NEWS

Proteins make light work of nerve control

There were audible gasps and spontaneous applause at a neuroscience meeting in Salt Lake City, Utah, in February, when Ed Boyden described a protein that switches off nerve firing when activated by light. And when Karl Deisseroth told the fuller story of the protein, called NpHR and published in this week's *Nature*, at Cold Spring Harbor in New York late last month, there was talk of a revolution in neuroscience. It is perhaps no surprise that intellectual-property disputes are looming.

The revolution could consign electrodes — neuroscience's staple tools — to the trash after a century of faithful service. They would be replaced by genetically engineered proteins that allow investigators to stimulate or inhibit very precise groups of nerves at the flick of a light switch. No previous technology has come close to this level of control and precision.

"It is incredibly exciting — now we can really start to investigate how different neuronal cell types contribute to the neural circuits that mediate all sorts of behaviours," says Carl Petersen of the EPFL Brain Mind Institute in Lausanne, Switzerland. Petersen has already received the NpHR protein from Deisseroth's lab at Stanford University in California and is rushing to use it in his research on sensory perception. "It is the best thing that has happened in neuroscience in a good long time."

This feeling of urgency pervades the field. The technology is so powerful that leaps are predicted in many areas. With such prizes to be won, there is also a rush to publish. Boyden, a former postdoc of Deisseroth's who left Stanford shortly after the NpHR work began and is now at the Massachusetts Institute of Technology (MIT) in Cambridge, hurried through a report last month on the activity of NpHR in cultured brain cells (X. Han and E. S. Boyden *PLoS One* **2,** e299; 2007). Boyden says he thinks the idea belongs to him, but both MIT and Stanford are pursuing patents.

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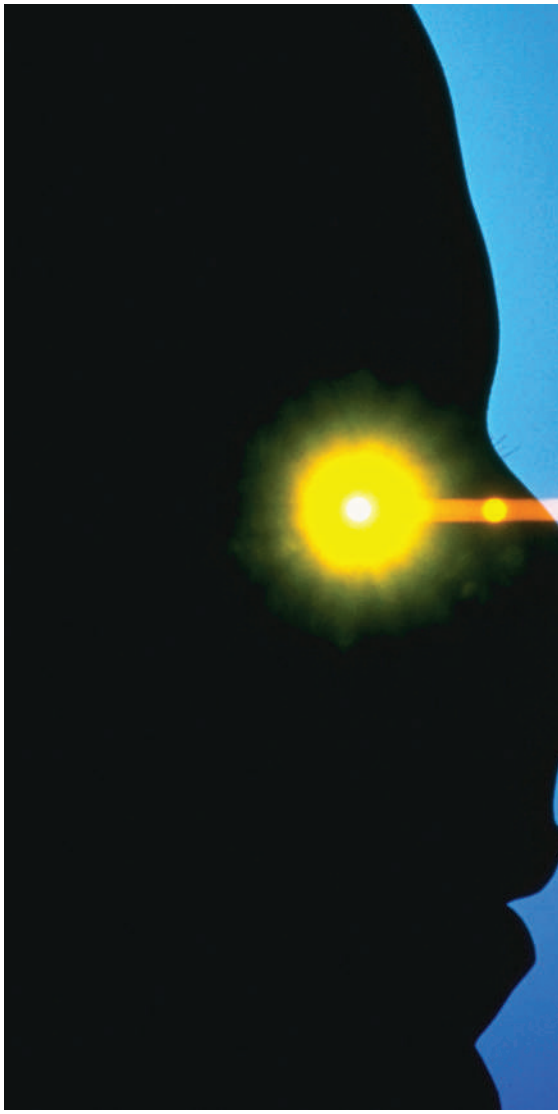
The *Nature* paper has resulted from a collaboration between researchers in Germany and at Stanford University. It extends the collaboration's 2005 work, conducted with Boyden, on a channel for positively charged ions (such as calcium) that is found in green algae and is activated by blue light. In that work, the researchers transplanted the channel, ChR2, into mammalian neurons. For the first time, it was possible to stimulate a nerve remotely at speeds close to normal neuronal transmission (E. S. Boyden *Nature Neurosci.* **8,** 1263–1268; 2005). Numerous research groups have already begun to use this 'on switch'.

The newly reported NpHR protein (see page 633) is exciting researchers even more. Identified in an archaeal species called *Natronomonas pharaonis*, it pumps chloride ions into cells, silencing physiological activity, when activated by yellow light. "The 'on switch' means we can replace the crude electrode, which stimulates all types of neurons in its vicinity," says Deisseroth. "But with the 'off switch' we can start to understand what is going on physiologically — or pathologically." By turning off sets of neurons in turn, researchers can investigate which ones are necessary, or sufficient, to elicit a particular behaviour or response.

Deisseroth and his colleagues have transferred the genes for NpHR and ChR2 into the nematode *Caenorhabditis elegans*, and can start the worms' swimming movements with flashes of blue light and stop them with yellow light. They also showed that functional proteins are produced when the genes are injected into the brains of young mice.

