Regenerative Medicine Translation:

The UK Bioentrepreneur Experience

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A thesis submitted for the degree of Doctor of Philosophy

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2010

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Declaration

I certify that the thesis I have presented for examination for the MPhil/PhD degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others.

I warrant that this authorisation does not, to the best of my belief, infringe the rights of any third party.

Acknowledgements

First of all, I would like to thank my doctoral supervisor Professor Sarah Franklin for invaluable advice throughout my research and her enormous support. Her guidance, patience and help have been critical to my challenge, which goes beyond this thesis and is about 'translating' a (previously hardcore) laboratory scientist into a sociologist.

This research would not have been possible without the bioentrepreneurs who agreed to be interviewed. All participants left their incredibly busy schedules to talk to me and I would like to express my gratitude. I am also grateful for the financial support of the Economic and Social Research Council.

I have benefited greatly from the BIOS intellectual community that I have been privileged to be part of. I thank all my friends and colleagues there with special thanks going to fellow 'traveller' Btihaj Ajana, and the older and wiser BIOsians Ayo Walhberg, David Reubi, Michael Barr, Kerstin Klein and Megan Clinch. Learning from them has been a pleasure.

I also owe my sincere thanks to Chris Mason and Ingrid Geesink whose advice and help at critical junctures of my research has been much appreciated.

Many of my friends, who have played a significant part in my life during the 'PhD years' deserve special thanks. They are: Vicky Malioka, Alexia Prodromidou, Nikos Prodromidis, Guy Burton, Constantinos Brikos and Isidoros Karatzas. Their friendship, advice, support and encouragement have been priceless.

Last but not least, I would like to thank my loving family, my parents Anna and Vassili Kaftantzi, and my sister Alkmini. This thesis is dedicated to my parents, who have constantly been there for me in every possible way. I am grateful for their love, their patience, their support and encouragement in all my endeavours, in the UK and elsewhere.

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Abstract

Regenerative Medicine is an emerging biomedical paradigm promising to radically change healthcare. For this to happen, basic science breakthroughs must be translated into the clinical setting and market. This thesis examines the evolving Regenerative Medicine Translation process from the perspective of UK-based bioentrepreneurs. While much is known about the views of scientists, clinicians and industry stakeholders, an understanding of what it is to be an RM entrepreneur and company founder and often drive the whole process has not been fully explored.

Based on interviews with bioentrepreneurs and other secondary sources this thesis explores three main 'areas' of the Regenerative Medicine Translation process: Funding, Regulation, and cross-disciplinary Collaboration. A variety of conceptual tools and social science analytical motifs are employed to explore the broad range of activities and roles undertaken by bioentrepreneurs. The exploration provides an in-depth look at individual experiences (at various stages of the clinical and commercial Translation process of their research) and sheds light on factors that influence the Translation process and the evolving role of bioentrepreneurs in it.

A main assumption throughout the thesis is that in the nascent field of Regenerative Medicine therapeutics (including cell-based and tissue-based), RM bioentrepreneurs are acting as crucial mediators of knowledge across the various scientific, institutional and professional domains. Their unique human capital (including scientific, clinical, regulatory and, often, business expertise) in combination with their formal status/position as founders of commercial entities aiming to commercialise new technologies, places them in a unique position between the bench, the clinic, and the industry from where they have the potential to elevate the available resources, facilitate Translation and promote innovation.

Findings from this investigation address voids in the understanding of RM Translation in the UK, provide insights not available through other types of stakeholder, and by means of lessons learned, potentially can help facilitate a cadre of more successful entrepreneurs and hence more successful Translation in the future.

List of Abbreviations

ACI	autologous chondrocyte implantation
ATMP	advanced therapy medicinal products
BBSRC	Biotechnology and Biological Sciences Research Council
BMRC	Biomedical Research Council (Singapore)
BSI	British Standards Institute
CB	cord blood
CBTs	cell-based therapeutics
CEO	chief executive officer
cGMP	current Good Manufacturing Practice
CHMP	Committee for Medicinal Products for Human Use
CMR	Centre for Medicine Research (US)
CSO	chief scientific officer
CTSAs	Clinical and Translational Science Awards
DG	Directorate General
DoH	Department of Health
DOR	disease-oriented research
DTI	Department of Trade and Industry
DUIS	Department for Innovation, Universities and Skills (UK)
EC	European Commission
EMA	European Medicines Agency (former EMEA)
ESRC	Economic and Social Research Council
EU	European Union
FDA	Food and Drug Administration (US)
FIH	first-in-human
FP7	Seventh Framework Programme

GMP	Good Manufacturing Practice
GTP	Good Tissue Practice
HES	Hospital Exemption Scheme
hESC	human embryonic stem cell
HFEA	Human Fertilization and Embryology Authority
HSC	haematopoietic stem cell
HTA	Human Tissue Authority (UK)
hTEPs	human tissue-engineered products
IND	investigational new drug
IP	intellectual property
IPRs	intellectual property rights
iPS	induced pluripotent stem (cells)
iSCNT	inter-species somatic cell nuclear transfer
ISCT	International Society for Cellular Therapy
ISSCR	International Society for Stem Cell Research
LDA	London Development Agency
LRMN	London Regenerative Medicine Network
LSE	living skin equivalent
MAAs	Marketing Authorisation Applications
MA-IMP	Manufacturing License for Investigational Medicinal Products
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MDD	Medical Devices Directive
MHRA	Medicines and Healthcare Products Regulatory Agency
MPD	Medicinal Product Directive
MRC	Medical Research Council (UK)

MSCs	mesenchymal stem cells
NHS	National Health Service
NIH	National Institutes of Health (US)
NIHR	National Institute of Health and Research (UK)
OECD	Organisation for Economic Cooperation and Development
OSCHR	Office for Strategic Coordination of Health Research (UK)
PAS	publicly available standard
PCT	Primary Care Trust
PI	principal investigator
POR	patient-oriented research
POST	Parliamentary Office of Science and Technology (UK)
Q&S	quality and safety
R&D	research and development
RATE	Regulatory Authority for Tissues and Embryos
RDA	Regional Development Agency
REC	Research Ethics Committee
RM	regenerative medicine
RMT	regenerative medicine translation
SCI	Stem Cell Initiative (UK), or UKSCI
SMEs	small and medium sized enterprises
SSCN	Scottish Stem Cell Network
STS	science and technology studies
TCD	Tissue and Cells Directive (EU)
TE	tissue engineering
TEPs	tissue-engineered products
TR	translational research
TTA	tissue transfer agreement

TTO	technology transfer office
UCL	University College London
UKXIRA	UK Xenotransplantation Interim Regulatory Authority
VC	venture capital
VCs	venture capitalists
WARF	Wisconsin Alumni Research Foundation

Chapter 1

The Three Arts of Translation: Funding, Regulation and Collaboration

This chapter begins with the story of the first stem cell transplant, as narrated by Professor Anthony Hollander from Bristol University, one of the scientists who took part in the breakthrough experiment/operation. Professor Anthony Hollander gave his presentation titled: 'Claudia's Trachea: Lessons Learned for Future Regenerative Medicine Strategies' at the London Regenerative Medicine Network[1] meeting in December 2008. I use the scientist's descriptions and comments to present the main themes of Funding, Regulation and Collaboration in the realm of Regenerative Medicine Translation and to provide a structure for presenting my empirical data and analysis in the three empirical chapters of the thesis (Chapters 4, 5 and 6).

In the second section of this chapter I briefly explain the rationale for this thesis and present the main research questions. The third section comprises the conceptual approach and the methodology that I followed, including descriptions of research settings (actors, timelines, and locations), data sources, analysis of interviews, research ethics and limitations of the study. In the final section I provide a brief overview of all the thesis chapters.

Claudia's Trachea: the Challenges from Breakthrough to Routine

> I got a phone call from Martin asking, "Would I help?" My first thought was – That's completely crazy. How can one go from the science that's

[1] The London Regenerative Medicine Network (LRMN) is a 'not-for-profit organisation' that was set up in 2005 by two internationally acknowledged leaders in the field of stem cells and regenerative medicine, Dr. Stephen Minger (King's College London) and Professor Chris Mason (University College London). The main objective of the Network is to provide a forum for all aspects of the new regenerative medicine technologies to be presented and discussed by holding evening meetings once a month, 11 months of the year. According to its website, the London Regenerative Medicine Network is the largest and most successful regenerative medicine network in the UK (if not globally) with a membership of over 4,500. Sponsorship has come from various sources including the London Development Agency (LDA), the UK Stem Cell Foundation, leading law firm Clifford Chance, as well as industry sponsors. The Network has showcased many 'high profile speakers of international calibre with interests and backgrounds from basic science, translational research, clinical sciences, biotechnology, the pharmaceutical industry or regulatory affairs'. For more information see: http://www.lrmn.com.

been done in several different countries and suddenly put it all together in a space of a few weeks and get it into a patient? It didn't seem at all the sensible thing that a career scientist like myself would do. Indeed, it could have been the end of my career, I suppose, if it had all gone pear-shaped. But I quickly realised that, actually, this was a golden opportunity not to just have the chance to intervene in the life of a lady who was at death's door, but also to do what I and many others have been saying in the media for years – which is that stem cells can help to save lives, can help to really improve the quality of life. And I did realise the importance of that moment and it was kind of a life changing moment for me. "Yes, let's go for it; let's see what we can do".

(Anthony Hollander, LRMN Meeting, Dec. 2008)

In the opening quotation, Professor Hollander explains to the audience his first reactions and thoughts when Professor Martin Birchall, an otolaryngology surgeon also from Bristol University,[2] called him on a Sunday afternoon to ask whether he would be interested in participating in an international collaborative project involving four research teams in three countries.[3] Paolo Macchiarini, a surgeon and clinical investigator based at the Department of General Thoracic Surgery, Hospital Clinic in Barcelona, had pioneered the research and now the perfect patient on whom to try the technique had arrived in his clinic.

In March 2008, Claudia Castillo, a 30-year-old Colombian woman, was admitted to hospital in Barcelona suffering from collapsed airways, following a severe case of tuberculosis. In such cases of end-stage bronchial disease, the only conventional option is to remove the affected lung and airway and perform a transplant (i.e. lungs and trachea from a donor[4]). At present, patients undergoing organ transplants must spend the rest of their lives on powerful drugs to suppress their immune systems. These drugs are necessary to avoid donor organ rejection but they can leave organ recipients vulnerable to other infections and complications. In order to save Castillo's life and, in addition, avoid the risks of immunosuppressant drugs, the doctors decided to try to tissue engineer a 'new' section of trachea containing the patient's own cells.

[2] Martin Birchall is currently Professor of Laryngology and consultant laryngologist at the Ear Institute (UCL) and the Royal National Throat Nose and Ear Hospital (RNTNEH).
[3] UK (Bristol team); Italy (Padua team, Milan team); and Spain (Barcelona team).
[4] The procedure is known as clinical allografting and the cells/organs used are from a donor (cadaver).

Engineering the 'new trachea' required an enormous coordinated effort among the different teams to ensure all necessary steps are executed and integrated in a timely manner. Initially, a scaffold was prepared by Italian scientists in Padua who took a section of trachea from a donor and repeatedly 'washed' it to remove all donor cells, leaving only a collagen 'scaffold'. Two types of cells were needed to line the scaffold and make it bio-compatible with the patient: chondrocytes (cartilage cells) derived from stem cells from Castillo's bone marrow that would line the outer surface; and epithelial cells, taken from a still healthy part of her trachea, to line the inner surface of the scaffold. These stem cells, from Castillo's bone marrow and airway, were taken to the University of Bristol, and grown to quantities necessary for the procedure. When ready, the cells were flown to Barcelona and placed within the decellularised scaffold in a bioreactor (developed for this purpose by a team in Milan), effectively making a windpipe in the lab. The final construct was cut and bent into the right shape, before finally being surgically grafted into Castillo in June 2008 at the Hospital Clinic in Barcelona by Professor Paolo Macchiarini who conceived the project.[5] No immune suppression medication was required because the raw materials came from Castillo herself and, within two months of the operation, Castillo had a normal lung function and was able to lead an independent life.

In his presentation, Hollander describes the initial feelings of caution and uncertainty he had over the outcome of the collaboration, as well as his concerns about the effect failure would have on his career (possibly even signalling its end). He refers to the 'crazy' choice he made as a 'career scientist' to agree to collaborate. His choice of words makes sense if one considers the early stage of these technologies, their novelty, and the challenges that would need to be faced in order for such a procedure to succeed. Paolo Macchiarini, the surgeon who designed the project, had only previously used pig and mouse models to develop and streamline the process in which autologous cells are seeded onto a decellularised donor tracheal scaffold and matured in a bioreactor. Encouraged by the *in vitro* generation of short but vital tracheal matrices, and by the absence of an immunological response to allografted and xenografted tracheal constructs in animals,[6] Macchiarini's ambitious aim was to bioengineer a human trachea and to attempt the application of this technology in a patient with end-stage airway disease.

[5] The transplantation was first reported in (Macchiarini et al., 2008).
[6] The publication describing the successful outcomes in animals is (Jungebluth et al., 2009).

This type of first-in-human (FIH) experimental intervention inevitably presents a series of risks and ethical challenges that if not entirely without precedent, are nonetheless distinctive, unfamiliar and unresolved.[7] Most of the risk is traceable to the character and degree of uncertainty in these translational interventions including issues of how to best predict and measure human response, how to assure safety, and how to manage and reduce any untoward outcomes. One has simply to look at the field of gene therapy to realise the degree of institutional and personal risk that is involved in early translational trials.[8] Had the participants failed to join up the steps and successfully complete the operation, or if indeed Castillo's body had rejected the transplanted 'new organ', then 'fingers would have been pointed'.

Indeed, the development of cell therapies and tissue engineered products has been, and continues to be, a long and risky trip, with both failures and successes readily reported by the media. Promises and predictions made by enthusiastic and ambitious scientists are communicated to the public through 'hyped' press releases, often conveying the impression that these therapies are safe and immediately available. In Hollander's own words' 'it was a golden opportunity [...] to do what I and many others have been saying in the media for years'.

However, experts in the field of regenerative medicine have drawn attention to this 'hype' and have stressed that unrealistic expectations and the premature use of technology could put patients at risk and as a result endanger public trust in new technology, jeopardising the future of the whole field (Braude et al., 2005; 2009a: 1011). Social scientists, on the other hand, who have explored these issues in relation to stem cell research, stress that 'it is a mistake to think that we can somehow factor out the hype, the media or the work of the imagination to exaggerate either the promises or the risks of new technology. This is not going to be possible, now or in the future, because it is precisely the importance of imagining a future yet-to-be that fundamentally defines the whole issue of the new genetics and society' (Franklin, 2001:

[7] Kimmelman, an Assistant Professor in the Social Studies of Medicine Unit, McGill University (Montreal, Canada), has explored these issues extensively in his book: *Gene Transfer and the Ethics of First-in-Human Research - Lost in Translation* (2010). Kimmelman uses the example of gene therapy to examine the ethical and policy dimensions of testing novel interventions in human beings for the first time. The book argues that many ethical frameworks devised for randomised controlled trials translate awkwardly to early phase human studies of novel therapies.

[8] In 1995, a high-level panel at the NIH faulted the gene therapy field for rushing into clinical trials (Orkin & Motulsky, 1995). In 2005, a gene therapy leading figure, James Wilson received a five-year, FDA-imposed ban on leading clinical trials. The ban followed the death of 18-year-old Jesse Gelsinger who died September 17, 1999, while participating in a trial of gene therapy (headed by Wilson) at the University of Pennsylvania Institute for Human Gene Therapy.

349). Hence, Castillo's successful transplantation could be seen by the public as providing the crucial new evidence that (at least) adult stem cells can offer genuine solutions to serious illness, boosting the arguments of scientists and vindicating the decisions of investors (public and/or private) to support the Translation of this kind of research.

Another key point to highlight here is that the tracheal transplant was achieved without any major formal funding, using only small local funds (Laurance, 2008). In the quote below, Hollander highlights the importance of a multidisciplinary team for the successful operation and points out the difficulty of securing funding for this type of high-risk, translational project:

> The reason this worked, it all came together, is because we had a multidisciplinary team. And that's a real take home message. We had Paolo [Macchiarini], driving things from the surgical point of view, the work on airways he'd been doing, we had Maria Teresa Conconi who developed the scaffold decellularisation process, we had our bioreactor experts in Milan and we had the Bristol team, myself and Martin [Birchall], doing the stem cell biology [...] So this was a multidisciplinary team. Scientists who have applied for grants to do this kind of work will know how extremely difficult it is to get pass review panels with this. I don't think we would have got a grant to do this, I don't think it would have passed. And we need to think really hard about that as a country. How the hell do we get this kind of multidisciplinary work funded properly without scientists from one discipline trashing your grant because he or she doesn't understand the science in another discipline? I don't know what the answer is, but if we are really going to do this sort of thing more frequently we have to resolve that one.
>
> **(Anthony Hollander, LRMN Meeting, Dec. 2008)**

Multidisciplinarity and the successful integration of the various 'parts' of the project were, according to Hollander, key to the success of the operation and yet, paradoxically, what made it hard to fund. Four research teams from three different locations/countries, managed by the surgeon and pioneer of the technique

(Macchiarini), integrated their methods, materials and expertise, as well as their small sources of funding, to produce a custom-made product on time. Despite the significance that cross-disciplinarity[9] seems to hold for this 'first' in RM Translation, Hollander maintains that this type of collaborative Translational Research is notoriously difficult to fund. He goes on to share his experience (and that of other researchers) of trying to get this type of research proposal through research evaluation panels, saying that it is not unheard of for reviewers to reject a cross-disciplinary research proposal only because they lack the relevant expertise and experience to conduct an appropriate evaluation.

Indeed, in the social sciences literature problems with research funding have been linked to the research evaluation process. In today's academia, evaluation is an integrated element of research, with the traditional peer review providing the gold standard of scientific evaluation. 'The peers are the judges'. However, the fairness of the principle of peer reviews has been questioned when it comes to cross-disciplinary research (Porter & Rossini, 1985), with authors reporting that funding structures with a strong peer review component tend to overfund mainstream research that follows established research lines, and peer reviewers to be risk averse and biased against speculative, unorthodox and cross-disciplinary research proposals.[10]

In addition, authors who have explored potential obstructions to cross-disciplinary research have emphasised the importance of 'mutual knowledge' between cross-disciplinary teams, if they are to succeed in their common endeavour. 'Insight into the basics of methodology, theories, epistemological and historical aspects of the others' disciplinary discourse is essential for understanding and respecting the position of collaborators from other fields. Conceptual compatibility is the basis for understanding and overcoming negative prejudices and creating respect' (Aagaard-Hansen & Ouma, 2002:432).

[9] In the rest of the thesis the term cross-disciplinarity will be used according to Rosenfield (1992); that is as a general designation for all the three terms (multidisciplinarity, interdisciplinarity, transdisciplinarity). Rosenfield's taxonomy describes three stages of progressive integration of the participating disciplines in terms of theories, methodologies and overall conceptual framework. She suggests that multidisciplinarity is present when researchers 'work in parallel or sequentially from disciplinary-specific bases to address common problems'. Interdisciplinarity consists of 'researchers working jointly but still from disciplinary-specific basis to address a common problem', whereas transdisciplinarity comprises 'researchers working jointly using a shared conceptual framework' that draws together concepts, theories, and approaches from the parent disciplines (Rosenfield, 1992). In addition to Rosenfield, Aagaard- Hansen and Ouma (2002) emphasise the significance of the time dimension on the process of progressive integration and propose that 'this is a gradual process in which the research group little by little moves in the direction of integration—from multi to transdisciplinarity and which takes place at different paces' (Aagaard-Hansen & Ouma, 2002:206).

[10] (Bourke & Butler, 1999; Horrobin, 1996; Langfeldt, 2006; Travis & Collins, 1991)

The same could possibly hold true for the fair and unbiased evaluation of cross-disciplinary proposals, something that, according to Hollander, is not really happening in the regenerative medicine (RM) field. From his comments it is obvious he considers it crucial that reviewers who are given the evaluation responsibility should have, in addition to their disciplinary competences, some kind of personal cross-disciplinary experience. This could be either in terms of double training (i.e. cross-disciplinary background) or in terms of practical involvement in similar projects.[11] In Hollander's view, funding agencies/research councils do not seem to have the appropriate expertise when it comes to evaluating cross-disciplinary research proposals. Hollander's account of grant application realities is in sharp contrast to the importance governments and their funding agencies place (or desire to be seen to place) on funding cross-disciplinary, highly innovative research, with many research councils and science administrators publishing guidelines[12] on how to facilitate and promote this agenda.

Another point to make here is that cross-disciplinary research is often thought of as highly innovative, off-the-beaten track, ground-breaking and thus as a 'high risk/high return' endeavour that might jeopardise one's academic and/or clinical career. This is especially true for Regenerative Medicine research as it has so far followed some controversial research avenues (e.g. hESCs), where the returns have been uncertain, distant, and often negative.[13] The concept of risk-taking is thus a necessary element of crossing disciplines and exploring new avenues of research in Regenerative Medicine. This approach to conducting research, however, unavoidably clashes with the standard pathways laid down for academic careers, mainly confined within disciplines. Academic researchers, clinical practitioners and bioengineers, three of the most important professional communities involved in Regenerative Medicine research, are all used to accumulating credit and constructing networks within their own disciplines in order to further their careers. 'Trespassing' into collaboration with other disciplines may be seen as a waste of time and resources that would best be spent in their own 'area'. Grit Laudel (2006a, 2006b), a sociologist from the Australian National University who has

[11] (McNeill et al., 2001)

[12] Research Councils UK (RCUK), 2006; Committee on Facilitating Interdisciplinary Research and Committee on Science, 2005; EURAB, 2004; OECD, 1998; Academy of Finland, 1997.

[13] In February 2009, researchers in Israel reported that a 13-year-old boy with ataxia telangectasia who had received injections of human foetal neural stem cells into his brain as part of an experimental treatment performed in a Russian clinic, four years after the treatment developed brain tumours apparently derived from the injected stem cells. This was the first report of a human brain tumour complicating neural stem cell therapy and concerns were raised over the safety of this experimental therapeutic approach (Amariglio et al., 2009).

investigated how researchers decide whether or not to propose risky research projects to sponsors, has found that many investigators will avoid high-risk topics/areas because they fear that the risk of failure (to obtain the grant) is too high. Failure to secure funding can be seriously detrimental, particularly to early-stage researchers or untenured academics. In the case of Claudia's trachea, the future of Birchall and Hollander's research (who were preparing their application to the European Union for grants to cover the next phase of the work) was heavily dependent on the outcome of this one operation.

In his discussion of the risks faced by high-profile, pioneering RM cases, Hollander also emphasised the crucial role 'flexible' regulation played in the successful realisation of the project:

> There was a lot of flexibility by the regulators. They worked with us and we got the permissions that we needed. I don't know if we would get that again. I actually don't know if we would have been able to do this operation here in the UK. I really just don't know that. But I simply make the point that if we are going to move forward in this field we are going to have to take some kind of risks with the patients on board with that. And I hope the regulatory environment, particularly with the new legislation[14] coming in January, doesn't prevent that. Because it could kill off this whole field and that would be a disaster in my mind. Actually, I think it would be unethical if that was the result.
>
> **(Anthony Hollander, LRMN Meeting, Dec. 2008)**

In this passage, Hollander expresses his concern about the way Translational Regenerative Medicine is conducted (or rather not conducted) under the current regulatory regime. Although he does acknowledge a degree of flexibility and collaboration on the part of Spanish regulators (as Barcelona was the place where the actual transplantation procedure was performed), he expresses uncertainty about whether this type of collaborative work involving research and clinical groups from different countries would be possible beyond the one-off case, or whether it could be eventually undertaken on a more routine basis in the UK. In the trachea project, the

[14] Hollander refers to the Europe-wide ATMP regulation.

UK's involvement was focused on developing the methods for growing human epithelial and mesenchymal stem cells (to be differentiated into chondrocytes) and carrying out the cell cultures, work belonging more in the realm of basic rather than Translational Research, and quite straightforwardly regulated in the UK. However, the surgery, which is the more 'translational part' of the project as it involved the actual application of the therapeutic construct into the patient, was performed in Spain.[15]

In Hollander's view, the UK is 'going to have to take some kind of risks with the patients on board with that', if it is going to move forward in the RM field. Indeed, what Hollander states is the very compelling argument for initiating first-in-human (FIH) trials and experimental clinical research in general: it is the results of these investigations that provide pivotal insights and allow the field to advance. In other words, only clinical trials will provide the necessary data to move forward and to optimise a cell therapy by recognising the best type of cell as well as the best delivery method for each disease.

Decisions to launch first-in-human (FIH) experiments are often marked by controversy. In truth, all forms of medical treatment are accompanied by the risk of unwanted side effects and cell therapies are no exception. Given the level of excitement surrounding Regenerative Medicine therapies, it is also not surprising that basic laboratory findings are being thrust forward into translational human studies at the earliest possible stage. There is, however, ongoing debate on this issue with many authors stating that we should be wary of prematurely pushing laboratory research into clinical practice (Chien, 2004; Wilson, 2009a, 2009b). In a 2009 *Science* article, James Wilson who led the gene therapy clinical trial shadowed in 1999 by the death of Jesse Gelsinger, expressed his growing concern that the field of stem cell research, like that of gene therapy, is getting ahead of itself. He says, 'I am concerned that expectations for the timeline have outpaced the field's actual state of development and threaten to undermine its success' (Wilson, 2009a:727). According to Wilson, the decision to initiate FIH is not just about ambitious investigators and desperate patients willing to accept greater uncertainty and higher risk, it is also about the fact that these trials make use of scarce social resources and adverse outcomes can 'initiate a chain of events that

[15] While the overall performance of Spanish biomedical research still lags behind that of the major international players, clinical research fares remarkably well in most comparisons. For example, papers on clinical medicine by Spanish authors indexed by Thomson Reuters between 2003 and 2007 received an average of 2.69 citations per paper, an impact 11% above the world average (Raya & Belmonte, 2009).

would seriously derail a field'[16] (2009a:727). Hence a cautious approach to Translational Research and its risks is justified not only by the duty to protect the welfare of the research subjects but also by the desire to safeguard the integrity of the broader research enterprise, and to protect the future of these innovative health technologies. Other experts believe that the risk of exposing patients to possible adverse outcomes of a new RM treatment must be weighed against the risk of depriving all patients of a novel and possibly effective treatment that will alleviate suffering and/or prolong life (Master et al., 2007).

Hollander also makes the point that this kind of collaborative, cross-border Translational Research is necessary to achieve the promises of Regenerative Medicine. However, he stresses that the future of this type of work is highly dependent on the new, EU-wide regulatory regime which came into force in December 2007[17] and aims to initiate harmonisation of standards for medicinal products (including RM cell based and tissue-engineered products/therapies). In Hollander's view, an unfavourable or dysfunctional regulatory landscape could seriously hamper collaborative translational efforts – an outcome he describes as disastrous and unethical as, he implies, it will severely retard, or even halt, the development of new life-saving options for patients such as Castillo, for whom conventional treatments are essentially worthless.

Reviewing Professor Hollander's presentation as a whole, it is clear that this landmark operation presents at least three crucial take-home lessons. First, it saved the life of Claudia Castillo, and transformed her existence from being virtually bed-ridden to a fit young woman who can resume the active life she once had. Second, it has demonstrated what stem cell technology, which has promised much but so far delivered little, can really do. And third, it is a remarkable example of international co-operation involving expertise from four teams in three countries.

In his 30-minute presentation, Hollander thus underscored what appear to be the three most important 'pillars' in the Translation of Regenerative Medicine: Funding, Regulation and cross-disciplinary Collaboration. My interviewees seem to be in agreement with Hollander's highlights since these three 'themes' also resonate

[16] Adverse events can damage public and investor confidence, initiate cumbersome oversight mechanisms in order to avoid further problems, and also close off promising research avenues.
[17] ATMP regulation came into force in December 2007 and became effective in December 2008.

repeatedly (along with a variety of other related issues) in the accounts of all informants in this study. Drawing on Hollander's description, I chose to use the themes of funding, regulation and collaboration as the three 'lenses' through which my informants recount their translational experiences in the Regenerative Medicine field: Chapter 4 addresses funding, Chapter 5 regulation and finally, Chapter 6 the theme of cross-disciplinary collaboration. The next section briefly presents the rationale of the thesis and the main research questions.

Briefly about the Thesis

This thesis examines the changing 'landscape' in the Regenerative Medicine research Translation process from the perspective of UK bioentrepreneurs. The thesis aims to characterise the varied nature of the contribution of bioentrepreneurs in the Regenerative Medicine Translation process and the various mechanisms through which it facilitates product innovation.[18]

While much is known about the views of scientists, clinicians and industry stakeholders,[19] limited research to date has focused on the experiences of bioentrepreneurs and founders in the UK Regenerative Medicine field. Research with scientists, clinicians and industry representatives is certainly important for understanding the interactions between these groups of stakeholders in relation to the context of the laboratory, the clinic and the market, but an understanding of what it is to be an RM entrepreneur and founder and to often 'drive' and 'coordinate' the whole Translation process has not been fully explored.

This research attempts to remedy this missing component by exploring what it is like to experience Regenerative Medicine Translation through this 'unique' and 'critical' position (role). The exploration provides an in-depth look at individual experiences (at various stages of the clinical and commercial Translation process) and sheds light on factors that influence the process and the evolving role of bioentrepreneurs in it. What is like to be a Regenerative Medicine entrepreneur in the UK? How do

[18] I will not be examining any performance implications of bioentrepreneur involvement/activity.
[19] (Plagnol et al., 2009). For relevant social studies see the literature review of the social science studies in the RM field provided in Chapter 3.

bioentrepreneurs conceptualise, describe and make sense of the Translation experience?

Entrepreneurs are often the principal investigators (PIs)[20] of the basic research being carried out and hence the ones responsible for identifying significant findings and recognising and evaluating opportunities for potential clinical and commercial Translation. They are the inventors of the technology, owners (or co-owners) of the IP and are often involved in the subsequent clinical experimentation of the products. They might simply be licensors of technology or, in some cases, founders of a spinout (or start-up company) and thus responsible for setting up a robust team comprising various types of expertise[21] that will have a good chance of 'seeing' the therapy/product to the clinic and or market.

Findings from this investigation address voids in the understanding of RM Translation in the UK, provide insights not available through other types of stakeholder participation, and by means of lessons learned, potentially can help facilitate a cadre of more successful bioentrepreneurs and hence more successful Translation in the future.

Fourteen entrepreneurs of various ages, undertaking various combinations of professional roles and based at diverse UK universities, research institutions, or corporate firms were interviewed. Data were enriched by commentaries from presentations taken from relevant conferences and meetings and from a number of informal conversations, as well as significant background research in the relevant academic and policy literatures.

For the purpose of this thesis, I define Regenerative Medicine bioentrepreneurs as principal investigators (PIs) in a Regenerative Medicine field who have one or both of the following characteristics:

- They have a patent on an RM invention (whether they have licensed it yet or not)

[20] Principal investigator (in the biomedical sciences) is the person designated as taking overall responsibility within the team of researchers for the design, conduct and reporting of the study. Principal Investigators are expected to lead and manage a research team, secure new research grants, liaise with stakeholders, publish, respond to with institutional issues and agendas, and maintain and develop their own research expertise. Frequently they simultaneously carry out a range of teaching and administrative duties too (PIs are also sometimes called Research Leaders).

[21] depending on area of research and phase of Translation.

- They have founded (or co-founded) an RM company at some point in their career. The company can be either an academic spinout or a start-up (corporate)

A main assumption throughout the thesis is that in the nascent field of Regenerative Medicine therapeutics, RM bioentrepreneurs are acting as crucial mediators of knowledge across the various scientific, institutional and professional domains. Their unique human capital (including scientific, clinical, regulatory and, often, business expertise) in combination with their formal status/position as founders of commercial entities aiming to commercialise new technologies, places them in a critical position between the bench, the clinic and the industry, from where they have the potential to elevate the available resources, facilitate Translation and promote innovation.

My main research questions are the following:

1. **How is Translation being conceptualised and practised by bioentrepreneurs in the Regenerative Medicine field in the UK?**
   A. What are the key challenges (problems) that need to be overcome and at which stage of the Translation process?
   B. How do bioentrepreneurs address each challenge?

2. **What are the translational models that bioentrepreneurs identify?**

(e.g. funding models, IP models, regulatory governance models, collaboration models)

3. **What is the importance of the bioentrepreneurs' contribution?**
   A. What are the resources bioentrepreneurs need to employ (financial, human, etc) in order to lead the products/therapies through clinical and commercial Translation?
   B. Do they relish their 'coordinating' role?

To address these research questions, in addition to drawing upon in-depth interviews with Regenerative Medicine bioentrepreneurs, I also use relevant documentary sources (see following section on Analytical and Methodological approach). Though the focus of the thesis is Translational Regenerative Medicine in the UK and the data collected are from and for UK-based research groups, bioentrepreneurs and companies, I also

examine sources and data from other countries (especially the US) as Regenerative Medicine is a 'global enterprise' .

The following section provides an explanation of the methodological and analytical (conceptual) approach I chose to follow in this study. More specifically, I begin with a description of the data sources I used and methods I employed. Afterwards, I introduce the (interview) research setting (actors, timelines and locations), explain the reasons behind my choice of participants and provide a justification of my grounded theory methodology. In the final section I provide a brief description of the analysis of the interviews, the ethical considerations and address the possible limitations of this work.

Methodological and Analytical Approach

Research Design (Data Sources/Methods)

In this section I review and reflect upon the research process and specific sources and methods used to capture my data. I continue with an introduction of the research setting and afterwards, I explain the main reasons behind my choice of informants.

For practical reasons, I focussed on three main data sources. These included interviews, documentary sources, and fieldwork conferences, meetings and workshops. Interviewing was chosen as the most appropriate technique to explore the specific research subject. Indeed, RM bioentrepreneurship and the role it seems to play in RM Translation is not an 'endeavour' that can be explored through academic journals, reports and surveys. Bioentrepreneurs, as the designated Translation champions, are presumably the best source of information about the phenomenon of Translation and the various challenges that seem to impede RM innovation (the drawback, of course, being the difficulty of recruiting interviewees). There are abundant documentary sources on RM, most of which are in the public domain. Documentary sources (such as legislation documents) provide a fundamental background and structure to the study. Finally, the data gathered during relevant conferences, workshops and meetings have been a particularly rich and crucial addition, as I had the opportunity to interact with diverse stakeholders, many of whom are leading figures in the RM field, thus

gaining access to opinions and views that I would not have had the opportunity to collect otherwise.

Documentary Sources

A wide variety of documentary sources were used. These include regulation sources, such as national and international regulatory guidelines, directives and codes of conduct (applicable to the UK context);[22] commercial sources such as websites[23] (including individual company websites), newsletters, commentaries, press releases and position papers on relevant regulation and commercialisation activities. Blog commentaries managed by Regenerative Medicine experts have also proven a rich and reliable source of information on the latest development in Regenerative Medicine R&D.[24] Many of the participants have also provided me with handouts and company leaflets. Scientific sources including scientific journal papers and reviews on specific Regenerative Medicine applications (for example skin systems, cardiac repair, etc.) were also very useful in gaining familiarity with the field and keeping up to date with the latest advances and breakthroughs. Finally, I also reviewed various government reports (e.g. the Cooksey Report, Pattison Report, POST publications, etc.), Research Councils' (for example the MRC) publications, and reports based on national, European and international studies (surveys) and initiatives.

Fieldwork Conferences/Meetings/Workshops

In addition to the formal semi-structured interviews, I had a number of informal and personal conversations with relevant actors at numerous fieldwork conferences.[25] Since

[22] These included official publications of the European Commission and EU legislation, directive and policy documents; MRC, EMA (former EMEA), HFEA, HTA publications and regulatory guidance documents.

[23] A website/newsletter I found especially useful is the 'Cell Therapy News' 'Cell Therapy News' is a free, weekly e-newsletter and website portal dedicated to providing the latest information affecting cellular therapies. The website portal supplies information about cell therapy products, jobs, events, publications, associations and regulatory bodies. The e-newsletter incorporates the most recent news from all areas of the field, from its science, research, and business news, to its regulatory affairs. The e-newsletter is published online weekly and sent to over 11,000+ subscribers globally (http://www.celltherapynews.com).

[24] One of the most useful blogs has been the 'Cell Therapy Blog' which includes business news and analysis for executives in the cell therapy and RM industry. The blog is 'run' by Lee Buckler a former attorney and Executive Director of the International Society for Cellular Therapy (ISCT) who is now a consultant on the business side of the cell therapy and regenerative medicine sector (http://celltherapyblog.blogspot.com).

[25] For example, I attended the Conference on the Commercial Translation of Regenerative Medicine that was organised by MarcusEvans on 16 and 17 November 2007. During the two-day conference 17 speakers presented on a variety of commercial Translation-related themes including: the latest R&D developments in the field of Regenerative Medicine, emerging regulation, the complexities of manufacturing RM products and the role of automation in realising the commercial dream, the structuring of reimbursement strategies and lessons learned from the current leading companies in the field.

these conversations were 'off-the-record', I have not quoted nor directly used the comments of these individuals, but I did use them to inform my analysis. Extensive field-notes were also produced based on observation and participation in these conversations, as well as my attendance at meetings and conferences. In addition, relevant documents were collected in the form of speakers' presentations, papers, company prospectuses and associated materials to generate an extensive database of sources relevant to this research. This generated a large amount of data on industry activities, cutting-edge clinical developments and regulatory issues that was not yet in the public domain and would not otherwise be available to me. Equally important during these meetings, was the opportunity to observe the various actors as they mingled and interacted with one another through the different 'stakeholder' networks and under one or more of their professional roles (e.g. scientist, clinician, business entrepreneur, or manufacturer/developer).

In addition to the above data, I recorded and transcribed three presentations from the London Regenerative Medicine Network meetings. The presentation details are the following (including speaker, title of presentation and date):

- Greg Bonfiglio, Founder and Managing Partner at Proteus Venture Partners, 'Commercialising Regenerative Medicine: Moving Great Science from Bench to Bedside', November 2008.
- Geoff MacKay, President and Chief Executive Officer (CEO) of Organogenesis, 'Applying Living Technology for Soft Tissue Regeneration: Research and Development, Manufacturing and Commercialisation', November 2008.
- Professor Anthony Hollander, University of Bristol, 'Claudia's Trachea: Lessons Learned for Future Regenerative Medicine Strategies', December 2008.

Interviewing (Actors, Timeline, Locations)

Interviews are generally considered to be the most suitable approach when seeking rich data illuminating experiences and attitudes. The drawbacks are that interviews are very

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Permission was granted to record 16 (out of 17 presentations) and the relevant question-and-answer sessions that followed, as well as the final panel discussion which lasted for an hour. All participants had been made aware that the presentations and discussions were being recorded and that the information might be used later on in publications. All recorded material was transcribed, and in combination with conference documentation and interview data, was used to inform analysis (MarcusEvans is an international business events and information company which, in collaboration with Professor Chris Mason (UCL), runs an annual commercially focussed regenerative medicine conference with the participation of the most acclaimed academics, practitioners and leading companies in the RM field).

time consuming to conduct and analyse. The interviews were conducted in two phases: the first phase consisted of seven interviews between September and December 2007 and the second phase consisted of seven interviews between October and December 2009. This timing apart from allowing me time to reflect on how to approach the next set of interviews also had other fortuitous advantages (described later).

My purpose in interviewing was to identify individuals, who through personal experience were involved in one or more parts of the RM Translation process, and to try and explore the perspectives and experiences regarding this process with them in a semi-structured dialogue that was recorded and then transcribed. In most cases, interviews developed into a format more typically recognised as a 'conversation with a purpose' (Burgess, 1988). Interview duration ranged from 60 to 80 minutes and took place at times and locations convenient to the interviewees (usually their academic office, hospital unit, or company premises).[26]

All transcripts were anonymised by replacing full names with codified initials. The interviewees' main professional roles (e.g. PI, founder, or clinician) are also mentioned under each quote along with the date (year) of the interview. Finally, people's names (e.g. colleagues/collaborators mentioned), company names and products have been replaced by simple descriptions such as [Colleague], [Company] and [Product]. A table with the coded initials and brief description of the roles of each interviewee can be found at the end of the thesis in the Appendices (Appendix 1, 'List of Interviewees').

[26] It would be difficult to overemphasise the challenges involved in acquiring interviews with many of the bioentrepreneurs included in this study. Because of their extremely busy schedules, it was often difficult to contact them at all, never mind to secure an appointment. Even once an appointment had been made (most of the time after 'intense' and long communication with the interviewee's secretary), it would often be changed at the last minute due to the unpredictable scheduling demands of the interviewee. There are numerous anecdotes to report, including one about the interviewee who, after failing to appear at the scheduled time and place of the interview, agreed to rearrange it for the same day and time the following week. However, in an attempt to 'squeeze' the interview into his schedule, he arranged to meet me in a (cardiac) intensive care unit in a room occupied by one of his colleagues, a few patients, and a few nurses reappearing every few minutes to ask him questions. In another case, the bioentrepreneur not only rearranged the interview three times (always with an e-mail and five minutes before I arrived at his office), but also, when we finally did manage to begin the interview, he disappeared intermittently into the operating theatre. Finally, I cannot but sympathise with the PI who, in response to my request for interview letter, wrote back stating: 'Thank you for your message. I am very sorry but I will not be able to help you at this time. I have a completely full diary for the next few months – partly as a result of trying to meet the requirements of the new ATMP regulations! I hope that you will be able to find the information you need elsewhere. Once again I am very sorry. I would normally be very happy to help with a project such as yours'.

Interview Responses

A number of individuals did not respond to request for interviews (despite follow-up letters), including five founding directors of well-known UK academic spinouts. A possible explanation is that many of these biotech entrepreneurs are high-status busy individuals, some of whom have already been interviewed numerous times about similar themes, so they felt that they have already contributed their views and chose not to take part. On the positive side, their opinions and views on thesis-relevant issues are available through a variety of sources, including journal interview articles, editorials, commentaries, books, on-line radio interview archives and blogs. I have used these materials to the extent feasible to this research and have referenced them appropriately.

Actors: Why Focus on Bioentrepreneurs?

My interest in the role of the RM inventors/bioentrepreneurs was sparked by previous research[27] during an MSc course where I had the opportunity of interviewing a number of different Regenerative Medicine stakeholders including basic research scientists, clinicians, bioentrepreneurs, bioengineers and others. In my experience, the majority of participants from other stakeholder groups, such as clinical researchers and biomedical scientists, while knowledgeable and experienced in the own field, are unfamiliar with Translation issues outside their 'area'. For example, basic scientists are well versed in the craft from stem cell cultures to the regulation and standards of fundamental laboratory research. They don't, however, have the contact with clinical centres which would inform them about the 'real' medical needs, and thus luck knowledge on the 'clinical side'. Clinicians, although aware of the medical needs of their patients, are often unaware of the cutting-edge laboratory-based developments. Both basic scientists and clinicians also seem to be unfamiliar with many issues relevant and necessary for Translation, such as regulation and IP. When asked about these issues,

[27] I have carried out relevant research in partial fulfilment of the requirements for the degree of MSc in Health Management (2002-2003) at Imperial College Business School, London. The study, which is called 'Stem Cell-Based Products: From Bench to Bedside', was conducted between May and September 2003 and in collaboration with NovaThera, an Imperial College spinout RM company. The study describes and analyses the journey of novel cell-based products beginning with the laboratory and ending with the market, including: intellectual property issues, the role of regulatory agencies for patient protection and public health, ethical and social considerations, legislation in the US, UK and other European countries. I have also carried out market and competition analysis towards business planning and commercialisation of a specific product called NovaLung. Qualitative research methodology was used to provide an overview of the market for NovaLung (at the time of research NovaLung was a candidate product under development).

which they consider to be 'outside their area', the most frequent responses would be something along the lines of: 'I am really not the best person to ask that'.

In contrast, bioentrepreneurs are, in a sense, at the centre of the sector and are, in a way, the protagonists in all the interactions in the changing terrain of Regenerative Medicine. They are, so to speak, the 'necessary glue' that will either make or break this sector. Their ability to develop new skill sets, to adapt these to rapidly evolving conditions, and to communicate their needs, and the needs of their sector, to a wide range of, often scientifically untrained, stakeholders, funders, and policymakers is at a premium as this field reaches its 'tipping point' (or not). Bioentrepreneurs are often principal investigators (PIs), usually heads of laboratory teams, who have pursued the commercialisation of one or more of their laboratory findings/inventions through founding a company. These bioentrepreneurs are, in my experience, the most 'knowledgeable' and informed actors in the process of Translation, with knowledge ranging from basic science, regulation, and manufacturing to business, intellectual property and financial expertise.

My focus on this unique type of actor is also supported by a recent study that has confirmed the importance and centrality of bioentrepreneurs in the RM Translation process. In the research study which was funded by the UK Engineering and Physical Sciences Research Council (EPSRC) and titled 'Enabling the Emergence of the Regenerative Medicine Industry in the UK', Livesey et al. (2008) made eight principal recommendations for government which they consider to be crucial to the long-term success of the industry. One of the recommendations states:

> Enhance research and training funding in RM to develop **'polymaths'** who can embrace all aspects of Regenerative Medicine and become the entrepreneurial focus for emerging companies

In outlining their recommendation, the authors continue:

> The demands of a multidisciplinary area like Regenerative Medicine are very high for those wishing to start and build a company. As well as having to have an understanding of the underlying biology, company founders will have to become conversant in process engineering,

> complex regulation and new product development for a difficult customer. ***Individuals with these skills are in short supply.*** The funding of doctoral training centres (DTCs) across a number of biology and healthcare related areas and in particular the recent £10 million funding for two DTCs related to Regenerative Medicine is a strong positive move. However, these research focused doctorates are likely to complete in 2012 and ***there is a need for talented personnel on a shorter time frame.*** Therefore we propose a Masters level qualification, possibly tied to a translational institute, specifically aimed at ***deepening the technical expertise of rising stars in the RM field while providing them with the business skills required to start and successfully grow a company.*** [emphasis added]

From the above excerpts, it is clear that the field of RM is in need of these 'polymaths'. The research acknowledges that those who are interested in starting and building an RM company as a vehicle to commercially translate their research inventions must possess many 'talents'. Starting with the essential biological knowledge, they must also become versed in bioprocess engineering, the ever-changing complex regulatory guidelines, and understand the process of 'new product development'. In addition to the scientific and technical expertise, RM polymaths must acquire business skills which are essential in order to 'start and successfully grow a company'. Although the report suggests that doctorates and Masters level qualifications focussed on the acquisition of those skills would be a viable solution, it also recognises that the 'there is a need for talented personnel on a shorter time frame'.

Indeed, all the participants are principal investigators (PIs) in a field under the definition of Regenerative Medicine and have experience of scientific work with one or more types of stem cells (i.e. adult, embryonic, foetal, cord blood), tissue research. Three out of 14 are also clinicians (i.e. clinically trained) while others have headed clinical trials (in RM or a relevant field) or have some kind of clinical involvement through clinical collaborations. In fact, all the respondents have mixed roles as they are involved in both basic and clinical research in order to achieve the objectives of Regenerative Medicine translational research. In addition, all fourteen interviewees have, at some point in their career, been involved with the commercial aspects of

Translational Research in addition to work on their discipline, either by licensing or founding a company. Finally, in addition to their academic, clinical and commercial expertise, all the participants can be considered as integral members of a diverse but close-knit research, policy and industry-shaping community. In other words, these actors are positioned at the 'heart' or 'hub' of contemporary RM technological innovation, characterised by close relationships and transactions between the academic, clinical and commercial 'space' of Regenerative Medicine.

In crafting an understanding of the role of the bioentrepreneur in the Translation process I use primarily 14 in-depth interviews, which comprise the core dataset of this study. It is also worth mentioning at the outset that although the dataset is comparatively small (due to the relatively small population of potential research subjects, their extremely busy schedules, and the consequent difficulty of acquiring interviews), this research was intentionally qualitative in focus, and is thus not intended as a representative survey or comprehensive overview. It is instead exploratory and indicative – seeking primarily to identify key factors influencing the Translation process in the context of Regenerative Medicine, which may in turn serve as a basis for further – potentially more representative or quantitative, research.

The following sections introduce the research methodology used for this study and how it has guided data collection, analysis and development of theory (conceptual framework). First a brief overview of the process of grounded theory is presented. The subsequent sections describe the interview data collection phases. The chapter concludes by explicating the analysis approach for the empirical data.

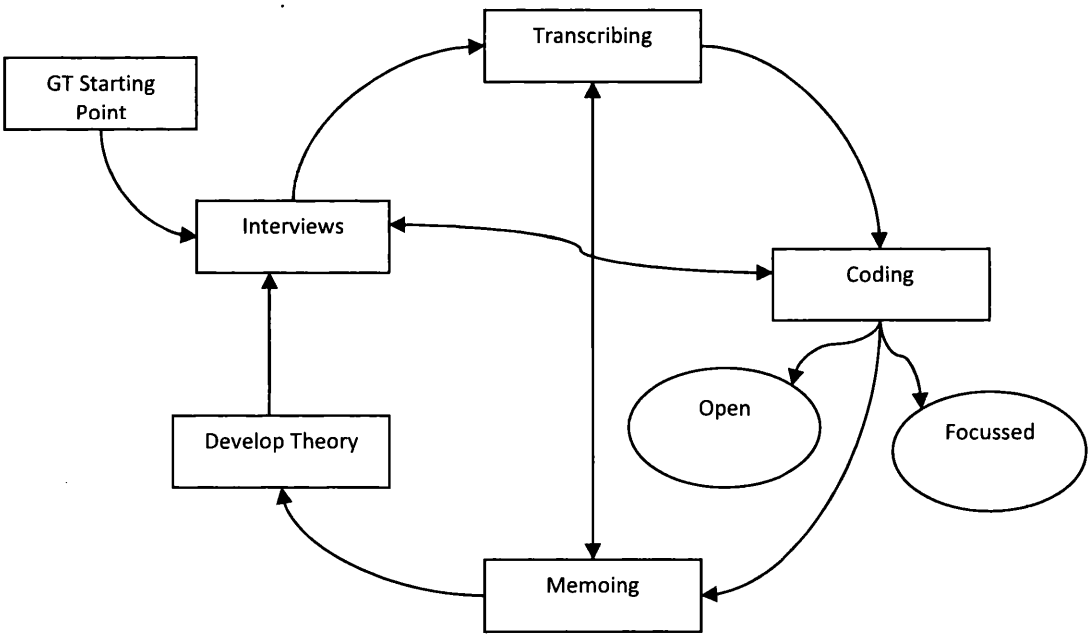
GT Methodology - A Brief Overview

Grounded theory is a qualitative research approach that was collaboratively developed by Barney Glasner and Anselm Strauss in the 1960's in their influential book 'The Discovery of Grounded Theory: Strategies for qualitative research' (1967).[28] What differentiates grounded theory from other qualitative research is that is explicitly emergent. In other words, GT methodology advocates creating new theory (consisting

[28] 'The Discovery of Grounded Theory' (1960) articulates the authors' research strategies for studies of patients dying in hospitals.

of interrelated concepts) based on the data rather than exploring data to test existing theories. In treating 'all as data' it applies a pragmatic approach, combining qualitative and quantitative data and data gathering methods to encourage a rich understanding of the situation under study and hence to enable the generation of theory. Interviews are typically the main source of the information the researcher will develop the theory from, but can also include other sources of data such as existing research literature and quantitative data (e.g. survey data)(Glaser & Strauss, 1967).

As the essential character of GT lies in the generation of theory from data by constant comparative, qualitative analysis, it is no surprise that it features a circular, interlinked, global rather than linear approach to the research process. A grounded theory study could be summarised graphically:



The GT approach provides a broad framework for the researcher to approach a phenomenon/problem beyond the confines of predetermined answers and thus enables a flexible and detailed in-depth study of issues that is unconstrained by predetermined categories of analysis. As a result, GT is particularly appropriate for exploratory studies like the one described in this thesis because it does not force the content (data) and process of the study into predetermined theories and structures.

Why Grounded Theory Methodology for this Study?

The decision to use grounded theory methodology was only taken after conducting the pilot (interview) study. An initial analysis of the two pilot interviews showed that it was not suitable to base the overall research study on existing theoretical models (as many of them have used either a diverse pool of stakeholders or have concentrated their attention on one or two specific aspects of the phenomenon of RM Translation). In this project the focus needed to be on bioentrepreneurs experiences and views on Translation and hence an inductive approach was chosen to explore the subject area through the informants' eyes. The decision to use grounded theory methodology was further supported by the dearth of existing theory regarding RM Translation.

Indeed, the fact that RM Translation is largely unexplored, with a dearth of social science studies currently addressing the 'area', had implications for the trajectory of my research. More specifically, when I began the research I considered my work as a mainly explorative study aiming to understand the phenomenon of Translation. The 'emerging' character of the project meant that at the beginning I was not completely certain which literature would turn out to be the most relevant.

Grounded theory scholars' have different opinions about the most suitable time at which to review the literature. For example, Glaser and Straus (1967) and Glaser (1978) recommend reading widely while avoiding the literature that is most closely related to the research study (which should be delayed until after completing analysis). Their concern is that the researcher will see his/her data through the lens of earlier ideas (often known as 'received theory').

In this study I have followed the advice of Charmaz (2006) and carried out an initial review of the literature before the first data collection (pilot interviews) took place. The main reason behind this approach was to learn whether any similar research had already been conducted in this area and to identify methodological approaches that have been followed. As a result, I read widely on the social science of Regenerative Medicine and on entrepreneurship which appeared to be the most relevant at that point. After I began collecting data (especially after I completed the first round of interviews) I was better equipped to pinpoint the literature most closely related to what I was discovering about this field from the actors most deeply embedded within it and

thus identify the theories, frameworks, and conceptual tools that would be most appropriate and useful to present and analyse my own data.

Use of GT Methodology (in this Study)

The data collection and analysis for this study followed a cyclical process typical for GT methodology, by using early findings to shape the on-going data collection. The pilot study involved two bioentrepreneur interviews. This preliminary data collection phase was then followed by seven more in-depth interviews that helped to explore issues raised in the pilot study. A second and final round of interviews (again seven in number) was undertaken exactly a year later (see section on 'Interviewing' earlier in the chapter).

Interviews- Sampling

GT methodology advocates a form of purposive sampling known as 'theoretical sampling'. According to theoretical sampling, participants in a study are selected according to criteria specified by the researcher and based on initial findings. In other words, early analysis of data indicates issues that need further exploration and thus the sampling process is guided by the ongoing data collection, analysis and theory development. Unlike the sampling done in quantitative investigations, theoretical sampling cannot be (entirely) planned before embarking on a grounded theory study. Instead, the specific sampling decisions should evolve during the research process itself.

In beginning the study, there were, however, a number of sampling matters that I could think about and plan. For example:

1- The group to study was chosen- that is bioentrepreneurs
2- The kinds of data to be used- interviews (mainly).
3- As I was studying an evolving process/phenomenon, I was considered useful to follow different individuals at varying points.

In drawing up this initial sample of participants I sought information from the following sources:

- Speakers' lists from past London Regenerative Medicine Network meetings and other conferences to identify people active in the areas in which I am interested
- Professor Chris Mason (UCL), a Regenerative Medicine translational investigator who has renowned UK and international expertise in the field (i.e. in both clinical and commercial RM Translation)

Once the project was underway, however, many of the initial decisions about sampling had to be changed. The most important deviation from GT methodology in this study is that decisions about interviews (bioentrepreneurs and companies) although modified according to the evolving theory they were also highly depended upon access.

Despite difficulties in securing interviews, the final list of potential participants included individuals and companies based in various UK universities.[29] In addition, the firms and research groups behind them represented a wide range of approaches to Regenerative Medicine, including scaffolds, cell therapies, tissue repair, combination therapies (i.e. cells and scaffolds combined) and cover a wide range of therapeutic areas, including wound care, ophthalmology, orthopaedics (bone and cartilage), aesthetics (skin and hair rejuvenation), production of clinical grade cell lines for therapies as well as for the drug discovery and toxicology arena.

Interviews- Preparation

The participants were contacted by an e-mail and the information sent out before the interview included a small summary of the project (background and objectives) and a description of the interviewing procedure. The consent form was also attached which ensured participants about anonymity and confidentiality of data collected (see Appendix 2).

Interviews- Pilot Study

In order to determine the most important issues of the Translation process according to bioentrepreneurs, preliminary interviews were carried out with two informants. The participants were selected based on the researcher's judgement. This pilot study was (as

[29] To preserve anonymity the universities are not named.

the rest of the interviews) guided by the ethical principles on research with human participants set out by the LSE/ESRC (as described in a later section under the heading 'Ethical Considerations').

The pilot interviews started with the basic research question: 'What is your experience with clinical and commercial Translation in the RM field?' I then encouraged the informants to provide open-ended general descriptions of their work for around 45 minutes without asking specific questions.[30] This increased the likelihood that the data primarily reflect the informant's own experience and priorities and were not (in any way) directed from the questions I asked. In this way, these initial interviews gave me the opportunity to explore 'Translation' over a broad context, to address multiple facets of the issue, and thus to bring to my attention various issues that I had not encountered before, giving me the opportunity to build an understanding of the real problems and challenges encountered in this complex and largely unexplored process that was led by my informants' own sense of what mattered most to them.

Development of Interview Questions

All first round interviewees were asked a similar set of questions that was developed based on findings from the pilot study. According to GT methodology guidelines interview questions should give as little guidance as possible in order to allow informants to talk about what is of importance to them regarding a given context.

The broad areas explored involved the current state of Regenerative Medicine in the UK, the participant's experience with regulation (e.g. regulatory agency representatives, guidelines, etc), experience with intellectual property (IP) (such as patenting and licensing of inventions), product/therapy design and development (including manufacturing issues), collaborations (between basic research, clinic and industry/company), how to get RM into the clinic through setting up an academic spinout company (funding issues, entrepreneurial spirit, integration of expertise, conflicts of interest issues), relationship with university and academic technology

[30] This interview approach is called 'convergent interviewing'. The convergent interviewing technique, although it has many uses, is most valuable when the researcher is in some doubt about the information which is to be collected. Also, if there is the intention to use surveys to collect information, convergent interviewing can help the researcher decide what questions to ask in the survey. 'Convergent interviewing enables researchers to determine the most important and/or key issues within a population rather than a full list of issues in an organization or barriers to change in a particular context' (Jepsen & Rodwell, 2008).

transfer offices (TTOs).[31] The interview questions can be found at the end of the thesis in the Appendices (Appendix 3, 'List of Interview Questions').

Following GT methodology all interviews were transcribed and coded (see 'Data Management and Analysis' below) immediately after they took place. Thus, initials findings from coding helped to (re)shape the questions/discussion for the subsequent (second round) interviews.

Data Management, Data Analysis and Theory Generation

For this study only a word processor (Microsoft Word) and pen and paper were used to manage the interview data. Interview transcripts were printed in the left hand two-thirds of the page, leaving one third of the page free for note-taking and coding.

Following GT methodology, interview coding was used to capture what was in the interview data. Interview coding is the first step of data analysis and it helps the researcher to move away from particular statements (in transcripts) to more abstract interpretations of the interview data (Charmaz, 2006). [32] After reading the transcripts the researcher needs to identify those phenomena/experiences/perspectives important to the participant and assign them a conceptual label, known as code. Several codes are then grouped into more abstract 'categories' which will form the basis of a new theory. In other words, 'coding is the pivotal link between collecting data and developing an emergent theory to explain these data. Through coding you begin to define what is happening in the data and begin to grapple with what it means' (Charmaz, 2006:46).

For the pilot study, *open coding* was performed using pen and paper (the use of qualitative software was judged to be unnecessary in this research project as the number of interviews is relatively small). Open coding is the part of the analysis concerned with identifying initial phenomena and producing a list of themes of

[31] I found that during my interactions with bioentrepreneurs my biological sciences background was very useful, as I was able to familiarise myself with each interviewee's (specific) field of research reasonably quickly and did not spend time trying to grasp scientific complexities that might have challenged a 'pure' sociologist. I was thus able to concentrate on the 'non-science' challenging issues such as IP and regulations. However, in order to avoid 'influencing' the interviewees' responses (for example, by encouraging their 'appetite' for elaborating on products and processes) and risk losing important data, I did not inform any of my interviewees about my background.

[32] GT methodology advocates using several coding techniques to examine informant's accounts at different levels: open coding, focused coding, axial coding and theoretical coding. For more details on the various techniques see Charmaz (2006).

importance to the respondent. The process involved working through each of the transcripts and using line-by-line coding to take note of themes and phenomena on the margins. Codes were attached to participants' words and statements in the transcript to capture what has been said. Some codes were very close to the respondents account (such as keywords or phrases, 'in vivo codes') while others were more abstract or conceptual.

Examples of ground theory codes, memos and visual representations provide an insight into how the final grounded theory categories were developed and how it led to the formulation of a substantive theory. In this case, a large number of initial and tentative codes were assigned to each of the two transcripts. Most of these codes could be grouped into 7 categories: 'regulation', 'funding', 'collaborations', 'intellectual property', 'business model', 'expertise', 'knowledge brokering and commitment'. An important part of the analysis at this stage was to keep track of how often the codes were used in the pilot interviews. These initial codes and the resulting categories later guided the development of the final categories (including the 'core' category).

In GT methodology it is important to verify all codes and categories that are assigned to interview data to ensure that they are applied in a consistent manner (Miles & Huberman, 1994). Ideally, a larger number of interviews would have been included in the pilot study in which case I would have the opportunity to open code them and compare between assigned codes.

After I had established some strong analytic directions through my initial (line-by-line) coding I began using *focused* coding to synthesize and explain larger segments of my data. Focussed coding involves using the most frequent and/or earlier codes (from open coding pilot interviews) to shift through large amounts of data from the next two interview phases. In other words, 'focused coding requires decisions about which initial codes make the most analytic sense to categorise data incisively and completely' (Charmaz, 2006:57). In short, the process of focussed coding is useful in determining the adequacy of the initial concepts/codes developed by applying them and testing them on further interview transcripts.

In short, my initial codes were modified and verified by being applied to further interviews transcripts but stayed alike for the most part. In other word, comparison between 'pilot interview' codes and 'first round interviews' codes has helped to clarify whether the codes were reliable and truly represented the empirical data. During the extended coding process some categories became more prevalent and some did not appear to have the 'importance' initially placed on them (mainly through my assumptions based on the initial literature review) and became redundant. For example the category 'ethics' which had been identified in the pilot study was not sufficiently prevalent as previously identified.

The second round of interviews helped to verify the initial codes further. This time focussed coding was adopted which is considered more directed and selective than open coding (used in pilot and first round transcripts).

Developing Categories and Memoing

All passages (quotes) that were assigned to a specific code and shared the same (or similar) characteristics were grouped together into more abstract categories (which could be interlinked and build the basis for a theory). In GT methodology the process of coding and developing categories is supported by writing memos. In effect, memos are notes kept by the researcher continuously while reading and coding the data in order to provide a record of thought and ideas and enable the researcher to reflect later on in the analysis on initial thoughts and hypothesis regarding categories, properties, and relationships between categories.

In this study, memoing continued in parallel with data collection, transcription, reading and coding. Memos were used to reflect about potential meanings of participants' statements and compare concepts identified in the transcripts to each other (code memos) and to the literature (theoretical memos). These memos were later consulted when establishing links between categories and 'building' the initial theoretical framework. The writing of memos was particularly useful as it allowed me to keep track of thoughts and ideas without the pressure of having to immediately decide where (if at all) and how these ideas fitted with the research findings and analysis .This system of coding and memoing was maintained for both rounds of interviews.

Sorting

In using GT methodology it is assumed that the theory/theoretical framework is concealed in the data 'waiting to be discovered'. While coding made visible some of its components and memoing added the relationships which linked the categories to each other it is through the process of sorting that I structured my 'theory'. For the actual sorting I worked to a large table and grouped the memos on the basis of similar categories or properties they addressed. Afterwards, I arranged the groups on the 'sorting plane' so as to reflect the relationships between them. Having done the coding, memoing and sorting, I began writing the first draft of my 'theory' by typing up the memos and integrating their 'notes' into a coherent argument.

Generation of Theory (Substantive Vs Formal Theory)

In general, the data was analysed by means of comparative methods and analytic deduction, revealing recurring themes or categories in the transcripts, in the literature and in fieldwork notes. The iterative process of constant comparison, multiple reading, coding, memo writing and creating categories and relationships (and further abstractions) (Glaser & Strauss, 1967; Strauss & Corbin, 1990) between them resulted in the emergence of the central themes of funding, regulation, collaboration, expertise, business models and innovation, and intellectual property. Central to this process is the link between bioentrepreneurs and the various stakeholder spheres and that (at least for the now) 'all things in Translation' occur in relation to them. In addition, each category or theme impacts on the others.

After months of analysing, comparing and revisiting the codes and categories and examining relevant literature, the research finally came together during the writing of the draft empririal chapters. As the research instrument in GT methodology is the researcher (Patton, 1990) the theory that has emerged is not the only possible one. What this thesis has tried to capture is the researchers understanding at a particular point in time- of specific incidents and the views of specific individuals regarding those incidents.

It is worth noting here that grounded theory may take several forms. One differentiation is between substantive and formal theory. 'Substantive theory is developed for a substantive or empirical area of sociological inquiry such as patient

care, race relations, professional education, delinquency or research organisations. By formal theory, we mean that developed for a formal, or conceptual, area of sociological inquiry, such as stigma, deviant behaviour, formal organisation, socialisation [...] rewards systems, or social mobility. Both types of theory may be considered as "middle-range". That is they fall between the "minor hypotheses" of everyday life and the "all-inclusive" grand theories' (Charmaz, 2006:32 and 33).

This thesis has developed a substantive theory as collection of data and interpretation focus on particular area: the relationship between RM translational research and UK bioentrepreneurs experience/perception of the regulatory/economic/and collaboration landscape. This thesis does not provide the scope to raise the specific substantive theory to a formal theory that would be generalisable across a wider area, such as other types of biomedical research (other than RM) or the status of RM TR in other countries.

GT Methodology- Criteria for Success

Glaser (1992) suggests two main criteria for judging the adequacy of the emerging theory: one, that it fits the situation; and two, that it works- that is, it helps the people in the situation to make sense of their experience and to manage the situation better.

GT Methodology- Limitations

Like any other research methodology, GT methodology has limitations. Some point out that the research can take considerable time and effort (due to the tedious coding process and memo writing as part of the analysis), and it can be difficult to predict the end, thus causing budgetary problems (Bartlett & Payne, 1997). Others consider as a limitation that the use of GT methodology to explore and explain a phenomenon and/or build a theory is a very subjective process which is highly dependent on the researcher's abilities (his/her 'theoretical sensitivity'). This study has followed the methodological guidance of Strauss and Corbin (1990) and Charmaz (2006) to collect and analyse the interview data. Finally, as GT sets out to find what theory accounts for the research situations as it is, findings are not generalisable.

Ethical Considerations

The London School of Economics and Political Science has a set of procedures in place to review proposed research for ethical accountability. The LSE research ethics policy document, which incorporates the minimum requirements as prescribed in the ESRC research ethics framework, aims to guide LSE researchers' thinking on research ethics issues and sets out the process for ethical review of research. Where a project is identified as involving human subjects all researchers (staff or students) are required to complete the Research Ethics review checklist which will determine the level of intervention required by the Research Ethics Committee (REC). In the proposal for this research to the Department of Sociology, and as part of my application for sponsorship to the Economic and Social Research Council (ESRC), I completed the self- assessment checklist and obtained the review and approval of my research supervisor and the Department (Sociology). In the subsequent carrying out of the project, I have made no changes to my objectives or methodological approach that would in any way modify the original self-assessment.

