



With foundation, community and industry partners, Pitt is planting seeds for a vibrant life sciences ecosystem in Pittsburgh. The new BioForge biomanufacturing center (preliminary rendering shown right) in Hazelwood will be a catalyst, creating new opportunities and attracting industry partners.



PHOTOGRAPHY: J&L PLANT IN HAZELWOOD; HEINZ HISTORY CENTER: TWO STEELWORKERS; UNIVERSITY OF PITTSBURGH; HAZELWOOD: RENDERING; DEPICTION; BIORANGE RENDERING; HOK.

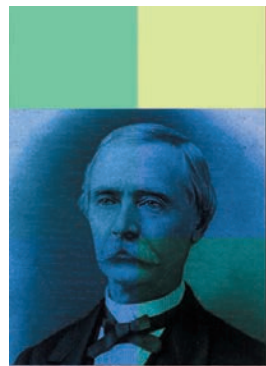
STEEL VALLEY TO BECOME BIO VALLEY

PITT AND PITTSBURGH CHART A BIOTECH CORRIDOR

BY CARA MASSET

PHOTO-ILLUSTRATION BY R.J. THOMPSON/UNIVERSITY OF PITTSBURGH

Patients who expected to live with blindness for the rest of their lives are back in action playing sports, reading signs and recognizing familiar faces. Some are driving cars again. Their turnarounds come from a novel gene therapy that's restoring sight for patients enrolled in clinical trials originating in Paris and conducted in Europe and the United States. These people are recovering from a form of blindness known as Leber hereditary optic neuropathy, which typically comes on in the teens and 20s.



“Eighty percent of patients get very significant vision improvement. Over 70% get partial but significant vision recovery,” says the University of Pittsburgh’s José-Alain Sahel, an MD, Distinguished Professor and chair of ophthalmology whose team developed the gene therapy. It’s the first treatment for the rare disease—and the first-ever gene therapy to target mitochondrial DNA, opening new treatment possibilities for other genetic mitochondrial diseases.

Dozens of patients in Sahel’s clinical trial are benefiting from the treatment, but he has had to ask some participants to wait as long as a year for doses to become available. Producing the gene therapy is among the biggest challenges for moving it—or any gene therapy—through trials and into the medical marketplace.

The global bioeconomy is in a manufacturing squeeze. Scientific and clinical advancements have prompted an explosion in the development of gene and cell therapies and other biological treatments over the past decade. (Broadly speaking, cell therapies transfer live cells into patients to treat diseases, while gene therapies transfer genetic material into patients to treat diseases.) Transitioning these living therapies from wet labs and animal models into clinical testing—and, if all goes well, widespread use for patients—requires manufacturing them in facilities where they can be purified for human safety and scaled up to clinically important levels.

But the processes are more complicated than manufacturing traditional pills, and few manufacturers have the specialized knowhow to make these clinical-grade therapies. Those that do have yearslong waitlists. Pitt scientists like Sahel are among the researchers worldwide who have had to wait in queues for their biological products to be manufactured. And there have been growing pains with quality control as manufacturers adapt to producing entirely new products. One Pitt research team outsourced the production of an antibody they’d developed for treating COVID-19 to an out-of-state manufacturer where it, frustratingly, failed to meet quality control standards. The researchers were among the very first to develop a monoclonal antibody for the disease, in 2020, yet they weren’t able to move it forward. (This during a pandemic, and in

the context of Operation Warp Speed, when the federal government made historic attempts to remove regulatory and other obstacles for promising COVID-19 therapies and vaccines.)

Beyond COVID, there’s work to be done to make next-generation treatments widely available.

“When you look at where life sciences research is going over the next decade, almost all of it is focused on biological products—gene therapy, cell-based therapy, mRNA-based therapy,” says Anantha Shekhar, Pitt’s senior vice chancellor for the health sciences and the John and Gertrude Petersen Dean of the School of Medicine. “These are very different types of technologies. We’re no longer going to be just making pills to give to patients. These are living products, most of them, and they have to be manufactured in a very different way. There is both significant unmet need and a huge bottleneck in capacity to manufacture them with current technologies.”

