SECOND SIGHT

Eye transplants are science fiction. A team of researchers wants to change that

By **Jennifer Couzin-Frankel**

In his first-floor lab at the University of Pittsburgh Medical Center (UPMC) in Pennsylvania, Vijay Gorantla is hunched over a blind pig. Under the glare of an operating room light, he's venturing into a shadowy landscape.

Gorantla's terrain is an elegant, tightly controlled 7.5-gram bundle of cells: the eye. Pigs and humans share similar ocular anatomy, and Gorantla, a plastic and reconstructive surgeon, has sliced this animal's optic nerve in two. Now the question is, can he help it see again?

When an eye is lost, darkness reigns. And those who treat eye trauma and disease are, in a sense, groping in the dark themselves. They have little to offer the young girl who tripped while trick-or-treating one Halloween night, cracking her skull and severing the optic nerve, or the 60-year-old who sees only light and shadows, because glaucoma has destroyed cells in that same conduit.

Physicians have transplanted hearts and lungs, faces and hands, a uterus, the abdominal wall. Now, Gorantla wants the eye on that list. He and his colleagues have their work cut out for them. The most daunting challenge is coaxing nerves to regenerate and connect the donor eye to the recipient's brain. But they must also establish blood flow to a transplanted eye; control how the immune system responds to it; and preserve the intricate mechanisms that keep the eye moist, blinking, and able to focus. No one has achieved success even in an animal, and Gorantla is starting from humble beginnings: removing a pig's eye and reattaching it.

Those holding the purse strings are ready to gamble. Last fall, the Department of Defense (DOD) awarded $1.25 million over 2 years to three centers, including Gorantla's, to develop animal models for whole-eye transplantation. In 2013, the National Eye Institute (NEI) in Bethesda, Maryland, announced the winner of its "audacious goal initiative," a reachable but ambitious target for eye research. The choice—"regenerate neurons and neural connections in the eye and visual system"—encompasses eye transplants, though isn't limited to them, says Paul Sieving, director of NEI. "Science fiction becomes reality eventually, doesn't it?"

Or, as Gorantla puts it, "if you don't think about something being a possibility, nothing can happen."

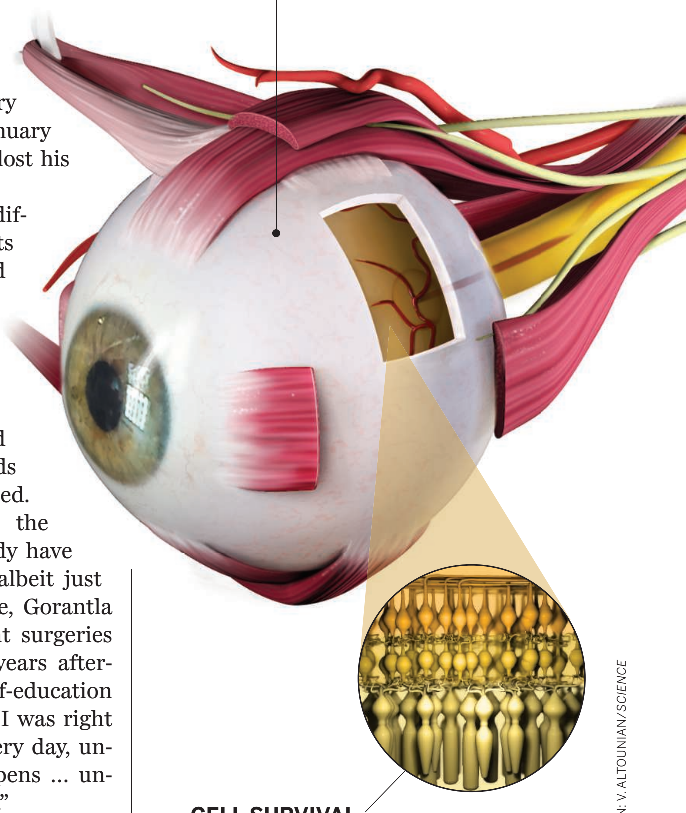
GORANTLA HAS HELD TIGHT to that motto since at least 1998, when he flew from Manchester, U.K., to Louisville, Kentucky. Fresh from surgical training in England, he was en route to one of the world's premier hand surgery programs. In the Manchester airport before his departure, Gorantla grabbed a copy of *Time*—and was startled to learn that his new home was gearing up for what would be the world's first successful hand transplant. The 15-hour surgery took place 6 months later, in January 1999, on a 37-year-old who had lost his hand in a fireworks accident.

