Stem cells have the potential to treat many diseases, including eye diseases. On December 5-6, 2016, the National Eye Institute (NEI) convened 75 leading stem cell researchers, clinicians, and relevant stakeholders from private foundations, the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH), to discuss the state of the science, progress, challenges and the pathways necessary to translate the science and technology of stem cells to clinical trials for therapy. Cell types discussed included bone marrow (BMSCs), adult stem cells, embryonic (ESCs), corneal limbal stem cells, neural and retinal progenitors and induced pluripotent stem cells (iPSCs).

Overview of the basic science of stem cells
The meeting opened with a comprehensive overview of the biology and types of stem cells. Varying levels of cell fate potential, from totipotent, pluripotent, multipotent, unipotent to determined were presented. Participants discussed the developmental origin and the biological function of mesenchymal stem cells (MSCs) as multipotent cells. Data presented showed that MSCs are not all the same. Analyses of MSCs taken from different tissues show that they have different transcriptomes and different differentiation capacities, and that there is no common, ubiquitous MSC. Paracrine, immunosuppressive and immunomodulatory effects of these so-called MSCs remain poorly understood. The origins of adult and embryonic stem cells were also reviewed and compared with iPSCs, which are pluripotent cells that have been reprogrammed from differentiated cells. Participants also discussed the history of how corneal limbal stem cells moved from an emerging scientific area with promise to an established therapy and what lessons were learned from that experience.

Replacement vs. rescue/repair strategies
The vision research community is engaged in using stem cells to rescue, repair or regenerate dead or dying cells. Studies are underway to replace the retinal pigment epithelium (RPE), the tissue that supports rod and cone photoreceptors (the light sensing cells of the eye). Chief challenges to replacement therapy include survival of the transplanted cells and integration in the microenvironment where host cells are degenerating. In such an environment, stem cell-derived RPE, delivered as a bolus of injected cells, often die after transplantation. Furthermore, recent reports using photoreceptor precursors suggest that transplanted cells do not replace lost cells or integrate into the retina, but rather they transfer some of their contents to recipient cells.

Several ongoing approaches incorporate the use of a scaffold to maximize RPE cell longevity and integration in the eye. Scientists have learned that survival is optimal when cells are delivered to transition zones, where diseased retinal tissue transitions into relatively healthy tissue. These current RPE replacement studies are informing efforts aimed at replacing neural retinal cells; photoreceptors and ganglion cells.
An alternate approach is the use of stem cells to rescue/repair diseased tissues. These cells appear to work by a paracrine effect, presumably through the release of small molecules/survival factors. Additional research is needed to characterize this mechanism. Use of stem cells to rescue tissues at earlier stages of disease should also be further explored. The participants noted the ethical challenges of testing such approaches on patients with usable vision. While there was some support for using non-eye cells (e.g. bone marrow cells) for their trophic paracrine support, there was greater enthusiasm for the tissue replacement approach.

**Cell Authenticity**

Workshop participants advocated for establishing best practices and optimal criteria to thoroughly characterize relatively differentiated cells *in vitro* to ensure authenticity (i.e. “Gold Standard”, e.g. human RPE cells) prior to transplantation into humans. This is important for determining the potential for tumorigenicity as well as studying efficacy and long term cell survival.

**Cell source: autologous vs. allogeneic**

The issue of immune rejection of transplanted cells is complicated and not well understood. Autologous cells from the patient are preferable due to fewer concerns about immune rejection, but the time and expense necessary to develop iPSCs from autologous sources are much greater. Nevertheless, development of an autologous iPSC-RPE therapy is nearing IND filing and clinical application. Alternatives to autologous sources were also considered including allogeneic approaches and an “off-the-shelf” strategy based on HLA characterization that would allow a single donor to serve as cell sources for many patients. 2

**Stem cell clinical trial requirements**

Participants were challenged to propose requirements for a well-designed human stem cell clinical trial. These include:

- Identifying target disease and a stage for treatment – Depending on the disease and stage, the cell therapy strategy might be different. Example: late-stage age-related macular degeneration (AMD) and retinitis pigmentosa (RP) would require RPE or photoreceptor replacement, whereas at earlier stages, a cyto-protective (paracrine) therapy may be appropriate.
- Developing a robust and controlled manufacturing process to determine batch to batch variability and clinical product purity.
- Developing release criteria to authenticate cell identity and define the mechanism of action of the cell therapy product – ensure that the cell meets its “critical quality attributes.” Examples: cell authentication, potency assays, potential mechanism of action.
- Designing toxicity and tumorigenicity studies of the clinical product to be used in patients using the clinical dose (human equivalent in an animal). These procedures must be GLP-qualified.
- Developing animal models to test efficacy and determine *in vivo* mechanism of action of the cell therapy product – Necessary to predict potential success or failure of the cell therapy product in patients. Efficacy endpoints in animal models should reflect the cell therapy product’s mechanism of action.
- Developing minimally invasive procedures to deliver the cell therapy products in the eye to minimize the possibility of adverse events. For example, leakage of cells from the sub-
retinal space to the vitreous cavity may lead to proliferative vitreoretinopathy (PVR); patch transplantation in the sub-retinal space increases the likelihood of retinal detachment.

- Creating clinical protocol including exclusion/inclusion criteria for patient selection – Various patient cohorts were considered.

**Unregulated stem cell clinics & educating the public**

Participants discussed the proliferation of unregulated or “rogue” stem cell clinics that offer unapproved non-monitored stem cell therapies, a topic recently addressed in a *New England Journal of Medicine* perspective by the FDA. Disastrous outcomes, in some cases enucleation of the eye, resulting from these untested therapies not only pose serious public health risks but also threaten to undermine progress in the field. Some of these clinics list their services on ClinicalTrials.gov, fostering the misperception that they are rigorous clinical trials with approval from the FDA or having NIH sponsorship. Both the CEO of the American Academy of Ophthalmology (AAO), the largest association of eye physicians and surgeons with a global community of 32,000 medical doctors, and the President of the American Academy of Retinal Specialists, the largest retina organization in the world, took strong stances on the issue of “stem cell tourism.” This is a broad problem rooted in the public domain and not consistent with scientific methods and validation. Participants discussed the ethics of using non-monitored stem cell methods on patients as well as approaches to increase public understanding of the hazards and current limitations of stem cell therapies, citing educational roles for professional societies and clarifying that registration on ClinicalTrials.gov does not denote FDA or NIH approval. NOTE: Regarding ClinicalTrials.gov, the NEI contacted the NIH Office of Science Policy (OSP) post-meeting. OSP staff are aware of this issue and have plans to post a statement on the ClinicalTrials.gov site when it is next upgraded.

**Possible roles for NEI/NIH**

Discussion of potential roles for NEI/NIH included: (1) continue to support rigorous clinical trials that elucidate critical next steps leading to therapy; (2) partner with other NIH institutes to support basic research to address stem cell toxicity/tumorigenicity and the optimal delivery devices and routes of stem cell and derived therapies; (3) along with the vision community, develop novel endpoints to assess treatment response that take into consideration daily function and quality of life in addition to visual acuity; (4) establish reference datasets to facilitate the authentication of cell types; and, (5) continue outreach efforts with professional organizations regarding their ongoing monitoring of unapproved stem cell ocular applications.

**References**