The need for investing in and expanding biomanufacturing was underscored in September when President Biden issued an executive order on the American bioeconomy. “It’s not enough to invent new technologies that save lives. We need to manufacture advanced biotechnologies here in the United States,” Biden said.

In the executive order, Biden’s administration laid out goals to support biomedical research that will “develop genetic engineering technologies and techniques to be able to write circuitry for cells and predictably program biology in the same way in which we write software and program computers” and “advance the science of scale-up production while reducing the obstacles for commercialization so that innovative technologies and products can reach markets faster.”

The president would be pleased to see what

Pittsburgh has planned.

Before long, Pitt will break ground for its own biomanufacturing facility, which will be known as BioForge. The futuristic “factory” for biological therapies will rise from Hazelwood Green, a former brownfield that was scrubbed and revitalized thanks to the persistent efforts of community groups and Almono, initially a consortium of four local foundations (which today includes the Heinz Endowments, the Richard King Mellon Foundation and Claude Worthington Benedum Foundation). Hazelwood Green is the site of the city’s last operating steel mill, run by LTV Steel (formerly Jones & Laughlin Steel), which closed in 1998. President Biden has given remarks there twice since 2020 on bolstering America’s future in manufacturing.

Hazelwood Green sits along the bank of the Monongahela River, a few miles upstream from Station Square’s monument to the steel industry’s revolutionary Bessemer process—fitting, because BioForge is being designed not only to meet urgent biomanufacturing needs but to revolutionize the biomanufacturing process itself.

THE WAY BACK STORY, AND THE BACK STORY

In 1811, William Kelly was born into an Irish immigrant family living in Pittsburgh. The region’s first iron mills began operating during his youth, and Kelly studied metallurgy at the Western University of Pennsylvania, which would become the University of Pittsburgh. He then joined his brother in running a dry goods company, a gig that involved business travel by canal boat, stage-coach and horseback. Train travel wasn’t yet widely available—a circumstance Kelly would ultimately help to change.

The family’s dry goods warehouse burned down, and around that time, Kelly had fallen for



Pitt alum William Kelly (far left) developed an approach to making a stronger metal from iron, steel. Today along the Monongahela, once a steel capital, a new industrial era is rising.

a Kentucky woman he met during his business travels. He married Mildred Gracy of Eddyville, Kentucky, and bought land in her hometown, where he applied his metallurgy expertise to open an ironworks. After a while, Kelly became concerned about the amount of timber his mill burned to make charcoal for the iron refining process. His crew of Chinese laborers knew about blowing air into molten pig iron to remove impurities, a method requiring less timber; they'd done that in China. So Kelly and his team worked on developing this pneumatic process. The resulting metal not only reduced timber costs but made a stronger metal—steel.

Civilizations had turned iron into steel for centuries through intensive small-scale production, but now Kelly was developing it in the context of the Industrial Revolution and taking steps toward mass production. He wasn't the only one. In 1855, Sir Henry Bessemer filed a patent in England for a similar pneumatic process.

The United States had largely been importing pricey iron rails from England, and the cheaper and stronger steel rails resulting from Kelly's and Bessemer's developments drove its railroad industry forward. Thousands of miles of new railroads catalyzed the industrial economy. Take the example of Hazelwood: After it earned a railroad track, its first steel mill set up shop.

Skip ahead almost 170 years to 2023 and a site just a mile or so northwest along the Monongahela. In a clean room in the Riviera building, a laboratory tech works at a hygienic stainless-steel bench (made possible by continued

advances in metallurgy). Clean rooms are the factory floors, as it were, for producing cell and gene therapies, but you won't find assembly lines with conveyor belts here. This sterile room of gleaming white and silver, built in compliance with the FDA's Good Manufacturing Practice (GMP) recommendations, features specialized appliances that wash cells or separate cells by type.

