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Team Awarded \$17 Million Grant to Develop Therapeutic Use of Adult Stem Cells to Treat Eye Diseases

By Mika Ono Benedyk

A group of scientists at The Scripps Research Institute has been awarded a five-year, \$17,037,185 grant from the National Eye Institute (NEI), part of the National Institutes of Health. The grant, starting June 1, 2007, will support the development of the use of adult stem cells as a therapy for treating the most common types of vision loss.

"We're extremely excited about this grant and by the confidence peer review and the NEI has placed in our project," said the initiative's principal investigator Martin Friedlander, a professor at Scripps Research and retina specialist at Scripps Clinic. "Our goal in the next five years is to develop this new approach to treating retinal diseases to the point it can be tested in the clinic. The project addresses a large unmet medical need—developing new treatments for patients who are losing their sight due to neovascular and degenerative retinal diseases."

Under the auspices of the new grant, titled "Adult Stem Cells for Therapy of Visual Disorders," the Friedlander lab will work with six other laboratory groups at Scripps Research—those of Laura Crisa, Glen Nemerow, Wolfram Ruf, Gary Siuzdak, Bruce Torbett, and William Balch. Together, this team will conduct the extensive and detailed pre-clinical work necessary for moving the potential therapy forward. The project will also explore novel technologies and approaches to understanding and developing treatments for retinal vascular and degenerative diseases, including diabetic retinopathy, age related macular degeneration, glaucoma, and retinitis pigmentosa.

A Promising New Approach

A leading cause of vision loss involves the abnormal formation of new blood vessels, a process called "neovascularization." In total, 2 to 3 million Americans suffer vision loss from neovascular eye disease. These include elderly patients with age-related macular degeneration (ARMD), patients with diabetes who suffer from diabetic retinopathy (DR), and infants born with a condition called retinopathy of prematurity (ROP).

Abnormal vasculature in the eye develops in response to "ischemia" (decreased blood flow and oxygen delivery due to abnormalities in small blood vessels as seen in diabetes and ROP) and inflammation (usually due to the abnormal deposition of angiogenic proteins and lipids as seen in ARMD). But, unlike in the heart or brain, where the extra blood vessels can have a benefit, in

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the eye the new vessels wreak havoc, leaking fluid and blood and leading to vision loss. Current treatments for neovascular eye diseases include thermal lasers and anti-angiogenic drugs, which are designed to prevent the growth of new vessels or to close, ablate, or remove abnormal vessels. Unfortunately, these treatments often fail to completely inhibit abnormal vascular growth, and may cause tissue injury and even exacerbate the underlying condition.

The Friedlander laboratory's approach, however, takes a dramatically different tack—repairing, rather than destroying, blood vessels. "By preserving existing vessels and normalizing the new ones," Friedlander says, "we hope to provide the eye with the oxygen it needs so it won't have to grow new, abnormal and potentially damaging, vessels."

In groundwork laid over the past decade, the Friedlander lab has used a number of models, including mice, to develop this new approach to treating neovascular eye diseases. This approach uses adult stem cells—pluripotent cells capable of differentiating into a variety of cell types—harvested from bone marrow (and potentially peripheral and cord blood). These adult stem cells are injected into an eye that is forming normal or abnormal blood vessels. Once in the eye, the Friedlander group has found that the stem cells migrate to sites of new blood vessel formation, where they can become blood vessel ("endothelial") or vessel-associated cells such as microglia. The endothelial cells can incorporate into the forming blood vessels and help to stabilize the growing vasculature, making it function more normally; the vessel-associated cells, or microglia, can exert a "paracrine" (helper) effect and facilitate normalization of leaking vessels.

One tantalizing twist to these results was the unexpected finding that, in addition to targeting and stabilizing blood vessels that would otherwise degenerate in the eye, adult stem cells can also rescue nerve cells in the surrounding tissue.

"Scientists are recognizing that blood vessels aren't simply conduits to deliver oxygen and remove metabolic waste products," notes Friedlander. "In addition, blood vessels produce molecules and exert actions which have profound paracrine effects on the neighboring tissue."

