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Special Commentary: Early Clinical Development of Cell Replacement Therapy: Considerations for the National Eye Institute Audacious Goals Initiative

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The National Eye Institute launched the Audacious Goals Initiative (AGI) in 2013 with the aim "to restore vision through the regeneration of neurons and neural connections in the eye and visual system." An AGI Town Hall held at the Association for Research in Vision and Ophthalmology Annual Meeting in 2016 brought together basic, translational, and clinical scientists to address the clinical implications of the AGI, with a particular emphasis on diseases amenable to regenerative medicine and strategies to deal with barriers to progess. An example of such a barrier is that replacement of lost neurons may be insufficient because damage to other neurons and non-neuronal cells is common in retinal and optic nerve disease. Reparative processes such as gliosis and fibrosis also can make it difficult to replenish and regenerate neurons. Other issues include choice of animal models, selecting appropriate endpoints, ethics of informed consent, and regulatory issues. Another area critical to next steps in the AGI is the choice of target diseases and the stage at which early development studies should be focused. For example, an advantage of doing clinical trials in patients with early disease is that supporting cellular and structural constituents are still likely to be present. However, regenerative studies in patients with late disease make it easier to detect the effects of replacement therapy against the background of severe visual loss, whereas it may be harder to detect incremental improvement in visual function in those with early disease and considerable remaining visual function. Achieving the goals of the AGI also requires preclinical advances, new imaging techniques, and optimizing translational issues. The work of the AGI is expected to take at least 10 years but should eventually result in therapies to restore some degree of vision to the blind. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Scientists have aspired for many years to cure blindness. Achieving this endeavor has been challenging, as many of the diseases associated with irreversible loss of vision involve retinal neurons, and most mammalian neurons do not regenerate. However, advances in stem cell technology and tissue engineering in the last several years have opened the possibility of replacing lost retinal neurons and restoring vision. As a result of these advances, as well as a challenge involving multiple stakeholders, the National Eye Institute (NEI) launched its Audacious Goals Initiative (AGI) in 2013 with the aim "to restore vision through the regeneration of neurons and neural connections in the eye and visual system." Since the inception of the AGI, the NEI has engaged the research community and organized several workshops and town halls to gather further input from the scientific community in specific areas critical to the AGI. These events have focused on bringing experts together in their respective fields to identify needs, gaps, and barriers to progress so as to further the AGI. Additional information on these events and the reports generated from them are available at www.nei.nih.gov/audacious. Brief updates on some of the preclinical and early clinical developments appear in the Updates section (Figs 1–4).

The most recent NEI Audacious Goals Initiative Town Hall was held at the annual meeting of the Association for Research in Vision and Ophthalmology in May 2016 in Seattle, Washington. Participants were asked by the NEI to help catalyze the important discussion about the clinical implications of the AGI, with a particular emphasis on diseases and disease states that are amenable to regenerative medicine.

To frame the discussion, the town hall began with presentations about which diseases of the visual system may be particularly wellsuited to regenerative medicine, followed by a free-ranging colloquy on possible pathways for clinical development, the pros and cons, the ethical issues, and the barriers to implementation, to propel the AGI from laboratory studies to clinical trials. This article provides a summary of the discussion that took place at the meeting, providing a perspective on the disease characteristics that need to be considered in these next phases of the AGI.

Identifying Barriers to Success

The potential barriers to success should be identified early, so that they can be mitigated. One specific barrier is that the

http://dx.doi.org/10.1016/j.ophtha.2017.02.017
ISSN 0161-6420/17

damaged neuronal circuitry present in late-stage disease is likely difficult to replace or reconnect. For the most part, regenerative strategies target one type of neuron, with the assumption that replacing it and connecting it to other neurons will suffice. However, in most chronic diseases other neuronal circuits are also damaged. This can include the loss of supporting cells, such as glia (astrocytes, oligodendrocytes), vascular supply, and retinal pigment epithelium (RPE). This is an area of active investigation in the regeneration field.

