



## SPEAKER ABSTRACTS

**NOTE: For complete speaker information, please visit:**

<https://www.btc.org/events-symposia-2018/wisconsin-stem-cell-symposium/>

### **Autologous iPS Cell Therapy for Macular Degeneration: From Bench-To-Bedside** **Kapil Bharti, Ph.D.**

Induced pluripotent stem (iPS) cells are a promising source of personalized therapy. These cells can provide immune-compatible autologous replacement tissue for the treatment of potentially all degenerative diseases. We are preparing for the first phase I clinical trial using iPS cell derived ocular tissue to treat age-related macular degeneration (AMD), one of the leading blinding diseases in the US. AMD is caused by the progressive degeneration of retinal pigment epithelium (RPE), a monolayer tissue that maintains vision by maintaining photoreceptor function and survival. Combining developmental biology with tissue engineering we have developed clinical-grade iPS cell derived RPE-patch on a biodegradable scaffold. This patch performs key RPE functions like phagocytosis of photoreceptor outer segments, ability to transport water from apical to basal side, and the ability to secrete cytokines in a polarized fashion. We confirmed the safety and efficacy of this replacement patch in animal models as part of a Phase I Investigational New Drug (IND)-application. Approval of this IND application will lead to transplantation of autologous iPS cell derived RPE-patch in patients with the advanced stage of AMD. Success of NEI autologous cell therapy project will help leverage other iPS cell-based trials making personalized cell therapy a common medical practice.

### **Sight for More Eyes: Development of Cell Therapies for Ocular Disease** **Dennis Clegg, Ph.D.**

One promising option for the treatment of ocular disease is to develop cellular therapies using RPE and neural retinal cells derived from pluripotent stem cells. One strategy for treating dry age related macular degeneration is to implant differentiated, polarized monolayers of hESC-RPE or iPS-RPE on an extracellular matrix-based scaffold, whereby cells are provided with a supportive substrate to stimulate cell survival, differentiation and function. We describe recent efforts to develop tissue constructs to replace ocular tissue and translate them to the clinic. A phase 1/2A clinical trial is currently underway to assess the safety of an implant consisting of a monolayer of H9 hESC-RPE on a synthetic scaffold.

## **Pluripotent Stem Cell Therapies - Challenges and Opportunities in Manufacturing, Quality and Regulatory** *Derek Hej, PhD*

Cell therapeutics derived from Pluripotent Stem Cells (PSCs) are poised to revolutionize medicine by providing the ability to replace a wide range of cell types that are affected by degenerative diseases. The addition of gene editing technologies provides the added ability to edit PSCs to create cell therapies with enhanced potency and safety. As these promising new cell therapies are advanced into clinical trials, several challenges face the field. Developing new methods for assessing the safety of PSC-derived cell therapies will be a key focus of translational researchers in the coming years. The development of new in vitro test methods will allow PSC therapies to advance into clinical trials more quickly and at a lower cost while minimizing the need to perform costly and time consuming animal studies. In addition to the advancements in manufacturing and testing technologies, the regulatory framework is evolving to allow for rapid development of promising cell therapies for devastating diseases under the FDA's Regenerative Medicine Advanced Therapeutics (RMAT) designation. As groups advance new PSC therapies into human clinical trials, it will be critical to recognize key areas of CMC that should be addressed early in cell therapy development and to continue to develop new technologies to address aspects of cell therapy process scalability and safety.

## **Critical Elements in the Development of Pluripotent Stem Cell Based Therapies for Human Degenerative Diseases: Examples in Neurological Diseases** *Jane S. Lebkowski, Ph.D.*

Pluripotent Stem Cells (PSCs) such as human embryonic stem cells can proliferate indefinitely yet, upon appropriate cues, differentiate into all somatic cell lineages. These two properties of PSCs enable the development of therapeutic cell populations which can be batch manufactured in central manufacturing facilities, cryopreserved, and distributed for "on demand" use at healthcare providers. Protocols have been developed to differentiate PSCs into neural, cardiomyocyte, islet, hematopoietic cell and other cell populations which have been shown to be functional in either in vitro or in vivo animal models of human disease. For example, PSCs have been differentiated into oligodendrocyte progenitor cells and retinal pigmented epithelial (RPE) cells that upon transplantation into animals with spinal cord injuries and a genetic retinal degenerative disorder, respectively, can support the survival, integration, and function of the cells leading to improved clinical outcome. Extensive preclinical studies have been completed to examine the activity, biodistribution, dosing, delivery, and potential toxicity and tumorigenicity of these cell implants. The safety and activity of these cell-based implants is now being tested in Phase 1/2a clinical trials in subjects with spinal cord injury and geographic atrophy. Critical elements including the manufacturing, preclinical development and clinical development PSC based therapies will be discussed with emphasis on preparing for first-in-human and advanced clinical studies.

## **1997-2017: Two Decades of Evolution in Stem Cell Therapy Regulation - *A pas de deux* Between Scientific Discovery and Policy**

***Richard McFarland, M.D., Ph.D.***

Classically, new FDA regulatory frameworks are generated during a fusillade of activity in response to discreet, notable incidents often termed public health crises. In fact, the history of the current biologics regulations in the United States dates back to an incident in 1901 involving a pediatric diphtheria epidemic caused by a manufacturing error in an early diphtheria vaccine. However, in the case of stem cell regulation it has been a more prolonged back and forth between scientific discovery and FDA regulation over the last 20 years. The evolution of the framework has been punctuated with new scientific discoveries repeatedly prompting potential need for tailoring of the regulatory framework to reflect the newly evolved science. This tailoring of the framework occurred both in the form of formal policy development, and more subtly through the case by case review of products as specific investigational applications were presented to the agency. The history of these two decades of dance, *a pas de deux* between conversation partners, which has resulted in the current regulatory framework for stem cell therapies in the United States will be described in the presentation. The current, relatively mature, framework attempts to provide the correct balance between two, sometimes seemingly at odds, missions of the FDA; namely to improve the public health by allowing the development of innovative products while at the same time protecting the public health from unsafe products.

