Vision hacker [1]

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As a child, Christina Fasser could ski, but she struggled with tennis. She also fumbled to find things in the dark. “I just thought, I’m clumsy,” she says. “I’m not as good as the others.”

Then came the news. At age 13, Fasser was diagnosed with retinitis pigmentosa, a degenerative eye disease that damages retina cells. For Fasser, the disease explained a lot. She wasn’t clumsy. Rather, she was night blind and lacked the 3D vision needed to play ball sports. “If you are born with a restricted visual field, you have no idea what it means to see fully,” she says.

There are no effective therapies available for Fasser’s retinitis pigmentosa, and the same holds true for patients with other inherited retinal disorders that degenerate the light-sensitive rods and cones of the retina, such as Leber’s congenital amaurosis and Usher Syndrome, though clinical trials are ongoing for some of these diseases. Approximately 2 million people worldwide suffer from these diseases and the life-limiting disabilities that accompany them, according to research from the Institut de la Vision in Paris, France.

Yet new hope is coming through research, particularly that of Botond Roska, a neurobiologist at the Friedrich Miescher Institute for Biomedical Research (FMI) in Basel, Switzerland, a research center affiliated with Novartis Institutes for BioMedical Research (NIBR) and with the University of Basel. Roska has found that the retina, a slip of light-sensitive tissue lining the eye, is actually an astonishingly complex biological computer. As a result, Roska has become a vision hacker of sorts, using the tools of neuroscience and genetics to reverse engineer the retina to understand how it functions and how disease-related damage might be repaired.

Understanding vision loss

Botond Roska, a neurobiologist at the FMI, has helped advance knowledge of the retina and retinal disorders.

In the mid-1990s, Roska emerged from medical school feeling uneasy. Being a doctor would sometimes require him to offer his patients therapies that he couldn't explain. "That's not what I wanted to do," he says. "I wanted to understand."

So Roska went back to school. He'd studied mathematics before medical school, and the eye offered a possible way to combine the two fields. At the University of California, Berkeley, he began what has turned into a decades-long quest to understand the retina. "Botond asks questions with a totally unbiased mind. He has an impressive mastery of the field, but he is also very interested in driving that knowledge forward to benefit patients," says ophthalmologist José-Alain Sahel, director of the Institut de la Vision, and one of Roska's longtime collaborators.

Roska teased apart the retina's wiring using probes that record the electrical signals sent through rod and cone cells in the retina in response to light. This work revealed that the retina contains 10 distinct layers of cells that form a complex signal processor that turns a wash of photons into a dozen parallel movie tracks. Those tracks, representing lines, motion, shadows, color, and more, are then streamed into the visual cortex of the brain through the optic nerve for assembly and interpretation.

Inherited retinal diseases interrupt this process before it starts by damaging light sensitive cells, leading to blindness. Like a smart phone with a broken screen, the remaining retina cells sit idle, waiting for a cue. These diseases result from a mutation in a single gene, though many different genes have been associated with Leber's congenital amaurosis and over 100 genes are known to cause retinitis pigmentosa. These diseases progress differently, but over time, they all degenerate rod and cone cells.

Roska learned the genetic techniques he needed to begin to grasp how these diseases progress from Connie Cepko, Professor of Genetics at Harvard Medical School, as a Junior Fellow at Harvard University in Cambridge, MA, in 2002. In 2005, he started in his own laboratory at the FMI. FMI investigators focus on the fundamental science Roska believes is

essential for progress. “You really have to dissect the different cell types and computations,” says Roska. “With that understanding, you get insights into potential therapies.”

A vision for restored vision

Roska had left his medical career behind, but as his understanding of the retina advanced, he saw an opportunity. “I realized that I can go back to medicine,” he says. “I can manipulate the retina, but now, perhaps, in patients.”

While disease may destroy the rods and cones of the retina, the cells that survive remain connected to the brain and give researchers a toehold for therapeutic intervention. “If you can stimulate the remaining cells in the retina, you might be able to restore some vision,” says Sahel.

In 2008, Roska began investigating the possibility of re-sensitizing cells in the retina to light using optogenetics. Optogenetics introduces instructions for the production of proteins that the cell isn’t naturally programmed to make. In this case, the instructions code for light-sensitive proteins found in algae and bacteria. These proteins are simple — when they sense light, they induce electrical activity in the cell.

The technique is often used in neuroscience research to probe the inner workings of the brain, but in this case, it restores sight. “The human retina is the perfect application for optogenetics,” says Roska. “It’s lost its light sensitivity, and you want to get it back.”

He first focused on bipolar cells, the layer of cells beneath the photoreceptors that many blindness-causing genetic diseases destroy. The experiment restored light-sensitivity in mice. In 2010, he restored light sensitivity to damaged but still living cone cells in mice with retinitis pigmentosa. “Together with José Sahel and other collaborators, we are going to try to bring both methods to humans,” he says.

Roska chose to use light-sensing proteins from simple organisms because the human light sensor is a much more complex system coded by about 20 genes. “We have to be modest in our goals,” says Roska. “If this approach helps patients see light, that’s a starting point.”

Towards a deeper understanding

Roska is still focused on understanding how diseases alter the human retina so that he can continue to develop new therapies. “Everything starts with understanding,” he says. “Then you can move ahead.”

One barrier has been that some human retinal diseases cannot be modeled in mice. For instance, Usher Syndrome causes deafness and blindness in humans, but mice with analogous mutations do not lose their sight. “The disease does not exist, so you can’t study it,” he says.

Recently, however, Roska made a key discovery that allowed him to take lab-grown retinas — complete 3D replicas of retinas grown from human stem cells — and make them light sensitive. He can now use these to model human retinas to study human disease.

Novartis biologists and Roska are developing new human models of retinal disease as tools for drug discovery. Much work remains to perfect the models for this purpose, yet the project fuels Roska’s ambition to make discoveries that eventually help patients.

For Fasser, Roska’s progress translates into hope. “His work has opened up completely new ways to look at restoration of vision,” she says.

Now totally blind, Fasser relies on modern technologies to function. She uses text-to-speech programs for reading, light detectors to light her home for visitors, and color sensors to choose clothing and sort the wash. But, as president of the advocacy group Retina International for over two decades, she has a loftier goal in mind. “To find a cure,” she says.

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