EERO LAMPINEN

Soon we could cure blindness, pain and brain diseases all at the flick of a switch, discovers **Teal Burrell**

Fixed by light

ED BOYDEN was a graduate student at Stanford University when he sparked a revolution. It was August 2004, 1 o'clock in the morning, and he was still in the lab, peering down a microscope at a single nerve cell. Curious to see how it would react, he flashed a blue light at it. Instantly, it fired. It was a defining moment, the birth of a technique that would revolutionise the study of brains and behaviour.

You may have heard of optogenetics. It's a procedure that makes neurons sensitive to light, enabling researchers to turn them on or off at the flick of a switch. Karl Deisseroth, who pioneered optogenetics with Boyden, gave an early demonstration of its power when he flashed a blue light on a mouse's brain – the right motor cortex to be precise – and found that the animal ran in circles, anticlockwise. When he turned off the light, it stopped.

Fast forward to February this year, and the revolution is upon us. In the first trial of its kind, doctors injected DNA from light-sensitive algae into a blind woman's eye in an attempt to restore her vision. This is the first time optogenetics has been tried in humans. It surely won't be the last. There are already other medical applications in the pipeline, including plans to alleviate chronic pain, nurse diseased brains back to health, and possibly even treat cancer – all at the flick of a switch. Boyden and Deisseroth's discovery is set to come out of the lab and into our lives.

Even without these developments, optogenetics has set the scientific world alight. The technique is used to study everything from learning and moving to seeing and breathing. It isn't just a step forward; it's a leap into new ways to address neuroscience's biggest mysteries. In 2010, optogenetics was called the "method of the year" by the journal *Nature Methods*. And this year Boyden, now at Massachusetts Institute of Technology, and Deisseroth were awarded the Breakthrough Prize in Life Sciences, worth $3 million each.

What makes optogenetics so exciting is the control it gives. Neurons are supplied with a gene, derived from algae or bacteria, that creates channels in their membranes. These open in response to light of a certain colour (often blue), allowing ions to pass into the neuron, either activating or deactivating it (see diagram, page 41). Researchers can control which neurons get the gene by tweaking the benign virus that delivers it. They can also control the application of light, supplied via a fibre-optic cable inserted near the light-sensitive cells. In research, this makes it possible to discover which circuits are responsible for different behaviours. Like puppet masters, researchers can take control: turn the light on and a mouse runs left, a rat remembers the path to a treat, a monkey looks directly at a target; off and the mouse stops, the rat forgets, the monkey stares into space.

Pinpoint precision

There are obvious hurdles to using this method in humans. But the precision it offers is tantalising. Current treatments for neurological diseases, such as drugs and electrical stimulation, are "a bit like playing the piano by hitting it with a mallet", says Andrew Jackson at Newcastle University in the UK. Optogenetics provides far more control. "We can actually start playing particular notes and at the same time be listening to what the rest of the orchestra is doing," he says.

Some researchers and doctors recognised the clinical potential of optogenetics right from the start. The eye is a logical place to start because it is open to light, removing the need for a fibre-optic implant. It's 10 years since Zhuo-Hua Pan of Wayne State University in Detroit, Michigan, showed that optogenetics could be used to restore vision to blind mice. "We talked at that point about some day in »

TINY SOLUTIONS TO BIG PROBLEMS

Optogenetics is a revolutionary way to manipulate nerve cells. It is used widely in the lab to explore how brains work, and has huge potential in medicine (see main story). But there are two main barriers to using it in humans: first, it requires gene therapy to make neurons sensitive to light; and second, you often need an implant to supply light to the sensitised neurons. Both these hurdles might be surmounted using nanoparticles.

Francisco Bezanilla at the University of Chicago is using gold nanoparticles to stimulate neurons without gene therapy, a method that has been called "optogenetics without genetics". When nanoparticles are exposed to light, they heat up, and neurons can be activated by heat. Bezanilla's method tags gold nanoparticles with antibodies so that they bind to specific types of neurons. He then applies light to heat the nanoparticles, stimulating the attached neurons. Bezanilla emphasises the technique's benefit to research, but sees no reason it couldn't work in the clinic.

Gang Han at the University of Massachusetts is using nanoparticles to tackle the second problem, the need for an implant to deliver light. Optogenetics generally uses blue light, which doesn't penetrate far into tissues because of its relatively short wavelength. But nanoparticles can be activated by infrared light, which penetrates deeper. Han calls the approach wireless optogenetics and is attempting to use it to treat cancer. He binds his nanoparticles to dendritic cells – immune cells that initiate an attack on cancerous cells – that have been made sensitive to blue light by gene therapy. When infrared light is shone on the nanoparticles, they convert it to blue light, activating the dendritic cells.

