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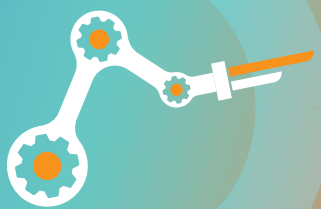
PENN Medicine

PUTTING DISCOVERIES TO WORK

A growing list of FDA-approved therapies is rooted in research at Penn Medicine.




Plus:

The New Science of Cancer Interception

Students Gather at the Nexus of Medicine, Tech, and Business

MAKING WHAT'S NEXT IN MEDICINE

By Karen L. Brooks

Since 2017, the FDA has approved more than two dozen new therapies with roots at Penn Medicine — almost half of which are first-in-class for their indications. Becoming a hub for drug research and development took a lot more than luck.

The news reached Abramson Cancer Center (ACC) Director Robert Vonderheide, MD, DPhil, at 11 a.m. on August 30, 2017: The U.S. Food and Drug Administration had officially approved a Penn Medicine-developed personalized cellular immune therapy.

Six hours later, Vonderheide was standing atop a coffee counter in the atrium of the Perelman Center for Advanced Medicine, addressing hundreds of jubilant faculty and staff members who had gathered for a now-iconic "flash mob" celebration of the milestone. Carl June, MD, and a team of scientists, physicians, and other dedicated staff had together turned a dream of using patients' own immune cells to treat their cancer, into a reality.

Vonderheide called the discovery "a 20-year overnight sensation." It would be a defining moment for Penn's identity as a place that incubates and brings to life some of the most transformative advances in modern medicine.

The approval of chimeric antigen receptor (CAR) T cell therapy didn't happen at Penn Medicine by chance. Nor did the others that followed. Since that day, other research that had been underway at Penn Medicine directly influenced at least two dozen more approvals granted to drugs and medical technologies — giving the stamp of safety and effectiveness needed for these treatments to be widely available to patients outside of clinical trials. Eleven of the advances documented to date represent the first in their classes: eight under cancer, two under gene therapy, and the revolutionary mRNA technology that powers COVID-19 vaccines around the world.

Penn Medicine faculty may lead this crucial work at different points across the continuum of discovery, from conducting pivotal discovery science in the lab which leads to licensing of compounds and technologies by commercial partners, to leading clinical trials of new therapies initially developed outside of Penn.

The list of Penn-linked approvals is growing with each passing year, and for good reason. Science has shifted toward more discoveries based on the underlying mechanism of disease, especially in cancer. Through a particularly robust clinical trial and commercialization infrastructure, Penn has further worked to smooth every part of the path from idea to implementation. And to ensure that state-of-the-art treatments reach the patients who need them, Penn Medicine teams have also kept focus on equity and access during clinical trials and after therapies are approved.

In the long view, Penn's emergence as a hub for drug research and development is a credit to both the culture and strategic choices going back decades, says Jon Epstein, MD, executive vice dean and chief scientific officer in the Perelman School of Medicine.

"Our leadership has been judicious about investing in a broad portfolio across a pipeline of development that might take 20 or 30 years," Epstein says. "People here embrace a no-risk, no-reward approach — they aren't afraid to take the long view and realize you have to back many different ideas to end up with just a few breakthrough therapies."

Barrier Free

Hiring Carl June — whose belief that the immune system could be trained to fight cancer was derided by naysayers — in 1999 is one of the risks Epstein references. At the time, nobody predicted June's work would change the entire trajectory of cancer care.

June began studying CAR T cell therapy in cancer in the late 1990s, and as signs of success grew, so did the breadth of collaborators at Penn Medicine and Children's Hospital of Philadelphia (CHOP) who brought the method into clinical trials. It would take nearly two decades to achieve FDA approval of the therapy in 2017 as a treatment for advanced acute lymphoblastic leukemia. The groundbreaking technique involves taking T cells — part of the immune system — from a patient's blood and engineering them to produce CARs before reinfusing them into the body. These new receptors latch onto unique antigens on the patient's tumor cells, killing them. Marketed by Novartis as Kymriah, the first CAR T cell therapy has proved lifesaving for many patients whose cancer has relapsed or failed to respond to other therapies. It has since garnered two additional approvals from the FDA to treat other forms of cancer.

