UPDATE

RICHARD C. ATKINSON LABORATORY FOR REGENERATIVE OPHTHALMOLOGY

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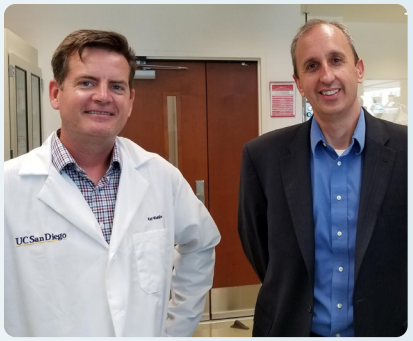


Drs. Wahlin and Welsbie study macular degeneration, optic nerve injury, neurodegeneration and vision loss. Ultimate goals are to develop new medications and gene therapy based strategies to interfere with deleterious genes preventing nerve cell death. Combined they have published hundreds of peer reviewed articles in all the major scientific publications

NEURO-REGENERATION
Goal: Identify factors to prevent optic nerve cell death and improve regeneration
Progress: Using a Shiley patient's blood, they created stem cells and turned them into mini-retinas for additional study. They found a set of genes that promotes regeneration when blocked.
Next step: Develop gene "instructions" to create new optic nerve cells to treat both glaucoma and macular degeneration.

CRISPR SCREENING
Goal: Remove one gene at a time from DNA in optic nerve cells and record the effect on its survival to find which genes increase survival.
Progress: After screening 700 genes, they identified a pair of genes that impacts optic nerve cell death. They removed these genes and found the optic nerve cells survive longer.
Next step: Understand the function of these genes.

IMPACT OF AGING ON RETINAL DISEASE AND THERAPIES
Goal: Determine genetically how and why older (aged) optic nerve cells degenerate and disconnect from the brain.
Progress: They developed a drug that blocks the damaging genes. A single injection of the drug leads to unprecedented long-term survival in rodent models of optic nerve degeneration.
Next step: Develop ways to insert the new drug into the eye in preparation for clinical trials. If successful, this will be the first non-pressure based strategy to help the optic nerve cells live longer.

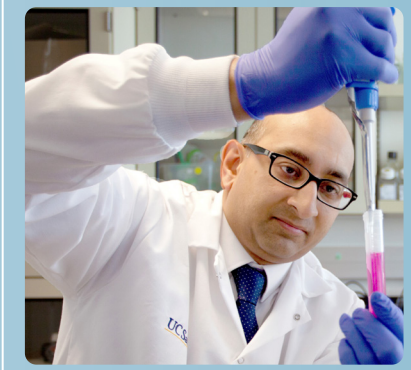
DRUG SCREENING FOR MACULAR DEGENERATION

Goal: Find new therapies for dry macular degeneration.
Progress: Using human stem cells to create retinal pigment epithelium cells-in-a-dish, they genetically modified the cells with CRISPR technology to have mutations that cause dry macular degeneration.
Next step: Develop a therapy to stop or interfere with the mutations leading to dry macular degeneration.

MODELING LEBER CONGENITAL AMAUROSIS

Goal: This disease affects children from birth and causes the death of retinal cells that are responsible for converting light to vision.
Progress: Utilizing the retinas-in-a-dish, they are modeling how this disease causes the death of the retinal cells.
Next step: Investigate this type of degeneration and find new treatment strategies.

Glaucoma is defined by the death of optic nerve cells that connect the brain and eye. Their loss leads to a progressive "disconnection" of the eye and vision loss. Thus, there are three goals for the development of new neuroprotective therapies: 1. Drugs that prevent optic nerve cell death; 2. Drugs that promote optic nerve cell regeneration; 3. Drugs that prevent optic nerve cell disconnection. The Welsbie lab has been interested in using high-throughput screening to identify drugs and drug targets for each of the three goals. For #1, we have identified a new drug target (i.e. "DLK" protein) and worked with industry to develop a new drug that is being tested in monkeys (it has already shown excellent activity in rodents). For #2, we have recently identified a set of new drug targets ("GCK-IV" proteins) and demonstrated that existing drugs that block GCK-IVs lead to impressive optic nerve cell regeneration. This work is currently under review for publication at the prestigious journal, *Proceedings of the National Academy of Science*. For #3, we are in the process of developing a new gene therapy approach to target a gene that is known to play a profound role in nerve cell degeneration. This work recently led to an invention disclosure with the University of California.



