BioMEMs Differentiation and Characterization of Human Embryonic Stem Cell (hESC)-Derived Cardiomyocytes

Project Contacts: Oscar Abilez, MD, General Surgery, Stanford Hospital (ojabilez@stanford.edu);
Feng Cao, PhD, Molecular Imaging Program at Stanford (fengcao@stanford.edu)

Objective: To design a bioMEMS substrate that can apply and measure electromechanical forces in the differentiation of hESCs into CMs

Hypothesis: Organized electromechanical stimulation on a microscale that mimics the *in vivo* development environment will play a role in directing hESCs toward a CM fate.

Clinical Relevance: Ischemic heart disease is the number one cause of morbidity and mortality in the United States[1]. Ischemic damage resulting from myocardial infarction is unable to regenerate in adult tissues. Cardiomyoplasty has recently emerged as a promising methodology for cardiac repair by transplanting cells at the site of damage[2]. Specifically, the delivery of CMs, which constitute 70-80% of the adult myocardium, may restore tissue viability and function to the myocardium. CMs derived from hESCs exhibit molecular, structural, electrophysiological and contractile properties similar to that of the nascent embryonic myocardium[3]. Human clinical trials of cardiomyoplasty have progressed forward with bone marrow stem cells (BMSC)[4, 5], skeletal myoblasts (SKM)[6], and endothelial progenitor cells (EPC)[7]. Preliminary results have reported improved myocardial function, however, the exact mechanisms for this process are poorly understood. Furthermore, other studies have challenged the ability of these adult stem cells to survive or engraft in the myocardium, suggesting these cells lack the ability to differentiate into functional cardiac cells and are not aptly conditioned to integrate into the existing architecture. Thus, the successful derivation and characterization of hESC-derived CMs may open doors to the rapidly progressing field of therapeutic cell transplantation.

Electromechanical Measurement: Microfabricated substrates can overcome the spatiotemporal resolution of traditional cell culture by enabling micrometer control over substrate composition and topology[8]. BioMEMS devices offer greater force resolution over other cell-measurement techniques, as well as active-sensing capability[9]. In the case of studying beating CMs, mechanical forces can be actively measured by micropatterning cell clusters called "embryoid bodies" (EBs) onto microscale sensors. Microelectrode arrays have been used to measure the electrophysiology of mouse ESC-CMs, and reported values are in the range of 500—1500μV[10]. BioMEMS offers the ability to combine mechanical and electrical measurement techniques on a single platform and monitor these quantities over time. Coupled characterization and imaging of CM precursors during proliferation on such a device could be used as a metric for assessing the range of forces that induce or maintain cardiac fate.

Challenges of Device Design & Fabrication:

- Characteristic size of CM precursors
- Force generation within the range of electrical and mechanical limits of CMs
- Coupled electrical stimulation and force sensing.
- Measurement calibration
- Efficient microelectrode-cell contact
- Biocompatibility—materials selection, passivation during fabrication, and packaging
- Integration into an active imaging platform

References

1. Thom, T., et al., *Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee.* Circulation, 2006. **113**(6): p. e85-151.
2. Pedrotty, D.M. and N. Bursac, *Cardiomyoplasty: the prospect of human stem cells.* IEEE Eng Med Biol Mag, 2005. **24**(3): p. 125-7.
3. Laflamme, M.A. and C.E. Murry, *Regenerating the heart.* Nat Biotechnol, 2005. **23**(7): p. 845-56.
4. Wollert, K.C., et al., *Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial.* Lancet, 2004. **364**(9429): p. 141-8.
5. Chen, S.L., et al., *Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction.* Am J Cardiol, 2004. **94**(1): p. 92-5.
6. Menasche, P., et al., *Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction.* J Am Coll Cardiol, 2003. **41**(7): p. 1078-83.
7. Schachinger, V.A., B. Britten, M.B. Honold, J. Lehmann, R. Teupe, C. Abolmaali, N.D. Vogl, T.J. Hofmann, W.K. Martin, H. Dimmeler, S. Zeiher, A.M., *Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial.* J Am Coll Cardiol, 2004. **44**(8): p. 1690-9.
8. Li, N., A. Tourovskaia, and A. Folch, *Biology on a chip: microfabrication for studying the behavior of cultured cells.* Crit Rev Biomed Eng, 2003. **31**(5-6): p. 423-88.
9. Grayson, A.C.S., R.S. Johnson, A.M. Flynn, N.T. Li, Y. Cima, M.J. Langer, R. *A bioMEMS review: MEMS technology for physiologically integrated devices*. in *Proceedings of the IEEE*. 2004.
10. Reppel, M., et al., *Microelectrode arrays: a new tool to measure embryonic heart activity.* J Electrocardiol, 2004. **37 Suppl**: p. 104-9.