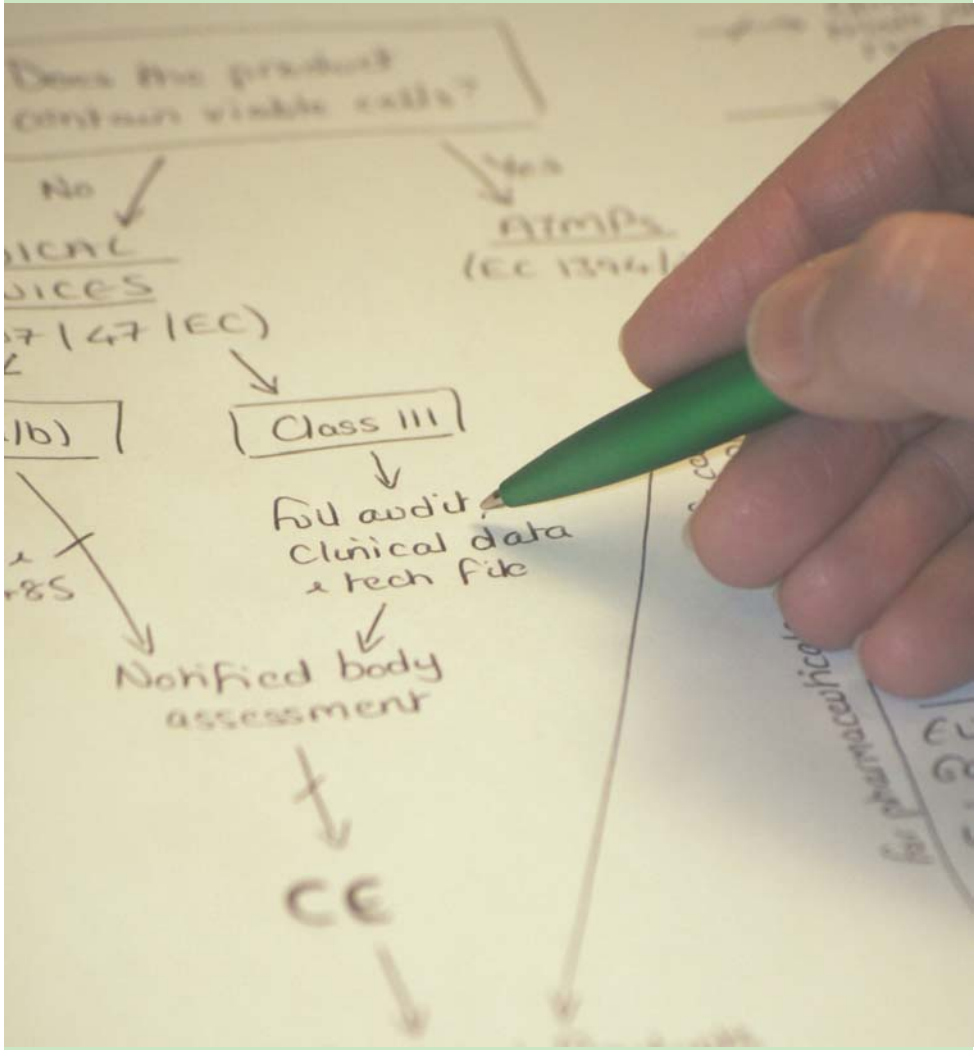
building a viable regenerative medicine industry

a guide for stakeholders



edited by David Williams, Richard Archer and Adrian Dent

remedi

building a viable regenerative medicine industry

a guide for stakeholders

edited by

David Williams,
Richard Archer
and
Adrian Dent

First published February 2010

Wolfson School of Mechanical and Manufacturing Engineering
Loughborough University
Leicestershire
LE11 3TU
UK

ISBN 978-1-907382-18-5

British Library Cataloguing-in-Publication Data
A catalogue record for this book is
available from the British Library.

Printed in Great Britain by
Design and Print Services
Marketing and Communications Department
Loughborough University
Leicestershire
LE11 3TU
UK

preface

Regenerative medicine (RM) is widely seen as the next major innovation in healthcare. The ability to repair and replace damaged cells and tissue, using emerging technologies such as stem cells, offers the potential of lifetime cures for unmet medical needs, including conditions such as Alzheimer's, heart failure, blindness and joint degeneration. The UK has a unique opportunity to build on its strong science lead to create and retain an industrial base in RM that will deliver long term health, wealth and employment. Estimates suggest, within a decade, a million UK patients, £5bn sales and 15,000 UK jobs in research and high value manufacturing.

There are barriers to the emergence of RM in the UK; the industry does not yet have a clear identity and visibility with mostly SME participants, the novel nature of the science and engineering means it is difficult for new companies to attract market investment and the regulatory environment is still evolving.

The key to RM is that the product is the process. Creation of novel manufacturing technologies and skills gives an opportunity to secure a long term industrial presence in the UK that captures the entire value stack. This book provides a guide for all stakeholders to seize the opportunity in achieving that outcome.

Richard Archer

Chairman, *remedi* Management Group, Loughborough University

February 2010

contents

acknowledgements

The work that is reported in this book is a consequence of the effort of the many people and organisations directly involved in *remedi* and also reflects wide interactions and discussions with the broader regenerative medicine community both in the UK and internationally. I would particularly like to acknowledge the contributions of the research teams at Loughborough, Birmingham, Cambridge, Liverpool, Nottingham and Ulster universities; our core industrial collaborators Critical Pharmaceuticals, Intercytex, Regentec and The Automation Partnership (TAP); and other partners including ABHI, emda, East Midlands NHS Innovations Hub, Medilink East Midlands, NHS Futures, NPL and NIBSC. I also thank those SMEs who have allowed us into their businesses to assist them a little and, importantly, to better understand the issues facing them as they grow.

The contribution and commitment of many talented individuals capable of working across the disciplines has been critical to *remedi;* my thanks to you all. A list of book contributors and work package managers appears overleaf - and the references cited in individual research areas show who really did the work. Thanks go to Eleri Bristow for her work on this book. I would particularly like to thank Richard Archer for his committed and visionary chairmanship and advocacy and Paul Hourd for delivering business led project management in an academic environment.

I must also acknowledge the significant funding and support of EPSRC from their Innovative Manufacturing and the Life Sciences Interface Programmes both for the *remedi* Grand Challenge and its successor, the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine. The new Centre, and the EPSRC Doctoral Training Centre in Regenerative Medicine, are collaborations of Loughborough, Nottingham and Keele universities. I would also like to acknowledge emda for their support of our more regionally centred initiatives and Loughborough University for its continued strategic support of our work.

David Williams, Loughborough, February 2010

about the contributors

The *remedi* Grand Challenge brought together research teams at Loughborough, Birmingham, Cambridge, Liverpool, Nottingham and Ulster universities. To detail the full team is not appropriate here, but we list the book contributors and research area managers below.

Richard Archer, formerly CEO of TAP, is an independent consultant. He is Chair of the BIA's RegenMed Industry Group, Chair of the *remedi* Management Group and a Senior Industrial Fellow at IfM in Cambridge.

John Crowe is Professor of Biomedical Engineering at Nottingham with expertise in novel optical instrumentation for measurement and monitoring characteristics of tissue scaffolds and cells.

Adrian Dent is an independent consultant and professional scientific writer. He has had a long association with manufacturing research and the work of many of the *remedi* partners.

Patrick Ginty now works at Loughborough, having previously been employed as a product development scientist at Regentec. He is working with SMEs and specialises in FDA/EU regulatory affairs.

Paul Hourd is the Loughborough-based *remedi* Project Manager with expertise in regulated clinical product development, quality systems and quality engineering approaches applied to GMP manufacturing processes.

Richard Lilford is Professor of Clinical Epidemiology at Birmingham and Director of the Birmingham Clinical Research Academy. He directs projects including the Birmingham & Black Country CLAHRC.

Finbarr Livesey is a member of the IfM in Cambridge and is the Director of the Centre for Industry and Government. His work focuses on how government policy (particularly for innovation) affects manufacturing.

Paul Martin is Reader in Science and Technology Studies at the School of Sociology and Social Policy, Nottingham. His research focuses on the dynamics of expectations in innovation.

Melissa Mather holds an NPL Strategic Research Fellowship at Nottingham. Her research has centred on the development of novel characterization techniques for use in regenerative medicine.

Helen McAteer, as part of Richard Lilford's team at Birmingham, defined the Headroom Method for determining cost effective investment in healthcare. She now works for the Birmingham Clinical Research Academy.

Brian Meenan is Professor of Biomedical Materials at Ulster and a member of the MATCH IMRC consortium. He particularly contributes to *remedi* through expertise in product characterisation.

Erin Rayment is a Research Associate in the Centre for Biological Engineering at Loughborough. Her research focuses on improving cell characterisation for manufacture of safe and effective cellular products.

Nick Rhodes is Reader in Tissue Engineering and Regenerative Medicine in the Faculty of Medicine at Liverpool and contributes, with Ulster and Nottingham, to the research on injectable scaffolds.

Emma Rowley is Senior Research Fellow at Nottingham's Business School. Her contribution to *remedi* was in exploring the factors influencing the clinical adoption and acceptability of RM products.

Kevin Shakesheff is Head of the School of Pharmacy at Nottingham. A prime mover in the creation of the *remedi* Grand Challenge, his expertise is in researching new scaffolds for tissue regeneration.

Robert Thomas holds an RCUK Fellowship at Loughborough and specialises in manufacturing processes for cell based products. He currently leads the Loughborough contribution to a major DARPA project.

Andy West is a Senior Lecturer in the Wolfson School at Loughborough and contributes to *remedi* his expertise in electronics, control and signal processing for healthcare systems.

David Williams is Professor in Healthcare Engineering at Loughborough and Director of the Research School of Health and Life Sciences. He leads both the *remedi* Grand Challenge and the RM Doctoral Training Centre.

introduction - the emerging industry

David Williams introduces the industry and the uncertainties associated with its emergence

executive summary

- Potential to revolutionise healthcare
- An emerging science-based industry
- 'One-to-many' translation important
- Reducing uncertainties key to SME and industry success

Regenerative medicines replace or regenerate human cells, tissues or organs to restore or establish normal function (Mason and Dunhill 2008)[1]. They have the potential to revolutionise methods of health care treatment and improve the quality of life for many. Regenerative Medicine (RM) is now established as an important branch of medicine – the industry is starting to enjoy commercial success with annual sales of over $1 billion; a large number of products are in clinical development having real long-term potential for public health benefit. The market shift to commercial products based on stem cells is likely to mature in the next 5-10 years, with a series of therapies for cardiovascular conditions - cancer, arthritis, and trauma - in the pipeline.

RM is an emerging industry with a unique opportunity to contribute to the health and wealth of the UK. It is a high value science-based manufacturing industry whose products tackle the consequences of aging and chronic disease. The industry, however, currently still faces a number of critical challenges including problems of commercial viability and

[1] Mason C and Dunnill P. A brief definition of regenerative medicine. Regenerative Medicine. 3(1), 1-5, 2008

company growth, limited revenue, and lack of investment. The key issue determining poor sales is the lack of clinical uptake of cell therapy products; this is mainly related to difficulties in establishing clinical utility and cost-effectiveness. Creating an appropriate evidence base is the key to addressing this deficit. Businesses therefore have a primary focus on successfully reaching 'first in man' clinical targets; this must be followed by the 'one-to-many' translation process, such that effective therapies can be produced at scale, and at a price society can afford.

Although effective therapies that demonstrate positive health outcomes are being developed, the key barriers facing firms relate to important aspects of the translation process. These include establishing closer collaboration with clinical end-users, greater regulatory certainty, clearer reimbursement policies based on economic evidence of the cost benefit of product solutions in application in the market place, rapid post-approval adoption, and the need to develop enabling technologies that lower manufacturing costs. Recent regulatory decisions also demand more clarity in the criteria that define product performance.

Solutions to these problems give significant commercial advantage; dissemination of these solutions to SMEs operating in the correct policy environment gives a unique opportunity for industry growth and retention at regional and national levels. The focus of the *remedi*[2] Grand Challenge was to improve our understanding of these processes particularly from a manufacturing perspective. This monograph seeks to communicate this learning in an accessible way for all stakeholders.

[2] *remedi* is one of the four Grand Challenge projects awarded by EPSRC in 2003. Grand Challenges are intended to address major research challenges with the potential for significant impact on national manufacturing priorities, and ambitions far greater than might be achieved by a single research team or in the span of a traditional research grant. The £8M *remedi* Grand Challenge portfolio, led by Loughborough, sought to demonstrate how established bio-science could be transformed into profitable commercial practice and generate affordable therapies while developing the science of manufacture.

a new kind of manufacturing industry

The emerging regenerative medicine industry is a new kind of manufacturing industry. It will use many biological materials as input and its products will frequently be living materials. Like the medical devices and pharmaceutical industries, it has different customers to those encountered in conventional manufacturing – the regulator, the payer, and the healthcare delivery process – and these create a different value system. The regulator and the choice of regulatory route define the new product introduction process and the cost to market; the payer and the healthcare delivery process define the value in the market. However, unlike the pharmaceutical and the medical device industries, the manufacturing process and the manufacturing and distribution system are complex and cost of goods may be significant. Products when they reach the market may also deliver cures instead of just managing symptoms. The benefit of these cures may transcend the traditional boundaries of acute, primary and social care.

We have found it useful to visualise the industry as trajectories of emergence (as shown overleaf) where value is released by the reduction of uncertainty with time in each of the trajectories as the technologies are applied to meaningful clinical applications. In addition to reduction of uncertainty along the technology trajectory, it has also been necessary to reduce the uncertainty associated with regulation and reimbursement. The reduction of uncertainty of business models and consequently investment models allows greater clarity, particularly in the opportunities for exit for early investors. Industry leadership has been critical to progress. Ultimate success will be demonstrated by evidence that allows viable rates of adoption of the technologies in clinical practice.

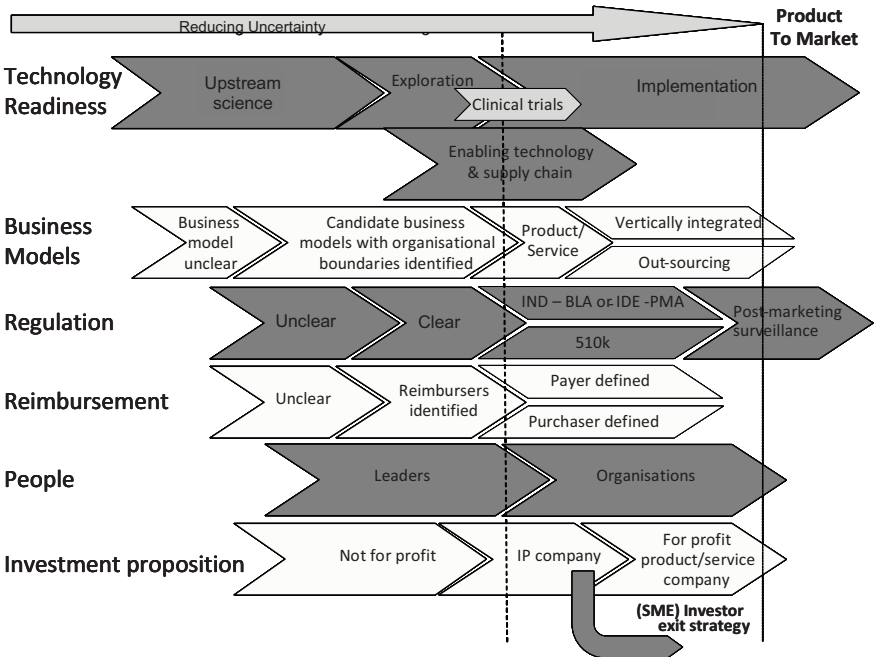


Figure 1. Trajectories for the emergence of Regenerative Medicine as an industry[3]

this book

The creation of businesses and an industry that can ultimately allow the healthcare and economic benefits of regenerative medicine to be realised is likely to be a long game. It will be a game with different rules, much uncertainty, and requiring significant negotiation between stakeholders to manage risk and reward. The intention of this book is to assist, in particular, emerging businesses to navigate some of the uncertainties and to inform the debate that balances risk and reward. The first part of this book summarises much of the learning from the *remedi* Grand Challenge

[3] Williams D. J., and Singh, P., Regenerative medicine, assisting the emergence of an industry, 15th Cambridge Technology Management Symposium - Creating Opportunities from Uncertainty: Navigating Industry Emergence, 24-25th September 2009.

as key lessons and the second part signposts our conventional academic deliverables.

