EP/C534247/1: REGENERATIVE MEDICINE – A NEW INDUSTRY, *remedi*, Narrative Final Report

September 2005 – February 2010

Professor David J Williams, Loughborough University (PI/Director), Richard Archer, Two BC (Chairman) and Dr Paul Hourd (Project Manager).

Executive Summary

remedi was one of the four Innovative Manufacturing Grand Challenge projects awarded by EPSRC. The *remedi* academic partners were Loughborough University and the Universities of Birmingham, Cambridge, Liverpool, Nottingham and Ulster.

Its vision was to demonstrate how established bio-science could be transformed into profitable commercial practice and generate affordable regenerative medicine (RM) therapies, while developing the science of manufacture – and in consequence an industry. The challenge focussed on understanding where such products give value and how the barriers to realising this value could be addressed. It aimed to demonstrate reproducible and cost-effective processes for the production of RM products taking advantage of emerging sensing and control techniques. It also aimed to create a community holding a shared vision for the industry, its products and future.

The Grand Challenge was a large - and rigorously planned and managed - project. It kept pace with the fast moving biological sciences – exemplified by its rapid, market and science-led, decisions to move into stem cells and then embryonic stem cells.

In terms of outcomes the *remedi* Grand Challenge has:

- Created and communicated a new multi-perspective understanding of the trajectory of the RM industry and its stakeholders, particularly for the UK.
- Driven development of the infrastructure of the industry including standards, advice to Government and regulators, and via the creation of a trade association.
- Delivered world firsts in manufacturing science of the processing and instrumentation of human stem cells and 3D tissue engineered structures.
- Determined generic issues faced by RM businesses and developed tools to assist them in new product introduction and GMP manufacturing.
- Worked with more than 15 businesses, primarily “high tech” SMEs, to progress therapeutics and create enabling technologies to reach global markets.
- Secured significant follow-up funding for translational research, innovative manufacturing research, GMP manufacturing and research training.
- Realised a cadre of people with commercial and regulatory awareness able to work on the translation of RM products from science to patient.
- Established a new way of working with multiple stakeholders, levels and disciplines with impact on both research focus and business transformation.

Introduction and background

Regenerative medicine (RM) 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 report describes the findings of a major research programme – *remedi* – that brought together multiple site, multidisciplinary university teams and stakeholders in the regenerative medicine business.

remedi was one of the four Grand Challenge projects awarded by EPSRC in 2003 from their Innovative Manufacturing and Life Sciences Interface Programmes. Grand Challenges were 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 *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 academic partners were Loughborough University and the Universities of Birmingham, Cambridge, Liverpool, Nottingham and Ulster.

remedi was organised as five work packages. Work package 1 with two components was focussed on understanding the market, the first component addressed market structure and barriers within the market and the second health economic issues, in particular pricing. Work package 2 focussed on the policy environment, particularly from a European regulatory perspective and from a UK level industry growth perspective. Work package 3 focussed on product processing with demonstrators/sub work packages in scaffold (3.1), cell (3.2) and tissue (3.3) processing. Work package 4 addressed characterisation and control particularly from a process perspective both acting as a "service" work package to work package 3 and addressing more novel work. Work package 5 encapsulated project management (5a) and subsequent work triggered by the mid-term review focussing on the growth of individual SME's and GMP and characterisation (5b) and with more speculative content in injectable scaffolds and in electrophysiology tools (5c).

remedi was structured as a combination of the EPSRC Grand Challenge award with financial support to the challenge from the Loughborough IMCRC. The EPSRC support ran from September 2005 to February 2010 including a six month extension, IMCRC support ran in parallel but extends to September 2010. The successor to *remedi*, the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine will begin on 1st September 2010.

Aims, Vision and Outcomes

The original vision of *remedi* was captured by its high level objectives that were to:

- Demonstrate how established bio-science can be transformed into profitable commercial practice and generate affordable therapies, while developing the science of manufacture.
- Determine the value of tissue engineered products to users in healthcare, define the market place and show how the development of regulation and industrial policy can maximise the benefit to the UK and patients.
- Create and demonstrate reproducible and cost-effective processes for the production of cells, scaffolds and tissue products that satisfy the regulator and take advantage of emerging process, sensing and control techniques.
- Construct a community that holds a shared vision for the industry and its products, and explores those visions practically.

In terms of outcomes the *remedi* Grand Challenge has:

- Created and communicated a new multi-perspective understanding of the trajectory of the RM industry and its stakeholders, particularly for the UK.
- Influenced and driven development of the infrastructure of the new industry including a new trade body (the RegenMed Industry Group (RIG) of the BioIndustry Association), advice to MHRA and the establishment of a BSi Standards Committee RGM1. Through RIG, *remedi* had fed key policy recommendations into The Office of Life Sciences at BIS, as reflected in Government policy papers for life science published in 2009/10.
- Delivered world firsts in manufacturing science of the processing and instrumentation of human stem cells and 3D tissue engineered structures, embracing new biology as it has emerged from the laboratory.
- Determined generic issues faced by RM businesses and developed tools to assist them to navigate and exploit differences in global regulation and create cost effective design of GMP manufacturing systems.
- Worked with more than 15 businesses, mostly “high tech” SMEs, to progress therapeutics and create enabling technologies to reach global markets.
- Secured significant follow-up funding for translational research, innovative manufacturing research, GMP manufacturing and research training from national and international sources.
- Realised a cadre of people with a commercial orientation capable of bridging from the science of the product and its application to the engineering of its manufacturing and realisation in the context of regulation and reimbursement. These “polymaths” potentially constitute the most critical output from the project.
- Established a new way of working with multiple stakeholders, levels and disciplines with significant impact on both research focus and business transformation.

remedi has proved transformational at an institutional level for Loughborough University, creating a multi-disciplinary team engaging the University in translational research at the leading edge of the interface of biology with engineering and with

significant impact on healthcare. It has also strongly influenced the development and implementation of a framework and policy for biological safety within the University. It has influenced the development of the other academic players including contributing to the triggering of EPSRC funded work in emerging industries at Cambridge.

remedi has also indirectly influenced regional, national and EU policy via parallel research activities, with input into programmes such as the Ministerial Medical Technology Strategy Group's SME Competiveness Study, The Dyson Ingenious Britain Report, the East Midlands Economic Strategy (2007-2012), the HaCIRIC Disruptive Innovation team and the EU Strategic Support Action Leadership as part of Manufuture, the key input to the design of manufacturing research in the FP7 NMP programme.

Industrial Collaboration

The key start-up industrial partners to *remedi* were RegenTec and Critical Pharmaceuticals (the key collaborators for work package 3.1) and The Automation Partnership (the key collaborators for work package 3.2). We were very unlucky to lose Smith & Nephew just before the original proposal submission (they were targeted as the key 3.3 collaborators). Initial network partners included ABHI, Medilink East Midlands, NHS Innovations East Midlands, emda, and NHS Futures, giving access to and representation of a wide group of industry, agencies and healthcare organisations.

As *remedi* gained momentum, key new collaborators joined the consortium. The UK National Stem Cell Bank (NIBSC) became a collaborator (particularly for work package 3.2) as it became clear that stem cell standardisation and supply were very important. Intercytex became the collaborator with a particular interest in tissue processing (work package 3.3). The National Physical Laboratory (NPL/LGC) became the key collaborator for the Characterisation and Control work package (work package 4) subsequently funding a Fellowship in the area. Other collaborators in this work package were Almac Diagnostics, Avalon Instruments (now Perkin Elmer) and J Y Horiba (now HORIBA Scientific).