Similar stories have played out on campus over and over. Jean Bennett, MD, PhD, and Albert Maguire, MD, were also "risky" hires whose ambitions vexed skeptics when they joined Penn's Scheie Eye Institute in 1992. But their determination and decades of work from basic science through to clinical trials at Penn and CHOP, paid off; in December 2017, less than four months after approving CAR T, the FDA approved the married team's treatment for a rare form of congenital blindness called Leber congenital amaurosis. Marketed as Luxturna, the therapy restores patients' eyesight by injecting a corrective gene directly into their eyes via a viral vector. It was the nation's first commercialized gene therapy — a term that encompasses a collection of techniques to modify a patient's DNA — for a genetic disease.

Eighteen months later, approval followed for Zolgensma, a gene therapy using a viral vector developed in the lab of James Wilson, MD, PhD, director of Penn's Gene Therapy Program and Orphan Disease Center, and studied in trials at CHOP, to correct spinal muscular atrophy — the number one genetic cause of infant mortality.

And in the most ubiquitous novel advance tied to Penn Medicine, in August 2021 the FDA gave its first full approval to an mRNA-based COVID-19 vaccine, which uses technology discovered more than 15 years earlier by longtime research partners Drew Weissman, MD, PhD, the Roberts Family Professor in Vaccine Research, and Katalin Karikó, PhD, an adjunct professor of Neurosurgery.

Recruiting faculty who dream big is essential to drug development, but there are other reasons Penn Medicine has connections to so many cutting-edge therapies. Among the top, says Vonderheide, is a strategic emphasis on translational research and eliminating barriers between laboratories and the clinic.

"Even our building design reflects that value. If you stand in the lobby of the Perelman Center for Advanced Medicine, you're within 100 yards of the labs where discoveries are being made, the clinics where clinicians are designing clinical trials and patients are getting therapies, and the offices where executives are working out financial models," he says. "We're a unified, integrated system committed to making science real for patients."

Financial investment from the health system is key to moving discoveries toward the clinic and helping more patients, Epstein adds, citing the Perelman School of Medicine's Clinical Cell and Vaccine Production Facility — where cell and gene biotherapeutics are manufactured to meet regulatory standards — as an example.

"The health system invested in what was only basic research at the time to build the good manufacturing practices facility that is necessary to produce things like CAR T cells safely so they can be put back into humans," he says. "Facilities like that cost a lot, and most medical schools can't afford them. But at Penn Medicine we integrate our clinical and research missions intentionally, for the sake of the patients who don't have the best clinical options today. We can't afford not to invest back into ongoing scientific discovery."

Next Generations

The FDA's approval of a drug doesn't mean its development ends, particularly in young and still-unfolding categories like cell and gene therapy and mRNA technology. Research around the world has proliferated in these new realms, where Penn Medicine faculty are still striving to push the science forward.

While CAR T cell therapy has revolutionized treatment for hematologic malignancies, researchers are still striving to use it successfully against solid tumors; getting the treatment to penetrate solid masses is one challenge, and it is harder to find unique antigen proteins to target on solid tumor cells. Faculty members are examining ways to overcome these limitations, such as delivering CAR T cells regionally and testing multivalent CARs, which simultaneously bind to multiple targets.

Researchers are also pursuing universal "off-the-shelf" versions of CAR T, which would spare patients from having to donate their own T cells for engineering — saving precious time while ensuring an abundance of high-quality cells to work with. And many are studying CAR T therapy in conditions other than cancer — including Epstein, who is evaluating CAR T cells' ability to treat fibrosis, which can affect any organ and is a major driver of heart failure.

In terms of gene therapy, most activity to date has tackled rare diseases, but some faculty are on a mission to change that — like cardiologist Kiran Musunuru, MD, PhD, MPH, ML, director of the Genetic and Epigenetic Origins of Disease Program. Musunuru is applying the gene editing technology CRISPR to fight the leading cause of death worldwide: cardiovascular disease. He has found that modifying genes in the liver can permanently reduce a person's cholesterol levels and protect against heart attack and stroke. Currently in a clinical trial in New Zealand and the U.K., this single shot could eventually work as a heart disease "vaccine."