Hand transplants were very different from the organ transplants that preceded them. "With a solid organ, the minute you transplant it" and reconnect the blood vessels, "it starts functioning," Gorantla explains. "All it needs is a blood supply." Hands include nerves, skin, bones, and bone marrow. Each of these needs to work for a transplant to succeed. Peripheral nerves connecting the new hand to the rest of the body have to regenerate—which they do, albeit just 1 millimeter a day. In Louisville, Gorantla assisted in two hand transplant surgeries and followed the patients for years afterward. "It was a process of self-education and discovery," he remembers. "I was right there in front of the patient every day, understanding how rejection happens … understanding how patients adapt."

In 2006, he relocated to UPMC to establish a hand transplant program there. Face transplants were just beginning, and

Restoring vision

Because of the eye's complex anatomy and its connection to the brain, transplants come with a host of hurdles.



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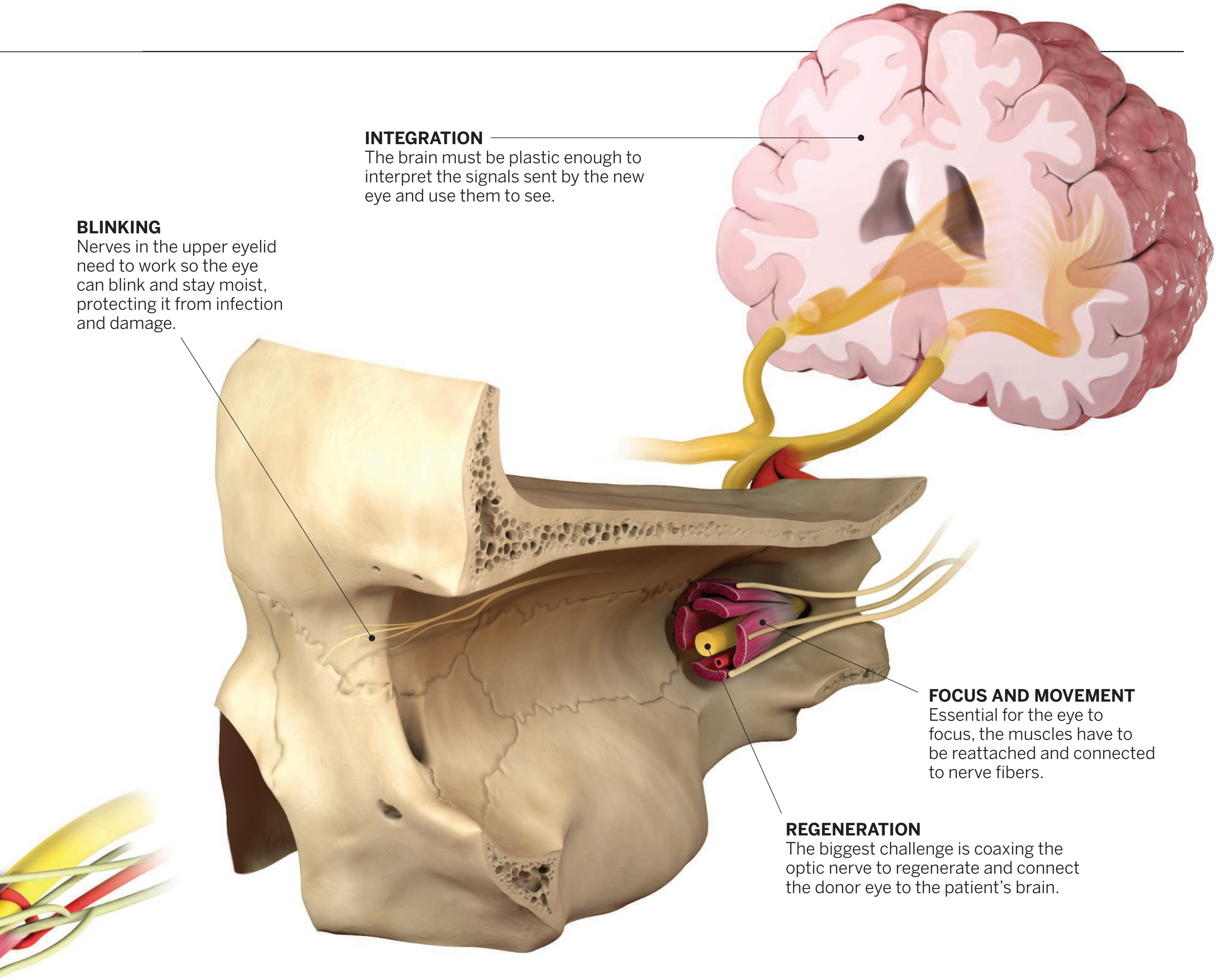

