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To celebrate the 20th anniversary of the journal, we have invited several leaders in the field of Tissue Engineering to submit their personal views on past, present and future directions of our discipline. These will appear throughout the anniversary year to celebrate our mutual accomplishments and to point the way toward a bright future for the field.

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The Editors, *Tissue Engineering Parts A, B and C*

The Biomaterials Conundrum in Tissue Engineering

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The development of biomaterials for use in tissue engineering processes has not so far followed a scientifically valid pathway; there have been no properly constituted specifications for these biomaterials, whose choice has often been dictated by the perceived need to comply with prior FDA approval for use of the materials in nontissue engineering applications. This short essay discusses the difficulties that have resulted in this approach and provides both conceptual and practical solutions for the future, based on sound principles of biocompatibility and the need to use tissue engineering templates that replicate the niche of the target cells.

Introduction: Why a Conundrum?

According to my own definition, tissue engineering is the creation of new tissues for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals.[1] This does not state, nor directly imply, that tissue engineering has to involve biomaterials. However, the delivery of those molecular and mechanical signals does not take place in a vacuum and there will usually have to be a vehicle that controls, with spatiotemporal accuracy, the relevant processes. For want of a better word, such vehicles have usually been described as scaffolds. I do not like the term scaffold as it conveys an old fashioned meaning of an inert external structure that is temporarily used to assist in the construction or repair of inanimate objects such as buildings, taking no part in the characteristics of the finished product. I prefer the term 'template' and I shall, in this article, describe why the concept behind this term, and the avoidance of the old-fashioned concepts of scaffold biomaterials, is so crucial in the next phase of tissue engineering development. That is why I refer to the current situation as a conundrum.

Concepts and Realities in Biomaterials

We have to start this discussion by reflecting on the nature of biomaterials themselves; this was the subject of a recent essay based on an analysis of trends in the development of materials for a variety of healthcare applications.[2] Historically, those healthcare applications involving biomaterials were initially the long-term implantable devices, such as used in orthopedic and dental reconstruction and the replacement or bypass of heart valves or blood vessels. Although many materials were evaluated and used clinically and lists of requirements of such materials were regularly

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published, experience gradually showed that success was most readily achieved with a combination of optimal mechanical properties and maximal chemical and biological inertness. The majority of devices within these categories today utilize a very small range of materials, such as titanium alloys, cobalt-chromium alloys, alumina, carbon, polyethylene, expanded polytetrafluoroethylene, and polyester textiles. That is the reality, inertness wins. Although we do use some materials for their special properties, such as shape memory alloys and thermoplastic elastomers, when we deviate from inertness, we have usually encountered problems. A detailed analysis of the biocompatibility of these materials within the context of these applications shows that, at maximal inertness, the host response is controlled by biomechanical factors and the release of particulate products, for example, wear debris from joint prostheses.[1]

We do see a hint that materials by themselves do not produce optimal results in all implantation situations, as vascular grafts need help from endothelial cells to generate superior neointima,[3] intravascular stents require help from antiproliferative drugs to control in-stent restenosis,[4] spinal fusion devices may give better outcomes when assisted by locally released bone morphogenetic proteins,[5] and thrombosis of heart valves is deterred by systemic anticoagulation.[6] Although these references make clear that the solutions have not been perfect, we see that the fundamental requirements of the biomaterials remain the same, and the achievement of the optimal and appropriate host response is influenced by biological and pharmaceutical factors, entirely consistent with the basic tenets of biocompatibility.[7]

Taking this argument a little further, biomaterials are no longer solely used in implantable devices, where mechanical and physical functionality dominate the requirements. Instead, we see biomaterials being used in drug, gene, and vaccine delivery systems, imaging and diagnostic systems and, of course, regenerative medicine applications, where quite different requirements apply.

Tissue Engineering Templates

This brings us to the crucial part of this conundrum. If the biocompatibility of implantable biomaterials is predicated on inertness, which implies a lack of any biological activity, how can such a fundamental tenet be translated into biomaterial applications for tissue engineering applications, where the materials, by definition, have to take part in the processes of cell stimulation? Clearly, a different concept is required.

