Institution: University of Sheffield

Unit of Assessment: 13C - Electrical and Electronic Engineering, Metallurgy and Materials: Materials Science and Engineering

Title of case study: The UK's first commercial source of cultured skin cells for difficult to manage burns patients

1. Summary of the impact

Research from the Department of Materials Science and Engineering led to healthcare impact through treatment of burns patients and those with chronic non-healing wounds using the culture and expansion of the patient's own skin cells. This impact was achieved by establishing a product, MySkin®, as the UK's first and only commercially available complete service for the culture and delivery of patient's skin cells. It is now used in 11 out of the UK's 12 major burns units for patients in danger of death from extensive burns. MySkin® benefits patients, clinicians and nurses and was Biomedical Product of the Year in 2008 (see Sky News video (2008) on www.Ilika.com).

2. Underpinning research

The majority of patients with burns injuries or ulcers can be handled using conventional skin grafting and wound treatments. However, for people that have over 60% burns, conventional treatments simply do not work. Cell therapy can be invaluable for patients with extensive full thickness burns (otherwise vulnerable to bacterial infection, sepsis and death) and many thousands of patients with chronic ulcers that do not heal with current best clinical practice.

The research undertaken by Professor Sheila MacNeil's team (University of Sheffield since 1976) developed a methodology with a sufficient performance and success rate to make it commercially viable and therefore clinically useful as a service to health practitioners.

The research arose from her longstanding collaboration with the Sheffield Burns Unit. This began in 1992 using the (then) best practice methodology of culturing human skin cells into small sheets for delivery to patients with extensive burns injuries. They undertook a 10-year clinical audit of this technique and concluded that it delivered poor performance in meeting clinical need. In particular these very delicate sheets of cells were difficult to handle and the success rate with them was poor. Also, it was very challenging to manage the timing of their production to the needs of the patients. All of the above explains why this cell therapy approach was not previously adopted for routine use in Burns Centres or Wound Care Centres in the UK.

Accordingly, from 1997 onwards MacNeil developed an improved, simpler and more robust methodology for delivering patient's skin cells from the laboratory to the patient [R1-6] through collaboration with Professor Robert Short (a surface science engineer in the Department of Materials Science & Engineering from 1995-2007). The product MySkin® was developed through a spinout company, Celltran Ltd, which ran from 2000 to 2008.

The underpinning technology was plasma polymerisation, which was used to make a surface that was attractive for the attachment of skin cells (keratinocytes) but not too adhesive so that cells placed in contact with the patient would readily leave the cell delivery carrier surface and transfer to the wound bed.

MacNeil's distinctive research contribution was that she led the team that started with a clinical problem - the need to provide a rapid barrier for patients who have lost extensive skin due to burns injuries. An analysis of the current technology was undertaken to provide cultured cell therapy to restore this barrier and a materials surface engineering solution was designed. The treatment method was refined through collaborations that involved the local hospitals with introduction to the clinic, and then developing MySkin® as the commercially sustainable product. Importantly, MacNeil provided the evidence base that supported the clinical adoption of this medical advance.

This work was supported by 14 grants running between 2003 and 2009 amounting to a total of £2,526,702 including EPSRC "Surfaces to enhance tissue culture of skin" October 1999 to September 2003. £110,922, R.M. France, S. MacNeil and G.J. Leggett and a Wellcome Catalyst Biomedical award to CellTran Ltd of £585,000 in September 2002.

3. References to the research

References that best indicate the quality of the research are indicated with asterisks (***):

R1*** R.M. France, R.D. Short, R.A. Dawson and S. MacNeil. Attachment of human keratinocytes to plasma co-polymers of acrylic acid/octa-1,7-diene and allyl amine/octa-1,7-diene. *Journal of Materials Chemistry* **8** (1998) 37-42. doi: 10.1039/A705098D

R2*** D.B. Haddow, D.A. Steele, R.D. Short, R.A. Dawson and S. MacNeil. Plasma polymerised surfaces for culture of human keratinocytes and transfer of cells to an in vitro wound bed model. *Journal of Biomedical Materials Research* **64A** (2003) 80-87. doi: 10.1002/jbm.a.10356