The first part begins with a perspective of the global market place and recent changes in the industry, chapter one; this is followed, in chapter two, by a discussion of the barriers to business growth from a UK perspective, highlighting the importance of regulation and reimbursement. The theme of reimbursement is pursued in the next two chapters, the first focuses on reimbursement in the US, the largest market in the world. The second, with an investment focus, describes a method of evaluating at an early stage the cost-effectiveness of a therapeutic in the context of the UK agency NICE, increasingly an international model for measuring cost effectiveness. UK SMEs must target global markets and therefore have to understand EU and US regulatory pathways - chapter five briefly describes and signposts these. As has already been emphasised for many regenerative medicine products - the product is the process – chapter six turns to manufacturing and quality issues. In chapter seven the significant and challenging issues of product characterisation are addressed. The first part of our book closes with a summary of the major challenges for an SME in the form of a discussion of the necessary evolution of its value proposition with time, and a short conclusion.

Part two of the book briefly summarises the outputs of the *remedi* Grand Challenge giving signposts to key publications and other deliverables thus allowing those interested to find out more.

One of our key outputs has, of course, been a significant number of talented people with a passion for translation and capable of working at the interfaces between new science with therapeutic promise and the clinic and industry.

The regenerative medicine therapeutic and its development is the focus of others. As will be clear from this book, our work targets the development of platforms enabling the commercialisation of the resulting promising therapeutics – the ‘one to many’ step.

the four key uncertainties

As with any emerging industry, there are a number of uncertainties that encumber growth and development. In regenerative medicine these uncertainties can be viewed as four fold and each one can have a significant impact on the other, making the situation more complex and demonstrating the necessity to retain the wider context when approaching each one individually.

Technology

Cell-based regenerative therapies are pushing the boundaries of modern medicine and, as a result, the industry is encumbered by a lack of both the enabling technologies and an infrastructure capable of supporting it. These "living" products vary greatly in their characteristics and sensitivity to their environment and so require specialised suppliers, storage requirements and manufacturing processes. These issues are particularly pertinent during clinical trials, with concerns over measuring and maintaining consistent quality during the supply of products to clinics in multiple locations. Safety and ethical considerations are also at the fore during clinical studies with methods of patient delivery/care and clinical trials protocols under close scrutiny from the authorities.

Market

The market for RM products has seen a shift from the "low hanging fruit" such as skin and hard tissue repair, to serving the major unmet clinical needs e.g. restoring eyesight, stroke treatments, etc. However, successfully reaching two of the largest markets (the US and the EU) is burdened by meeting the clinical requirements of payers/purchasers and demonstrating that cell-based products can be sufficiently cost-effective, especially in the UK. The perceived cost-saving benefit of RM is that it can cure or better manage the underlying cause of disorders and diseases so that the healthcare providers save money in the long term; the problem being that this proven cost-benefit data will not be available for some time, thus indicating the requirement for new reimbursement models. Furthermore, the pathways to clinical adoption are also not clear, with potential new surgical practices and methods of delivery requiring a paradigm shift in the way that both healthcare providers and clinicians approach patient care.

Regulation

A large proportion of the FDA and EU regulations that must be followed in order to gain marketing approval for medicinal and non-medicinal cellular products are taken from the pharmaceutical regulations. This results in a lack of specificity that encumbers the transposition of these requirements into a form that can be used in the development of cell-based products. Although some specific legislation is provided in the form of 21 CFR Part 1271 (US) and the ATMP regulation (EU), many of the specific GMP, GCP and post-marketing regulations that are required to fully implement them have yet to be provided. In addition, there are currently no published international standards available to guide the testing and manufacture of cell based products. This increases the regulatory burden upon developers by limiting their understanding of how they must fulfil the regulatory requirements and creating uncertainty over their business practices.

Finance

The RM industry sector has attracted proportionately less investment than the average for the biotechnology sector. Investors are driven by any one of a range of investment mandates, which in turn influence their stance towards the type of investment and approach to investment-risk management. The uncertainties described above for the RM industry result in both a lack of clarity as to the actual size of the risk as well as an understanding of the options that could be deployed to mitigate the risk. The impact of these uncertainties has been to deter any significant level of commitment from the financial markets.

the market opportunity

Paul Martin uses the results of an industry survey to summarise the market opportunity for the cell therapy industry

executive summary

- Size and structure of the cell therapy industry
- A growing number of products and their targets
- Industry/clinical collaboration is key to success
- Be realistic about expectations

Great hopes currently surround the emerging field of regenerative medicine and the use of cells as therapeutic agents. In particular, much attention had been paid to the potential of novel stem cell based therapies, following a number of major scientific breakthroughs and media reports of potential new cures. These therapies have become the focus of a new sector of the biotechnology industry, which faces a number of major challenges in translating the promise of these scientific advances into widely used medical products. This chapter summarises the findings of a survey of the cell therapy industry completed in January 2009 that set out to assess the current state of private sector activity, the prospects for the future of the industry and the main challenges it currently faces.

Careful definitions of tissue engineering, regenerative medicine and cell therapy were used to provide a sound basis for the industry survey. A key difference was drawn between *primary* (cell based) products and *secondary* products that provided structural components (matrices, scaffolds and biocompatible materials) to enable cell growth. Another important set of distinctions was made between: A) non-stem cell based *first generation* products and a *second generation* of products based on stem cell technology; and B) *autologous products* (based on a patient's

own cells) and *allogeneic products* (based on cells from an unrelated donor). These categories proved a valuable way of segmenting and analysing the industry and its dynamics.

the structure of the cell therapy industry

The cell therapy sector has increased significantly over the last five years and was composed of 138 primary firms and 49 secondary firms at the start of 2009. The survey also identified 177 cord blood banks. The latter were not profiled in detail as they are not directly involved in developing new therapies. The UK ranks in the top three countries in the world with 15 firms working in this area.

However, the sub-structure of the cell therapy industry has changed very substantially over the last five years and is now dominated by firms working on stem cells (71% of all primary firms). No new firms working on non-stem cell therapies have been founded since 2002. The shift to stem cells is also associated with a greater emphasis on allogeneic products across the industry.

The cell therapy industry is also highly geographically concentrated. It is dominated by US firms, which together with German and UK companies account for ~75% of the primary industry. US firms are older and more mature. The European industry has lagged behind, but whilst it made good progress in narrowing the US lead in the late 1990s, growth in the EU has stalled in recent years. This is largely due to the shift to stem cell technology, which the US dominates, and suggests further entrenchment of its competitive advantage over Europe.

The cell therapy sector is relatively well established compared to other parts of the biotechnology industry, as measured by age of firms, number of public companies and products on the market. Despite this, there is a very high level of turnover and commercial failure amongst primary firms.

Furthermore, there are problems with company growth and the primary sector remains dominated by small companies. Both these features are largely due to problems getting access to finance. In contrast, there are a greater number of medium-sized secondary firms, reflecting their commercial success.

disease targets

The most popular disease target worked on by firms was cardiovascular conditions. This was followed by classical tissue engineering applications in skin, bone and cartilage, and metabolic disorders. The only clinical areas that fell outside the broad field of tissue engineering were CNS diseases and blood/immune disorders (including some haematological cancers). The latter mainly relates to the application of haematopoietic and cord blood stem cells, an area with a long pedigree stretching back to the 1980s. It therefore appears that the transition from tissue engineering to regenerative medicine that has been marked by the application of stem cell technology has not yet led to a dramatic shift in the diseases targeted by industry.

Over 50 firms are working on different types of adult stem cells, compared to ~20 firms working on human embryonic stem cells (hESCs) and less than 15 on cord blood stem cells. This highlights the fact that most commercial activity is in the adult stem cell area and this is even more marked when looking at products in clinical development.

products on the market

The cell therapy industry is unusual compared to other biotechnologies in having a relatively large number of companies with products on the market (48 out of 187). However, this is very unequally distributed: 30 of the 49 secondary firms have launched products, whereas only 18 of the 138 primary firms had marketed products. Of this latter group, only two stem cell firms have therapies for sale.

A total of 97 products were identified by the survey, of which 88 were for skin, bone or cartilage. Most products were sold by small firms and the development time to market was 5-10 years. Product sales were broken down by product type:

- *Autologous first generation (non-stem cell) products* – The survey identified 17 autologous cell-based products (13 for cartilage repair; three for skin repair of burns and chronic wounds, and one for bone grafting). Sales of these products have been very limited, with only one product (Carticel) treating more than a 1,000 patients a year. There are a number of reasons for this including poor product specification, lack of clinical evidence of utility and the high cost of manufacturing.
- *Allogeneic first generation (non-stem cell) products* – Five allogeneic products were identified by the survey, of which four were for skin repair. These have generated significant sales and cell-based products for the active treatment of chronic skin wounds now have an established market. Organogenesis' Apligraf is currently used on 35,000 patients a year and has been used on over 200,000 patients in total since 1998. However, it is unclear if this success can be extended to other therapeutic areas as issues of transplant rejection from unmatched tissue donors are not a major issue with skin repair, but may be far more important for other indications.
- *Second generation (stem cell based) products* – Only two products based on stem cell technology had been launched at the time of the survey. These have only been on the market for a few years and have limited sales of less than $20M a year. It would be premature to make a judgment about likely peak sales of these or other stem cell based therapies that might reach the market in the next few years.
- *Secondary products* – In contrast to the relatively poor sales for primary products, the sales of a number of secondary products are significant totalling over $750M a year. Sales of the leading bone related secondary products were over $180M in 2007 and secondary skin products $300M. The most successful product in this category was Integra Dermal Regeneration Template.

Taken together, sales of primary products (containing cells) totalled no more than $100M a year. When combined with sales of secondary products (> $750M a year) and the cord blood banking industry (sales of $200M a year), this gives an industry total of over $1 billion a year.

industry pipeline

There were 120 primary products in clinical development at the time of the survey. 53% were either Pilots, Phase I or Phase I/II; 28% were in Phase II; and 19% were in Phase III. Of the primary products in clinical development 35% were non-stem cell based and 65% used stem cells. Trials of primary non-stem cell therapies (autologous and allogeneic) and secondary products were mainly for classical tissue engineering conditions (skin, bone and cartilage). However, there were a number of trials for cardiovascular disorders. The clinical development of stem cell therapies was slightly different, split between classical tissue engineering conditions (28 trials), cardiovascular disorders (30 trials) and diseases treated by haematopoietic stem cells (13 trials, mainly for cancer). Only three trials were for metabolic conditions and one was for a CNS disorder. No clinical trial involving human embryonic stem cells had started by January 2009.

Based on the number of different products in clinical development, approximately 28 new products might reach the market in the next 5-10 years. Of these, six might be for cardiovascular conditions, 16 for classical tissue engineering and six for other indications, mainly cancer.

industry collaborations

Collaboration between companies is a good index of industrial activity and alliances with large companies are important for the development and growth of small firms. There were a total of 411 cell therapy deals between 1987 and the end of 2008. The great majority of these were formed after 2000. 14% of deals involved first generation primary product

firms, 57% deals involved second generation stem cell firms and technology, and 29% were with secondary product companies. There are significantly fewer alliances per firm/year than in other parts of the biotechnology industry, with few sizeable alliances with large money transactions (>$10M) taking place.

One of the most important features of the pattern of collaborations was the lack of investment from large companies. In total, large firms formed 99 alliances in cell therapy since the mid-1980s. Of these, 33% were with pharmaceutical and biotechnology companies, with only six biotechnology companies and three pharmaceutical companies making more than one deal in the whole industry since it was founded. However, there are some signs that this might be starting to change. In addition, ten large device companies have invested in the sector forming a total of 50 collaborations. More recently, a number of major reagent and equipment firms have also invested in the stem cell industry. The key issue determining poor sales is the lack of clinical uptake of cell therapy products and this is mainly related to difficulties establishing clinical utility and cost-effectiveness. Creating an appropriate evidence base is the key to addressing this deficit.

conclusions

These findings point to a significant risk of market failure for a number of types of cell therapy. Whilst the sales of non-stem cell allogeneic and secondary therapies appear sufficient to sustain companies working in these areas, this is not the case for non-stem cell autologous and most stem cell based therapies. The historic high level of company failure in this sector looks set to continue, but with far fewer new firms taking their place. Unless this situation changes, the industry will contract and the progress needed to develop important cell therapies will be adversely affected. Another key conclusion is that the barriers facing the industry are largely structural rather than technical. These include establishing closer collaboration with clinical end-users, the funding of clinical studies, greater regulatory certainty and clearer reimbursement policies. In addition, there is the need to develop enabling technologies that could

lower manufacturing costs. None of the barriers have changed as a result of the shift to stem cells as the underlying technology in the sector, but each can be addressed by public policy. A comprehensive package of policies therefore needs to be developed that address the risk of market failure and the structural barriers facing firms. These might include:

- Greater emphasis of public-private partnerships (PPPs) around particular therapies that are at risk of market failure, in which the costs and risks of development are shared in return for part of the profits/royalties or lower cost access to products. PPPs are already being created in relation to hESCs and should be extended to other areas;
- Help with the credit available to small firms and greater public support for R&D costs;
- Much more direct financial support for clinical studies that will help develop the evidence base required to establish clinical utility and cost-effectiveness;
- Experiments with provisional reimbursement that would open up access to the NHS whilst linking final market approval and the price paid for a product to clinical outcomes;
- Speeding up the adoption of a clearly defined and well supported regulatory framework;
- Increased public funding for the development of enabling manufacturing technologies to reduce the cost of cell therapies.

At the same time it is important that a more realistic set of expectations is adopted about the level of resourcing and length of time needed to realise the potential of a cell therapy. The history of the field is one of incremental change and the slow build-up of the social, technical and clinical infrastructure required to develop products that offer significant improvement in patient care. As with many other novel biotechnologies, long-term success will depend on the public sector playing a major role in supporting private companies through the difficult early stages of the translation process.

barriers and bottlenecks

Emma Rowley summarises the findings of an interview study of the academic, industry and clinical communities, which set out to examine the barriers to the commercialisation and utilisation of regenerative medicine products in the UK

executive summary

- Translation of regenerative medicine from invention to market is possible
- Clinical utility and clinical need must be designed into products
- Reimbursement processes must be clear
- Close involvement with the regulator at an early stage is desirable

In carrying out this research it was our intention to examine some of the underlying barriers that have curtailed the development of the regenerative medicine industry in the UK. Interview data from 54 academics, clinicians and industry managers demonstrated that UK academic regenerative medicine is thriving. Unfortunately, lack of access to capital, regulatory hurdles, and a lack of clinical evidence on (cost) effectiveness is leading to problems with utilisation and reimbursement. This is compounded by an NHS culture that is considered to be unsupportive in utilising innovative products, and does not provide an attractive environment for the commercialisation of regenerative medicine products.

There are strong reasons to believe that the key organisational and institutional barriers to the commercialisation and utilisation of regenerative medicine can be overcome with effective public policy. The number of products available for use demonstrates that the translation of regenerative medicine from invention to market is possible. However, the successful translation of regenerative medicine towards adoption has proved more difficult and is in urgent need of further attention. We believe that a key reason has been that clinical utility and clinical need have not been designed into the products to a sufficient extent. This has resulted in invention without adoption.

In order to address these barriers a more realistic and robust understanding of the process of translation is needed. The data from this research suggests that the most challenging problems occur after product launch, most notably the difficulty of demonstrating clinical utility. Based on the interview data the following policy recommendations have been suggested:

technology

- The scientific, clinical, industrial, media and policy communities involved in regenerative medicine need to take care to ensure they present more realistic expectations about the future prospects of the field. This is essential to maintain public support.
- There should be an ongoing commitment to real increases in the public funding of basic research in the field of regenerative medicine.
- New institutional arrangements and funding mechanisms need to be established to enable much greater input of clinicians into the innovation process so that clinical suitability is designed into new products at an early stage of development.
- Companies developing novel regenerative medicine therapies need to ensure that the needs of clinical end users and the particular setting in which a technology will be used are taken into account during the

specification and design of products. This is best ensured through interaction and engagement with both expert and non-specialist clinicians at an early stage.

market

- The NHS, industry and universities should pilot the joint funding of a series of 'knowledge translators' who would have the role of establishing local networks in leading research centres aimed at fostering greater collaboration in regenerative medicine.
- Improved reimbursement policies and procedures, which include the full costs and savings offered across the whole treatment path/patient journey provided by novel therapies such as regenerative medicine, need to be developed. Experiments should be undertaken with provisional reimbursement that would open up access to the NHS whilst linking final market approval and the price paid for a product to clinical outcomes.
- A review of the NHS as a customer of innovation should be undertaken, with a particular focus on the purchasing/commissioning procedures and the NICE tariff system to explore ways in which the adoption of novel technologies can be better supported.
- A comprehensive training programme should be made available for all staff involved in working with regenerative medicine products.
- A pilot project should be established to explore the extent to which the National Blood Service distribution infrastructure can be used as part of a dedicated supply chain for cell-based and other regenerative medicine products.

regulation

- Universities, the Biotechnology Industry Association and the research councils should work together to draw up guidelines for the licensing of intellectual property to ensure improved access whilst protecting the rights of patent holders.