The technician carefully extracts immune T-cells from a tumor that was removed from a patient at UPMC Hillman Cancer Center a few days prior. Over the following month, he will create a personalized therapy for the woman, who is participating in a clinical trial for tumor-infiltrating lymphocyte (TIL) therapy led by Udai Kammula, Pitt associate professor of surgery. The technician will select the patient's T-cells that are the most effective at attacking her tumor and then multiply those T-cells from the millions to the billions.

After the resulting product goes through multiple quality control checks to ensure its efficacy and make sure it hasn't been contaminated with bacteria, it will be hand-delivered to Hillman, where doctors will administer it to the same patient and, hopefully, eradicate her cancer. The results of the TIL trial are promising so far, with regression of metastases in many cancer types.

The clean room for TIL trials is part of Hillman's Immunologic Monitoring and Cellular Products Laboratory (IMCPL), founded in the 1980s as a pathology labora-

tory. Its most recent evolution and 2021 expansion quadrupled its clean rooms and added better capabilities for gene and cell therapy fabrication. IMCPL is probably the largest such lab in an academic medical center, and teams of international scientists from Korea to Croatia regularly visit to learn how they can build their own facilities. Yet it's a precursor of what's to come along the Monongahela.

Hillman founded the IMCPL back when cell and gene therapies were

still in their early experimental phases. At the time, some success with such therapies had been achieved in animal models and rare clinical uses, but those largely remained good ideas rather than viable treatments. The gene editing techniques in existence were complicated, and the safety of patients who might be helped by gene therapy was a serious concern, as evidenced by the tragic death of an 18-year-old clinical trial participant in Philadelphia in the 1990s. The scientific community continued honing their methods, and clinical trials began demonstrating the safety and efficacy of newer cell and gene therapy approaches. A landmark change came in 2017 when the FDA approved the first cell and gene therapies for commercial use.

The agency has since approved 27 cell and gene therapy products—and it expects to soon approve 10 to 20 such products per year, based on an assessment of the current pipeline and clinical success rates.

UPMC Hillman Cancer Center was the first clinical site in the Pittsburgh region to offer FDA-approved CAR T-cell therapies, with the IMCPL responsible for preparing and shipping patient cells to pharmaceutical companies for genetic modification and then verifying that the cells were in top clinical condition upon return to Pittsburgh. ("CAR" stands for chimeric antigen receptor. The CAR T-cell approach is similar to Kammula's TIL in that clinicians extract a patient's natural immune T-cells and use them to create a per-

“BioForge puts another flag in the ground around reasons why industry partners would want to come to the region—there’s now a capability that doesn’t exist in many places.”

sonalized therapy for the patient.)

The Hillman and IMCPL teams have since administered more than 100 CAR T-cell treatments, a significant number because the whole process for each patient takes upward of a month or two.

But what if the process could be reduced to, daresay, 24 hours? That’s the sort of question that will be tackled at BioForge.

“A WONDERFUL ENVIRONMENT”

Pitt and Carnegie Mellon are already neighbors along Pittsburgh’s Forbes-Fifth corridor, and they’ll soon become neighbors at Hazelwood Green, where Carnegie Mellon’s advanced manufacturing innovation facility is the lead tenant at Mill 19, a modern facility built inside the exoskeleton of the original Jones & Laughlin Hazelwood Works (later LTV Coke Works). The facility, led by Sandra DeVincent Wolf, is known as the Carnegie Mellon Manufacturing Futures Institute.

Wolf, who most recently hosted President Biden at Mill 19 in 2022, is excited to watch BioForge rise across the street from her Mill 19 office and expects to partner with Pitt on taking biomanufacturing to new heights. Faculty at the Manufacturing Futures Institute have already made big strides in biomanufacturing—such as figuring out 3D printing of soft and biological materials. “It’s hard to print squishy materials because they don’t support themselves,” says Wolf.

Shekhar says locating the front doors of Pitt’s BioForge and Carnegie Mellon’s Manufacturing Futures Institute across the street from each other will be a boon for biomanufacturing.

“There’s very little being done in terms of disrupting the existing slow and painful technologies that biomanufacturing is using right now,” Shekhar says.

