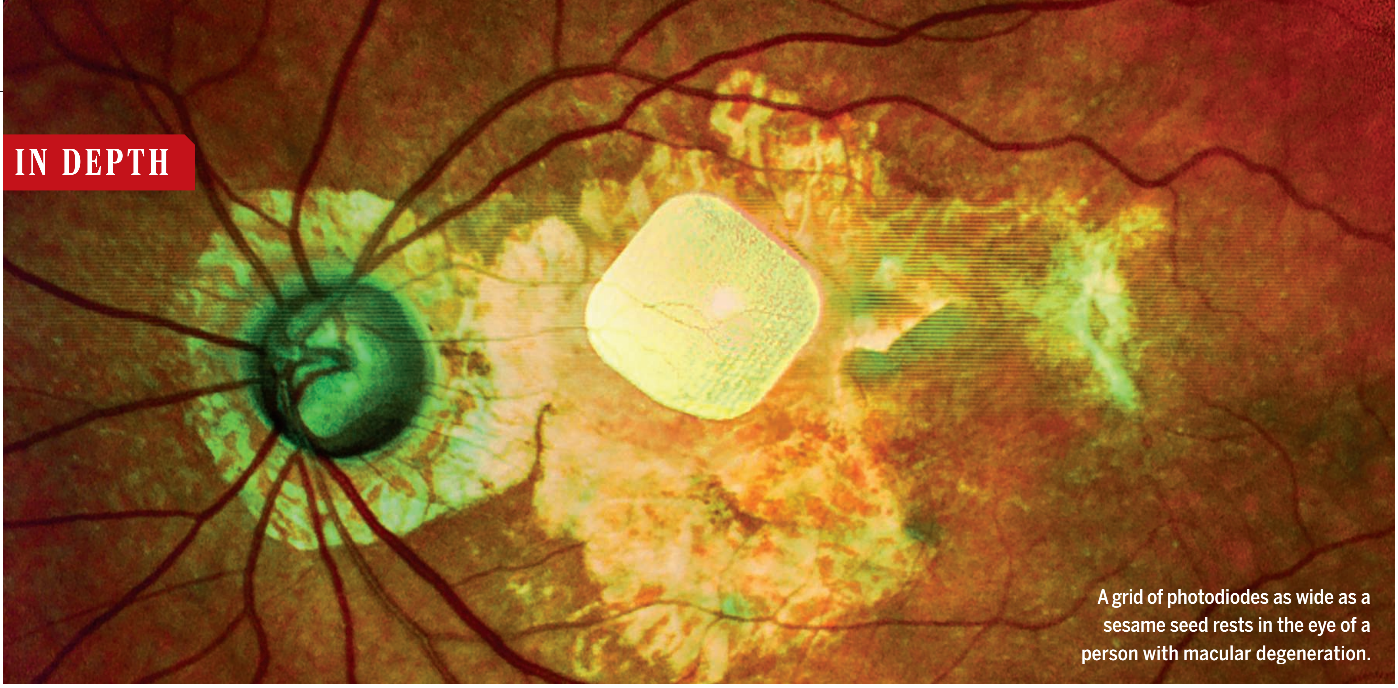
IN DEPTH



A grid of photodiodes as wide as a sesame seed rests in the eye of a person with macular degeneration.

NEUROSCIENCE

Next-generation artificial vision comes into view

Researchers hone techniques to restore sight by stimulating the retina or brain

By **Kelly Servick**, *in Chicago, Illinois*

In 2014, U.S. regulators approved a futuristic treatment for blindness. The device, called Argus II, sends signals from a glasses-mounted camera to a roughly 3-by-5-millimeter grid of electrodes at the back of eye. Its job: Replace signals from light-sensing cells lost in the genetic condition retinitis pigmentosa. The implant's maker, Second Sight, estimates that about 350 people in the world now use it. Argus II offers a relatively crude form of artificial vision; users see diffuse spots of light called phosphenes. "None of the patients gave up their white cane or guide dog," says Daniel Palanker, a physicist who works on visual prostheses at Stanford University in Palo Alto, California. "It's a very low bar."

