

<p><b>Institution: Loughborough University</b></p>
<p><b>Unit of Assessment: B12 Aeronautical, Mechanical, Chemical and Manufacturing Engineering</b></p>
<p><b>Title of case study: Manufacturing systems for therapeutic human stem cells to improve health and quality of life</b></p>
<p><b>1. Summary of the impact</b> (indicative maximum 100 words)</p> <p>Since 2003 Loughborough University has worked with industry to create future manufacturing systems to enable large scale production of human stem cells. The research, development and demonstration of consistent, optimised, automated expansion in culture of human stem cells at Loughborough has led to the commercial sale by July 2013 of 47 systems worth £20.1M to companies developing stem cell-based and other therapies. Their use is contributing to the health and quality of life of patients, whilst creating a new industry sector with significant economic and employment benefits. Loughborough leads internationally and nationally in this emerging field with research at significant scale contributing new manufacturing and regulatory science and standards.</p> <p><b>2. Underpinning research</b> (indicative maximum 500 words)</p> <p>Research at Loughborough University since 2005 has generated new and important methods of automatically and consistently culturing human stem cells for therapeutic use. These cells are key to regenerative therapies that replace or regenerate human cells, tissues and organs. It is predicted these developments will transform healthcare and the creation of a new industry sector is envisaged, as is evidenced by the creation of the Cell Therapy Catapult. The research arose from the industrial experience of Professor David Williams in terms of addressing scale-up challenges towards the end of pharmaceutical product life cycles. Returning to academia in 2003 as an EPSRC funded Research Chair at Loughborough he committed to address the automation, process design and scale-up challenges for emerging industries, in particular those commercialising regenerative medicines.</p> <p>Williams headed the EPSRC Grand Challenge in Regenerative Medicine – <i>remedi</i> [Grant Ref EP/C534247/1][<b>G3.1</b>], which began in 2005. The most significant work package of <i>remedi</i> addressed systems for the automation of therapeutic human stem cell culture. It was a collaboration of Loughborough’s manufacturing, quality, process, process design and biological engineering skills. The Automation Partnership (now TAP Biosystems) providing machine design skills, and multiple user partners who provided key understanding of the requirements for the manufactured product. Following the specification of a machine by the collaborating partners it was constructed and installed at Loughborough University in 2006.</p> <p>With user collaborators, the consistent automated adherent culture of human mesenchymal stem cells (hMSC) [<b>3.1</b>], human embryonic stem cells (hESC) [<b>3.2</b>], human foetal progenitor cells [<b>3.3</b>], cord blood derived stem cells and smooth muscle cells was demonstrated at the level of quality required by clinical and commercial therapeutic use. Also, quality engineering and process design techniques were applied for the first time to improve the quality of stem cell bio-processing, including the measurement and comparison of manual and automated culture Process Capability (Cpk) [<b>3.4</b>], methods of product characterisation [<b>3.5</b>] and use of Design of Experiments including Taguchi Screening Experiments and Response Surface Methods to improve process consistency and product quality and reduce the Cost of Goods as summarised in [<b>3.6</b>].</p> <p>The work has been executed within a quality system for translational research allowing transfer to an industrial environment requiring the use of Good Manufacturing Practice (GMP), essential for therapeutics.</p> <p>Since the initial transformative research in <i>remedi</i> (2005-2010) [<b>G3.1</b>], research has continued with EPSRC [<b>G3.5-7</b>, <b>G3.11-13</b>], BBSRC BRIC [<b>G3.2</b>], TSB [<b>G3.8</b>], MRC UKRMP [<b>G3.14-15</b>], Darpa [<b>G3.4</b>] as well as other funding [<b>G3.3</b>, <b>G3.9</b>, <b>G3.10</b>]. Although other universities have been involved with some of these grants, the most significant of these activities in manufacturing are and have been Loughborough led.</p>

