The redemption

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On Sept 17. 1999, Jesse Gelsinger died after receiving an experimental gene therapy from James Wilson's lab at the University of Pennsylvania. That tragedy waylaid Wilson's career and almost shut down the whole field. Wilson and his team put their heads down and spent the next decade searching for safer gene therapies. Today, his lab's $70 million annual budget and bevy of biotech partnerships are fueling the gene therapy explosion.

The resurgence was never a sure thing. Here's how it happened.

# of James Wilson

RYAN CROSS, C&EN BOSTON

I. The visit

Stephen Squinto vividly remembers his first visit to James Wilson's lab—if it can even be called that. Wilson directs the Gene Therapy Program and the Orphan Disease Center, which together staff an army of more than 200 people spread across multiple floors of multiple buildings at the University of Pennsylvania. In 2017, Squinto scoped it out on behalf of OrbiMed Advisors, a health-focused private equity firm.

The investor walked through rows and rows of lab benches—standard biology fare, to be sure, but at an immense scale. Multiple rooms had been converted into small manufacturing suites that churn out AAVs—the adeno-associated viruses that act as molecular mail trucks for delivering therapeutic genes into cells. Another site housed the many animals—mice, monkeys, cats, and dogs—in which the experimental AAV gene therapies are tested. And almost everyone Squinto met was a staff scientist. Wilson trained only a handful of PhD students at a time.

Squinto was astounded. "He runs his gene therapy center like you'd run a very efficient company," he thought. With Wilson's infrastructure and decades of know-how, any spin-off company financed by Squinto's firm could hit the ground running. "It's all here," he told Wilson. "And I am willing to pay for it."

Over the next few months, the duo negotiated an intimate arrangement: they would form a new company, and Wilson's lab at Penn would function as its R&D arm. They'd begin by further developing gene therapies for five rare neurological diseases. Once Penn finished testing the therapies in monkeys, the biotech firm would take the data and petition the US Food and Drug Administration for permission to begin clinical trials in humans.

After raising additional cash from other investors, Passage Bio officially launched in February with $115.5 million. This month, the start-up raised an additional $110 million. It plans on testing three of its gene therapies in humans next year.

"Things are happening so fast," Wilson says with a touch of awe.

For anyone familiar with the slow crawl of drug development, gene therapy is moving at lightning speed. The approval of the first two gene therapies in the US and promising clinical data on many more have supercharged the field. Money, hard to raise not long ago, is flooding into academic labs and companies developing gene therapies. The FDA can barely keep up with the growing pipeline, and it anticipates receiving more than 200 applications from groups that want to test new cell and gene therapies next year. The pace is a source of both excitement and anxiety for anyone who's weathered gene therapy's peaks and troughs over the past 3 decades.

And of all the field's pioneers, 64-year-old Wilson may feel that tension more strongly than anyone.

Twenty years ago, a young man named Jesse Gelsinger was injected with a large dose of gene-shuttling viruses designed in Wilson's lab. The experimental treatment was created to treat a rare metabolic liver disease. The goal was to deliver a working copy of the teenager's broken gene, but the viruses threw his immune system into overdrive. Four days after being treated, Gelsinger died. It was the first public tragedy of a highly hyped field.

As details about Gelsinger's death emerged, the entire enterprise of gene therapy began to crumble. The Gelsinger family filed a lawsuit. Investor money dried up, and start-ups shuttered. Wilson found himself at the center of multiple investigations. He was stripped of his titles, his gene therapy center was disbanded, and he was barred from doing any more clinical trials until 2010. "Every other week there was another shoe to drop," Wilson recalls. "People were in full-on retreat from having anything to do with the field."

Despite that—or perhaps because of it—Wilson's downsized and outcast lab kept plugging away with a newfound focus on finding safer viruses. Their work led to the discovery and dissemination of new AAVs, including one used in the recently approved gene therapy Zolgensma, which saves the lives of infants born with an otherwise fatal neurological disease.

And Zolgensma is just the beginning. By Penn's latest count, some 42 companies are using AAVs that fall under Wilson's patents, covering nearly 100 drug development programs. Eleven of those firms have obtained licenses from Regenxbio, a firm that Wilson cofounded in 2009 to commercialize his technology. As more gene therapies start hitting the market in the coming decade, the university anticipates that it will effectively be printing cash.

"Ten years ago, no one would touch Jim with a 10-foot pole," says Regenxbio's CEO, Ken Mills. "Now everyone is happy to work with Jim and gives him a lot of money."