But it was a start. He and others are now aiming to raise the bar with more precise ways of stimulating cells in the eye or brain. At the annual meeting of the Society for Neuroscience here last month, scientists shared progress from several such efforts. Some have already advanced to human trials—"a real, final test," Palanker says. "It's exciting times."

Several common disorders steal vision by destroying photoreceptors, the first cells in a relay of information from the eye to the brain. The other players in the relay often remain intact: the so-called bipolar cells, which receive photoreceptors' signals; the retinal ganglion cells, which form the optic nerve and carry those signals to the brain; and the multilayered visual cortex at the back of the brain, which organizes the information into meaningful sight.

Because adjacent points in space project onto adjacent points on the retina, and eventually activate neighboring points in an early processing area of the visual cortex, a scene can be mapped onto a spatial pattern of signals. But this mapping gets more complex along the relay, so some researchers aim to activate cells as close to the start as possible.

Palanker's team has designed a retinal implant of about 400 photodiodes or "pixels" that replaces some of the retina's spatial map. A video stream of the outside world is shown on the inside of a pair of glasses in near-infrared light, which the implant's pixels convert into electrical signals to stimulate the retina's bipolar cells. The Paris-based company Pixium Vision is testing the device in five people who have the photoreceptor-destroying disease macular degeneration.

At last month's meeting, Palanker presented videos showing that participants who had been implanted with the prosthesis for about 1 year could recognize objects on a table and read printed or on-screen letters. The artificial vision is good enough to make out the title of a book, Palanker says, though not the words on its pages. His team is now working to shrink the photodiodes—creating finer pixels and sharper vision—without losing too much signal strength.

To push to higher precision than electrical stimulation of the eye can achieve, other teams are turning to optogenetics, a technique for activating cells with light. In a clinical trial by Paris-based GenSight Biologics, researchers have injected a harmless virus carrying the gene for a light-sensitive protein into the eyes of five people with retinitis pigmentosa. Retinal ganglion cells that take up the gene can then respond to red light projected into the eye. Whether the trial participants will gain useful vision should become clear next year, says José-Alain Sahel, an ophthalmologist and neuroscientist testing the technology at the University of Pittsburgh School of Medicine in Pennsylvania and the Vision Institute in Paris.

But therapies targeting retinal cells won't help people who have lost much of their eye to injury or have severe damage to the optic nerve from conditions such as glaucoma.

Second Sight aims to treat these patients with Orion, an implant of 60 electrodes that sits directly on the visual cortex and feeds the brain signals from a glasses-mounted video camera. Four of five blind patients who have had the implant for about 1 year could better locate a roughly fist-size white square on a black screen. All five were better able to detect the direction in which a white bar moved across the screen. "We're encouraged," says Jessy Dorn, director of scientific research at the company in Sylmar, California.

Electrodes that sit on the brain's surface have drawbacks. Because it takes a relatively strong current to activate the target neurons in the tissue below, activating multiple elec-

PHOTO: PIXIUM VISION SA/PARIS

trodes at once risks triggering a seizure. And neighboring electrodes can stimulate the tissue between them, fusing two discrete visual points into a blob. But at the meeting, Second Sight's collaborators at Baylor College of Medicine in Houston, Texas, presented evidence that the 60 electrodes could create phosphenes at more than 60 locations. To create extra phosphenes, the scientists employed a technique known as current steering, which is already used to enhance pitch perception with cochlear implants.

Electrodes that penetrate deeper into the visual cortex could get closer to target neurons and use a lower current to activate multiple points in the tissue simultaneously with greater precision. Last month, Xing Chen, a neuroscientist in Pieter Roelfsema's lab at the Netherlands Institute for Neuroscience in Amsterdam, presented tests of implants containing 1000 of these penetrating electrodes in two sighted monkeys. The animals could indicate which of two letters the researchers had just flashed into their "mind's eye" by stimulating sets of 10 to 15 electrodes. Roelfsema hopes to start human trials by 2023.

Stephen Macknik, a neuroscientist at the State University of New York's Downstate Health Sciences University in New York City, cautions that the brain will eventually form a scar around implanted wires, walling them off from their target neurons. Electrode implants are "ruining the cortex for all other implants in the future," he says, "and at best, [the user is] not going to see much." Optogenetics, he says, promises much sharper vision. At the meeting, Macknik presented plans for a technology called OBServ, which would add a light-sensitive opsin gene to neurons that reach into the visual cortex from a signal waystation at the base of the brain. Those cells, he explained, could be activated with light shined from the brain's surface.

