

SUMMER 2023

PENN Medicine

A large, white silhouette of a human figure stands against a vibrant blue background. The silhouette is filled with a dense, colorful pattern of various shapes, including gears, stars, and virus-like particles in shades of yellow, orange, red, and green. The overall theme is related to health, medicine, and the immune system.

THE IMMUNE HEALTH ISSUE

A new platform
for monitoring
health and treating
disease, an age of
immunotherapies,
and more.



THE PREP

BACK ON THE COURT

After a three-year hiatus, the annual Perelman School of Medicine Faculty vs. Students Basketball Game returned to the University of Pennsylvania's Palestra this spring. The students, in red, and faculty, in blue, wore jerseys originally printed for the 2020 game that was scuttled by the spread of COVID-19.

Now, when they aren't facing off on the court, faculty and medical students are taking their shots at transforming medicine in the pandemic's wake. Microbiology Professor Scott Hensley, PhD, pictured above shooting the jump shot, is among them—developing a new, universal mRNA influenza vaccine that could prevent future pandemic outbreaks of that virus. (See more on p. 24.)

As for the game, the students won the day, 59 to 54.



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PENN MEDICINE

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By Christina Hernandez Sherwood

Breaking the code of the immune system could provide a new fundamental way of understanding, treating, and preventing every type of disease. Penn Medicine is investing in key discoveries and building infrastructure to make that bold idea a reality.

24 Viruses vs. Vaccines, the Perennial Rematch

By Tomas Weber

Inside the evolutionary arms race that explains why we get annual flu and COVID-19 vaccinations—and the scientific quest for a “one and done” alternative.

30 Building on the Body's Wisdom

*By Wynne Parry, Carol R. Cool, Kirsten Weir,
and Christina Hernandez Sherwood*

Treatments that manipulate or repair the immune system are becoming more commonplace. An age of immunotherapy is underway in medicine, starting with lifesaving cancer treatments and radiating out to have wider impacts.

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The Immune Health Issue

The words “Immune Health” are ones you might expect to see on the cover of a health and fitness magazine in the grocery store checkout line, probably paired with an active verb like “boost” and followed by some tips that involve supplements or superfoods.

At Penn Medicine, they mean something different and far more powerful.

Immune Health® is a term trademarked by Penn as a new area of scientific discovery and medical care that our scientists and physicians are actively bringing into existence, along with a growing list of partners across academia and industry. Scientists at Penn Medicine are deeply profiling individual immune systems to understand how they function as a unique fingerprint, a piece of your health-and-disease puzzle that’s unique to you, but also a key to new ways of thinking about health care.

The vision they are working toward is comparable to the way genetics has suffused medicine in recent years. Most people know that their individual genetic sequence is as unique as a fingerprint. For the last two decades, medical science has used our growing understanding of patterns within those fingerprints to develop more personalized treatments. Patterns among people’s genetics are commonplace and important in different ways. Some groups of people share gene variants that cause genetic diseases. Some groups with similar genetic patterns share risks for other diseases, or they may react differently to certain medications. When you develop cancer, your doctor may have the tumor’s genome sequenced to see how its DNA mutated to make it grow, and to show where its weaknesses lie—because plenty of cancer treatments are designed to target specific mutations in a tumor.

This is all routine in medicine today. New discoveries are constantly uncovering new connections between genetic variations and better medical treatments to help us prevent, intercept, or treat diseases when they develop. It’s also a remarkable shift, just within the span of the current century, that has saved and extended countless lives.

Now Penn Medicine wants to do it all over again, but looking instead at the immune system—its unique patterns in individuals as it surveils, learns, and responds to threats; its common patterns in groups of people; and how to connect those patterns to more customized medical treatments or prevention. This issue’s cover story (p. 12) details more of how, why the immune system is such a compelling subject for this approach, and what initial steps Penn teams have come so far in the early stages of bringing that vision to life.



There aren’t many other places in the world where this type of Immune Health work could get underway today. The rest of this issue is filled with stories that give the context and history around Penn’s leadership in an astonishing breadth of discovery for a single institution, from its role in the history of vaccine development in the past century (p. 4) to understanding why different people react differently to vaccines and developing new ones that protect may protect universally against all influenza viruses or coronaviruses (p. 24). Penn’s leadership also notably includes developing chimeric antigen receptor T cell therapy (CAR T) that programs the body’s immune cells to fight cancer—and someday soon, scientists hope, other diseases. A collection of stories beginning on p. 30 shows the impact of this and other types of immunotherapies, both on patients who have already been cured of their disease, and on scientists and physicians who are still working to create better treatments. Autoimmune diseases are among the important targets of these varied approaches, with significant support totaling \$60 million since 2021 from Stewart and Judy Colton powering the Colton Center for Autoimmunity at Penn.

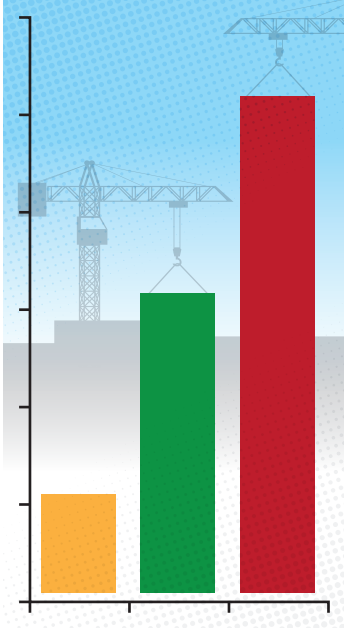
Immune Health is an area where Penn Medicine and our partners are investing major effort because our teams have the track record and the expertise to keep growing in this area, and they have the commitment to keep putting discoveries to work. Scientists, physicians, patients, industry partners, and philanthropists all have a role in making it happen. I hope that the stories on these pages will help inspire you to connect with this work as it unfolds in the years ahead.

RE

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BUILDING BETTER BENCHMARKS

Penn Medicine is developing new, transparent metrics of quality health care and medical education in lieu of participating in an outside ranking system.



This year, Penn Medicine announced plans to withdraw from voluntary participation in the *U.S. News and World Report* annual “Best Medical Schools” and “Best Hospitals” rankings.

“The rankings measure the wrong things,” wrote J. Larry Jameson, MD, PhD, executive vice president of the University for the Health System and dean of the Perelman School of Medicine, announcing the decision to withdraw from the medical school rankings in January.

Likewise, Penn Medicine leaders say the publication’s hospital rankings represent an outdated view of health care, failing to capture the full breadth of “care everywhere” services. Modern medicine goes far beyond hospital walls. Today’s health systems provide primary care along with advanced care—from surgeries to cancer treatment to kidney dialysis—in outpatient facilities, in patients’ homes, and through virtual platforms or remote monitoring.

“Health care is evolving at an unprecedented pace, and the ways performance is measured must also change. The ‘Best Hospitals’ rankings don’t account for all of the elements essential to improving patient outcomes, such as research, innovation, or value-based care,” said Kevin B. Mahoney, CEO of the University of Pennsylvania Health System, in announcing the health system’s withdrawal from participation in these rankings in June.

Over the next year, Penn Medicine will develop a public-facing dashboard, including evidence-based measures like readmission and infection rates and quality data for emerging areas, including home care and telemedicine, to be updated annually. Penn Medicine will also continue to engage health system and hospital peers nationwide to standardize quality and performance reporting. Data about the medical school will be included on the Perelman School of Medicine admissions site.

CENTRALIZED EXPERTISE FOR MENTAL HEALTH CARE

With a new crisis response center serving West Philadelphia, Penn Medicine will bring together emergency, inpatient and outpatient psychiatric care on the same campus.

Penn Medicine is launching a new community mental health hub at the Hospital of the University of Pennsylvania–Cedar Avenue (HUP Cedar), co-locating inpatient and outpatient psychiatric care with a new crisis response center (CRC) at the facility. The multi-year plan will put crucial psychiatric and substance use care in easy reach for West and Southwest Philadelphia. The new CRC is expected to provide an estimated 4,000 patient visits each year. Co-locating these services will enable a seamless transition of care for patients, eliminating the wait time and additional steps required to transfer patients to inpatient units at other facilities—a common occurrence in a city where emergency psychiatric resources remain in short supply.

The steps will create two comprehensive, fully integrated mental health hubs at Penn Medicine facilities in Philadelphia, offering emergency mental health services and inpatient and outpatient care at both HUP Cedar and Pennsylvania Hospital, which has operated a CRC since 1999. Together, Pennsylvania Hospital and HUP Cedar will have 73 licensed inpatient psychiatric beds and 16 beds for substance use treatment. Additional space at HUP Cedar will allow for expansion of coordinated services over the next five years, at a time when both mental illness and drug and alcohol dependence are surging in the city.



A HISTORY MURAL THAT POINTS TO THE FUTURE

A new display in Penn's Smilow Center for Translational Research provides a history of breathtaking discoveries.

For more than half a century, Penn Medicine, with its neighbors the Children's Hospital of Philadelphia (CHOP) and the Wistar Institute, has been a leader in vaccine development—making significant contributions to improve the health and wellness of people in our region and around the world.

A new mural now on display in the lobby of Penn Medicine's Smilow Center for Translational Research, "Vaccine Development in Philadelphia," pays tribute to that impact and those who are still making history today. Its timeline spans from vaccine discoveries of the 1960s to the work forming the foundation of immune health initiatives and new universal vaccines for influenza and coronaviruses (detailed later in this issue). The Perelman School of Medicine Portrait Review Committee supported the development of the mural. Established in 2020 as an advisory committee to PSOM Dean J. Larry Jameson, MD, PhD, and Chief Scientific Officer Jonathan Epstein, MD, this group works to diversify the visual representation of Penn Medicine's trailblazing leaders on campus. In telling the story of the history of vaccines, they sought to amplify diverse teams in science that increasingly drive this work, to feature the voices of more scientists and physicians who are women and people of color, and to celebrate Penn Medicine's commitment to equitable access to vaccines in underserved communities.

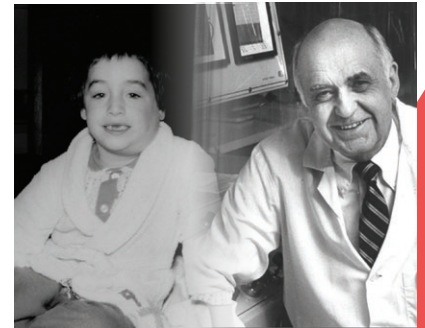
The story and images on these two pages represent an excerpt of the full mural.

1968

MEASLES, MUMPS, RUBELLA

Maurice R. Hilleman, PhD, DSc, an adjunct faculty member in Pediatrics at the Perelman School of Medicine at Penn and a Merck scientist, helped to develop over 40 vaccines.

Maurice R. Hilleman, PhD, DSc developed the mumps vaccine after isolating a viable mumps strain from daughter Jeryl Lynn Hilleman (below) during her sickness



2020

COVID-19

The mRNA technology pioneered by Penn Medicine scientists Katalin Karikó, PhD and Drew Weissman, MD, PhD is recognized for enabling the rapid development of highly effective COVID-19 vaccines. To date, hundreds of millions of doses of mRNA COVID-19 vaccines have been administered in the United States and around the world.



Scientists Katalin Karikó, PhD and Drew Weissman, MD, PhD in 2021



"The impact of vaccination on the health of the world's peoples is hard to exaggerate. With the exception of safe water, no other modality has had such a major effect on mortality reduction and population growth."

SUSAN & STANLEY A. PLOTKIN, MD
A Short History of Vaccination,
in Vaccines 1st Edition

1971



Stanley A. Plotkin, MD, Hilary Koprowski, MD, and Tadeusz Wiktor, VMD inoculating themselves with the rabies vaccine

RABIES

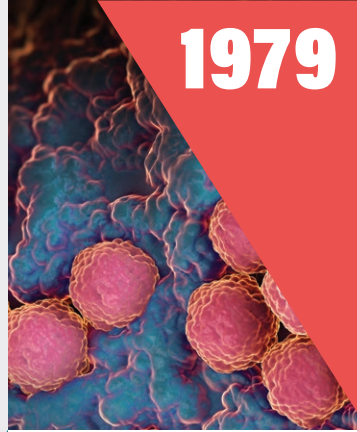
In 1971, Hilary Koprowski, MD and Tadeusz Wiktor, VMD of The Wistar Institute, and Stanley A. Plotkin, MD of Wistar/Penn/CHOP produced a highly effective human vaccine in human embryonic cells and even inoculated themselves to test its safety.

1976

PNEUMOCOCCUS

Robert Austrian, MD, Chair of Medical Research at the University of Pennsylvania, began identifying different strains of pneumococcal bacteria, eventually finding dozens of serotypes. In 1976, he reported that a pneumococcal vaccine that he developed had proven safe and effective in clinical trials. Austrian's pneumococcal vaccine, which was licensed by the FDA in 1977, would soon prevent a common cause of pneumonia, sepsis, and meningitis in the U.S. and the world.

1979



RUBELLA

The rubella vaccine licensed in 1969 was replaced in the United States by Stanley A. Plotkin, MD's [Wistar/Penn/CHOP] newly licensed RA27/3 vaccine, which was safer. Plotkin's vaccine also replaced the original rubella vaccine in the combined MMR shot and is still used today.

2006

ROTAVIRUS

The Centers for Disease Control and Prevention recommends routine infant immunization with three doses of the rotavirus vaccine, live, oral, pentavalent (trade name RotaTaq), developed by H. Fred Clark, VMD, PhD [Wistar], Stanley A. Plotkin, MD [Wistar/Penn/CHOP], and Paul A. Offit, MD [Wistar/Penn/CHOP].

H. Fred Clark, VMD, PhD and Paul A. Offit, MD (below)



ONGOING EFFORTS

COMMUNITY ENGAGEMENT



"As Black leaders at Penn Medicine, we recognized our unique position to address our community directly: to own the past mistakes of the medical profession, acknowledge present-day racism in healthcare and offer an opportunity for conversation about the vaccine with trusted messengers."

FLORENCIA GREER POLITE, MD & EUGENIA SOUTH, MD, MSHP

From Los Angeles Times Op-Ed: "Vaccine hesitancy is common among Black healthcare workers. We're trying to resolve it." Feb. 19, 2021

After hosting its first COVID-19 community vaccine clinic in mid-February 2021 at a church in West Philadelphia, Penn Medicine sponsored dozens more events at schools, recreation centers, and even professional sporting events. The goal was to "meet people where they are" with the vaccine.



DEAN J. LARRY JAMESON, MD, PhD

"Through research fueled by a desire to solve clinical challenges, we have developed groundbreaking vaccine platforms with the power to save lives and transform health care. Looking ahead, we can envision a future where vaccines are used to treat a wide range of illnesses, representing hope and progress in our mission to improve health for all."

CONTINUOUS ADVANCEMENTS IN VACCINE DEVELOPMENT FOR:



HERPES



UNIVERSAL FLU



CANCER



AIDS



THE LONG ROAD TO LONG-COVID RECOVERY

Penn Medicine physicians are working with patients with lingering symptoms after COVID-19 infection to improve their quality of life and gain insights into this mysterious and frustrating condition.

Frantz Dickerson developed COVID-19 in the fall of 2020 and spent a few days in the hospital. After returning to work a few weeks later, he realized his ability to function was impaired by lingering exhaustion and one of the hallmarks of long COVID, “brain fog”—a frustrating lack of mental acuity. “My brain was like a 10-lane highway before COVID, and suddenly, it was a 2-lane road with a traffic jam,” Dickerson said.

Long COVID is one of the most mysterious and frustrating aspects of COVID-19, with symptoms that linger weeks or even months after the body has cleared the infection. Estimates suggest that perhaps one in every four people who has recovered from COVID may be struggling with long COVID. Other common symptoms include difficulty breathing, joint pain, headaches, and gastrointestinal problems.

For nearly three years, Penn Medicine’s Post-COVID Assessment and Recovery Clinic has worked with patients like Dickerson as they navigated an unfamiliar path to recovery, typically after they are referred by a primary care doctor.

“One of the challenges of treating long COVID is that it presents differently in each patient, so every patient is treated individually,” explains the clinic’s leader, Benjamin Abramoff, MD, an assistant professor of Physical Medicine and Rehabilitation in the Perelman School of Medicine. “So we focus on treating symptoms and improving day-to-day quality of life and function.”

With a combination of physical therapy, cognitive behavioral therapy, headache management techniques, and in some

cases medication, the clinical team helps patients develop coping mechanisms and restore function. Dickerson sought help from Abramoff’s clinic and after months of grueling work to recover both energy and mental clarity, he reports that not only are his symptoms gone, but that he feels better than he did before COVID: “It feels like I have a couple extra lanes on the highway now.”

For patients whose main symptoms are associated with the brain and nervous system, Penn Medicine’s Neuro COVID Clinic offers more specialized expertise. The only one of its kind in the Philadelphia region, it focuses specifically on brain fog, headaches, memory issues, fatigue, and more neurological and psychological aspects of long COVID. So far, they have treated more than 300 patients, and learned that improvement can be a realistic expectation for many patients, although it may take up to two years.

“At this point, we don’t know what makes one patient more likely to suffer from neurological symptoms of long COVID, or what indicates better rates of recovery,” said Dennis Kolson, MD, PhD, a professor of Neurology and Microbiology and part of the Neuro COVID Clinic. “We hope that the work we do at our clinic can help us understand this better, and help develop tailored treatments that lead to better outcomes for patients in the future.”

UNCOVERING HIDDEN IMMUNE CONNECTIONS

What role does the immune system play when some people with psoriasis go on to develop inflammatory arthritis?

The skin and the joints are seemingly unrelated organs. Yet about a third of the 8 million Americans with the skin condition psoriasis will eventually develop psoriatic arthritis. In this disease, the body's immune system causes painful inflammation in the joints in addition to the overproduction of skin cells that creates itchy, scaly psoriasis plaques. But how?

This seeming paradox has intrigued Alexis Ogdie-Beatty, MD, MSCE'12, since early in medical residency at Penn, when she met her mentor, the renowned rheumatologist H. Ralph Schumacher, Jr., MD'59. Then, during fellowship (also at Penn), she met dermatologist Joel Gelfand, MD, MSCE'03. "As he talked about psoriatic arthritis, I realized this was the perfect focus of study to help me understand inflammatory joint disease because, unlike other people with arthritis, some of these patients were destined to develop this condition," said Ogdie, who is now director of the Penn Psoriatic Arthritis and Spondyloarthritis Program and the Center for Clinical Epidemiology and Biostatistics. "We know there is some connection, but why and for whom?"