It's an astounding comeback for Wilson's career and gene therapy in general. And while some people praise him for catalyzing the field's resurgence, others still blame him for its near demise 20 years ago. But one thing is clear. Gene therapy is back in business, and you can't tell the story of how it happened without Wilson.

II. The fall

On Dec. 22, 1998, Paul Gelsinger walked into his home in Tuscon, Arizona, to find his teenage son Jesse vomiting uncontrollably. Jesse was suffering from yet another of his medical episodes. He was born with a rare genetic mutation that left him with low levels of an enzyme called ornithine transcarbamylase (OTC), which is needed to properly metabolize nitrogen—a crucial building block of proteins. Because of that broken gene and deficient enzyme, Jesse had dangerously high levels of ammonia in his blood.

Jesse was in and out of the hospital over the holidays, seizing, vomiting, and not getting any better. It wasn't his first hospitalization, but this time was especially scary. The doctors kept him in an induced coma for 2 days while waiting for his body to stabilize. After Jesse regained consciousness in January, he developed a new appreciation for the gravity of his condition. In June, he would turn 18, making him eligible for an experimental gene therapy trial for OTC deficiency that he'd first heard about in September 1998.

By the fall of 1999, the OTC deficiency study was one of seven underway at the Institute for Human Gene Therapy in Philadelphia. The largest center of its kind, it was housed at Penn and led by Wilson.

The center fulfilled an ambition that started when Wilson was an MD-PhD student at the University of Michigan Medical School in the early 1980s and witnessed the devastating consequences of rare genetic diseases firsthand. It left him yearning to create cures—not mere treatments.

At that time, the first experimental inklings of gene therapy suggested it was possible, and scientists were racing to turn the idea into a reality. When Wilson graduated in 1984, he was itching to get into the lab to work on the problem but was stuck completing his residency first. "I actually thought, believe it or not, that by the time I finished my internship that the problem would be solved," he says.

Gene therapy is conceptually simple: since genetic diseases are caused by faulty genes, giving someone a functional copy of that

gene could provide a onetime fix. The challenge is actually getting the therapeutic genes into the body. Wilson and others stuffed them into hollowed-out adenoviruses—which are naturally adept at infiltrating cells to propagate their own genes. Wilson saw gene therapy as a less extreme option than some contemporary treatments. Surgeons were already transplanting whole livers into kids with OTC deficiency to restore that missing enzyme. Why not just transfer the gene instead?

Compared with some people with OTC deficiency, Jesse had it good. His liver produced low levels of the enzyme. Still, Jesse had just had a close call with death. After discussing the gene therapy trial with his doctor at a semiannual checkup in April 1999, he decided to volunteer for Wilson's study. According to his father, Jesse said the worst-case scenario was that he would die "and maybe help doctors figure out a way to save sick babies."

In September, Jesse flew to Philadelphia to begin the trial. A Penn surgeon walked him through the protocol, and a few days later, on Sept. 13, injected him with a large dose of gene-stuffed viruses: 600 billion per kilogram of his body weight. A young woman had recently received the same dose. So far, high fevers and flu-like symptoms were the most common side effects. Jesse was the 18th patient in the study, and the last.

Jesse's health deteriorated quickly. His immune system flared up and his organs failed. Despite attempts to save his life, 4 days after the injection, on Sept. 17, he was declared brain dead, and his family gave permission to remove life support.

Although clinical trials fail all the time, and in fact, other people would die during experimental gene therapy trials, Jesse's death tapped into fears about the risks of genetic alteration. Regulatory authorities swept in to investigate the tragedy. Suddenly, all the attention was on Wilson and his lab.

"He runs his gene therapy center like you'd run a very efficient company."

—Stephen Squinto, interim CEO, Passage Bio

"Jim was a high-profile golden boy," says Tachi Yamada, one of his mentors at the University of Michigan. "And you know what happens to high-profile golden boys. One little slip and everybody jumps on them."

Wilson never met Jesse. A few years earlier, the university had barred Wilson from interacting with patients because he founded a biotech company called Genovo, which provided funding to the institute that led the clinical trials and held rights to commercialize his discoveries. After Jesse's death, the connection fostered allegations that Wilson had acted recklessly for profit. It became a sticking point in the media.

