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

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ABSTRACT

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? This report summarizes input from the meeting and serves as guidance for future funding of research that focuses on optic nerve regeneration.

INTRODUCTION

The NEI's Audacious Goals Initiative (AGI) program initiated in 2012. At that time, the AGI began by soliciting big ideas suitable to bring the energy of the eye and vision research community into one or more audacious goals. Initially nearly 500 proposed ideas were reviewed by 80 outside extramural scientists, whittled down to 10 prizes, and divided into 7 groups. The single audacious goal chosen was to regenerate neurons and their neural connections in the eye and visual system, and this was subsequently separated into two primary goals, replacing degenerated photoreceptors, and regenerating axons in the optic nerve.

Injury 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. Thus the AGI's goal of restoring vision through promoting successful optic nerve regeneration recognizes the critical importance of understanding and reversing regenerative failure.

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 D.C. The workshop was chaired by Jeffrey Goldberg, University of California San Diego, and William Guido, University of Louisville. The meeting was sponsored by the NEI with planning oversight by the AGI Steering Committee and AGI Liaison Steven Becker.

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 four-hour roundtable discussion, the workshop reviewed the current state of the science and addressed knowledge gaps in and barriers to scientific progress. It also identified key areas for discovery research. Here we capture the major points emphasized through the workshop as critical to achieving the goal of restoring vision by optic nerve regeneration.

STEPS TO OPTIC NERVE REGENERATION

The workshop organized its initial discussion by outlining what it will take to restore vision in optic neuropathies, and what must happen to rescue an injured or dying retinal ganglion cell (RGC). The workshop participants first outlined the factors necessary for promoting successful

optic nerve regeneration and restoration of vision. These include RGC survival, axon growth and guidance, central target selection, and synapse formation and circuit integration.

RGC survival

Without a fundamental understanding of the mechanisms underlying RGC survival, regeneration is not possible. Thus, preventing RGCs from degeneration and subsequent death in the face of injury or disease is a critical first step. The field has made considerable progress in dissecting molecular pathways involved with RGC survival and death, and in a number of pre-clinical models of human diseases, RGC death can be slowed or prevented, at least over short time periods (Danesh-Myer 2011; Chan and Goldberg 2012). While a number of candidate therapies have been evaluated in animals, their translation to humans with various optic neuropathies is lacking.

A related area of considerable interest identified by workshop participants dealt with RGC cell type specificity. RGCs can be divided into different types based on morphology, receptive field properties and more recently by genetic markers (Masland 2012; Sanes and Masland, 2015). The use of genetic markers to tag and study specific RGC types is still a nascent area of research, but by all accounts one that harbors great potential for identifying new pathways relevant to RGC survival (as well as axon growth and targeting, discussed below). A number of related questions were identified as high priority. For example, do different RGC types exhibit varying degrees of vulnerability to injury or disease? Alternatively do some types show more regenerative capacity than others?

RGC response to insult was also discussed, as the molecular pathophysiology of different insults, be they glaucomatous, ischemic, traumatic, inflammatory, or others, are still subject to intense investigation. Whether RGCs become hyper- or hypo-active after insult remains to be determined. Although there was consensus that such questions hold great promise, it was also acknowledged that understanding the molecular pathophysiology of disease is in some ways independent of promoting survival and regeneration. Thus, developing therapeutic approaches to restore vision may not require a complete understanding of the underlying causes of disease.

Axon growth

When considering axon regeneration, both short and long distance growth must be addressed. Proximal growth deals largely with the growth across an injury site (for example at the optic nerve head or along the optic nerve), while long-distance growth deals with issues related to axon guidance along central visual pathways.

Considerable progress has been made in identifying candidate molecules that can stimulate axons to grow short distances and across an optic nerve injury site (Pernet and Schwab 2014; Lu et al., 2014). Investigators are also exploring how modifications to the optic nerve injury site could regulate axon growth. Manipulation of local glial, vascular and inflammatory responses all deserve additional attention. The consensus of workshop participants suggested that although a number of promising molecular manipulations can promote growth, 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 that can eventually lead to appropriate target selection, while at the same time preventing aberrant growth and sprouting. Success in this area while promising has been limited (deLima et al., 2012; Li et al., 2015). While much progress has been made to understand the mechanisms underlying the guidance of developing axons, little is known about how regenerating axons perform these tasks

after injury (Giger et al., 2010; Liu et al., 2011; Pernet and Schwab, 2014). Moreover, it is not clear whether the mechanisms regulating the guidance of regenerating axons in the adult are similar to those that govern developing ones. Workshop participants generally dismissed the premise or at least the requirement that regenerative axon growth should have to recapitulate developmental axon growth.

There are three important "selection" steps to consider: what pathway to choose, what target to innervate, and finally, what neurons to form specific synaptic connections with Goodman and Shatz, 1993). The initial steps of axon guidance (pathway and target selection) are likely to rely on molecular guidance cues/gradients that either attract or repel growing axons. For example, a major challenge highlighted by workshop participants was to understand how regenerating axons traverse through the optic chiasm. What are the mechanisms that guide midline decisions, to cross or project ipsilaterally to travel centrally in the optic tract? In regenerating axons, what steps need to be taken to prevent an aberrant projection from developing and innervating the spared/undamaged retina or inappropriate areas in the brain?

