QUT seeks to heal wounds without scars

David Leavesley, Sean McElwain, Graeme George, Zee Upton

Tissue Repair and Regeneration Program, Science Research Centre, Queensland University of Technology, 2 George Street, Brisbane, Queensland, 4000, AUSTRALIA.

Correspondance: z.upton@qut.edu.au

Treatment of wounds represents a significant challenge at all levels of our society, in terms of cost (physical, emotional and financial) to patients, the economy and to the wider Australian and global communities. Despite this, relatively little research is directed at this hidden health problem. The Tissue Repair & Regeneration team at QUT is addressing this challenge using advanced biotechnological, biomaterials and bioengineering strategies. Our interdisciplinary team is focussed on delivering practical innovations in wound healing, with an emphasis on diabetic and venous ulcers, as well as burns. This 'snapshot' of our research briefly describes some of the research projects we are pursuing at QUT: interactions of growth factors with other components of the extracellular milieu in tissues; cellular mechanisms associated with wound healing and scar remediation; diagnostic and prognostic markers of healing; novel, relevant, *ex vivo* 3D skin equivalent models for pre-clinical evaluation of new wound therapeutics; and the design and production of "smart" bioactive wound dressings. The overall goal of our research is to generate new technologies and wound management interventions that keep patients healthy and obviate their need to depend upon the cost-intensive hospital-based health care sector.

- **Structural and functional investigation of growth factor- and vitronectin-binding receptor cooperation in modifying cellular function.**

We have previously reported that growth factors interact with the extracellular matrix glycoprotein, vitronectin. Further, complexes of growth factors with vitronectin (generically referred to as VitroGro®) result in enhanced cell proliferation and migration leading us to evaluate this technology for: serum-free cell and tissue culture; surface coating of implanted prostheses; and other repair and regeneration applications. Using microarray and proteomic approaches we are also probing the fundamental mechanistic elements behind why presentation of growth factors bound to ECM proteins, such as vitronectin, enhances cell proliferation and migration. In addition we are currently completing pre-clinical *in vivo* evaluations of these complexes as a topical therapy for deep partial thickness burns and for diabetic ulcers. We want to understand how skin cells respond to the complexes in the conditions of the *in vivo* diabetic wound environment: namely in the presence of wound exudates', high concentrations of insulin and glucose, and low oxygen.

Insert Fig 1 here.

Identifying the relationship between biochemical markers and wound healing in chronic venous leg ulcers treated with compression therapy.

In allied projects we are also investigating the relationship between biochemical markers in wound fluid and wound healing in chronic venous leg ulcers treated with compression therapy. Again, the application of advanced proteomic techniques are being applied to analyse biochemical markers in sequential wound fluid samples collected from patients during the course of compression therapy. The aim of this project is to identify fluid and/or tissue indicators associated with improved or delayed healing. The identification of biochemical changes indicative of healing at various time points will provide basic information about the complex and changing wound environment and contribute to the development of models to predict healing in individuals and facilitate the development of new clinical management approaches.

- **Elucidating mechanisms underlying the effective use of hyperbaric oxygen as a therapy for wound healing**

Related to the previous project, we are also characterising the dynamic changes in wound fluid and repairing tissue anatomy during, and following, hyperbaric oxygen (HBO) treatment of chronic ulcers and non-healing wounds. These data will provide a novel window into the biochemical and cellular changes associated with the anecdotal benefits of hyperbaric oxygen therapy.

Insert Fig 2 here.

- ***In vitro* evaluation of the potential of novel silicones for scar remediation.**

In addition to the pressing need to dissect the cellular aspects of wound healing, there is a parallel need to understand the process that underlies scarring. Silicone gel sheets are known to reduce the size and severity of scars that result from burns by an unknown mechanism. We believe that the decrease in scar tissue is due to the egress of specific silicone species from the sheet into the healing tissue. These silicones interact with fibroblasts present during granulation tissue remodelling and possibly modify the production of collagens. This project has identified novel characteristics of some silicones that penetrate the skin and is examining the effect of these novel silicone species on the synthesis and organisation of collagen by fibroblasts derived from normal, keloid and hypertrophic scars. In collaboration with chemists and biomaterials scientists we plan to exploit these silicones as an effective scar remediation therapy. This project is providing an opportunity to explore how nanoscale structures, such as these silicones, can impact on cellular processes.

