Institution: University of Southampton		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: 01-01 Therapeutic and commercial translation of skeletal stem cells for new approaches to orthopaedic treatment		
Period when the underpinning research was undertaken: 2002 – 2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Richard Oreffo Douglas Dunlop Jonathan Dawson Nicholas Evans	Professor of Musculoskeletal Science Professor of Orthopaedic Surgery (Category C) EPSRC Research Fellow Associate Professor of Bioengineering	February 1999 – present November 2004 – present October 2004 – present November 2011 – present
Period when the claimed impact occurred: May 2014 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Pioneering research by the Stem Cell Group at the University of Southampton has led to the use of skeletal stem cells and novel biomaterial scaffolds in the treatment of bone damage and disease. This has benefited a hard-to-treat patient cohort, generated economic impact and inspired far-reaching public engagement activities.

In 2014 the Group undertook the first stem-cell augmented 3D-printed titanium hip replacement, which demonstrated positive clinical outcomes. A further 20 of the most challenging patients were treated with this procedure; evaluations showed sustained quality of life improvements and long-term cost savings for the NHS. The procedures generated significant commercial revenue growth for a Nasdaq-listed 3D printing company.

Patented research was commercialised through the formation of a spin out company, which raised GBP870,000 in private and public sector investment and created 3.5 FTE employment roles.

In parallel, the Group engaged more than 600,000 people in its novel Stem Cell Mountain public engagement exhibit, increasing understanding of stem cell biology and regenerative medicine; it marked the University's first partnership with Winchester Science Centre and led to 11 further collaborations worth GBP500,000. Stem cell workshops run by the Group had a demonstrable influence on inspiring GSCE students to pursue further STEM-related study or careers.

2. Underpinning research

As the world's population ages, the rates of bone and joint illness or injury rise. In the UK, one in two women and one in five men will suffer a fracture after the age of 50, costing the NHS billions of pounds each year. Hip replacements are one of the most common joint replacement procedures; however, many of those surgeries need corrections – in 2018 there were 106,116 hip replacements in the UK with 8,324 (8%) of them needing revisions. New treatments that enable the skeleton to heal better are needed to meet this escalating need and save costs.

Stem cell research at the University of Southampton has demonstrated the efficacy and patient benefit of using patients' own bone stem cells together with innovative biocompatible scaffolds at the point of injury to transform approaches to orthopaedic treatment. Starting in 2002, Professor Richard Oreffo demonstrated a patient's own stem cells, identified by surface marker STRO-1, had a large capacity to form bone *in vitro* [**3.1**]. Working with patient samples from University Hospital Southampton, Oreffo was able to isolate human skeletal stem cells [**3.2**] and optimise their expansion and characterisation with work identifying the physical conditions necessary to optimise their growth [**3.3**].

Work from Oreffo and Professor Douglas Dunlop led to demonstration of the survival and applicability of using a patient's own cells in bone impaction grafting in *in vivo* models and in human patients [**3.4**]. To facilitate large bone repair defects, they combined stem cells and bone graft with 3D printed scaffold templates. In 2014, Oreffo and Dunlop translated this into clinical practice and undertook the first concentrated autologous skeletal stem cell augmentation onto the porous surface of a 3D custom-made revision total hip replacement. Following this landmark operation in the UK, Oreffo and Dunlop have followed a case series of treated patients; they showed significant patient-reported clinical and radiological improvements in 11 patients in 2018 [**3.5**]. To date 20 patients have been treated with this approach.

In parallel with this work, Dr Jonathan Dawson and Oreffo developed novel biomaterials to augment bone repair and, to the best of their knowledge, were the first group worldwide to use novel nanoclay gels, in 2011, as a biomaterial for bone repair [**3.6**]. Specifically, they have shown the ability for bone induction at physiological doses of bone morphogenetic protein, (BMP2), the current osteoinductive therapeutic agent; which has fallen from favour following widely publicised damaging side-effects. This has been patent protected and two additional patents are under submission. This approach and the associated patent family formed the basis of University of Southampton spin out company Renovos Biologics Limited in 2017.

