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Six NIH-funded projects aim to identify biological factors that affect neural regeneration

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The National Institutes of Health will fund six projects to identify biological factors that affect neural regeneration in the retina. The projects are part of the National Eye Institute (NEI) Audacious Goals Initiative (AGI), a targeted effort to restore vision by regenerating neurons and their connections in the eye and visual system. These projects will receive a total of $12.4 million over three years, pending availability of funds.

"Understanding factors that mediate the regeneration of neurons and the growth of axons is crucial for the development of breakthrough therapies for blinding diseases. What we learn through these projects will have a health impact beyond vision," said Paul A. Sieving, M.D., Ph.D., director of NEI, part of NIH.
Most irreversible blindness results from the loss of neurons in the retina, which is the light-sensitive tissue in the back of the eye. Many common eye diseases, including age-related macular degeneration, glaucoma and diabetic retinopathy, put these cells at risk. Once these neurons are gone, humans have little if any capacity to replace them.

These six projects will add to the knowledge base from several recent key advances. Researchers recently reported a technique that increases the regenerative capacity of retinal axons in a mouse model of optic nerve injury, a model commonly used to study glaucoma and other optic neuropathies. Progress also has been made in identifying factors that either stimulate or inhibit regeneration of neurons required for vision. The newly-funded projects will further this area of research by identifying cues that guide axons to appropriate targets in the brain, allowing functional connections to re-establish between the eye and the visual processing system.

The six projects include:
Molecular discovery for optic nerve regeneration
(EY027261-01)
Principal investigators: Jeffrey L. Goldberg, M.D., Ph.D., Andrew D. Huberman, Ph.D., Stanford University, Palo Alto, California; Larry Benowitz, Ph.D., Harvard University, Cambridge, Massachusetts; Hollis Cline, Ph.D., Scripps Research Institute, La Jolla, California

Goldberg and colleagues have demonstrated through a series of interventions in mice with optic nerve injury that they can successfully regenerate retinal ganglion cells axons, which form the optic nerve that transmits visual information from the retina to the brain. In this next research phase they hope to identify genes and proteins that help or hinder this ability of retinal ganglion cells to regenerate, grow axons to a target and become functional in mice. Promising molecular candidates will be investigated in longer-term animal studies designed to assess changes in the animals' vision.

Screening for molecules that promote photoreceptor synaptogenesis
(EY027266-01)
Principal investigators: Donald J. Zack, M.D., Ph.D., Johns Hopkins University, Baltimore; David Gamm, M.D., Ph.D., University of Wisconsin, Madison

Zack, Gamm, and their teams plan to study precursor photoreceptor cells derived from human stem cells to determine what factors help coax them into becoming fully developed and connected photoreceptor cells. They expect their studies to identify a list of small molecules and candidate genes that contribute to the ability of photoreceptor cells to home in on their appropriate target cells in the retina, known as bipolar cells. In a healthy eye, bipolar cells receive signals from photoreceptor cells across a synapse and then transmit this information either directly or indirectly to retinal ganglion cells. Generating appropriate synapses between photoreceptor and bipolar cells is an essential step in restoring vision through photoreceptor transplantation.

Evaluation of novel targets for retinal ganglion cell axon regeneration
(EY027256-01)
Principal investigator: Stephen M. Strittmatter, M.D., Ph.D., Yale University, New Haven, Connecticut

Strittmatter and his team also are searching for genes that contribute to the regeneration of axons from retinal

ganglion cells. Starting with 450 candidate genes, culled from more than 17,000, they will test each candidate in a mouse optic nerve injury model, to see if any act as mediators of regeneration. Positive genes will then be validated by looking to see if they are also active in the C. elegans worm, an indication that a gene's function is preserved across species. The strongest gene candidates will then be analyzed in greater detail to better understand their molecular action.

Novel activators of regeneration in Muller glia
(EY027265-01)

Principal investigators: Edward M. Levine, Ph.D.; James G. Patton, Ph.D.; David J. Calkins, Ph.D. Vanderbilt University School of Medicine, Nashville, Tennessee

Levine and his colleagues are investigating exogenous and endogenous factors—that is, factors with an external or internal origin—that contribute to the successful reprogramming of supportive cells in the retina called Muller glia. In zebrafish, Muller glia can give rise to photoreceptor cells after injury to the retina. First, the investigators plan to test a novel combination of pharmacological agents and genetic manipulation for the ability to reprogram Muller glia in mice. If the therapy is successful, they will then study the conditions that support regeneration by determining which genes are turned on or off in regenerating zebrafish and mouse Muller glia. A second component of their project will look at the role of exosomes, tiny cell-secreted vesicles commonly found in blood and other bodily fluids, in promoting regeneration.

Comparative transcriptomic and epigenomic analyses of Muller glia reprogramming
(EY027267-01)
Principal investigators: David R. Hyde, Ph.D., University of Notre Dame, South Bend, Indiana; John D. Ash, Ph.D., University of Florida, Gainesville; Andy J. Fischer, Ph.D., Ohio State University, Columbus; Seth Blackshaw, Ph.D., and Jiang Qian, Ph.D., Johns Hopkins University, Baltimore

In zebrafish and chicks, retinal damage induces Muller glia to reprogram and re-enter the cell cycle to produce neuronal progenitor cells, which are capable of moving to damaged retinal tissue and turning into the missing neuronal cell types. While Muller glia can initiate a regenerative response in the damaged zebrafish and chick retinas, mammalian Muller glia cannot, thereby preventing retinal regeneration and restoration of vision in humans and other mammals. Hyde and his colleagues are comparing the capacity of Muller glia cells from zebrafish, chicks and mice to perform this type of reprogramming. From the Muller glia in each animal, they will determine what gene activity is upregulated or downregulated (transcriptomics), as well as look for modifications to the genomic DNA (epigenomics), during retinal development and in response to different forms of retinal damage. These types of cross-species comparisons are designed to detect differences in gene expression, as well as to identify potential regulators that control Muller glia reprogramming. This work will shed light on why some species possess the ability to regenerate their damaged retinas while humans cannot.

Novel targets to promote RGC axon regeneration: Insights from unique retinal ganglion cell cohorts
(EY027257-01)
Principal investigators: Kevin Park, Ph.D.; Vance Lemmon, Ph.D.; Sanjoy Bhattacharya, Ph.D., University of Miami Miller School of Medicine

Park and Lemmon are using RNA sequencing in cultured mouse retinal ganglion cells to identify differences in the expression of genes in regenerative versus non-regenerative retinal ganglion cells. In parallel, Park and Bhattacharya will use mass spectrometry to determine what lipids (or fat molecules) may give subclasses of retinal ganglion cells more robust regenerative capacities. The researchers will then perform a set of experiments aimed at understanding the function of the genes found to be involved in regeneration. The most promising gene candidates will be used as a therapy aimed at regenerating the optic nerve in a mouse model with optic nerve injury.

Source:
NIH, National Eye Institute (NEI)