- Regulatory agencies, including the European Medicines Agency (EMEA) and the Medicines and Healthcare products Regulatory Agency (MHRA), should give regenerative medicine a much higher priority, with improved resourcing and clear points of contact in this area to help streamline the working of the Advanced Therapeutic Medicinal Products (ATMP) regulations and ensure reduced cost of compliance and time to market.
- Regulators should make greater efforts to clarify, stabilise and harmonise the key concepts and terms used to describe regenerative medicine science, technology and products.

finance

- Greater public funding should be made available to support the clinical and product development stages of the translation process. In particular, dedicated funding should be made available to help develop new production technologies based on automated cell and tissue processing. To achieve this consideration should be given to experimenting with novel forms of public-private partnership and risk/benefit sharing mechanisms.
- Greater funding needs to be made available for studies aimed at creating a clinical evidence base, including cost-effectiveness. In addition, a standing committee of leading clinical researchers, health economists, regulators, NHS commissioners and research funders should be established to consider the type of evidence requirements that need to be established in the field of cell-based and regenerative therapies.

reimbursement in the US

Patrick Ginty summarises the reimbursement strategies within the US – the largest market for RM products

executive summary

- Coverage and payment drive reimbursement
- Variety of public and private payers
- SMEs should engage payers early in process
- SMEs must meet payers clinical requirements

context

Instead of being burdened by the pitfalls of socialised medicine in the UK and negotiating multiple reimbursement pathways in Europe, many UK companies continue to target the US as it remains the single biggest market for regenerative medicine. However, targeting the US market is one thing and being successful is another. The mechanisms for selling products in the US are still seen as a “black box” to many and as a result are poorly understood, particularly outside of the US. Therefore SMEs targeting the US market should understand both the mechanisms for reimbursement and the requirements of the US payers and incorporate them into their product development strategy in order to enhance their chances of commercial success.

fundamentals of the US reimbursement system: coverage, payment and coding

In the US, reimbursement is driven by coverage and payment. Coverage represents the treatable conditions and limitations of use established by a payer for medically necessary applications of regenerative products. Payment relates to how, and how much, the payer is willing to pay for such applications of the regenerative product. The cost of healthcare is split between a mixture of public and private payers with the dominance of the latter making it unique amongst other healthcare systems around the globe. Public payers, most notably the Centre for Medicaid and Medicare Services (CMS), are largely restricted to those over the age of 65 (Medicare) or those with low income or disabilities (Medicaid). Therefore, the vast majority of healthcare in the US is funded through private payers that can be either for profit (e.g. CIGNA) or not for profit organizations (e.g. Blue Cross/Blue Shield). Reimbursement codes are the alphanumeric systems that send information from providers to payers about what was provided, presenting a description of diagnoses, medical services, items and supplies. They are used when referencing coverage decisions and payment rates and are used on insurance claims to enable payers to pay healthcare providers. Codes are specific to surgical or medical procedures but are not specific to the discrete products which may be used with those procedures. Whilst attaining a product code is an important step in the process of gaining reimbursement, it should be noted that this is not in itself a guarantee of reimbursement.

important considerations for developers of regenerative products

The traditional ethos amongst the developers and manufacturers of regenerative products is that the success or failure of a new technology is

based on gaining marketing approval from the regulator. However, it has also become increasingly clear that US payers are now demanding a level of clinical evidence that at least equals or even exceeds that required by the FDA. Payers, whether public or private, may want to see a breadth of clinical evidence ranging from anecdotal safety studies through to large double-blinded multi-centre trials. Payers care about effectiveness and not just efficacy; in other words, they want to know that it *does* work and not just that it *can* work in a specific population. Therefore, the main challenges for manufacturers in the field of RM are (a) producing the large volume of high quality data demanded by the payers/FDA with limited financial resources and (b) conducting large multi-centre trials with environmentally labile biological products and the consequent supply chain and logistical barriers.

In the US, Medicare coverage is determined on a local or a national level, but it is perhaps more strategic to "think local" and establish reimbursement coverage incrementally by targeting the US region by region. The US is broken down into 20 local coverage regions which are based upon population clusters and not state lines. Local Coverage Decisions (LCDs) are made for each of these regions by intermediary bodies who employ clinical experts to make decisions over reimbursement. These local coverage decision makers potentially represent the line of least resistance to a developer/manufacturer. National Coverage Decisions (NCDs) are far more difficult to achieve, as it is more challenging to show efficacy on a national basis given the breadth of clinical data required. The theory is that by approaching each intermediary body individually, the uptake of a product on a national level will be facilitated by a "snowball" effect whereby other regional bodies will follow suit. These LCDs will be made by clinical experts and the scientific directors of the intermediaries/payers, with clinical effectiveness top of the agenda. However, the cost of goods is also crucial to successful reimbursement at a rate that will provide both profits for the manufacturer and cost effectiveness for the payer. One of the most

common requests directed at manufacturers is for cost data demonstrating that either the technology contributes to lowering overall costs associated with the current standard of care, or that the clinical benefits alone provide justification for the increase in overall treatment costs. From January 2008, CMS started to take into account certain stem cell processing codes for the first time, for which they collected cost data on cell processing procedures to determine hospital outpatient reimbursement rates. In this regard, it is imperative that CMS is supplied with precise cost data which accurately reflects the true cost of these procedures as future revenue will be based on these cell processing charges. If the scientific director of a payer or intermediary refuses to reimburse a product completely, there is still a formal hearing and appeal process in place for the manufacturer. However, even when a favourable coverage decision is given for a product and a reimbursement rate is set, this rate is not permanent, as CMS can change the payment amount. Another note of caution is that the uses of a product approved by the FDA do not necessarily establish the scope of reimbursement coverage. For example, an LCD or private payer may cover only some of the intended use of a product approved by the FDA, with the result that some product uses permitted by the FDA will not be considered reimbursable.

company strategy

Traditionally, the customer most in need of satisfying during the product development process has been thought of as the regulator, with the challenge of reimbursement being tackled after product approval is given. However, given the lack of uniformity between the regulator and the payer, the reimbursement strategy must be considered with equal if not more importance. SMEs in the field of RM must use their resources wisely as there is no real precedent for success and investment is limited due to the high risks associated with regenerative products. For early stage companies (or even before the decision to start up), reimbursement

consultants in the US can be of value in helping the company to understand the real market size i.e. the patient population. Spending time and funds at this stage may ultimately determine whether the company is viable or not and prevent money from being wasted on a product that will not be reimbursed. This may help establish credibility of the company's story (or vice versa) from an investment point of view. It is crucial that both CMS and private payers are engaged at an early stage with contact made with the intermediary bodies that govern LCDs. Private payers can pay up to 20-30% more than the CMS threshold with private payers such as CIGNA basing their reimbursement and payment decisions on the CMS model. Therefore, determination of the CMS model could give clues as to private payers' thresholds and manufacturers can adjust their price accordingly. Further down the line, clinical trial design should consider the requirements of the payers, so either an investigational new drug (IND) or an investigational device exemption (IDE) application must take this into account as it may have implications for the level of investment needed to successfully complete clinical trials. When seeking reimbursement decisions from intermediary bodies, it may be diligent to target those that are historically more open to new or comparable technologies and innovation before "invading" additional territories. Post-FDA approval, gaining the correct code for a product can be crucial to gaining a satisfactory reimbursement rate as many codes are associated with low reimbursement thresholds. New codes can be generated to permit this threshold to be raised or existing codes can be combined to create a new threshold. However, this is a moving target with constant tariff negotiations with payers required, so continued vigilance is required on the part of the manufacturer.

cost effective investment

Richard Lilford and Helen McAteer describe the Headroom Method that determines the maximum cost of a technology that is still cost-effective in the UK

executive summary

- Worldwide increase in health economic analysis
- Critical to understand the healthcare purchaser
- In the UK NICE assess whether an increase in cost is justified by a sufficient increase in effectiveness
- Early assessment of cost-effectiveness can inform investment decisions

introduction

Health economics is concerned with issues relating to the scarcity of resources. It provides the tools necessary to assess the most efficient use of available resources in the allocation of health and healthcare and is defined in terms of costs and outcomes.

Health services increasingly use health economic analysis to guide purchasing and reimbursement decisions. The National Institute for Health and Clinical Excellence (NICE) uses this approach to asses the incremental cost-effectiveness ratio (ICER) of the technology. This is the extra cost per extra unit of benefit achieved when comparing one technology against another. It determines whether an increase in cost is justified by a sufficient increase in effectiveness. Decisions are made based on a

threshold level for an ICER. Our purpose was to adapt cost-effectiveness analysis to inform investments and development decisions.

applying health economics early in the development cycle

Cost-effectiveness analysis is typically conducted once the product has been developed i.e. by the demand side. In the case of a technology yet to be developed, or in early stages of development, the very nature of the product is uncertain and no effectiveness studies have been conducted. We argue for the adoption of health economics early in development i.e. by the supply side. This will help inform investment decisions and indicate which products have greatest potential.

Here, we describe a simple threshold approach to the problem of supply side analysis, termed the **Headroom Method**, which estimates the maximum cost at which a technology can be brought to market and still be considered cost-effective. Our examples are from regenerative products.

the headroom method

The headroom method simply looks at the potential of a clinically defined market. Instead of asking, *"How cost-effective will the technology be?*" we ask, *"Would it be cost-effective if it works as well as one would hope?"* In other words, optimistic assumptions are made about the incremental effectiveness of the proposed treatment over the best alternative. We then ask, *"At what cost would this new technology be cost-effective?*" This gives the maximum potential cost of the new treatment (including development costs), factoring in any health service savings.

If this cost is too low then investment funds should be channelled elsewhere. Of course, the reverse is not true - the new technology might still fail despite adequate headroom. For example, it might turn out to be less effective or more expensive than hoped, or novel competing

alternatives may emerge. However, the headroom method can lower the risk of embarking on an investment that is doomed from the outset.

The headroom method provides a framework to support investment decisions. The stages are summarised below.

Strategic Considerations

Tools such as PEST (political, economic, social, technological) and SWOT (strengths, weaknesses, opportunities, threats) analysis exist for structuring and defining a business situation. This process can provide some rigour to decision making and exclude obviously futile schemes. In RM there is an additional specific question you must ask yourself, *"What changes to the regulations are in the pipeline?"* If the technology is not ruled out at this stage, then the investigation should move to the next stage with a study of the clinical problem and an analysis of how the technology may help.

Defining the Clinical Problem

There is always a limit on how cost effective a new technology may be. The epidemiology and clinical features of the condition limit the potential benefit. All the conditions where a new technology may have an application need to be examined, at least to the point where it is clear there is a material clinical problem to be solved. A clearly defined clinical need based on a clear understanding of the strengths and weaknesses of current treatment is crucial to the uptake of a new technology. The following issues should be clarified:

Statement of technology – a precise description of technologies being considered, including any uncertainties; e.g. it is uncertain whether a tissue engineered bladder becomes re-innervated.

Disease context – a precise description of disease and natural history, including analysis of disease sub-groups where the technology may be more or less applicable; e.g. there may be a greater need for TE bone for non-union of fractures than for spinal fusion.

Prevalence and incidence – hospital episode statistics and a literature search can be useful here. The data needs to be broken down by relevant sub-groups since the effectiveness gap may vary by sub-group, as it does in hernia repair.

Current treatments – the current gold standard is the comparator for the new technology. However, new developments must also be reviewed as this may change the shape of the market; e.g. the availability of specific growth factors is replacing the need for complicated bone scaffolds.

Effectiveness of available treatments – The effectiveness, including any side effects and complications, must be clearly described. In particular, side effects which could potentially be avoided by the new treatment should be identified; e.g. a TE solution to repair complex hernias would avoid adhesions and infections, a complication of current treatment.

headroom analysis

The headroom analysis involves two aspects:

1. **Establishing the effectiveness gap –** the room for improvement in effectiveness between the current best treatment and that which the new technology might plausibly achieve.
2. **Calculating the headroom –** the maximum incremental cost (maximum additional cost compared to the current best treatment) of the new technology which could still be considered cost effective. This is based on optimistic but plausible estimates of the effectiveness of the technology being assessed.

Firstly, we must cover some basic health economics principles:

1. Incremental Cost-Effectiveness Ratio (ICER)

Cost-effectiveness analysis aims to quantify the ICER, the extra cost per extra unit of benefit when comparing one technology against another -

most often done on a cost per quality adjusted life year (QALY) basis (discussed below).

The comparator should always be the current gold standard treatment. Only an improvement on this performance, in terms of cost-effectiveness, will support the reimbursement of a new technology.

An ICER is calculated using incremental cost (ΔC) and incremental effectiveness (ΔE) to give a cost per additional unit of effectiveness, or an incremental cost per QALY (equation 1).

Equation 1: $ICER = \Delta C / \Delta E$

2. Quality Adjusted Life Year (QALY)

A QALY is a measure that accounts for both *quantity* and *quality* of life generated by healthcare. Quantity is measured in years and quality is measured by health utilities. Health utility measures the strength of an individual's preference for a particular health outcome. It is measured on a scale from 0, death, to 1, perfect health. A greater preference for a particular health outcome will result in a greater utility for that health outcome. A year of perfect health is worth 1 i.e. 1 QALY is equal to 1 year of perfect health. Incremental QALY gain ($\Delta QALY$) is a function of improvement in health utility ($\Delta Utility$) and duration over which improvement is sustained (equation 2).

Equation 2: $\Delta QALY = \Delta Utility$ x duration of time (years) with that health state

calculating headroom

Now we can calculate the headroom *(maxΔcost)* – the maximum additional cost of new treatment over the comparator (current gold standard) for the new treatment to be deemed cost-effective. We rearrange equation 1 into equation 3. We substitute 'ICER' with 'WTP

(willingness to pay) threshold'. Where, *WTP threshold* is the maximum threshold for the ICER i.e. the maximum the healthcare provider is WTP for 1 QALY. In the UK, we assume this is £30,000 per QALY, and *max∆QALY* is the *effectiveness gap* - the maximum additional benefit that could be obtained from the new treatment (see below).

Equation 3: max ΔCost = WTP threshold x max ΔQALY

estimating the maximum ΔQALY – the effectiveness gap

When the current treatment is sub-optimal, an effectiveness gap can be estimated. For those conditions with treatments which are ineffective for large proportions of patients or have significant side effects, the maximum potential increase in effectiveness over the current treatment may be used as the optimistic assumption. Specifically we are looking for those side effects that could be eliminated by the new treatment – these should have been identified during the definition of the clinical problem.

Two steps are required to calculate the effectiveness gap (maxΔQALY):

1. Health utility associated with the current treatment

Having defined the clinical problem and existing treatment it is possible to identify the clinical outcome that the new treatment should improve. Next, it is necessary to identify the health utility associated with that clinical outcome. Health utilities can be identified in the literature or in the database of utilities held by Tufts University. If not, the utility values will have to be established using formal methods.

Finally, we define the effectiveness gap. Since we do not know the true effectiveness of our new technology, we assume the most optimistic scenario (the new technology returns the patient to perfect health, a health utility of 1), so we subtract the utility value we identified from 1.

2. Estimation of duration of the improvement in effectiveness

The next step is to identify the maximum potential duration of the clinical benefit expected from the new treatment. If there is no difference in life expectancy, only the duration of the improvement in clinical benefit is taken into account i.e. the duration of the side effects of the current treatment that would be abolished by the new treatment. If there is likely to be a difference in life expectancy then this must be included in the calculation.

Now we can populate equation 3 and calculate the headroom (maxΔcost).

return on investment (RoI)

For those technologies that appear to have headroom, continuing development and investment would appear to be justified. At this stage, interest is focussed on whether or not the technology has the potential to succeed, once bought to market. RoI may be affected by the rarity of a condition or because it occurs only in economies unable to support high cost remedies. The revenue that can be generated is a function of the headroom, the likely cost and volumes (equation 4), where max ΔCost is the headroom and C' is the expected cost of production.

Equation 4: Revenue = (max ΔCost – C') x Volume

conclusion

Following the headroom analysis, two further possibilities exist:

1. The investor can make an intuitive decision to invest based on the outcome of the headroom method.
2. The investor can perform more formal value of investment analysis.

The framework discussed here provides a structure for investment decisions. The headroom analysis is useful as a barrier to misguidedly investing in those technologies which are unlikely to be cost-effective. If

there is little or no chance the technology could be marketed at a price that would keep the maximum incremental cost (maxΔcost) below the threshold the technology should not attract further investment. It should be noted that the value of applying these methods is dependent on the planned technologies being aimed at the third party payer.

As development proceeds it is important to revisit economic analysis with new information regarding likely effectiveness of the technology as it becomes available. Continual economic assessment at various stages of development will enable more accurate predictions of a product's cost-effectiveness and hence its market potential.