3. References to the research

3.1. Howard D, Partridge K, Yang X, Clarke NM, Okubo Y, Bessho K, Howdle SM, Shakesheff KM, Oreffo RO. Immunoselection and adenoviral genetic modulation of human osteoprogenitors: in vivo bone formation on PLA scaffold. Biochem Biophys Res Commun. 2002 Nov 29;299(2):208-15. https://doi.org/10.1016/S0006-291X(02)02561-5

3.2 Mirmalek-Sani SH, Tare RS, Morgan SM, Roach HI, Wilson DI, Hanley NA, Oreffo RO. Characterization and multipotentiality of human fetal femur-derived cells: implications for skeletal tissue regeneration. Stem Cells. 2006 Apr;24(4):1042-53. https://doi.org/10.1634/stemcells.2005-0368

3.3. MJ Dalby, N Gadegaard, R Tare, A Andar, MO Riehle, P Herzyk, CDW Wilkinson, Oreffo ROC (2007). The control of human mesenchymal cell differentiation using nanoscale symmetry and disorder. Nature Materials Dec 6 (12):997-1003. https://doi.org/10.1038/nmat2013 Nature Materials top 20 paper in last 10 years)

3.4 Tilley S, Bolland BJ, Partridge K, New AM, Latham JM, Dunlop DG, Oreffo RO. Taking tissue-engineering principles into theater: augmentation of impacted allograft with human bone marrow stromal cells. Regen Med. 2006 Sep;1(5):685-92. https://doi.org/10.2217/17460751.1.5.685

3.5 Goriainov V, McEwan JK, Oreffo RO, Dunlop DG. Application of 3D-printed patient-specific skeletal implants augmented with autologous skeletal stem cells. Regen Med. 2018 Apr;13(3):283-294. https://doi.org/10.2217/rme-2017-0127

3.6 Dawson JI, Kanczler JM, Yang XB, Attard GS, Oreffo RO. Clay gels for the delivery of regenerative microenvironments. Adv. Mater. 2011 Aug 2;23(29):3304-8. https://doi.org/10.1002/adma.201100968 *Recommended (**) F1000 Prime*

Grants:

MRC-AMED MR/V00543X/1 GBP582,765

Innovate UK Smart Grant TS/V005472/1 GBP206,788 (Renovos GBP144,863; UoS GBP61,925)

BBSRC – BB/S019480/1 GBP563,091

BBSRC – BB/P017711/1 GBP675,553

UKRMP II – MR/R015651/1 GBP4,092,161 with 719,660 to Southampton

EPSRC – EP/R014213/1 GBP909,511

Innovate UK Project Grant GBP296,563 (Renovos 195460; UoS 101,103)

EPSRC – Early Career Fellowship GBP1,320,173.17 (JID 2014-2019)

EPSRC – Early Career Fellowship (ext.) £802,691.38 (JID 2019-2022)

EPSRC – EP/R013594/1 GBP449,173 Project Grant to NDE 2018-2021

4. Details of the impact

The Stem Cell Group's research on biomaterials, stem cells and regenerative medicine led to ground-breaking, cost-saving approaches to clinical practice that have significantly enhanced patients' quality of life. It has had an economic impact through the formation of a spinout company to commercialise the next generation of biomaterial treatments. Through creative public engagement initiatives, it has increased the public's understanding of stem cells and enjoyment of science, inspired a series of collaborations between the University and Winchester Science Centre, and stimulated interest among GSCE students in STEM study and careers.

Improving quality of life for hard-to-treat patients through pioneering, cost-saving changes to clinical practice

The underpinning research led to the first patient in the UK being treated with a stem-cell augmented 3D-printed hip replacement in 2014. This was reported widely in the national and international media, including reports on the BBC, Sky News, Research Councils and industrial organisations [**5.1**]. The patient, 71-year-old Meryl Richards from Hampshire, had undergone six hip operations since a traffic accident in 1977. In December 2020, seven years after the surgery, Mrs Richards remains pain free and mobile.

Subsequently, 20 patients have been treated in Southampton using this technique, some of whom contacted the Southampton team directly after reading the 2014 media reports. Follow-up studies, including an 11-patient case series published in 2018, demonstrated the impact of this treatment. New bone was formed in challenging clinical cases, important as these large custom-made 3D printed implants are usually an operation of last resort in patients with reduced biological potential, caused by previous implant effects and increasing patient age [**5.2**].