## Impact case study (REF3b)

Loughborough University researchers were David J Williams (Professor, 2003 to date), Robert J Thomas (Research Associate, RCUK Fellow, Lecturer, Senior Lecturer, EPSRC Early Career Fellow 2006 to date), Yang Liu (Research Associate, RCUK Fellow, Lecturer, Senior Lecturer 2006 to date), Paul Hourd (Research Associate 2005 to date), Amit Chandra (Research Associate 2005 to date), Elizabeth Ratcliffe (Research Associate 2008 to date), Erin Rayment (Research Associate 2008 - 2010), Patrick Ginty (Research Associate 2008 to 2013), Jasmin Kee (PhD student 2006 - 2009), Pawanbir Singh (PhD student 2007 - 2010). Williams, Hourd, Kee and Chandra worked from manufacturing and quality engineering perspectives; Thomas, Liu, Ratcliffe, Rayment at the biology engineering interface and Williams, Hourd, Singh and Ginty integrated the commercial, clinical and evolving regulatory science and standards environments.

### 3. References to the research (indicative maximum of six references)

- 3.1. Thomas RJ, Chandra A, Liu Y, Hourd P, Conway P, Williams DJ, Manufacture of a human mesenchymal stem cell population using an automated cell culture platform, *Cytotechnology*, 55 (2007) 31-39; DOI: 10.1007/s10616-007-9091-2. Impact factor 1.35.
- 3.2. Thomas RJ, Anderson D, Chandra A, Smith NM, Young LE, Williams DJ, Denning C, Automated, Scalable Culture of Human Embryonic Stem Cells in Feeder-Free Conditions, *Biotech and Bioeng*, 102 (2009) 1636-1644; DOI: 10.1002/bit.22187. Impact factor 3.65.**
- 3.3. Thomas RJ, Hope AD, Hourd P, Baradez M, Miljan EA, Sinden JD, Williams DJ, Automated, serum-free production of CTX0E03: a therapeutic clinical grade human neural stem cell line, *Biotech Letters*, 31 (2009) 1167–1172; DOI: 10.1007/s10529-009-9989-1. Impact factor: 1.85.
- 3.4. Liu Y, Hourd P, Chandra A, Williams DJ, Human cell culture process capability: a comparison of manual and automated production, *JTERM*, 4 (2010) 45-54; DOI: 10.1002/term.217. Impact factor 2.83.
- 3.5. Rayment EA, Williams DJ, Mind the Gap: Challenges in characterising and quantifying cell- and tissue-based therapies for clinical translation, *Stem Cells*, 28 (2010) 996–1004; DOI 10.1002/stem.416. Impact factor 7.70.**
- 3.6. Williams DJ, Thomas RJ, Hourd P, Chandra A, Ratcliffe E, Liu Y, Rayment EA, Archer RA , Precision manufacturing for clinical-quality regenerative medicines, *Phil. Trans. R. Soc. A*, 370(1973) (2012) 3924-3949; DOI:10.1098/rsta.2011.0049. Impact factor 3.11.**

The significance of the research is indicated by the total award of £37M over an 8 year period, see below, and invited presentations internationally (including Auckland (New Zealand), Boston (US), Bremen (Germany), Erlangen (Germany), Hilton Head (US), Hong Kong, Leipzig (Germany), Madrid (Spain), Singapore, Stuttgart (Germany), Wroclaw (Poland)). Loughborough was also the only academic institution invited to give oral evidence on manufacturing to the 2012-2013 House of Lords Select Committee on Regenerative Medicine [5.4, 5.5], a clear indicator of national academic leadership in the field.

#### Key Research Grants:

- G3.1** 2005-2010 EPSRC Remedi Grand Challenge Regenerative Medicine – A New Industry £7M (Williams).
- G3.2** 2008-2011 BBSRC/BRIC Developing scalable and standardised manufacturing methods for human pluripotent stem cells £377k – Hewitt (Loughborough University), Thomas, Williams & Young, Denning (University of Nottingham).
- G3.3** 2008- 2010 emda Centre for Biological Engineering Facility £650k – Williams (Loughborough University).
- G3.4** 2008-2012 Darpa Large Scale Human Placenta Progenitor Cell-Derived Erythrocyte Production – Continuous Red Blood Cell Production Phase 1 & Phase 2 £2.13M – Thomas & Williams (Loughborough University).
- G3.5** 2008-2017 EPSRC LSI DTC's Doctoral Training Centre in Regenerative Medicine £6.1M – Williams (Loughborough University), Shakesheff (University of Nottingham), El Haj (Keele University).
- G3.6** 2010-2017 EPSRC E-TERM Cross Disciplinary Research Landscape Award £2.9M – Williams (Loughborough University), Fisher (University of Leeds), Shakesheff (University of Nottingham), El Haj (Keele University), McNeil (University of Sheffield), Genever (University of

## Impact case study (REF3b)

York) .