This method has not yet been tried in humans. But because it allows you to control exactly when and where the immune response is activated, it might result in a cancer treatment with fewer side effects. It also moves therapeutic optogenetics beyond the neuron, which means we can potentially use it to treat a whole host of conditions. Already, others are starting to manipulate heart tissue in animals, creating optogenetic pacemakers. "There is a lot of promise relevant to optogenetics, not only in neuroscience," says Han.

the far-distant future contemplating human trials," says David Birch, at the Retina Foundation of the Southwest in Dallas.

That time has come. Birch, working with the company RetroSense Therapeutics, injected a virus carrying genes from light-sensitive algae into one eye of a woman with retinitis pigmentosa, an inherited form of blindness in which the retina's light-sensing cells degenerate. The hope is that ganglion cells – a few stops further down the visual pathway but still in the retina – will take up the virus, develop light-sensitive channels, and send visual signals to the brain, bypassing the lost retinal cells (see diagram, below right). The trial is in its first phases, so safety is a priority. To begin with, the woman has been given a relatively low dose of the gene. Her progress will be monitored over the coming year and she may get two further doses. RetroSense hopes to treat 15 people in all.

Turning off pain

At this early stage there are no controls or placebo groups. Participants are warned of the risks and told there's no guarantee, with many motivated to take part in the hope that research on the inherited disorder will help family members. If anyone does regain some vision, it will be a gradual rather than instantaneous process, as the brain learns to interpret signals straight from the ganglion cells. "We're making a brand new light-sensitive palette," says Birch. "It's going to be a whole new way of responding to light and they're going to have to learn to see." That may sound drastic, but there are currently few therapeutic options for blind people. "This is by far the most promising," says Birch.

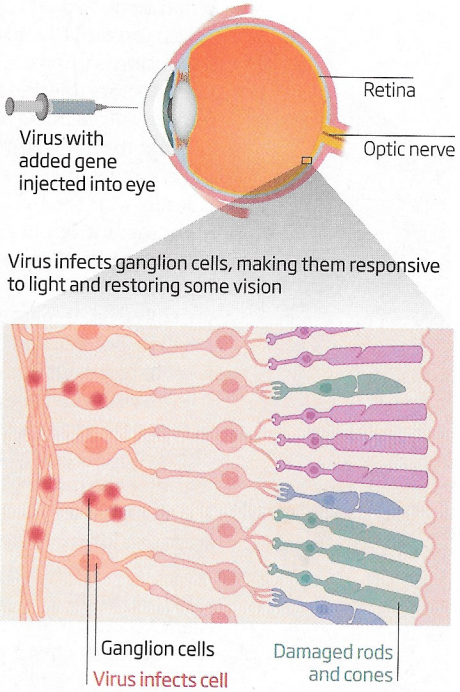
Another area where optogenetics has potential is in the treatment of chronic pain. This is traditionally treated with drugs, but these are limited by side effects, such as drowsiness and lethargy, and the potential for addiction and overdose. Optogenetics could sidestep these problems by targeting pain directly, and with no need for an implant. That's because the sensory neurons that transmit touch and pain signals to the brain lie just under the skin, so light can reach them. "They are tantalisingly poised, just sitting there waiting to be optogenetically modulated," says Chris Towne. Having achieved this in mice in Deisseroth's lab, he has now joined biotechnology company Circuit Therapeutics in Menlo Park, California, to try to move the technique to the clinic.

Last December, Circuit Therapeutics received a $2.7 million grant from the DARPA, the US military's research agency, to develop a treatment for chronic pain, both for the many veterans with pain from nerve trauma and the general population. The company is currently doing animal studies and hopes to start a human trial within two years. First in line are likely to be people with mechanical allodynia, for whom a soft touch can feel intensely painful. After receiving the gene therapy, they will wear a light patch on their skin that can be turned on to deactivate the nerves below whenever they are in pain.

Getting a gene into a neuron involves harnessing your gene to an adeno-associated virus (AAV), which is small and harmless, and allowing the virus to infect the neurons in question. Otherwise known as gene therapy, it worries some people because it introduces a foreign gene into the body. But with neurons, Jackson points out, the risk is minimal because they don't divide as other cells do. It only goes into the neurons you want, so the new gene should spread no further. Even so, we don't yet know how the human body will react to genes from bacteria and algae. Studies in monkeys show no signs of toxicity or immune reactions, so Towne is optimistic.

A cure for blindness?

A woman with the eye disease retinitis pigmentosa recently became the first person to receive optogenetic therapy



"People have been very surprised by how tolerated these foreign proteins have been," he says.

