

The retina is key to both sensing and processing our visual world. Yet, as part of the central nervous system, it does not lend itself easily to transplant or regeneration.

OPHTHALMOLOGY REENVISIONED

BY ELAINE VITONE

COMING TO LIGHT

If you're ever unfortunate enough to land in a neurologist's exam room, one of the first things your doc will do is shine an ophthalmoscope in your eyes. Peering through each pupil, she'll spy a dome ablaze in sunset hues, four spindly veins branching out from the radiant "sun" that is the start of your optic nerve. This simple examination is one of the quickest ways to check in on your brain, because that dome—your retina—is a part of it, pushed out of your primitive central nervous system in-the-making a mere month into your becoming you.

Our eyes are central and essential to us. At just two and a half centimeters in diameter within our full-grown skulls, they hold nearly 70 percent of all our sensory receptors and helm almost half of our cerebral cortex.

And the retina is where the story starts.

It's the film in the camera. The place that first catches light along its spectacular conversion: from our encounters with our visual world to the sparks of our understanding. And somehow, in a process that still eludes scientists, the retina performs some local processing of the input it receives, as well, making it both hardware and software.

ILLUSTRATION | MICHELLE LEVEILLE

The nerves in your arms and legs are resilient; injure them and they can rebuild. But damage to the retina and optic nerve is permanent; because like your spine, they are part of your central nervous system. They don't easily lend themselves to transplant, either, unlike the cornea. Thus many diseases of the retina and optic nerve remain untreatable.

Changing that, experts say, will require an all-hands-on-deck approach: developmental biologists, stem cell biologists, physiologists, neuroscientists, mathematicians, engineers, pharmacologists, and surgeons all charging full force—and most importantly, doing it together. They'll need a common physical space, first of all, to get together on common scientific ground, as well as support and encouragement to test new ideas—even the bold, way-out-there ones that are a far cry from what most scientists in the grind of the grant life cycle would call "safe."

And all of this, says the University of Pittsburgh's Jeff Gross, is happening right here.

"We keep feeling like somebody should be saying 'No' at some point," he says. "They're really letting us do this."

By 2022, the whole department, which is now scattered across Biomedical Science Tower 3 and the Eye and Ear Institute, will set up shop along with rehabilitation medicine colleagues in UPMC's planned vision and rehabilitation hospital in Uptown. The nine-story, 410,000 square-foot facility was painstakingly designed to spec with both patients and scientists in mind, "room by room and bench by bench," Gross says.

There will be floors for both basic and clinical research, as well as surgical and medical care for ophthalmology patients. (More on the facility's patient-centered design and unique clinical offerings on page 30.) Spaces for teaching, spaces for incubating start-ups, and spaces for collaboration.

Gross, professor of ophthalmology and the E. Ronald Salvitti Professor in Ophthalmology Research, is scientific matchmaker in chief for a rapidly expanding cadre of Pitt scientists at the vanguard of vision-restoration research. In the past three years, the ophthalmology department has hired 18 new faculty members, with more to come. They're asking fundamental questions: How do photoreceptors within the retina stay alive? How do connections between the optic nerve and brain develop? How does the brain decipher the patterns of light in our sights? How do all of the structures of the eye develop in the first place?

And if and when any of the above fails—then what?

"Can you find ways to stimulate the regeneration?" says Gross. "Or can you supplement or bypass [damaged eye structures] through [electronic prosthetic] devices? Or gene therapy? Can you give [patients] something to repair dying photoreceptors? The department is focused on each of these issues—in different but overlapping ways."

The aggressive recruitment effort and bold new facility to match are the brain children of José-Alain Sahel, Pitt's chair of the Department of Ophthalmology, who came to Pitt three years ago from Paris.

Sahel speaks often of the tremendous support he's receiving to help him realize his vision. The new tower, which will be located next to UPMC Mercy, is part of UPMC's $2 billion investment in new specialty hospitals in the region. "The effort that UPMC is making in building this fully integrated facility is currently unique in the country," he says. And on the University of Pittsburgh side, Sahel is quick to add, Chancellor Patrick Gallagher has backed the ophthalmology department's expansion wholeheartedly as an area of strategic importance.