However, further difficulties can arise as the technology nears market:

- Uncertainties – a major barrier to adoption of technology is the requirement to provide sufficient evidence of effectiveness. Evidence on effectiveness should ideally come from randomised control trials.
- Silo budgets – silo budgeting is a major barrier to adoption. The segmentation of healthcare delivery by departments means you have to provide an economic argument for a single department. This is often very difficult, because while the cost may lie in one department, the benefit is accrued in another. For example, less invasive surgery may increase cost in the operating theatre, yet the benefit and cost saving is made on the ward. Ultimately a more joined-up system is required.
- Business strategy – some products will aim at more than one application e.g. bone morphogenic proteins. Each application may have a different ICER and headroom. Furthermore, the first application might not necessarily be the 'big one'.

regulation

Patrick Ginty describes the EU and US regulatory pathways, and considers the issues facing UK SMEs

executive summary

- Cell therapies regulated under 1394/2007 (EU)
- Cell therapies regulated under 21 CFR 1271 (US)
- Specific GMP requirements are lacking
- Regulatory route dictates necessary resource

The term 'regenerative medicine' cannot be found in any regulatory document. Therefore, commercialising products with regenerative medicine applications requires the selection of a suitable regulatory conformance route that best fits the technology and its application (Figs 1 & 2). In the EU the requirements are provided by the European Commission (EC) whilst in the US, they are provided under title 21 of the Code of Federal Regulations (CFR 21). Regulatory language is underscored.

regulatory pathways

Cell and Tissue-Based Therapies (EU)

The advanced therapy medicinal products (ATMP) regulation (EC 1394/2007) is a piece of legislation that covers both tissue engineering products (TEPs) and cellular products that have not been engineered (somatic cell therapy medicinal products). Cells or tissues are considered "engineered" if they have been substantially manipulated and/or are not intended for autologous and homogenous use. Products that contain both viable cells and a device component will be classified as combined products with both components requiring separate marketing

authorisations. All ATMPs are required to show safety and efficacy through approved clinical studies.

Medical Devices (EU)

In the EU, medical devices are defined as those products which do not achieve their principal intended action in or on the human body by pharmacological, immunological or metabolic means. Therefore, the European medical device directives principally apply to tissue repair scaffolds and biomaterials that perform a more structural function. Medical devices are classified based upon their risk and regulated under the medical device directive (93/42/EEC, as amended by 2007/47/EC in March 2010). In order to market a new medical device, it is required to go through the CE marking process whereby a technology assessment is carried out by independent notified bodies that test the device to ensure that it meets the EU requirements.

Cell and Tissue-Based Therapies (US)

Viable cell and tissue-based products must follow the regulatory route for human cells, tissues and cell and tissue-based products (HCT/Ps). If the product is minimally manipulated, intended for homologous/autologous use and not combined with a drug or device, it will be regulated under section 361 of the public health service act. However, most products will not meet these strict criteria and will be regulated under section 351 of the Public Health Service Act. Under section 351, the HCT/P is subject to clinical assessment under an Investigational New Drug (IND) application before marketing approval can be granted via a Biologics License Application (BLA).

Medical Devices (US)

510(k) pre-market notification is a regulatory route for medium-risk medical devices that show substantial equivalence (SE) to a predicate Class II device that has been given marketing approval in the US since May 1976. SE is determined by the device's intended use and technological characteristics, evidence for which must be submitted to the FDA 90 days prior to marketing. The 510(k) pathway is usually reserved for scaffold and

biomaterial-based devices that perform a structural function. Pre-market approval (PMA) is a regulatory route for Class III medical devices. This means that they are not substantially equivalent (NSE) to an existing Class II device and pose a significant risk to human health and/or provide a life supporting/sustaining function. Therefore the device is subject to pre-approval by the FDA to ensure that the device is both safe and effective which is demonstrated through the collection of clinical data under an Investigational Device Exemption (IDE). A product regulated under a PMA may often contain an active drug or biologic provided that this drug/biologic does not provide the primary therapeutic effect.

regulatory uncertainty

A large proportion of the conformance requirements for cell- and tissue-based products are borrowed from the pharmaceutical regulations (Figs 1 & 2). As a result, they lack a number of key specific requirements that encumber their transposition into a form that can be used in the development of cell- and tissue-based products. Although some specific legislation is provided in the HCT/P and ATMP regulations, many of the specific good manufacturing practice (GMP) and post-marketing regulations that are required to fully implement them have yet to be promulgated. This is especially detrimental given the requirement for GMP-grade material to be used in both clinical studies and the final commercial-grade product. In addition, there are currently no published international standards documents available to guide the testing and manufacture of ATMPs or HCT/Ps. These deficiencies increase the regulatory burden upon developers by limiting their understanding of how they must fulfil the requirements and creating uncertainty over their business practices and best use of resources. The medical device regulations are more clear cut in both the US and EU, provided that the device is not combined with a viable cell component. These combined products (EU) or combination products (US) have the additional complication of having to follow multiple sets of GMP regulations at some

stage of the process, even if the aim is to produce the two components as a single entity.

considerations and strategies for SMEs

In order to achieve commercial success, it is essential that all of the potential regulatory pathways are understood and considered before key business decisions are made, as the regulatory burden is heavily linked to resource and will define the business model for the company (table 1). The requirement for clinical studies to support the majority of cell- and tissue-based products requires a significant amount of investment and a thorough knowledge of the regulatory requirements. However, as indicated by the medical device pathways, regenerative products do not necessarily require clinical studies to gain marketing approval and this is the certainly the case for the majority of products marketed via the 510(k) PMN route (table 2).

Table 1. Regulatory burden and time to market for cell- and device-based products

	Device-based	*Cell-based*
Technology	No viable cell component, largely structural function	Viable cell component, provides biological therapeutic effect
Approval Route	510(k), PMA, CE Mark	IND-BLA, ATMP
Regulatory Burden	Low to medium, little or no clinical data required for Class II and some Class III	Relatively high, clinical data required for majority of products
Speed to Market	Faster, 2-3 years for Class II and 5-7 years for PMA	Slower, ~10-15 years

This allows them to reach the market more quickly and provide a demonstrator to investors and other larger companies that there is value in the technology and the business. Similarly, the CE marking process in the EU allows many devices, including some Class III devices, to be approved without the need for new clinical studies, as they can rely on existing clinical data provided there is a significant similarity between the new product and that used to collect the original clinical data. In addition,

medical devices can be used as a pre-cursor to a more complex biological product with the initial device acting as a stepping stone to a more ambitious long-term product pipeline. For example, these products are often simple biomaterial-based products that, whilst having limited clinical impact in the short-term, may provide a suitable scaffold for the delivery and support of an ATMP/HCT/P in the long-term.

Table 2. Exemplar products with regenerative medicine applications

Regulatory pathway	*EU-approved products*	*US-approved products*	*Regenerative medicine application*	
			EU	US
Class II medical device	Kerraglove (Ark Therapeutics) (Class IIb)	Actifuse (Apatech)	Non-invasive wound healing device	Scaffold device for bone regeneration
Class III medical device	Chondromimetic (Orthomimetics)	IN-FUSE (Medtronic)	Osteochondral plug for knee joint repair	Bone graft for spinal repair
ATMP (EU) HCT/P (US)	Chondrocelect (Tigenix)	Carticel (Genzyme)	Viable autologous cellular therapy products for cartilage repair	

In addition to utilising the device regulations, developers of ATMPs/HCT/Ps should ensure that they use all available means to enhance their chances of commercial success. For example, as the costs of development are likely to be high given the limited investment for regenerative medicine SMEs, product reimbursement may provide a significant barrier, especially as it is not tied in with regulatory approval. Therefore, clinical trial design and cost of goods should take into account the requirements of the business, the regulator and those who will ultimately reimburse the product. This regulatory burden can also be shared by the strategic use of contract manufacturing and research organisations that have both GMP facilities and capabilities that cannot be resourced “in-house”. It should also be noted that the European Medicines Agency provides incentives for SMEs with ATMPs such as a 50 % reduction in the marketing application fee and a free certification service for all relevant quality and non-clinical data.

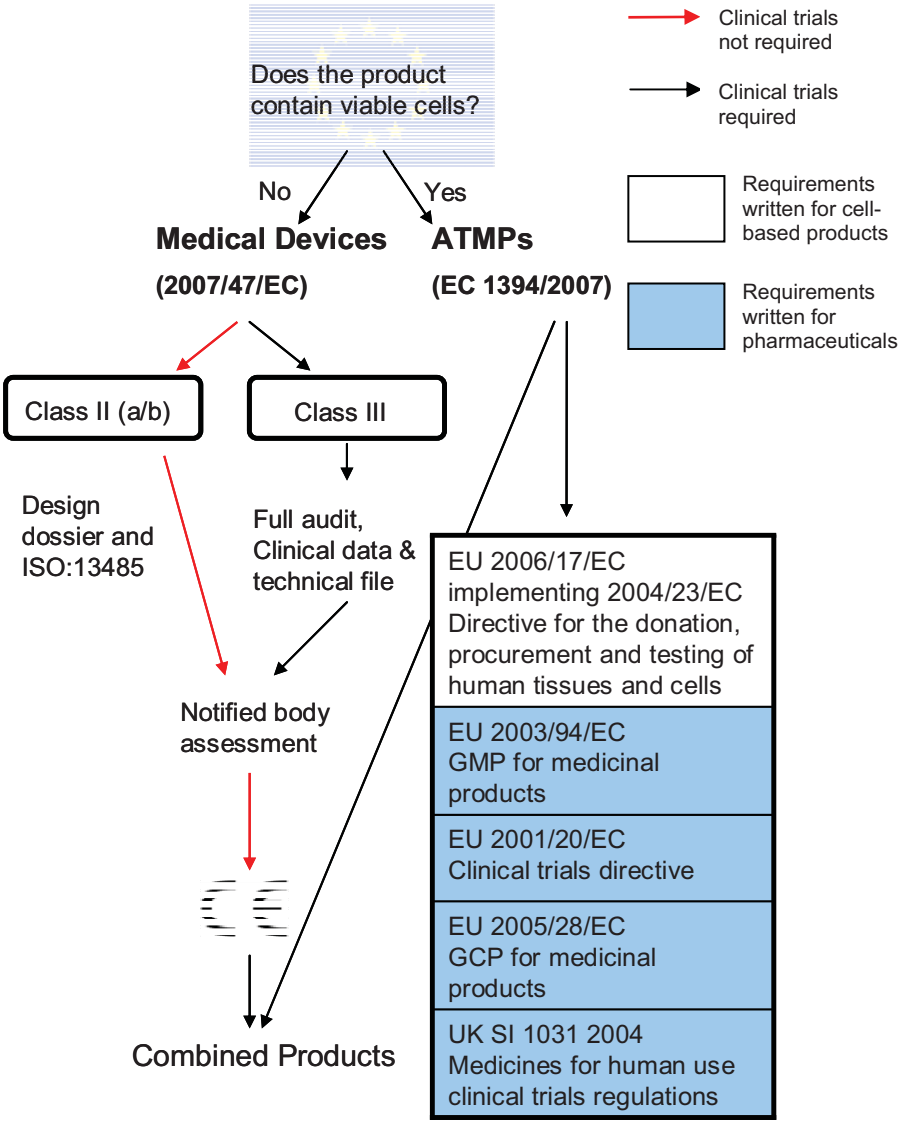


Figure 1. Regulatory conformance routes for regenerative medicine products in the EU

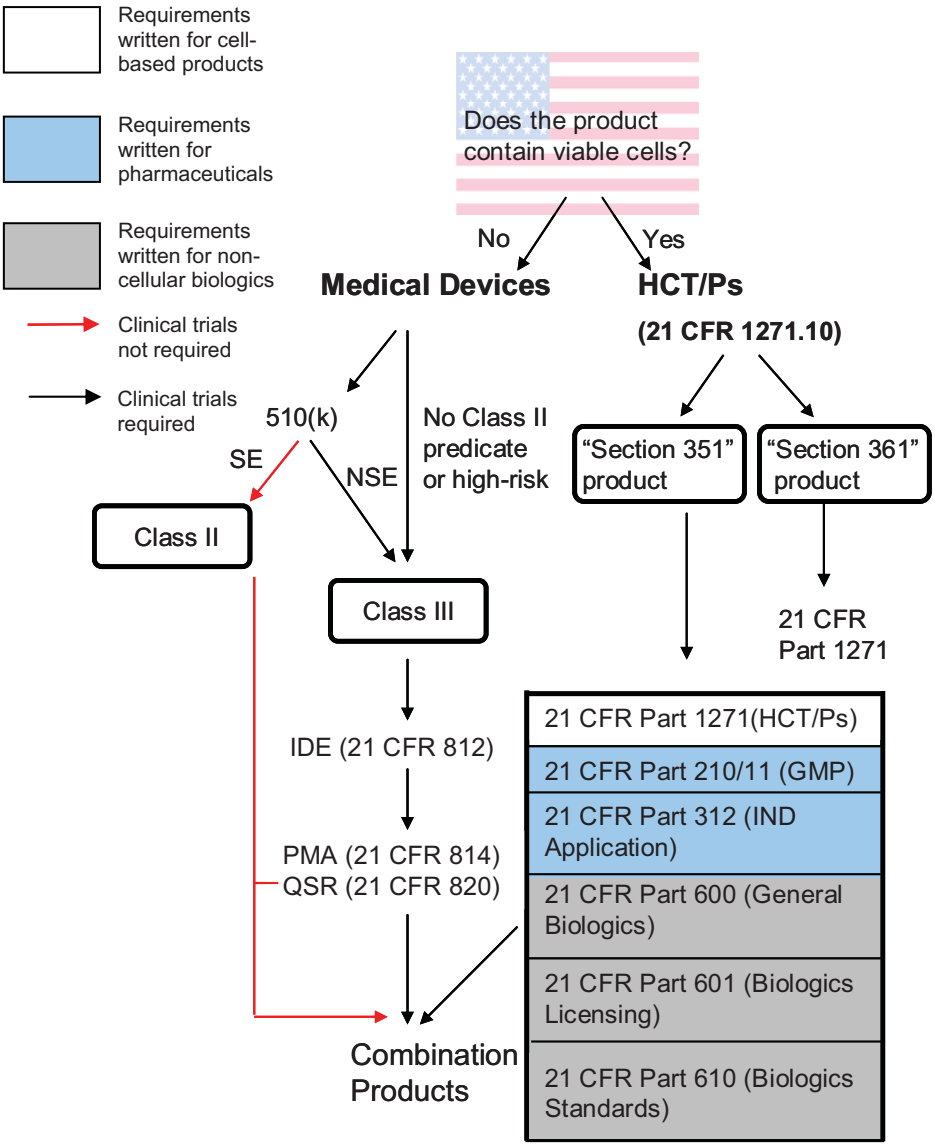


Figure 2. Regulatory conformance routes for regenerative medicine products in the US

manufacture of RM products

Robert Thomas and Erin Rayment describe the approach to automation, process design and equipment/environment validation for cell based product manufacture

executive summary

- Manufacturing variation needs to be tightly monitored and controlled
- Process automation is a key way to achieve the required consistency
- Systematic statistical analysis is critical to understanding cell responses
- Manufacturing to GMP standards is onerous and will include a quality control plan

introduction – the manufacturing challenge

Regenerative medicine and tissue engineering are maturing through a translational phase from lab-based experimental disciplines to a nascent industry. Projected clinical demand indicates that within the next decade this industry will need to responsively and economically provide a diverse range of RM products, many of which will incorporate living cells, to a large market. This transformation is driving a need for robust manufacturing systems for cell-based products that can meet the stringent regulatory requirements imposed on medical product manufacture.

The requirement to manufacture living products for RM applications poses significant new challenges. These challenges revolve around the complexity of the living product and its sensitivity to environmental conditions. A living cell is in a constant state of change in response to its environment, and therefore maintaining product quality requires precise

process control. Cell products always incorporate some degree of heterogeneity due to different micro-environments in the manufacturing process. Furthermore, the complexity of a living cell defies comprehensive definition; measurement of product quality is usually based on average population values of surrogate markers (i.e. critical gene or protein expression) that are at best indicative of critical product attributes (therapeutic efficacy, safety).

Many of the solutions and technologies that have been developed for conventional biologics manufacture cannot be applied to cell therapies. Large volume suspension bioreactors that are well characterised for cell line production are not readily adapted to the culture of adherent cell types such as those required for most cellular products. As the cells themselves, rather than a culture by-product, are the product, conventional downstream purification also has limited use. The greater sensitivity of the therapeutic cells and the difficulty of product measurement enforce greater reliance on process understanding and control to guarantee product safety and efficacy.

Achieving a controlled and characterised manufacturing process for cell based therapies requires the development of new technologies, tools and techniques, as well as the transfer of manufacturing experience from diverse older industries. In addition to the technical challenges outlined, manufacturing equipment, processes and facilities must be compliant with good manufacturing practice (GMP), the stringent regulatory framework controlling therapeutic product manufacture.

the *remedi* method

Variation in the manufactured RM product can come from two sources: process input material and process conditions. If identical batches of input material are subject to identical processing conditions they will produce identical product. Relative to conventional pharmaceutical or biologic production, both input material variation and process condition variation have been poorly controlled in cell therapy manufacture. Although the

complexities are specific to the RM industry, generic methods from other industries, in particular process automation and systematic process improvement methods, are instructive for approaching this challenge.