Cortical optogenetic systems such as OBServ won't reach the clinic anytime soon. Researchers still need to demonstrate that a virus can safely and reliably endow particular neurons with an opsin gene that sticks around for years. They'll also need to implant a highly precise, yet compact, device under the skull that flashes light into the brain while reading out neural activity to calibrate stimulation on the fly.

But one of the biggest barriers to beaming ultraprecise vision into the brain, many researchers say, is much more fundamental: discovering which stimulation patterns the brain will be able to interpret. "We don't think that just because you had, say, a million electrodes or perfect spatial optogenetic activation, everything is just solved," says Baylor neuroscientist William Bosking. "We need to learn how to talk to the cortex." ■

ENVIRONMENT

Mystery oil spill threatens marine sanctuary in Brazil

Months after its release, crude oil has reached Abrolhos Bank, a biodiversity hot spot in the southern Atlantic Ocean

By **Herton Escobar**

Marine scientists in Brazil are closely monitoring a mysterious oil spill that threatens the largest biodiversity hot spot in the southern Atlantic Ocean. The region, known as the Abrolhos Bank, shelters almost 9000 square kilometers of reefs along the central part of the Brazilian coastline and is home to iconic species such as Brazilian brain coral (*Mussismilia braziliensis*) and the endangered blue parrotfish (*Scarus trispinosus*).

Thousands of tons of crude oil residue from an unknown source began to wash up on Brazil's northeast seaboard in late August, contaminating hundreds of beaches, estuaries, reefs, and mangroves along a 2500-kilometer stretch of shoreline. On 2 November, the first small blobs of petroleum were discovered on rocky islands in the Abrolhos Marine National Park archipelago, 60 kilometers offshore.

A volunteer cleans oil at a beach in Brazil's Bahia state on 2 November.

PHOTO: ANTONELLO VENERI/AFP VIA GETTY IMAGES

"The oil is coming. How much of it will land here and what ecosystems will be impacted remains to be seen; but it could be tragic," says Rodrigo Leão Moura, a marine scientist at the Federal University of Rio de Janeiro (UFRJ) in Rio de Janeiro, who is monitoring the crisis. A fleet of navy ships is patrolling the region, looking to contain and remove any large incoming oil patches.

Environmentalists and others had criticized the Brazilian government for not responding quickly or strongly enough to the first wave of contamination. Although it eventually deployed ships and troops to help with the cleanup, the administration also tried to blame nongovernmental organizations and left-wing conspirators for the crisis. Minister of the Environment Ricardo Salles even tweeted a picture of a Greenpeace ship on 24 October, suggesting—without any proof—that it was responsible for the spill.

The real source may have finally come to light. On 1 November, the Brazilian Federal Police released the name of a suspect: the *Bouboulina*, a Greek tanker that skirted northeast Brazil in late July, carrying 1 million barrels of crude oil from Venezuela to Malaysia. Chemical analysis of the crude had indicated it was from Venezuela and, according to the police investigation, satellite images show a large oil slick appearing offshore on 29 July, about 730 kilometers off the coast of Paraíba state, just as the *Bouboulina* passed by.

The company that operates the ship denies responsibility and says the *Bouboulina* delivered all its cargo to Malaysia. But computer simulations run by UFRJ's engineering institute based on the distribution of the oil along the coast also point to an offshore source about 700 kilometers away that started to spill oil about 1 month before it hit land, UFRJ oceanographer Luiz Assad says.

Federal investigators estimated the *Bouboulina* released—either accidentally or intentionally—about 2500 tons of crude oil, but it's unknown how accurate that estimate is or how much of the spill will reach land. Any amount of oil that reaches Abrolhos is reason for concern, says marine biologist Ronaldo Francini Filho of the Federal University of Paraíba in João Pessoa, whose team was planning to inspect the reefs with a remotely operated vehicle this week. "It's an extremely sensitive environment, already suffering the effects of climate change and other anthropogenic impacts," Francini Filho says. ■

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Science

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Science **366** (6466), 671-672.
DOI: 10.1126/science.366.6466.671

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.