And when it comes to mRNA, "we're working on every imaginable infectious disease," says Weissman, who back in 2005, alongside Karikó, discovered how to modify mRNA so it could be used safely and effectively in vaccines and

therapeutics. Even before COVID-19 struck, Weissman's lab group had set up mRNA vaccine clinical trials for herpes, HIV, and influenza. The many avenues they are currently exploring include a universal flu vaccine that covers all 20 known subtypes of influenza virus and an all-in-one "pan-coronavirus" vaccine that would be effective against any new variants yet to emerge.

People suffering with a broad range of life-threatening illnesses today hold onto hope that tomorrow will bring a new therapy that will save their life. Across Penn Medicine, researchers are focused on developing new medicines to address their unmet needs.

"With Penn at the forefront, the application of these first-in-class therapies to a broader array of other diseases is just around the corner. Penn Medicine's scientific impact — and the worldwide attention it commands — have never been greater," says J. Larry Jameson, MD, PhD, executive vice president of the University of Pennsylvania for the Health System and dean of the Perelman School of Medicine. "It is a tremendous point of pride that innovation born within our laboratories is being deployed to save lives across the world, and we are committed to fostering breakthroughs that will continue to redefine medicine as the 21st century unfolds."

Drew Weissman, MD, PhD, and Katalin Karikó, PhD, made fundamental discoveries that made it possible to use mRNA for vaccines and therapies — a technique used to develop two of the first approved COVID-19 vaccines.

THE PATH FROM INNOVATION TO IMPLEMENTATION

Penn's infrastructure in both supporting clinical research and forging commercial partnerships smooths the way from idea to approval.

In the sea of smiling faces at the August 2017 CAR T flash mob celebration, John Swartley, MBA, PhD, was beaming as much as everyone else — but not just because of Kymriah's approval. His grin was sparked by memories of one of the first meetings he had at Penn, right after joining the institution in 2007.

The meeting was with a "very frustrated" Carl June.

"Carl was struggling to find funding for this phase one study — the study that eventually became the *New England Journal of Medicine* article that kicked off the whole CAR T revolution," Swartley remembers. "Fifteen to 20 years ago, you really could not raise money for cell and gene therapy. But he knew the world was going to wake up to it, and part of my job was to believe him before everyone else did."

Swartley was hired into Penn's Center for Technology Transfer (CTT), a "more or less traditional, transactional tech transfer group" that managed the patenting and licensing processes for any intellectual property developed university-wide. Gradually, he helped transform it into the Penn Center for Innovation (PCI), which still serves those functions but is now equally focused on building relationships between faculty innovators and the private sector.

"Faculty know to disclose big discoveries to us, but also to come to us if they're looking for sponsored research or thinking that maybe they should start their own company — whatever's the best way to take their program forward and get it to patients," says Swartley, who today is associate vice provost for research at Penn and PCI's managing director. "PCI comes in at the earliest stages of these discussions and also brings opportunities to faculty without being asked. We're the matchmaker, the intermediary — the enzyme that helps make a reaction happen. But we're not consumed in the reaction, so then we go off and find another partnership to build."

The Slow Motion of Drug Development

These days, PCI handles around 750 commercial agreements annually, about three-quarters of which involve Penn Medicine. Such agreements can prime early discoveries like new medicines for success years — sometimes decades — before the words "FDA approval" are ever uttered.

Drug development generally moves at a snail's pace, with therapies taking an average of 10 to 15 years and costing upwards of $1 billion to trudge from concept to market. For every drug that "makes it," more than 5,000 fail.

Anyone working in academic medical research is aware of the long and winding pathway an experimental therapy must traverse before securing approval. Often, the journey begins once a disease mechanism is identified, and then the search for a target molecule to fix it begins in the laboratory. Testing begins in cells outside the body before progressing in animal models. A small-scale phase 1 clinical trial then examines a compound's safety in humans, followed by a phase 2 trial that measures its effectiveness and a large-scale phase 3 trial studying it in various populations, dosages, and combinations with other drugs.

While PCI manages all of the intellectual property coming out of Penn as a whole, Penn Medicine has its own discrete resources for supporting faculty research efforts as they push new therapies through the pipeline. The dozen staff members on the PSOM Office of Clinical Research's (OCR) regulatory team, all of whom have regulatory backgrounds and graduate degrees in biomedical science, guide researchers in designing their projects with a view toward FDA approval — offering know-how that doesn't exist in most academic organizations, according to Emma Meagher, MD, senior vice dean for clinical and translational research, who oversees PSOM's clinical research infrastructure.