Process automation has been a key mechanism for achieving controlled and standardised processes in many manufacturing industries. Automation also enables scale-out of production with predictable process variation and therefore predictable process costs, in marked contrast to scale-up of manual laboratory operator processing. Systematic process improvement methods, such as the 'six sigma' approach, have been developed in electronics and automotive manufacturing in order to understand and control sources of process variation and thereby reduce the rate of defective products.

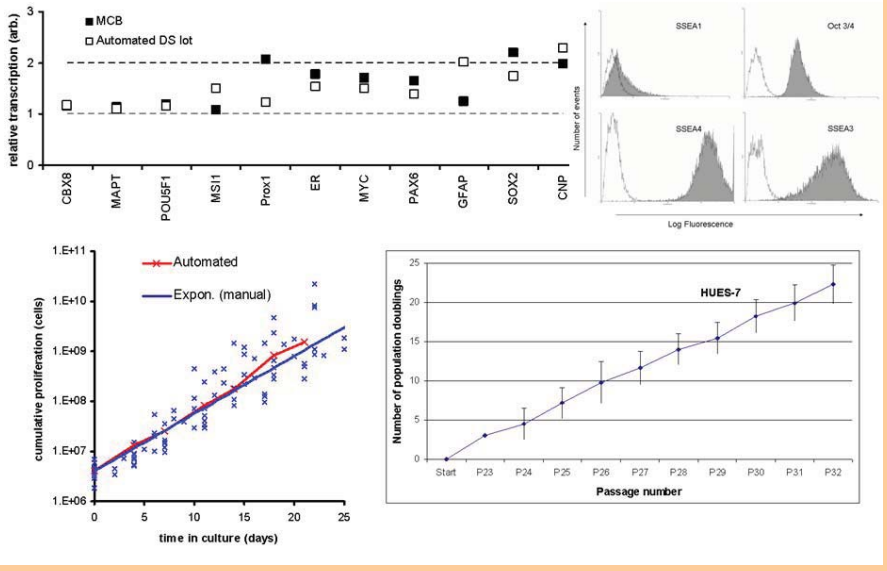
automated manufacture

The first step undertaken in the *remedi* manufacturing research programme was therefore to remove manual operator processing from the manufacture process of important therapeutic cell types and bring the processes under machine control. The *remedi* collaboration identified the CompacT SelecT robotic flask handling platform as the best candidate production technology to remove operator variation from the manufacturing process. The CompacT SelecT consists of a robotic arm in a clean processing environment adjacent to an incubator. The system can carry out most cell processing activities on bar code tracked adherent cell culture flasks with relatively few deviations from conventional manual processing protocols. This similarity to manual flask processing increases confidence that cell product quality will not be affected and makes process automation of clinically advanced flask based processes, (where important historical process data exists) feasible.

We selected key therapeutic cell types and associated commercial and academic partners ('customers') to demonstrate the efficacy of automated cell production using the CompacT SelecT. Successful automated production protocols were developed for human mesenchymal stem cells

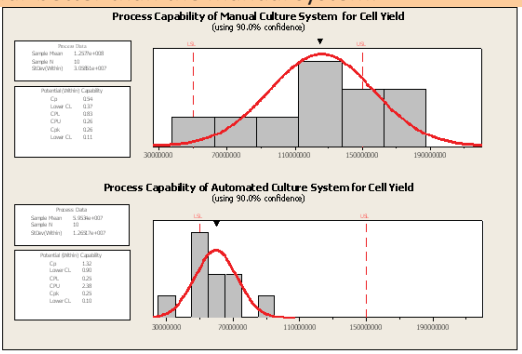
and human embryonic stem cells, as these represent the cell stock source for a significant proportion of cell therapies under development. We also developed automated production protocols for niche proprietary cell lines and products including neural stem cells and smooth muscle progenitor cells with commercial collaborators. The cell types chosen were intentionally diverse. They covered examples of both autologous and allogeneic applications, different handling requirements, and clinically acceptable production protocols. The automated production methods developed produced cells that met stringent quality specifications identified by the customer including cell proliferation, viability, genetic stability, biological markers and differentiation potency (Box 1).

Box 1: Automated cell processing produced high quality populations of regenerative medicine cell types. The left-hand graphs show growth rates and quality markers for a proprietary clinical neural stem cell during automated processing compared to the gold standard manual process. The right-hand graph shows example growth rate and quality markers of embryonic stem cells during automated processing.



In parallel it was important to demonstrate the improved reproducibility (using the accepted manufacturing metric of process capability) achieved through moving from manual to automated production. Data in Box 2 shows the process capability of manual compared to automated production for an exemplar cell line manufacture process. The process capability result is important for two main reasons. Firstly, it shows the automated process is in control, i.e. the variation is stable, and therefore enables the application of powerful statistical tools for process analysis. It also provides a probability of batch failure allowing predictable production costs at scale.

Box 2: Analysis of process capability of automated vs manual cell production showed substantially lower process variation in the automated system. An intervention to adjust the process location (mean) of the automated process was successful. The table shows that the potential CpK of the automated process with centred mean is far better than the manual system.

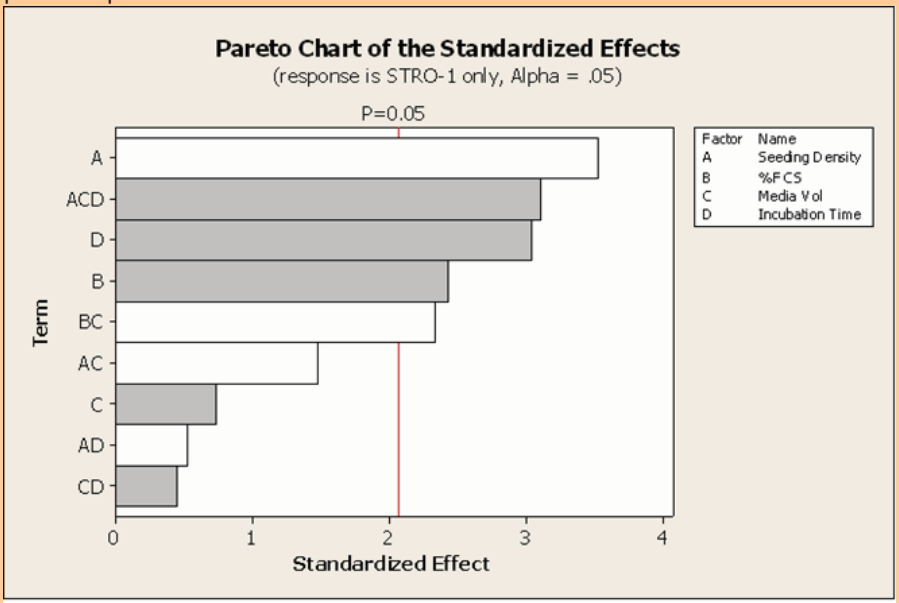


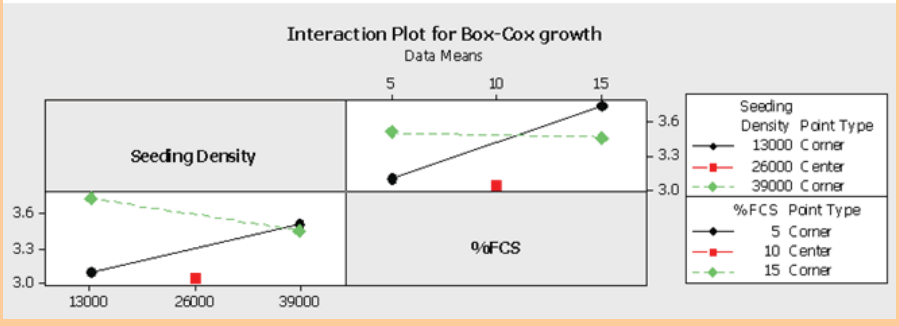
Culture System	Potential Capability	Actual Capability	Process Performance	Process Location (mean)	Process Variability	Improvement Intervention	Process Improvement compared to Manual System	
							Order of magnitude	% Defects
Manual	Cp = 0.55	Cpk = 0.26	Not capable	Centred	Poor	Reduce variability	-	21%
Automated	Cp = 1.32	Cpk = 0.25	Adequate capability	Off-centre	Good	Adjust process location	0	23%
Automated potential (centred mean)	Cp = 1.32	Cpk = 1.32	Good capability	Centred	Good	None	3	< 0.01%

automated process improvement

In the *remedi* programme we demonstrated the value of systematic process improvement methods as a tool for achieving controlled and optimised automated manufacturing processes. We used a 'six sigma' type approach as a framework for applying statistically designed experiments (DOE) in automated mesenchymal stem cell production. The six sigma method helps maintain a systematic approach to process improvement. It involves definition of critical to quality process attributes, measurement of the process performance, analysis of process performance, a *data driven* process improvement intervention and, finally, process monitoring to demonstrate maintained control post improvement. The power of DOE is to identify major process input effects on critical process outputs in the analysis phase with high experimental efficiency (i.e. results per experimental run). These multivariate experiments can also identify where input parameters are not independent (i.e. their individual effects are dependent on the levels of another parameter). This is critical data for achieving an optimal process as some input factors cannot be optimised independently. Data in Box 3 outlines the DOE analysis of critical process input variables for the automated production of mesenchymal stem cells. Particularly important is the observed interaction between serum concentration and cell density. This shows the potential to reduce the use of undesirable production components such as serum with improved process understanding and proves the futility of attempting process analysis using one-factor-at-a-time experimental approaches.

Box 3: Analysis of the automated production of hMSCs was conducted within a systematic process improvement framework. Statistically designed experiments showed the most important parameters determining expression of hMSC markers. The analysis also identified critical interaction between process input parameters (i.e. seeding density and serum concentration) that effect cell growth and quality. This illustrates the importance of process understanding for achieving process optimisation and control.





achieving GMP standards of cell manufacture

As the automated process development work has progressed, consideration has been given to the challenge of a production system that could meet the regulatory requirements for clinical production. Regulatory authorities demand stringent validation of equipment and facilities used in the production of therapeutic products for human application. Therefore, the transition of facilities and automation from non-GMP applications to GMP-validated equipment requires careful consideration of the processing machine, as well as the surrounding laboratory environment. Furthermore, the segregation of individual cell types, whether cell lines or individual patient cells, is pivotal to maintaining quality of cell- and tissue-based products. If cross-contamination were to occur between individual patient samples, there would be the potential risk of adverse reactions due to the transfer of patient disease from one cell to another, or even negative immune reactions due to the body recognising cells as non-self. However, in terms of manufacturing multiple autologous therapies concurrently, the cost of complete segregation of patients' cells in dedicated incubators and biosafety cabinets may make the cost of such therapies prohibitive.

From a regulatory perspective, full qualification of reagents and source materials is required, together with appropriate manufacturing controls to ensure consistency and product quality of each cell lot. Environmental monitoring is of the utmost importance, with air quality, water quality, laboratory design and personnel training and compliance all critical to product safety. For example, FDA standards classify a critical area, i.e. an area in which a product is exposed to environmental conditions during manipulations, as requiring a per-cubic-metre particle count of <3520 in a size range of 0.5 µm and larger. Furthermore, a quality control (QC) plan also needs to be put into place to ensure proper manufacturing oversight, as well as provide the following functions:

- Examination of the various production components (21 CFR 211.84(a));
- Review and approval of production procedures, testing procedures and acceptance criteria (21 CFR 211.22(c));
- Assessment of each clinical batch based on a cumulative review of completed production records and other relevant information (21 CFR 211.22(a), 21 CFR 211.165, 21 CFR 211.192); and
- Investigation and initiation of corrective actions if unexpected results or errors occur during production (21 CFR 211.22(a), 21 CFR 211.192).

This QC plan then acts to prevent, detect and correct any deficiencies that may produce poor quality or unsafe products, such as the transmission of adventitious infectious agents. Finally, it is important that the QC plan establishes internal audits at planned intervals, and takes into account relative risk factors, previous audit results and corrective actions, with the completion of an annual audit of the complete operation.

the way forward

Once this has been addressed, the current biggest challenge for manufacturers of cell- and tissue-based therapies is in the development of representative potency assays to evaluate the final product. According to a recent FDA guidance document, potency assays must be specific, quantitative, meet pre-defined criteria, include appropriate standards and controls, be fully validated and measure both identity and strength of all active ingredients. Therefore, due to the inherent heterogeneity in the cells themselves, these requirements can only be met if the product is fully defined and manufactured to the same consistent standards. This consistency will rely on strong quality systems controlling both the product and the manufacturing process itself. One way to combat this problem is through the concept of quality by design (QbD).

QbD focuses on building quality into the product through a thorough understanding of both the product and process, combined with a clear

knowledge of manufacturing risks along with appropriate mitigation strategies. This system can aid manufacturers by reducing time to approvals, but can also build significant cost into the manufacturing process through the volume of testing required throughout production. Therefore, the choice of quality system needs to be carefully selected to maximise quality and minimise cost. Once this quality system is in place, potency assays can be developed as *in vitro* surrogate assays for the eventual efficacy of the therapy *in vivo*. Since the manufacturing process is now controlled, any variations in results will be due to the potency of the cells themselves, whether it be their potential to form colonies, or their ability to secrete proteins in response to specific stimuli. In addition to this, there needs to be a strong focus on real-time monitoring of product manufacture and non-destructive testing methods that will avoid cell wastage through onerous quality testing regimes. By improving these techniques, the cost of cell- and tissue-based therapies should be reduced, as fewer cells will be needed to provide an effective treatment, as well as to provide the evidence to satisfy the regulator that the treatment will be safe and effective.

RM product characterisation

Melissa Mather, with Erin Rayment, discusses the characterisation processes critical to regulatory approval

executive summary

- Characterisation of RM products is essential
- Suitable surrogate *in vitro* tools are needed
- Rapid non invasive tools are also needed
- Stakeholder input is vital in characterisation

introduction

Characterisation is fundamental to the demonstration of adherence to good manufacturing practice (GMP) and underpins efforts to obtain product regulatory approval. Specifically, there is a need to demonstrate safety, efficacy and purity of manufacture of regenerative therapies. Safety is of prime concern to ensure therapies do not have a deleterious effect on the patient. Efficacy generally refers to the ability of a product to cause a functional response in the patient, and is related to the potency of the therapy. Purity of manufacture assessments can be used to determine the quality and capability of manufacturing processes. Suitable characterisation strategies will depend on the type of product being assessed. Appropriate tools and techniques for the assessment of devices, cell-based therapies and combination products, are discussed below and shown in Table 1.

devices

Devices include products that do not contain any biologics or drugs and whose primary mode of action is not biochemical. Scaffolds, which take the role of a surrogate extracellular matrix, are the main devices used in

regenerative medicine. These can be composed of natural materials, synthetic materials or a combination of both.

Safety

Sterilisation is important for any product being used in the body; such devices should be free from any unintentionally introduced adventitious infectious agents. Here, conventional microbiological testing can be used along with PCR-based assays for rapid detection. Assessment of the device cytotoxicity should also be made, which requires that cells be cultured whilst in contact with it *in vitro*. *In vivo* studies via animal models will also be applicable to assess the inflammatory response of any device that comes into contact with the body. Further, assessment of any degradation products and/or leachables from the product needs to be made under conditions representative of the *in vivo* environment. Typically, toxicological data should be consulted to assess whether degradation products and leachables cause risk. Finally, an assessment of the mechanical stability of devices designed to bear load will need to be made.

Efficacy

The primary function of devices in regenerative medicine is to support cell and tissue regeneration. It is therefore important to assess the device's ability to facilitate cell migration, and nutrient and waste transport, as well as to act as a physical barrier or mechanical support. Devices can also modulate cell function through suitable topography or mechanical cues. In terms of cell migration, imaging techniques at various time points are suitable for some devices, however, for others where there is insufficient contrast or resolution in the imaging system, the sample should be fixed and sliced to enable conventional histology or microscopy. Nutrient and waste transport can be studied using a number of methods and examples include a simple diffusion cell, optical density studies, fluorescent recovery after photo-bleaching (FRAP) and Nuclear Magnetic Resonance (NMR) techniques. Mechanical properties of devices can be assessed by applying a known load (either static or dynamic) to the sample and determining the resulting strain.

Purity of Manufacture

The quality of a device can be assessed by determining the capabilities of the manufacturing system. Here, assessment of the device's structural characteristics and composition is important. Ideally, measurement tools should enable the device to be interrogated during and at the end of the manufacturing process. Non-destructive testing techniques, which include a range of imaging and spectroscopy methods, are well suited to interrogate devices during the manufacturing process. Often techniques which require either the sampling or destruction of the device can provide a richer source of information, and as such, should be considered for assessing the purity of the device at the end of manufacture.

cell-based products

Cell-based products involve the use of either a single cell type or a combination of cell types to provide a positive therapeutic response once implanted in the patient. These cells are hypothesised to act in several ways *in vivo*, including: repairing the function of the surrounding tissue by acting as replacement cells; by secreting various growth-promoting agents to encourage surrounding cells to act as repair agents; and by mobilising existing niche stem cell populations to migrate to the affected area to repair the site of damage.

