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Special Collection: Closing the Gaps in Skin Wound Healing.

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Title:

Special Collection: Closing the Gaps in Skin Wound Healing

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Skin is the largest and most accessible organ in the body and any compromise in its integrity results in a healing cascade. Often, underlying pathologies hamper these cascades. A tissue-engineering approach has the potential to attenuate healing in these compromised wounds. Solutions for dermal wound healing has direct clinical impact in addressing other compromised wounds in other clinical targets where matrix deposition, fibrosis or angiogenesis needs to be modulated. From some of the earlier reports in the field, it was clear that a carefully selected extracellular matrix mimic is needed to house fibroblast cells. These cells can be provided *in vitro* or conditions in template can be engineered for permissible migration *in vivo*. This approach allows for formation of a dermis-like layer and an epidermal layer. However, large skin lesions due to traumatic injuries or burns and chronic wounds that are refractory to treatment remain a critical clinical challenge. In particular, chronic diabetic skin ulcers are an increasing concern; the World Health Organisation estimates that Type I and II diabetes affects 350 million people globally(1). Diabetic foot ulcers (DFUs) occur in 15% of these diabetic patients and, if they remain chronic, have the devastating consequence of lower-leg amputation. Along with the aforementioned wound pathologies, therapies to address healing of these diabetic foot ulcers have been a subject of research in the field to develop increasingly effective solutions to these recalcitrant wounds. Bioactive factors that can direct or accelerate tissue formation are being studied and are being incorporated in tissue rudiments.

In this special collection, we highlight some of the exciting new approaches to skin tissue engineering published in the last year in the journal. In addition, there is an increasing drive towards rapid tissue vascularization to heal compromised wounds, as

well as a need for more accurate *in vitro* models for testing. This special collection includes manuscripts that tackle the following key challenges:

1. Optimising scaffold design
2. Rapid vascularization of implanted tissue
3. Identifying key regulatory factors
4. More accurate *in vitro* models

A review by Delgado et al. explores various approaches to crosslinking the frequently employed extracellular matrix mimic, collagen, and makes a case to develop novel methods to minimise the foreign body reaction(2). In a second paper that explores scaffolds, Peng et al. freeze-dry mesenchymal stem cell supernatant to yield a membrane that is rich in cytokines, has low toxicity and significantly accelerates wound healing through enhanced epithelialization and neovascularisation(3).

The important effects of enhanced vascularisation are echoed by several other papers in this collection that focus on prevascularization of scaffolds to enhance the rapid uptake and integration of tissue. This is achieved by incorporation of endothelial cells within matrices (Alekseeva et al.(4), Helmedag et al.(5), and Sánchez-Muñoz et al.(6)) or by 3-D printing vasculature into skin grafts (Yanez et al.(7)). An interesting emerging theme from these manuscripts and others is the requirement for additional cell types (e.g., fibroblasts) to support the endothelialisation process.

Along with cell-loaded scaffolds, novel combinations of scaffolds and bioactive factors are still under investigation. For example, a bFGF/decellularised pig peritoneal membrane construct that has the potential for off-the-shelf use is presented(8), as well as the use of a novel stimulatory factor, Macrophage Stimulating Protein (MSP)(9).

Inspired by the effectiveness of adipose-derived stem cells in wound healing, Zhao et al. demonstrated the presence of MSP receptors on dermal fibroblasts and the potential for MSP to stimulate fibroblast proliferation, migration and matrix synthesis *in vitro* and *in vivo*(9).

In addition to these manuscripts that focus on developing products for skin repair, we have included three methodology manuscripts to reflect the increasing drive to develop more realistic *in vitro* models. The first, by Maione et al., uses patient-derived fibroblasts (including diabetic fibroblasts) and presents a suite of *in vitro* and *in vivo* screening models of chronic wound healing, including: the endothelial sprouting assay, a 3-D human skin equivalent model, and a re-epithelialization model, which can be used to interrogate interventions(10). Mohiti-Asli et al., present a co-culture system to explore the effects of antibiotic/antimicrobial interventions *in vitro* on skin wound healing by incorporating *Staphylococcus aureus* into 3-D skin tissue healing mimics(11). Finally, the acceleration of extracellular matrix production and, specifically, of the dermal-epidermal junction formation by exploiting macromolecular crowding, as shown by Benny et al., motivates the application of macromolecular crowding in *in vitro* models(12).

Recent advances in the skin tissue-engineering field have seen significant efforts to enhance the efficacy of treatments through novel agent(s) selection or combinations. The field has now reached a point where a standardisation of models is being achieved; however, it is becoming increasingly important to test these exciting potential interventions with realistic models that match clinical scenarios including diabetes and infection. As various tissue-engineering products are tested in more

clinically relevant scenarios, we expect that the optimum products and design principles for these more select applications should become clearer. The manuscripts presented in this special collection have advanced the field towards answering this goal in the past year and we are hopeful that these, and future, approaches will see enhanced clinical relevance.

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