

Retina Research Foundation Newsletter is published three times per year: Spring, Summer and Fall.

# **The Audacious Goal of Retina Regeneration**

Cells of the human retina are not replaced, so if they are damaged or degenerate, vision may be diminished or lost all together. The NIH/National Eye Institute's **Audacious Goals Initiative (AGI)** stimulates research dedicated to regenerating the light-sensitive retina and its connections to the brain, bold and daring work to be sure, and necessary ground work for reversing vision loss due to retina degeneration. The initiative is driving therapeutic development from different perspectives, including noninvasive imaging to study the cells of the eye and response to therapies, regenerative factors discovery, and promotion of innovative animal models for testing therapies and bridge the gap between basic research and human clinical trials.

The regenerative discovery projects explore opportunities within specific retinal cell types essential for sight: 1) photoreceptors, the light sensing cells of the retina; 2) retinal ganglion cells (RGCs) that relay information from the photoreceptors to the brain through the optic nerve; 3) Müller glia cells that support retina neuron structure and function and may be reprogramed after other cell type injury.

RRF supports unique research opportunities seeking to answer these same questions of retinal regeneration, and often focuses on developing young investigators as they collect the preliminary data necessary to apply for funding by the NHI/NEI. RRF also provides research funding to established vision scientists through nationally recognized awards such as the Award of Merit in Retina Research given in collaboration with the Retina Society. The most recent recipient of the RRF Award of Merit is **Russell Van Gelder, MD, PhD**, who researches retina regeneration and currently serves on the NEI's five member AGI Steering Committee.

In his award lecture given at the Retina Society's annual meeting, "Prospects for Vision Restoration in Outer Retinal Degeneration," Dr. Van Gelder discussed



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2020 RRF Award of Merit Recipient



Russell Van Gelder, MD, PhD Professor and Chairman of the Department of Ophthalmology University of Washington Seattle, WA

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the possibilities for restoring sight to people blinded by retinal degenerative diseases such as age-related macular degeneration or retinitis pigmentosa.

Dr. Van Gelder summarized the current approaches to vision restoration: stem cell replacement of damaged cells; electronic chips to simulate and transmit light receptivity to the brain; and light sensing protein (optogenetic) gene therapy, noting that all approaches face significant challenges to becoming established therapies. For gene therapy to successfully treat retinal degeneration, effective delivery methods must be developed to get the therapy to target retina cells, and because gene therapy is designed to change the functionality of how cells perform, significant consideration must be given to the implication that gene therapy patients may be precluded from receiving future, more effective therapies when they become available.

Replacing damaged **retinal ganglion cells (RGCs)** using precursor stem cells still remains beyond reach and as of now, no stem cell-based replacement treatment has received FDA approval. Audacious Goal Initiative researchers are trying different strategies including: using stem cells to grow RGCs that would then be transplanted to a patient's retina, or recruiting other cell types in a patient's retina for reprogramming into RGCs, something some amphibians and zebrafish do naturally. Potential cell type candidates for reprogramming include retinal pigment epithelial (RPE) cells, Müller glia cells and amacrine cells. The key to unlocking these cell types already found in eye tissue as sources for RGC reprogramming is understanding the cues that direct their maturation and integration with other cells.

Dr. Van Gelder is pursuing a different approach to restoring retina function. His lab is investigating the therapeutic potential of synthetic small-molecule photoswitches for restoring light sensitivity to degenerated retinas. Dr. Van Gelder is concentrating on determining how retinal ganglion cells can sense light and using these discoveries to treat blindness.

"The concept of restoring vision to someone who's blind from retinitis pigmentosa, or from dry age-related macular degeneration, still falls into the category of miracle. We need to turn to science if we're going to have the miracle of vision restoration for these patients become a reality"

#### Russell Van Gelder, MD, PhD

Photoswitches are compounds that are chemically sensitive to light, and change to block voltage-gated potassium channels, which triggers depolarization of neurons and causes them to fire and send a signal. Dr. Van Gelder's lab has studied three generations of these synthetic pharmacologic compounds with successive improvement and some do appear to work in animals. Dr. Van Gelder is hopeful about transition of this research to human clinical trials in the next several years.