In late November, Wilson flew to Arizona to meet Paul Gelsinger. They went out for a hike in the desert, and Gelsinger recalls that Wilson was going on about his institute, how morale was low after the tragedy, that he was losing people. "I had to stop him and say, 'Jim, things could be a lot worse. You could lose a child.'" Wilson backed off. He had four kids himself. "He's an ambitious guy," Gelsinger says. "And that's what got him in trouble."

Gene therapy's fall and rise

James Wilson's career closely follows the story of gene therapy's near demise and current explosion. These are key events that shaped his career and the field.

- **March 1993:** Wilson is recruited to lead the newly founded Institute for Human Gene Therapy (IHGT) at the University of Pennsylvania.
- **Sept. 17, 1999:** Jesse Gelsinger dies 4 days after being dosed with an experimental gene therapy for ornithine transcarbamylase (OTC) deficiency. The study of 18 patients is stopped.
- **Jan. 2000:** The US Food and Drug Administration shuts down all clinical trials at the IHGT.
- **July 2000:** GlaxoSmithKline begins funding Wilson's efforts to develop safer gene therapies in exchange for the rights to any of his team's discoveries.
- **April 2002:** Wilson steps down as director of the IHGT, and soon thereafter the institute is disbanded.
- **Aug. 2002:** Wilson's lab publishes the discovery of safer and more effective gene-delivery viruses called AAV7 and AAV8.
- **Oct. 2003:** Wilson's lab publishes a report explaining the role of the innate immune system in Gelsinger's fatal response to the OTC gene therapy.
- **June 2004:** Wilson's lab reveals a new virus called AAV9 that later becomes widely used for gene therapy.
- **Feb. 2005:** The FDA, the Department of Health and Human Services, and the Department of Justice complete their investigation of Gelsinger's death and settle with Wilson and Penn. Penn is fined, and Wilson is barred from clinical trials for 5 years.
- **March 2009:** Wilson secures the rights to his AAVs from GSK and launches the start-up Regenxbio.
- **Feb. 2010:** Wilson's federal restrictions on running clinical trials are lifted.
- **May 2014:** Nationwide Children's Hospital begins a clinical trial using Wilson's AAV9 for a spinal muscular atrophy (SMA) gene therapy.
- **Nov. 2017:** The Nationwide Children's Hospital SMA clinical trial is published, and the treatment is hailed as a long-awaited, lifesaving gene therapy.
- **Dec. 2017:** Luxturna, a treatment using AAV2 to deliver a gene for inherited blindness, becomes the first viral-based gene therapy approved by the FDA. It costs $850,000 for a pair of injections.
- **Jan. 2018:** Wilson resigns from the scientific advisory board of Solid Biosciences over concerns about the safety of its Duchenne muscular dystrophy gene therapy.
- **Feb. 2018:** Wilson publishes a paper exposing the risks of high doses of AAVs.
- **Feb. 2019:** Wilson's start-up Passage Bio launches with $115.5 million to develop gene therapies for rare neurological diseases. The firm raises another $110 million in September.
- **May 24, 2019:** The FDA approves the SMA gene therapy, now named Zolgensma. It is the first commercial gene therapy to use one of Wilson's new AAVs. It costs $2.1 million for a onetime dose.
- **May 29, 2019:** Amicus Therapeutics expands an ongoing partnership with Wilson's lab to work on gene therapies for more than a dozen diseases and provides $50 million for basic discovery work.

Sources: Companies, *The Oxford Textbook of Clinical Research Ethics*, the University of Pennsylvania, scientific papers.

At first, Gelsinger believed Wilson acted in his son's best interest. That changed soon after their hike. The FDA issued a scalding report outlining dozens of mistakes or failures by Wilson's team to follow protocol and in early 2000 shut down all clinical trials at Penn's gene therapy center. Later that year, the Gelsinger family sued Penn—Gelsinger had come to believe Wilson's ties to Genovo and his rush to be first in curing a genetic disease had caused the researcher to take an unnecessary risk with his son's life. Although that lawsuit was resolved out of court in just 6 weeks, investigations by Penn, the FDA, and the Department of Justice lingered for years.

Support for the field overall floundered. It was particularly frustrating for a small group of researchers who had been championing the use of a different kind of gene-delivery vehicle: adeno-associated viruses—the AAVs. Despite their similar names, AAVs are unrelated to the adenoviruses that Wilson used. AAVs were first discovered as contaminants of adenovirus samples in 1965. But many virologists thought studying them was a waste of time since they weren't associated with any diseases. That fact would later make them gene therapy's greatest asset.