In 2008, Sahel founded Institut de la Vision in Paris. That colossal venture is in the same vein as what UPMC and Pitt are planning. In its first 10 years, the Paris institute launched several companies and created 1,000 jobs.

Sahel continues to advise his colleagues in Paris and has established a robust collaboration between the institute and its academic partner—the Sorbonne's scientific and medical school known as Université Pierre et Marie Curie—and Pitt/UPMC.

Before Pitt/UPMC even hitched their wagons to Paris, they had particular strengths in corneal biology, infectious disease research, immunology, drug delivery, neuroscience, information technology, engineering, and ocular biomechanics. Pitt is also home to the Louis J. Fox Center for Vision Restoration, perhaps the first multidisciplinary research program dedicated to optic nerve regeneration in the nation, which Gross directs.

In a nascent field known as cortical vision, scientists hope to learn to circumnavigate damaged eyes and optic nerves, placing electronic prostheses in their stead. This will require a deeper understanding of the seeing brain and how it works in tandem with our bodily hardware.

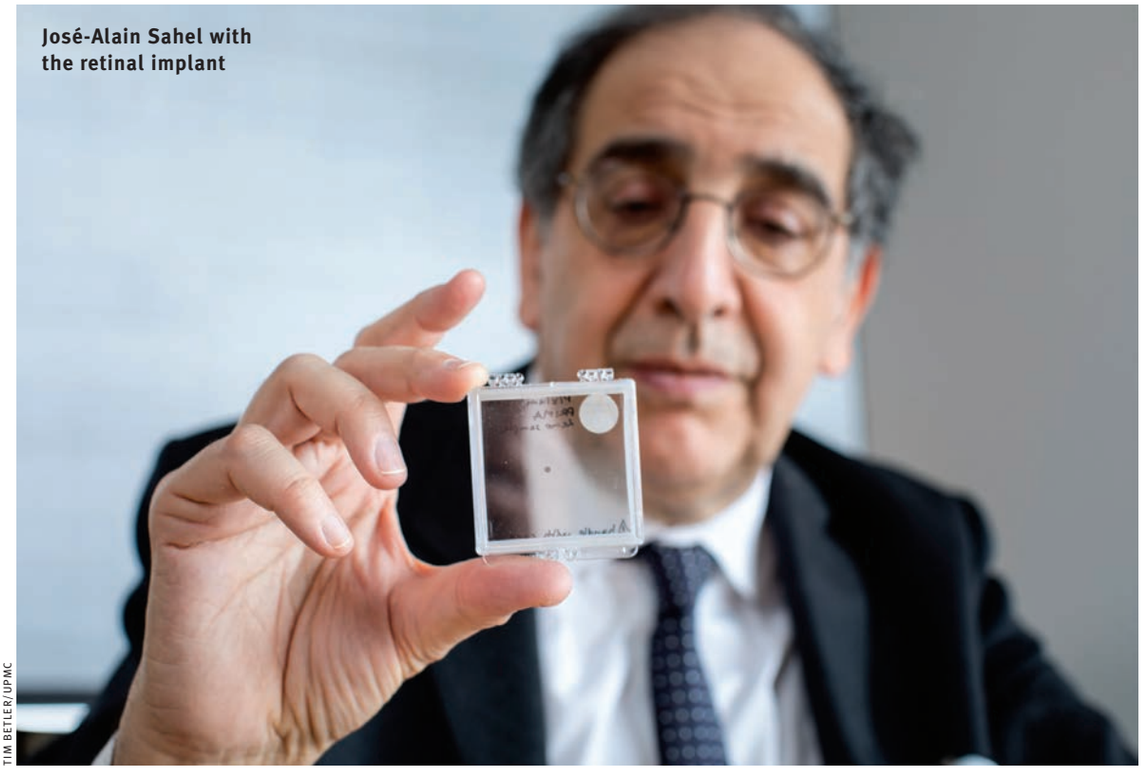
And now, the new intercontinental partnership is likely the largest biomedical research undertaking of ophthalmology in the world.

John Dowling, the Gordon and Llura Gund Research Professor of Neurosciences at Harvard University, mentor to Sahel, and luminary in the field of retinal biology, says this is exactly what he expected, because Sahel "has great taste in science. He knows the people who are likely to be very successful."

With Sahel at the helm, Dowling says, Pitt is on the path to number one in ophthalmology in the country, no question.