This rescue effect opens the door to using adult stem cell therapy to treat additional types of visual disorders. These could include degenerative diseases such as retinitis pigmentosa, a progressive eye disease affecting the rods and cones in the retina, and age-related macular degeneration, a condition that gradually destroys sharp, central vision and is the leading cause of vision loss in Americans age 60 and older. Glaucoma, in which increased intraocular pressure can lead to loss of neurons and eventually to blindness, may also be amenable to treatment with these stem cells.

Up Next

While initial results have been promising, much work remains to be done before the adult stem cell therapy is ready to test in humans—and that's where the new NEI grant comes in.

One critical detail the team will be working out is the development of procedures for extracting cells from a patient, purifying them, and putting them back into the eye. Such procedures must meet the strict quality control guidelines set by the U.S. Food and Drug Administration generally known as "good laboratory practices" or GLP. Developing practices that meet these standards is a task Friedlander calls "a real engineering challenge."

The team will also address the issues of expanding the adult stem cell therapy to larger eyes, determining appropriate dosage and verifying that the adult stem

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cells will diffuse over a larger area. In addition, the team will define and characterize the pharmacokinetic, toxicological, and pharmacological properties of the stem cells after injection into the eye, a necessary step to taking the therapy to the clinic.

- Importantly, some of the work supported by the grant will address the fundamental question of the underlying mechanisms of the proposed therapy.
- "We want to learn how these cells do what they do," says Friedlander. "By understanding the molecular events initiated by these cells, we hope we might improve upon the individual cells themselves."

One intriguing possibility that will be explored under the grant is that stem cells could be engineered to express additional therapeutic molecules to further enhance neuroprotection or to interfere with the proliferation of blood vessels. If successful, this approach could have broad treatment implications not only for eye disease, but also for some types of tumors. "We know that these particular stem cells like to target certain connective tissue cells of the central nervous system (CNS) called glia," adds Friedlander. "It turns out that most neovascular eye diseases have an associated gliosis (proliferation of glial cells) and we can exploit this affinity by targeting the injected cells to these sites. Glioblastoma multiforme, a highly malignant brain tumor, is another CNS disease to which we can target these cells. In collaboration with neurosurgeon Faith Barnett, we have shown that it may be possible to use these cells to deliver potent anti-angiogenic molecules to the tumor and, thus, kill it."

A major strength of the new grant is bringing together expertise from a variety of fields represented in different Scripps Research labs to address the use of stem cell therapy for treating vision loss. The project combines expertise from the Friedlander lab in retinal vascular and degenerative biology, stem cells, and disease; from the Torbett and Crisa labs on differentiation and transcriptional regulation of myeloid progenitor cells; from the Ruf lab in vascular endothelial protease and protease activated receptor signaling; from the Nemerow and Siuzdak groups in molecular tools for the modification and analysis of progenitor cells; and from the Balch lab on the cell biology of retinal pigmented epithelial cells. In addition, a member of the Friedlander lab, Scientific Associate Mohammed El Kalay, brings decades of experience with cell-based engineering to the task of developing good laboratory practices. Close collaborations with laboratory, biotech and clinical groups in San Diego, New York, London, Paris and Jerusalem bring additional expertise and resources that will greatly benefit the overall program and more rapidly facilitate translation from the laboratory to the clinic, a significant component of this particular NEI program designed to support "collaborative research for the therapy of visual disorders."

"This program has enabled my group to collaborate with several highly talented investigators here at Scripps and other institutions, many of whom were not previously working in the field of vision research," says Friedlander.

"Together, we make a strong and highly complementary team. I'm determined we will bring this potential therapy to the point of being tested in the clinic. To date, we have cured many mice, but whether it will work or not in humans is another story—but that's what we want to find out. This is an extraordinary opportunity to take highly novel laboratory concepts, test them experimentally, and translate them into therapies for the treatment of blinding eye diseases."

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