"The community got a black eye and the funding dried up because Wall Street couldn't distinguish between adenovirus and adeno-associated virus," says Richard Jude Samulski, director of the University of North Carolina's Gene Therapy Center. "We had to pay a Wilson tax on the field."

"I have nightmares all the time. I am afraid, seriously, that the field is moving too fast."

—Guangping Gao, director, Horae Gene Therapy Center, University of Massachusetts

III. Discovery

Wilson's old mentor Yamada watched the fallout from the OTC deficiency trial with dismay. Jesse Gelsinger's death brought scrutiny and skepticism to the entire field of gene therapy, and Wilson was its lightning rod. Wilson stopped going to conferences—he was no longer invited to speak—and for years he avoided the press. "I think lesser personalities would have been destroyed," says Nelson Wivel, a deputy director in Wilson's lab at that time. "But Jim's pretty tough."

Yamada, meanwhile, had recently left academia to become head of R&D at GlaxoSmithKline. To Yamada, the focus on Wilson's conflict of interest because of Genovo was overblown. "The whole field was miscast as profiteers, a truly inappropriate demonizing of very important science," Yamada says. "I hate that kind of thing."

Soon after Jesse's death, Wilson and Yamada had a long discussion about what to do next. "You need to find out what caused the problem," Yamada advised.

Before the OTC deficiency trial began, Wilson's lab had struggled to control the immune response to the delivery viruses in lab animals. One iteration of the therapy even killed monkeys at high doses, so Wilson asked one of his researchers, Guangping Gao, to develop a crippled adenovirus—one that delivered genes but didn't trigger the immune system's T cells to attack the liver. When Jesse's body began breaking down within a day of the adenovirus injection, Wilson knew that T cells couldn't be the culprit, since they take a week or more to mount their attack.

The problem appeared to be with a different branch of our bodies' defenses, called the innate immune system. Wilson's group never considered that the innate immune system would present an issue, and there was no obvious way to redesign adenoviruses around it. Wilson's mission became finding safer gene-delivery vehicles, ones that didn't ignite the innate immune system. He laid out a plan to convert what remained of his lab into a discovery shop, but he'd need money.

"I never felt that I would walk away from science," Wilson says. "I was concerned that I would not be allowed to do it."

Yamada thought Wilson was gene therapy's best hope, and he was already drafting a plan to fund Wilson's lab. "From Jim's standpoint, it looked pretty easy," Yamada says. Inside GSK, it was a hard sell. Many felt that gene therapy just wasn't ready for prime time. Others worried about the perception of GSK working with a scientist disbarred by the FDA. Yamada was ready to overrule everyone, if needed, but it didn't come to that.

In July 2000, the GSK cash arrived, allowing Wilson's lab to begin developing a new generation of safer gene therapies in full force. The $29.4 million that GSK provided Wilson over the next 9 years was a lifeline, but it came with strings attached: the big pharma firm owned the rights to discoveries made with its money.

It didn't take long for Wilson's lab to make progress. The group had already dabbled in using AAVs as alternatives to adenoviruses. In the previous 35 years, scientists had discovered only six variants of AAVs, and although they seemed safe, none of them were particularly good at delivering genes.

In July 2001, a year after the GSK money first arrived, Gao began fishing for new AAVs using a technique called polymerase chain reaction to pull fragments of the viral DNA from monkey tissue. When Gao first presented the data at a lab meeting in mid-December, Wilson was skeptical. Later that afternoon, Wilson walked into Gao's office and drilled him on his methods and interpretations. Finally, Wilson conceded, "Guangping, I think you stepped on a gold mine," Gao recalls.

Wilson asked another scientist to repeat the experiment. When the results held up, Wilson called the team together on a Saturday in spring 2002 to review the results. In the course of the afternoon, the team began realizing that they had stumbled upon a new, highly diverse family of AAVs—more than 100 of them. But would they be better than the existing six?

Before he knew it, 5:00 p.m. had rolled around. Wilson remembered he had promised to take his 11-year-old son, Matt, to see a sci-fi flick—one that his mom wouldn't take him to see—and he was running late. They made it to the movie, *Resident Evil*, in the nick of time. For a brief moment, Wilson was able to get his mind off the viruses, but it didn't last long. On screen, a genetically engineered virus escaped and, of course, turned everyone into zombies.

"Oh my God, you got to be kidding me," Wilson recalls thinking. "Why couldn't I be watching *Snow White* or something right now?"