The *remedi* collaboration governance was constructed so that much of the generic work was in the public domain and such that key collaborators acted as gatekeepers for broader dissemination and collaboration in more sensitive areas. All collaborators had the opportunity to influence all work packages. Our industrial collaborators were thought leaders and the academics learned much from them. Key advice on the approach to NHS ethics was given by the regional NHS hub, NHS Innovations East Midlands.

remedi worked via case examples with further SMEs and up stream academic scientists. For work package 3.2 this was to identify, understand and resolve generic process problems for cell supply for cell therapies through collaborations with Oreffo of the University of Southampton (mesenchymal cell therapies), ReNeuron (allogeneic stem cell therapies), Cook Myosite (autologous cell therapies), Andrews and Moore of the University of Sheffield (embryonic cancer cell lines), NIBSC and Denning and Young of the University of Nottingham (embryonic stem cell lines). For work package 5b this focused on more commercial and business growth issues for

both UK and US based businesses and included significant interactions with the additional SMEs, Bioceramic Therapeutics, Future Health Technologies, Orthomimetics and Keranetics. Keranetics is a spin out from one of the major US centres for RM, Wake Forest University. *remedi* has worked with both UK and US SMEs, the intent of this approach was to understand whether the major issues facing these businesses were the same and to encourage inward investments. Informal collaborations with the McGowan Institute and one of its associated businesses, Pepper Hamilton, have significantly improved our understanding of reimbursement in the US. Of greatest significance was the emergence of Pfizer as a major entrant into RM, the first major pharmaceutical company to visibly make that strategy change. Based in the UK, Pfizer RM collaborated informally on a number of aspects of *remedi* and will be a major player going forward into the new EPSRC Centre.

remedi also worked with other key agencies, including TSB and BIS, to support dissemination and influencing. Two key activities were formulated, promoted and significantly influenced by the Challenge, the BioIndustry Association RegenMed Industry Group, and the BSI-RGM1 Regenerative Medicines Standards Committee. These in turn have actively influenced the landscape and used *remedi* as a touchstone.

remedi has also driven or been involved in a number of national and international industrial and academic workshops, the most significant of which have been: the 2007 Australian Academy of Technical Sciences (ATSE) stem cell workshop; the exploitation focussed discussion panel at Termis Europe 2007; the Stem Cells for Safer Medicines (SC4SM) call road mapping process in 2008; the MHRA Topics Selection Panel ATMP workshop 2008; the Economic & Social Research (ESRC) stem cell initiative workshop 2008; and the Tissue & Cell Engineering Society (TCES) pre-symposium workshop on manufacturing in 2009.

A summary table showing the most significant industrial collaborations within *remedi* is attached as Appendix 1.

Management

The Grand Challenge was clearly not an Innovative Manufacturing Research Centre, it was essentially a large - and rigorously planned and managed - project with a mid term review. The project kept to its vision and aggressively kept up to date with the emerging biological sciences – exemplified by its rapid, market and science-led, decision to move into stem cells and then embryonic stem cells. This has been vindicated by the quality of publications and level of international recognition.

remedi was chaired by an industrialist, Richard Archer, and included a healthcare industry experienced project manager, Paul Hourd. It was project managed in professional style by a quarterly, minuted board meeting, working from board reports prepared by work package and reporting progress to agreed deliverables. The board was chaired by Richard Archer and attended by work package managers or their representative. This was highly structured by academic standards, but light touch in comparison to an “industrial strength” board meeting.

It became apparent early in *remedi* that there would be significant biological consumables costs that were not anticipated in the proposal, this required transfer across budget headings. The learning from this has been included in the costing of the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine.

remedi infrastructure also required management and quality systems development, especially at Loughborough as facilities grew from a small laboratory to the construction of the Centre for Biological Engineering, which includes a GMP specification suite. This multidisciplinary Research Centre, bridging the fields of engineering and biology and integrating the research work of three departments: the Department of Chemical Engineering, the Wolfson School of Mechanical and Manufacturing Engineering and the Department of Electronic and Electrical Engineering, was opened by Lord Robert Winston on 1st October 2009.

Many RAs and PhD students have been associated with *remedi*. One of the major outputs of *remedi* is a community of young researchers who are comfortable working at disciplinary boundaries and with others from other backgrounds from biological and clinical to engineering and commercial. Informal networking and results reporting was encouraged and enabled by researcher led "Research Associate (RA) days" held twice a year. These were preceded by a dinner attended by the Chairman and PI, allowing informal interaction and, by after dinner speeches, the reinforcement of key messages.

Strong leadership from the chairman, who acted as the chair of an SME would, and his access to an international business network was very important to ensuring the relevance and timeliness of *remedi* output.

Future Development and Funding

Future funding has been secured by many of the *remedi* academic partners. The most notable funding includes the securing of an EPSRC Doctoral Training Centre in Regenerative Medicine between Loughborough, Nottingham and Keele (£6.1m) and subsequently the EPSRC Centre for Innovative Manufacturing (£6.3m FEC) by the same partners, announced by the Prime Minister in January 2010. These allow for a complementary research training activity and reinvention of the research pipeline. Further research support has been forthcoming for academic partners from EPSRC, TSB, BBSRC, BRIC, MRC and internationally from DARPA. Significant regional support has been secured by Ulster (with Galway), Loughborough (including an automated GMP facility) and Nottingham. Discussions have taken place on the funding of a regional downstream translational regenerative medicine institute in the East Midlands, these are now stalled following the change of government. Individual universities have made considerable infrastructural investments.

The EPSRC DTC and new Centre for Innovative Manufacturing together provide the core of the way forward. They will be driven to deliver international level science and wide impact across the UK and lead to sustainable long term capability in the UK.

Commentary on the individual work packages

This section captures the major outputs by work package. This summary complements the book prepared for the *remedi* closing conference (Williams, Archer and Dent 2010) and gives traceability of output by the selected key publications presented with each work package. Some publications are still in preparation or in the publication pipeline, in particular those publications associated with Work Package 5. Some brief *remedi* people stories are attached as Appendix 2. Impact cases by work package are also attached to this report as Appendix 3.

Work package 1: Understanding the market (Nottingham and Birmingham)

The intent of the work within work package 1 at Nottingham was to understand the market, market evolution and barriers to reaching the market. The understanding developed was captured in two significant public domain reports (1.1 and 1.2) available for web download. Learning in respect of barriers was also published in Plagnol et al (1.3). Major lessons arising from this were the rapid movement of the industry into stem cells, structural issues in the UK associated with adoption by the NHS and an increasing number of small company - large company relationships. This work was significantly geared by understanding generated from related work in stem cells and cord blood.

The intent of the work at Birmingham was to develop methods for entrepreneurs and investors in order to understand the scale of the market and clinical opportunity before beginning the development process. This led to the development of the headroom method for evaluating the value of an RM therapeutic against the incumbent essentially by reverse engineering the NICE reimbursement process. The method is described in Cosh et al (1.4) and its application shown in McAteer et al (1.5). Birmingham also delivered a number of deep case studies of the opportunities for RM products in key therapeutic areas, references (1.6-1.7). The preparation of these showed that deep clinical knowledge was required to understand and refine the niche for a putative product and that this also required considerable expert, brokered clinical discussion to secure some consensus of perspective. Again this work was highly geared by exposure of the researchers to the EU STEPs project and co-funding under MATCH. The reports from this work have considerable value and should be more broadly circulated as part of the current national work to establish NHS priorities for regenerative medicine. The work is now widely recognised in the health economics community and the researchers have since undertaken a number of consulting and advisory exercises for UK SMEs.

1.1 Martin, P., Hawskey, R. and Turner, A., 2009, The Commercial Development of Cell Therapy – Lessons for the Future? Survey of the Cell Therapy Industry and the Main Products in Use and Development Part 1: Summary of findings, Institute for Science and Society, University of Nottingham, www.nottingham.ac.uk/iss/regenmed

1.2 Rowley, E. and Martin, P., 2009, Barriers to the Commercialisation and Utilisation of Regenerative Medicine, Institute for Science and Society, University of Nottingham, www.nottingham.ac.uk/iss/regenmed

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

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

1.5 McAteer, H.L., Cosh, E., Freeman, G., Pandit, A., Wood, P. & Lilford, R., 2007, 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, 343-349.