That regulatory expertise is a layer on top of the support that clinical research offices routinely provide academic health centers for the essential elements of simply running a clinical trial, which is not simple at all. Services range from participant recruitment and staff training to financial planning to legal guidance through compliance and contracting for

Carl June, MD, spoke before the flash mob that gathered in August 2017 to celebrate the approval of the first CAR T cellular therapy.

corporate-sponsored trials. By streamlining all of the processes involved in clinical research, Penn's OCR empowers faculty to conduct higher-impact trials that boost clinical discovery and offer patients more advanced treatment options and opportunities.

"As academics, we write grants, we publish papers, we execute research — but we don't necessarily do that through the lens of, 'How would this actually get reduced into clinical practice? What are the requirements I need to demonstrate to get there? How would this be manufactured, and what would scale-up look like?'" Meagher says. "There has been an enormous investment in taking Penn's scientific heft and enabling its translation toward product development by hiring people who have a deep understanding of how regulatory authorities consider new drugs and devices."

Partners in the Path to Approval

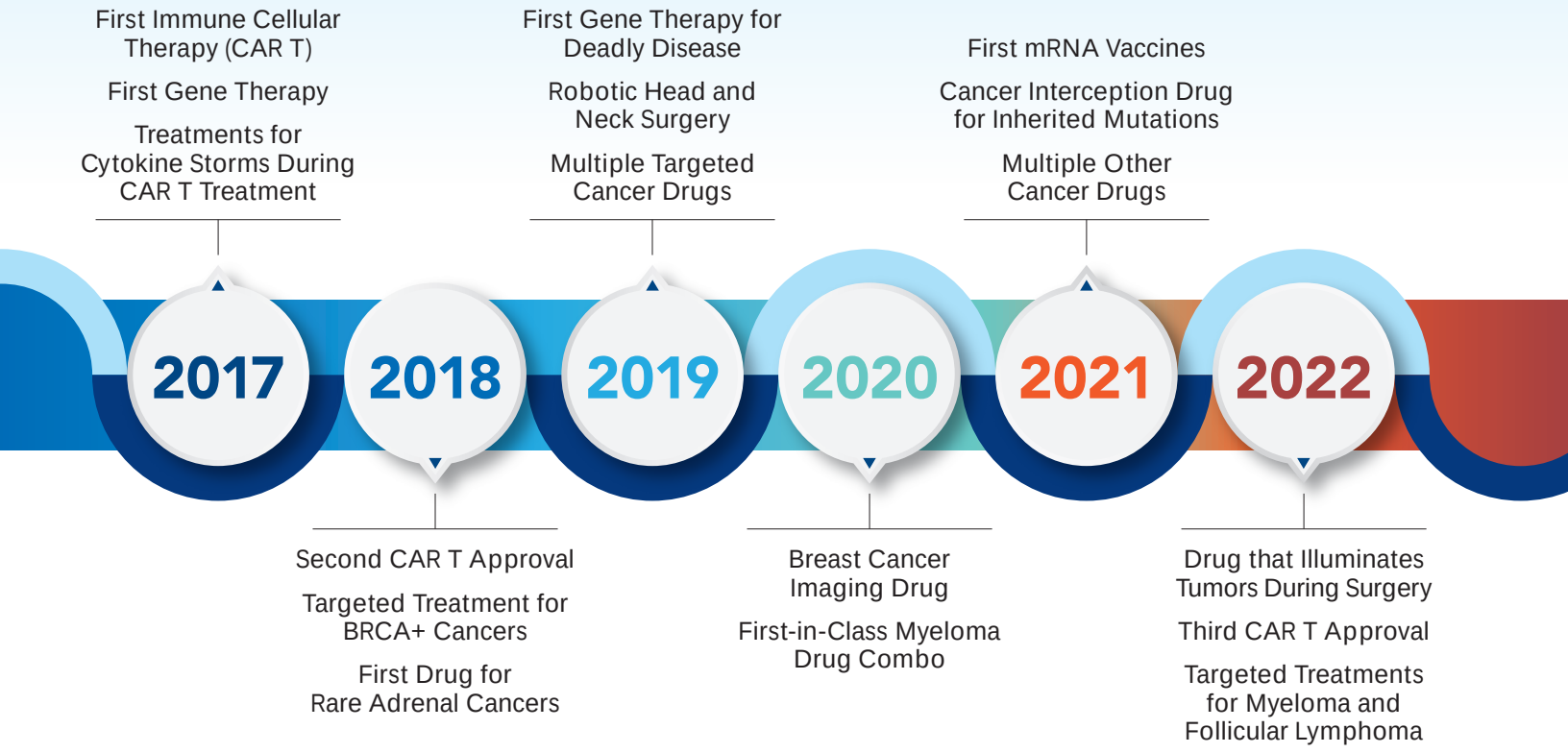
The expansion of PCI — now about three times the size of its predecessor, the CTT — has empowered researchers to accelerate the advancement of their discoveries by positioning them as active research and development partners with pharmaceutical and biotech companies.