Systematic Study of an Autoimmune Disease

Arthritis and psoriasis are both immune-mediated diseases. "The immune system gets turned on for reasons that we don't fully understand, and then we can't really turn it off," Ogdie said. "We have therapies that suppress the immune system, but they never fully reverse the inflammatory process."

Now, through these related but distinct conditions which comprise psoriatic arthritis, scientists are starting to understand how different parts of the immune system "talk" to each other. "It turns out there are cells that communicate with both the skin and the joints and may even travel between them," Ogdie said. "It's a fascinating interaction between very different cell populations that has broader implications."

Her team's discoveries in this area benefit from the collaborations, resources, and expertise of colleagues from Dermatology and Rheumatology at Penn, collaborators across the country, and the Center for Clinical Epidemiology and Biostatistics (CCEB), which Ogdie has directed since 2022.

Taking an epidemiological approach, Ogdie has been researching whether dermatologists should treat psoriasis more aggressively in patients who have other conditions that might contribute to the development of psoriatic arthritis in collaboration with Jose Scher, MD from New York University, Joseph Merola from Brigham and Women's



Alexis Ogdie, MD, MSCE

Hospital, and others. The team has since launched a randomized clinical trial to address this question. Understanding the patterns of the risk factors and which ones seem to precede the psoriatic arthritis diagnosis is the key way that epidemiology informs this research.

These studies have been exploring whether the electronic medical record (EMR) can be used to alert the provider when a patient with psoriasis comes in with depression, anxiety, obesity, or other known risk factors of psoriatic arthritis. "The EMR can then prompt the provider to ask the patient about any joint pain or swelling," Ogdie said. "That way, the provider can start the patient on an effective therapy for psoriasis that could potentially delay or prevent the onset of clinical joint symptoms."

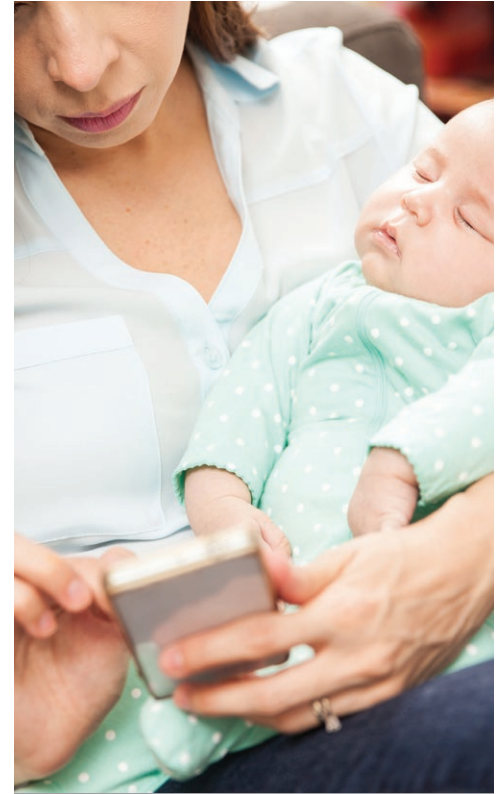
The CCEB's multidisciplinary approach—and its focus on research questions that improve patient outcomes—have broader implications for medical research than just psoriatic arthritis, Ogdie said. "We focus on risk, why people develop diseases and how these complex pieces can fit together to create a clinical symptom for a patient sitting in front of you," she said. "We're also designing new types of trials to help us get the right therapy for the right patient by incorporating what patients and clinicians actually need."

— Darcy Lewis

PREVENTING PREECLAMPSIA VIA TEXT MESSAGE

A blood pressure cuff and a cell phone may be all a new mom needs to prevent some major complications after childbirth, with the right supports set up on the other end of that phone line. Six months after delivery, new mothers with high blood pressure were less likely to have post-partum complications, hospitalizations, and incurred less health care costs if they participated in a remote blood pressure monitoring program, compared to a similar group of mothers who did not. Heart Safe Motherhood is a two-way text message-based program created and studied at Penn Medicine, which makes blood pressure monitoring after giving birth more convenient and links patients directly with their care teams from home. The program is in use in all of Penn Medicine's birthing hospitals. The new study was published in the journal *Obstetrics and Gynecology*.

"Our previous work showed that Heart Safe Motherhood made important blood pressure monitoring easier and eliminated racial disparities in obtaining blood pressures in the two weeks after giving birth," said study author Adi Hirshberg, MD, an associate professor of Obstetrics and Gynecology in the Perelman School of Medicine. "What this study really solidified is that the benefits continue long-term. Close but remote tracking of blood pressure during this short yet pivotal time led to healthier moms months later."



PHYSICIAN PROMPTS

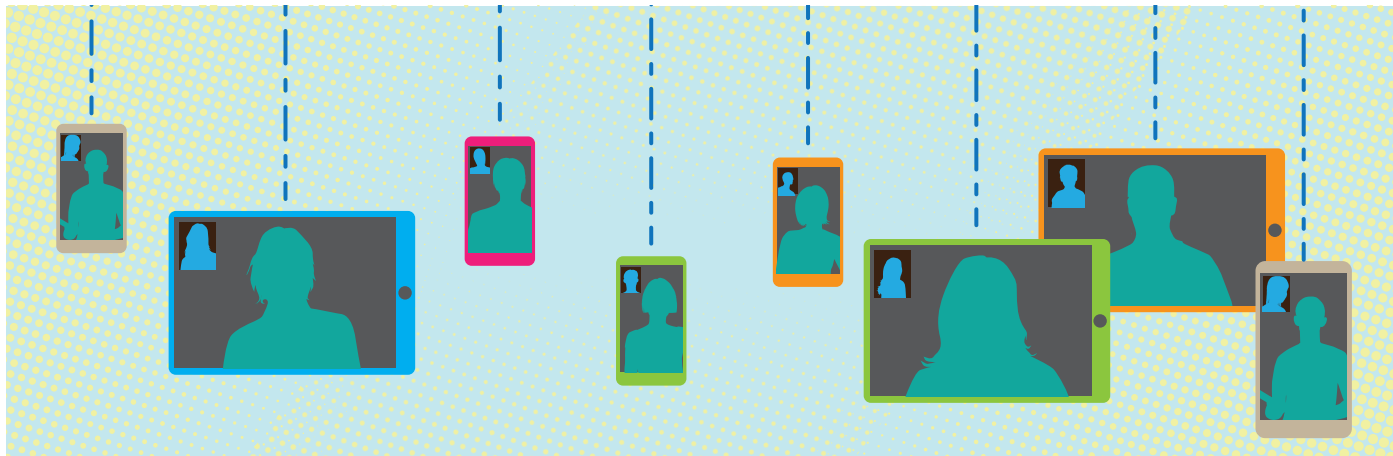


A 'NUDGE' CAN HELP MORE CANCER PATIENTS QUIT SMOKING

More than half of patients who smoke prior to their cancer diagnosis continue to smoke after they are diagnosed. Routine, evidence-based tobacco use treatment reduces the risk of death caused by cancer and other health issues. But only about half of cancer centers identify patient tobacco use and even fewer engage patients directly in a tobacco use treatment strategy. Recently, researchers from Penn Medicine and Children's Hospital of Philadelphia (CHOP) reported in the *Journal of Clinical Oncology* that cancer patients were significantly more likely to receive treatment for tobacco use when "nudges" to provide tobacco treatment were directed at clinicians through the electronic health record.

The findings strengthen the case for using behavioral economics, or targeting predictable patterns in human decision-making to overcome barriers to changes in behavior, to improve outcomes for patients treated for cancer.

"Oncologists are faced with the challenge of responding to each patient's individual cancer," said first author Brian Jenssen, MD, MSHP'16, an assistant professor of Pediatrics at Penn and primary care pediatrician at CHOP, and a member of the Abramson Cancer Center's Tobacco and Environmental Carcinogenesis Program. "We wanted to see if we could develop a strategy for making their lives as easy as possible by providing simple, timely nudges to help patients engage in tobacco use treatment options."



MAKING CARE EASIER BENEFITS THE BOTTOM LINE

Penn Medicine study shows that when health system staff use telemedicine for their own care needs, costs drop significantly.

Even before the COVID-19 pandemic ushered in a new era for telemedicine, virtual visits were a money-saver when health system employees took advantage of them. That's the finding of a recent analysis published in the *American Journal of Managed Care*.

When University of Pennsylvania Health System employees scheduled visits with Penn Medicine OnDemand, a 24/7, co-payment-free telemedicine program, the cost of their care dropped 23 percent compared with in-person visits for the same conditions, the study found—from an average of \$493 per visit in person at primary care offices, emergency departments, or urgent care clinics, to \$380 per visit via the telemedicine program.

"The conditions most often handled by OnDemand are low acuity—non-urgent or semi-urgent issues like respiratory infections, sinus infections, and allergies—but incredibly common, so any kind of cost reduction can make a huge difference," said the study's lead researcher, Krisda Chaityachati, MD, MPH, MSHP, an adjunct assistant professor of Medicine in the Perelman School of Medicine, who previously served as medical director of Penn Medicine OnDemand and now is the physician lead for Value-based Care and Innovation at Verily.

The study analyzed de-identified data from almost 11,000 total visits by Penn Medicine employees who used the company-sponsored insurance plan. The researchers compared 5,413 visits to Penn's OnDemand telemedicine service with 5,413 that were conducted in-person between July 2017 and December 2019, a period chosen to avoid confusion with changes enacted in response to the COVID-19 pandemic.

More Care Can Still Mean Savings

"The program made care easier, and it lowered the costs of delivering each episode of care," said David Asch, MD, MBA, the John Morgan Professor of Medicine and senior vice dean for strategic initiatives in the Perelman School of Medicine, and the study's senior author. "But making care easier makes for more care: People who might otherwise have let that sore throat go without a check-up may seek one when it's just a phone call away."

Despite increased demand for overall 10% more virtual appointments, there was still a decrease in "unit cost" per appointment. The net effect was hundreds of thousands of dollars in savings for the health system. The study authors argued that health systems are uniquely positioned for their telemedicine offerings to drive savings: They can leverage their own providers, make in-system/in-network referrals, and better organize follow-up care.

The public's growing comfort level with using telemedicine in the aftermath of the COVID-19 pandemic could translate to greater use of care at reduced costs, the authors suggest.

"These days, people seem willing to jump in," Chaityachati said. "We made care easier while saving money, and we think the savings could be higher in the future."

A LIVING LABORATORY

From tissue samples to genomic data, the Penn Medicine BioBank is harnessing the power of more than a quarter of a million Penn Medicine patients to make important discoveries that improve care.



Penn Medicine BioBank Co-Directors Marylyn Ritchie, PhD, and Daniel Rader, MD

“Would you like to take part in the Penn Medicine BioBank?” This question now greets any and every adult patient at Penn Medicine when they check in for an appointment, electronically through the myPennMedicine web portal or at clinics across the region. Those who say “yes” go on to be part of a remarkably powerful living laboratory. The Penn Medicine BioBank (PMBB) helps clinicians and scientists improve, formulate, and address key research topics, from genetics to chemotherapy to COVID-19.

The Penn Medicine BioBank recently surpassed 250,000 patient participants, and it continues to grow.

The idea behind the BioBank is relatively, perhaps deceptively, simple: a program that facilitates the preservation of the medical data and specimens—including blood, urine, and other bodily fluid and tissue samples—that are collected as part of routine patient care, then makes them available for research purposes. The result is a rich repository of material and information with nearly countless scientific applications.

“Every clinical interaction gets captured in our electronic health record,” said PMBB Co-Director Marylyn Ritchie, PhD, who is also vice president for Research Informatics for the University of Pennsylvania Health System and director of the Institute for Biomedical Informatics at the Perelman School of Medicine (PSOM) at the University of Pennsylvania. “We don’t recruit people with specific diseases; some have

diseases, some are healthy. This creates opportunities to ask a lot of different research questions.”

New Research Possibilities Connect Discovery to Care

One of the most promising uses of the Penn Medicine BioBank is genetic research.

“Typically with genetic research, you enroll a bunch of people with diabetes, for example, and a bunch of control participants without diabetes, and then you look across their genome to examine the differences between the two,” explained PMBB Co-Director Daniel Rader, MD, who serves as chair of the Department of Genetics and chief of the Division of Translational Medicine and Human Genetics for PSOM. “What PMBB allows you to do is flip that on its head. You now have access to genomic data for many thousands of people, so you can ask the question in reverse. An investigator who’s worked on gene X for the last 30 years may have done work in mouse models or cells, but they can now say, ‘I want to know all the people in the BioBank who have mutations in gene X.’”

When the COVID-19 pandemic threw a wrench into many research operations, PMBB, with its pre-existing collection of specimens and data, facilitated important research in the era of social distancing. “Early in the pandemic, we were

able to pull bio-specimens for virology and immunology that we needed at a time when you couldn't recruit people for studies," Ritchie said. "We already had great specimens as well as nice research and papers from the BioBank."

A biobank's specimens and data are a powerful resource for all sorts of research questions, not just those prompted by a pandemic emergency. They can help identify rare genetic mutations that are connected to disease symptoms, for example, or combinations of relatively common variants that connect with a risk of diabetes.

A single-institution biobank like Penn's is also a crucial starting point for finding opportunities to improve patient care in systematic ways. One example is in pharmacogenomics, or the prescribing of drugs based on knowledge of patients' different susceptibility to their effects, or tendency to have side effects, depending on their genes. "We were seeing a lot of patients carrying DNA variations that would change their response to a given drug," Ritchie said.

A team led by Sony Tuteja, PharmD, a research assistant professor of Medicine, used the BioBank to estimate how many patients had genetic variants that would impact the types of drugs they should receive. As a result, they were able to home in on two classes of chemotherapy drugs that caused major side effects for a subset of patients with a particular genetic variant. They went on to create a pathway for all patients to get timely genetic testing before they receive these drugs. Physicians then have the insight they need to prescribe the right dose of chemotherapy for each patient based on their DNA.

Diversity and Scale

As one of just a handful of single-institution biobanks in the nation, PMBB is unusual. What puts it in a class by itself, however, is the racial, socioeconomic, and medical diversity of its participant population. For example, a total of 17% of PMBB participants—over 40,000 patients—are Black, higher than any other biobank of its kind, leaders said. Broadly speaking, Black patients have been historically underrepresented in clinical research trials. Greater inclusivity in trials—across not just ancestry or ethnicity but also socioeconomic status and other factors—is widely recognized as a critical tool in reducing health disparities and developing treatments and approaches that are more effective for more people.


As PMBB leaders and their colleagues worked in recent years to scale up the BioBank to its current size, one key challenge loomed over the others: a new, universal, online model for soliciting and securing patient consent. This project took on new urgency during the COVID-19 pandemic, with solutions ultimately increasing convenience and enrollments in the BioBank.


Setting up this streamlined electronic consent process was a collaborative process led and piloted at the Abramson Cancer Center by Katherine Nathanson, MD, the Pearl Bassar Professor for BRCA-Related Research and deputy director of Penn Medicine's Abramson Cancer Center, along with


Power in Numbers

The PMBB mainly operates through PennChart, Penn Medicine's electronic health record (EHR) system. Every adult patient visiting one of Penn Medicine's six hospitals or dozens of other clinical sites is eligible to enroll, a process that is now easier than ever thanks to streamlined patient consent processes in myPennMedicine, the system's digital patient portal. Along with physical biospecimens, the BioBank holds a wealth of imaging, survey, and medication data—just about any piece of information captured by the EHR.

With 250,000+ patients enrolled in the Penn Medicine BioBank, the information these patients have provided for research includes:


70,000+
patients' blood and
tissue samples


10 million
diagnoses


44,000
clinical genomic
sequences


6.3 million
medication orders


47 million
clinical visits
documented


3.6 million
procedures

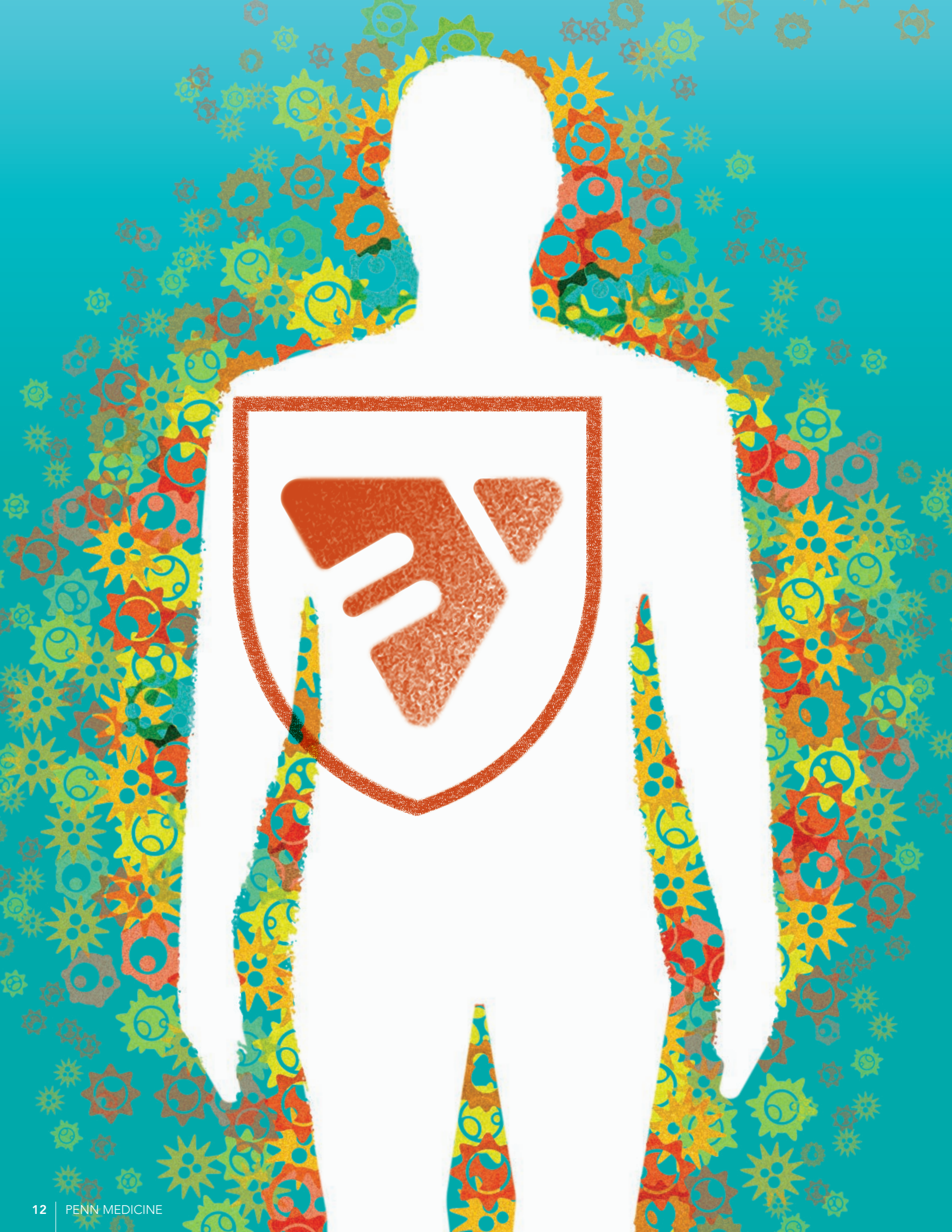
Researchers can use this data and these samples to ask all sorts of questions—from finding biospecimens to study for virology research early in the COVID-19 pandemic, to understanding how often patients are prescribed drugs whose dosing could be affected by their genetic variants.

