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Sculpting Cells with Light

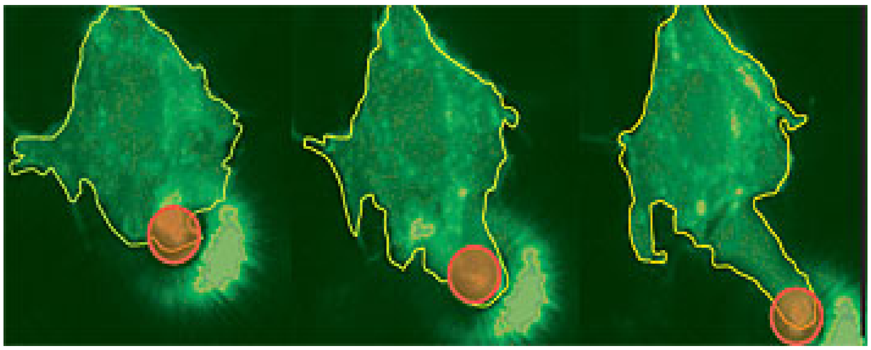

Image Title: Focusing a red laser at the periphery of a fibroblast cell induces the cell to grow outwards towards the illuminated point via the phytochrome remote control system. The laser point is slowly moved outward as the protrusion grows to "extrude" the surface of the cell about thirty micrometers from from the cell body. - Anselm Levskaya

With the flick of a laser beam, scientists can now sculpt cells into new shapes. The power to manipulate cells at will comes courtesy of a new genetically encoded switch that lets researchers use light to control a cell's shape and movement.

The switch gives biologists exquisite control over cell behavior, and they can now use brief pulses of laser light to start and stop cell movement or to restrict movement to specific regions of a cell.

"We've shown we can borrow a switch that evolved in plants, and link it to mammalian cell processes to create a kind of light-controlled dial to direct cell movement."
- Wendell A. Lim

Researchers built the switch using a light-sensitive protein from *Arabidopsis thaliana*, a plant in the mustard family. Using some clever genetic engineering in living mammalian cells, the researchers delicately linked the light-responsive plant protein to mammalian proteins that regulate cell movement. In essence, they created a hybrid protein that causes mammalian cells to move in response to red or infrared kinds of light. According to the Wendell Lim, a Howard Hughes Medical Institute researcher at the University of California, San Francisco (UCSF), this setup acts as a "universal remote control," which they envision using to control a host of cellular processes.

"We've shown we can borrow a switch that evolved in plants, and link it to mammalian cell processes to create a kind of light-controlled dial to direct cell movement," said Lim. "We can use this tool to better study how metastatic cancer cells move through the body. The technique also points to ways that we might use light to, for example, guide regrowing nerve cells so that they make the right connections."

The technique, which was described September 13, 2009, in an advanced online publication of the journal *Nature*, offers a way to scrutinize a range of normal and defective processes that require cell movement, from blood clotting to metastasis. Lim, who is a synthetic biologist, collaborated on the studies with UCSF colleague Christopher Voigt. The new technique unites Lim's focus on manipulating mammalian signaling pathways with Voigt's expertise in programming cells to perform complex, coordinated tasks for pharmaceutical and industrial applications. Anselm Levskaya, a graduate student who works in both Lim's and Voigt's laboratories, is the first author of the paper.

Researchers are just beginning to learn how to use light to manipulate cell behavior, but there have already been several striking examples of the power of this technology. For instance, a technique developed earlier by Karl Deisseroth at Stanford University – now an HHMI Early Career Scientist – permits scientists to insert a light-sensitive protein from algae into mammalian neurons and use it to precisely control neuronal activity with a laser beam. And in August 2009, Klaus Hahn's lab at the University of North Carolina reported another way of controlling cell movement with light. Now, Lim and Voigt have expanded biologists' light-activated toolkit, providing a means to control cell movement that may be adaptable toa range of other cellular processes.

Their approach hinges on a specific type of phytochrome -- proteins that plants use to regulate seed germination, shade avoidance, and other processes in response to light. In plant cells, the protein changes shape when exposed to red light, but returns to its normal state in infrared light.

Lim and his colleagues knew that cell movement begins when the right proteins arrive at the cell membrane. They reasoned that if they could link the plant phytochrome to specific regulatory proteins that cause mammalian cells to move, they might be able to develop a switch that could turn movement on or off in response to light.

They set up their system in such a way that shining red light on the hybrid phytochrome/regulatory protein would cause it to migrate to the cell’s outer membrane, where it could alter the structure of the cell’s cytoskeleton. That alteration would, in turn, cause the cell to change shape or move. In contrast, infrared light would quickly stop the migration of the hybrid protein to the outer membrane. So by toggling between the two wavelengths of light, scientists could turn cell movement on and off. Using a laser beam, which can be directed at a precise location within the cell, the scientists can sculpt cell shape down to a resolution of one micron -- about one-10,000th of an inch.

By exposing the cells to different patterns of light, Lim and his colleagues showed they could control the movement of mouse connective tissue cells with great precision. Exposing a round cell to red light caused long extensions known as lamellipodia to project from its edges. In one experiment, they focused red light on only a small section of a cell, managing to induce only that small region to protrude from the bulk of the cell, as if it were melted cheese being pulled from a pizza.

“It’s tremendously exciting that we can control cell shape and movement with a novel and non-invasive input such as light,” Lim said. “If you’re trying to understand complex processes like metastasis or development, it’s a great advantage to have a dial – a light-controlled knob -- you can turn to activate just one place.” While these studies were done in cells grown in the laboratory, Lim is now collaborating with other researchers to use the light-triggered switch in live animals, opening up even more possibilities for study.

He is equally enthusiastic about using the same strategy to design light-programmable systems to control other cellular processes that involve recruiting proteins to new locations or to new partners. Linking the phytochrome to a variety of signaling proteins could therefore be a powerful way to manipulate cell behavior. “Because that is a generic cell mechanism, you could in theory use the light-controlled switch to manipulate a range of functions, such as cell division or turning genes on and off -- like a universal remote,” he said.