## **Most Common Retinal Degenerative Diseases**

The most common retinal degenerative diseases are Age-related Macular Degeneration (AMD) and Retinitis Pigmentosa (RP). AMD causes the loss

of central vision, while RP causes the loss of peripheral vision.

In AMD, build-up of toxic materials, age or environmentally caused degradation of cells, deteriorates the tissue adjacent to the retina called the retinal pigment epithelium (RPE). The RPE provides essential support for retinal function. By 2050, the conservative estimate of the number of people with AMD in the U.S. is expected to be 5.4 million (NIH/NEI). Due to the aging of the U.S. population, some sources indicate prevalence will be up to four times larger.

Retinitis pigmentosa also causes damage to the RPE, which has a very limited ability to regenerate. Consequently, degeneration of these cells leads to photoreceptor

death and irreversible blindness. Retinitis pigmentosa is not prevalent and considered rare, and it is generally estimated that this genetic disease affects one in 4,000 individuals in the U.S.

The views of individuals with different vision anomalies (courtesy of NIH)

In many cases, individuals do not realize how serious the changes taking

place in their vision are until irreversible damage has already occurred. Many eye diseases are asymptomatic in the early stages when treatment may prevent or delay disease onset, so early detection is extremely important. The early stages of both diseases are clinically evident, and these changes can be found during an annual visit to your ophthalmologist. If you do have the early stages of these diseases, your doctor will work with you to determine the best treatment, which may be complex and sometimes urgent.

Source: sciencedirect.com





#### **RRF** Grant Researcher



James R. Monaghan, PhD Northeastern University Boston, MA



The Axolotl, a feathery-gilled Mexican salamander

# **Researching Retina Regeneration With Assistance From the Axolotl**

Dr. James Monaghan's lab at Northeastern University in Boston, MA, might appear a little different from others supported by RRF because it is. Dr. Monaghan researches the complex tissue regeneration that salamanders are capable of, including retinal regeneration.

Humans cannot recover from retinal damage, but Mexican axolotl salamanders can regrow their entire retinas; in fact they are capable of regenerating complete appendages and other vital structures. Dr. Monaghan's research seeks to understand the cellular and molecular mechanisms that enable these salamanders to replace damaged or destroyed retina tissues,



Photo by Matthew Modoono, Northeastern University

knowledge essential for possible translation of those mechanisms into future cures for degenerative diseases of the human retina.

With funding from RRF, Dr. Monaghan's team has developed a technique that reveals cell types in the axolotl retina and their associated gene activity, useful for understanding the mechanisms behind regeneration at the molecular level. Preliminary data suggests that the **Notch signaling pathway** may dictate what types of cells regrow in the new retina, and the research team confirmed that the regenerated retina re-establishes its connection with the brain, which is necessary for functionality. Additionally, Dr. Monaghan's research documented the new discovery that the axolotl retina contains a type of glial cell that may serve as a stem cell during salamander retinal regeneration.

Currently, Dr. Monaghan is investigating how **Notch signaling** controls retina cell regrowth after an injury and how the newly discovered stem cells drive regeneration of the retina. By learning which elements enable axolotl cells to behave this way, perhaps those elements may be applied to human stem cell therapy and retinal regeneration in the future.

#### What is Notch signaling?

Notch signaling occurs in all animal species and promotes neural cell differentiation. It plays a major role in the regulation of embryonic development. The **Notch signaling pathway** is a cell signaling system that has remained relatively unchanged across various biological species. Cell signaling is the ability of a cell to receive, process, and transmit signals internally and externally across cell membranes in its environment. Notch signaling promotes the rapid increase of signaling during neurogenesis, the process by which nervous system cells, neurons, are produced by their precursor neural stem cells (NSCs).

# Yale Scientists Find Dozens Of Genes That Block Nerve Cell Regeneration

By screening 400 mouse genes, Yale School of Medicine researchers have identified 40 genes actively involved in suppressing the regeneration of the axon, the long nerve fiber in central nervous system cells. By editing out one of those genes, they were able to **restore axons in ocular nerves** of mice damaged by glaucoma.

The ability to silence gene expression using RNA techniques combined with new gene editing technologies capable of removing single genes to gauge their functional impact has allowed researchers to greatly expand their search for genes involved in suppressing regrowth of neurons.