1.6 McAteer, H. L., Griffin, D., Donnell, S., Scammell, B., Kon, E., Stirling, A., and Lilford, R., 2007, The Current Clinical Opportunities for Regenerative Medicine in Bone, www.haps.bham.ac.uk/publichealth/methodology/hes/

1.7 Chilton, P., McAteer, H. L., and Lilford, R., 2010, The current application of cell therapy in neurodegenerative disorders, www.haps.bham.ac.uk/publichealth/methodology/hes/

Work package 2: Policy environment (Cambridge)

The intent of work package 2 was to understand the requirements at a policy level in order to influence industry growth and was completed in the first two years of the challenge. This had a focus on understanding and communicating the international regulatory landscape, see for example references 2.1-2.3, 2.5 and on national policy for industry growth. This led to a *remedi* policy report (2.4) that much influenced the BIGT Refresh, OLS papers and TSB plans in grant funding for regenerative medicine. Outputs also figure in UKTI international marketing material for UK technology expertise. Influencing was assisted by brokering with key individuals. The outputs of this work package were integrated with those of work package 1 at Nottingham to produce Plagnol et al (1.3).

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

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

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

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

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

Work package 3: Processing for product (Nottingham)

Work package 3 concentrated on processing issues with demonstrator projects in scaffolds, cells and tissues as below.

3.1 Scaffolds (Nottingham and Loughborough)

The aim of this work package was to take a novel patented process for the manufacture of scaffolds (porous matrices), translate it towards clinical application (3.1.4) and optimise both the materials used (3.1.1, 3.1.7) and the process conditions (see work package 4). This required the construction of a novel instrumented reactor and studies of scaffold formation with time. Statistical approaches were used to measure process capability for this (3.1.2) and other scaffold types (3.1.3). Subsequently scaffolds have been applied with some success both with (3.1.5, 3.1.8) and without biomaterial additions (3.1.6.). The analysis of process capability indices helped the RegenTec Group identify critical areas for process improvement and control and is to be used to support their 510k US regulatory approval submission. The material arising is now in early clinical evaluation at the University of Southampton. The University of Nottingham and RegenTec received a Medical Futures Award in London 2008 that reflected *remedi*'s input as a key outcome from this work package.

3.1.1 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., 2007, Control of pore size and structure of tissue engineering scaffolds produced by supercritical fluid processing, European Cells and Materials, Vol. 14, pp 64-77.

3.1.2 Chandra, A., White, L.J., Hourd, P., Shakesheff, K., Liu (Chaozong), C. and Williams, D.J., 2007, "Establishing the process capability of a super critical fluid scaffold manufacturing process", Proceedings of Termis NA 2007, Termis NA 2007, Toronto, Canada, June.

3.1.3 Liu, C.Z., Han, Z.W., Hourd, P. and Czernuszka, J.T., 2008, "On the process capability of the solid free-form fabrication: a case study of scaffold moulds for tissue engineering", Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 222(3), 377-391.

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

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

3.1.6 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., 2008, 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.

3.1.7 C. Gualandi, L. J. White, L. Chen, R. A. Gross, K. M. Shakesheff, S. M. Howdle & M. Scandola, 2010, Scaffold for tissue engineering fabricated by non-isothermal supercritical carbon dioxide foaming of a highly crystalline polyester, Acta Biomaterialia, 6, 130-136, 2010.

3.1.8 Kanczler, J. M., Ginty, P. J., White, L. J., Clarke, N. M. P., Howdle, S. M., Shakesheff, K. M., & Oreffo, R. O. C., 2010, The effect of the delivery of vascular endothelial growth factor and bone morphogenetic protein-2 to osteoprogenitor cell populations on bone formation, Biomaterials, 31, 1242 – 1250.

3.2 Cells (Loughborough)

This was perhaps the most visible of the *remedi* work packages. Its original intent was twofold: i) to demonstrate that conventional manufacturing automation and quality approaches could be applied to cellular feed stocks for regenerative medicine and cellular therapeutics, and ii) to demonstrate that emerging and potentially challenging biology could be reduced to practice in an engineering setting. Its primary and gatekeeper collaborator was The Automation Partnership (TAP).

It has involved the co-development, evaluation and demonstration of an automated production system (a smaller version of a discovery based machine refocused on the production of therapeutics in smaller businesses), *remedi* being the recipient of the first and prototype machine. Some thirty of these £500k machines have now been sold by TAP, many to stem cell processing applications globally. This system ("CompacT SelecT") has now been used to demonstrate the measurement of process capability for cell culture (3.2.3), the use of designed experiments for cell culture process design (3.2.8) and the use of response surface methods for cell culture process design (3.2.9). This has also required significant measurement system analysis, see for example Liu et al (3.2.2) and focus on increasing machine reliability.

It has also been used for the automated culture of many regenerative medicine and related cell types. This has included, in the early part of *remedi*, murine embryonic stem cells (with Stem Cell Sciences), human osteoblastic cell lines, human embryonic cancer cell lines and fibroblast cell lines. With this track record established, work progressed to more important cell types, including human mesenchymal stem cells derived from bone marrow (3.2.1) and cord blood (3.2.5), progenitor cells (3.2.4, 3.2.7) and human embryonic stem cell lines (3.2.6). This later work was in collaboration with academic scientific partners Oreffo of Southampton, and Denning and Young of Nottingham, and the industrial collaborators ReNeuron (3.2.7 and the

press releases that followed its publication) and Cook Myosite (a US SME). ReNeuron were our allogeneic (stroke, foetal cortex derived neural progenitor) therapeutic case study partner and Cook Myosite our autologous, "batch of one", (bladder, smooth muscle cells) therapeutic partner. These collaborations were particularly significant as they established the critical to quality characteristics required for the cultured cells. ReNeuron will be initiating the first ever UK trial of a stem cell therapy later in 2010 – the process to produce cells for the therapy has been optimised by the Loughborough team.

The work has established landmark precedents in the automated and scalable production of cell stocks and products for RM. These include the market dominating mesenchymal and human embryonic 'platform' stem cell types, as well as proprietary smooth muscle progenitor and neural stem cells. The latter two processes were engineered to demanding manufacturing specifications set by industrial partners, including production volumes and gene and surface marker expression profiles. The automated system is programmable and therefore provides a platform to engineer regenerative medicine production processes toward higher quality and more economic outputs at an industrially relevant scale. Most notably, work in this area included the first definition of process capability (CpK) for an RM cell production process, and the first applications of statistically designed experiments in a systematic process improvement framework to characterise and control the manufacturing process. The understanding gained from these approaches will be critical to control regulatory and economic risk in highly complex cell based product manufacture. The impact of this work has been recognized through the award of the 2009 Institution of Chemical Engineers International Prize for Innovation and Excellence in Bioprocessing.

This work has required the development of a new laboratory infrastructure (twice!) as well as process transfer techniques and, as publications authorship shows, has required work by multi-disciplinary teams spanning from engineering to biology.

Work to address the research challenges inherent in a GMP version of the automated platform have been addressed in Work Package 5b.

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

3.2.2 Liu, Y., Hourd, P. and Williams, D.J., 2007, "Measurement System Capability: A Comparison of Manual and Automated Cell Counting Systems", Tissue Engineering (Abstract No 263), 13(7), 1722.

3.2.3 Thomas, R.J., Hourd, P. and Williams, D.J., 2008, 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, 148-155.

3.2.4 Liu, Y., Chandra, A. and Williams, D.J., 2008, "Automated culture of endothelial progenitors derived from mononuclear cells of human peripheral blood and bone marrow", Online Abstract Database for Termis NA 2008, 091, Termis NA 2008, San Diego, http://www.termis.org/na2008/abstract_search/091.pdf.
3.2.5 Singh, P., Thomas, R.J. and Williams, D.J., 2008, "(OP 21) Automated Culture of Umbilical Cord Blood Derived Progenitor Cells", Tissue Engineering: Part A, 14(5), 701.

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

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

3.2.8 Liu, Y., Hourd, P., Chandra, A. and Williams, D.J., 2010, Human cell culture process capability: a comparison of manual and automated production, J Tissue Eng Regen Med, 4, 2010, 45-54.

3.2.9 Ratcliffe, E., Rayment, E., Hourd, P., Williams, D. J., and Thomas, R. J., Application of a Response Surface Methodology to the scalable, automated expansion of human embryonic stem cells for prediction of a high cell quality, economic production strategy. In preparation.

3.3 Tissues (Loughborough)

This work package was more speculative than the other two in WP3 and targeted increasing our understanding of manufacturing of tissue engineered constructs containing both cells and matrix and included a significant modelling component. As *remedi* evolved, it began to have two components centred on understanding the growth of tissue products requiring the creation of Extra Cellular Matrix (ECM), one with confidential components in collaboration with Intercytex and the second non-confidential demonstrator focussing on intervertebral disc. A parallel mathematical modelling programme explored the growth of tissues and ECM components in culture.

