INTO A WORLD
Hat may be the oldest eye hospital in Europe opened in 1260, a few years after the Seventh Crusade. Louis IX of France established the 300-bed infirmary for the poor just to the west of Paris’s great fortress. From that dark age of blood and chaos, Centre Hospitalier National D’ophtalmologie des Quinze-Vingts survived into the modern era. (Its current home is still just a short drive from the former fortress, which you know as the Louvre.)

A few blocks from the hospital is an inspired work all its own, a research facility known as Institut de la Vision. Constructed as a patchwork of hundreds of unique panes of glass, their varying sizes and textures playing on the natural light that floods the building, the institute houses a legion of cellular biologists, physiologists, pharmacologists, surgeons, engineers, and others who are working to halt and reverse the effects of diseases that leave millions in the dark.
Inherited and acquired blinding diseases of the retina—the part of the eye that’s now the largest subfield within ophthalmology—remain untreatable. But that’s likely to change soon. Gene therapy and stem cell therapy are in clinical trials, and an electronic prosthetic device was recently approved by the U.S. Food and Drug Administration. At the forefront of these and other biomedical achievements is the founding director of this institute—this empire, as one colleague put it—José-Alain Sahel, who is the University of Pittsburgh’s new chair of ophthalmology as of July 1.

Sahel will continue to advise his colleagues in France from his new home. His move here marries Pitt and UPMC to the institute and its academic partner, the Sorbonne’s scientific and medical school known as Université Pierre et Marie Curie. And Sahel’s many collaborators across the United States and Europe say this union will strengthen each of its member entities: in Pittsburgh, the country’s largest payer-provider health care system affiliated with an academic center; in Paris, one of the largest centers of translational research on eye disease worldwide.

Sahel expects they’ll make this “marriage” official in the fall, when Yves Lévy, director of INSERM—the French equivalent of the National Institutes of Health—and Jean Chambaz, president of Université Pierre et Marie Curie, are slated to visit the University of Pittsburgh. They’ll iron out the details of the partnership in a meeting with Patrick Gallagher, chancellor and CEO of Pitt, Jeffrey Romoff, president and CEO of UPMC, and Arthur S. Levine, senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine, among others.

Sahel is quick to note that his initial decision to leave Paris was for personal reasons—not at all because he was unhappy in his work there. “It’s a total blessing. I love it every day. Every minute,” he says in a French accent. He’s talking via Skype in his book-filled home office on a June afternoon, just before his trans-Atlantic move. (Well, it’s afternoon in Pittsburgh, anyway—he’s a night owl.)

Sahel had plenty of offers, he admits. But chose Pitt for the truly unique opportunity it presented:

In Pittsburgh, he could build upon the strength and success of Pitt’s clinical and research realms—for which he credits his predecessor, Joel S. Schuman, the new ophthalmology chair at New York University’s Langone Medical Center, and Levine. (“You don’t meet a dean like that [but once] in your life. He’s amazing. He knows what translational research is. And his support has been exceptional.”) Sahel could also build on the strengths of the city itself: The uniquely collegial relationship between Pitt and its neighbor, Carnegie Mellon University. The growing technology industry, which includes an outpost of Google, as well as Uber’s robotic car development operations. The nexus of big data and machine learning, of precision medicine and translational science.

And he was drawn by the urgency of the moment for this region, which has a large elderly population. Macular degeneration—the leading cause of vision loss in the United States—is on the rise. Cognitive loss, dependence, depression, and trauma are all compounded by this as-of-yet-uncurable, age-related assault to the senses.

Without prompting, just about everyone I talked to predicted that Sahel would build a Pittsburgh equivalent to the Institut de la Vision that will attract researchers from all over the world. And when I ask the man himself about this, he says that it is indeed a goal. However, he says, “I like to tell people the future is promising, but it’s not today. We have to start working now.”

