Engineering Immunotherapy through Biomaterials: From Stem Cells to Vaccines

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Statement of Purpose: Recent advances in immunotherapy have opened up novel ways to manipulate the immune system and treat a variety of complex disorders including infectious diseases and cancer. Our laboratory focuses on developing engineering concepts and biomaterial-based strategies to manipulate the immune system both at the cellular as well as the system level. Specifically, our goals are two fold: first to understand the developmental pathways of immune cells from progenitor cells to eventually generate readily transplanatable, disease specific immune-effector cells and second to create effective carriers for antigens and adjuvants that can modulate and "train" the immune system to fight specific diseases. We present here results from our work on (a) manipulating embryonic stem cells using polymer scaffolds and bioreactors to generate hematopoietic progenitors and dendritic cells (b) microfabrication of spatio-temporally patterned polymer scaffolds for directing stem cells into multiple lineages (c) generating T cells from hematopoietic stem cells using biomaterial-directed notch signaling and (d) creating novel drug and vaccine delivery vehicles for dendritic cell-targeted or environmentally responsive release of antigens and adjuvants.

Results:

Hemtapoiesis from ES cells: We have demonstrated that mouse embryonic stem cells form embryoid bodies (EBs) within 3D tantalum-based scaffolds and undergo improved hematopoiesis, especially under dynamic
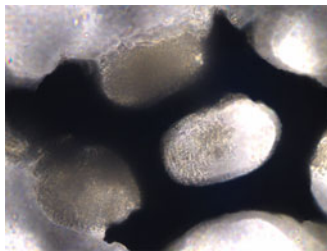

culture conditions. As shown in figure 1, the EBs interact closely with the scaffold biomaterial during the differentiation process. We have further shown, using PLGA scaffolds, that scaffold physical properties (e.g. pore size, compression modulus etc.) could play an important role in modulating spontaneous hematopoietic differentiation of ES cells.

Figure 1: Interaction of EBs with scaffold materials

Microfabrication of Tissue Engineering Scaffolds: We have developed a laser-based and a digital micro-mirror device-based system to fabricate polymer scaffolds with precise, pre-designed spatially patterns of growth factors and ECM molecules. The
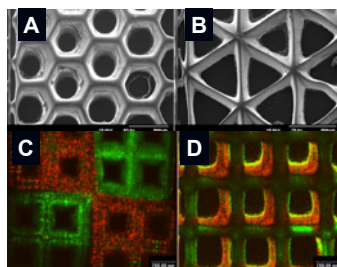

Figure 2: Spatially patterned complex scaffold structure

goal is to create complex tissue microenvironments that might allow a single stem cell population to differentiate into multiple lineages in pre-set patterns. As shown in figure 2, precise spatial patterns as well as complex internal architectures can be readily generated in these scaffolds.

Notch signaling biomaterials for T cell generation: We have recently shown that controlled notch signaling can be induced in bone marrow derived stem cells using magnetic microbeads functionalized with the notch ligand DLL4 and that such signaling, along with paracrine signals from stromal cells is sufficient and necessary to generate early T cells from stem cells (figure 3). Our ultimate goal here is to generate antigen-specific T cells for immunotherapy using ligand-directed signaling of progenitor cells.
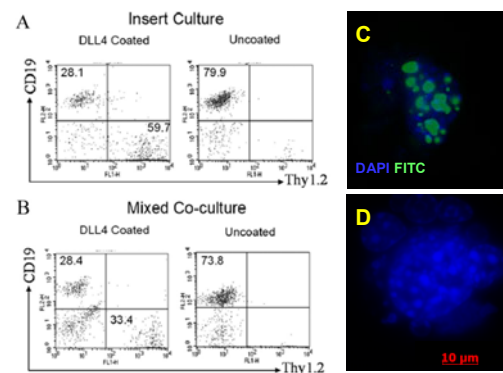

Figure 3: Notch signaling through biomaterials

Delivery of vaccines and adjuvants using micro and nanocarriers: We have developed surface-functionalized polymer microparticles for the delivery of multiple immunostimulatory (DNA and protein antigens) and immunomodulatory (adjuvants e.g. SiRNA, CpG and MPL) agents in a single carrier. These particles have shown significant efficacy in a mouse model of B cell lymphoma. We have also created modified polysachharides carrying secondary and tertiary amines for efficient gene delivery. More recently we have focused on novel nanomanufacturing techniques, including step & flash nanoimprint lithography to create highly monodisperse, disease-responsive, degradable nanocarriers of precise size and shapes (figure 4).
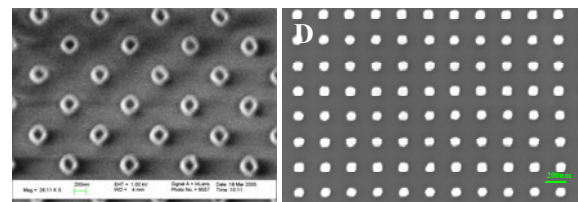

Figure 4: Nanoimprinted drug delivery particles