**G3.7** 2010-2015 EPSRC Centre for Innovative Manufacturing in Regenerative Medicine £5.3M - Williams (Loughborough University), Shakesheff (University of Nottingham), El Haj (Keele University).

**G3.8** 2010-2011 TSB GMP Automated Stem Cell Culture £198k – Williams (Loughborough University).

**G3.9** 2011-2012 KTA Supporting the Improvement and Optimisation of Cell Culture for Regenerative Medicine Products Companies £91k – Williams (Loughborough University).

**G3.10** 2011-2012 KTA Supporting the Establishment and Validation of a Regulated Manufacturing Facility for Contract Research and Manufacturing of Cell Therapies £142k – Williams (Loughborough University).

**G3.11** 2012-2015 EPSRC National Centre Uplift £534k – Williams (Loughborough University).

**G3.12** 2013-2018 EPSRC Early Career Fellowship £1.5M – Thomas (Loughborough University).

**G3.13** 2013-2018 EPSRC Manufacturing Fellowship £1.08M – Medcalf (Loughborough University).

**G3.14** 2013-2017 MRC/UKRMP The Pluripotent Stem Cell Platform £5.6M – Andrews (Sheffield University), Smith (Cambridge University) and Williams (Loughborough University).

**G3.15** 2013-2017 MRC/UKRMP The Pluripotent Stem Cell Platform Capital Investment £3.1M – Andrews (Sheffield University), Smith (Cambridge University) and Williams (Loughborough University).

#### 4. Details of the impact (indicative maximum 750 words)

Our research as cited in **[3.1-3]** led to the creation and application of an automated system, the Compact SelecT, to the culture of large numbers of human stem cells. This is now being put to use internationally to develop therapeutics **[5.1]**. As of July 2013, 47 of these systems worth £20.1M have been sold in laboratory and GMP configurations and are being used to benefit current and future patients by both enabling translational research and manufacturing therapeutics. TAP are in discussions with potential purchasers of 50 further systems with half of these to be applied to either cell therapy development or stem cell research. As a result of the orders, TAP Biosystems and their build partners have created 15-20 new jobs **[5.2]**.

The Loughborough research uniquely allows the transfer of manual stem cell culture processes to automation and pioneered process design techniques for their subsequent optimisation. The research was collaborative with the science base, manufacturing industry and its suppliers and end users and designed with embedded direct dissemination routes.

After some initial work, human (h) dermal fibroblasts were cultured on the automated Compact SelecT in collaboration with Intercytex (2006-2009), human smooth muscle cells with Cook Myocyte (US) (2008-2009), hMSC with Oreffo of Southampton (2006, **[3.1]**), foetally derived neural progenitors with Reneuron (2008-2009, **[3.3]**), hESC (differentiated to cardiomyocytes) with Denning and Young of Nottingham (2008-2009, **[3.2]**) and latterly human induced pluripotent stem cells (hiPSC) with Vallier and Pederson of Cambridge (2011-2013) and GMP grade hESC cells with WiCell (US) (2012-2013). Consequently the work has significantly contributed to the development of cell-based therapeutics for blood replacement, stroke and degenerative diseases of the brain, leukaemia and other cancers and tissue repair including for the bladder **[5.1]**.

The product launched by TAP Biosystems has a global reach: 40% of the systems sold are in Europe and 60% in the US with concentrations on the East (MA) and West Coasts (CA) **[5.2]**, and new markets are emerging in Russia, China and Korea. Loughborough further enabled the exploitation process by demonstrating the capability of the machine to culture complex cell types of significance to customers and to operate to GMP.

