

# Report on the National Eye Institute Audacious Goals Initiative: Regenerating the Optic Nerve

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See the appendix for the participants of the NEI Audacious Goals Initiative Workshop.

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The National Eye Institute (NEI) hosted a workshop on November 19, 2014, as part of the Audacious Goals Initiative (AGI), an NEI-led effort to rapidly expand therapies for eye diseases through coordinated research funding. The central audacious goal aims to demonstrate by 2025 the restoration of usable vision in humans through the regeneration of neurons and neural connections in the eye and visual system. This workshop focused on identifying promising strategies for optic nerve regeneration. Its principal objective was to solicit input on future AGI-related funding announcements, and specifically to ask, where are we now in our scientific progress, and what progress should we reach for in the coming years? A full report was generated as a white paper posted on the NEI Web site; this report summarizes the discussion and outcomes from the meeting and serves as guidance for future funding of research that focuses on optic nerve regeneration.

Keywords: optic nerve, regeneration, goals, National Eye Institute, vision restoration

**I**njury to or neurodegeneration of the optic nerve underlies vision loss in many diseases, including glaucoma, ischemic and traumatic optic neuropathies, as well as retinal artery or vein occlusions, and many others. Normally, in humans and indeed in all mammals, there is no regenerative response, and the failure of injured or degenerating retinal ganglion cells (RGCs) to reconnect their axons through the optic nerve to their natural targets in the brain explains the irreversibility of such vision loss. A full white paper was published by these authors and is available on the National Eye Institute (NEI) Web site (in the public domain; available at [https://nei.nih.gov/audacious/optic\\_nerve](https://nei.nih.gov/audacious/optic_nerve)).

The NEI's Audacious Goals Initiative (AGI) program was initiated in 2012, searching for big ideas to bring the energy of the eye and vision research community into a chosen single audacious goal: to restore vision by regenerating neurons and their neural connections in the eye and visual system. To understand progress to date in the sciences relevant to optic nerve regeneration, and more specifically to identify focal areas for funding, the NEI convened a workshop in November 2014 in Washington, DC. Participants (see appendix) represented a variety of research areas relevant to optic nerve regeneration, from developmental neurobiology to visual processing. Over the course of a 4-hour roundtable discussion, the workshop reviewed the current state of the science and addressed knowledge gaps in and barriers to scientific progress (Tables 1 and 2), and identified key areas for discovery research.

## STEPS TO OPTIC NERVE REGENERATION

What will it take to restore vision in optic neuropathies, and what must happen to rescue an injured or dying RGC? Workshop participants outlined steps necessary for promoting successful optic nerve regeneration and restoration of vision.

### RGC Survival

Survival is obviously a requirement for cellular or axon regeneration; thus, preventing RGCs from degeneration and subsequent death in the face of injury or disease is a critical first step. Retinal ganglion cell response to insult was also discussed, as the molecular pathophysiology of different insults, be they glaucomatous, ischemic, traumatic, inflammatory, or others, is still the subject of intense investigation. Although such questions hold great promise, developing therapeutic approaches to restore vision may not always require a complete understanding of the underlying causes of disease. Considerable progress in dissecting molecular pathways involved with RGC death in a number of preclinical models of human diseases has been made,<sup>1,2</sup> although translational testing in humans with various optic neuropathies has been slow to follow.

A related area of considerable interest is RGC-type specificity. Retinal ganglion cells can be divided into different types based on morphology, receptive field properties, and more recently, by genetic markers.<sup>3,4</sup> Important questions were

**TABLE 1.** Gaps in Knowledge and Other Unknowns

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Lack of information about mechanisms underlying disease and injury-related regeneration
Why do retinal axons exhibit a weak capacity to regenerate? Are RGCs unique in their inability to regenerate?
How do retinal axons regenerate? What are the mechanisms of transport and trafficking?
Is regeneration of RGC type-specific?
What is the role of RGC activity after injury?
What are the relevant cues that guide long-range growth, target selection, and synapse formation?
How do nonneuronal factors, such as glia or extracellular matrices, influence regeneration?
Experimental models: standards and uniformity
Optic nerve crush (useful to evaluate regenerative therapies, but far less common in humans than ischemic or pressure-induced injuries)
Intraocular pressure (good for quantifying cell death and axon loss but less reproducible and more challenging for studying regenerative growth or restoration of vision)
Ischemic optic neuropathies (reproducible but less well studied)
Cell culture models
Timing of delivery of therapies, importance of finding “postinjury” efficacy
Comparative and standardization issues (age, onset of injury, response to injury)
Animal Models
Species selection: utility of fish, rabbit, rodent, non-human primate models
Need for translational bridges to humans
Early-phase human testing to help define goals and approaches
Outcomes
Behavioral assays linking structure to function
How many neural connections are enough?
Can “vision” areas be targeted?