All the documentary sources used in this thesis are either publicly available or have been voluntarily provided by the participants (e.g. company data, leaflets, reports). By design, the research is not seeking either sensitive or proprietary information, and during the interviews I have not requested, nor have I encountered, ethically sensitive data. When and where commercially sensitive information has been mentioned by participants in the flow of the interview, it was used to gain further insight into the issues under discussion and has not been cited anywhere in the thesis.

In all formal interviews, I have asked permission to record and offered the participants the option to review and modify the resulting interview transcript for accuracy of information. I have also provided the interviewees with a consent form briefly describing the title and purpose of the project, the option to subsequently withdraw parts of or the whole interview, and also guaranteeing confidentiality and anonymisation in publications and presentations. Each consent form was signed by me and the participant.

Analysis of Findings

Data collected from documentary sources and fieldwork conferences/meetings/ workshops were compared to the grounded theory categories identified in the interviews in order to support the analysis of findings. The findings from empirical data were then compared to the reviewed literature (Chapters 4, 5 and 6), which lead to conclusions and recommendations (Chapter 7).

Limitations of Research

The relatively small number of bioentrepreneur interviews may be considered a limitation of the study. However, this may be justified by the fact that the area of Regenerative Medicine therapeutics is just emerging in the UK and elsewhere and interviewees were selected to represent individuals with renowned national as well as international expertise. Secondly, there are only a handful of UK companies involved with clinical Translation of Regenerative Medicine research and even fewer (academic) groups/companies with products on the market (i.e. commercial Translation). Finally, this is a qualitative constructed grounded theory study; therefore findings are not generalisable.

Chapter Summary and Conclusion

This chapter has introduced the three main 'themes' of interest (funding, regulation, collaboration) and discussed the choice of grounded theory methodology as a suitable research methodology for this study. It is necessary to capture the views of bioentrepreneurs, as bioentrepreneurs are critical to the process of Translation and they appear to integrate resources and mediate communication between other stakeholder groups such as biomedical scientists, clinicians, business people and industry representatives.

A grounded theory methodology has been followed and a grounded theory has been developed to provide an explanation for the phenomenon under study: the relationship between 'enhanced' Translation and bioentrepreneurs' perceptions of funding (schemes), regulation (guideline, compliance, harmonisation attempts), and collaboration (exploitation and integration of expertise). The emerging theory can be

categorised as 'substantive' rather than 'formal' since the collection of data and their interpretation focus on the explanation of a particular area (RM Translation through the perspective of bioentrepreneurs).

The chapter has explained in detail each of the data collection methods (sources and phases) including sampling, ethical considerations and methodological limitations. The iterative cycle of data collection and analysis is an essential element of grounded theory methodology and has helped to shape the ongoing data collection as well as the development of the final 'theory'. The last section below offers a brief breakdown of the rest of the thesis chapters.

Overview of Chapters

In the section below, I offer a brief breakdown of the rest of the thesis chapters.

Chapter Two – Regenerative Medicine and Translational Research

Chapter two is divided into two parts. In the first part ('Understanding Regenerative Medicine'), I trace the emergence of Regenerative Medicine as the new and exciting 'paradigm shift' in biomedicine, its current status in the UK, as well as its potential to revolutionise medical practice as a novel and unique source of healthcare innovation. In the second part ('Understanding Translational Research'), I provide a detailed explanation of the phenomenon of Translation in biomedicine in general and its significance. Finally, I introduce the unique combination of these two paradigms – the case of Regenerative Medicine Translational Research (RM TR) which is the central focus of this thesis.

Chapter Three – The Social Science Perspective

This chapter examines the literature on the social science studies of Translational Regenerative Medicine and positions my research within this general landscape. Starting with a brief introduction into the social science studies of Regenerative Medicine in general and an explanation of the current influx of interest and funding in relevant research areas (especially in the UK), I then continue to review in more detail those studies that focus on Translational Regenerative Medicine (i.e. social studies of the 'Bench-to-Bedside'). These studies draw from a wide variety of sociological

perspectives (e.g. sociology of expectations, boundary work, etc) and employ different theoretical tools and concepts. This chapter establishes the 'location' of my research relative to the existing literature and suggests how the thesis will contribute to the 'bench-to-bedside' area of scholarship by developing a richer description of the mechanisms embedded in scientific and technological progress aimed at the development and commercialisation of Regenerative Medicine therapeutics.

Chapters four, five, and six discuss the main empirical findings of my research.

Chapter Four – The Art of Funding

As mentioned earlier, funding appears to be one of the fundamental pillars in Translation. In Chapter 4, I present and examine the views of my respondents on the funding of RM Translation in the UK, including issues of availability and potential sources of capital such as public funds, private venture capital and big pharma industry investments. The bioentrepreneurs' perspective on the continuing search for a 'viable' business model for RM Translation is also discussed with particular reference to the role of RM intellectual property as a foundation for such a model.

Chapter Five – The Art of Regulation

Chapter 5 explores the views of bioentrepreneurs on the theme of regulation. Given the fact that I have conducted my data collection in two distinct 'phases' the data includes evidence of the 'dynamic' regulatory landscape and the efforts of my respondents (and consequently of other stakeholders) to adjust. I begin by delineating the main problems faced and narrated by respondents during the first phase of data collection which I term the 'era of uncertainty'. I then examine the bioentrepreneurs' perspectives on the interaction with regulators and guidelines and discuss their perceptions about the effects of compliance on their work and consequently RM innovation. In the final part of the chapter, I draw from the empirical data to discuss issues that were repeatedly raised in the interviews such as the issue of animal models, the type of cells used – autologous or allogeneic, and study their significance in the process of Translation.

Chapter Six – The Art of Collaboration

Chapter 6 is in a way a study of the respondents themselves as I delve into their 'lived' experience as bioentrepreneurs focussing on the more 'practical' activities behind Translation. This 'practical' side of the Translation includes the building of the entrepreneurial team, integration of necessary expertise, and the various other collaborations that respondents have mentioned. Bioentrepreneurs admit to playing the role of 'Research Translators' hence in effect 'driving' and coordinating the Translation process (both clinical and commercial) which (as claimed by my informants) is often paradoxically hampered by the university and research sponsors themselves. Drawing from their narratives it appears that, in terms of competitive advantage 'value', the most significant type of collaboration for bioentrepreneurs (and their teams) to engage in is collaboration with clinicians. In the final part of the chapter, I examine why clinician feedback is considered invaluable for the development of the therapies and I use the data to build a model that allows evaluation of the importance of three 'conditions' in the Translation process: clinical practice, product/therapy design, and timing of therapy delivery.

Chapter Seven – Thesis Conclusion

In Chapter 7, I endeavour to bring the entire story together, drawing conclusions designed not only to demonstrate the 'centrality' and importance of the role of the bioentrepreneur as an actor in the RM Translation, but also the utility of a variety of social theoretic tools to explore and characterise it. I will also draw some tentative conclusions from and for all three 'areas' under investigation, namely funding, regulation, and collaboration and their significance for successful Regenerative Medicine innovation. I will finally argue that the bioentrepreneur- focussed perspective offered in this thesis provides an important basis for understanding the phenomenon of Translation.

Chapter 2

Regenerative Medicine and Translational Research

Introduction

Over the last century, increased demographics and the global epidemic of chronic degenerative diseases have put an increasing burden on healthcare systems (Cortese, 2007; Waldman & Terzic, 2007). According to data from the Merck Institute of Aging and Health, 'The United States is experiencing a longevity revolution and as the baby boomers approach retirement age, they are touching off an age wave that will double the number of Americans over age 65 to more than 70 million by 2030. Individual life expectancy is also increasing and the older population is growing much more rapidly than the entire population of the United States'.[33] In addition, 'the average 75-year-old suffers from 3 chronic conditions and takes 5 prescription medications'.[34] The predictions concerning US demographics, along with the high prevalence of chronic disease, are mirrored in most developed countries, including the UK. The expected population growth, in combination with the fact that the aging population is particularly susceptible to degenerative diseases, equates to added healthcare responsibility which will undoubtedly challenge healthcare systems across the globe, already stretched by an expansion of expenditure. These continuing rises in healthcare costs, in combination with social pressures for better treatments of serious diseases, have left many people frustrated by the slow rate at which new basic research knowledge translates into new products and therapies in both the pharmaceutical and biotechnology industry (Nightingale & Martin, 2004).

The paradoxical situation of having a successful 'front end' of the product development process (i.e. prolific basic research and inventions) followed by a decline in the innovative output (i.e. new products and therapies) at the 'back end' of the

[33] Centres for Disease Control and Prevention, Merk Institute of Aging and Health. The State of Aging and Health in America 2007. Washington, D.C.: Merk Institute of Aging and Health, 2007. Available at http://www.silverbook.org. Accessed March 2009.

[34] Centres for Disease Control and Prevention, Merck Institute of Aging and Health. The State of Aging and Health in America 2004. Washington, D.C.: Merck Institute of Aging and Health, 2004. Available at http://www.silverbook.org. Accessed March 2009.

development process, raises an obvious question: will continued heavy investment in basic research lead to the much-needed new therapies, at effective cost levels, across a wider range of diseases and, at the same time, limit the growth of health care spending? The answer to this question is starting to become evident in the fairly recent emergence of two major paradigm shifts in biomedicine, namely Regenerative Medicine (RM) and Translational Research (TR).

Understanding Regenerative Medicine

Various healthcare programs have been devised and implemented by nations in order to address the increasing medical needs and manage the cost of dealing with chronic disease. The current standard of care for age-related conditions is largely based on palliative therapies and the use of pharmaceutical drugs. With a few exceptions (such as antibiotics), most drugs can be divided into two categories: those which provide symptomatic relief and those that treat asymptomatic conditions, such as hypertension and hyperlipidimia, which are risk factors for other diseases (Sakurada et al., 2008). However, there are still many acute or chronic intractable degenerative diseases/conditions such as Parkinson's disease, myocardial ischemia, stroke, diabetes, blindness, arthritis and others, for which no adequate treatment is available. In some of these cases, it might be possible to address the tissue degeneration or organ dysfunction associated with the condition through the transplantation of donor-derived tissues and organs. Transplantation therapies, however, are crucially limited by a shortage of transplantable organs, tissues and cells. Even in cases where the organs are available, the necessary immunosuppressive medication has many side effects, including a reduction in life expectancy of ten years on average (Hollander et al., 2009).

In short, despite the dedicated efforts to reduce the economic burden on healthcare, the situation stands to worsen. A large number of conditions have no available drug treatments, and even in cases where a pharmacotherapy approach is available, it allows patients to survive with a prolonged course of their disease, thus contributing to the expansion of healthcare expenditure.

Regenerative Medicine is seen by many to have the potential to address this healthcare 'bottleneck' by ameliorating the disease outcome and reducing the burden of chronic therapy. Unlike drugs that 'work' by providing symptomatic relief, Regenerative Medicine interventions aim to treat the root cause of the disease linked to progressive cell destruction and irreversible loss of tissue function (Daley & Scadden, 2008). In other words, instead of simply mitigating the symptoms as traditional (pharmaco)therapy approaches do, RM aims to repair the underlying pathobiology or restore/replace the native cellular architecture and organ function (Waldman et al., 2007). In short, RM is widely seen as a new transformative paradigm in biomedicine which, driven largely by curative objectives, has the potential to reverse the daunting forecasts and decrease the burden of disease which is paid for in both human and economic terms.

What is Regenerative Medicine?

Regenerative Medicine is a new and rapidly developing interdisciplinary branch of medicine, typically characterised by a convergence of disciplines such as cell biology, biochemistry, molecular embryology, immunology, advanced materials science, engineering and medicine.[35] Since the term was first coined, there have been various attempts to define the field as well as map its relationship with 'a good deal of prior activity', especially in the fields of Tissue Engineering, bone marrow and organ transplants, surgical implants (such as artificial hips), and increasingly sophisticated biomaterial scaffolds (Mason & Dunnill, 2008). Of the lengthy definitions in the scientific literature, the one by Greenwood et al. (2006) is probably the most clear and comprehensive:

> Regenerative Medicine is an emerging interdisciplinary field of research and clinical applications focussed on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including

[35] For a detailed account of the way the various disciplines that currently comprise Regenerative Medicine came together see the study by Viola et al. (2004) conducted for the National Science Foundation (Available online at http://www.nsf.gov/pubs/2004/nsf0450/start.htm) or the World Technology Evaluation Centre (WTEC) Report of Tissue Engineering conducted by a panel of leading U.S. experts and describing the research and development activities in the United States, Japan, and Western Europe (McIntire et al., 2002).
(Available online at: http://www.wtec.org/loyola/te/final/te_final.pdf).

> congenital defects, disease, trauma, and aging. It uses a combination of several technological approaches that moves it beyond transplantation and replacement therapies. These approaches include, but are not limited to, use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering and advanced cell therapy (2006:1497)

Perhaps the simplest definition of Regenerative Medicine has been published in an editorial of the journal *Regenerative Medicine* by two leading figures in the field, University College of London's (UCL) Chris Mason and Peter Dunnill. It states: 'Regenerative Medicine replaces or regenerates human cells, tissues or organs, to restore or establish normal function' (Mason & Dunnill, 2008:4). According to Mason and Dunnill, as the field grows and there is a need to carry governments and public opinion along, lengthy definitions are confusing and 'not the sort of thing scientists, start-ups or advocates can say succinctly when a pharma executive, government minister or member of the public asks for clarification' (Mason & Dunnill, 2008:1). Instead, a short and to the point definition can be a starting point and provide clarity to the nature of the field, which is vital for the move toward the industrial context. Finally, perhaps the most widely accepted representation of the field among the UK RM community, is depicted in a diagram by Intercytex Chief Scientific Officer Dr Paul Kemp (see Figure.1). According to this definition, Regenerative Medicine is the 'umbrella term' which embraces cell therapies, tissue engineering, biomaterials[36] (e.g. matrices/scaffolds) and regeneration stimulating compounds (e.g. growth factors, differentiation factors, other key proteins). The final RM product can involve any combination of these components.

[36] Biomaterials are materials that can influence, by physical or chemical means, the organisation, growth, and differentiation of cells in the process of forming the desired tissue. A company working with such acellular matrices is Integra, UK (http://www.integra-ls.com).

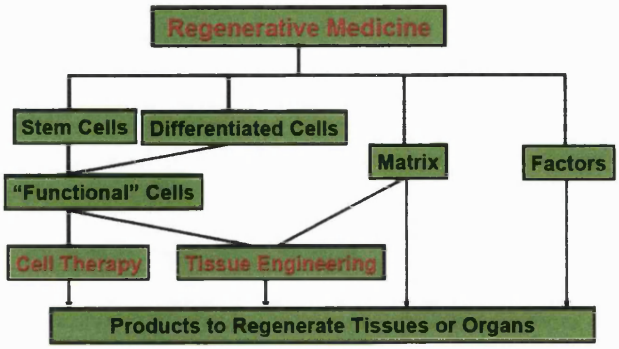


Figure.1. This diagram is taken from Dr Paul Kemp's presentation at the London Regenerative Medicine Network Meeting (June 2007).

As also becomes obvious from Figure.1, the central focus of Regenerative Medicine is human cells, irrespective of the components/combination used. These may be somatic, adult stem or embryo-derived cells as well as the recently discovered induced pluripotent stem cells (iPS) (Takahashi et al., 2007; Yu et al., 2007), that is cells that have been reprogrammed from adult cells and display embryonic-like features (pluripotency). Depending on the source of the cells, products and therapies can also be autologous or allogeneic. In autologous therapies it is the patients' own cells that are isolated, purified and/or expanded, stored and reintroduced into the patient. This means that there are no immune rejection problems or risks of disease transmission, but the bioprocessing is complex. In allogeneic therapies, on the other hand, the cells are isolated from (related or unrelated) donors, and although these cells allow for easier bioprocessing, rejection and the potential for disease transmission are serious hurdles to overcome. In addition to having a therapeutic application, RM products can have a diagnostic application where the cells or tissue(s) are used as a biosensor or for the development and testing of drugs (for example screening for novel drug candidates, testing drug metabolism, uptake and toxicity or identifying novel genes as drug targets)(Hellman, 2008).

Cell therapy (that is cell suspension, without scaffolding) has been available for several decades. Most of this therapy was and continues to be autologous, typified by bone marrow transplants. Clinical allogeneic cell therapy currently utilises unrelated bone

marrow, umbilical-cord blood (Fanning et al., 2008), or mesenchymal stem cell (MSC) transplants.

In contrast to cell therapies, which involve delivering 'doses' of cells to patients, Tissue Engineering (TE) involves incorporating the cells into a three-dimensional structure using a temporary scaffold (for example a tube to create a blood vessel). Current autologous approaches to cell-based tissue engineering include: cultured autologous epithelial cells from skin such as Epicel® (Genzyme Biosyrgery, Cambridge, MA), MySkin (CellTran, UK) and CellSpray® (Avita), as treatments for chronic wounds and life-threatening burns; cultured autologous chondrocytes from articular cartilage, such as Carticel® (Genzyme BioSurgery, Cambridge, MA) as a treatment for focal defects in articular cartilage of the knee. All the above treatments are based on an autologous expansion service approach which carries a number of disadvantages, the most critical being the significant turnaround time in providing enough product for treatment and the high cost when compared to conventional treatments (Daniels & Roberts, 2006). A more attractive approach to developing commercially viable products is based on the use of allogeneic cells and involves the production of standard 'off-the-shelf' products similar to the ones produced by traditional pharmaceutical development. Only few bioengineered live tissue products of this type have emerged in the market, the most famous being Apligraf® (Organogenesis, US/ Novartis, EU), Dermagraft® (Advanced BioHealing, La Jolla, CA), and Trancyte® (Smith & Nephew)(Parenteau, 1999).

According to Intercytex's chief scientific officer Dr Paul Kemp, every product already on the market or currently in development can be represented in the 'whole-cell bioprocessing matrix' comprising of just four quadrants (see Figure.2 below). 'You can either use allogeneic cells or autologous. You can put these in as a single-cell suspension or you can make a construct from them. There are four quadrants to this. I have asked numerous people within the industry whether there is another segment to the field, and there is simply not' (Kemp, 2006a:2). Kemp also points out that the manufacturing facilities for the four types of product would be very different, as would be the cost. From the matrix, it is clear that the cheapest to produce is allogeneic single cell suspensions, then allogeneic constructs, followed by autologous single cell suspensions and finally autologous constructs, which are the most costly (Kemp, 2006a, 2006b).

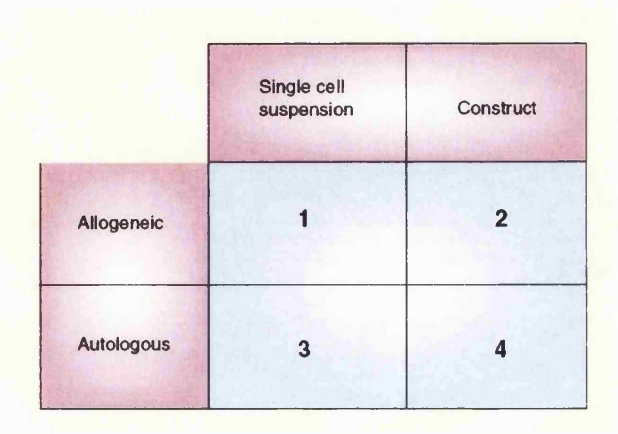


Figure.2. Each quadrant is numbered according to the cost of each approach to whole-cell bioprocessing (1: least costly, 4: most expensive). Diagram taken from Kemp, P. (2006) 'Cell therapy- Back on the up-curve', Regenerative Medicine 1(1): 9-14.

In short, RM therapeutics, whether cell therapies or cell-based constructs, are very different to the pharmaceutical and biotechnology products. A phrase regularly quoted in scientific articles regarding RM product development and manufacturing is that 'the process defines the product' or 'the product is the process'. As noted by Nancy Parenteau (Parenteau BioConsultants) who has written extensively on the commercial development of stem cell therapeutics: 'Cells, unlike biological molecules and chemical entities, are complex, dynamic and interactive and the design of the therapeutic product (i.e. its components, how they are derived and processed) becomes particularly important. It can mean the difference between an effective product and one that fails to meet clinical and regulatory standards' (Parenteau, 2009:601). Mason and Hoare (2007) also emphasise the importance of the bioprocess for cell therapies and call for a workable and at the same time rigorous regulatory framework. The authors view such a regulatory framework as a target inseparable from bioprocess and suggest that everyone stands to gain from consistency and harmonisation. The following section briefly describes such standardisation and harmonisation attempts.

Regenerative Medicine Product Regulation

Appropriate regulation of RM therapeutics is essential to ensure public safety and trust while minimising unnecessary barriers to product development. At the moment, RM research is entering a critical 'transition period' as the first stem-cell based products are beginning the process of seeking approval for testing and marketing (Fox, 2008). In July 2010, the US Food and Drug Administration (FDA) cleared Geron Corporation (Menlo Park, CA) to proceed with its much heralded GRNOPC1 trial, which would have been the first use of hESCs in humans, thus lifting a hold placed in May 2008 and again in early summer of 2009 (Alper, 2009).[37]

In the UK, ReNeuron Group Plc has also received approval from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) to conduct a first-in-man trial of a stem cell therapy to treat stroke (Pilcher, 2009). Other companies are also at various stages of developing and testing stem cell products (Langreth & Herper, 2008), which means that questions about the adequacy of the regulatory framework applicable to the products of RM cell-based technology are becoming increasingly important.

Weaknesses of the existing regulatory frameworks include a poor fit between established product categories (such as drugs, medical devices, biologics) and emerging RM technologies, as well as variation between markets/jurisdictions. Since a primary goal of the RM community is the establishment of a global industry that enables companies to manufacture and market products across national borders (Salter, 2009b; Salter, 2009c; Salter et al., 2006), a harmonised international regulatory approach is crucial.

Currently, a number of regulatory approaches are being developed in North America, Europe and the East (Singapore, China, Japan, and India) and several harmonisation initiatives already exist. Most notably, the new European Advanced Therapy Medicinal Products (ATMP) regulation,[38] that became effective from December 2008 and will be managed by the European Medicines Agency (EMA). Apart from formal legislation, harmonisation may take other forms, ranging from informal cooperation for the

[37] At the time of submission (September 2010), Geron's Phase I trial was on. On 30 July 2010, Geron announced that the U.S. Food and Drug Administration (FDA) has notified the company that the clinical hold placed on Geron's Investigational New Drug (IND) application has been lifted.

[38] EC. Regulation (EC) No 1394 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, [2007] O.J. L 324/121. Available at: http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/advanced_en.htm

development of common technical requirements or mutual recognition agreements (Von Tigerstrom, 2007). Important harmonisation attempts have also been undertaken at the international level, by the International Society for Stem Cell Research (ISSCR),[39] the International Conference on the Harmonisation of Technical Requirements for Registration of pharmaceuticals (ICH),[40] and also at a more 'local' (UK) level, such as the PAS83[41] and PAS84[42] guidance documents, published by the British Standards Institute (BSI). A more in-depth explanation of the RM regulatory landscape is given in Chapter 5, where it serves as the background for the analysis of my empirical data regarding interviewees' perceptions on the effect of regulations on translational Regenerative Medicine innovation.

The Regen Industry: the Ups and Downs...and Ups

The RegenMed (or simply Regen[43]) industry is the industry which develops, manufactures and sells Regenerative Medicine products. Mason and Dunnill (2008) note the fact that the Regen industry has to be distinguished from Regenerative Medicine in that although centred on human cells, it also draws on other science and technology such as biomaterials for Tissue Engineering. The origins of the Regen industry can be traced back to the Tissue Engineering industry, now only a part[44] of the much broader Regen sector.

When discussing the progress of Regenerative Medicine industry, field experts (Kemp, 2006a) draw attention to a cycle that so often characterises novel medical research:

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[39] The International Society for Stem Cell Research (ISSCR) has published two documents so far: Guidelines for the Conduct of Human Embryonic Stem Cell Research, Version 1: December 21 (2006). Available at: http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf and Guidelines for the Clinical Translation of Stem Cells, December 3, (2008). Available at:
http://www.isscr.org/clinical_trans/pdfs/ISSCRGLClinicalTrans.pdf

[40] Although the ICH has not yet formulated any guidelines specific to stem cell-based products, a number of its guidelines on biotechnology products are relevant to this area. For further information see Catalano, J. 2006 'The International Conference on Harmonization (ICH) and its Relevance to Cell Therapy. ISCT 6th Annual Somatic Cell Therapy Symposium (http://www.fda.gov/cber/genetherapy/isct092506jc.htm).'

[41] PAS83: Guidance on Codes of Practice, Standardised Methods and Regulations for Cell-based Therapeutics, from Basic Research to Clinical Application. DTI in collaboration with British Standards Institute, UK. November (2006).

[42] PAS84: Regenerative Medicine. Glossary. (2006). PAS84 provides clear guidance on the meaning of terminology currently used in the UK by industry, regulators, government and academia with the aim of helping the key stakeholders to communicate more effectively and allow the commercialisation of the new technology to take place more efficiently and safely.

[43] The shorthand 'Regen' has been used in a similar way to the terms 'Pharma' and 'Biotech' as routinely used to describe companies in the pharmaceutical and biotechnology sectors, respectively.

[44] Regen industry (just like Regenerative Medicine) is an umbrella term which incorporates cell therapies and tissue engineering. The difference between these two types of therapy is that cell therapies, in general, will involve 'doses' of cells to patients; tissue engineering involves incorporating the cells into a three-dimensional structure using a temporary scaffold, for example a tube to create a vessel (Mason, 2005).

initial hype, a subsequent trough of disappointment, and final emergence of viable technology.[45] This depiction of the Regenerative Medicine industry is largely based on the concept of 'Gartner Inc.'s Hype Cycle' which was first coined in 1995 by Gartner.[46] The Gartner Cycle shows the over-enthusiasm ('hype') and disappointment that typically happens with emerging technologies, as well as the way these technologies move beyond the 'Trough of Disillusionment' phase to become widely accepted and commercially successful.

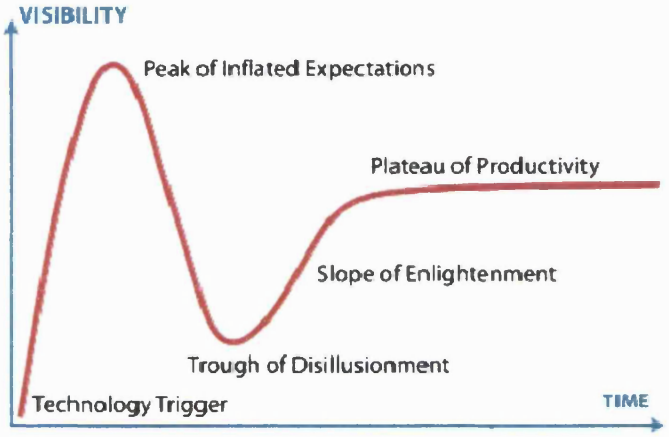

Figure.3. shows 'Gartner's Hype Cycle of Emerging Technologies'

The first phase of the industry's development, running from the early 1990s through 2001, represented a period of considerable excitement, during which research in the field was rapidly expanding at the universities and there was also considerable activity on the commercial front. The products that made it to the market during that period were largely living skin substitutes (Parenteau, 1999) including Apligraf, Dermagraft and Trancyte, and were developed by pioneering companies such as Advanced Tissue Science and Organogenesis. The second phase, between 2001 and 2002, corresponds to the 'trough of disillusionment' part of the Hype Cycle, when 'things went very wrong, very quickly' and several factors combined to make this period 'the worst of times' for tissue engineering (Lysaght & Hazlehurst, 2004). New products were hampered by delays in regulatory and reimbursement approval, and a variety of less-than-optimal business management decisions were made that left several of the early

[45] Presentation by Gregory A. Bonfiglio, Proteus Venture Partners, 'Venture Funding for RM Companies', California Institute for Regenerative Medicine ICOC Loan Task Force, January 16, 2008.
[46] For further details on Gartner see the company homepage available at http://www.gartner.com/

companies experiencing severe financial problems (Nerem, 2006). December 2002 marked the end of the 'hyped' and 'troubled' periods of the RM industry, what is now known as RegenMed 1.0 and the transition to the third part of the Curve, the 'slope of enlightment' towards the plateau of productivity, widely known as RegenMed 2.0. In fact by 2006,

> Tissue Engineering had largely been replaced by cell therapy. The focus has switched from whole organs grown in the laboratory at uneconomic cost to cell therapies where cells alone are surgically implanted to restore damaged and diseased organs: *in vivo* Tissue Engineering. This dramatic refocusing occurred because of a number of major factors but principally: the high cost associated with growing whole organs for weeks or months in facilities operating according to Good Manufacturing Processes (GMP), the complexity of bioprocessing solid organs, market opportunities and stem cells (Mason, 2007: 25).

Finally, in contrast to RegenMed 1.0 companies which were almost all focussed on research, RegenMed 2.0 industry[i] is almost exclusively focussed on translating science into commercial products, thus integrating the science into the healthcare system[47](Mason, 2007).

Regenerative Medicine in the UK

The UK is widely recognised as having strong research activity in the Regenerative Medicine area, including world class capability in stem cells and Tissue Engineering, and is considered to have a leading position (in basic research) relative to most Western economies, including the United States. This UK lead is mainly attributed to the informed and open approach towards Regenerative Medicine work that combines a strong ethical basis with informed regulatory policies, substantial and well directed basic research funding, and a strong interest in consulting the public and securing its support (Livesey, et al., 2008). The need to maintain this competitive advantage has been widely recognised by all stakeholders and is a central theme to almost all recently

[47] Presentation given by Eric C. Faulkner, Senior Director, US Market Access & Reimbursement, 'Financing for Cell Therapy Companies: Importance of Reimbursement Planning for Product Success', International Society for Cellular Therapy, 18 May 2008, Miami, Florida.

published policies regarding current progress and future directions of the Regenerative Medicine field.

In March 2005, for example, the UK Government's Chancellor of the Exchequer Gordon Brown announced the launch of the UK Stem Cell Initiative (UKSCI) during his pre-budget statement. The requirement was for the development of a ten-year research and development strategy for UK Stem Cell Research, from 2006 to 2016, which will 'make the UK the most scientifically and commercially productive location for this activity over the coming decade, and which commands the support of public and private research funders, practitioners and commercial partners' (UKSCI Report, 2005:103). Sir John Pattison was asked to chair the process, together with Dr John Connolly (Department of Health, Secretary to the UKSCI) and a high-level advisory panel.[48] Eight months later, in November 2005, and after a wide consultation with universities, research institutions and industry, the Report and Recommendations of the UKSCI was published,[49] providing the world's first blueprint for the future of stem cell platform technologies and Regenerative Medicine therapies (Mason, 2006). While launching the report, Sir Pattison described the challenges facing Regenerative Medicine research in the UK and said:

> During the pioneering phases of any new medical treatments, there are often substantial gaps in our knowledge, leading to a perception that the research is "high-risk". This is certainly true for stem cell therapies. However, **we must foster those who pioneer the applied aspects of our strong basic science, if we are to make significant contributions to its global development.** It is essential, therefore, that the UK is supportive of early clinical trials, provided they are of sufficient quality. This will help to develop our breadth of expertise and

[48] The panel included Professor Colin Blakemore (Chief Executive, Medical Research Council), Professor Julia Goodfellow (Chief Executive, Biotechnology and Biological Sciences Research Council), Ms Diana Garnham (Chief Executive, Association of Medical Research Charities), Professor Sir Christopher Evans (UK Stem Cell Foundation), Dr Peter Mountford (Chief Executive, Stem Cell Sciences (UK) Ltd), Professor Sally Davies (Director of Research, Department of Health), Dr Mark Walport (Director, The Wellcome Trust), Dr Peter Arnold (Director of Technology, Smith and Nephew,UK), Dr Fiona Watt (The Academy of Medical Sciences), Lord May of Oxford (UK Stem Cell Foundation).

[49] UK Stem Cell Initiative Report and Recommendations, November 2005. Available online at: *www.advisorybodies.doh.gov.uk/uksc.*

> knowledge of clinical aspects of stem cell research
> [emphasis added]
> (UKSCI Press Notice, 1 December, 2005:2)

This call for attention to the 'applied' aspects of the Regenerative Medicine science is evidence of the policy-makers' concern that increased support of the science base and the creation of greater capacity for invention alone, are unlikely to secure the competitive advantage on the RM world stage. Indeed, in a review of UK health research funding, led by Sir David Cooksey and published in December 2006, a gap between the pace of change in basic research and its application to healthcare practice was evident (Cooksey, 2006). The review highlighted the fact that although major advances in basic science (including Regenerative Medicine science) and patentable inventions are self-evident, translating these advances into commercially viable innovations remains problematic. In other words, if Regenerative Medicine in the UK (and elsewhere) is to have a major effect in the lives of patients and the economy, it must find ways to close this gap between invention and innovation, between basic research and clinical practice, and ensure that all scientific breakthroughs happening in UK laboratories are swiftly and efficiently translated into healthcare benefits for the public.

The following section ('Understanding Translational Research') begins with an explanation of what Translational Research is and provides a description of the emerging 'status' of Translational Research (TR) in biomedicine. I identify and explain existing definitions of Translational Research (including clarification of which definition is being used in the context of this thesis). The aim of this section is to provide the reader with a brief, but comprehensive introduction to the concept of 'Translation', which is central to this thesis. I continue with an exploration of the literature on the nature of the Translation process (bidirectional and iterative) as well as some of the potential issues and obstacles that have kept positive basic research findings from translating into therapies. Gaining an insight into the above issues will facilitate the understanding of the remaining chapters which examine Translation through the lens of Sociology and Science and Technology Studies (STS). Finally, I introduce the case of Translational Research in the Regenerative Medicine (or RM TR) which is the focus of this thesis.

Understanding Translational Research (TR)

The emphasis on 'translating' science into practical applications began in 1980 through US code legislation. The Stevenson-Wyndler Technology Innovation Act (1980) made 'technology transfer' (i.e. using existing research knowledge to fulfil public and private needs) a mission of the federal Government. In addition, the enactment of the Bayh-Dole Patent and Trademark Act within the same year, allowed universities to retain certain rights to their inventions so as to provide incentives for researchers to create products and services that would benefit the public (Sussman et al., 2006). In biomedicine, the term Translational Research (Translational Science/ Translational Medicine) can be traced back to the early 1990s in the literature describing biology-based attempts to find new drugs for cancer. Since then, the concept has found its way into the literature concerned with almost all areas of medicine (e.g. cardiology, psychiatry, neurology) and it has been the subject of multiple catchphrases such as 'lost in Translation', 'crossing the valley of death', 'bridging the gap', 'walking the bridge', and most notably 'from bench to bedside'. But what exactly is (biomedical) Translational Research (TR)?

Until recently, two types of research have dominated the literature, basic research and applied research. Basic research has many different meanings and definitions, and alternative terms such as 'fundamental', 'curiosity-driven', 'blue skies', 'autonomous' and 'researcher-controlled'. Sometimes, authors refer to basic research meaning both 'curiosity-driven' research (undertaken primarily to acquire new knowledge) and 'strategic' research (undertaken with some instrumental application in mind, although the precise process or product is not yet known) (Salter & Martin, 2001).

Sociologist Jane Calvert (2006) who has examined the history of the basic science concept, argues that it is a flexible and ambiguous term which, in practice, is used selectively by scientists and policy-makers in a variety of contexts so as to protect and promote their interests (e.g. to protect their work from demands of applicability and to justify funding). Whatever the term used, though, the popular understanding in biomedicine is that basic research is based on a hypothesis about how biology works and takes place in a laboratory, while clinical research is applied research, and determines whether known biological mechanisms apply to a disease or treatment.

Nobel Laureates Joseph Goldstein and Michael Brown (1997) have distinguished basic research from Disease-Oriented Research (DOR)[50] and Patient-Oriented Research (POR), describing the latter as 'being performed by physicians who observe, analyse, and manage individual patients. As a rule of thumb, if the investigator shakes hands with the patient in the course of the research, that scientist is performing POR' (Goldstein & Brown, 1997:2805 and 2086).

The relationship between basic and applied (including clinical) research has also been famously depicted as the 'Pasteur's Quadrant' by Donald Stoke in his 1997 homonymous book. In the book, the author considers how viewing research as a continuum from basic to applied, assumes that progress only builds in one direction, when advances in technologies (i.e. technological breakthroughs) can also reverse the direction and lead to better understanding of basic research theories.

In recent years, the term Translational Research (TR) or 'Bench-to-Bedside' has come into use in various disciplines, to describe the not always so distinct borderline between the two ends (i.e. basic and applied research) of the research continuum. Different stakeholders have different meanings for Translational Research (TR). For some, TR refers to the enterprise of harnessing knowledge from basic science to produce drugs, devices and treatment options for patients. In this case, the endpoint of TR is the production of a promising new treatment that can be used clinically or commercially. For others, mainly health services researchers and public health investigators who consider health as the primary outcome, TR is about ensuring that the knowledge and new treatments/products actually reach the populations for whom they are intended, through timely and proper implementation (Woolf, 2008). Referring to these different types of TR by the same name has become a source of some confusion in the relevant literatures, and this confusion is discussed later in this chapter.

[50] Goldstein and Brown define DOR as 'research that is targeted toward the understanding of the pathogenesis or treatment of a disease, but does not require direct contact between the patient and the scientist. It may use patient materials such as cultured cells or DNA samples, but not the whole patient' (Goldstein & Brown, 1997:2805 and 2806).

Translational Research: a Global Priority?

Currently, Translational Research is considered an integral part of all aspects of biomedical research, a new 'paradigm shift' of the way science is done, and a new movement in funding direction. Stephen Curry, a US business consultant for translational science and medicine notes: 'at its core is the identification of a funding category for making public money available to facilitate the movement of an idea from bench to bedside' (Curry, 2008). In the United States, for example, Translational Research has been recognised as a funding priority in both the Food and Drug Administration's Critical Path Initiative[51] (FDA, 2004) and the National Institutes of Health's (NIH) agenda, through the NIH Roadmap[52] (Zerhouni, 2003) and the launch of the Clinical and Translational Science Awards (CTSAs) program in 2006 (Zerhouni & Alving, 2006). In Canada, research and knowledge Translation are the focus of the Canadian Institutes of Health Research (CIHR) work. The CIHR, which was created in 2000 and is the government agency responsible for funding heath research in Canada has a budget of $928.6 million (2008-09) and its mandate is:

> To excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge and its **translation** into improved health for Canadians, more effective health services and products and a strengthened Canadian health-care system[53] [emphasis added]

In Singapore, the Biomedical Research Council (BMRC) which was established in October 2000, has created a number of research consortia[54] to coordinate and drive Translational Research at the national level, in what are considered strategic thematic areas. Similarly, in the EU, Translational Research has become a centrepiece of the European Commission's £6 billion Seventh Framework Programme (FP7) health research budget. The FP7 is running from 2007 to 2013 and states:

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[51] FDA Report, 'Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products', Food and Drug Administration, US Department of Health and Human Services, March 2004 and updated version 2006. Available at:
http://www.fda.gov/ScienceResearch/SpecialTopics/ criticalPathInitiative/CriticalPathOpportunitiesReports/default.htm.

[52] For more details on the NHI roadmap see: http://nihroadmap.nih.gov

[53] Statement on website: http://www.cihr-irsc.gc.ca/e/7263.html (Accessed March 2009).

[54] The consortia that have been set up to date include, among others, the Singapore Stem Cell Consortium (SSCC) and the Experimental Therapeutics Centre (ETC). Details on website:
http://www.a-star.edu.sg/biomedical_sciences/170-Strategic-Initiatives-Translational-Research.

> Citizens will benefit from European health research since its emphasis will be put on: **translational research** (i.e. the translation of basic discoveries into clinical applications), the development and validation of new therapies, methods for health promotion and prevention including the promotion of healthy ageing, diagnostic tools and medical technologies, and sustainable and efficient healthcare systems.[55] [emphasis added]

In the United Kingdom, Translational Research has been prioritised in a 2006 review of health research funding which places considerable emphasis on the need to translate the results of basic research along the pathway to new innovations, products and healthcare services (Cooksey, 2006). The increasing shift in UK biomedicine towards translational goals is also evident in the establishment – by the National Institute for Health Research (NIHR) – of five biomedical research centres devoted to Translational Research at a cost of £450 over five years (Lord & Trembath, 2007; Travis, 2007).

Outside central government, a range of other organisations also support Translation, such as the research councils, mainly the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). Indeed, promoting and strengthening Translational Research has become a key priority for the MRC in recent years. Following several specific initiatives, as well as the publication of the Cooksey Review (2006), members of the MRC community came together in February 2007, to review the role of the Council in TR and discuss what more is needed to support and accelerate the Translation of medical research. During the workshop[56] Professor Blakemore, Chief Executive of the MRC (at the time), outlined how the Council has been shifting its emphasis in funding[57] in order to strengthen clinical and Translational Research. To achieve this, the MRC has supported a number of initiatives[58] which included: additional funding for large-scale clinical trials (£9m), for experimental research (£15m), biomarkers (£10m), implementation research (£1m),

[55] Statement on website http://ec.europa.eu/research/fp7/index_en.cfm?pg=health.
[56] MRC Workshop, 'Accelerating the Translation of Medical Research', 20-21 February 2007, Latimer House, Bucks.
[57] In 2004-2005 approximately 80% of the MRC's research portfolio was in basic laboratory and population health research.
[58] These initiatives have been published in the 2006/07-2007/08 MRC Delivery Plan. See http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002472 (Accessed June 15 2009).

MRC Centres grants (£15m), Clinical Research Training Fellowships awards and additional studentships.

MRC Technology which has been set up to support the intramural MRC research portfolio so that scientific discoveries are translated into commercial products, has also expanded its activities, including the development of a new, pilot category of staff called 'Research Translators'. Their role is 'to facilitate the translation of research by applying their expertise and knowledge of the Translation process and brokering partnerships/collaborations between scientists and other stakeholders in order to progress research findings towards development and delivery of new healthcare interventions' (MRC Workshop, 2007:15). Charities such as the Wellcome Trust and private foundations and organisations are also investing in Translational Research (e.g. Avla BioVentures Ltd, UK) (DTI, June 2007).

The shift to a 'translational agenda' is thus a noticeable trend in many of the world's leading industrial nations. In addition to private entities, governments and individual states (such as California and New Jersey)[59] increasingly want to see a return on the very large sums of money they commit to research (Levine, 2006). The long-cherished freedom of the research funding agencies to choose their 'areas' of activity has disappeared under the pressure of the numerous healthcare challenges, with academics, clinicians, and policy-makers realising that the only way to secure strong funding for both basic and Translational Research is to produce successful commercial outcomes, reduce the currently spiralling healthcare costs and/or have a major impact on patients' quality of life.

Translational Research: Success or Failure?

During the past decade and following the complete sequencing of the human genome there has been an exponential growth in basic research aimed at understanding the underlying nature of disease and developing novel forms of therapy. This has led to major scientific accomplishments in diverse fields such as molecular genetics and cell biology, and in the development of revolutionary forms of treatment such as RNA

[59] see California Proposition 71: The California Stem Cell Research and Cures Act, 2004; The Economic Benefits of the New Jersey Stem Cell Research Initiative Report, Seneca and Irving, 2005; UK Stem Cell Initiative Report and Recommendations (2005), Department of Health, UK.

interference, gene therapy and stem cells (Chanda & Caldwell, 2003). When considering the explosion of basic science discoveries along with the recent emphasis on Translational Research, it is not surprising that there is a high expectation of immediate therapeutic benefits in a wide range of disease states many of which have no current effective treatment (Bubela, 2006; Ioannidis, 2006; Nerem, 2006). However, it remains unclear if TR, this new 'paradigm shift', has been living up to expectations. Indeed, despite the astounding advances that have been accomplished in the laboratory, and despite the cross-stakeholder (governments, funding agencies, researchers, clinicians, industry, and the public) commitment, the translation of bench research findings to clinically relevant and effective therapies has proven neither simple nor assured.

Indeed, as the pharmaceutical and biotechnology industry has fallen dramatically short of its own expectations, virtually everyone has been concerned with the so-called 'innovation deficit' or 'productivity gap' – that is the reduction of the number of medicines entering the market on a year-by-year basis, as well as the ever-increasing R&D expenditure that compounds the issue (Drews, 1998; Drews, 2000). Recent research from the multinational management consulting and accounting firm Accenture and the Centre for Medicine Research (CRM) International has suggested that 'only 3% of projects aimed at new targets will enter preclinical development compared to 17% for projects aimed on established targets' (Carney, 2005:1011).

This innovation decline, identified in the pharmaceutical and biotech R&D setting, has been also evident in the more academic setting, where the translation rate of major basic science promises to clinical applications has been insufficient and disappointing. In their 2003 paper, Contopoulos-Ioannidis et al. (2003) have examined what is referred to as the 'rate' of Translation by looking at how often and how fast original basic research findings translate into clinical development and use. To address this question, they evaluated a sample of basic research publications in highly cited journals that had presented findings showing a clear clinical promise and then studied whether the original expectations materialised over a period of twenty years. Their study provided considerable evidence that even the most promising basic science findings take a long time to translate into clinical experimentation, with subsequent adoption into clinical practice being even rarer.

But why is the rate of translation so low? Why is it that current developments in basic discovery sciences, published in thousands of discipline-specific journals and in combination with high levels of public and private investment, have not been mirrored by the same level of progress in understanding the clinical basis of disease and ultimately the development of novel effective therapies? The effort to diagnose the 'failure of Translation' and explain the decline in biomedical innovation has become something of a cottage industry within the literature of innovation, and it is here where the social sciences may be able to make a significant contribution. In order to do so, however, it could be useful to first briefly review the Translational Research literature in order to pinpoint and clarify the exact meaning and setting of Translational Research that is going to be explored in this thesis.

Definitions and Nomenclature Issues

The question of how to define Translational Research remains controversial. Many academics have voiced concerns that the first challenge of TR is one of language and meaning (Liang, 2003). As the terms Translation and Translational Research, 'Knowledge Translation', 'Knowledge and Technology Transfer', 'Knowledge Dissemination', 'Diffusion' and 'Implementation' are used interchangeably to mean sometimes similar and sometimes different things in the literature, they become a source of confusion. This is especially true for the funding agencies who are in need of a consensus terminology in order to recognise the gaps and address them with the Translational Research investments (Kerner, 2006).

The distinction between two main types of TR was articulated for the first time by the Institute of Medicine's Clinical Research Roundtable.[60] This series of roundtables (first convened in June 2000) was attended by a diverse group of stakeholders involved in basic and clinical research and its purpose was to promote dialogue, exchange of experts' views and collaboration on the issues faced by the 'Clinical Research Enterprise'.[61] As a result of these discussions, the Roundtable participants introduced a distinction between two types of Translational Research, T1 and T2. In addition, they

[60] Clinical Research Roundtable homepage available at: http://www.iom.edu/?id=19179 (Accessed June 15, 2009).

[61] The Clinical Investigator Workforce: Clinical Research Roundtable Symposium I. National Academy Press: Washington, DC. 2001; Public Confidence and Involvement in Clinical Research, Clinical Research Roundtable Symposium II. National Academy Press: Washington, DC. 2001; Exploring the Map of Clinical Research for the coming Decade. Clinical Research Roundtable Symposium III. National Academy Press: Washington, DC. 2001.

identified two major obstacles, or 'Translational Blocks', that impede efforts across the clinical research continuum to apply science for better human health. 'Translational block 1' was described as impeding T1 or 'the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans' (Sung et al., 2003: 1279). The second block 'affects the translation of results from clinical studies into everyday clinical practice and health decision making' (Sung, et al., 2003: 1279), namely T2.

A more pragmatic definition of Translational Research based on the fact that different stakeholders look at different aspects of the issue, is supported by Littman et al. (2007), who have been looking at Translational Research in the context of the pharmaceutical industry and drug development. For academia, for example, 'Translational Research represents a general desire to test novel ideas generated by basic investigation with the hope of turning them into useful clinical applications. For academic purposes, Translational Research also responds to the need of identifying novel scientific hypotheses relevant to human pathology through direct observation of humans and their diseases' (Littman, et al., 2007: 218). For the people more directly involved in clinical practice, such as physicians and patients, Translational Research represents 'the need to accelerate the capture of benefits from research in daily medical practice' (2007:218). And finally, for the commercial sector, 'Translational Research is a process aimed at expediting the development of known entities, particularly in the early phases, and/or identifying ways of making an early 'go/no-go' decision when the cost of product development is still relatively contained' (2007:218).

For this thesis, a limited definition of Translational Research is used, namely the 'bench to bedside' model of harnessing knowledge from basic sciences to produce new drugs, devices, and other clinical applications for patients. In other words, the end point of Translational Research is the production of a promising new product/treatment that can be used clinically or successfully commercialised ('brought to the market'). This definition is conceptually closer to the T1 term described above and is best suited to describe the Translational route in Regenerative Medicine and cell-based therapeutics (CBTs) field where research is still very much work-in-progress, most products/ therapies are still on the basic discovery, early development or clinical

trials stage and only a relatively small proportion of products have made it to the clinic and/or market.

In view of the fact that there are not many clinically and commercially successful cases yet to investigate and from which to draw conclusions, it is not surprising that T2 in the Regenerative Medicine field has largely been ignored so far by the scientific and health policy research literature. It has, however, been discussed by a substantial body of the sociological and STS literature exploring the effects of new technological advances on society and debating issues (such as equitable access) that might emerge once proof of principle exists and the first therapeutic products/treatments reach the clinic.

To sum up, there are a number of different terms and definitions/meanings of TR that correspond to a variety of points along the research continuum. Establishing which term and definition one is using is perhaps the first critical step to take in exploring Translational Research as each 'area' has its own characteristics (actors, settings, timelines) and raises its own set of issues. Indeed, much of the literature on Translational Research has been concerned with the identification of different barriers/obstacles for Translational Research across the various 'areas' as well as with finding ways to better translate basic biomedical achievements into practical benefits. Some of these barriers are explored in the following section.

Barriers to Translational Research

Scientific authors and commentators have identified various reasons for the Translation deficit. For example, the inability of translational investigators to take into account the complexity of human physiology and disease surfaces in the Marincola (2003) editorial when introducing the *Journal of Translational Medicine.* For Marincola, however, the obstacles are as much technical and methodological as they are conceptual or disciplinary. He identifies the limitations of animal models resembling human diseases as one of the most serious hurdles in Translational Medicine. In their attempt to facilitate the mathematical prediction of a given treatment outcome, many basic scientists prefer to simplify the biology of the models through standardisation of the genetic make-up of animal and diseases. As a result, the models no longer

represent the basic essence of human diseases and hence do not work as well in humans as they did in the preclinical settings. According to Marincola, Translational Medicine is a bidirectional process, from bench to bedside and from bedside to bench, but unfortunately, bedside-to-bench efforts are hindered because 'the scientific aspects are poorly understood by full time clinicians and the difficulty of dealing with humans poorly appreciated by basic scientist' (Marincola, 2003: 1). Rather than overcoming these misunderstandings, over-simplified animal models exacerbate them.

Apart from the calls for greater *in-vitro* and *in-vivo* connectivity, several other barriers are identified in the literature regarding TR. These include economic hurdles (i.e. funding of product development through to profitability), regulatory barriers, intellectual property (IP) obstacles, lack of metrics, and lack of infrastructure and TR training (Horig et al., 2005; Mankoff et al., 2004). The following section explores and discusses the apparent bidirectional nature of Translational Research and the role it plays in innovation.

On the Complexity and Non-linearity of Translational Research

In the previous sections, I have elaborated on the origin, definitions, terms and various meanings of the TR concept. As it is obvious from this review, Translational Research, as currently used in biomedicine, refers to a one-way, linear process through which the findings of basic science are applied to clinical problems.[62] However, this view of Translational Research has been increasingly doubted by many, including basic scientists and clinicians as well as social scientists, who argue that it portrays patient-oriented investigation as a process that is at best simplistic and at worst intellectually derivative.

For example, Peter Stacpoole (Professor of Medicine and Director of the General Clinical Research Centre, University of Florida) in a commentary in 2001 states that the term 'bench-to-bedside' evokes a fundamentally misleading and harmful paradigm for describing patient-oriented investigation and those who conduct it. Implicit in the

[62] Even the Pattison report, which in 2005 provided an agenda for research within the UK in the field of stem cells and more broadly RM, adopts a largely linear model of innovation. The diagrammatic representation of the 'stem cell therapy development and production process' comprises one-way arrows depicting the move of innovation(s) from R&D, to clinical research and finally to clinical practice (Pattison, 2005).

bench-to-bedside notion is, he suggests, the assumption of a linear and unidirectional process of biomedical experimentation, by which so-called Translational Research is 'necessarily preceded by and dependent on the creativity and hypothesis testing percolating up from laboratories conducting basic research' (Stacpoole, 2001: 616). Stacpoole continues by pointing out that biomedical investigation simply does not always work that way, and it is often the wonder and curiosity of observers of the clinical phenomenology of human disease that 'ignites the creative spark and inspires both clinically and non-clinically trained experimenters to undertake relevant hypothesis testing' (2001:616). In other words, according to Stacpoole, the quest for answers oscillates within and between the bench and the clinical arenas, in a process that he describes as highly iterative and palindromic.

Elliot Gershon (1998), a Professor of Psychiatry and Human Genetics at the University of Chicago, also criticises the linear model of TR even further, noting that the prevailing directional bias that most important discoveries are made in the laboratory and then applied to the clinic, is a costly one. This is because 'it enshrines an antagonistic "two cultures" mentality in the vast segment of society related to biomedicine, and inhibits intellectual voyages of discovery that do not go in the prescribed way, thus inhibiting rather than stimulating scientific progress' (Gershon, 1998: 96).

Damian O'Connell and David Roblin (2006) (from pharmaceutical giant Pfizer) also emphasise the non-linearity of Translational Research (within the context of the biopharmaceutical industry and drug development) and highlight the importance of a 'bi-directional dialogue' between research scientists and clinicians that would ensure the timely removal of poor candidate compounds and facilitate the identification and acceleration of 'good' compounds that fulfil a medical need, hence overcoming the pharmaceutical industries R&D attrition where 'failure is many times more likely than success' (O'Connell & Roblin, 2006: 833).[63]

[63] The FDA estimates that just a 10% improvement in predicting a product's failure in clinical trials could save 100 million dollars in development costs per drug. See: FDA 2004 'Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products': US Department of Health and Human Services, Food and Drug Administration.

From a social science perspective and with a focus on the RM field (and specifically HSCs[64]), Paul Martin, Nik Brown and Alison Kraft (2008) question the imagined trajectories of 'bench to bedside' and present an RM reality characterised by rather the inverse, namely 'bedside to bench'. Their analysis, which is based on a detailed historical and empirical study of the development of HSCs spanning several decades (1950 to the present), explores the way the relationship between the bench and the clinic has changed during this period and what implications are there for understanding the knowledge production and application, in other words Translation.

The non-linearity of Translation has also been argued from a business and commercialisation perspective. In his book on 'Commercialising Successful Biomedical Technologies: Basic Principles of the Development of Drugs, Diagnostics and Devices', Shreefal Mehta[65] – a US 'inventor/researcher-turned-CEO' – addresses the practical limitations of using a linear model ('a linear roadmap') to organise the iterative and path-dependent process of biomedical product development. Mehta points out that 'the linear roadmap shows the components that must be accessed to build a sound commercialisation plan, but the processes are all carried out in parallel, with shifting emphasis on each component as one proceeds down the plan'. In short, Mehta points out the inevitable fact that feedback from one component will ultimately influence or change the understanding of another previously researched component.[66]

In short, there are compelling arguments to suggest that Translational Research cannot be adequately represented by the 'bench-to-bedside' concept and has increasingly been described as a 'bench-to-bedside-to-bench-to-industry-to-bench' process. This iterative and complex nature of Translational Research that emerges from the scientific and other literature, is an important concept in this thesis, and I use it in later chapters as a background in order to identify and explain innovation in the Regenerative Medicine (RM) therapeutics field.

[64] Haematopoietic Stem Cells (HSCs)

[65] Shreefal Mehta was awarded the New York capital region's Future Business Leaders '40 under 40' Award in 2006. He has lectured at international conferences, been quoted in business and trade magazines (*Economist, The Scientist,* etc), been widely published in leading journals such as *Nature Biotechnology,* and has taught executive management and multidisciplinary classes on commercialising biotechnology.

[66] For example, limited access to IP rights may change market strategy, which in turn may alter the regulatory pathway required to develop an FDA-approved product.

Indeed, Regenerative Medicine is considered by many to be a poster child for Translational Research. Maienschein et al. (2008), for example, have argued that contemporary stem cell research is being shaped by the pressures of Translation more than any other biomedical field, precisely because the research is developing at the same time as the demand for results. As the emphasis on harnessing laboratory findings has coincided with this 'new era in biology and medicine' (Keller, 2005) there is in no longer the possibility of what is called 'pure' or 'curiosity-driven' exploration of stem cell science. As Maienschein et al. (2008) note, by changing our understanding of fundamental biological concepts, stem cell research has also changed the expectations about what and how fast things can reach the clinic (or the market). As such, 'stem cell research outcomes may well set the agenda for future funding initiatives and change the ways in which Translational Research is understood, by both scientists and the public' (Maienschein et al., 2008).

A vital role in this understanding of Regenerative Medicine is undoubtedly being played by the social sciences and the way they are exploring both Regenerative Medicine as a new promising treatment paradigm and Translational Research. In the next chapter, first I briefly review the social science literature for Regenerative Medicine in general and then provide a more detailed review of the social studies which have focussed on the 'bench-to-bedside' paradigm of RM and other relevant aspects (for example social science research on RM regulation).

Chapter 3

The Social Science Perspective

Introduction

In this chapter, I provide a review of the social science literature that is relevant to my thesis and that will help the reader to better conceptualise the research problem and questions that have been mentioned in the first chapter, as well as understand the rationale behind the study and the intended contribution to the knowledge of the specific field.

The purpose of this review is twofold. First, it is to identify sociological work concerned with the emerging field of Regenerative Medicine and identify and present some of the central research streams that have emerged. This part briefly reviews the most relevant social science studies that have addressed the RM paradigm including a variety of perspectives (e.g. political perspective) and methodological approaches, and thus provides the reader with the background to understand my research and puts my 'line of enquiry' into context. Second, it is to identify the most influential researchers and research groups in the (more narrow) field of RM Translational Research, critically describe their work and reflect on the main sociological theories and concepts that have been used to examine the paradigm 'of bench-to-bedside'. In other words, in this part I identify the pieces of sociological work that are the most relevant to my research, explain why this is and finally explain what motivated my research and guided its 'structure'.

The review of the literature (in addition to its value in developing my research rationale) has also provided me with methodological insights regarding how to 'go about' exploring the specific part of the phenomenon (Translation) I was interested in and also how to capture the particular perspective on which I wanted to focus.

Coverage

Deciding how wide to cast the net was a critical step in conducting the review. As an initial approach I read widely on the social science of RM to try and gain an understanding of the central issues that have emerged and the approaches that people in the field have taken to explore and address them. The next step was to identify the studies that appeared to be the most relevant to what I had already proposed to do and use them to justify it, develop it and refine my research design. Once the first empirical data had been collected and themes emerged I decided it was essential for the review to cover additional areas that although not characterised as directly belonging to the 'bed-to- bedside' sociological research space, they are in many ways relevant and useful in its exploration. For example, I have also reviewed sociological research on RM regulation and the recent articles analysing and debating the emergence of an 'ethos of Translation'. Finally, I have read extensively from the entrepreneurship literature and have included many references in the empirical chapters. A full review however, is beyond the scope of this thesis. I do review and recommend one study that I found the most relevant, in terms of settings, and the most useful, in terms of structure, methodology followed and concepts.

Although the above description might give the impression of a linear and ordered process, in reality, the process of reviewing the literature has been continuous and iterative throughout the writing of the thesis; as new references were identified and retrieved it became necessary to examine some themes in more detail.

Organisation Format

There are many formats in which to organise a review (for example the historical format, the conceptual format, and the methodological format) (Hart, 1998). For the purposes of this review the 'conceptual' is the most appropriate format as it allows the review to be organised according to the various theories, concepts and analytical motifs in the literature. A historical and methodological approach cannot be justified because of the recent emergence of the phenomenon (RM in general and the 'bench to bedside' more specifically) under study and the dearth of social science studies that have addressed it (so far).

Data Collection Method

My data collection process began with an electronic search in social science databases (IBSS) and the Internet. Among the search terms used were: Regenerative Medicine, Translation, Translational Research, stem cells, cell therapies, cell therapeutics, commercialisation, clinical and commercial translation. Electronic searches lead to about 40 percent of the articles that eventually comprised my review. The remaining 60 percent was located by searching the references of the articles that were retrieved, determining which of those were relevant and searching through them too. In order to ensure that I included all relevant studies, I also searched for literature reviews that had already addressed the same research area and explored related sets of questions.[67]

In the next section, I briefly review social science studies that I think are the most pivotal in the RM field, this will provide the necessary background for the reader and aid their understanding not only of the research context, but also the analysis and discussion in the empirical chapters (Chapters 4, 5 and 6). For reasons of clarity I have classified the reviewed sociological work under a few broad, distinct but interrelated streams of research.

Social Science of Regenerative Medicine

The social sciences have launched a large number of studies into the sociological perspectives of Regenerative Medicine aiming to explore, map, and understand it, often help direct its governance and regulation, and ultimately facilitate the achievement of its goals.

In the UK and in recognition of the importance of the social science perspective for the developments in Regenerative Medicine, the Economic and Social Research Council (ESRC) set up in 2005 (until 2009), the Social Science Stem Cell Initiative (SCI) to the value of £1.7 million. Through this funding, the SCI sought to build research capacity and raise awareness within the UK social community of the significance of this emerging field. The SCI has supported a substantial number of social science projects involving various themes related to stem cell research, including

[67] As far as I am aware, only one review of sociological work on Translation has been published so far. See Wainwright et al. (2009), where sociological work in the RM field is categorised under seven broad themes. I have found this categorisation useful and I am using a similar format.

the issues of stem cell regulation, innovation, materials and research practices standardisation, and the dynamics of expectations and public engagement.

On the whole, the growing (and relevant) social science literature on Regenerative Medicine (RM) can be classified as belonging to one (or a combination) of the following research streams.[68] The streams include:

1. Research on the themes of regulation, legislation, and policy frameworks;
2. Research focusing on the development of the notion of 'tissue economies' and tissue commodification;
3. Sociological research that relates stem cell research to the social world of reproductive technologies;
4. Research on the media representation of the RM field and the relationship between the public (perceptions, debates) and ethics;
5. Socio-political perspectives and the theme of governance (biopolitics);
6. Research on intellectual property issues related to RM.

In the following paragraphs I briefly review what I consider to be the pivotal studies and most influential contributions in each stream of research. The aim is provide a picture of the whole field and help the reader to position my own work.

Focussing on the themes of regulation of Regenerative Medicine, a number of social scientists have examined the regulatory and legislative frameworks for stem cell research in various countries, including Germany and the US (Gottweis, 2002), Israel (Prainsack, 2006), Singapore (Kian & Leng, 2005), or have written reviews of various national policy frameworks (Liddell & Wallace, 2005), or have explored the development of the policy framework itself (Parry, 2003).

The relationships between regulation and policy formation (from a more empirical basis), has been largely explored by Alex Faulkner, Ingrid Geesink, Julie Kent and David Fitzpatrick. In their paper Faulkner and colleagues (2008) examine the risks that are formulated in the zone of tissue engineering (TE) and whether those risks are

[68] The research streams or 'themes' in RM are the same as those identified in Wainwright et al. (2009). However, in their 2009 publication there is one stream that I will not be reviewing and includes the more 'cultural' perspective on the field of RM.

reflected in emerging regulatory policy in Europe. According to the authors, scientific and industrial actors formulate the risks of TE in three primary frames (technological safety risk; therapeutic efficacy risk; and economic risk) and these frames are mobilised selectively during the EU process of regulatory regime building. Additionally, Faulkner (2009) presents a detailed account of the debate and development of regulatory policy for therapeutic TE in EU policy institutions and stakeholder networks, exploring how jurisdiction of an emergent zone has been formed through such negotiations and thus essentially providing a counter-example to the common view that regulation 'lags behind' innovation.

The same team (Kent et al., 2006) employs the concepts of 'biovalue', 'biocapital' and 'intercorporeality' (Waldby, 2002a, 2002b) to examine the significance of autologous applications of tissue engineering for the personal identity of its end users. The authors explore the issue in relation to the tissue-engineered autologous chondrocyte implantation (ACI) technique. According to Kent et al. (2006), the implications for 'self' of autologous 'self-repair' technologies such as ACI are very different to that of allogeneic multi-donor/multi-recipient technologies where analytic concepts such as biovalue and intercorporeality are much more applicable.

One important stream of research is focussed on the theme of tissue commodification and 'tissue economies' (as defined by Catherine Waldby). Waldby (2002b) examines social and philosophical implications of stem cell technologies, including transformations in the concept of health/healthy body, particularly in the temporality of ageing and social indebtedness. Using cord blood banking as a case study, Waldby (2006) argues that the technical economy of Regenerative Medicine is not socially neutral. Cord blood banking exists in two distinct forms – an allogeneic tissue network based on gifting to public cord blood banks and a private autologous cord blood account. In her analysis, Waldby suggests that private cord blood banking not only does not conform to the logic of gift economies, but also the form of possession/property relationship it creates is novel in the contemporary field of human tissue biopolitics.

Other scholars to have contributed significantly in this research stream are David Resnik (2002) and Peter Glasner (2005) who have focused on the commercial potential

of RM and the resulting ethical dimensions. Resnik (2002) draws attention to the shift of the human embryonic debate from fundamental questions such as whether the research should be done at all, to what he sees as the next stage of the debate: the battle for property rights relating to human embryonic stem cells. Sociologist Peter Glasner (2005) from Cardiff University, uses Waldby's model of 'tissue economy' (predicated on the gifting of spare embryos by family members to stem cell researchers) to conceptualise the supply chain from stem cells to therapeutic applications.

Another stream of research, explores the relationship of RM, and specifically human stem cell research, with reproductive technologies. Sarah Franklin from the London School of Economics (2006) explores the question of embryo donation to stem cell research from the perspective of the increased proximity between stem cell derivation and the process of *in-vitro* fertilisation (IVF). Franklin uses a model of 'double reproductive value' to explore what forms of exchange and flow are occurring, and how these are defined and negotiated in the context of a national hES cell coordination network of practitioners (hESCCO).[69]

Sociological research on media representations and public concerns about embryonic stem cells has been carried out by Williams et al. (2003) and Kitzinger and Williams (2005) who explore how the debate about embryo stem cell research is played out in the UK national press and TV news media.

Pivotal studies in the research stream of public debates and ethics include Margaret Sleeboom-Faulkner's (2008) (University of Sussex) examination of hESC debates in Japan. In her study Sleeboom-Faulkner notes that although the debate is considered crucial by policy-makers in Japan, it is found to be monopolised by the voices of a few social groups. These social groups either clearly support or oppose hESC research. Nevertheless, according to the author, 'the public debate is carried on mainly by political interest groups that amplify and mis-quote the minority voices. These interest groups capitalize on the hopes placed on hESC in promoting financial and political support, at the same time as they aim to cure disease' (Sleeboom-Faulkner, 2008: 285).

[69] Network of human embryonic stem cell coordinators (hESCCO).