"We're no longer just a contracting entity whose work ends with throwing a discovery over the fence. We're officially joint developers of our own technologies, especially when it's something like a groundbreaking cell or gene therapy, because without our faculty members' skills and expertise, these types of transformative innovations don't work," Swartley explains. "Penn helps its faculty embrace roles as collaborative co-development equals rather than waiting for an outside company to swoop in and take over."

In many cases, PCI's role is to support faculty in founding their own startups. Successful Penn Medicine spinout com-

TRANSLATING DISCOVERY INTO MEDICINE

Year after year, more therapies rooted at Penn gain approval by the Food and Drug Administration.



A comprehensive list of FDA approvals from the last decade based on Penn research is currently under development. To see a list and description of cancer-related approvals documented since 2017, visit PennMedicine.org/magazine.

panies developing cellular therapies such as Tmunity (now a division of Kite, a Gilead Company), Carisma Therapeutics, and Capstan Therapeutics, are all excellent examples of this, Swartley points out. Further developing promising technologies through a startup can be a wiser strategy for commercializing the technology than immediately licensing it to an existing company, he says, because startups (and the types of firms that invest in them) are often more comfortable with the myriad risks inherent in early-stage product development. And because startup companies need early financial investment to grow, since 2018, Penn Medicine has supported a growing number of these faculty-led spinoff companies through the Penn Medicine Co-Investment Program. As of the end of the 2022 fiscal year, the program had invested over $35.5 million in nine Penn Medicine spinouts that have gone on to cumulatively raise over $1.4 billion in capital.

As a basic scientist himself, Jon Epstein remembers that early in his career, he routinely imagined "somebody else — probably a pharmaceutical company — taking my discovery and running with it."

"I thought someday they'd read a paper I'd written and go make a new medicine," Epstein recalls. "But being at Penn has changed me. Now, I think I could make a new therapy here."

No matter how far down the testing and development pathway an investigator's project perseveres, Meagher says it demands doggedness and drive to navigate the laboratory, clinical, and entrepreneurial routes involved in drug discovery: "It takes a combination of incredible passion for and curiosity in the science, an unbelievable sense of optimism, and being able to take the knocks — to have an inherent resilience to bounce back up again even if nothing is ever going to go the way you want it to go."

Except sometimes, eventually, things do go the way a researcher wants — like they did for June. Two years after first lamenting to Swartley about his lack of funding, June secured just enough private funding to treat three patients in an initial trial. Then, in 2012, two years after those remarkable first results were published — with support from Swartley and his team — Penn signed an agreement with Novartis to accelerate research, development, and commercialization of CAR therapies.

Five years after that, their voices joined the chorus of cheers at the CAR T approval flash mob event.

And the rest is history that is still making history.

FROM SERENDIPITY TO SCIENCE-DRIVEN DRUG DESIGN

The approval of CAR T cell therapy ushered in a new era for cancer treatment.