IV. Dissemination

Gao and the team spent the next year feverishly trying to understand and test the new AAVs. Their first study isolated only fragments of AAV capsid sequences—the genetic code for the outer shells of the viruses—so they still had to isolate the full sequences, turn them into usable viruses, and test them in animals. The first two they picked, dubbed AAV7 and AAV8, were 10–100 times as good at getting genes into cells as the six previously known viruses. A virus that Gao discovered in 2003 called AAV9 seemed even better.

At first, Wilson struggled to get the work published. "Gene therapy was still under the shadow of Jesse Gelsinger," Gao says. People had lost faith not only in Wilson's lab but also in the field as a whole. Furthermore, it was almost preposterous that no one had discovered these allegedly new viruses before.

Eventually, in March 2002, the Penn researchers convinced Thomas Shenk, a respected virologist at Princeton University, to review the paper for the *Proceedings of the National Academy of Sciences of the United States of America*, where it was published online that August. That same year, a bright student named Luk Vandenberghe joined Wilson's lab—although other scientists warned him against it. He remained Wilson's only graduate student for several years. That period was a blur of isolating, characterizing, and testing new AAVs, Vandenberghe recalls. "I sometimes called it the gulag of the Wilson lab," he jokes.

Wilson was eager to get the new viruses into the hands of other researchers who could independently show that they were up to snuff, but he met a roadblock. GSK held the rights to the viruses, and the drug company wasn't interested in sharing. The firm didn't want other groups filing patents based on the technology; more importantly, GSK was worried that a sloppy experiment would put patients, and the whole field, in peril.

Wilson was furious. "It was not acceptable that we would limit distribution of these," he recalls. "I was really intent on getting these things in the hands of everyone." He argued that academics had an obligation to share their source materials and that anyone who wanted to use the AAVs could reverse engineer them anyway. "I basically bullied my way through," he says. Eventually GSK let Penn distribute AAVs to academics under material transfer agreements.

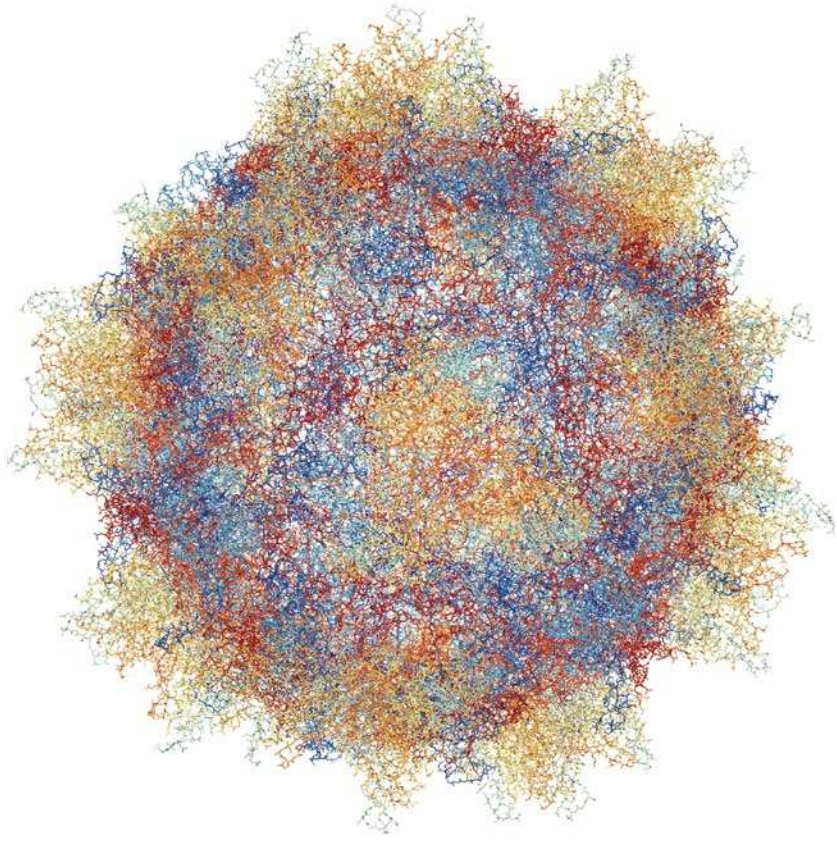
Over the next few years, Penn's viral vector center became the Amazon of AAV. Penn scientists churned out thousands of AAV preps a year that they used internally and distributed to others. "These things were being sent out left, right, and center," Vandenberghe says. "At some point we were concerned that even though we generated it, we weren't going to make the most interesting observations on our own technology."