Safety

As with devices, the sterility of cell-based products also needs to be assured. For this purpose, existing quantification techniques for measuring safety parameters such as bacterial and fungal load, virus contamination and endotoxin levels appear to be sensitive enough to prevent adverse patient events. For cell-based products, contamination from culture media also needs to be tested for and eliminated. In addition, cells are often passaged for extended amplification times, which can lead to cellular senescence, as well as genetic and epigenetic changes. Although suitable techniques with the necessary precision to assess these risks exist, many require long incubation times and thus new rapid test methods are required. There are currently a number of methods available to monitor

the interactions that occur between cells with their environment *in vitro*, including those based on the assessment of immunochemical and biomolecular markers. However, whereas each has its own merits, no one provides for the non-invasive, rapid, specific and non-destructive analysis of living cells. Of the techniques that might provide some of these attributes, Raman spectroscopy has shown promise, as evidenced by its increasing utility in the life sciences sector in recent years. One of the drivers for this transformation has been the evolution of the instrumentation to the stage where the technique's potential can be realised in complex solutions.

In the case of allogeneic therapies, where cells are derived from an unrelated donor, the autoimmune response needs to be assessed, particularly to determine if immunosuppressants will be needed. Another concern regarding safety measurements is the current inability to remove all unwanted cells. For this to occur, current cell detection methods will need to be sensitive enough to detect as few as tens of cells in a large cell suspension. Considering that current advanced cell sorters claim to only have a sensitivity limit of 98%, there needs to be significant advances in this technology to ensure patient safety. However, the multiple purification steps required to ensure a sufficient standard of quality may add significant costs to the product, in terms of reagents, work hours and also initial cell numbers required to give a purified product.

The role of these cell based products and in particular the evaluation of human mesenchymal stem cells for cell-based therapies in tissue injury and degenerative diseases requires rapid accurate evaluation of cell source quality at a level that satisfies the stringent guidelines laid down by the regulators. DNA microarray technology can be used as a technique to assess relevant cellular pathways, such as senescence, as well as the recognised genetic changes that have been shown to occur with the extensive *ex vivo* expansion that is a prerequisite to obtain the cell numbers that are necessary for human cell-based therapy protocols.

Understanding the genes that dictate the special properties of stem cells has implications for both stem cell biology and regenerative medicine. The information obtained in this way will ensure the quality of the cells and the specificity of differentiation is maintained as well as providing the assessment of mixed phenotypes. Microarray analysis measures the global expression of genes and can thereby provide insight into the genetic processes expressed in stem cells. Microarray data from tissue-specific reference files can be compared to microarray data of stem cells making it possible to identify similarities in particular phenotypes while also revealing other novel signatures. Hence, microarray analysis can be used to better understand stem cell differentiation and make a significant contribution to the biosafety issues of future cell-based therapies and regenerative medicine products.

Efficacy

Proper characterisation and understanding of cell function is the most important factor in determining whether a cell-based therapy will function effectively *in vivo*. However, as complete characterisation of some cell processes are still unknown, it is very difficult to accurately predict every consequence of a particular cell once placed within a patient. Efficacy tests should always be cell-specific and, ideally, test the function of the cell that will be required in an *in vivo* situation. In some cases, *in vitro* assays can be used as surrogate measures. Such measures can often provide more sensitive and useful data than *in vivo* trials in an animal model. Clinical endpoints have to be defined at an early stage to allow for proper evaluation of cell-based therapies in patient trials. For cell-based treatments, the end-points will have to be patient-specific, relative to the age of the patient, as well as being related to when the disease was diagnosed to account for how any existing complications will affect the treatment outcome. However, due to the complexity of several clinical applications, optimal efficacy measurements may evolve over time due to improved clinical information available to inform the decision. Quantifying efficacy measurements is another challenge for product developers, but can only be focussed upon once appropriate specific functional assays have been identified. With regards to *in vitro* testing, the sensitivity of

measurements will always depend on the detection system that is being used. Therefore the design of the functional assay, and identifying its key output requirements, is likely to be more challenging than the sensitivity of the detection system itself.

Purity of Manufacture

Many scientists consider cell viability as the primary factor for determining the cellular effect of these advanced therapies once implanted in the body. This can be measured using various simple assays, as well as more sophisticated measures of cell metabolic activity - with both providing quantitative data. However, most of these viability percentages simply measure how many cells are “alive”, not how many cells are actively metabolising and playing a productive role in their environment. In terms of these advanced therapies, identifying the cell phenotype, function and perhaps mode of action will be critical for specific clinical applications. Biomarkers may be important in distinguishing different cell phenotypes, but they do not always provide a correlation to cell function. Therefore, in terms of cell-based therapies, how the cells act in the body might be more important than their immunophenotype *in vitro*. Cellular morphology can also be used to analyse cell populations using various microscopy techniques to determine if cells appear true to their phenotype.

To meet product specifications, cell number and cell viability measurements must be accurate so that specific product dose can be determined. However, the accuracy of cell counts can also be quite variable, from both manual and automated systems. Therefore, while automated cell counting systems have several advantages over manual counting, improvements still need to be made. Of note, the final product acceptance range should be carefully considered as the limitations of the machine must be taken into account. This may include the tolerancing of specifications, as well as factoring in measurement system errors that may contribute to misleading data. An extremely narrow range might cause products to be rejected due to these inaccuracies rather than actual product failure.

combination products

Combination products include two or more separately regulated components, i.e. drug/device, biologic/device, drug/biologic, or drug/device/biologic. In most regenerative medicine applications, this will involve the combination of a device and a biologic, e.g. a scaffold that is seeded with cells. These therapies require stringent regulatory processes as the risk of contamination or cross-contamination is higher than that of products that can undergo a terminal sterilisation step.

Safety

Safety requirements that apply to each component of a combination product should also be applied when they are used together as a single product. Thus, test methods detailed in the previous sections should be applied to these products. In addition, if the product contains a drug the release of this agent needs to be considered as patient safety may be compromised in the case of an over- or under-dose. Studies of release rate should be carried out in conditions that mimic the *in vivo* environment (both physiologically and mechanically). Tests could be performed by placing the combination product in a culture environment and either periodically assaying aliquots of the release media or performing non-invasive measurements of the released media (e.g. fluorescence measurements).

Efficacy

Here, suitable test methods will depend upon which component of the combination product has the main therapeutic action. For example, in a drug-loaded scaffold, the rate of scaffold degradation or dissolution will play a primary role in determining efficacy. Whilst in a tissue-based product composed of a biomaterial and cells, both components are likely to play a key role in product function. Thus, a number of complementary techniques should be used to fully assess product efficacy. Further, in the selection of measurement tools preference should be given to those techniques that enable the product to be assessed in an environment representative of the site of its intended use.

Purity of Manufacture

As with cell-based products, combination products that contain a biologic should undergo tests which assess cell viability and phenotype. Here, the use of conventional testing methods may be limited if difficulties arise in isolating cells from other components of the product. Thus, test methods that do not require isolation of cells will be more practical (e.g. fluorescent markers and microscopy). As with devices, the quality of some combination products will require assessment of structure and composition. Here, it will be important to assess the impact that other components have on the product structure and composition, e.g. cells may obstruct voids in scaffolds over time and modulate the composition of surrogate matrices. Therefore, imaging and spectroscopy techniques with sufficient contrast to resolve each component of the combination product will be useful.

conclusion

There are many challenges associated with characterising regenerative therapies. From a regulatory perspective, these advanced treatments must not only be safe and effective for their designated indication, but must also be made by high quality manufacturing processes. Whilst a number of existing technologies are available to characterise regenerative therapies, many are time consuming, expensive and disruptive. In general, there is a need to identify suitable surrogate *in vitro* tools, define clinical endpoints early on and develop product specifications that can be met by current manufacturing processes. In conclusion, there is a need for improved stakeholder involvement in product characterisation, to allow the manufacture of the best possible regenerative therapies within the shortest timeframe.

Table 1

Technique	Analysis Capability	Device	Cell-based	Combination	Safety	Efficacy	Purity of Manufacture
Broth & agar	Bacterial growth	✓	✓	✓	✓		
PCR assay	Bacterial and viral presence	✓	✓	✓	✓		
Blood pathology testing	Donor contamination of biologics		✓	✓	✓		
***In vitro* culture**	Cytotoxicity, endotoxin	✓	✓	✓	✓		
GTL banding of metaphase spreads	Karyotyping		✓	✓	✓		
Fluorescence *in situ* hybridisation	Karyotyping		✓	✓	✓		
Flow cytometry	Cell number, viability and phenotyping		✓	✓			✓
Animal models	Toxicology, immune response, cell effectiveness	✓	✓	✓	✓	✓	✓
ELISA	Cell effectiveness		✓	✓		✓	
Trypan blue assay	Cell number and viability		✓	✓			✓
Metabolic assay	Cell viability		✓	✓			✓
Optical microscopy (including fluorescence)	Morphology, structure and function	✓	✓	✓		✓	✓
Histology	Morphology, structure and composition	✓	✓	✓	✓	✓	✓
Diffusion cell	Diffusion of nutrients and waste	✓		✓		✓	
FRAP	Diffusion of nutrients and waste	✓		✓		✓	
NMR techniques	Spectroscopy: composition; Imaging: structure and diffusion	✓		✓		✓	✓
Compression testing	Mechanical properties	✓		✓	✓	✓	✓
Optical spectroscopy (Including Raman)	Composition, Cell Viability	✓	✓	✓		✓	✓
DNA Microarray Technology - qPCR	Gene expression, SNP analysis		✓	✓	✓	✓	✓

the value proposition for SMEs

Patrick Ginty summarises the challenges for SMEs and Government

executive summary

- SMEs must please a multiplicity of customers
- Value proposition is quality, safety and efficacy; *and* cost-effectiveness
- Success in first in man trials is a key value demonstrator
- Reducing cost and risk is key to success

components of the value proposition

Future success in the regenerative medicine field will depend on an SME's ability to manage risk, attract investment and achieve key technical and financial milestones at specific points in the lifecycle of a new technology. In order to achieve this, a multiplicity of customers and stakeholders (i.e. investors, regulators, payers, clinicians and ultimately patients) must be satisfied through the demonstration of value in the parts of the business that are most relevant to each of them. This demonstration of value is best described as the value proposition (VP) and is defined as 'the benefits offered to the customer, minus the cost and risk'.

Quality, Safety and Efficacy; Regulatory Approval

Three core elements of a successful VP are defined by the regulator and provide the basis to meeting the key customer requirements of *quality, safety and efficacy*.

Demonstration of these three elements, together with cost-effectiveness, at key stages in the development of the business/product will provide evidence to investors that the business/product is commercially viable, thus reducing risk and enhancing the probability of a satisfactory return on investment (ROI). The most important milestones associated with gaining investment are; (1) the successful completion of *animal efficacy studies*, (2) the completion of *'first in man' trials* and (3) *regulatory approval.* These key value inflection points demonstrate safety, efficacy and quality (built into the process in the form of GLP and GMP) with regulatory approval showing that one very critical barrier i.e. clinical trials, has been successfully negotiated. Without any of these key demonstrators, the company has little to offer to investors as the real value of IP in the field of cellular therapeutics has yet to be determined.

Cost-effectiveness

Showing value to both the payer and clinician for adoption may be the most challenging part of the VP as the requirements for efficacy and *cost-effectiveness* are relative to any incumbent technology, the clinical pathway and the size of the market (as discussed at length in Chapter 4). Therefore, SMEs need to assess the relative efficacy needed to achieve cost effectiveness for either an addressable market of sufficient size or an unmet clinical need. This will determine both the reimbursement flexibility and acceptable cost of goods (COGs) and thus determine the pricing structure and resultant ROI. New enabling technologies may be the key to reducing COGs that are driven by R&D costs, such as the removal of bottlenecks from the manufacturing process or cheaper/faster testing methods that improve efficiency and ultimately deliver the *ability to supply* at the product volumes required. However, reducing COGs during the R&D phase is challenging, as much of the costs are incurred through achieving regulatory compliance/approval and are therefore 'non-negotiable'. Therefore a lot of emphasis will be shifted onto the efficacy of the product, placing a heavy burden on those SMEs that develop products

that must show greater efficacy and cost-effectiveness than that of the current standard of care.

the product pipeline and investor returns

The issue of the size of product/platform pipelines remains open to debate. It can be surmised that a large product pipeline adds value to the business and potentially provides multiple revenue avenues that are attractive to investors. However, having a broad number of platforms in development can significantly increase cash burn, especially if the company is not close to commercialisation, due to the increased costs incurred by numerous regulatory submissions, clinical trials and manufacturing processes. A single technology platform that can provide products with a range of indications is a more attractive option, as it is less likely to involve this multiplicity of costs and allows the company to remain focussed. Conversely, a single product may be viewed as risky by investors as there is little to fall back on, but it can be justified provided that key components of the VP are in place, i.e. there is compelling evidence to suggest that it will be a commercial success. As a further note of caution, it should be remembered that many customer requirements are prone to change. For example, the demands for continued regulatory compliance and justification of pricing are moving targets and will require constant attention in the post-market phase.

conclusion

executive summary

- Successful RM products will reach the market but translation is slow
- Rate of routine adoption remains a significant investment risk
- Intervention is required to support small business growth

There can be no doubt that, given sufficient time, very important and successful RM products will be brought to market to the benefit of the patient, the healthcare provider, the reimburser, and, not least, the originating company and its investors. This translational process is, however, currently slow, immature and unproven, with few exemplars of success that market investors can compare against (as covered in Chapter 1). The availability of a positive value proposition is, consequently, a necessary but not sufficient condition for success, particularly where a product passes all the approval and reimbursement criteria, but for whatever reason takes much longer than anticipated in the business plan to become adopted as the standard approach.

There remains a critical role for Government over the next three to five years if these opportunities are to be exploited in a timely way for the broad benefit of the UK both in healthcare delivered by the NHS and new business and industry growth. This has been clearly recognised in the Blueprint published by The Office for Life Sciences in July 2009, in which RM was specifically identified as a strategic priority for company investment stimulus, increased funding of manufacturing research – *the product is the process* – and targeted grants from the Technology Strategy Board.

remedi – the Grand Challenge

remedi is one of four Grand Challenge projects awarded by EPSRC in 2003. Grand Challenges are intended to address major research challenges with the potential for significant impact on national manufacturing priorities, and ambitions far greater than might be achieved by a single research team or in the span of a traditional research grant. *remedi,* led by Loughborough, brought together research teams from Nottingham, Cambridge, Birmingham, Ulster and Liverpool, together with a growing number of companies and organisations associated with the realisation of Regenerative Medicine as an industry. The £8M portfolio of research areas sought to demonstrate how established bio-science could be transformed into profitable commercial practice and generate affordable therapies while developing the science of manufacture. The specific objectives were to:

- determine the value of tissue engineered products to users in healthcare, thus defining the market place, and show how the development of regulation and industrial policy can maximise economic benefit while protecting patients
- create and demonstrate reproducible cost effective processes for the scaleable production of cells, scaffolds, and tissue products that satisfy the regulator and take advantage of emerging sensing and control techniques
- construct a community that integrates the Challenge programme and generates a shared vision for the industry and its future products and explores these visions practically. It will develop techniques to enable life science and manufacturing professionals in SMEs to create cost effective manufacturing systems, pre-clinically, while managing biological risk.

This second part of the book summarises the research areas (or 'workpackages') that contributed to the *remedi* portfolio, together with their outputs and impact. For each area, key publications are listed together with contact details for those who led the research.

understanding the market (University of Nottingham)

Aims

This work area was a horizontal activity that contributed to all others. Its central theme explored what tissue engineered /regenerative medicine products were on the market and how they are being adopted by users in healthcare settings. The research:

- Surveyed the tissue engineering industry and the main products in use and development;
- Analysed the needs of clinical users in relation to tissue engineered products;
- Assessed the main factors shaping the adoption and acceptability of tissue engineered products;
- Disseminated findings to key stakeholders.

Achievements

The main research findings were published in two major reports (below) in April 2009. The first described the commercial development of cell therapy internationally and mapped the industry structure, the products on the market and in development, and the pattern of industry collaboration. It highlighted the risk of market failure and made a number of recommendations about how public policy might support the sector. The second report was based on a qualitative study of clinical adoption of regenerative medicine products in the NHS. It identified the main barriers to successful adoption and made a series of recommendations about how these might be overcome.

Future directions

In addition to the reports a number of papers have either been published or are in preparation. Direct outcomes include a meeting with senior managers at the National Blood Service to brief them on opportunities in the regenerative medicine area (this followed a specific recommendation in the Barriers report).

Impact

The industry survey highlighted both the economic potential of the regenerative medicine industry and the challenges it faces. This has provided a valuable evidence base for policy making and the report was circulated throughout government. The Barriers report explored how the NHS could better adopt innovative cell based therapies and identified the main institutional barriers to innovation, thus making a significant contribution to policy formation and NHS practice.

