7.342 Cell-material Crosstalk: Engineering Cell-Instructive Biomaterials

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(Laboratories of Robert Langer and Dan Anderson)

Fall 2013. Wednesdays, 11 am - 1 pm. (*Class time is flexible*.) Room 68-150.

Course Description

Biomaterials are substances that have been designed to direct the course of any therapeutic or diagnostic procedure by controlling interactions with biological systems. A large toolbox of non-biological materials has been engineered to study cell behavior at the cell-material interface. In this course, we will examine how this interface can be leveraged to study cellular systems and generate novel therapeutics. A critical evaluation of the primary research literature will be used to frame discussions about the interactions between cells and biomaterials. In particular, we will discuss how cell behavior can be altered by controlling biochemical and biophysical cues of substrate materials, how new organs and tissues can be produced by the use of structured scaffolds that direct cells into organized forms, and how specific patterning of materials can enable biological processes to be studied and altered at the single-cell level. We will also consider the applications at patterned cell-material interfaces to build artificial systems, such as organs-on-a-chip, which can be used to perform preclinical tests for the activity and toxicity of drug candidates. Also, we will discuss the combination of non-biological materials with genetic material (DNA and RNA), which can be a robust approach to modifying gene expression at the level of cells, tissues, or organs. We hope that your introduction to the cell-materials interface will inspire you to work at the intersection of biology and engineering and that you will help pioneer new and improved strategies to engineer this interface for functional applications.

Prerequisites

This course is open to students interested in engineering and biology. Prerequisites are 7.03, 7.05, 7.06, *or* 7.28, *or* permission of the instructors.

Course Format

For each class, students will be assigned to read two papers. Students should formulate two questions per paper and send them by email to the instructors the night before each class. During each session, we will discuss as a group the articles as well as address the emailed questions, with emphasis placed on the experimental design, the use of control experiments, the details of experimental methodology, and the interpretation of experimental data. At the end of each session, the instructors will briefly introduce the papers for the next week.

Course Objectives

The main objectives of this course are to 1) introduce students to the primary scientific literature and the process of reading research publications, and 2) expose students to the rapidly developing field of cell-instructive biomaterials. Course objectives will be met through class discussions and take-home/in-class assignments. By the end of the semester students should be able to:

- Read, comprehend, critically analyze, and integrate knowledge concerning primary research articles
- Understand how to search for primary research articles relevant to the field of biomaterials using online tools (PubMed, Google Scholar, Scopus, MIT Library eJournals, etc.)
- Orally present papers from the primary scientific literature and engage classmates in discussion
- Define a cell-instructive biomaterial (in the context of this class)
- Identify several techniques scientists use in the design of cell-instructive biomaterials

Assignments
There will be two assignments for this course:

Written Assignment (due October 23, 2013):
Students will be provided with only the figures and captions from a published paper and asked to interpret the data in the form of an abstract describing the paper. The abstract should provide a brief introduction to the paper's topic, a summary of the results, and an interpretation of the significance of the results. PLEASE DO NOT LOOK UP THE PAPER.

Oral Assignment (presented on December 11, 2013):
Students will be provided with a list of articles selected by the course instructors but not discussed in class. From this list, students will select one paper to discuss in a 10-minute presentation, followed by a 5-minute discussion with the class. The presentation should provide a critical analysis, rather than just a summary, of the data, the controls, and the published interpretations. The presenter should also discuss the relevance of the paper to the course topic and the field, whether the authors' conclusions were justified, and what would be a good follow-up experiment/future study.

Grading
Grading for this course is pass/fail and will depend on student attendance, preparedness, participation in class discussions, and completion of the required assignments.