Gorantla wondered whether he might take them on. The candidates he met were often Iraq War veterans, their faces blown away.

Although Gorantla could offer these veterans a new face, many had lost their eyes as well, and he couldn't restore their sight. For them, as for other blind people, the preferred strategy for navigating the world is a Seeing Eye dog. "We've outsourced it," says Andrew Huberman, a neuroscientist at the University of California, San Diego (UCSD). "That's the best thing we've got."

So rather than dive into face transplants, Gorantla focused on vision. About 5 years ago, he began broaching the subject of eye transplants with ophthalmologists. "I thought, 'It's crazy,' " remembers Joel Schuman, director of the eye center at UPMC. "The barriers to success are very high." The greatest: Parts of the eye belong to the central nervous system, and unlike peripheral nerves in the hands and face, the central nervous system was thought incapable of repairing itself. Gorantla was eager to defy dogma. "People said I was too disruptive; they distanced themselves from me," he recalls.

He turned to history. Digging into medical archives, Gorantla uncovered illustrations and handwritten notes from 1885, when a Parisian ophthalmologist had transplanted a rabbit's eye into a young girl. Other efforts followed. All failed miserably, of course— "the rabbit eye was rejected immediately," Gorantla says. But still, the early attempts "really gave me confidence to get back on track. … I was not being completely stupid" to consider this.

MORE THAN A MILLION retinal ganglion cells form a layer in the retina of the human eye. Running from each is a nerve fiber called an axon that stretches back into the brain. Together, these fibers assemble into the optic nerve, "a cable of 1 million phone wires," as NEI's Sieving describes it.

In *Nature* in 2011, Harvard University neuroscientist Zhigang He and his colleagues described crushing the optic nerve of mice and deleting two genes in their retinal ganglion cells. Losing those two genes helped neurons sense stress and proliferate, and, remarkably, they activated a host of others that prompted at least 10% of the nerves to regenerate. The work was replicated by other labs, confirming that "it's possible to get mouse axons to regenerate long distance," says Ben Barres, a neuroscientist at Stanford University in Palo Alto, California, who wasn't directly involved.

But did the newly sprouted nerve fibers travel to the right place? In 2012, Harvard neuroscientist Larry Benowitz, working independently, supplied early evidence that they did, at least partially: The axons reached into visual centers of the brain. Preliminary data hinted that the pupils of the mice responded to light, suggesting they had regained some vision, albeit a minuscule amount. In a dif-

Surgeons Kia Washington and Vijay Gorantla (*right*) at the University of Pittsburgh are hoping pigs and rats will offer an eye transplant road map.

ferent Harvard lab, He is studying how the regenerated nerves function, performing electrophysiology on the cells and behavior studies on his animals.

Also unknown is how many nerve cells must regenerate so the eyes can see. "The brain is exceptionally good at taking relatively deprived input and making the most of it," says UCSD's Huberman, but no one knows what the minimum number is. When cochlear implants were introduced to restore hearing, many scientists were shocked that they work with as few as 16 electrodes applied to the auditory nerve. "Everyone thought it would take thousands of electrodes to stimulate thousands of nerve fibers for this to happen," says John Dowling, a neuroscientist at Harvard who studies the retina.