Ritchie and Rader, as well as Michael Feldman, MD, PhD, now at Indiana University School of Medicine.

Ritchie and Rader envision PMBB participants ultimately topping 1 million. That BioBank evolution—and the scientific breakthroughs it facilitates—continues with each passing day.

"We get new specimens every day," Ritchie said. "Every clinical interaction gets captured in the electronic health record. This infrastructure is organic in that way, and that to me is what makes it a living laboratory. The data will live on for years to come and continue to grow."

— Scott Harris



THE IMMUNE HEALTH FUTURE, TODAY

By Christina Hernandez Sherwood

Breaking the code of the immune system could provide a new fundamental way of understanding, treating, and preventing every type of disease. Penn Medicine is investing in key discoveries and building infrastructure to make that bold idea a reality.

You can imagine the scene as an older gentleman lifts a thick, creamy envelope from his mailbox, seeing his own name written in richly scripted lettering. He beams with pride and gratitude at the sight of his granddaughter's wedding invitation. Yet his next thought is a sober and serious one. Would he be taking his life in his hands by attending the ceremony?


This grandfather lives with primary progressive multiple sclerosis (MS), an autoimmune disorder that he controls with a medicine that depletes his body of the type of immune cells that make antibodies. So while he has completed his COVID-19 vaccine course, his immune system function isn't very strong—and the invitation has arrived at a time when COVID-19 is still spreading rapidly.

"In the past, all we could do was [measure] the antibody response," said Amit Bar-Or, MD, the Melissa and Paul Anderson President's Distinguished Professor in Neurology at the Perelman School of Medicine, and chief of the Multiple Sclerosis division. "If that person didn't have a good antibody response, which is likely because of the treatment they're

on, we'd shrug our shoulders and say, 'Maybe you shouldn't go because we don't know if you're protected.'"

Today, though, Bar-Or can take a deeper dive into his patients' individual immune systems to give them far more nuanced recommendations. A clinical test for immune cells produced in response to the COVID-19 vaccine or to the SARS-CoV-2 virus itself—not just antibodies—was one of the first applied clinical initiatives of a major new Immune Health® project at Penn Medicine. Doctors were able to order this test and receive actionable answers through the Penn Medicine electronic health record for patients like the grandfather with MS.

"With a simple test and an algorithm we can have a very different discussion," Bar-Or said. A test result showing low T cells, for instance, would tell Bar-Or his patient may get a meaningful jolt in immunity from a vaccine booster, while low antibody levels would suggest passive antibody therapy is more helpful. Or, the test might show his body is already



well primed to protect him, making it reasonably safe to attend the wedding.

This COVID-19 immunity test is only the beginning.

Physicians and scientists at Penn Medicine are imagining a future where patients can get a precise picture of their immune systems' activity to guide treatment decisions. They are working to bring the idea of Immune Health to life as a new area of medicine. In labs, in complex data models, and in the clinic, they are beginning to make sense of the depth and breadth of the immune system's millions of as-yet-undeciphered signals to improve health and treat illnesses of all types.

Penn Medicine registered the trademark for the term "Immune Health" in recognition of the potential impact of this research area and its likelihood to draw non-academic partners as collaborators in its growth. Today, at the south end of Penn's medical campus, seven stories of research space are being added atop an office building at 3600 Civic Center Boulevard, including three floors dedicated to Immune Health, autoimmunity, and immunology research.

The concept behind the whole project, said E. John Wherry, PhD, director of Penn Medicine's Institute for Immunology and Immune Health (I³H), "is to listen to the immune system, to profile the immune system, and use those individual patient immune fingerprints to diagnose and treat diseases as diverse as immune-related diseases, cancer, cardiovascular disease, Alzheimer's, and many others."

The challenge is vast. Each person's immune system is far more complex than antibodies and T cells alone. The immune system is made of multiple interwoven layers of complex defenders—from our skin and mucous membranes to microscopic memory B cells that never forget a childhood infection—meant to fortify our bodies from germs and disease. It is a sophisticated system that learns and adapts over our lifetimes in numerous ways, and it also falters and fails in some ways we understand and others that remain mysterious. And each person's intricate internal battlefield is in some way unique.

The immune system is not just a set of defensive barricades, either. It's also a potential source of deep insight about a person's physiological functioning and responses to medical treatments.

"The immune system is sensing and keeping track of basically all tissues and all cells in our body all the time,"

Wherry said. "It is surveying the body, trying to clean up any invaders and restore homeostasis by maintaining good health."

"Our goal is to essentially break the code of the immune system," said Jonathan Epstein, MD, executive vice dean of the Perelman School of Medicine and chief scientific officer at Penn Medicine. "By doing so, we believe we will be able to determine your state of health and your response to therapies in essentially every human disease."


Untangling Millions of Messages

Measuring and making sense of the immune system is a crucial step in Penn Medicine's Immune Health platform.

An individual's immune system—constantly adapting and responding to its environment—is sending millions of messages, such as a spiked fever during an infection. Most of these messages are still confounding to researchers. The challenge is to find ways to untangle those numerous signals in ways that broaden and deepen physicians' understanding of patients' health and response to disease.

Researchers across Penn Medicine, with the backing of I³H, are endeavoring to do so by tracking patients' immune responses across the disease spectrum and, in some cases, partnering with informatics experts to use advanced artificial intelligence algorithms and machine-learning models to predict outcomes. Among the efforts: studying whether dietary interventions could enhance the efficiency of some cancer treatments, using immune signals to help determine MS treatments, and even testing a cancer prevention vaccine.

"The immune system operates very much like the nervous system in monitoring just about everything that goes on physiologically in our body," Wherry said. "Unlike the nervous system, the immune system is mobile. Cells move around, survey different tissues, interpret their environment and then respond or, importantly, choose not to respond. In some ways, this cell movement is our opportunity. The blood system is the highway of the immune system, but also allows easy sampling, of at least a subset, of the cells in the immune system. If we know how to listen to the language of the immune system, we can use it to tell us about physiological changes that may not be obvious otherwise."

A man and a woman are standing outdoors in front of a modern building with large glass windows and metal panels. The man, on the left, has a beard and is wearing a dark blue blazer over a white shirt and khaki pants. The woman, on the right, is wearing glasses, a black top, a grey plaid blazer, and black pants. They are both smiling at the camera. The background shows the building's facade and some greenery in the foreground.

E. John Wherry, PhD, directs Penn Medicine's Institute for Immunology and Immune Health, working with Allie Greenplate, PhD, the institute's director of Strategic Alliances and Operations.



Seven additional stories of research space are being added atop 3600 Civic Center Boulevard, an office building at the south end of Penn's medical campus in University City that opened just five years ago. Three of the new floors will be dedicated to Immune Health, immunology, and autoimmune research.

Leading the Way in Cancer Immunotherapy and COVID-19

Penn Medicine arrived at this moment due to a combination of leadership in immune-based discoveries in cancer and recent advances using immune health insights to treat patients who were severely ill with COVID-19.

Much of Wherry's own research for years had emphasized understanding patients' immune responses to cancer and to cancer treatments that work by activating the immune system. Other Penn Medicine researchers—notably Carl June, MD, the Richard W. Vague Professor in Immunotherapy, along with many other collaborators—were pioneers of chimeric antigen receptor T cell (CAR T) cancer therapy, in which a patient's own immune cells are reprogrammed to fight cancer cells. Once the first CAR T therapy was approved by the Food and Drug Administration in 2017, Robert H. Vonderheide, MD, DPhil, director of Penn Medicine's Abramson Cancer Center and an immunotherapy researcher himself, said the Penn immunology community felt the moment had truly arrived to look for the clinical impacts they could have with the immune system beyond cancer.

"We realized there is this huge discrepancy between what we were measuring routinely in a tube of blood from a patient versus the billions of parameters that we can measure with the same tube of blood in a research lab 500 yards away," Vonderheide said. "That was the start of immune health."

The field truly began to explode at Penn three years later when COVID-19 struck. As doctors around the world were scrambling to find the best ways to treat severely ill patients, Wherry, who is also chair of Systems Pharmacology and Translational Therapeutics, thought his research approach for cancer patients could be applicable to combatting the new virus. His study of cancer patients' immune signals to predict their response to certain treatments accelerated care for patients who were racing the clock.

So when, early in the pandemic, critical care physicians were struggling to effectively treat hospitalized COVID-19 patients, Wherry jumped into action. Leveraging the work already being done on a smaller and slower scale in cancer, Wherry and Michael Betts, PhD, a Penn microbiologist studying immunology in human infection and diseases, established the COVID-19 Processing Unit to use patients' individual immune responses to the virus to help inform their treatment. In the clinic, they partnered

with Nuala Meyer, MD, MS, a critical care physician treating patients with COVID-19 in the intensive care unit. Meyer headed a laboratory with experience quickly enrolling critically ill patients into a clinical trial to study sepsis, and she was well versed in how immunology could fill in gaps in clinical knowledge.

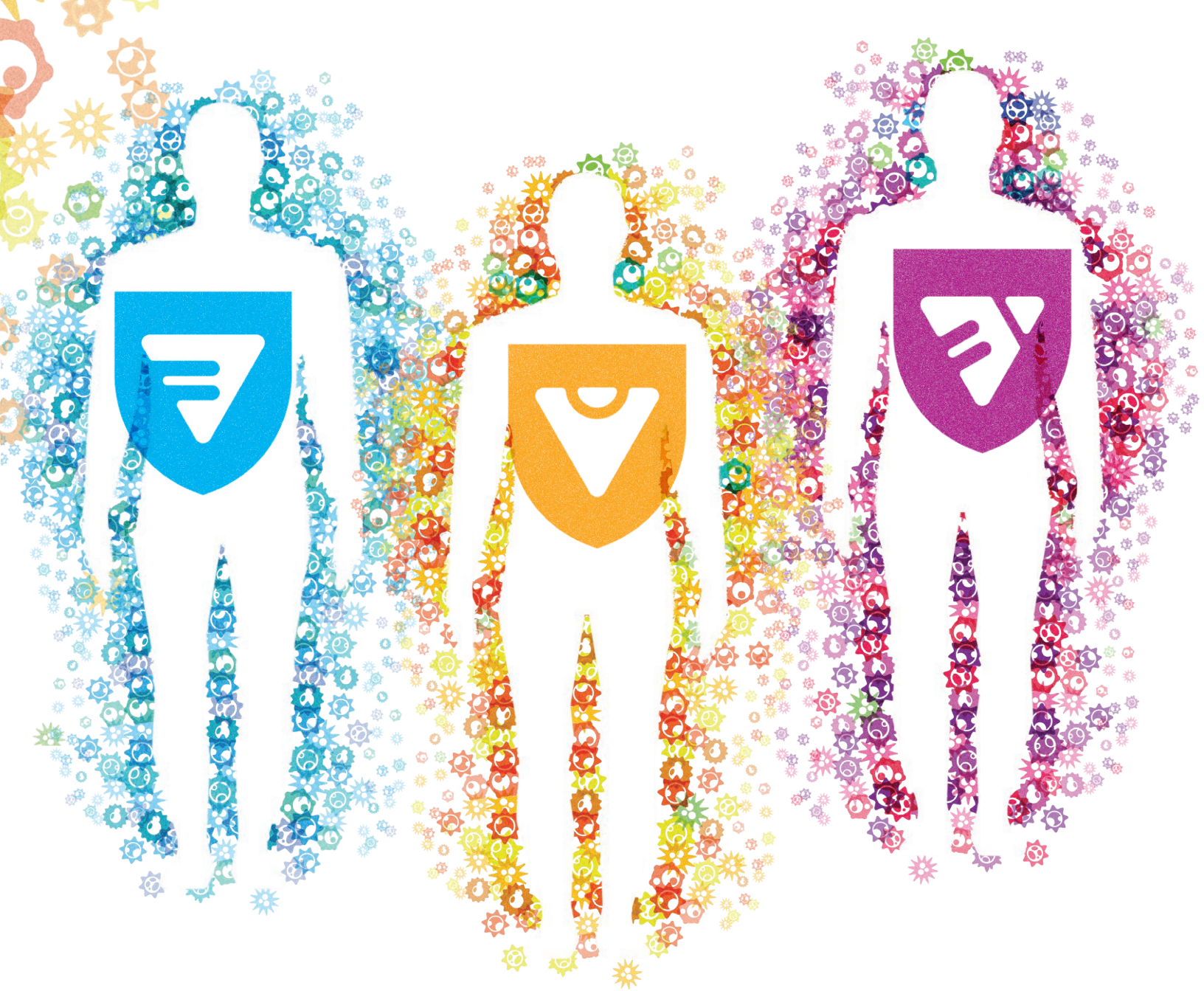
For Wherry and others in Penn's immunology community, the pandemic presented a once-in-a-lifetime opportunity to show how their work could extend far beyond cancer. "We've been saying for a number of years that the immune system matters, and that it should be a key to helping to diagnose [and treat] diseases," he said. "If there was ever an opportunity to put our money where our mouth is and test whether what we've been saying is true, this is when we have to do it."

The team of more than two dozen highly trained researchers who made up the COVID-19 Processing Unit first processed peripheral blood and plasma samples from hospitalized patients with COVID-19 to extract immune cells. Then, they ran an assay called flow cytometry to measure the activation of the 30 or so immune cell types in the blood, more or less evenly divided into innate—or hardwired—cells, and adaptive cells, such as T cells and B cells (the cells that make antibodies). Because each immune cell type can exist in various forms of activation and anywhere throughout the body—for instance, a single B cell from the lungs of a person who recently received the COVID-19 vaccine might be very active, while a B cell from an unvaccinated person's lymph nodes might be in a resting state—the team produced a data set of thousands of features of each patient's immune system.

Each patient's immune response was charted on an immune map with the responses of other hospitalized COVID-19 patients, which is when the team noticed some surprising, and important, patterns. Unlike in most other viruses, the COVID-19 patients' immune systems were not responding to the virus in a uniformly predictable way. Instead, the patients' immune activity patterns seem to cluster in a few distinct groups. They published these findings in *Science* in July 2020.

One group of patients was characterized by their overactive immune systems—with severe inflammation, high levels of activated T cells, and a large number of plasmablasts (a type of B cell actively producing antibodies). Another group had what doctors deemed an appropriate viral response to COVID-19: Their immune systems activated to fight the virus, but not to the extent that the immune system was causing harm. The third group had a low, almost negligible, immune response.

The first group—those with overactive immune responses—were likely to see the best results from steroid



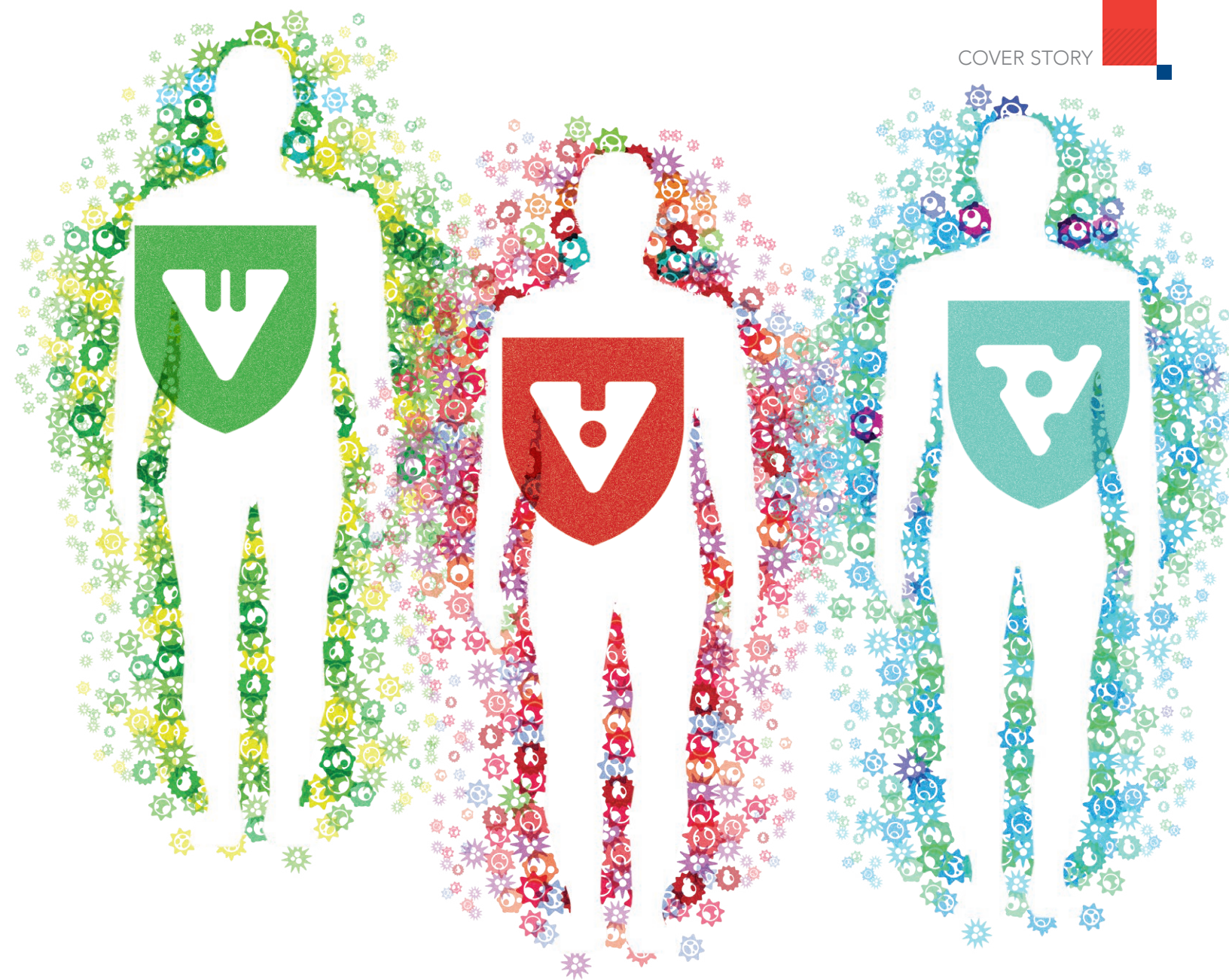
treatment, while the group with little to no immune response might not see such benefits from steroids, which would further suppress their immune systems. It was a finding consistent with subsequent clinical trials that helped the overwhelmed front-line physicians make informed treatment decisions for their patients amid a global pandemic.