“With Pitt and Carnegie Mellon expertise, we can not only do routine manufacturing, but we can start to add robotics into it or add artificial intelligence and add new biological pathways so that the manufacturing itself can transform—so that we’re able to make faster, cheaper and safer products. That’s the real long-term value.”

Shekhar’s team has recruited ElevateBio, an experienced biomanufacturing company head-

quartered near Boston, as an anchor tenant and partner at BioForge.

ElevateBio was founded in 2017 to address the need for biomanufacturing brought on by the new frontier of genetic medicines. “There are more than 1,400 companies currently developing cell and gene therapies focused on treating or curing otherwise intractable diseases,” says David Hallal, the company’s cofounder and CEO. “We felt like the world really needed an end-to-end solution to help any number of these companies or academic medical centers to advance their cell and gene therapies.”

ElevateBio offers a range of technologies (gene editing, induced pluripotent stem cells, RNA-, cell- and vector-engineering) and R&D and regulatory expertise. Shekhar recruited the company for BioForge precisely because of its breadth of offerings and interest in partnering directly with academic investigators.

Hallal’s team has been talking with Sahel and other researchers from across the life sciences, as well as Wolf’s team at Carnegie Mellon. And it’s already partnering with BlueSphere Bio, a drug-development startup based along the Monongahela spun out of the Pitt lab of UPMC Endowed Professor and Distinguished Professor of Immunology Mark Shlomchik, an MD, PhD. BlueSphere uses proprietary platforms to rapidly identify T-cell targets and manufacture T-cell products for personalized cancer therapy. The 63-person company has been working with ElevateBio to manufacture its novel treatment that only attacks cancerous tissue.

“Our manufacturing process is very complicated,” says Keir Loiacono, BlueSphere CEO. “ElevateBio hit it out of the park on the first try.”

Loiacono says they will submit an investigational new drug application to the FDA later this year; they plan to first apply their T-cell therapy, in combination with stem cells, to treat the high-risk acute myeloid leukemia, often called AML.

Access to ElevateBio should help small companies here get their novel treatment ideas to patients.

“We want our staff to be working closely with the local team in Pittsburgh. We are focusing on generating new ways of manufacturing and creating know-how to advance

these technologies forward,” says Hallal.

BioForge will be ElevateBio’s first manufacturing location outside of its Boston-area headquarters. Hallal, a 35-year veteran of the life sciences industry, has popped into Pittsburgh for conferences and business trips a number of times over the years. He is excited to plant an ElevateBio footprint in the city.

“With research, innovation and health care at its core, Pittsburgh has always struck me with its great alignment between UPMC, University of Pittsburgh, Carnegie Mellon—and even the insurance community,” he says. “It creates a wonderful environment for innovation and delivery of transformative therapies to patients with severe and debilitating conditions.”

As Hallal notes, the relationship between the University of Pittsburgh and UPMC is unique among academic medical centers nationwide. UPMC operates its hospitals and its own insurance organization (of 4.5 million members) under a single roof, a setup known in organizational lingo as an integrated delivery and finance system. That gives it some latitude to experiment and be entrepreneurial. Its investment arm, UPMC Enterprises, has underwritten \$800 million in the development of mostly digital technologies and pledged \$1 billion toward life sciences startups, including BlueSphere Bio.