His plan for the present is twopronged: First and foremost, make changes for patients’ immediate benefit by improving access to, and comprehensiveness of, ophthalmologic care—notably for age-related macular degeneration, genetic retinal degenerations, and other diseases of the retina, which require advanced approaches. To do so, he’ll leverage Pitt’s main clinical and research hub in Pittsburgh’s Oakland neighborhood, as well as UPMC’s many community clinics. (He’s sensitive to the fact that for many people within this patient population, venturing out for doctor’s visits isn’t easy.) Meanwhile, he’ll exploit technologies that can extend Pitt/UPMC’s reach even further. “We have an opportunity to build a model of medicine,” he says.

Second: Make connections. There’s a tendency to view ophthalmology as an island all its own, notes Sahel. But really, it’s a part of neuroscience, and relevant to much more.

“The eye is an approachable part of the brain,” he says, quoting his mentor, John Dowling. “And a lot of diseases that affect many parts of the body affect the eye, too.” Here is an organ with sophisticated vasculature and immunology. Pharmacology is integral to managing eye disease, and biomaterials are becoming increasingly important—for drug delivery, for biocompatible systems. And perhaps most important, in his view, is what happens after the therapy—rehabilitation. Sahel sees treatment as a beginning, not an end. “When a patient comes into your
office, he’s not asking you a cellular biology question. He’s asking you about his real life.”

Scientists from other top institutions are already expressing interest in coming here to work with Sahel—one interview in Pittsburgh about every other day. Perhaps they have such faith in the next act of Sahel’s career because of the compelling story of the previous ones, which he performed starting with far less—virtually nothing, save his talents, notably that of bridge-building. “I built the institute with many people,” he says. “So I can do it here—with many people.”

When Sahel was 6, the family moved from Algeria to Rodez, in Southern France. In his quick recounting, he focuses more on the upsides of the move and what they made of it than their journey there, which had to have been harrowing amid Algeria’s bloody War of Independence. (Rodez was “very cold, but full of very nice people,” he says.)

Initially, he had no designs on becoming an eye doctor. The young Sahel went to Université de Paris for his MD and was planning to do a pediatric oncology residency in Strasbourg, 500 kilometers to the east. By then, 1980, he was married, and the family’s first child was on the way. So he decided to stay put for a rotation. It was more or less happenstance that he chose to do it in ophthalmology, but within a few months, he was hooked.

“First, the eye is very delicate. It’s beautiful, the retina especially.” Second, he saw in ophthalmology a rare opportunity to be both a people person and a polymath—a clinician deeply invested in patients’ quality and enjoyment of life, and also a student of the world. (His interests are “everything from medicine, to
surgery, to neuroscience, to poetry, to art,” he says, referencing blind poets like John Milton and Jorge Luis Borges. “I like that you can be both broad and deep at the same time.”) When he did move to Strasbourg, he performed residency rotations in neurology and neurosurgery before starting his core ophthalmology training, ever eager to learn more.

The clinic was frustrating. Half the patients who walked into his office would walk out happy, knowing there was a relatively easy surgical fix for what ailed them—a cataract, a detached retina. But for the other half, he was delivering the devastating news that their sight was slipping away, sometimes shockingly fast, well. Without cones, the patient can no longer read, recognize faces, or see the blue of the sky.

As Sahel was beginning his academic career, a handful of genes had been identified as culprits in RP—but only in rods. None had been found in cones at the time (nor have more than a handful since—and more than 60 RP genes are known today). It didn’t make sense.

And it wasn’t fair—we live in a world of light, he says. For that, we need our cones.

“If you protect the cones, people don’t become blind. . . . I thought that if we could find a mechanism explaining the loss of cones, that would be great.”

At first, Sahel and his institute colleague Serge Picaud chased a neurotoxicity hypothesis. They did find some neurotoxicity at work, and published on that, but it was not enough to explain RP. So next, they looked at calcium overload as another possibility, and published in Nature Medicine their findings that, yes, if an overload of calcium burdens the cells, rods and cones die. But that clearly wasn’t the whole story, either.