A review of all 20 patients presented at the Wessex Gauvain Society Annual Meeting in 2020 showed no one needed to have their implant replaced or suffered any dislocations or fractures. Pre-operation, many of these patients were immobile, with some reliant on a wheelchair. Post operation, there was significant improvement in the patients' Oxford Hip Score, a patient reported outcome measuring hip function and pain with return to much improved mobility level. [**5.3**] To date no implants have been revised. As orthopaedic revision burden increases, the frequency of the most challenging cases has increased with nearly 33% of revisions being re revisions. These re revisions are three times more likely to fail. Given there are 3,150 revisions a year, albeit not generally as complex as the Southampton group's series, a 6% revision rate after 12 months would save the NHS GBP1.6m if we used our stem cell 3D implant approach. Assuming a best case scenario, application across all 3,150 patients, at 50% implant survival enhancement, would save the NHS GBP34.8m. The UoS series resulted in 100% survival which equates to GBP3.2m saving for the NHS. If applied only to complex revisions such as Southampton's, then assuming 10% were of similar complexity, this would still save the NHS a total of GBP3.5m. The intervention has therefore transformed patient lives and demonstrated significant cost savings, through fewer revisions, as well as improved patient quality of life.

Delivering economic impact through clinical innovations and commercialisation of underpinning research

Oreffo and Dunlop's 3D-printed hip research was responsible for significant commercial revenue growth for Materialise NV, the Nasdaq-listed company which produced the hip implant. Brigitte de Vet-Veithen, Vice President of Materialise Medical, wrote: '*The research from Prof. Dunlop and the University of Southampton Bone Research Group has contributed to create strong clinical outcomes of our personalized aMace implant. Their work has helped us to better position this solution in the market and as such expand the treatment to more patients in need to break the revision cycle. The resulting growth of our aMace implant has over proportionally contributed to the 17.6% revenue growth of Materialise's medical devices and services in 2019.*' [**5.4**]

Oreffo and Dawson co-founded spin out Renovos Biologics Limited, a regenerative medicine company, in 2017; the underpinning science outlined in [**3.6**] was protected in a patent family [**5.5**, **5.6**]. Renovos is pioneering its nanoclay gel technology platform Renovite®, which addresses an unmet clinical need for long-term tissue regeneration for patients with debilitating bone and joint conditions; it acts as injectable scaffold that attracts cells and localises and retains delivered biologics at ultra-low doses for safer and more efficient regenerative medicine applications. Market research with key opinion leaders affirmed the commercial and clinical potential of the technology. For example, Prof Ashraf Ayoub, Oral and Maxillofacial Surgery, Glasgow, recognised the USP of the nanoclay gels, stressing the '*huge need for an injectable and easy to apply delivery material for bone morphogenetic protein*'. Steve Charlesbois, Director of Orthobiologics, Cook Regentec, stated: '*This biomaterial has big potential in orthobiologics delivery*' and Ian Dunkley, Senior R&D Engineer at Medtronic, emphasised '*the need for a safe delivery carrier that stays where it's delivered' and endorsed the minimally invasive delivery technology as an approach that 'aligns with [their] strategy*'.

This demonstrable unmet clinical need has resulted in Renovos raising GBP870,000 from public (e.g. Innovate UK) and private sector funding to the end of the impact period. This included a GBP140,000 investment in February 2020 by charity Orthopaedic Research UK and healthcare accelerator HS [**5.7**]. Dr James Somauroo, HS Founding Partner, said: '*It quickly became apparent that Renovos has the potential to fundamentally change the way extremely powerful and sometimes harmful drugs are given around bone. During the interview phase we were impressed by the immense knowledge and expertise of the team and we're now excited to join the journey and to use our networks to help take them to the next level.*' [**5.7**].

Renevos' other commercial propositions include the supply of primary mesenchymal stem cells for research and the delivery of contract research to those carrying out R&D in biomaterials and orthopaedic compounds [**5.6**]. Renovos has generated initial sales of skeletal stem cells worth GBP24,500 via a licensing agreement with European distributor Caltag Medsystems [**5.6**]. This commercial activity enabled the company to create 3.5 FTE employment positions (two scientists, a development manager, Executive Chairman and an administrative role).

Increasing public understanding of stem cell biology and stimulating interest in STEM study and employment

A series of workshops and lab visits for teenagers, based on the Southampton group's published work and research interests in clay biomaterials and stem cells, took place between 2014 and 2019. Led by Dr Nick Evans, in partnership with educational charity The Smallpeice Trust, 142 students aged 15 to 16 completed workshops; 91.6% of males and 85.3% of females agreed with the statement: '*This course has increased your interest in engineering generally*', and 48.3% of males and 54.9% of females agreed with the statement: '*This course has persuaded you to follow a career in this field of engineering*.' Of those students who selected science or engineering degrees at university and participated in the Southampton course during the REF period, 84.8% (28/33) said the course had '*increased interest in the subject*' and 26.8% (9/34) said the course directly '*influenced (their) degree choice*' [**5.8**].