In one memorable instance, Meyer called the COVID-19 Processing Unit with an urgent request on a Friday afternoon: Could the team map the immune state of a patient whose case was confounding physicians? By Sunday morning, the COVID-19 Processing Unit told Meyer that her patient mapped to the hyperactive immune response group.

“It gave us a lot of insight about that patient’s immune status,” Meyer said. “It was convening the right minds... to give us a sense for which features of this patient’s immune system seemed out of balance. It shows the potential for this type of work.”

For a single patient, the COVID-19 Processing Unit team’s analysis—along with a review of the patient’s clinical data—took 12 to 24 hours. “We had a team of about 6 to 10 people working in shifts 24 hours a day,” Wherry said. “To make immune health functional from a clinical perspective, this had to be real-time.”

In just three months, the COVID-19 Processing Unit analyzed the immune responses of some 750 patients. “It was team science done in a new way,” said Allie Greenplate, PhD, director of Strategic Alliances and Operations for I³H and an adjunct assistant professor of Systems Pharmacology and Translational Therapeutics, who was then part of the COVID-19 Processing Unit as a post-doctoral researcher in Wherry’s lab. “Looking in detail at the immune system and discovering something about a person’s biology [has been done before]. What was unique was the ability to return the results to a physician in real time. To do it at the scale we did, I think, is still something that hasn’t been done elsewhere.”



Immune Health Fingerprints

The methods the Penn Medicine teams put in place to analyze individual patients' blood and plasma samples for their immune cells' activity and map those patterns into groupings had clear implications for patients beyond COVID-19, and even beyond cancer, where immune-based treatments are already most advanced. Once the pace of "emergency response science" slowed down, Wherry said the COVID-19 Processing Unit team that saw potential in scaling up the systems they had built.

"The core infrastructure of immune health is disease agnostic," he said. "The immune landscape analysis that we applied in COVID, we can apply to cancer, to autoimmunity or allergy. We get to look at all of those fingerprints across all patients."

Researchers and clinicians see potential to better understand connections across conditions by creating large-scale immune

landscape maps, like the one used to understand how different patients responded to COVID-19, by categorizing individual patients' "immune fingerprints" into immune subgroups across diseases. For instance, Wherry said, the weakened immune system of a cancer patient is, in many ways, actually the inverse of the overactivated immune system of a person with an autoimmune disorder. "There's this subgroup of cancer patients that didn't respond to this immune-stimulating drug," he said. "Well, there are some autoimmune patients who fall in that same category. Maybe the drugs that didn't work in cancer will now work in autoimmunity."

Among the first steps to realizing this ambitious vision was to streamline the process used during the pandemic into a more scalable and sustainable system. The I³H team simplified assays, standardized workflows, added support, organized teams, and embedded quality control into the process. Another change: Without the urgency of COVID-19,

researchers could relax their timelines. “We could return results on the scale of days to weeks,” Wherry said, “and still be real-time for the patients to use that information for treatment choices.”

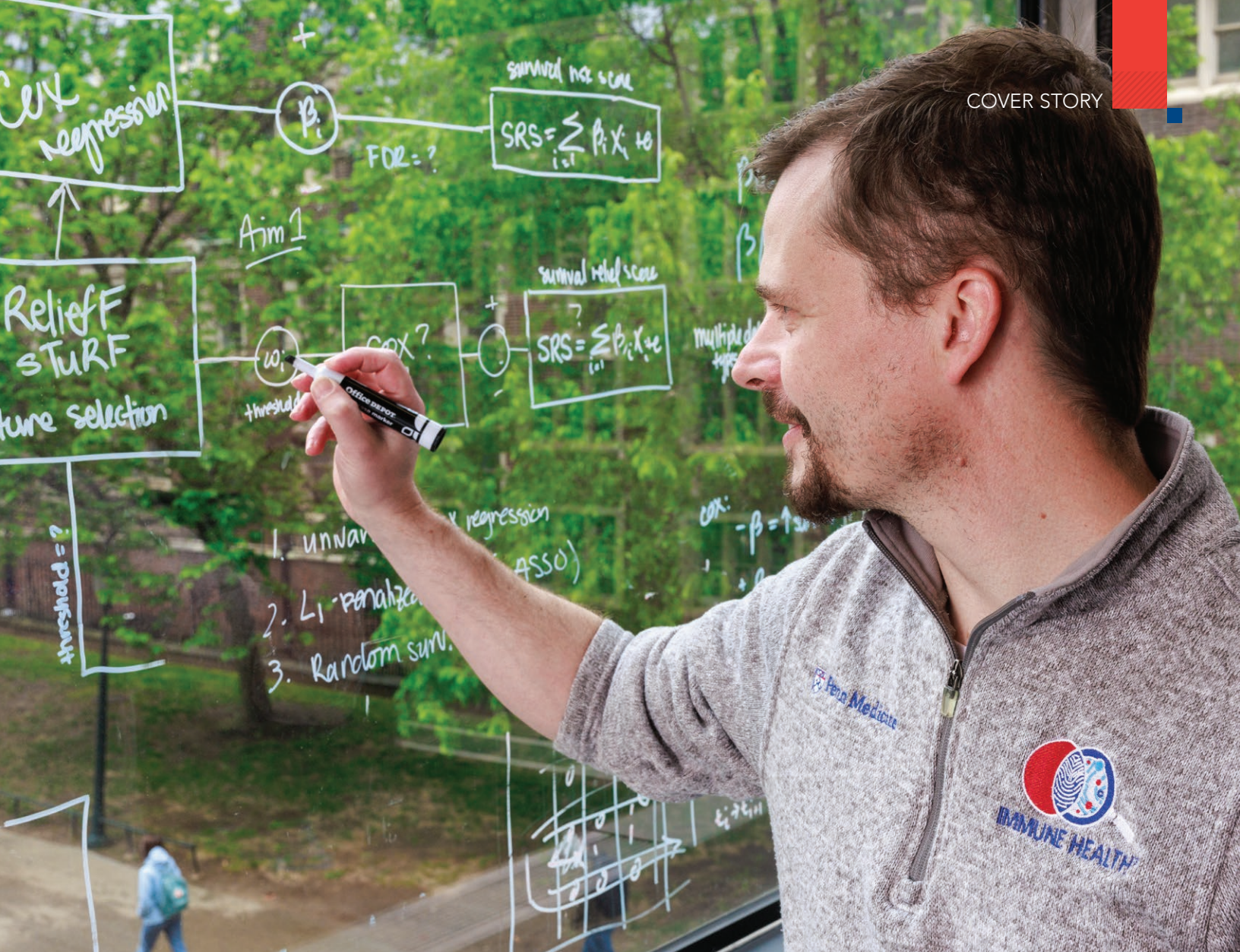
That’s how it worked for Bar-Or’s work in COVID-19 immunity, where he led a key study published in *Nature Medicine* in 2021 showing that MS patients taking drugs that suppressed their immune systems’ production of antibodies still gained robust protective T cell responses to the COVID vaccines. His next I³H partnership will focus on getting the patients the right MS treatments for their own body’s immune type. There are a number of FDA-approved therapies available for MS, but doctors have little guidance about which work best for individual patients. Mapping out how different patients respond to the various treatments could help doctors better target their therapies—just as they did with extra COVID-19 protection.

Autoimmune diseases like MS are among I³H’s first targets because they are fundamentally diseases of the immune system itself. Autoimmune diseases, including rheumatoid arthritis, lupus, and Graves’ disease, affect almost three times the number of people with cancer but

receive seven times less funding, Greenplate said. At Penn, however, generous gifts totaling \$60 million from Judy and Stewart Colton in 2021 and 2022 established and accelerated the Colton Center for Autoimmunity, which will partner with I³H. Penn researchers are already making advances in multiple approaches that arm the immune system to fight autoimmune disorders, such as a modified version of CAR T therapy for the autoimmune skin condition pemphigus vulgaris and for myasthenia gravis, a neuromuscular condition.

Another researcher is working to understand long COVID—perhaps the world’s newest autoimmune disease. With blood samples offering few clues about why some people develop long COVID, researchers in the laboratory of Michela Locci, PhD, an assistant professor of Microbiology at the Perelman School of Medicine, are adapting a tool from basic science to a question with clinical implications. Locci’s lab uses a fine needle aspirate (FNA) method to collect samples from the cervical lymph nodes of COVID-19 survivors and study their ongoing immune responses in the lymphoid





tissue. A closer look at these immune cells might help clarify what's causing some survivors to develop long COVID.

Locci said she believes the study is the first attempt to use FNAs to study immune responses to long COVID infection in humans. "I could not think of a better place to conduct immune health-related studies than Penn," she said. "This increased focus on immune health will act as a propeller to facilitate human immunology studies with potential to guide clinical decisions."

Creating Tools for Immune Health Research

Building new tools and adapting existing ones to the challenges of immune health are among the most crucial aspects of the work.

Penn Medicine patients have an important role to contribute to immune health research. Greenplate is hoping to

make it easy for many patients to get involved by expanding on the model of the Penn Medicine BioBank, which already aggregates a wide range of clinical data from nearly a quarter of a million Penn patients along with tens of thousands of biological samples from those patients, for use in observational research. The Penn Medicine BioBank was established in 2012 but has grown rapidly in recent years since the option to consent to participate was built into the electronic patient portal for every Penn Medicine patient at every location, during the COVID-19 pandemic. Patients who opt into participating in the Penn Medicine BioBank have extra blood collected the next time they are scheduled for a blood draw in the course of their care, as well as any leftover tissue from biopsies saved for research. To date, about 44,000 of these patients have genomic data associated with their (anonymized) clinical histories, including diagnoses, visits, and clinical test results, available for researchers to study using the BioBank. (See related story on p. 10.)



"I would love to see not only your genetic information, but your immune profile as part of your medical record," Greenplate said.

But first there are regulatory considerations to address before bringing research data to patients in a clinical setting. Research laboratories, where immune health breakthroughs are made, don't have the clinical laboratory certification needed to return their data into patient's medical records,

Greenplate said. One option currently being studied by Angela Bradbury, MD, a Perelman School of Medicine associate professor of Hematology/Oncology and Medical Ethics and Health Policy, is asking patients if they are willing to receive research data.

So, while Greenplate envisions someday giving patients access to their immune health testing data inside their electronic medical records, "We'll probably start on a smaller

The Immune System's All-Stars

The immune system is made up of dozens of types of cells that surveil for threats, communicate with one another, and defend and protect the body in a variety of ways.

Broadly Defensive INNATE IMMUNE CELLS

This hardwired part of the immune system is quick to respond to injuries, viruses, bacteria, and more.



NEUTROPHILS and **MACROPHAGES** are like patrol officers responding first to an immediate threat. Both types of cells destroy viruses and bacteria soon after they are detected. Macrophages also release molecules called cytokines that cause inflammation and make it easier for more immune cells to reach the area.



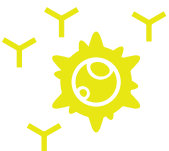
DENDRITIC CELLS act like crime scene investigators. They break invader cells apart and bring their uniquely detectable component molecules and pieces, or antigens, back to the adaptive immune system to learn more about the enemy.

Specialized Learning ADAPTIVE IMMUNE CELLS

The adaptive immune system is trained against specific threats, and also learns and retains a memory of antigens it has encountered before.



T CELLS are the body's specialized immune soldiers. They are a type of white blood cell that will destroy the body's own cells when necessary if it detects that cell is infected or damaged. They can also direct the activities of many other parts of the immune system.



B CELLS multiply in high numbers when fighting off an infection or invader, and produce antibodies, which are specialized protein molecules that are custom-made by the body to latch onto and neutralize or destroy viruses, toxins, and any foreign molecules that are perceived as a threat.

scale with research data,” she said. “Then, depending on the response, consider whether it’s worth the cost of making it an insurance reimbursable test.”

Making sense of that research data to arrive at useful insights for patients is itself another large area still scaling up. The informatics team at I³H is building an infrastructure of data management, sharing, and analysis that will make their discoveries not only possible, but also actionable. Dokyoon Kim, PhD, an assistant professor of Informatics in Biostatistics and Epidemiology, does work that integrates electronic health record information with various biomedical data sources such as biobanks, medical imaging, and different types of genomics and other “multi-omics” data, to predict disease outcomes. Now, as I³H associate director of Informatics, Kim is leveraging artificial intelligence to further enhance his clinical risk prediction models. “If we have well-trained multimodal AI models,” Kim said, “we could bridge the gap between clinicians and data scientists, opening doors to broad applications including personalized medicine.”

Building those immune health data and prediction models into a standardized and scalable database is a multidisciplinary collaboration—encompassing data scientists and software engineers, immunologists, and phlebotomists—led by Joost Wagenaar, PhD, also an assistant professor of Informatics. The goal is a comprehensive data ecosystem combining multimodal clinical and research data that is easily accessible. Imagine the power of a database, Wagenaar said, that enables a physician to pull a quick analysis of patients on a specific medication or a scientist to build a cohort of information for drug discovery.

“What if all of the data is at your fingertips, and all you have to do is ask the right question?” Wagenaar said. “Would we be able to accelerate research? Would we be able to get to cures for patients faster? I think the answer is yes. Immune health is an extremely good use case where we can demonstrate that.”

Using Immune Health to Guide Medical Treatment

The ultimate goal of the work scientists and informaticists are doing in the lab is to untangle the thousands of immune signals into clear clinical messages. It’s only then that immune health data will be truly useful for doctors and patients.

Greenplate imagines “immune boards,” modeled on cancer’s tumor boards, that would bring together physicians and scientists to examine a patient’s immune health data and make decisions on how to move their care forward.

The I³H informatics team is also working to develop a streamlined Immune Health dashboard that can integrate with

the electronic medical record. They have already created an Immune Health tab in Penn Medicine’s electronic health record that provides a home for test orders and test results like the COVID-19 immunity test. Their goal is to give clinicians easy access to immune health insights that offer meaningful guidance for patient care, as they work to identify and validate more of these measures.

“We don’t want to put those 100,000 features of your immune system in the electronic medical record,” Wherry said. “We want to find out which two or so features can tell whether you’re going to respond to a new MS drug better than one of the other drugs that could be used. That’s the actionable choice.”

In cancer—where immune health has a long history—some groundbreaking developments are perhaps close at hand. The field as a whole has made rapid advancements in recent years thanks to the explosion of immunotherapy research. Those developments, combined with mRNA and other gene therapy technology, bring the possibility of a cancer prevention vaccine within reach, Vonderheide said. One in the works at Penn is for individuals at high risk for breast cancer because of their genetic mutations. “There’s an active clinical trial using DNA to treat those individuals,” he said, “and boost their immune systems to intercept and prevent cancer.”

Vonderheide’s own research is showing the potential of treatments customized to an individual patient’s immune health. His team published a paper in *Nature Medicine* last year showing that certain patients with newly diagnosed metastatic pancreatic cancer responded extremely well to different combinations of chemotherapy and immunotherapy treatment. Depending on their immune health baseline, some patients responded well to combination A, while others found success with combination B.

Vonderheide’s team is following up on this finding with a forthcoming prospective study—selecting each trial participant’s treatment according to the predicted outcome. “That’s precision oncology,” he said. “We do that all the time, but mostly with the genetic sequence of the tumor.” This time, though, it’s entirely based on the patient’s immune system.

“This is really where the rubber meets the road,” he said. “We meet a patient and we say, ‘Based on your immune health, we think this therapy is best for you.’” □

► Find more information online at PennMedicine.org/magazine/ImmuneHealth.

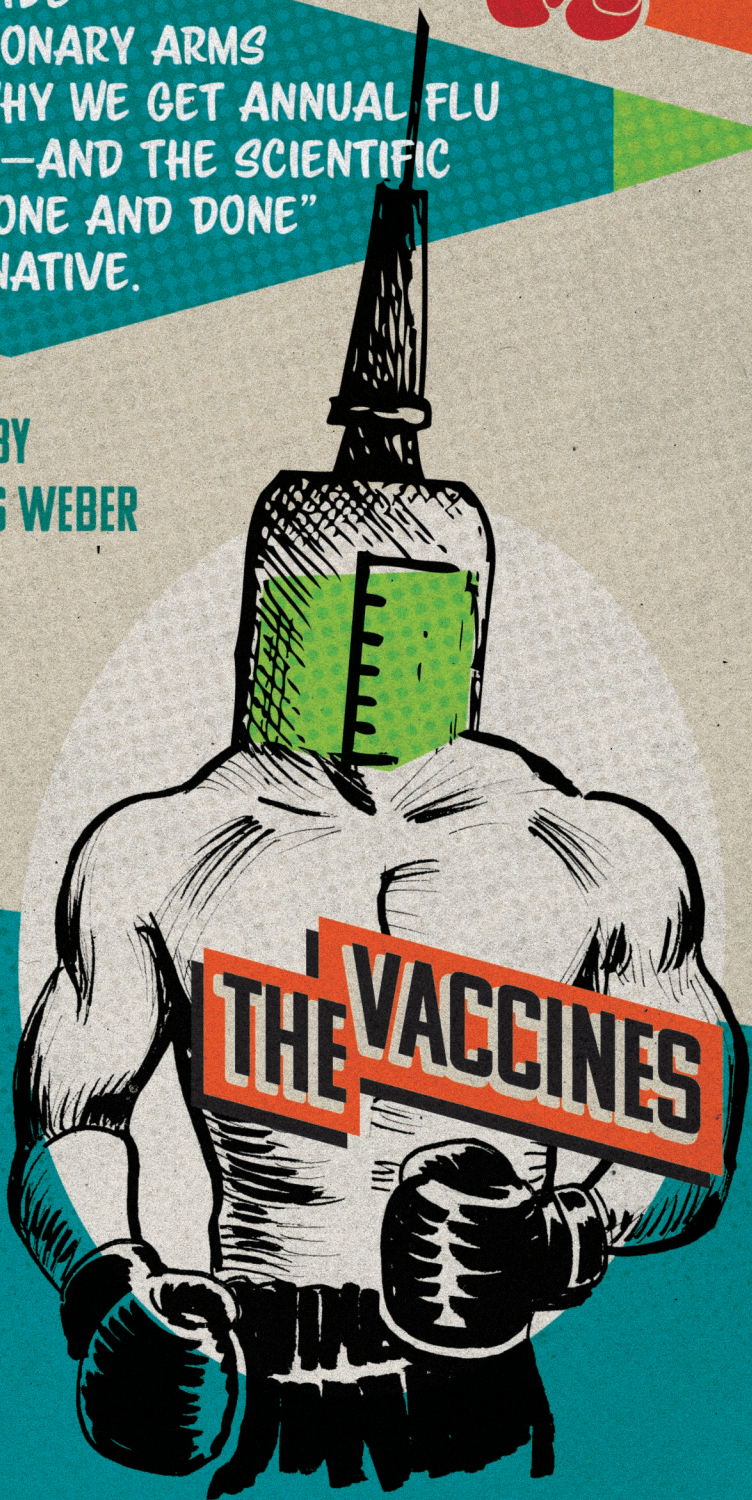
VIRUSES vs. VACCINES

THE PERENNIAL REMATCH



INSIDE
THE EVOLUTIONARY ARMS
RACE THAT EXPLAINS WHY WE GET ANNUAL FLU
AND COVID VACCINES—AND THE SCIENTIFIC
QUEST FOR A “ONE AND DONE”
ALTERNATIVE.