Thus it will be important to identify guidance cues in a regenerative environment and determine whether successful guidance of regenerating axons requires a re-introduction and/or a remodeling of guidance molecules. Indeed, some axon growth-promoting regenerative therapies may introduce guidance problems while others may not, suggesting that all regenerative therapies may not be equal.

Selecting the proper target in the brain is also a daunting task given that there are up to a dozen different subcortical targets for regenerating RGCs to choose from (Dhande and Huberman, 2012). As pointed out by many workshop participants, since target selection is cell type specific, getting specific RGC types to innervate the appropriate target may be crucial. 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.

Additionally, workshop participants identified a number of other important questions. What roles do spared or degenerating axons play in regeneration, and do they serve as adequate pioneers to steer the growth of regenerating axons? To what extent in humans or in animal models does age or type of insult affect the propensity of regeneration? Are growth promoters and/or repressors needed, and do they need to be intrinsically programmed or applied exogenously? Finally, what role does neural activity play in promoting axon regeneration?

Synapse formation and circuit integration

Ultimately to restore visual function, regenerating axons must find the right target and then form precise patterns of connectivity with neurons in central visual targets. Although great progress has been made in determining how synapses form during early development, our understanding of how regenerating axons in the adult animal might form synapses and become re-integrated into existing or remodeled circuits remain largely unknown. Workshop participants discussed the importance of defining the microenvironment of synapse formation (priming, adhesive, inductive, stabilizing factors), understanding the role of activity in guiding the precision of connectivity, and finally, knowing the degree of cell type-specific targeting needed to achieve functional recovery. Indeed the relationship between restoration of synaptic transmission and degree of behavioral recovery is also not known.

GAPS IN SCIENTIFIC KNOWLEDGE AND BARRIERS TO PROGRESS

The workshop's main focus was to identify and elaborate on the present gaps of knowledge in the area of optic nerve regeneration. Based on the workshop discussion we found that many knowledge gaps could be grouped into a few general areas: fundamental mechanisms underlying disease and injury-related regeneration, standardization and uniformity among different experimental models, species selection and translation to humans, and finally, measurable outcomes (Box 1).

Mechanisms underlying regeneration

There was a strong sentiment among the workshop participants that fundamental gaps remain in our understanding of the underlying failure of regeneration in disease or after injury. How are some retinal axons induced to regenerate, and why do others exhibit only a weak capacity to do so even when presented with strong stimuli? Other important gaps include the cell type specificity of regeneration, the potential role activity plays in augmenting regeneration, and whether long range growth and target selection require specific guidance cues similar to those encountered during development.

Experimental models

Thus far RGC survival and regeneration has been examined in a variety of animal models, including optic nerve crush, cut, and ischemia, as well as intraocular pressure-induced insults relating to glaucoma. All of these have advantages and disadvantages in providing good models for discovery research and/or mimicking human diseases. For example, optic nerve crush models are extremely useful to evaluate regenerative therapies, but in humans, such injuries are far less common than ischemic or pressure-induced injuries. In contrast, intraocular pressure models are very good for quantifying cell death and axon loss but are less reproducible, and are considerably more challenging for studying regenerative growth or restoration of vision. This is particularly evident from the ongoing discussion among glaucoma researchers when trying to identify what axons are injured by raising eye pressure. This barrier to progress, discovering which axon was injured at what time, remains a major limitation to studying the promotion of axon regeneration in glaucoma models.

Barriers to progress were also identified in the lack of standardization of animal models. Non-standardized models provide some advantages: the opportunity to explore alternative models of nerve regeneration in order to explore a range of regenerative therapies, and the probability that a regenerative therapy that works more robustly in a variety of models might be more likely to translate to human conditions. However, standardized techniques are also important, particularly to attract new investigators to the field. In addition we must consider the duration of insult, and the length of the assay to study survival and regeneration. Testing of therapeutics should include both pre- and post-injury treatment testing, to mimic human acute and chronic injuries, respectively. Similarly, as we know little about how regenerative potential changes with aging, particularly after development, attempts to model regeneration in younger and older animals should be compared.

Finally, the lack of functional, behavioral assays for rodents and primates is also a barrier. Clearly the evidence for anatomic recovery should be the first priority, but workshop participants also emphasized that functional recovery needs to be closely followed up thereafter. Robust functional assays are needed for proof of principle in animal models to facilitate translation to human testing. These could bridge the hierarchy of priorities for restored function, from visual discrimination or acuity tasks at the top, down to circadian or pupillary light responses lower down in priority.