It is of no surprise that the majority of the first group of tissue engineering products to be used clinically involved biodegradable polymeric materials that had previously formed parts of existing medical products such as surgical sutures; prior FDA approval for other devices became the first and most important specification for what were then called tissue engineering scaffolds. However, a surgical suture was not designed to take part, biologically, in wound healing; it was required to hold tissues together mechanically and then degrade and resorb with minimal host response. Nothing could be further from the main requirement of a tissue engineering biomaterial, which should be to actively take part in the process of tissue regeneration.

Let us consider this from a slightly different perspective. We routinely see in this journal microphotographs of polymeric or ceramic tissue engineering scaffolds that have been produced by techniques such as those of solid free form fabrication. The question arises as to whether those microscale porous structures, which we intend to facilitate the delivery of a systematic combination of molecular and mechanical signals to target cells, actually replicate the natural environment of those target cells? In other words, do these structures replicate the niche of the target cells? Moreover, the niche of the target cells, especially but not exclusively stem cells, changes with time during the process of extracellular matrix expression. If the biomaterial was undergoing degradation and resorption, would its degradation profile be consistent with the profile of cell niche maturation? The answer to these questions is almost certainly no.

It may well be that some tissue engineering processes that involve classical degradable polymers such as poly(glycolic acid) and polycaprolactone do allow the generation of some functional tissue, but I suggest that this happens in spite of rather than because of the choice of material. More specifically, the tissue engineering field has progressed in the absence of any clearly delineated specifications for tissue engineering biomaterials or tissue engineering templates. I suggest that we now define these specifications; some may be considered as mandatory in the sense that they apply to all situations, while others are specific to individual cases. The following lists are offered for discussions

Mandatory specifications for tissue engineering templates

- The material should be capable of recapitulating the architecture of the niche of the target cells.
- Since the cell niche is changeable over time, the material should be capable of adapting to the constantly changing microenvironment.
- The material should have elastic properties, particularly stiffness, which favor mechanical signaling to the target cells, to optimize differentiation, proliferation, and gene expression.
- The material should have optimal surface or interfacial energy characteristics to facilitate cell adhesion and function.
- The material should be capable of orchestrating molecular signaling to the target cells, either by directing endogenous molecules or delivering exogenous molecules.
- The material should be of a physical form that provides the appropriate shape and size to the regenerated tissue.
- The material should be capable of forming into an architecture that optimizes cell, nutrient, gas, and biomolecule transport, either *ex vivo* or *in vivo* or both, and facilitates blood vessel and nerve development.
- The material should be intrinsically noncytotoxic and nonimmunogenic, and minimally proinflammatory.

Optional specifications for tissue engineering templates

- The material should be degradable if that is desired, with appropriate degradation kinetics and appropriate morphological and chemical degradation profiles.
- The material should be injectable if that is desired, with the appropriate rheological characteristics and transformation mechanisms and kinetics.

- Where necessary, the material should be compatible with the processing techniques that simultaneously pattern both the material and living cells.
- Where multiple cell types are involved, the material properties should be tunable to accommodate variable cellular requirements, with spatiotemporal control as appropriate.
- When used in a significantly stressed *in vivo* environment, the material must have sufficient strength and toughness.
- In those situations where the biomaterial encapsulates cells, optimal diffusion characteristics concerning key molecules are required.

Conclusions and Perspectives

The concept of replicating the cell niche introduced above is consistent with the trend of recent years. The architecture of tissue engineering templates has been changing, with a move toward hybrid macro- and nanoscale structures and toward hydrogels based on tissues, tissue-derived, or tissue-mimicking components. These include injectable peptide-based hydrogels,[8] biomimetic hydrogels,[9] and decellularized tissues.[10] In such materials, great care has to be taken to avoid undesirable host responses, again consistent with the basic principles of biocompatibility, for example, through immunological responses with xenogeneic-derived substances, but this is not the main driving force or specification for their development. In this study, the appropriate host response[7] is not no response, but that which is optimal for the stimulation of those target cells within a recognizable, niche-mimicking, microenvironment.

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