Additional benefits and outcomes

As part of this work area associated studentship funding has been awarded to a PhD student (Richard Elliott) to examine public perceptions of the acceptability of regenerative medicine products. Dr Emma Rowley has now also secured a translational research role working in the NIHR CLAHRC NDL (Collaboration for Leadership in Applied Health Research and Care – Nottinghamshire, Derbyshire, and Lincolnshire).

Information sources

http://www.nottingham.ac.uk/iss/research/Current-Research-Projects/Staff_projects/regenmed/reports_publications.htm

Key references

The Commercial Development of Cell Therapy – Lessons for the Future? Survey of the Cell Therapy Industry and the Main Products in Use and Development, Paul Martin, Ruth Hawksley and Andrew Turner, April 2009, download from site above

Barriers to the Commercialisation of Regenerative Medicine in the UK, Emma Rowley and Paul Martin, April 2009, download from site above

Plagnol, A.C., Rowley, E., Martin, P., and Livesey, F., Industry perceptions of barriers to commercialization of regenerative medicine products in the UK, Regenerative Medicine, Vol.4, No. 4, 549-559, July 2009

Contact for more information

Paul Martin: paul.martin@nottingham.ac.uk 0115 951 5419

Emma Rowley: emma.rowley@nottingham.ac.uk 0115 846 8144

assessing cost-effectiveness (University of Birmingham)

Aims

Our remit was to conduct health economic analysis to guide the development of regenerative medicine therapies and as far as possible make these easily understood by industrial partners. We have set out to take health economics to the supply side of the health economy.

Achievements

Firstly, we have produced generic methods for health economic analysis at the supply side. Secondly, we have produced worked examples of these methods using clinical applications of RM therapies for urogenital defects, bone and cartilage defects, abdominal wall defects, and neurodegenerative disorders.

Future directions

Our approach to health economics at the supply side has been well received in the industrial community. Over the course of our work we have been contacted by a number of RM and TE companies and asked to help them better understand how their products might withstand future health economic scrutiny. Further dissemination activities are planned. In addition our work on using health economics to inform supply side analysis will be continued more broadly under the MATCH (Multidisciplinary Assessment of Technology Centre for Healthcare) IMRC banner.

Impact

It is a waste of resources to produce products that will not be purchased and used. The industry and the nation as a whole will benefit by application of the approach to give a better match between supply and user need.

Additional benefits and outcomes

Helen McAteer is on target to achieve a PhD based on this work. She has also recently secured new employment in the NHS working for the Birmingham Clinical Research Academy, a role which will assist clinicians and academics to conduct translational research.

Information sources

Further information and a full description of the method is available on: http://www.haps.bham.ac.uk/publichealth/methodology/hes/remedi.shtml

Key references

Cosh, E., Girling, A., Lilford, R., McAteer, H.L., Young, T., Investing in New Medical Technologies: A decision framework. Journal of Commercial Biotechnology, 13(4): 263-71, 2007

McAteer, H.L., Cosh, E., Freeman, G., Pandit, A., Wood, P. & Lilford, R., Cost-effectiveness analysis at the development phase of a potential health technology: examples based on tissue engineering of bladder and urethra, Journal of Tissue Engineering and Regenerative Medicine, Volume 1, Issue 5, Pages:343-349, September/October 2007

Contact for more information

Prof Richard Lilford: r.j.lilford@bham.ac.uk 0121 414 6772
(PA Cathy Hill: c.hill@bham.ac.uk 0121 414 8695)
Helen McAteer: h.l.mcateer@bham.ac.uk 0121 414 9096

the policy environment (University of Cambridge)

Aims

This work area was concerned with identifying the key policy/regulatory barriers and enablers that exist for RM products in the UK, and with exploring possible changes and improvements to the regulatory and policy infrastructure. The research:

- investigated the state of policy and regulation towards RM globally
- developed alternative policy and regulatory frameworks for RM in the UK
- looked into some of the economic aspects of RM firms in the UK to support the development of regulatory and policy recommendations

Achievements

The regulatory work led to the publication of a number of working and journal papers which identified the lack of clarity and predictability of the pre-existing regulatory framework for RM products at the EU-UK level. It further included an analysis of the strengths and weaknesses of the regulation put in place by EU regulators and engaged in a forward-looking approach to explore how this regulation would impact on the RM industry landscape. The economic work included a study which revealed that scientific research in RM was thriving in the UK but that key issues, like the lack of access to capital and regulatory hurdles, did not provide a good environment for the commercialisation of RM products. These findings were integrated with those in the market understanding study and published in a journal paper.

From a policy perspective, the main research findings were published in a policy report in 2008. This report provided a snapshot of the industry and its possible potential for the UK and outlined recommendations for public investment and support to assist in its development to the benefit of the UK economy.

Future directions

The findings from the *remedi* project have been used as the basis of one of the case studies adopted by the Emerging Industries Programme, a research project at the Institute for Manufacturing at the University of Cambridge. This programme explores how emerging technologies can be fostered in an optimal way in the UK.

Impact

The policy report was well received. The BioIndustry Association acknowledged the valuable contribution it made to the review of the Bioscience 2015 report. Some direct work has also been done with the RM industry through two consultancies for TAP and MagneCell.

Information sources

http://www.ifm.eng.cam.ac.uk/cig/

Key references

Brevignon, L. & Livesey, F., Regulation of tissue-engineered products in the European Union: where are we heading?, Regenerative Medicine, Vol 1., No. 5, pp. 709 – 714, 2006

Brevignon, L. & Livesey, F., What can be learnt from the Japanese regulatory approach to tissue engineered products?, Regenerative Medicine, Vol.2, No.6, 967-971, 2007

Kulkarni, R. P., Livesey, F. & Brévignon-Dodin, L., Will regulation determine the science agenda? A look at human embryonic stem cells (hESC), Regenerative Medicine, Vol.2, No.5, 839-844, 2007

Brévignon-Dodin, L. & Singh, P., ATMP in practice: toward a new industry landscape in tissue engineering, Journal of Commercial Biotechnology, Vol.1, No.15, 59-65, January 2009

Finbarr Livesey, Anke Zimmermann, Laure Brévignon-Dodin & Mike Gregory, Policy report: Enabling the emergence of the regenerative medicine industry in the UK, 2009

Contact for more information

Finbarr Livesey: tfl20@eng.cam.ac.uk 01223 748258

Laure Dodin: ld308@eng.cam.ac.uk 01223 339739

scaffold manufacture (University of Nottingham)

Aims

Scaffolds are materials that can stimulate regeneration of tissue within the body. They are complex structures that have been developed in laboratories using bespoke and small batch manufacturing methods. The *remedi* project aimed to generate protocols for the manufacture of scaffolds with high reproducibility and with the potential for large scale production. In addition, scaffolds provide an interface with the pharmaceutical industry as they act as controlled drug delivery systems for biopharmaceuticals. *remedi* aimed to demonstrate the reproducible formation of composites of scaffolds and growth factors.

Achievements

Standard protocols for the formation of scaffolds with average porosities of 70% and mechanical properties suitable for bone repair.

Delivery of bone morphogenetic protein 2 (BMP2) and vascular endothelial growth factor from scaffolds. 14 peer-reviewed papers have been published to date.

Future directions

The Medical Research Council and RegenTec Ltd (UK based SME) have funded further trials of the scaffolds in hip arthroplasty at Southampton University. This could lead to project launch within 3 years.

Critical Pharmaceuticals (UK based SME) has utilised know-how from *remedi* to understand the influence of viscosity on its manufacturing process.

Impact

Enhanced the scientific foundation of 2 UK SMEs. Both companies have raised investment during the *remedi* project and have progressed products towards launch.

The MRC funded work promises to decrease the cost of certain hip surgeries and improve surgical procedures.

New collaboration with Queensland University of Technology to develop weight bearing porous scaffolds.

Additional benefits and outcomes

One postdoctoral scientist from this work area, Dr Tai, received a prestigious International Fellowship and has a permanent academic position.

Information sources

www.regentec.net
http://www.nottingham.ac.uk/cbs/

Key references

Tai, H., Mather, M.L., Howard, D., Wang, W., White, L. J., Crowe, J.A., Morgan, S.P., Chandra, A., Williams, D.J., Howdle, S.M. and Shakesheff, K.M., Control of pore size and structure of tissue engineering scaffolds produced by supercritical fluid processing, European Cells and Materials, Vol. 14, pp 64-77, 2007

Ginty, P.J., Barry, J.J.A., White, L.J., Howdle, S.M.and Shakesheff, K.M., Controlling protein release from scaffolds using polymer blends and composites, European Journal Of Pharmaceutics and Biopharmaceutics, 68 (1):82-89, 2008

Davies, O.R., Lewis, A.L., Whitaker, M.J., Tai, H.Y., Shakesheff, K.M. and Howdle, S.M., Applications of supercritical CO2 in the fabrication of polymer systems for drug delivery and tissue engineering, Advanced Drug Delivery Reviews, 60 (3):373-387, 2008

Bolland, B.J.R.F., Kanczler, J.M., Ginty, P.J., Howdle, S.M., Shakesheff, K.M., Dunlop, D.G. and Oreffo, R.O.C., The application of human bone marrow stromal cells and poly(DL-lactic acid) as a biological bone graft extender in impaction bone grafting, Biomaterials, 29 (22):3221-3227, 2008

Contact for more information

Prof Kevin Shakesheff: kevin.shakesheff@nottingham.ac.uk 0115 951 5104
Prof Steve Howdle: steve.howdle@nottingham.ac.uk 0115 951 3486

therapeutic cell culture automation (Loughborough University)

Aims

This work area created process demonstrators for the automated culture and volume processing of human cell types of commercial, therapeutic and scientific value. The demonstrators included application of key quality engineering techniques to improve process capability.

Achievements

Specified the prototype CompacT SelecT automated cell culture machine design to allow the scaleable production of cellular therapeutic products.
Demonstrated the automated, scaleable culture of: human bone marrow and umbilical cord blood derived hMSCs; multiple hESC lines in serum-free or feeder-free conditions; two 'near to clinic' commercial cell types, verified against commercially relevant endpoints; differentiated otic progenitor cells from hESCs for application to hearing disorder therapy; and human endothelial progenitor cells for drug screening applications.
Defined effective methods of designing and operating cell culture manufacturing processes including: first demonstration of the application of process capability analysis to establish and compare short-term process capability of manual and automated human cell culture processes; first use of capability statistics to demonstrate improvement in process performance of manual culture systems on the automated platform; short-term process capability studies for a scalable commercial cell culture process; the application of a statistically designed full-factorial screening experiment (DOE) to investigate the effect of critical input variables on cell population growth and functionality in an automated culture process for primary bone marrow derived hMSCs; and the application of Response Surface Methodology to optimise a model stem cell culture process for reduction in Cost of Goods.

Future directions

Exploitation of much of the work is via the collaborating partners. The research has fed directly into teaching particularly via the new collaborative Doctoral Training Centre (DTC) in Regenerative Medicine. BRIC funding has secured the continuation and expansion of the hESC bioprocessing work with Nottingham University. A DARPA funded project for fieldable blood production systems has increased international collaboration.

Impact

With other work packages, this work has demonstrated measurable impact on SME partners (Cook Myosite, Reneuron, Stem Cell Sciences and TAP), and UK and international upstream science. TAP in particular have benefitted by selling a significant number of machines.

Additional benefits and outcomes

2 RAs in this area, Dr Thomas and Dr Liu, have now secured UKRC Fellowships. Dr Thomas has won the 2009 IChemE Award for Innovation and Excellence in Bioprocessing. The UK National Stem Cell Bank also joined *remedi* as a collaborator.

Information sources

http://www.lboro.ac.uk/research/lcbe/
http://www.reneuron.com/news__events/news/document_186_237.php

Key references

Liu, Y., Hourd, P., Chandra, A. and Williams, D.J., Human cell culture process capability: a comparison of manual and automated production, J Tissue Eng Regen Med 2009, DOI: 10.1002/term.217

Thomas, R.J., Chandra, A., Liu, Y., Hourd, P., Conway, P.P. and Williams, D.J., Manufacture of a human mesenchymal stem cell population using an automated cell culture platform, Cytotechnology, 55(1), pp 31-39, September 2007

Thomas, R.J., Hourd, P. and Williams, D.J., Application of process quality engineering techniques to improve the understanding of the in-vitro processing of stem cells for therapeutic use, Journal of Biotechnology, Volume 136, Issues 3-4, 10 pp 148-155, September 2008

Thomas, R.J., Anderson, D., Chandra, A., Smith, N.M., Young, L.E., Williams, D.J. and Denning, C., Automated, Scalable Culture of Human Embryonic Stem Cells in Feeder-Free Conditions, Biotechnology and Bioengineering, Vol. 102, No. 6, 1636-1644, April 15 2009

Thomas, R. J., Hope, A. D., Hourd, P., Baradez, M., Miljan, E. A., Sinden, J. D. and Williams, D. J., Automated, serum-free production of CTX0E03: a therapeutic clinical grade human neural stem cell line, Biotechnology Letters, 31:1167–1172, 2009

Contact for more information

Robert Thomas: R.J.Thomas@lboro.ac.uk 01509 227601
Paul Hourd: P.Hourd@lboro.ac.uk 01509 564890
Prof David Williams: D.J.Williams@lboro.ac.uk 01509 227668

manufacture of tissue engineered constructs (Loughborough University)

Aims

To build process demonstrators and models of the variation in the volume manufacture of first generation tissue engineered products requiring cell growth and extracellular matrix (ECM) deposition within a scaffold matrix. To understand the principles of process design in the presence of biological variation. To understand the effects of mechanical stimulation.

Achievements

Design, specification and implementation of a novel, physiologically informed triaxial dynamic bioreactor system to enable demonstration of the effect of mechanical stimulation on tissue growth in the presence of biological variation. Implementation and validation of a novel validated phenomenological model of growth of orthopaedic tissue cultured in a rotating bioreactor. Characterisation of the structure and biochemical composition of a commercially manufactured living dermal equivalent (ICX-SKN) construct and the evolution and enhancement of its mechanical properties during the process. The outcome of this research has led to a step change improvement in both the properties of the commercial construct and the processing time. This work area has been one of the most challenging of *remedi*; in consequence efforts have been made to understand and communicate these challenges.

Future directions

The knowledge and learning from the experimental bioreactor programme combined with the outcomes of both the cartilage modelling work and SKN construct work will be used to inform the engineering science/interface research agenda for mechanical stimulation of tissue constructs. Workshops will be used to further explore this. A further industry collaborative TSB project has been secured, 'Packaging Platform for Cell and Tissue Based Therapies', which includes understanding the effect of mechanical stimulation during transport.

Impact

Demonstrated a world first in the design and operation of a physiologically informed triaxial orthopaedic bioreactor.

Demonstrated measurable impact on core partner (Intercytex) and UK and international upstream science. Novel work in the use of mechano-transduction to improve properties of constructs is subject to a patent application.

Additional benefits and outcomes

Two of the research assistants in this area, Dr Immanuel Sebastine and Dr Chaozong Liu have secured university lectureships/senior lectureships. Dr Jasmin Kee is now employed as the engineer in the future project group of one of the most well known and successful RM companies.

Information sources

http://www.lboro.ac.uk/research/lcbe/

Key references

Archer, R. and Williams, D.J., Why Tissue Engineering Needs Process Engineering, Nature Biotechnology, 23, pp 1353-1355, November 2005

Nikolaev, N.I., Obradovic, B., Versteeg, H.K., Lemon, G. and Williams, D.J., A Validated Model of GAG Deposition, Cell Distribution, and Growth of Tissue Engineered Cartilage Cultured in a Rotating Bioreactor, Biotechnology and Bioengineering, 2009, DOI 10.1002/bit.22581

Liu, Y. and Williams, D. J., Incorporation of Hydroxyapatite Sol Into Collagen Gel to Regulate the Contraction Mediated by Human Bone Marrow-Derived Stromal Cells, IEEE Transactions on Nanobioscience, to appear

Sebastine, I.M., Liu, Y., Win Naing, M., Pearson, E.A., Dingmann, D. and Williams, D.J., Design and Validation of a 3D Tissue Manufacturing System: The Dynamic Triaxial Bioreactor, Online Abstract Database for Termis NA 2008, 120, Termis NA 2008, San Diego, December 2008

Naing, M. W., Liu, Y. and Williams, D. J., O6 Towards a Physiologically Informed Bioreactor Engineering Challenges & Compromises, Tissue and Cell Engineering Society Conference, University of Glasgow, July 8-10 2009

Contact for more information

Prof David Williams: D.J.Williams@lboro.ac.uk 01509 227668

sensing and characterisation (University of Nottingham)

Aims

This work area sought to develop appropriate methods of assessing the characteristics and quality of regenerative medicine manufacturing processes and products.

Research outcomes achieved

Increased understanding of mechanisms that influence the pore size and structure of tissue engineered scaffolds produced by supercritical fluid processing via optical and ultrasonic monitoring.

Demonstration of an increase in the structural stability of tissue engineered skin via application of ultrasound based mechanical stimulation.

Development of an integrated environmental and mechanical sensing and logging instrument housed in a standard culture flask to assess incubator and robotic cell culture machine performance.