Animal Models: Species Selection
There is concern that successful therapeutic intervention developed in rodent or lower vertebrate models does not or cannot translate well to human pathological conditions. Given the paucity of work on nonhuman primate models, there was strong consensus that this is a much needed critical first step. Little work has been done to extend optic nerve regeneration to a non-human primate model, largely considered a critical step to translating research in rodent towards human testing. Researchers are developing primate models and looking for fidelity to human diseases, but questions remain about what species to use to drive this work forward. For example, marmosets are very small and easy to work with, although not much is known about their retinal and brain cell types. On the other hand, the macaque is better understood at the level of cells and circuits, but is a challenging model for a number of reasons, including an intraluminal membrane that is a barrier to drug or gene delivery in the eye. Although research has progressed in primate retinal physiology, almost nothing is known about axonal regeneration in non-human primates. There was consensus that the best candidate therapies should be tested in primates, with input from scientists focused on clinical translation.

In the other evolutionary direction, lower vertebrates including fish demonstrate endogenous RGC regeneration, but it is unclear how that happens. What can be learned from RGC regeneration in fish? How is the fish model translatable to humans? Discovery- based approaches to identify unknown factors in axon regeneration would be useful in this regard. Historical work on non-mammalian species may have fallen out of favor due to the many differences between fish and mammals, but updated scientific approaches may revive such comparative research and demonstrate new value.

Animal Models: 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 improvement is a big step, but it will 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 timeframe.

OPPORTUNITIES IN HOW WE DO SCIENCE

Closely related to these gaps in knowledge was the discussion of which of these are significant barriers to progress (Box 2), which led to brainstorming how, as a field, scientists in a variety of areas might come together to make major progress towards optic nerve regeneration and vision restoration.

Development and Dissemination of Tools and Technologies
A number of barriers to progress were identified in the limited access to specialized and expensive technologies. New progress in valuable approaches including in vivo imaging in

animals and humans, correlated light and electron microscopy (EM), 3D reconstruction from EM are examples. Robust viral vector technology including preparation of expensive materials would be necessary to accelerate progress across many laboratories, as would access to compound libraries and better non-viral methods of cell transduction in vivo. The lack of ability to image RGCs and their axons in vivo is another important barrier to overcome. Identification and imaging of biomarkers preceding RGC death might provide a way to test regenerative therapy. For many of these including EM and viral gene vector production, the establishment of core resources might be a way to expand the reach of such new technologies.

Building a Culture of Collaboration through Grant Mechanisms
New strategies for data sharing and collaborative research were emphasized, highlighting research consortiums, reproducibility studies, avenues for reporting negative results, and facilitated entry points for scientists or trainees who do not normally study RGC regeneration per se but are in related fields. It was generally felt that new RFA mechanisms that enable larger collaborative groups, as well as the use of contracts that could build imaging and molecular cores as mentioned above, would both greatly accelerate progress. Other discussion revolved around government (e.g., NIH), academia, foundations, and industry coming together to fund research.

Areas for Open-Ended/Non-Hypothesis Driven/Discovery Research
Mechanisms are also needed to encourage high throughput discovery research to move forward, even knowing that the payoff might not be immediate. NIH applications are likely to be more heavily favored when they have clear hypotheses and are not “fishing expeditions,” but there is much to discover in the field of optic nerve regeneration. Participants were asked to think of opportunities for discovery research that could benefit from specific NEI support. This could include generating and testing molecular targets through drug and gene screening, as well as high-content and high-throughput advances in imaging and gene delivery. Groups with dozens of researchers each could do such work in parallel if a mechanism to fund such an approach were supported.

At the same time, an openness to innovation was also emphasized. For example, an alternative approach raised during the workshop to get around the challenge of axon regeneration could be to focus on the plasticity of the central circuit. Can central visual plasticity be marshaled to restore vision? Such questions, although outside the explicit goal of promoting optic nerve regeneration, might yet restore vision in the same targeted diseases.

A VIEW TO THE FUTURE

At the end of the workshop, participants distilled the discussion into a consensus plan. Immediate goals included extending work to enhance regeneration in current animal models, to solve issues relating to axon guidance and central targeting, and to cross into human testing for both biomarker validation and for candidate therapeutic testing. Other first-move approaches included building resource centers and expanding functional or behavioral testing assays in pre-clinical 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.

BOX 1:

GAPS IN KNOWLEDGE AND OTHER UNKNOWNS

- 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? Mechanisms of transport and trafficking?
  - Is regeneration 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 non-neuronal factors such as glia or extracellular matrices influence regeneration?
- Experimental models: Standards and Uniformity
  - Optic nerve crush
  - Ischemic lesion
  - Intraocular pressure
  - Disease/Degeneration
  - Cell culture models
  - Timing of delivery of therapies, importance of finding “post-injury” 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
  - The 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?

BOX 2:

BARRIERS TO PROGRESS

- Science/Technology
  - Development of functional and behavioral assays
  - Better viral/non-viral manipulation of inhibitor/regenerative signaling pathways
  - Need molecular markers for primate and human retina
  - Need 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
- Non-Scientific/Sociologic
  - Better mechanisms to build teams or promote collaborative research
  - Need to improve communication of positive AND negative results
  - Resource sharing, e.g., core facilities for viruses, ultrastructure, compound libraries, and behavioral assays
  - Dissemination of standard models
- Achieving Final Goals
  - Bridge basic research to clinical research
  - Early phase testing (need to learn from human patient experiments)
  - Need to innovate and test human biomarkers of regenerative biology

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