Then the team wondered whether there might be crosstalk between the cells. Did the health of the one population depend on the health of the other? Could the rods somehow be important for the cones’ survival?

Sahel and Saddek Mohand-Said, his then-PhD student who is now an associate professor at Pierre et Marie-Curie Université, transplanted isolated rods into an animal model of advanced RP, and found that although it didn’t completely stop cone death, it did delay it by half—and not just at the site of the transplant, but all over the retina. Which raised the question: Could there be a diffusible factor, something the rods were releasing that protected the cones? They cultured the two cell types together and found that was exactly the case, publishing their red-letter findings in PNAS in 1998.

The team then recruited a molecular biologist, Thierry Léveillard—who’s now the director of research at INSERM—and for six years, they systematically cloned every known gene in the retina, then screened thousands of their products before they found what they were looking for: RdCVF, or rod-derived cone viability factor. They showed that when they injected RdCVF into the retina of an animal model of RP, photoreceptor cell death slowed down.

Last year, two decades of work culminated in a Cell paper, wherein the team led by Léveillard at last identified the receptor of RdCVF—and revealed exactly why RdCVF is so crucial for cones. Without it, cones are unable to absorb the glucose they need to survive. And their ability to regenerate their outermost segments, which catch and process light, may suffer, as well.

A clinical trial for a novel treatment targeting this mechanism is slated to begin in 2017 (with major and continuing support of Foundation Fighting Blindness). If all goes well, people with RP will soon finally have a way to protect their vision. A single injection of this cell-saving therapy, a vector introducing copies of a gene that’s essentially an all-purpose RdCVF factory, is expected to work for several years, slowing cone death and perhaps even reversing it. Best of all, any patient with RP stands to benefit, regardless of which mutation ails him, provided he still has at least 5 percent of his cones intact. And the treatment may help patients with other retinal conditions, as well.

When Sahel started his lab, it was a moonlighting gig—just him and a part-time tech-
nician making the most of evenings, weekends, and other stolen moments in a surgeon's crammed schedule. Bit by bit, he chased down the money to snowball the Strasbourg group to some 30 people, cellular biologists and ophthalmologic electrophysiologists and others all simmering together in a scintillating interprofessional stew. They cooked up papers, gained momentum, learned from one another, had a ball. And when Sahel accepted a chair position 15 years ago at France's national eye hospital, all but one member of his team came with him.

Quinze-Vingts brought Sahel to Paris with the promise of breaking ground on a new research center. But he arrived to find that the money had fallen through. Within a few years, with the support of Quinze-Vingts, he raised it from a variety of government, industry, and nonprofit sources and carved out a magnificent, 120,000-square-foot space that opened in 2008.

And then, just two months later, it burned in a disastrous fire.

Sahel mentions this in our Skype chat only in passing—that his decades-long dream went up in flames. He uses the same soft-spoken, measured, yet incredibly fast cadence with which he recalls any other event in his long and storied career, his mind and mouth moving a kilometer a minute. (He was just as calm on the phone the day after the fire—No problem. Don't worry. We'll fix it—says close collaborator and friend Botond Roska, a neuroscientist and group leader at the Friedrich Miescher Institute for Biomedical Research and professor at the University of Basel in Switzerland.)

And fix it they did, reopening in 2010. From their original team of 30 people, Institut de la Vision has since grown tenfold. And by all accounts, their operation is a wonder to behold:

Computer scientists conjure up mathematical models of how the eye works. Developmental biologists refine new treatments using stem cell therapy (Sahel expects they'll be in clinical trials by 2018), as well as efforts to transplant and re-innervate the entire organ of the eye. (Pitt is already a partner and leader in the latter, a long-haul effort that's just beginning—more on that later.) Molecular biologists and geneticists work to pinpoint mechanisms of heritable disorders. A vision function department teases out how information is processed in the retina and the brain. A therapeutics and pathophysiology department develops new treatments for conditions like glaucoma and diabetic retinopathies. Pharmacological researchers, currently at work on some 140 projects, have 10 drug candidates either in or on their way to clinical trials. And eight startup companies—some of which include Sahel as a cofounder—are cutting their teeth. (One was acquired for $500 million, and two have gone public.)