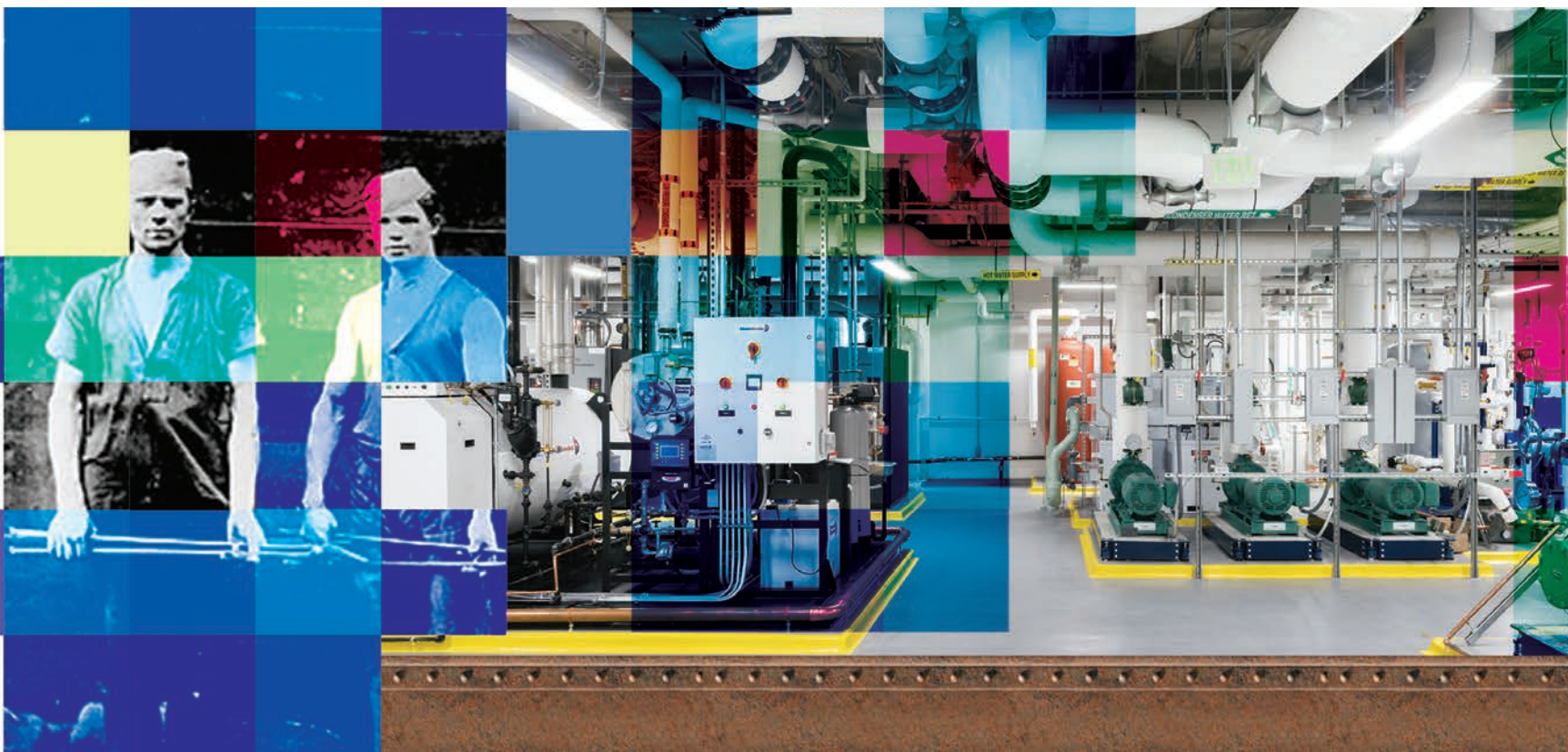
“We’ve long realized the need to commercialize innovations so that we can transform care globally while reinvesting in our mission,” says Leslie Davis, president and CEO of UPMC. “Pitt is a committed and integral partner in bringing this vision to life for the health of our region and all communities that we serve.

“BioForge is a game-changer for our region,” Davis adds. “It will help us save lives, create jobs and build new technologies right here in Pittsburgh.”

ANOTHER FLAG IN THE GROUND

Pitt’s BioForge will be constructed with funding from the Richard King Mellon Foundation, which made its largest single-use gift ever, a \$100 million grant, to build it. The grant will disperse \$10 million per year over the next decade. “The foundation is making a historic bet on Pittsburgh to lead nationally in the life sciences,”





STEELWORKERS: UNIVERSITY OF PITTSBURGH; ELEVATEBIO: BEN GERO PHOTOGRAPHY.

Sam Reiman, Richard King Mellon Foundation director, said when the gift was announced.

