CLINICA 1179 October 28 2005

Tissue engineering – a new technology that needs a new business model

Tissue engineering is based on complex and intrinsically risky concepts, and it is difficult to define exactly the product that is being sold. It is essential to find new business models for this field to speed its realisation as a commercially viable sector, says Professor David Williams, director of the UK Centre for Tissue Engineering at the University of Liverpool

I am writing this article just as one of the leading conferences on tissue engineering is about to start. The venue is Shanghai. Not so long ago, it would have been surprising to see such a major event in the realm of advanced medical technologies taking place in China, but now we find that there is massive interest and investment in this part of the world in the new therapies of regenerative medicine.

In a short lecture tour prior to the conference, I encountered several audiences, each of several hundreds of informed students and senior scientists, thoroughly engrossed in these technologies. One has to wonder why there is so much interest when the recent history of this area shows that, so far, we have, collectively, failed to realise the potential of tissue engineering, either in terms of routine clinical success or profitable commercialisation.

Everyone working in the healthcare industrial sector is well aware of the high-profile failures of the original tissue engineering companies and of the difficulties others are facing in obtaining any reasonable return on their investments.

But why is this, and how can business models be arranged to provide sounder financial bases for the products and processes of tissue engineering?

Let us start at the beginning. What is tissue engineering and why should it provide so many problems?

Tissue engineering is, along with cell therapy and gene therapy, one of the processes of regenerative medicine, where the objective is to persuade the human body to *regenerate* diseased or damaged tissues and organs, through mechanisms of cell signalling. Crucially, this is different from medical device technologies, which aim to *replace* damaged tissues or organs, typically through the use of implantable replacement prostheses.

Adult bodies have largely lost the ability to regenerate tissues and organs – skin and bone can regenerate themselves as part of a repair process to some extent, and a few other parts of the body have limited regenerative capacity. But in general, evolution relieved us of that mechanism, so that injured tissues are usually repaired by non-functional scar tissue. In tissue engineering, we actively aim to switch back on those mechanisms of the generation of new functional tissue, mechanisms which we had as a growing embryo, foetus or infant, but which we then lost.

Significantly different to devices

My conceptual definition of tissue engineering is the persuasion of the body to heal itself, through the delivery to the appropriate site of cells of molecular signals and/or supporting structures. Two things strike one immediately about the difference between tissue engineering and medical device technology: the first is that tissue engineering is a far more complex and intrinsically risky concept, since it involves the active encouragement of cells to do certain things that are no longer normal for them; and secondly, tissue engineering is centred far more on a process than on a product. With this in mind, consider the logistics of the commercialisation of medical devices and assess how these can be transferred to tissue engineering.

If tissue engineering is all about persuading the body to heal itself, where is the product, how is the process regulated?

Ignoring for a moment some of the complexities of drug-device combinations and other products that exist at the boundaries of classifications, the procedures for manufacture, intellectual property protection, quality control, regulation and reimbursement for the vast majority of medical devices are relatively straightforward in most jurisdictions.

An implantable medical device is a manufactured article that can be marketed and sold to recognisable clients or customers. It can be tested, qualified by well-rehearsed regulatory rules, standards and guidelines, and sold through traditional routes, with reasonably fair reimbursement mechanisms. In short, a medical device is a product and it is controlled by the practices of normal commerce and the professional marketplace.

If tissue engineering is all about persuading the body to heal itself, where is the product, how is the process regulated, and how do we charge for this persuasion process in the commercial world? These are the questions at the heart of the tissue engineering debate.

Autologous tissue engineering

To start to formulate the answers to these questions, and to get a little deeper insight into the technical issues involved, let us consider the two main, currently popular, paradigms of tissue engineering processes. The first is autologous tissue engineering, in which the patient's own cells are used for tissue regeneration.

This concept has the advantage of completely avoiding adverse immune responses to any regenerated tissues; but the logistics and costs soon look forbidding. We have two primary sources of autologous cells. These can be either: fully differentiated cells from the tissue in question (eg chondrocytes for cartilage and osteoblasts for bone); or stem cells, isolated from bone marrow, or perhaps fat (from liposuction) or even blood – either peripheral blood for adults

in urgent need of therapy, or from stored cord blood in the case of children with far-sighted parents who are able and willing to pay for storage of such blood for the required decades.

These cells, wherever derived, have to be manipulated – typically involving sophisticated sorting techniques, expansion and/or differentiation. This has to be done patient-by-patient in secure sterile conditions. Then the cells have to be given the correct signalling, usually in a dedicated bioreactor, involving the application of molecular signals, for example from growth factors, cytokines or via gene transfection, and usually assisted by mechanical signals, transmitted by shear stresses in the fluid phase of the bioreactor, the cells usually being seeded into a substrate scaffold or matrix for this purpose.