R3*** M. Moustafa, C. Simpson, M. Glover, R.A. Dawson, S. Tesfaye, F.M. Creagh, D. Haddow, R.D. Short, S. Heller and S. MacNeil. A new autologous keratinocyte dressing treatment for non-healing diabetic neuropathic foot ulcers. *Diabetic Medicine* **21(7)** (2004) 786-789. doi: 10.1111/j.1464-5491.2004.01166.x

R4 N. Zhu, R.M. Warner, C. Simpson, M. Glover, C.A. Hernon, T.M. Brotherson, D.R. Ralston, J. Kelly S. Fraser and S. MacNeil. Treatment of Burns and Chronic Wounds Using a New Cell Transfer Dressing for Delivery of Autologous Keratinocytes. *European Journal of Plastic Surgery* **28** (2005) 319 – 330. doi: 10.1007/s00238-005-0777-4

R5 M. Moustafa, A.J. Bullock, F.M. Creagh, S. Heller, W. Jeffcoate, F. Game, C. Amery, S. Tesfaye, Z. Ince, D.B. Haddow and S. MacNeil. Randomized, controlled, single-blind study on use of autologous keratinocytes on a transfer dressing to treat nonhealing diabetic ulcers. *Regenerative Medicine* **2(6)** (2007) 887-902. doi: 10.2217/17460751.2.6.887

R6 N.G. Walker, A.R. Mistry, L.E. Smith, P.C. Eves, G. Tsaknakis, S. Forster, S.M. Watt, S. MacNeil. A Chemically-defined Carrier for the Delivery of Human Mesenchymal Stem/Stromal Cells to Skin Wounds. *Tissue Engineering Part C: Methods* **18(2)** (2012) 143-155. doi: 10.1089/ten.tec.2011.0037

4. Details of the impact

The research led to the development of an evidence-based, commercially available, cell therapy. This therapy has delivered major healthcare impact for patients [S1-S4]. The continued commercial availability attests to the resilience of the product and the economic model developed for its sustainability. Essentially the product is designed for use only with 'difficult to treat' patients. Fortunately the number of patients with very severe burns in the UK is low but the impact for these patients is substantial. Few tissue-engineering companies achieve the translation of research into effective products. This was achieved by the initial spinout company, called Celltran Ltd, which ran from 2000 to 2008. Building on the clinical success of MySkin®, Celltran was acquired by York Pharma in 2008 and then Ilika in 2009 to further stimulate growth in the company. The latter company formed a subsidiary Altrika Ltd to focus on MySkin® and a related product Cryoskin.

Impacts on patients and practitioners:

The commercial availability of MySkin® from 2004 to the present time has benefited patients, clinicians (burns surgeons, diabetologists) and dressing nurses using this product to treat patients. Thanks to Prof MacNeil's proactive approach to disseminating her results at meetings of burns and wound healing professionals in the UK from 2004 to the present day, the clinical community has been made aware of the sound evidence base and the potential benefits of the technology, leading to the gradual adoption of the therapy by practitioners in these areas and use of the products on patients (MySkin® has been used to treat over 300 cases since 2008, with each patient requiring

up to 50 treatments by MySkin®). The major health impact of this research has been the improved outcomes of UK patients with extensive burns - increasing their chances of survival. The technology has offered burns surgeons in the UK the potentially life-saving option of a cell expansion and delivery service for treating those patients who are *in extremis* and in danger of death because of the extent of their burns injuries. This is the *only* commercial service that burns surgeons can access for treatment of patients if conventional therapies fail, and (as noted by the head of the Sheffield Burns Unit, below) patients with major burns represent a real clinical challenge. For these patients, getting swift barrier function is essential and difficult. The use of cultured cell therapy leads to improved health outcomes through greatly reduced risk of infection and death and shortened stays in hospital [S2]. The Operations Director of Altrika Ltd says "*Use of the cultured cell technology in burns units has been increasing since 2008 due to the growing evidence base that early intervention of these therapeutic approaches can be cost effective, coupled with efficiencies in cost of manufacture that make the approach more sustainable for a wider patient cohort. Altrika recently added the burns units in Birmingham and Manchester to its list of customers, bringing the total number of burns centres in England / the UK who have used this cell therapy to 11 out of 12, with 6 of these being regular repeat users*" [S1].