Kinsey Casey, Pitt associate vice chancellor for economic development in the health sciences who is playing a key role in establishing BioForge and connecting its partners, says the investment is part of a broader effort to raise Pittsburgh's prospects. She points to a 2017 Brookings report concluding that Pittsburgh is ripe for expansion in innovation and technology domains but is missing a key sector which is—ironically, considering the city's heritage—industry, notably biomanufacturing.

“Part of this strategy is to develop an ecosystem. BioForge is serving as a catalyst,” she says.

Evan Facher, a PhD, MBA, vice chancellor for innovation and entrepreneurship at Pitt and associate dean for commercial translation in the School of Medicine, says there is a need for the University to invest in projects leading to commercial partnerships.

“When we talk about Pitt from a funding perspective, we typically focus on federal funding and NIH funding. In those areas we're top five, top 10 in the U.S. But when we look at how much research funding comes in from industry partners, we're just inside the top 50,” he says. “BioForge puts another flag in the ground around reasons why industry partners would come to the region—because there's now a unique capability that doesn't exist in many places,” adds Facher, who also directs the University's Innovation Institute.

Blueprints are still being drawn for the 180,000-square-foot biomanufacturing facil-

ity that will include plenty of clean rooms, negative pressure rooms and all the necessary equipment for making biological treatments. ElevateBio is expected to lease about 130,000 square feet as part of its investment.

AT THE FRONT OF THE QUEUE

But BioForge is not solely about the facility, Casey says. “We don't want it to just be that shining building in Hazelwood Green that everyone's like, ‘I don't know what happens in there. It's basically magic,’” she says.

In October 2022, lab technicians flew in from ElevateBio's Massachusetts hub to talk with local high schoolers about biomanufacturing careers during a Manufacturing Day event at Mill 19. An effort to build workforce training programs aimed at Hazelwood residents for BioForge is underway. Pitt's partnership with ElevateBio is expected to generate more than 170 permanent full-time jobs, 900 construction jobs and 360 off-site support jobs. Pitt will also partner with local residents to create a community engagement center in the neighborhood.

BioForge will put Pittsburghers at the front of the queue in more ways than one.

“Having local biomanufacturing is critical to helping local patients first,” Shekhar says. “Wherever manufacturing capabilities are, hospitals or universities in the region have the first access to the products for their patients. We'll be able to do the first testing of all these products here, and we will be becoming world

experts in these treatments.”

Constructing the large-scale biomanufacturing site portends a new era of translational medicine at Pitt. Shekhar and his team are looking ahead toward creating a more robust infrastructure for multisite and late-phase clinical trials, exploring ways to prepare primary care physicians to offer gene and cell therapies as they become more commonplace and preparing health sciences students to practice in this new environment.

BioForge's grand opening is targeted for 2027. Pitt scientists we talked to can't wait to walk into a large-scale biomanufacturing site in their own backyard.

Sahel has several projects in need of biomanufacturing for what he anticipates will be the first-ever clinical trials for treating certain forms of blindness. Likewise, his colleague Leah Byrne, PhD assistant professor of ophthalmology who specializes in engineering biological vehicles for gene therapy, is ready to get started. (See page 22.)