AAV-based gene therapy was approved in Europe in 2012. Although not yet allowed in the US, Towne thinks that will change soon, following some successful clinical trials. It is already approved for trials in Parkinson's disease, another condition that could be a prime target for optogenetic therapy. Parkinson's is a degenerative disease

"This is the first time optogenetics has been tried in humans"

that affects brain cells connected with movement, causing tremor and problems with coordination and movement. It is currently treated using deep brain stimulation (DBS), in which an electrode is implanted into the damaged area. Although this method reduces the tremor, it is a blunt tool, stimulating all the cells near the electrode and leaving some people with severe mood changes and depression.

More recently, researchers have tried to mend faulty neurons in people with Parkinson's using gene therapy, so an optogenetic clinical trial could follow soon. The plan is to implant an optical fibre smaller than the DBS electrode within an existing DBS device. The risks could still outweigh the benefits, though. "I think the bar's kind of high for an optogenetic therapy," says Boyden. "Since it needs a gene therapy, there has to be a good reason for doing that."

Others have a more fundamental concern about gene therapy: it is irreversible. "No one would want to remove [an added gene] given the current knowledge that we have," says ethicist Frederic Gilbert of the University of Tasmania, Australia. "That would be too complicated, too risky." This concern may eventually be allayed by the development of "optogenetics without genetics" (see "Tiny solutions to big problems", left). For now, one group of researchers has found a workaround.

The project, called Controlling Abnormal Network Dynamics using Optogenetics (CANDO), aims to use optogenetics to treat focal epilepsy – a form of epilepsy in which seizures begin in a specific area of the brain. Surgically removing this region is currently a treatment of last resort if the condition fails to respond to medication. The optogenetic approach would involve continuously monitoring the brain via an implanted electrode. When a seizure begins, flashes of light would act to regulate the network back to normal, turning neurons on or off as necessary. Only particular cells within the seizure focus would be genetically engineered, leaving the surrounding networks intact. "If it didn't work for whatever reason, the person could then have the seizure focus surgically resected, which would mean cutting out both the implanted device and also any of the tissue that had been genetically modified," says Jackson, a principal investigator on CANDO. In this case, reversing the therapy follows similar steps to an existing treatment.

Blindness, chronic pain, Parkinson's and epilepsy are all promising places to start, but this is still highly experimental research. "It's pretty exciting; it's great innovative science," says Gilbert. "But we have to keep our feet on the ground." Gene therapy and implant surgery are not the only concerns. "We don't know yet what it means for brain cells to get a laser shooting at them for a long time," he says. In the lab, animals have responded well, but scaling up to the larger human brain could require more light. "Getting enough light into the brain without also heating the brain to a point that might be dangerous is one of the big engineering challenges," says Jackson.

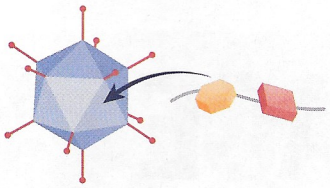
Then there's the sheer complexity of the human brain. "You really have to know a lot about which cell types are involved and how you want to control them to help repair a disease," says Boyden. "We just know so little." So while he's excited by the prospects for optogenetics, he is continuing to use it to find out more about how the brain works.

Nobody doubts the potential of this breakthrough technology. But the idea that it could ever be used to treat human disorders has been hotly contested for years – 2016 will bring some answers. ■

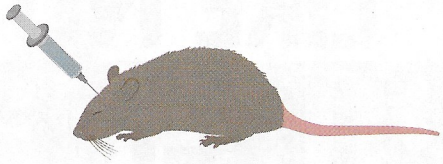
Teal Burrell is a writer based in Washington DC

Mind control

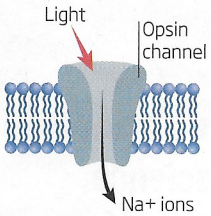
Optogenetics allows researchers to turn nerve cells on and off at the flick of a switch



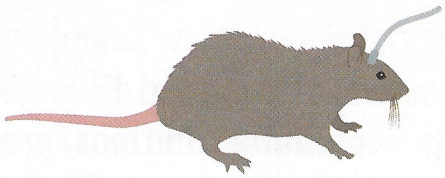
1 A gene encoding light-sensitive ion channels is inserted into a virus



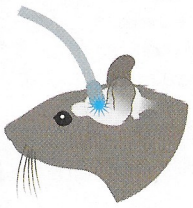
2 The virus is injected into an animal's brain, where it infects only the type of neurons it is designed to target



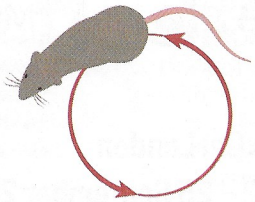
3 The neurons express the gene, creating ion channels in cell membranes



4 A fibre-optic cable and electrode are inserted near the target cells



5 When laser light of a specific wavelength is switched on, the ion channels open and ions pass into the neuron, either activating or deactivating it



6 Researchers record how this affects the animal's behaviour