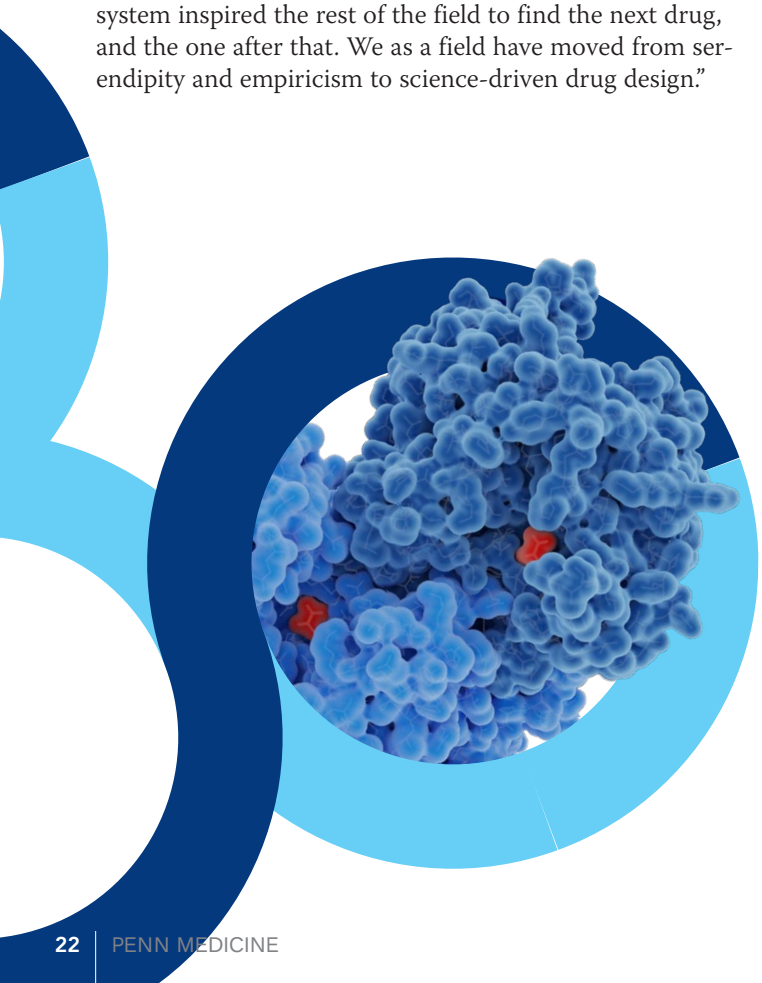
In the five years since the FDA's initial approval of CAR T cell therapy, Penn Medicine has gleaned 20 additional approvals related to drugs and techniques to treat or detect cancer.

Rather than being the single disease class many people refer to, "cancer" is a blanket term that covers more than 100 distinct diseases, many of which have little in common aside from originating with rapidly dividing cells. Since different cancers demand different treatments, it follows that a large number of new therapies emerging from any institution would fall under the oncology umbrella.

But why so many in just this five-year period?

The volume makes sense, says ACC Director Robert Vonderheide, attributing the flurry to a recent "explosion" in knowledge about cancer biology.

"Much of that knowledge is about the immune system's ability to attack cancer, which people seriously doubted until about 20 years ago. As soon as we had a clinical validation for this Achilles heel in cancer, the dam burst for ideas about other ways to exploit that vulnerability to come forward," he says. "The first drug that came out to activate the immune system inspired the rest of the field to find the next drug, and the one after that. We as a field have moved from serendipity and empiricism to science-driven drug design."



The first CAR T cell therapy approval invigorated faculty interested in finding new ways to harness the immune system to fight cancer.

"An approval like that makes what you're working on more of a reality," says Avery Posey, PhD, an assistant professor of Systems Pharmacology and Translational Therapeutics whose lab team spends much of its time trying to identify more specific antigens for solid tumors and also studies ways to optimize engineered donor T cells. "It brings a new perspective, showing that your work is more than basic research and can actually become drugs that impact patients' lives. That's a real motivator to keep pushing forward."

Honing new immunotherapies is a priority among Penn researchers, but not all of the recently approved cancer-care tools developed at the institution engage the immune system. Faculty have explored and introduced widely varying approaches to improving the standard of care for cancer patients.

For example, there's olaparib (marketed as Lynparza), which is used in ovarian and breast cancers, most commonly those involving an inherited BRCA gene mutation. The oral medication works by targeting PARP, an enzyme in the body that helps to repair damaged cells — including cancer cells. By inhibiting PARP, the drug stops the repair of cancerous cells to prevent them from growing. The drug's approvals in 2014, 2018, and 2022 were based on trials led or co-led by Susan Domchek, MD, executive director of the Basser Center for BRCA at the ACC.