This process has to be controlled and monitored. It may take several weeks for those chosen cells to express sufficient extracellular matrix, ie the basis of the regenerated tissue, to be used clinically through the reimplantation of this new tissue engineering "construct", back into the patient from whom the cells were initially derived.

The costs of this dedicated, customised, process may be significant and the risks are high. There are risks of contamination and infectivity, of poor quality tissue that may not be functional, of adverse responses to degrading scaffold materials and of logistics errors. And finally, which is the product and how can it be sold in order to recover those costs and make a profit?

Is the scaffold the product, or the growth factor? The bioreactor, or the construct? None of these make commercial sense. A few grams of a scaffold made of a commodity polymer or ceramic can hardly be sold for thousands of euros, and can we really ask a patient to buy back a piece of their own tissue in the form of a construct?

Which reimbursement scheme is going to pay for a more expensive form of treatment?

Even more importantly, if the condition for which we are using this process is treatable by other, albeit less successful but much cheaper therapies, which reimbursement scheme is going to pay for this particularly expensive form of treatment?

The now classic example of this is the treatment for the diabetic foot ulcer, where it is now appearing possible for autologous tissue engineering to provide an effective treatment in some patients, but possibly at a very significant financial cost. If success is not guaranteed, and if the alternative treatment is the regular but inexpensive palliative cleansing and replacement dressings, we can see that reimbursement becomes a significant factor.

Allogeneic tissue engineering

Now consider the alternative, which is indeed what most commercial tissue engineering companies did with the first generation of tissue engineering products, especially those for skin regeneration. This involves allogeneic cells, derived from a human donor and expanded into cell lines, which provide the basis for an off-the-shelf product.

The manufacturing phase here is quite straightforward, involving procedures of cell sourcing and cell culture, and can be done with a variety of differentiated cells such as fibroblasts and keratinocytes. These cells can be seeded onto a suitable scaffold or matrix, typically a synthetic biodegradable polymer or a natural biopolymer such as collagen or a hyaluronic acid derivative. This product can then be frozen and stored, waiting for use in a patient.

Once applied to an appropriate tissue site, for example the surface of a burns wound, this cell and scaffold combination can initiate the regeneration of new tissue. This explanation is, of course, much simplified. There is usually a need to assist these cells with some signalling processes, often supplied during the pre-implantation phase by the use of murine cells that are able to secrete cytokines that stimulate the human cells.

Since this allogeneic route offers off-the-shelf products rather than customised and individualised pieces of tissues, it automatically sounds more commercially attractive. However, that has not proven to be the case so far. Neither the science nor the manufacturing technology is trivial, nor has it been inexpensive.

The demonstration of clinical effectiveness and safety have been very difficult, and reimbursement and regulatory policies have been chasing each other around in circles – clinical effectiveness is required before reimbursement, but the cost implications of clinical trials have been financially overwhelming without reimbursement.

Tissue engineering will not survive commercially if it is based on selling a product

Superimposed on this has been the inability of regulatory bodies to decide, with one voice, how to deal with these new products, the FDA, the European Commission, the Australian TGA, the Japanese PAL, the Chinese CFDA and others all, so far, either taking their own position, or possibly no position at all on this matter. There are commercial products in this allogeneic paradigm, but it is still process-driven, and both regulation and business models have had to recognise this.

What next?

So where do we go from here? Tissue engineering will not survive commercially if it is based on selling a product, be that a scaffold, a cytokine or growth factor. Instead, it will have to be based on the provision of a complete service.

That service will involve the whole process from cell sourcing to final treatment of the patient, but it is unlikely that this will be efficient if it deals with only one kind of tissue or one kind of clinical condition. However, although the precise conditions under which each cell type produces tissue are different, the principles are very similar, and process control will follow a common pattern.

In other words, it should be possible for one service facility to cover a wide range of conditions, meeting the requirements for economy-of-scale.

I suggest that this will be best done on a regional basis and be attached to major regional clinical centres, the essential skills of such a centre being those of cell manipulation, under GMP type control, linked to normal specialist-based clinical units (orthopaedics, cardiovascular etc). Both the facility and each type of procedure would be subject to regulatory control and surveillance.

It is not impossible for the types of companies currently engaged in tissue engineering to be the owners and managers of these regional tissue engineering service facilities – indeed this could be a preferable solution since it is they, rather than hospitals, that have the skills to obtain regulatory approval and operate commercially-sound businesses.

In spite of the limited clinical and commercial success so far, I do believe that tissue engineering has a good future, but only if the clinical outcomes prove good enough and returns on investment can be realised. I suggest that the business models involving such regional centres provides a rational way forward.