Syllabus at-a-glance

Date/Topic	Summary	Papers
September 4, 2013 **Class #1: Introduction to the course**	We will go over the syllabus, including expectations and goals of the class, an overview of the course, and an introduction to the first two papers. We will also discuss strategies for reading primary scientific papers.	
September 11, 2013 **Class #2: Mechanobiology of Materials**	The mechanical properties and stiffness of a material have a direct effect on cell function and stem cell lineage. We will discuss two papers that demonstrate creative approaches to preparing material substrates that allow one to determine the effect of substrate mechanical properties on cell behavior. The first paper uses a simple hydrogel substrate that can be tuned to different stiffnesses and thereby control differentiation of stem cells toward a specific lineage. The second uses a patterned substrate of micron-sized posts that have variable deformability, creating surfaces of varying stiffness and resulting in changes in cell behavior.	**1)** Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix Elasticity Directs Stem Cell Lineage Specification. *Cell* **126**, 677-689 (2006). **2)** Fu J, Wang K, Yang MT, Desai RA, Yu X, Liu Z, Chen CS. Mechanical regulation of cell function with geometrically modulated elastomeric substrates. *Nature Protocols* **7** 733-736 (2010).
September 18, 2013 **Class #3: Controlling cell morphology**	Substrate geometry plays a major role in the biophysical regulation of cell function. Micro-patterning techniques have allowed scientists to study the effects of surface topography on numerous cell types. We will discuss two examples of how surface shape influences cell proliferation and differentiation. The first paper demonstrates how vascular endothelial cell shape governs whether individual cells grow or die, independent of cell adhesion factors. The second paper demonstrates how cell shape, independent of soluble factors, has a strong influence on the differentiation of human mesenchymal stem cells (MSCs) from bone marrow.	**1)** Chen CS, Mrksich M, Huang S, Whitesides GM, Ingber DE. Geometric control of cell life and death. *Science* **276**, 1425-1428 (1997). **2)** Kilian KA, Bugarija B, Lahn BT, Mrksich M. Geometric cues for directing the differentiation of mesenchymal stem cells. *PNAS* **107 (11)**, 4872-4877 (2010).
September 25, 2013 **Class #4: Altering gene expression**	Advances in the field of nanoparticle carriers for small interfering RNA have demonstrated enormous potential in modifying gene expression. This approach might enable disease to be treated at a genetic level. Here we will read two examples of papers that have developed carriers for siRNAs,	**1)** Love KT, Mahon KP, Levins CG, Whitehead KA, Querbes W, Dorkin JR, Qin J, Cantley W, Qin LL, Racie T, Frank-Kamenetsky M, Yip KN, Alvarez R,Sah DW, de Fougerolles A, Fitzgerald K, Koteliansky V, Akinc A, Langer R, Anderson DG. Lipid-like materials for low-dose, *in vivo*

	demonstrating functional silencing in animal models. The first paper demonstrates the use of a broad library-based approach to find ultra-high efficiency siRNA carriers, and demonstrates therapeutic efficacy in a non-human primate model. The second paper discuses the use of a nanoparticle carrier to deliver siRNA, which laid the groundwork for the first evidence of an siRNA therapy success in human clinical trials.	gene silencing. *PNAS* **107** 1864-1869 (2010). **2)** Hu-Lieskovan S, Heidel JD, Bartless DW, Davis ME, Triche TJ. Sequence-specific knockdown of EWS-FLI1 by targeted, nonviral delivery of small interfering RNA inhibits tumor growth in a murine model of metastatic Ewing's Sarcoma. *Cancer Research*. **65** 8984-8992 (2005).
October 2, 2013 **Class #5: Biomimetic signaling**	Integrins are transmembrane cell receptors that play an important role in helping cells attach to their local microenvironment. Studies of integrin binding to extracellular matrix (ECM) proteins led to the discovery of small signaling domains composed of specific amino acid residues within long-chain ECM proteins. These oligopeptides were found to elicit similar cell responses as the long-chain proteins. We will discuss two papers in which "biomimetic" sequences have been used to modify the surface of biomaterials. In the first paper, hydrogels functionalized with cell adhesion peptides are used to control the attachement and morphology of marrow stromal cells. The second paper uses self-assembling nanofibers displaying cell adhesion ligands to study effects of cell adhesion, spreading, and migration.	**1)** Shin H, Jo S, Mikos AG. Modulation of marrow stromal osteoblast adhesion on biomimetic olio[poly(ethylene glycol) fumarate] hydrogels modified with Arg-Gly-Asp pepties and a poly(ethylene glycol) spacer. *Journal of Biomedical Materials Research Part A* **61 (2)**, 169-179 (2002). **2)** Storrie H, Guler MO, Abu-Amara SN, Volberg T, Rao M, Geiger B, Stupp SI. Supramolecular crafting of cell adhesion. *Biomaterials* **28**, 4608-4618 (2007).
October 9, 2013 **Class #6: Single Cell phenopyping** **Distribute Written Assignment**	Traditional methods of screening cells for phenotypic alterations involve bulk methods (PCR, western blotting, etc.). Advances in material design and patterning now make it possible to study cell behavior and function on the scale of a single (or few) cells. This approach allows one to examine the effects of different parameters on cell behavior and obtain information that might be lost if one simply looks at the overall bulk response. In the first paper, a nanowell array is used to capture individual T cells so they can be phenotyped on an individual basis. The second paper uses arrays of small droplets of different polymers to determine their effects on the differentiation of embryonic stem	**1)** Torres AJ, Contento RL, Gordo S, Wucherpfennig KW, Love JC. Functional single-cell analysis of T-cell activation by supported lipid bilayer-tethered ligands on arrays of nanowells. *Lab on a Chip*. **13**, 90-99 (2013). **2)** Anderson DG, Levenberg S, Langer R. Nanoliter-scale synthesis of arrayed biomaterials and application to human embryonic stem cells. *Nature Biotechnology*. **22,** 863-868 (2004).