The research on stem cell differentiation to bone led to the conception and creation of a large exhibit to communicate stem cell potential and differentiation. The 'Stem Cell Mountain' was designed by Dawson and Dr Ben Ward, CEO at the Winchester Science Centre (WSC), in the University's first formal collaborative partnership with WSC in 2014. It has since been taken to around 30 festivals including Glastonbury, Cheltenham Science Festival and Countryfile Live. During an impact assessment across six events in 2015, the exhibit was seen by 21,100 people and facilitated in-depth engagement with 7,450 people on the subject of stem cells and regenerative medicine [**5.9**].

Due to its popularity, additional funding from Dawson's fellowship and WSC workshop funds were allocated to build a permanent replica, which continues to be resident at the Winchester Science Centre (WSC) . During an assessment period undertaken by WSC between 30 April 2015 and 29 November 2018, it reached 613,219 people (133,960 school children, year R-year 9, and 450,709 members of the public). The Stem Cell Mountain consistently receives positive user feedback. Representative examples include: 'The stem cell mountain – thank you for having this idea. It's such a clever way to explain the concept'; 'Such a simple way to represent a very complicated thing'; 'We need science like this in school. It's so much more interesting'; 'I was considering doing a PhD at one point – I didn't think I'd reconsider it here' [**5.9**].

As the first successful partnership between the University and WSC, the Stem Cell Mountain led to 11 more joint projects amounting to a value of GBP500,000 and a formal memorandum of understanding between the two organisations in a public engagement partnership inaugurated by the Vice-Chancellor in September 2017. Dr Ben Ward sums up its success: '*It has been instrumental in trail blazing an ongoing and fruitful collaborative relationship between our two organisations'* and *'The Stem Cell Mountain is now one of our most popular exhibits with our visitors, and we see it as a perfect example of how we blend education with fun at the Centre - engaging children and adults alike with science.'* [**5.10**]

5. Sources to corroborate the impact

5.1 Media evaluation report from the University of Southampton documenting the audience reach of this translational milestone in 2014, for example:

a. http://www.bbc.co.uk/news/uk-england-hampshire-27436039

b. https://news.sky.com/story/3d-printer-used-to-make-womans-hip-joint-10405257

5.2. A follow-up study demonstrating patient reported benefits of 3D printed stem-cell augmented hip in 11 patients. Goriainov V, McEwan JK, Oreffo RO, Dunlop DG. Application of 3D-printed patient-specific skeletal implants augmented with autologous skeletal stem cells. Regen Med. 2018 Apr;13(3):283-294. https://doi.org/10.2217/rme-2017-0127 Epub 1 May 2018.

5.3 Wessex Gauvain Society: V Goriainov, L King, ROC Oreffo, DG Dunlop. 3D-Printed Custom Cup-Cage For Treatment Of Massive Acetabular Defects, With And Without Pelvic Discontinuity: Early Results Of Our First 20 Consecutive Cases. 2020. PDF abstract supplied.

5.4 Corroborating statement from Brigitte de Vet-Veithen, Vice President of Materialise Medical.

5.5 A patent family based on the use of Laponite clay gels to deliver the biologic drug, BMP2.

https://worldwide.espacenet.com/patent/search?q=pn%3DUS10245350B2

a. United States Patent Number 10,245,350; Polymer-clay composite and organoclay; University of Southampton.

b. US Publication of United States Divisional Patent Application Number 16/274,047. Polymer-clay composite and organoclay. Case Ref 13483/US DIVa.

c. Patent Application 1407248.2 – International PCT filed: "Polymer-Clay composite and Organoclay"; Patent Application No. 1815369.2 – New United Kingdom "Spontaneous 3D micropatterning of proteins in self-assembling nanoclay gels for tissue regeneration"; University of Southampton owned.

5.6 Company website for Renovos Biologics Limited and licensing of technology to distributor.

a. https://renovos.co.uk/

b. https://www.caltagmedsystems.co.uk/renovos/

5.7 Orthopaedic Research UK announces first start-up investment: https://www.oruk.org/news/orthopaedic-research-uk-announces-first-startup-investment/

5.8 Corroborating statement from CEO of The Smallpeice Trust

5.9 Stem Cell Evaluation report provided by Winchester Science Centre

5.10 Corroborating statement from CEO of Winchester Science Centre