Photoswitches could restore sight to blind retinas

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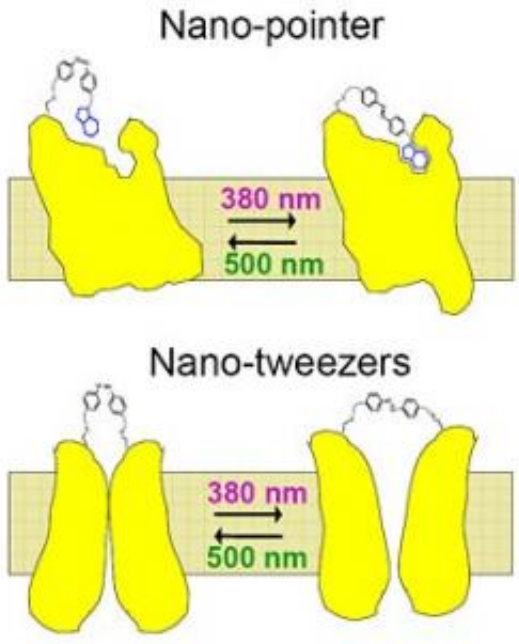

A molecule that changes shape when zapped by light (pair of black hexagons) has many uses. At top, it can be used to stuff a molecule into the active site of an enzyme, either activating or inactivating the enzyme. At bottom, it can be used to force two molecules together, like a nanotweezer. Different colors of light force these transitions: light with a wavelength of 500 nanometers (green) kinks the molecule; 380 nanometer-wavelength light (ultraviolet) unkinks it. (UC Berkeley)

A research center newly created by the University of California, Berkeley, and Lawrence Berkeley National Laboratory aims to put light-

sensitive switches in the body's cells that can be flipped on and off as easily as a remote control operates a TV.

Optical switches like these could trigger a chemical reaction, initiate a muscle contraction, activate a drug or stimulate a nerve cell - all at the flash of a light.

One major goal of the UC Berkeley-LBNL Nanomedicine Development Center is to equip cells of the retina with photoswitches, essentially making blind nerve cells see, restoring light sensitivity in people with degenerative blindness such as macular degeneration.

"We're asking the question, 'Can you control biological nanomolecules - in other words, proteins - with light?'" said center director and neurobiologist Ehud Y. Isacoff, professor of molecular and cell biology and chair of the Graduate Group in Biophysics at UC Berkeley. "If we can control them by light, then we could develop treatments for eye or skin diseases, even blood diseases, that can be activated by light. This challenge lies at the frontier of nanomedicine."

The research got off the ground this month thanks to a $6 million, five-year grant from the National Institutes of Health (NIH), part of a nanomedicine initiative within NIH's Roadmap for Medical Research. The initiative, which has funded eight Nanomedicine Development Centers around the country, including one last year at UCSF that involves UC Berkeley collaborators, is designed to "take cutting edge technology from one branch of science - nanotechnology - and apply it to another - medicine," according to Isacoff.

The nanoscience breakthrough at the core of the research was developed at UC Berkeley and LBNL over the past several years by neuroscientist Richard Kramer, professor of molecular and cell biology, Dirk Trauner, professor of chemistry, and Isacoff - all three members of the Physical

Bioscience Division of LBNL. It involves altering an ion channel commonly found in nerve cells so that the channel turns the cell on when zapped by green light and turns the cell off when hit by ultraviolet light.

The researchers demonstrated in 2004 that they could turn cultured nerve cells on and off with this optical switch. Since then, with UC Berkeley Professor of Vision Science and Optometry John Flannery, they've injected photoswitches into the eyes of rats that have a disease that kills their rods and cones, and have restored some light sensitivity to the remaining retinal cells.

Isacoff, Kramer, Flannery and Trauner have now joined forces with 9 other researchers from UC Berkeley and LBNL, as well as from Stanford University, Scripps Institution of Oceanography and the California Institute of Technology, to perfect this fundamental development and bring it closer to medical application. Their group, centered around the optical control of biological function, will develop viruses that can carry the photoswitches into the correct cells, new types of photoswitches based on other chemical structures, and strategies for achieving the desired control of cell processes.

"The research will focus on one major application: restoring the response to light in the eyes of people who have lost their photoreceptor cells, in particular, the rods and cones in the most sensitive part of the retina," Isacoff said. "We plan to develop the tools to create a new layer of optically active cells for the retina."

Loss of photoreceptors - the light detectors in the retina - is the major cause of blindness in the United States. One in four people over age 65 suffers vision loss as a result of this condition, the most common diagnosis being macular degeneration.

The chemistry at the core of the photoswitch is a molecule - an

azobenzene compound - that changes its shape when illuminated by light of different colors. Kramer, Trauner and Isacoff created a channel called SPARK, for Synthetic Photoisomerizable Azobenzene-Regulated K (potassium) channel, by attaching the azobenzene compound to a broken potassium channel, which is a valve found in nerve cells. When attached, one end of the compound sticks in the channel pore and blocks it like a drain plug. When hit with UV light, the molecule kinks and pulls the plug, allowing ions to flow through the channel and activate the nerve cell. Green light unkinks it and replugs the channel, blocking ion flow.

Isacoff said that this same photoswitch could be attached to a variety of proteins to push or pull them into various shapes, even making a protein bend in half like a tweezer.

In 2006, in a cover article in the new journal *Nature Chemical Biology*, the researchers described for the first time a re-engineered glutamate receptor that is sensitive to light, which complements the SPARK channel because the same color of light will turn one on while turning the other off.

"Now we have photochemical tools for an on switch and an off switch for nerve cells," Kramer said. "This will allow us to simulate the natural activity of the healthy retina, which has on cells and off cells that respond to light in opposite ways."

Isacoff, Kramer, Trauner and their colleagues are experimenting with other molecules that can force shape changes, looking for improved ways to attach shape-changing molecules to proteins, developing means to shuttle these photoswitches into cells, building artificial genes that can be inserted into a cell's DNA to express the photoswitches in the correct cell, and searching for ways to get light into areas of the body not possible to illuminate directly.

"I'm struck by how versatile this approach seems to be," Isacoff said, noting its applications for screening, diagnosing and treating disease. "I'm convinced that we'll come up with a therapy that will work in the clinic."

Source: University of California - Berkeley