There's also pafolacianine (marketed as Cytalux), the first FDA-approved agent that illuminates ovarian cancer and lung cancer lesions during surgery, enabling surgeons to find and remove cancerous tissue. Penn investigators Janos Tanyi, MD, PhD, and Sunil Singhal, MD, led its Phase 2 and 3 clinical trials leading to approval. And belzutifan (marketed as Welirig), the first treatment of its kind for treating von Hippel-Lindau disease-associated tumors, such as those in renal cell carcinoma and central nervous system hemangioblastomas — a drug with Penn connections from basic science discovery about cancer hypoxia through to the definitive clinical trial leading to its approval.

On Jan. 12, 2023, the American Cancer Society released its annual compilation of cancer facts and trends, which reported

Sunil Singhal, MD (right), led trials of pafolacianine, an agent that lights up lung cancer tumors to help surgeons find and remove cancerous tissue. Photo credit: Addison Geary.

that since its peak in 1991, cancer mortality in the U.S. has dropped 33 percent.

"That's almost 4 million deaths averted. Clearly, something dramatic has changed the outlook for patients with cancer in this country in the last 30 years," Vonderheide says. "Much of that has to do with new therapies, which were all unknown drugs in a phase one clinical trial at some point. Every single drug you see advertised on TV — once upon a time, some patient somewhere was the first patient ever treated with it. This is why we do what we do."

Because of high mortality outcomes among cancer patients who haven't responded to conventional therapies, risk tolerance in cancer clinical trials tends to be higher than in trials testing novel therapies for non-cancer conditions, Emma Meagher explains

"High-risk, and potentially high-reward, trials happen frequently in cancer for that reason and oftentimes can move more quickly," Meagher says.

Just because a new drug is first tested and approved to treat cancer doesn't mean it can only treat cancer, though. Many therapies that start in oncology eventually have broader disease applications — like CAR T cell therapy, which is already showing promise with other diagnoses, like the autoimmune disease lupus.

CAR T cell therapy's potential translation to other diseases is "a rumble that is beginning to sound like thunder in autoimmune disorders, neurological conditions, rheumatological conditions, and dermatological conditions, among others where immune mechanisms are implicated," she adds. "We're beginning to see momentum in using what is currently considered a cancer therapy well outside of the oncology space, and I predict that Penn will be a real leader in this area."

PUTTING ADVANCES WITHIN REACH

Treatments and vaccines are only useful in the hands of people who need them.

Despite Penn's track record developing therapies that make it onto the market, faculty remain humbled by one basic tenet: Advances mean nothing if patients can't access them.

"If our goal is to improve human health, we cannot call ourselves successful unless we bring the fruits of our labor to bear as broadly as possible on people suffering from the conditions that interventions are designed to treat," Meagher says.

In the U.S., manufacturers are free to set prices for brand-name drugs and launch novel products at the highest rates, with gene therapies often costing millions and CAR T treatments approaching the half-million-dollar range. Although some manufacturers offer payment assistance programs, these expenses burden state and federal health programs, private insurers, and uninsured or under-insured patients facing out-of-pocket costs.

Commercialized drug prices are beyond an academic institution's control, but researchers — including many at Penn — are exploring advances that would make cutting-edge treatments more easily available to everyone who needs them. In the case of CAR T, for example, those working to develop a universal version of the therapy understand they can drive down costs by transforming a time-intensive, personalized treatment that requires a patient to donate their own T cells into one where an existing bank of cells could be used to treat many patients.

Many U.S. cancer patients who are eligible for today's FDA-approved CAR T therapies do not actually receive the treatment or end up waiting months to begin the process as their disease worsens. Honing an "off-the-shelf" version of CAR T therapy would also curb the extensive wait times and manufacturing limitations that prevent many patients from getting the treatment.

Clinical Trial Outreach

Racial and ethnic health disparities also stoke accessibility concerns. Black Americans are less likely than any other group to receive CAR T cell therapy — a trend rooted in gaps in income, education, housing, job security, and proximity to high-quality medical centers. These same social determinants of health have also led to their underrepresentation in CAR T and all kinds of clinical trials; Black patients account for just 5 percent of clinical trial participants nationwide.

"Black patients' historically low participation in trials means that, compared to white individuals, they have less

access to some of the most advanced new treatments," says Carmen Guerra, MD, MSCE, vice chair of diversity and inclusion in the Department of Medicine and associate director of diversity and outreach at the ACC.