One strand of the work, in collaboration with Intercytex, was aimed at improving the process to manufacture its ICX-SKN skin product, a human extracellular collagen matrix created by human fibroblasts. Key outputs for this work have been the thesis (3.3.5) describing the development of the microstructure of ICX SKN and methods of improving its mechanical properties using mechanical stimulation in collaboration with Nottingham, a patent application is in progress. Some of the non-confidential content of this work has been published (3.3.3). The balance will be published following clarification of the patent status.

A significant programme of work to mathematically model the growth of cartilage has been carried out in collaboration with Obradovic, Belgrade (formerly of MIT). This, captured in publication 3.3.6, has generated a validated systems biology model of the culture and growth of a tissue product allowing understanding of the mechanisms by which the key ECM components are generated and retained within the construct during culture and construct growth. This piece of most original work has created a model of tissue growth that can be used both predictively and to explore the effects of different growth models.

The final major component of this work package is an engineering demonstrator of physiologically informed tissue product culture aimed at the culture of intervertebral disc products. This required deep understanding of the influence of mechano-transduction in this particular structure (see for example 3.3.1, preliminary experiments in collaboration with Reilly, Sheffield (3.3.2)), and the co-development and procurement of a novel programmable triaxial stress bio-reactor system. Commissioning and proving this platform has proved very challenging but progress has been made with both engineering issues and with the product configuration such that results are emerging (3.3.8). This work will proceed after the challenge, the experimental platform being used by PhD students.

Parallel work on the automation of production of novel three dimensional constructs using the CompacT SelecT platform has also been carried out with some success. It has been used to automatically produce 3D angiogenesis tissue models that may be suitable as an alternative to animal models for cancer drug screening (3.3.4) and to develop scaffold structures that allow constructs to retain their geometry during the culture process even in the presence of cells driving contraction (3.3.7).

3.3.1 Sebastine, I.M. and Williams, D.J., 2006, "The Role of Mechanical Stimulation in Engineering of Extracellular Matrix (ECM)", Proceedings of the 28th IEEE EMBS Annual International Conference, New York City, USA, September, pp 3648-3651,

3.3.2 Sebastine, I.M., Sittichokechaiwut, A., Clarke, D.A., Williams, C., Reilly, G.C. and Williams, D.J., 2008, "(P 142) Effects of Frequency and Loading Duration on Mechanically Modulated Collagen Production by Osteoblasts in Bone Tissue Engineering", Tissue Engineering: Part A: 14(5), 844.

3.3.3 Kee, J., Johnson, P.A. and Williams, D.J., 2008, "Characterisation of ICX-SKN during Manufacturing for Process Optimisation and Product Improvement", Online Abstract Database for Termis NA 2008, 026, Termis NA 2008, San Diego, December.

3.3.4 Liu, Y., Chandra, A., and Williams, D. J., 2009, Endothelial Progenitor Expansion and 3D Angiogenesis Model Fabrication: An Automated Process Using the CompacT SelecT Platform, NC3R Conference, London, April.

3.3.5 Kee, J., 2009, Process Characterisation of a Manufactured Living Dermal Equivalent (ICX-SKN) and use of Ultrasound for Product Improvement, Confidential PhD Thesis, Loughborough University.

3.3.6 Nikolaev, N.I., Obradovic, B., Versteeg, H.K., Lemon, G. and Williams, D.J., 2010, A Validated Model of GAG Deposition, Cell Distribution, and Growth of Tissue Engineered Cartilage Cultured in a Rotating Bioreactor, Biotechnology and Bioengineering, 105, 842-853.

3.3.7 Liu, Y. and Williams, D. J., 2010, Incorporation of Hydroxyapatite Sol Into Collagen Gel to Regulate the Contraction Mediated by Human Bone Marrow-Derived Stromal Cells, IEEE Transactions on Nanobioscience, 9, 1-11.

3.3.8 Naing, M. W., Liu, L., Sebastine, I. M., Sidney, L., Morris, D. E., Mather, M. L., Dingmann, D., Williams, C., and Williams, D. J., Physiologically informed mechanical stimulation: challenges and early results on commercial scaffolds for nucleus pulposus tissue engineering, in preparation.

Work Package 4: Characterisation and Control (Nottingham and Ulster)

Work package 4 included a number of styles of working, the preparation of reviews (4.1), service oriented work packages supplying instrumentation techniques to the three process demonstrators and more novel work investigating the application of ultrasound, Raman, and gene chip techniques. Work on scaffolds included the application of ultrasound monitoring (4.2), image based characterisation of porous scaffolds as they formed (4.3, 4.4), the use of micro CT and particularly the understanding of thresholding (4.6). Work on cell culture created a smart flask to allow instrumentation and in-process observation of the automated cell culture process (4.9) and work on tissue culture created unique instrumentation for the triaxial stress bioreactor system (3.3.8) and explored the use of polarised imaging to view collagen (4.5). Work on Raman spectroscopy included its application to cell (4.10) and tissue characterisation (4.5), this proved extremely challenging. The work package progressively engaged more deeply with NPL who ultimately supported a research fellowship at Nottingham with a particular focus on the characterisation of gels (4.8). Collaboration with NPL also assisted interactions with international standards forming bodies including NIST and ASTM. Work at Ulster was carried out in collaboration with Almac Diagnostics, Perkin Elmer and J Y Horiba. Promising work in the application of gene chips (4.7) continues.

4.1 Mather, M.L., Morgan, S.P. and Crowe, J.A., 2007, Meeting the needs of monitoring in tissue engineering, Regenerative Medicine, 2 (2), 145-160.

4.2 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., 2008, Ultrasonic monitoring of foamed polymeric tissue scaffold fabrication, Journal of Materials Science-Materials In Medicine, 19 (9):3071-3080.

4.3 Mather, M.L., Morgan, S.P., White, L.J., Tai, H., Kockenberger, W., Howdle, S.M., Shakesheff, K.M. and Crowe, J.A., 2008, Image-based characterization of foamed polymeric tissue scaffolds, Biomedical Materials, 3 (1): Art No. 015011.

4.4 Mather, M.L., Brion, M., White, L.J., Shakesheff, K.M., Howdle, S.M., Morgan, S.P. and Crowe, J.A., 2009, Time-Lapsed Imaging for In-Process Evaluation of Supercritical Fluid Processing of Tissue Engineering Scaffolds, Biotechnology Progress, 25 (4):1176-1183.

4.5 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., 2009, 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.

4.6 Morris, D.E., Mather, M.L. and Crowe, J.A., 2009, Generation and simulated imaging of pseudo-scaffolds to aid characterisation by X-ray micro CT, Biomaterials, Volume 30, Issue 25, 4233-4246, September.

4.7 G.A. Burke, M.M. McCafferty and B.J. Meenan, 2009, Requirements for Microarray Based Gene Expression Analysis of Human Mesenchymal Stem Cells in Tissue Engineering and Regenerative Medicine, Proceedings of the 22nd European Conference on Biomaterials, Lausanne.

4.8 M Farrugia, Mather M, Crowe J, Morgan S, Alexander C, 2010, Ultrasound monitoring of sol-gel transitions in Pluronic F127 hydrogels, Termis, Galway, Ireland, 13-17 June.

4.9 A Rabi, JA Crowe, ML Mather, DE Morris, A Chandra, 2010, Wireless Monitoring System For Cell Culture Processes, TERMIS, Galway, Ireland, 13-17 June.

4.10 A.R. Boyd, G.A. Burke and B.J. Meenan, Monitoring Cellular Behaviour using Raman Spectroscopy for Tissue Engineering and Regenerative Medicine Applications, Journal of Materials Science: Materials in Medicine DOI 10.1007/s10856-009-3965-00.

Work Package 5: Facilitating the growth of the industry

5a Project Management

As discussed above, work package 5 contained the project management and networking aspects and formed the mechanism to progress work following the mid-term/two year review. Following the mid-term review, two work packages were designed each with two components, 5.2 focussed on SME requirements and 5.3 on more speculative product led research.