In a similar vein, Beatrix Rubin (2008) examines how the concept of 'therapeutic promise' serves to draw attention to the central role of medical proposal in the discourse of hESC research and how it initiates an alliance between bioethics and science in an endeavour that both shapes and ensures the continuation of hESC research. The author uses the discourse of hESC research as a case study to show 'how proposals for novel therapies have framed and stabilised the initiation, reception, and implementation of a novel biomedical research domain (such as hESC) in the Western systems of science and policy (Rubin, 2008: 25). Evans et al. (2009) use diabetes stem cell research as a case study to examine how the hopes and uncertainties associated with its complex research agenda are understood by different groups, including researchers involved in the work themselves, public supporters, and public opponents of the research. In their analysis, they show that the difference in the understanding of the potential of stem cell research is a result of the way scientific progress is being communicated, both among the experts themselves and from the experts towards the public. Kotchetkova et al. (2008) compare focus group data on perceptions of stem cell research with survey-based representations of public opinion.

Patients' perceptions of embryo donation to stem cell research have been extensively explored in the UK and European context. For example, Sarah Parry (2006) from the University of Edinburgh investigates the views of people involved in UK fertility programmes who may be approached to donate their embryos for stem cell research. She argues that that participants' views are context-bound, born out of lived experiences both within the clinic and wider society. In particular, Parry argues that people's understandings of embryos as potential lives and the context in which embryos are created, have direct implications for their views about donating embryos for stem cell research. Haimes and Luce (2006) explore the views and experience of people (in the UK and Switzerland) asked to donate embryos for research.

The theme of patenting and intellectual property regulation in the UK, EU and US has also been intensively examined. The majority of the articles address the ethics of patenting, with most focussing on the ethics of patenting human embryonic stem cells (Chapman, 2009). David Resnik (2002) considers arguments for and against patenting, while others have sought to empirically research the perceived impact of the patenting regime (as well as commercialisation agendas) on the stem cell community (of Canada)

(Caulfield et al., 2008). Matthew Herder (2006) from Loyola University, Chicago, examines US and European patent systems, illustrating discrepancies in the patentability of hESC technologies and identifying potential negative consequences associated with efforts to make available hESC research tools for basic research purposes while at same time strengthening the position of certain patent-holders' rights. Herder (2009) also analyses and compares two recent initiatives in the field of stem cell research – 'Stem Cells for Safer Medicines' (SC4SM) based in the United Kingdom and the cross-border Canada–California 'Cancer Stem Cell Consortium' (CSCC) – in order to examine the reasons why any of these research initiative elects to adopt a particular approach to patenting, licensing, data and materials dissemination.

From a (bio)politics perspective Brian Salter (2007) examines the basis of the conflict in hESC science between patenting and morality at national and international levels, and the manifestations of those tensions in European patenting policy. He argues that a new type of expertise and authority is needed to negotiate the inevitable plurality of the economic and cultural moralities that are shaping EU patent policy and discusses how bioethics is a promising candidate for this new governance role. In another article, Salter (2008) analyses the approach of the emerging economies of China and India to innovation in stem cell science and their distinctive contribution to the dynamics of the global political competition.

In the next section, I examine the work of the most influential researchers and research groups in the field of translational Regenerative Medicine. The aim is to describe and examine previous research, identify the central issues under investigation and explicate the lines of argument most relevant to my work.

Social Science of Regenerative Medicine TR

As mentioned in Chapter 1, Translational Research is quickly becoming an integral part of all kinds of biomedical research and has become a funding priority for governments and relevant institutions across the globe including the National Institutes of Health (NIH) and the California Institute for Regenerative Medicine (CIRM) in the US; the Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council (BBSRC) and Wellcome Trust in the UK. With the ultimate aim of taking basic scientific discoveries that happen in the lab and converting them into clinical, economic and social benefits, translational efforts are under pressure to achieve their goal not only promptly but also transparently and under regulatory regimes that guarantee that results are safe and ethical to use.

In fact, in recognition of the important role the social sciences can play in the study of Translational Research (especially in the Regenerative Medicine field), special fellowships were set up by the UK Economic and Social Research Council (ESRC) to support research specifically on the theme of stem cell Translation. Study areas have ranged from the IVF–embryo interface and the processes and obstacles of product development, to commercial models and the emerging politics of a global stem cell bioeconomy.

Given the fact that Regenerative Medicine TR ('bench to bedside' paradigm) is a recently recognised concept/phenomenon (at least in the sense that is currently used by all stakeholders), it is no surprise that there are, to date, few sociological studies that have thoroughly addressed it. These studies have focussed on a wide variety of aspects and issues, have employed an array of concepts (borrowed from different research traditions) and have followed various methodological approaches. Overall, I have identified four broad 'research areas' that are (in terms of conceptual tools) the most useful to my own work. Each of the following sections provides a review of what I identify as the most influential studies in each of these areas.

A large part of sociological research in RM TR (bench-to-bedside) has been drawing on the sociology of expectations in order to explore a range of questions about the role of expectations in shaping scientific, technological, commercial, and social trajectories of stem cell research. The sociology of technological expectations is a relatively new

field within Science and Technology Studies, that builds on previous work on the social shaping of technology (MacKenzie & Wajcman, 1999) and with the general aim of examining how expectations of the future and other future-oriented claims (promises or 'visions') are an important resource in the creation of new technologies (Guise, 1999; Martin, 1995; Van Lente, 1993; Van Lente & Rip, 1998).

A number of studies on expectation dynamics have shown how, especially in the early stages of a technology's development, expectations play a crucial part in building interest, enrolling support and winning legitimacy, defining roles, constructing mutually binding obligations, informing agendas and commercial decisions and attracting investment (Walsh, 2002). In other words, expectations are thought to be a 'constitutive force' (or 'performative') as far as they coordinate actions in the present in order to realise a particular future (Borup et al., 2006; Brown et al., 2000). In this sense, expectations are considered by many as a particularly important analytical object when studying the bench-to-bedside interactions as both stem cell innovation and Translation are highly 'future-orientated' endeavours in need of ongoing financial and public support during what is a (possibly) long waiting time, before any benefits come to be realised.

Over the last five years a series of social science research papers have thoroughly examined aspects of the TR process employing concepts from the sociology of expectations and focusing on their 'performative' nature. Among the most influential groups are social scientists from King's College who have published widely on the subject, focussing on the field of stem cell research and specifically on the area of diabetes mellitus. For this group, 'stem cell science as a potential cure for diabetes, is a prime example of the increasing pressures of linking the bench and the bedside through Translational Research' (Wainwright et al. 2007: 252).

Beginning with their 2006 paper, Steven Wainwright, Clare Williams, Mike Michael, Bobbie Farsides and Alan Cribb (2006) explore the views of biomedical scientists on the prospects for and problems of Translational Research in the field of stem cells and specifically in the area of diabetes. The focus of their research is not only on institutional influences on the interactions between scientists and clinicians but also on stem cell science itself as barrier to developing treatments (both are areas which

scientists themselves saw as central in relation to stem cell science as a therapy for diabetes). Wainwright et al. (2006) draw on interviews and ethnographic work with scientists from one leading beta cell[70] laboratory in the UK, and their aim is to 'unpack a number of discourses that construct expectations about the trajectory from bench to bedside' (2006:2052). Among their findings is that, as Translational Research is becoming increasingly important in the shaping of basic scientific research, scientists seem to perceive that a number of institutional influences affect their interaction with clinicians (who carry out clinical research on the same field). The scientists understand these influences to be either in the form of 'external influences' (e.g. governmental, commercial, and so on) or in terms of the 'two cultures' of medicine and science, as they are perpetuated by important institutional factors – such as the way clinicians and scientists are trained and the way medical schools and research communities 'operate'. Despite these 'negative' influences, the authors found evidence of willingness to 'bridge' the perceived difference and collaborate in view of the benefits that would arise from successful interaction (collaboration).

The second part of the study investigates the theme of biomedical science itself as a major problem of imagined future stem cell (diabetes) therapies. In this part of their investigation, the authors' findings suggest that 'scientific' problems such as controlling the behaviour of (embryonic) stem cells, genetically modifying them and translating findings from animal models to humans, are perceived as responsible for dampening scientists expectations and in some cases even re-directing them to different stem cell 'futures' such as the use of stem cells as research tools (as opposed to being used as therapeutic transplants). Throughout the paper Wainwright and colleagues (2006) highlight the 'performative' nature of the discourses of expectations on the prospects for the Translation of research from bench to bedside. They conclude that 'scientists weave a complex tapestry of expectations' and that 'enactments of material expectations (about research outcomes) are partially structured by expectations about institutional (e.g. funders') expectations about the prospects for stem cell therapy. Conversely, institutional expectations about the possibility of collaboration are enabled by expectations about the successful manipulation of stem cells. The institutional and the material are thereby intimately entwined' (2006:2062).

[70] Beta cells are insulin-secreting cells that are destroyed in diabetes by the patient's autoimmune system.

Keeping the focus on the 'performative' nature of expectations Steven Wainwright, Mike Michael and Clare Williams (2008) have explored the role expectations play in the possible emergence of a new paradigm of Regenerative Medicine, the 'disease in a dish' approach to stem cell Translation. As opposed to the 'cell transplant' translation model (where stem cells themselves comprise the therapy), under the 'disease in a dish' model, hES cells will be used as tools for investigating the mechanisms of disease as well as enabling the development and testing of new drugs. Drawing on the sociology of expectations, and particularly the concept of 'expectational capital', as well as from Bourdieu's 'habitus', 'capital', and 'field' concepts, the authors argue that scientists' persuasive promises are used to advance their interests in the new 'disease in a dish' approach, hence promoting (and stabilising) it over the option of the until-recently dominant 'cell transplant' translation model and its so far 'unfulfilled expectations'. Wainwright and colleagues draw on over sixty interviews with scientists and clinicians in leading labs of the UK and US and explore their views on the bench-to-bedside interface in the fields of neuroscience and diabetes. In justifying their theoretical approach of combining the sociology of expectations with Bourdieu's concepts the authors state: 'If Bourdieu can provide a sense of the structure that characterises the field of stem cell research, the sociology of expectations can allow us to show how the future of this structure is performed in order to effect change in the present' (2008: 960).

Other scholars have looked at the constitutive character of expectations with regard to the long tradition of clinical innovation associated with the area of blood stem cells (haematopoietic stem cells, HSCs) in order to explore their role in what is truly the first and only (so far) routine application of stem cells in clinical practice. In examining the way biological entities like HSCs 'become the focus and bearers of future value in contemporary global stem cell economies', Nik Brown, Alison Kraft and Paul Martin (2006) have turned to the past to explore the way current expectations of stem cells are historically constituted. Again, drawing on perspectives in the 'sociology of expectations', the authors chart the 'promissory pasts' of HSCs through four different narratives: their place in blood transfusion, their role in bone marrow transplantation, their importance in gene therapy, and finally their role in the more recent areas of Tissue Engineering and Regenerative Medicine. By tracking the emergence and transformation of the HSC through 'a long series of cycles of hope and

disappointment', the authors have shown how past expectations are embedded in current networks and knowledge, in the same way that current expectations will be constituted in the construction of biological futures.

In another paper, the same team – Paul Martin, Nik Brown and Alison Kraft (2008) – question the 'imagined trajectories of bench to bedside' in the field of Regenerative Medicine and instead, advocate a Translation model based on the two-way flow of knowledge. Drawing on Anderson's notion of 'imagined communities' (Anderson, 1983) they develop the concept of 'communities of promise' and employ it to explore how clinical developments really emerge. Using HSCs as their case study, they examine the changing relationships between the bench and the bedside (i.e. the scientific and clinical communities of promise) over time and conclude that clinical experimentation, by 'feeding back' into basic laboratory research, facilitates innovation and is an equally crucial driver (to basic laboratory work) in the production of knowledge.

Several scholars have been exploring the role of expectations in stem cell innovation and Translation by focusing on a recently created 'branch' of the stem cell enterprise, the banking of cord blood (CB) stem cells. Nik Brown and Alison Kraft (2006), for example, have explored the growing phenomenon of cord blood (CB) banking by addressing the relationship between what they call 'imagination' and 'materiality' – in other words, the way in which current expectations of a future stem cell revolution are embodied (materialised) in the ever-increasing number of deposited cord blood samples. In their attempt to delve into the promissory dynamics of expectations of CB banking, they have employed a variety of concepts that have previously proven useful in unpacking the dynamics and sociological examination of other bio-phenomena (e.g. donation, processing and use of embryos, ova, tissue, etc).

For example, using the concepts of 'capitalisation' and 'biovalue', Nik Brown and Alison Kraft (2006) study the way promises and expectations in the worlds of CB banking work to connect the present and future value of this novel type of biological investment. Through the lens of the 'cord blood debate', which contrasts public banking and its ethos of altruistic donation to private banking as a form of 'personal property/investment', the authors are examining how the futures and expectations attached to the banking of cord blood are restructured and the implications this

restructuring is having or will have for the wider contemporary tissue economies. In the words of the authors, 'capitalisation can be seen to take the form of a shift away from the shared public ownership of a collective future resource and towards a greater privatisation of the storage for personal use and also commercial profit' (2006:318).

According to Brown and Kraft (2006), cord blood services are also part of what has been termed 'the political economy of hope', which resolves around the idea of 'a shared culture of images and understandings about the promise of medicine and the importance of personal or collective action in the face of potential pathology' (Brown & Kraft, 2006: 319). As the authors point out, there is a growing concern that in the case of CB banking this 'action' (i.e. the decision to bank the cord blood) is in danger of appearing to be more the result of the emotional manipulation of parents during the anxiety of childbirth than promotion of a 'legitimate precaution against the possibility – however unlikely – of the future clinical utility of banked cord blood' (2006:320).

Drawing from qualitative interview data Brown and Kraft (2006) also provide evidence of how the cord blood industry is interfering with understandings of family, kinship and blood ties, as well as 'new' parental duties towards an uncertain, risky future. Taking advantage of an 'increasingly geneticised causality of disease' the industry is seen to manufacture future familial disease risk and then present its services as an essential step towards safeguarding the potential treatments. Building on the expectations of future therapeutic potential, the risk of a future disease and kinship responsibilities, cord blood banking is promoted as a vital form of 'insurance' that parents are advised to take to ensure that their child (and perhaps other family members) takes advantage of future medical therapies.

Exploring further the dynamics across public and private CB sectors, and drawing on data from a global survey of the cord blood banking industry, Paul Martin, Nik Brown and Andrew Turner (2008) provide a detailed analysis of the construction of expectations in each case and the way public and private organisations are trying to create value for their prospective customers. According to the authors, public CB banking and its support of present-oriented, evidenced-based existing applications of cord blood stem cells is operating with a body of claims that can be characterised as a 'regime of truth'. As Martin and colleagues (2008) suggest, public banks 'refrain from

mobilising the future in constructing biovalue and stress instead currently proven therapeutics within a regime of truth oriented to the moral economy of altruistic mutuality' (Martin, Brown, & Turner, 2008: 137). In sharp contrast to this 'regime of truth', stands a body of both present but mainly future claims that can be characterised as the 'regime of hope', under which commercial cord blood banking has been operating. Recent findings about the plasticity of cord blood cells have hinted at a change of their role from 'just an alternative' to conventional bone marrow transplants for children to a potential therapy for a number of degenerative diseases in both adults and children, and have spurred rapid development of the commercial CB sector. While distinguishing between the two regimes of value, Martin and colleagues point to the entangling of the two regimes in the case of private banks that are operating the so-called 'hybrid model' where the choice between truth and hope, present and future is left to the customer.

In addition to their 'performative' nature, expectations are also thought to be temporally and spatially 'situated' (Brown, 2003). More specifically, they appear to have a temporal patterning over time, involving stages such as hypes and disappointments, and they are also different (at any one time) for the many groups or communities involved. In this section, I review a number of social science studies which have analysed Regenerative Medicine Translational Research, by identifying and conceptually employing this characteristic of expectations.

One recent study that addresses Translation this way is Kitzinger's (2008) study[71] which examines how experts in the field of stem cell science attempt to set expectations and manage disappointment during the innovation process. Focussing on the period 2000–2005, the author navigates her analysis from the initial times of visionary promises (2000) to the moments of breakthrough offered by a group of Korean scientists (2005), and finally to the 2005–2006 period of setback and disappointment as the Korean achievements were exposed as fraudulent. The work of Kitzinger shows that promises/hopes are more than just a 'tool' to be used in rhetorical representations of the future in order to mobilise resources and win support during the early stages of stem cell innovation process. In short, through the study of the Hwang scandal, Kitzinger (2008) illustrates how, even at later stages of the stem

[71] This study is located within the growing literature of expectations, as well as within the media studies literature.

cell innovation process – and especially during periods of failure/setback – expectations could be readjusted to the new reality and realigned towards a new future, so as to rescue hope and support of the stem cell innovation process as a whole.

Departing from the sociology of expectations but still with the focus on diabetes stem cell research, Steven Wainwright and Clare Williams (2008) from King's College develop a 'geography of science' framework as a new way to examine the interactions between the bench and the bedside. Their approach is based on David Livingstone's 'geographical perspective' which they use to explore what they call 'stem cell landscapes in the making'. The authors illustrate some of the transformations of the places[72] of stem cell science, explore the influence that place/space has on the production, shaping, content circulation and consumption of science, and finally they 'deconstruct the stem cell transplant approach to diabetes to illuminate some of the ways in which "space matters" in the field of stem cells and diabetes' (Wainwright & Williams, 2008: 164).

RM Translational Research and Ethics ('Translational Ethics')

In recognition of the many challenges that RM Translational Research faces as it crosses disciplines and other professional and institutional boundaries, many scholars have turned their attention to the ethical issues that are raised across the whole continuum of Translation. Given the fact that Translational Research is in need of ongoing financial support in order to achieve its goals, these issues must be addressed if the process is to secure legitimacy and win the trust and support of policy-makers, investors and the public.

Steven Wainwright, Clare Williams, Mike Michael, Bobbie Farsides and Alan Cribb (2006), for example, have empirically explored the ethical views of biomedical scientists on stem cell research and how these views are grounded in routine practice in the laboratory setting. The study focuses on the views of biomedical scientists on the (ethical) sources of human embryos and stem cells, scientists' perceptions of the human embryos and stem cells and, finally, scientists' perceptions of the current regulatory frameworks governing stem cell research. Building on Gieryn's 'boundary-

[72] Both physical/material spaces and 'disciplinary' spaces.

work' concept (Gieryn, 1983, 1999), the authors introduce the concept of 'ethical boundary-work' which they claim is becoming an integral part of the routine practice and performance of biomedical science. According to Wainwright and colleagues (2007), scientists have various practical ways of engaging with the 'ethics' of their work in order to conduct themselves in a 'complicated, political, moral and epistemic context. These practical ways ('practical ethics') include the use of different sources of embryos and stem cells as well as deferring 'ethical responsibility' from the 'space' of the laboratory to the 'space' of public regulatory bodies such the HFEA, the MRC and the Tissue Bank. Scientists consider that these regulatory authorities are responsible for the constant surveillance of the work being carried out, and for reassuring both the scientific community and the public that the research is being conducted legally and to high ethical standards. As the authors point out, the notion of 'ethical boundary-work' that has been developed in this piece of research has taken a form quite distinct from Gieryn's original concept, in that instead of defending scientific expertise by demarcating it from non-science, it de-privileges scientists by relocating their 'ethical work' to 'outsiders' (such as the regulatory bodies mentioned above).

The same team (Cribb, Wainwright, Williams, Farsides and Michael, 2008) has also examined how the socially produced and institutionally constructed roles/positions of the basic scientist and clinician, 'dictate' somewhat different ethical positions. According to the authors, stem cell experimental Translational Research and treatment are an ideal case when exploring what they call the 'uneven ethical terrain', as Translational Research (TR) by definition involves 'work done inside and across role positions that are constructed within, and defined by the differentiated ethical spaces of the scientific and the clinical' (Cribb et al., 2008: 351). The focus of the study is on two ethical issues: the use of experimental therapies and the responsible presentation of claims for innovative RM therapies. The authors argue that the normative structures[73] produced by the institutions, and the organisation of the scientific and the clinical, construct different ethical spaces and role positions, leading to what they term 'division of ethical labour'. According to Cribb and colleagues, this 'division' turns the application of science into a series of negotiations and collisions between the two ethical value fields, and challenges the establishment of effective collaborative relationships that are essential for successful Translational Research.

[73] Including role-related goals, obligations and disposition between the lab scientists and the clinicians.

In addition to the above studies that draw on empirical work to explore aspects of the Regenerative Medicine Translation, there are several other studies that address the same issues albeit in a theoretical way. For example, in addition to the problems that arise from the 'division of ethics', there are other challenges that are created by the 'homogenisation' of the ethics of the field. According to Woods (2008), 'bringing together all aspects of stem cell science under one rubric homogenises the field but obscures important moral distinctions between clinical application and experimental laboratory science' (Woods, 2008: 845). Reflecting upon the argument for the use of established but still risky stem cell therapies (e.g. HSC transplantation), Woods points out that the same ethical reasoning should not be used for the moral justification of future but still theoretical therapies. In other words, in Woods' view, the consequentialist reasoning in the form of risk-benefit evaluation that seems so robust in the context of an actual clinical application (even 'risky' ones) 'becomes attenuated and overshadowed by other important considerations in the more esoteric context of hES cell research' (2008:846), not least because of its still speculative and unproven nature.

Exploring the theme of Translational Research and bioethics, Shapiro and Layde (2008) emphasise the importance of integrating bioethics into each stage of translational and clinical research. This is, according to these authors, an essential step both for maximising the beneficial impact of scientific advances and for guarding against the potential deleterious medical and societal consequences of such advances. According to Shapiro and Layde, bioethics has the potential to play a critical role in what they identify as a 4-stage Translation process including basic research; preclinical studies and first-in-human trials; incorporation of results into clinical and community best practices; and finally, the fourth stage of refining best clinical practices. More specifically, the authors note that at the earliest stage of basic research studies, bioethics input is critical in addressing issues such as whether to limit certain areas of scientific inquiry, while at the second stage bioethics input is critical for the responsible conduct and reporting of human subjects research, including the management of conflict of interest issues that arise from industry collaborations. Although the authors' discussion and framework have been inspired by the whole spectrum of the evolving discipline of Translation, their conclusions are perfectly suited to the Regenerative Medicine field, which could potentially benefit by applying their recommendations for

assuring appropriate bioethics input is firmly incorporated into scientific agendas and Translational science initiatives.

Robert, Maienschein and Laubichler (2006) from the School of Life Sciences and Center for Biology and Society (Arizona State University) call for a more integrated approach to bioethics, which they name 'systems bioethics'. This approach, the authors argue, can provide a useful framework to address ethical and policy issues in controversial fields where there is significant pressure to generate clinical applications fast, as in stem cell research. In contrast to traditional bioethics, which is based on the atomistic analysis of particular aspects of the ethics of genetics, genomics and developmental biology, systems bioethics aims to integrate aspects of the history and philosophy of science, religious studies, experimental and clinical medicine, economics, political theory and the social studies of science (much as systems biology brings together different methodologies and experimental approaches, in an integrative way to study the complex interactions of living entities). The authors note that although this new approach to bioethical enquiry could be applied to other controversial research (e.g. gene therapy), it stands to be especially useful in the case of stem cells because stem cells as such 'are cultivated precisely to change, and therefore must be intrinsically dynamic and potentially unpredictable in some ways that may influence our decisions about the potential risks and benefits of applications' (Robert et al., 2006: 20).

Translational Research and Ethos ('Translational Ethos')

A different and recent body of literature that I have found useful for my research is that which has debated Maienschein's notion of the 'ethos of Translation'. Jane Maienschein, Mary Sunderland, Rachel Ankeny and Jason Scott Robert (2008) argue that the widespread push to Translational Research that is being imposed upon the biomedical sciences by government, funding agencies, institutions and patient advocacy groups, is bringing a new social contract for the way science works in society. The authors contrast this new social contract with the traditional social contract for science articulated by Vannevar Bush in his *Science the Endless Frontier* (1945), and which is based on the support of basic science and the assumption that 'applied' results will inevitably follow. In short, the authors argue that by subscribing to the new social

contract, accepting the translational imperative and building end goals into the research from the start, scientists might unwillingly distort science. Furthering their argument, Maienschein and colleagues also suggest that the pressure of Translation could also import a negative effect into the ethical discourses in biomedical science because it 'is taking the Translation as [an] unquestioned desirable goal and trying to make ethics fit' (Maienschein et al. 2008: 50).

Schwab and Satin (2008), however, question the above argument on the potentially distorting epistemic fit that accompanies translational demands and suggest that more precise conceptions of Translational Research as well as more diverse conceptions of science and bioethical discussion are needed to gain perspective on the potential impact of Translational Research on both science and bioethics. Zubin Master and Vural Ozdenir (2008) accept the 'silent' emergence of Maienschein's 'translational ethos' and that it may inadvertedly affect certain types of basic research that do not fall under the 'popular' Translation trend. However, they also point out that this kind of 'promissory practices' (such as Translation) are not a new phenomenon in the biomedical sciences where scientists are subject to hyper-competition and have to favour certain types of research programmes.

Finally, Audrey Chapman (2008), a Professor of Medical Humanities and Ethics at University of Connecticut, offers a completely different view, suggesting that it is more likely that the translational imperative will enhance the role of ethics in medical research. In her analysis, she uses the NIH's model of a clinical and Translational Research Institute as an example, and notes that in its calls for applications for funding it has identified clinical research ethics as a central programme area, hence making ethics 'a partner in training scientists, the research process, the development of therapeutic applications, clinical testing, and the diffusion of products' (Chapman, 2008:65).

RM Translational Research: Regulation and Standards

The themes of RM TR and regulation have been explored in various combinations and with a reference to standards, uncertainty, harmonisation, regulatory policy innovation and governance. For example, STS scholars Lena Eriksson and Andrew Webster

(2008) from the University of York, examine the development of standards in the stem cell field, the challenges of stabilising them through collaborative work, and the different epistemic values the discovery of various types of standards hold. Their study focusses on the international joint effort of the International Stem Cell Initiative (ISCI) taking place in various labs across the world to analyse the role that standards play in futures of stem cell research as imagined/constructed by stem cell scientists. As hESC research is an international enterprise, standardisation[74] is necessary to enhance collaboration between different research groups as well as to facilitate the production of comparable data, which will, in turn, speed up the pace of research and move the field closer to the clinical applications (therapies).

According to Eriksson and Webster (2008), the whole imagined landscape of stem cell research from the lab to the clinic is characterised by uncertainties which they have termed 'unknowns'. Unknowns are of three different types, the 'known unknowns', the 'knowable unknowns' and the 'unknown unknowns' – each located at a different phase of the stem cell research trajectory and posing different types of challenge and reward. The 'known unknowns', which are the focus of the ISCI's work, refer to the procedures and substances used in the derivation and maintenance of stem cells, the variation of which could potentially 'make a material difference' by changing the biological properties of the cells. In this respect, the known unknowns are, as the authors point out, 'a seemingly stable future soon to be present' (Eriksson & Webster, 2008: 58). In other words the scientists do not yet have the answers to their questions (on standards for protocols and materials) but they do have a very clear idea of what they are looking for. Despite the fact that the 'discovery' of these 'known unknowns' is an absolute requirement before the research moves to the next phase, it is apparently been considered as of low epistemic value by the scientific community, when compared to the 'knowable unknowns'. The 'knowable unknowns' in hESC research are the cells lines themselves and the salient scientific questions about their behaviour that the scientists are trying to answer. According to Eriksson and Webster (2008), these 'knowable unknowns' occupy a different layer of futurity on the imagined landscape, are of higher epistemic currency, but will only become a reality (a present), if the 'known unknowns' are stabilised first. The final type of uncertainties are the

[74] This task of standardisation (which has been assumed by the International Stem Cell Initiative) aims to develop a set of standardised criteria for the derivation, characterisation and maintenance of stem cell lines, through a comparative study of all hESC lines currently in use.

potential clinical applications of stem cell research, what the authors term 'unknown unknowns', which are seen as the more distant and more unstable part of the future. In the case of the 'unknown unknowns', the discovery payoff might be even higher but their high-risk nature means that they are a 'futurity whose ontological status is very uncertain indeed and in contrast to the 'known unknowns' it might never come about at all' (2008:64). Webster and Eriksson (2008) also explore the ways in which this form of governance-by-standards approach acts to manage uncertainty in the 'unstable' regulatory landscape of, initially, 'basic innovation' and eventually clinical application of hESC-based therapies.

Another recent piece of research has also examined the role of 'regulatory standards' in shaping and securing a certain future. More specifically, in a recent paper that draws on empirical research conducted at the UK Stem Cell Bank, Neil Stephens, Paul Atkinson and Peter Glasner (2008) explore the role of the UK Stem Cell Bank in sustaining stem cell hopes and protecting the future vision of stem cell science. Work with human embryonic stem cells (hESCs) is politically controversial and a number of public concerns in relation to the source and use of hESCs could be seen as threatening to the present and future of stem cell science. The fear of a potential collapse of public support and associated loss of social legitimacy for stem cell work has led the UK Bank to assume a 'regulatory role' that involves accrediting the ethical status of each potential donation to the Bank, quality checking donated cells and screening requests to access already deposited material. In the authors' words, the role of the Bank is performed through strategies that 'involve a complex temporal interplay: securing accounts of the past (both technical and social), while validating the regulatory legitimacy of the present' and all this 'in an effort to shape an imagined future of safe and publicly acceptable stem cell science' (Stephens et al., 2008: 46). In short, this study shows how promises about detailed ethical scrutiny and tight regulation help address public fears and solidify social networks that are essential to the work of the Bank.

Linda Hogle (2009) from the University of Wisconsin-Madison also examines attempts to develop consensus standards, reference methods and classifications rubrics, but in this case the focus is on the field of tissue engineering (TE) in the US. Hogle (2009) analyses the collective formal and informal processes that were employed to determine

what would count as relevant and objective evidence in the regulation of human tissue-engineered products. According to Hogle, although they were meant to provide 'procedural certainty' and create order, attempts to standardise and classify ambiguous products had unintended consequences, including challenges to fundamental assumptions about bodily interactions with technologies and reconsiderations of the institutional forms through which medical therapies have long been evaluated. In short, Hogle's work highlights the way political-industrial assemblages participate in socially negotiated forms of objectivity and argues that they are inseparable from the way new technologies take shape.

Another pivotal study on RM Translation and innovation that is related to the regulation of IP was published in 2009 by Olivia Harvey from the University of New South Wales (Sydney). Harvey (2009) examines hESC science in the US with a view to understanding the relationship between Translation in hESC science, the overall biotechnology innovation system, and how the State might intervene in this process to enhance competitive advantage. The main argument put forward by Harvey (2009) is that the adoption of the biotech innovation model by hESC research is one of the problems with US hESC research. According to Harvey, the normal processes of biotechnology innovation are further complicated in respect to hESC by the complications associated with patenting, the special cultural and political sensitivities, and finally by the uneven regulatory arrangements across the US that have an impact upon the networks and opportunities available to scientists and investors. In other words, the biotech innovation model ignores the specificities of hESC development and, at the same time, exacerbates the existing limitations to the long-term success of the hESC research in the US.

The Literature on Entrepreneurs

Over recent years, there has been a dramatic rise in entrepreneurial activity at universities (Wright et al., 2007) in the form of patenting, licensing, research joint ventures with private companies and the creation of spin-outs. The increase in entrepreneurial activity in universities has been matched by a concomitant increase in scholarly interest in this topic (Rothermael et al., 2007). Academic entrepreneurship is an interdisciplinary topic which can be studied using mixed methods (i.e. both

quantitative and qualitative analysis) and can draw on theories and concepts from economics, sociology and management.

The literature on entrepreneurship is large and beyond the scope of the current thesis. However, as the focus of this thesis (informant-wise) is on entrepreneurs – namely bioentrepreneurs – I consider it useful to briefly review one study that I found 'conceptually' useful and that could perhaps also be used as an inspiration for future research that would integrate theories and perspectives (from the sociology of expectations and entrepreneurship), hence benefiting from and eventually contributing to other research traditions.

In general, there is a relative dearth of studies that have focussed on the resource accumulation behaviour reported by nascent entrepreneurs who seek to commercialise their research. According to Paul Westhead (Director for the Centre of Entrepreneurship, Nottingham University Business School) and Harry Matlay (Birmingham University Business School) (2005), attitudinal, resource, operational and strategic barriers must be overcome by nascent entrepreneurs who, according to the authors, have no assets of business ownership experience to leverage (including financial resources, social and business networks) (Westhead & Matlay, 2005).

One of the few studies (as far as I am aware) that have explored these issues in the context of biomedicine is the study of the Medici Fellowship scheme by Simon Mosey, Paul Westhead and Andy Lockett. Mosey and colleagues (2007) have explored the success of a university technology transfer boosting scheme that was based on the introduction of 'knowledge brokers' in five research-intensive UK universities. The Medici Fellowship scheme was a short-term intervention to address the barriers to the Higher Education Institutions' (HEI) commercialisation process. More specifically, the scheme sought to 'engender a culture change within Biomedical faculty towards the commercialisation of their research, to address perceptions of negative attitudes towards commercialisation amongst faculty, and to help academics to accumulate resources to support the process of commercialisation' (Mosey et al. 2007: 364). In short, the aim of the scheme was to broaden the social capital of academics, which could be drawn upon to leverage resources available in practitioner networks (that is non-academics such as business individuals, customers and so on). The scheme

provided training 'which demystified the "language of business" [...] 'experimental learning was facilitated, which proactively encourages individuals to deal with the opportunities and threats that need to be considered when commercialising an idea from a university setting' and 'context specific skills were accumulated and the Fellows were encouraged to "learn by doing"' (2007:364). According to the authors' findings, 'fellows who accumulated human and social capital were able to act as agents of attitudinal change in their host institutions. Although they did not markedly change the culture towards commercialisation, they addressed several structural holes by creating weak ties with external actors who provided early-stage funding, market and legal information and potential customers' (2007:360). In monitoring the outcomes associated with this novel 'structured training initiative' that aimed to facilitate academic biomedical research Translation, Mosey et al. (2007) were guided by theoretical insights from human and social capital theory.

Overall, theoretical perspectives from human and social capital literatures are being increasingly used to explore and gain insights into the role of, and the barriers faced by, novice entrepreneurs. Thus, future research on the phenomenon of RM Translation could benefit greatly from combining what could be termed 'traditional' analytical tools (for example drawn from the sociology of expectations) with concepts widely used and useful in the entrepreneurship literature (and elsewhere), such as social and human capital, and social networks.

The Literature on Sociotechnical Networks, Techno-economic Networks (TENs) and Heterogeneous Engineering

This section provides an account of the key social science literature that this thesis aims to make a contribution to and presents the theoretical framework that is used to frame the empirical findings of the research in the conclusion of the thesis (Chapter 7). In designing my empirical study I drew on various ideas and research streams. The following paragraphs summarise these research streams and describe the theoretical tools and concepts I found useful for investigating the complex nature of the RM Translation process, drawing on work of Thomas Hughes, John Law and Michel Callon. All three authors advocate similar approaches to understanding technological innovation.

In particular, the historian of technology Thomas Hughes, understands technological innovation and stabilisation in terms of a system metaphor and proposes to think of technologies as if they were not only material artifacts within a separate technical sphere, but sociotechnical systems (Hughes, 1986; Hughes, 1987) . In the systems approach, the argument is that 'those who build artifacts do not concern themselves with artifacts alone but must also consider the way in which these artifacts relate to social, economic, political and scientific factors. *All* these factors are interrelated and all are potentially malleable' [emphasis in the original] (Law, 1987: 112).

Additionally, in Thomas Hughes' systems approach 'innovators are best seen as system builders: they juggle a wide range of variables as they attempt to relate the variables in an enduring whole. From time to time strategic problems arise that stand in the way of the smooth working or extension of the system. Using a military metaphor, Hughes talks of these problems as reverse salients,[75] and he shows the way in which bioentrepreneurs tend to focus on such problems and juxtapose social, technical, and economic variables as they search for a solution' (Law, 1987: 112).

[75] In his seminal book, *Networks of power: Electrification in western society, 1880-1930,* Thomas Hughes introduces the concept in the analysis of technological systems whereby the reverse salient refers to a component of the system that, due to its insufficient development, hampers the progress or prevents fulfilment of potential development of the collective system. Hughes' book is a study of Edison and illustrates both the systemic nature of much technological activity and the importance of the concept of reverse salient.

Sociologist John Law's own approach- 'network' approach[76]- in turn, borrows much from Hughes' system building perspective. Law, in addition, emphasises that in explanations of technological change and innovation the social should not be privileged nor be perceived 'as standing by itself behind the system being build and exercising a special influence on its development'. [77] In other words, Law thinks that 'the dominant factor in the growth and evolution of the system is a purely contingent matter and can only be determined by empirical means' (1987:113). Indeed, he suggests that other factors -natural, economic, or technical may at times explain better the final shape of artifacts in question as well as the social structure that results.

Law also argues that 'the stability and form of artifacts should be seen as a function of the interaction between heterogeneous elements as these are shaped and assimilated into a network' and that 'an explanation of technological forms rests on a study of both the conditions and the tactics of system building' (Law, 1987: 113). Because the tactics depend, as Hughes has suggested, 'on the interrelation of a range of disparate elements of varying degrees of malleability' Law calls such activity 'heterogeneous engineering' and suggests that 'the product can be seen as a *network* of juxtaposed components' [emphasis in the original] (1987:113).

Yet, according to Law, large-scale heterogeneous engineering is not easy. This is because the 'elements in the network are difficult to tame and hold in place [...] vigilance and surveillance have to be maintained, or else the elements will fall out of the line and the network will start to crumble (1987:114). Hence, 'system builders seek to create a network of heterogeneous but mutually sustaining elements. They seek to dissociate hostile forces and to associate them with their enterprise by transforming them' (1987:121).

To sum up, Thomas Hughes' system approach emphasizes a comprehensive viewpoint highlighting the interaction among heterogeneous parts and John Law's 'heterogeneous engineering' stresses a holistic viewpoint that allows us to understand

[76] Law's 'network' approach has been developed in relation to secondary empirical material about the technology of the fifteenth and sixteenth century Portuguese maritime expansion. See Law, J. (1987). Technology and Heterogeneous Engineering: The Case of Portuguese Expansion. In T. P. H. W.E. Bijker, and T.J. Pinch (Ed.), *The Social Construction of Technological Systems: New Directions in the Sociology and History of Technology* (pp. 111-134). Cambridge, MA: MIT.

[77] Contrary to social constructivism approaches who work on the assumption that the social lies behind and directs the growth and stabilisation of artifacts.

the underlying mechanisms of sociotechnical systems. Both concepts/theories of 'sociotechnical network' and 'heterogeneous engineering' easily lend themselves to the study of RM Translation through the perspective of bioentrepreneurs and their academic enterprises. I will consider the Translation of RM therapeutics (through founding of RM spinouts or start-ups) as an example of what John Law calls a 'network'. The 'core' of this 'network' is formed by the RM under development.

Figure.3 shows the structure of what I consider 'sociotechnical network' in this study. The central element consists of the bioentrepreneur, the company s/he has founded and the therapy/product that is being translated. The five peripheral elements consist of the five different 'spaces' (stakeholder groups) that are also involved in the process. The small (white) circles include the issues that have been mentioned in the narratives of the respondents as the most influential factors in the interaction between the two 'interacting elements'.

Figure.3 'Sociotechnical Network for RM Translation'

Several other authors have also used the concept of 'heterogeneous engineering' to explore the evolution of sociotechnical systems. For example, in his book '*Inventing Accuracy: a Historical Sociology of Nuclear Missile Guidance*', Donald MacKenzie (1990) examines the development of nuclear missile guidance systems as a historical product and social creation.[78] MacKenzie's theoretical model is created in the context of discussing nuclear missile guidance and his prime example of successful heterogeneous engineering is Charles Draper, Director of the Instrumentation Laboratory at MIT and of the key proponents of inertial missile guidance. He shows how Draper used 'heterogeneous engineering' to successfully develop inertial missile guidance system during the Cold War. Using Law's concept of 'heterogeneous engineering' to describe the complete 'set of skills' that is needed to succeed in promoting a specific technology, he states:

> 'People had to be engineered too- persuaded to suspend their doubts, induced to provide resources, trained and motivated to play their parts in a production process unprecedented in its demands. Successfully inventing the technology, turned out to be heterogeneous, the engineering of the social as well as the physical world' (MacKenzie, 1990: 28).

In other words, the author suggests that for a technology to be successful its proponents must create interest for it and obtain resources. Additionally, they must create an institutional framework in which progress can be made and at the same time train the employees and the public.

Following the 1990 publication of 'Inventing Accuracy', MacKenzie produced- a wide ranging collection of his (most recent) previously published work under the title 'Knowing Machines: Essays on Technical Change'. In a chapter entitled 'The Charismatic Engineer', MacKenzie and co-author Boelie Elzen describe the 'heterogeneous' work of Seymour Gray- the engineer whose name has become associated with the invention of the supercomputer. In their discussion of Cray's work, they introduce the notion of 'charisma'- a phenomenon, that according to the

[78] Previous studies of guidance systems have tended to view them from the technological deterministic perspective- that is that idea that guidance systems evolved to increasing missile accuracy, and that that nuclear strategies are determined by this technology (MacKenzie rejects this view).

authors, 'is little touched upon in the social studies of technology' (MacKenzie, 1996: 135).

The authors interpret Cray's charisma as a matter of forging a network. In short, they describe his continuous efforts to build the world's fastest computer and in doing so, places himself at the intersection of what could be seen as two contrasting worlds (networks). The first is the more stabilised world of previous efforts where customers demand hardware modifications, software and end-user support. The second is the uncertain journey towards higher speeds during which he constantly has to attempt to enrol the technology and hence gain the support of his colleagues. At every hurdle that could hinder his quest for a faster computer, Cray tried to 'shake off' the constraints by building networks, forming alliances and placing himself at the front of this network.

In an article he published in 2001,[79] John Krige, a historian of science and Kranzberg Professor of History, Technology and Society at the Georgia Institute of Technology (Atlanta), has also used the concept of 'heterogeneous engineering' to describe the work of Carlo Rubio who, together with Simon van der Meer, won the 1984 Nobel Prize for physics.[80] In their press release the Royal Swedish Academy recognised that there was more to this achievement than sheer intellectual insight and technological achievement. They write: 'Such qualities had to be embedded in a technological, managerial, institutional and political infrastructure' (Krige, 2001: 425). In his paper, Krige captures the 'salient' features of that infrastructure by suggesting that at least one of the laureates- Carlo Rubio- 'should be viewed, not only as a physicist, but also as a "heterogeneous engineer", who succeeded in mobilising the human and material resources needed to attain his objectives' (Krige, 2001:425). In short, Rubbia's ability to mobilise the necessary resources so as to bring that idea to fruition was essential to success.

Another research tradition that has been developed to examine the process of innovation and diffusion through the various interactions between the world of science, technology and the marketplace and which provides useful theoretical tools

[79] Krige, J. (2001). The 1984 Nobel Physics Prize for Heterogeneous Engineering, *Minerva* (Vol. 39, pp. 425-443): Springer Netherlands.

[80] Both Carlo Rubio and Simon van der Meer were based at CERN (the European organisation for Nuclear Research) and won the prize for their decisive contributions to the 'large project' that led to the identification of two important fundamental particles.

for the study of RM Translation is that of techno-economic network (TENs). As mentioned at the beginning of the chapter, in addition to Hughes and Law, Michel Callon (Centre de Sociologie de l'Innovation, Ecole des Mines de Paris) has also explored the heterogeneous processes of social and technical change, and in particular the dynamics of techno-economic networks (TENs).

Callon defines a TEN as 'a coordinated set of heterogeneous actors (public laboratories, technical research centres, industrial firm, financial organisations, users and public authorities) which participate collectively in the development and diffusion of innovations, and which via numerous interactions, organise the relationships between scientifico-technical research and the market' [...] A network is also not limited to just the (heterogeneous) actors who make it up. A whole set of intermediaries[81] circulates between them' (Callon et al., 1992: 216). More importantly, TENs are what Callon calls 'polycentric' networks which 'can be characterised simultaneously by a great degree of strategic autonomy for the various actors/organisations composing it and by mechanisms for integration and coordination that enable each actor to profit from the collaborative work with the other partners' (1992:216).

TENs are a useful framework to examine the work of RM bioentrepreneurs for two main reasons: first, unlike Hughes' and Law's sociotechnical systems, it has been specifically 'designed' to include the notion of the market (as one of the three main poles of the network) and second, it suggests the existence of actors (and thus intermediaries) that are 'not necessarily assignable to a particular category of organisation or institution' (Callon et al., 1992: 222). In that sense, the TEN theory has been developed to deal with 'role' overlaps as seen in the case of RM bioentrepreneurs. Finally, the distinction between incomplete and chained network, dispersed and convergent network, and short and long network is useful when investigating the dynamics of the RM Translation (network(s)).

Another concept that I found useful in the analysis of the RM bioentrepreneur sociotechnical network, particularly for explicating the (dynamics of) interaction between product developers and clinicians, is that of 'concurrent engineering'. In their

[81] Intermediaries give material content to the links uniting the actors and can be written documents, incorporated skills, money or more or less developed technical objects.

1997 article on 'social embedding of new products', Jasper Deuten from the School of Philosophy and Social Sciences, University of Twente and colleagues present a new management approach that allows managers within a firm to include, what the authors call 'societal embedding', in the management of product creation process (PCP). In the authors' words: 'one need not fatalistically await whatever societal embedding of one's product will result, but can anticipate and actively work towards desirable societal embedding. Thus in addition to, and integrated with Product Creation Process (PCP), one can think and act in terms of processes that create social embedding, i.e. "societal embedding creation processes" (SECP)' (Deuten et al., 1997: 131).

According to Deuten and colleagues (1997), in sectors like biotechnology, 'where integration in business chains and public acceptability are major issues, firms have taken up the challenge of such an integrated management approach (PCP+SECP), even if in a partial and not always successful way' (1997:131). This integrated approach, the authors suggest, is already much better than current practices, in which issues of societal embedding are bracketed until a late stage in the process (i.e. when potential damaging consequences of innovation cannot be avoided). They state:

> Product creation managers will often have a sequential approach[82] to the environment [...] when management is forced, as in biotechnology, to deal with alignments with the wider society, this is still taken up in later stages of the PCP, or not all (1997:134).

A principal way, in the authors' opinion, to manage the uncertain innovation journey of a product is to use 'concurrent engineering'. The term 'concurrent engineering implies intensive interaction between upstream and downstream functions, and upstream and downstream are regarded as parallel, rather than sequential processes. Furthermore, concurrent engineering implies integration of functions. Cross-functional teams are used to stimulate integration. Concurrent engineering is a reaction to changes in business environment (increasing international competition, decreasing

[82] The web of alignments in which the new product is to be embedded is gradually filled in. 'In many cases management of PCP wants to clarify the functional and technical aspects of the new product before it makes alignments with other parts of the environment. [...] in the early stages alignments with the business environment are seen as the most relevant. Only after the product concept is more definite do links with the regulation environment become important. Alignments with the wider society are only put on the agenda in later stages of the PCP, in particular if resistance of the public is expected, or becomes manifest' (Deuten, Rip & Jelsma, 1997:134).

product cycles etc.). Managing for societal quality implies that pressures in the regulation environment and wider society have to be taken into account as well' (1997:136).

In this thesis, I argue that In the same way that Deuten et al. (1997) view societal embedding as a broader notion of success for biotechnology products, bioentrepreneurs (in this study) view the 'clinical embedding' of RM products. In the same way that extended concurrent engineering is introduced by Deuten et al. as a management approach to make sure that societal embedding creation processes (SECP) are managed as a simultaneous and integral part of the Product Creation Process (PCP) from the start, respondents in this study propose what is, in fact, extended concurrent engineering between clinicians and bioentrepreneurs/product developers.[83]

Chapter Conclusion

My research has been motivated by a lack of information about the 'world' of bioentrepreneurs and their role in RM Translation, and by the more 'practical concerns' (barriers, failures, delays) of the RM Translation process as identified in the literature and as I understood them from personal communication with stakeholders during conferences and meetings.

So far most of the studies looking at the 'bed-to-bedside' paradigm have followed a similar structure. For example, they have focussed on a small number of questions/themes and have collected data from what would be a large and varied pool of RM stakeholders (often including biomedical scientists and/or clinicians and/or industry representatives). My study has been structured in very much the opposite way. More specifically, I chose my interview informants from just one 'pool' of stakeholders – namely bioentrepreneurs who hold critical and influential positions – and explore how they experience the Translation process and (unlike previous studies) address a wide range of themes. In fact the wider-than-normal range of themes that were

[83] Both notions also resonate with Gibbons et al.'s (1994) argument of a macro level shift towards a more socially robust 'Mode 2' form of knowledge production characterised by the active involvement of multiple social and scientific groups.

addressed (e.g. funding, regulation, collaboration, IP) is a logical consequence of the multifaceted role of the interviewees and is itself an empirical finding.

As many of the recent studies in the field have drawn on the sociology of expectations and related concepts to analyse their findings, I felt slightly biased and was tempted to incorporate it into my analysis. Looking carefully at the data, though, I soon felt I could not justify its use satisfactorily, despite sometimes coming across themes and issues in the narratives that could have possibly benefited from its use. However, these occurrences were limited. One reason for the lack of such 'expectations-related findings' might be that bioentrepreneurs are less likely to either understand or communicate an 'overblown' potential of a technology or be themselves 'hyped' about either basic scientific breakthroughs or technological developments. Their distinct position in the 'centre' of the RM TR field, which involves constant updates about the laboratory advances, the clinical setting (and clinical challenges) and the realities of the market, may help to dampen their expectations to a larger degree than is observed in other types of stakeholders.

Instead, I have sought to address the lack of knowledge and the practical concerns that I identified in two ways: first by relating the concerns with the rest of the relevant sociological research – mainly through the process of comparing and contrasting – and second, by identifying a variety of conceptual tools and analytical motifs that I either used in the 'original version' or I have moulded them in ways that I thought would best serve and advance my analysis. In some cases, and where I thought it would be useful in exploring and explaining the phenomenon (RM Translation) as well as the data that were coming in, I synthesised terms and concepts afresh.

Chapter 4

The Art of Funding

Introduction

The first chapter introduced the story of the first ever stem cell transplant and identified the three most important elements for successful realisation of such pioneering interventions: sufficient Funding, reasonably 'flexible' Regulation and effective and efficient cross-disciplinary Collaboration. This chapter discusses the first of these elements – Funding – and explores the experience and views of UK RM bioentrepreneurs about funding in Regenerative Medicine Translation.

The chapter is structured as follows: the first section provides a brief description of the biomedical research funding sources in the UK; this will provide the necessary background in order to conceptualise the issues reported by the informants later on. The second section examines the perceived lack of public translational funds for RM in the UK; the third and fourth sections examine the views of interviewees on the two emerging (alternative) sources of capital, namely venture capital and biopharmaceutical industry investments; finally, the two last sections explore how bioentrepreneurs experience and participate in the efforts of the RM industry to identify and/or create a 'viable' and hence fundable business model and their perceptions about the role IPRs (patents) appear to play in these efforts.

To begin to appreciate the problem of the so called 'equity gap'[84] that has plagued the Translational Research (TR) arena, as much in Regenerative Medicine as in other biomedical research fields, it is useful to understand the way medical research is funded in the UK. For instance, the overwhelming majority of *basic* biomedical research has, so far, been the preserve of laboratory-based scientists at universities or other research institutions. This type of research benefits from having a wide variety of funders and funding mechanisms from public sector, charities and occasionally the health industry. For example, in terms of the public sector, the key funders of *basic* research are the

[84] Ray Oakey, Director of the Centre for Research on Entrepreneurship and Innovation Management at Manchester Business School has coined the term 'equity gap'. See (Oakey, 2003).

Biotechnology and Biological Sciences Research Council (BBSRC) and the Medical Research Council (MRC). Very substantial spending in *basic* biomedical research (including Regenerative Medicine *basic* research), is also undertaken by charities with three of the largest funders being the Wellcome Trust, the British Heart Foundation (BHF) and Cancer Research UK. *Applied* research,[85] on the other hand, is primarily taking place in clinical settings and involves human volunteers. The main funders of UK *applied* research are the Health Departments of England, Wales, Scotland and Northern Ireland (Cooksey, 2006). This well-established but inflexible UK biomedical funding structure is unfortunately detrimental for the emerging paradigm of Translational Research which occupies the phase in the research continuum between *basic* and *applied* research. Translational Research helps turn early-stage innovations into therapies or products by advancing the innovation to the point where it becomes attractive for others (such as venture capital firms, industry, public–private partnerships) to take up the challenge of developing a product for the market.

Given the increasing emphasis of governments and publics on tangible medical breakthroughs that can only happen if the findings from heavily (publicly) funded *basic* research are 'translated' to the clinical setting, it is not surprising that the UK biomedical funding scheme has been widely criticised. In fact, in a consultation meeting for the Cooksey Review[86] held at the Royal Society in 2006, it was acknowledged that 'although the BBSRC and the MRC offer some opportunities in Translational Research, current funding to help move ideas from the laboratory is limited and research councils are still perceived as being weak at supporting Translational Research'.[87] In short, by not providing enough 'earmarked' funds for the translational phase, the UK places Translation in, what many respondents and others in the field, call the 'equity gap' or, how it is often referred to in scientific commentaries and literature, the 'valley of death'[88] (Butler, 2008; Woolf, 2008). The

[85] Applied research covers a wide range of activities including: research into prevention, detection, and diagnosis of a disease; research for the development of interventions; the subsequent evaluation of those interventions (also known as Health Technology Assessment, HTA); research into the management of disease; and finally, the provision of health and social care services (Cooksey, 2006).

[86] In March 2006, the Chancellor of the Exchequer and the Secretaries of State for Health and Trade and Industry invited Sir David Cooksey to undertake an independent review to advise on the best design and institutional arrangements for the public funding of health research in the UK.

[87] Consultation Meeting for the Cooksey Report Review: 'Lost in Translation', the Royal Society, London, 31 July 2006.

[88] The 'valley of death' concept is not exclusive to the Regenerative Medicine field. It is often used to refer to the chasm that exists between basic researchers and clinicians/physicians both in terms of communication and collaboration, as well as funding-wise. In the literature it is also referred to as the first gap in Translational Research or Translation Gap 1 or G1. TG1 spans key preclinical animal studies through to the end of successful Phase 3 trial.

following section focuses on how interviewees perceive the 'equity gap' in RM TR and how they think it might be possible to remedy the situation.

Translational Research and its Status of 'In-Between'

Asked about the challenges associated with Regenerative Medicine Translation, one of the first issues brought up by all interviewees is the apparent 'funding gap' that they encounter when it comes to translating research findings from the laboratory to the clinic and/or market. One interviewee explains:

> One of the biggest challenges is funding of Translation. Because that's sort of in the interface between what research councils would do and what venture capitalists would do. So Translation suffers from this so-called 'equity gap'. And that's a very serious issue which the TSB [Technology Strategy Board][89] is trying to plug now with serious cash injections.[90] But you know, in other countries these projects are taken up much sooner by venture capital. And in the UK, there is no venture capital for Regenerative Medicine and very, very little for biotech in general. So this is a big issue for the country. I think the UK has to fix that.
>
> **(XB, PI/CEO/Founder of Start-up, 2009)**

XB is the founder and Chief Executive Officer (CEO) of a non-academic, small biotechnology company that has developed and holds exclusive intellectual property rights (IPRs) for technologies in the field of Regenerative Medicine and stem cell research in particular. At the time of the interview, XB informed me that his company had recently secured a significant investment from a London-based venture capital fund that backs fast-growing small and medium-sized companies.[91] In describing the difficulties of funding Regenerative Medicine Translational Research (RM TR) in the

[89] The Technology Strategy Board (TSB) (formerly part of the Department of Trade and Industry, DTI) is an executive non-departmental public body (NDPB), established by the Government in 2007 and sponsored by the Department for Business, Innovation and Skills (BIS). The activities of the Technology Strategy Board are jointly supported and funded by BIS and other government departments, the devolved administrations, regional development agencies (RDAs) and research councils.

[90] For example, in November 2007, the Technology Strategy Board (TSB) announced a 'Cell Therapy' competition for projects which look to translate bioscience research into more robust methods for regenerative healing.

[91] As XB mentioned the VC investment followed on a grant from the DTI's Technology Programme (In 2004, the UK Government established a 10-year investment framework for science and innovation programmes. £320 million in grant funding has been available to UK businesses to support R&D projects between 2005 and 2008).

UK, XB emphasises its 'in-between status'. He explains how Translational Research falls outside the remit of research councils and, at the same time, it is too risky to attract funding from venture capitals and industry (pharma/biotech). While discussing the hurdles and delays his company faced in raising the necessary capital, he also commented on the role of venture capitalists which, he thinks, is limited in the UK compared to other countries.

In addition to the unanimous identification of the 'equity gap', the majority of the respondents also gave accounts that portray a confused understanding over which UK research council or charity funds what type and stage of research. LM, a principal investigator (PI) in the wound-management field who is also the founder of a spin-out company, describes her experience of trying to fund her team's translational efforts (that is early-stage prototype development of living skin equivalent (LSE) technology and its transfer to the clinical setting).[92]

> I was working with a colleague, Professor [Name], and we were tackling the problem of how to get patient skin cells from the laboratory to the patient, as fast as possible and as flexible as possible [...] We began doing that as a research project and got funding from the BBSRC [Biotechnology and Biological Sciences Research Council]. And then we got to the point where it [the construct] was working and we tried to get further funding. At that point, we applied to the Wellcome Trust and they turned down the grant and said: "Well listen, this is not research anymore, it is product development".
>
> **(LM, PI/Founder of Spin-out, 2007)**

LM explains how she and a colleague carried out basic research for their product funded by the Biotechnology and Biological Sciences Research Council (BBSRC), traditionally a sponsor for a variety of basic Regenerative Medicine research projects (including skin Tissue Engineering). After getting satisfactory results and proving that their product 'was working', LM and her colleague began their efforts to clinically translate it. According to LM, their application, this time to the Wellcome Trust, for grant money was quickly rejected as the charity considered the proposed work 'product

[92] LM's company has at least one product in the market available for use by clinicians.

development', which means it was outside the realm of 'research' and thus ineligible for the Wellcome Trust's 'research' grant money.

The Wellcome Trust however, was not the only UK 'sponsor' to have displayed such 'tunnel vision' as to what Translational Research really involves. It seems that projects that have ceased being hypothesis-based basic research and are trying to move into the clinical application phase will not be considered for funding by most UK research councils. In the quote below the same bioentrepreneur who was turned down by the Wellcome Trust recalls her experience of applying to the Medical Research Council (MRC), again seeking support for translational work.

> We have had grants turned down by the MRC [Medical Research Council], when we have tried to go to the clinic, because they said "it is not hypothesis driven". With a colleague of mine in London, Dr [Name], we applied for a couple of grants [MRC grants] and each was turned down. One [reviewer] said that it was not scientific enough. My colleague was going to translate cells through to cornea, clinically, and ours was for vitiligo[93] patients. They said it was not hypothesis driven. And this is not what we need for the UK to really pull things together. So there needs to be an understanding of what Translational Research is. In research councils there is a certain amount of snobbishness. They would be happier to look at blue sky stuff, cute science. If you write a good grant in these areas your chances of getting it funded are good. If you say: "actually we've done all of these bits and now we really need to go to the patient", your chances of getting it funded are very low. So that is a big gap. [...] We have scientists who are capable of pulling together things that will work, but to try and find a funding route for that is difficult. And really we need to be able to fund this small-scale, proof-of-concept [phase], prior to commercialisation.
>
> **(LM, PI/Founder of Spin-out, 2007)**

LM explains how her grant application was rejected by the MRC reviewers for not being 'scientific enough'. A colleague of hers in London, also interested in translating

[93] Vitiligo is a chronic disorder that causes depigmentation of patches of skin. It occurs when melanocytes, the cells responsible for skin pigmentation, die or are unable to function.

her findings to the clinical setting, was treated to the same response by the MRC. LM's frustration on the subject is clear and she blames the research councils and charities for not understanding what Translational Research really is. She also mentions the snobbishness of reviewers and their bias towards basic research that produces pure 'Big Science'. To an extent, her narrative echoes Professor Hollander's statement in Chapter 1, where he highlights the difficulty of having cross-disciplinary Translational Research funded. As far as LM is concerned, applications for 'safe', bench-based and blue-sky research have higher chances of being successful than risky, clinical research involving human subjects.

Another bioentrepreneur expresses the same feeling of sponsor – and grant-related uncertainty when it comes to applying for Translational Research funding. This informant reflects on the funding 'intricacies' of trying to deliver clinical-grade human stem cells.

> Then you have to put in all the aspects of how you are going to deliver clinical-grade cells, what way you are going to manufacture them, where are you going to get support for that. Which isn't cutting-edge research, it's fairly mundane, but it takes a lot of time and you have to then comply with all the compliance and validation and everything. So it is expensive to set up and the route for something like the MRC is quite difficult. Because you couldn't apply for a project grant for that. A project grant is mainly for basic research and this is not basic research, it is applied research. It is not so easy to see how you can get funding for it. I am never quite sure whether it should be academics who do that or companies, or a bit of both. I think the thing is that embryonic stem cells have come very much from an academic background...so it is one of those areas.
>
> **(GL, PI/Clinical involvement/Co-Founder of Spin-out, 2007)**

Clinical grade cell production, like the one undertaken by GL's team, necessitates adhering to current good manufacturing practices (cGMP)[94] to ensure the delivery of a

[94] Current Good Manufacturing Practice (cGMP) is a quality assurance system used in the pharmaceutical industry. It ensures that the end product meets preset specifications. GMP covers manufacturing and testing of the final product. It also requires traceability of raw materials and that production follows validated standard operating procedures (SOPs).

cell product/therapy that is safe, reproducible, and efficient. As the cell therapy production encompasses purification, manipulation, culture, characterisation, and delivery of cells, all parts of the production process must be defined and quality controlled.[95] Therefore, for academic centres, spin-outs and private companies who are moving towards exploiting the full potential of cells, needs arise for the development of the infrastructure necessary to support these investigations. Careful consideration of the design and building of the infrastructure is not only significant in terms of the large capital investment involved but, more importantly, in terms of the facility's role in achieving regulatory compliance.[96]

A common belief among stakeholders in the RM field is that the knowledge-base for new developments in Regenerative Medicine and stem cell research generally resides in the academic community and in small biotechnology companies with a substantial research capacity or those well connected to academic research groups (e.g. spin-outs).[97] This is also clearly acknowledged in GL's phrase 'I think the thing is that embryonic stem cells have come very much from an academic background...so it is one of those areas...'. Still, despite academia's 'competitive advantage' provided by 'cutting-edge' knowledge and 'know-how', the lack of appropriate funding means that the academic community is less prepared for the expensive and highly regulated aspects of product development, particularly those related to RM manufacturing. As GL explains, building and maintenance of such infrastructure and complying with the regulations is expensive, takes time and is not in the realm of what the research councils would normally fund.

ZL below, stresses the importance of securing 'good preclinical data' and the 'catch-22' of achieving proof-of-principle: animal studies are expensive to run, but it is very challenging to raise external financial support without them (and their positive results).

> They [funding problems] are pretty large. One is funding the animal studies to get proof-of-principle, which are expensive and take time. If they are successful, then it is really setting up the preliminary clinical trials which are also going to be very expensive. And there is a sort of funding

[95] For a detailed description on the production of clinical hESCs see (Unger et al., 2008).
[96] An article describing in detail the regulatory environment surrounding the infrastructure support for cell therapy and practical aspects for design consideration is (Dietz et al., 2007).
[97] This belief has also been confirmed at conversations I had with various Regenerative Medicine stakeholders including clinicians, industry people and biomedical researchers.

> gap. It takes time to get those animal studies completed so, in the meantime, the main challenge is really supporting them until you can get good [animal trial] results. Because getting investment in that early stage is really difficult.
>
> **(ZL, PI/Clinician/Licensor of RM technology, 2007)**

In commenting on the high 'burn rate' of capital while waiting for the necessary preclinical (animal) data and regulatory approval to proceed, ZL underlined how the lack of funding (for time-consuming and expensive animal studies) makes survival particularly difficult for any corporate company with limited financial flexibility (McKernan et al., 2010), and even more so for small academic spin-outs.

Since the publication of the Cooksey Review in 2006 and the identification of Translational Research funding problems and shortages (in life sciences in general), more initiatives and publicly-funded schemes[98] have been set up including: the NHS Innovation Hubs;[99] Regional Development Agencies;[100] the creation of the new virtual office for Life Sciences within the Department for Innovation, Universities and Skills (DIUS) to address key issues affecting the biotechnology, pharmaceutical and medical devices sectors. More specifically for RM Translational Research, the Medical Research Council announced a new translational stem cell research programme aiming to fund Translational Research to the tune of £10 million per year by 2010/2011, in addition to the establishment of the MRC Technology (i.e. the 'commercialisation arm' of the MRC); the Technology Strategy Board announced a 'Cell Therapy' competition with the focus on creating better 'methods' and cell therapy production processes. Charities have also introduced Translation-specific awards, such as the Wellcome Trust Translation Awards and the Wellcome Strategic Translation Awards;[101] this is response-mode funding, designed to bridge the funding gap in the commercialisation of new technologies in the biomedical arena. According to the Award's application

[98] For a list of the publicly-funded schemes in the UK go the following website: http://www.hml- treasury.gov.uk/d/cooksey_review_background_paper_examples_publicly_funded_schemes.pdf

[99] Commercialisation of innovations arising from within the NHS is managed by the Innovation Hubs in England, most of which are funded by the Department for Innovation, University and Skills (DIUS) and Office of Science and Technology (OST), via the Public Sector Research Exploitation (PSRE) scheme, and by the Department of Health (DH).

[100] For more information on England's Regional Development Agencies see: Cooksey, 2006. http://www.englandsrdas.com/visit_rdas. For more information on Scotland's RDAS (Scottish Enterprise and Highlands and Islands Enterprise (HIE)) see: http://www.scottish-enterprise.com and http://www.hie.co.uk respectively.

[101] For more information see: http://www.wellcome.ac.uk/Funding/Technology-transfer/Awards/Translation-Awards/index.htm and http://www.wellcome.ac.uk/Funding/Technology-transfer/Awards/Strategic-Translation-Awards/index.htm

guidelines 'projects must address an unmet need in healthcare or in applied medical research, offer a potential new solution, and have a realistic expectation that the innovation will be developed further by the market'.

Despite officially 'dedicating' part of their funds for Translational Research (TR), it appears that neither research councils nor charities have convinced the translational investigators and bioentrepreneurs. In the following excerpt, a bioentrepreneur specifically criticises the Medical Research Council's (MRC) funding scheme, and argues that what it seeks to fund is not 'real' Translation, but 'reverse' Translation.

> The MRC tend to consider 'reverse' Translation more than Translation. So they are more interested in the samples coming from patients who are receiving these products going back into basic research to find out something more about the process, rather than funding the actual research Translation itself. So I think that's the biggest challenge.
>
> **Kaftantzi**: What about the MRC Translational Stem Cell Research Committee (TSCRC) awards?
>
> Yes, they call them Translational Awards, but what the MRC has traditionally funded as a 'translational project' is 'reverse' Translation. So the people who sit on the awarding committees are all basic scientists. And they all want access to materials from patients who've been treated for something. They don't want to pay for the conduct of the trial, the fact that you need regulatory affairs officers, you need CROs [Contract Research Organisations],[102] etc. Several of us have stood up at meetings and decried this. Whenever we have a large enough audience we make a fuss about it.
>
> **(LK, PI/Founder of Start-up, 2009)**

[102] Contract Research Organisation, also called a Clinical Research Organisation, (CRO) is a service organisation that provides support to the pharmaceutical and biotechnology industries. CROs offer clients a wide range of 'outsourced' pharmaceutical research services to aid in the drug and medical device research and development process. Services offered by CROs include: product development, formulation and manufacturing; clinical trial management (preclinical through Phase IV); preclinical, toxicology, and clinical laboratory services for processing trial samples; data management, biostatistics and medical writing services for preparation of an FDA New Drug Application (NDA); regulatory affairs support; and many other complementary services. CROs range from large, international full service organisations to small, niche specialty groups and can offer their clients the experience of moving a new drug or device from its conception to FDA marketing approval without the drug sponsor having to maintain staff for these services.

