National Institutes of Health

NIH Common Fund Center for Regenerative Medicine

Virtual Workshop Summary Report – May 6, 2014

5/6/2014

NIH Common Fund Center for Regenerative Medicine (CRM)
NIH CRM Virtual Workshop
May 6, 2014, 3 pm to 5 pm EDT

Introduction and Overview

The NIH Common Fund (CF) launched the NIH Center for Regenerative Medicine (CRM) in 2010 in an effort to build an internationally renowned hub of stem cell activity within the NIH Intramural Research Program (IRP). NIH CF programs are intended to be Transformative, Catalytic, Synergistic, Cross-cutting, and Unique. In general, these programs are expected to transform the way a broad spectrum of health research is conducted. Moreover, initiatives are intended to be catalytic by providing limited term investments in strategic areas to stimulate further research through other mechanisms.

The overarching goal of the CRM is to resolve translational challenges associated with the use of induced pluripotent stem cells (iPSCs). The CRM will deliver to the community methods and best practices for translation of iPSCs, leveraging resources on the NIH campus and working with collaborators on diverse cell types. During the first 2-3 years, the center awarded a number of small pilot grants to IRP investigators to encourage them to develop projects using iPSCs. One of these, led by Dr. Kapil Bharti at NEI, was selected through peer review in 2013 to expand and take the next step toward a clinical application as a Therapeutic Challenge Award. Other accomplishments of the Center to date include the development of protocols, contracts for stem cell services and storage, standard consent forms, training courses, and other services. Many iPSC lines have been generated, and more investigators in the NIH IRP are working in this area.

Currently, the CRM is at a transition point. Over the past two years the many challenges to the use of iPSCs in therapy have become clearer, and of these, the methodological and technical challenges align with the expertise and mission of the National Center for Advancing Translational Sciences (NCATS). Therefore, NCATs, together with the Office of Strategic Coordination (OSC) that oversees the Common Fund, held a virtual workshop in May 2014 to discuss the many recommendations that had been made. The participants included experts from academics, industry, societies, and other federal government agencies (see Appendix 1 for the list of participants). The goal was for the participants to provide input regarding the high priority gaps and challenges in this area that could be addressed by a focused effort from the NIH in the next few years.

To establish context for this conversation, a small working group of NIH staff developed a short list of challenges derived from the community-generated white papers and review articles (see Appendices 2 and 3). This list was circulated to the participants prior to the workshop, and several individuals provided written input in lieu of participating in the workshop. The list was not intended to be exhaustive. Thus, this workshop provided an opportunity for participants to share their ideas about additional gaps, opportunities, and challenges.

Summary

Although many challenges to the development of iPSC therapies were described, three specific needs were mentioned repeatedly:

1. **Methods to produce mature differentiated cells with high efficiency.** Current differentiation protocols suffer from low efficiency and incomplete differentiation. For some lineages, culture in three-dimensions increases efficiency and enables differentiation and maturation to adult phenotypes, but these methods are not well established or standardized. Differentiation protocols, including those that utilize three-dimensional culture, need to be optimized for diverse lineages, with molecular and/or functional diagnostics (including epigenomic, proteomic, and transcriptional profiles) defined for each differentiation stage. While some companies can produce certain differentiated lineages at high volume, standardization of specific endpoints is lacking. The improvement in differentiation protocols combined with standardized profiles for each differentiation stage would be broadly enabling.

2. **Methods to assess heterogeneity of cultures.** Heterogeneity is inherent in the differentiation process, as differentiation occurs in less than 100% of the cells and individual cells influence their neighbors. Assessing this heterogeneity is critical for development of iPSC therapies. Methods must be in place to detect undifferentiated cells at each step. Defining robust standards and methods to identify different subpopulations of cells will also be critical, since different populations are more or less effective in different assays or pre-clinical tests, such as wound healing or immunomodulation.