5b SME and Industry Growth

Following the mid term review work package 5b continued much of the industry and SME facing work including contributing to the GMP manufacturing solution, a GMP version of the automated platform used in work package 3.2 within a GMP specification facility.

Work was carried out at an overall industry helicopter level including: the construction of models for industry emergence and growth (5b.3) within a strong clinical context (5b.1); contributions to the debates on characterisation (5b.6) and standardisation, via the RGM1 committee, essential in such a young industry; and on reimbursement in the US market (5b.7), the largest and most significant target market for UK business start ups in the area. This work stream significantly influenced the recent TSB regenerative medicine value systems call via its generation of the “parallel uncertainties” model.

Work also proceeded at a more pragmatic company level (5b.2) to understand the issues faced by small RM product companies at start up via case studies with Bioceramic Therapeutics, Future Health Technologies, Intercytex, Keranetics (US SME) and Orthomimetics. The generic learning from these case studies has been captured in two ways for communication to small businesses, in the *remedi* stakeholder handbook (5b.5) and in papers (5b.8, 5b.9) giving an overview of the issues and addressing an industrial and SME audience, as well as other supporting material in preparation for publication.

The GMP manufacturing solution has required the specification and procurement of a second generation TAP CompacT SelecT machine and construction of a further laboratory facility, the capital cost of which has been borne by Loughborough University and its RDA, emda. It is important to recognise that the validation of this machine system has raised important scientific and engineering challenges, particularly the extreme level of process reliability required for GMP and management of potential contamination and cross contamination from living materials at the scale of human cells. It should be noted that this work has been carried out within an environment of considerable regulatory uncertainty and has required frequent interaction with the UK regulator. This has required experimentation on both the first and second systems and the development of novel methods of measuring contamination that emulate the behaviour of living materials (5b.4). TAP confirm that they have, as a consequence, significantly increased their knowledge of good manufacturing practice (GMP) issues surrounding stem cell based therapies. As a direct result of this, TAP has developed the world's first high throughput autologous cell therapy production platform. They confirm that this would not have been possible without Loughborough's input to the creation of the supporting data for the associated validation package. This is a new market for TAP and two of these platforms have been sold to date.

Key further elements of this work are now progressing via two industry collaborative TSB projects focussed on GMP manufacture of cell therapies and on regenerative medicine value systems. The balance, funded by the IMCRC contribution to *remedi*, closes in September 2010.

The GMP specification automated cell culture facility that will result from the combination of the EPSRC, University, TSB and emda funding forms a unique national asset. The exploitation mechanism for this asset remains under continuous review, the next steps being contingent on market readiness.

5b.1 Singh, P. and Williams, D.J., "Cell therapies: realising the potential of this new dimension to medical therapeutics", Journal of Tissue Engineering & Regenerative Medicine, Vol 2, 2008, 307-319.

5b.2 Williams, D.J., "Commercialisation of Regenerative Medicine Therapies: What else needs to be done when the science looks promising?", UKNSCN Second Annual Scientific Conference Abstracts, UK National Stem Cell Network Second Annual Scientific Conference 6-8th April 2009, University of Oxford Examination Schools, 6th April 2009, 13.

5b.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.

5b.4 Thomas, D., Dayala, H., Stacey, A., Rayment, E., Ratcliffe, E., and Chandra, A. 2009 GMP CompacT CellBase System Testing Biological Experimental Programme, TAP-8075-30-011 Issue 2.00, December.

5b.5 Williams D. J., Archer, R. and Dent, A., Building A Viable Regenerative Medicine Industry, A Guide for Stakeholders, Loughborough University, 2010, pp 95, ISBN 978-1-907383-18-15.

5b.6 *Spotlight Paper:* Rayment, E. A., and Williams, D. J., 2010, Mind the Gap: Challenges in Characterising and Quantifying Cell- and Tissue-Based Therapies for Clinical Translation, Stem Cells, 28, 996-1004.

5b.7 Ginty P. J., Singh P. B., Smith D., Hourd P. and Williams D. J., 2010, Achieving Reimbursement for Regenerative Medicine Products in the USA, Regenerative Medicine, 5, 463-469.

5b.8. Rayment, E. A., Ginty P. J., and Williams, D. J., When the science isn't enough: issues surrounding the realisation of cell- and tissue- based therapies, at review for Nature Biotechnology.

5b.9. Ginty, P. J., Hourd, P. and Williams, D. J., 2010, Minimizing Risk When Taking Regenerative Medicine Products to Market: Lessons Learned from the *remedi* Project, in Preparation for Regenerative Medicine.

5c.i Speculative product led research: Injectable Scaffolds that Control Mesenchymal Stem Cell Differentiation (Liverpool, Nottingham, Ulster).

This work package has successfully developed strategies and methods for the bio-functionalisation of injectable scaffolds to promote bone regeneration and repair for applications in orthopaedic medicine. The collaboration has surface engineered RegenTec's novel injectable scaffold through inclusion of chemical amine components in the scaffold chemistry. This significantly enhances the propensity of the scaffold to induce osteogenic cell phenotypic expression on mesenchymal stem cells in the form of increased expression of osteogenic genes and secretion of proteins that direct bone formation. Work has determined that the amine plasma modified particulates that form the scaffold significantly upregulated osteogenic markers at the MRNA level throughout the 28 days experiment and culminated in positive Von Kosa staining for calcified extracellular matrix deposits. Cell adhesion and spreading were also enhanced by the specific amine surface treatment. This work will be showcased as a podium presentation at the July UK Society for Biomaterials meeting with posters at TCES in Manchester in July and at the European Society for Biomaterials in Tampere in September 2010. A manuscript is in preparation. This work has succeeded in stimulating the coordinated and sustained differentiation of mesenchymal stem cells in a 3D environment without the use of diffusible growth factors that can support ectopic bone formation. This development may have considerable relevance and significant impact on the potential for clinical application of an injectable osteoinductive scaffold.

5c.ii Speculative product led research: Cell Friendly Electrophysiological Characterisation of Cells and Cell Therapies using Novel Modular Multi Electrode Array Systems (Loughborough).

Work in collaboration with Denning, Nottingham, and Grant, Genes to Cognition Group, Sanger Institute, funded by the IMCRC contribution to *remedi* is realising a scaleable, 'cell friendly' modular multi electrode array system (MEA) for the rapid measurement of electrophysiological function of cells in vitro applied as an enabling technology for use in cell therapeutic characterisation manufacturing process development and control. Feasibility of the system is being tested by application to the real-time evaluation of the electrical properties of human neuronal and cardiomyocyte cells and their electrical response to various input stimuli in vitro (5c.2.ii.1 and 5c.2.ii.2).

5c.2.ii.1 Segura Velandia, D. M., Flaherty, O. M., Conway, P. P., Hutt, D. A., Cui, X., West, A. A., 2010, Real-Time Signal Processing For Microelectrode Arrays for Cardiomyocytes, Paper to be presented at IEEE Engineering in Medicine and Biology, August 31 - September 4, 2010, Buenos Aires, Argentina.

5c.2.ii.2 Flaherty, O. M., Segura Velandia, D. M., Cui, X., Hutt, D. A., Conway, P. P., West, A. A., 2010, Enterprise modelling applied to protocols employed in the acquisition and analysis of electrophysiological cardiomyocyte data using in vitro multielectrode arrays, Paper to be presented at IEEE Engineering in Medicine and Biology, August 31 - September 4, 2010, Buenos Aires, Argentina.

DTA Allocation

The DTA contribution associated with *remedi* has been used to gear activities at all collaborating universities. The allocation was distributed competitively (but equitably) via proposals to the *remedi* board. Unfortunately Ulster was not eligible for funding via this route. It is important to recognise that PhD students made many important and distinctive contributions. PhD students were included in the "RA Days" and had their own distinctive events, including on thesis writing for translational research. PhD students and their topics are as below. Destinations of graduated students include the regenerative medicine industry (Kee, Organogenesis and Singh, Stem Cell Technologies) and translational research in a hospital environment (McAteer, Birmingham CLAHRC).