To better diversify clinical studies, the ACC recently conducted a five-year community engagement study that reached more than 10,000 individuals through marketing campaigns tailored to minority cultures; wellness forums and events in Black communities; partnerships with Lyft and Ride Health to reduce transportation barriers; and patient education efforts. By the end of the project, the number of Black patients in Penn's cancer clinical trials had doubled.

Additionally, the ACC piloted a Cancer Clinical Trials Community Ambassador Program that trained Black cancer survivors and caregivers in how to inform their networks about the importance of clinical research; a Genentech Innovation Grant launched in February is now fueling a study to determine how effective these peer ambassadors are when matched with newly diagnosed or relapsed breast cancer patients. And a first-of-its-kind collaboration with the Lazarex Cancer Foundation allows Penn to reimburse trial participants for gas, parking, plane or bus tickets, hotels, and other out-of-pocket travel and lodging costs related to clinical trial participation for the patient and a companion.

"There is financial toxicity associated with participating in a clinical trial, even though the actual treatment is covered by research dollars," Guerra says. "We're working to eliminate obstacles one by one to make sure people can get the treatments they need. Addressing inequities is like an onion — we peel off one layer of barriers, then see what's underneath so we can address the next layer."

Global access concerns abound, as well. Outside the U.S. and other economically stable nations like China, Australia, Singapore, and the United Kingdom, CAR T cell therapy is unavailable. Penn Medicine and CHOP have begun to partner with low- and middle-income nations in an attempt to facilitate global equity in CAR T cell research and treatment. Their first agreement is with Costa Rica's Social Security Program, the Caja Costarricense de Seguro Social; the partners will bring adult and pediatric patients to Penn or CHOP, where their immune cells will be collected for manufacturing into CAR T cells. Then, those cells will be returned to Costa Rica for infusion as part of a trial to be conducted there.

Democratizing Vaccine Access

Even when drugs are relatively affordable and easy to produce, racial disparities persist — disparities Penn Medicine is striving to overcome. Following the approval of mRNA vaccines against COVID-19, for instance, the health system worked with partners in West and Southwest Philadelphia to bring vaccines directly to their predominantly Black communities in spaces like gyms and public schools, and later moved portable "hyperlocal" clinics between locations like fast-food restaurants and retail parking lots in neighborhoods where many residents remained unvaccinated.

And like with CAR T, the global distribution of mRNA vaccines is far from equitable. By the end of 2022, at least three-quarters of the population in dozens of countries had been fully vaccinated — but in many others, mostly in Africa, only small fractions had received vaccines. More than three years after COVID-19 first emerged, close to one-third of the global population has not yet had a single dose. That's a big problem, says Weissman, who has collaborated on research and drug development with more than 200 academic and biotech labs "on every continent except Antarctica" and has helped foreign governments set up Good Manufacturing Practices (GMP) sites where scientists in underserved areas are trained to produce and administer vaccines. Working with investigators at the vaccine center at Chulalongkorn University in Bangkok, he established a quality manufacturing center to produce an mRNA COVID-19 vaccine for Thailand and seven surrounding low- and middle-income countries, and he has done similar work in Africa and eastern Europe.

"Part of the failure in clearing COVID-19 has been a lack of vaccine access in many regions of the world where unchecked virus replication led to new variants," he explains. "Local groups and governments being able to make their own RNA vaccines is critical for equity. I also believe these GMP sites will offer regions the ability to make vaccines against local diseases that Big Pharma has no interest in, such as dengue and tularemia in Southeast Asia, and malaria and a variety of local pathogens in Africa."

More Work to Be Done

Efforts at Penn to understand gaps in new drug access go as far as examining how and where products end up being prescribed. For example, researchers found in a spring 2022 study of the first-ever mutation-targeted bladder cancer drug that it was being used by fewer than half of patients who tested positive for the gene mutation in question and qualified to take it. Fewer than half of those potentially eligible even underwent testing.

The next step: figuring out why more people aren't accessing a drug that could extend or save their lives and how to help close the gap — in this example, by advocating for more genetic testing and education for treating physicians.

"In academics, our incentive mechanism is to publish, to write grants, to see patients, and to teach," Meagher says. "But if community isn't an integral, systematic part of our processes, we aren't doing our jobs to the best of our ability. If you believe what you're working on is important, you must bring it to all the people it will benefit." ⛉