"He is a builder."

Gross says Dowling is just one of many advisory board members from around the world who've come to visit the exploding, reenvisioned department and left gushing at its promise, swept up in the feeling that this is the precipice of something huge.



José-Alain Sahel with the retinal implant

TIM BETLER/UPMC

MIND'S EYE

In a worst-case scenario, like a blast from a roadside bomb, the eyes and optic nerves might be destroyed altogether. But remember, the retina is an extension of the brain. Eyes and their wiring exist, essentially, to do our cerebral cortex's bidding.

"The brain," says Jeff Gross, "is what really sees."

In a nascent field known as cortical vision, scientists hope to learn to circumnavigate damaged eyes and optic nerves, placing electronic prostheses in their stead. This will require a deeper understanding of the seeing brain and how it works in tandem with our bodily hardware. "It's a long way off," says Gross. "But the pieces are all there."

In July, Pitt's ophthalmology department was awarded a $6 million grant from the Richard King Mellon Foundation. The massive gift will support Pitt in developing a Cortical Vision Program, through which it can recruit several neuroscientists researching vision and visual computation.

The latter, Gross explains, is the mathematical side of neuroscience—eavesdropping on, and computational modeling of, neurons within the networks. Visual computation demands a variety of approaches. "Some neuroscience, some math, some engineering," he says.

Gross adds that cortical vision will be the ophthalmology department's biggest area of expansion in the next couple of years. The first of these new hires, Patrick Mayo, was recently recruited from Duke University and will join the department in spring 2020.

FIXIN' CHIPS

If your brain is the computer, your retinas are chips. So, before José-Alain Sahel came to Pittsburgh, he and Stanford University's Daniel Palanker collaborated on a potential new therapy that could replace nature's chips with electronic ones. The latest and most promising iteration of that therapy is a retinal prosthetic device known as PRIMA, commercialized by Pixium Vision. Clinical trial organizers are now actively recruiting patients with end-stage atrophic dry age-related macular degeneration (AMD) for a three-year clinical feasibility study here in Pittsburgh. Study volunteers are already participating in France.

The new chip, a surgical implant, is pinhead sized, and, at 30 microns, no thicker than a human hair. The visual information goes from special glasses with a camera to a computer in the patient's pocket, then back to the glasses, where an infrared light beams the signal to the implanted chip. From there, patterns of light are sent to the brain. With training, patients could learn to use the chip to enhance their visual function—that's the hope.

This technology has a 25-year history. Previous attempts, though, either haven't worked or have fallen short of offering any meaningful improvement in vision. But PRIMA is expected to surpass its progenitors: It's the first wireless model. With 378 electrodes, hundreds more than on other chips, it's expected to drastically improve image quality. And it's the first chip to be surgically implanted under the area of macular degeneration, as opposed to on top of the retina or outside of the eye.

Joseph Martel, an assistant professor of ophthalmology at Pitt, is the principal investigator and will perform the delicate implantation procedure. He notes that while none of the study participants, who are legally blind, will suddenly be able to get behind the wheel, the technology has enormous potential to enhance quality of life.

"In these people who can't even see light, even if you can restore their ability to see shadows or a hand right in front of them, that's a very meaningful improvement."

ALGAE WIZ


Martel

Retinitis pigmentosa (RP), a leading cause of blindness worldwide, can result from any one of hundreds of molecular miscalculations. These missteps sabotage the production of a crucial protein, the absence of which robs photoreceptors of their function or causes them to die prematurely.

Experts are testing a wholly new workaround in a five-year safety and dose-escalation trial at three sites: UPMC here in Pittsburgh, Institut de la Vision in Paris, and Moorfields Eye Hospital in London. Using a technology called optogenetics, they'll target specific cells and reprogram them to become factories for a protein borrowed from nature—a light-sensitive substance usually only found in algae.

The reprogrammed cells, then, can detect light at specific wavelengths, which they can "see" using a specially designed set of glasses. The specs are equipped with a built-in camera, as well as a projection system. It's all linked to a pocket-size computer that generates images of the world around the person, in real time. (For more on the camera technology, see the next section.)