Name	Institution	PhD Thesis Title	Work package link
Olivia Flaherty	Loughborough University	An examination of biological laboratory protocols identifying and addressing end user requirements	5c
Jasmin Kee	Loughborough University	Process Characterisation of a Manufactured Living Dermal Equivalent (ICX-SKN) and use of Ultrasound for Product Improvement	3.3
Pawan Bir Singh	Loughborough University	Enabling Late-Stage Translation of Regenerative Medicine based Products	3.2/5b
Helen McAteer	University of Birmingham	The use of health economics in the early evaluation of regenerative medicine therapies	1.2
Richard Elliott	University of Nottingham	The Cultural Framing and Public Perception of Regenerative Medicine Products	1.1
Abdel Rabi	University of Nottingham	Online monitoring for the optimization of cells culture	4
Mario Farrugia	University of Nottingham	Ultrasonic Gelation of Injectable Scaffolds for Regenerative Medicine	4
Qun Zhu	University of Nottingham	Rotating Orthogonal Polarization Imaging	4
Fiona Lewis	University of Liverpool	In vitro models to assess the potential of chemically modified polymer substrates at the nano scale	5c
Sandra Fawcett	University of Liverpool	Novel chemical modification systems to provide enhanced cell recruitment, proliferation and differentiation for applications in Regenerative Medicine	5c

Table: PhD topics of *remedi* associated students

Conclusion – Benchmarking *remedi*

By July 2007 *remedi* was already internationally competitive and on trajectory to be world leading (IMCRC International Review, July 07).

Since then *remedi* has been recognised both nationally and internationally for its novel perspective in RM, its leadership in manufacturing science and the impact on SMEs. It has influenced policy and new initiatives; in industry and science funding with EPSRC, BIS, the Office of Life Sciences and TSB, in regulation with MHRA and standards with BSi. It has assisted in the creation of a new industry association RIG, the RegenMed Industry Group, of BIA, and has supported its chair.

The vision of *remedi* has been recognised by a Nature Biotechnology Paper (C.1) and keynote invitations to a number of conferences including the CIRP General Assembly, Kobe, 2006 (C.2); Euspen, Bremen, 2007 (C.3); and Intelligent Production

Systems of the Future, Stuttgart, 2010 (C.4). The winning of the Medical Futures Award in London 2008 and the Institution of Chemical Engineers Bioprocessing Award in 2009; invitations to present at the UK Focus for Biomedical Engineering Briefing Seminar in Regenerative Medicine, 2009, and the Royal Society Ultra-Precision Engineering Discussion Meeting, 2011; and the impact of the *remedi* dissemination conference held jointly with the BIA in February of 2010 confirm the national leadership position of *remedi*.

Feedback from industry and the engagement of industry in the successor proposal to *remedi* have demonstrated the value and impact of *remedi* to industry and the wider community – the proposal includes 35 letters of support. Referees comments on the Centre proposal reflected wide awareness of the *remedi* activity and universal acknowledgement of the brand and its research importance.

The destination of *remedi* researchers to academic lectureship and fellowship positions and positions in relevant science based businesses further confirms impact.

An invitation to serve on the Johnson and Johnson Scientific Council for Regenerative Medicine in April 2010, the visibility of *remedi* in the EPSRC review of Manufacturing in April 2010 and the securing of a second phase of DARPA funding in "blood pharming", confirm the international status of *remedi*. Major US RM translational institutes acknowledge the unique and critical insights that *remedi* has generated and the *remedi* way of working has been much praised by key advocates as far away as New Zealand. The volume of high quality publications in high impact factor journals now arising from *remedi* work emphasises the academic quality of the work, especially when it is recognised that *remedi* publishes in journals with a significantly higher impact factor than the usual mainstream academic manufacturing journals.

The most important lessons from r*emedi* are that:

- The Grand Challenge approach can be transformational. Taking a strategic and focused approach while accepting and managing some risk allows movement from an unassuming position to one of national and international visibility, influence, and leadership in a relatively short time.
- The academic environment will respond to a more structured management process and a more industrial leadership style, this being necessary for an effective and co-ordinated approach to a problem of scale and complexity requiring the application of significant resource.
- Multidisciplinary teams take time to build and time to learn each others' cultures, values and skills. Some thrive in this environment, some are less comfortable. Ultimately multidisciplinary working delivers solutions to richer problems and delivers more interesting and adventurous science.
- Applied or problem driven science in collaboration should be driven by a mix of industrial and academic requirements and should recognise the role of industry to both pose problems of value and, in particular, to provide intellectual leadership, this is not solely the domain of the academic.

remedi is fortunate to be able to continue via its successor, the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, and the closely coupled EPSRC Life Sciences Interface Doctoral Training Centre in Regenerative Medicine. Our challenge will be to maintain the level of transformational change and impact that *remedi* has delivered and to convert this to a sustainable long term UK capability.

C.1 Archer, R. and Williams, D.J., 2005, Why Tissue Engineering Needs Process Engineering, Nature Biotechnology, 23, pp 1353-1355, November 2005.

C.2 Williams, D.J., Ratchev, S., Chandra, A. and Hirani, H., 2006, "The Application of Assembly and Automation Technologies to Healthcare Products", CIRP Annals - Manufacturing Technology, 55/2, 617-642.

C.3 Williams, D.J, Hourd, P.C., Archer, J. R., 2007, Applications of Precision Engineering within the Medical Engineering Sector, Proceedings of the 7th International Conference and 9th Annual General Meeting of the European Society for Precision Engineering and Nanotechnology, Bremen, May, 5-21.

C.4 Williams, D.J., Production Systems for Regenerative Medicine, Stuttgart Competence Forum, Intelligent Production Systems of the Future, November 4, 2010.

Acknowledgements

The work that is reported here 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. We 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, NHS Innovations East Midlands, Medilink East Midlands, NHS Futures, NPL and NIBSC. We 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*; our thanks to you all.

Appendices

Appendix 1. Summary of industrial collaboration in *remedi*

Appendix 2. People Stories

Appendix 3. Impact Cases (using EPSRC Success Story Format)

Appendix 1. Summary of industrial collaboration in remedi

Work Package	Primary Collaborators	Collaborator Contribution	Additional Collaborators	Contribution
Market evolution (1)	Network	Input to interviews and cases	-	-
Health economics (1)	Network & Clinicians	Input to interviews and cases	Consultancies for Intercytex, Magnecell, Orthomimetics (Tigenix), Sofradim, TAP	-
Policy (2)	Network	Input to interviews and cases	Consultancies for Magnecell and TAP	-
Scaffold Processing (3)	Critical Pharmaceuticals	£100k	-	-
	RegenTec Group	£260k	-	-
Cell Processing (3)	TAP	£1580k	Cook Myosite (US)	IP, therapeutic cell types & consumables value £150k
			National Stem Cell Bank, NIBSC	Additional key network partner
			Reneuron	IP, therapeutic cell types & consumables value £250k
			Stem Cell Sciences (Stem Cell Inc)	IP in automated of murine stem cell culture
Construct processing (3)	Intercytex	£275k		
Characterisation (4)	NPL	Strategic Research Fellowship	Almac Diagnostics	Instrument development contributions
			Avalon Instruments	Instrument development contributions
			JY Horiba	Instrument development contributions
Management (5)	Network	Meeting attendance	BIA	Co-sponsorship of closing conference
SME growth (5)	Network	Input to interviews and cases	Avlar Bioventures	Access to commercial data
			Bioceramic Therapeutics (RepRegen Ltd)	Deep access to commercial data
			BSi	Additional key network partner
			Future Health Technologies	Access to commercial data
			Intercytex	Access to commercial data
			Keranetics (US)	Deep access to commercial data
			Orthomimetics (Tigenix)	Access to commercial data
			Pepper Hamilton (US)	Access to commercial data
Automated GMP (5)	Network, emda			emda capital funding £650k
Injectable Scaffolds (5)	RegenTec Group			
Electrophysiology (5)	Network	-	-	-

The *remedi* network includes both the named network collaborators in the original proposal (ABHI, Medilink East Midlands, NHS Innovations East Midlands, and NHS Futures) and a broad network of industry and agency stakeholders. The scale of the broader *remedi* nework is indicated by the more than 110 attendees at the *remedi* closing conference.