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October 16, 2013 **Class #7: Organs-on-a-chip**	Advances in microengineering technologies have led to the development of "organs-on-a-chip." Using microfluidic techniques, researchers can create small devices that mimic organs in the body. This advanced technology opens up the potential for rapid drug screening using human cell lines. We will discuss two examples in which this technology has been used to recapitulate organ level functions of the heart and lungs on a chip.	**1)** Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber D. Reconstituting organ-level lung functions on a chip. *Science* **328**, 1662-1667 (2010). **2)** Grosberg A, Alford PW, McCain ML, Parker KK. Ensembles of engineered cardiac tissues for physiological and pharmacological study: heart on a chip. *Lab on a Chip* **11**, 4165-4173 (2011).
October 23, 2013 **Class #8: Targeting with nanoparticles** **Written Assignment due** **Handout list of papers for oral presentations**	Nanoparticles have demonstrated the potential to serve as targeting therapies for disease. One method to ensure that a payload enclosed in a nanoparticle reaches its target is to functionalize the particle surface with targeting groups. This is most often done using antibodies, but here we will examine some creative non-antibody strategies for nanoparticle targeting. The first uses aptamers, oligonucleotide sequences with binding specificity for prostate cancer cells, to deliver encapsulated chemotherapy to tumors. The second uses chlorotoxin, a toxin derived from scorpion venom, to target particles to brain tumors across the blood-brain barrier.	**1)** Farokhzad OC, Cheng J, Teply BA, Serifi I, Jon S, Kantoff PW, Richie JP, Langer R. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy *in vivo*. *PNAS* **103** 6315-6320 (2006). **2)** Kievit FM, Veiseh O, Fang C, Bhattarai N, Lee D, Ellenbogen RG, Zhang M. Chlorotoxin labeled magnetic nanovectors for targeted gene delivery to glioma. *ACS Nano*. **4** 4587-4594 (2010).
October 30, 2013 **Class #9: Materials for**	Non-biological materials have been developed to address challenges in	**1)** Manolova V, Flace A, Bauer M, Schwarz K, Saudan P,

