A synthetic skin scaffold to treat full-thickness wounds

Dr Julian Dye discusses the development of an artificial skin product that shows rapid blood vessel formation.

An independent UK-based charity has spent several years developing a synthetic 'off-the-shelf' skin scaffold which could prove effective at wound healing. The charity, known as RAFT (the Restoration of Appearance and Function Trust), is unique among many medical charities in the sense that it raises money for its own research institute and team of researchers.

Regeneration of full-thickness skin

The basic concept of Smart Matrix™ is to encourage rapid in-growth of blood vessels and has been designed to be used in the treatment of a variety of full-thickness skin wounds. These include combat injuries, burns, and chronic wounds, ranging from diabetic ulcers to pressure sores. Working in the dermal layer of skin, RAFT also claims that Smart Matrix would reduce scarring and the need for further surgery.

'When a burn or chronic wound severely damages skin, the body can never regenerate full-thickness skin,' says Dr Julian Dye, Smart Matrix project leader.

Skin graft limitations

Traditionally, surgical intervention involved grafting skin from other parts of the body to treat the burn or wound. However, in the case of burns there might not be enough healthy skin left to provide grafting material due to the large size of the burn. This can be a limiting factor in some cases.

'For some patients, conventional grafts risk simply creating a new wound site elsewhere on the body, which cannot heal completely,' explains Dr Dye. 'This is most problematic in elderly patients with pressure sores and people with diabetic or other chronic ulcers.'

A new artificial skin product

Work on the Smart Matrix has been ongoing at RAFT's laboratory for nearly eight years.

'I joined RAFT in 2001 as a post-doctoral research scientist and was appointed Group Leader in 2004,' says Dr Dye, who has a background in endothelial biology — biology of the skin cells that form blood vessels.

'The initial motivation to pursue the idea of a "Smart Matrix" was hearing from plastic surgeons about the clinical limitations and failures of existing artificial skin products.

'However, witnessing the reality of what patients needing surgical skin reconstruction undergo, and talking with patients who had survived and endured prolonged suffering from wound infections, made me appreciate the urgency of this need and it continues to spur us forward.'

In drawing up criteria for what they had in mind, RAFT came up with the following list:

- A synthetic material that reliably 'integrates' with the body
- Rapid growth of blood capillaries into the material
- Possibility for rapid wound closure
- Ability to minimise scar formation
- A product that is easy to store and available to surgeons off-the-shelf.

'We looked at existing artificial skin products, the use of donor skin and tissue engineering of new skin; although each has its own advantages, there are disadvantages as well,' says Dr Dye.

One form of biomaterial used for treating large wound areas is donor skin, harvested post-mortem and processed for safety and preservation. It does provide a biocompatible wound cover, but will be rejected in two-to-three weeks. In itself, donor skin is too dense to provide an effective structure for capillary growth and integration. Also, despite thorough processing procedures and screening measures, there are concerns about the possibility of transmitting diseases.

Epidermal cells (keratinocytes) can be cultured from a small skin biopsy and expanded into sheets of cells suitable for autografting. However, this method entails a delay of 3–6 weeks before these cells will be ready for grafting.

'The hypothesis that drove the development of the synthetic skin scaffold was the idea that a biomaterial, which supported the rapid growth of blood capillaries [angiogenesis], would show an improved rate of integration and cellularisation compared with available scaffolds,' says Dr Dye.

Fibrin as a biomaterial

In screening a variety of possible ways to stimulate capillary formation, RAFT identified fibrin as a potent extracellular matrix material when compared with collagen. Understanding the difference in cellular responses to fibrin and collagen was important in helping to develop a more effective biomaterial.

'We went on to devise a porous composite material based on fibrin and developed a manufacturing process to

make a dermal scaffold we called "Smart Matrix"', says Dr Dye.

His team found that this biomaterial promotes rapid ingress of capillary-forming cells (endothelial cells) — a critical first step in forming new capillaries.

Improving wound healing

At this stage, the big question was whether the material would improve wound healing.

'Our proof-of-concept in vivo evaluations of prototype scaffolds showed that the material vascularised significantly faster, with new blood vessels forming up to 10 times the depth of that seen in clinically used collagen-based material,' says Dr Dye. 'Also, the qualitative histological results indicate improved formation of a neodermis.

'During the last two years we have gained statistical evidence for accelerated and potentially improved wound healing with the skin scaffold compared with the commercial standard. Importantly, we have seen that blood vessel formation does, indeed, occur very rapidly and extensively within the scaffold.

'We have discovered how to further accelerate the formation of new blood capillaries, and the overall rate of cell ingrowth, by optimising the physical structure and porosity of the scaffold. This has enabled the material to support a single-stage integration with a split thickness skin graft, regenerating the full-thickness of skin within one week.

'This is important because if it can be achieved clinically this will reduce the number of surgical operations that patients need to undergo and may reduce the incidence of infection.'

Finding a clinical manufacturer

At this point, the scaffold is ready to be turned over to a clinical manufacturer to be produced under strict regulatory controls. Patient trials will follow.

Dr Dye has had the initial meetings with a UK-based manufacturer and RAFT has begun detailed planning on how it will transfer over workbench technology to the company.

'This approach has taken a long time to establish, but we hope that patients will benefit in the end,' he says. 'The scaffold must be made under the strict regulatory framework for medical products (GMP) which RAFT does not have. We are a research laboratory, not a manufacturing plant. Every aspect of the manufacturing process must be scrutinised — it's very stringent and very expensive to do.'

However, because the Sheffield-based facility is licensed to manufacture items in the strictest of conditions, the scaffold produced there can be supplied for patient trials anywhere. This will greatly simplify the whole process and hopefully get the scaffold to patients quicker.

'In pre-clinical trials with experimental wounds, the scaffold has integrated into the wounds exactly as we were hoping it would,' says Dr Dye. 'This provided us with more evidence of the reliability of Smart Matrix in restoring a full-thickness of skin in a single step.'

For more details of the findings of this study visit www.raft.ac.uk

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A processing step in manufacturing the Smart Matrix biomaterial — translation of the process into a clean room environment is the next stage in bringing the product into the clinic.