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identified as high priority: do different RGC types exhibit varying degrees of vulnerability to injury or disease? Do some types show more regenerative capacity than others?

### Axon Growth

Both short (across an injury site) and long distance growth (back to central visual targets) must be addressed and may involve separate signaling pathways. Considerable progress has been made in identifying candidate molecules that stimulate axons to grow across an optic nerve injury site.<sup>5,6</sup> Manipulation of local glial, vascular, and inflammatory responses all deserve additional attention, and testing combinatorial therapies and evaluating the quality of regenerative growth, including axon guidance, remain largely unexplored and should represent a major objective of the AGI. Indeed, the next major challenge is to encourage long distance growth to appropriate targets while minimizing aberrant growth and sprouting.<sup>7,8</sup> While much progress has been made to understand the mechanisms underlying guidance, target selection, and synapse formation of developing axons, little is known about how regenerating axons perform after injury.<sup>6,9,10</sup> Workshop participants generally dismissed the requirement that regenerative axon growth should necessarily recapitulate developmental patterning regarding pathway choice, target selection from the dozen different subcortical targets for regenerating RGCs to choose from,<sup>11</sup> or specificity of synaptic connectivity.<sup>12</sup> In regenerating axons, what steps need to be taken to prevent an aberrant projection from developing and innervating the spared/undamaged retina or inappropriate

**TABLE 2.** Barriers to Progress/Current Needs

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Science/Technology
Development of better functional and behavioral assays;
Improved viral/nonviral manipulation of inhibitory/regenerative signaling pathways;
Validated molecular markers for primate and human retina;
Better tools/technologies to perform in vivo deep brain imaging;
More “omics” approaches to provide genomic and proteomic resources for higher throughput screening and discovery research.
Nonscientific/Sociologic
Improved mechanisms to build teams or promote collaborative research;
Improved communication of positive AND negative results;
Shared resources (e.g., core facilities for viruses, ultrastructure, compound libraries, behavioral assays);
Dissemination of standard models.
Achieving final goals
Bridges from basic research to clinical research;
Begin early phase testing (need to learn from human patient experiments);
Support to identify and test innovative human biomarkers of regenerative biology.

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areas in the brain? Since target selection is cell-type specific, getting specific RGC types to innervate the appropriate target and become reintegrated into existing or remodeled circuits may be crucial, although questions on circuit reintegration in the adult are largely unstudied. Thus, it will be important to identify guidance cues and synapse formation signaling pathways in a regenerative environment. Indeed, some axon growth-promoting regenerative therapies may introduce guidance or synapse formation problems, while others may not, suggesting that all regenerative therapies may not be equal. Within this context, however, there was discussion that RGC innervation of brain targets subserving image formation may be more important than promoting regeneration of RGCs dedicated to non-image-forming functions such as pupillary light response or photoentrainment of circadian rhythm.

### GAPS IN SCIENTIFIC KNOWLEDGE AND BARRIERS TO PROGRESS

The workshop’s subsequent focus was to identify and elaborate on the present gaps of knowledge in the area of optic nerve regeneration; these are summarized in Table 1. Closely related to these gaps in knowledge was the discussion of which of these are significant barriers to progress, summarized in Table 2. Overcoming these gaps will help bring scientists together across disciplines to make major progress toward optic nerve regeneration and vision restoration.

### TRANSLATION TO HUMAN DISEASE

Perhaps most limiting in reaching the goal of restoring vision in humans is the lack of translational research and early phase human testing in RGC survival and regeneration. Research across other body systems has already demonstrated that human testing is extremely important, and certainly human patients with optic nerve diseases are eager to participate in appropriately vetted trials of new therapeutic candidates. Such initial testing of candidate therapies in humans will begin to address critical questions, such as: How important are fine points of circuit integration? Is it enough to give someone light perception or improve contrast sensitivity? Functional im-

provement is a big step, but it will also be necessary to perform human trials to learn how to measure axon regeneration and visual restoration in patients. Similarly, the workshop participants noted that, as a field, we should think backwards from the “clinic-of-the-future.” Having biomarkers for RGC function will be extremely important, as will having a delivery system with demonstrated safety. Moving treatments into human testing was identified as something that could be done quickly, within 5 years, and would help the field determine how to conduct clinical trials in a shorter time frame.

## A VIEW TO THE FUTURE

Based on workshop consensus, immediate goals should include extending work to enhance regeneration in current animal models, solving axon guidance and central targeting in regeneration, and crossing into human testing for both validating biomarkers and testing candidate therapies. Other first-move approaches should include building resource centers and expanding functional or behavioral testing assays in preclinical models. The group appreciated that although disease pathophysiology remains an important separate goal, one therapeutic solution might ultimately address many different optic neuropathies, and that identifying candidate therapies should be a major focus of the AGI.

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## APPENDIX

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