## **Cardiovascular Progenitors from Human Pluripotent Stem Cells for the Treatment of Heart Failure: A Translational Experience**

***Philippe Menasché, M.D., Ph.D.***

The rationale for using pluripotent, and particularly embryonic stem cells (ESC), in patients with heart failure primarily stems from the assumption that regeneration of scarred myocardium likely requires the supply of cells phenotypically matched to the target tissue, regardless of whether they act by generating a new myocardial tissue or, more likely, by harnessing endogenous repair pathways. This approach is made possible by the intrinsic pluripotentiality of ESC which allows to drive their fate in vitro towards a cardiac lineage. Consequently, our program has targeted the generation of early cardiac progenitors which, experimentally, have proven their ability to differentiate into cardiomyocytes in a clinically relevant scenario of allogeneic transplantation in nonhuman primates. The clinical translation of this program has entailed a stepwise approach including the following steps : (1) the expansion of hESC to generate cell banks under Good Manufacturing Practice conditions (GMP); (2) a growth factor-induced cardiac specification; (3) the purification of committed cells by immunomagnetic sorting to yield a SSEA-1-positive cell population strongly expressing Isl-1 taken as a marker of their early stage of differentiation; (4) the incorporation of these cells into a fibrin scaffold intended to be epicardially delivered onto the infarcted area; and (5) a safety assessment focused on (i) the loss of teratoma-forming cells and (ii) the absence of cytogenetic abnormalities and of microbiological contamination. Put together, these data have led to the first-in-man clinical trial of transplantation of these SSEA-1+ progenitors in 6 patients with severe left ventricular dysfunction and otherwise candidates for a coronary artery bypass operation. The primary end point was safety at one year and focused on (1) cardiac or off-target tumor, assessed by imaging (computerized tomography and 18F-FDG positron emission tomography scans), (2) arrhythmias, detected by serial interrogations of the cardioverter-defibrillators implanted in all patients, and (3) alloimmunization, assessed by the presence of donor-specific antibodies. One patient died early postoperatively from treatment-unrelated comorbidities. All others had uneventful recoveries. With a current median follow-up of 18 months, no tumor has been detected and none of the patients presented arrhythmias. Three of them

developed a clinically silent alloimmunization. All patients were symptomatically improved with an increased systolic motion of the cell-treated segments. This trial demonstrates the technical feasibility of producing clinical-grade hESC-derived cardiovascular progenitors and supports their short- and medium-term safety, thereby setting the grounds for adequately powered efficacy studies. However, our parallel experimental findings that the cardioprotective effects of these ESC-derived cardiovascular progenitors could be duplicated by the sole injection of the extracellular vesicles that they secrete also open the way to a new paradigm of cell-based a-cellular therapy whereby pluripotent stem cell-derived differentiated derivatives could be assigned the new role of exclusive in vitro producers of a purified secretome considered as the “active substance.

### **Development of a Stem Cell Derived Pancreatic Islet Cell Therapy for the Treatment of Diabetes**

***Felicia Pagliuca, Ph.D.***

Semma Therapeutics is a preclinical stage biotechnology company with the mission to transform the treatment of diabetes through development of stem cell derived pancreatic islets, including insulin-producing beta cells, to be used as a cell replacement therapy. Diabetes results from the dysfunction and/or destruction of the insulin-producing beta cells in the pancreatic islet. The development of replacement sources of beta cells, combined with effective methods of delivery back into the patient’s body, has the potential to “cure” the disease. Recent breakthroughs have enabled virtually unlimited production of replacement beta cells through pluripotent stem cell differentiation. At Semma, we are focused on further optimization and innovation in differentiation technologies, manufacturing scale-up, and characterization of stem cell derived islets in preclinical studies in order to move into clinical trials. In parallel, we have engineered innovative encapsulation solutions, using novel materials and device configurations, to solve the challenge of delivering and protecting these therapeutics from immune destruction. Ongoing development activities are focused on bringing this novel product to first in human clinical trials.

### **Universal Donor Stem Cells**

***David Russell, M.D., Ph.D.***

The clinical use of pluripotent stem cell (PSC)-derived products is limited by allogeneic rejection, primarily due to differences in the diverse human leukocyte antigen (HLA) genes, and the use of autologous induced PSCs or the establishment of HLA-typed PSC banks are problematic due to the large number of cGMP-grade cell lines that must be prepared, characterized, and approved by regulatory agencies. I will describe an approach for generating universal donor PSCs, which allows a single PSC-derived cell product to be used in multiple recipients. Gene editing with recombinant adeno-associated virus vectors is used to efficiently alter genes involved in HLA expression, without the use of potentially genotoxic nucleases. Through this process, we eliminate cell surface expression of polymorphic HLA class I and class II molecules, which prevents peptide presentation to T cells and recognition by anti-HLA antibodies. Gene editing is also used to reintroduce a non-polymorphic class I molecule and thereby prevent lysis by Natural Killer cells. These HLA-engineered universal donor cells resist allogeneic responses of NK, B and T cells, both in vitro and in vivo in humanized mouse models. Universal donor PSCs can be differentiated into diverse therapeutic cell products that are compatible with all recipients, and they allow the production of off-the-shelf cellular therapy products for many indications.

### **Developing a Pluripotent Stem Cell-based Therapy for Parkinson’s Disease**

***Lorenz Studer, M.D.***

[TBA]