BY
TOMAS WEBER



The worst pandemic in the last century was caused by a coronavirus, which came as a surprise to many. Influenza was long thought to pose a greater risk. “Before 2020,” said Scott Hensley, PhD’06, a professor of Microbiology at the Perelman School of Medicine, “if you had asked any virologist what virus they worried about the most, the answer would have been almost exclusively flu.”

It would have been a reasonable assessment. Flu is a devious killer. Globally, it causes around 400,000 deaths each year. While we have decades of experience creating vaccines against the influenza virus, flu, ever-shifting, still catches us on the back foot each season. Year after year, it ducks and weaves to evade human ingenuity.

The viral strains responsible for pandemic outbreaks are generally new ones that first infected humans from an animal host—and these jumps can be hard to predict. Still, every year, we rush to make a new flu vaccine against strains that are already known to be circulating in human populations. Most flu vaccine components are produced in fertilized chicken eggs. The process takes between six to eight months—so slow that it relies on some guesswork about which of the circulating strains might dominate during the upcoming flu season. Representative strains are chosen and injected into fertilized eggs, where the viruses multiply, and are then extracted, inactivated, and purified. The vaccine must then be tested, packed, and distributed.

At the culmination of these annual formulations, over half of all adult Americans get a new flu vaccine every season.

Why, though, do we have to repeatedly protect ourselves against new variants of a familiar virus? From just a handful of shots in early childhood, we have managed to beat back other viruses, including polio, hepatitis, measles, and rubella. Whether we received flu vaccines in childhood or not, most

of us caught flu at an early age, and we mounted very good antibody responses to the virus.

The same relatively unusual pattern of annual vaccination may become the norm with SARS-CoV-2, the virus that causes COVID-19. Earlier this year, officials in the Centers for Disease Control and Prevention recommended that updated booster vaccines be given each year, particularly to high-risk groups. (Compared with flu, though, the manufacturing process is likely nimbler, given the greater flexibility of the mRNA platform.) Still, only about 20% of U.S. adults have received the 2022 bivalent booster shot against the Omicron variant, with an updated formulation expected for fall 2023 to help manage COVID-19 as an endemic disease. Why do new viral variants keep dodging our blows? Why can’t we seem to land a knockout punch, taking care of flu and COVID-19 once and for all?

Why Do We Need New Vaccines Year After Year?

One common explanation for why we need repeated annual flu vaccines, and why we may need periodic boosters against COVID-19, is that these viruses mutate rapidly. And it’s true: They are “master shapeshifters,” said Hensley. As they replicate, the viruses acquire genetic changes that trigger alterations to their proteins. But the slippery, fast-evolving nature of flu and coronaviruses, Hensley said, is not enough to explain how they keep managing to fight off our assaults.

Other viruses mutate quickly, too, but pose much less of a threat. The measles virus, for instance, is constantly acquiring random changes, but its mutations do not usually permit it to get past the defenses most of us have from the



Scott Hensley, PhD, studies “original antigenic sin,” or the tendency of our immune systems to retain immunity that is specifically attuned to the earliest strains of a virus, such as influenza, that we were exposed to.

measles vaccine. With flu, though, and potentially also with COVID-19, we are constantly being reinfecting. What explains it?

The answer, Hensley said, is that flu and coronaviruses seem to be very tolerant of change. For a virus to change and still be capable of infecting a host population, the virus must maintain critical functions such as attaching to host cells. A high rate of change must be combined with great tolerance for transformation. Most viruses aren’t like that at all.

“With many viruses, when mutations crop up, they just kill the virus, and that’s the end of the show,” Hensley said. Not so with flu and coronaviruses. “Flu and SARS-CoV-2 have this uncanny ability to acquire mutations and still be able to replicate efficiently,” he said. “These viruses evolve to avoid human immunity while maintaining functions critical for viral replication.”

It’s natural selection at work: Certain mutations help the virus to gain a stronger foothold, enabling it to better replicate and spread, evading the immunity human populations

had previously picked up from exposure to older varieties and vaccines designed for other strains. But there is another reason why evolution can knock back our best efforts to fight these viruses. Vaccines are designed to protect us from pathogens that we already know about and that are circulating in humans. They don’t usually protect us from brand-new strains that come from animal populations.

“Most novel viruses that emerge in human populations are zoonotic,” meaning transmitted from animals, said Louise Moncla, PhD, an assistant professor of Pathobiology at the Penn School of Veterinary Medicine, whose research is focused on understanding what characteristics of avian flu strains affect their potential to infect humans.

Major flu pandemics, including the 1918 pandemic and 2009’s H1N1 outbreak, have been caused by cross-species transmission. Coronaviruses, too, are common in other animal species and sometimes spill over to humans, as was the case with SARS-CoV-2. But it is not easy for a zoonotic virus to successfully infect humans and transmit among us, Moncla explained. The factors which may cause it to do so are poorly understood, making cross-species transmission perilously hard to predict—meaning it’s difficult to plan ahead for human vaccines against these animal viruses.

A Trick of the Immune System Memory

There is another reason why flu is so good at sneaking around our defenses when it so often mutates. Immunologists call it “original antigenic sin,” and scientists at Penn are helping to deliver us from it.

Our immune systems have a long memory. Our earliest childhood infections provide us with memory B and T cells that stick with us for life. This is a good thing. It allows us to retain immunity over an entire lifespan. But our immunological memory can also cause serious problems when the opponent our immune system encounters looks a little bit different than the one it is primed to remember.

Our immune systems are shaped by the very first flu variant we were exposed to as children. “Viruses circulating in the late 1970s, when I was born,” said Hensley, “are quite different from viruses that were circulating about a decade ago, when my kids were born. So my kids have different immune memory than me.”

Our immunological memory continues to influence our responses to fresh variants, in the form of either vaccines or live viruses. The immune responses of different individuals, then, might target different parts of the virus. “My kids and I might mount the same number of antibodies against this year’s flu vaccine strain. But my antibodies likely target a different region of that vaccine compared to my kids.”

The immune system targets those regions of the antigen that were imprinted at the time of the original exposure. Immune responses, then, can be dangerously narrow. With all your eggs in one basket, Hensley said, “you may be one [viral] mutation away from becoming susceptible again.”

Original antigenic sin also affects our response to COVID-19. Our first exposure to SARS-CoV-2, or to a COVID-19 vaccine designed to mimic the original pandemic strain, could potentially make it harder to pivot to new strains. Although Omicron-targeted booster vaccines offer strong protection, there is some evidence that immune imprinting may have reduced their effectiveness.

To shed light on how susceptibility differs across individuals, Hensley is working closely with Laurel J. Glaser, MD, PhD, an assistant professor of Clinical Pathology and Laboratory Medicine at the Perelman School of Medicine. For the last few years, Glaser and Hensley have been collecting virus

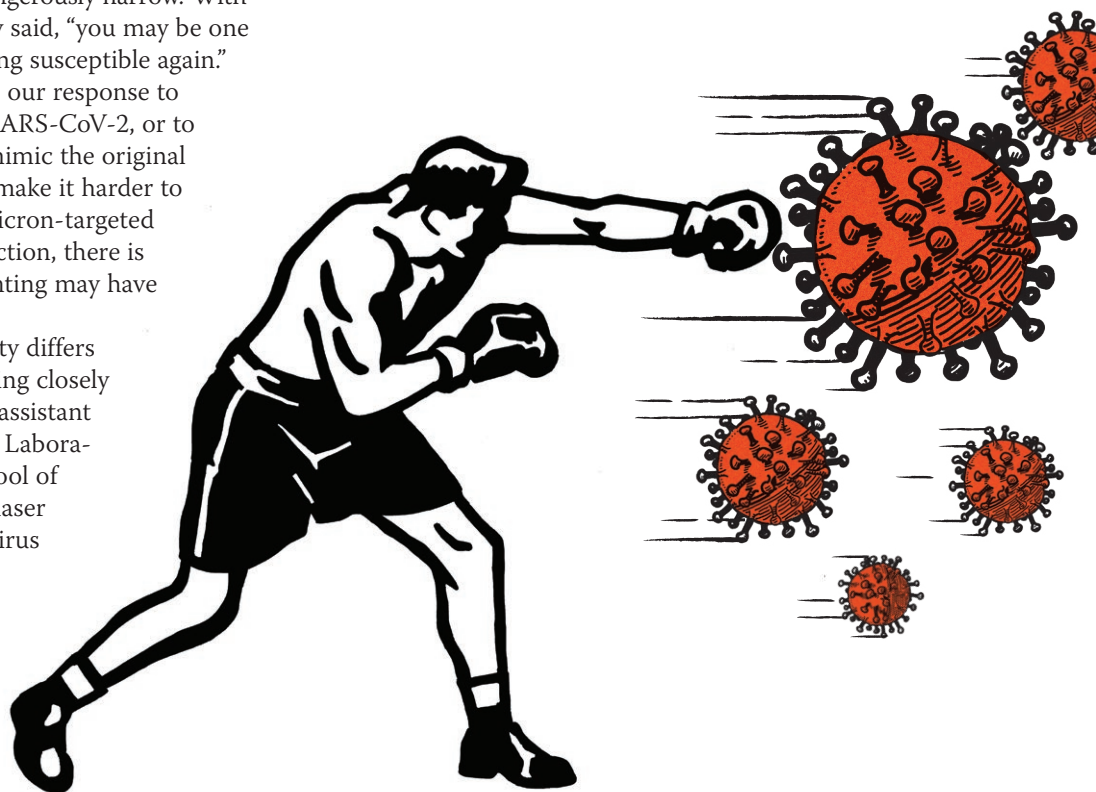
and serum samples from flu-infected patients at the Hospital of the University of Pennsylvania (HUP).

They are completing studies to determine if influenza viruses are evolving to evade antibody responses that are unique to each individual. “The question,” Hensley said, “is simple. If I get infected with the flu virus and show up at HUP, do I have an antibody response that is unique to me, that has allowed that infection?”

This work is uncovering how individuals respond to different flu variants in distinct ways, and they have discovered a similar pattern with COVID-19. Evidence is emerging that different people have specific susceptibilities to new variants of SARS-CoV-2 due to immune imprinting. “Specificity,” said Hensley, “means everything when it comes down to a virus that is rapidly changing.”

Armed with knowledge of different antibody specificities, Hensley anticipates that in the future it may be possible to predict an individual’s susceptibility to emerging variants based on their year of birth and their immune history. Different people may even get different vaccines, he said, “to fill the immunological gaps each of us may have.”

But personalized vaccines, though a real possibility, are not the ultimate goal for Hensley and other Penn Medicine scientists. Their vision? A single, universal flu vaccine, offering equal protection against all variants, regardless of an individual’s immune history. And a single coronavirus vaccine, not just for new variants of COVID-19, but for future zoonotic strains that have yet to emerge. These dreams are edging closer to reality.



Can We Get One-Time, Universal Vaccines?

The promise of a universal flu vaccine has its roots in earlier, ground-breaking work by scientists at Penn Medicine. In 2005, Drew Weissman, MD, PhD, the Roberts Family Professor in Vaccine Research and director of Vaccine Research at Penn Medicine, and Katalin Karikó, PhD, an adjunct professor of Neurosurgery, made a discovery that would go on to save millions of lives.

Karikó and Weissman found that messenger ribonucleic acid (mRNA), the molecule that carries sequences for synthesizing proteins, could be modified and successfully delivered via vaccination to elicit an immune response. Fifteen years later, as a new virus, SARS-CoV-2, was spreading around the world, Weissman and Karikó's mRNA technology, which turns cells into powerful factories for building proteins to stimulate the immune system, was licensed by Moderna and Pfizer-BioNTech for use in their COVID-19 vaccines.

"It turns out it's very potent," said Weissman, of their mRNA technology. mRNA produces proteins over a long period of time, which is necessary for a strong antibody response. Plus, the delivery vehicles for mRNA, lipid nanoparticles, act as adjuvants, meaning they stimulate the immune response in a way that makes the vaccine more effective.

"You combine those two things together, and it becomes an incredibly potent vaccine," Weissman said. And, compared with seasonal flu vaccines, "it's very easy to make, and very inexpensive."

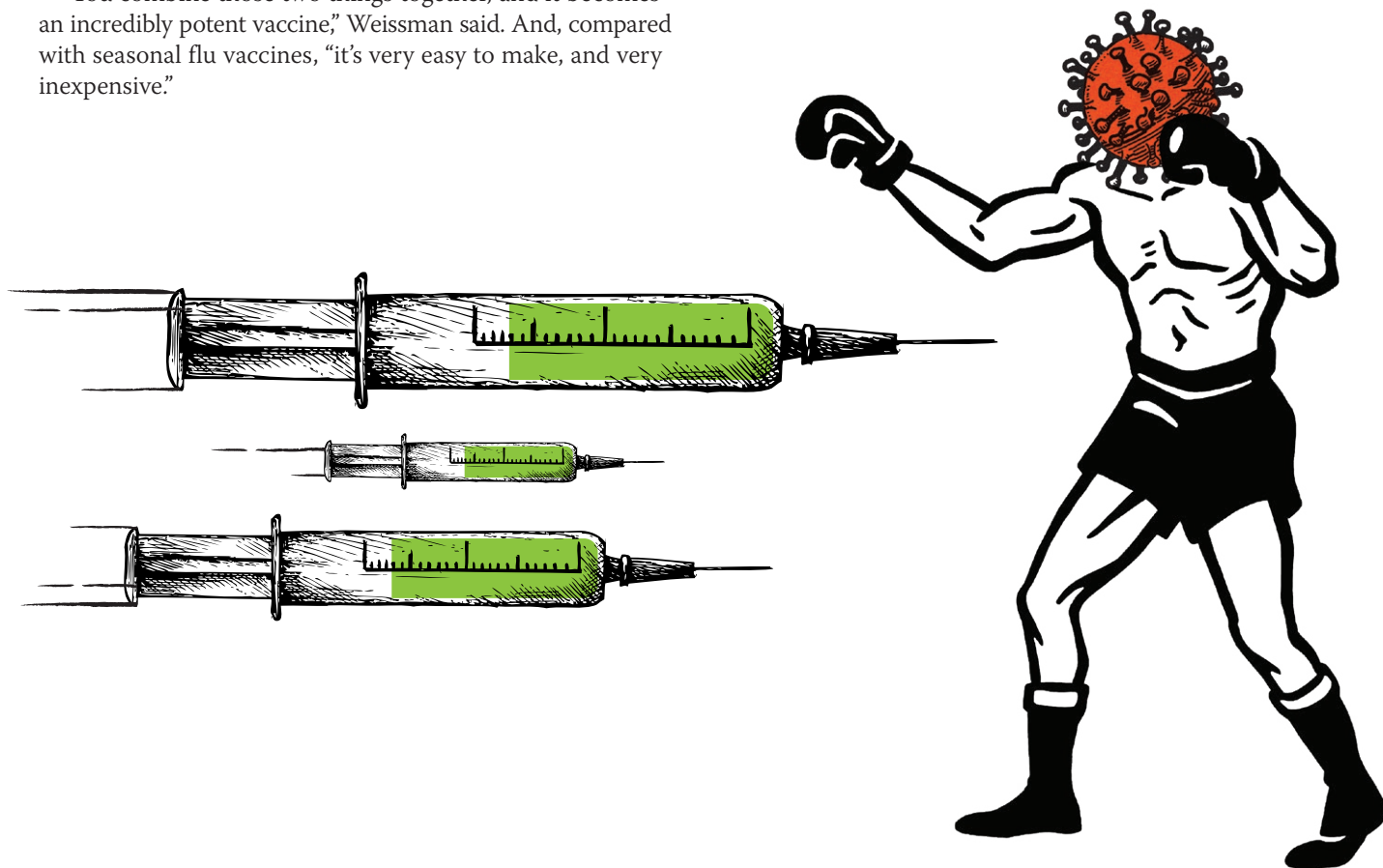
Towards the end of 2020, as the trials of the mRNA COVID-19 vaccines were showing a high level of protection, Karikó and Weissman did not take a break to celebrate. In the battle against diseases from malaria and HIV to genital herpes and norovirus, there was not a moment to spare.

"Their discovery really transformed vaccinology," Hensley said. "The mRNA platform opens doors to areas that we really struggled with in the past." And one of those entrances led straight to universal vaccines against variable viruses.

Three years before the COVID-19 pandemic, Hensley had a thought. Maybe Weissman and Karikó's mRNA technology could be harnessed to make a vaccine against all 20 known influenza subtypes and lineages. "Wouldn't it be neat," Hensley remembers writing in an email to Weissman, "if we could make a vaccine against all 20 of those components?"