They were right. Other researchers used the shared AAVs to make some of the most exciting discoveries of the coming decade. For instance, a group at Nationwide Children's Hospital in Ohio found that AAV9 was able to cross the protective blood-brain barrier that normally keeps drugs—and viruses—out. A team at St. Jude Children's Research Hospital and University College London developed an experimental gene therapy for hemophilia B using AAV8.

As more groups began using Wilson's viruses, it grew clear that they would want commercial licenses to develop bona fide gene therapies. Again, GSK wouldn't budge. Worse, Wilson also caught wind that his GSK funding would be winding down. He told some lawyer friends, Allan Fox and Daniel Kiser, about his dilemma, and they came up to Penn in November 2007, along with their protégé, Ken Mills, to help Wilson figure out how he could get the rights to his viruses back.

After more than a year of negotiating, the group eventually wrangled the rights to Wilson's AAVs back in March 2009 and housed them in a new firm later named Regenxbio. The paperwork for the company made its purpose clear: to commercialize Wilson's technology.

Six and a half years later, a *Philadelphia Inquirer* reporter called Paul Gelsinger, asking if he had seen Wilson on the news. Regenxbio had gone public on the Nasdaq Stock Market on Sept. 17, 2015—the 16th anniversary of Jesse's death. Videos of the event showed Wilson clapping alongside Mills—the CEO of Regenxbio—who rang the opening bell amid falling confetti. Gelsinger was shocked that anyone could be so insensitive or unaware of their actions. "It told me that it really was all about the money."



The structure of AAV9, a virus discovered in Wilson's lab and later used for the commercial gene therapy Zolgensma

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V. Resurgence

Wilson's son Matt recalls the moment when gene therapy was on the up and up. Over dinner at a Mexican restaurant in 2011, his dad, James, was talking about a hemophilia gene therapy. That the conversation had veered to viruses was typical: Matt grew up in a house saturated with science. His dad read the Ebola virus thriller *The Hot Zone* aloud to him as a kid. When Matt was 16, he began working in his dad's lab. "I was cheap labor," he quips. He

later assumed a lead role at his father's company Scout Bio, which is developing gene therapies for cats and dogs.

Matt would often hear about the latest struggles and successes of using viruses to deliver therapeutic genes. At the restaurant, his father was explaining the stunning results of a clinical trial underway at UCL that used AAV8. "He had a huge smile on his face, kicked back, and emphasized how much this was going to change the field," Matt recalls. When the paper was published in December 2011, James Wilson exclaimed, "Merry Christmas for hemophilia!"

That data woke up investors to gene therapy. It would take another few years for the financial floodgates to open, but when they did, a decade's worth of development that had been parked on university shelves would be ripe for the picking.

James Wilson had redefined his career once by shifting from clinical pioneer to toolmaker. Now that his long ban from running clinical trials had ended, he saw an opportunity to evolve again.

"Should we morph to support the industry as it tries to get back on its feet?" Wilson recalls asking his group. "It was a major redo, and we were hesitant." It would mean expanding the staff to include toxicologists, study directors, alliance managers, and other well-paid professionals required to turn scientific ideas into experimental therapies ready to test in humans. "We basically had to become a hybrid of industry and the academy," Wilson says.

Both Penn and Wilson's team were supportive, and as his operations grew, Wilson developed a mantra that he repeats to himself several times each day: "innovate, execute, and diversify." His team started using AAV8 and AAV9 to create experimental gene therapies for a bevy of rare diseases. In 2013, several programs from his lab—including one for Jesse Gelsinger's disease, OTC deficiency—formed the basis of a Regenxbio spin-off called Dimension Therapeutics. A year later, Regenxbio boosted its funding of Wilson's lab. The company wanted to kick-start its own pipeline of clinical programs instead of just supplying AAVs to others.

And after years of operating in relative isolation, Wilson started hearing from drug companies. His lab's many biotech partners include Biogen, Johnson & Johnson, Moderna, and Precision BioSciences, with programs running the gamut from common conditions like Alzheimer's to rare diseases, including OTC deficiency. Wilson's already-large annual budget ballooned from several million during his GSK years to a breathtaking $70 million today.