LK cites the MRC award strategy as a failure of the translational funding system in the UK and explains that the biomedical community avoids acknowledging the problem, perhaps in part, because the system as it stands, supports 'superb basic science' and the majority of people who sit on the award committees (deciding on the fate of the funds) are basic scientists. In LK's opinion, basic scientists are mainly interested in getting access to the clinical samples in an attempt to gain insights into the 'performance' of the product (cells) that may help refine the experiment in its next iteration. In other words, what LK implies, is that basic scientists have few incentives to move out of their comfort zone and get involved with expensive human trials and all the associated complex regulatory, manufacturing, and even intellectual property issues. LK sounds sensitive to the need for reform, and mentions how he and few of his colleagues repeatedly try to attract attention to this problem.

LK's account supports the image of a basic biomedical research enterprise which has evolved its own dynamic and it is favoured (or in a way favours itself through the composition of the awarding committee) by research council funding. His account resonates well with Professor Hollander's point in Chapter 1, regarding peer review evaluation for funding and the preference for research projects that are closer to the evaluators' own discipline and, generally, of 'low risk'. This view is also supported by Young and colleagues (2008) who argue that peer review of journal articles is one subtle way this funding attitude is perpetuated. Their work suggests that the incentive structure built around the impact and citations, favours reiteration of popular work, that is, more and more detailed mouse experiments, and that it can be difficult and dangerous for a career to move into a new arena, especially when human study is expensive of time and money.

LK's critique of the MRC Translational Awards also questions the recently emerging discourse of biomedical 'Knowledge Translation'.[103] The proponents of this position describe a shift away from unidirectional research findings utilisation in the clinical setting toward more interactive models of knowledge transfer. The shift began when a growing number of scholars in biomedical, clinical and social sciences have noted that models involving linear, unidirectional and passive flow of information from research laboratories to clinical settings have not properly addressed the gap between research

[103] As described in Chapter 2, in the section titled 'On the Complexity and Non-Linearity of TR'.

and practice (Jacobson et al., 2003). The failings of previous models led some researchers to advocate broad and interactive models of knowledge (and research) Translation. The discourse, although relevant to all biomedical research (Baumbusch et al., 2008; Ledford, 2008; Nussenblatt et al., 2010; Stacpoole, 2001), in recent years, has taken centre-stage in the Regenerative Medicine therapeutics field.[104] This is mainly due to the unique characteristics of cells as 'drugs' and 'therapeutics' and the prerequisite to 'watch' them work *in vivo* to be certain of their safety and effectiveness.

Key to this interactive model of Knowledge Translation (KT), as envisaged for the Regenerative Medicine field, is the concept of 'reverse' Translation (mentioned by interviewee LK). Under the notion of reverse Translation, successful clinical trials, unexpected clinical responses, and even failed trials, can all stimulate new hypotheses and inspire new avenues of basic research. According to a recent editorial by Mason and Manzotti (2010), Translation is a cyclical process and reverse Translation is undoubtedly a very important part of it. According to the authors, 'the resulting clinical data must be fed back to the basic scientists in order to generate new hypotheses for the next round of research and Translation – a continuous revolving cycle fostering advances in both basic discovery and routine clinical practice' (Mason & Manzotti, 2010: 153).

The theme of 'bidirectionality', specifically in the field of Regenerative Medicine Translation and through the lens of STS, has also recently been explored by sociologists Paul Martin (Nottingham), Nik Brown and Alison Kraft (York) (2008). Using the development (over a 50-year period) of haematopoietic stem cells (HSCs) as their case study, Martin et al. (2008) examine the changing relationship between basic science and the clinical research community. Drawing from the sociology of expectations and concepts such as 'imagined communities' (Anderson, 1983), they develop the concept of 'communities of promises'[105] (formed around emerging technologies) and use them to question the, up until recently, popular unidirectional and linear model of knowledge production and innovation in biomedicine, suitably referred to as the 'bench-to-bedside' model. Their analysis, which is in agreement with an increasing number of scientific commentaries, concludes that clinical

[104] (Mason & Manzotti, 2010).
[105] In this case, basic science communities and clinical communities.

experimentation is as important for innovation as science is, thus supporting a dynamic, two-way innovation model for Regenerative Medicine.

Without rejecting the reverse Translation notion and the significance of the bidirectional flow of information it represents, LK is one of three bioentrepreneurs challenging the idea that reverse Translation is, as he states, 'everything'. Having experienced first-hand the MRC's 'funding preferences', he calls for a balance between the two types of Translation. Although he seems to appreciate the benefits of feeding clinical data and materials back to basic scientists, he emphasises the equal importance of pressing ahead with clinical trials (for example, Phases I, II and III), as well as dealing with manufacturing and regulatory issues, things that are often 'overlooked' by the MRC and its funding strategy.

Continuing with the theme of public funding, three bioentrepreneurs were keen to offer their views on how the situation might improve for RM Translational Research. For example, LM below, explains how 'joined-up thinking'[106] (on the part of research councils and the NHS) could facilitate potential collaborations between biomedical researchers and clinical practitioners and boost clinical Translation, through allowing the combination and/or sharing of their resources and funds.

> We need more joined-up thinking on how we fund Translational Research. Because my way of looking at it, is this: many of the patients that we are using skin for – and there are colleagues who are using cartilage, etc – they are NHS patients who have the problems. So chronic non-healing ulcers, major burns etc, etc. We have clinical staff that treats those patients under the NHS and they often wish they had something else they could give the patients like cultured cells or chondrocytes. Many of those NHS staff also need to do research to progress their careers. And we also have research council funding. Now many of the research

[106] The 'joined-up thinking' approach advocated by bioentrepreneurs is partly fulfilled by the establishment in January 2007 of the Office for Strategic Co-ordination of Health Research (OSCHR). The establishment of the OSCHR was a key recommendation in the Cooksey 2006 Review, and its aim was to 'take an overview of the budgetary division and research strategies of both the MRC and the NIHR'. In other words, the OSCHR was established to unify, distribute and control clinical research funds from the Department of Health (delivered through the NIHR) and the Department for Innovation, Universities and Skills (delivered through the MRC), and hence establish a more coherent strategic approach to funding, especially focussing on the case of Translational Research. The OSCHR published its first progress report in November 2008. The report can be accessed at:
http://www.nihr.ac.uk/files/pdfs/OSCHR_Progress_Report_18.11.08.pdf

> councils will not fund clinical research. And the NHS has got very little research funds. But it has got the problem of the patients and it has got the clinical staff and the willingness to do research. So the only way I have managed to move into the clinic is by pulling those together, using very little money. Now what we really need, is more joined-up thinking between the NHS research budget holders and the research councils. And there needs to be recognition that having money earmarked for getting stuff into the clinic safely, small-scale pilot studies, not commercial, is one of the most creative things the UK could do. Because we have all the skill sets to do that, but we have barriers at every stage.
> **(LM, PI/Founder of Spin-out, 2007)**

As LM emphasises in this passage, 'combined' (council and NHS) and 'earmarked' funds for Translational Research would help create a sustainable, seamless process between basic researchers in academic departments and surgeons/clinicians that promotes collaborations and accelerates innovations. The clinical environment has traditionally not been very supportive of Translational Research. As a result of limited time to devote to research (due to teaching and clinical responsibilities), small budgets and lack of readily available resources to test technologies and develop product prototypes, it is no surprise that creative approaches to address crucial improvements in patient care do not often progress out of the idea stage. On the other hand, academic scientists who have the time and resources to conduct research, have limited experience in a clinical environment and often lack the understanding of which medical problems really need addressing and how the clinical setting places constraints on potential solutions.

The need for 'joined-up thinking' has also been identified by another interviewee, LK, who advocates for more financial support (again combined between research councils and NHS) for principal investigators to perform first-in-human (FIH) experimental trials.

> I think the MRC and the NHS research funds should be focussed more towards Translational Research, and by that I mean first-in-man Translational Research [...] I think we need to encourage academics to

> do more than one-off first-in-man, and provide them with the facilities. At the moment the concept is that you have this brilliant idea...so for example if we take my product, [Product], I would have treated three patients, and shown that the cells engrafted, that the patients didn't die and that there was reduction in tumour. I would then stop everything and look for a commercial partner to pick it up and run with it. And I'd walk away from it. Because as an academic this is what I am supposed to do. Because I need to get one decent paper in one big journal, and then move on into something new.
>
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

Here LK talks about the tendency of RM investigators to end their research work at the FIH stage, if not earlier at the animal studies. He identifies two main problems behind this tendency. First, most of the investigators have neither the necessary facilities nor the funds to perform this kind of trial. Second, he believes it is the academic publications and career rewards 'culture' that sustain the above strategy. According to LK, academics need to publish a certain number of papers in certain high-impact journals, so they are 'better off' halting research before the FIH stage and looking for commercial partners to carry them out instead, while they pursue something new. Commenting further, he explains how his 'ethos' – that is, to change clinical practice – requires that he does things differently from 'normal' academics:

> Now my ethos is that I want to change clinical practice. So I want to run a fifteen-patient Phase-I trial and then a Phase-II trial or Phase-III. And that is completely outside most universities' ethos and most university researchers.

FIH experimental trials will usually include few people (perhaps 1-3) and, if successful, investigators could move to a Phase I trial including around 10-15 volunteers. As pointed out by LK, Phase I (and Phase II and III) trials are 'completely outside most university ethos and most university researchers'. LK continues, explaining the reason behind the reluctance of sponsors (public and private) to fund clinical trials, especially in academia:

> I think there is a problem with getting funding for Phase I/Phase II trials in academia. They are expensive compared to most academic products that one puts forward and they are high risk. They also don't tend to get publications in high-impact journals because they are clinical trials. So consequently it's not something that is readily funded by the MRC or any of the research councils. And I think there is a big gap there between the basic research and the true Translational Research.
>
> [...] So there needs to be understanding that academics need not just the money to do it, but they need to be reviewed in a different way in terms of their career structure, their returns to government or how 'academic' you are. It shouldn't be whether you got a paper in *Nature Medicine* this month or next month. It should be over a series of deliverables.
>
> [...] And we need to have the capacity, either in partnership with industry or on our own to manufacture RM products for up to fifteen patients at a trial. Not one or two [patients] in a very inadequate space.
>
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

Phase I clinical trials are considered 'high risk' both ethically and financially. This means that, even if successful, they will not secure the much needed high-impact publications that would justify a research council's investment and, perhaps even more importantly, capture the 'academic' credits for PIs, as required by the current career progression system. Yet, concentrating on publications so as to satisfy their 'reviewers' is clearly distracting and discouraging RM bioentrepreneurs from engaging with 'serious' Translation, which LK considers to be past the proof-of-principle and FIH stage. He also advocates better support of the manufacturing process in order for PIs to be able to progress from three patients to around fifteen.

The changes that LK proposes are large and challenging for the system and even if decisions are made to implement them (or something similar) it will no doubt take time. However, the pace of the RM breakthroughs at the bench does not seem to be slowing down so the need for principal investigators to bravely turn into bioentrepreneurs and drive the process, often completely unassisted, is clearly there and it is huge. As LK admits though: 'the complexity of taking the fantastically, wizzy

cell therapy product that you've invented and putting it into a small manufacturing entity is completely beyond most academics, they don't understand it'.

LK's insightful commentary is very useful in understanding how a start-up bioentrepreneur thinks of other bioentrepreneurs (specifically those involved with academic spin-outs) and 'normal' PI's, relative to clinical and commercial Translation. As LK suggests, what distinguishes him from investigators who have no interest in moving Translation beyond the first-in-man stage and those who will 'simply' (unprepared and unskilled) spin out a company, is a different 'ethos'. It is from this 'ethos' that stems the 'desire to change clinical practice' and the only way to achieve that is to strive and get one's research to as advanced a stage as possible, towards being a 'real technology' with a 'real benefit'.

The concept of 'translational ethos' has been recently in the forefront of Regenerative Medicine debates. Maienschein et al. (2008) have written about this ethos in the context of stem cell research which they claim has 'superseded genomics as the translational object of choice' (Maienschein, et al., 2008: 43). Referring to the 'translational ethos', the authors express concern about the appearance of a 'new social contract for the way science works in society'. According to this contract: 'Instead of implicit promissory results scientists must promise specific results up front. Moreover, they must produce results sooner rather than later and more specifically targeted for particular ends rather than the general good. Finally, there is now far more guidance from public investors. The result is an ethos of Translation' (2008:43).

Maienschein et al. (2008) critically interrogate this translational imperative and the pressure that comes with it to ask particular kinds of questions (and reach particular kinds of results), and wonder whether this imperative is undercutting scientists' abilities to engage in other kinds of research. The authors are concerned that 'public, political, and industrial demands, particularly with regard to what the products of the research should be, shape the landscape within which the research trajectory is determined, and that landscape is dominated by various demands for translation' (2008:49) and claim that today's Translational Research 'builds certain (and sometimes dubious) end goals into the research from the start' (2008:49).

Maienschein et al.'s (2008) analysis of the effects of the translational ethos on bioentrepreneurs suggests that they are driving the clinical and commercial Translation process so that it conforms to the external demands of others such as sponsors and/or the market. LK's account, however, could not be further from this speculation. The impression given by LK's narrative is that he is 'driving' the Translation process against all odds. In other words, the route he has chosen – a decision he attributes to his 'ethos' – is clearly the difficult one, 'against the current'. Instead of conforming to the lack of sufficient financial and infrastructure support (for clinical trials) and to the academic evaluation system like his colleagues, LK chooses to pursue Phase-I clinical trials which will bring him closer to external funding and perhaps the successful Translation of his work.

Summary

It is undoubtedly the case that many bioentrepreneurs interviewed for this study perceive a profound lack of funding in UK RM TR.[107] All the interviewees, without exception, reported difficulty in securing funds which is not credited to competition, but instead to an apparent 'mismatch' between the translational work principal investigators claim to carry out and the kinds of projects research councils and charities are 'interested' in sponsoring. The consensus among the bioentrepreneurs I interviewed is that UK research councils (which handle the bulk of public funds for universities and research institutions) and UK charities, often favour basic 'scientific' research at the expense of Translational Research. Yet the 'favouring' and continual expansion of basic research has been criticised before, with critics stating: 'the problem may be that Big Science is inappropriate for generating medical progress. The dominant research paradigm has been termed the 'basic to applied' model, and is (roughly) the assumption that expanding 'basic' medical research leads predictably to an increasing frequency of 'applied' clinical breakthroughs. The continuing failure to sustain therapeutic progress is making it increasingly apparent that these assumptions are, at best, only partially valid' (Charlton & Andras, 2005: 54).

Another theme to emerge in the discussion concerning public funding of Translation, is 'bidirectionallity'. Although most of the respondents with whom I had the

[107] In truth, the dearth of 'translational capital' does not seem to be specific to Regenerative Medicine, but the fact that all my informants are part of the RM paradigm does not allow for generalisation.

opportunity to talk described 'bidirectionality' in an inherently 'positive light', some bioentrepreneurs argue that the focus on the bedside-to-bench knowledge Translation that takes advantage of clinical feedback has led to the overlooking of important 'forward-looking' translational activities (such FIH, and Phase I, II, III clinical trials) and their requirements, such as regulatory and business expertise. Together, then, critics of the Translation process identify both 'internal' and 'external' factors that may be impeding more successful Translation, and more financial support for this sector.

Two of the respondents were keen to propose a solution to the dearth of translational public funds (due to their misdirection) by advocating a 'joined-up' thinking (and subsequently funding) approach between the research councils and the NHS, the main sponsors of basic and applied research respectively. By combining the financial resources of the two ends of the research continuum (basic and applied), much as they combine their expertise, research councils and the NHS could possibly serve the 'funding needs' of Translation. With this proposal in mind, this chapter now turns to the views of bioentrepreneurs on the role of venture capital in Regenerative Medicine Translation in the UK.

Venture Capital: The 'Later-Stage' Attitude

From the bioentrepreneurs' accounts so far, it is clear that the strategies and schemes that have been set up by the UK Government have not managed to bear enough of the risk of early-stage investment in Regenerative Medicine Translation. As mentioned earlier, new high-technology business ventures such as Regenerative Medicine start-up firms can have very high capital requirements (e.g. GMP facilities), returns are often much delayed compared to other more established science and technology areas, and bioentrepreneurs often have few or no assets available beyond their own knowledge capital. This situation leaves few choices if principal investigators want to transform their research into clinical applications. They are dependent upon 'risk' capital provided by venture capitalists or investments from industry (especially from large, established pharmaceutical firms).

In the absence of adequate public funding, successful identification of potential private sponsors is crucial, and yet is not the same as actually securing the funds, as many spin-

out founders know too well. Indeed, it is common knowledge within the community of start-up bioentrepreneurs interviewed for this study that venture capital groups, as well as big pharma, have largely held back from investing in companies focussed on Regenerative Medicine (Parson, 2008). In this section, my focus is the bioentrepreneurs' experience of engaging with venture capital while trying to raise funds for Translation. The next section includes a discussion of informants' views on the emerging role of industry in the Translational Regenerative Medicine field.

Asked about alternative sources of funds, all bioentrepreneurs interviewed for this study expressed dismay at how venture capital is operating in the UK. According to the interviewee below, the reason why venture capital is not a good candidate for filling the 'equity gap' is that most venture capitalists prefer to enter the process further 'downstream', ideally after proof-of-principle has been achieved in the clinic. This 'later-stage' attitude and the problem it poses for Translation funding is evident in the following quote by LM:

> It [UK Government] needs to seriously put research funding into translational work and not just talk about it. Because a common, common problem is that when you go for commercial money for a company they always wish you were further down the line and you were actually "caught" into the clinic. [...] It is actually very difficult for academic researchers to fund Translational research.
> **(LM, PI/ Founder of Spin-out, 2007)**

The level of technology development that the venture capitalist community is typically looking for, is also pinpointed below, by Greg Bonfiglio, during a presentation at a London Regenerative Medicine Network meeting in November 2008. Bonfiglio is the founder and Managing Partner of Proteus Venture Partners (Palo Alto, California), a venture fund focussing solely on stem cell and Regenerative Medicine companies. He has extensive experience in the commercialisation of Regenerative Medicine research and is considered an international leader in the field.

> We are trying to find a post where the core technology, the core concept has already been established. And by that, do I mean: do you have to be

> in the FDA? No. Do you have to be working your FDA program up? No. But you do need to know what your technology is and you need to have some sense of what are the most appropriate therapeutic applications for it. It needs animal data. You need to have enough data to gather so you can talk intelligently with the FDA in one of those pre-IND [Investigational New Drug] application meetings. If you are not there, you are probably not going to attract venture capital money. Because you are just too early. You could attract money from angel investors or friends and family, which is how you should be doing it, or grant money. But you are probably not going to attract the interest of most venture capital funds.
>
> **(Greg Bonfiglio, LRMN Meeting, 2008)**

A company's life cycle may be divided into different phases based on the time of maturity involved (European Venture Capital Association, 2006). The seed phase comprises the establishment of the company, during which the technology and business model are developed. This initial phase would normally involve a modest capital requirement, and is often financed either by friends, family and/or the so-called business angels[108] (sometimes referred to as 'angel investors'). Once the core technology and business models have been developed, then the company is said to move into the 'start-up' phase. During the start-up phase the technology should be verified, the product is considered to be in a 'prelaunch' state, and the organisation/ company will normally be built up with business expertise. The start-up phase is the most capital intensive, and the need arises for external, professional funders such as venture capitalists to join financially, or perhaps even take an active role in the business (Dobloug, 2008).

Commenting on behalf of his venture capital firm regarding Regenerative Medicine companies and their expectations of VC support, Bonfiglio points out that the product/therapy under development does not necessarily need to have FDA-approved data for safety and efficacy. It is, however, necessary for the research teams/companies

[108] The term 'business angels' was coined to describe the activities of individual investors who specialise in providing finance to new start-ups and early-stage firms in return for an (often substantial) equity stake. Business angels are, typically, wealthy individuals, often with significant previous managerial or entrepreneurial experience. They differ from venture capitalists in generally being sole investors, often reliant on their own finance, rather than managing a fund; it is, however, becoming increasingly common for business angels to create groups and organise themselves in networks and syndicates in order to search for and make investments. Definition sourced from Sainsbury Review (Sainsbury, 2007: 83).

to have key pre-clinical (animal studies) data and to have a solid knowledge of the product and all its potential therapeutic applications – preferably more than one (as a strategy to maximise the chances of success). According to Bonfiglio, only if these conditions are met is the technology considered 'de-risked' to the point where it is potentially attractive to venture capitalists.

Another risk factor is described by the interviewee below, who perceives the absence of venture capital in the RM field to be the result of the way RM companies have secured funding in the past, which, he implies, has led to failure of the ventures and has also generated distrust between the venture capitalists and the current Regenerative Medicine (RM) research and development community.

> For us, as academics – and I feel very strongly – that Regenerative Medicine is a very high-risk field. And as we've seen, there've been lots of train crashes with Regenerative Medicine companies and I think that, largely because they started too soon, they raced off on a field of euphoria, obtained funding from wherever, and then not delivered. And then the problem is this is still a very academic field. The success we are having with our [Product Name] is [because] the academic proof-of-principle was done before the company picked it up.
> [...] There is a famous phrase that: "Venture capital should not be adventure capital". Most of these [academic RM spin-outs] have been complete adventures.
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

LK admits that Regenerative Medicine is still a very academic and high-risk field. By this, he means that cell therapies under development – like the already existing cell therapies (largely from bone marrow), have been generally, so far, relying on academic-based clinical trials the cost of which is large for either academia (spin-outs) or start-ups to bear. Yet, according to LK, most of the Regenerative Medicine spin-outs so far have sought venture capital and/or industry funding too soon, before establishing proof-of-principle for their technologies. He mentions the company he founded – a non-academic firm – and highlights the fact that the product technology was acquired

for further development by a biotechnology company, after proof-of-concept had been achieved.

The importance of venture capital in relation to the development of entrepreneurship and innovation has long been reported in the social literature. But why is it so difficult for biotech companies, and specifically Regenerative Medicine companies, to raise adequate funding from private equity sources, such as venture capital? A surfeit of scientific/technical, ethical, legal and political problems make Regenerative Medicine companies a difficult pitch to venture capitalists. Indeed, as Regenerative Medicine research (including hESCs, iPS and other types of cells) is a relatively new area of endeavour, academic groups and companies developing these kinds of products face several types of risk, including technological risk, manufacturing risk, regulatory risk, and risk of failure in proceeding through clinical trials (Giebel, 2005).[109]

A final type of risk, and no doubt a distinctive risk factor for 'emerging' technologies, is the timeline for investor exit.[110] The intrinsic uncertainty of the lengthy development process of an innovative health technology challenges the flow of supporting finance in such a high-risk field (Perin, 2005).[111] The concentration of key patents into the hands of few commercial entities, in addition to the unclear, non-harmonised IP landscape might also help to dampen investor enthusiasm. This factor has been exacerbated by increasing global financial insecurity, a generalised risk factor that has hit the whole biotech sector hard as venture capital dries up (Browning, 2009). According to Ernst and Young the crisis has reduced venture capital to $16 billion in 2008, a 46% decrease compared with 2007 (Ernst&Young, 2007, 2009).

Thus, with less money to 'go round', it is no surprise that venture capitalists are becoming increasingly risk averse. As a result, biotech and regenerative companies are having to adjust to a situation where low-risk projects are favoured over high-risk ones, and the high-risk ones will probably have to be delayed and will require government or

[109] Giebel is a Venture Partner at SV Life Sciences, a venture capital firm focused on healthcare investing. He was cofounder and formerly CEO of Cythera Inc., a human embryonic stem cell company.

[110] Venture capitalists in biotech in general have a time horizon of about three years for a particular investment–nowhere near the ten or twelve years most companies take to get their first drug on the market. In addition, because they need to spread their risks, not even the largest funds can afford to sink a vast sum into any one start-up. According to data from the National Venture Capital Association on fund investment policies, the average investment in a biotech firm is about $3 million. The average maximum is $20 million (Pisano, 2006a, 2006b).

[111] Nicola Perin (June 2005), The Global Commercialisation of UK Stem Cell Research. A report prepared as part of an internship with the Biotechnology Team at UK Trade and Investment (DTI).

charity support in order to progress (Karberg, 2009). At the moment, however, it seems that none of the research councils[112] are very keen to bear the risk to adequately support this part of the Translation phase. Nevertheless, throwing, high-risk projects overboard may not suffice, and the whole dependence on venture capital and risk-averse research council funding may have to change. Finding new sources of long-term financing for translating research into therapeutics will be essential for maintaining innovation. An example of such a source could be large pharmaceutical or biotechnology firms looking to get involved with the new and promising Regenerative Medicine technologies, a scenario which is discussed in the next section.

Summary

Most bioentrepreneurs seem to have a realistic understanding about a company's potential to attract venture capital money. It clearly depends on the stage of the research, and all the bioentrepreneurs I spoke to have had quite a lot of contact with both venture capitalist firms or have attended relevant workshops and conferences. They are also aware that the 'capital problem' is typically even greater than normal in the Regenerative Medicine field where there is high knowledge intensity (with new scientific breakthroughs revealed every day – able to completely obliviate previous techniques and materials) and where neither the product nor the potential manufacturing process has been tested in market. In short, bioentrepreneurs perceive venture capital as perhaps the least possible funding option and instead are directing their efforts to sources that seem more 'accessible' such as Regional Development Agencies, as mentioned by many respondents.

In the next section, I build a picture of how bioentrepreneurs look at the role big pharma has played so far in terms of investment in the regenerative therapeutics field, and if and how this role has evolved. Where does a founder's choice for business model (commercialisation route) depend? How does the choice of business model and research agenda influence industry's investment decisions? And how industry investment strategies, in turn, affect a principal investigator's (basic and translational) research agendas?

[112] Research councils, even when they are keen, often require multiple rounds of grant applications to enable a novel product to reach a mature stage that is attractive for private investment.

Big Pharma: From 'Simply Watching' to 'Taking an Interest'

Given the current financial crisis and the fact that both public and venture capital funding appear to be problematic for Translational RM, many companies who are running low on cash are seeking funding from non-traditional sources such as big pharma. The 'non-traditional' characterisation stems from the fact that normally RegenMed companies with their R&D pipelines would be considered a threat to pharma, as RegenMed products have the potential to cure diseases, which was previously unthinkable. Big pharma, on the other hand, is in need of 'new growth engines' for their business and RegenMed companies and spin-outs could help fill this gap. Up to 2007 when I conducted the first half on the interviews, investments in the clinical and commercial Translation of Regenerative Medicine therapeutics had been modest. Since 2007 however, big pharma has been aggressively investing in the RegenMed space. For example, in 2008 Novartis and Roche invested in Cellerix in Spain, Johnson & Johnson invested in Tengion, Pfizer invested $3 million in Eyecyte. Large established biotech and medical devices companies have also made deals with RegenMed firms such as Genzyme with Osiris, Novo Nordisk with Cellartis, and GE Healthcare with Geron and Cytori (Smith, 2009).

In this section, I present the views of UK bioentrepreneurs on pharma and its role in the RM Translation field. What do they think about big pharma's initial hesitance, its current changed 'funding attitude' and how their own translational work is influenced by the changing landscape.

In the following quote, the informant reveals the 'watch-and-wait' attitude portrayed by the pharmaceutical industry towards investment in the regenerative therapeutics field. Interestingly, the informant describes the 'challenging' business model (involving venture capital) her company has followed to develop their pipeline and compares it to one where a 'big pharma company' is involved.

> That's another one of the problems. I think it is very difficult for the RM companies to identify a model that works well. The model that we followed is a challenging one. That is, develop your first product, get it out into the market and start making revenue while trying to get enough venture capital funding to develop the next products coming through.

> You could say that a better model, in theory it sounds easier, is if you developed a technology that you sold on to bigger companies. There the problem is, I will say in all honesty, we have very few big companies in the UK who are seriously interested in the Regenerative Medicine area. I think the majority are still sitting on their hands and watching. They go to the meetings to find out what goes on, but they are not buying.
> **(LM, PI/Founder of Spin-out, 2007)**

The appeal of having a big pharmaceutical (or biotech/medical device) company involved in a RegenMed company's technology commercialisation pathway is shared by all informants. Technology is licensed or acquired, usually in a one-off deal with the pharma company, and the academic or corporate (research) team can either move on into something different or can continue working with the 'parent' company on the same technology, though this time with newfound resources (financial, regulatory, business, possibly infrastructure – things that are simply non-existent in small start-up firms). In contrast to this 'easier model' as described by LM, venture capital involvement means that the company must go through rounds of raising investment, the difficulty of which has been discussed in the previous section. Later on, LM also made a reference to the Smith & Nephew[113] case, in which the corresponding company attempted to enter the Tissue Engineering market 'a couple of times and failed to break out. They ended up saying it was too expensive and too difficult'. It is difficult to say, though, how much past failures like the Smith & Nephew case have actually influenced the current risk-averse attitude shown until recently by pharma, and how much it is simply the 'uncertain nature' of RM therapeutics that has kept big pharma away.

The next quotation sheds a bit more light on the current 'state of affairs' between pharma and RegenMed companies, albeit from the bioentrepreneur perspective.

> I think it has been particularly difficult for Translation because the people who have the largest amounts of money are not seeing a good business model in some of these cells. For bone marrow cells, for example, where you are injecting the cells back to the same people: it is difficult for a

[113] It must be noted, however, that Smith & Nephew is a medical device company and not a pharmaceutical company.

> drug company to see where they can make the money on that. It is a little bit easier with the stem cells and the patches but there are patent issues in Europe. You are not supposed to patent hESCs, so they can't have that as their business model. So I think they are struggling to find the business model. And for cardiac, in particular, I mean for the bone marrow trials, which are relatively straightforward, it's about £10,000 per patient. Now most of the trials for drugs are looking at thousands of patients, not hundreds of patients. So you need the power of the trials, so it is getting somebody to pay for those big trials.
>
> **(RG, PI, 2009)**

RG is an academic principal investigator (PI) working in the area of cardiac Regenerative Medicine. In her narrative above, she points out the difficulty for investors, including large pharmaceutical companies who have the most to spend, in identifying RM Translation as a profitable business. As with any other area of biotech, in Regenerative Medicine investors need to be able to calculate and manage the risk involved in their investment decisions. In other words, a Regenerative Medicine company's business model must address the issue of risk stacking (i.e. how much risk can the company offset before success becomes completely improbable). Yet at the moment in RM, the high level of uncertainty that characterises the innovation path from biomedical science to its therapeutic applications means that there is no acceptable commercial model on which investors can draw when making their judgements, and 'the technological novelty of the field challenges the skills and inventiveness of the business community as much as those of science' (Salter, 2009a: 405). In short, the fact that tissue engineering and cell therapy development processes are far removed from current R&D expertise and the established business model which pharma has been following so far is, according to RG, the reason behind their hesitance to invest.

Now, in RG's broader field (i.e. cardiac disease), the development of an effective stem cell therapy will offer hope to patients with cardiac disease who have otherwise limited options.[114] Along with the new hope for the 'difficult to treat' cases, the potential of

[114] Current treatment options include heart transplantation, drug therapies, or some type of medical device. In fact, often these three types of therapy are complementary, each addressing a particular feature of heart disease, with the treatment escalating and becoming more invasive as the heart failure worsens. Despite having proved to improve the function of a

stem cell therapy, however, has created a new situation (compared to previous therapeutic development processes). For example, small molecules such as beta blockers or calcium antagonists were developed with funding from the pharmaceutical company that owned the intellectual property in the molecule. As RG points out, autologous bone marrow cells themselves, however, have no value as intellectual property so their commercialisation as such is not possible. Cardiac patches[115] on the other hand, she presumes, might be easier to consider as products, as their design is closer to the concept of constructs/medical devices. Yet again, pharma considers them problematic for investment as the IP patent landscape in Europe is still filled with uncertainty. Therefore, according to RG, pharma (and commercial sources in general) are unlikely to fund expensive clinical trials unless ownership becomes more transparent and secure.[116] Without the 'power of the trials' the chances for product commercialisation significantly decrease.[117]

The following respondent uncovers a similar understanding of the reasons behind pharma's attitude towards (not supporting) Regenerative Medicine Translation. Unlike RG, however, he makes no mention of IP concerns, emphasising instead the 'lack of fit' between RM and the pharma business model.

> I think the problem with most Regenerative Medicines is that...I know that Geron will say in every meeting – "one-offs, patient-specific products are not ever going to fly". That's rubbish. It is just a business model that has not been considered by big pharma because it is so far outside their expertise. And what they are familiar with is pharmaceuticals based on another white pill-type programme. And that's not the way we are going to go with this, we are running out of other white pills basically. I think if big pharma [companies] are going to survive they will have to embrace some of this. There are some good

damaged heart, none of these currently available treatment combinations has demonstrated an ability to regenerate the cardiac muscles within the scarred regions of the infarcted heart.

[115] Engineered 'cell patches' which comprise of cells seeded on a biomaterial that can be used to adhere and replace/regenerate the 'dead' area of the heart. In this approach the possibility is being explored that materials may not simply act as a support for the delivered cell implants, but may also add value by changing for example cell survival, cell integration or by prevention of mechanical or electrical remodelling of the failing heart. Although this techniques shows promise, research is still needed to determine suitable cell source, biomaterials and optimal implantation time post-infraction.

[116] For instance, if the treatment process is combined with a patentable preparation or delivery system.

[117] Clinical trials are generally viewed as a sign that a company has progressed to the next stage and investors usually perceive it as very important validation of a technology and team. Indeed, venture investors often measure a small biotech company's suitability for investment based on the estimated time to the clinic. (Parenteau BioConsultants, No Date).

> models of...for example, things like Regenerative Medicine structures, three-dimensional structures, constructs that can be manufactured which then can be seeded with cell therapies.
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

As LK points out, the preference of the industry for allogeneic (off-the-shelf) products in part explains its 'aversion' towards autologous, patient-specific therapies. For the time being, Regenerative Medicine start-ups and small biotechs looking for funds might be making themselves more 'attractive' to potential investors, he implies, if they choose to focus on the development of universal, allogeneic products. LK clearly suggests that this difference in preference stems from the fact that allogeneic products resemble the development and production of pharmaceuticals. This resemblance, he claims, makes them better candidates to integrate into the pharma industry which has built its technological capabilities and fortunes in a highly specialised and expensive research and development trajectory.

Nevertheless, the situation might be about to change drastically as pharmaceutical innovation in R&D has been experiencing a steep decline in the last decade and the sector is accused of not coming up with the expected innovations. As LK notes, big pharma is running out of small white pills. In fact, fully integrated drug discovery companies are increasingly being confronted by disruptive life-science technologies coming from both public sector research organisations and small-medium biotechnology companies. In other words, as big pharma companies struggle to cope with the innovation deficit, rising R&D costs and cost containment pressures, small RM companies are providing new hope for the healthcare industry's pipelines. As LK implies, the pressure from the various technological and commercial challenges, as well as the social pressure for the Translation of science into the most effective and beneficial clinical products, will make pharmaceutical companies reconsider the 'white pill' approach. The respondent is using the pill metaphor to give emphasis, in a way, to the difference in the two therapeutic approaches. One approach involves a white pill, universal and mass produced; the other a cell solution (or construct), customised and individually prepared.

The image/metaphor of the pill is a very common metaphor that is used in reference to the pharmaceutical industry and the nature of its R&D.[118] In fact, medical and healthcare discourse is full of metaphors that help to articulate the unique features of diseases, medical interventions, relationships, treatments, and so on. For example, 'magic bullets' for antibiotics, the 'Holy Grail' for various treatments. A metaphor specific to the RM field has been proposed by Burns (2009): the stem cell 'superhero'. Burns uses the concept/metaphor of 'superheroes' to capture what is unique about stem cell therapies because he claims old metaphors such as magic bullets, holy grails and miracle cures do not capture 'the new conceptual paradigm that supports the notion of stem cell cure' (Burns, 2009: 428).

The conceptual distinction between a 'Holy Grail' pharmaceutical treatment and the 'heroic' stem cell cure features widely in the social sciences. Pharma's favourite 'treatment' rationale is serviced by its familiar small-molecule 'blockbuster' therapies that have so far dominated the healthcare industry. The vast majority of these products are currently being developed in-house and are small-molecule, prolonged treatments in complex, but high value, therapeutic areas such as oncology, cardiovascular, and those concerned with the central nervous system and depression. In contrast, the objective of novel therapeutics such as (stem) cell therapies is to provide a 'one-off treatment' that will ideally lead to cure. According to social scientist James Mittra (Innogen ESRC Centre, Edinburgh) (2005), who has been studying the pharma and biotech industry extensively, although traditional big pharma companies do currently appear to prefer treatment to cure (that is pills to cell therapies), in the long term, change will be inevitable. In Mittra's words: 'to develop a cure for diabetes, heart disease or cancer would represent a fundamental change to its [pharma's] traditional business model and could potentially render existing high-value therapies redundant. To invest money and resources into a paradigm of prevention and cure big pharma companies would have to perceive either realistic commercial benefits, or potentially significant losses accruing from a failure to adapt and change' (Mittra, 2005: 33). This view seems to agree with LK's prediction that 'if they [big pharma companies] are going to survive, they will have to embrace some of this [cell therapeutics]'.

[118] For example, the image of the 'pill' is recalled in the title of a book by Merrill Goozner: The $800 Million Pill: The Truth behind the Cost of New Drugs. In his book, Goozner explores the process of drug development using case studies that recount the discovery, development and eventual commercialisation of a number of significant drugs; $800 million is the average cost of each new discovery.

In his commentary, LK also mentions the 'opinion' of Geron, an internationally famous, California-based, biotech company[119] which, in his view, exemplifies the way most large biotech and pharma firms 'think'. Geron's lead product candidate is GRNOPC1. The immune-privileged characteristics of the hESC-derived cells used in it, provide the rationale for GRNOPC1 to be developed as an off-the-shelf, allogeneic cell therapy, which according to LK is closer to the drug development process and thus likely to attract the interest of large pharmaceutical firms. In May 2009, two months after President Obama lifted the restriction banning federal funding of research using embryonic stem cells, Geron did indeed 'attract attention'. But it was not the attention of a pharma company and not for the development of therapeutics. Instead, Geron teamed up with GE Healthcare, a 17 billion dollar unit of General Electric Company headquartered in the UK. The aim of the partnership is to use an existing batch of Geron's stem cells to develop sample human cells that drug companies could use to test the toxicity of new drugs early in the development process, before they are ready for animal testing or human clinical trials.[120]

In general, the commercial use of human embryonic stem cells as tools for drug discovery and development is considered more imminent than the 'traditional' cell replacement model. According to this translational model (and its corresponding business model), physiologically relevant human cells (derived from human embryonic stem cells) are used as the basis for creating novel and improved *in vitro* disease models. The hope is that using these models in drug R&D will lead to better precision and more cost-effective assays, ultimately leading to lower attrition rates and safer new drugs, as well as reducing the need for *in vivo* experimentation (Sartipy et al., 2007).

In their examination of this new paradigm of Regenerative Medicine which they call the 'disease in a dish' approach to stem cell Translation – sociologists Steven Wainwright, Mike Michael and Clare Williams (2008) confirm that, indeed, potential transplant therapies are not a priority for pharma for two reasons. One of the reasons

[119] Geron Corporation is investigating whether human embryonic stem cells can be used safely to repair nerve tissue in patients with spinal cord injuries. Its lead product GRNOPC1 has surmounted numerous hurdles before finally receiving the 'go ahead' from the FDA as the world's first hESCs clinical trial. On 30 July 2010, Geron announced that the US Food and Drug Administration (FDA) has notified the company that the clinical hold placed on Geron's Investigational New Drug (IND) application has been lifted and the company's Phase I clinical trial of GRNOPC1 in patients with acute spinal cord injury may proceed.
(http://www.geron.com/media/pressview.aspx?id=1229)(Accessed August 2010).

[120] 'GE teams up with Geron for Stem Cell Research' by Scott Malone. Reuters News (www.reuters.com)

echoes RG's account: cell therapies are out of pharma's 'comfort zone' which comprises expertise in translating small molecules to the clinic. The other, is that pharma is reluctant to be associated with the 'controversial hESCs, since it might negatively affect their share price. In addition, Wainwright et al. (2008) argue that experts (scientists and clinicians) in the stem cell field use persuasive promises in order to advance their interests in the new 'disease in a dish' approach to stem cell Translation, hence promoting it over the traditional and 'failed' 'cell transplant' approach.

The recent interest displayed by big pharma has been noted by many experts, not least by venture capitalists, who have been assigned to keep a watchful eye over the future of the sector in order to spot potential threats and opportunities. Gregory Bonfiglio, Managing Director of Proteus Venture Capital, believes that the 'change of mind' displayed by pharmaceutical giants like Pfizer, is saying a lot about the future of the industry and the role that big pharma is planning to play:

> Pfizer is a watershed event for the industry because it's a very clear stake in the ground by big pharma that "We believe in this technology, we can build a franchise around it". And consider what Pfizer is. Within the next year they are going to lose 2 billion dollars of revenue. We are talking about laying off massive numbers of people, 25-30,000 people, shutting down major parts of their operation. Where are they focussing their energy? Regenerative Medicines. To people watching the field that says a lot about where they think this field is going. And it's not just Pfizer. GSK just put 25 million dollars into the Harvard Stem Cell Institute. Novartis has got a programme...I think this technology is the future and they [pharma firms] are now beginning to recognise it.
>
> **(Greg Bonfiglio, LRMN Meeting, 2009)**

As mentioned at the beginning of this section, in the past big pharma has shied away from investing in stem cell technologies, but according to respondents' accounts and other experts, Pfizer's move confirms that attitudes are gradually starting to change. Several pharmaceutical companies have started to take notice of research advances in

the Regenerative Medicine field and their proximity to reaching the market. In 2008, UK-based GlaxoSmithKline signed a $25 million five-year deal with Harvard Stem Cell Institute with the initial aim of harnessing stem cell technology for drug screening (Alamo-Bethencourt, 2008). The venture funds of Switzerland-based Novartis and Roche helped bankroll Cellerix, a Madrid-based company testing stem cells from fat to treat rare skin conditions. Roche has also began a collaboration with a Wisconsin stem cell company, Cellular Dynamics International, to use cardiac cells (derived from embryonic stem cells) to test drug candidates for toxicity. GE Healthcare has also recently entered into a global exclusive licence and alliance agreement with Geron Corporation and Cytori Therapeutics (Baker, 2010; Ledford, 2008; Winter, 2009).[121]

Alain Vertes, Global Alliance Director of Roche, believes that this emerging trend of pharma companies to partner with RM firms is due to the fact that the field of regenerative cell-based therapies is now reaching 'critical maturity'.[122] By this, he means that the mechanistic fundamentals of these new therapies – safety and efficacy – are now sufficiently well understood to allow the design of appropriate research and development strategies. This is also supported by the numerous[123] clinical trials that have been launched by the biotechnology industry in order to test the regenerative/curative potential of autologous or allogeneic cell preparations in a variety of diseases (Carpenter et al., 2009; Giordano et al., 2007). According to Vertes, this observation of 'critical maturity' in the field of RM, constitutes a 'tipping point', since the potential for radical innovation that live stem cell therapeutics represent could now be efficiently integrated within large pharmaceutical companies. In the author's own words: 'early adoption of live stem cell therapeutics by large pharmaceutical companies will enable them to apply their core strengths and success factors to the development of these novel therapeutics, thus providing not only competitive edge to the early entrants as they build internal resources, expertise and field awareness, but providing also an important thrust forward to the entire arena as these companies leverage their

[121] Most of these collaborations between big pharma and RM biotech, however, stop short, for the moment, of using cells directly for therapy and instead concentrate on developing drug screening and other research tools. The exceptions are Johnson & Johnson who has invested in Novocell's therapeutic project, and Osiris Therapeutics which dominates the adult stem cell space and has been paid $130 million upfront (with another $1.2 billion to be paid in potential milestones) by the biotech Genzyme, for the development of two late-stage adult stem cell treatments (Prochymal and Chondrogen).

[122] Vertes (2010) uses the annual number of scientific publications in a given technology – (SC: all stem cells; mAb (monoclonal antibodies); MSCs (Mesenchymal Stem Cells), etc. – and its growth rate, as indicators of the scientific maturity of a given field. After a field has reached maturity, Vertes suggests that incremental innovation rather than disruptive innovation is likely to occur (Vertes, 2010).

[123] There are over 800 clinical trials ongoing under a broad-based definition of CBTs (Cell-Based Therapeutics) (McAllister et al., 2008).

scale, global presence, long-term vision, and deep clinical development expertise' (Vertes, 2010: 156).

The result is perceived by some industry commentators as a 'win-win' situation. Regen companies often struggle with product development and commercialisation, given the lack of money (especially after the recent fall-out in the economy) and their relative inexperience with clinical development, regulatory affairs and commercialisation. Large pharma, on the other hand, is in need of a new platform that can bring innovative products down the pipelines and drive revenue growth (given the number of products going off-patents in the next few years)(Smith, 2009).

Summary

Until recently, bioentrepreneurs have perceived big pharma as an unlikely sponsor. Those interviewees working with embryonic stem cells have mentioned intellectual property issues as a 'thorn' in investing strategies. Bioentrepreneurs working on autologous cell therapies based on the service model (instead of allogeneic products) believe the logistics, costs and financial returns of such a therapeutic approach are unlikely to be attractive to the pharma industry. Finally, all interviewees admitted that they are witnessing some very important developments, although not in therapeutics. Large pharmaceutical companies are showing interest in the 'safe' translational model based on using stem cells as tools in the drug discovery process. The move of the pharma industry to embrace Regenerative Medicine technologies, even if it is through the 'disease in a dish' approach, is considered by bioentrepreneurs and other experts in the field as unavoidable, given the low productivity of pharma's R&D and the promising results of RM research.

In the next section, I present empirical data on the various ways UK bioentrepreneurs are dealing with the lack of funding identified in the three previous sections of this chapter and their struggle to identify or create a 'viable' business model – the 'ticket' for securing financial support and forwarding their products to market.

In Search of a 'Viable' Business Model

Everyone involved with the Regenerative Medicine sector, including all my informants, is well aware of the high-profile failures of the 'first wave' of Tissue Engineering companies and of the difficulties the industry[124] has been facing in obtaining reasonable returns on investments. Regenerative Medicine therapeutics, including tissue-engineered products and cell therapies, are based on intrinsically complex (scientifically and technically) processes and it is difficult to define exactly what is the product that is being sold. In fact, in order to show how markedly different RM products are from pharmaceutical and biotechnological products, and the importance of bioprocessing for the final 'result' a key phrase is often used: 'the product is the process'.[125]

Professor David Williams, Director of the UK Centre for Tissue Engineering at the University of Liverpool, has commented on the difficulty of defining, costing and subsequently commercialising the resulting products. His concerns and comments are referring to tissue-engineered products, but they are equally true for most (if not all) Regenerative Medicine therapeutics. He states:

> If tissue engineering is all about persuading the body to heal itself, where is the product? How is this process regulated and how do we charge for this persuasion process in the commercial world? [...] Is the scaffold the product, or the growth factor? The bioreactor, or the construct? None of these makes commercial sense. A few grams of a scaffold made of a commodity polymer or ceramic can hardly be sold for thousands of euros, and can you really ask a patient to buy back a piece of their own tissue in the form of a construct? (Williams, 2005: 8 and 9)

According to David Williams (2005) it is essential to find business models for the field in order to speed its realisation as a commercially viable sector. In this section, I present the views and perceptions of interviewees as they navigate the 'daunting

[124] The previously Tissue Engineering (TE) industry is now part of the broader Regenerative Medicine industry called RegenMed.

[125] The implications of the 'product is the process' conceptualisation for the regulation of cell-based products and therapies are discussed in detail in Chapter 5.

waters' of business models. Their experiences seem to be highly dependent on the type of therapy they are developing and the type of company they are involved with.

It is interesting to mention here that two of the participants were not comfortable talking about business models as they perceived the information to be of a confidential nature. Despite reassuring them about confidentiality and complete anonymity, they still chose not to discuss the theme in the detail I would have liked, so I had to limit myself to relevant information that they 'let slip' while talking about other closely related issues.

Interviewee XB talks about the business model followed by his company:

> We develop platform technologies at this point. We have two different platform technologies, both focus on stem cells. For the longer-term business model, on the therapeutic side, the decision was to go for small molecule therapeutics that cause regeneration. And that differentiates us from all the other stem cell companies, except maybe from one or two now entering the same arena. But it is difficult to stay away from the cell therapy, I think, particularly in the UK, because a lot of the incentives that are being offered to companies in the Regenerative Medicine field are specifically for cell therapy...so we may have to revisit that.
> **(XB, PI/CEO/Founder of Start-up, 2009)**

XB, a founder and chief scientific officer (CSO) of a (non-academic) RM start-up, explains that his company has been focussing on platform stem cell technologies and that his team has created a technology that is able to identify small molecules that act on cells to regenerate them. The research, as XB points out, has been carried out in collaboration with a large pharmaceutical company and, as he claims, there are not many companies that operate in the same 'area'. He finally explains that although this is a 'viable' business model at the moment, his company may 'have to revisit' the idea of developing cell therapies, as their development seems to be favoured by UK public funders.

Another interviewee, GL (an academic founder), gives his own explanation for the choice of business model:

> [Company]'s model is still cell therapy rather than using tools for drug discovery. The reason for that is, really, from an investment point of view it [developing therapies] is risky but it has bigger returns in the end.
> **(GL, PI/Clinical involvement/Founder of Spin-out, 2007)**

GL explains that his company has chosen to focus on the therapeutics field, instead of pursuing the 'drug discovery' business model, in which stem cell lines are sold to institutions and private companies for testing the effectiveness and toxicity of drugs. He explains that the reason behind the choice is the potential for bigger returns, although he is aware of the increased risk in terms of attracting (the often risk-averse) investment, and surviving the failures, delays, costs and uncertainties of the field. Asked whether he and his co-founder are planning to 'experiment' with any other business model in the (near or far) future he says:

> We are sort of looking at that. But the problem is that with a small company you can become very diffused if you are looking at tools as well. And you end up not doing any of that properly, so in a way you have to be focussed. I mean, in a way, it'd be nice to support everything by tools but that is also tricky for that reason [becoming diffused]. So we are not very big, we are just trying to get to the next stage.
> **(GL, PI/Clinical involvement/Founder of Spin-out, 2007)**

Although GL admits that their research and, consequently, their business strategy is not 'fixed' and they are 'open' to other commercial Translation models, he stresses the fact that the company is a small academic spin-out. This suggests that although, ideally, it would be useful to concurrently develop and commercialise 'drug discovery' tools along with cell therapeutics, in order to secure profits and help fund their long-term clinical product development, realistically it is difficult (if not impossible) to do so because the company is too small to diversify. He points out that if a small company like theirs 'spreads' its R&D agenda and hence its resources (financial, human, etc.) towards too many goals, it runs the risk of 'not doing any of that properly'. Thus, and

is so often the case, although the financing of a longer-term translational goal by a shorter-term one might be desirable, it is not feasible due to challenges of scale.

A very different perspective is provided by PK who is involved with a medium sized RM start-up. According to PK, his company is prepared to follow a variety of 'complementary' business avenues in order to financially sustain an innovative research and development trajectory and a 'rich' product pipeline. PK comments:

> And there isn't one model, it's a whole mixed bag from one end of the spectrum, making something and selling it yourself, to the other end of the spectrum, doing a bit of research and then selling the data. And there's everything in between, you know, taking it to certain stages. And what we are probably going to follow, and probably everyone else I think, is a mixture [of business models]. You will do some of it [R&D] all [by] yourself – hopefully in some products in some regions – and you will license out some technologies from riskier products in other regions, and everything in between. So the same product could be treated differently in different regions. For example, you could sell it yourself in your home territory [UK] or in Europe say. You could have a distribution agreement in which it's purely distributed in somewhere like America, and you could have a licensing agreement in Asia where your licensing partner's got to get it through their regulatory system.
>
> **(PK, PI/CSO/Founder of Start-up, 2007)**

PK suggests that, eventually, the majority of RM R&D groups and companies will have to follow a 'mixture' of business models in order to survive. This means that although some of the products will follow the traditional route of being developed and sold by the same firm, other products – usually the 'risky' ones – could be licensed out to other companies at various stages of their development. Indeed, 'mixed bag' commercialisation strategies, like the one described by PK, are often employed by biotech companies as a way to gain quick returns on investment from short-term projects. In the case of RM start-up firms, such 'short-term' strategies could involve development of cell lines ('bio-tools') or culture media, and be of assistance in funding longer-term R&D projects such as the development of cell therapeutics. Interestingly,

PK associates a product's 'commercial viability' with regulation, by emphasising that for certain regions (markets) where the regulatory system is 'unknown', it is more advisable to license the product so then it is the licensing partner that has to 'get it through their regulatory system'.

In general, during the majority of the interviews and as business models were discussed by bioentrepreneurs, their comments gave the impression of flexible, 'uncertain structures' that they could easily change given an adequate reason, whether it is access to additional financial resources, a 'valuable' collaboration opportunity, a profitable deal or sometimes as a desperate last move for economic survival.

In the following quote, LK describes the type of business model he thinks will dominate the RM field in the future:

> My vision is that we will have a small number of service companies that will be able to get cells from individual patients on behalf of healthcare providers, either manipulating the cells, or put them on the scaffolds they buy from somewhere else, or into devices they buy from industry, to make these products available to patients. But I think we are going to be faced a lot with patient-specific products. And I don't think we should shy away from that, if there is a model for delivering those [patient-specific products]. And I am working with a number of US companies on patient-specific products, so I don't think there is a major problem there. Our [Product] has been hugely popular. The American company [Name of Company] bought the patent for that. And [Company] have raised an enormous amount of money on the back of our Phase I/Phase II trial. The investors have not been big pharma, but once you start seeing the sort of results we are seeing, I think they will be looking at ways of picking that up. In the same way that Pfizer RM has been set up, as part of Pfizer.
>
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

LK believes that the future of commercial Regenerative Medicine will not be based on selling a product but will have to be based on the provision of a complete service, with

the focus on autologous, patient-specific treatments. These treatments might be cell therapies, tissue-engineered applications or combinations of cells and medical device, but they will all be process driven and will be provided by established service centres/companies. LK also gives the example of one product that has been developed by his research team, through a company he co-founded, and has been licensed to a clinical-stage biopharmaceutical company which 'shepherds promising therapies through the drug development process'. The product/therapy is based on a three-step process during which cells are harvested from a patient, processed accordingly, and then reintroduced back into the patient. LK also expresses his certainty that once the clinical outcomes prove good enough and satisfactory returns on investment realised, then big pharmaceutical firms will start showing more interest. His mentions the case of pharmaceutical giant Pfizer which decided to expand its interest in stem cell business and, in the beginning of 2009, launched a new dedicated R&D unit – Pfizer Regenerative Medicine.[126]

The concept for the provision of a full service has been quite popular in the RM field especially in Europe (Bock et al., 2003). Other authors have also proposed models where the service involves the whole process from cell sourcing to the final treatment of the patient, with David Williams, Director of the UK Centre for Tissue Engineering at the University of Liverpool, suggesting that 'it should be possible for one service facility to cover a wide range of conditions, meeting the requirements for economy-of-scale' (Williams, 2005: 9). Greg Bonfiglio, Managing Partner of Proteus Venture Partners, who is considered a leading authority in RM commercial Translation, is also confident about managing to 'build' a successful business model around the provision of autologous cell therapy services, as opposed to the dominant view of selling an allogeneic product.

> There's been a lot of debate as the industry is maturing and we are now thinking more seriously about commercialisation issues; there's been a lot of debate whether you can build a business around autologous cells. I

[126] Pfizer's Regenerative Medicine Programme has been set up to look for small molecules that are able to alter cell fate and differentiation during neurogenesis in the brain. The New York-based company planned to spend more than $100 million on the new initiative, which aimed to employ 70 researchers based at two facilities, in Cambridge, Massachusetts, and Cambridge, UK. The UK group focuses on neural and sensory disorders, whereas the US team concentrates on endocrine and cardiac research. In-house researchers work with both embryonic and adult stem cells. It is useful to note though that, so far, Pfizer RM unit is focused exclusively on using stem cells to develop new medicines and not therapeutics.

> believe that you can. Fundamentally the challenge around autologous cells is that it is a service product, a service business, it doesn't scale, cost of goods is very high, and your manufacturing lot is one. Because you are building cells for the individual. You are not building cells in a bottle which you can sell to millions of people. You take cells from one individual and put them back into that individual. Can you build a business model around that? A lot of people have said "No, you can't". I don't believe that. I think you can.
>
> **(Greg Bonfiglio, Proteus Venture Capital, LRMN, 2009)**

It is interesting to record a different view as expressed in a presentation at the London Regenerative Medicine Network meeting, by Geoff MacKay, President and CEO at Organogenesis Inc. since 2003. Organogenesis Inc. (Canton, Massachusetts) is a Regenerative Medicine company that focuses on developing cell therapies that induce soft tissue regeneration for multiple applications. The company's flagship product is Apligraf, a human skin equivalent containing living allogeneic cells. Unlike technologies where autologous cells are cultured to provide an epidermal layer, Apligraf is available without the delay involved in culturing autologous cells and avoids the need for skin grafting and consequent creation of donor/patient wound sites. Asked by a member of the audience whether the company is thinking of entering the autologous cell therapies field, Geoff MacKay replied:

> We've debated this. I think regardless of which way the field goes a company, in my opinion, has to commit, and you kind of have to commit early. Because the 'animal' that we've built is an allogeneic company. And so where immunology precludes us from going, we don't go. So there are a number of applications where having an allogeneic delivery might not be appropriate but in the field of wound healing, I think that is perfectly appropriate. Our thinking is, you know some of the comments about tumourogenicity, we sort of view the optimal target product profile in this field as – if you can deliver allogeneic cells to kick-start a wound and then eventually leave, then you have no oncogenicity issues to even talk about [...] What we want it [Apligraf] to do is: we want to put it there, do its job, stimulate, transfer a chronic wound into an acute [wound], and

> then go away. And as long as it does that, we are happy. So if there are autologous strategies that can increase the efficacious or the safety profile, then we'd be in a conundrum. Because we sort of build this whole manufacturing suite to be allogeneic. And its our belief that in this particular area an autologous strategy wouldn't work.
> **(Geoff McKay, Organogenesis, LRMN, 2009)**

MacKay's account is a testament to the close relationship between the RM product under development, the 'building' (infrastructure) of the company and, most importantly, the potential (of the product) for integration within the healthcare system. As MacKay explains, Organogenesis is a company 'built for a purpose': to produce products that induce soft tissue regeneration. Normally, allogeneic donor-derived cell therapies require immunologic compatibility between donor and recipient (patient), condemning them to have limited commercial potential. Apligraf, however, belongs to a number of products whose development is based on cell types that do not appear to give rise to an immune response. As MacKay points out, this is the main reason the company is focussing on Apligraf and 'steers away' from 'immunologically' problematic areas. Allogeneic products have also very different manufacturing requirements to autologous therapies. In fact, allogeneic (universal) products are usually amenable to bulk manufacturing and can take advantage of technology used to produce biotechnology products. It thus makes sense that the company infrastructure depends on the product and the processing that it requires.

Another important point in MacKay's description is the relationship revealed between the therapeutic area, type of product, and potential for integration into the healthcare system.

> If you are going to cure diabetes we'll build hospitals for you. But if you are going to close a chronic wound, the healthcare system isn't going to change around you. You have to change around the healthcare system and that gets you back to allogeneic cells.
> **(Geoff McKay, Organogenesis, LRMN, 2009)**

In general there is a reluctance to pay for expensive treatments when much less expensive treatments exist, even if they provide inferior benefits (Williams, 2005). Therefore, the commercial success (or not) of a product, in this case Apligraf, depends on the costs of development and production and on the willingness of the healthcare system to pay for these services. As implied by MacKay, the fact that Apligraf is one of many options for patients in the wound management field is in a way imposing the only profitable model to follow and that is the allogeneic business model. In the last quote below, MacKay highlights the importance of keeping the R&D of the company focussed in the emerging and volatile field of RM:

> Although we do have some process patents on how to amplify and manage the cells in the cell banks, really, the majority of the IP [intellectual property] is on the 3D construct. [...] We call it a technology platform simply because, as you can imagine, it can be customised to a number of different applications, and like a lot of RM companies we can err on the side of being greedy. We can try to look at what to do and, on a white board, you can probably think of thirty applications [of the product] [...] but then we don't think that we will be able to execute them all properly [...] what we try to do is to focus, and we put a few filters on our business. The first filter is soft tissue. So, using these allogeneic cells, the primary focus of the company is wound healing with our flagship [product] being Apligraf.
>
> **(Geoff McKay, Organogenesis, at LRMN Meeting, 2009)**

Again, it is interesting that despite leading a large and established international company, MacKay's account echoes that of GL, who is talking on behalf of a small academic spin-out. Both MacKay and GL perceive the concurrent development of multiple applications as 'risky' in terms of 'stretching' resources and not being able to execute each and every application 'properly'.

Summary

There is an understanding in the RM bioentrepreneur community that there must a clear commercialisation route and a robust business model behind any cell therapy

approach in order for Translation to succeed and returns on investment to be realised. According to many authors (including the statements of interviewees in the previous sections on pharma involvement) the industry is still struggling with the identification of a business model that makes economic sense, and the debate is still raging whether a personalised, serviced-based (autologous) or an 'off-the-shelf' (allogeneic) type of therapy will dominate the RM market. In this section, I highlighted challenges related to choice of cell therapy approach and related business model(s). My aim was to show how bioentrepreneurs perceive business models in RM, what are the most important factors for them to consider, and on what basis they make their strategic decisions concerning which research agenda and business models to follow. Indeed, several of the informants reveal a preference for the cell therapy development. Among the reasons that they give is the potential for larger financial returns and the apparent preference of public funders for cell therapeutics (as opposed to stem cell-based tools for drug discovery research).

There is also no consensus within the community of informants over the need to focus a company's R&D. A number of interviewees and other experts (such as Organogenesis' Geoff MacKay) underscore the importance of concentrating financial and human resources on a single product. Others are advocating a 'mixture' of business models in order to increase returns and hence the chances of the company's survival. Although it is difficult to say which strategy is best overall, it is safe to assume that RM bioentrepreneurs are following whichever they think fits best with the type of product under development, the scale of their activities and their financial situation.

Intellectual Property as a Foundation for Business

Many respondents mentioned difficulties associated with IP rights, ownership and the freedom to operate in the intellectual space, and argued that it is not always clear who owns the final product. This uncertainty around intellectual property creates problems for principal investigators at various stages of the Translation process, including when they are 'pitching' candidate pipelines to investors. Below, US-based venture capitalist Greg Bonfiglio explains the importance of protecting IP rights (usually patents) for attracting venture capital (VC) financing.

> At a minimum you need to be able to establish that you have freedom to operate. No venture capitalist is going to invest in a company only to find themselves embroiled in an IP lawsuit. You can worry about building your bigger fence or your walls later, but you have to show freedom to operate otherwise you are not going to get their (i.e. VCs') attention.
> **(Greg Bonfiglio, Founder and Managing Director of Proteus Venture Capital, LRMN, 2008)**

According to Bonfiglio, for a regenerative company (whether academic spin-out or corporate start-up) to draw investment it must have a business plan that both outlines a credible IP strategy capable of protecting the company's products through issued patents[127] and at the same time gives the company freedom to operate with regard to the product development process. Freedom to operate, which Bonfiglio suggests would be the first concern to address, requires a detailed analysis of all of the IP in the field of Regenerative Medicine, and a detailed identification of what would interfere not only with the company's freedom to operate in the present but also its ability to patent products in the future.[128] In the words of another venture capitalist, Lutz Giebel, a venture partner at SV Life Sciences and former founder and CEO of Cythera Inc. (a human embryonic stem cell company): 'for a new stem cell enterprise to get off the ground, a well-thought licensing[129] and cross-licensing strategy is a must' (Giebel, 2005: 799).

Indeed, all the spin-out companies that the interviewees have founded are based on some form of intellectual property, either in the form of a filed or granted patent or know-how. For the majority of these companies the tangible product has yet to appear

[127] 'A patent is a form of intellectual property right (IPR) which confers on the holder the right to exclude others from making, using, or commercialising a patented invention without prior permission from the inventor/patentee. The most important part of the patent is a list of claims, which are carefully written descriptions of the invention that also define the limits of the application. There are two types of claims: product (or 'composition of matter') claims and process claims. Of the two, the former are generally more powerful because they cover the matter itself regardless of how it is made, obtained or used'. Definition sourced from (Loring & Campbell, 2006).

[128] Patent laws can help promote the progress of science and technology, by protecting the financial interests of inventors or companies and thus allowing them to make their knowledge available to the public. In addition to this openness which can facilitate collaboration and trust among scientists, there are also some economic benefits as patents offer incentives to researchers and sponsors (especially commercial sponsors) to conduct and finance research, by allowing them to profit from it. In fact, patents granted by national and/or international patent agencies such as the United States Patent and Trademark Office (PTO) and the European Patent Office (EPO) respectively, 'protect' an invention for a specified period (usually 20 years), keeping potential competitors out of a niche market while the inventor(s) reap the rewards of the innovation. In other words, IP supports future revenue streams and erects barriers to competition.

[129] The conventional route to market for university intellectual property (IP) has been through licensing the rights to use technological discoveries controlled by university-owned patents.

and the economic value is embedded in the potential application of knowledge.[130] Thus evaluating these intangible assets (patents) can be an important incentive for positive early-stage investment decisions. As Brian Salter (2007) from King's College clarifies in his study of the relationship between patenting human stem cell science and cultural politics in Europe, 'the economic significance of patents is further enhanced by the need for new forms of knowledge to compete for attention in an increasingly global venture capital market with its own clear demands: investors, often institutional investors, make their decision in the light of the patents held by companies. For capitalisation of new knowledge to occur, then, investors need to be reassured that the value of the knowledge, as opposed to the value of the eventual product, is in the hands of the company concerned. Investors are likely to be particularly sensitive to the patenting issue in high risk areas such as early-stage development of health biotechnologies where the science is very new and the potential therapies very distant' (Salter, 2007: 302). In other words, a stem cell company's quality of protected IP is intimately tied up with the company's perceived value to investors, partners, and/or acquirers (Barrett & Crawford, 2002).

There are other authors, however, who argue that the biotechnology innovation system, based on VC-led exploitation of intellectual property, does not seem to be functioning in the case of US hESC research (nor in European hESC research for that matter). According to Olivia Harvey (2009) from the University of South Wales (Sydney), the uncertainty surrounding stem cell patenting in US, European, and Asian markets is the reason why the traditional approach of raising finance based on securing intellectual property and selling it on for maximum profits appears to be problematic for the stem cell field.

Venture capitalists are trained to 'watch' the field (in this case Regenerative Medicine academic research), recognise opportunities and pursue investments. In contrast, bioentrepreneurs usually come from a life sciences background and are heavily immersed in basic and often clinical research. Surprisingly, however, they did not fall short on IP knowledge and 'how to go about' IP rights. GL's comment below is short and straight to the point:

[130] Some of the companies, however, do have products on the market.