Weissman, in a response sent within 10 minutes, agreed, and the two scientists decided to join their labs together to work on a universal flu vaccine. With funding from the National Institutes of Health, their goal was to devise a new vaccine that would offer protection against newly evolved flu strains, as well as new zoonotic variants. "We were trying to make pan-influenza vaccines that can tolerate mutations and new viruses," Weissman said.

Hensley and Weissman's teams injected mice and ferrets with an mRNA vaccine that encoded antigens from the 20 subtypes and lineages. This caused their cells to make copies of hemagglutinin, an important surface protein of the flu virus, corresponding to each variant.





Katalin Karikó, PhD, and Drew Weissman, MD, PhD, developed technology with mRNA that was crucial to the development of COVID-19 vaccines. Now, Weissman is continuing to develop potential universal flu and coronavirus vaccines based using mRNA.

When COVID-19 struck, the team had to put the project on the backburner as their laboratories turned their attention to SARS-CoV-2. But last year, they published their results in a paper in *Science*. The vaccine worked.

The mRNA caused the animals to produce antibodies that remained detectable for at least four months. It reduced symptoms of disease and provided a high protection against death across all the different strains. Plus, the results seemed unaffected by previous flu infection, indicating that Hensley and Weissman may have solved a problem arising from original antigenic sin.

Clinical trials are due to start within the next two years. If successful, Weissman anticipates the vaccine would be most effective when delivered to young children. “That way, they would have protection starting from the beginning of their lives,” he said. “If you immunize kids and you make them resistant to flu, you’ve saved them a potentially lifelong history of influenza infections.”

The elderly, too, would benefit. Compared with other vaccines, mRNA works very well in the oldest sections of the population. And eventually, said Weissman, “everybody in the world would be vaccinated, making flu much less of an issue.”

Weissman’s lab has also already helped to produce a pan-coronavirus vaccine that has been shown to be effective against several different coronaviruses in monkeys. The team is currently applying for funding for clinical trials. As well as helping beat back existing, frequently mutating viruses like SARS-CoV-2, a pan-coronavirus vaccine would also be a powerful weapon to stop the next zoonotic pandemic in its tracks.


Even if the trials go well, some hurdles will remain for universal vaccines. Ensuring everybody has access to the vaccine, wherever in the world they live, will be a challenge. “The fear,” Weissman said, “is it’ll be available in the U.S. and Europe and other high-income countries, but not in low- and middle-income countries.”

Ensuring worldwide access to vaccines has long been one of Weissman’s passions. He has spent years developing mRNA vaccine factories across the globe that make and distribute vaccines locally. “We currently have 18 production sites, either running or being built, across the world.” Among them is a site in Ukraine which, Weissman noted, “is pretty incredible.”

One pressing question is whether new universal flu and coronavirus vaccines would replace the seasonal or annual vaccines we currently use. Or would they just complement them? And would we have to get boosters?

“It depends how well they work,” Weissman said. Ultimately, though, Weissman is optimistic that their universal flu vaccine will offer a high degree of protection against future mutations and pandemic strains. “In theory, it could be a replacement,” he said. “If the vaccine works, you won’t need yearly injections.” □

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BUILDING ON THE BODY'S WISDOM

Treatments that manipulate or repair the immune system are becoming more commonplace. An age of immunotherapy is underway in medicine, starting with lifesaving cancer treatments and radiating out to have wider impacts.

What if, with a little assistance, the body already possessed the means to overcome many of the diseases that afflict humanity?

Whether protecting against internal or external threats or becoming the source of the problem by acting up, the immune system plays a role in many, if not most medical conditions. The concept of manipulating it has a long history. More than two centuries ago, the first vaccine accomplished this by preparing the immune system to fight smallpox.

Scientific understanding of the immune system has grown immensely since then; however, this insight hasn't always translated to proper recognition of its role until recently.

Advancements in immunotherapy—a field dedicated to manipulating the immune system—have exploded especially over the last decade, empowered by basic biological discoveries.

“We have a huge diversity of ways the immune system can function. If we understand how to trigger it correctly, we have an amazing toolkit already prebuilt for us in the body,” said E. John Wherry, PhD, the Richard and Barbara Schiffrin President’s Distinguished Professor, chair of Systems Pharmacology and Translational Therapeutics, and director of Penn’s Institute for Immunology and Immune Health and Colton Center for Autoimmunity.

Penn Medicine is among those at the forefront in this current age of immunotherapy, seeking to build on an institutional legacy of leadership in the field.

Transforming Cancer Care

About 25 years ago, many doubted the importance of the immune system's interaction with cancer, according to Robert Vonderheide, MD, DPhil, director of the Abramson Cancer Center at the University of Pennsylvania. "I was advised as a young faculty member by colleagues elsewhere not to study immunotherapy because it wasn't going anywhere," he said. "But Penn embraced this concept, the main reason I wanted to start my lab here."

Since he established his laboratory in 2001, attitudes everywhere have shifted. "A very common phone call I'll get now as cancer center director is from another institution saying 'We'd like to establish or extend an immunotherapy unit. What was your secret to success?' And I say we started 20 years ago," he said.

The sea change began with the discoveries of specific mechanisms involved in the immune system's response to cancer. Researchers then began seeking to disrupt, or augment, those processes, leading to two seminal developments, according to Vonderheide.

The first, lab-grown immune proteins known as monoclonal antibodies, attack molecular targets in tumor cells and within the immune system. The earliest monoclonal antibodies, such as Herceptin, bound cancer cells and led to cell death directly. Then came second-generation monoclonal antibodies, designed to bind immune cells, and led to immune activation in a variety of ways. One of the most significant of these immunotherapy antibodies for cancer patients has been a treatment that latches onto proteins on T cells, specifically a protein called PD-1, that inhibits the immune cells' tumor-fighting capacity. By interfering with PD-1, the antibodies remove the "brake pedal" on the T cells so they are able to destroy the cancer.

Carl June, MD, and a team of colleagues at Penn Medicine pioneered the subsequent breakthrough in cancer immunotherapy: a cell-based therapy known as CAR T. In CAR T, a patient's T cells are altered to sport cancer-seeking receptors called chimeric antigen receptors, or CARs.

In the decade plus since a Penn Medicine team successfully treated three adult leukemia patients, the FDA has approved six CAR T therapies for leukemia, lymphoma, and multiple myeloma. For substantial numbers of blood cancer patients, CAR T can eradicate signs of cancer. Some even see their malignancies remain at bay for such extended periods that researchers cautiously describe CAR T's effects as "curative."

The promise of more applications for immunotherapies has emerged. As detailed in the pages that follow, efforts seek to, for example, adapt CAR T to fight solid tumors, revive war-weary T cells that have lost their ability to fight cancer, and—in a line of work Vonderheide finds most exciting—devise vaccines that use genetic material from cancer to prime the immune system to fight off these malignancies.



Autoimmunity, Infection, and More

While cancer treatments employ the most advanced arsenal of immunotherapies, patients with other disorders are also benefiting from this strategy. Monoclonal antibodies, for instance, are used to treat an assortment of disorders, from migraines to COVID-19 to inflammatory skin disease. Many of these therapies directly intervene in activity within the immune system.

Experimental studies, meanwhile, are exploring a host of cutting-edge applications. For HIV, researchers at Penn Medicine and elsewhere are looking to adapt CAR T so the modified immune cells can seek out and destroy virus-infected cells. Penn Medicine researchers are also investigating CAR T's capacity to eliminate the immunological resistance that causes some people's bodies to reject organ transplants. And clinical trials are now underway to test a version of CAR T adapted to treat certain autoimmune diseases.

CAR T is highly adaptable to more types of disease treatments in the future because all sorts of different artificial receptors could potentially be designed to enhance a variety of immune cells in a wide variety of ways.

The diversity of these efforts—and the way this technology has diffused outward from its initial application in cancer—speaks to the collaborative culture nurtured at Penn Medicine, according to Vonderheide.

"We are an epicenter of this movement, and we're not done yet," he said.

— Introduction by Wynne Parry



Next: Walter Styer's life has been forever changed thanks to the then-experimental immune therapy that wiped out his cancer.



LIFE, GAINED

By Carol R. Cool

Walter Styer's life-filled years, after being the 10th patient in an early trial, are a testament to the impact of CAR T cell immunotherapy.

When Walter Styer isn't still working at the family propane business, he fills his days tending his half acre filled with string beans, zucchini, corn, and tomatoes.

Styer, 89, has been able to enjoy this active life for the past 11 years thanks only to the experimental immunotherapy treatment he and his family call a miracle.

Trial and Error—and Success

In 2012, after four years of treatment for chronic lymphocytic leukemia, Styer's oncologist told him he was "running out of bullets." He found his way to a clinical trial of CAR T cell therapy led by David Porter, MD, at Penn Medicine's Abramson Cancer Center (ACC).

Styer, his family, and even his oncologist worried that being 78 years old would prohibit his participation in the study. But the ACC team assuaged their fears. "We were so early in the trial, we had no idea if age impacted outcomes," said Porter, "so we didn't think age should preclude Walter."

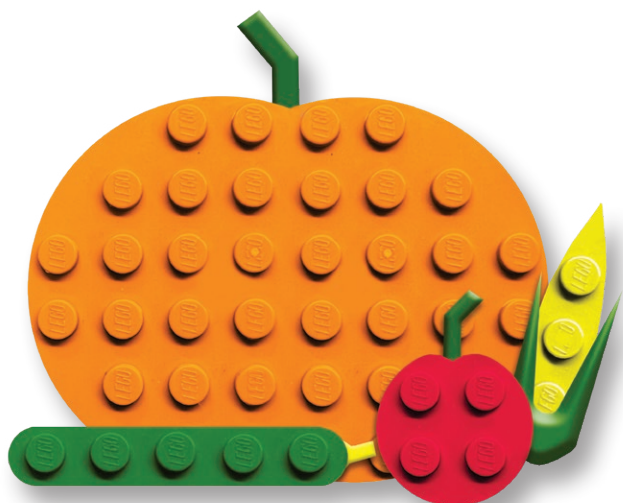
He enrolled as the trial's 10th participant.

In June 2012, Styer received his first infusion of CAR T cells, but follow-up tests showed the cancer was still present, and the CAR T cells were not. Not ready to give up, Styer received a second infusion in August. This time, after 52 days, his body responded with fevers that required him to go to the hospital. Tests then showed CAR T cells were growing and killing his leukemia. His swollen lymph nodes and tumor masses would all eventually disappear.

That trial and others that followed ultimately led to the CAR T treatment developed at Penn receiving U.S. Food and Drug Administration (FDA) approval in 2017. Now



This year, Styer taught one of his great-granddaughters how to ride a two-wheeled bike, just as he had patiently taught her mother and grandmother before her.



marketed by Novartis as Kymriah (tisagenlecleucel), the drug is curing previously incurable leukemia and lymphoma. It was the first of six now-approved CAR T therapies available for patients outside of clinical trials.

“Walter was truly a pioneer,” said Porter. “This trial sparked an entirely new field of cancer medicine.”

Lots of Life Left

Cancer-free, Styer continues living a life filled with the things important to him—his family and his faith.

“I’ve been so blessed to be in the study,” says Styer, “and to enjoy 68 years of marriage with Sarah.” These past 11 years, they’ve celebrated the weddings of grandchildren, attended graduations, and welcomed 11 great-grandchildren.



Walter Styer with his wife of 68 years, Sarah

This year, Walter taught one of his great-granddaughters how to ride a two-wheeled bike, just as he had patiently taught her mother and grandmother before her.

In the summer months, Styer maintains the family pool and mows nine-and-a-half acres across his own property and that of three of his children. Every fall, he drives the hayride tractor at his family’s harvest party. Over the years, Porter and others from Styer’s Penn Medicine team have accepted the invitation to join the fun.

“I am most grateful to have had the opportunity to participate in this study,” says Styer. “Because of it, I’ve gained life—a normal, active life.”



Next: Scientists are working to adapt CAR T beyond blood cancers to help patients with solid tumors like breast cancer.



ENGINEERING THE IMMUNE SYSTEM TO TACKLE

SOLID TUMORS

By Kirsten Weir

Scientists are still learning how to help CAR T cells evade the body's defenses so they can effectively treat cancers in the breasts, brain, lungs, pancreas, and other organs.

CAR T cell therapy is one of the heroes that ushered in the age of immunotherapies, bringing long-lasting remissions and cures for patients with blood cancers like leukemias and lymphomas. But there are many more cancer foes it has yet to defeat. Designing CAR T cells to destroy solid tumors—which account for 90% of all cancers—has proved much trickier.

In CAR therapy, a patient's T cells are removed, altered, then returned to the body, where they seek out and kill cancer cells. In a petri dish, that process works for any type of cancer, including solid tumors. Getting it to work in the body, though, has been a different story.

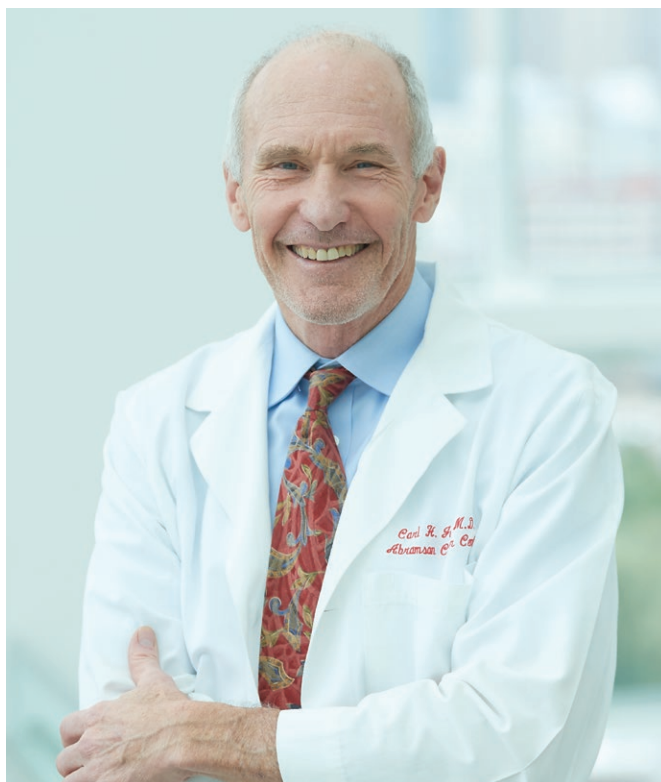
"Each type of tumor has its own little ways of evading the immune system," said Carl June, MD, the Richard W. Vague Professor in Immunotherapy at the Perelman School of Medicine and director of the Center for Cellular Immunotherapies at Penn Medicine's Abramson Cancer Center, who led the team that developed what became the first U.S. Food and Drug Administration–approved CAR T cell therapy. "So there won't be one silver-bullet CAR T therapy that targets all types of tumors."

But Penn Medicine researchers are making steady progress, with an extensive portfolio of clinical trials testing the treatment in solid tumors and other approaches in the pipeline. "Our toolbox is full of new ways to engineer cells. We have all the tools required to solve the problem of solid tumors," June said.

How Brain Cancer CAR T Homes in on Hard-to-Target Solid Tumors

Many solid tumors are naturally hostile to T cells. Part of that hostility is what June calls the medieval castle problem: "Just like castles have a moat, tumors are surrounded by scars made of collagen," he explained. It's tough for T cells to cross that barrier. When cells do make it past, they often find themselves surrounded by immunosuppressive cells and molecules that are primed to wipe out marauding immune cells—including T cells. "You have to teach the cells to go there and proliferate in that hostile environment," June said.

Another challenge is that solid tumors aren't as easy a target for CAR T cells to lock onto. CAR T cells are programmed to seek out specific proteins, or antigens, on a cancer cell's surface. In a disease like leukemia, most cancer cells are made of a single cell type (such as B cells) that all express the same antigen. A solid tumor, however, is made up of different cell types, with different mutations, expressing different antigens. It's more challenging to design a CAR therapy for heterogeneous tumors like this, targeting several antigens at once.



Carl June, MD, pioneered CAR T cell therapy for blood cancers with a team of colleagues at Penn Medicine and continues to explore new uses for the approach.

Challenging, but not impossible. Donald M. O'Rourke, MD, the John Templeton, Jr., MD Professor in Neurosurgery and director of the Glioblastoma Translational Center of Excellence at the Abramson Cancer Center, and colleagues are currently testing a "dual target" CAR that goes after two antigens expressed by the brain cancer glioblastoma multiforme (GBM).

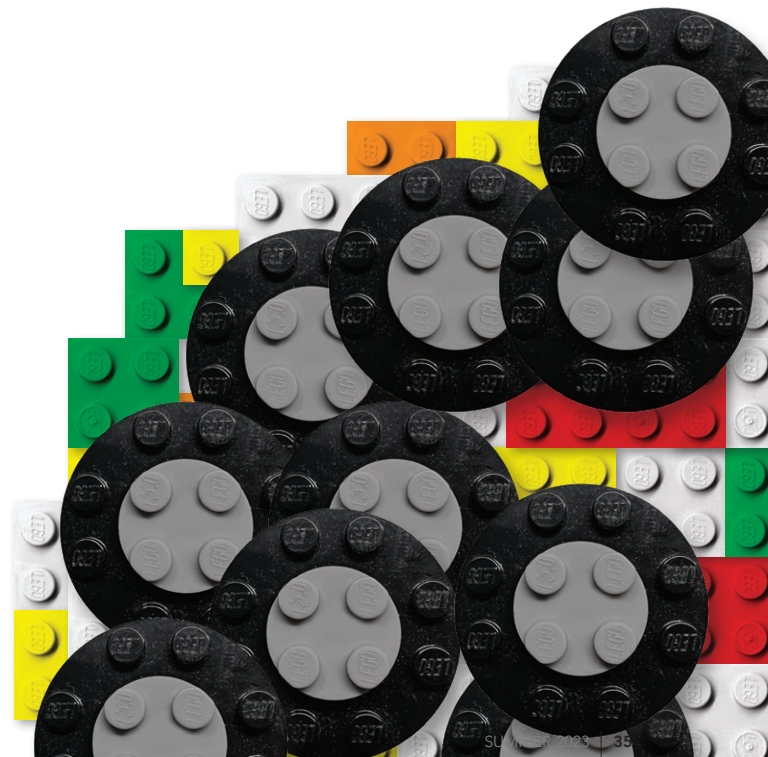
GBM has long been one of oncology's fiercest foes. Rather than growing in a well-defined ball, these tumors

send out invasive projections that infiltrate nearby cells. It's virtually impossible for surgeons to remove them completely, and tumors almost always recur soon after treatment. Despite decades of research, the median survival time for GBM patients is just 15 months. "We need a therapy that can expand in the body and home in on the regions that the cancer has invaded," O'Rourke said. "And the only thing that can do that is an activated T cell."