- **Bioactive polymers for wound healing applications**

Another major aim of the QUT Tissue Repair and Regeneration team is to develop novel bioactive polymeric dressings for application in wound healing. One strategy is focused on releasing bioactive agents from provisional carriers (eg. biodegradable polymers) using cell-activated linkers such as protease sensitive cleavage sites. Our second strategy is the development of two distinct polymeric delivery systems in a multicomponent bandage. One component will release cell-stimulatory agents and/or adjuvants as the other component, a responsive hydrogel, is designed to passivate wound exudates which otherwise may reduce the activity of the wound healing agents.

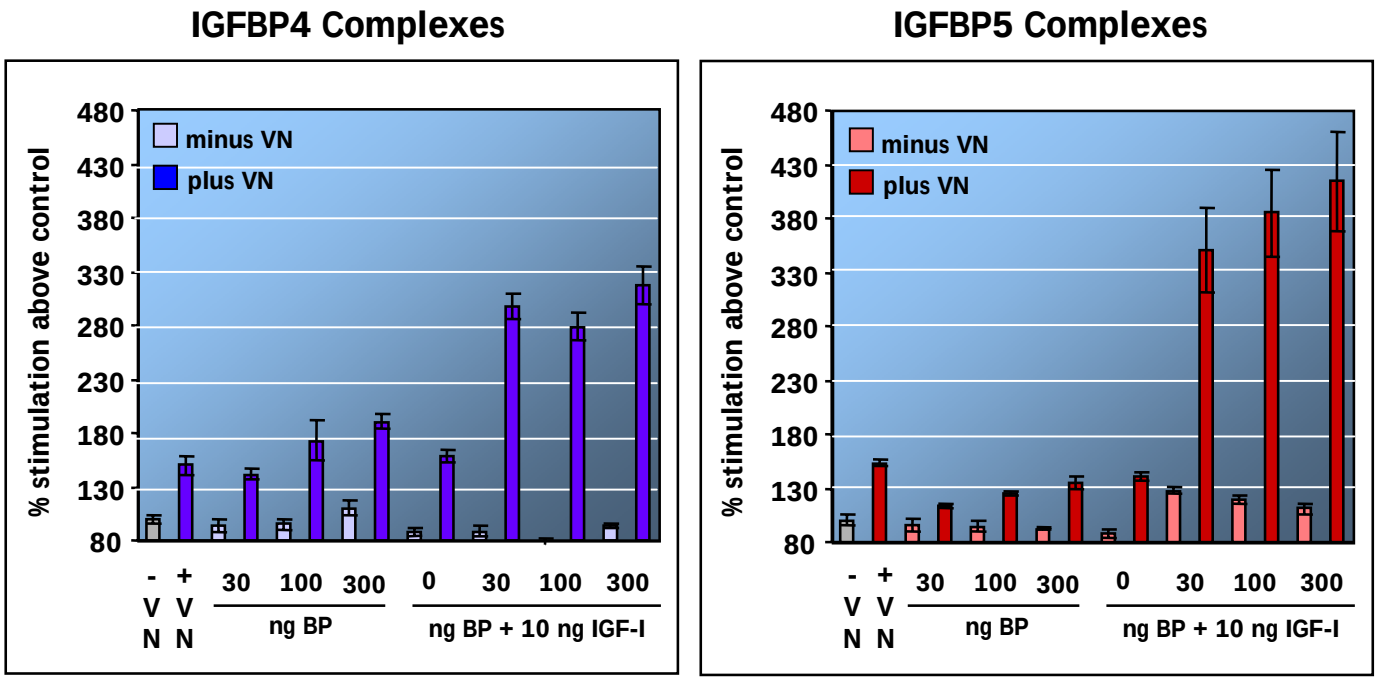

Fig 1. VitroGro® stimulates the migration of keratinocytes.

Migration of keratinocytes were assayed with, or without, vitronectin in serum-free basal media in Transwell™. Maximal migration is observed only when all three components of the complex are presented together to cells.