> I think you need to patent to protect and also to provide room to work in a certain area.
>
> **(GL, PI/Clinical involvement/Co-founder of Spin-out, 2007)**

In addition to the concerns raised over freedom (or lack of freedom) to operate in the field and the consequences for the progress of basic research, interviewees expressed concerns over the potential exploitation of generated IP and the ownership of future products. The quote below belongs to a principal investigator who is also co-founder of a Regenerative Medicine academic spin-out.

> If we are talking about developing a product, then in business circles you need to establish who owns the product. And it is not enough to just say that X and Y funded the product and kind of leave it hanging as to who owns it.
>
> **(NC, PI/CSO/Co-founder of Spin-out, 2007)**

One of the company's chief aims is to commercialise initially research-grade, and subsequently clinical-grade human embryonic stem (hES) cell lines. Research-grade lines can be used in basic Regenerative Medicine research while clinical-grade lines can be used for the development of clinical applications in humans or drug discovery tools. NC underscores the necessity of establishing ownership during the development of any such product. His comments echo Bonfiglio's advice on the importance of securing freedom to operate by 'building fences' to protect, and thus exploit, the company's innovations. In other words, intellectual property ownership is very important to successful innovation models ('Pharma', 'Biotech' and 'RegenMed') and is a driving force behind private investment. Investors are looking to capture some or all of the economic value associated with an innovation, and intellectual property rights – mainly patents – are an important method.

For example, QN reflects on the importance of IP and technology transfer for the university, and praises the strategy that has been put in place in order to achieve the best possible results.

> One of the things we do really well here is IP, SMEs, spin-out activity, licensing, patenting. The University is really good at that. Behind Stanford and Cambridge we are the third best at capital actual realisation of SMEs [small and medium enterprises]. We have a strategy and panels in place to help drive that programme. And it [IP] is something that is discussed very early on. It's expensive so you can't afford to just let it drift.
>
> **(QN, PI/Founder of Spin-out, 2009)**

QN's increased 'IP awareness' stems from the fact that apart from his role as principal investigator and co-founder of a spin-out, he is also a leading member of the university's technology transfer board/committee, which is responsible for the commercialisation of life science innovations as well as technologies from other academic departments including engineering and physics.

Another founder of a spin-out talks about the approach she follows with the IP of her team's work:

> I think it [patenting] is a very, very valuable thing to do. As an academic researcher I would always think about patenting my research. Even when I did not have a company involvement, I would always think when we were close to something interesting: "Is that something we should patent?". And many times we decide not to go there because we wouldn't think it would be too interesting. If we thought it was interesting, we would then go into the University [Technology Transfer Office (TTO)] and get them to look at it [the candidate IP].
>
> **(LM, PI/Founder of Spin-out, 2007)**

For LM, IP awareness seems to have started long before the establishment of her company. She explains how she deals with 'interesting' and 'patentable' findings and how she might rely on further expert advice form the university's technology transfer office before taking the final decision whether to pursue a patent or not.

Below, are the comments on IP from the only person (out of the 14 interviewed) who is not involved with a company, although she did think about the possibility of creating a company after 'intense pressure from the University'. RG describes the way she views intellectual property in relation to her work and how that relates to the work of others.

> But I would most likely hand it on...I would hand on the intellectual property that I have generated. Most likely I would not make any money out of it myself, and it would be simply that the work that I have done feeds into the choice of cell, growth medium, scaffold and how they are combined. So mine would be part of a much larger intellectual effort to understand what's the best way to deliver that [product] to the heart [...] I wanted to get patents on things but the TTO didn't agree with me. So I didn't get anything from that. And [there are] other things I know I am never going to get any money from and I want to just do, in terms of patents they [University and TTO] are very fussy about the IP then.
>
> **(RG, PI, 2009)**

RG is an academic principal investigator working on an off-the-shelf product for cardiac regeneration and she is also very involved in clinical work. Earlier in the interview, she talked about her aversion to spin-out companies because of colleagues' accounts of the difficulties associated with being involved in the commercialisation of their inventions. On one hand, she seems quite firm in her choice to 'hand on' the intellectual property her team generates, that is to license it to someone (to use it and/or develop it further), and on the other hand, she seems uncertain about making a personal profit. She implies that if there is any money to be made it will, in all probability, go to the university. However, she is aware that her work, possibly in the form of a publication, will 'feed into' the work of other laboratory and clinical teams.

RG's knowledge of IP seems somewhat hazy and uncertain compared to the definite answers the rest of the interviewees gave. It would be safe, I think, to assume that the 'negative' experiences of other PIs-turned-bioentrepreneurs have influenced her attitude on 'spinning-out', and perhaps in turn, deprived her of the further IP

knowledge she would have acquired had she gone ahead and founded a spin-out. RG is also one of two interviewees to perceive IP as potentially crippling her R&D. In the quote below, she reflects on how 'external' IPRs might potentially delay or completely block the progress of her research.

> I think it [IP] inhibits it [research] actually. The patent that's the most nuisance to us is the Geron patent on cardiac myocytes. Although we do have a non-profit-making collaborative agreement with them, so we are fine with that, but we see that their patent – if they chose to apply it – could inhibit the field greatly.
> **(RG, PI, 2009)**

As a research scientist working in the field of cardiac regeneration, RG describes the 'Geron patent' on cardiac myocytes as causing the 'most nuisance'. Her account is consistent with the feeling of threat described by many researchers who are working on certain types of hESCs. This threat, although 'potential' (as it has not been realised yet at least to its 'full extent') seems to be big enough to make these investigators feel that IP might actually 'inhibit innovation' in their field. Even though at the time of the interview RG admits to having a non-profit agreement in place that appears to allow the smooth operation of laboratory and product development research, it is clear that she still worries about any future changes in the IP landscape that would endanger the continuity of her team's work. Her concerns are not unreasonable, as in the US licensing is not compulsory, which means that patent holders have the choice of licensing on their own terms or even not to license at all.

Access to hESCs is presently mediated by a political, legal and economic infrastructure assembled on the foundation of thee seminal US patents[131] (Rabin, 2005). The patents, also known as the WARF patents, have been assigned by their inventor, James Thomson, to the Wisconsin Alumni Research Foundation (WARF) (Madison, US) and are unique in the sense that the patents have claims on the hESCs themselves and not just on the method of deriving them. According to Jeanne Loring (founding Director, Center for Regenerative Medicine, Scripps Research Institute, LaJolla, CA) and

[131] Between 1998 and 2006, the University of Wisconsin-Madison was awarded three US patents: US Patent Nos. 5,843,780; 6,200,806; and 7,029,913. Before amendment and re-examination, these patents together covered the entirety of all stem cells, no matter how the cells were derived.

Campbell (based at McDermott, Will & Emery, LLP, Washington, DC), by patenting ES cells, 'WARF has the right to exclude everyone else in the United States from making, using, selling, offering for sale, or importing any ES cells covered by the claims until 2015. The right of exclusivity is rooted in the US Constitution and was intended to benefit society by encouraging innovation while discouraging secrecy on the part of the inventors' (Loring & Campbell, 2006: 1716).

RG's view is shared by many in the field as the WARF patents and their exclusive licensing have been the subject of much controversy[132] in the literature (Rabin, 2005; Regalado & Hamilton, 2006; Taymor et al., 2006).[133] The main criticism is that, although embryonic stem cells are precisely the type of broadly applicable enabling technology that, as general matter, should be licensed non-exclusively in the interest of promoting future research and product development, the Wisconsin Alumni Research Foundation (WARF) chose to license exclusively some of the most critical commercial rights under the patent (Rai & Eisenberg, 2003). In short, WARF signed a worldwide commercial license with Geron (who funded James Thomson' original research on embryonic stem cells) giving it exclusive rights to its patented method for isolating primate and human ES cells and for three[134] cell lines developed from them: neural cells, cardiomyocytes and pancreatic islet cells (it also gave Geron non-exclusive rights to develop products and commercialise research products based on other cell types)(Pollack, 2002).

Thus, in order to work with these embryonic stem cell technologies, academic researchers and commercial companies must negotiate with Geron and agree to sharing profits from their applications. Not surprisingly, the WARF–Geron licensing strategy (and as a result the patenting strategy) led to series of re-examinations and litigations (Fitt, 2009) and prompted intense criticism which stands today. For example, Fiona Murray from the Sloan School of Management, who has published widely on science commercialisation, IP, innovation and entrepreneurship (particularly in the areas of genomics and Regenerative Medicine) writes: 'Human embryonic stem cells with their potential both for expanding our understanding of biology and for

[132] Another reason why the WARF patents are controversial has to do with the moral and cultural significance attached to the human embryo. This part of the controversy is beyond the scope of this thesis. For articles addressing the ethics of patenting hES cells see (Chapman, 2009) and (Salter, 2007).

[133] Anonymous. (2007). Burning bridges. Nature Biotechnology, 25(1), 2.

[134] The initial number of cell types under the exclusive license was six, but after intense criticism from the media and pressure from the NIH, WARF sued Geron and managed to reduce the cell types to three.

commercial use, represent a classic example of knowledge that should be accessible to both academia and industry. Although it ought to be possible to create a stem cell market that provides rapid, unconditional access to academic researchers and more circumscribed access to commercial scientists, along with higher prices and profit sharing, the University of Wisconsin has instead imposed terms and conditions on academic researchers that, I believe, represent an encroachment of private sector barriers on the free exchange of ideas' (Murray, 2007: 2342).

The following respondent revealed a more defiant attitude toward this situation, implicitly proposing that the EU establish an alternative to the US patent system:

> In Europe you are not allowed to patent an embryonic stem cell. So we don't care about Geron. But for the US market it is an issue. We've reached our own deals with Kings College London and University of Sheffield to access their cell lines and use them commercially, and while we are doing that in Europe we don't need any further licences.
> **(XB, PI/CEO/Founder of Start-up, 2009)**

XB is aware of the IP issues but because of the already decided market for his company's products, he does not appear to be as concerned as RG. He confirms having secured an agreement with the relevant authorities in the UK in order to work lawfully with the necessary cells/lines. The company's future products, he says, are going to be legal as long as they are marketed in the EU. So far, the US is the only country to have allowed hESCs to be so broadly patented, and as a result patents rights can only be enforced in the US. However, 'hESCs and any derivatives/products made in another country, immediately become subject to the US patent law if they are imported into the United States' (Loring & Campbell, 2006: 1716). Unlike the US Patent and Trademark Office which has granted many patents, including patents on culture methods, differentiated cells derived from hESCs cells, and even hESCs per se, the European Patent Office (EPO) has not granted a single patent that makes direct hESCs claims (Porter et al., 2006).

In short, not all respondents have the same awareness regarding IP rights. There seems to be a connection between IP awareness, the professional roles held by the

respondents, the type of product they are developing and also the university where those respondents are based. People who have founded companies are very aware of the IP 'nuts and bolts', and the majority admitted they were keen to spot any opportunity and look into it, perhaps even seek the advice of the university's technology transfer office (TTO). The bioentrepreneur who was also member of the university's commercialisation committee, displayed, not surprisingly, the highest awareness of all the informants, and was very keen to discuss 'IP opportunities'. Informants were also familiar with the potentially 'threatening' patenting strategies of others that could seriously affect their ability to do research, and the two people with products nearing the market were very familiar with the limitations and 'freedoms' of their potential market's IP landscape.

The cost associated with patenting was also discussed by almost all interviewees. Individual international patents can run into the thousands of pounds and returns will only be realised if the patent is licensed or, in case of a company (spin-out or start-up), if the product is successfully developed and commercialised. One informant, GL, comments:

> The problem with patenting is that it costs a lot of money. So [Company] had to make decisions on which patents it is definitely going to hold on to and which others it might have to drop because of the cost of putting applications through.
> **(GL, PI/Clinical involvement/Co-founder of Spin-out, 2007)**

Below, LM talks about the need of small and cash-starved spin-outs to make important decisions on which patents they are going to pursue and which they will just have to forgo.

> From a company perspective the issues are slightly different. If you were a company with plenty of money to spend you would patent a lot more things than you would as an academic. Because quite quickly it comes down to money, not lack of ideas. But you haven't got the money. You may set up quite a few patents that couple of years down the line when

> they become expensive you may have to let them go down. Scientifically they may be fine, but you just can't keep them going commercially.
> [...]So a university can't afford to follow through on patents. They can generally just get you to the patent filing, but if you haven't been able to find the funding – which usually means a commercial interest – to support the patent a few years down the line, then you have to let it go down. I don't really know on the academic front whether UK universities are less able to support patents than, say, American or other European, but that might be the case. Small spin-outs will lose out on patenting opportunities as they haven't got the cash.
> **(LM, PI/Founder of Spin-out, 2007)**

LM's comments confirm, once again, the significance of IP for attracting funding and how the cost of patenting can burden small firms. As she explains, big companies in the field have better chance of protecting their ideas simply because they can afford to do it. For academic spin-outs or small corporate start-ups on the other hand, it is more difficult. Capital in small firms is scarce and hence the need arises to prioritise between which patents are absolutely crucial and which could be 'left out' from the firm's patent portfolio. The university will usually help with the initial patent filling application but then external financing is essential in order to continue supporting the patents. In short, LM, from her firm-founding experience, captures the difference between big and small firms and suggests that the latter are clearly disadvantaged when it comes to protecting their IP as they 'haven't got the cash'.

A few informants mentioned patent pooling as a 'desirable' way to facilitate access to IP and reduce cost and inefficiencies. NC gives his view below:

> I would be in favour of the concept of patent pooling where the technology is an underpinning technology that would be used by many. There are aspects associated, say, with cell culture generally – to maintain the cells or devices to facilitate their expansion, purification, differentiation – one could rightly put under the banner of being suitable to be collected as a pool so that, you know, private entities can reasonably access that to [be able to] work. And that just benefits

> everyone. By contrast, I think there are other technologies which, the closer they are to actually creating a tangible product that could plug into other technologies, [for which] the proper thing is to provide some type of protection in exchange for the investment that has been made to develop them. Bottom-line, none of this technology gets to the bedside unless there is private investment. So we need to strike a balance [on] how we get there.
>
> **(NC, PI/CSO/Founder of Spin-out, 2007)**

It is often the case that patents in biomedicine, perhaps even more so in Regenerative Medicine, cover complementary technologies. For example: a product, a method of obtaining or manufacturing the product, and a method of using/delivering the product. In such cases where complementary technologies are owned by different patentees, in order to use the technology (and avoid infringement), one is required to obtain licenses from each patent owner (Esmond et al., 2006). This can be confusing, time consuming and expensive.[135] So instead of struggling with the 'foggy' and 'dispersed' IP landscape, complementary technologies can be 'integrated' through the structuring and implementation of patent pools. A patent pool is an arrangement in which one or more patent owners agree to license certain of their patents to one another and/or third parties (Ebersole et al., 2005). NC suggests structuring and implementing patent pools for what he calls 'underpinning technologies' that could be used freely by many, while reserving the 'normal' patenting for cases where there is a tangible product.

Summary

Several respondents mentioned difficulties associated with IPRs, ownership and the freedom to operate. Properly evaluating and protecting the 'intangible' IP assets is, according to the interviewees, of paramount importance for small 'high-tech' and early-stage companies such as the RM spin-outs and small start-ups that dominate the UK RegenMed industry, as they can represent an attractive investment opportunity for external sponsors.

[135] Another relevant concern is that if one of patent holder decides not to license at all (or requires an unreasonably high price), then this will block the progress of research and hinder later discoveries. This is especially true for 'breakthrough' patents with very broad claims that threat to dominate markets.

Another point that has emerged in this section is that IP awareness varies among bioentrepreneurs, and it appears to be associated with a bioentrepreneur's combination of roles as well as the type(s) of products s/he is developing. For example, individuals working on hESCs are wary of any potential future changes in the WARF IP policies and are concerned about the effects these changes could have on the progress of their own research. Furthermore, interviewees whose products are nearing commercialisation are familiar with the 'legal' complications that might arise while promoting their products in different markets (countries).

Finally, the high cost of patent applications has been repeatedly cited as the main reason for bioentrepreneurs not pursuing all the patents that would be 'advisable' to pursue. As many informants explained, applying for patents is perhaps easier in the case of medium sized start-ups who have the financial resources to 'follow patents though', as opposed to 'cash-starved' spin-outs (or small start-ups) that are instead 'forced' to prioritise their IP and only 'protect' what they consider absolutely necessary.

Chapter Conclusion

In this chapter, I have attempted to chart some of the key factors identified by the participants in this study, concerning the funding of UK's Regenerative Medicine Translational Research. This chapter thus outlines the significant obstacles to successful Translation as they are perceived and experienced by a 'critical' and 'central' group of actors, namely RM bioentrepreneurs in the UK.

In the first section of this chapter, I examined how bioentrepreneurs experience the lack of translational funds: to what do they attribute this shortfall for what is widely perceived to be one of the highest priority arenas of biomedical innovation? How in their opinion might the situation be rectified?

The account I have offered has drawn on the testimonies of bioentrepreneurs who have had their applications to fund translational projects repeatedly rejected by research councils and charities, despite these sponsors advocating a commitment to Translational Research in the UK. Judging from the investigators' accounts, the funding pathways are unclear and strewn with obstacles. While funding for hypothesis-

based, basic research seems easier to secure, projects that are pursuing high-risk Translational Research are perceived as difficult to fund. Even in cases of earmarked funds such as the MRC translational awards, the emphasis on the practice of reverse Translation is perceived as favouring, once again, basic research. Recommendations to rectify the situation include combining the two main streams of public funding for basic and applied research (i.e. research council and NHS funds) to promote integration of skills and collaboration between basic scientists and clinicians, thus facilitating Translational Research.

In the second and third sections, I considered the views and experiences of bioentrepreneurs with the only two other alternatives sources of funds (in the absence of public funding), namely venture capital or support from industry (pharma/ biotech investments). As I have shown, venture capital was characterised as a 'later-stage' source with most bioentrepreneurs reluctant to pursue it. There is also evidence that relates this reluctance to past, rushed and disorganised attempts of colleagues to spin-out VC-backed companies that eventually led to failures and have 'troubled' the VC community.

Like venture capital, until recently, big pharma involvement was also perceived as improbable and fraught with difficulties. The main reason behind this perception, according to bioentrepreneurs, is that large established pharma firms have traditionally been operating a business model based on small molecule production, a type of product that differs markedly from the development and production of cell therapeutics. However, a recent increase in interest, evident through the announcement of partnerships, investments and other direct activities in the field of RM, have led bioentrepreneurs to believe that industry funding is becoming an increasing possibility. With the focus of pharma on the development of drug discovery tools instead of cell therapeutics, however, many investigators seem willing to reconsider research agendas and 'reconstruct' business models in order to become more 'attractive' (possibly to the detriment of cell therapy development approaches).

In the fourth section, I explored how bioentrepreneurs understand and conceptualise the much-debated 'viable' RM business model in order to attract the attention of the various funders. As Translation struggles from the lack of public funding, increasingly

conservative venture capitalists and 'cautious', 'risk-averse' industry, bioentrepreneurs try to push forward untested forms of therapy that everyone knows will be expensive to produce and implement. From the data, it is evident that the main 'problem' with identifying a profitable business model is the diversity of products, processes and therapeutic areas that UK bioentrepreneurs work on. This makes the existence of one 'ideal' model improbable. It is notable that in the case of Apligraf as described by MacKay the successful business model operated by Organogenesis is based on the absence of immunogenicity in the case of the specific cells used (which supports the rationale of an off-the-self product) and the cost and effectiveness of other competitive therapies on offer for the same condition.

In the final section I examined intellectual property and the importance bioentrepreneurs attribute to it as a foundation for creating a 'translational' business. Clarity of ownership and freedom to operate are the two most important features of IP identified by bioentrepreneurs. In general IP awareness varies among investigators and is also relevant to their own scientific activities.[136] There is also evidence that bioentrepreneurs perceive the cost of IP as limiting, with two informants proposing patent pooling as a way to reduce costs.

As a whole, these observations contradict Jane Maienschein and colleagues' (2008) portrayal of a bioentrepreneurial drive to Translation that is potentially restricting basic research agendas. To the contrary, as mentioned above, it appears to many UK bioentrepreneurs that basic research is easier to fund than Translation. At the same time, Translation still 'looks like' basic research to big pharma and to many venture capitalists.

As a result, and in a manner that is consistent with the following chapters, the picture that emerges of both small-scale and successful 'breakthrough' bioentrepreneurs in the RM area is that they face a series of funding challenges that require them constantly to balance conflicting agendas. Because of their small scale they must be rigorously focussed on a limited – or even a single – R&D trajectory, and yet they must be flexible enough to change and adapt – often quickly – to new opportunities that arise. At the same time, in order to finance their research and product development, they

[136] Activities might include a variety of professional roles, types of cells/products they work with, markets they are pursuing.

have to simultaneously be monitoring on several different fronts. They must be working both toward their clinical 'catch', and backwards to protect a patent trail behind them. They must be focussed on an immediate, local market, and yet also bear in mind the need potentially to expand that market considerably in the future. Above all, they must be monitoring – in addition to funding opportunities and strategies – the co-dependent changes affecting regulation and cross-disciplinary (local, national and international) collaborations. It is to these two areas that the next chapters now turn.

Chapter 5

The Art of Regulation

Introduction

Regenerative Medicine science and technology is highly varied and complex in terms of the different materials used and their potential therapeutic applications. The variety of emerging technologies being developed, coupled with their 'novel' and 'uncertain' nature and the pressure for Translation, pose a significant challenge for institutions responsible for their regulation and governance, as well as innovators and other key stakeholders. Indeed, quite different approaches have been taken by policy and regulatory authorities in national and international contexts.

So far, the largest part of the (scientific, legal and social science) literature has focussed on what is called 'upstream' regulation – that is regulation of fundamental Regenerative Medicine research. It is important to emphasise here that my focus in this chapter (and thesis in general) is on 'downstream regulation' – that is regulation during product (prototype) development and during the critical step of beginning clinical experimentation (in humans).

As half of the interviews were conducted in late 2007, before the seminal ATMP regulation came into force,[137] and half were conducted between October and December 2009, when the implementation of the ATMP regulation was 'in full swing', I had the chance to see how the experience of the field is changing – from confusion and widespread uncertainty to the flexible and highly variable interpretation of the long-awaited 'new regulation'.

In this chapter, I explore the experience of UK bioentrepreneurs in dealing with 'downstream' regulation of novel Regenerative Medicine therapeutics in the context of uncertainty. The following section briefly describes the product/therapy classificatory categories and the evolving regulatory landscape before and during the period of data

[137] The Advanced Therapy Medicinal Products (ATMP) Regulation came into force in December 2007 and became effective in December 2008.

collection. In other words, it provides the context for understanding the implications of regulation for bioentrepreneurs' attempts at Translation. Section 2 examines how bioentrepreneurs deal with uncertainty over potential regulatory routes and regulatory agency oversight. Section 3 explores the collaboration between regulators and bioentrepreneurs, focussing in particular on the claims of interviewees about helping to shape emerging regulation. In section 4, the bioentrepreneurs' efforts to comply with regulatory guidelines, the 'cost' of compliance, as well as the informants' views on the transition to a whole new 'promising' and 'long-awaited' regulatory infrastructure are discussed and analysed. Finally, section 5, considers the challenges bioentrepreneurs face depending on the nature of their products (i.e. autologous or allogeneic) and the relationship between regulation, product testing and the (unconvincing) 'truth' of the animal models.

Classifying Therapeutics: From the Existing to the Novel

According to the legal framework that exists in most developed countries, the regulatory route that a medical product follows, from the laboratory up until its approval for clinical trials and marketing authorisation, will depend on how the product is classified under the relevant legislation. The traditional categories of therapeutic products include drugs (medicines or medicinal products), medical devices, and, in some jurisdictions, biological products (biologics).

In general, before a new medical product can be released, it has to be approved for market release by the relevant Regulatory Authority. In the US, for example, the Food and Drug Administration (FDA) is the regulatory body responsible for overseeing healthcare products. In the UK, it is the Medicines and Healthcare Products Regulatory Agency (MHRA) – a government body which was set up in 2003 to bring together the functions of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). So not surprisingly, until recently, medical products were regulated either as medicinal products (such as drugs) or medical devices (for example pacemakers).

However, with the emergence of advanced therapy products (that is gene therapy, cell-based and tissue-engineered products), the crucial question was posed (in the EU):[138] should they be required to meet the criteria of the Medicinal Product Directive (MPD) or the less demanding[139] Medical Devices Directive (MDD)? The majority of Regenerative Medicine products, however, fell between these two categories. It soon became obvious that neither of the two product types was a good fit for the 'emerging' technologies and it might be necessary to produce new European legislation to adequately cover them.

Because of their borderline nature, cell and tissue-based products raised a number of concerns for the regulators, most importantly the risk of contamination and disease transmission. The fact that many of these products contain viable cells means that they cannot be sterilised using conventional sterilisation techniques, hence the need arises to 'quality assure' the whole production process from the provenance of the raw materials to the point of product application. In the presence of such risks and concerns and in the absence of appropriate and Europe-wide legislation, several countries started developing their own approaches to regulation. The resulting regulatory divergence and market fragmentation across Member States has not only hampered the development of the TE and subsequently Regenerative Medicine industry (RegenMed), but also made availability of existing products in different European countries very patchy.

In response to the various voices and calls for review of the regulatory system and its harmonisation, in 2002, the European Commission (Directorate General Enterprise) launched a public consultation to assess the need for a legislative framework for human tissue engineering and tissue-engineered products. The consultation brought to light the numerous difficulties in categorising new products and highlighted a broad consensus (in particular amongst industry and governments) in favour of a detailed,

[138] In contrast to the EU, in the US, the FDA had anticipated the need for new regulatory pathways that are able to deal with products that involve living cells and are different from conventional pharmaceuticals and medical devices. Consequently, it set up new 'regulatory routes' for the so called 'biologics' and 'hybrid' (combination) products, including cell-based therapies and tissue-engineered products. In 1997, the FDA released the Proposed Approach to Regulation of Cellular and Tissue-Based Products with the aim of establishing a new, comprehensive regulation. The regulatory structure of the 'Proposed Approach' is tiered and risk-based in that products thought to present greater risk receive more regulatory oversight, require more extensive controls in manufacturing and clinical studies, and more rigorous product characterisation. Products thought to present less risk are stringently regulated, but less so than higher-risk products.

[139] Regulating a product under the medical devices regulations is generally considered less burdensome because, unlike medicines, medical devices are not automatically subject to a clinical trial. This is because it is often impractical and unnecessary to test them in this way and safety and performance can be based on laboratory tests.

harmonised EU regulatory framework that will specifically and comprehensively address both the existing and any future advanced therapy products. In particular, participants stressed the need for the new initiative to include these products which at the time of the consultation period (2002-2004) did not fall clearly or entirely within the scope of existing legislation. These included products derived from genes and cells which have had a poor working definition (mostly classified as pharmaceuticals) and tissue-engineered products (TEPs)[140] that were not explicitly covered by the existing legal framework and fell in a regulatory gap somewhere in between Directive 93/42/EEC on Medical Devices and Directive 2001/83/EC on Medicinal Products. The consultation paper states:

> At present, the lack of a comprehensive, clear and uniform regulatory framework creates legal uncertainties and leads to a fragmentation of the tissue engineering market: similar products are regulated differently in the various Member States, different safety requirements may apply and patients can be denied access to products which are readily available in other countries.
> (European Commission Consultation Paper, 2004: 3)[141]

Responding to industry concerns over lack of harmonisation in the cell-based and tissue-based therapeutics arena, the European Commission[142] began its first step towards addressing the situation by developing a new core regulation – Regulation (EC) No 1394/2007[143] – the Advanced Therapy Medicinal Products regulation (in this thesis referred to as 'ATMP regulation'). According to the regulation, an Advanced Therapy Medicinal Product (ATMP) is defined as 'a gene therapy, somatic cell therapy or tissue engineered product (TEP) (or combinations thereof), that claims to have a

[140] Gene therapy and somatic cell therapy products had previously been included in an amended annex to the main Directive on Medicinal Products (2001/83/EC), but the ATMP regulation (1394/2007) is the first instrument to specifically cover Tissue-Engineered Products (TEPs).
[141] Proposal for a Harmonised Regulatory Framework on Human tissue Engineered Products, European Commission, DG Enterprise Consultation Paper, Brussels, 6 April 2004. Available at:
http://ec.europa.eu/health/files/advtherapies/docs/consultation_paper-2008-07-22_en.pdf
(Accessed in June 2010).
[142] A number of international initiatives such as the International Society for Stem Cell Research (ISSCR) and the International Stem Cell Forum are also working on harmonisation processes. These initiatives mainly work towards the harmonisation of technical standards and safety requirements as a way to help international collaboration despite the 'regulatory patchwork' presented by national research policies. The majority of these harmonisation attempts are focused on developing scientific and ethical standards and practices for the conduct and governance of basic Regenerative Medicine research. The exception is the release in 2008 of the by ISSCR of the Guidelines for the Clinical Translation of Stem Cells.
[143] EC, Regulation (EC) No 1394 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, [2007] O.J. L 324/121.

medicinal function'. By clearly defining these three groups of products and laying down 'specific rules concerning the authorisation, supervision and pharmaco-vigilance of advanced therapy medicinal products', the new regulation aims to provide clarity to stakeholders (oversight agencies, regulators, academics and companies that work in the area) on issues related to approvals, labelling, monitoring, and risk management; ensure a high level of health protection; provide legal certainty, harmonise market access and improve availability for European patients, as well as foster competitiveness with pharmaceutical and biotechnology industry outside the EU. In short, the regulation which entered into force in December 2007 and became effective in December 2008, requires anybody wishing to market an ATMP within the EU to seek authorisation from the EMA (European Medicines Agency, formerly EMEA) and lays the foundation for a harmonised regulatory regime applicable for all Member States in the European community.

It is useful to also clarify here the relationship between the ATMP regulation and the EU Tissue and Cells Directive (EU TCD). In the UK, use of human cells and tissue is regulated by the Human Tissue Authority (HTA) under the EU TCD, the first attempt to establish a harmonised approach to the regulation of tissues and cells across Europe. The EU TCD is made up of three Directives: the parent Directive (2004/23/EC) which provides the framework legislation and two technical Directives (2006/17/EC and 2006/86/EC), which provide the detailed requirements of the EU TCD. The Directives set a benchmark for the standards[144] that must be met when carrying out any activity involving tissues and cells for human application (patient treatment). The three Directives were fully implemented into UK law on 5 July 2007,[145] via the Human Tissue Regulations 2007 (also known as the Quality and Safety for Human Application or Q&S Regulations).

In 2007, the Human Tissue Authority's (HTA) remit was extended by the Q&S Regulations to include the regulation of procurement, testing, processing, storage,

[144] The EU Tissue and Cells Directive sets out the standards for the quality and safety of the donation, procurement, testing, processing, preservation, storage and safety of human tissues and cells. It covers tissues such as bone marrow, sperm, eggs, embryos, umbilical cord blood, bone and heart valves. It excludes blood, blood products and organs, which are covered by other European legislation.

[145] The Directive came into force in April 2004 and was to be fully implemented into UK law by 7 April 2006. The completion of the implementation process, however, was delayed, due to the fact that the Directive was dependent on two technical Directives which were still being drafted by the late summer of 2006. At the time, the UK Department of Health (DoH) decided to transpose the Directive (and its two accompanying technical Directives) through two sets of Regulations that will amend the Human Tissue Act 2004 and the Human Fertilisation and Embryology Act 1990.

distribution and import/export of tissues and cells for human application (establishments where these activities are carried out would normally need a license). The HTA is still (since 1997) the body responsible for ensuring that human cells or tissue used in ATMPs are donated, procured, and tested in an appropriate manner. However, the subsequent stages of clinical research involving ATMPs, including the manufacture, storage and distribution of products would be regulated (and licensed) by the MHRA.

Summary

In this section, I have provided an overview of the changing regulatory landscape in the field of Regenerative Medicine and the challenges that the 'emerging technologies' have posed to both developers/companies and regulators. Indeed, the majority of RM products contain living cells and thus do not fit in the category of medicinal products and cannot be regulated as a medical device either. However, with the increasing presence of these combination RM products in the EU R&D agendas, most Member States proceeded to develop and adopt variable national policies in order to fill the perceived gap between medical devices and drugs. The main reason behind the policies was to address important safety issues including the risk of infection, risk of cancer formation and rejection risk. It soon became apparent though, that the resulting 'patchwork' of national guidelines made the development of 'advanced products' for the common EU market difficult. After a long process of negotiations and drafting, the EU introduced its new ATMP regulation which became effective in December 2008 and covers all products under the ATMP definition.

In this transition phase (roughly between 2003 to date [2010]), from the old, inadequate regulation to the novel ATMP guidelines (and their 'in-progress' implementation), it is particularly important that people involved with the development of such 'advanced therapies', be able to adapt to the fragmented situation while also preparing for future requirements. It is in the next section that I examine this ability of UK bioentrepreneurs by focussing on the way my respondents perceive and deal with the regulatory uncertainty during the clinical translation of their research findings. The majority of interviewees admit to feelings of uncertainty and frustration over the

classification of their products as well as confusion over disparities and overlaps in the regulatory oversight of the relevant regulatory authorities.

The Era of Uncertainty

As noted at the beginning of this chapter, half of the interviews were conducted between October and December 2007, just before the ATMP regulation came into force (December 2007). This first wave of interviews suggested that all the informants were confused and dismayed about product/therapy classification, regulatory agency jurisdiction and responsibilities. At the same time, the interviewees also shared a somewhat conservative optimism with regard to the upcoming regulation (ATMP).

When asked about the challenges of working with regulators and classifying their products for regulatory purposes, most of the interviewees had a version of the view that is nicely illustrated by RB's answer below:

> They have to put you into one box or another. And the box is medicine or device. And everybody knows that for the majority of these [novel Regenerative Medicine products] neither of those categories are a good fit.
> **(RB, PI/Founder of Spin-out, 2007)**

This perception of 'category confusion' is characteristic of the EU context where, as mentioned earlier, tissue-engineered (hybrid/combination) products should be 'made to fit' into one of the two existing categories: drug or device (Faulkner et al., 2003). LM, a principal investigator (PI) in the wound care field and founder of a Regenerative Medicine spin-out, also conveys the uncertainty of bioentrepreneurs over commercialisation and regulatory strategies for the regenerative therapeutics field.

> Everybody waits for everybody else to make a decision. So when you write a grant they will say "How are you going to commercialise this? What regulatory route you are going to take?" And you think "I wish I knew". So it is not a culture in which it is easy to move things forward clinically. **(LM, PI/Founder of Spin-out, 2007)**

The above extract confirms not only the tight relationship between regulation and the commercialisation trajectory but, more importantly, the significance of 'early on' product classification for a research project's 'financial viability'. Under the pressure for Translation and 'outcomes', most (translational) grant applications in the UK require applicants to include this kind of information in their application form, but as LM admits, the overall culture is not being very accommodating. What she really implies is that at an early Translation phase neither the regulators nor the potential funders are being helpful as 'everybody waits for everybody else to make a decision'.

As an example, below is part of the application guidelines for those seeking to apply for the Wellcome Trust Translation Awards which 'are response-mode funding designed to bridge the funding gap in the commercialisation of new technologies in the biomedical area':[146]

> ***Commercialisation Strategy***
>
> What are the strategy and plans for attainment of a commercial exit, and how will they be implemented? What is the rationale behind this route? What are the outputs going to be (e.g. platform technology description, product descriptions)? Are there any clinical, manufacturing, regulatory or marketing issues known that may affect the ability to deliver the product to market?
>
> ***Current or Downstream Regulatory Considerations or Risks***
>
> Evidence that the regulatory requirements are known and being accounted for in the product development
>
> (Wellcome Trust Translation Awards, Application Guidelines)[147]

It is clear from the type of information required by the application form, that the bar for funding is very high. With both public and private investors looking for rapid liquidity to arise from successful clinical and commercial projects, issues such as commercialisation and regulatory strategy are deemed critically important and the need

[146] Candidate Projects for the Wellcome Trust Translation Awards must address an unmet need in healthcare or in applied medical research, offer a potential new solution, and have a realistic expectation that the innovation will be developed further by the market. More information is available at:
http://www.wellcome.ac.uk/Funding/Technology-transfer/Awards/Translation-Awards/index.htm

[147] The Application Guidelines document is available at:
http://www.wellcome.ac.uk/Funding/Technology-transfer/Awards/Translation-Awards/index.htm
(Accessed May 2010).

to be considered early in a project's life is proved by their inclusion in the grant application forms.

To understand bioentrepreneurs' frustration with the 'confusing' classificatory and regulatory regimes, it is necessary to explain that how a product gets classified (under the 'two tier' system) has crucial implications for its whole journey from the laboratory to the clinic and market. For example, products that are classified as medical devices and are reviewed as such will have to satisfy the safety and efficacy requirements of the Medical Devices Directive (EC Directive 93/42/EEC). These requirements are generally considered less burdensome that the ones required by the Medicinal Products Directive (Directive 2001/83/EC), are less expensive to satisfy (in terms of developing and manufacturing the product) and thus lead to a quicker and 'easier' regulatory approval.[148] As seen in more detail later on, the categorisation of a product can also be very significant for its financial 'survival' (and hence the survival of the company) as investors will, in most cases, choose to invest in products that will 'sail through' the regulatory approval process as quickly as possible. Swift regulatory approval means that products will reach the market sooner and start bringing in the rapid return-on-investment that motivates most (if not all) sponsors.

This preference for a 'simple' product profile shown by both sponsors and developers, however, seems to be limited to the regulatory (approval) arena. As Linda Hogle (2009) suggests: 'to meet the expectations in all [...] arenas [i.e. public and private payers and clinicians], producers might want to position their products differently for regulatory purposes than for marketing or other purposes. They seek the fastest, least burdensome and lowest cost regulatory route, while for marketability they claim unique product properties in order to receive a higher reimbursement rate code and to be adopted by clinicians wanting improvements over existing treatments' (Hogle, 2009: 722). This 'audience-tailored' characterisation of products is based on what Hogle describes as a certain amount of 'interpretative flexibility' applied to all product-related knowledge and data produced.

[148] It is claimed that 'the quickest and least costly regulatory pathway is a device' and it has been estimated that 'once products have undergone development and are ready for their key preclinical animal studies, it is likely to take 5 years and $30–$200 million as a device, and 8 years and $50–$300 million as a biologic or drug' (Hunziker et al., 2006: 3354).

LM's description of how she managed to have her product approved in the UK by the Medicines and Healthcare Products Agency (MHRA) provides a useful illustration of how tissue-engineered and other novel regenerative therapeutics have been 'dis-serviced' by the 'old', two-pillar classification system. LM credits early communication and collaboration with the regulatory authority for eventually managing to 'bring' the product to the clinical setting, despite the blurred regulatory landscape.

Kaftantzi: So how was [Product Name] approved?

That was an interesting one! We had meetings with the MHRA. We went and presented our work to them. And we showed them that it was autologous keratinocytes on an inert polymer-type carrier. Now, if it were the carrier alone, it would have been a device. But it isn't [alone]. The carrier alone doesn't work. It is the carrier with cells. So they looked at what we are doing, we showed them that it worked clinically. Then they wrote back to us saying they had reviewed it internally, this was in 2002-2003. They wrote us a letter back and said that they had looked at it, and that in their opinion it was not a device and it was not a medicine. But, providing it was autologous and we did it from clean rooms under protocols approved by them, we could continue supplying it and selling it to patients. So really, it was the fact that it was autologous and that we were working within the framework at that time – which was clean rooms – approved by them.

(LM, PI/Founder of Spin-out, 2007)

LM's product comprises a synthetic carrier (scaffold) which is seeded with the patient's cells (keratinocytes) and cultured *in vitro*. The entire entity is then grafted onto the patient (on a skin ulcer or burn) where biomolecules in the product actively recruit the patient's own cells to the site to initiate wound-healing processes. In other words, the product includes a scaffold, which means it has structural components like a device, it contains living cells like a biological, and it delivers molecules at the site of 'damage' like a drug.[149] The complexity of both the product and the actual healing process is an

[149] A similar product to the one developed by MN's company and currently present in the international market is Dermagraft. Dermagraft has famously suffered from inconsistencies in the regulatory and marketing approach due to the

indication of the difficulties biomedical researchers, clinicians, and regulators face when they seek to categorise these types of therapy.

LM's account of how her company's flagship product was approved in the UK, exemplifies the way cell-based and tissue-engineered products have been allowed to reach the UK market before the development of Europe-wide (or even UK-wide) 'appropriate regulation'. As long as products were safe and effective, that is they 'worked clinically', as stated by LM, then they could be manufactured in approved facilities and under established protocols and be offered to patients. *Autologous*, though, is a key word and its importance in manufacturing and, consequently, regulation will be analysed later in the chapter.

Despite having success with that particular product and 'getting it through the regulatory haze', LM sounds frustrated and blames the luck of 'universal' regulations for 'arbitrary' classification performed by regulators which, she implies, is not beneficial for the field.

> It's actually very, very difficult to get a regulatory opinion on where your product falls and you will find identical products have been given different opinions even in the UK and that's very, very frustrating! They are dealt on a case-by-case basis, which I think is fine, but it's a bit arbitrary at the moment.
>
> **(LM, PI/Founder of Spin-out, 2007)**

LM's comments suggest that product developers, companies and, most importantly, sponsors are losing trust in the system as 'similar' products, after having been judged on a case-by-case basis, are being directed to follow quite 'dissimilar' regulatory approval routes. NC, principal investigator and founder of a spin-out focussing on the production of research and clinical hESC lines, shares this view and emphasises the need for regulatory harmonisation across Europe:

> You could say that a harmonised market, no matter what the decision, will be easier to deal with than different decisions in different countries. I

hybrid nature as a kind of device/biologic. For more information on the development history of Dermagraft see (Stuart, 2008).

> think that the one thing that the commercial environment can't cope with is uncertainty. So uncertainty in the regulatory environment is possibly the worst thing.
>
> **(NC, PI/Founder of Spin-out, 2007)**

Now, judging from the answers and narratives of all my (first wave) informants, uncertainty over product classification and regulatory route is intimately linked to uncertainty over which UK regulatory authority governs which type of product/therapy and which part of the product development process. The following is a quote from a principal investigator who is also a spin-out company's founding director and largely involved in reproductive clinical work.

> The regulatory aspect is not very clear at the moment with hESCs. I do not think that's really held [Spin-out Company] up because it is not in a position [to commercialise a product yet]. But it has held up the [Academic Research Centre] to which [Spin-out Company] contracts to. Because, for instance, for the clinical development of clinical grade cells we have been in limbo, not knowing [...] The uncertainty surrounds which regulatory authority is actually regulating development of clinical grade hESCs. I was at a meeting the other day and it is still not clear whether it is going to be the HTA or the MHRA really. And which Directive it will come under exactly. The HFEA are also involved but really they are only interested in the embryo. Once you destroy the embryo to make the embryonic stem cell lines they are not interested. So that bit [embryo research] is fairly well controlled. The bit after that is problematic. The HTA and the MHRA are involved but the interpretation of what your cells are [i.e. research or clinical grade] has a big influence on which Directive you are going for.
>
> **(GL, PI/Clinical involvement/Founder of Spin-out, 2007)**

GL's research group is working on the area of the derivation and differentiation of human embryonic stem cells (hESCs). Apart from research work on the differentiation of hESCs to specific cells (such as insulin secreting cells), the Research Centre is also working on the derivation of clinical-grade human embryonic stem cell (hESC) lines

that can be used by other researchers as tools for research. For this 'clinical-grade' work, the group is in possession of a clean room facility so that the generation of human ES cell lines can meet the standards for clinical treatment (i.e. Good Manufacturing Practice, GMP).

When asked to explain 'which agency governs what part of the Research Centre's and subsequently the company's work', GL, admitted that 'it is not clear'. Regulating the development of clinical-grade cell lines appeared to be especially problematic, with GL describing how they have been 'in limbo' lately, 'not knowing' how and from whom their 'clinical-grade' work ought to be regulated. He mentions his participation in a meeting and points to the general feeling of confusion matched by other colleagues attending. Although GL is clearly uncertain about the role of the HTA and the MHRA in the development of the 'clinical-grade' lines, he seems to have a clear view of the role and responsibilities of the third regulatory authority he mentioned – the HFEA. The HFEA (along with the HTA) is one of the UK's competent authorities for the EU Tissue and Cells Directive (EU TCD) and licenses and monitors centres that conduct *in vitro* fertilisation, donor insemination and embryo research.[150] GL confidently explains that 'really they are only interested in the embryo' and 'once you destroy the embryo to make the embryonic stem cell lines they are not interested'. Overall GL perceives the oversight work and responsibilities of the HFEA clear-cut and 'fairly well controlled', emphasising the overlap and ambiguity that characterises the rest of the production process.

Similar comments are made by another interviewee, who also works on the production of clinical-grade human embryonic stem cells. His company too is interested in selling clinical-grade hESC lines as tools for other laboratories and companies. In addition to criticising the confusion over 'who governs what', he mentions the need for the creation of a clear, harmonised, structure that 'recognises' and covers the type of work that his company is already doing (research-grade derivation), as well as the new aspects that they are starting to focus on (clinical-grade derivation).

[150] The other competent authority, HTA, regulates the removal, storage, use and disposal of human bodies, organs and tissues from both the living and deceased (i.e. other than gametes and embryos, which are covered by the HFEA).

> The UK still has to work hard to keep pace. So for example, to do the work that we are doing right now we get a licence from the HFEA [Human Fertilisation and Embryology Agency] and, very soon, that is going to be complemented by a need for licence from the HTA [Human Tissue Authority]. And there is duplication there. What is being asked of individuals, demonstration of quality assurance standards, etc. is basically twice as much work for the people involved, so ultimately we need to create a harmonised structure. On top of that, if you go with what the HFEA is concerned about really, is derivation of cells for research. The first version of the licence that I hold is titled 'Enabling technologies for human embryo stem cell derivation'. But now the development is towards therapeutic-grade cells. At some point there needs to be recognition that what we are doing, the licence that we are seeking is not for research but it is actually for production of a therapeutic product. And there are nuances that I think then need to be addressed.
>
> **(NC, PI/CSO/Founder of Spin-out, 2007)**

NC is describing the challenge of the transition from 'research-grade' to 'clinical-grade' work under what he perceives as confusing, overlapping and non-harmonised guidelines. The current licence he holds is for derivation of research-grade lines, but as his company changes focus he will need to go to 'yet another regulatory authority' and demonstrate 'once again' the necessary quality assurance standards.

The concern over 'duplication' of work revealed by NC (in 2007), had also been reported in the media and in commentaries (published in scientific journals) by many stakeholders at the time, and had been very controversial. In fact, in December 2006, the UK Government published a White Paper under the title *Review of the Human Fertilisation and Embryology Act*,[151] in which it set out its plan for the HFEA and the HTA to merge and form a single regulatory body, the Regulatory Authority for Tissues and Embryos (RATE), covering the whole of reproduction technology, pathology, anatomy, transplantation and the use and storage of human tissue. The arguments that

[151] Review of the Human Fertilisation and Embryology Act: Proposals for revised legislation (including establishment of the Regulatory Authority for Tissue and Embryos). Department of Health (DoH), London: Stationary Office, 2006.

had been put forward in support of the merger had been political (for example, reducing the number of regulatory bodies by one) and financial.[152]

Curiously, the proposed 'RATE' merger surfaces in the narratives of many informants with another interviewee commenting even more explicitly on it:

> They were going to merge the HFEA [Human Fertilisation and Embryology Authority] and the HTA [Human Tissue Authority]. But that's been stopped, which is probably a good idea. I don't think it was going to work how it was. Because the HFEA really governs all the patients attending IVF [In-Vitro Fertilisation] clinics, mainly. They do cover the research, but it is really quite a small aspect of what they do, in a way. I mean it is important because they regulate all embryo research, but the HFEA come from a way of protecting patients who are going to IVF units. So a lot of the governance is related to that, which is a bit different to the HTA. So I am not sure it would have come together very well. But on the other hand, having lots of different agencies is not particularly useful either. We've also had ongoing discussions with the MHRA for about three years but they haven't really come to any decision, so this has been a problem.
>
> **(GL, PI/Clinical Involvement/Co-founder of Spin-out, 2007)**

As GL suggests, the problem with the merger is the different 'concerns' of the two bodies, with HFEA's main concern being the protection of IVF patients who donate the embryos (from which the embryonic stem cells are subsequently derived). From GL's reflection, it is clear that he, like other respondents, is facing the dilemma between having to deal with reducing the 'arms length bodies' by one, but running the risk of not having 'enough expertise in the central authority to appropriately regulate the difficult areas it would have to address'. As another interviewee puts it: 'It might, actually, lead to a more expensive and less efficient system'.

Institutional hybrids such as RATE have proven to be important objects of social science critique before. Brown and Michael (2004), for example, examine the

[152] Although it has been argued that equal financial savings could be made by other changes short of merging the bodies.

establishment of such an institutional hybrid body – the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) – for regulating transpecies transplantation and discuss the scope and limitations of its 'hybridity'. In their analysis, Brown and Michael suggest that hybrid institutions are 'risky creatures' as they face many risks such as 'whether or not their terms of reference are adequate to cover the kinds of new combinations arising in bioscience, whether they are sufficiently representative of all the relevant regulatory bodies' (Brown & Michael, 2004: 209). Their analysis seems to agree with the concerns of bioentrepreneurs (and others) whether the establishment of RATE would have been an appropriate and effective solution to the 'duplication of work' concerns at the time.

Summary

The regulatory landscape is changing and the bioentrepreneurs are attempting to make sense of the changes. There are frequent calls for harmonisation and more 'straightforward' regulation. One of the main problems identified by bioentrepreneurs is the difficulty of classifying their products. As mentioned earlier, the category under which a product is classified has large implications for the way a product is subsequently tested and approved. Up until late 2007, in the absence of a coherent European regulatory framework, similar cell-based products could potentially be subjected to different regulatory regimes and decisions, even in the same country (if evaluated at a different time), leading to confusion and frustration – especially in view of the positive relationship between a clear, regulatory route and investment potential for a product/company. To emphasise the need for advance knowledge of the potential regulatory (and commercialisation) route, many informants mentioned how grant applications require the inclusion of the relevant information in order to allocate funding.

In the narratives of bioentrepreneurs, uncertainty over regulatory route is coupled with uncertainty over the work and regulatory jurisdiction of the main UK competent authorities for RM research and development such as the HTA, the MHRA and the HFEA. Out of the three agencies, the work of the HFEA is perceived by the entrepreneurs as the most 'clear-cut' with responsibilities ending at the point of embryo destruction. The HTA and the MHRA on the other hand are 'uncertain'

actors, perceived by many interviewees as 'duplicating' work and frustratingly wasting investigators' and companies' precious time and resources. Interestingly, the current (at the time) proposal for merging the HTA and HFEA surfaced in many interviews but discussion with the informants revealed mixed feelings and there was no consensus on whether merging the bodies would facilitate or hamper activity in the field.

Bioentrepreneurs interested in pursuing the production of clinical-grade cell lines have also spoken about the difficulty of making the transition from research-grade to clinical-grade lines under the current regulation. The concerns raised highlight the impact of regulatory uncertainty on innovation and commercialisation. The finding also points to another interesting change in the regulatory landscape: the focus of the regulation is no longer on the source of the cell lines, as this is an issue in the embryonic debate that appears to have been 'solved'. The focus of the (downstream) regulation is on assuring the 'quality' of the hESC lines especially when they are destined for therapeutic application and must be of 'clinical-grade'.

Co-Shaping the Regulatory Landscape

It would be easy to form the impression from the preceding section that bioentrepreneurs are involved as passive actors in the regulatory time and space. However, in addition to the narratives and the framing of the regulatory 'hurdles', there are also parallel stories about the way many of these challenges have been handled in order to realise the translational objectives.

Intrigued about the way they deal with this uncertainty at the practical level (when they are asking for examination of a product for example), I asked the informants about their interaction with the regulatory authorities. A bioentrepreneur replies below and explains his belief that regulatory uncertainty stems from the fact that regulators themselves are uncertain and inexperienced when it comes to 'evaluating' this new kind of 'entities':

> So the regulators ask loads of questions. You know, it went from drugs and devices, then biologics, and then what? The move from drugs to biologics was a big move when they did it, because you're talking about

> proteins and synthesised products. But the move from biologics to cells is even bigger. Biologics are a single molecular entity, they're one thing and they're not changing. Once it's made, it's made. It just sits there slowly degrading, but sits there. Cells are dynamic things, changing by the moment.
>
> **(NJ, PI/CSO/Founder of Start-up, 2007)**

NJ attributes the 'state of confusion' to the fact that cell therapies, especially stem cell-based therapies, are very different to medical devices, biologics and drugs, which is what the regulators are 'used to' so far. Thus, traditional approaches to regulation that have proven effective for the latter are not well suited to the 'novel biological products' where the mechanism of action is still poorly understood; where most products are used as a component of a complex therapeutic strategy in which it is difficult to isolate and access its contribution (for example in a conventional clinical trial); and, finally, where the field is advancing at a rapid pace that is incompatible with the time frame for the approval of traditional medical products (Gee, 2002). This 'novelty' is the reason, he later explains, that regulators default on 'I wonder what if' type of questions. His comments were mostly applied to the EU regulatory landscape, as he seemed to be more convinced by the approach followed by the US Food and Drug Administration (FDA). Still, from his perspective, the confusion in the regulatory system is 'understandable'. He continues:

> It's a dual-edged sword at the moment. The confusion in the regulatory system is understandable, it's not that they're doing anything wrong. You can play it to your advantage in a way because in industries like ours you can actually, direct it. So you can influence it. If we were a start-up drug manufacturer now, we would just have to follow the rules. We wouldn't have any chance of changing the rules. Whereas, [in the new area] we have chances you know, and they [regulators] come and seek advice all the time.
>
> **(NJ, CSO/Founder of Start-up, 2007)**

NJ seems to believe that the uncertainty that dominates the regulatory landscape in the UK (as well as the EU) is a 'dual-edged' sword and could also work to the advantage of

the scientists and ultimately the field. In contrast to having to comply with an already established regulatory framework, as would be case for a company entering the pharmaceutical industry and drug development field, in the cell therapy field, investigators and small companies have the opportunity to influence and perhaps even, 'direct' the work of the regulatory agencies. To illustrate this work-in-progress participatory attitude that, he believes, is also encouraged by the regulators, he provides an example from his own company:

> And I'll show you, you talk [about] automation; I'll show you in a minute because we're actively in consultation with the MHRA [Medicines and Healthcare Product Regulatory Agency] at the moment about this automation. Because it's a robot that we developed for one purpose and we're using it to try and see if we can do it for another purpose. And we're doing this in consultation with the MHRA.
> **(NJ, PI/CSO/Founder of Start-up, 2007)**

In other words, according to NJ, it might be the case that embarking upon early consultations with the appropriate regulatory authority is not only a way to avoid committing precious time and funds on the 'wrong' innovation process but is also a way to be involved in the formulation of the policies. By filtering the regulatory guidelines through their personal, first-hand experience of developing cell therapy products and by providing input to the relevant agencies, RM investigators and budding companies, are in way shaping expectations of these agencies and might be actually lowering the barriers for their own future commercial product candidates.

The bioentrepreneurs' 'claim' of co-shaping regulation with regulators has been recently confirmed by the 'other side' (albeit in the medicines field). In a 2010 *Nature* article,[153] regulatory experts from the European Medicines Agency (EMA) commenting on the drug approval success rates in Europe, have mentioned interaction between regulators and sponsor companies as a way to 'remedy' the gap between regulatory expectations and product development strategies and hence increase the regulatory success rates. The experts highlight the fact that such interaction is not mandatory in the EU and only 60% of the Marketing Authorisation Applications (MAAs) are

[153] (Eichler et al., 2010).

currently preceded by scientific advice from the EMA's Committee for Medicinal Products for Human Use (CHMP). The importance of such 'dialogue' early on and repeatedly at major transition points, as well as compliance with advice given by the CHMP seemed to be a predictor of positive MAAs outcomes (Regnstrom et al., 2010).

NJ's account also resonates with scholars' suggestions in the social science literature that there is a shift toward a more 'participative ethos' in 'building' regulation as well as changes in the relationships between science, industry and state regulation. For example, Salter and Jones (2002) argue that in the field of genetics ethical concerns and the role of the consumer citizen are becoming increasingly influential, deflecting the attention from the promotion of innovation and industrial development, which used to be the first priority. Additionally, Kent and Faulkner in their 2006 analysis of the regulation of human implant (breast and hip) technologies argue that we may be witnessing (at least in the UK) 'a move towards a more user-oriented shaping of regulation' (Kent & Faulkner, 2002: 205).

In the case of the nascent RegenMed industry, the bioentrepreneur can also be considered as a type of 'user'[154] who is increasingly gaining 'power'. Not yet members of an established industry (such as pharma and biotech), the founders and (often) Chief Scientific Officers of small RM companies are collaborating with the regulatory authorities and help to 'co-shape' the emerging regulation. This collaboration makes sense, as both the 'know-how' and the 'maturing' (bioprocessing) infrastructure are 'constructed' and, at least for the time being, 'monopolised' by these small companies that are the lifeblood of the RM field.

NJ's perception, on the other hand, over the rigidness of the pharmaceutical industry and its 'set' regulatory framework is not groundless. Abraham and Lewis (2002), for example, argue that in the area of pharmaceutical regulation, despite consumers' growing activism and the associated challenges to medical autonomy and dominance (by questioning the social viability of medical expertise in industry and the regulatory state), 'the evidence that these challenges have been accompanied by societal changes, such as increased power for consumers of medicines in terms of citizenship rights or a

[154] Although, technically, bioentrepreneurs are not users of RM products, in the sense that patients and clinicians are, because of the early stage of the RegenMed industry, its representation predominantly through SMEs and the multifaceted nature of the bioentrepreneurs (often scientist, clinician and manager) who are leading the field, I argue that they can be considered as a type of 'user' with regard to the regulation.

significant decline in medical authority within the regulatory state, is limited' (2002:82). In other words, the long-established pharmaceutical regulation – shielded behind the medical authority and the interests of the producers (industry) – is perceived as being 'immune' to the 'user' (patient) interests. It is not surprising then that in the face of such a scenario, where small RM companies are entering an already established industry (much like pharma), NJ perceives his group (i.e. bioentrepreneurs) as having much less 'power' and fewer opportunities to co-shape the regulation that will inevitably define their businesses' future. In short, it could be said that unlike Abraham and Lewis' 'active citizenship' in pharma that is dampened by the 'biased' regulatory state, 'active entrepreneurship' in RegenMed instead seems to be more 'influential' and 'productive', facilitated by the early stage of the science, the early stage of the industry and hence the early stage of the regulation itself.

Another interviewee, LM, reflects on her experience with regulators and comments on her perception of their attempts to create 'a third pillar' of regulation in order to accommodate the tissue-engineered and other combination products that did not seem to 'fit' either the medical device or the drug category. More specifically, she describes how regulators, challenged by the 'novelty' of the emerging RM technologies, default on 'lifting the safety bar higher and higher and higher' hence running the risk of producing something 'so difficult' that will discourage investigators from clinically translating their findings. She notes:

> Because the conundrum for regulators is that they can only regulate things they know about – that they have been around for a while. And then, how do we ever bring [forward] something new that doesn't quite fit...? I do appreciate it from a regulator's point of view, but I think that if the regulation goes to always lifting the safety bar higher and higher and higher, we will end up with something so difficult. I know many of my academic colleagues in the UK would not think of doing TE research that went to the clinic because they view it as too difficult.
>
> I think we've got to say this [regulation] is something we hope [...] will succeed, but we hope it will succeed and end up with something that is sensible, rather than something that is so prohibiting that nobody can do

anything. Something that recognises that we need to develop products in the area. You have to support innovation while also making sure that everything that goes forward is safe. What we really want is some sort of "light-touch" regulation while we are developing products.

(LM, PI/Founder of Spin-out, 2007)

LM appears to share NJ's understanding of the regulators' attitude towards novel technologies that challenge the existing guidelines and expertise. In addition, she emphasises the need to create a framework that balances the requirements for safety and quality with the need for progress and innovation in the Regenerative Medicine field. Unreasonably high safety standards and too-restrictive regulations will end up stifling, if not completely 'killing' the field. She sums up a view held by most interviewees, when she says 'what we really want is some sort of *"light-touch"* regulation *while* we are developing products'.

The term 'light-touch' regulation can theoretically be employed in both a narrow context – such as the development of a specific therapy/product – and in a broader context, such as a whole discipline/field (for example Regenerative Medicine) or indeed the whole biotech sector. As LM uses the term, it seems to imply a call for flexibility and open-mindedness toward the emerging technologies (and their risks), plus a call for a kind of continuous, investigator-friendly guidance from the regulators. In other words, the term conveys the image of a constant, back-and-forth communication between the product developers/manufacturers and the regulators so as to produce an outcome that is 'in accordance' and 'approved'.

In general, the term 'light-touch' regulation as employed by LM is useful for highlighting the challenges associated with restrictive and inflexible legislation, and emphasising the need for regulatory guidelines that allow a rapid response to scientific advances – especially in rapidly progressing scientific or technological fields such as RM. Indeed, the significance of this mode of regulation ('light-touch') becomes obvious in view of recent advances in the stem cell research field, such as induced pluripotent stem cells (iPSCs), inter-species somatic cell nuclear transfer (iSCNT), and embryonic stem cells derived from parthenogenetic embryos and from embryos

generated from isolated blastomeres.[155] All these techniques were not even contemplated during the political and scientific debates that led to the current regulation.

The discussion of the challenge of regulating rapidly changing science has also been raised recently by a group of stem-cell biologists and law scholars from the University of Toronto, Canada (Rugg-Gunn, Ogbogu, Rossant and Caulfield), who are using stem cell legislation in Canada as a model and who attempt to demonstrate how broad-based prohibitive legislation can unintentionally restrict research direction.[156] They note:

> The law is also often a terribly blunt and clumsy tool. It not only lags behind the advances of science but can create unintended hurdles in front of it. Legislation can quickly become an anachronism, no longer reflecting the social mood or scientific realities. If scientific legislation is crafted without careful attention to the underlying science, it may run aground when faced new scientific realities [...] whether one advocates a cautious or permissive approach to regulation, it is important to craft legislative provisions that retain the ability to capture the nuances and unpredictable turns inevitably associated with scientific progress.
> (Rugg-Gunn et al., 2009: 285 and 288)

In other words, there is a call for regulators to strike the difficult balance between appropriate guarantees on the safety and quality of therapies, while at the same time allowing for a certain degree of flexibility in order to keep pace with the technological innovation.

For many of my informants, part of the 'toughness' of the regulations was also the endless paperwork that accompanied the regulations. Indeed, the multifaceted role of bioentrepreneurs as principal investigators, often as heads of experimental (sometimes even clinical) trials, and as company 'managers' assigns them the unfortunate task of

[155] For an overview of the legal status of novel cell technologies/techniques such as iPSCs, inter-species somatic cell nuclear transfer (iSCNT), and others (in Canada) see: (Ogbogu & Rugg-Gunn, 2008).
[156] The group's (i.e. Rugg et al.) interest in 'prohibitive' and 'lagging-behind' regulation seems to have been raised by the fact that, in Canada, the reproductive technologies legislation that also governs embryonic stem cell (hESC) research came into force a decade after the publication of the Royal Commission that called for its enactment.

arranging for licences, filing in endless forms and preparing all sorts of applications. The interviewee HR is principal investigator and clinician in orthopaedics[157] specialising in autologous chondrocyte implantation (ACI). Like other bioentrepreneurs, he recognises that the 'novelty' of most cell-based treatments is undeniably contributing to the 'over-regulation' and the bureaucracy, but he also thinks that better management of the situation could avoid a lot of 'red tape'.

> We have so much bureaucracy now. One of the problems has been that it is a new treatment so it is quite difficult for the regulators/authorities to know what to do. Because they don't know if there are problems with it [the new therapy] or not. Now fortunately this new treatment hasn't ever killed anyone or caused much trouble and a lot of people are very happy with it [...] so the regulatory authorities still want to provide a framework. And the EU TCD [Tissue and Cells Directive] came up with some quite good suggestions. But these are being interpreted by each country in Europe in a different way, and in the UK they've become very burdensome. There is a lot of bureaucracy [...] so this is bad management. So I think we need to invite people from Singapore to come and run licensing in the UK. Because they [regulators in Singapore] have managed to arrange things efficiently and cost effectively.
>
> **(HR, PI/Clinician/Co-founder of Manufacturing Facility, 2009)**

HR is frustrated by the bureaucracy. On the one hand, he recognises the regulations as necessary and well intentioned, and on the other he expresses his disapproval of how the guidelines have been set up and interpreted in the UK. He perceives the 'burdensome' regulation as a result of 'bad management' (through equally bad interpretation), and suggests that the UK could solve the 'problem' by inviting people from 'Singapore to come and run licensing in the UK' because 'they have managed to arrange things efficiently and cost effectively'.

In addition to discouraging academic researchers from clinically translating their bench findings, there is the impression from many interviewees that burdensome regulations

[157] Orthopaedics is the field primarily concerned with the treatment and correction of diseases and injuries of the musculoskeletal system.

are perhaps even more critical in the case of companies who are attempting to enter the field. The quote below is from a scientist also working in orthopaedics.

> We are aware of the complex problems of working with a cell-based strategy compared to a device. From an industry perspective, they are much more interested in a device than a cell-based product, because of the regulatory authority requirements [for cell-based products] – and working with these dreams of paperwork – that will have to be met and approved. GMP facilities, category 2, HTA [Human Tissue Authority] licences and MHRA [Medicines & Healthcare Products Regulatory Agency]. So we are aware of all that, and from my perspective [i.e. academia] it doesn't change my research programme. I think if we were a commercial entity, it will probably focus quite dramatically what we try to do. But based here at the university, it doesn't affect my programme.
>
> **(QN, PI/Founder of Spin-out, 2009)**

In the quote above, QN is well aware of the expensive regulatory compliance and the associated 'bureaucracy' when it comes to cell therapies. Regulations need not only to be formulated but, to be meaningful, must also be enforced. This unavoidable involvement with the bureaucratic apparatus – these 'dreams of paperwork that will have to be met and approved' is, he claims, the reason behind the preference[158] of the industry for developing devices (implants) as opposed to cell-based approaches. Although he admits that such regulatory concerns do not direct his own academic work, in the sense that he would not change the product therapy his group is working on, he points out that for a company (spin-out or start up) the effect would be different. His comments suggest that stringent regulatory requirements impose additional costs on industry (companies) thus stifling innovation. This is presumably caused by redirection of funds and efforts towards compliance with regulations, instead of towards commercially oriented innovation. In short, what QN suggests, is that although burdensome regulations might not determine the science agenda of a

[158] Interestingly, although RO's view on the preference of industry for devices instead of cell-based approaches holds true for most of Regenerative Medicines subfields, it does not agree with recent market reports that consider the development of stem cell therapies to treat orthopaedic disorders to be advancing at a rapid pace. The promise of being able to regenerate multiple tissue types critical to proper musculoskeletal function has lead industry forecasters to predict that the market for orthopaedic-focussed stem cell therapies will grow from its current (2010) size of $110 million to £950 million by 2012. Espicom Healthcare Intelligence is a provider of business intelligence services (http://www.espicom.com). See: (Espicom, 2008).

predominantly publicly funded academic group (like his own group), it could be a seriously limiting factor to the commercialisation strategy of a small RM company with limited resources (financial, administrative, etc.) looking to develop Regenerative Medicine products.

In short, it could be said that tough regulatory R&D requirements and bureaucracy steer R&D strategy for commercial entities away from 'high regulatory requirements' products (i.e. cell-based) towards 'low regulatory requirements' products (i.e. medical devices). This steering activity makes sense as it supports the idea of a product commercialisation trajectory that needs to be 'easy to the eye of regulation' at early development stages (when scientific/technical challenges are plenty).