Wilson isn't alone in his close ties to biotech. A handful of academics with an entrepreneurial bent have turned their biomedical labs into start-up incubators, fueled by troops of precocious graduate students and postdocs. Yet Wilson's lab stands apart for its scale and for his heavy reliance on more experienced scientists that develop dozens of experimental gene therapies in parallel. The lab's goal is gathering enough data to support investigational new drug (IND) applications—the documentation that must be submitted to the FDA before beginning clinical trials in humans—for its biotech partners.

"These are intense efforts that normally take place at drug development companies," explains Vandenberghe, who started his own lab at Massachusetts Eye and Ear in 2012. "Now there is an academic group trying to compete with that, and frankly, service them." In his estimation, Wilson's lab has largely become an "IND warehouse."

Although each experimental gene therapy must be tested anew, it should be relatively straightforward to crank out several more programs that use the same AAV, each just packed with a different gene. "This is really going to lead to a simplification of the drug development process," Wilson says.

In fact, it already has. In 2016, Wilson's lab recruited Juliette Hordeaux, an expert on lysosomal storage disorders, to head up an effort to develop gene therapies for a collection of 60 related rare diseases, each caused by a mutation in a different gene. Her team is already working on 12 of them. "When you are a scientist working here, you feel like nothing is impossible," she says.

"Ten years ago, no one would touch Jim with a 10-foot pole. Now everyone is happy to work with Jim and gives him a lot of money."

—Ken Mills, CEO, Regenxbio

VI. Warnings

Jerry Mendell breathed a sigh of relief. In May 2014, the neurologist at Nationwide Children's Hospital in Ohio gave a baby an injection of viruses—some 67 trillion viruses per kilogram of body weight, more than 100 times the dose of adenoviruses that killed Jesse Gelsinger 15 years before. These viruses were supposed to be safer, though; they were AAV9.

That infant was born with spinal muscular atrophy, a normally fatal neurodegenerative disease. Immediately after the injection, the infant seemed to be doing fine. But a few weeks later, the child's liver enzyme levels skyrocketed. Mendell suspected that although some AAV9 reached the infant's neurons, most of the viruses were getting stuck in the liver, where they were causing massive inflammation. "All that was going through my mind was Jesse Gelsinger all over again and the end of AAV," Mendell recalls.

Fortunately, Mendell was able to suppress the inflammation with prednisone, a steroid that is now proactively given to infants receiving gene therapy. The results of the 15-patient study, published in November 2017, showed that all infants were still alive at 20 months. Some were even able to sit, speak, and walk. At last, gene therapy was saving lives.

That December, the FDA approved the first-ever viral gene therapy in the US, a treatment for inherited blindness that uses AAV2. And in April 2018, the Swiss drug giant Novartis agreed to pay $8.7 billion for a company called AveXis, the Nationwide Children's Hospital spin-off working to commercialize the spinal muscular atrophy therapy, now known as Zolgensma. That therapy was approved for sale this May. Gene therapy hype is now back

in full swing, and the rekindled excitement is dredging up old concerns.

"Jim has been very worried about these high doses," Mendell says.

In February 2018, Wilson published a small study showing that high doses of a virus similar to AAV9 caused such severe toxicity in monkeys and piglets that the animals had to be euthanized. Two weeks before, he also quietly resigned from the scientific advisory board of Solid Biosciences, a company using high doses of AAV9 for muscular dystrophy treatments.

Wilson admits that scientists still don't totally understand why AAV becomes toxic at a certain dose, but it is clear that without more effective gene-delivery vessels, high doses may be the only way to correct enough cells for some conditions, particularly muscle diseases. High doses also create the additional hurdle of simply manufacturing enough of the viruses for a treatment. Those concerns have guided the strategy of Wilson's new company, Passage Bio, which is focused on rare genetic neurological conditions.

"We've tried to choose diseases for which very, very low doses are going to be required," says OrbiMed's Squinto, the firm's interim CEO. The company also plans on injecting AAVs directly into the cerebrospinal fluid, which should require smaller doses than the systemic injections used in Zolgensma. "Jim is at the point in his career where he is not going to take too many chances anymore," Squinto says. "We are going to know as much as we can before going into human experimentation."

The resurgence of gene therapy has reawakened Paul Gelsinger's concerns about its safety too. Last year, when he learned that Ultragenyx Pharmaceutical was running a new clinical trial for OTC deficiency, he emailed the firm, hoping it was being more careful than Wilson was 2 decades earlier.

