Propositions

Cellular Modifications and Interventions for the Damaged Heart

1. Insulin-like growth factors promote Brachyury$^+$ early mesodermal proliferation *in vitro* through selective phosphorylation of a downstream Akt pathway. Treatment with insulin-like growth factors steers embryonic stem cell differentiation towards an Nkx2.5$^+$ cardiac progenitor cell-fate. *(this thesis)*

2. In an *in vitro* cardiac fibrosis model, forced cellular fusion of neonatal rat ventricular myocytes with human ventricular scar cells markedly decreases arrhythmogenicity through several mechanisms, including improved coupling, improved excitability and increased repolarization force. *(this thesis)*

3. Down-regulation of connexin 43 leads to conduction slowing and formation of phase islands of spatially discordant action potential duration alternans. Presence of adjacent alternans phase islands of opposite phase creates a vulnerable substrate for wavebreak formation and re-entry initiation. *(this thesis)*

4. Optogenetic engineering of atrial cardiomyocytes can terminate re-entry by brief light pulses. *(this thesis)*

5. The combination of three transcription factors, Gata4, Mef2c, and Tbx5, can rapidly and efficiently induce cardiomyocyte-like cells from postnatal cardiac and dermal fibroblasts. iCMs were similar to neonatal cardiomyocytes in global gene expression profile, electrophysiologically, and could contract spontaneously, demonstrating that functional cardiomyocytes can be generated from differentiated somatic cells by defined factors. *(Ieda M., et. al. Cell. 2010;142:375-386)*

6. Minimally invasive *TBX18* gene transfer creates physiologically relevant pacemaker activity in complete heart block, providing evidence for therapeutic somatic reprogramming in a clinically relevant disease model. *(Hu Y.F., et. al. Sci Transl Med. 2014;6:245)*

7. Our study also provides reassurance about the arrhythmogenic risk of cardiac repair with immature stem cell-derived cardiomyocytes. We observed an arrhythmia-suppressive effect that was unique to cardiomyocyte grafts and occurred despite incomplete host-graft coupling. *(Shiba Y., et. al. Nature. 2012;489:322-325)*

8. Human embryonic stem-cell derived cardiomyocytes can remuscularize substantial amounts of the infarcted monkey heart. Comparable remuscularization of a human heart should be possible, but potential arrhythmic complications need to be overcome. *(Chong J.J., et. al. Nature. 2014;510:273-277)*

9. Curious that we spend more time congratulating people who have succeeded than encouraging people who have not. *(Neil deGrasse Tyson, Twitter January 23, 2012)*

10. Your time is limited, so don't waste it living someone else's life. Don't be trapped by dogma – which is living with the results of other people's thinking. Don't let the noise of others' opinions drown out your inner voice. And most important, have the courage to follow your heart and intuition. *(Steve Jobs, Stanford Commencement address June 12, 2005)*

11. We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do. *(Atul Gawande, Complications: a surgeon's notes on an imperfect science)*

12. At the end of a PhD training, you should not forget to stop w(o/a)ndering.

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