vaccination	the efficacy of current vaccine and immunotherapy technologies. The thought is that these materials can more specifically target the delivery of antigens to antigen presenting cells (i.e. dendritic cells), to in turn, induce T-cell immunity. Here we discuss two papers describing biomaterial vehicles for targeted antigen delivery. The first paper discusses the effect of nanoparticles diameter on cell targeting. In the second paper, adjuvant- and antigen- loaded nanoparticles are used to target dendritic cells.	Bachmann M. Nanoparticles target distinct dendritic cell populations according to their size. *Eur. J. Immunol.* **38**, 1404-1413 (2008). **2)** Scott EA, Stano A, Gillard M, Maio-Liu AC, Swartz MA, Hubbell JA. Dendritic cell activation and T cell priming with adjuvant- and antigen- loaded oxidation-sensitive polymersomes. *Biomaterials* **33 (26)**, 6211-6219 (2012).
November 6, 2013 **Class #10:** **Visit to Langer Research Lab**	A behind the scenes look at some of the biomaterials science research focused on the cell-material interface in the laboratory of Bob Langer.	
November 13, 2013 **Class #11: Engineering vascular structure** **Finalize choice of paper for oral presentation**	In this next series of classes, we will draw on our knowledge of biophysical and biochemical cues to discuss ways in which researchers design higher ordered tissue structures. In this class, we will discuss tissue engineered vascular structures. The first paper uses synthetic polymer meshes to culture smooth muscle cells under pulsatile media flow conditions in a bioreactor. The second paper describes a fully biological tissue engineering technology to fabricate small-diameter tubular vascular grafts via rapid prototyping techniques.	**1)** Niklason LE, Gao J, Abbott WM, Hirschi KK, Houser S, Marini R, Langer R. Functional arteries grown *in vitro*. *Science* **284**, 489-493 (1999). **2)** Norotte C, Marga FS, Niklason LE, Gorgacs G. Scaffold-free vascular tissue engineering using bioprinting. *Biomaterials* **30(30)**, 5910-5917 (2009).
November 20, 2013 **Class #12: Repairing the nervous system**	Because of a lack of regenerative capacity, restoring function to the damaged central nervous system is a challenging task. Materials can participate in this process by delivering soluble or matrix cues that promote the growth of new neurons across an injured segment of spinal cord. We will discuss such methods in this class. From the first paper, we will examine the implantation of a scaffold into a spinal cord injury site that releases a soluble factor known to promote the growth of neurons. From the second paper, we will read about an injectable gel that delivers immobilized cues to growing neurons and helps to promote improved motor function following spinal cord injury.	**1)** Taylor SJ, Sakiyama-Elbert SE. Effect of controlled delivery of neurotrophin-3 from fibrin on spinal cord injury in a long term model. *J Controlled Release*. **116** 204-210 (2006). 2) Tysseling-Mattiace VM, Sahni V, Niece KL, Birch D, Czeisler C, Fehlings MG, Stupp SI, Kessler JA. Self-assembling nanofibers inhibit glial scar formation and promote axon elongation after spinal cord injury. *Journal of Neuroscience* **28** 3814-3823 (2008).
November 27, 2013 **Class #13: Bioinspired**	Researchers have drawn inspiration from the sophisticated structure and	**1)** Kim DH, Seo CH, Han K, Kwon KW, Levchenko A, Suh

Materials	complex hierarchical organization of many materials found in nature to create living tissues. We will discuss ways in which researchers try to mimic these structures to achieve scaffold functionality and also develop new technologies. In the first paper, *in vivo* like extracellular matrix (ECM) architectures inspired the design of topographically tailored substrate to study the migration of cells. The second paper drew inspiration from jellyfish physiology to engineer muscular pumps.	KY. Guided cell migration on microtextured substrates with variable local density and anisotropy. *Adv. Funct. Mater.* **19**, 1579-1586 (2009). **2)** Nawroth JC, Lee H, Feinberg AW, Ripplinger CM, McCain ML, Grosberg A, Dabiri JO, Parker KK. A tissue-engineered jellyfish with biomimetic propulsion. *Nature Biotech* **30**, 792-797 (2012).
December 4, 2013 **Class #14: Cell-like materials**	Materials that circulate through the body disguised as cells could have applications for many new therapies. Here we discuss two approaches that have been used to create artificial red blood cells, either by controlling mechanical properties or controlling surface characteristics. In the first paper, materials are made into the size, shape, and stiffness of red blood cells to achieve long-term circulation. In the second paper, a polymeric material is coated with the membrane of a red blood cell, which facilitates improved circulation of the particles.	**1)** Merkel TJ, Jones SW, Herlihy KP, Kersey FR, Shields AR, Napier M, Luft JC, Wu H, Zamboni WC, Wang AZ, Bear JE, DeSimone JM. Using mechanobiological mimcry of red blood cells to extend circulation times of hydrogel microparticles. *PNAS* **108** 586-591 (2011). **2)** Hu CJ, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *PNAS* **108** 10980-10985 (2011).
December 11, 2013 **Final Class** **Oral Presentations**	After the oral presentations, we will discuss the course in general, including an overview of what we have learned about engineering cell-instructive biomaterials	