New patients are entered into a genetic registry and tested for eye-function benchmarks and eye structure, using the latest and greatest imaging devices—including one that can show high-resolution images of the back of the retina, at the level of individual cells. All of this information is funneled into the laboratories, which are busily working on hundreds of different forms of blinding disease. As new treatment possibilities emerge, they go right into the pipeline, says Jean Bennett of the University of Pennsylvania. She laughs, saying, "It's a really incredible empire."

As much of the workspace as possible is shared. Virtually every department is involved in every project. The cafeteria is centrally located. There are no mandatory dinner meetings—but, mon ami, while at work, everyone works together, hopefully for the joy of it.

These are things Sahel planned to the letter, with “almost amusing attention to detail,” says Roska, “right down to how much light enters the building.” But he was on to something: “You can have a lunch with somebody who initially thinks that you're a complete idiot,” says Roska. “And the next day, he thinks that you are just an idiot, and then the third day he thinks that, well, maybe not an idiot. And then you start to talk. There is a point where you see light, . . . some place for collaboration. . . . It takes a lot of effort and discussion to find a common point."

"You go to him with some large idea that you would have no clue how to ever [fund] or organize," says Roska, "and he listens. And if he thinks it's a good idea, he just makes it happen. I've seen it so, so, so many times. . . . He builds
up trust around him. You know where the money goes. It goes to translational research.”

Sahel, with Oregon Health & Science University’s Richard Webler, was the first to conduct gene therapy trials for Stargardt disease, the most common form of inherited juvenile macular degeneration, as well as for Usher syndrome, which can render people both blind and deaf. And now, he has brought to fruition a gene therapy trial for a mitochondrial disease known as LHON (Leber hereditary optic neuropathy). It’s an optic nerve disorder that usually strikes boys in adolescence. They lose vision in one eye, and then weeks or months later, the other eye follows. But with this new therapy—a technique Sahel and Marisol Corral-Debrinski at INSERM developed to transport reparative RNA to the damaged mitochondria—some patients have regained some vision. A new study is now under way at seven sites across the United States and Europe.

For people who have little or no vision left, Sahel and Roska have worked for 10 years perfecting a technique called optogenetic vision restoration. It harnesses dormant cones or other retinal cells, using what are called optogenetic sensors, unique proteins that can transduce light to spark neural responses. Once delivered to the retina (via an injection of a viral vector), the optogenetic sensors target the chosen cell type and kick-start the cells into producing a light-sensitizing protein usually found only in archaea. Then, the patient is fitted with a special set of glasses. Built into them is both a sophisticated camera to capture images of the world around her and a projection system to send these images into her eyes, at just the right intensity and wavelength to stimulate the transformed retinal cells and send meaningful signals to the brain. (A cell phone–sized computer in her pocket links it all together.) This therapeutic approach has the potential to help a range of visually impaired or blind patients, regardless of what mutation they have.

And then, there’s the artificial retina, known as Argus II. In a collaboration with the University of Southern California’s Mark Humayun, one of the co-inventors of the technology, and Avinoam Safran, an emeritus professor at Université de Genève, Sahel’s group was the first in Europe to run clinical trials on the device, which has since been approved by the FDA. This fall, Sahel’s team will begin a clinical trial of a new and improved version they designed with Stanford’s Daniel Palanker and an institute-incubated startup called Pixium Vision.

Sahel believes it’s important that when patients are outfitted with these experimental devices, they aren’t just observed for their visual acuity. (In the classic example, flash cards. “Which way is the letter pointing?” and so on.) Rather, they are invited to participate in the research as they practice using their new visual function in a safe environment that mimics everyday life.

