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Review

Skin regeneration: The complexities of translation into clinical practise☆

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ABSTRACT

The integration of engineering into biological science has resulted in the capacity to provide tissue engineered solutions for tissue damage. Skin regeneration remains the goal of skin repair to reduce the long term consequences of scarring to the individual. A scar is abnormal in its architecture, chemistry and cell phenotype, tissue engineering of scaffolds and cells opens up the potential of tissue regeneration into the future. Tissue engineering solutions have been applied to skin many decades despite technical success the clinical application has been modest.

To realise the potential of the developing technologies needs alignment of not only the science and engineering but also the commercial upscaling of production in a safe and regulated framework for clinical use. In addition the education and training for the introduction of new technology within the health system is essential, bringing together the technology and systems for utilisation to optimise the patient outcome.

This article is part of a Directed Issue entitled: Regenerative Medicine: The challenge of translation.

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1. Introduction

Skin is a complex organ with cells derived from all embryological layers with an extracellular matrix and skin adnexal structures specific to the varying body sites (Hoath et al., 2003). The skin is known to change in response to ageing and a wide range of pathologies (Sugihara et al., 1991). Skin trauma is commonplace and regeneration of the skin without functional or aesthetic deficit, rather than scar, remains the ultimate goal of skin repair. In considering the complexities of translating techniques of tissue regeneration into clinical practice it is important to learn from the drivers of the development of the technology and the history to date (Bannasch et al., 2003). Also essential to the understanding is the natural history of the pathophysiology of the skin conditions needing treatment and the implication of using regenerative technology on the outcome and life of the patient.

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The clinical problem is the limited capacity of skin to regenerate after injury, although it is continually replaced under normal conditions with the general morphology being retained over the years, to heal by regeneration remains elusive in all but minor trauma (Fuchs, 2007). When the capacity to repair is overwhelmed the resulting scar is often debilitating, restricting normal function or impacting negatively on the psyche of the individual (Bayat et al., 2003; Rumsey et al., 2003)

To heal a skin defect it is essential to have a source of cells capable of proliferating into the range of specialist skin cells together with an extracellular matrix (ECM) framework for the cells to attach and develop into skin tissue. However to facilitate regeneration such that we restore the skin to the pre injured state we have to understand the drivers of tissue organisation. The 3D information of the wound shape and character of the given body site and a mechanism to guide self-organisation into the tissue construct specific to the body site and characteristics of the individual need to be considered (Metcalfe and Ferguson, 2007). The complexity extends beyond the simple reconstitution of the epidermal and dermal layers onto the interplay of the signalling and cues for expression of cell phenotype (Nath and Hyun, 2004).

There are many questions we need to answer as we progress towards understanding the complex relationships in healing to guide the tissue regenerated solution along the path to a normal skin not scar (Gibran et al., 2007). The complexity of wound healing has been written about since ancient times with a range of interventions advocated (Reed and Clark, 1985). Despite all efforts we are still in a situation today where we routinely fail to facilitate a regenerative solution and the result of healing is a significant scar (Wood, 2012a,b).

With the development of laboratory based cell and tissue expansion techniques came the opportunity to explore the concept of tissue engineered skin replacements (MacNeil, 2007). Initially driven by the need to achieve skin healing in situations where such extensive areas of skin injury such that traditional techniques were inadequate such as in massive burn injuries (Singer and Clark, 1999). As the techniques were adapted for clinical use the focus evolved to include consideration of improvement in functional and aesthetic outcomes (Mustoe et al., 2002).

For a tissue engineering solution to be successful it is clear that an in-depth working knowledge of the biology of the tissue is essential (Babu and Wells, 2001). Skin has been considered simplistically as a layered structure such that epidermis provides the waterproof external surface with the underlying dermal structure giving the capacity to withstand wear and tear. This is reflected in the early work in the area of dermal scaffolds and epithelial culture (Klama-Baryła et al., 2008). Both epidermal replacement using cultured epidermal autograft (CEA) (Atiyeh and Costagliola, 2007) and dermal repair using tissue guided regeneration by a dermal scaffold, Integra™ were both successfully used clinically (Burke et al., 1981) since the early 1980s.

However, there are a number of cell types within the skin, each with specific and often interrelated functions (Ulrich et al., 2007). The potential solutions to skin replacement have developed along a number of pathways aiming to provide a range of solutions to the clinical problem. From cells in suspension to composite structures of cells and ECM and more recently 3D printing of multiple cell types, the range of solutions have both common and specific barriers to implementation (Horch et al., 2005). When using in the clinical setting it is vital to consider the specific pathophysiology, what can be salvaged and what elements of skin are needed to drive to a regenerative repair (Black et al., 2005). Further, there are issues relating to the technology include the source of materials and cells for clinical use, the environment of manufacture, the regulations around the systems and environment (Johnson et al., 2007).

The skin defect cannot be considered in isolation as we move into the clinical setting. The responses of an individual to a given injury or pathology are variable and in treating the patient it is essential to consider the regenerative capacity on multiple levels, the pre-injury condition of the patient, the systemic response to the injury, the wound and the cells within the wound. Understanding the clinical indications and patient preparation is key to success in choosing the technology to optimise the outcome (Munster and Smith-Meek, 1994). It is clear that lack of understanding of either the patient needs or the technology will create a barrier to clinical implementation associated with suboptimal results (Hamburg and Collins, 2010).

The clinical implementation of any technology in itself has layers of complexity related to the patient safety and efficacy and related to system within which the treatment is delivered. The regulation of the regenerative technologies has evolved rapidly building on previous strategies and often requiring new approaches to facilitate the timely use whilst maintaining the highest standard possible (Rosenblatt, 2012).

We live in a time of exponential growth in the science and technology discoveries many of which could and do change lives. However, the cost of delivering health is also climbing at an unprecedented rate. As scientists and clinicians we need to be aware to the cost implications of potential solutions to ensure that clinical implementation is realistic (Chandra and Skinner, 2001).

Three decades since the clinical introduction of tissue regenerative technologies for skin repair in the area of burn wound healing, it is timely to review the progress to date. It is also clear from the experiences of the last three decades that many of the proposed tissue regenerative skin solutions are disruptive technologies (Martin, 1997). It is essential that the regenerative therapies should not only be designed for a specific clinical problem, be reproducible and reliable, but also be linked to an education and training programme such that it realises its full clinical potential (Haynes, 1998).

The review will explore the barriers to clinical implementation related to:

- Skin regenerative technology.
- Clinical patient pathway.
- Systems involved in health delivery.

The goal is successful delivery of tissue regenerative strategies into clinical use in the future.

2. Skin regenerative technology

The essential factors to achieve skin replacement include a source of cell's capable of differentiating into the tissue along with an ECM capable of supporting the cells, the signalling systems for tissue formation (Martinez-Hernandez, 1988). The ECM scaffold is integral to tissue integrity, we know that the physical shape and chemical composition of the environment of a cells influence their phenotype (Parkinson et al., 2009). The skin has multiple functions related to the multiple cell types, to this time a complete skin replication for clinical use has not been achieved. Despite intense efforts the tissue engineered replacement of skin adnexal structures are not yet in clinical use (Spector and Glat, 2007).

The ideal needs for tissue regeneration skin replacement solutions continue to be debated (Boyce et al., 2001). A key to the clinical implementation is the understanding of the technology with a clear knowledge of the clinical indication when designing the solution which emphasises the need to work in close collaboration with teams of scientists and clinicians. Although the ultimate goal remains the replacement of the skin construct, specific to body site of the individual, tailored to treat the pathological, all the available