Appendix 2. People Stories

Jasmin Kee

I am currently working as a Process Engineer for Organogenesis Inc. in Canton, Massachusetts, USA. My main projects focus on scale-up and automation of manufacturing processes for production of the next generation living human skin equivalent. I am part of a small team responsible for the development of a new 100,000sqft manufacturing facility from grass roots, which will house automated production lines for current and future products. I am also responsible for the development and scale up of closed systems for mammalian cell culture processes.

As part of the *remedi* Grand Challenge – Regenerative Medicine: A New Industry, I undertook a PhD at Loughborough University, supervised by Professor David J. Williams. My PhD "Process Characterisation of a Manufactured Living Skin Equivalent (ICX-SKN) and Product Improvement using Ultrasound" was sponsored by Intercytex, a UK Healthcare Company, and co-supervised by Dr Paul Kemp (Chief Operating Officer) and Dr Penny Johnson (R&D Director). My PhD showed how the biochemical composition and mechanical properties of the developmental Intercytex skin product (ICX-SKN) changed during the manufacturing process. This identified areas of further research aimed at improving the manufacturing process. The second part of my PhD showed that the biochemical and mechanical properties of ICX-SKN could be significantly enhanced by the application of ultrasound under specific acoustic conditions.

My participation in *remedi* has enabled me to change career direction from working as a Process Engineer in fast moving consumer goods companies to the life science and regenerative medicine industry. My PhD experience opened my eyes to the complexities of combining engineering principles and the manufacture of life science products, as well as the financial, regulatory, manufacturing and basic science challenges that need to be met for the growth of the industry. Through the *remedi* community I have met inspiring people from very different backgrounds, working together to bring the benefits of regenerative medicine to everyday life. Most importantly, I have made good friends and colleagues who I look forward to working with in the future.

Immanuel Sebastine

I am currently working as a Senior Lecturer in Chemical and Bioprocess Engineering within the School of Science and Engineering at Teesside University, UK. As a Senior Lecturer, I teach core Chemical Engineering subjects to BEng students and also supervise design and research projects. Shortly after joining the School, I implemented 'tissue engineering and regenerative medicine' as a key component of the Bio-manufacturing module that I teach as part of the MSc Biotechnology course. I am also involved in a collaborative research project in the area of bio-processing of cellulose and lignocelluloses.

As Postdoctoral Research Associate at Loughborough University, I worked for *remedi* in the field of 3D tissue engineering, focused mainly on specifying and subsequently testing the design of a novel and complex Dynamic Triaxial Loading Bioreactor (manufactured by BOSE Electroforce, USA) and on identifying growth conditions (cells, scaffolds and mechanical stimulation) for tissue engineered intervertebral disc (IVD). This work involved an investigation of the effects of mechanical stimulation on chondrocytes loaded on polyurethane scaffolds.

The time I spent with the *remedi* research group provided me with the experience and confidence to continue independent research in new research topics within Biotechnology & Healthcare Engineering. Through *remedi* I was able to attend and present papers at various international conferences and meetings, facilitating contact with other leading research groups and improving my technical writing and communication skills. The overall experience and knowledge I gained from the *remedi* research group has helped me to further my academic career, as I continue to apply the skills and experience gained to my new teaching and research activities at Teesside University.

Emma Rowley

I am Senior Research Fellow and Theme Manager for the Collaboration for Leadership in Applied Health Research and Care – Nottinghamshire, Derbyshire and Lincolnshire (CLAHRC-NDL) Implementation Theme, employed by Nottingham University Business School. CLAHRC-NDL is an NIHR funded applied Health Research Unit, with the aim of closing Cooksey's 2nd translation gap (funding 2008-2013 IRO £17.5 million), working across 12 health and social care partners in Nottinghamshire, Derbyshire and Lincolnshire in the UK. As Implementation Theme Manager, I lead a team of four social scientists, reporting to the Director of CLAHRC-NDL. We are responsible for carrying out the Implementation analysis in 16 clinical studies, ensuring that the new service innovations being designed are fit for purpose and meet the needs of the context in which they are to be introduced. This involves carrying out qualitative research into the barriers and facilitators to the translation, introduction and adoption of new medical services into a range of different health and social care settings. In addition to this, I oversee four case studies of existing service innovations (in primary care, mental health, children's services and stroke rehabilitation) to identify learning points for good and bad translation practice. I am also responsible for the CLAHRC-NDL development and education programme, a structured series of learning events open to all staff, seconded NHS staff and partner organizations, and have oversight management of the internal evaluation of CLAHRC-NDL and our Diffusion Fellow programme, whereby staff from NHS and local authority partners (~30 individuals) are seconded for one day per week to work alongside researchers and assist in translating research into practice.

My *remedi* work, as the researcher on Work Package 1.1 “Understanding the market”, saw me undertake an in-depth qualitative study of stakeholder’s perceptions to the barriers and facilitators to the commercialization and utilization of regenerative medicine products.

The work I carried out as part of *remedi* further added to my experience and expertise in the translation and contextual utilization of innovative medical technologies. The experience gained working as part of a multi-disciplinary, geographically diverse research group has been incredibly useful since!

Amit Chandra

I am a Research Associate in the Healthcare Engineering Group at the Centre for Biological Engineering (CBE) at Loughborough University. One of my roles involves the development of a clean room facility (the 'Cell Therapy Manufacturing Facility'), which aims to provide the manufacturing capability for the preparation of Good Manufacturing Practice (GMP) compliant batches of somatic cell therapeutic medicinal products for Phase I, II, and III clinical trials, regulated by the MHRA (Medicines and Healthcare Products Regulatory Agency). I have recently helped to win a TSB project that will fund some of the validation activities for this facility. I currently manage the Loughborough component of this project and as Technical Manager lead a small team that supports all the facility qualification activities within the validation programme. Additionally, I am a named researcher in the new EPSRC Centre for Innovative Manufacturing in Regenerative Medicine. As a part of this, I will be involved in the platform activity, contributing to case studies that aim to influence public policy, regulation and the value system and to a research activity within the hospital platform theme.

Along with personal funding from the TSB project on Maxillofacial therapies, I was a key researcher in the *remedi* Grand Challenge project from its inception in September 2005. I initially started work in *remedi* within Workpackage 3.1, collaborating with Nottingham University researchers in quantifying the capability of the supercritical fluid process for the manufacture of scaffolds. I was also the "chief engineer" for Workpackage 3.2, and in collaboration with The Automation Partnership (TAP), contributed to the procurement, installation and qualification of an automated cell culture system ('the first Compact Select machine manufactured by TAP'). This was installed in the Healthcare Engineering laboratories in the Wolfson School of Mechanical and Manufacturing Engineering and subsequently transferred to the CBE. I have also taken part in many collaborative research projects which have included researchers working in teams from multidisciplinary backgrounds.

As a consequence of my role in the Grand Challenge, I have developed engineering expertise applied to automated stem cell culture, a key competence of the Healthcare Engineering Group. This has required me to gain skills in biology and cell biology, which, in working with the other members of the group, has allowed me to apply these skills to the development and validation of the clean room facilities at the CBE. These combined engineering and biology skills, together with my experience of working with clinicians, will be key to fulfilling my role within the new Centre, which is scheduled to start in September 2010.

Appendix 3. Impact Cases (using EPSRC Success Story Format)

- Birmingham – WP1: Understanding the Market
- Nottingham – WP1: Understanding the Market
- Cambridge – WP2: Policy Environment
- Nottingham – WP3(i): Scaffolds
- Loughborough – WP3(ii): Cells
- Loughborough – WP3(iii): Tissues
- Nottingham – WP4: Characterisation and Control
- Ulster – WP4: Characterisation and Control
- Loughborough – WP5: Facilitating the growth of the Industry
    - 5a) Project Management
- Loughborough – WP5: Facilitating the growth of the Industry
    - 5b) SME and Industry Growth
- Liverpool, Nottingham & Ulster - WP5: Facilitating the growth of the Industry
    - 5c.i) Speculative product led research: Injectable Scaffolds
- Loughborough – WP5: Facilitating the growth of the Industry
    - 5c.ii) Speculative product led research: Electrophysiological Characterisation

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Birmingham – WP1: Understanding the Market**

2. Summary of Case Study/Research Project

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.

