

TRANSLATING TISSUE ENGINEERING TO THE CLINIC

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Tissue engineering of skin is almost 25 years old. Based on a 1975 methodology for the production of thin sheets of integrated keratinocytes (cultured epithelial autografts, CEA) cells have been expanded in the laboratory and used successfully in the treatment of patients with extensive full thickness burns since the early 80s. However, attempts at developing commercial tissue engineered products have achieved only modest success. Unfortunately this has impacted negatively on perceptions of what is possible in this field. Thus the field has gone from a basic pragmatic approach into over inflated commercial expectations. Despite this, cultured cells and tissue engineered skin have significant benefits to offer patients with extensive burns and patients with chronic non-healing ulcers.

The approach that we have been working on within the University of Sheffield since the early 90s is to take existing methodologies for culturing keratinocytes and delivering them to patients and for making reconstructed human skin and seek to develop approaches which are significant improvements on these technologies with a view to making them more patient and clinician friendly. Thus for cultured epithelial autografts, through the spin-out company CellTran Ltd, we have sought to improve on this early methodology for culturing cells and transferring them from the laboratory to the patient. Using a chemically defined plasma polymerised surface containing 20% carboxylic acid groups, cells can be delivered on this surface to patients following initial expansion in the laboratory using conventional methodologies (1). This approach has been tried for repeated applications of autologous keratinocytes for chronic non-healing diabetic foot ulcers with considerable success (2) and more recently has been launched (Myskin) for the treatment of patients with extensive burns injuries. Supplying the cells on an easy to handle polymer disc obviates the necessity of the surgeon or district nurse handling spray-on cells or fragile sheets of cultured cells. The application of Myskin to the wound bed has also been made compatible with other ongoing treatment regimes for burns therapy and chronic wounds.

With respect to reconstructed skin, beginning initially with skin based on sterilised de-epidermalised donor dermis, we have reconstructed skin with either epidermal keratinocytes and fibroblasts or oral mucosa keratinocytes and fibroblasts and have preliminary data with the use of both in reconstructive surgery. Based on this our current plans are to replace the human dermis with a synthetic biodegradable scaffold produced by electrospinning and our research on this shows that its

possible to culture keratinocytes, fibroblasts and endothelial cells together in electrospun 3D scaffolds under serum free conditions with a promising degree of cell organisation.



Fig. 1: This shows the appearance of a diabetic foot ulcer which had been non-healing for 3 years and then after 7 applications of Myskin. Myskin was delivered once per week to fit in with the patient's visit to a diabetic foot clinic.

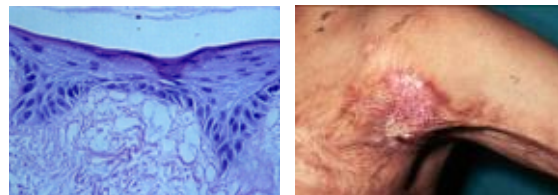


Fig 2: This shows the appearance of reconstructed human skin which was grafted into the axilla of a patient who had suffered skin contraction due to earlier burns injuries. As can be seen the reconstructed skin has survived and become vascularised but is beginning to contract.

REFERENCES: ¹France, R.M., Short, R.D., Dawson, R.A. and Mac Neil, S. (1998) Attachment of human keratinocytes to plasma co-polymers of acrylic acid/octa-1,7-diene and allyl amine/octa-1,7-diene. *J. Materials Chemistry* **8**, 37-42. ²Higham, MC, Dawson, R, Szabo, M, Short, R, Haddow, DB and MacNeil, S.(2003) "Development of a stable chemically defined surface for the culture of human keratinocytes under serum free conditions for clinical use". *Tissue Engineering* **9**, 919-930 ³Moustafa M, Simpson C, Glover M, Dawson RA, Tesfaye S, Creagh FM, Haddow D, Short R, Heller S and Mac Neil S. (2004) A new autologous keratinocyte dressing treatment for non-healing diabetic neuropathic foot ulcers. *Diabetic Medicine* **21**,786-789.