Light-controlled genes and neurons poised for clinical trials

As a human trial of optogenetics for retinal diseases begins, researchers eye other applications.

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Optogenetic therapies use light to control the behaviour of neurons and genes.

Every time something poked its foot, the mouse jumped in pain. Researchers at Circuit Therapeutics, a start-up company in Menlo Park, California, had made the animal hypersensitive to touch by tying off a nerve in its leg. But when they shone a yellow light on its foot while poking it, the mouse did not react.

The treatment is one of several nearing clinical use that draw on optogenetics — a technique in which light is used to control genes and neuron firing. In March, RetroSense Therapeutics of Ann Arbor, Michigan, began the first clinical-safety trial of an optogenetic therapy to treat the vision disorder retinitis pigmentosa.

Many scientists are waiting to see how the trial turns out before they decide how to move forward with their own research on a number of different applications. “I think it will embolden people if there’s good news,” says Robert Gereau, a pain researcher at Washington University in St Louis, Missouri. “It opens up a whole new range of possiblilities for how to treat neurological diseases.”

Retinitis pigmentosa destroys photoreceptors in the eye. RetroSense's treatment seeks to compensate for this loss by conferring light sensitivity to retinal ganglion cells, which normally help to pass visual signals from photoreceptors to the brain. The therapy involves injecting patients who are blind or mostly blind with viruses carrying genes that encode light-sensitive proteins called opsins. The cells fire when stimulated with blue light, passing the visual information to the brain.

Chief executive Sean Ainsworth says that the company has injected several individuals in the United States with the treatment, and plans to enroll a total of 15 blind patients in its trial. RetroSense will follow them for two years, but may release some preliminary data later this year.

Rival company GenSight Biologics in Paris is attempting to treat retinitis pigmentosa with an opsin protein that responds to red light, which is less harsh on the eyes than blue light. At a meeting of the Association for Research in Vision and Ophthalmology in Seattle, Washington, earlier this month, GenSight researchers presented data showing that injecting a gene-carrying virus into healthy monkeys made their retinal ganglion cells responsive to light. Chief executive Bernard Gilly says that GenSight hopes to begin a small human trial early in 2017.

Neither company developing retinitis pigmentosa therapies expects patients to fully recover their vision. But Gilly and Ainsworth both say that the trials will be a success if participants gain the ability to navigate independently or even recognize faces.

Light touch

The eye is an enticing target for optogenetic therapies, in part because immune cells can't enter the eye to attack the foreign proteins introduced during such treatments. But Circuit Therapeutics is taking a different approach with its pain therapy, relying on light's ability to pass through the skin.

"The nerves are tantalizingly poised at the surface of the skin, just waiting," says Chris Towne, the company's head of gene therapy. He presented preliminary data on the treatment on 4 May at a meeting of the American Society of Gene and Cell Therapy in Washington DC.

Unlike the retina therapies, Circuit Therapeutics' treatment uses opsins that prevent neurons from firing. Shining yellow light on mice with these proteins reduces pain by preventing pain signals from travelling to the brain. Towne hopes that the approach, now being tested in pigs, will be the first non-retinal optogenetic therapy to reach the clinic. He envisions a light-producing patch that humans with severe pain sensitivity could wear on the skin and trigger when they perform a painful activity.

Researchers still have to determine how well opsins would function in human tissue and whether they will be toxic, but Gereau, who is also pursuing optogenetics for pain relief, says that the results are promising. In a paper in press at *Nature Protocols*, his group showed that flashing light at similar opsins inserted into the neurons of donated human organs can activate them or prevent them from firing.

Other applications are not far behind. Stimulating neurons in the inner ear with light has been shown to restore some neuron function in deaf mice. Some researchers are developing light-emitting implants that trigger nerves to control bladder function and vocal cords. Many others hope to use optogenetics to treat Parkinson's disease and other brain disorders. Such a therapy would be similar to, but more precise than, current deep-brain-stimulation devices that trigger neuron firing.

Martin Fussenegger, a biologist at the Swiss Federal Institute of Technology in Zurich (ETH Zurich), says that scientists pursuing optogenetic therapies still face some technical challenges. These include developing smaller, less obtrusive light-emitting implants, and addressing the risk that optogenetic treatment could overheat neurons.

Still, researchers such as neuroscientist Ivan Soltesz of Stanford University in California are watching industry developments closely. He hopes to use optogenetics to stop seizures through a system that automatically flashes a light when a device detects brain patterns that indicate a seizure is about to start or is in progress. Such seizure-detection technologies have worked in animals[3], and early trials of similar systems that use deep brain stimulation for this purpose are promising.

Soltesz says that optogenetics could allow more precise targeting of the right neurons, if scientists can deliver functioning opsins into brain cells. "As soon as I see that it's feasible I'm all over it," he says.

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