



the neurobiology of glaucoma

— SIMON W.M. JOHN —

WHEN HHMI INVESTIGATOR SIMON W.M. JOHN, AN EXPERIMENTAL GENETICIST WITH PARTICULAR EXPERTISE IN MOUSE STUDIES, DECIDED TO FOCUS HIS RESEARCH LENS ON GLAUCOMA, HE FOUND A CLEAN SLATE. RELEVANT MOUSE STUDIES—AND TECHNOLOGIES—DIDN'T EXIST. THE CHALLENGES PROVED IRRESISTIBLE. JOHN HAS SPENT A DECADE AT THE JACKSON LABORATORY IN BAR HARBOR, MAINE, IMPROVING THE POWER OF MOUSE MODELS FOR STUDYING GLAUCOMA, A GROUP OF DISEASES CHARACTERIZED BY THE DEATH OF NERVE CELLS THAT CONNECT THE EYE TO THE BRAIN. HERE, HE TALKS ABOUT RECENT DIRECTIONS IN HIS WORK.

Using mouse models and genetics is very important for understanding the neurobiology of glaucoma and the involvement of elevated intraocular pressure (IOP) in the disease. Our research has helped overcome reluctance to using mouse models. We created the first method for measuring IOP in mice, which was a big hurdle, and we developed mouse models of inherited glaucoma to illuminate some of the genes and pathways involved in the disease.

We have identified several genes that induce high IOP, but we now know that IOP is not the only issue. Some

people have high IOP and no glaucoma, while patients with glaucoma sometimes have low pressure. We need to identify those individuals whose optic nerves are more sensitive to increases in pressure. We also want to understand what changes are taking place in the optic-nerve head as well as in the retina.

I would like to see more translation of our research into the clinical setting, and in that regard I've been talking with clinicians in various places. We need to be resourceful

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and energetic to make that happen—for example, our research has shown that *Bax* is a gene that needs exploration in the human population. Is it a susceptibility gene in humans? *Bax* codes for the BAX protein and induces apoptosis. To explore retinal ganglion cell death, Richard T. Libby, a postdoc in my lab, crossed our glaucoma-prone mice with mice deficient in BAX to generate mice that were either completely missing BAX or had lower amounts of it. Importantly, even the mice missing just one copy of the *Bax* gene are profoundly protected from glaucoma because the nerve cells in the retina do not die. These mice don't lack BAX, they just have lower levels of it—a more realistic model for treating humans since it is easier to reduce the levels of a protein in patients than completely turn it off. We want to encourage clinicians to look at BAX inhibitors to see if they might be helpful for glaucoma patients.

Our discovery of the role of the tyrosinase gene is another area ripe for a clinical look. We discovered that mice with a mutation in the tyrosinase gene, coupled with a second culprit gene, *Cyp1b1*, had severe eye-drainage structure malformations similar to those that cause glaucoma in people. When we put L-DOPA, a product of tyrosinase, in the drinking water of pregnant mice deficient in CYP1B1 and tyrosinase, their pups did not have severe structural abnormalities. We want clinicians to take this result and run with it, though it may be safer to modulate the tyrosinase gene than to directly manipulate L-DOPA.

David K. Dueker is a clinician in Saudi Arabia, where early-onset glaucoma involving CYP1B1 is common, often resulting in childhood blindness. Dave would like to study the impact of fava beans, a dietary staple in the region that is rich in L-DOPA. He wants to ask: “If a woman with the CYP1B1 mutation has a baby with a milder form of glaucoma, was she eating a lot of fava beans? That is, was she medicating herself with L-DOPA without knowing it?” We'd like to complement this epidemiology with mouse studies, which I hope can do his patients some good. These L-DOPA studies may also help patients with glaucoma caused by several other genes that affect tyrosine hydroxylase, another enzyme that makes L-DOPA. Disturbances in L-DOPA may be a unifying theme in these glaucoma cases.

The last area I want to mention is furthest from clinical application, but still very exciting. Through serendipity, we discovered that radiation plus bone-marrow transfer in mice provides *complete* protection from glaucoma! While studying a form of the disease called pigmentary glaucoma, we observed that none of the glaucoma-prone mice we irradiated had any glaucoma damage. This was a hugely surprising outcome that we just couldn't fathom. So we did it a second and third time, and got the same results. In about 96 percent of the animals, protection was complete. We seemed to stop the disease dead in its tracks—long-term.

This effect doesn't seem to be unique to the mouse strain. A group studying atom-bomb survivors of Hiroshima and Nagasaki found that the people with the highest radiation exposures seemed to be protected from glaucoma. Now our challenge is to understand the mechanisms involved. Maybe there's a way those mechanisms can be “bottled” and turned into medications or preventive measures down the road. ■

-Interview by Cori Vanchieri-

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[VALERIE MIZRAHI]

and has led people who can afford it to retreat into secure neighborhoods protected by barbed wire fencing—not a great way to live. The safety of my family is foremost in my mind at all times, of course, but you can't let the fear of crime dominate your life. Also, I don't worry about the safety of my staff and students—at least, not during normal working hours—because my lab site is very secure. I do worry a little about their safety after hours, but most of them have grown up in Johannesburg or lived here for a while, so they tend to be street-smart.

HHMI: WHY DON'T YOU LEAVE?

VM: I am a second-generation African, and South Africa is my home. I love the beauty of this country, its sounds, its smells, and the wonderful climate. Every time I step off a plane here, I feel glad to be home. There is also the issue of relative impact. The reality is that I can make more of a difference here than elsewhere.

HHMI: WHAT WOULD YOU LIKE TO BE REMEMBERED FOR?

VM: Actually, I want to be put out of business by my graduates—by students

like Limenako Matsoso and Betty Mowa, two talented black African women who are working toward their Ph.D.s in my lab.

Betty is from the Limpopo Province of northeastern South Africa. She is in her first year of doctoral studies and has won a prestigious bursary, which is like a graduate fellowship, from the South African government.

Limenako is from Lesotho, a small independent country located completely within South Africa. She played a central role in establishing DNA microarray technology in our lab, using a partial-genome microarray of *Mycobacterium smegmatis*—a close cousin of the organism that causes TB. Because the *M. smegmatis* microarray was constructed by former HHMI international research scholar Ross Coppel in Australia, the requisite interaction with our Australian colleagues exposed Limenako to the world of international collaborative science. After completing her Ph.D. this year, she plans to do postdoctoral training in the United States, but I want her to know that she can then come home and do great science here. ■

-Interview by Jennifer Boeth Donovan-

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hoping to disseminate the academy's ideas across the country.

“We see this as a unique opportunity that goes beyond simply providing money,” says Peter J. Bruns, HHMI vice president for grants and special programs. “Our network of scientists and educators are contributing ideas and their own findings, so this experiment in science education is not going it alone.”

The 9th- and 10th-grade academy curriculum is designed to meet Virginia state standards, which are based on national science standards. Fortunately, Virginia doesn't require earth science, biology, and chemistry to be taken in the traditional sequence, Wolfe says, although students must pass a test at the end of each course. He isn't worried about these exams. “Our kids will have such a strong understanding of the sciences,” he says, “that they'll be able to handle anything the tests throw at them and probably a whole lot more.” ■

-Jennifer Boeth Donovan-