# Switching to a cure

Renowned scientist Dr. Philippe Monnier and his team at Krembil are developing an injection that could dramatically improve the lives of patients

*Marjo Johne*

What if, with one injection, doctors could turn off the molecular switch that triggers the death of the eye's photoreceptors – those neuron cells in the retina that enable vision by processing and transmitting visual information to the brain?

"It would significantly improve the lives of patients with conditions such as retinitis pigmentosa, glaucoma and age-related macular degeneration," says Dr. Philippe Monnier, a senior scientist at the Krembil Research Institute. "Eye diseases dramatically impact quality of life, and the older you get, the higher your chances of developing an eye disease such as glaucoma."

More than a decade ago, Dr. Monnier led a research team that made an intriguing discovery: when the eye's photoreceptor cells are stressed – usually because of a malfunction caused by an injury or a gene mutation – proteins known as neogenins activate a pathway that leads to the death of these cells.

"These are proteins that will tell your eye how to connect with the brain, and dictate where to establish and stop the connection," explains Dr. Monnier. "What we discovered was a higher presence of neogenin in diseased photoreceptor cells, and we believe that these neogenin proteins are basically telling the cells, 'No, you cannot regenerate – you're going to die.'"

Today, Dr. Monnier and his team of researchers at Krembil are working on a therapy that they hope can stop neogenin proteins from activating photoreceptor cell death. The scientists have developed a peptide called 4IG that, when injected into the retina, successfully blocked the death-inducing function of neogenin proteins in photoreceptor cells that are diseased with retinitis pigmentosa. Peptides are fundamental components of cells that carry out important biological functions.

Laboratory tests show that effects could be detected in as little as two weeks, says Dr. Monnier. An injection with 4IG improved photoreceptor cell survival and structure, and led to better vision.

"The improvement was very dramatic," says Dr. Monnier. "The peptides, which are these small protein fragments, blocked the neogenin pathway that would normally lead to photoreceptor cell death."

While the lab tests have focused primarily on retinitis pigmentosa, the findings may also be relevant for other eye conditions.

"We could have well identified a molecular switch that is critical for cell death in multiple eye diseases," says Dr. Monnier. "We have a lot of indications which tell us that by targeting this specific pathway, we can not only protect photoreceptors, but also other cell types in the eye that are important for diseases such as glaucoma and age-related macular degeneration."

Jason Charish, a project lead in Dr. Monnier's research into neogenin blockers for retinitis pigmentosa, notes that the study findings – and, most importantly, the potential for a cure – also have implications that go beyond the eyes.

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– Dr. Philippe Monnier

Krembil scientists believe neogenins may also play a critical role in multiple sclerosis (MS) and in stroke, says Mr. Charish, a PhD student at the University of Toronto.

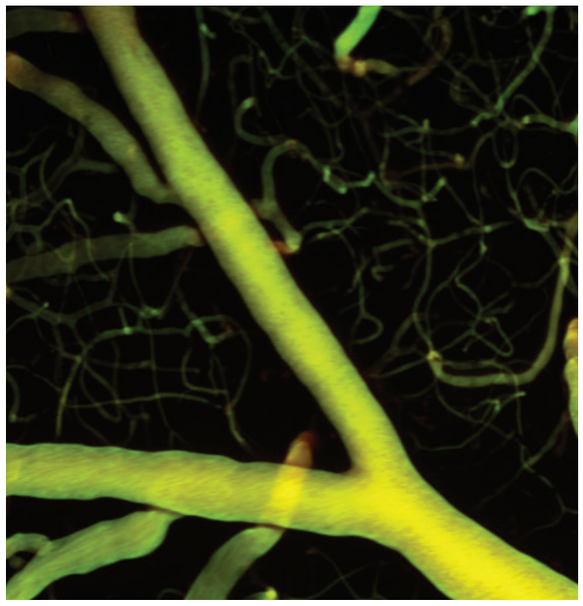
"Other members of the lab have also looked at MS and stroke models, and we see potential applications of the therapy in these diseases as well," he says.

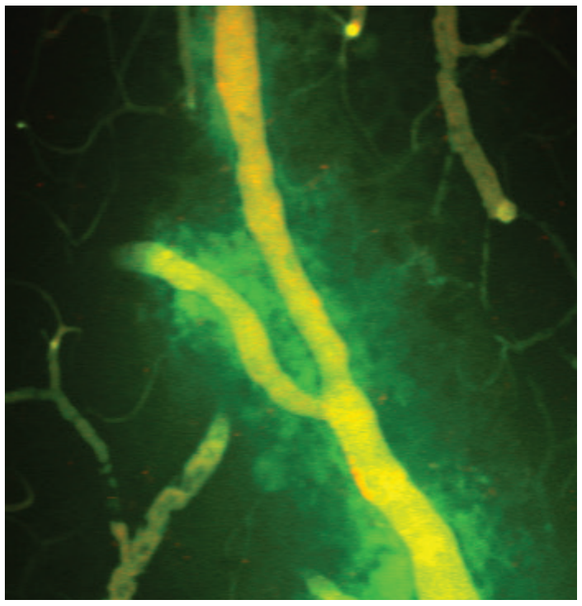
Dr. Monnier says the application of 4IG produced an unexpected finding: neogenins were also responsible for maintaining the blood-brain barrier – a protective membrane that prevents harmful substances from entering the brain.

"The blood-brain barrier prevents a lot of bad things from happening. For example, it prevents the immune system from going into your brain," he says. "In multiple sclerosis, the immune system is somehow able to cross the barrier and attack the brain. So if we can restore the barrier, then we prevent immune system cells from [targeting] the brain."

Krembil is now working to take 4IG from the lab into clinical practice. Dr. Monnier and his team are preparing to test 4IG for preclinical safety. They have also partnered with a pharmaceutical company to eventually produce and market 4IG as a drug.

"Our goal is, in four to five years, to be able to turn 4IG into a drug that can be administered to patients," says Dr. Monnier. ■





*Left: blood vessels in the brain. The blood-brain barrier is functioning well. Right: a cloud around the blood vessels indicating that the blood-brain barrier is no longer functional. This is seen in a model for MS, where the blood-brain barrier stops working.*