Optogenetics has 'completely changed neuroscience'

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It's getting harder to find the line between science and science fiction. One of the hot research techniques these days, "optogenetics," uses gene therapy to deliver light-sensitive proteins to specific cells. Then researchers use light to control the cells. The field got its start in the brain, where scientists have demonstrated the technique by making contented mice fly into a rage - a remarkable, if slightly creepy, achievement.

Brian Chow, a University of Pennsylvania bioengineer, has bigger ambitions than that.

He wants to develop optogenetic tools that help scientists unlock the secrets of all kinds of cells by triggering discrete cellular activities on demand, say the expression of a gene or the activation of a protein.

Scientists have never had that kind of control over specific cell functions before. Drugs affect large numbers of different kinds of cells. Electricity can be used in a small region, but not just one cell type. Brain imaging studies have let scientists see which parts of the brain were active during certain activities, but they couldn't tell what role they played.

Optogenetics - the combination of optics and genetics - lets researchers see exactly what specific cells do, and control when they do it.

"It just fundamentally allows us to answer questions we have not been able to answer in the past," Chow said.

"The promise of it is demonstrating causality as opposed to correlation."

Within each cell, there are "at least" hundreds of separate actions taking place, he said. Being able to switch them on and off individually would help scientists figure out how cells "make decisions." Scientists would understand how the body works in a far more detailed way, possibly unveiling myriad drug targets in the process. Of course, there is also the hope that optogenetics can be used directly as a therapy, but there are challenges with that.

Chow, who trained at MIT with Edward Boyden, one of the researchers credited with creating optogenetics - it got its name in 2006 - is one of a handful of scientists using the method in the Philadelphia area. "Hundreds if not thousands" of labs are using it elsewhere, he said.

"Part of the reason why optogenetics has grown in the way that it has is because the tools work fairly well across labs, across the world," said Chow, 35, a Cherry Hill, N.J., native who planned to be a high school teacher when he left home to study chemistry at Stanford.

"It's completely changed neuroscience," said David Meaney, bioengineering chair at the University of Pennsylvania. But, he added, "most of the impact will go well beyond neuroscience."

The brain alone may have a thousand different cell types assembled in a mind-bogglingly complex communication network. Optogenetics, combined with new imaging techniques, will help unravel how the brain works at a time when the United States and Europe have made it a priority.

Among many other things, scientists have been using optogenetics to learn more about appetite, anxiety, depression, memory, attention span, movement, stress, epilepsy and schizophrenia. Chow said it also is being

used to study heart, kidney, and muscle cells.

Locally, Javier Medina, a Penn neuroscientist, is using optogenetics to study how animals learn and control movements. The technique helped him make mice blink on command. Ultimately, the goal is to repair injuries. "You can't fix things until you understand how they work when they normally work," he said.

Andrew Spence, who in November moved to Temple University from Royal Veterinary College in London, is also interested in movement. The neuroengineer will soon resume his work using optogenetics in mouse legs to study the relationship between sensory input and motion. The research could lead to better robots or prosthetic limbs.

Optogenetics is "accelerating the pace of discovery in neuroscience dramatically," Spence said. "It is already unraveling some long-standing mysteries in neuroscience."

The technique melds basic biological science with gene therapy. It involves inserting light-sensitive proteins called opsins from algae, bacteria, fungi, and other living things into different kinds of cells in a wide range of organisms.

"We get to think about the entire tree of life every day," Chow said.

The cells must then be exposed to an internal light source, such as a light tube inserted in the brain.

While researchers initially used blue light, Chow said there are proteins that respond to the whole spectrum of light. He's particularly interested in finding proteins that are activated by red light because it penetrates tissue more deeply than other colors. He was part of a team that affected mouse brain function by shining a red light outside the skull.

His current work focuses on finding more and better proteins that can do more than just make neurons fire. "The cells in our bodies do a lot more than that," Chow said. He wants to control all kinds of intracellular signaling pathways. He calls that "virtual pharmacology," although he sees the testing as a way to "emulate" a drug, not replace one.

He's also interested in how algae use light detection to swim.

Whether optogenetics can be used as a treatment is "to be determined," Chow said. There are potential logistical issues with implanting light sources, safety concerns about gene therapy, and possible allergic reactions to foreign proteins.

He thinks the technique's best treatment potential now is for inherited forms of blindness. Human eyes naturally contain light-sensitive cells that degenerate in certain forms of blindness.

That's where Jean Bennett, a Penn professor of ophthalmology, comes in. She's using the technique in animals to deliver light-sensitive proteins to cells that normally wouldn't have them as a way to compensate for degeneration of photo-receptor cells. She said her team already has evidence that it has been able to restore some vision in mice, and "promising data" in large animals. She thinks the approach is at least three years from testing in humans.

Optogenetics has the potential to help people with blindness caused by a variety of genetic defects, as well as diabetic retinopathy and macular degeneration, Bennett said. In its current form, it won't restore clear vision, but could help people navigate independently.

"You wouldn't want to go this route unless you'd exhausted all other options," she said.