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academic: Richard Lilford
Collaborators included a wide network of Clinicians, especially orthopaedic and neurosurgeons. Magnecell, Orthomimetics, Intercytex, Sofradim.
MATCH
STEPS (EU Project)

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

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.

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Nottingham – WP1: Understanding the Market**

2. Summary of Case Study/Research Project

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).

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academic: Paul Martin
Collaborators included a wide range of industry, patient and user, clinical and academic stakeholders contributing to confidential interviews.

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

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).

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

Paul Martin: paul.martin@nottingham.ac.uk 0115 951 5419
Emma Rowley: emma.rowley@nottingham.ac.uk 0115 846 8144

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Cambridge – WP2: Policy Environment**

2. Summary of Case Study/Research Project

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.

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge

Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academic: Finbarr Livesey
Collaborators included a wide range of industry, government and academic stakeholders via confidential interviews and two workshops.

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

Informal parallel research in emerging industry.

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

Finbarr Livesey: tfl20@eng.cam.ac.uk 01223 748258
Laure Dodin: ld308@eng.cam.ac.uk 01223 339739

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Nottingham – WP3(i): Scaffolds – generation of robust processes for the manufacture of drug eluting scaffolds and their materials**

2. Summary of Case Study/Research Project

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.

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academics: Kevin Shakesheff, Steve Howdle.
Collaborators: Richard Oreffo (Southampton University; Critical Pharmaceuticals and Regentec (SMEs).

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

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

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Loughborough – WP3(ii): Cells – process discovery, optimisation and continuous improvement for the manufacture of cellular feedstocks**

2. Summary of Case Study/Research Project

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.

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academics: David Williams (Loughborough Uni), Lorraine Young & Chris Denning (Uni of Nottingham)
Collaborators: The Automation Partnership, Cook Myosite, ReNeuron, Stem Cell Sciences, Intercytex, Future Health Technologies, AQIX, NIBSC (Stem Cell Bank), Uni of Sheffield (Peter Andrews & Harry Moore), Uni of Southampton (Richard Oreffo).

6. Evidence of impact on the economy and/or society

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.

David Newble, CEO of The Automation Partnership, stated:
The Automation Partnership and the overall regenerative medicine industry have benefited significantly from this programme. One of the first deliverables was development of a new automated cell culture system, the specification for which was developed in collaboration with Loughborough University, for smaller biotechnology companies. Over thirty systems have been sold since at a price of around five hundred thousand pounds per system. The manufacture of these systems is carried out in the UK.

As part of the project Loughborough University retained the development system and has used this to work closely with a number of emerging regenerative medicine companies and academics to demonstrate that complex stem cell culture protocols can be automated. This work was very valuable for a number of reasons:

- Regenerative medicine companies, such as Reneuron, were able to demonstrate that their production processes could be automated cost effectively enabling their business plans,

- Academics have demonstrated that highly sensitive human embryonic stem cells can be cultured on an automated platform,

- TAP significantly increased its knowledge of good manufacturing practice (GMP) issues surrounding stem cell based therapies. As a direct result TAP have developed the world's first high throughput autologous cell therapy production platform. This would not have been possible without Loughborough's input to the creation of the supporting data for the associated validation package. This is a new market for TAP and two of these platforms have been sold to date.

Finally, as a result of the remedi project both TAP and Loughborough have built their positions as industry leaders in the automation and scale up of stem cell based therapies. This is demonstrated by the fact that they have been chosen as partners in a significant US Defence Establishment Research Projects Agency (DARPA) project to develop a platform to produce red blood at therapeutic volumes. This will bring several million dollars of investment into the UK and has the potential to bring significant additional investment in as further work is done to address this multi-billion dollar market opportunity.

7. Benefits to researchers, students, or collaborators

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 on behalf of the Wolfson School of Mechanical & Manufacturing Engineering. The UK National Stem Cell Bank also joined *remedi* as a collaborator.

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Loughborough – WP3(iii): Tissues – engineering models of the variation in the manufacturing of first generation tissue engineered products requiring cell growth and extracellular matrix deposition within a scaffold matrix**

2. Summary of Case Study/Research Project

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.

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academic: David Williams
Collaborators: Intercytex, Uni of Sheffield (Gwen Reilly), Uni of Manchester (Judith Hoyland & Steve Richardson)

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

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.

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Nottingham – WP4: Characterisation and Control**

2. Summary of Case Study/Research Project

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.

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

NPL Fellowship support.

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academics: John Crowe, Steven Morgan
Collaborators: National Physical Laboratory, Critical Pharmaceuticals, The Automation Partnership, Intercytex, ReNeuron, Regentec, MATCH.

6. Evidence of impact on the economy and/or society

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

7. Benefits to researchers, students, or collaborators

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).

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

Prof John Crowe: john.crowe@nottingham.ac.uk 0115 951 5590

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Ulster – WP4 Characterisation and Control**

2. Summary of Case Study/Research Project

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.

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

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academic: Brian Meenan
Collaborators: Almac Diagnostics (NI), Avalon Instruments (now Perkin Elmer), JY Horiba, National University

of Ireland - Galway, MATCH.

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

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.

8. Background information and relevant website(s)

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

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Loughborough – WP5: Facilitating the growth of the Industry 5a) Community building and project management**

2. Summary of Case Study/Research Project

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, the recent announcement of funding for the new Loughborough-led EPSRC Centre for Innovative Manufacturing in Regenerative Medicine allows the research to be taken forward.

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academic: David Williams
Collaborators: The Automation Partnership, RegenTec, Critical Pharmaceuticals, Association of British Healthcare Industries, Medilink East Midlands, East Midlands NHS Innovations Hub, East Midlands Development Agency, NHS Confederation, Intercytex, National Physical Laboratory, NIBSC, BioIndustry Assocation (RIG), BSI, McGowan Institute for Regenerative Medicine, Keele University (Alicia El Haj)

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

Significant contributions to systemic change within Loughborough University.

8. Background 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

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Loughborough – WP5: Facilitating the growth of the Industry 5b) Manufacturing systems analysis and redesign to re-engineer bench based processes; manufacturing systems and process design methods for bio-intensive products; risk and cost analysis**

2. Summary of Case Study/Research Project

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.

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academic: David Williams
Collaborators: The Automation Partnership, KeraNetics, BioCeramic Therapeutics, Orthomimetics, Intercytex, RegenTec, Critical Pharmaceuticals, Pepper Hamilton.

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

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.

8. Background information and relevant website(s)

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Liverpool, Nottingham & Ulster – WP5: Facilitating the growth of the Industry**
5c): Exploring the challenges in the realisation of visionary tissue engineered products

2. Summary of Case Study/Research Project

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.

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academics: Nick Rhodes & John Hunt (Liverpool), Brian Meenan (Ulster) & Kevin Shakesheff (Nottingham)

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators

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.

8. Background information and relevant website(s)

9. Who should we contact for more information? *(Include email and tel. number)*

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

EPSRC Engineering and Physical Sciences Research Council

EPSRC Success Story Form

Have an example of how EPSRC-funded research has had a positive impact on society or the economy?

Please fill in the following form and return it to rachel.blackford@epsrc.ac.uk

1. University **Loughborough – WP5: Facilitating the growth of the Industry**
5c) Exploring the challenges in the realisation of visionary tissue engineered products

2. Summary of Case Study/Research Project

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.

3. EPSRC support *(Amount, type(s) of grant or scheme, grant references (if applicable), date)*

Part of EPSRC Regenerative Medicine – A new Industry – Grand Challenge
Ref: EP/C534247/1 Dates: 01/07/2005 – 28/02/2010

4. Other sources of significant sponsorship (if applicable) *(Amount, sponsoring organisation, date)*

-

5. Names of key academics and any collaborators *(Include organisation details)*

Key Academics: Kevin Shakesheff, Nick Rhodes, Brian Meenan

6. Evidence of impact on the economy and/or society

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.

7. Benefits to researchers, students, or collaborators
8. Background information and relevant website(s)
9. Who should we contact for more information? *(Include email and tel. number)* Andrew West: A.A.West@lboro.ac.uk 01509 227550