The Head of the Burns Unit Sheffield Hospitals says in referring to MySkin® - "*The transition of MySkin® from research to the clinic, provided through the company CellTran, provided a commercial service that I or other burns surgeons could access for the treatment of our patients. At its establishment, it was the first such commercially available skin service in the UK and to the best of my knowledge it's still the only commercially available skin cell service. Thus the company established a valuable clinical resource, which we use for those extensively burned patients who can't be easily managed with conventional skin grafting alone. It is only appropriate to use cultured cell therapy for patients with major burns, these patients represent a real clinical challenge and it is good to know that in the UK there is a useful resource based on expanding the patient's cells in the laboratory which clinicians can access*" [S2].

The other health impact has been on patients with chronic non-healing ulcers, which have failed to heal despite best clinical practice. Patients with access to cultured cell therapy have benefited from the availability of the service - cell therapy can stimulate wounds to heal and restore quality of life. For these patients [S4] MySkin® greatly improves their quality of life and reduces hospital (or home) treatment costs.

Economic impact:

The cell therapy was developed through a University of Sheffield spin-out company, Celltran Ltd, which was formed in 2000 for the sole purpose of developing and commercialising the underpinning research, including providing a strong clinical evidence base for the culture and delivery of patients' skin cells for clinical benefit. The first product was launched as MySkin® in 2004. The product is produced in a GMP facility in Sheffield and has been selling consistently since its launch, commercialised through a number of different companies:

- Celltran was formed in 2000 and commercialised the technology from launch in 2004 through to late 2008. The company created 16 jobs and raised £4 million in investment income from 2004 until 2008. This supported a team of 16 surface engineers, cell biologists and clinical staff (burns surgeons, wound care nurses and staff involved in the study of diabetic ulcers) and staff who set up and ran clean rooms and engaged in all aspects of the commercialisation of this technology.
- In October 2008 the IP and GMP facility were purchased by York Pharma for £70k plus royalties for 5 years; the greater of £100k (20k per year) or 10% of revenues generated.
- In September 2009, Ilika bought the GMP facility, setting up a wholly owned subsidiary Altrika, solely to commercialise this technology (http://www.ilika.com/history.aspx).

In December 2012, Altrika was bought by Adiposet Ltd, a medical logistics and service company and continues to commercialise both MySkin® and CryoSkin. Altrika currently employs 6 people.

5. Sources to corroborate the impact

S1. Operations Director of the University of Sheffield spin-out company CellTran Ltd which ran from 2000 to 2009. He then became Operations Director of the company Altrika Limited who currently produce MySkin® and a related product (Cryoskin) for the UK market. MacNeil worked closely with the Operations Director in the development (as can be seen from our joint publications) and commercialisation of the product MySkin® while MacNeil was a founder Director of Celltran until 2007. The Operations Director can confirm the impact of having a commercially available cell delivery service on the UK clinical community who purchased this service and on how, having established this Company, we were able to attract development awards from Research Organisations (BBSRC and the Wellcome Trust) and Venture Capitalists.

S2. Consultant Burns Surgeon and Head of the Burns Unit Sheffield Hospitals, who contributed to the initial development and evaluation on MySkin® in burns patients.

S3. Consultant Burns Surgeon Manchester Children's Hospital who uses MySkin® for the management of major burns and has been a regular purchaser of MySkin® for use in major burns for several years.

S4. NHS Consultant Diabetician, Sheffield Hospitals, who was involved in the first main clinical evaluation of MySkin® for diabetic ulcers. *(He was involved in the initial clinical evaluation of MySkin® in the management of patients with non-healing diabetic ulcers).*

(*The above clinicians will also be able confirm that this was the first and only source of cultured skin therapy available to help them treat patients in the UK. Indeed it remains the only commercially available service for culture of autologous skin cells for clinical use in the UK).*