

Biomaterial Scaffold Design for Engineering Human Tissues

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Statement of Purpose: The overall objective of tissue engineering is to fully restore the lost tissue function. Engineered tissues of sufficiently high fidelity can also provide physiologically relevant yet controllable models for fundamental research - for example, to study stem cells in a native-like three-dimensional context of development or disease. The utility of tissue engineering depends on our ability to predictably direct the cells to express the right phenotype in the right place and at the right time. My laboratory is interested in biophysical regulation of cell differentiation and functional assembly by an integrated use of biomaterial scaffolds and bioreactors (Grayson 2009a). This talk will discuss advanced technologies for regulation of stem cell fate and function, with focus on scaffold design for engineering human tissue grafts. We will use two distinctly different tissues of great clinical interest - heart muscle (myocardium) and bone - to illustrate how the specific biological requirements for the formation of a given tissue can be met through the design of cell environment.

Methods: To regulate cell differentiation and assembly, cells are cultured within a 3D scaffold, using a bioreactor (Fig. 1). In studies of cell differentiation factors, we have used custom-designed hydrogels (Gerecht 2007) and microarray bioreactors with perfusion, electrical and mechanical stimulation (Freytes 2009).

For *tissue engineering of bone*, common cell sources are adult human mesenchymal stem cells (hMSCs). The scaffolds extensively used in our work are made of decellularized bone and mineralized silk fibroin. Anatomically shaped scaffolds are generated using digitized clinical images, seeded with human mesenchymal stem cells, and cultured with interstitial flow of culture medium (Grayson 2009b). A novel bioreactor with an “anatomical” culture chamber was designed to enable controllable perfusion throughout clinically sized engineered constructs.

For *tissue engineering of myocardium*, hMSCs are used if only vascularization is to be achieved, while embryonic type and iPS cells are required for engineering of the muscle. The main types of scaffolds used in our cardiac tissue engineering work include fully decellularized human myocardium, functionalized hydrogels, and channeled elastomers (Radisic 2006). The bioreactor systems are designed to provide medium perfusion, electrical and mechanical stimulation (Freytes 2009).

Results: We are observing that the same factors that regulate tissue development *in vivo* (cell and scaffold derived, molecular, physical) can be used to direct cell fate and tissue assembly *in vitro*. A “biomimetic” tissue engineering approach has been developed to direct cell differentiation using scaffolds (cell-instructive templates for tissue formation) and bioreactors (controllable environments providing molecular and physical signals).

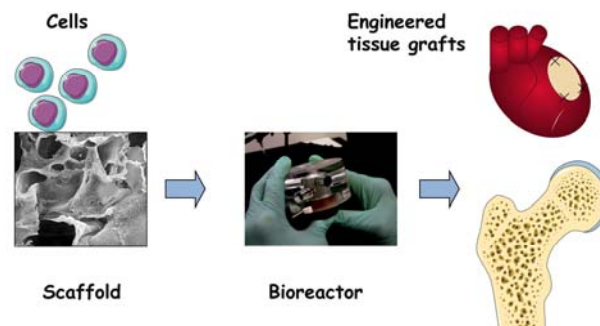


Figure 1. Cell – scaffold – bioreactor system for tissue engineering: human stem or progenitor cells (the actual “tissue engineers”) are cultured in a biomaterial scaffold (structural and logistic template for tissue formation), using a bioreactor (environmental control, molecular and physical signaling). The scaffold and bioreactor are designed to meet the biological and functional requirements for the formation of a specific tissue.

The system described in Fig. 1 was utilized for tissue engineering of human temporomandibular joint grafts. After five weeks of cultivation, the grafts contained viable cells at a physiologic density, forming confluent layers of lamellar bone, mineralized matrix and osteoids. Using the same approach, we studied the formation of cardiac grafts and their implantation in a nude rat model of cardiac ischemia. Cardiogenic and vasculogenic cells were induced to differentiate and form synchronously contractile grafts in channeled scaffolds by combined effects of molecular, electrical and mechanical stimuli.

Conclusions: The availability of fully biological tissue grafts, customized to meet the needs of a specific patient and clinical situation, would radically change the way we currently treat tissue loss due to trauma, disease or congenital defects. Scaffold design remains one of the most critical steps towards engineering functional tissues. Our current technologies enable the creation of scaffolds that mimic native tissue matrix and thereby enable the mobilization of the full regenerative potential of the cells. Many of the remaining challenges – tissue vascularization with immediate blood flow, creation of structurally and mechanically anisotropic tissues, full integration with the formation of interfaces – will likely be met only after developing a new generation of biomaterial scaffolds.

References:

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