Getting T cell therapies ready to test in GBM patients hasn't been easy. On top of the other defenses that solid tumors put up against CAR T, the brain has its own mechanisms to keep T cells away, O'Rourke said. "The body isn't designed to tolerate inflammation in the brain." But in previous research, his team discovered that GBM seems to be more vulnerable to CAR therapy after the cancer recurs. One patient they treated with CAR T cells for recurrent GBM lived for 36 months.

Building on those successes, O'Rourke is leading a clinical trial testing the dual target CAR in patients with recurrent GBM. To help as many of the engineered cells as possible reach their target, they'll deliver the T cells directly into the spinal fluid. It's the third in a series of small trials, and with each one, the researchers chip away at GBM's stubborn barricades. The patients recognize that this new therapy is unlikely to erase their tumors completely. But their participation offers hope that they may gain more quality months or years, and allows them to be a part of finding a future cure

Continues on next page





Surgeon Julia Tchou, MD, PhD, is leading a clinical trial in which CAR T cells are injected directly into breast cancer tumors.

for this devastating disease. “Each patient is a treasure trove of data,” O’Rourke said. “It’s been a slow build, but we’re learning a lot.”

Trial Gives a Boost of CAR T After Surgery for Breast Cancer

Getting CAR T cells past a tumor’s defenses is one challenge. Making sure they don’t go after innocent targets is another. A decade ago, June and colleagues including Julia Tchou, MD, PhD, a professor of Clinical Surgery and director of breast surgery research at Penn Medicine, discovered that the hard-to-treat triple negative breast cancer expresses the surface protein mesothelin. It could be a good target for T cells—except that noncancerous cells can also express mesothelin, increasing the risk of serious side effects if the engineered cells attacked healthy tissue.

Tchou and June took a creative route around that roadblock. They developed a special gel containing CAR T cells that could be painted into tissues left behind after tumor removal. In mouse models of breast cancer and pancreatic cancer, the gel showed impressive results: Residual cancer vanished in 19 of 20 mice, without affecting wound healing or causing

other side effects. “The results in animals were surprisingly good,” Tchou said.

Now her team is launching a trial of patients with locally advanced or metastatic triple negative breast cancer. Rather than apply the gel, they’re injecting CAR T cells directly into the tumors. (If all goes well, studies of the gel may follow.) Researchers biopsy the tumors before and after treatment so they can make detailed comparisons. “We’ll be able to do these really deep analyses and learn how the CAR T cells are behaving—and whether the tumor tissues are shrinking or changing,” Tchou said.

It’s a small pilot, she cautions, and just one step on the long road to making CAR T a go-to for solid tumors. But the approach has potential for all sorts of tumors that are difficult for surgeons to remove completely, including cancers of the brain, lung, and pancreas. “In the future, if we can deliver this type of treatment at the site during surgery, patients might be able to avoid chemotherapy and radiation,” Tchou said. “That would be a huge breakthrough.”

Meanwhile, researchers across Penn are working on complementary approaches to make CAR T more effective, including new techniques to break down the collagen “moat” surrounding tumors, and new rapid manufacturing methods that allow T cells to be reinfused into patients in just a few days rather than several weeks. Penn Medicine is

“At a high level, CAR T is a fairly simple concept. It’s very modular, like building with Legos.”

– Vijay Bhoj, MD, PhD

Assistant Professor, Pathology
and Laboratory Medicine

Studies CAR T for Autoimmune
Disease and Transplant Resistance

a place where such revolutions can happen—especially in the field of CAR T immunotherapy, which was born in those very labs. “When we started, there wasn’t a workforce of people who knew how to do this. Over the past 25 years, we’ve developed a huge talent base and an amazing infrastructure,” June said. “I’m optimistic cell therapies will be used for all kinds of solid cancers. The only unknown is when.”

CAR T THERAPIES BEYOND CANCER

Six different CAR T cell therapies are now approved to treat various types of blood cancers, but researchers' quest to use this "living drug" immune therapy for more diseases isn't limited to other cancers. As research at Penn and elsewhere moves into early-stage clinical trials, it's no longer just a theoretical possibility: CAR T cell therapy is making waves for a wide array of common and chronic diseases.

"Essentially it boils down to two questions," said Carl June, MD, the Richard W. Vague Professor in Immunotherapy at the Perelman School of Medicine and director of the Center for Cellular Immunotherapies in the Abramson Cancer Center. "Can we identify a population of cells that are bad? And can we target them specifically? Whether that's asthma or chronic diseases or lupus, if you can find a bad population of cells and get rid of them, then CAR T cells could be therapeutic in that context."

► **Read more about the progress, challenges, and opportunities for CAR T cell therapies beyond cancer in a Q&A with June and Daniel Barker, a fourth-year graduate student studying in June's lab, online at PennMedicine.org/blog.**



CANCER VACCINES TO STOP TUMORS BEFORE THEY START

Just over a decade ago, the idea of using the immune system to attack and destroy tumors seemed like a pipe dream—and today it is not only proven science for certain cancers, but an exploding field.

Already, there are several approved cancer treatment vaccines that fight back against advanced cancers such as prostate cancer and melanoma.

But what about using the immune system to prevent early cancers from taking hold? Research here, too, is proliferating. At the Basser Center for BRCA at Penn's Abramson Cancer Center, Susan Domchek, MD, is leading a pioneering study testing a new cancer vaccine in women with *BRCA1* and *BRCA2* mutations. In an initial trial, patients who were in remission after previously having cancer were vaccinated, with the goal of preventing recurrence. Now, BRCA-positive participants who've never had cancer are enrolling in this trial, in hopes that the vaccine can stop precursor lesions

before they grow into breast cancer tumors. If the approach is successful, it could open the door for intercepting the various cancers associated with BRCA mutations.

This work at the new Basser Cancer Interception Institute, part of the Basser Center for BRCA, and other efforts to intercept cancer, were highlighted in the Spring 2023 issue.

► **Find it online at PennMedicine.org/magazine.**



Next: With a deeper understanding of the immune system, there are growing possibilities to selectively turn down only the parts that malfunction in autoimmune diseases—with hopes for lasting results.



THE IMMUNOTHERAPY REVOLUTION FOR AUTOIMMUNE DISEASES

By Wynne Parry

With a deeper understanding of the immune system, there are growing possibilities to selectively turn down only the parts that malfunction—with hopes to someday cure these conditions.

Autoimmune diseases are a conundrum: Sometimes instead of protecting the body, the immune system turns against it. The target of its wrath varies depending on the condition. To alleviate patients' suffering, doctors must dampen the immune system. However, lacking the means to selectively target only the parts that are misbehaving, they have no choice but to broadly impair the body's defenses, opening the door to potentially life-threatening malignancies and infections..

This tradeoff has long frustrated Aimee Payne, MD, PhD, a professor of Dermatology in the Perelman School of Medicine at the University of Pennsylvania, who treats and studies pemphigus vulgaris, an autoimmune condition that causes the skin to blister and peel because immune proteins known as antibodies attack an adhesive molecule in skin, desmoglein 3.

"Why are we wiping out all of the immune cells, including the good immune cells that are helping to protect someone?" she said. "We should just be able to identify the ones causing pemphigus or another autoimmune disease and eliminate them with laser focus."

New research, including that by her lab, is striving to make such precision treatments a reality for pemphigus and certain other conditions. These experimental efforts belong to a larger wave of advancements in immunotherapy driven by basic discoveries about the body's defensive system and the development of new techniques for manipulating it.

Just as Penn Medicine has established itself as an epicenter for the revolution in immunotherapy that has transformed cancer medicine, the institution has now set its sights on autoimmunity, a category that includes more than 80 disorders affecting more than 20 million people in the U.S. Working at the leading edge of the field, Payne and other Penn Medicine researchers aim to bring less damaging, longer lasting—perhaps even permanent—relief to patients by addressing the source of their disease.

Two gifts from Stewart and Judy Colton totaling \$60 million since 2021 have bolstered this effort, establishing Penn Medicine's new Colton Center for Autoimmunity. The center supports researchers as they dive deeply into mechanisms underlying autoimmune diseases, and so identify the basis for new therapies.

These immune-targeting approaches can directly address the misguided activity at the heart of autoimmune conditions,



and more, according to E. John Wherry, PhD, director of Penn's Colton Center and Institute for Immunology & Immune Health and chair of Systems Pharmacology and Translational Therapeutics. Immunotherapies also have the potential to harness the immune system's inherent ability to remember past threats. By tapping into immunological memory, immune-based drugs could potentially have effects that endure long after patients have stopped taking them.

"We're not talking about treating autoimmunity, we're talking about curing the disease and making a permanent change in the body," Wherry said.

A Discovery Suggests a Path for More Selective Therapies

Devising new immune-targeting therapies requires a deep understanding of the intricacies of the immune system. In a study published in *Science Immunology* in April, a team led by immunology researcher Neil Romberg, MD identified a promising subtlety in the lineages of T cells.

Within clusters of cells known as germinal centers, T cells help B cells produce antibodies tuned to latch onto targets on invading microbes or, in cases of autoimmunity, on the body's own cells. A specific population of T cells, known as T follicular regulatory (Tfr) cells, oversees this process.

"Historically, people have thought that a single type of Tfr cells maintains protective immune responses to microbes while also directing them away from self-injury," said Romberg, an associate professor of Pediatrics in the Perelman School

Aimee Payne, MD, PhD, is working to discover immune-targeting therapies for autoimmune skin conditions.



of Medicine and clinical immunologist at Children's Hospital of Philadelphia (CHOP).

Using tonsils collected from healthy patients, the researchers instead identified two types of Tfr cells that appear to split up these tasks. One descends out of cell lineages known to calm the immune response. The second line of Tfrs originates from a variety of T cells that promotes the production of antibodies. Unlike their counterparts, these more combative Tfrs sport a marker protein known as CD38.

With this differentiation in mind, Romberg envisions devising ways to selectively manipulate these populations, with the goal of improving the immune system's ability to tolerate whatever it has mistakenly labeled an enemy—without affecting its ability to protect the body in general.

"What if we could be uncompromising in the way we apply these therapies," he said, "so we don't have to accept these tradeoffs?"

Tweaking CAR-T to Treat Autoimmunity

The breakthrough that established Penn Medicine's pre-eminence in cell-based immunotherapy, the development of CAR T, is now providing a basis for new approaches to certain autoimmune disorders.

CAR T endows T cells with artificial receptors (chimeric antigen receptors, or CARs) so they can find and destroy cells the receptor is designed to bind to, such as B cells that run amok in leukemia and lymphoma. Because pemphigus also results from B cell activity, Payne's lab has long looked to these blood cancers for inspiration. Roughly a decade ago, when the first early trials of CAR T had begun to show success, Christoph Ellebrecht, MD, then a research fellow in Payne's lab and now an assistant professor of Dermatology, suggested adapting that method to treat pemphigus vulgaris and other autoimmune diseases. If CAR T could wipe out cancerous B cells, why not other problematic B cells?

Payne recognized the potential. "My reaction was—that's brilliant," she said.

Ellebrecht initially worked on his idea with Vijay Bhoj, MD, PhD, then a postdoc in Michael Milone's lab and now an assistant professor of Pathology and Laboratory Medicine. Conventional CAR T seeks to eradicate all of a patient's B cells;

together with Payne and Milone, they sought to make their version more selective by topping the receptor with the skin protein desmoglein 3, the target of the antibodies in pemphigus.

"The idea is that the receptor will only bind to the bad antibody-expressing B cells and specifically kill those, not the B cells that protect against tetanus infections, COVID-19, measles, and whatnot," Bhoj said.

A spinoff company co-founded by Payne and Milone, Cabaletta Bio, has clinical trials underway testing therapies based on this strategy, dubbed CAAR T for chimeric auto-antibody receptor, for specific subtypes of pemphigus and myasthenia gravis, a neuromuscular condition. Meanwhile, other applications are in the works.

Bhoj recognized CAAR T's potential to remedy a blood condition he treats. In the autoimmune form of thrombotic thrombocytopenic purpura (TTP), antibodies attack an enzyme, ADAMTS13, that prevents the formation of blood clots. When this enzyme is depleted, clotting interferes with blood flow in small vessels throughout the body. His group is now testing an experimental CAAR T treatment for this condition in animal models.

While the straightforward, well-defined dynamics underlying pemphigus vulgaris, TTP, and certain other autoimmune diseases lend themselves to CAAR T, the causes of many others do not. In some of these cases, however, preliminary research suggests a conventional CAR T approach has promise. In one recent study based in Germany, five patients with lupus, a disorder in which antibodies attack DNA, went into remission after their T cells were engineered to wipe out their B cells.

These cell-based immunotherapies are still in experimental stages for patients, with plenty more potential therapies still under investigation that are not yet ready for clinical testing. But researchers hold out hope that they could eventually have impacts on autoimmune diseases as real as those for cancer.

Bhoj thinks of a patient he saw recently. Although he has received conventional B cell depleting therapy, the man came into the hospital in late May with his fourth relapse.

In contrast, evidence from CAR T suggests these engineered cells can more effectively infiltrate the body to find their targets and persist for long periods, perhaps indefinitely, within it.

"I'm working on it because I think there is a potential that these approaches could be curative," Bhoj said. "There are no guarantees, but it's good to aim high." □



ENERGIZING THE IMMUNE ARMY

By Christina Hernandez Sherwood

A phenomenon known as “T cell exhaustion” has stymied some efforts to develop powerful immune-based therapies. E. John Wherry, PhD, describes how researchers are learning to manipulate this complex process.



Sometimes dubbed “the soldiers of immunity,” T cells are among the most ruthless warriors in the immune system’s arsenal. These powerhouse fighters have the unique ability to periscope into individual cells to see what’s lurking inside. If the T cells spot a pathogen, they attack, destroying not only the foreign invader but the entire cell containing it. Of course, this “shock and awe” approach to viral warfare has its limits: T cells waging long-term battles eventually succumb to exhaustion, losing their full power to fight back.

What causes T cells to become exhausted?

With a typical infection, T cells get control of the virus and eliminate it completely. In the process, the T cells cause a good bit of damage, which is what makes you feel sick.

In T cell exhaustion, the immune system switches from destroying everything to eliminate the pathogen to learning how to manage it. T cells sit in this under-responsive state. They’re not inert. They’re partially responsive. It’s as though the body’s defense goal has changed to keep the virus in check without causing too much damage along the way.

What happens biologically in T cell exhaustion?

It is a very active process over several weeks of chronic stimulation. The T cells turn on brakes, or checkpoints. They’re being actively restrained. After weeks of chronic stimulation, they go down a separate path of differentiation in ways that become progressively more irreversible.

Can medical treatments revive exhausted T cells?

If those brakes or checkpoints are taken away, the T cells can experience a burst of activity again. We can restore some function, essentially reinvigorating exhausted T cells to at least temporarily perform their immune functions more efficiently.

T cell exhaustion has been a major barrier for cancer treatments. Nobel Prize-winning work from James Allison and Tasuku Honjo to partially reinvigorate these exhausted T cells was the breakthrough in human therapeutics. We’re now seeing drugs like YERVOY, KEYTRUDA, and OPDIVO that are curing cancer patients.

How are your lab and others at Penn working with T cell exhaustion to treat diseases?

We’re excited about opportunities to reprogram these cells. Some of these efforts are aimed at understanding and then reversing the stable epigenetics (or gene control) in these cells. We’re collaborating with experts in the Epigenetics Institute at Penn and our colleagues doing great work with CRISPR gene-editing technology. We’re using concepts of cellular and genome engineering to pick apart the internal wiring of exhausted T cells, and then use what we’ve learned to induce or build better T cells. We’re also excited to understand more about how these T cell exhaustion targeting therapeutics like checkpoint blockades work in people.

Elsewhere at Penn, we’re seeing work on how other parts of the immune system play a role in T cell exhaustion. We’re learning from Andy Minn’s lab about chronic inflammation as a contributor to T cell exhaustion. We’re learning from Carl June and others in the CAR T cell space about genes and pathways that could be targeted to avoid or overcome exhaustion. Other work from June’s group has used receptors that respond to certain growth factors to try to keep T cells from becoming exhausted.

There’s work at Penn that spans the whole spectrum, from the basic fundamental science of how one cell type becomes another, or becomes permanent in its identity, all the way to very clinically applied aspects of avoiding, reversing and understanding exhaustion in T cells that are active in the human body.

This is the soul of Penn’s scientific enterprise. With every patient treated, there’s an opportunity (and almost obligation) to learn, and clinicians and researchers at Penn thrive on this generation of new knowledge that will help improve current treatments and develop new ones. That makes Penn ground zero for not only translating great basic science into patients, but doing fundamental discovery in a patient being treated with an innovative drug. ▢

PHILANTHROPY GIVES IMMUNE HEALTH ITS MOMENT

From a global pandemic, we learned that it took more than our decades of investment in basic and translational science to keep the health of millions safe and our labs operating at the leading edge of medicine.

During those earliest days, leaders across Penn Medicine turned to the resources generously provided by its community of donors: annual unrestricted and newly created COVID-19 funds, as well as the Dean's Innovation Fund (DIF).

It was because of Penn Medicine's ability to put these gifts to immediate use that the next immune revolution is now underway. And the tremendous donor support behind these efforts—especially through support for the DIF—began promoting a culture shift among Penn Medicine's scientists, bringing to the fore the notion that the larger world is interested and invested in their work.

"The sense of possibility—of being able to say to our best people, go for it—is difficult to quantify, but enormously valuable," said J. Larry Jameson, MD, PhD, dean of the Perelman School of Medicine.

A Critical Pivot

When the World Health Organization declared COVID-19 a global pandemic in March 2020, the world turned to scientists to better understand the virus' impact on patients, how to treat it, and how vaccines might prevent it—and Penn Medicine's philanthropic first responders immediately stepped up to help. In a tremendous outpouring of support, more than 400 donors came together to enable the development of critical infrastructure and processes and drive rapid scientific progress, laying the foundation for

Penn's experts to fight the pandemic. By July 2021, we had raised \$14.8 million from 550 donors to support COVID-19 research efforts. Our philanthropic partners have helped us answer critical early questions—and pose even better ones—and continue to drive us forward as we study the nature of the immune response to COVID-19 and deliver findings that impact the broader community.