Sahel’s biggest inspiration for this soup-to-nuts approach to science wasn’t a scientist, but twentieth century historian Walter Benjamin, one of the earliest proponents of transdisciplinary teaching in philosophy, history, and art. For Sahel, the borders between academic divisions and departments are fluid, the ends of some studies blurring into the beginnings of others.

But it is all the same thing, and all for the patients.

Sahel has been a unifying force in the field from the start, says Bennett, the physician-scientist at Penn, who first met Sahel more than two decades ago. They were both waiting in the wings for conference presentations on the promise of gene therapy for blinding diseases—a dream on which they would eventually collaborate. “I immediately realized that this was a person who was very, very ambitious, yet incredibly humble and self-effacing, and brilliant, and determined to make a difference in the lives of people who are facing blindness.”

Bennett and Sahel became acquainted at that international ophthalmology conference—fittingly, she says, in Germany, not far from the felled Berlin Wall. Soon after that meeting, Sahel decided it was time to join U.S. and European forces behind the common goal of turning bench research into meaningful clinical trials. So he scared up funding to host a huge meeting, which he called Curing Blindness: Reaching Across the Atlantic. It was held in the French Senate in Palais du Luxembourg, a grand and gilded space where daylight streams through the domed ceiling.

“First of all, I don’t know how he managed to do all that!” she says. “But it really set the pace going forward.”

The meeting succeeded in chipping away at old walls of rivalry and ultimately birthing multiple organizations and collaborations.

“I view it as a historic event,” Bennett notes. “Everyone [agreed] to move forward, together.”

Four weeks after Sahel’s arrival in Pittsburgh, we talk again, this time face-to-face in his office at the Pittsburgh Eye and Ear Institute, sandwiched between his many meetings. Among his goals—tap into UPMC and Pitt’s strengths and lay the groundwork for new approaches to treatment and research on retinal disease here, from neuroprotection to vision restoration. He’s been busy.

Face-time with all of his faculty and staff. Site visits. Chats with Pitt chairs like Angela Gronenborn of structural biology, Lawrence Wechsler of neurology, Peter Strick of neurobiology, Jonas Johnson of otolaryngology, and Gwendolyn Sowa of physical medicine and rehabilitation. With Jeremy Berg, former National Institute of General Medical Sciences director who is Pitt’s associate vice chancellor for science strategy and planning (and was just named editor-in-chief of Science—see p. 30). And with Martial Hebert, head of Carnegie Mellon’s Robotics Institute (a fellow Frenchman who’s been in Pittsburgh for 30 years—“We spoke in English,” Sahel says, looking down with a smile).

Sahel met with Andrew Schwartz, Distinguished Professor of Neurobiology, and Robert Friedlander, neurological surgery chair and Walter E. Dandy Professor, to discuss future collaborations regarding robotic vision.

He convened with the chancellor and, that same day, with an award-winning app developer.

This afternoon, Sahel will talk with Kia Washington, the young Pitt surgeon whose work Science called him to comment on a year and a half ago, before he knew thing one about Pittsburgh.

Washington, an assistant professor of plastic surgery and associate director of the hand transplantation program at Pitt and UPMC, developed the world’s first viable model of orthotopic rodent eye transplantation. A multi-institutional consortium with Stanford, Paris, and Harvard is behind this very long-term project; the consortium formed months before Sahel arrived.

“But now the hub is going to be here,” he says, “because we’re bringing everything together—people like Jeff Gross, head of the Fox Center, Vijay Gorantla, and other experts in optic nerve regeneration, immunology, neuroscience, surgery, biomaterials, many areas.”

Coming together like this is what Pitt people have become known for.

And, notes Sahel, “This is what I love to do—to integrate, to view the question as a global question, and then see what pieces we need, and how the puzzle will fit in the end.”