The Biomarker Initiative: 2013 Progress Report

By the Catalyst for a Cure Researchers: Alfredo Dubra, PhD, Medical College of Wisconsin; Jeffrey Goldberg, MD, PhD, University of California, San Diego; Andrew Huberman, PhD, University of California, San Diego; and Vivek Srinivasan, PhD, University of California, Davis.

How can we better diagnose or track the progression of glaucoma? Our goal is to identify novel biomarkers for glaucoma that report on the health of the retina and optic nerve and to image these biomarkers in the clinic. This goal requires a highly collaborative crossover between imaging/engineering, physics, retinal cell biology, neurobiology, and clinical ophthalmology.

The Catalyst for a Cure Biomarker Initiative brings together four laboratories to form a single team with broad expertise in these areas. Drs. Huberman and Goldberg study retinal circuitry and neurobiology. Drs. Dubra and Srinivasan have expertise in biomedical imaging and engineering. Dr. Goldberg is also a clinically trained glaucoma specialist. Key laboratory personnel were also recruited to work together on this endeavor. In the early stages of the initiative, the team's strategy has been to cast a wide net, investigating diverse candidate biomarkers, and during the first year the team has shown considerable progress.

The Search for an Early or Progressive Marker

Retinal ganglion cells (RGCs), the cells that degenerate and are responsible for vision loss in glaucoma, have been divided into many subtypes and certain subtypes may get injured or die first in glaucoma. We have completed a detailed and systematic analysis of RGC subtypes, and preliminary results show that one subtype changes its shape much earlier in the disease. Can an early biomarker be found in the tight biological coupling between neurons, astrocytes and blood vessel cells? We have identified candidate markers for vascular endothelial cells to "report" on nearby RGCs and devised an approach to confirm the best hits.

The Development of Novel Imaging Approaches

Can non-invasive imaging be developed for biomarker identification? We have started a comprehensive study of the microscopic structural changes that take place in the living glaucomatous retina using an ophthalmic adaptive optics instrument. In collaboration with others, the group visualized the nerve fiber layer and the retinal blood vessels that support them with a clarity not seen before in vivo at a microscopic scale. The team also developed techniques that will be used to image inner retinal metabolism and RGC axon transport non-invasively. We are also developing model systems and tools to study the intrinsic light
scattering and hemodynamic changes in response to light stimuli which may more directly assess RGC function than standard visual field testing. Imaging of metabolism and functional dynamics may reveal the earliest biomarkers of RGCs that are "sick" but can still be saved through appropriate interventions.

The discovery of improved biomarkers for early detection or disease progression has the potential to radically change treatment of glaucoma.