Another interviewee talked about a similar problem he faced in the bioentrepreneur (developer)/regulator partnership and that, he believes, stems from regulatory authorities recruiting the wrong expert to act as advisor (on the agency's behalf). LK explains:

> In the UK the MHRA are extremely helpful now. They have certainly changed their position over the last five years and we have excellent relationships with the MHRA. I think the problem is more at the European level and the complexity of the CHMP [Committee for Medicinal Products for Human Use][159] interactions. Everybody is learning, and certainly one example I can think of [is] where I was asked by a company to work with them – and go with them to their presentation with the EMA, to be an external adviser with an expertise in a particular field – and the person, the expert that the CHMP had identified is someone I know very well, [and who] certainly no one in the field [would] identify [...] as an expert; and yet to CHMP he was an expert. And his lack of understanding and lack of knowledge of the field was whoooof!... But he had been identified because of a particular status

[159] The CHMP plays a vital role in the marketing procedures for medicines in the European Union. For example, in the 'Community' or 'centralised' procedure, the CHMP is responsible for conducting the initial assessment of medicinal products for which a Community-wide marketing authorisation is sought. The CHMP operates by establishing a number of working parties at the beginning of each three-year mandate. These working parties have expertise in a particular scientific field, and are composed of members selected from the European experts list maintained by the EMEA. The CHMP consults its working parties on scientific issues relating to their particular field of expertise, and delegates certain tasks to them associated with the scientific evaluation of marketing authorisation applications or drafting and revision of scientific guidance documents.

> he held at the time...he was the chairman of an international body...he was appointed because he was chairman, so he had absolutely no idea [about] the specifics, and he actually clouded the issues. So there will be issues there where regulators aren't sufficiently informed to get the appropriate expert to represent them in discussions in a field which...some of these [fields] are very, very narrow, so the field of expertise is [also] very narrow and tight, and you only ever have a small number of experts that are true experts. So that, I think, was the only time where we had a real problem with knowledge.
>
> **(LK, PI/Clinical Involvement/Founder of Start-up, 2009)**

In this quotation, LK emphasises the 'excellent' working relationship with the MHRA and explains how problems he encountered had not been with the UK regulatory agency, but rather with the Committee for Medicinal Products for Human Use (CHMP) – that is the European body responsible for the scientific assessment of products and for granting marketing authorisations. LK describes how he was asked to be an external advisor to a company and join their presentation and subsequent negotiations with EMA (European Medicines Agency). He then expresses dismay at CHMP's choice of expert to conduct the specific evaluation. In his view, EMA inappropriately chose someone based on their current high-profile status and not, as they claim to do, according to the 'strength of their qualifications and expertise with regard to the evaluation of medicinal products'. Interestingly, he points out that he personally knows that person and he believes 'no one in the field [would] identify that person as an expert'.

LK repeatedly referred to his example as 'a knowledge barrier' case, emphasising the complete ignorance of the so-called 'expert' and his ability to 'cloud' the issues instead of clarifying them. In other words, he seems to imply that, although the scientific assessment work conducted by the CHMP is subject to an internal peer-review system, the system will only be as good as the choice of reviewers it recruits. According to LK, the danger of regulatory agencies to 'mis-recruit' experts increases when fields are relatively new and narrow, as is the case with cell therapeutics. 'True experts', as he calls them, are few.

As a last point, a few informants brought up the theme of 'difficult' regulation of Translation in the UK compared to more 'appealing' overseas regulation. As founders of companies that need to not only survive financially but also 'turn a profit', it makes sense that bioentrepreneurs will look for successful cases and draw lessons from their experience. In the following quote, SP suggests that large UK companies could avoid regulatory uncertainties by moving their operations to the United States or wherever a system might be more accommodating to their development and commercialisation strategies.

> The UK could quite rapidly lose out depending on the regulatory decisions. All the hard work could be blocked if you find out that you cannot move things forward to get things to the clinic. Now if you are a company with deep enough pockets you could take the view "Well we are not going to develop for the UK market we are going to develop things for the States". So if you are really big company you can say "We are not worried about getting to the clinic or the market in the UK, we will look at the world stage". But small companies cannot afford to do that. You will find when you talk about Intercytex and Renovo that they have strong connections with the States which is how they manage most of their funding.
>
> **(SP, PI/Founder of Spin-out, 2007)**

According to SP, small RM companies do not have many options when it comes to regulation and compliance. In contrast, he mentions the case of two large, fairly established UK RM companies with 'connections', as he points out, in the States. Ironically though, in early 2009, Intercytex suffered a potentially damaging setback following the failure of a key product in the latter stages of clinical trials.[160] The Cambridge company (which has another UK base in Manchester and a US facility in Boston) announced that the Phase III study of its treatment for venous leg ulcers – Cyzact – failed to meet its primary endpoint. As a result of that 'failure' the company did not manage to raise the necessary funds to continue operation and ceased all activities.[161] The Intercytex story proves how critical 'science' still is in the development of RM products, a view that contrasts with comments some interviewees have made,

[160] The 396-patient Phase III trial was a three-arm study conducted in the US, the UK and Canada.
[161] http://www.businessweekly.co.uk/life-sciences-archive/intercytex-hit-by-product-failure.html

stating: 'it just may be that science is the least of our problems' in order to highlight their view that regulation is 'what is stifling innovation and progress'.

Summary

The majority of bioentrepreneurs attribute part of the uncertainty over classification to the novelty of the emerging Regenerative Medicine products and the inexperience of the regulators. A few perceive the uncertainty as a 'dual-edged' sword with bioentrepreneurs casting themselves as crucial 'shapers' influencing the expectations of the regulatory authorities, instead of being passive recipients of regulatory guidelines. This 'co-shaping' is encouraged by the regulators, with early and frequent collaboration between developers and regulators being cited as a factor that increases the chances of successful regulatory approval. This kind of active participation in the creation of regulation is perceived as possible because of the early-stage of the RegenMed industry and the fact that regulatory guidelines have to be concurrently produced along with the RM science. Interviewees have also emphasised the importance of 'light-touch' regulation when it comes to uncertain technologies such as cell-based therapies, as a balance needs to be struck between safety and the need for innovation and progress.

Bioentrepreneurs at the helm both of academic and corporate research groups and companies trying to translate their research findings into the clinical setting, feel overwhelmed by the apparently 'endless' regulatory requirements that apply. Tough regulatory requirements and related bureaucracy were perceived as 'discouraging' and burdensome for academic groups/companies, although not to the point of decisively changing the research agenda. However, in the case of purely commercial entities, bioentrepreneurs were more concerned, suggesting that regulation might steer the research agenda away from cell-based therapeutics and towards less complex technologies such as medical devices. In general, regulatory bureaucracy was criticised for discouraging many principal investigators from entering the clinical Translation arena altogether.

The Effects of Compliance

On the basis of the ongoing conundrums reported by bioentrepreneurs in the previous sections, it can be concluded that the importance of standardising regulations for Regenerative Medicine developers has become increasingly obvious, yet also more complicated. All the interviewees for this study agreed that normalisation through regulatory standards is imperative across the field. The pressure to meet heightened regulatory compliance in such a fast-changing field is felt especially urgently by bioentrepreneurs, since they are the ones responsible for the task, and also the first to see their circumstances benefit or decline as a result of regulatory set-backs or delays.

The following section addresses the attempts of the interviewed bioentrepreneurs to comply with various regulations, including the new ATMP guidelines. Many bioentrepreneurs talk about the challenges and 'cost' of compliance. They disclose their feelings about the pressure they feel to comply with the ever-changing regulations and also criticise the lack of guidance and support from the government (and the relevant agencies). In the absence of adequate help and infrastructure, several informants raise concerns about 'wastage' of time and resources as well as the consequent impact on people's careers. With regard to the ATMP specifically, a few respondents point to the 'still-work-in-progress' status of the regulation (despite being in effect from December 2008), and highlight the significance of a 'careful' interpretation, and hence implementation, of the ATMP-based harmonisation during the transition period.

Below, LM shares her experience of trying to deliver a cell therapy, initially from an academic and, subsequently, from a spin-out company setting. LM is a principal investigator (PI) who leads her own group in a research institute. Her team's research has a strong translational interest in developing skin tissue engineering which will benefit patients, alongside fundamental work to develop new understanding and tools in the area of wound healing, burns and various skin conditions. LM is also a founder of a RM company that has at least one product in the market, available for use by medical professionals. Below, she describes attempts, both of hers and others' laboratories, to set up 'clean rooms' for aseptic manufacturing:

> When the Department of Health made it clear that if you were going to deliver cells to patients they had to be from clean rooms I think we were one of the first [research] groups and companies to have clean rooms up and running. So we set up clean rooms in 2003 and our first product – [Product] – was available commercially from about 2004 from clean rooms. Other colleagues of mine also set up clean rooms around the same time. It was a very clumsy operation. The Department of Health said "Here is how it must be, do it". We all got together and said "We can't do it overnight! You mean we have to stop treating burns patients?". "No", they said, "we do not mean that. We will give you another year". So they gave us another year to find the funding and set up the clean rooms. To be quite blunt, it caused enormous stress to the groups that took it on. People have lost jobs, it has impacted on careers, and it's been really difficult.
>
> **(LM, PI/Founder of Spin-out, 2007)**

It is interesting to note here that compliance attempts described by LM precede the adoption not only of the EU TCD Directive which came into force on 7 April 2004, but also of the Human Tissue Act (HTA) of 2004. Yet, her account echoes those of other bioentrepreneurs who aimed to comply with the subsequent EU Tissue and Cells Directive (TCD) and with the more recent ATMP regulation.

Now, both the HTA (2004) and the EU TCD (2007) require that production of tissues and cells, either in clinical studies or patient therapy, must be manufactured under observance of strict GMP (Good Manufacturing Practice) conditions in the so-called 'clean rooms'.[162] This is because, the culture of cells (in this case skin cells) and many other cell types involves their exposure to the atmosphere, for instance during feeding. Hence, measures must be taken to prevent the risk of particulate or microbiological contamination. The costs of building or refurbishing existing laboratories are substantial and are followed by major costs associated with monitoring and restocking of the clean-room and employment of trained personnel.

[162] GMP facilities or 'clean rooms' are relied on to control environmental contamination and thereby generate a sterile product. As post-process sterilisation is largely incompatible with maintenance of cell therapy product potency, aseptic techniques are used throughout product manufacture to control contamination. Maintaining aseptic technique is what drives the design, construction and function of GMP facilities.

From the interviewee's description it is obvious that the 'GMP-compliance' process was uncharted territory for her and her colleagues. She admits that their attempts to comply have been 'clumsy' and they were not supported financially nor guided by the Department of Health. She also notes the impact the whole process had on the careers of people who were involved as, she implies, compliance took a lot of extra time and effort that had to be directed away from the research work and the treatment of patients.

Equally interesting is how LM views regulatory compliance as far more hindering than any scientific and technical challenges in her field:

> Where we are right now, the scientific challenge of developing new products is actually the attractive and somewhat easier bit. People have been culturing adult skin cells since 1995. They have been using skin cells therapeutically since 1982, so compared to the stem cell world this is a fairly mature technology. To develop new products in the area is entirely possible. We could develop many more products than we could afford to take down the line. The biggest challenge to us in developing new products is actually the regulatory issues and the ever-changing regulatory environment.
>
> **(LM, PI/Founder of Spin-out, 2007)**

LM explains how the science part of her work is the 'attractive' and 'somewhat easier bit'. She refers to the long and established science of her field and contrasts it to the very 'novel' science of stem cells, characterised by uncertainty and unpredictability. Admittedly, LM is working in a scientific arena where there are far fewer scientific and technical uncertainties than those faced by hESC researchers. Still, novel biomaterials (e.g. for scaffolds) and novel combination products have their own risks and it is impossible to say that all 'technological' risks can be eliminated. LM notes that, given the relatively well established science, to develop 'new products is entirely possible' and that they could actually 'develop many more' if it was not for the 'unattractive' part of her work, which is the regulation.

LM's suggestion that it is the ever-changing regulation and the pressure to comply that are actually hampering innovation in the RM field is matched by other UK bioentrepreneurs as well as other investigators. More specifically, Dr Julie Daniels, reader in stem cell biology and Director of 'Cells for Sight Tissue Bank', Moorfields Eye Hospital (London, UK), in an article she published with colleagues, describes their experience of trying to comply with the Directives (in this case the EU TCD) and gaining regulatory approval, in the hope that it 'may help colleagues who are developing innovative academic research-driven stem cell therapies regarding donor consent, raw materials, quality assurance, laboratory specification, indemnity and funding' (Daniels et al., 2006: 715). Their account and long list of requirements is a proof of the time and effort required for regulatory compliance. In a different quote that sums up the views of many of my respondents the authors state: 'In our experience, gaining regulatory approval has been as great a hurdle as surmounting the scientific challenges of stem cell therapy' and at the end of the article they conclude: 'No doubt, the loss of some activities will have prevented the delivery of poor quality cell and tissue products to patients, and this can only be a good thing. However, we are left to wonder how many innovative new therapy programs borne out of government- and charity-funded research in UK universities may have been abandoned owing to the pressures of an ever-changing regulatory environment and lack of infrastructure to support it'(2006:718).

Along with the pressure felt and the difficulties of compliance, a few interviewees highlighted the 'expected' differences in the interpretation of regulations across Member States and discussed the impact these differences might have on the overall attempt for normalisation. GL's statement is simple but characteristic:

> The EU Directive is quite reasonably clear actually, but how do you implement it? Maybe open to interpretation really.
> **(GL, PI/Clinical Involvement/Founder of Spin-out, 2007)**

According to Article 29 of the ATMP regulation, all ATMPs that are on the Community market in accordance with national or Community legislation will have to comply with the new legislation by December 2011 (ATMPs other than tissue-engineered products) or 30 December 2012 (tissue-engineered products). LK, who is

well versed in the regulations through a number of key positions he holds in national and international oversight committees, explains how the regulation of ATMPs across the EU is becoming clearer, but no less arduous in terms of compliance at the level of delivery.

> The regulations for 1394 [ATMP regulations] were enacted in the UK law on the 7th of January this year [2009] but the implementation guidelines only came out from the MHRA in July [2009] and the closing date for discussion of those was the 16th of September [2009]. And only now [November 2009] I am having conversations with the MHRA about interpreting those opinions. And I suspect it will be decided early next year how they are going to deal with them in the UK. But *they will be different* to every Member State [emphasis added]
>
> **(LK, PI/Clinical Involvement/Founder of Start-up, 2009)**

Almost a year after the regulation became effective, LK implies that it is still too early to determine how the new regulation works, because much depends on the details of its implementation – in other words how each country 'interprets' the regulations in their attempt to 'adopt' them through national laws and guidelines. Below, LK draws attention to problems that he has experienced during the 'implementation phase' of the new ATMP regulation because of different interpretations of the regulation by different countries:

> So, for example, the Hospital Exemption Scheme (HES) in the 1394[163] in the UK you are going to have to apply for an MHRA production licence for your HES licence or use the currently existing "specials" licence. Well I know for a fact that the Dutch are not going to implement it in that way. And it will be very difficult for us to import products that are made under HES. Well for one, you can't export products made under the HES and yet many cell therapies, particularly transplantation cell therapies, we currently ship them all over the world. So, I am using mesenchymal stem cells (MSCs) as an example. One of my colleagues in London needed an MSC product for one of their patients and we didn't

[163] '1394' refers to the ATMP Regulation

> have one. No one else in London had one. The only one we could identify was in Utrecht. Now Utrecht then shipped it over. They would not be able to do that if they are manufacturing under a HES, they couldn't send it to the UK. So equally, if the lab in the UK was making their MSCs under the HES they couldn't receive MSCs from somewhere else. So you have to have a "specials" licence. And that means that the manufacturer has to have a "specials" licence.[164] And in academia at the moment there is only one academic that I am aware of in the UK that has an MHRA IMP manufacturing licence[165] and the "MHRA specials" licence. They just don't exist [...] so those are the sort of barriers that I have been around, and will be increasingly raised if we are not careful.
>
> **(LK, PI/Clinical Involvement/Founder of Start-up, 2009)**

LK describes a situation where the 'new regulation', specifically the HES, would have blocked the application of an ATMP, rather than facilitate it. His perspective is informed by personal communication and discussions on the implementation of the new regulation with various experts from Holland, who are interpreting it in a different way. He explains how cell transplantation therapies such as MSCs – that, so far, have been routinely transported from one country to another, based on need – will now, if classified under the HES, be prevented from being imported and exported.

As mentioned in the introduction to this chapter, once a product is classified as an ATMP, the procurement of the starting material and the subsequent storage of the product are regulated by the HTA (under the Tissues and Cells Directive), but the production is regulated by the MHRA and requires one or more of three licences depending on the intended use of the ATMP. The options available include: the Hospital Exemption Scheme (HES) manufacturing licence; the 'specials' manufacturing licence; and the manufacturing licence for Investigational Medicinal

[164] A 'specials' manufacturing licence allows the manufacture of ATMPs for treatment of patients with clinical need which cannot be addressed by any licensed medical product. In this case the product can be released for use by the quality control person of the lab.

[165] MA-IMP (Manufacturing Licence for Investigational Medicinal Products) – this licence is required if the applicant is planning to use the ATMP as part of a clinical trial. ATMPs produced under an IMP licence require a comprehensive 'product specification file' which details the manufacturing process, the quality-control assays associated with the manufacture, and a product definition against which each product can be accessed to determine whether it is fit for release (for infusion). The IMP licence allows the import and export of ATMPs. In addition, ATMPs that have been manufactured as IMPs can, upon completion of successful clinical trials, become a licensed medicinal product and can be commercialised.

Products (MA-IMP). All three licensing options also require full cGMP compliance (Lowdell, 2009).

Out of the three newly introduced licences, the hospital exemption scheme (HES) licence has been in the centre of a debate[166] since the draft version of the ATMP regulation with companies (SMEs) claiming that, because of the rule, they face 'unfair competition' from hospitals. According to the HES, hospitals will not be subject to the regulation where they prepare advanced therapies in-house, and where these therapies are developed 'on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient'.[167] In other words, these 'one-off' patient-specific treatments will be exempted from applying for the central EU marketing product Marketing Authorisation. Instead, the regulation stipulates that ATMPs 'manufactured under the HES must be authorised by the Member State' – that is the MHRA in the UK.

Although the HES rule appears to enjoy clinical acceptance, according to LK's narrative there is 'catch': ATMPs manufactured under the HES licence cannot be imported or exported. If a situation was to unfold like in the case described by LK, the turn of events would be ironic, if one considers the objective of the ATMP regulation which is to allow free movement of products around Europe, whilst guaranteeing an equally high level of safety for patients. As a last comment, LK implies that, increasingly, as researchers and agencies recognise the need for importing and exporting ATMPs, the value of the HES within the regulations will diminish substantially. In short, LK's example confirms the need for careful implementation of

[166] Industry stakeholders have raised concerns about HES and the subsequent creation of a two-tier system favouring hospitals and a need to 'level the playing field'. While products produced by private companies will be subjected to rigorous expert scientific evaluation, hospitals could manufacture the same type of product with much less evaluation. According to industry insiders the HES rule not only leads to a situation of unfair competition between private enterprises and hospitals, but it also poses risks in terms of product reliability and safety. On the other hand, clinicians argue that the HES will minimise the impact of the new ATMP regulations in hospitals, provide freedom of activity and promote innovation (Brévignon-Dodin & Singh, 2009). For example, according to Paul Hatton at the Centre for Biomaterials and Tissue Engineering (University of Sheffield School of Dentistry) the exemption offers an opportunity for hospitals to contribute to the development of commercial therapies. He states: 'I can see why industry might feel that hospitals might have an unfair advantage in the development of advanced therapies, but custom/named patient exemption for hospitals is not a new concept and the types of therapies developed in this way will, in the main, be different to those developed by industry' (Sheridan, 2006: 480).

[167] 'ATMP Guidance (20 April 2010)' document (the document includes guidance on the UK's arrangements under the Hospital Exemption Scheme (HES). Accessed on May 2010 at:
http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm

the 'new regulations' through 'trial and error'. The majority of interviewees suggested that 'application and practice' is the only way to test, refine and ultimately improve the regulation.

The importance of Member State 'interpretation' for successful harmonisation, underscored by bioentrepreneurs, is not new in the EU. Commenting on a report[168] about the effect of harmonisation on innovation in the European medical devices industry (published in 2000), Steg and Thumm (2001) note:

> It must be noted that although the basic prerequisites are in place today, the positive effects have not yet developed to their full potential. At present companies are still greatly influenced by the negative effect of transition. Further actions appear to be necessary so that a comprehensive harmonisation of the interpretation, practical application, and enforcement of the new institutional framework at the level of different member states and players can be achieved and that the expected positive effects of the new institutional framework can be realised fully.
> (Steg & Thumm, 2001: 430)

In short, according to Steg and Thumm, the successful harmonisation that will assist the innovation and commercialisation process is not enough in itself. After the establishment of universal and 'appropriate' rules and guidelines, innovators and companies have to endure a difficult transition period that appears to have negative effects. As the authors highlight, harmonisation needs to be followed by 'further actions' crucially supporting the interpretation, practical application and ultimately, the enforcement of the 'harmonised' guidelines/legislation. Only then will the positive effects of the harmonisation be 'realised fully'.

[168] Report compiled in April 2000 by VDI/VDE-IT (Teltow, Germany), Technopolis, (Brighton, UK) and the Institute for Prospective Studies (Seville, Spain) for the European Commission's Directorate General Enterprise.

Summary

To sum up, it is through use that regulations get revised and refined.[169] Regulators must therefore work together with bioentrepreneurs/developers to ensure that the new regulation in place is practicable. The bioentrepreneurs in my sample admit to feeling increasingly pressured because of the need to comply with ever-changing standards and protocols, and describe the impact of regulatory compliance on their time and energy, and subsequently on their careers. Although they all agree that harmonisation is critical for the growth of the field, the majority also believe that better guidance and support on behalf of the competent authorities would benefit the process immensely and hence help the small but innovation-intensive RM firms (like the ones they have founded). All interviewees feel that 'proper' interpretation of guidelines is as important as harmonisation itself, and a few describe facing interpretation-introduced hurdles after the new ATMP regulation became effective. However, they all seem to be aware that this is, once again, a transition period and that by the end of the EC full-implementation deadlines, most of the 'thorny' places in the EU regulatory landscape will have been smoothed out through regulator/ developer collaboration. For this kind of collaboration to be effective, though, authorities must ensure that they are advised by suitably qualified members. A few bioentrepreneurs have voiced concerns over an apparent shortage of people with expertise and experience in the emerging technologies, implying conflicts of interests and competition issues (possibly coming from relevant fields such as pharma or medical devices). According to bioentrepreneurs, these kinds of interactions would only further complicate an already complex and difficult task.

The Cells, the Process and the Models

As noted earlier, the word 'autologous' raises particular issues in the context of Translation. A key factor mentioned by many of the bioentrepreneurs interviewed for this study, and perceived to profoundly influence product regulation during Clinical Translation, is whether the cells are patient-specific (autologous) or universal (allogeneic). In autologous therapies stem cells are sourced from the patient, manipulated, and then returned to the patient. In contrast, in allogeneic therapies stem cells are harvested from a donor (or donors), manipulated, expanded and may be

[169] Interestingly, the process for US regulation for tissue-based products has been underway for almost 10 years.

stored in a tissue bank or as a stem cell line, in order to form the basis of 'off-the-shelf' products and treat a large number of recipients (patients). Both autologous and allogeneic products may be combined with manufactured biomaterials to form a 'combination' technology.

Below is a quote from an academic bioentrepreneur who is using autologous products (living skin equivalent) to treat ulcers and burns. LM gives her opinion on the different 'treatment' autologous and allogeneic cells receive from regulatory agencies.

> I would say that until recently the UK regulatory environment was one where you could hold a sensible dialogue and certainly with respect to getting autologous products to patients, entirely possible. Where I think the UK regulatory environment is so difficult is when you start to talk about allogeneic products.
> **(LM, PI/Founder of Spin-out, 2007)**

In LM's experience, investigators like herself can 'hold a sensible dialogue' as far as autologous products are concerned. This 'easy' and 'sensible' attitude shown by regulators, presumably originates from the fact that LM is using autologous products that have less rigorous requirements for testing[170] and on a small scale.

Yet, another interviewee's response seems to up-end the whole impression that autologous products are easier to regulate and thus more attractive to develop. Interestingly, he is a non-academic bioentrepreneur, founder and Chief Scientific Officer (CSO) of a RM start-up (corporate). He states:

> In [Company Name] we are developing both autologous and allogeneic products and the regulatory issues are somewhat different. The main issue with autologous [products and therapies] is the fact that you are growing cells from more than one patient at the same time in the same facility, so there is the theoretical risk that you could be infecting patient A with some virus that patient B has got. So process controls are critical to ensure that this cannot take place [...] With autologous, it's every day

[170] Autologous products are generally regarded as less risky, in terms of public health, compared to allogeneic products because the process only involves one patient, who is both the donor and recipient of the cells.

> is a new day. You don't know what's coming in. So not only have we got to protect ourselves, we've got to protect all the other patients from contaminating patients. So we assume everyone is contaminating. We don't wait to find out if they are. We just assume they are. [...] The concerns are more addressable with allogeneic products because it is standard to produce huge cell banks and test them extensively to ensure that they are virus free.
>
> **(NJ, PI/CSO/Founder of Start-up, 2007)**

In the quote above, NJ explains the different regulatory concerns that his company has to address during the production of autologous and allogeneic cells. According to NJ, managing the logistics of autologous therapies is challenging for his company as every patient effectively constitutes their own 'batch'. In view of the fact that the company's facilities are processing material (cells) from more than one patient, rigorous Good Manufacturing Practice (GMP) standards need to be in place, to ensure that patient samples are kept apart in the clean room in order to prevent cross-contamination. As NJ later explains, implementing and running a quality control system is more difficult if the process is autologous. Processes such as in-process-control, sterility assays, endotoxin, mycoplasma, viability and potency all come as standard requirements from a regulatory perspective. None of these are cheap and, if the product is autologous, they all need to be performed on a patient-by-patient basis. What this means is that both the manufacturing and the quality control process are extremely space- and labour-intensive. Overall, economies of scale and reductions of costs are difficult to implement in autologous production, with the overall consequence of having high (per patient) cost of goods. Allogeneic products, in contrast, seem to carry great benefits for his company's manufacturing and commercialisation strategy. Despite their requirement for cell expansion, allogeneic products are more amenable to automation, can be quality controlled en masse, and thus the costs of manufacturing are easier to recover.[171]

The two preceding statements illustrate different conceptions of the regulatory experience for the approval of Regenerative Medicine therapeutics. The former, reflects the conception of an academic-based bioentrepreneur with a relatively small

[171] For a comprehensive review of the advantages and disadvantages of autologous and allogeneic cells in Regenerative Medicine applications see (Mason & Dunnill, 2009).

academic team/spin-out seeking to take her product towards the clinic. In LM's case, it makes sense to go for autologous products as she is operating on a small (academic) scale and she feels she can hold a 'sensible dialogue' with regulators in terms of having them approved. Also, given the low (individual) risk of infection associated with autologous therapies, 'strict' manufacturing procedures are not critical in her case. The second account reflects a rather conventional corporate start-up view from the RM industry. In NJ's industrial setting, the high standards required by regulatory approval are 'easier' and more cost effective to achieve through the production of allogeneic products.

Two social science studies have made relevant findings, and each partly echoes my informant's perceptions. First, Faulkner et al. (2008) have made a similar finding regarding the relationship between the type of TE therapy to be developed and the type of organisation involved. The perceptions noted in their study are those of research and clinical scientists in the RM field. The authors write: 'larger companies tend to fund both kind of research activity [...] potential profitability of allogeneic is one primary motivation in the TE sector [...] the autologous, service-based model may be seen as commercially weak in the longer term, more suited to small scale activity by academics in partnership with clinicians and industry' (Faulkner, et al., 2008: 209). In short, there is the perception among their informants that the marketplace was structured along the lines of academic groups producing autologous therapies and commercial groups focussing on allogeneic, off-the-shelf products.

The second social science study to have partly similar findings is by sociologist Julie Kent and colleagues (2006) who, although they make no reference to the type of therapy under production (i.e. allogeneic or autologous), describe a two-culture perception regarding the setting of production (academic/industrial) and the strict management and control of the manufacturing processes. They write:

> There are two quite diverse characterisations of the production of tissue engineered products. One is that it is a relatively low tech activity, which can be carried out with minimal resources and in an uncontrolled environment. In contrast, the same activities are sometimes characterised as highly technical, specialised and requiring strict controls, risk

> management, safety standards and quality assurance procedures. We see what has become custom and practice, on the one hand in the social world of the clinic and tissue bank, and, on the other, in the regulated industrial setting [...] Manufacturers downplay any role of standards and protocols in the clinic and tissue bank while emphasising the 'cleaner' and more rigorous procedures embodied in manufacturing practices. Of course such a distinction is far from straightforward but it does point to a feature of the two cultures (Kent, et al., 2006: 8).

Kent et al. (2006) point to a 'two-culture' representation of producing Regenerative Medicine products. One representation involves the academic/clinic setting (like the one LM is operating) with 'minimal resources' and a relatively 'uncontrolled environment'. The other representation involves the industrial setting (like the one NJ is operating), where the standards and protocols appear to play a pivotal role (presumably to achieve the much desired 'reproducibility') and the manufacturing processes are 'rigorous' (to ensure safety and quality of products).

The following narrative by LK seems to nicely complement the previous accounts by LM and NJ, by being 'somewhere in the middle'. More specifically, although LK works on autologous stem cell therapies in the field of cancer Regenerative Medicine he is beginning to move his service from an academic small scale to a larger-scale operation. In the following extract he talks about issues that arise from the complexity of the cell therapy development process, and how they have an impact on the work of his company – especially now that they are looking to expand their service.

> Most of the products that I intend to make over the next ten years will always be focussed on a single donor, single patient. So they will be directed products. Now at the moment we are restricted in terms of the number of directed products we can make because the processes are complex. So, for example, my Technology and Strategy Award for the moment will be used to take a complex process that makes a patient-specific product and engineer that down to a less complex process. [This] still makes a patient-specific product, but [it] does it in a more streamlined fashion, so you can produce more. So that's a scale-up, but

> it's not industrial scale-up, as [in] single donor–multiple patients – like a chondrocyte product or "off-the-shelf" product. We are not ever going to go down the route of the "off-the-shelf" [product].
> **(LK, PI/Clinical Involvement/Founder of Start-up, 2009)**

As LK explains, his interest lies in simplifying the complex manufacturing process that he currently operates to a 'less complex' one that makes the same type and amount of product but 'in a more streamlined fashion'. This will enable his company to 'service' more patients, but still on a 'same donor–same recipient' (autologous) basis.[172] He mentions the translational award that he has secured in order to fund the project, and points out the difference between his approach and that of scaling-up allogeneic therapies, where the challenge is to expand the donor's cells to as large quantities as possible (in order to be able to service a large population with the same 'type' product).

LK's kind of translational work is, in a sense, at the centre of the Regenerative Medicine debate over the lack of a commercially viable business model and whether the (autologous) service-based model will ever be profitable. It is also directly related to the popular conceptualisation circulating in the cell therapies field that 'the product is the process'. This conceptualisation, which is based on the solid interdependency between a cell-based product and the process through which it has been developed and produced, has unique consequences for all parts of its development and commercialisation process. In other words, unlike pharmaceuticals and biologics, a cell-based product is in the 'making' from the time the cells are sourced up to the point of application to the patient. From harvesting conditions, culture conditions, manipulation (isolation, differentiation), scale-up/automation (expansion), storage, transportation, delivery/application to interaction with the host, are all key components. Careful selection and quality assurance of every component at every step is crucial to ensure the safety and effectiveness of the process and, ultimately, the product in the clinical setting.

In addition to their allogeneic/autologous concerns and how they affect the process of Translation from their perspective, a few interviewees brought up the issue of animal models in RM. Below, I present the views of bioentrepreneurs on the reliability of

[172] This approach is associated with autologous therapies, and is often referred to in some commentaries and scientific articles as 'scale-out' (as opposed to scale-up of allogeneic therapies).

animal models as a basis for RM clinical Translation, and their opinions on the 'changing order' of future early clinical human experimentation.

As the field of stem cell research and Regenerative Medicine is rapidly moving towards translation to the clinical setting, it is no surprise that it becomes dependent on animal hosts for assaying the safety and potential therapeutic efficacy in models of the disease. However, judging by the bioentrepreneurs accounts, their validity and hence usefulness in the case of Regenerative Medicine therapeutics is contentious.

The following quote is from a scientist working in the area of cancer stem cell research.

> And traditionally once [their use is] proven there are [antibodies] in animal models. But increasingly in Regenerative Medicine there is not a valid animal model and the EU has understood that.
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

LK's view is shared by principal investigator RG who cites animal models as one of the 'technical challenges' of translating cell-based products. According to RG, animal models cannot be of use in Regenerative Medicine because RM therapeutics are crucially dependent on the environment in which they end up.

> I would also point out another technical challenge which is particularly true of translating human cells. Which is – the animal models don't work. Because if you put some human cells into an animal, you have to immuno-suppress the animal. If you put them into a human you might not – depending on if you have done your work correctly – there are autologous cells. So you can't really test them under the same conditions. [...] The immuno-suppressants are very, very active molecules, we have done some work on this. The same is true for the patch things.[173] Animal models are now all wrong. You need something with the structure and size of the human heart. So you have to move to large animal models very quickly, which is difficult. So the scale is wrong for small animal

[173] Cardiac patches that are being developed by her team.

> models, and you've got all the immune challenges that are wrong for human cells. It is a bit like the monoclonal antibody story. You can't really test your actual product in an animal. You could test the concept, but you can't test the product under the same circumstances in an animal. **(RG, PI, 2009)**

RG mentions her own experience of trying to develop cell-based cardiac patches for the regeneration of the heart after cardiac disease. She explains how 'wrong' the animal models are in this case, both in term of 'context' and 'structure'. Immuno-suppressing the animal model in order to test the cells, 'de-natures' it in a way, as it creates a safe but at the same time 'unrealistic' context. The animal model, is also 'structurally wrong', as finding a model with a heart similar in size to a human heart becomes, logistically and ethically, more problematic. RG mentions the 'antibody story' which is discussed below in more detail by LK in his discussion about how regulatory agencies are starting to come to terms with the preclinical data and the 'animal model reality' in Regenerative Medicine product development.

> I mean one of the great things to come out of the C28 scandal up at Northwick Park was that all of the assays that the regulators wanted were done on that antibody. And I was one of three people that were asked by different regulatory authorities to comment on that trial, from different EU countries. All three of us, independently said: "The animal model doesn't test the safety of the antibody in any way, shape or form". And of course we had the disaster at Northwick Park. Now that has led the EU and the FDA to question their traditional acceptance of pharmaco-toxicology studies on biologics. And they are beginning to realise, and we have realised, that animal models are not always appropriate. Certainly in one of my trials, which is running in the UK at the moment and is about to open in the US, both the FDA [Food and Drug Administration, US] and the MHRA [Medicines and Healthcare Products Agency, UK] have accepted that the preclinical data is all basic laboratory data, there is no animal model. So it is straight to human, because there is no animal model for that particular product. And we are going to see a lot more of that. **(LK, PI/Clinical Involvement/Founder of Start-up, 2009)**

In his comments, LK is making reference to the events at the Parexel Clinical Pharmacology Unit (housed at the Northwick Park Hospital) in London, where six volunteers were left seriously ill after taking part in the first trial in humans of the drug TGN1412.[174] [175] LK mentions the adverse effects associated with the TGN1412 Phase-1 trial to highlight the fact that the predictive value of animal models is limited and that regulatory agencies will increasingly have to recognise that. He emphasises the fact that despite the use of a series of murine, nonhuman primate studies and even *ex-vivo* human cell assays, the immunological models used in TGN1412 preclinal testing were of insufficient predictive power to anticipate the serious adverse events in humans. Interestingly, the MHRA, has since said that an 'unpredicted biological action' and not the manufacture or administration of the drug was to blame for the adverse reactions seen (*BMJ*, 2006; 332: 1290, 3 June).

In LK's view, in biologics and cell therapies (as it is also the case with drug development programs), moving from preclinical animal testing to human clinical trials is a critical juncture. Hence, when extrapolating preclinical testing results to the clinical setting, it is important to recognise and appreciate both the relevant attributes and the limitations of a selected animal model of disease/injury. According to LK, events like the Northwick Park scandal have prompted regulatory agencies to 'question their traditional acceptance of pharmaco-toxicology studies on biologics' and realise that 'animal models are not always appropriate'. As cell therapies are becoming more common and are starting to be tested across the globe, regulatory, as well as scientific, principles for cell therapy development and approval of clinical trials require re-evaluation. The informant implied that the number of 'straight-to-human' trials will increase in the future and that regulators and other stakeholders will have to implement other modes of regulatory oversight, perhaps, in the absence of appropriate animal models, by the identification of surrogate markers that are more predictive of risk factors in human volunteers.

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[174] TGN1412 is a fully humanised monoclonal antibody designed to bind to CD28, a cell surface molecule on T cells which play a role in a variety of cell mediated immune reactions.

[175] On 13 March 2006, eight healthy volunteers were admitted to the Parexel Unit as the first of four cohorts in order to be administered with escalating doses of the drug. Within one hour of being given the TGN1412 intravenously, six of the participants started reporting increasingly severe manifestations of cytokine release syndrome and by midnight of that day, all six volunteers developed multi-organ failure and were admitted to the hospital's intensive care unit. The two out of the eight men who were given placebo showed no sign of illness (Suntharalingam et al., 2006). The drug was being developed for the treatment of autoimmune and inflammatory diseases and leukaemia by the German company TeGenero and the trial had been approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) and a local ethics committee (Nada & Somberg, 2007).

My findings on the views of bioentrepreneurs on animal models echo findings of other social science studies which also focus on aspects of the TR process. For example, Steven Wainwright, Clare Williams, Mike Michael, Bobbie Farsides and Alan Cribb (from King's College London) and Mike Michael (from Goldsmith's) (2006) in their study of biomedical scientists expectation in the field of stem cell research for diabetes report and examine similar concerns of their interviewees about the transfer of rigorous experimental studies in animals to clinical studies in humans. According to the authors, in the views of biomedical scientists a boundary is drawn between interviewees who support rigorous animal modelling and those who question whether animal studies will ever lead to similar and thus more clinically relevant studies with human cells. Wainwright and colleagues (2006) conclude that 'the tension between the relevance of "human studies" and the rigour of "animal experiments" colours expectations for future cell transplant therapies. Our scientists see the target of ES [embryonic stem cell]-driven cell therapies as something that may be unachievable, except in very specific and limited areas. In contrast, they see the prospects for significant scientific breakthroughs from stem cells in understanding basic cell and developmental biology as achievable' (Wainwright, et al., 2006: 2061).

The animal models controversy, although increasingly prominent, is not unique to the RM field (Pound et al., 2004).[176] In fact, human clinical trials are essential and mandatory because animal studies do not predict with sufficient certainty what would be the outcome in humans. Hackam and Redelmeier (2006) clinicians at the Department of Medicine, University of Toronto, set out to understand why animal experiments often fail to replicate when tested in rigorous human trials. In a review of animal studies (studies that were published in seven leading scientific journals of high impact), they found that only about a third of the highly cited animal research translated at the level of human randomised trials, and only one-tenth of the interventions were finally approved for use in patients. In another systematic review that was published in the *British Medical Journal* a year later, Perel and colleagues (2007)

[176] The authors of this paper include one sociologist (Pound, Department of Social Medicine, Bristol University) and three epidemiologists. According to the authors, the ideas in this paper have developed through the authors' involvement in conducting systematic reviews and clinical trials, in reviewing animal studies before trials, and in examining the reasons behind their failure to find successful treatments for stroke and brain injury. The authors question the validity of animal studies, highlight that many animal trials have been of poor methodological quality and call for systematic reviews to become routine in order to ensure the best use of existing animal data as well as improve the estimates of effect from animal experiments.

compared treatment effects and found that the therapeutic efficacy in animals does not always translate into the clinical domain .

The literature on the value of animal disease models in reliably informing human studies provides a number of reasons that may explain the disparity between the results of animal models and human clinical trials.[177] One of the most obvious reasons also mentioned by my informants is what scientists call the 'lack of external validity' or 'generalisability' of most animal models. In short, both terms refer to the fact that animal models to do not sufficiently reflect disease in humans simply because they do not adequately mimic human pathophysiology. From the age, size and lifespan of an animal to the workings of the immune system, all models present a partial-only match with the human organism. The 'lack of external validity' is of special significance in the case of Regenerative Medicine, where the 'product is the process'. In other words, given that in RM the 'process' refers to the whole journey of the cells from their sourcing to their application on/in the patient, it makes sense that the final step of the biological interaction between implant and host is crucial in determining the outcome. Therefore, according to the bioentrepreneurs, the only 'adequate' model to test RM cell-based therapeutics is humans themselves.

Summary

To summarise, there is evidence of a 'two cultures' mentality in the RM Translation field. The bioentrepreneurs in my sample that are based in academia and clinic show a preference for small-scale autologous therapies. In contrast, bioentrepreneurs who are involved in start-up companies (considered as an industrial setting) are 'favouring' the production of universal (allogeneic) products. Interestingly though, each group perceives their choice as the 'easier' to manage in terms of regulatory compliance and thus approval. The issue of animal models has also surfaced in the narratives and appears to be of special significance to my informants. In fact, a few of them, having already completed the 'necessary' animal studies, have now moved into the early clinical experimentation arena and can talk comparatively about the performance of their product in both animal models and humans. Overall, the general perception (as confirmed by informants from at least four different disease areas) is that animal

[177] For a discussion see (Van der Worp et al., 2010).

models are not a reliable model for most RM therapies and more support and guidance must be directed toward encouraging investigators to pursue early human experimentation (i.e. FIH) and Phase I clinical trials.

Chapter Conclusion

In this chapter I have explored the views of 14 UK bioentrepreneurs in relation to regulation during Translation of Regenerative Medicine therapeutics (cell- and tissue-based). I have used the concepts of regulation, uncertainty, innovation, harmonisation, interpretation and compliance to develop this analysis.

As a first finding, I identified three sources of uncertainty for RM UK bioentrepreneurs: the classification of their products; the regulatory route during development; and finally, the regulatory authority overseeing each part of the development process. How do bioentrepreneurs overcome this product classification uncertainty? What roles do the relevant regulatory agencies such as HFEA, MHRA and HTA play in the RM Translation process? I conclude the following:

Before the drafting and the subsequent introduction of the ATMP regulation, bioentrepreneurs working on cell-based and tissue-engineered products in the UK had to interact with regulators on a product-by-product basis. The result of the interaction would be an agreement over the characteristics of the product (classification) and, in the frequent case of not being able to categorise the product under the existing regulations, an agreement on the conditions and the methods/protocols under which the therapies ought to be produced in order to secure future regulatory approval. The overall impression from the respondents' narratives is that uncertainty, combined with a pressure to comply with an influx of guidelines (often without adequate guidance and infrastructure to support it), means that regulation is not a means to 'control' innovation, but rather another hurdle in Translation that has to be overcome.

In terms of the uncertainty surrounding the regulatory agencies, it seems to be more prevalent in the accounts of the interviews I conducted in 2007 compared to those of the 2009 informants. In late 2009, the issue of the HTA-HFEA that surfaced in many of the 2007 interviews had already been resolved (by the merger not going ahead) and

the ATMP regulation was already well into the implementation phase. The introduction of the ATMP regulation meant not only clear and comprehensive definitions for the classification of the novel RM technologies but, more importantly, a clearly defined regulatory route for each type of product comprising the distinct jurisdiction of the HTA, the MHRA and the European Medicines Agency (EMA).

The second finding is that RM bioentrepreneurs present themselves as active shapers of regulations. According to their testimonies, through early and close engagement with the regulatory authorities, they have the opportunity to raise their concerns, negotiate standards, outcomes and timelines, and most importantly, 'link' the regulators with the realities of science and product development as a means to 'ground' their expectations and hence assist them in producing stringent but also practical regulatory guidelines. This is consistent with bioentrepreneurs' perception of an ideal mode of regulation, accurately described by a term several respondents used – 'light-touch' regulation. The use of this term endorses a continuous collaboration with the regulators who will advise and gradually guide (and apparently be guided by) the developers through a consistent yet flexible system.

In so far as bioentrepreneurs' (developers) manufacturing input is sought and included in the drawing-up of regulatory guidelines (and consequently in policy decisions), the evidence for a 'participative ethos' (to borrow the Salter and Jones 2002 concept) is strong. This strong direct involvement that is revealed in respondents' accounts also agrees with cases discussed by Kent and Faulkner (2002) and Kent (2003) where a consumer movement grew up around breast implant use which contributed to calls for revision of the Medical Devices Directive (MDD) and provided some evidence of a more 'user-oriented' approach to regulation. Given the nascent state of the RegenMed industry and the limited availability of research, development and manufacturing expertise, as well as necessary infrastructure (for example automation, manufacturing equipment), it is not surprising that the feedback of RM bioentrepreneurs in the forefront of cell therapy production is considered important, allowing them to display a form of 'active (bio)entrepreneurship' similar to the what Abraham and Lewis have called 'active citizenship' (Abraham & Lewis, 2002).

Also, from a policy perspective, this second finding raises a number of questions regarding the extent to which emerging RM regulatory policy is shaped by bioentrepreneurs in the UK. At the moment the bioentrepreneurs' input and the 'co-shaping' process appear to have an 'informal' character, but perhaps in the light of future research, a more 'formal' part could be established. This part would benefit from the multifaceted role of the bioentrepreneur and his/her participation in, and coordination of, all aspects of the Translation process.

A third finding is that according to the type of cells (autologous or allogeneic) used in the development of the product, bioentrepreneurs seem to anticipate an 'easy' or 'difficult' regulatory approval. However, this anticipation is not straightforward, as it appears to depend on whether the bioentrepreneur is operating from an academic or industrial setting. Academia-based respondents perceive the autologous regulatory approval as 'requiring comparatively lower production standards' and hence is more 'manageable', while informants who founded corporate start-ups and manufacture products on a comparatively larger scale, think that the 'high' safety and quality standards necessary in an industrial setting for regulatory approval are easier to address in the case of allogeneic products. This point compares intriguingly with recent findings reported by Kent et al. (2006), indicating that there is a two-culture perception associated with the setting of production (academic/industrial) and the management and control of the manufacturing processes.

A fourth and final finding of this chapter is that many respondents have openly questioned the value of animal models in Regenerative Medicine Translational Research. The development, use and interpretation of data from preclinical models remain a complex challenge and an imperfect science, and available animal models are generally considered deficient (according to the scientific literature) in accurately predicting the clinical performance of a product in humans. My findings however lead me to suggest that this 'liability' in clinical Translation is perceived by bioentrepreneurs to be increasingly worse in RM clinical Translation, because of the special dependency between the product, the process, and the final therapeutic outcome. In fact, several respondents instead of advocating 'a need for innovation in model system', suggest that the only way to really advance the Regenerative Medicine field is to direct clinical experimentation to human subjects, as this is the optimal way to test and refine the

therapies. However, it should be noted that the sample of interviewees, as chosen from the UK bioentrepreneur community, is in a way narrowly focussed in terms of disease areas and types of product. Thus, it is difficult to generalise beyond the respondent's research areas in deciding whether this 'dissatisfaction' with the animal models is true for other disease areas at the forefront of RM science.

Chapter 6

The Art of Collaboration

Introduction

Guided by Hollander's description of the first in the world stem cell transplantation and the powerful messages that have been unveiled regarding successful translational outcomes, Chapters 4 and 5 have explored the views of UK bioentrepreneurs with regard to the themes of funding and regulation of Regenerative Medicine Translation. This chapter will examine the last of the 'emerging' key elements credited for breakthrough outcomes and necessary to realise the potential of Regenerative Medicine: cross-disciplinary collaboration.

In the context of Claudia Castillo's transplantation, cross-disciplinary collaboration meant efficient integration of expertise among the different teams from different countries, in order to successfully treat the patient using novel technology. This type of cross-disciplinarity requires collaboration among 'actors' from various science disciplines such as stem cell biologists, bioengineers and clinicians in order to translate the technology efficiently and successfully. I call this type of cross-disciplinarity 'scientific cross-disciplinarity'. In general, collaborations that are based on 'scientific cross-disciplinarity' are effective in achieving high-impact developments on national and international scales because of their speed in producing innovative high-quality data and combining them, at a level no single discipline or team could have done by itself. The crucial importance of this type of collaboration, which requires a considerable degree of carefully timed, large-scale recombinant expertise, is a factor identified by participants in this study as critical to successful clinical Translation in the context of RM.

Despite the importance of collaborative Translational Research in accelerating Regenerative Medicine research benefits, up until recently there were no official funding streams in the UK to support such endeavours. Similarly, at the international level, there have been relatively few funding bodies prepared to support international

collaborations between multiple and widely dispersed public and private teams; for example, the European Framework Programme has launched a few such collaborative initiatives and in the US the National Institutes of Health (NIH). Unfortunately, in addition to being limited in number, these initiatives have been fiercely competitive and not specifically targeted to provide the support necessary for Translational Research (and, presumably, even fewer funding opportunities available specifically for Regenerative Medicine (RM) Translational Research).

In fact, it is only in 2008 that the spirit of international collaborations in Regenerative Medicine research and Translation has begun to take hold, as nations realised they have much to gain by working together. As a result, cross-border research relationships have begun to be forged with participating nations aiming to connect to the global supply of ideas, contribute, adopt and adapt to important innovations. For example, a pioneer in setting up international collaboration agreements to co-fund stem cell research is the California Institute for Regenerative Medicine (CIRM), which in 2008 began to sign agreements with various US states and nations across the world.[178] The aim of the CIRM strategy is to accelerate the path from research bench to the clinic by enabling scientists from different nations to jointly submit research team applications and hence foster global academic–industry collaborations that are, according to CIRM strategists including their President, Alan Trounson, 'structured in a manner that is more focussed than these relationships have been in the past' (Trounson et al., 2010: 513). In the context of such agreements, CIRM awarded 14 Disease Team Awards (involving some level of academic–industry partnership) in October 2009 to the average value of $16 million each. The aim for these 'disease teams' is to achieve the completion of an Investigational New Drug (IND) application within four years and begin a clinical trial.

The objectives of the CIRM collaborative awards confirm that a new set of initiatives to boost international collaborations extending beyond what Claudia's case has achieved is now well under way. While Claudia's case was a 'one-off' success which

[178] Nations who have signed such agreements with CIRM include Australia (State of Victoria), Canada (through the Canadian Cancer Stem Cell Consortium (CCSC), the Spanish Ministry of Science and Innovation, the German Ministry of Education and Research, the Chinese Ministry of Science and Technology, the Japanese Science and Technology (JST) Organisation, the US state of Maryland and the New York Stem Cell Foundation (Sornberger, 2009). Finally, in the UK, the Medical Research Council (MRC) has also signed a collaborative agreement with the CIRM, similar to the Canadian deal. For more details on the California-UK collaborative opportunity in translational stem cell research see the following: http://www.mrc.ac.uk/Fundingopportunities/Calls/MRC_CIRM/MRC005564.

involved only scientific and clinical teams and sought the treatment of a single patient, the CIRM initiative has also enlisted the support of the industry, ethicists, government, and patient groups in order to bring therapies to the market – that is, to commercially translate them. This in turn suggests that in the case of commercial Translation, the need for successful integration of knowledge domains extends further than just the scientific expertise often involved in Regenerative Medicine basic research, to domains such as regulation and business. This type of cross-disciplinarity, which I call 'commercial' cross-disciplinarity, relies upon successful integration of scientific, clinical and subsequently business expertise, and is necessary for commercially exploiting a novel regenerative technology. I further suggest below that there is a need for 'scientific' and 'commercial' cross-disciplinarity to emerge at distinct time-points during the process of Translation, while the former (scientific cross-disciplinarity) still appears to be a prerequisite for the latter (commercial cross-disciplinarity).

Identifying a successful model for commercial cross-disciplinarity, and successful Translation, however, is different from actually achieving it. In the sections that follow, I explore a number of issues related to collaboration that emerged out of the bioentrepreneurs' accounts of Translation collected for this study. These 'collaboration factors' include: the role(s) of the bioentrepreneurs in the absence of adequate support for Translation; the parts played by the university and the Technology Transfer Office and their impact on Translation partnerships and collaborations; the value derived from the 'evolving' composition of the entrepreneurial team; and finally, the unique contribution of clinical input in achieving timely and relevant RM therapy development and production.

More specifically, in the next (second) section, I discuss the perception of the bioentrepreneurs that there is a dearth of people appropriately trained and qualified to perform 'knowledge broker' duties, despite the desperate need identified by various stakeholders in the field for support of this kind. I also provide evidence that in the absence of 'official' Research Translators, 'knowledge and research brokering' activity must be performed by bioentrepreneurs themselves, almost always in a 'trial-and-error' fashion. In other words, bioentrepreneurs must assume the roles of the 'Knowledge Translator' and the 'Boundary-Crosser' in order to 'sail' the company 'through a sea of translational challenges'. In the meantime, these nascent entrepreneurs are not only

'forced' to acquire new expertise (for example business, regulatory, IP, market awareness) but they also have to re-direct resources, energy and time away from their 'normal' activities (such as teaching, basic or clinical research) in order to 'fill the shoes' of the (non-existant) Translators. Although most of the time this role is taken on voluntarily, I present a range of views regarding the 'new-found' role and various levels of commitment to serving it. In the third section, I explore the role of the university and the Technology Transfer Offices as it unfolds though the interviewees' narratives, shedding light on the murky area of technology transfer activities, and their effects on translational collaborations in the Regenerative Medicine field. In the fourth section, I argue that – in the absence of adequate and robust funding for Translation, well-established, long-term national and/or international collaborations, and well-defined regulatory requirements (as seen in Chapter 5) – it is essential to integrate sufficiently diverse and innovative expertise in the 'entrepreneurial team' to address the challenges of the Translation process (and its missing staff). In the fifth section, I delve into the one kind of collaboration that has emerged as the most decisive in the process of RM Translation – the collaboration between the bioentrepreneurs/developers and the clinical community. Drawing from my data, I identify three elements/conditions that need to converge in order for RM Translation to successfully occur and use them to construct a 'braided translational model'. In the final section, I discuss my findings, draw my conclusions and say how this research contributes to previous work.

Bioentrepreneurs as 'Research Translators': A Layer Missing?

In 2007, the Medical Research Council launched a small Translational Research (TR) pilot scheme.[179] The scheme involved the dissemination of a small number of research funds through institutions in the UK and appointed three Translational Research facilitators. Their job was to ease the exploitation of basic research findings into health-related applications that would one day provide tangible benefits. One of the

[179] The pilot scheme was designed to run along massively funded, highly acclaimed centres funded by the National Institutes for Health Research (NIHR) and was planned to be critically evaluated after two years. Nowadays, according to the MRC website a new cadre of 'research translators' exists, 'who have the skills and expertise to help scientists exploit their research findings'. The role of these translators is to facilitate knowledge transfer across all stages of the research pipeline and in areas where the potential for commercial exploitation is not apparent. According to the MRC, 'they will take a proactive approach seeking out ideas for further translation and brokering links with other researchers, industry and healthcare organisations. They will work at all levels of the translational process from basic research to policy, practice or healthcare delivery'.
(http://www.mrc.ac.uk/Ourresearch/Industry/index.htm). (Accessed May 2010).

three 'Research Translators' was Julie Lotharius who was based at Kings College London.

In a statement she contributed to a Nature network forum in June 2008, Lotharius identifies one of the key factors mentioned by many of the bioentrepreneurs interviewed for this study, namely that of defining what 'Translation' is, exactly. This difficulty – paradoxically of translating Translation – underscores a fundamental confusion among investigators (as described and discussed in Chapter 4) and indeed among sponsors of Translational Research about what makes Translation *translational.* In the following statement, Lotharius highlights the need for more 'Knowledge Broker' positions like hers, in order for Translation to get the critical support that it needs for prompt and successful transfer of research breakthroughs to the clinical setting. In her statement, Lotharius asks why more baseline support is not available to provide, in effect, a new kind of *translational infrastructure*:

> I do not exaggerate when I say 90% of my applicants still ask me what Translational Research is, and giving them a one-line explanation is just not possible. Translational Research is a continuum, a fuzzy transition from basic research to proof-of-concept trials in man, to clinical application, to routine health practice. How do we expect people to do something that they don't understand? So why not invest a little more of the £1.7 billion earmarked for Translational Research (TR) in the UK for people like me, willing to work on the sidelines, dealing with scientists on a day-to-day basis, reading applications, providing feedback, helping them find resources no one at the university seems to have time to help them find, searching funding databases, establishing industry links, providing intellectual property advice, and sometimes just a few words of encouragement...or maybe the directors can do that.
>
> **(Julie Lotharius, June 2008)**

However, additional infrastructure alone is also not enough – especially since it remains unclear to many in the translational sector what exactly it involves (Lotharius points out the fact that the majority of the investigators (biomedical and clinical) who are pursuing 'translational' grants are not even certain themselves of what exactly

Translational Research actually is). She explains how she spends most of her time telling researchers that what they are proposing to do 'is not really translational' simply 'because the application includes a few buzzwords such as "disease prevention", "risk" and "biomarkers"'. Lotharius appeals for the creation of more positions like hers that have the task of helping basic and clinical investigators translate their findings. According to her description of the role, Research Translators facilitate Translation through helping investigators to integrate various components of the process such as funding guidance, IP advice, and providing networking help to establish university–industry collaborations. All of these tasks, although critical and decisive for a successful outcome, clearly require special training and expertise and they can be far too time consuming to be performed by principal investigators themselves in addition to their busy research and/or clinical schedule.

To highlight the challenging nature of her task, which involves having to give face-to-face feedback to the 'rejected' researchers, Lotharius explains how 'sometimes just a few words of encouragement' could also prove useful. Her ironic comment referring to the Directors' 'words of encouragement', reveals a deeply held belief among many of the stakeholders I have spoken to (including many of my interviewees), that the process of Translation is perhaps better managed by people who are personally involved in the process and have a 'sense of it'. Directors and generally people in high administrative/managerial posts are considered by principal investigators to be disengaged from translational activity and thus ill-suited to give advice and allocate money (which they often do).

However, it is not only a new translational infrastructure that is needed, according to Lotharius: it is also a new translational *culture*. In addition to drawing attention to the poor understanding of the Translation concept by many PIs, and the failure of public funders to appoint proper and ample 'facilitators' to implement this concept in practical terms, Lotharius criticises the way the translational system is currently *conceptualised* by commenting on a recent report in *Nature Reviews Drug Discovery* praising large clinical translation networks. The article,[180] entitled 'Building the bridge from bench to bedside' (2008) reports on and praises the creation of large networks for clinical trials, the erection of large clinical centres and the increasing number of clinical

[180] Adams, J. U. 2008 'Building the bridge from bench to bedside', *Nature Reviews Drug Discovery* 7(6): 463-464.

scientist posts being opened in the UK. In response to this 'mis-directed' investment, Lotharius writes: 'while indeed very laudable, this is Translational Research (TR) at the very end of the spectrum, where millions of pounds have already been invested and are currently being overseen and locally disseminated by a select group of people in government and academia, mostly directors of this and that and the other. What we must not forget, however is that Translational Research involves a change in research culture starting form the bottom up, and re-education of scientists working at the bench about what bench to bedside really is'. In short, Lotharius advocates a shift in the focus of the translational system towards a more thoroughly integrated conceptual model of what Translation actually involves. She clearly suggests that such a shift would be better achieved by refraining from committing large investments in generic infrastructure, and by carefully directing much smaller investments to change the base level culture of biomedical scientists and clinical investigators, including their 'education' on the real meaning of Translational Research.

In the rest of this section, I explore how bioentrepreneurs perceive this lack of guidance and support identified by Lotharius who has not only been a part of the 'system', but as one of the only three MRC 'Knowledge Brokers' she is able to reveal a unique 'insider's' perspective on the state of UK Translational Research. Bioentrepreneurs, on the other hand, can be considered to be on the 'outside' of the system, though still having a unique perspective of their own, as determined by their multifaceted role.

Lotharius' call for more 'Research Translators' has been matched by many respondents in the sample who acknowledge that individuals with these diverse and integrating 'entrepreneurial' skills, although 'highly essential', are in short supply in the Regenerative Medicine field. As a consequence, several informants described the many challenges and hurdles they faced before reaching the stage in the Translation process where they are now (some with licensed products and others with established companies and/or products in the pipeline, clinic or market). LM, herself a founder and principal investigator, explains how she 'wished' there were more 'entrepreneurially skilled' people to help her with the process of clinical and commercial Translation.

> If I had three wishes, my first one would be that the UK had got more people with an entrepreneurial interest in doing this. Not just a commercial interest. Now when you get money from a venture capital firm their interest is primarily commercial. What I really wish is that the UK had a bigger number of people who are really interested in working alongside the scientists to find the best funding route. So that the people who have the experience of having done that, work with the academics.
> **(LM, PI/Founder of Spin-out, 2007)**

Branding the involvement of more 'Research Translators' as her first wish, bears evidence of the difficulties LM faced and the importance she assigns to this type of translational expertise and the support it could provide to budding bioentrepreneurs. It is also interesting how LM distinguishes 'entrepreneurial interest' from 'just a commercial interest' which, she claims, is expressed by venture capitalists and generally commercial sponsors. Her preference towards 'entrepreneurial interest' implies that the expertise should ideally come from governmental sources; for example, from research councils like the MRC who are distributing translational grants, or perhaps they could be recruited by the universities themselves. Commercially sourced translational expertise is, presumably, perceived by LM as more profit-oriented, a feature that could potentially clash with the priorities of the principal investigators themselves.

This difference in culture, based on a more- and a less profit-driven Translation has also been part of bioentrepreneurs' narratives on the role of the Technology Transfer Office (TTO) executives. TTO executives are a recently added force in UK Universities and have various responsibilities including alerting scientists on research commercialisation opportunities and providing advice and guidance on intellectual property (IP) issues. Many interviewees mentioned TTOs (and their representing universities) as 'frustratingly' profit-driven and have blamed them for various translational obstacles including stifling of external collaborations (e.g. with industry, other universities, etc.)

In LM's view, experience is also very critical for Translational activities and she emphasises that the 'posts' should be assigned to 'people who have the experience of having done that before'. It is worth noting here that when Julie Lotharius was

appointed by the MRC as a pilot 'Research Translator' she had five years experience in the pharmaceutical industry translating newly identified and validated disease targets into clinical development. In Lotharius' own words, she had 'knowledge few people in academia would generally come across'.

LM continues by describing her efforts to create the spin-out and thus establish a commercialisation route for her Regenerative Medicine research. Below, she explains how a fellow RM company founder held a meeting[181] at his University in 2007 and invited many UK bioentrepreneurs so they could all discuss their experiences and learn from each other.

> A colleague of mine, Professor [Name], held a meeting on spin-outs and technology transfer earlier this year and, at the end of it, he invited people who had spin-outs to come and talk to say what was their experience, etc. And many of us, who were academic founders of companies, we all said that we felt we had reinvented the wheel in starting the spin-out company. That we had made mistakes, that they were obvious in hindsight, and that we just didn't have the skill set to make a good job of this. I am not saying that we failed. I think we all got there, but we were all aware how clumsy it was. And what I would say is that the academics that are doing the spin-outs usually do have a very good sense of where they have expertise, know-how. And I do not think that we are being arrogant in saying "oh the business bit is easy"; I don't think we are saying that. We are saying "we wish we had help here". So if we had more entrepreneurs who are really interested in working in the sector in the UK, who can work alongside the academics with the idea that they wish to commercialise, I think things would go much better. I think it's a whole layer of people we are largely missing.
>
> **(LM, PI/Founder of Spin-out, 2007)**

LM's account provides an insight into how the bioentrepreneurs' experience Translation, and how they share this 'lived experience' with each other. LM uses the

[181] I was very intrigued to learn about this meeting which unfortunately had just taken place before my interview with LM. No doubt it would have been a very enriching experience for me too, to actually attend and observe how 'lessons learned' are communicated among bioentrepreneurs.

analogy of 'reinventing the wheel' to describe how she and her colleagues felt when they embarked on the creation of their spin-outs. She admits that everyone has made mistakes and that the whole 'spinning out' process has been, in fact, 'clumsy', but that she doesn't feel like she and the others have 'failed'. In her opinion, it is clear that the novice bioentrepreneurs simply did not have the 'skill set' to 'make a good job of this'. LM also believes that people in her position are very aware of their 'strengths' and 'weaknesses' and are not overambitious with their roles and goals. In a way, she confirms the impression that I have from talking to bioentrepreneurs that they, in a sense, 'went with the stream'. In other words, upon identifying a clinical or commercial opportunity in their research and with the 'encouragement' of the university's administrators, they decided to pursue it. In the absence of both internal and external appropriate help and guidance though, it seems that nascent bioentrepreneurs have been improvising, each drawing their own 'clumsy' but 'edifying' journey. LM admits that they 'needed help' and had they had been offered some, she believes 'things would have gone much better'. So she calls for this 'layer of people' that she says is missing. In short, she calls for people with the interest, willingness and experience to work alongside principal investigators like her, to facilitate and speed up Translation of research findings to the market.

Yet in the absence of this 'layer of people', PIs-turned-bioentrepreneurs that have already gone through some stage of Translation, and perhaps even succeeded in creating a company, perceive the process to be challenging and time consuming. In principle, academic entrepreneurs may bring a strong commitment to the technology in the face of hurdles and setbacks that confront the process of Translation and commercialisation. Their involvement may bring scope for greater 'technical capacity' together with potential benefits arising from a continuing relationship with the technology source such as cross-licensing (Radosevich, 1995). On the downside, novice bioentrepreneurs often lack the business knowledge and experience necessary to initiate the 'entrepreneurial activity'. In fact, universities have been found to be more successful when the entrepreneurs have experience of transferring products to the market. Furthermore, academic-based entrepreneurs (which dominate my sample), may have the tendency to focus on the technical aspects of the innovation to the detriment of the business aspects (Radosevich, 1995, 2009).

Thus it is no surprise that, when discussing the level of involvement and commitment, my interviewees expressed a wide range of ambivalent views and feelings toward the challenges of Translation. In theory, all respondents' accounts advocate the notion of Translation, but after a closer look at the various narratives, the question about degree of involvement and dedication to the various phases of the Translation process is raised. In the following section I provide examples of the 'mixed feelings' and consequently mixed attitudes (of my informants) toward translational challenges. I have labelled the respondents accordingly and positioned them on a scale ranging from the 'enthusiast', 'eager', 'keen', to the 'uninterested' or 'dismissive' RM bioentrepreneur.

(Keen)

'Keen' bioentrepreneurs are well aware of the benefits of Translation and are receptive to the advice of universities and the TTOs. Upon recognising a commercial opportunity in their research they very keen to explore it further, although they are also eager to emphasise that the commercialisation objective is not 'driving their research agenda'.

Indeed, most of the respondents said they were very interested in getting involved in the technology transfer and commercialisation route and admitted to making an effort to acquire 'additional skills' in order to engage with clinicians and industry. QN sums up the view of most interviewees in relation to commercial Translation (through licensing and/or spinning-out a firm):

> I think if the opportunity arises we are very, very keen to harness that potential, but it is not our sole driver.
> **(QN, PI/Founder of Spin-out, 2009)**

(Reluctant or Accidental)

'Reluctant' or 'accidental' bioentrepreneurs will recognise the opportunity, but it is highly unlikely that they will pursue it without the extra help and advice of the university. Frequently lacking the business expertise to induce commercial Translation on their own, reluctant bioentrepreneurs display a preference towards the 'scientific'

and 'technical' part of the innovation and seem more comfortable in the knowledge that the business part is being 'taken care of' by business professionals.