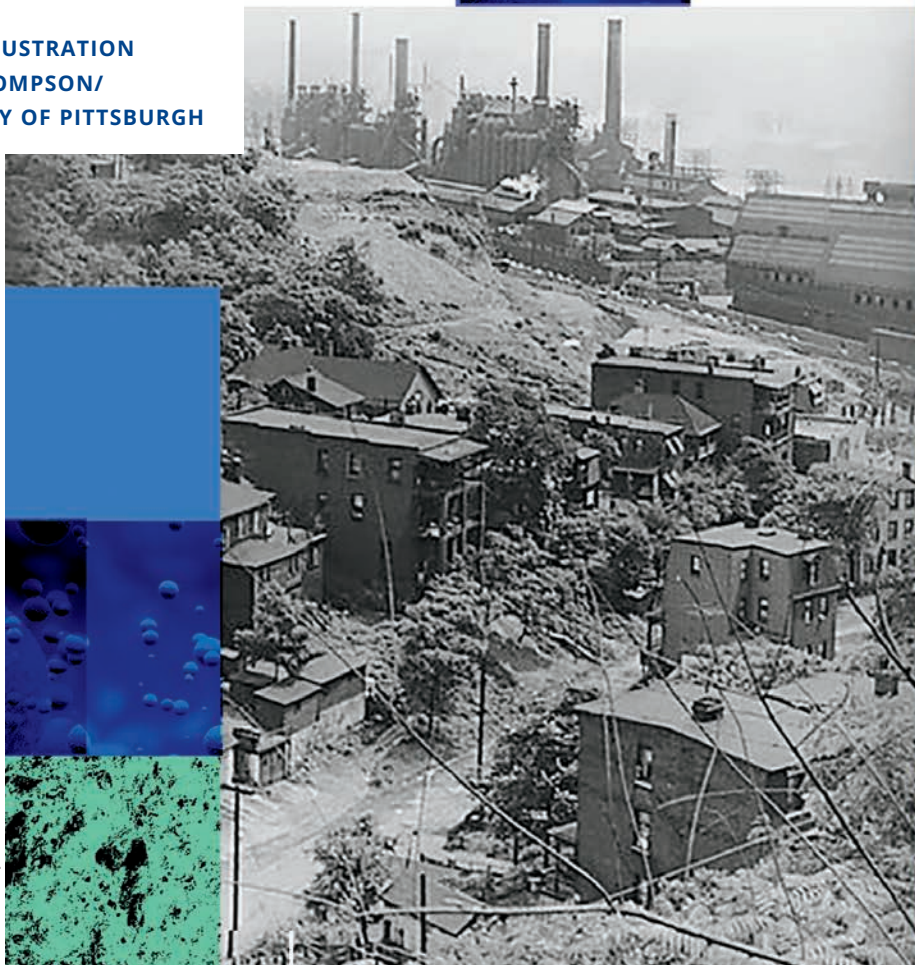
“Having direct access to ElevateBio here in Pittsburgh will allow us to make sure that the purification is optimal. That close collaborative relationship is going to lead to the success of the production,” Byrne says.

“This is a really unique opportunity to be here in Pittsburgh at this moment, right while biotech is just taking off. I really think we have all the ingredients that we need to make this a center for biomanufacturing.” ■

Erica Lloyd contributed to this report.

PHOTO-ILLUSTRATION
BY R.J. THOMPSON/
UNIVERSITY OF PITTSBURGH

HISTORIC HAZELWOOD: KINGSLEY ASSOCIATION/UNIVERSITY OF PITTSBURGH. ACTIVITIES DURING BIG TENT EVENT: JAMES KNOX PHOTOGRAPHY. RENDERING OF FUTURE HAZELWOOD: DEPICTION.



FERTILE GROUND FOR LIFE SCIENCES STARTUPS

"I never thought I would form a company in my life," says Pitt ophthalmology chair José-Alain Sahel. "But it just happens that if you want to deliver therapies to patients, it's the only way to make things happen."



Sahel

Sahel, an MD and Distinguished Professor, receives emails every day from people around the world who ask if he has treatments that will restore their vision. In most cases, the answer is: "Not yet." But in some cases, he's able to respond with a satisfying: "Yes." Sahel and collaborators are creating interventions for a wide range of diseases that cause vision impairment and blindness. He has launched a dozen companies to commercialize those therapies.



Byrne

Recently, along with Leah Byrne, a PhD assistant professor of ophthalmology, and Paul Sieving from the University of California, Davis (former director of the National Eye Institute), Sahel cofounded Avista Therapeutics. Byrne engineers vehicles—called AAVs (adeno-associated virus vectors)—to deliver genetic materials into eye cells for restoring vision. Avista is commercializing products based on her AAV engineering platform, which is nicknamed scAAVengr.

The scAAVengr method, which is still in preclinical development, investigates the performance of multiple AAVs in thousands of cells by tagging every AAV with a barcode and then evaluating whether each cell receives the needed genetic material from the AAV and

expresses it. Byrne uses scAAVengr for vision research, though—"The platform could be applied to any tissue type, including the brain, heart, liver, kidney," she says.