Interleukin-22, one of the 40 genes studied is responsible for producing an immune system regulator. Elimination of this immune mediator altered the expression of many neuronal regeneration genes and greatly increased axon regeneration in mouse models of glaucoma. Future research will explore how modifying or blocking those 40 genes might affect the repair of neurons damaged by stroke and traumatic brain and spinal cord injuries.

The research was funded in part by National Eye Institute's Audacious Goals Initiative.



Directionally, light signals move from the eye through the axon (part of the optic nerve) connecting to the brain



Axons extending from the eye (left side of photos) to the brain (right side of photos) in the optic nerve after the nerve has been crushed. In the control, untreated case (top photo), very few nerve fibers succeed in growing back. After suppression of Interlukin-22 (II22) in the retina, many more axons can regenerate from the injury (bottom photo). (Image: Strittmatter lab, Yale)

#### Source: news.yale.edu

Retina Research Foundation is dedicated to the eradication of retina disease through programs in research and education.
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# **Katharine W. Orton Joins RRF Board of Directors**



Kathy Orton

In April 2021, Kathy Orton became the newest member of the RRF Board of Directors. Her interest in the work of the Foundation spans 30 years from when she agreed to first serve as an RRF Advisory Trustee and intersects with her professional experience in finance and her dedication to the cultural and health care institutions of Houston.

Mrs. Orton's ties to the Houston health care community are deep-rooted, reaching back to her time as Chairman and CEO of Texas Commerce Medical Bank, which was an acknowledged leader specializing in financing for medical

professionals and institutions in the Texas Medical Center. Later, as a Managing Director at JPMorgan Chase, she originated and managed a multibillion dollar portfolio of credit facilities that provided tax exempt financing



to government and not for profit entities. Up until her recent retirement, Mrs. Orton was a Senior Vice President and Regional Manager of the Wells Fargo Healthcare Financial Services Group, working with clients throughout Texas, Colorado, Oklahoma, Louisiana and Arkansas.

Mrs. Orton is a highly respected leader serving our city in many capacities. In addition to RRF, she is on the Alley Theatre Board of Directors, a member of the Development Board of The University of Texas Health Science Center, and active with the United Way and the Museum of Fine Arts, Houston. She has previously volunteered her expertise and time as a

board member with numerous other Houston health care, arts and charitable organizations.

A sports enthusiast, Kathy enjoys the occasional break from the local heat and humidity and gets away to spend time in the mountains of Colorado where she, her husband, John, and their two grown daughters pursue many of their favorite outdoor activities, including skiing, golfing and hiking.



John and Kathy Orton

# **It's Summer, Are Your Eyes Protected?**



Years of chronic sunlight exposure can increase the risk of developing a cataract, a clouding of the eye lens that typically occurs with aging. Similarly, studies funded in part by the NEI, link ultra-violet (UV) sun light damage to a process called oxidative stress that hastens retinal degeneration.

While major studies show no conclusive evidence that overexposure to the sun directly causes macular degeneration, some findings suggest at least an association between AMD and cumulative eye damage from overexposure to

both UV and high energy visible (HEV) or "blue" light.

Most of your exposure to blue light occurs when you're outside during the day because sunlight is the main source of blue light. There are additional artificial sources of blue light as well including computer and phone screens, and fluorescent and LED lights.

The cornea and lens of the eye are effective at blocking UV rays from reaching



The Spectrum of

Visible and Non-Visible

the light-sensitive retina at the back of the eyeball. But virtually 100% of blue light passes through these structures and reaches the retina. In animal laboratory studies, blue light has been shown to be harmful to light-sensitive cells like those in the retina. The damage resembles that caused by macular degeneration, which can lead to permanent vision loss. More research is needed to determine how much blue light from sunlight and digital devices is "too much" blue light for the retina. This summer, stay



on the safe-side and always wear UV protective sunglasses when you are outdoors, and when you are indoors and looking at a device screen, consider wearing computer glasses to filter out blue light. Remember, it is cumulative exposure to UV and blue light that is possibly detrimental to retina tissues.

Source: NEI, optomerytimes.com



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