The therapy will be delivered via a viral vector, injected into "the jelly part of the eye," says Joseph Martel, the surgeon for the trial. He notes that other therapeutic approaches have been delivered under the retina—which is far trickier, not to mention riskier. The jelly, however, is a piece of cake. No one has to fly to Pittsburgh or Paris to learn the technique. And it takes minutes, not hours.

"These patients that we contact for these trials," Martel adds, "they're quite enthusiastic about participating. It's refreshing and definitely a nice change from previous visits where we were basically telling patients that . . . there's nothing we can do."

A NEW LENS

Consider the sea squirt.

As a little tyke, it's a freely moving being—a wee cyclops with a tail. And then, when it's ready to settle down with itself (it's hermaphroditic) and make some little squirts of its own, it finds a nice rock somewhere to retire, basically, as a sea sponge. In its new life chapter, its first order of business: eat its own eye. Then, in short order, its brain.

These fascinating creatures have an important lesson for us, says Ryad Benosman, professor of ophthalmology at Pitt, as well as an adjunct faculty member in the Robotics Institute of Carnegie Mellon. And that is: Anything that moves, sees. And Benosman, a world authority on computer vision, has come to realize, the thing most worth seeing is: movement.

Benosman, a mathematician by training, has undergone an unlikely metamorphosis of his own. He worked for years in robotics, designing omnidirectional systems. But as his frustrations mounted over the limitations of his prototypes (Exposure! Motion blur! File size! Power!), he grew curious about how this process comes so naturally to us and our kin in nature.

"Suddenly, around 2003, I understood that the problem was that if you want to really understand brains, you have to work with real brains," he says.

So, at his kitchen table, he began a self-guided exploration of the far-off field of physiology, focusing (ahem) on the eye. This organ, he found, has evolved the most across species, with efficiency robotics couldn't hold a candle to.


Benosman

After years of study, it dawned on him that brains simply don't care about what cameras churn through massive amounts of data and power to do, i.e., build hi-res renderings of every single point of light in the sky, blade of grass beneath our feet, and everything in between.

Instead, says Benosman, "You get information only when something happens." The stuff of real substance for the seeing brain is: change.

And if nothing changes, moves, or happens? Then the seeing brain idles. Nothing spent, nothing wasted.

Benosman conceived of a new type of sensor that captures and records only changes within a visual field between time points. He'd entered a discipline known as neuromorphic event-driven computation.

But it was all theoretical, he says, for years. Then José-Alain Sahel invited him to join Institut de la Vision in 2008. By 2015, Benosman had 45 people on his team, churning out implants, chipping away at optogenetic stimulation, building cameras and retinal prostheses (see previous sections for more on these technologies).

When Benosman presents on his work at conferences, there's a video he likes to play: a split screen showing the same drive through a tunnel in Paris, filmed by two different cameras side-by-side. On the left is a conventional camera. Though rendered in full color, it's kind of a mess. Scenes come at it too fast, causing blurry, pixelated blobs. And as the car emerges from the tunnel to the open air, the daylight completely blinds the camera.

On the right, using Benosman's invention, it's entirely different. There's no color—it's more of a flat plane of gray overlaid with what looks a little bit like a pen-and-ink outline of the edges of all that moves past the car. But there's no motion blur from computational catch-up. The important stuff is all there: individual tiles of the tunnel that locate the car in the space, and then, outside, streets and curbs and buildings of the intersection at what a Parisian would recognize as the Gare de Lyon. And there's no white-out of exposure, either. Light, dark, inside, outside, this camera doesn't care.

Benosman's innovation seeded a start-up called PROPHESEE, which produces cameras for driverless cars. The machine-vision technology mimics how our brains see.


da Silva

HATCHING PLANS

Hope and Terzo, the peregrine falcon couple who call the Cathedral of Learning their home, have vision far superior to our own. They can spot their next meal a mile away. And here's another fun fact: In each of their retinas, they have two structures that confer superfine-detailed vision. We humans only have one. For us, that structure is known as the fovea. The fowl equivalent is called the high-acuity area. (Fovea refers to the Latin "pit"; there are no actual pits in bird eyes.)

In the dome of the retina, this high-acuity area is a tiny spot within a little yellowish structure in the center called the macula. For us, the fovea contains about 200,000 cones—photoreceptor cells used during daylight conditions—compared to the whopping 6.4 million cones throughout the rest of the retina. And yet in humans, this tiny structure, which amounts to less than 1 percent of our entire retinal surface, has fully 50 percent of our visual cortex dedicated to processing what it takes in. In fact, losing a significant amount of nonfoveal cones is sometimes not even noticeable. But with foveal cones, it sure is.