Avista intends to collaborate on AAV manufacturing with ElevateBio at BioForge. (See page 16 story.)

At this stage, Avista is funded primarily by UPMC Enterprises. This innovation arm of the health system plans to invest \$1 billion in life sciences startups by 2024, according to Jeanne Cunicelli, president of UPMC Enterprises and a veteran venture capitalist.

Pitt and UPMC have been collaborating on commercialization since the 1990s, says surgeon Timothy Billiar, the George Vance Foster Professor, as well as chief scientific officer and executive vice president of UPMC. He's chaired Pitt's Department of Surgery for 24 years. In the early days, the commercialization focus was on digital products. About six years ago, Pitt and UPMC created a more formal structure for biological technologies, benefiting from Cunicelli's "very disciplined mindset around how to invest," says Billiar. Several of the resulting companies have already made significant progress and have partnerships with, or been acquired by, pharmaceutical companies.

Avista is partnering with Roche, notes Rob Lin, a PhD who is CEO of Avista and helped fund its early research when he was vice president at UPMC Enterprises.

Moving breakthroughs into the clinic so they can



Billiar



Cunicelli

Hazelwood yesterday, today and the vision for tomorrow. By partnering with the community, brownfields will be transformed to public green spaces and a life sciences and advanced manufacturing corridor.



MIRACLE MAKERS

Associate professor of medicine Yen-Michael Hsu, an MD, PhD, once oversaw a blood bank—blood transfers, dating back to the ancients, are among the oldest known uses of living cells. He says the most exciting part of his role today as director of the Immunologic Monitoring and Cellular Products Laboratory (IMCPL) at UPMC Hillman Cancer Center is working with investigators on the newest ways of making miracles with living cells.

Projects underway in the laboratory's clean rooms include modifying dendritic immune cells for an HIV vaccine, as well as modifying regulatory dendritic immune cells so patients are better able to accept organ transplants. One of the lab's most successful achievements, Hsu says, has been developing tumor-infiltrating lymphocyte (TIL) therapy. (See page 16 story.)

Hsu's team is also collaborating with ophthalmology colleague Gary Yam, a PhD research associate professor, to prepare corneal stem cells for clinical trials—carrying on research that the late James Funderburgh pioneered in India to treat patients who could no longer see because of corneal scarring. (Tune in to the 2016 Pitt Medcast about it.) Before Funderburgh died in 2019, he invited Yam, who had been studying similar aspects of the cornea in Singapore, to replace him as principal investigator of Pitt's Corneal Regeneration Laboratory.

Yam is training staff at the IMCPL to spot the different layers of stem cells in the cornea. Their primary cellular experience is in immune cells for oncology therapies. Eye cells are an exciting new challenge for the team, says Hsu.

The idea, Yam says, is to ultimately create a simple paste of restorative stem cells that can be applied to a patient's eye and fix scarring on the cornea—a feat that would eliminate the need for invasive corneal transplants that only last for a decade or so, while also providing an option for patients in countries where corneal transplants are unavailable. —CM



benefit patients is a top priority for Dean Anantha Shekhar, an MD, PhD whose own discoveries for psychiatric disorders have been spun off Shekhar into startups. In 2022, he brought



Evan Facher, a PhD and MBA who was already Pitt's vice chancellor for innovation and entrepreneurship, onto his leadership team as associate dean for commercial translation in the School of Medicine. Among other charges, Facher helps discern which med school innovations are truly ripe for commercialization. (In fiscal year 2022 alone, Pitt Med researchers filed 251 patent applications.)

Facher's team welcomes new companies into a dynamic business environment through LifeX, an organization founded by Pitt that helps early stage life sciences companies in the region secure funding.

Pittsburgh's progress and ambition are exciting for clinicians like Sahel who are eager to respond with "yes" when patients ask: "Do you have any treatments to help me?" —Cara Masset



Hsu



Yam



Funderburgh