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Light Switch for Bladder Control

A startup is developing molecular "light switches" for clinical use.

By Emily Singer

A startup out of Case Western Reserve University in Cleveland plans to commercialize molecular "light switches," (http://www.technologyreview.com/biomedicine/18488/) a genetic technology that has rapidly taken root in the research world. Initially developed in 2006, the technology involves injecting small snips of DNA into living animals to allow specific neurons to be controlled with light. The company, called LucCell, will focus first on developing therapies to restore bladder control in paralyzed people.

The effort signals a growing interest in developing these unique research tools for clinical use. Ed Boyden (http://www.technologyreview.com/tr35/Profile.aspx?TRID=454) , a neuroscientist at MIT and one of the original inventors of the technology, formed a startup (http://www.technologyreview.com/biomedicine/22720/) earlier this year to develop new therapies for blindness. (Boyden is a columnist (http://www.technologyreview.com/blog/boyden/) for Technology Review.) "It's exciting to see interest in pushing this technology, which was considered a powerful basic science tool, into the clinic," says Boyden.

The molecular light switches contain a gene for a light-sensitive protein derived from algae, called channelrhodopsin-2, as well as molecular instructions that limit its expression to a specific subset of cells. The gene is delivered to the target tissue via a virus, much like in gene therapy.Once taken up into the cell, the DNA triggers production of a protein that activates the cell when exposed to light.

The approach has become one of the hottest new tools in neuroscience, and it is being used across the globe to study psychiatric and neurological disorders such as depression, addiction, and epilepsy, as well as normal brain functions such as movement and memory.

LucCell will focus primarily on breathing and bladder function in paralyzed people. In both cases, signals from the brain can no longer reach the relevant muscles. The idea is to make the neurons controlling those muscles light-sensitive; the cells could then be turned on or off with an implanted light source. "We believe the light-switch technology could be most readily applied to those targets because they require just one or two muscles -- the diaphragm for breathing, and the external sphincter for bladder

function," says Jerry Silver, a neuroscientist at Case Western and president of LucCell. "I'm really optimistic that we can help people." Silver is running the company with two colleagues at Case Western, Stefan Herlitze and Evan Deneris.

Last year, Silver and his collaborators showed that channelrhodopsin could be used to restore breathing function in paralyzed rodents. Researchers first recreated a high-level spinal cord injury in rodents, paralyzing half of the diaphragm. They then injected the switch into the spinal cord, near the nerves that control the crippled muscle. Shining light on those cells triggered muscle contractions in the diaphragm. "The paper shows remarkable recovery of breathing function on the side of the animal with impaired function that lasted for a day even after light was turned off," says Silver.

The researchers are also working on restoring bladder control, a problem for a large percentage of paralyzed people. To empty the bladder, a signal from the brain travels down the spinal cord, signaling the sphincter to relax and release urine. That connection is severed in spinal cord injury, preventing normal urination. "A very powerful local circuit keeps the sphincter closed," says Silver, "which is why patients have to catheterize themselves" -- a process that can lead to infections and other complications. "This is high on the list of things people with paralysis would like to see fixed."

The researchers are now testing a slightly different molecular light switch called vertebrate rhodopsin 4, which turns cells off in response to light rather than activating them. Injecting the gene into the neurons that control the sphincter would allow those cells to be turned off in response to light, allowing the sphincter muscle to relax.

Ultimately, the researchers would like to combine this off-switch with a mechanism to squeeze the bladder, another part of normal urination. "We could put an on-switch into the nucleus that squeezes the bladder, or we could work with people who squeeze the bladder using functional electrical stimulation (http://www.technologyreview.com/biomedicine/17842/) ," says Silver. In functional electrical stimulation, implanted electrodes are used to control paralyzed muscles.

Researchers still must surmount several obstacles to develop the technology into a practical treatment. They will need to figure out how to safely deliver both the DNA and the light to the appropriate nerve cells. LucCell is developing a version of the light switches that are delivered using viruses already common in human gene therapies. The researchers are collaborating with Boyden to modify an implantable light source made from a miniature laser or LED attached to an optical fiber.

"The biggest challenge will be safety," says Karl Deisseroth, a neuroscientist at Stanford who was not involved in the research. "You have to worry about things like possibility of rare but serious immune reactions to the proteins and devices." Because

the protein is derived from algae, there is some concern it could trigger an immune response or prove toxic to the cell in the long term. Earlier this year, Boyden and his collaborators published the first paper testing the channelrhodopsin technology in primates, expressing the protein in the frontal cortex of macaque monkeys. The animals showed no unusual signs of damage nine months later. But given the novelty of the technology, extensive safety testing will likely be required.

Upcoming Events

Lab to Market Workshop (http://www.technologyreview.com/emtech/09/workshop.aspx)
Cambridge, MA
Tuesday, September 22, 2009
http://www.technologyreview.com/emtech/09/workshop.aspx (http://www.technologyreview.com/emtech/09/workshop.aspx)

EmTech 09 (http://www.technologyreview.com/emtech)
Cambridge, MA
Tuesday, September 22, 2009 - Thursday, September 24, 2009
http://www.technologyreview.com/emtech (http://www.technologyreview.com/emtech)

Nanotech Europe 2009 (http://www.nanotech.net)
Berlin, Germany
Monday, September 28, 2009 - Wednesday, September 30, 2009
http://www.nanotech.net (http://www.nanotech.net)

2009 Medical Innovation Summit (http://www.ClevelandClinic.org/innovations/summit)
Cleveland, OH
Monday, October 05, 2009 - Wednesday, October 07, 2009
http://www.ClevelandClinic.org/innovations/summit (http://www.ClevelandClinic.org/innovations/summit)

Optimizing Innovation 2009 (http://www.connecting-group.com/Web/EventOverview.aspx?Identificador=6)
New York, NY
Wednesday, October 21, 2009 - Thursday, October 22, 2009
http://www.connecting-group.com/Web/EventOverview.aspx?Identificador=6 (http://www.connecting-group.com/Web/EventOverview.aspx?Identificador=6)