Dr. Borooah leads a laboratory research program developing novel therapies for inherited retinal degenerations and age-related macular degeneration. His successes include the demonstration of long term retinal protection using gene therapy in a model of childhood inherited retinal disease. His research accomplishments have been honored with multiple prestigious awards including a Rowling scholarship for translational medicine, a Foundation Fighting Blindness career development award and a Fulbright scholarship.

UNDERSTANDING THE CAUSE OF SUBRETINAL DEPOSITS WHICH RESULT IN MACULAR DEGENERATION

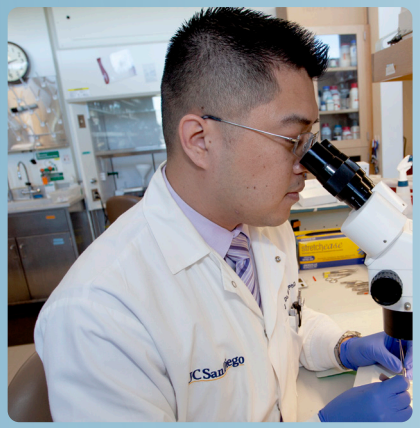
Goal: Identify the cause of disease using models of Dry and Wet macular degeneration
Progress: He identified changes in the immune system which are associated with subretinal deposits.
Next step: Repurpose FDA approved drugs to target the immune cells associated with macular degeneration to slow/prevent degeneration.

EARLY-ONSET INHERITED RETINAL DEGENERATION

Goal: Initiate gene replacement therapy for children going blind with inherited retinal disease.
Progress: Using gene replacement therapy, he slowed retinal degeneration in a laboratory model.
Next step: Develop clinical trials using gene therapy to preserve remaining vision in patients.

LATE-ONSET INHERITED RETINAL DEGENERATION

Goal: Use CRISPR gene editing to correct faulty genes which cause sight loss.
Progress: He has completed a long-term natural history study to identify the best time to treat patients with retinal degeneration.
Next step: The laboratory has recently developed retinal cells from patient stem cells. He will use this 'disease in a dish' model to test the effectiveness of gene correction. If successful, the plan is to translate this to clinical trials to treat disease to prevent sight loss.



Dr. Do has a scientific interest in regenerating the optic nerve and is developing research programs to restore vision. He uses novel stem cell technologies to replace components of the eye that are lost in glaucoma and to regenerate lost connections between the eye and the brain. His long-term goal is to develop translational therapies to restore vision and to help patients with blinding diseases.

STEM CELL DIFFERENTIATION

Goal: Restore vision by regenerating the connections (optic nerve stem cells) between the eye and the brain.
Progress: He developed a method to have optic nerve cells receive input from other nerve cells
Next step: Facilitate cell transplantation to improve survival of optic nerve cells.

TRANSPLANTATION

Goal: Develop process for transplanted cells to survive and grow within the eye that has macular degeneration or glaucoma eventually leading to whole eye transplantation.
Progress: He has developed methods to transplant stem cells into the injured optic nerve to reconnect the eye to the brain.
Next step: Further incorporate stem cells into the eye for vision.

Vision loss in glaucoma and many other eye diseases occur due to the loss of connections between the eye and the brain. Following injury, the cells responsible for making these connections that form the optic nerve are not replaced. Therefore, the consequential vision loss from losing these cells and connections are permanent. Regenerating the optic nerve is necessary to restoring vision. Our work focuses on adapting stem cells to achieve this goal using various approaches.

Stem cells have the potential to become any cell type in the body, including the cells critical for connecting the eye and the brain. One of our strategies is to produce these specialized cells using stem cells in the lab and then directly transplant them into the eye. To achieve this, we have identified the barriers in the eye that prevent lab-produced cells from being successfully transplanted and are developing methods to remove these barriers. Additionally, using genetic tools and high-throughput screening, we will enhance the ability of the transplanted cells to be successfully transplanted into the eye. The goal of this work is to restore vision by directly replacing the cells that are lost in glaucoma and retinal diseases.

In an alternative strategy to replacing cells by direct transplantation into the eye, we are also developing a novel use of stem cells to regenerate the optic nerve. The ability to regenerate the optic nerve would allow for a number of therapies to restore vision, including whole eye transplantation. We have developed methods to successfully transplant stem cells into the injured optic nerve. The optic nerve transplanted stem cells reform connections with the eye and extend connections toward the brain, acting as an "extension cord" for the optic nerve. Ongoing work will evaluate methods to further integrate optic nerve transplanted stem cells with the visual system and eventually achieve the goal of successful whole eye transplantation.