(Image courtesy of Caroline Hyde)

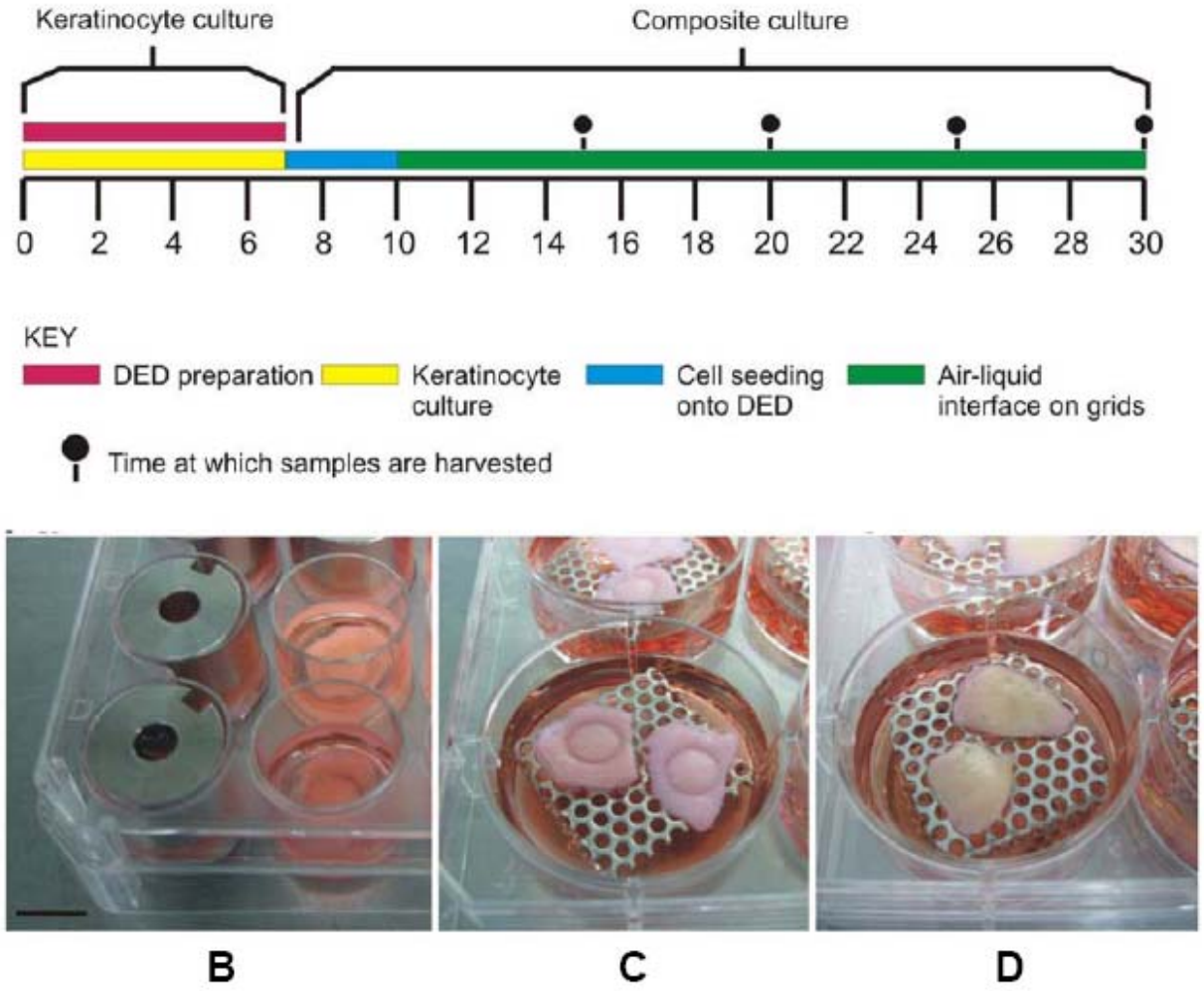

Fig 2. Human skin equivalent construct for *in vitro* skin repair and regeneration studies.

A. Timeline of the model construction. **B.** Steel rings are used to seed keratinocytes on top of the centre of the deepithelised dermis (DED) in a 24-well culture dish. Scale bar: 5 mm. **C.** Grids are used to bring the HSE to the air-liquid interface after the rings are removed. **D.** Model after 10 days culture at the air-liquid interface.

Method adapted from that previously reported by Huang *et al*., Wound Repair Regen 2004, **12**:276-287.

(Image courtesy of Gemma Topping)