For years, the National Eye Institute has supported scientists attempting to grow new retinas, to relieve patients facing macular degeneration, the leading cause of visual impairment and blindness in the developed world.

And it's working . . . almost. These seedlings of tissues, sprouted from stem cells, build layers of photoreceptors, ganglion cells, and interneurons. Unfortunately, however, no fovea-like structures.

But Susana da Silva, assistant professor of ophthalmology who joined Pitt this spring, thinks she knows why.

During her postdoc in the lab of Harvard University's Connie Cepko, da Silva studied retinal development in chickens. Because, as it turns out, uber vision is for the birds, broadly, and not just Hope, Terzo, and their high-flying friends. Chickens also have high-acuity areas like our foveae; but mice, zebra fish, and many other animal models frequently used in scientific studies do not.

By 2017, da Silva had identified the particular ingredients that can make or break chick high-acuity area development: retinoic acid (or rather, a complete absence thereof in a very specific spot) and FGF8. Then, she checked to see if the same was true in humans. And much to her delight, she found that it was.

"To our knowledge," says da Silva, "it's the first ever described molecular signature of the early human fovea."

Here at Pitt, she's setting up her lab, hatching plans, and preparing to follow through on her findings. She'll ask: What is downstream of retinoic acid and FGF8? Can these particular ingredients be tweaked to finally incubate new high-acuity areas in a dish? What signals do cells send to one another to decide on their fates?

"Development is all about the right time and the right place," says da Silva. Genetic manipulation is especially tough in these particularly tight time windows. Also, retinoic acid and FGF8 are all over the place during development, like in nascent limbs. Which is all to say: She has her work cut out for her. But nonetheless, da Silva is thrilled at the prospect of (sorry) pecking away at it.

SEE NEW PEOPLE, HEAR NEW PEOPLE


Gross

Of the many challenges in modern ophthalmology, regenerating the optic nerve is perhaps the most daunting. Pitt is growing a team of recruits with this bold goal in their sights. Among them, notably, is Takaaki Kuwajima, research assistant professor of ophthalmology who won a highly competitive, $125,000 career development award from Research to Prevent Blindness.

At the same time, says Jeff Gross, Pitt's Louis J. Fox Center for Vision Restoration director, no one is under the delusion that any one department or even one institution can go it alone toward a challenge this formidable.

Gross, a self-described cynic, apologizes. "I feel like I drank the Kool-Aid. But it's true. People really want to work together. I think that's the expectation," not just within the department, but the neuroscience community citywide.

Each year, the Fox Center has a conference—a 25-person think tank on optic nerve regeneration that invites experts from around the world. Stars from Institut de la Vision are now in regular attendance.

"We also bring in people who are studying regeneration in other parts of the central nervous system," says Gross. For example, Pitt's Thanos Tzounopoulos, an authority on the auditory nerve who is director of the Pittsburgh Hearing Research Center and Endowed Professor of Otolaryngology. It might sound (ahem) surprising given the specialized nature of these areas, however, says Gross, "Many of the parameters are the same."

There's plenty of cross talk between Pitt and its fellow Pittsburgh higher-ed institutions, as well—something unheard of in other cities. Each quarter, vision scientists from Pitt, Carnegie Mellon University, and Duquesne University get together, a couple of representatives from each institution giving a brief overview of their work.

"It's a bit like science speed-dating," says Marlene Behrmann, professor of psychology at Carnegie Mellon who is also an adjunct professor at Pitt. The scholars share tips, tricks, and technical and analytical approaches. The institutions put their heads together during candidate searches, as well, to fill in gaps.

Behrmann, who studies plasticity in the visual system following surgery for epilepsy, has a strong collaboration with Taylor Abel and Christina Patterson at Pitt and UPMC. She points out that the Pitt-CMU connection is longstanding, citing the Center for the Neural Basis of Cognition and other joint programs. And now, that cooperative relationship between the neighbors is "zoomed in many-fold," she says.

