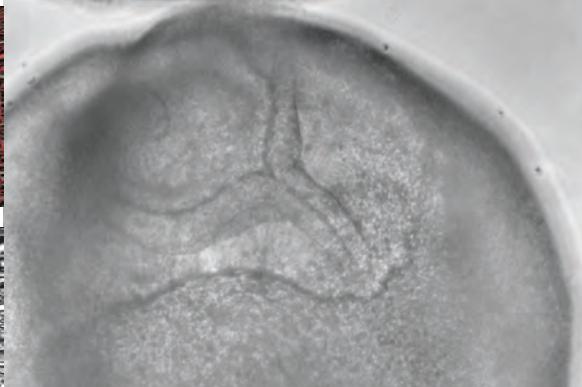


Richard C. Atkinson

Laboratory for Regenerative Ophthalmology

2016 Update



Stem cell derived '3D optic cup' illustrating the entire eye at early stages of development



Pluripotent stem cell derived fluorescent reporter mini-retinas genetically engineered to identify early stages of retina formation

Retinal degenerative (RD) diseases, such as age-related macular degeneration (AMD), retinitis pigmentosa (RP), and Leber's congenital amaurosis (LCA), as well as glaucoma, are blinding disorders, that unfortunately, are untreatable once photoreceptors or ganglion cells are lost. The remarkable regenerative capacity of pluripotent stem cells (PSCs) is demonstrated by recent studies showing that such cells can give rise to a multitude of tissues found throughout the body including cells that form the eye. Retinas derived from such stem cells offer enormous potential to generate new cells and tissue for transplantation, a system to address the origins of disease and a platform to screen for drugs that could block the disease process.

Under the direction of **Karl Wahlin, PhD**, the Richard C. Atkinson Laboratory for Regenerative Ophthalmology at the Shiley Eye Institute has been developing new strategies for vision repair using pluripotent stem cells. Using stem cell derived human 3D "mini-retinas", genetic engineering and drug screening, his lab is investigating new ways to better understand how the human retina forms and how genetic defects cause human retinal disease. The so-called 3D "mini-retinas" that are being developed in his lab resemble actual retinas of people and with recently developed genome engineering tools, his lab

uses 'precision molecular scissors' to introduce fluorescent markers into cells in order to track their development. These fluorescent reporters are now helping his team to systematically optimize the microenvironment of cultured stem cell derived mini-retinas and in some cases have already improved our understanding of the biology of eye formation. For example, by tweaking oxygen levels to mimic the conditions normally experienced by a living human embryo, they were able to exploit the fluorescent signature of retina reporters to confirm that such conditions also improved the outcome of early eye development in experimental settings. These findings are encouraging results that will hopefully lead to more efficient ways to generate transplant ready retinal cells.

Over the past year, the laboratory has also used this DNA editing approach to introduce mutations into laboratory grown stem cells in order to create human retinal disease models, including for childhood onset LCA. Sometimes referred to as the "disease-in-a-dish" approach, this method is one of the best opportunities to study the close to 300 mutations that result in retinal degenerations. While still in early phases, these "disease-in-a-dish" models are under active development as a first step towards identifying neuroprotective compounds to block or even reverse the degenerative condition.

Over the past year, the team in the Atkinson Laboratory for Regenerative Ophthalmology has also assembled sophisticated high throughput imaging and liquid handling tools for drug discovery and functional genomic screens to explore the mechanism that allows a cell to transform from an undifferentiated progenitor to mature photoreceptors, RPE and ganglion cells. These tools are essential for high throughput approaches to identify neuroprotective pathways applicable to glaucoma, RP and AMD. The fluorescent cell type reporters that have been developed will allow researchers at Shiley to visualize living cells under a variety of experimental conditions allowing for more efficient generation of high purity pools of photoreceptor and ganglion cell precursor cells.

An example of the work currently being conducted in his lab is a pilot screen of close to 400 drug compounds that was used to uncover at least one new pathway involved in the generation of new retinal cells. The success of this relatively small pilot screen sets the stage for larger screens in which thousands of compounds will be tested simultaneously. It is hoped that this translational work will enhance our ability to find treatments for many of the retinal degenerations including macular degeneration, glaucoma and other eye diseases that are currently incurable.