3. **Methods to assess and facilitate safety.** Molecular definition of "safe" iPSCs and their derivatives is a requirement. Correlation between the molecular profile of a cell and tumor-inducing phenotype is a high priority need. Development of methods to monitor cell migration *in vivo* is also essential. Since most cells fail to engraft at the implantation site, development of standard materials to facilitate engraftment and assays to assess engraftment and follow the behavior of engrafted cells are also needed. Three dimensional culture methods will also be important for safety studies, since these are likely to predict cell behavior *in vivo* more reliably.

Additional Areas of Opportunity

The following subjects emerged from the workshop as areas of opportunity that met the criteria of being 1) a specific challenge or roadblock faced by the field, 2) an area where the NIH could make a lasting contribution in the next 4 years, and/or 3) an area that is not being adequately addressed elsewhere. These are listed in no particular order and workshop participants did not prioritize among these issues.

Understanding the Basic Biology of iPSCs

Although the development of more robust differentiation protocols and the establishment of standard molecular diagnostics for each stage of differentiation will contribute to the

basic understanding of stem cells, many workshop participants voiced a need for additional basic science. Understanding intercellular interactions during the differentiation process and how heterogeneous populations of cells may ultimately be required for therapeutic benefit will ultimately be important for new therapy development.

Derivation of iPSCs

Various workshop participants expressed the need for automated expansion of iPSCs and methods for deriving the cells that do not induce mutations or use oncogenes. Although some participants called for banks of iPSCs to be generated from different HLA groups, participants were mixed in their views of the relative benefit of autologous approaches versus therapies that utilize banked cells from HLA-matched individuals. Multiple groups around the world are developing large HLA banks of iPSCs. A related goal was design of genetically engineered cells that would be useful for all patients. Development of standards for GMP derivation, expansion, and differentiation were also identified as needs. Although not directly related to use of iPSCs for cell therapies, some participants voiced the need for libraries of genetically diverse iPSCs, coupled with development of cellular screening assays that would allow iPSCs and their derivatives to be used in pharmacogenomic preclinical assessment of new drugs.

Technology Development and Discovery

Engineered iPSC lines that would not be rejected after implantation and cells that could be easily tracked were two concepts within the broader need for reagent and technology development. Methods to switch research grade cell lines to GMP grade was also identified as an important technical challenge.

iPSC Core Facility

This concept would involve creation of a central hub to facilitate the availability of cells, ease intellectual property issues, and facilitate the dissemination of knowledge to help basic researchers take on translational challenges. This hub could help share information between partners and might help guide researchers in the next steps of preparing for a clinical trial, an area that is foreign to most researchers interested in the basic biology of iPSCs. Access to patients and criteria for patient stratification were identified as challenges that could be facilitated by a consulting consortium.

Appendix 1: Webinar Workshop Participants (listed alphabetically)

This list includes the names of those individuals who attended the workshop in person, those who provided verbal input during the webinar, and those who appeared on the webinar participant list.