"In my view, a field grows exponentially when you have a critical mass of individuals," Behrmann says, each scholar carving out a particular niche, but with interests so intertwined. She adds that her own work has been enhanced enormously by Pittsburgh's neuroscience community.

"We've reached critical mass." ■

Views of the planned UPMC Vision and Rehabilitation Tower—in the Pittsburgh skyline and (top right) from Boulevard of the Allies.

Architecture renderings by HOK



SNEAK PEEK

At the moment, the UPMC Vision and Rehabilitation Tower is merely a gaping hole in the earth, clattering with construction in the shadow of UPMC Mercy. Come 2022, a nine-story, 410,000-square-foot facility will put Pitt ophthalmology researchers under the same roof with patients in an extraordinary space.

The team at HOK, the architects for the project, has carefully selected lighting, materials, textures, and audio throughout the planned building to help patients with visual impairments in navigating the spaces. For example, Chris Downey, a blind architect at HOK, introduced elements like sound as wayfinding.

Pitt's Department of Physical Medicine and Rehabilitation, chaired by Gwendolyn Sowa, was instrumental in the process, as well, and will have a presence on the fourth floor of the completed facility. Neurorehabilitation services will aid patients with low vision. A space for Pitt's Rehab Neural Engineering Labs will connect those investigators with ophthalmology researchers and clinicians.

The rehabilitation expertise is key; many diseases affecting vision also involve other senses, as well as balance, mobility, and cognition, explains José-Alain Sahel, Pitt's chair of ophthalmology.

"It's a bold plan," says Sowa. "We believe that no other location in the world has paired vision and rehabilitation together in this way."

Sahel says patients will benefit from new imaging technologies, an area of great interest for his department. When he joined Pitt three years ago, Sahel's very first recruit was Ethan Rossi, a world leader in what's called adaptive optics. (Kunal Dansingani, Syed Mahmood Shah, and Jay Chhablani have also since joined the clinical imaging dream team.) Rossi is developing tools to visualize individual cells within a patient's retina, a capability that would enable Pitt ophthalmologists to quantify how well a given therapy is working. It could also help detect disease much earlier, which could improve outcomes.

Sahel is a firm believer that treatment is a beginning, not an end. Thus, the campus will feature a rooftop garden with test ramps and stairs, as well as an apartment and an indoor street scene, dubbed the street lab. In these spaces, patients will put new therapies and assistive technologies through the paces of everyday life, safely, with the support of the rehabilitation team.

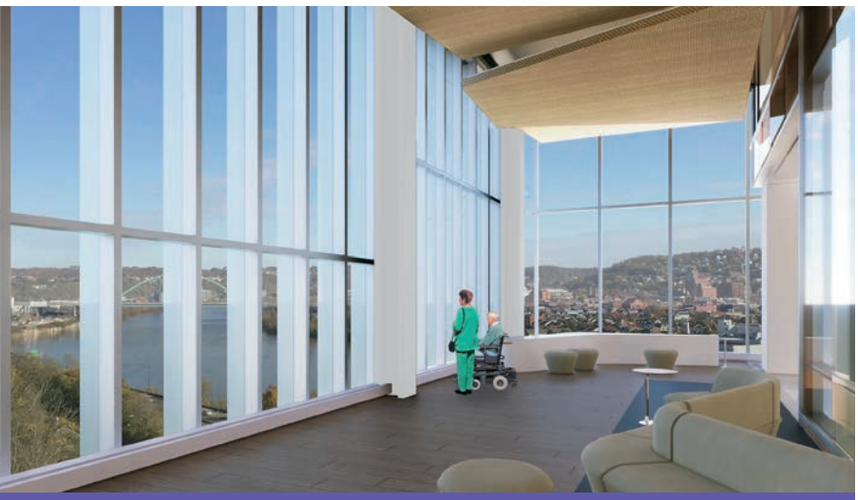
The street lab will feel a bit like a TV set—and in a sense it will be, cameras training on patient volunteers to measure their progress, step by tentative step, on the path toward a better drug or prototype, and a more independent life. —*Elaine Vitone*



UPMC Mercy is gaining the new Uptown facility as part of UPMC's $2 billion investment in new specialty hospitals in the region.









ABOVE: A view from the hospital, expected to open in 2022.

RIGHT: The building is designed to encourage collaboration, from the ground floor to the rooftop garden.