In addition to his research, Deisseroth holds a weekly psychiatric clinic, in which he assesses whether severely depressed patients are suitable for a treatment called deep-brain stimulation. In this procedure, electrodes are implanted deep in the brain to try to activate the neuronal circuits that lift mood. But the technique is crude and experimental, and Deisseroth says that the plight of his patients made him want to find something better.

The light-operated proteins might eventually replace electrodes in deep-brain stimulation, allowing physicians to hit just those neurons relevant to the disease being treated, although this would require a safe way to transfer the proteins into human brain cells. The technique could also have shorter-term clinical implications. For example, Gary Matthews of the State University of New York at Stony Brook hopes to use the switches to persuade retinal neurons, which don't respond directly to light, to mimic the responses elicited by rods and cones, to see whether this could help restore vision.



Light-activated proteins could provide a fresh perspective on how nerve cells work.

But the immediate use for the technology will be dissecting the role of different types of neurons in the circuits of both healthy and diseased brains. Deisseroth plans to use mice that express both proteins to identify targets relevant to depression, whereas Boyden plans work on mouse models of epilepsy, depression and Parkinson's disease.

Both researchers are distributing the NpHR protein to colleagues around the world, such as Sergey Kasparov at the University of Bristol, UK, who studies neurotransmitter release. When Kasparov heard about Deisseroth's work, he jettisoned a complicated plan to silence neurons that use noradrenaline as a transmitter: "The question we were posing is better answered by

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the light-activated protein technology."

Another researcher keen to use the protein is David Kleinfeld of the University of California, San Diego, who is tracing the neuronal pathways that mediate touch sensations. "I moved very quickly to get a material-transfer agreement after we heard Deisseroth talk about the work," he says. "We are really psyched up about it."

But Petersen cautions that the intellectual-property issues surrounding such a significant technology "should be huge". So far, the parties involved are commenting little on the conflicting claims. Deisseroth points out that Boyden was supported by his Stanford lab when the work on NpHR began there. But both claims may have to fight their way round a 1991 patent awarded to Japanese scientists, which broadly covers light-activated channels. ■

Alison Abbott

Car emissions are EPA's problem

In a major victory for environmentalists, the US Supreme Court this week ruled that the federal government must regulate carbon dioxide emitted from cars and trucks.

In a strongly worded opinion issued on 2 April, the justices brushed aside insistence from the Environmental Protection Agency (EPA) that it did not have the authority under the Clean Air Act to regulate greenhouse-gas emissions from vehicles. They also disagreed with the agency's contention that even if it had the authority, it doesn't have to regulate if it doesn't want to.

"The use of the word 'judgment' is not a roving license to ignore the statutory text," wrote Justice John Stevens. "Under the clear terms of the Clean Air Act, EPA can avoid taking further action only if it determines that greenhouse gases do not contribute to climate change or if it provides some reasonable explanation as to why it cannot or will not exercise its discretion to determine whether they do."

Led by Massachusetts, the case was brought by several states, a handful of environmental groups and American Samoa. They argued that climate change was, among other things, causing the sea to rise up and swallow some states' territory and that the EPA was breaking the law by refusing to consider greenhouse gases as 'pollutants', which it has to regulate under the Clean Air Act.

The EPA denied this on a number of grounds, including appealing to the intentions of Congress when creating the act, and the desirability of using the promise of reducing emissions as a lever to force developing countries to do the same — something that wouldn't be possible if the EPA was already regulating them (see *Nature* 443, 486–487; 2006).

Lead author of the petition for Massachusetts, Lisa Heinzerling of Georgetown University Law Center in Washington DC, is naturally pleased with the outcome: "On every single issue we won, and I think we won big."

The ruling means that the EPA must now evaluate greenhouse gases and determine whether they are "air pollution which may reasonably be anticipated to endanger public health or welfare". If it finds that they are, it must regulate them. But there is no timeline for how quickly it must do this. The EPA under the Bush administration "will not move on it at all", says David Bookbinder, director of climate litigation at environmental group the Sierra Club, who was among the petitioners. "They have 18 months [left], they are a lame duck; they are not interested in climate-change regulation."

It is more likely that the next US president will begin to regulate greenhouse-gas emissions through the Clean Air Act, he says, if Congress doesn't get there first by passing climate-change laws. Certainly, many of the Democrats in Congress would love to regulate emissions in a similar manner to the European Union's Emission Trading Scheme.

Senator Barbara Boxer (Democrat, California), head of the Senate Committee on Environment and Public Works, plans to call EPA officials to Capitol Hill later this month to ask them how they will begin regulating climate change. In a statement, she said: "We now have a two-track process for addressing global warming — comprehensive legislation and administrative action."

The EPA is "reviewing the court's decision to determine the appropriate course of action", says spokeswoman Jennifer Wood, adding that "the Bush administration has an unparalleled financial, international and domestic commitment to reducing greenhouse-gas emissions" — a slightly bizarre contention, to say the least. ■

Emma Marris

M. BLAKE/REUTERS

The Environmental Protection Agency now faces the task of regulating greenhouse-gas emissions from vehicles.