Indeed, a few bioentrepreneurs admitted to being less enthusiastic about entering the product development and commercialisation process and stated that they would have preferred to keep a focus on the 'science-side of things'. In short, although these informants too were interested in seeing their research being translated and willing to facilitate, they expressed 'mild dysphoria' about having to become involved with the 'operationalisation', in a sense, of the Translation process. One such scientist and founder states:

> It depends how much you want to jump into the company as well. [Name of co-founder] and I, although we founded the company, we remain at the science part. For the moment anyway. We might get more involved if [Company] gets properly funded. At the moment it is at a difficult phase...although we've been going for years.
> **(GL, PI/Clinical Involvement/Founder of Spin-out, 2007)**

GL could be described as a reluctant or accidental bioentrepreneur. He admits that, along with his co-founder, they prefer to remain focussed at the 'science part'. His statement suggests that the availability and nature of external funding his company has so far, plays a critical role in his involvement with the commercialisation activities. Perhaps this could also be seen as a conundrum: if they are properly funded, they will consider becoming more involved with their company and hence with the Translation of their research. But the possibility of reaching that extra financial support is, presumably, directly related to the effort they put in fundraising and thus their level of involvement with the company beyond what they call the 'scientific part'.

Indeed, the commitment of the principal investigator/inventor may be particularly important in dealing with the uncertainty surrounding the Regenerative Medicine technology in its early stage. Normally, in a pure or orthodox spin-out (Nicolaou & Birley, 2003) the academic becomes highly committed to the development of the venture. However as seen in the case of GL and his co-founder they may not be the best candidate or they may not be interested in assuming the role of the commercial

Translation champion (instead focussing on clinical Translation or their other 'core' academic activities).

(Eager)

'Eager' or 'enthusiastic' entrepreneurs are actively involved with the company and also seek to interact with 'entities' outside their academic environment such as business expertise, regulatory professionals, industry and funders. Bioentrepreneur enthusiasts embrace their role more than any other category, seek to learn the 'language' of other stakeholders with the aim of interacting more efficiently, and seem to enjoy actively pursuing all avenues of the Translation process. Their perception of the Translation process is characteristically informed by the broader social and economic benefits of research commercialisation, as opposed to simply following the guidance of the university administrators.

So a few bioentrepreneurs were clearly more eager to be involved with the commercial Translation of their findings and the creation of a company:

> So there was seed-corn available for spin-out companies and my colleague Professor [Name] was very keen to have the experience of developing a spin-out.
> **(LM, PI/Founder of Spin-out, 2007)**

(Enthusiast)

RB is what I would call a bioentrepreneur 'enthusiast'. Below, he describes how he enjoys working at the interface between academia and industry and highlights the need for and importance of people who are able to cross disciplines, especially in a field like Regenerative Medicine. He notes:

> It hasn't been easy getting to this point and it will not be easy getting to the next point at all. It is high risk, it is very challenging, from my personal point of view, I am learning an awful lot. I am happy in doing it because I actually think you need individuals who can cross the disciplines. And, actually, I get most out of working at the interface between the three disciplines [biology, chemistry and engineering]. It is

> one of the reasons why I think the technology we have developed has been very successful. We've been working at the interface between biology, chemistry and engineering, and I have been working at the interface between academia and industry. That is very challenging but it's also very exciting [...] I am very lucky working with some very good people. For me, the challenge of getting out of the laboratory, something that we have developed on the bench, into the real world – that is a real success. To see one of our products, which we have developed, being used by others in the field, and is helping them do their research is personally inspiring. But it is also great for the economy and job creation, business development and so on. So many positive things really.
>
> **(RB, PI/Founder of Spin-out, 2007)**

RB acknowledges that it has not been an easy 'journey', from 2002 when his company was first incorporated to the day of the interview in 2007, when it was fairly well established. As RB explained earlier, the initial basic research behind the firm was supported by research council grants and then a Department of Trade and Industry (DTI) Smart grant was awarded to further exemplify the use of the technology. RB spent a couple of years setting up the spin-out, during which relevant IP was filed by the university and licensed to the company, and access to university facilities was arranged (at commercial rates). After the first couple of years however, in 2004, a reassessment of the company's market offering was performed that resulted in the introduction of new R&D. The reasons that prompted the reassessment, as RB clarified, included: insecure IP (given the European position on stem cell patents); lack of defined product; market potential for the product was difficult to identify and not clearly defined. Consequently, the risk for investors was seen to be high. In contrast, the newly introduced R&D was considered to have clearly defined commercial outputs, a demonstrated demand for both technology and products and thus easily defined markets. All these, according to RB, meant that he was more likely to secure favourable investment propositions.

The years of transition from a commercially 'naive' spin-out to an established firm with significant financial offers and 'deals under consideration', seem to have been educational for RB. Although he finds the Translation (through transition) process

risky and challenging, he emphasises the fact that he is 'learning an awful lot'. He is definitely one of the interviewees to relish the 'bioentrepreneur' role and to appreciate its 'boundary-crossing' features. In fact, it is to the cross-disciplinary work between the various research and business teams that he attributes the success of both the technology and the company. He refers to the contribution of three disciplines – stem cell biology, chemistry, engineering – as responsible for the innovative and competitive product portfolio and then he credits his own work between academia and industry for securing access to expertise and, even more importantly, to revenue streams and prospects of early licensing deals. RB describes the work as 'exciting' and himself as 'lucky' to be able to work with a diverse group of people and succeed in transferring the product from the 'bench' to the 'real world'. The broader implications of Translation on the local (and wider) economy are also very important to him.[182]

It is clear that RB recognises the importance of both 'scientific' and 'commercial' cross-disciplinarity and he is well versed on the approach he needs to follow to achieve it. He, like LM and the colleagues that attended the spin-out workshop, thinks it is also very important to communicate to others the 'lessons learned' from the cross-collaboration and Translation experience. Going over a leaflet he gave me during the interview – it is actually a print-out of slides from a presentation he had just given (at a conference) on the 'Issues facing a spin-out stem cell company' – I read:

> *Our Aims*:
>
> (a) To create innovative methods to enhance the differentiation and function of cultured cells and to improve the accuracy and representation of assays.
>
> (b) To develop technologies which are versatile and have multiple applications.
>
> *Our Approach*: to form *multidisciplinary collaborations* that introduce new skills and expertise from different fields which bring innovations and new ways to solve problems [emphasis added]

The combination of 'Aims' and 'Approach' is a testament to RB's belief that cross-disciplinary collaborations and integration of scientific and commercial expertise build

[182] Most spin-outs are unlikely to serve national markets, yet taken as a whole, university ventures do have significant implications for creating local employment and revenue generation (Clarysse et al., 2005).

value into the company and encourage the innovation that is necessary to develop successful Regenerative Medicine technologies. Another informant, NC, gives his own (sceptical) interpretation about the relationship between academia and bio-entrepreneurship in the field of Regenerative Medicine:

> Ultimately it comes down to a grass roots level of scientists needing to be able to get on and engage with each other productively, and that can be problematic. Because to be a good scientist, doesn't necessarily make you good at anything else. I think that there are a few individuals that might have other talents but for the most part, I think the majority of individuals are very, very focussed on the intricacies of, you know, the science that they do and they have a very tunnel vision.
>
> **(NC, PI/CSO/Founder of Spin-out, 2007)**

In modern science, being scientifically brilliant is necessary but it is not sufficient. In most fields, a scientist who cannot recruit, work with and communicate with colleagues or who cannot attract resources and manage them as obtained, is considered a bad overall 'performer'. According to NC, many principal investigators (and potential bioentrepreneurs) are so focussed on their scientific work that he judges them to have 'a tunnel vision'. The process of clinically and commercially translating basic science findings requires skills that NC believes are 'foreign' to most academics. These include negotiation and business skills, intellectual property awareness, and market knowledge, all of which may be a prerequisite for the scientist's ability to recognise the commercial value of the new knowledge and therefore to engage in its Translation (Vohora et al., 2004). In short, in NC's view, the majority of PIs are mainly inspired and motivated by the science and overlook the commercial side, which is equally important for funnelling their Regenerative Medicine inventions to the patients and market.

Finally, 'uninterested' bioentrepreneurs might just prefer to concentrate on their 'core' academic activities and stay outside the Translational arena, or they might have been discouraged by the accounts of others (as in the case of one of my interviewees) who have had trouble or even failed to translate their research findings altogether.

RG is the only one of the respondents who turned down the idea of commercialising her Regenerative Medicine product by spinning out a company (despite pressure from the university). She admits to have been discouraged by other bioentrepreneurs' stories.

> There have been people who have spun-out companies and I know, having talked to them, that they are very shocked by the process. Particularly with some of the things where they haven't realised that they are personally liable for any losses and things of that nature. I know people who have tried to [spin-out a company] and they have been rather overwhelmed by the process.
> **(RG, PI, 2009)**

RG mentions the accounts of colleagues who have tried to translate their research findings commercially through spin-outs and admit they have been 'overwhelmed by the process'.

'Dismissive'

Another possibility that I have encountered involves a bioentrepreneur who is dismissive not of the 'Translation-through-company-creation' process, but of what he perceives as an interfering and coercive attitude of the university towards commercial exploitation of its research. Instead, this interviewee proposes a more 'conservative' approach that involves the creation of a company (preferably non-academic) only when the technology has sufficiently matured and the appropriate people (mainly professional managers) have 'come on board'. LK, a PI, head of RM clinical trials and founder, laments the pressure of the universities to translate Regenerative Medicine research through spin-outs:

> There are a lot of struggling companies out there, a lot of academic spin-outs. Some of them, I would think, are just [a result of] the naivety of the universities. Actually, some of them should never have been span-out. Judging by things that I read and from the conversations I have with people, they are so naïve. They want funding for gathering data that they could get through an internet search, or ringing up an academic like me

> to answer their questions. I think there is a lot of naivety out there. I think there are far too many spin-out companies; most of them will never turn over a profit and most of them should never have been span-out.
> **(LK, PI/Clinical Involvement/Founder of Start-up, 2009)**

LK is the founder of a RM start-up company (non-academic) and talks about the 'spin-out mentality' that dominates universities. He brands the whole strategy, including the resulting companies, 'naïve'. In LK's view, principal investigators in the Regenerative Medicine field are rushing – sometimes through their own initiative but more often pressured by their academic institutions – to create spin-out companies.[183] The result, he explains, is the creation of companies that have no 'added-value', will 'never turn over a profit' and 'should never have been span-out' in the first place. In short, LK suggests that, while it is relatively easy to create a legal entity, the act of setting up the company does not necessarily mean that it will succeed in generating wealth. LK's view is in agreement with a report published in the UK at the end of 2003 – the UK Treasury-sponsored Lambert Review of business–university collaboration – which considered that too many university spin-outs were being created and that greater focus should be placed on identifying whether a spin-out was the most appropriate means to exploit technological inventions produced in universities (*Lambert Review of Business-University Collaboration*, 2003).

Summary

As the data for this study and numerous other analyses have shown, there is an urgent need for more 'Research Translators' (and this need is identified by all the bioentrepreneurs interviewed for this study). According to the interviewees, 'Research Translators' must be adequately trained and experienced in Translation, and willing to work alongside the scientists (PIs, potential bioentrepreneurs) to help them translate their findings. Currently this critical 'layer' of people is seen to be missing from UK universities, with the lack certainly being felt in the RM field. In the absence of this 'helping hand' infrastructure, novice RM bioentrepreneurs must assume the responsibilities of 'Knowledge Brokers', although with varying levels of involvement

[183] A study by British Venture Capital Association showed that no less than 435 spin-out companies have been created from university research since 1999. Two-thirds of these have only attracted seed funding, with just a handful taking the next steps to raise significant sums to take their plans further. More details can be found at: http:www.grothbusiness.co.uk/news/fundraising-deals/24358/university-challenges.html.(Accessed February 2010).

and dedication – and almost always on a trial-and-error basis. This is a situation also characterised as under-defined by commentators such as Lotharius. It is not only a question of getting more specialist-trained translational 'assistants' into the mix, but also inculcating a stronger sense of what 'good' Translation consists of within the sector. As a result of both these gaps – the missing infrastructure and the as-yet emergent 'culture' of translation – it is not surprising that bioentrepreneurs, such as those interviewed for this study, frequently express frustration and ambivalence about the translational challenges they face. Indeed, in some respects it is surprising there is any enthusiasm at all for ploughing forward into this morass of obstacles. I nonetheless came across a wide range of attitudes toward translational challenges among Regenerative Medicine bioentrepreneurs. I have termed these categories 'keen', 'reluctant/accidental', 'eager/ enthusiastic', and finally 'uninterested' or 'dismissive'.

From carefully examining the bioentrepreneurs' narratives, under which 'category' a bioentrepreneur would be eventually classified has to do with a person's character (i.e. some are simply more entrepreneurial than others), but also with their experience of interacting with the university for the purposes of Regenerative Medicine Translation. In the following section, I explore the role of the university in the process of RM Translation and how this role is perceived by bioentrepreneurs, as the one 'driving' the Translation process.

The Role of the University in RM Translation: Help or Hurdle?

> I'm a scientist by training and I think scientists will always find a way around that and find a way to collaborate internationally. The interesting part comes when you start trying to spin out products and intellectual property. That's when it can get, shall we say, interesting.[184]
> **(Dr. Marilyn Robertson, Scottish Stem Cell Network (SCCN) Executive Director)**

In the quote above, Dr Robertson, SSCN Executive Director, talks about the Scottish experience of forging (cross-border) collaborations and implies that collaborations are

[184] Quote taken from (Sornberger, 2009: 185).

'easier' at the level of fundamental research when the issues of ownership and profit are not yet at the forefront. Since enabling collaborations is one of SSCN's key aims, it is very important that Robertson recognises that the translational system is built in a way that encourages not only universities but also nations to pursue Translation for their own economic benefit and hence in their own terms.

In the same vein, while discussing the theme of collaborations, a key point that emerged in my interviews is the role of the university in the process of RM Translation, through the increasing influence of intellectual property rights (IPRs) on the creation of (national and/or international) translational partnerships and collaborations. Many of the interviewees deplored the strategies followed by the universities and their Technology Transfer Offices (TTOs).[185]

Technology Transfer Offices are the intermediaries through which university science is commercialised. Recent research suggests that Technology Transfer Offices vary in their mandates and capabilities.[186] Although TTOs' primary activity remains licensing, they are also often involved in negotiating multi-party research contracts, establishing and facilitating the operation of incubator services, and actively investing in and managing university spin-outs.[187]

When asked about their relationship with the university/TTO and the help they have received during their RM translational efforts, my respondents were at pains to describe the lack of guidance and support, as well as the barriers the university involvement is introducing. Indeed, the majority of informants criticised the stringent university IP policies (mainly patents and material transfer agreements) and gave

[185] Much has been written about the need in a knowledge-based economy to exploit university-originated innovation and the need to improve the process. As also mentioned in Chapter 2 about the origins and global priority of Translation, the landscape is changing, with TTOs gaining an increasingly important position in academia, both in terms of power and numbers. In addition, interest in spin-outs has been driven by legislative changes such as the Bayh-Dole Act (US). For a collection of articles on the role of TTOs and the rise of entrepreneurial activity at universities see the special issue in the Journal of Industrial and Corporate Change, Volume 16, Number 4.

[186] The subject of the role of the TTOs in the context of changing university–industry relations and commercialisation of academic R&D is very large. In the case of spin-outs, the bulk of research has focussed on firm creation, with less emphasis on understanding of what is required to grow these ventures and 'make' them successful. For a good review (from the management literature) of organisation interactions involving universities and firms that result in the commercialisation of research and technology, see (Markman et al., 2008).

[187] Sometimes the TTOs have been found to enact a proactive role in championing novel (and often controversial) technologies. For example, a study by Sanjay Jain (University of Wisconsin-Madison, US) and Gerard George (Imperial College Business School, UK) examines the case of a TTO–WARF taking on the role of the institutional entrepreneur to support the development of hESCs technology. The authors argue that, in cases like the WARF and hESCs, 'the commercialisation challenge for the TTOs can go beyond patenting and licensing or creating start-ups and involves building legitimacy for the novel technology' (Jain & George, 2007).

examples of how these policies affect their (mainly) external collaborations with industry, hospitals, and other academic institutions. Below, a bioentrepreneur reflects on his experience of founding a spin-out company in order to translate his research.

> It has not been a positive experience. It's been a very frustrating experience, because these [TTO executives] are people who tend to be very pragmatic and see things from a very traditional perspective. So I would be lying to you, if I told you that the creation of [Company] has been easy. Primarily because the university has had a very dogmatic view that anything that they are involved with – where, for example, the lead contribution scientifically is from their organisation – then they [think that they] own everything. And if you are talking about trying to merge collective interest, that's not a helpful starting point. They also have this desire to control the distribution of intellectual property. And again there is 'two-sidedness' here. On the one hand, there is all this verbal acknowledgment of the need to publicly promote, enhance the dissemination [of IP] for public benefit, but at the same time there is a desire to maximise the financial return to the university. And those two are not necessarily consistent if you need multiple partners to deliver on an objective.
>
> **(NC, PI/ CSO/Founder of Spin-out, 2007)**

NC admits that setting up the spin-out company in order to commercially exploit the teams' laboratory 'know-how' 'has not been a positive experience'. He cites the 'dogmatic' attitude of the university, conveyed through the IP policies, as the main reason behind many of the difficulties he encountered in creating the company. He also criticises the university for being overprotective of the work done under its auspices, which stems from the perception that 'they own everything'. This rigid attitude towards (material and intellectual) ownership, aims to maximise the institution's financial returns but, as NC suggests, this is problematic when 'you are talking about trying to merge collective interest' (as in the case of translational collaborations and partnerships). NC also points to the 'two-sidedness' of the university's 'behaviour' regarding the distribution of intellectual property. On the one hand, the university is verbally advocating the (free) dissemination of the resulting IP,

but one the other hand, they are accused by bioentrepreneurs and other scientists of over-patenting and over-protecting the university's 'work'. This behaviour is clearly not helpful when 'you need multiple partners to deliver on an objective', and many of my interviewees feel that it discourages external partners from pursuing translational collaborations.

Indeed, the distribution of intellectual property rights (IPRs) within a partnership is not trivial since it has the objective of securing the future development and competitive advantage of both parties. Issues such as who gains the right to further develop and economically exploit the output, and to what extent the use of the know-how accumulated in the relationship should be restricted in other business contexts need to be addressed in contract negotiations.[188] Also, a restrictive contract (from either side), might cancel the benefits envisaged by a potential partner, leading to the collapse of the partnership. Therefore, in a sense, the 'commercial cross-disciplinarity' that is achieved and subsequently displayed through the entrepreneurial effort of the founders and the formation of a commercial entity (like a spin-out company), is at the same time undermined by university policies. As read in the quote below, the bulk of the blame is directed towards the technology transfer executives and the senior academics who they often consult.

> At the risk of being slanderous, I am not convinced that the people who are in Technology Transfer Offices (TTOs) have the vision to be the most effective in their role. So we are talking, essentially, middle management posts that are receiving guidance from senior academics, heads of departments, etc. Now these academics may have been good scientists, and may have been good academic or clinical leaders, but are not necessarily versed in business development.
>
> **(NC, PI/ Founder of Spin-out, 2007)**

NC is very frank about his opinion of the technology transfer executives and how they 'operate' in the commercialisation trajectory. He typecasts them as 'middle management posts' which are essentially guided by the advice of senior academics from relevant departments of the university (depending on the product). From NC's

[188] (Paija, 2003).

perspective, these senior academics who are (frequently) not research-active any more and who have been reassigned to high-level administrative posts such as heads of departments (or research institutes), are not qualified to guide Translation either. In other words, the essential business development expertise that NC believes to be lacking in nascent academic ventures, cannot be satisfactorily provided by the TTOs, neither by the way they are staffed nor by the way they operate. To be fair, my interviews do provide evidence of a few bioentrepreneurs who said they were satisfied with the help and advice from the TTO.[189] Yet far more common were expressions of growing frustration among investigators.

In the same vein, a principal investigator based at a top London university with a very 'active' Technology Transfer Office grumbles:

> I just had lots of grief from them mostly. As far as I can tell I am never going to get any money out of anything. All they do is they stop me working with people. I wanted to get patents on things but the TTO didn't agree with me. So I didn't get anything from that. And other things I know I am never going to get any money from and I want to just do, in terms of patents they are very fussy about the IP then.
>
> **(RG, PI, 2009)**

RG thinks that the university's TTO is hindering her work through its strict IP policies. She recalls how she has had disagreements with the Office on what 'stuff' she should and should not patent, and blames them for being 'fussy about the IP'. Yet, more importantly, she feels that the IP policies being followed and the strict regulations that are in place to govern the research conduct of staff, are preventing her from pursuing essential collaborations. Like other PIs, she is at odds with her TTO and does not see it as enhancing collaboration – or other aspects of her work. In effect, rather than being helpful, the TTO is yet another obstacle.

LK provides a similar but more detailed account of the way intellectual property rights, and especially the way they are managed (by the university), create barriers in Regenerative Medicine Translation. In this case, both sides of the 'potential'

[189] It is hard to tell whether the rare positive comments that I have heard about the TTO's help and advice are true, or the result of a politically correct answer about the institution in which the PIs are based.

collaboration – university and hospital – are eager to ensure they 'harvest the fruit' in the partnership, but ultimately have the opposite effect.

> Universities tend to overestimate. Well, they've been beaten before and they've lost a lot of potential IP through not protecting it. And what happened is that there has been a reaction towards the other way and they believe that IP is everything. I've just had a long discussion over access to tissues from patients, and one of the hospitals that I deal with believes that a blood sample or a tissue sample that has been derived from a patient in their institution carries with it some intellectual property. So if I discover something from it, they want to share the IP. As far as I am concerned, an inert piece of tissue can't have any intellect, therefore doesn't have any intellectual property. If I or my colleagues think of something from that [piece of tissue], develop something from that, that property is with the person who generated the intellect behind it [final product] and not with the actual substance. But tissue agreements[190] are the sort of thing that ties it [IP] up for a very, very long time. The university is not happy to give its IP to the hospital just on the basis that the hospital provided a bone marrow biopsy.
>
> **(LK, PI/ Founder of Start-up, 2009)**

According to LK, the universities' increasing trend to overprotect IP is a way to ensure that they are 'making the most' of the research they are funding and that they do not lose out to other universities, hospitals, or industry. This 'over-protectiveness', LK claims, is a result of previous losses in revenues that universities have incurred by showing a 'flexible' attitude towards IPRs. He then describes how he recently had to abandon a potential collaboration, because the hospital made IP claims over the donated tissue to be used in LK's experiments. The university, on the other hand, was not prepared to 'share' the IP. According to LK, the 'property is with the person who generated the intellect behind it [product] and not with the actual substance [tissue]', implying that the hospital's request to retain IP on the grounds that it performed the biopsy and extracted 'a piece of tissue' was illogical.

[190] By 'tissue agreements' LK refers to Material Transfer Agreements (MTAs).

It is worth noting that in his description LK specifically mentions 'tissue agreements' (Material Transfer Agreements) and how 'they tie IP up for a very, very long time'. An MTA is a contract that governs the transfer/exchange of material such as human tissue (cell lines, plasmids or reagents) from the custodian (provider) to a third party (recipient). For the provider, a material transfer agreement (MTA) provides several comforts including restricting the use of the material to non-commercial research, and reducing the provider's legal liability for the recipient's use of the material. Additionally, the terms of the MTA can help the provider to gain access to the results of the research, both for information purposes and for commercial exploitation. According to legal and social scholars, in the case of Regenerative Medicine and stem cell research in particular, 'patents do not necessarily pose the greatest hurdles to research over time; physical property rights, as controlled and enforced through material transfer agreements, are often the most difficult to overcome' (O'Connor, 2006: 1052).[191] Indeed, there are several empirical surveys where researchers express greater frustration with material transfer agreements than patents *per se*,[192] while others suggest that these two proprietary means of maintaining control and extracting rents are 'mutually reinforcing'.

The above sample of interviews repeatedly suggest that strict IP policies followed by UK universities in the field of RM research (and presumably in other areas of biomedicine) are creating 'barriers' and impede the flow of materials and information between research teams and other RM Translation stakeholders such as clinical centres (hospitals) and industry. This overemphasis on academic IP has also been identified recently in an independent report to the 'Funders' Forum' of the Department for Innovation Universities and Skills (DUIS).[193] The report, titled 'Streamlining University-Business Collaborative Research Negotiations', was published in August 2007 and states:

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[191] Sean O'Connor, Associate Director of the Centre for Advanced Studies and Research on IP (CASPIP), University of Washington School of Law, explains the relationship between IP and MTAs, using the case of the control of stem cell patents and stem cell lines by Wisconsin Alumni Research Foundations (WARF) and its affiliate WiCell Research Institute. See: O'Connor, S. M. 2006 'The Use of MTAs to Control Commercialization of Stem Cell Diagnostics and Therapeutics', *Berkeley Technology Law Journal* 21 (3).

[192] The most commonly cited surveys were performed by Walsh and colleagues and included academic researchers working within the life sciences generally. A more recent survey conducted by Timothy Caulfield is specific to the Canadian stem cell researchers, but essentially replicates Walsh et al.'s core findings. See: (Walsh et al., 2005; Walsh et al., 2003) and (Caulfield, et al., 2008).

[193] The Department for Innovation, Universities and Skills (DIUS) was a UK government department created on 28 June 2007 to take over some of the functions of the Department of Education and Skills and of the Department of Trade and Industry (DTI). In June 2009, the DIUS was merged with the Department for Business, Enterprise and Regulatory Reform (BERR) into the newly formed Department for Business, Innovation and Skills (BIS).

> It is important that adequate protection is made for Intellectual Property, but we feel that both universities and businesses are guilty on occasions of putting excessive emphasis on ensuring their own ideal outcome from the negotiation in relation to IP, when it is often not even the most important aspect of the research collaboration [...] there is confusion as to whether the primary aim of collaborative research should be to generate income for universities or to create benefit for the wider economy; and it is not always clear what public research funders expect to see as an appropriate outcome in relation to IP.
> (Funder's Forum Report, August 2007)[194]

The above passage again echoes the views of RM entrepreneurs who seem to believe that the strenuous efforts that are made by government and research councils to foster collaborations in Regenerative Medicine – for example by establishing RM Translational Research collaboration grants[195] – might indeed be hindered by strict IP policies imposed by universities or the funders themselves.

In short, bioentrepreneurs perceive IP (patents and MTAs) as a major obstacle to enhanced collaboration and, consequently, their translational work. From the interviewees' accounts, there is no doubt that the majority think they are on a different wavelength from TTOs regarding Translation-related priorities. This divergence of views and priorities sometimes ends in tense relations with the TTO representatives, as informants feel they are limited by IP and related policies in terms of collaborations and expertise and cannot fulfil their 'true potential'. The main problem lies behind the idea of enhanced collaboration, which not only includes additional expertise and the pursuit of scientific excellence, but also involves the sharing (or matching) of funds by potential collaborators, which could speed up both research and development. However, as exemplified by Dr Robertson's comment in the opening quote, it is the same financial contributions and need to protect a collaborator's investment that impedes or completely halts the efforts.

[194] Following on from discussions at the Funders Forum Plenary Conference in November 2006 a small working group drawn from universities and business, led by Peter Saraga, looked at the issue of university/business collaborative negotiations. The results were published in August 2007 in a report titled 'Streamlining University/ Business Collaborative Research Negotiations'. The report can be accessed at:
http://www.dius.gov.uk/policies/science/science-funding/funders-forum/reports
[195] For example the CIRM–MRC translational stem cell research collaboration grants.

The above discussion also brings into relief an omission in writings about 'successful' RM Translation definition and understanding, namely, that successful Translation for one stakeholder may not proceed in parallel with, or may even be in a collision course with, other social worlds and downstream, implicated actors. In other words, it might be the case that for the PIs-turned bioentrepreneurs the objective is to enlist the input (through collaborations) of necessary people and 'get stuff done'. For the TTO it might be to protect the universities' research budgets, secure the highest possible return on investment and/or protect future streams of revenue. Finally, for the government the objective might be to 'look good' by promoting itself as the distributor of free knowledge and IP and hence a 'bottleneck solver'. In short, it could be argued that Translation may appear to be under-defined not only because people do not know 'what it is' 'and what it involves', but because people have very different ideas about 'what it is for' – in other words its main objectives.

To add to the pessimism on collaborations, in a recent comprehensive analysis of the Regenerative Medicine and stem cell research field (including proprietary domains) three authors – Winickoff, Assistant Professor of Bioethics and Society at the University of California, Berkeley, Saha from Whitehead Institute (Cambridge, MA), and Graff, Assistant Professor of Economics at Colorado State University (2009) – have reached the conclusion that stem cell research is an exploding field that 'is characterised by a lack of any deeply collaborative architecture, yet it is the field that requires more coordination than others due to the particular trajectory of its development' (Winickoff et al., 2009: 57 and 58). In order to support their claim, the authors describe how 'in response to dominant patterns of propertisation, competition, and decentralisation in the modern life sciences, new forms of 'open and collaborative" research have, as if by necessity, recently emerged' (2009:57). These forms of collaboration, pooling and sharing can mainly be located in fields like open source bioinformatics software, genomic and other databases, and to a lesser extent wet-lab biology.[196] According to Winickoff and colleagues, however, these important efforts emanating from either public or private sector initiatives (or at the interface of the two) remain the exception rather than the rule, and broad areas of biomedical research such as RM have yet to experiment with such 'novel collaborative architectures'. In fact, the

[196] Specific 'collaboration' examples mentioned by authors include the Human Genome Project and International Haplotype Map Project and the BioBricks Foundation at MIT which seek to coordinate a synthetic biology 'commons'. For an overview of some of these efforts see (Rai, 2005).

authors suggest that such a collaborative architecture would be most useful to regenerative research and industry as it seems that not only proprietary, but also technical, regulatory and ethical complications seem to 'cloud the prospects for stem cell R&D to a greater extent than other fields in the life sciences' (2009:58).

Yet, one interviewee mentioned her involvement in what could be called an 'antidote' to the lack of coordination in the RM IP field. She states:

> Interestingly, a paradigm that I am involved with is the Stem Cells for Safer Medicines (SC4SM) paradigm.[197] This [initiative] supports that free protocols should be generated from its academia–industry collaborations and be made available to the Stem Cells for Safer Medicines collaborators without charge. So it is a shared IP.
> **(RG, PI, 2009)**

Stem Cells for Safer Medicines (SC4SM) Ltd is a not-for-profit public–private collaboration with participation by the UK Government[198] and pharmaceutical companies.[199] SC4SM Ltd, in its Intellectual Property policy statement, has set out the principles which govern the relationship between the 'Company', its members and third parties, with regard to intellectual property (IP) rights. The existence of a 'cell bank' like SC4SM should, in principle, facilitate the exchange of materials and data (for example by mitigating transaction costs), relative to a world where scientists and institutions are left to negotiate the terms and conditions of transfer on a case-by-case basis. The operation of SC4SM is based on what is known in the literature as 'protective commons' (or 'contractually reconstructed research commons').[200] In short, participating members in SC4SM are 'entitled to utilise the intellectual property

[197] The initiative was developed as a direct follow up to the report of the UK Stem Cell Initiative, chaired by Sir John Pattison and published in November 2005 (SC4SM website, www.sc4sm.org). Initial research would focus on the development of 'open standards, methodologies and services in the field of stem cells'. The long-term objective of the collaboration, however, is to develop a bank of differentiated human cell lines to be used in early drug discovery to provide early identification and elimination of potential toxicity issues before clinical testing.

[198] Government participation includes the Department of Health, the Department for Innovation, Universities and Skills, the Scottish Government, the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC).

[199] AstraZeneca, GlaxoSmithKline and Hoffman-La Roche are the founding private sector members of the consortium.

[200] For an in-depth discussion of the concept of 'contractually reconstructed research commons' see (Reichman & Uhlir, 2003).

contributed by other members as well as any new intellectual property generated as research projects unfold'.[201]

According to Mathew Herder, a legal scholar from Loyola University, Chicago, both the (UK-based) SC4SM initiative and the Canadian Stem Cell Consortium (CSCC) initiative, are two nascent initiatives that have escaped the study by Winickoff and colleagues. In his own study, Herder examines the extent to which initiatives such as SC4SM and the (similar) Canadian Stem Cell Consortium (CSCC) initiative 'are able to create conditions conducive to scientific collaboration based upon their (observable) approach to stem cell-related data, materials, patenting, and licensing, and in spite of the real world constraints they each face' (Herder, 2009: 18).

In addition to the concerns over academia's restrictive IP policies and their burden on RM translational collaborations, the academic metrics system traditionally used in the UK is also criticised. A principal investigator from a prestigious London university speaks of the difficulties the metric system imposes on fostering a culture of cooperation, interdependence and shared intellectual efforts, all very important for Translational Research and even more so for the uniquely cross-disciplinary Regenerative Medicine Translational Research. RG states:

> One of the barriers is the metrics system of academics keeping their jobs. And the university is very clear on this. You have to publish a certain number of papers in impact journal above 5, and you have to be first or last author. Now, many of these experiments require multidisciplinary things, they require lots of collaborations, in fact lots of people. So you have a paper with 12 or 15 people on and you can have two first joint or two last joint authors or whatever, but a lot of people in the middle they don't get credited. I have a lot of complaints from my collaborators in the Physics or whatever Department because they are never the initiators of the biological question, they are only suppliers of a technique so they don't get that first or last authorship. Everybody is saying that we ought to be moving to a model where, like physics, where you can have 20 people on paper and they all get credit.[...] So if you are going to start

[201] Entities that are not participants in the SC4SM may be allowed access to resources, but they are not entitled to those per se.

> throwing people out on the basis that they were not first author then you are very much discouraging them from interacting. And this particular thing [Regenerative Medicine Translational Research] needs interaction.
> **(RG, PI, 2009)**

RG comments on the 'academic outcomes' required and evaluated by the university for career progression, and how the current metrics system is hindering collaborative Translational Research. As RG explains, bioengineers and materials scientists, although absolutely essential for the realisation of many RM projects, are rarely the 'initiators' of the 'biological question'. Therefore, according to the current system, they are 'seen' as mere providers of a technique and are constrained to the 'less rewarding' middle authorships. In RG's view, by following a system that acknowledges only the first and last authors of a publication, potential collaborators are understandably discouraged from forging collaborations with lots of participants and in cross-disciplinary projects. To overcome this hurdle, RG suggests a shift to models of publication followed in other disciplines such as physics where, she claims, all contributors in a paper are credited equally. Such an approach will undoubtedly encourage interactions between scientists and foster RM Translation, which by definition is highly cross-disciplinary and depends on many people accumulating and integrating their expertise.

Summary

The bioentrepreneurs in my sample perceive the role of the university and its TTO as predominantly limiting. The two main areas identified as problematic are the IPRs and ownership, and the metrics system. Several interviewees criticise the IP policy of their universities as 'strict' and 'over-protective', suggesting that it erects barriers to forming partnerships as all parties would like to have a claim in the patents rights. A few informants mentioned tensions between them and the university/TTO, while others passed judgement on what they perceive as 'two-sidedness' between what the university and Government promote and what their IP policies actually embody. My results mirror findings reported in a recent study (Funder's Forum Report, August 2007) of IP over-protection as displayed by both academia and business.

The UK metrics system and its emphasis on publications are also under the respondents' spotlight. Interviewees suggest that the biased authorship credit that is allocated in cases of multi-authored scientific publications such as those frequently published in the Regenerative Medicine field, is discouraging scientists such as bioengineers, materials scientists, chemist and often clinicians, from contributing to RM translational projects.

Cross-disciplinary and cross-border collaborations are, without doubt, of critical importance in RM as they give research teams, spin-outs, and (on a larger scale) nations the opportunity to combine their own scientific, technical, regulatory and conceptual advances with that of others, thus facilitating the generation of novel insights that could potentially speed up Translation and innovation. Although this 'picture' of an ideal collaborative climate is (theoretically) promoted by all stakeholders in order for RMT to receive the much needed infrastructural support (as defined by Julie Lotharius earlier in the chapter), in reality, the university, which is supposed to be the main source of that support, is more often an impediment. A further point to have emerged is the conviction of bioentrepreneurs that RM Translation is best managed by people who are actively involved in the process. This view echoes Lotharius' statement in the previous section, in which she suggests that directors, heads and generally people in high managerial and administrative posts are not the ideal people to advise on, design, or allocate funds to translational strategies. Instead, people who are more similar to the bioentrepreneurs themselves, on the boundaries of science, medicine, academia and business, are perhaps better suited to guide RM Translation.

In short, according to the bioentrepreneurs who are first in the line of the 'IP wars', it is often a case of under-definition of what RM TR involves and how it could best be achieved – that is, through collaborative and cross-disciplinary work. From the accounts of the informants it is difficult to avoid wondering whether it is 'naïve' to think the sector will ever be that 'joined up'. Perhaps this is also what really distinguishes bioentrepreneurs from all other stakeholders. They are truly very unusually dedicated people with unique communicative and collaborative skills and, equally important, they are willing to get into the fray.

In the following section, I examine the views of bioentrepreneurs on skills, accumulation of expertise, composition of the enterpreneurial team and collaborations. What is the importance of those factors in the Translation process? Which of these factors facilitate and which impede the Translation process and how?

The Value of a Cross-Disciplinary Team

Translational support officers, government programmes, TTOs and University research support offices may all be more or less of use to the RMT bioentrepreneur. But at the end of the day, it is often the immediate team with which such individuals work that most profoundly determines their success or failure. Excellent cross-disciplinary teamwork can overcome numerous externally imposed barriers. But lack of such teamwork cannot be compensated for by any external supports. In this sense, a strong team is the true kernel of successful RM Translation.

This theme is reflected in the interviews, which contain frequent references to teams and teamwork. The theme of collaborations in relation to the composition and expertise of the translational team surfaced several times when participants were asked about the strengths of their research and company (with regard to Translation). In this section, the crucial issue of teamwork is examined with a view to identifying the key factors bioentrepreneurs themselves prioritised.

As one interviewee describes her experience of collaboration between stem cell biologists, bioengineers and clinicians, it is clear that an emphasis on the significance of cross-disciplinary collaboration during RM Translation is both constant and cumulative – extending from the early project planning to its successful completion, and encompassing everything from basic problem solving to long-term strategy along the way:

> We start [collaborating] from when we prepare a project proposal and go to someone to get funded. We have initial talks about what's the best strategy, what each [team] can bring to the table and then we put it in a project proposal, which may or may not be funded. And then, if we have it funded, we have regular meetings to try and work out the details [of the

translational project]. For example, "The rat heart is this size; can you trim your material to that size? Can you make it stiffer?" You know, these kinds of questions. So, we all take the experience from each experiment and carry it forward to the next experiment.

(RG, PI, 2009)

RG describes how she and her team of stem cell biologists collaborate with a number of teams from different disciplines including bioengineers, biomaterials scientists, and clinicians, initially to write a comprehensive and 'viable' translational proposal and, subsequently, if funding is secured, to perform experimental work (i.e. animal studies and pilot human experimentation). RG explains how the collaborators have meetings to discuss everyone's contribution and how each contribution fits into the overall progress. Her narrative about 'regular meetings', 'working out details' and generally back-and-forth questions and answers between the various teams is proof of the degree of cross-disciplinary, efficient communication and work that must occur in order for Regenerative Medicine translational projects to come to fruition.

As she emphasises, there are several benefits that follow from having many collaborators. First and foremost, with expertise on major developmental pathways, stem cell biology, chemical and biomaterial know-how, and 'eyes' on clinical applications, the group covers a lot of territory. This scientific synergy makes it possible to deal quickly with any particular challenge that may appear. In addition, each scientist 'brings to the table' a different portfolio of IP, which is useful if the research moves to the phase of commercial Translation. Not surprisingly, the breadth of the interaction inspires new ways of thinking that can ultimately strengthen the academic pathway that each of the collaborating scientists is following. This type of collaboration could be classified under what I have termed in the introduction to this chapter: 'scientific cross-disciplinarity'. 'Scientific' cross-disciplinarity involves collaboration only among scientists (of various disciplines) and clinicians (as is the case with RG's team), and in order to engage in it, bioentrepreneurs need not have acquired neither business skills nor market knowledge (as opposed to 'commercial' cross-disciplinarity which involves business skills and market knowledge).

While discussing his experience of making the transition to the clinic, another spin-out founder links the evolution of the composition of the enterpreneurial team behind the venture to the challenge of securing early-stage funding. He notes:

> Establishing the company was really made possible by the merger of two abilities, provided by myself and my co-founder. So on the one hand, there needs to be an appreciation of the science, there needs to be an experience with the regulatory process, which is essentially what I provide. At the same time, I was struggling to secure funding for this work because the research councils, which traditionally would have been the first stop for shopping, were not seeing this as a priority or within their remit. So it was becoming necessary to present the work and the prospect not as a research proposal, but as a business opportunity. At that point then, I was rapidly getting out of my depth. Although I did certainly make an effort to engage with both venture capital and the regional development agency (RDA), really, I only was successful with the latter, when I brought onboard my co-founder who has background in accountancy and in business development.
>
> **(NC, PI/CSO/Founder of Spin-out, 2007)**

NC describes his attempt to found a spin-out company in order to move from small-scale production of research-grade human embryonic stem cell (hESC) lines to large-scale manufacturing of clinical-grade lines.[202] The short-term aim of NC's company is to commercially supply these lines as research tools to other academic institutions and/or private companies. According to NC, securing research council funding (such as he had already received in the academic setting to create the research-grade lines) proved highly problematic when he decided to move towards 'clinical-grade' work and the creation of a spin-out. As NC explains, funding was eventually secured from the Regional Development Agency, but only after the additional (business) expertise was brought into the team. NC's account would be an example of what I have called

[202] While research-grade hESC lines are a valuable resource for fundamental stem cell research, their use in developing clinical therapies is compromised by the fact that they were derived using animal feeder cells or in media containing animal components, which presents a risk of xenogeneic contamination. There is therefore a clear imperative to generate clinical-grade (or GMP) human embryonic stem cell lines for therapeutic applications. The early establishment of banked clinical-grade lines will also enable developmental and preclinical work to be undertaken on exactly the same stock of cells that might eventually be used in clinical trials and therapy.

'commercial cross-disciplinarity', as it is the addition of 'business knowledge' in the team's 'knowledge pool' that seems to give credibility to the new commercial venture.

In the same vein, LK expresses his disapproval of the universities' strategy to 'roll out' companies when technologies are 'premature' and the venture team is not adequately staffed to deal with the commercialisation requirements.

> So many SMEs are being rolled out from the universities with insufficient capital, with no expertise [i.e. commercial/business expertise], with a really academic approach that everything can be done on a shoestring by everyone working a little bit longer, rather that saying "No, we need a professional team here and then we really can do it".
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

LK criticises what he calls 'the academic approach' to commercial Translation which seems to require 'everyone working a little bit longer' instead of recruiting business and regulatory professionals. He continues and reflects on the development trajectory of the company he co-founded, a start-up, explaining the reasons behind its 'prosperity'.

> And that is why [Company's Name] is working, because it was not a spin-out, it was a company in its own right that was set up by businessmen, to take [to the market] initially one product that had already gone through thirty patients. It wasn't first-in-man, proof-of-principle; it was thirty patients. And they could go out and say "Look, that works, because we've got the clinical data to show that it works!" And that's not true of every other RegenMed product that has gone out into the market.
> **(LK, PI/Clinical involvement/Founder of Start-up, 2009)**

LK credits the involvement of professional business expertise as well as the advanced development stage of the product for the company's success. He clearly suggests that when a product successfully passes the first-in-human (FIH) stage and there are the clinical data to 'show that it works', it then automatically becomes more 'viable' as the foundation of an SME that will be attractive to external investors. This trajectory, he says, is hardly the case for the majority of the RegenMed products, which are spun-out

from academia without the necessary expertise, and are usually in a too-early development stage to be attractive to investors. Securing the available funds and facilities for FIH experimental trials does not, however, guarantee successful Translation. If the principal investigators are to become bioentrepreneurs and devote their time to the commercial Translation process, they must also be 'reviewed in a different way' in terms of their 'academic performance'. This last point resonates with the respondents' views reported earlier on the publication bias and its damaging effect on translational collaborations.

RB reveals a similar understanding to NC and LK, of the importance of acquiring business skills and expertise in order to further the Translation process.

> The thing is that the company has developed its technology and it got to the point – and I realised this earlier this year – where it needed the commercial expertise to go into the real world and spin-out into real business. And to do that you require a skill set which comes with people that have commercial expertise, who can network, who know how to strike a deal. Since the placement of these two individuals the company has changed dramatically. We have now investors knocking on our door to give us money rather than the other way around. Word has spread very quickly. We are also now talking to a multinational company to strike a licensing deal in the US for our technology. There is a very strong possibility that an early-stage deal can be negotiated.
>
> **(RB, PI/Founder of Spin-out, 2007)**

According to RB, moving his research from the bench to the 'real world' in the form of a 'real business', requires the engagement of business people who are well versed in networking and closing deals. As a result of their recruitment, the company's financial state of affairs has started to improve, with RB revealing that the company has now investors 'knocking on its door' and expressing an interest instead of the other way around (which had been the case until that point). He also mentions the possibility of negotiating an early-stage deal with a US company, implying that the business expertise has significantly boosted the team's translational efforts.

Indeed, one of the key issues of concern at the early phase of the Translation process when the decision has been made to proceed and test the application of a laboratory findings into the clinic, is the issue of leveraging the necessary human resources for the successful launch of the venture. Many scholars in the literature of university- industry relations have already emphasized the different rules and norms that prevail in business and academic or research environments (Van Dierdonck et al., 1990) while others have shown that human and financial resources of spinouts tend to be closely interrelated (Heirman & Clarysse, 2004). Additionally, in the venture capital literature, Muzyka et al. (1996) provide evidence that when new ventures apply for early-stage venture capital funds, the question of a well balanced team[203] with sufficient business experience is often raised by the potential investors in order to evaluate a project.

Many bioentrepreneurs in the sample have also stressed the importance of 'common language' in the collaborative translational efforts (both for raising financial capital and initiating Translation towards the clinic). Indeed, in the organisational literature, specialisation and the existence of discipline boundaries are associated with the evolution of local norms, values and 'languages' tailored to the requirements of the disciplines' work (March & Simon, 1993). Communicating across disciplinary (or organisational) boundaries requires learning the local coding schemes and 'languages' as well as the specialised conceptual frameworks in order to achieve effective processing of information (Tushman & Scanlan, 1981). This need for a common language is illustrated in the following two quotes:

> Essentially we were able to couch the initiative [founding proposal for RM company] in terms that the business people could relate to.
> **(NC, PI/CSO/Founder of Spin-out, 2007)**

NC explains how he and his 'business savvy' co-founder managed to secure capital. RB shares NC's view:

> And that's when the company is a real business in a sense. And what is very interesting is that we are very lucky and we got the right [business]

[203] The question, now, of what exactly is meant by an 'entrepreneurial team' has been the matter of a considerable debate and many scholars have published their own definitions (Gartner et al., 2004). According to Vanaelst et al. (2006) this confusion is related to the fact that entrepreneurial teams are too often investigated within a static framework and neglect the evolutionary aspects of entrepreneurial team formation and development.

> people in and involved and they know how to speak to the appropriate partners and make it happen.
> **(RB, PI/Founder of Spin-out, 2007)**

RB credits the transition of his team's research work into a 'real business' to the 'right people' who got involved and they 'know how to speak to the appropriate partners and make it happen'. According to another interviewee, who has been working in the interface of Regenerative Medicine, chemistry and materials, 'talking the same language' is very important and needs time and effort in order to work. He states:

> Especially when you are dealing with people from different backgrounds. You have to be able to talk the same language and be able to engage – and that requires a learning process from both sides.
> **(MF, PI/Founder of Spin-out, 2007)**

Learning each other's 'language' is, obviously, a crucial 'activity' in order for what I have termed 'commercial cross-disciplinarity' to succeed. The scientists from various disciplines, as well as the 'business' or 'industry people', might have to study at least parts of the other's field to understand not only the 'words' but also the other's motivation, thoughts and impact on value creation. This is, of course, a two-way process and thus, according to MF, requires time and effort from both sides. In fact, all the bioentrepreneurs I have interviewed have admitted to being gradually building-up these 'language' skills through the various collaborations and interactions with diverse communities, all necessary for Translation to succeed.

Summary

All respondents acknowledged the importance of accumulating and integrating diverse expertise for their translational efforts. Each collaborator (scientist, clinician, business professional) brings a different type of 'knowledge' and only through successful integration (via frequent communication and meetings) can RM projects be fully realised. Several bioentrepreneurs report that invoking business expertise has made their RM ventures more attractive to investors. Finally, bioentrepreneurs spoke of the need of 'forming' common language with collaborators – either clinicians, investors, or

industry – seeking to communicate better with the 'other side', induce the creation of jointly formed ideas and consequently be in a better position to invite the other side's support.

Although engaging business expertise is perceived as a crucial step for commercial Translation, by far the most important type of collaboration, as confirmed by all interviewees, is collaboration with clinicians. The bioentrepreneurs I interviewed seem conscious of the need to produce clinically relevant results (products/therapies) and stress the importance of early and close collaboration with the future 'users' of the technologies under development. The next section explores the dynamic relationship between PIs-turned-bioentrepreneurs and clinicians, and draws on empirical data to generate a Regenerative Medicine Translational model that has both 'longitudinal' and 'current' features.

Collaboration with Clinicians

According to all interviewees, the involvement of clinical collaborators is of unrivalled importance in Regenerative Medicine Translation. In the following passage, NC explains how collaboration with clinical services and integration of clinical experience contributes in setting up an attractive investment opportunity that might help secure (private and/or public) capital. NC notes:

> I think the clinical interface is very important. I mean clinical translation is a really big header. The fact that we have not sorted out translation yet...To do so, I would argue that we need to take the [Company] paradigm and raise it up a couple of notches. We need to see that type of integration between the academic centre, the clinical service and private investment. This is something that myself and others [in the RM field] are working on. What I am hoping [Company] will be able to do is to position itself in a way that private companies will come in and see; see the elite contributions of an academic pipeline and clinical experience as a desirable setting to make an investment. Perhaps by acquiring the product in the first instance, but then in the second instance, to assist in

actually 'taking' the product to the clinic. **(NC, PI/ Founder of Spin-out, 2007)**

NC is the founder and Chief Scientific Officer (CSO) of a Regenerative Medicine company that isolates hESCs to the standards required for clinical applications and makes them available, either for the development of cell therapies for clinical applications or for drug discovery research. His company is unique in that it is operating as a partner of a larger network which includes the university (from which the company has spun-out) and an NHS specialist provider. The latter is providing the clinical and regulatory expertise and ensures that the cells produced by the spin-out company comply with Good Manufacturing Practice standards (required for the cells to be of 'clinical grade').

NC refers to Translation as a 'big header' implying that it is difficult to solve and that the failure to do attracts much attention (because it is recognised unanimously by all stakeholders as a priority). He believes that the translational strategy that his company is following, which is characterised by integration of the academic centre, the spin-out and the clinical service is an attractive proposition for investors who, NC hopes, will recognise the 'elite contributions of an academic pipeline and clinical experience as a desirable setting to make an investment'. In other words, in NC's opinion, demonstrating collaboration between physicians, who can argue from first-hand experience that a need for a product/therapy exists, and a biomedical scientist who can devise an effective biotechnological solution can be very powerful, especially when a spin-out is trying to convince an investor that an idea is both technically and economically sound.

Another informant expresses a similar appreciation for the clinician's input in the Translation process:

> We have clinicians embedded in the projects, often working on the animal work as well, and thinking about it in terms of what they see clinically. In addition, the heads of most of the divisions in the Medical School are clinicians and they are often working at the bedside so we have a lot of clinical input, you know, embedded in the whole process.
> **(RG, PI, 2009)**

RG highlights the fact of 'having clinicians embedded in the projects' and 'in the whole process' of developing the products. The dominant conception among interviewees is that clinicians are familiar with the patients' needs – from 'working at the bedside' – and they are also the ones that will eventually deliver ('use') the therapy. Hence, consulting clinicians increases the chances of the product being correctly designed and developed, and consequently adopted for use, if commercial Translation is also successful. In the same vein, a founder talks about what she considers to be the strengths of the team behind the company which help boost translational efforts:

> We have got strengths in surface technology, in skin cell culture, and in wound management. And a particular strength of the company is that we have worked very, very closely with clinicians to develop our product and our next products.
>
> **(LM, PI/Founder of Spin-out, 2007)**

The timing of initiating clinical collaborations is also considered important. For example, early communication with clinicians has been mentioned by many interviewees as a success factor. GL states:

> [...] maybe academically we can push more for translation. I think also more active collaborative research with the clinicians who will deliver whatever we are going to do. For instance, for the work on the eye that we are doing with Professor [Name] at [University]: we have a project in collaboration with his group. The [Spin-out] and the [Academic Centre] are involved too. They got the surgeons and the downstream [clinical work] and we are doing the upstream [fundamental research]. I think it is very important you marry that up as early as possible if you are going to get it to work [Translation].
>
> **(GL, PI/Clinician involvement/Founder of Spin-out, 2007)**

GL describes his first-hand experience of working with clinicians on a cell-based product. GL's team is responsible for what he calls the 'upstream' part, while the collaborating surgeons are addressing the 'downstream' challenges – that is, the ones closer to the actual delivery of the therapy. In GL's opinion it is important to 'marry'

basic research with clinical work 'as early as possible' to increase the chances of a product's success. Clearly, the input from the clinicians and surgeons who are familiar with the medical needs of patients and will be applying the therapy is considered critical.

In the case of one bioentrepreneur, geographical distance between the department of biomedical research located in the university campus and the clinical department located approximately 20 miles away, added an additional degree of complexity which eventually led to a termination of the bioentrepreneur/clinic synergy.

> We worked with some clinicians in [Region] but we found it frustrating. For one, it was geographically difficult and, of course, their [clinicians'] interests are the patients. And we were getting tissues which were very inconsistent. It [collaboration] didn't work at all, so we quickly dropped that. What you need to do is to have your clinician next door.
> **(RB, PI/Founder of Spin-out, 2007)**

RB admits that he found working with clinicians 'frustrating' for two main reasons: firstly, because of the geographic distance and secondly, because of a kind of 'cultural distance', suggesting that the clinicians have different priorities to the PIs and that the clinicians' focus on patients needs was 'interfering' with PIs' priority of getting consistent tissues necessary for research and subsequent product development. In other words, RB views 'clinician culture' as a barrier to the cross-disciplinary work, as he highlights the different interests of his team and those of the clinical practitioners. His account echoes other social science studies of RM Translational Research by Wainwright et al. (2006), who have explored some of the key institutional differences that stem cell scientists perceive as affecting their interactions with clinicians. According to the authors 'the scientists' views of clinicians reflect the scientific pursuit of rigorous experimental research, and the more "black box" approach of medicine, where improving patient outcomes is often seen as more important than unravelling mechanisms' (Wainwright, et al., 2006: 2057). Yet despite underscoring these different 'cultures' between clinicians and basic scientists (including PIs) RB goes on to mention the value of having the 'clinician next door' for 'easy' and timely feedback.

The perception of a positive relationship between clinical input and the enhanced chance of therapy adoption is further strengthened by the comments of one bioentrepreneur active in the field of regenerative orthopaedics. QN notes:

> I think it has to make a difference for the clinicians. They are busy, and speaking from an orthopaedic perspective there are a number of things that already work really well. In terms of what we are trying to do, it has to provide added value whether it's quicker application, greater longevity or enhanced efficacy.
> **(QN, PI/Founder of spin-out, 2009)**

For the clinician deciding to change the therapeutic product s/he is using and therefore the current practice, there must be a strong incentive present, such as better outcomes for patients or significant savings in terms of cost. In certain disease areas, such as the one QN is working on, there are a number of products and therapeutic strategies that are considered to 'work really well', hence the new candidate product must provide 'added value' and make a difference for both the patient and the clinician. The same investigator continues:

> When you have a hip replacement it is usually – I should stress – not a life or death situation, so in that respect, yes, you want to make sure that if you are advocating a cell-based strategy that is certainly doing no harm. There are lots of wonderful hip implants that work. So it's not life threatening in that respect. So you have to be sure that there is really no harm and it is real added efficacy. And that informs what we do.
> **(QN, PI/Founder of Spin-out, 2009)**

According to all my respondents, the majority of clinicians with whom they collaborate would be highly reluctant to adopt the emerging cell-based therapeutics unless their safety and efficacy have been sufficiently proven. This is especially true for areas, as QN explains, where there are already a number of products that have been used for years and thus their safety and efficacy have been firmly established. This aversion to 'novelty' and 'uncertainty', however, is normally less evident in disease areas and/or patient cases where there traditional approaches have had a poor outcome.

Overall, collaboration with clinicians has been mentioned by all interviewees as being crucial to the product development process and providing unique competitive advantage. By closely examining the accounts of the bioentrepreneurs specifically on the theme of bioentrepreneur (developer)/clinician interactions, I was able to observe three necessary 'conditions' in order for Regenerative Medicine Translation to occur.

As a first condition, the therapy/product must 'fit' into the current clinical practice. In other words, the application of the 'emerging product' will usually be dependent upon an array of complementary treatments which must have reached a point in their progress that allows the new product to be integrated in the 'overall therapy', ideally in a seamless fashion. If the product is radically innovative there is the possibility (as in the case of Dermagraft described later on) that it will be 'ahead of its time' and consequently its adoption will be delayed until a better 'match' is achieved with the complementary therapeutic interventions. This 'matching' (or 'treatment harmonisation') process appears to be a longitudinal one as therapeutic interventions vary in their pace of progress and degree of innovativeness. This first 'condition' is also relevant to the notion of individual clinician practice, as the more often the surgeon is applying the product the better he/she becomes at using it, the better the integration with the complementary treatments and thus the better the overall outcome. I term this condition 'best performance practice'.

A second 'condition', closely related to the first, is that the product must be optimally designed in terms of meeting both the physical needs of the treatment (and therefore the patient) and the needs of the 'users' (physicians/surgeons/nurses) by becoming increasingly user-friendly through repeated redesigning and redevelopment. I have termed this 'condition' 'best performance design'.

The third and final condition is related to what I have called 'best performance timing'. For all autologous products and allogeneic products with a shelf-life (i.e. not cryopreserved)[204], the application of the therapy must be perfectly coordinated with the health state of the patient, which in many cases might change unexpectedly, hence rending the treatment unusable. Finally, by using the words 'best performance' I mean

[204] Cryopreservation is the maintenance of the viability of cells, tissues and organs by the process of controlled cooling and storing at very low temperatures and subsequent re-warming.

to show that there might be cases where two of the 'conditions' are fully satisfied and one is 'underperforming'. In such cases the treatment might still go ahead but presumably the chances of clinical success are lower compared to the scenario where all the conditions are fully met.

In the following section, I explore the bioentrepreneur narratives to reveal the interdependent nature of these three 'conditions' and how they must all 'converge' in order for the cell-based treatment to be realised. At the end of this, I construct a theoretical 'braid' model of Translation which is specifically based on bioentrepreneur (developer)/clinician interaction.

A 'Braid' Model for Cell-therapy Translation?

Best Performance 'Practice'

A principal investigator, active in the wound-healing and burns field, is commenting on the importance of collaborating with surgeons to design and develop a product that is compatible with current clinical practice.

> Without naming products, there have been tissue engineered products that were designed in the lab that were works of art, but when you come to take them into the clinic it would have meant that clinicians had to change how they normally treated the patient, alter their practice. It was obvious that there wasn't any clinical input into what sort of product was needed. You got to have that user interface. If you make something that is a Rolls Royce but the clinician can, really, only handle a Mini, it is no good.
>
> **(LM, PI/Founder of Spin-out, 2007)**

LM explains how crucial it is for the RM product under development to 'fit' with the way clinicians are used to working and the protocols they follow. Application of complex therapies such as RM therapies, require long and intense training so a product incompatible with the rest of the practice or significantly different from what clinicians have been using (even if more effective) will still meet resistance from the 'users'.

In addition to LM's account above, a product example from the literature – Dermagraft – could also demonstrate the dynamics between product complexity and current clinical practice. Dermagraft, is a cryo-preserved human fibroblast dermal substitute approved for the treatment of diabetic foot ulcers, once considered the poster child for failure in tissue engineering. Dermagraft was initially developed by a US company – Advanced Tissue Sciences (ATS) which, in the absence of significant sales in 2001, started to cave in under the costs of manufacturing and supporting its products. In 2002, ATS filed for bankruptcy and transferred all rights for Dermagraft to Smith & Nephew. Three years later, in 2005, when Smith & Nephew failed to gain FDA approval for the additional indication of venous leg ulcers, Dermagraft, which had also been deemed very expensive and difficult to reimburse, was once again dropped. In June 2006, the product was acquired by a small company, Advanced BioHealing, who also bought the former ATS manufacturing facility and equipment, and employed most of the former ATS employees. The company, who changed nothing from the manufacturing process (which was both GMP and FDA approved), managed to ship its first product to customers in February 2007.

According to David Armstrong, an American podiatric surgeon and researcher, most widely known for his work in the diabetic foot, amputation prevention and wound healing, Dermagraft has had so many 'troubles' simply because it has been 'a product ahead of its time'. In the February 2008 issue of *Start-up* magazine, and in a review article on Dermagraft,[205] Armstrong was quoted on the reason why Dermagraft had not been able, during the 'troubled' times described above, to reach its clinical potential and its true market. He states:

> Ten years ago, when this product was emerging, the standard of care was to put gauze on wounds, an unchanged practise for the last three hundred years. When this product and a couple of others like it came on the market, it was a big change for a lot of clinicians. But now there are basic tenets of care, like appropriate surgical intervention, appropriate relief of pressure and protection that are now being married with technology **(David Armstrong, renown podiatric surgeon, 2008)**

[205] (Stuart, 2008).

Therefore, in Armstrong's view, it is the progress in the general standards of wound bed preparation and consequent changes in clinical practice that are now fostering the uptake of products like Dermagraft and lead to their adoption by physicians and their commercial success.

A relevant key point emerging from respondents' narratives, is that the efficacy of Regenerative Medicine therapies, in addition to being dependent on current standards of care and routine clinical practice, depends heavily on the surgeons' 'surgical expertise' (many interviewees, in fact, referred to the new successful therapies being transplanted as 'regenerative surgery'). Indeed, Regenerative Medicine therapeutics famously differ from previous medicines such as biopharmaceuticals and small molecules in two ways: first, they involve living cells or tissue and, second, there is a closer connection between the clinical practitioner harvesting or administering the cells and the patients. As one interviewee points out, 'the clinical application of these products is not science anymore, it is engineering'. In other words, because of the unique nature of cell-based therapeutics, the more experienced clinicians and surgeons become on delivering them, the more successful the therapies will start to be. Notes a founder and Chief Scientific Officer:

> First example of cell therapies is organ transplantation. It works, it's been around for 50 years now and it's saved many, many lives. For example even this morning on the radio, you know, [Hospital Name] stopped doing heart transplants because the death rate's gone up from one in ten to seven in 20. Hearts are still the same you know, the success rate of heart transplants is not because people have been getting better hearts. It's because people [clinicians] have been getting better at using [transplanting] them. And it's the same in all cell therapies and it's going to get more and more, that reiterative loop.
>
> **(NJ, CSO/Founder of Start-up)**

NJ uses the example of organ transplantation to underline the crucial relationship between product and clinical delivery (application) in the case of cell and tissue-based therapeutics. Unlike pills and medical devices which are mass produced and 'used' (consumed) roughly the same way, RM therapeutics and their associated benefits

depend highly on the skills and knowledge of the person – clinician, nurse, or surgeon – who delivers them. This means that even in the case of automating the entire production, possible with many types of RM therapeutics (albeit not all), there will often be the 'variable', 'manual' application.

This surgical expertise-dependent 'variability' is added to the risk-laden and provisional nature of cell therapies for whom the key to clinical utility lies in the ability (of scientists and clinicians) to proliferate cells (hESCs) down a specific differentiation path and retain control over that complex process in clinical applications. This is, as sociologists Eriksson and Webster (2008) from York University have argued, an attempt to deal with the 'unknown unknowns'. According to Webster and Errikson (2008), differentiation down a pathway with known clinical utility is a different matter to standardising biomarkers (which they call 'known unknowns'), it involves 'dealing with uncertainties *in vivo* and will require considerable input from clinical scientists in monitoring as yet unknown effects of the use of hESC implants' (Webster & Eriksson, 2008: 108). In other words, the authors argue that 'what goes on in the lab is never closed off, or finished even when encased in a black-boxed process or product' and conclude that 'the basic science in these cases of differentiations and engraftment is in a sense unfinished and can only come to some sort of closure by hanging on the coat tails of its applications' (2008:109).

Best Performance (Product) Design

A second point that has emerged from the bioentrepreneurs' narratives is the 'value' of a carefully thought-out, designed and 'constructed' cell-based product. The following interview extract provides a detailed account of the series of incremental innovations that take place while the product is being developed, clinically tested, and then re-designed/re-developed to fit the patient's needs and the requirements of the surgeons:

> [Product], our chronic wound care product, has gone through four iterations now. It's still the same product as far as the regulators are concerned, which is amazing because it wouldn't happen with a drug. It started out as little, little disks because for chronic wounds, surgeons take pinch grafts. I don't know if you know, they pinch the skin up and just cut it off. They take this little sliver of skin and then pepper it all over

the wound and hope that the skin grows out and covers it; and it works fine. So we thought we'll make synthetic pinch grafts in a way. A little pot of them [synthetic pinch grafts] and you can just pop them on [the wound]. That was the first one [design] and the problem was when you did that, they all fell off. So you had to dress it. You had to put them [synthetic pinch grafts] on and hold them horizontal while you put the dressing on which was awkward. So instead, we made just one big one [synthetic skin graft] in a big disk, put that on and it stays on. You can turn your hand upside down and the [Product] is stuck – it was too big. It was seven centimetres in diameter and they had to cut off some, so it was expensive and they [surgeons] were already thinking: "We're throwing all this really expensive stuff away". So the next generation was five centimetres. It was in a flat pack so that the pack could hold it because it's not solid, it's jelly-like. If it was in a tube, it would all wash up, because you've got to wash it and you've got to peel it out; and that again would be awkward. So it sits on the backing of foil. The surgeon just opens it up, pops it on. That [design version] was really good. But when you would turn it upside down and you would be looking at foil, and you've got to try and remember where the wound is, and then all you see is foil. So the third generation is a clear, transparent thing.

(NJ, CSO/Founder of Start-up, 2007)

NJ describes in detail the way his company has been using the clinicians' feedback to 'evolve' their wound care product. His narrative is a fascinating example of the process of refining a cell therapy in a mode not previously envisaged in the pharma and biotech industry. The step-by-step re-designing of the 'physical' product – although as he explains the actual properties remain fundamentally the same – is evidence of the clinical concerns and innovation being systematically incorporated towards a more user-friendly and ultimately more successful therapy. His account also proves that Regenerative Medicine product developers are very concerned about the various features of the product that can contribute to clinical uptake and therefore its success on the market.