Understanding how to manufacture stem cell based products is one of the key critical translational steps required to allow such therapies to reach the market and for successful business investment and sector growth. The new manufacturing science researched at Loughborough has allowed the reduction to practice of complex research laboratory based biological processes.

## Impact case study (REF3b)

This capability has significantly influenced the development of the new Cell Therapies Catapult. The Group was joint leader of one of the three bids, reaching the final round of the subsequently withdrawn academic competition for leadership of the Catapult during 2011. The Catapult was then created in a top-down process by the Technology Strategy Board with a CEO being appointed in April of 2012 and a Chairman in September 2012. An MOU establishing a strategic collaboration between the Cell Therapies Catapult and the manufacturing, automation and process capability at Loughborough University was signed on 21<sup>st</sup> January 2013 [5.6].

Further, Williams chaired the meeting (09/07/08) that led to the founding of the Regenerative Medicine RGM/1 committee of BSI. Whilst creating the first two Publically Available Specifications, PAS, (PAS 83 and 84) was straightforward being solely descriptive of the status quo, a third, PAS 93 on Cell Characterisation [5.7], was more problematic, requiring a Loughborough intervention [5.8] to meet the needs of the innovative businesses. It is important to recognise that this third PAS [5.7] is the first of its kind in the world and is likely to lead to an ISO standard.

Our track record was also key to securing essential follow-on research funding, in particular the leadership of major national consortia including The EPSRC Centre for Innovative Manufacturing in Regenerative Medicine (2010) [G3.7], its uplift to act as a national centre (2012) [G3.11], the translational research fellowship programme, the EPSRC ETERM Cross Disciplinary Landscape Award (2010) [G3.6], the EPSRC Early Career Fellowship of Dr Robert Thomas (2013) and other subsequent grants [G3.2-5, G3.8-10, G3.13-15].

The work has also generated a large number of skilled individuals with contributing research assistants and PhD graduates from the group being employed as lecturers and senior lecturers (Thomas and Liu, Loughborough) in academia and as technical and commercial professionals in international translational and technology transfer organisations (Rayment, Griffith University, Australia; Ginty, Cell Therapy Catapult) and businesses (Kee, Organogenesis, US; Singh, Stem Cell Technologies, Canada) with a consequent impact on technology translation.

### 5. Sources to corroborate the impact (indicative maximum of 10 references)

The following sources of corroboration can be made available at request:

- 5.1 Therapeutic Development: Example press release <http://www.reneuron.com/press-release/reneuron-successfully-automates-its-stem-cell-manufacturing-process-09-04-09>.
- 5.2 Commercial Exploitation of Automation: TAP Biosystems, Royston, SG8 5YW
- 5.3 Economic Impact of Research: EPSRC Economic Impact of the Innovative Manufacturing Research Centres, DTZ, 15<sup>th</sup> April 2011. <http://www.epsrc.ac.uk/SiteCollectionDocuments/Publications/reports/EconomicImpactOfTheMRCs.pdf> Page 45: Table showing total impact of Regenerative Medicine Grand Challenge new product £21.5M sales to date, Leverage of £28M of follow-on funding (between all partners). (Additional potential share of market, 0.5% worth £650M p.a.)
- 5.4 Policy Impact.  
Oral Evidence to the House of Lords Select Committee in Regenerative Medicine. Weblink to session <http://www.parliamentlive.tv/Main/Player.aspx?meetingId=12149>;
- 5.5 Policy Impact. Web link to Report of House of Lords Select Committee on Regenerative Medicine <http://www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/23.pdf>
- 5.6 Relationship with Cell Therapies Catapult/MOU.  
Cell Therapy Catapult, Guy's Hospital, Great Maze Pond, London SE1 9RT London,  
Web link to press release <http://www.innovateuk.org/content/news/cell-therapy-catapult-loughborough-university-to-c.ashx>
- 5.7 Standards  
PAS 93:2011, Characterization of human cells for clinical applications, BSI, 2011. ISBN 9780580698507. <http://shop.bsigroup.com/en/ProductDetail/?pid=00000000030213318>  
Centre for Biological Engineering contribution acknowledged on page iv.
- 5.8 Characterisation Standards Influence on PAS 93  
BSI, 389 Chiswick High Road, London, W4 4AL