Time lapse imaging of neuronal stem cell culture and development of mathematical models of this process.

Theoretical investigation of how the key variables of X-ray micro CT imaging affect the estimation of porosity (and hence other characteristics) of tissue engineered scaffolds.

Achievements

RegenTec have benefitted from the increased understanding of the factors that influence tissue engineered scaffold formation.

Intercytex are applying for a patent on the ultrasound stimulation of tissue engineered skin.

TAP were closely involved with the development of the sensing and logging 'SMART flask' that is currently being used by a number of researchers at Nottingham and Loughborough.

Discussions are being held with Reneuron to continue both time lapse imaging and modelling. Links with the University of Sheffield have been established concerning the application of their agent based modelling software to this problem. A proposal, inspired by this work, has been submitted to the Wellcome Trust's Technology Development Fund.

Experimental validation of the theoretical models of factors influencing the quality of X-ray micro CT images, and hence estimates of scaffold parameters, is almost complete.

Impact
Collaboration with industry has aided production of enhanced products that should result in both increased sales and greater patient satisfaction.

Additional benefits and outcomes
NPL joined *remedi* as a core partner and Dr Melissa Mather subsequently secured a fellowship at the NPL on the use of hydrogels in healthcare. Dr Mather has produced a draft standard guide for ASTM International on the characterisation of hydrogels used in regenerative medicine (WK21927).

Information Sources
http://news.bbc.co.uk/1/hi/health/7834028.stm

Key references
Mather, M.L., Morgan, S.P. and Crowe, J.A., Meeting the needs of monitoring in tissue engineering, Regenerative Medicine, 2 (2), 145-160, 2007
Mather, M.L., Crowe, J.A., Morgan, S.P., White, L.J., Kalashnikov, A.N., Ivchenko, V.G., Howdle, S.M. and Shakesheff, K.M., Ultrasonic monitoring of foamed polymeric tissue scaffold fabrication, Journal of Materials Science-Materials In Medicine, 19 (9):3071-3080, 2008
Mather, M.L., Morgan, S.P., White, L.J., Tai, H., Kockenberger, W., Howdle, S.M., Shakesheff, K.M. and Crowe, J.A., Image-based characterization of foamed polymeric tissue scaffolds, Biomedical Materials, 3 (1): Art No. 015011, 2008
Mather, M.L., Brion, M., White, L.J., Shakesheff, K.M., Howdle, S.M., Morgan, S.P. and Crowe, J.A., Time-Lapsed Imaging for In-Process Evaluation of Supercritical Fluid Processing of Tissue Engineering Scaffolds, Biotechnology Progress, 25 (4):1176-1183, 2009
Morris, D.E., Mather, M.L. and Crowe, J.A., Generation and simulated imaging of pseudo-scaffolds to aid characterisation by X-ray micro CT, Biomaterials, Volume 30, Issue 25, 4233-4246, September 2009
Mather, M.L., Morgan, S.P., Morris, D.E., Zhu, Q., Kee, J., Zoladek, A., Crowe, J.A., Notingher, I., Williams, D.J. and Johnson, P.A., Raman spectroscopy and rotating orthogonal polarization imaging for non-destructive tracking of collagen deposition in tissue engineered skin and tendon, Optics in Tissue Engineering and Regenerative Medicine III, Proc. of SPIE, 7179, 71790A - 1 to 10, 12th February 2009

Contact for more information
Prof John Crowe: john.crowe@nottingham.ac.uk 0115 951 5590

control and characterisation (University of Ulster)

Aims

Activities at Ulster focussed on the control and characterisation of cellular products for tissue engineering and regenerative medicine. In particular, Raman spectroscopy has been used to assess cell function in a real-time, non-destructive context and to indicate the presence or otherwise of contaminants in culture. A commercial DNA Microarray platform has been employed to examine gene expression in adult stem cells as a function of passage number in both normal and osteogenic media conditions. The programme of work sought to determine and demonstrate the instrumental sensitivity required to characterise, monitor, evaluate and control such cellular products in both manual and automated cell culture.

Achievements

Research outputs include two working papers, the results of a workshop on the characterisation of osteoblast cell types. Research on the application of Raman for cell analysis has been accepted for publication in the Journal of Material Science – Materials in Medicine. Research findings on both the Raman and Microarray studies have been presented at the World Biomaterials Congress 2008, ESB 2008 & 2009 and UKSB 2008 & 2009, and at the Northern Ireland Bioengineering Society meetings in 2008 & 2009. Invited oral presentations, which included substantial *remedi* outputs, have been delivered at the UK Surface Analysis Forum meeting in 2008 and the UK Surface Science of Biologically Important Interfaces Group meeting in 2009.

Future directions

Work in Raman is proceeding under a National Access Programme Award, enabling access to facilities at the Tyndall Institute, Cork, Ireland. A submission to EPSRC for development of a dedicated optical platform for Raman analysis of adult stem cells in culture has been referred to the BBSRC for review. A 3 year PhD project has also been funded through the Department of Education and Learning (DEL) in NI to develop further the work undertaken from the preliminary Microarray studies.

Impact

Collaboration has been undertaken with several companies during the course of the r*emedi* research work at Ulster. In particular, a strong relationship has been developed with Almac Diagnostics (NI). Interaction with the company continues and discussions are taking place on the development of specialist microarray products for use in Tissue Engineering and Regenerative Medicine, similar to those that the company currently employ in oncology diagnosis. In addition, Avalon Instruments (now Perkin Elmer) and JY Horiba, have both provided collaborative assistance to the Raman activities and this support is on-going via their contributions to the BBSRC proposal.

Additional benefits and outcomes

Researchers from the University of Ulster have benefitted directly from their involvement in the *remedi* project through promotions for PDRA staff and the appointment of the main researcher on the grant at Ulster, Dr George Burke, to a Lectureship position. In addition, the *remedi* project contributed to the Biomaterials & Tissue Engineering Group at Ulster securing infrastructural funding from the Department of Education & Learning (DEL) in Northern Ireland to establish a collaboration with the National University of Ireland, Galway in Functional Biomaterials.

Information sources

NIBEC, University of Ulster - http://www.nibec.ulster.ac.uk/
Almac Diagnostic Ltd. - http://www.almacgroup.com/diagnostics/

Key references

Burke, G.A., Boyd, A.R., Meenan and B.J., Raman spectroscopy as a diagnostic tool for regenerative medicine and tissue engineering, 8th World Biomaterials Congress, Amsterdam, 28th May – 1st June 2008

Contact for more information

Prof Brian Meenan: bj.meenan@ulster.ac.uk 02890 368939

growing the community and the capability (Loughborough University)

Aims

This activity sought: to integrate the work of the challenge, enable communication, promote debate and to make the work of the challenge accessible and of value to SMEs; to build communities within the challenge and with the wider industrial and academic community; to build bridges between the life sciences and manufacturing communities nationally and internationally; to install a project management and co-ordination process; and, following the mid term review, to embed the emerging capability.

Achievements

Strong project leadership and the installation of a Project Management system, including quarterly Management Group meetings, biannual Steering Group meetings and coordinated networking and dissemination has provided effective monitoring, control and change management within the project and significant impact on the external environment including government and other agencies. International academic impacts have included branded sessions at Termis conferences, plenary presentations at CIRP Kobe, Euspen Bremen, World Congress Leipzig and *remedi* being seen as the model for such research in New Zealand.

Securing of additional financial and physical resource at Loughborough University and partner universities to embed new capability, as follows: Creation of the Centre for Biological Engineering (CBE), with Loughborough University strategic investment (£1.2m) and emda support (£650k) for the new facility completed in January 2009. The EPSRC Life Sciences Interface Doctoral Training Centre in Regenerative Medicine (£6.1M) led by a consortium of Loughborough, Keele and Nottingham Universities which together with other UK Government (TSB, BRIC) and non-industrial (DARPA) funded projects are focussed on PhD training, and national, international and SME collaboration. Successor UK Government (TSB) funded projects have been secured to allow further progress in Regenerative Medicine Value Systems research. Significant intellectual property is held as know-how and patenting opportunities are being reviewed. Opportunities for spin-outs have been explored - but due diligence has shown these should not be progressed.

Future directions
In addition to the above, work is in progress following the recent announcement of funding for the new Loughborough-led EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, and to secure emda funding for an Institute for Regenerative Medicine in translation (including manufacturing) and exploitation.

Impact
Via this work package and in collaboration with BIA/RIG, *remedi* continues to influence policy formulation and new initiatives: in industry and science funding with Department of Business, Innovation and Skills (BIS), Office for Life Sciences (OLS) and TSB; in regulation with MHRA (The Topics Group); and in standards with BSI (the RGM1 Committee). It has assisted in the creation of a new industry association RIG, the Regenerative Medicine Industry Group, of BIA, and supports its Chair. It has continued influence on UK and European research policy (Manufuture and Medical Devices) and standards (PAS 83, BSI definitions group).
Creation of a viable regenerative medicine industry gives a unique opportunity to deliver health, create wealth and tackle the aging demographic.

Additional benefits and outcomes
Significant contributions to systemic change within Loughborough University.

Any other information and relevant website(s)
CBE website: http://www.lboro.ac.uk/research/lcbe/
remedi website: www.remedigc.org
http://www.lboro.ac.uk/departments/cg/research/regen/dtc.html
Radio New Zealand Interview, June 2009 -
http://www.radionz.co.nz/national/programmes/ourchangingworld/20090528
TAP Podcast June 2009 -
http://www.automationpartnership.com/20years/podcast.htm

Contact for more information
Prof David Williams: D.J.Williams@lboro.ac.uk 01509 227668

growing SMEs (Loughborough University)

Aims

This SME facing research began following the mid term (two year) review of *remedi*. It has focussed on understanding how RM SMEs can be assisted to grow and deliver next generation products. It takes account of regulation and reimbursement, with a focus on business model related issues and manufacturing including characterisation. It is desk, interview and action research based, with industry case studies in the UK and the US (to establish differences and market conditions) and also uses the Loughborough GMP facility as an SME facing technology transfer demonstrator that will ultimately deliver manufacturing capacity for SMEs and others. The action research process combines real work, understanding, generalisation and influencing. This document is a key output of this work.

Achievements

Work has identified that the early stages of the New Product Introduction Process are particularly problematic because of uncertainties in the investment model, market and time to market, and the ultimate product value proposition. Industry investment readiness and industry emergence models have been created and grounded by a hearing therapy study. Work in characterisation has identified the likely requirements of future products and perhaps more significantly that there must be negotiation between the regulated and the regulator on these requirements. Business planning, with the construction and implementation of the Loughborough GMP facility and procurement of a novel 'GMP ready' automated production system (Cellbase) from TAP, has emphasised both the uncertainty and non-therapy specific requirements for characterisation when manufacturing an RM therapy. In addition to those mentioned in other work areas direct case studies of significance have been carried out with Bioceramic Therapeutics, Critical Pharmaceuticals, Keranetics, Orthomimetics and Regentec. Following a number of conference presentations, publications are in progress that capture early stage issues, US reimbursement approaches and the issues of characterisation. In parallel, as a consequence of both *remedi* and *remedi* stakeholder influence, national agencies and mechanisms have emerged including OLS, BIA-RIG, RGM/1 of BSI, TSB and the MHRA Topics Group. A key role of *remedi* has been to represent the perspective of SMEs in these bodies and seek to influence either their direction or resource allocation.

Future directions

remedi has continuing involvement in, and initiation of, regional and national initiatives. When seeking to influence, emphasis focuses on the need to reach both European and US markets, the opportunities and issues associated with the NHS as a market, on capacity for negotiation between the regulator and the regulated, the requirement to focus on manufacturing and cost of goods as well as first in man, and the financial fragility of the sector. This perspective is taken forward into taught programmes at undergraduate and post graduate levels.

Impact

This work has demonstrated measurable impact on SME partners, UK and international upstream science, national and international standards and the network. It is having a direct impact on its SME partners by assisting their regenerative medicine and automation product development activity via this work package and within other work areas. It is assisting the growth of an industry by actively influencing from a strong evidence base the position of regenerative medicine SMEs in many fora.

A significant capability has been built in the automated processing of human cells within the CBE at Loughborough; this, combined with regional funding for an automated GMP manufacturing facility at the University, give Loughborough the opportunity in the near future to offer GMP therapeutic cell culture services to SMEs and others.

Additional benefits and outcomes

Relevant career development for the SME facing researchers, regulatory and GMP compliance training of three Loughborough Research Associates. One of the graduating PhDs working in this area has secured employment with one of the leading international stem cell media companies.

Contact for more information

Prof David Williams: D.J.Williams@lboro.ac.uk 01509 227668

injectable scaffolds (Universities of Liverpool, Nottingham and Ulster)

Aims

Current materials used for repairing bone defects generally do not satisfy the necessary clinical requirements. This work area aims to explore the hypothesis that, through surface modification to Regentec's novel injectable scaffold, its propensity to induce the expression of osteogenic phenotypes in mesenchymal stem cells cultured within the scaffold may be greatly enhanced.

Achievements

From a number of different chemical modifications, two in particular have been shown to significantly increase the expression of osteogenic genes and the secretion of proteins important in bone formation, in the absence of any adverse effects on injectable scaffold function.

Future directions

The results of the current study will be used as the basis for research to investigate further enhancements to the osteogenic profile of injectable scaffolds for acellular *in situ* regenerative medicine applications.

Impact

The exploitation of scaffolds that are inherently significantly osteogenic without having to release biological molecules and without the need for the implantation of cells would be a significant advance in terms of cost and efficacy, and could be swiftly exploited in many clinical applications that require the rapid repair of bone defects. It is anticipated that the chemical technology may be appropriate for licensing which could result in widespread adoption. Furthermore, it is anticipated that the technology will be adapted for other tissue types in the future.

Additional benefits and outcomes

Increased osteogenic expression of mesenchymal stem cells cultured on the scaffolds in this study will point to strategies available for other researchers to pursue for improving the expression of phenotypes of other cell lineages.

Contact for more information

Nick Rhodes: npr@liverpool.ac.uk 0151 706 4211
Prof John Hunt: huntja@liverpool.ac.uk 0151 706 5264
Prof Brian Meenan: bj.meenan@ulster.ac.uk 02890 368939
Prof Kevin Shakesheff: kevin.shakesheff@nottingham.ac.uk 0115 951 5104

electrophysiological cell characterisation (Loughborough University)

Aims

The determination of the feasibility of a cell friendly electrophysiological characterisation system that will enable the integrated monitoring of electrical and optical parameters associated with cell development. The final system is to be supported by a suite of configuration software tools to enable the end user to customise the solution (e.g. electrode layout, signal pre-processing and analysis) and scale (i.e. readily increase the number of *(parallel)* recording wells) depending on the requirements of cell development.

Achievements

- Formal modelling of detailed end user experimental process and analysis techniques
- Automatic extraction of features relevant to cardiac and neuronal cell development
- Design, implementation and test of novel component-based electrode array hardware and software architecture
- Embedding of cardiac and neuronal processing functionality within target cell monitoring component-based hardware

Future directions

The results of the current feasibility study will be used to develop the next generation of component-based electrophysiological monitoring systems for large-scale cell characterisation studies. The embedding of end user best practices, experiential knowledge and analysis capability within the components will support rapid, high quality, low cost industrial exploitation.

Impact

Significant reductions in the time and cost of undertaking electrophysiological analysis is envisaged with the current system. Quality of cell cultures will be increased by ensuring that all of the analysis is undertaken within the incubator eliminating unwanted external disturbances. Embedded end user knowledge is expected to enable rapid, large scale academic and industrial adoption and expansion of system capability.

Contact for more information

Andrew West: A.A.West@lboro.ac.uk 01509 227550

Regenerative medicine is widely seen as the next major innovation in healthcare. The ability to repair and replace damaged cells and tissue has great potential, for society and business and as an industry. The science behind regenerative medicine is rapidly becoming established, but the industry required to underpin the clinical realisation of regenerative medicine is lagging behind. This book describes the findings of a major five-year research programme – *remedi* – that brought together university teams and stakeholders in the regenerative medicine business. It explores the practices that will enable the UK and, in particular, its SMEs to build a viable new industry that can exploit new science against a backdrop of financial, regulatory, technological and market uncertainties.

EPSRC
Engineering and Physical Sciences Research Council

remedi is one of the four Grand Challenge projects awarded by EPSRC in 2003 from their Innovative Manufacturing and the Life Sciences Interface Programmes. Grand Challenges are intended to address major research challenges with the potential for significant impact on national manufacturing priorities, and ambitions far greater than might be achieved by a single research team or in the span of a traditional research grant. The £8M *remedi* Grand Challenge portfolio sought to demonstrate how established bio-science could be transformed into profitable commercial practice and generate affordable therapies while developing the science of manufacture.

remedi is a collaboration of:

Loughborough University
University of Birmingham
University of Cambridge
University of Liverpool
The University of Nottingham
University of Ulster

together with industry and agency partners.

remedi

ISBN 978-1-907382-18-5