The discovery that the optic nerve can regenerate has raised hopes, and not just for transplants: Eye transplants are far in the future, and they'll be appropriate for only a subset of blind individuals. But even if the transplants never succeed, the regeneration studies could help drive "all sorts of spinoff science and technology," says Jeffrey Goldberg, a neuroscientist and ophthalmologist at UCSD. Those might include ways to combine regenerative techniques with treatments for vision loss like retinal prostheses, gene therapy, or stem cells to replace cells that have been lost.

In 2012, Benowitz and Goldberg, who also works in optic nerve regeneration, were invited to speak at the University of Pittsburgh's Fox Center for Vision Restoration. "Vijay was in the audience," Benowitz says. Afterward, the surgeon approached the neuroscientist to evangelize on eye transplants.

The following year, the three began to collaborate. Quickly, the group expanded to include other neuroscientists, surgeons, and ophthalmologists. Researchers at nine institutions joined with Pitt. To augment their funding from DOD, they're seeking grant money from foundations and government sources. It's "like our moonshot," Pitt ophthalmologist Schuman says, recalling the famous speech by John F. Kennedy in 1961, when Schuman was 2 years old. Transplanting an eye may take longer to achieve than the decade Kennedy promised for the moon landing, he acknowledges, "but I'm sure that we're going to reach" it, too.

Even some of the doubters have come around. Fifteen years ago José-Alain Sahel, director of the Vision Institute in Paris, regarded his countrymen's failed rabbit eye experiments 130 years ago as the first and last word on the matter. A gifted student of his was desperate to graft an eye; Sahel told her the project was outlandish and, with no other goals in mind, she quit science after finishing her Ph.D. Now he's collaborating with the researchers at Pitt, Harvard, and UCSD. "All of this is no longer deemed impossible, it is just a huge, huge crazy effort," he says.

EARLY STEPS TO BRIDGE fantasy and reality are being plotted in a lab not far from Gorantla's, where a young plastic and reconstructive surgeon, Kia Washington, is transplanting the eyes and faces of rats. It's the first eye transplant model in a warm-blooded animal. Washington is focused on reattaching dozens of blood vessels, muscle fibers, and the optic nerve. Many of the fibers are less than a millimeter in diameter. To keep immune reactions at bay, she uses genetically identical rats as donors and recipients, much like the first successful kidney transplant in 1954 from a brother to his identical twin.

"It doesn't look like there's function" in the rat eyes, Washington says, but she isn't surprised, because she hasn't tried to induce nerve regeneration. Using cutting-edge optical imaging with Schuman's help, she's found that the transplanted eyes look healthy—even if, practically speaking, they're useless. "You can actually see blood flow in the eye and in the retina," she says, and MRIs suggest the eyes produce moisture as they're supposed to. As her work progresses, Washington expects to team up with her neuroscientist collaborators to stimulate optic-nerve regeneration. Assessing the outcome will require new kinds of imaging tools, such as measuring how retinal cells grow in real time. NEI plans to release $5 million to fund several imaging awards this spring.

A rat eye is too small to transplant on its own, so Washington combines it with facial tissue from the same donor. This is how Gorantla imagines the first eye transplants: a combination of face and eye for a patient who's lost both. "You have nothing to lose," because immunosuppressants are already part of the face transplant package, Gorantla notes. The team is readying its first paper, describing Washington's rat eye transplants, for publication. And Washington is about to shift to genetically diverse animals, so she can study how to manage the expected immune response to the transplant.

For his part, Gorantla is ramping up his pig model—and, thinking far ahead, considering where human donor eyes might come from. "The common criteria for organ donors is brain death," he says, and "most of the donors have significant brain trauma or head trauma." That's worrying when it comes to eyes, because brain damage can inflict injury on the optic nerve. One group of collaborators, at the L V Prasad Eye Institute in Hyderabad, India, is testing eye function in brain-dead individuals on ventilators in an intensive care unit. Gorantla is also considering how best to preserve the eye once it's removed—right now, a human retina lives only about 4 hours outside the body.

"There's so much we don't know," Gorantla says. "We don't even know what we don't know." In a way, that's what excites him the most. ■