Ultragenyx CEO Emil Kakkis invited Gelsinger and his wife to visit the firm in Cambridge, Massachusetts. During their visit in May, Kakkis showed Gelsinger a conference room dedicated to Jesse. A plaque displaying his name and picture hang by the door. "The point is to make us walk in the room and remember," Kakkis says.

Ultragenyx got the OTC deficiency program when it acquired Dimension Therapeutics in 2017, although the firm doesn't advertise that the program's origins lie in Wilson's lab.

Wilson says he thought a lot about whether continuing to work on the disease would create conflicts or distractions from the goal of curing patients. "But we're working on so many other liver metabolic diseases," he says. "Is it fair for us to avoid developing a potential curative therapy for OTC deficiency because of the past?" The answer, he says, is no.

VII. Legacy

On June 4, 2019, the Penn Center for Innovation, the university's technology transfer office, hosted an event showcasing Penn start-ups and highlighting some of the university's greatest successes. The week prior, Amicus Therapeutics expanded a rare-disease partnership with Wilson's lab, giving the drug company rights to gene therapy programs for 18 rare diseases, plus the majority of the 60 lysosomal storage disorders that Hordeaux's team is working on.

To top it all off, Amicus also agreed to pay Wilson's lab $10 million a year for 5 years to expand his work to improve gene therapies and develop the next generation of AAVs. Wilson recently moved his discovery team to a commercial building down the street. On that June evening, Jeffrey Castelli, the head of gene therapy at Amicus, told the crowd that his company would move in too—and hire up to 200 people across three floors.

Penn is proud of its prowess in translating academic work into medicines, and it's not bashful about the financial benefits, either. "At Penn Medicine, we are the most for-profit nonprofit in the world," Kevin Mahoney, then CEO-elect, told the room.

The excitement expressed about academic-industry partnerships that night is a dramatic shift from the mood at the turn of the century. "When I first came to Penn, working with a company was bad, evil," Wilson says. "What has changed significantly is the value that academic institutions place in partnering with industry," he adds. "It's not only accepted but encouraged, because it's the right thing to do."

The university's leadership certainly agrees. "We are not going to be a passive participant in the process of translating the potential of our science into goods, products, services," says John Swartley, director of the Penn Center for Innovation. "The Wilson lab and gene therapy are almost unprecedented examples of how that potential can translate into a lot of activity."

Today, Wilson's gene therapy center is larger than ever. He says it has about 80 open positions, including veterinarians, IND application writers, and even an intellectual property scientist. Wilson has expanded his armamentarium to include messenger RNA therapy, which is like a temporary version of gene therapy, as well as gene editing, which can make precise changes to genes instead of replacing them wholesale.

And his new company, Scout Bio, is developing gene therapies to treat anemia, atopic dermatitis, and chronic pain in pets. Successful treatments might provide a stepping stone for using gene therapy on more common diseases in humans.

Wilson has been thinking about his legacy and what's kept him committed to gene therapy all these years. "My motivation was to help patients because of my early experiences as a physician, so that is my driver," he says. "But my passion is science."

Yet Jesse Gelsinger—a man he never met—is an inescapable part of Wilson's legacy. Jesse's story is the subject of textbook chapters on bioethics and a case study in law journals. Two years ago, when Paul Gelsinger's daughter was taking a graduate genetics course at the University of Arizona, her professor used Jesse's story as an example of science gone awry and a lack of informed consent. "It is so amazing how his memory has held on and is so alive still," Gelsinger says.

Depending on whom you ask, Jesse's death either catalyzed a bold rethinking of gene therapy or simply slowed down the inevitable march of progress that would have occurred with or without Wilson. "I think a lot of us sit back at meetings thinking about where the field would be if we hadn't gone through that episode," UNC's Samulski says. "We lost a generation of patients that we could have helped."

Some still worry that history could repeat itself. "I have nightmares all the time," says Gao, who is now director of a gene therapy center at the University of Massachusetts. "I am afraid, seriously, that the field is moving too fast, that people may not be careful enough, and that something like Jesse Gelsinger will happen again."

"Research has risk. Things go wrong," Ultragenyx's Kakkis says. "The question is, in the fire and ashes of all of that, can you rise up again and do something to fix the problem?"

Today, Wilson keeps a framed quote in his office next to a photo of himself from his football days. It's part of a Theodore Roosevelt speech from 1910 known as "The Man in the Arena": "It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood." ■