James (Jim) Anderson, Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), NIH
Christopher (Chris) Austin, National Center for Advancing Translational Sciences (NCATS), NIH
Kapil Bharti, National Eye Institute (NEI) Intramural Research Program (IRP), NIH
Manfred Boehm, National Heart, Lung and Blood Institute, (NHLBI), Intramural Research Program (IRP), NIH
Roberto Bolli, University of Louisville
Steve Bauer, Federal Drug Administration (FDA)
Dennis Clegg, UC Santa Barbara
Laura Cole, National Institute on Deafness and Other Communication Disorders (NIDCD), NIH
Christine Colvis, National Center for Advancing Translational Sciences (NCATS), NIH
Stephanie Courchesne Schlink, Office of Strategic Coordination (OSC), Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), NIH
Eileen Dolan, University of Chicago
Paul Doran, Cellular Dynamics International
Melissa Green Parker, Office of Strategic Coordination (OSC), Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), NIH
Rob Harriman, Office of Portfolio Analysis (OPA), Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), NIH
Jocelyn Kaiser, Science Magazine
Lillian Kuo, National Center for Advancing Translational Sciences (NCATS), NIH
Patricia (Trish) Labosky, Office of Strategic Coordination (OSC), Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), NIH
Jeanne Loring, Scripps Research Institute
Tenneille Ludwig, WiCell Stem Cell Bank
Nadya Lumelsky, National Institute for Dental and Craniofacial Research (NIDCR), NIH
John McKew, National Center for Advancing Translational Sciences (NCATS), Intramural Research Program (IRP), NIH
Vanessa Ott, Cellular Dynamics International
David Owens, National Institute of Neurological Disorders and Stroke (NINDS), NIH
David Panchision, National Institute of Mental Health (NIMH), NIH
Byron Peterson, University of Florida
Pamela Gehron Robey, National Institute for Dental and Craniofacial Research (NIDCR) Intramural Research Program (IRP), NIH
Anna Rossoshek, National Center for Advancing Translational Sciences (NCATS), NIH
David Russell, University of Washington
Michael Sheldon, Director of Stem Cell Laboratories, RUCDR Infinite Biologics, Rutgers
Anton Simeonov, National Center for Advancing Translational Sciences (NCATS), Intramural Research Program (IRP), NIH
Marge Sutherland, National Institute of Neurological Disorders and Stroke (NINDS), NIH
Clive Svendsen, Cedars-Sinai Medical Center
Evan Snyder, Sanford Burnham Medical Research Institute
Danilo (Dan) Tagle, National Center for Advancing Translational Sciences (NCATS), NIH
Sally Temple, Neural Stem Cell Institute

John Thomas, National Heart, Lung and Blood Institute (NHLBI), NIH
James Thomson, University of Wisconsin
Keith Wonnacott, Federal Drug Administration (FDA)
Elizabeth (Betsy) Wilder, Office of Strategic Coordination (OSC), Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), NIH
Sean Wu, Stanford University School of Medicine
Elias Zambidis, Johns Hopkins University

Appendix 2: Topics selected as a starting point for the workshop, derived from papers in Appendix 3

1) Methods/technology challenges in production of iPS cell therapy.

- Methods for expanding cells to large numbers
- Methods for making the growth microenvironment more hospitable
- Methods for closed volume reduction
- Methods for improving cell yield
- Small molecules to replace growth factors and cytokines
- Synthetic matrices to replace biological ones
- Methods to provide cells in final formulation media

2) Methods/technology challenges in characterization of iPS cell therapy.

- Assays to analyze cell heterogeneity
- Monitoring of interactions between cells and their microenvironment
- Computational tools for data analysis
- Imaging methods for potency assays
- Live imaging of single cells to screen differentiation protocols
- Methods for monitoring cell migration using reporter-gene imaging strategies

3) Opportunities. The outstanding opportunities in this research area.

4) Gaps and challenges. Any additional areas to prioritize.

Appendix 3: Community-generated white papers and review articles

- Stem Cells: Future Scientific and Medical Opportunities, a report by the ASCB Stem Cell Task Force, November 2013. http://www.ascb.org/stemcellrevolution
- UK Strategy for Regenerative Medicine. http://www.mrc.ac.uk/news-events/publications/regenerative-medicine-strategypdf/
- Key Tools and Technology Hurdles in Advancing Stem-Cell Therapies, a White Paper by California Institute for Regenerative Medicine, Alliance for Regenerative Medicine, Cell Therapy Catapult, June 2013. http://www.cirm.ca.gov/sites/default/files/files/funding_page/Key-Tools-Tech-Hurdles-in-Advancing-Stem-Cell-Therapies.pdf
- *Stem Cell Research: Trends and Perspectives on the Evolving International Landscape.* Jointly prepared by EuroStemCell, Kyoto University's Institute for Integrated Cell-Material Sciences (WPI-iCeMS), and Elsevier. http://www.elsevier.com/online-tools/research-intelligence/resource-library/resources/stem-cell-research-trends-and-perspectives-on-the-evolving-international-landscape

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