A similar 'evolutionary' process, echoing many of the considerations addressed in NJ's description, has been responsible for the development of Dermagraft (Mansbridge, 2006). Dermagraft has been developed and approved as a medical device. From the beginning, the design concept was to be an allogeneic, viable dermal replacement product with a long shelf-life (approximately 6 months). In addition to the standard cell and tissue-engineered considerations (such as pH control, changing medium, and gas exchange) the designers of Dermagraft also considered factors to make the product safe and easy to use by the treating physicians. Perhaps the most significant decision concerning these two aims, was the decision to make the bioreactor (i.e. the vessel in which the cells are grown) part of the final packaging thus avoiding post-growth handling of the product and minimising contamination. In addition to meeting all of the clinician's aseptic conditions requirements, the bioreactor ensures user convenience by opening in such a way that the product is well exposed and can be easily rinsed prior to application. Finally, as a further assistance to practitioners, the individual bioreactor pockets are translucent and accept ink, which means that an outline can be traced on them and a suitably sized piece of the unit may be cut out. As a consequence of its design concept, Dermagraft has also the potential for scale-up production and automation which are crucially important for commercial viability.

Both NJ's account detailing the step-by-step development of his company's wound care product and the Dermagraft 'story' as reported in the scientific literature, illustrate the same type of process. A process of constant communication between developers and surgeons, leading to a gradual readjustment of the product's physical dimensions and packaging until the 'ideal' design is attained.

Yet, as one would think that such a degree of communication and 'productive' collaboration between UK developers and UK surgeons would be enough to translate the product to the market, in reality the Regenerative Medicine market presents further challenges. Indeed, as different countries follow different practical approaches to therapy for the same type of problem, it is necessary for companies (and the founders and R&D groups behind them) that have international market aspirations, to tap into a diverse pool of clinical guidance and advice. This is the only way to create products that will satisfy a wide range of therapeutic approaches and clinical protocols.

From conversations with various stakeholders (as well as from my respondents) I reached the understanding that bioentrepreneurs engaged in academic clinical Translation will receive feedback and advice from their collaborating clinic (or clinicians embedded in the project as mentioned earlier). Non-academic RM companies, in turn, will usually have either a standard clinical advisory board or would seek to assemble ad-hoc, product- and/or region-specific clinical panels. One respondent explains the strategy followed by his (non-academic) RM start-up company when it comes to seeking clinical input for the design of the product:

> And it's not just with the UK. We do it with Americans and UK people and non-UK Europeans because medical practice is very different in kind of those three areas. For example, I just met with someone yesterday, a surgeon, burns surgeon, for our [Product Name], the skin product. We're looking to use that for basal cell carcinoma removal. The standard practice in the UK is you cut it out and you let it go, just leave it. You know, it just contracts and heals up. Standard practice in Europe is to use flaps and try and close it. In the US they use grafts and flaps but they don't just leave it. So if we just took the UK view of the world, we'd be producing a product that everyone else said: "We don't do it that way". So yes, we get a lot of feedback in from doctors, we have panels of them. We don't have standard medical panels because we don't want to. We want to keep going out in different areas, for different products and at different times, in order to get more input around what's needed. And [this is how] the product changes.
>
> **(NJ, CSO/Founder of Start-up, 2007)**

NJ explains how critical it is to have knowledge of the market (users) for whom the products are being developed. What is 'standard practice' in one European country is not necessarily followed in another. Therefore, it is crucial to engage with 'users' repeatedly, at 'different areas' (markets) and 'at different times' to ensure capitalising on the best knowledge available and targeting innovation.

Indeed, innovation is increasingly being viewed as a complex and iterative process of direct producer-user interaction, and users who have so far been confined to passive

recipients of products are also being increasingly appreciated as reflexive actors, actively involved in the evaluation, modification, and sometimes even invention of products. In recent years scholars from many disciplines have emphasised the role of users in innovation processes in general, and in the biomedical innovation field in particular.[206]

'Best-Performance Timing'

Even with the creation of a product that is carefully designed to fit the 'physical' needs of the clinical problem, be user-friendly and compatible with current clinical practice, RM therapy success is still not guaranteed. In addition to being dependent on the 'environment' (i.e. current practice, clinicians'/surgeons' skills, product design), many RM products, mainly autologous, are also time-dependent. In other words, autologous products must be delivered promptly and in perfect coordination with the patient and clinician needs (unlike the majority of allogeneic products that can be stored, usually cryopreserved).

In the following quotation, a bioentrepreneur who is working on autologous epithelial grafts (autografts) describes the difficulties of working with them because of their inflexible delivery schedule:

> How we you used to do this is we take a small biopsy from the patient, we would grow the cells and then we would wait until they form an integrated sheet of cells and then we detach the sheet enzymatically, put it on some backing dressing and deliver it to the patient. Now we could not deliver the cells until all the cells were joined together and formed a sheet and that took a minimum of 9 days. But then we had to use the cells within 3 days otherwise they would not attach to the patients. So in terms of their useful shelf life it was a very, very difficult product to

[206] The engagement of users (stakeholders) in market-oriented sectors, such as the pharmaceutical and medical device industry, has been shown in the literature to have a range of positive effects for companies and their futures. For example, the ability of companies to keep track of the needs and wishes of users not only could enhance the adoption rate of their products, but it could also lead to significant modifications and improvements, if they make use of the user's 'experiential knowledge' (Caron-Flinterman et al., 2005). Chatterji and colleagues (2008), in turn, provide evidence that physicians contribute to medical device innovation. As the authors note, practising clinicians represent an important source of 'external' knowledge and innovation as they have the best insights regarding unmet clinical needs and the clearest sense of the most feasible solution to a particular problem. Involvement in activities such as clinical trials and product testing is one of the means by which clinicians can learn about the new technology. Their knowledge is derived from using the device – they know what is problematic, which improvement would be most critical, and which solutions are preferable from the perspective of the end user (i.e. physicians or patients depending on the type of the device).

> manage. Because you had to fine-tune the production of the cell sheets to be just right to the needs of the patient. And what used to happen is that we would make a plan...and I worked very, very closely with burn surgeons in [Hospital] for whom we were delivering the cells... and we would make a plan and we would set off to deliver cells to an agreed time-point. And then the patient's condition would change and instead of the patient going to theatre Wednesday they would say "The patient has developed a fever, we cannot take him on Wednesday, we might take them on Friday, and is that ok? And I have to say, "No it's not ok, because the cells are now past the point at which they detach and there was not sufficient time for us to start again". So basically, how we used to deliver the cells was very inflexible in terms of the timing. Everything was about getting the cells to the right possible condition, but it was not a very good fit with the needs of this critically ill group of patients whose condition could change day by day. So it became clear that we could not change the patients, so we had to change the product.
>
> **(LM, PI/Founder of Spin-out, 2007)**

LM narrates in detail the process of producing autografts – from the moment of the initial biopsy to the application of the product. As mentioned earlier in the thesis, autologous therapies are based on the same donor–same recipient approach –meaning that a sample (biopsy) of healthy cells are sourced from the patient, then expanded for a certain period (depending on the quantity of tissue/cells needed in each case) and then when 'ready', re-introduced to the same individual. The whole process, however, is crucially time-dependent and this is a feature that is 'incompatible' with some of the conditions bioentrepreneurs seek to treat such as burns. The usual problem, as noted by LM, being an unpredictable deterioration of a burn patient's condition that may require rearranging the time of surgery (application), and hence rendering the whole cell product unusable. Not being able to guarantee a perfect fit between the state/quality of the cells and the condition of the patients deems the whole approach 'inflexible' and ineffective. Therefore the search continues for LM's team to 'change' and improve the product as 'it became clear that we could not change the patients' and the unpredictable nature of burns.

LM's account perfectly illustrates the critical relationship between a cell therapy product and the timing of its delivery. In addition to being provided in a convenient format, autologous cells or autologous engineered tissue must be available to a schedule workable to the physician or surgeon. Sometimes it might be possible for the surgical team to access the status of a patient's bioprocessed material, and to try and schedule the application so as to gain maximum efficiency. In other cases, it might be possible for the bioprocess team to 'slow down' (e.g. by lowering the temperature) the growth of the cells in order to match the surgical team's schedule or, more importantly, the patient's condition. In cases where none of the above 'time adjustments' is possible, the autologous bioprocessed material exceeds its shelf-life and can no longer be used for treatment. A new biopsy will have to be taken and the bioprocessing will have to be repeated. Hernon et al. (2006) undertook a clinical audit of cultured epithelial autografts (CEA) use in a burns unit in Sheffield and have shown that the extent of wastage between CEA production and delivery to patients was nearly fifty percent (Hernon et al., 2006).

Allogeneic therapies are subject to time restrictions too. With the exception of cryo-preserved cell products that can be employed at a very short notice and be applied again soon after they thawed, most allogeneic therapies that have a shelf-life are subject to similar time limitations as autologous products. During a presentation of his company's translational milestones Geoff MacKay, President and Chief Executive Officer of Organogenesis, describes the challenges they faced in order to be able to ship their flagship allogeneic wound care product (Apligraf) to customers (clinics). Although, MacKay speaks on behalf of a large RM company which has shipped more than 200,000 treatments so far, the process of reaching that stage does not differ much from LM's account who is working in a small-scale academic setting. Both stories begin with a 'time-dependent' product and narrate the challenge of fitting cell therapy supply around an unpredictable demand. Said MacKay:

> And, you know, some of the mundane things like "How do you get it from A to B in a reliable way?", are things that we really had to get our heads around. Initially, we were shipping our product with 3 to 5 days shelf-life. So it would get to the clinic, but by the time it got to the clinic if the patient did not show up, if there was a snowstorm, if the doctor

just chose not to treat because the wound wasn't ready, it created anxiety on the side of the customer. So what we wanted to do is we wanted to lengthen our shelf-life to go from 3-5 days to 10-15 days. But the issue is that the fixed variable is our release criteria. We can't go to FDA and say we've decided that we want to have 90% survivability instead of 95%. Something had to change. [But] that is [release criteria] in stone. And so it's really by getting a much better handle on controlling the environment that we can enhance the shelf-life of the product. And we looked at many different temperature ranges for the products and we were able to establish an exact temperature range where the shelf-life, the viability of the cells and the histology of the cells would remain intact for 15 days, instead of 5 days. The challenge was [that] there can only be a +/- 2 degrees Celsius variation or that [cell viability] doesn't hold [...]And so with that as a challenge, our process engineers were able to put together a really neat technology package. We went to NASA and we got really space-age technology – so we were able to accomplish that. And then the next challenge is "How you do it in an environmentally friendly manner?" And we've done the best that we could there. And also "How do you make it as small as possible?" because weight equals money and that [cost] just gets passed on. We want to become standard-of-care, so we have to drive down costs. So, you know, something as banal as a shipper has actually been a priority project for us. We are very pleased that we've been able to demonstrate that you can get this [Apligraf] around the world.

(Geoff MacKay, Organogenesis, LRMN, 2008)

Like LM, MacKay explains the need to 'proof' product supply from unpredictable changes such as the fluctuating condition of the patient, the schedule of the surgeon or even the weather. According to MacKay, the one thing in the production process that is 'written in stone' and has to remain stable is the release criteria, as approved by the Food and Drug Administration (FDA). The 'fixed' released criteria leave the developers with the challenge of 'adjusting' the rest of the product's features to withstand delays. MacKay describes how Organogenesis' process engineers experimented with different temperatures and how they sought advice and state-of-

the-art 'shipping technology' from NASA in order to maintain a 'target' temperature that safeguards the cells' viability to the point of delivery. Yet, all these adjustments must also be made in an environment-friendly and cost effective way. This way Organogenesis not only sustains a profile of a 'socially responsible corporation', but also paves the way to become the standard-of-care by lowering production costs and establishing itself as an attractive option to healthcare payers. Both NJ's description and MacKay's account attest to the existence of the third condition that has to be met in order for cell-based therapies 'to perform their best'.

The challenge in Regenerative Medicine Translation lies in converting ideas and inventions into products that will eventually lead to improvements in patient care. However, as has been demonstrated by the many attempts to convert laboratory findings into Regenerative Medicine products, scientific strategies will not be effectively translated unless they agree with clinical practice and patient care. In other words, scientific and clinical strategies must be woven together in terms of both specific *outcomes* and *timelines*. Drawing on the narratives of bioentrepreneurs with regard to clinical collaborations and input in the phase of product (prototype) development, I have shown that there are there three conditions that must converge in order for the therapy to succeed: 'best-performance practice', 'best-performance design' and 'best-performance timing'. In cases where one of these conditions is absent or underperforms, the chances of therapy success are significantly lower and the whole Translation process is endangered.

Chapter Conclusion

This chapter provides a number of findings that contribute to a more textured understanding of the role of successful collaboration in RMT. While the factors influencing successful and unsuccessful collaboration identified by the bioentrepreneurs interviewed for this study do not point to any one single model of translation, they do help us to understand the priority issues in developing successful translational 'culture' from the point of view of those who are currently most intimately involved with the challenges defining this sector of bio-innovation. Moreover, while many of the themes in this chapter overlap with those of other

chapters, the theme of collaboration is revealed to have many specific features that would repay further qualitative study.

First, drawing on bioentrepreneurs' narratives, I have identified a profound lack of people appropriately trained to support scientists, clinicians and budding bioentrepreneurs in their translational efforts. The need for this 'layer' of entrepreneurial people is clearly articulated in the narratives of most interviewees, who also express their wish to 'source' these people from non-commercial entities to avoid any possible conflicts between what are perceived as the 'profit-driven' commercial approach to Translation and the more 'outcome-driven' approach followed by academia-based bioentrepreneurs.

My data also suggest that some bioentrepreneurs are more committed to the 'commercial' part of Regenerative Medicine Translation than others. Although all interviewees were highly supportive of the notion of Translation the narratives reveal fairly different levels of commitment towards the practical activities involved and the 'additional' skills that have to be acquired.

Another suggestion that emerges is that bioentrepreneurs are resentful of the way universities and TTOs manage intellectual property rights, which has a significant (negative) impact on RM translational collaborations. This 'bad management' is frequently linked (in the respondents' accounts) to the fact that the 'wrong' and 'unqualified' people are designing and guiding university policies. These people, who act from high-level administrative posts, are by definition disengaged from the actual Translation process and thus have no real sense of how it should be promoted and facilitated. Such findings prompt a rethinking of the way patents and material transfer agreements (MTAs) are managed, and at the same time provide recommendations about the way Translation might be better guided by 'actors' such as bioentrepreneurs who have been involved in all aspects of the process and have displayed the necessary 'boundary-crossing' skills which are critical for accumulating and successfully integrating all kinds of expertise.

It is also worth reiterating at this point why I have called my model 'the braid model of Translation': Drawing on the empirical data I identified three conditions that must all

'converge' in order for RM to succeed: the first condition, which I called 'best-performance practice'; the second condition called, 'best-performance design'; and the third and final condition, 'best-performance timing'. Ideally all three conditions would converge so that a cell-based product has the 'optimum' design, is compatible with the clinical practice and is also delivered in a timely fashion perfectly suiting the patient condition. It is important to note that the 'model' I have identified is not uniformly found across all RM therapies and products. The application of the model is clearly most highly pronounced in disease areas where the patient's condition is unstable and unpredictable and is limited to RM products/therapies that are autologous or allogeneic with a limited shelf-life.

Finally, caution is needed here: my research has explored the perspective of one group of 'stakeholders' which, although central and critical, cannot fully capture or represent the entire 'phenomenon' of Translation. More specifically, the research cannot said to document all types of interactions and collaborations between basic biomedical scientists, principal investigators, clinicians, and business professionals involved in the various phases of clinical and commercial Regenerative Medicine Translation. What it does provide, however, is a picture of the bioentrepreneurial 'logics' that characterise small Regenerative Medicine companies in the UK and the founders and the teams behind them.

Chapter 7

Thesis Conclusion

Introduction

Understanding the process of Translation is crucial to understanding Regenerative Medicine (RM) innovation. This research has explored the process of Regenerative Medicine Translation in the UK through the perspective of bioentrepreneurs. It has addressed issues of funding (Chapter 4), regulation (Chapter 5) and collaboration (Chapter 6) and related these to successful (or not successful) translational RM outcomes. Such matters are central to discussion about the development, application and commercialisation of RM products and therapies both in the UK and global arena. This thesis has also demonstrated how bioentrepreneurs in the UK perceive and respond to the translational challenges and how they comprehend, negotiate and 'evolve' their own role in the translational landscape.

Aim of Chapter

In this final chapter, I first briefly summarise the contents of the thesis. I then revisit the aims and objectives of this study as presented in chapter 1 ('research questions') and through briefly summarising the empirical findings I discuss the contributions of this PhD research to sociological research in the field of translational RM and to ideas and concepts of sociology in general. Afterwards, I reflect on the strengths and weaknesses of this study. In the two final sections, I highlight the implications of the study for future research as well as the implications for policy along with some tentative recommendations.

Brief Summary of Thesis

This thesis began with the story of the first in the world stem cell-based tissue-engineered organ replacement as narrated by one of the scientists that took part in the 'breakthrough experiment'- Professor Anthony Hollander, a stem cell biologist from

Bristol University, UK. Hollander's presentation was accurately titled 'Claudia's Trachea: Lessons Learned for Future Regenerative Medicine Strategies', a title which inspired me to do exactly what the professor's presentation called for: use 'Claudia' story' to identify and investigate the factors that appear to play the most critical role in the successful Translation of RM technology. Indeed, three factors emerged from Hollander's narrative – funding, regulation, and collaboration. These factors (which were also confirmed later on by the empirical data) served as the three 'lenses' through which my interviewees were asked to view Translation and share their experiences.

An explanation for my choice of actors to study, namely RM bioentrepreneurs was provided in chapter 1. There are two main reasons behind this choice. First, in view of previous relevant research where I had the opportunity to interview other types of RM stakeholder (including clinicians, basic scientists, bioengineers and industry representatives) I gained the impression that bioentrepreneurs are in possession of the most wide ranging knowledge and skills on RMT. Second, their unique position and responsibilities between the laboratory, the clinic, a spinout company, and the industry, requires them to work across the 'boundaries' between disciplines and specialisations 'where most innovation happens' (Leonard- Barton, 1995).

The importance of Regenerative Medicine as the new and promising treatment paradigm has been established in chapter 2. Indeed, RM is widely seen as the next major source of innovation in healthcare and it is applicable to numerous diseases and conditions, many of them currently incurable. They include genetic diseases, cancer, various autoimmune conditions, diabetes, renal failure, and spinal injury. In addition, as the population ages, age-related conditions such as stroke, cardiovascular and neurodegenerative conditions (Alzheimer's, Parkinson's disease), bone degeneration and type-2 diabetes become more common. As organs fail they need to be repaired or replaced and the potential for new medical breakthroughs that could improve the lives of individuals is huge. Furthermore, as the result of successful RM would be new therapies that offer a short course or a one-off treatment, the overall impact of decreasing the prevalence and the current treatment costs of these diseases is potentially extremely large.

The UK has so far been considered to have a leading position in the RM fundamental research mainly attributed to the informed and open approach towards RM work that combines a strong ethical basis with informed regulatory policies as well as substantial basic research funding. However, as recently identified in the Cooksey Review, the Translation of major advances in laboratory science to successful healthcare innovations and consequently patient benefits remains problematic. In response to this 'diagnosis', increasing amounts of budgets and political willpower were dedicated to expanding the RM innovation field. The process of Translation became a significant component in this ambition.

In the second half of chapter 2, I have provided a detailed explanation of the phenomenon of Translational Research including the 'meaning' of the term and how it has been used in various health-related disciplines, its emerging status as a global priority, the inherent difficulty in quantifying it (rate), the numerous definitions and the frequent use of inconsistent nomenclature (in different contexts), as well as the barriers to TR that have been reported in the scientific, social and other relevant literature. Finally, I briefly described two related characteristic features of TR- complexity and non-linearity- that were important for understanding the empirical chapters, and introduced RM translational research which, according to many, rightfully holds the title of 'poster child' for the phenomenon of TR.

In chapter 3, I have provided a review of the relevant social science literature and have positioned my own research and contribution. The chapter has two main sections: the first section I described sociological research in the area of RM in general. Considering the large volume of research in the field of RM, I had to carefully choose to include those works that are meaningfully-related to my own research and would by some means offer a helpful insight into issues and themes relevant to my work. All these social science studies, although not directly addressing the phenomenon of RM Translation, are nonetheless very important as both a source and clarification of sociological concepts and contexts that are useful when exploring the more narrow area of RM TR.

The second section comprises a review of the social studies of RM translational research (the so-called paradigm from 'bench to bedside'). As both RM and TR are

considered nascent paradigm shifts in medicine it is no surprise that so far there are only a few social science studies that have sought to explore them. These studies have drawn on a variety of concepts from various research traditions such as the sociology of expectations, boundary work, regulation and standards, and ethics. To complement the sociological research described above I review recently emergent literature on what scholars have called 'translational ethos'. The last area of sociological literature that I review (in Chapter 3) is the literature on 'sociotechnical networks and heterogeneous engineering' and is the research area where this study aims to contribute the most.

Chapters four, five and six present the empirical findings of the research. The thesis concludes with chapter seven where theoretical arguments and empirical findings are weaved together to provide the answers to the research questions presented in chapter one and thus satisfy the objectives of this study.

Research Questions Revisited

As explained in chapter 3, the process of RM Translation has been at the forefront of sociological research since the development of the first cell therapies and tissue engineering products. In most cases, the phenomenon of Translation has been studied and understood in terms of various stakeholders' perspectives including biomedical scientists, clinical practitioners, regulators and individuals working in the biotechnology or pharmaceutical industry. However, as it has been observed in the relevant literature, Translation is not a phenomenon that just happens. Against this background, this thesis set out to investigate the role of a specific group of stakeholders- bioentrepreneurs- in the Translation process with a view of understanding the phenomenon through the eyes of these very 'central' actors and identifying best practices that could assist in facilitating their work and hence the process of Translation.

In order to clearly spell out the contribution of the study to 'sociological research' it is useful to restate the research questions and use them as a 'scaffold' on which to organise and present the empirical findings. The following four questions (and their sub-questions) constituted the focus of this research:

1. **How is Translation being conceptualised and practised by bioentrepreneurs in the Regenerative Medicine field in the UK?**
    a. What are the key challenges (problems) that need to be overcome and at which stage of the Translation process?
    b. How do bioentrepreneurs address each challenge?

2. **What are the translational models that bioentrepreneurs identify?**
    (e.g. funding models, IP models, regulatory governance models, collaboration models)

3. **What is the importance of the bioentrepreneurs' contribution?**
    a. What are the resources bioentrepreneurs need to employ (financial, human, etc) in order to lead the products/therapies through clinical and commercial Translation?
    b. Do they relish their 'coordinating' role?

In order to answer the above questions, the thesis took as its starting point a 'sociotechnical network' and 'heterogeneous engineering' approach on the RM spinout creation process that is integrating the social, individual, technical and economic dimensions. By bringing the theoretical arguments (Chapter 3) and empirical findings (Chapter 4, 5, and 6) together, answers to the research questions can now be put forward.

The Challenge of Funding

One of the main barriers identified by bioentrepreneurs as hindering RM Translation is the funding deficit for translational projects. As a response, my research has sought to unravel the origin and dimensions of this deficit as perceived by RM bioentrepreneurs who have made attempts to clinically and/or commercially translate promising laboratory outcomes. The main finding is that bioentrepreneurs attribute the profound lack of translational funds to an incorrect understanding on behalf of public funders of what TR really involves and the subsequent misallocation of supposedly 'translational funds' to what bioentrepreneurs claim to be basic (fundamental) RM research.

In the absence of successful public funding strategies and in light of the widely shared feeling of TR funding uncertainty, I sought to explore the views of my informants with regard to the other two alternative sources of capital, namely venture capital and industry investments. My findings suggest that informants perceive venture capital as the least likely funding source for their RM translational activities. According to the majority of the bioentrepreneurs in this study, venture capitalists have 'closed their minds' to early-stage investing (required by RM spinouts and small start-ups) and are looking for low risk and short-term investments (again not a feature compatible with the long-term development trajectory involved in RM therapeutics).

For few of the informants the fall in the number of available VC funding opportunities is a logical and expected consequence of a dent in the early RM companies track records caused by poor returns and the consequent bursting of the RM technology 'bubble'. In short, the perception that dominates amongst the informants in this study is that there is a serious shortage of risk capital that can be accessed by RM spinouts planning commercial Translation. This restricts growth and hence threatens to undermine the UK's position in the RM field compared to other countries (such as the US) where VC early-stage investing is a dynamic and strong part of the economy.

Perhaps this profound lack of risk capital is one reason why more 'non traditional' sources of capital who are not so concerned with historic performance indicators, but can recognise the technology's potential, have emerged and are being considered; for example, big pharma and, to a lesser extent, the biotechnology industry. Indeed, according to interviewees, the drug industry 'is keener on stem-cell technologies than ever before'. Pharma's interest however is not in using stem cell for developing replacement tissues. Instead, the wave of new partnerships recently announced by big pharmaceutical firms aim to use stem cells as tools for the screening of drug candidates.

The use of stem cell-based tools in conventional drug discovery programs is varied, but is based on the reproducibility of deriving clinically relevant cell types (as diverse as cardiac myocytes, sensory neurons, pancreatic progenitors, and so on) and using them to test the safety and effectiveness of candidate drug substances. The approach is often referred to as 'disease in a dish' model of Translation and it applies the pharmaceutical

strength in the R&D of small or large molecule projects to find novel therapeutics that modify endogenous stem/progenitor cell fate. Given the fact that the 'disease in a dish' paradigm is able to profit from the strength of biopharmaceutical companies, the commitment to Regenerative Medicine based on combining drug discovery and stem cell platforms that is taking hold across the industry, appears not to be a surprise to bioentrepreneurs. However, the majority seem to believe that ultimately cell replacement therapies will start to become of particular relevance, as bio-pharmaceutical companies move away from a focus on palliative treatment and seek opportunities in disease modifications and eventually personalised, custom-made replacement RM therapy.

At present, however, pharma's involvement appears to be obscured, especially with regard to small academic spinouts, with significant factors comprising insufficient demonstration of efficacy, regulatory and safety concerns as well as lack of familiarity with the complexity of developing a cell-based product and the business model for commercialising it (including the 'downstream' challenges of distribution, delivery, reimbursement).

It may well be that the funding strategies followed by UK research councils and biomedical research charities need reassessment. Indeed, it is probably a lack of understanding from both sides- the funders and the technology developers- about what translational research really involves and consequently how it could best be funded.

How is the Funding Challenge Addressed?

Respondents admit to following a variety of funding strategies in order to transfer their findings from the laboratory to the clinic. These include trying to persuade public sponsors that their work is in the realm of TR and creating the 'right' heterogeneous entrepreneurial team that will inspire trust to private funders and will attract the necessary resources. A few interviewees have admitted to considering the possibility of changing their research agendas and focussing on the creation of what they perceive as 'attractive' products favoured by public (cell therapies) or private sponsors (e.g. cell based drug discovery tools).

What are the Translational Models that Bioentrepreneurs Identify?

Even in the presence of abundant funding, it has proved difficult to translate the concepts and paradigms of RM into clinically successful procedures and, even more importantly, into commercially viable products or processes. Indeed, it is well known in the RM sector that after a great deal of promise and hype in the early 1990's (back then the TE industry), the industry failed to provide the anticipated novel products. Much of the blame for this failure has been directed towards the business models and their slow response to the changing conditions including a product development trajectory that was far longer than originally envisaged. Even at this stage, no universally applicable business model has been identified for RM and as noted earlier in the thesis, this uncertainty has been partly blamed for many of the difficulties still faced by the RegenMed industry. In the respondents' accounts we can see a divergence of views and practices with regards to business models.

First, there is a divergence of views dependent upon whether a venture should concentrate on cell therapeutics and follow a long-term Translation trajectory or whether it should focus on short-term (quick economics returns) business models such as those based on the development of stem cell-based drug discovery tools. Informants mentioned various reasons to justify their choices including the preference shown by public funders for cell therapies, the potential for bigger returns and the importance for concentrating on a technology instead of diversifying and risking becoming diffused. Overall however, no consensus could be reached among the bioentrepreneurs, which lends credence to my claim that there is probably no ideal business model for RM- at least at this stage- and that it makes sense for RM teams and companies to operate business models as diverse as the products they are developing and labouring to bring to the market.

Second, even among those who chose to develop cell therapeutics there was a divergence of views dependent upon whether the future of RM will be in the (allogeneic) product-based or (autologous) service-based industry. In the former case, allogeneic (universal) products could be supplied to healthcare facilities in a way similar to that for drugs or devices. In the later, we could imagine the commercial RM service operating within the healthcare facility, deriving cells from patients, expanding them, combining them with scaffolds (matrices, growth factors or other biomaterials and

substances) in order to provide a customised service. Again there is no obvious consensus that emerges from the narratives. Some interviewees seem to be convinced that the allogeneic, off-the-shelf approaches will dominate as they represent technologies that are more comparable to molecular pharmaceuticals, hence is possible to envisage a similar production, quality assurance process and commercialisation. Others however are more convinced by the autologous, service based approach and doubt that in certain areas RM will ever survive commercially if it based on selling a product.

However, despite their beliefs about which business model is going to dominate, they all seem to be aware of the 'volatility' of the sector and they also appear willing to 'change and adapt'. Indeed, bioentrepreneurs seem to be aware that changing business models, extending or often limiting their range of candidate products, changing and expanding their scientific and technical expertise and even changing the content and direction of their research are all plausible scenarios that might become reality in light of necessary 'survival decisions'.

This pronounced divergence of views seems to cut to the very heart of the complexity and techno-scientific uncertainty that characterises RM science at this stage. Perhaps it is through further scientific and technical progress and breakthroughs that some of the current challenges will be met and a few distinct, 'safe' and 'tested' business models will start to emerge from the hazy commercial landscape. It is perhaps then that sponsors will also become less cautious and more will eventually step in to support the ventures, Translation and hence the sector.

The Challenge of IP

As commercial RM remains a paradigm in search of product success, one way to clear-up the 'cloudy' commercial landscape is to clarify issues of intellectual property rights and ownership. At the end of Chapter 4, I have shown how bioentrepreneurs understand and approach intellectual property rights (IPRs) in the context of research, product development and commercialisation.

The two main IP-related issues that have emerged from the narratives include the freedom to operate in the RM field and the ability to protect their own work and exploit their 'market exclusivities'. As it is the case with other types of small high-tech ventures, RM spinouts are based and centred on the development of proprietary technology or know-how protected by patents which makes IP one of the key components in attracting finance.

Once more, informants' views diverged depending on the type of product under development and the type of company through which they operate. In general, submitting 'expensive' patent applications and 'eating' from the spinout's limited financial resources is perceived as problematic by academic-based founders, although views are different when it comes to larger RM start-ups (these can afford to submit patent application 'as a precaution' even for developments that are considered of relatively little importance in the current context of business goals). A few interviewees perceive the field- especially hESCs- to be particularly vulnerable to patent thickets, potentially 'slowing down' and skewing the overall development of new products, in addition to dampening investor interest in commercialisation.

How is the Challenge of IP Addressed?

To avoid the high costs associated with patenting, respondents stressed the need to prioritize which patents are 'critical' for product development and must be protected and which patents will have to be 'dropped'. Clearly, this is not an easy decision to make especially when the product is at the very early stages of Translation and neither scientific nor technical aspects have been 'stabilised'. One informant claimed to have avoided the 'IP hurdle' by avoiding the markets were the relevant patents hold.

What are the Translational Models that Bioentrepreneurs Identify?

The respondents mentioned two IP access systems that they think would facilitate access to IP by reducing the costs and inefficiencies identified above: patent pools and the already established (in the UK) SC4SM model. As described earlier (chapter 4), a patent pool is an arrangement between two or more patent holders in which the relevant patents are licensed jointly as a 'package'. Obtaining a single license from the

pool means that the licensee has access to all the IP covered by the patents in the pool. The UK-based SC4SM model described by one of the participants, operates in a very similar way to patent pools based on managing the collectives rights of all of its members, thus avoiding potential coordination failure among its members (and other 'external' IP owners) and minimising high transaction costs usually associated with upstream/downstream licensing.

The Challenge of Regulation

In Chapter 5, I have shown how RM bioentrepreneurs deal with regulatory uncertainty during development and Translation of their products, how they actively contribute to the building of regulatory infrastructure and finally what they perceive as the biggest regulation-related obstacles that need to be overcome before successful RM Translation is realised. In addition, the fact that I collected my empirical data in two different time points (before and after the seminal ATMP regulation) gave me the opportunity to compare perceptions and attitudes among the participants and how these have evolved during this very important period of transition for the RM field. A number of significant concluding points have emerged and are discussed below.

For the majority of the interviewees before the ATMP regulation came into force, the regulatory picture was cloudy. Informants were primarily concerned with the classification of their products/therapies and appeared frustrated by arbitrary product classification and lack of harmonisation. This frustration and uncertainty apparently spilled over into regulatory authority jurisdiction and the perceived 'duplication' of work that seemed to burden and discourage translational efforts. All informants stressed the need for harmonisation and looked forward (albeit with caution) to the new (ATMP) regulations that were expected to clarify the classification criteria and streamline the route to approval.

I have also shown that regulatory compliance without guidance and appropriate infrastructure to support it is a significant burden to the bioentrepreneur community and the teams behind the ventures. With numerous new 'discoveries' every day the pressure to control them and safeguard the public has lead to an influx of guidelines. Overall, the pressure to comply with the ever-changing regulation is sometimes seen as

distorting the necessary balance between necessary regulation and the need for progress and innovation. It is not an exaggeration to say that regulation was seen by the (first round) interviewees, as yet another hurdle to overcome in addition to the scientific and technical challenges of product development.

How is the Challenge of Regulation Addressed?

In a significant departure from other studies and other fields (e.g. pharma industry), bioentrepreneurs/developers in RM claim to play a decisive role in the shaping of the emerging regulatory landscape. Either through being involved in discussions and negotiations with regulators over the classification of their candidate products (mainly before the introduction of ATMP regulation) or providing input on the use, safety and effectiveness of manufacturing/automation equipment and protocols, the informants present themselves as 'active shapers' of what is seen as 'work-in-progress' regulation.

In other words, the bioentrepreneurs in this study clearly confirm that they are far from passive recipients of guidelines and protocols. On the contrary, they describe how they seek early collaboration with the regulators and how they 'educate' the regulators on the novel technologies. This kind of 'synergy' between the 'regulating' and the 'regulated' (stakeholder) communities is perhaps unavoidable in such a scientifically and technologically revolutionary paradigm where the notion of expertise is virtually redefined everyday.[207] In short, this co-shaping of regulation that is welcomed by bioentrepreneur/developers and encouraged by regulators, indicates a more participatory approach and signals perhaps an age where bioentrepreneurs will have a more formal role in the regulation and, consequently, the regulatory policy formation process.

In the context of RM Translation as a 'network', even the regulators are important suppliers of problems, knowledge and skills. On the one hand, product developers seek early communication with regulatory agencies and on the other hand, agencies send their teams to learn from developers in order to try and produce practical

[207] Indeed, informants have drawn attention to occasional 'mistakes' of regulatory authorities in appointing advisers- on the basis of their professional status- but who would not be regarded as 'true experts' in field. The overall perception is that the recruitment of non experts clouds the developer-regulator communication and hence delays and even endangers the RM field.

guidelines. Consequently, regulatory guidelines are 'constructed' as a collaborative effort in which 'heterogeneous engineers' from the RM company and regulators negotiate, experiment, and design. Since the respective competences of RM developers and regulators are complementary, their collaboration represents a proper example of how heterogeneity may be achieved through institutional arrangements. Judging from the respondents' narratives this 'co-shaping' of regulation is no simple process of knowledge integration. Instead, it is presented as a series of problem-solving negotiations in which different kinds of knowledge are debated and checked and where the outcome also depends on the persuasive ability of the 'heterogeneous engineers' (bioentrepreneurs) involved. As noted by one interviewee, in these early stages of the RM science and industry the artifacts (in this case an automated manufacturing machine) which are being built are characterised by a substantial level of flexible interpretation. In other words, in many cases, although the physical design of a technology may be stabilised (in the sense that there is a more or less fixed technical design), the applications may be negotiable. This flexible interpretation of the fixed design means that 'problems' (standards, technical guidelines, reagents) will keep changing and what counts as relevant expertise and equipment is rather open.

What are the Translational Models that Bioentrepreneurs Identify?

Another important point to have emerged from this part of the study is the existence of a complex relationship between the type of product under development and the perception of a future regulatory approval that is either 'easy' or 'difficult' to achieve. I have shown that informant perceptions of an 'easy' or 'difficult' regulatory route are not straightforward- that is they are not simply related to the type of cells autologous or allogeneic used and the therapeutic approach followed but are also dependant upon the setting of therapy production such as academia or industry. In short, academia-based bioentrepreneurs perceive autologous approaches as more manageable in terms of standard compliance and regulatory approval, while start-up founders who operate on a larger scale seemed to believe that because of their 'logistics', allogeneic products 'make more sense'.

One more repeating theme to have emerged from the fieldwork and the only case where all informant views seem to have converged is the predictability of animal

models in RM TR. Indeed, although in other biomedical fields the debate is still raging about methods to evaluate the clinical relevance of basic animal studies and whether and to what extent animal models can predict with sufficient certainty what will happen in humans, in the case of the RM bioentrepreneur community, the verdict is unanimous. Animal models simply do not work. The disparity between animal models and human clinical trials in the RM field is perceived as insurmountable because of the 'special' relationship between the cells, the host and the therapeutic outcome. Interviewees called for more guidelines and support in pursuing FIH experimentation, which they perceive as the only useful way to evaluate the cell-based therapies.

The Challenge of (Effective) Collaboration

Bioentrepreneurs in this study expressed dismay on stringent IP policies and claimed that universities, research sponsors and other translational entities such as hospitals, are increasingly seen to overestimate their IP assets. This, in turn appears to distort business decisions which nowadays are inextricably linked to decisions of cross-departmental, cross-institutional and, perhaps most importantly, international collaborations. Therefore, one of the main conclusions to be drawn here is that the existing IP policies operated by many UK universities (as well as public research funders) are inhibiting valuable translational collaborations. Although it is legitimate for academic institutions to seek to capture some of the economic value associated with an innovation (in the creation of which they have invested), it is equally important to be aware of other issues too and evaluate them in a balanced way.

In the context of RM Translation as a sociotechnical system, the reverse salient (Hughes, 1983) is a useful concept for analysing overreaching IP policies. Although not a technical element (in line with the sociotechnical standpoint), IP policy is a factor (subsystem) of the system that appears to hamper the progress of the system (through hindering translational collaborations, and hence Translation). Given the fact that reverse salients limit system development, the further progress of the system lies in the correction of the reverse salient, where correction can be attained through either incremental or radical innovation- in this case a review of the IP policies. In the case or RM IP, the reverse salient refers to an extremely complex situation where individuals (biomedical researchers, patent holders, TTO executives), material forces (patents,

material transfer agreements) and other factors, all have distinctive, causal forces and play their part in the process.

In addition to the IP-related hurdles, the different 'cultures' of biomedical researchers, clinicians and industry have also been mentioned by a few interviewees as a barrier to successful collaborations. For example, clinical practitioners work in different timescales to basic researchers and appear to have different (more patient focussed) objectives, whereas commercial sponsors such as venture capitalists and industry show a more risk averse funding attitude and a clear orientation towards products and route that will ensure lower costs and 'quick- returns'.

How is the Challenge of (Effective) Collaboration Addressed?

To overcome the hurdles placed by stringent and 'unrealistic' university IP policies, bioentrepreneurs feel they have to 'argue' the with university technology transfer offices about IP, potential collaborations and rules of research contact. As informants claim, this is often a frustrating process and more often than not results in the cancellation of the collaboration.

Despite admitting to the 'different culture' hurdles, respondents emphasize that there are certain types of collaborations that lend credibility to the venture such as the involvement of business and clinical expertise. Especially clinical expertise are considered as the only way to ensure that the product under development is clinically relevant, which increases the possibility that it will be adopted by the clinical community. Additionally, many interviewees have suggested that the involvement of clinicians in the innovation team, makes it easier to secure financial and other resources. Not surprisingly then, bioentrepreneurs have sought strategies to ensure that communication/collaboration with RM clinical investigators is arranged early on in the therapy development process and that clinical advice is incorporated in the 'design' of the therapy. In short, as with the cases of successful 'societal embedding' (of a biotechnology product) where societal actors are given an early on constructive role, in RM 'concurrent engineering' is encouraged between product developers (bioentrepreneurs) and clinicians. In other words, clinicians are given a constructive role and hence the chance to contribute (early on) to the product development

process; this includes contributions which signal difficulties and may lead to shifts in the design of the product/therapy, up to decisions to halt the development altogether.

What are the Translational Models that Bioentrepreneurs Identify?

My findings suggest that there is some basis to the fear, often voiced by the critics of university industry relations, that salient IP-related obstacles impede translational collaboration in the RM field. Furthermore, like any large and diffuse organisation, it is difficult to identify (let alone intervene and change) how decisions are made within a university and this, according to interviewees, makes IP negotiations a time consuming, unpredictable and often frustrating process. Thus, a key message emanating from the informants' accounts is that less emphasis must be given to monetary returns and more emphasis on operating an IP system that does not 'frighten off' potential collaborators and, therefore, weakens future prospects of the bioentrepreneurs' efforts.

At the last section of the chapter six ('The Art of Collaboration'), I contemplate a translational model based on what is perceived as the most important type of collaboration for Translation- that is the collaboration of bioentrepreneurs/developers with clinicians. Drawing on data from the interviews and the literature it is not difficult to see that a number of 'conditions' must converge in order for clinical Translation to be realised. To some extent the 'translational model' I identify de-privileges the 'empowered' position of bioentrepreneurs in the Translation process by involving a level of external and uncontrollable factors. In short, according to the model, apart from the optimal product design and the optimal product delivery, there is one more condition to be met- the product must 'agree' with current clinical practice. This condition is largely out of the product developers' control. It is perhaps what happens in the case of radical innovations in biomedical practice where it may take some time before they are adopted by clinicians and their benefits realised.

What is the importance of the bioentrepreneurs' contribution? (Research Question 3)

What are the resources bioentrepreneurs need to employ (financial, human, etc) in order to lead the products/therapies through clinical and commercial Translation?

Chapter 6 commences with the perceived lack of 'Research Translators' currently available in the UK and in the RM field in particular. Research Translators are defined by the Medical Research Council (MRC) who created both the post and the term, as cross-disciplinary individuals with experience and skills in 'facilitating the Translation of basic research finding into tangible health benefits'. The suggestion that emerges from my data is that, in the absence of such qualified individuals, RM bioentrepreneurs like the ones interviewed for this study, are 'encouraged' to assume the 'knowledge broker' role that is so critical in achieving successful Translation outcomes.

If the process of RM Translation can, in fact, be depicted as a sociotechnical network (as described by Hughes and Law), then bioentrepreneurs are the creators of this network- the system builders and the heterogeneous engineers. The concept of 'heterogeneous engineering' has been coined by John Law (who was inspired by the work of Michel Callon and Bruno Latour in actor-network theory ANT). While the term 'engineering' as it is used in (ANT) may be best described as 'getting to work', the adjective heterogeneous emphasises that this 'getting to work' takes hybrid manoeuvres mixing and coordinating people and things.

As stated earlier, RM bioentrepreneurs (often) assume voluntarily the role of 'heterogeneous engineer' in order to steer their findings through the process of Translation. According to MacKenzie (1996) and his discussion of Seymour Cray as the 'charismatic engineer', invention is the bringing together of many resources and building of heterogeneous networks. Brilliance, charisma or great leadership is in placing oneself at the front of these networks.

RM bioentrepreneurs are builders of Translation networks and do 'heterogeneous engineering'. It must be emphasised, however, that (in this case), the outcome of heterogeneous engineering is not only the RM product that is developed. Even more importantly, it is the creation of the 'Translation network' itself. In other words, for successful (therapy) Translation bioentrepreneurs must simultaneously build artifacts and the environments in which those artefacts can function. In fact, (at least) in the case of RM Translation neither of these activities can be done on their own.
Law's networks and Hughes's (sociotechnical) systems bundle many different actors and resources together. System builders need scientific and technical knowledge but

they also need financial, material, and social resources. For network creators, nothing can be reduced to only one dimension and technology requires heterogeneous engineering of a dramatic diversity of elements (Bucciarelli, 1994; Law, 1987). In the same way, successful RM Translation draws on multiple types of resources and simultaneously addresses multiple domains. The scientist-turned-entrepreneur faces scientific, technical, social (legal, regulatory) and economic obstacles all at once and has to bind solutions to these problems together in a configuration that 'works'. To do this s/he must also enrol any number of actors, not all of whom may be immediately compatible (with the rest of the network).

Not surprisingly, large-scale heterogeneous engineering (like the one necessary for Translation) is difficult (Law, 1987). Law's network approach stresses this by noting that 'there is almost always some degree of divergence between what the elements of a system would do if left to their own devices and what they are obliged, encouraged, or forced to do when they are enrolled within the network' (Law, 1987: 114). In short, in Law's scenario, 'the environment within which a network is build may be treated as hostile, and heterogeneous engineering may be treated as the association of unhelpful elements' (1987:114). This description fits well with the narratives of bioentrepreneurs who have mentioned the interaction with actors who have different cultures (e.g. clinicians), different objectives (e.g. universities seeking to maximize return on investment), different reward structures (e.g. VCs attracted by short term returns), and regulators (interested in maintaining public trust in the regulatory system).

Given that heterogeneous engineering is a difficult task it is interesting to have unravelled a variety of attitudes towards performing it. Indeed, my data suggest that some bioentrepreneurs are more committed to this 'operational part' of Translation than others. Indeed, a variety of different commitment levels have emerged ranging from what I have termed bioentrepreneur 'enthusiast' to the expression of a very hesitant or even dismissive attitude toward translational endeavours, especially those that involve the creation of commercial entities such as academic spinouts or small RM start-ups. However, even when including the cases of the few informants that expressed their reluctance toward creating a company, the founders that I have interviewed, are indeed what I would call 'above the average' entrepreneurial, displaying 'networking', 'organising' and 'integrating' skills.

The Contribution of the Thesis to Concepts and Theories in Sociology

In the previous sections, I drew the main threads from approaches (theories) on sociotechnical systems (Hughes, Law, Callon, MacKenzie) and applied them to the study of RM Translation. This is not to say however that all concepts and ideas from these approaches have been utilised. Only those that seemed to provide the most fruitful analysis for comparison and insights for the study of RM Translation were chosen. In this section, I summarise the findings from the comparison and spell out the contribution of my work to concepts and theories in Sociology (particularly the social study of networks/sociotechnical systems).

As I have already mentioned in chapter 3 (in the description of the theoretical framework), I consider the process of RM Translation as an example of what Thomas Hughes calls a sociotechnical system. The core 'element' of the system is the RM product/therapy under development as well as the network itself. Five more 'elements' of the network exist around this core element namely- regulation/regulatory bodies, public sponsors (research councils, charities), commercial sponsors (VCs, industry), academia/biomedical researchers, clinic/physicians.

Similarly to technological systems that can be hampered by reverse salients, Translation networks are also plagued by them. Drawing on the respondents' narratives a number of reverse salients can be identified: for instance, stringent university and sponsor IP policies which hinder translational collaborations and increase the cost of research and development. By maintaining these policies as part of the network, the whole system's output performance is compromised. A similar threat may be seen in the case of the ever-changing regulatory guidelines. The continuous effort to comply with the guidelines consumes valuable resources and holds the system back from attaining that higher output performance.

In this study, the creators of the network- the heterogeneous engineers and the system builders- are the scientists-become- entrepreneurs. The main argument of the thesis is that there would be no successful clinical or commercial RM Translation if it was not for the 'weaving' and mobilising of bioentrepreneurs and the subsequent creation of their heterogeneous networks. So, in this view, the task of sociology is to characterise these networks in their heterogeneity, examine the interactions between the various

actors (and if and how these interactions are mediated) and finally, explore how it is that they come to be patterned to generate effects like organisations, standards, legislation, alliances, patents and therapies.

Overall, the thesis aimed to make a contribution to our understanding of the work of the bioentrepreneurs as key actors in the Translation process and the 'heterogeneous' factors that critically shape the Translation process itself. The study is unique in integrating a story about these factors into a single narrative and it highlights a number of important policy lessons that could help further refine the process of Translation in this promising area of biomedicine.

Implications of Research for Policy

Several policy implications of this study have been identified. In the following paragraphs, I summarise the views of respondents on what they perceive as the biggest hurdles for RM Translation in the UK and I make a few recommendations for overcoming them.

Increasing Dedicated Funding for RM TR

From the interviewees accounts there is no question that the UK biomedical science excels in basic RM research. Inside the community of bioentrepreneurs there is a strong conviction, however, that greater levels of funding have to be dedicated translational research especially for the support of animal studies, early-stage human experimentation and clinical trials. Moving their work from the lab bench towards prototypes, to a larger and faster scale and ultimately patients is proving extremely difficult hence discouraging many scientists from entering the field altogether.

One possible solution, would involve funding agencies across the discovery- product development continuum expanding existing interagency partnerships and establishing new ones. Given the different priorities (and missions) of research (e.g. councils, charities) versus application sponsors (NHS), limited resources are available from all parties. Hence collaborative development of investment priorities (in the field of TR) and pooling resources may be the only way to ensure that an adequate investment is

made in the critical area of RM TR. In other words, setting aside what is currently been seen (by bioentrepreneurs) as competing agendas will enable biomedical research sponsors and service funding agencies to develop coordinated translation programs thus integrating research with practice. Furthermore, such funding arrangements/schemes will ensure that the novel products being developed are actually informed by lessons learned from basic research as well as medical practice.

Changes in University and Funder Intellectual Property (IP) Policy

Although all respondents agree that patents are important in attracting private sector investment, the majority have also drawn attention to the negative impact university and sponsor IP policy can have on building research and industry translational collaborations in the field of RM. More specifically, bioentrepreneurs have criticised the emphasis given by universities and funders on legal contractual agreements for the exchange/sharing of scientific materials and reagents and believe that they are slowing down the pace of Translation, discouraging researchers from collaborating, and constraining the freedom of small enterprises (such as university spinouts) from operating.

The need to improve the management of IP by both universities and sponsors has been identified by all informants. Universities, research funders and clinical services providers (NHS) must address the issue by collaboratively drawing guidelines that will both ensure acknowledgement in downstream research and protection of the inventors' rights but at the same time avoid excessive rights of ownership in research results and/or demanding agreements that are overreaching and overprotecting (based on the fear of losing financial returns even when perceived as improbable by inventors/bioentrepreneurs themselves). This way, all relevant parties (universities, hospitals, firms) will save time and resources and will be able to concentrate on the development of much needed therapies.

Addressing Regulatory Uncertainty

Prior to the introduction of the ATMP regulation, regulatory uncertainty both in terms of regulatory agency jurisdiction and product development guidelines was identified as one of the main hurdles for RM Translation. Bioentrepreneurs reported a desire within

their community for greater overall clarity regarding the current legislation, guidance and standards to be used. The interviewees felt that there was a need for greater standardization and harmonisation in scientific and technical areas that would endure fair classification of products and avoid unnecessary delays and costs in the development and approval of products. Apart from the perceived lack of standards and manufacturing guidelines, part of the uncertainty was also based on the role of regulatory agencies such as the HTA, HFEA, MHRA, and EMA and the overlap of their regulatory jurisdictions.

Development and introduction of the ATMP was welcomed by these key members of the RM community and it was anticipated to make researchers and developers feel more reassured about the clinical and commercial Translation of RM therapeutics. However, bioentrepreneurs interviewed after the ATMP regulation came into force, although satisfied with the introduction of formal and comprehensive guidelines they admitted to being concerned about the potential differences in interpretation of the guidelines as well as the enormous effort required to comply with the new regulation.

In order to address the concerns of bioentrepreneurs (and other stakeholders), regulatory agencies such as MHRA, HTA, HFEA and EMA must provide clear guidance to the RM community across the whole spectrum including the process of research, development, trials and commercialisation/approval of cell therapy products. This not only requires to identify regulations and guidelines and link them to the corresponding stage of therapy production but to provide the bioentrepreneur community with the essential resources (documents, financial resources, personnel) that will expedite the Translation process.

Fostering Collaborations between RM TR Stakeholders

All respondents acknowledged the importance of fostering effective collaborations between the various 'spaces' of Translation- academia, clinic, industry, regulators. As mentioned previously this could be facilitated through establishing collaboration schemes with shared/combine funding and by more efficient management of university IP.

All bioentrepreneurs agreed that collaboration with clinicians is especially important as it increase the chances of the product being correctly designed and developed hence minimising costs and increasing the possibility that it will be adopted for use when finalised (that is its efficacy and safety proven). Thus, early on collaboration with clinicians should be encouraged through schemes that cross institution and national borders with the aim to acquire the most relevant and up-to-date clinical input.

Employing 'Research Translators'

Crucial to fostering collaboration during Translation is the role of 'research translators' as piloted by the MRC. According to bioentrepreneurs, research translators that are adequately trained and experienced in the process could promote the understanding of what TR really is, therefore changing the various cultures across the Translation spectrum, and could also be the crucial link between TR funders, basic researchers and product developers. This will not only take the 'knowledge brokering' load of the shoulders of bioentrepreneurs but it will also speed up the process and avoid costly R&D and commercialisation errors. These research translators which would (ideally) be appointed in common by sponsors, academia and the clinical community, could create 'Knowledge Brokering Networks' (or Networks of Translation') that will enhance communications and collaboration between UK universities, spinout companies, NHS and the industry.

Formalising the Role of Bioentrepreneurs in Policy Shaping

Bioentrepreneurs are at the forefront of Translation and have the skills and knowledge to facilitate the process. According to their accounts, their role is critical for successful translational outcomes especially through what they see as 'active shaping of relevant regulation'. Policy makers should seek to exploit this valuable resource of expertise by formalising the role of bioentrepreneurs in building regulatory guidelines. This is especially important in the short term as the introduction and training of the 'research translators' will take time and the call of the RM community for help in this area is rather urgent. Furthermore, the importance of having the 'right' people at the right 'post' has been noted by many participants who have also claimed that it is often the

case that non-experts are employed and instead of facilitating the process they 'end up clouding the regulatory issues even more'.

Strengths and Limitations of Thesis

The previous sections identified key factors that promote or prevent the progress of RM Translation in the UK and explored the dynamics of the Translation 'network' aiming to promote the development and commercialisation of RM therapies. It concluded by outlining some policy recommendations.

Against the general lack of systematic data analysis supporting theoretical arguments about the area of RM Translation in general, this thesis succeeded in putting forward a conceptual framework substantiated by empirical evidence for describing and analysing the process of RM Translation in the UK. Its focus on bioentrepreneurs provided a perspective that has not been fully explored before.

Following on from the thesis strengths above, it could be seen as limitation that only a small-scale theory was developed. A PhD thesis does not provide the scope or resources to raise this very specific theory to a more generalised level such as for example a formal grounded theory. This conceptual framework also remains to be validated by other researchers working in other contexts (e.g. other countries). These new contexts would also provide opportunities to refine the methodological approach adopted by this study and to assert its trustworthiness.

As mentioned earlier, the findings and analysis of this study are based on a limited number of respondents. Teams of researchers, as opposed to a single one, would be able to engage with more participants, collect more data and engage in a more 'varied' and perhaps precise analysis and interpretation. The additional data resulting form such studies would indeed enrich the corpus of narratives and would enable the development of a more robust substantive theory.

Finally it needs to be remarked that the author of this study was relatively new to using grounded theory methodology when conducting this research project. Thus, it could be seen as a limitation that considerable time and resources were spend on reading

literature about GT methodology and learning how to analyse data. Nevertheless, the research process- data collection and analysis- has been a very valuable experience that will be of assistance in carrying out similar future projects.

Directions For Future Research

As the work for this thesis progressed, a number of areas deserving future research revealed themselves. In particular, one way to extend the research would be to look into the similarities and differences between the two main empirical sources used in this study- that is the 14 interviews and the three observations of talks from the LRMN. Additionally, the LRMN provides an archive of its presentations throughout the years (in audio format) so there is the possibility for further data collection. More could also be made from the various informal discussions that I have had over the years at this LRMN meetings and the notes that I have kept regarding bioentrepreneur and other stakeholder statements.

One way to explore these data would be to 'use' Hilgartner's 'Science on Stage' study[208] which provides an insightful and useful approach to understanding the production of science advice by bodies like the American National Academy of Science. In his study, Stephen Hilgartner employs Goffman's dramaturgical theory as the framework for his analysis of three National Academy Committee reports on diet and health. In short, 'by creative use of the metaphor of the theatre, Hilgartner examines the production of science and advice and reveals the social machinery involved in its production. He views science advice as a form of drama, and reports, recommendations and criticisms of science advice as performances. He makes the case that expert authority is constituted through strategic impression management and very deliberate control over what is displayed publicly and what is concealed from the audience' (Dersken, 2001:pgs n/a).

Hilgartner's methodological approach and the metaphor of frontstage and backstage could prove very useful as RM is a nascent biomedical field (and nascent industry) and as such it is especially dependent on expert advice. Exploring the process by which the advice is produced, contested and maintained would shed light into decision processes

[208] Hilgartner, S. (2000). *Science on Stage: Expert Advice as Public Drama*. Standford, CA: Standford University Press.

that often remain deliberately hidden from view and are thus little understood. Comparing the personal account of bioentrepreneurs given at the interviews with talks or presentations (of the same individuals) at a LRMN (or other Translation-relevant) meetings, would provide social science with an insight about the degree (if any) of enclosure and disclosure of information in the RM field and the role that it plays in the shaping of knowledge and advice, and subsequently the effect in the shaping of the trajectory of the RM field (including scientific, technological, economic, social, ethical and legal aspects).

Another way to examine the data could utilise the literature on the dynamics of Translation as examined by several authors including Alberto Cambrosio and Bourret and colleagues in the context of oncology and cancer genetics. In particular, Pascale Bourret and colleagues (2006) examine the founding and development of a French bioclinical collective- the Groupe Genetique et Cancer (GGC)- that coordinates and structures the activities of most French actors in cancer genetics and operates simultaneously in the clinical, research, and regulatory domains. The authors are interested in understanding the development of hybrid biomedical collectives (such as GGC) whose activities bridge the research, clinical, and regulatory domains, thus raising epistemic issues that are intimately connected to the evolving material and organisational arrangements that characterise these collectives. 'Within these collectives a heterogeneous set of actors interacts in a number of ways by establishing flexible collaborative arrangements at the national and international level. These interactions give rise to novel practices, engendering and regulating the human [...] and nonhuman [...] entities mobilised by bioclinical activities' (Bourret et al., 2006: 432).

According to Bouret et al (2006), 'collaborative networks offer a strategic empirical starting point for the investigation of new biomedical developments that avoids the twin pitfalls of focussing only on research, strictly defined, or on clinical work, looking instead at the alignment between these activities and at the role played by regulation in this respect' (Bourret, et al., 2006: 457). As the authors emphasize, when they speak of new biomedical collectives they refer to more than simply team work within hospitals. In their view, biomedical collectives (such as the GGC in their article) 'cannot be equated to a mere lobbying institution or a learned society since it obviously engages in collaborative research activities leading to joint publications, nor can it be reduced to a

research network since its activities bridge clinical and laboratory work; the GGC has, moreover, become a policy actor by producing guidelines and regulations that have been officially endorsed. The group, in other words, structures and channels its members' activities by simultaneously producing the (regulatory) environment within which it acts' (2006:457).The notions of biomedical collectives and collaborative networks as described by Bourret et al. (2006) fit well with the phenomenon of RM Translation and might be useful in examining the emerging role of bioentrepreneurs as 'co-shapers' of regulation.

Although heterogeneous maps allow Bourret and colleagues (2006) to inspect the constitutive dynamics of the GGC as a sociotechnical network, there is at least one important way in which it differs from my analysis and that is scale. Single RM spinouts and start-ups navigating the Translation process do not have the scale of the GGC. Perhaps as a next stage the analysis presented in this study could be expanded to include the activities of national networks and consortia focussing on RM Translation and commercialisation such as the LRMN which in essence brings all types of stakeholders in contact with one another and thus gives the opportunity to bioentrepreneurs to form their own (so far mainly) informal networks.

Apart from the above research directions, many of which will require additional data collection and further examination of the relevant literature, a short term plan to build onto this study would be to create an executive summary of the thesis and request the feedback of the study's participants. How do participants think of the questions and their own answers now? What do they think about the answers of other respondents and were they what they expected them to be? Have they been through important changes (for example: does the company still exist, have their roles evolved, and have they managed to clinically or commercially translate any products/therapies, etc.). Such an approach will give me the opportunity to identify which issues examined in this thesis are still at the forefront of UK RM Translation (as experienced by bioentrepreneurs), which issues have been 'solved' and which are those key issues that have started to emerge and would require immediate addressing by all stakeholders including sociologists studying the field of RM.

Concluding Words

This research concludes that at present in the UK, in the absence of adequate institutional support, bioentrepreneurs are central to the 'mission' of Regenerative Medicine Translation and that they have assumed the critical role of weaving the translational 'web'. In other words, bioentrepreneurs are seen to use a variety of means, routes and 'combinations', which according to them are the most appropriate, for achieving the desired translational outcomes. These bioentrepreneurial 'strategies' involve getting therapies to the clinic in an uncertain economic and regulatory climate, providing therapy development and manufacture input and helping shape the emerging regulatory infrastructure, and creating small companies that have the potential to be the vanguards in the 'art' of RM Translation.

Appendix 1

List of Interviewees

	Coded Initials	Brief Description of Role(s)
		2007
1	NC	PI/CSO/Founder of Spinout, 2007
2	NJ	PI/CSO/Founder of Start-up, 2007
3	GL	PI/Clinical Involvement/Co-founder of Spinout, 2007
4	RB	PI/Founder of Spinout, 2007
5	LM	PI/Founder of Spinout, 2007
6	ME	PI/Co-founder of Spinout, 2007
		2009
7	QN	PI/Founder of Spinout, 2009
8	HR	PI/Clinician/Co-founder of Manufacturing Facility, 2009
9	EJ	PI/Co-founder of Manufacturing Facility, 2009
10	RG	PI, 2009
11	MF	PI/Clinician/Founder of Spinout, 2009
12	XB	PI/CEO/Founder of Start-up, 2009
13	LK	PI/Clinical involvement/Founder of Start-up, 2009
14	ZL	PI/Clinician/Licensor of RM technology through an independent Start-Up, 2009

Appendix 2

LSE BIOS

London School of Economics and Political Science

BIOS Centre for the Study of Bioscience, Biomedicine, Biotechnology and Society

Informed Consent to Participate in a Research Study:

"Regenerative Medicine Translation: The UK Bioentrepreneur Experience"

A. PURPOSE AND BACKGROUND

Regenerative medicine, tissue engineering, and stem cell technologies are emerging as potentially revolutionary new ways to treat disease and injury, with wide ranging medical benefits. Successful outcomes of this research depend not only on clinical viability and safety, but also on commercialisation. However, commercial regenerative medicine (with the exception of a few tissue-engineered products) is still in an early yet critical phase. In their efforts to develop, produce and distribute their products both institutions and private biotech companies stumble across frustrating and potentially crippling obstacles that reflect both the controversial nature of this research and the underdeveloped nature of the Translation process itself.

While a great deal of attention has been orientated towards 'ethical' issues, the route to successful translation involves many other areas such as funding, regulation and quality control. This study aims to identify the key factors that affect the process of Translation and commercialisation of Regenerative Medicine products. The research will be a study between UK universities and their RM commercialisation efforts and will be done mainly by interviews with RM bionentrepreneurs to gain an understanding of the Translation, to determine current practices in this area and also to document their experiences of the journey/transfer of cell-based research from the bench to the market.

The researcher, Lamprini Kaftantzi, is a doctoral student at BIOS.

B. PROCEDURES

If you agree to participate in this study, the following will occur:

1. You will be interviewed for approximately 1 hour by the project researcher about the theme(s) described in Section A of this form.
2. The interview will be recorded with a digital voice recorder to ensure accuracy in reporting your statements.
3. The interview will take place at a time and place convenient to you.

4. You will be sent a copy of the transcript to correct or modify.
5. The researcher may contact you later by e-mail to clarify any interview answers.

C. CONFIDENTIALITY

The research data will be kept in a secure location and only the researcher will have access. Upon the agreement of the participants the researcher would prefer not to anonymise the data as it will make the research findings more informative and valuable to the target audience. However, in the case of a participant wishing to preserve his/her anonymity, all identifying information will be removed.

D. QUESTIONS

You have spoken with the researcher about this study and have had you questions answered. If you have any further questions about the study, you may contact the researcher by e-mail at l.kaftantzi@lse.ac.uk.

E. CONSENT

You have been given a copy of this consent form to keep. The signed consent in this study will confirm that you agree:

1. To be interviewed by the project researcher at a time and place of your choosing;
2. To allow the researcher to transcribe the interview and to copy relevant documents or other material that you may provide her/him with;
3. To use these materials in publications subject to the following conditions (please add or delete as appropriate):

    A. That during the interview you may indicate any topics on which you do not wish to be publicly quoted or transcribed;
    B. That you will be sent a transcript of the interview to correct or modify before it is used for any research purposes;
    C. That you retain the right to restrain access to all of the materials you provide, in whatever manner you see fit;
    D. That you can withdraw portions from the interview at any time;
    E. That you may terminate the interview at any time.

Subject to the above conditions, I give my consent to points 1-3.

Signature of Participant: Date:

Signature of Researcher: Date:

Appendix 3

List of Interview Questions

-BACKGROUND-

1. **If you could please tell me briefly about your positions and background**

Basic Researcher/ Clinician/ Head of trials/ Translational Investigator/ Bioentrepreneur/ Founder

2. **What do you understand by the term Regenerative Medicine 'Translation' and how do you relate your work to that?**

3. **What are the projects/ applications that you are currently developing?**

(allogeneic/ autologous, limitations, process)

-Focus on TRANSLATION-

4. **What would you say are the main challenges in product/therapy development? (or in other words, the Translational challenges of the field?)**

Scientific/ Technical Challenges – including manufacturing and scale-up
Regulatory Challenges/ Business Challenges in Product Development/ IP Challenges (ownership issues)

5. **What do you think the UK needs to do in order to improve the process of Regenerative Medicine Translation?**

(for example, what kind of policy interventions would improve the general outcome for the field?)

-FUNDING-

6. **What kind of funding is most important for your work during the R&D and Translation phase?**

NHS / Research Council (Research grant)/ Regional Development Agency/ Venture capital/ Industry investments/ Combination

7. **How did you 'go about' raising the capital?**

-COLLABORATIONS-

8. **RM is a very cross-disciplinary field. What collaborations do you have and what form do these collaborations take?**

Academic/ Industry collaborations (Pharma, biotech)
Clinical/ Regulatory, National/International collaborations

9. **Do you feel that there are any barriers in these types of collaborations?**

(knowledge, culture, ethics, IP)

-REGULATION-

10. **How would you describe the current RM regulation in the UK? Do you think it facilitates or impedes innovation?**

11. **How would you describe your experience with regulatory requirements? Have encountered any specific issues? If so what kind of issues?**

12. **Which regulatory agencies do you communicate with?**

13. **Do you have the chance to give feedback to the agencies on the Regulation?** (panels, committees, etc.)

14. **What is your opinion about the EU attempts of standardisation and harmonisation?**

15. **What is your experience with GMP/ATMP/EU TCD compliance? Did you find it challenging?**

-IP-

16. **What is your opinion on patenting in RM? Do you think it enhances or inhibits innovation?**

-COMPANY-

17. **How would you describe your role in the creation of the company?**

-UNIVERSITY/TTOs-

18. **Have you had any contact/collaboration with the Technology Transfer Office (for the purposes of translation)? If yes, what is your experience?**

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