National Eye Institute Audacious Goals Initiative Workshop

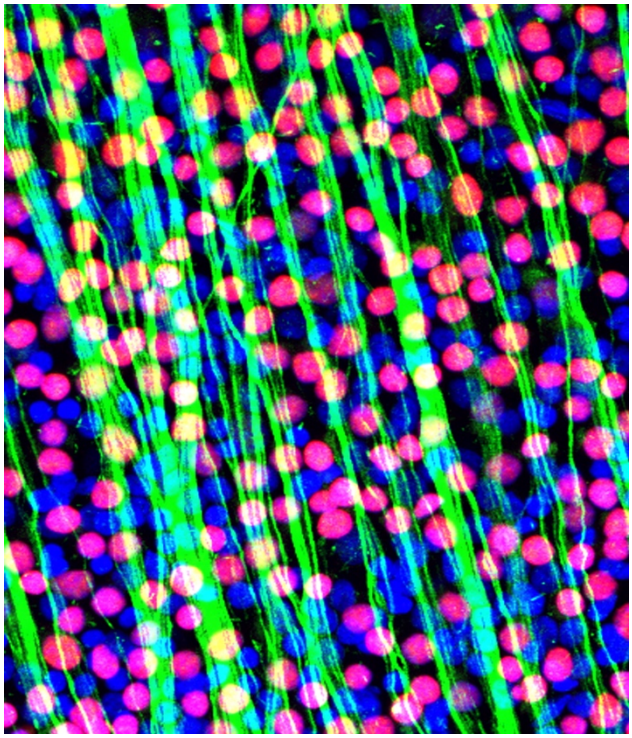
Understanding Human Retina Biology and Perception

Executive Summary

September 15, 2021

Background

The NEI's audacious goal is to replace damaged retinal cells, re-establish their connections to the visual centers in the brain, and restore vision. A milestone toward achieving this goal is to develop regenerative therapies for blinding diseases that mature to the point of being testable in human clinical trials. Outcome measures to establish the safety and efficacy of regenerative therapies will require proof of successful transplantation of therapeutic cells, survival of transplanted and endogenous cells, circuit reconnection, and vision improvement. The overarching objective of this exploratory workshop, held February 7, 2020, was to identify gaps in our knowledge regarding human retinal biology resulting in limitations to achieve visual restoration and percepton of light, motion, form and color. The workshop also aimed to identify current barriers to progress and to discuss new or existing technologies, shared resources or other factors hindering translation to human studies. Overall, the topic of the workshop was perceived as large in scope for one workshop. A number of limitations and new opportunities were identified as summarized below.



Caption: Retinal ganglion cell soma (Brn3a, Red) and their axons (pNFH, green) counterstained with DAPI (blue) from a piece of wholemount thirteen-lined ground squirrel retina. Imaged by Francisco M. Nadal-Nicolás (Wei Li Lab/NEI)

Understanding the biology and regenerative capacity of distinct cell types in the human retina

Studies are underway to develop a useful cell atlas of the human retina. However, there is a lack of understanding of which human retinal cells are most vulnerable in disease and how many of them have to be replaced to restore functional vision. In-depth molecular analyses to further understand differences between resilient and vulnerable cells as well as their regenerative capacity would be useful. To this end, there is a tremendous need for NIH-facilitated resources to enhance

the availability of human retinal tissue in excellent conditions for research. In addition, a better understanding of the precise connectivity of the transplanted cells within the retina and with brain targets will be critical to ensure circuit functionality. New retinal prosthetics, currently in clinical trials, could shed light on which cells are being stimulated and the range of visual function restoration experienced. An important consideration is the status of visual pathways and centers in the brain, which are likely to undergo remodeling in conditions of reduced or absence of visual input at different disease stages. It will be critical to implement neuroprotective strategies to preserve the structure and function of remaining cells as they can improve the milieu and enhance connectivity of the engrafted cells.

Selection of target cells and disease(s)

A disease or small group of diseases needs to be selected as the initial targets of the AGI efforts to identify next steps towards human studies. The most prevalent diseases affecting photoreceptors and retinal ganglion cells are age-related macular degeneration and glaucoma, respectively, therefore these are logical targets. The natural history of the chosen diseases must be characterized to enable clinical trials that can distinguish therapeutic effects from natural disease progression. In-depth structural and functional characteristics of the diseased retina is needed to determine the stage of the target disease(s) with the greatest potential for a clinically significant outcome. Research must pinpoint the most functional visual circuits in the lateral geniculate nucleus and cortex and in various disease states to enable clinical trials to use functional imaging (e.g., fMRI) and psychophysical approaches to demonstrate vision improvement. Research is needed to develop psychophysical methods to monitor disease progression and therapeutic efficacy. The ultimate goal of developing human regenerative therapies will necessitate a mechanism that supports a multi-disciplinary approach in which cell biologists, ophthalmologists, psychophysicists, patients, and sponsors work together to tackle this challenge.

Optimizing the retinal microenvironment to enhance survival, integration, and regeneration

What can be done to create growth-friendly microenvironments for transplanted cells? The retina, optic nerve, and brain microenvironments change with disease progression. Inflammation, oxidative stress, and metabolic dysregulation will affect not only the transplanted cells but also surviving neurons and glia that are essential for tissue function. A better understanding of how the microenvironment in the human retina and visual pathways change during disease onset and progression will be essential to increase the success of transplantation efforts. Future studies should focus on in-depth analyses of disease processes including gene and protein expression, lipid composition, extracellular matrix, immune response, oxidative damage, nutrient and vascular deficits in the human retina, optic nerve, and brain targets. Saving or rejuvenating surviving cells in degenerative disease is likely more promising in the near term than cell replacement for some diseases, such as glaucoma. The scarcity of human donor tissue has been a significant barrier to answering these questions. Human tissues need to be more available for research studies, and we need improved protocols for preserving tissue at the time of collection.

Creating better non-human primate (NHP) models of human disease

Some retinal circuits are unique to humans and NHPs including the fovea, which is required for high-level functions such as reading and recognizing faces. A better understanding of primate-specific circuits is crucial for evaluating the potential of cell-based therapies to treat human

blinding disorders. The development of NHP models that reproduce the onset, progression, and pathological signatures of eye diseases is needed to obtain insights into human retinal biology and perception. Studies are needed to explore the possibility of creating relevant and useful NHP models of target disease(s) by making diseased patches of retina (e.g. using viral-mediated gene delivery) to investigate retinal and cortical circuitry. In addition, molecular analysis of resilient versus vulnerable cells and circuits as well as natural history data from these NHP models will be required to evaluate their usefulness to test the therapeutic potential of regenerative strategies.

Conclusions

This workshop revealed crucial issues that need resolution before stem cell transplantation can be tested in human clinical trials. A better understanding of the natural history and progression of blinding conditions in humans as well as insights into disease mechanisms are required to select the most amenable disease(s) for transplantation/regenerative therapies. The scarcity of research quality human tissue is a major limitation. Studies are needed to better define and validate the structural/functional outcome measures and perception (e.g. imaging, psychophysics) to monitor the effect of regenerative therapies in humans. In addition, clear and reproducible readouts from cell transplantation studies in NHP models are urgently needed to move forward. Several issues addressed in previous AGI workshops, including a limited understanding of the diseased retinal microenvironment, shortcomings of current functional human retinal imaging, and lack of translation-enabling NHP models, were also identified here and remain barriers for substantial progress.

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NEI leads the federal government's research on the visual system and eye diseases. NEI supports basic and clinical science programs to develop sight-saving treatments and address special needs of people with vision loss. For more information, visit https://www.nei.nih.gov/.

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