A second specific barrier is that as a result of the disease process, there may be gliosis and/or fibrosis, with aberrant remodeling of tissues. This scar formation can further serve as a barrier to regeneration, although recent work in spinal cord regeneration suggests that glial scars may have a more complex role in regeneration than previously thought and could even contribute to a pro-regenerative environment.[2]

One of the most difficult barriers is determining the clinical development pathway needed to translate regenerative methods developed in the laboratory to human patients, and it is this barrier that we will address in further detail here. Identifying the best diseases in which to test regenerative approaches is a key step. Determining the balance between early-stage safety trials in end-stage disease and trials that are capable of demonstrating efficacy in early-stage disease is complex. The assessment of success in the early stages of translation is critical. Most studies of drug therapies take place in phase 2 or phase 3 clinical trials involving hundreds to thousands of patients. In contrast, the early stages of assessing new AGI therapies will probably involve a small number of volunteers. Under these circumstances, there is a substantial risk of a false-positive result (i.e., an apparent effect of the therapy where one does not exist) or a false-negative result (i.e., a perceived lack of efficacy when there is actually success) buried in the noise of the measurement technique. A placebo effect must also be considered. These issues are addressed below and are summarized in Table 1.

Translation Considerations: Target Diseases

There are 2 classes of diseases that are targets for the AGI. One is retinal disease, where the target cell is the photoreceptor, the RPE, or both. The other is optic nerve disease, where the target cell is the retinal ganglion cell (RGC) and its axon.

Retinal Diseases

There are multiple retinal diseases that are targets for regenerative therapies. Two of the most relevant to cell-replacement therapy are age-related macular degeneration (AMD) and inherited retinal degenerations. The most common cause of irreversible blindness in most developed countries is AMD. Although AMD does not result in complete blindness, the involvement of the central retina drastically reduces the quality of life of patients with this disease. New therapies such as anti-angiogenic drugs have improved the visual outcome in many patients, but long-term follow-up suggests that most patients end up with poor vision; this is likely due to continued progression of the neurodegenerative disease.[3,4] In addition, there are patients who lose vision as a result of either early fibrovascular scarring from neovascular macular degeneration or from advanced non-neovascular AMD, or geographic atrophy. These patients would be candidates for restoration of vision targeted to the macula.

A second group of retinal diseases are the inherited retinal degenerations, such as retinitis pigmentosa. These typically progress over years, beginning in the periphery and eventually involving central vision. Ultimately, complete blindness can occur. Some forms present earlier and with a more severe course, e.g., Leber congenital amaurosis. These patients could benefit from improvement in either central or peripheral vision.

A third group are diseases where trophic factor-mediated cell rescue may be particularly effective in the early stages, e.g., diabetic retinopathy or acute retinal detachment. In diabetic retinopathy there is early alteration of neuronal connections, and in acute retinal detachment there is separation of the neural retina from the underlying. Both may be mitigated by paracrine-delivered trophic support in the acute stages, while cell-replacement therapy may be less helpful in the late stages because of structural changes associated with the disease.

Optic Neuropathies

Optic neuropathies are the other main class of eye diseases suitable for regenerative therapies. The most common cause of irreversible blindness worldwide and the second most common in developed countries is glaucomatous optic neuropathy, or glaucoma. Glaucoma is characterized by progressive injury to the RGC axon occurring at the optic nerve, with consequent loss of the rest of the axon and the RGC body. The disease typically occurs over decades. In the chronic stages, there may be loss of the afferent (retinal bipolar cells) and efferent (lateral geniculate) neurons. Because complete blindness occurs in a substantial number of patients with glaucoma, any restoration of visual function may have a significant effect on quality of life.

The most common acute optic neuropathy in younger patients is optic neuritis, most commonly associated with multiple sclerosis. There is usually return of vision after resolution of episodes early in the disease, but permanent visual deficits can occur as a result of multiple attacks or chronic optic neuritis. In contrast, the most common acute optic neuropathy in older individuals is anterior ischemic optic neuropathy. Unlike optic neuritis, the visual loss in anterior ischemic optic neuropathy does not usually improve. Depending on whether anterior ischemic optic neuropathy is associated with giant cell arteritis or not, the degree of vision loss can be substantial, and there can be complete loss of light perception with minimal likelihood of recovery. Many of these patients are bilaterally blind and would benefit from any degree of visual restoration.

There are 2 common hereditary optic neuropathies, Leber hereditary optic neuropathy and dominant optic atrophy. Both are bilateral, have varying degrees of visual loss, and are infrequently associated with complete loss of vision. Traumatic optic neuropathy is sudden, is unilateral or bilateral, and can appear clinically to be reversible in the first days to weeks. After that time, the visual loss is