CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

iPSC repository for drug development and disease modeling

Introduction – the Opportunity and the Challenge

The California Institute for Regenerative Medicine (CIRM) is charged with supporting the development of cures and therapies based on stem cell science. Moving an innovative technology into the clinic involves years of development, intensive resource investment, and navigating an evolving regulatory landscape. An external review of CIRM's strategy, policies and procedures was conducted in 2010 to provide external, objective perspective and advice on CIRM's past performance and recommendations on changes to enable long term success. The purpose of the review was to position CIRM and California as a global leader in translating outstanding stem cell science into the clinic, and included among the recommendations were the following:

- Maintain focus on meaningful, targeted scientific excellence
- Adopt a more aggressively proactive approach to identifying innovative projects across the stem cell therapeutic landscape that shows promise for moving into translational research, clinical trials and product development
- Ensure serious engagement with industry

In 2006 the generation of induced pluripotent stem cells (iPSCs) from somatic cells through retroviral-driven expression of four embryonic transcription factors initiated a revolution in resource development for both the exploration of the cellular basis of human disease and for therapeutic discovery. Rapid advances in iPSC reprogramming technology focused on integration-free methods such as transfection of episomal plasmids, non-integrating viral vectors, small molecule inhibitors, synthetic RNAs, miRNAs, and protein-driven iPSC induction can now circumvent concerns associated with viral integration including oncogene reactivation, and the generation of insertional mutations. iPSC technology is emerging as an unprecedented opportunity in biomedical research, disease modeling, drug discovery and regenerative medicine. However, to harness the full potential of this technology, issues regarding iPSC resource availability, standardization of iPSC resource quality, iPSC line variability, mutational load as a result of reprogramming, differentiation efficiencies, and reproducibility of cellular phenotypes across iPSC lines and laboratories, still need to be addressed.

Recent breakthroughs in the ability to generate human induced pluripotent stem cells (iPSC) by reprogramming of somatic cells are having a dramatic impact on biomedical research. iPSC lines are being generated from patients with a host of intractable diseases, from autism to heart disease to diabetes. These valuable pluripotent cell lines can be differentiated into cells that were previously inaccessible to researchers, such as human brain and heart cells, that carry the same genetic background as a patient with a specific disorder. iPSC and their derivates can be used to understand the biological properties of human cells, to generate in vitro models of human diseases, and to develop high-throughput screens to identify potential therapeutics or drug toxicities. The promise offered by iPSC is that studying human cells, which may reflect a disease phenotype more accurately than previous

cellular models or animal models, will make therapeutic drug discovery faster, more efficient, and eventually, customizable to individual patients.

Analysis of iPSC opportunity

In November 2010 CIRM organized a workshop with leaders in the field of stem cell research and regenerative medicine to assess the value of supporting more formal iPSC banking efforts. The focus of an iPSC bank would be to increase the number and quality of human cell lines available for activities such as in vitro disease modeling and high-throughput screening, although not cell therapy at this stage. Participants were asked for advice on the elements that would increase the impact of such a bank on therapeutic development. Two independent banking needs were identified: 1) repository to bank iPSC generated by the research community in California; and 2) a more comprehensive effort to generate new iPSC for targeted diseases for disease modeling and in vitro screening.

At the national level, the National Institute of Neurological Disorders and Stroke (NINDS), through the American Recovery and Reinvestment Act of 2009, the Grand Opportunities grants program supported large scale research projects to accelerate critical breakthroughs, early and applied research on cutting edge technologies and new approaches to improve the synergy and interactions among multi and interdisciplinary research teams. Through the initiative, NINDS funded 3 consortia, to develop well-characterized publically available, iPSC lines for Huntington's Disease (HD) and familial forms of Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS). This consortium approach enabled rapid resource and analytical tool development, and the initial identification of cellular phenotypes associated with late-onset neurodegenerative disease in iPSC derived neuronal cultures. All fibroblast lines and iPSC lines developed through the ALS, PD, and HD consortia will be available through the NINDS repository at Coriell. In 2010, NINDS held two workshops for iPSC consortia investigators, non-government organizations and industry representatives to discuss the progress of consortia in developing iPSC disease-specific lines and protocols or methodologies for cell-type specific differentiation and lineage analysis. The workshops also provided industry perspectives regarding the challenges that remain for the utilization of patient-derived iPSC lines in the drug development process.

A primary goal of this initiative is to facilitate the scientific evaluation of iPSC resources for drug discovery purposes and to increase the number of lines, types of mutations, reporter modifications, maintenance and differentiation protocols and cell line characterization that are broadly available to the community as research resources. This initiative is intended to be a partnership with government, non-government organizations and pharmaceutical companies interested in advancing drug discovery efforts for neurodegenerative diseases.

The General Solution

Features of a solution include a sustainable, high quality national research resource where investigators, working collaboratively with academia, industry and patient advocacy foundations, can develop the standards and framework for the deposit and the utilization of well-characterized iPSC lines from patients with serious/life threatening diseases and conditions, and relevant control lines. The lines would be utilized to develop disease models that would more accurately mimic the human disease condition, and accelerate the development and use of more efficient/predictive screens for drug discovery and development. A collaborative effort of the major stakeholders is essential for more rapid progress in the field.

Benefits to CIRM – opportunity to play a role in a national effort, while leveraging resources and expertise; access to CIRM-funded investigators of a national resource in iPSC, as well as opportunities for more in-depth interactions with industry, translational scientists, and patient advocacy engagement, all focused on increasing the knowledge of strategic therapeutic areas and catalyzing the development of more accurate and predictive screens for drug discovery and development. The proposal aligns with CIRM's mission and directly addresses several key ERP recommendations.

The Proposed Solution and Call to Action

The specific proposal is for a two-step project:

Step One – CIRM to present concept to engage with NINDS in a public private partnership focused on iPSC for neurodegenerative diseases at the ICOC science committee, and the GWG in April; if concept reviewed favorably, concept to be presented at the ICOC May board. Time line solicitation for proposals to be submitted to NINDS in June, 2011(California investigators could submit applications, summary statements from NIH review to CIRM), with funding in the fall of 2011. Proposed budget for CIRM is $150k/year x 2 years and the dollars would be directed to California based investigators. This would leverage existing resources and expertise, provide a national platform for CIRM and align with CIRM's mission. CIRM would have representation on the public private partnership panel. The agreement would be documented in a MOU between CIRM and the Foundation for NIH. The budget for NINDS for all of the partners is $4.5 million in FY 2011, with subsequent year budget to be based on appropriations to the NINDS.

Step Two – CIRM to present a concept to the ICOC in the Fall, 2011, for funding of an iPSC repository for disease modeling and drug discovery/development across additional disease areas (e.g., other than neurodegenerative diseases). CIRM would build upon knowledge gained from the repository in neurodegenerative diseases, and provide a repository to bank existing iPSC lines from California investigators, and the generation of new iPSC lines from targeted diseases excluding neurodegenerative disease so as not to duplicate efforts and CIRM resources.