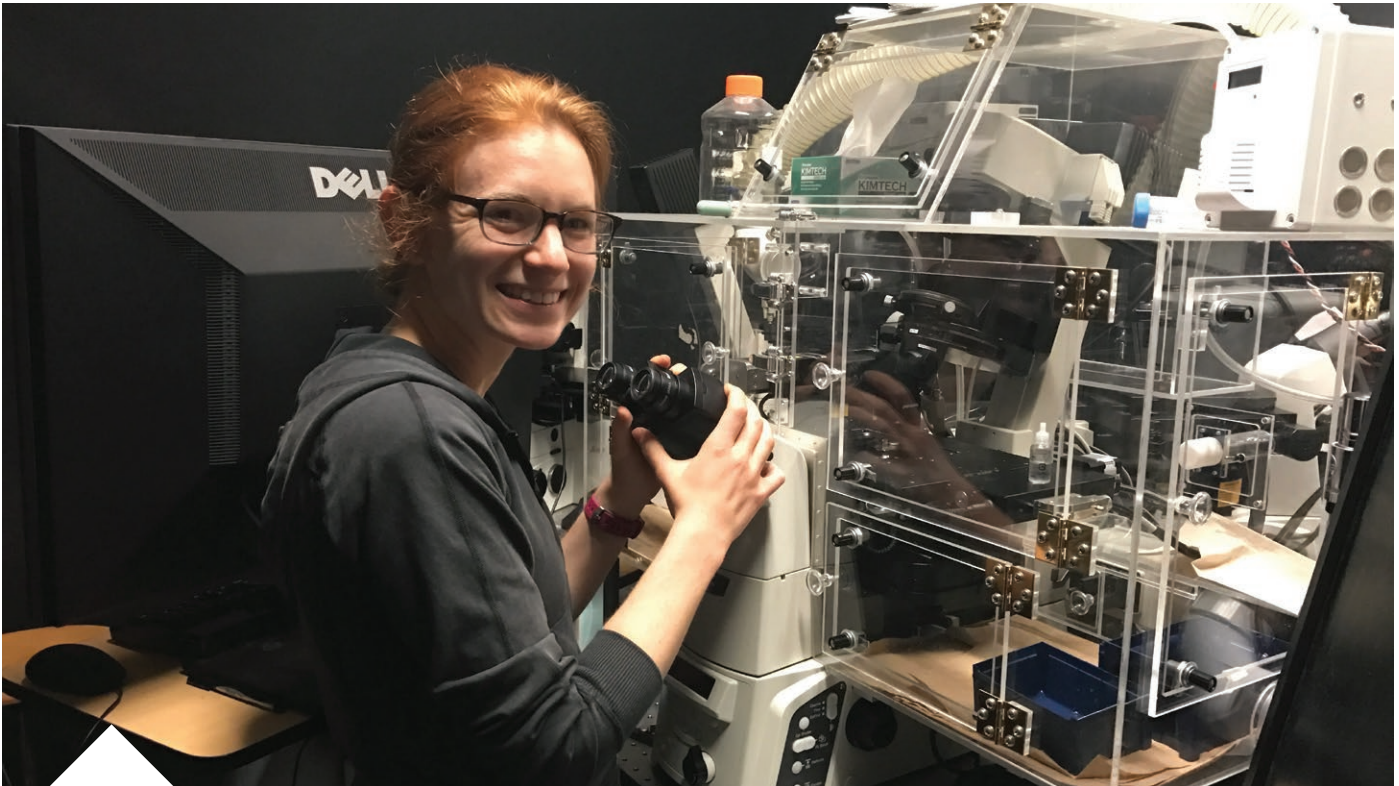
E. John Wherry, PhD, the Richard and Barbara Schiffrin President's Distinguished Professor, continues building on foundational gifts from generous donors, as well as his breakthrough findings related to distinct immune responses to the virus and the role of prior COVID-19 infection on a

person's immune response to receiving a COVID-19 vaccine. In Spring 2020, Scott Hensley, PhD, made key findings that added important evidence to our understanding of the immune response to COVID-19 and what might prevent or fight off infection. This work, paired with Hensley's expertise in the field of flu research, will help Penn Medicine play a leadership role in preparing for future pandemics.

"The sense of possibility—of being able to say to our best people, go for it—is difficult to quantify, but enormously valuable."

– J. Larry Jameson, MD, PhD





Sydney M. Shaffer, MD, PhD

Catalyzing Discovery

Gifts to the Dean's Innovation Fund (DIF) provide flexible resources that enable investment in the most promising high-risk, high-reward projects in Penn Medicine's research portfolio, and many COVID-19 projects were supported by the DIF in the early days of the pandemic. The DIF enables researchers to rapidly explore new areas of investigation, setting in motion brilliant ideas that have the potential to improve human health.

Recognizing the importance of the discovery science phase of research, forward-looking Wharton alum Joel M. Greenblatt, W'79, WG'80, made a gift to establish the DIF in 2016, providing unrestricted early-stage funding to be directed to young investigators. When Jed Hart, W'89, entered the picture as the second donor to the Fund, Penn Medicine built on this momentum by creating Penn's Council for Discovery Science. With active and deeply dedicated members who have to date pledged more than \$9.4 million to support the DIF, the Council for Discovery Science demonstrates the sustainability of this donor-powered funding model.



Daniel Rader, MD

RESEARCH IMPACTS

The projects the Dean's Innovation Fund supported at an early stage have gone on to generate **\$243 million** in subsequent investment.

Achievements of the investigators supported through the Dean's Innovation Fund from FY18–FY22 include:



1 first-in-human clinical trial



11 patent applications



2 pending FDA approvals



56 academic papers published, that have already been cited over 5,350 times & 8 additional pending publications



5 start-up companies



To date, members of the Council for Discovery Science have pledged over **\$8.7 million** to support the Dean's Innovation Fund.

“The Dean's Innovation Fund was extremely powerful in accelerating our work and letting us be as bold as we could be in our scientific explorations. Being bold is what is needed—and not always easy to do through conventional funding mechanisms,” said Ben Black, PhD. The DIF has enabled Black to explore using artificial chromosomes to engineer the human genome, a concept with immense potential for new therapies.

Also supported by DIF funding, Sarah Tishkoff, PhD, the David and Lyn Silfen University Professor in Genetics and Biology, and Daniel Rader, MD, the Seymour Gray Professor of Molecular Medicine, have enrolled 700 people to date in a study that could provide insights into the susceptibility to COVID-19 in different global populations. Norbert Pardi, PhD, and Hao Shen, PhD, are using mRNA technology to explore a new vaccine for influenza virus. Sydney M. Shaffer, MD, PhD, analyzed autopsy tissue using RNA FISH, an extremely powerful technique for studying RNA viruses that allowed her team to visualize active infection at a cellular level to determine which cells and tissues showed signs of COVID-19 infection and progression, providing key insights in the earliest days of the pandemic.

Donor support for the DIF has accelerated a range of innovative research projects that have generated \$243 million in subsequent investment. More than 50% of DIF awards have supported early and mid-career faculty at key inflection points in their careers, and from FY18–FY22, investigator accomplishments included one first-in-human clinical trial, 11 patent applications, two pending FDA approvals, 56 academic papers published, and five start-up companies—all remarkable successes that would not be possible without our philanthropic partners.

The ripple effects from this donor support have gone even further in concept and impact, spurring on the creation the Penn Center for Genome Integrity (PCGI) and the Center of Excellence for Influenza Research and Response (CEIRR), as well as continued discovery within the Penn Center for Research on Coronavirus and Other Emerging Pathogens, the Institute for Immunology & Immune Health (I³H), and other Penn-led initiatives.

► To learn more about supporting the Dean's Innovation Fund, please contact Sarah Gilmour at 215-573-9803 or sarahra@upenn.edu.

Progress Notes will resume with the next issue.

Send your progress notes and photos to:

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1940s

Frederick Warren Coe, MD'44, an internal medicine physician; June 10.

Coe graduated from Ohio Wesleyan College in zoology and chemistry in 1941. While in medical school, he was inducted into the Army during WWII, and later graduated in 1944. He entered the Army after completing an internship, serving for more than three years as a first lieutenant in Puerto Rico and on several transport ships, demobilizing returning U.S. troops. He returned for his residency in internal medicine at Presbyterian Hospital in Philadelphia. He then entered private practice in Maryland, before being recalled to complete his military obligation in the Public Health Service.



Coe served two years in San Francisco, then spent several months serving on a minesweeper surveying the sea floor in the Aleutian Islands. After completing his service, he returned to private practice in Bethesda, MD. In 1958, he moved to Marin County, CA, first working in private practice, then at Yountville Veterans Home, and Sonoma State Hospital until his retirement in 1992.

1950s

Frederick Jones Jr., MD'56, a pulmonologist; April 23. He began his medical career with an internship at Pennsylvania Hospital and completed his residency at the University of Michigan. He then served as a U.S. Air Force physician, first at Dyess AFB, Abilene, TX and then at Scott AFB, Belleville, IL, before being honorably discharged as a major.

In 1965, Jones accepted a position at Geisinger Medical Center (Danville, PA), where he became a renowned pulmonary medicine expert. He was one of the original chest medicine specialists at Geisinger, pioneering many procedures imported from leading academic centers, and helping to establish the first intensive care units at the hospital. After leading the thoracic medicine section, he was appointed as chief of Medicine. Jones authored dozens of publications ranging from original research and case reports to medically related poetry. He made important contributions toward the understanding of several diseases of local significance, including Black Lung disease of coal miners, Legionnaire's Disease, and tuberculosis. He also trained hundreds of physicians and served leadership roles in many professional societies. He developed a passion for collecting medical antiques, building a museum-quality collection. In recent years, he donated a large array of microscopes to Geisinger and gifted other pieces to institutions, such as the Montgomery House.

Richard Nevin Rupp, MD'58, an otolaryngologist; Jan. 23. After attending medical school, Rupp, an ROTC alumnus, transitioned into the U.S. Army. He was stationed in San Antonio and began his medical career at Brooke Army Medical Center. Nevin was transferred to Walter Reed Medical Center

in Washington, DC, and later was posted overseas in Nürnberg, Germany. In 1967, he returned to San Antonio and Brooke Army Medical Center in Houston, where he rose to the rank of lieutenant colonel and served as chief of Otolaryngology. In 1970, Nevin left the Army for private practice as an ear, nose, and throat doctor, but continued to serve in the Army Reserves and rose to the rank of colonel.

1960s

McIver Edwards, Jr., MD'62, emeritus professor of Anesthesia; Jan. 13.

Edwards studied biology at the Massachusetts Institute of Technology (Cambridge, MA), graduating in 1956. He served as first lieutenant in the U.S. Army Chemical Corps at Fort McClellan in Alabama, then completed medical school at the University of Pennsylvania in 1962. He went on to specialize in anesthesia at Penn, where he practiced and taught for 39 years, during 10 of which he served as chief of Anesthesia at the VA hospital of Philadelphia.

Edward W. Lieberman, MD'62, a radiologist; Jan. 31.

Commissioned as a naval officer during medical school, Lieberman completed his internship at the United State Naval Hospital in Chelsea, MA. He was personally selected by Admiral Hyman Rickover to join the new Polaris nuclear submarine program as a medical officer on the U.S.S. Lewis and Clark, based out of Norfolk, VA. He then completed a radiology residency at Albert Einstein Hospital (Bronx, NY), where he earned certification in diagnostic radiology and radiation oncology. Lieberman practiced radiology with Jersey



Shore Radiology Associates from 1970 to 2000 and served as the corporation's long-time treasurer, managing pension investments for 20 years. He also helped Central Jersey Radiologists open the first independent MRI facility in Monmouth County.

Michael Altman, MD'63, a pulmonologist; Sept. 18.

After earning his medical degree, Altman returned to his undergraduate alma mater of the University of Pittsburgh for residency in Internal Medicine. He stayed at Pitt for a research fellowship in pulmonary diseases, focusing on physiologic and biochemical adaptations to hypoxemia, which included studying diving reflexes in harbor seals. He also served in the U.S. Air Force for two years, first serving at the School of Aerospace Medicine in San Antonio, then at the hospital at the Korat Royal Thai Airforce Base in Thailand.

Altman was on the faculty at the Temple University Medical School for two years before moving to The Ohio State University School of Medicine in Columbus, where he became director of the Independent Study Program—a computer-based, self-paced program for medical school years 1 & 2. In 1985, he became associate dean for Education Programs and a member of the Pulmonary Division of the Department of Medicine at Northwestern University in Chicago. In 1990, he took on the newly designed position of associate dean for Medical Informatics and Computer-Assisted Learning.

1970s

Edith A. McFadden, MD⁷⁹, GME'84, an otolaryngologist; April 12.

McFadden earned a BS in Chemistry from Cabrini College in 1965. In 1979, she graduated from the University of Pennsylvania School of Medicine, where she also completed her residency in Otolaryngology—Head and Neck Surgery.

1980s

Murray Grossman, MD, GME'89, director of the Penn Frontotemporal Degeneration Center; April 4.

Grossman earned his EdD in 1977 at the Boston VA Aphasia Research Center, followed by a postdoctoral fellowship at the Massachusetts Institute of Technology (Cambridge, MA). He earned his medical degree from McGill University (Montreal, Canada) in 1985, and completed his residency at



the University of Pennsylvania School of Medicine's Department of Neurology in 1989. He remained at Penn for his entire career and founded the Penn Frontotemporal Degeneration (FTD) Center in 2010. Grossman conducted seminal linguistics studies and worked on emerging treatments for FTD, Alzheimer's disease, and related dementias, shaping the modern diagnostic criteria for primary progressive aphasia and related disorders. He authored more than 600 publications during his career.

FACULTY

Christopher (Casey) Brown, PhD, associate professor of Genetics; March 18.

Brown completed his undergraduate studies at the University of Nebraska, followed by his PhD at Stanford University (Stanford, CA), and post-doctoral research



fellowship at the University of Chicago. While serving as an associate professor of Genetics at the University of Pennsylvania, he held a leadership role in the Genomics and Computational Biology Graduate Group.

Brown's work centered on approaches to understanding how human genetic variation controls gene expression. While his focus was initially on expression in the liver, these studies quickly expanded to a wide array of cell types and tissues. He was involved in multiple research collaborations, generating several landmark publications and garnering substantial NIH funding. He was a pivotal member of the Genotype-Tissue Expression Consortium, a nationwide multi-center effort that was established to explore the basis for gene regulatory pathways in numerous tissue types.

McIver Edwards, Jr., MD. See Class of 1962.

Murray Grossman, MD. See Class of 1989.

LEGACY GIVING

New Face of Planned Giving

The door is always open for a conversation with Robert Vosburgh, JD, Penn Medicine's new executive director of planned giving. No stranger to Penn, over the past decade he has worked with donors across campus to create legacies that will propel the university into its future.



"We are here to help educate and inform people so they can articulate their philanthropic vision and ambitions," Vosburgh says of his team's responsibilities. "We help our donors become better consumers of legal and financial services, which enables them to enlist their trusted advisors to accomplish all their planning goals."

Vosburgh began his career at the Metropolitan Museum of Art, helping to research the provenance of looted art and artifacts. This inspired him to combine his background in medieval history and material culture with a law degree. "I've been really fortunate to use my interest in law to help people effectuate their charitable intent and realize philanthropic ambitions that they thought were impossible," Vosburgh says. "What's most rewarding is when people realize that they can do a lot more than they imagined."

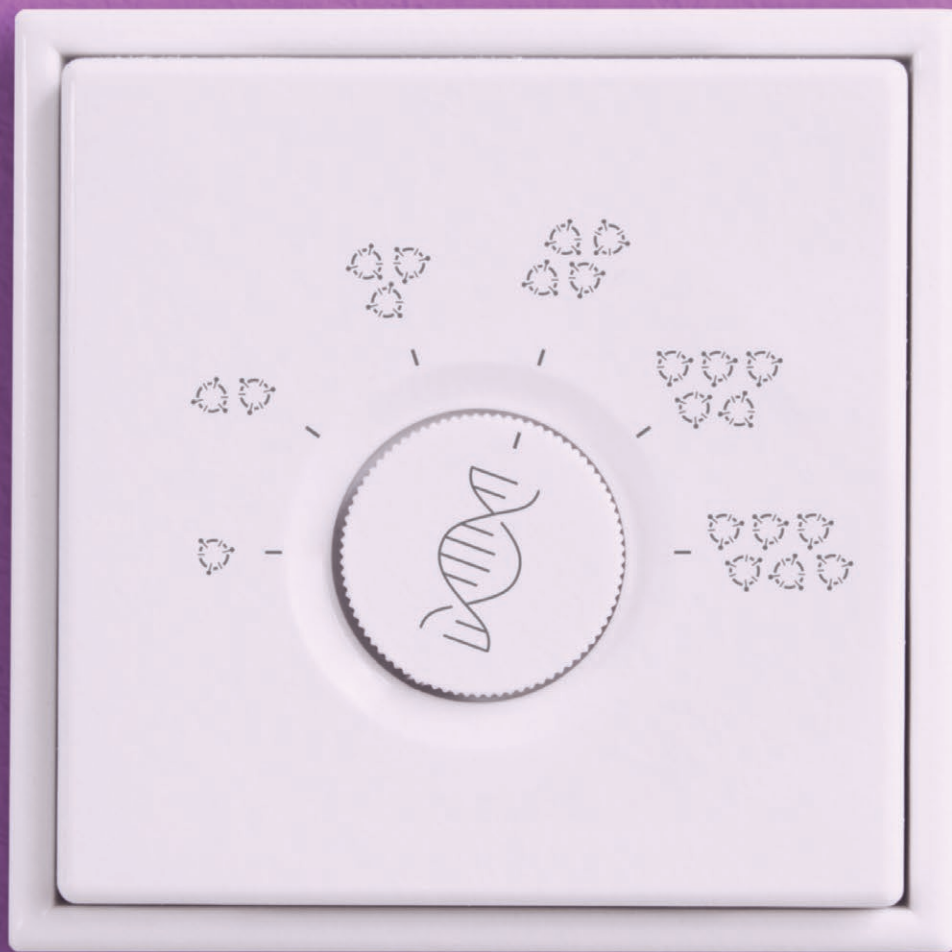
Planned giving may seem like a laundry list of complex instruments, from charitable gift annuities to IRA rollovers to charitable remainder trusts, to name only a few ways that donors have supported Penn Medicine. As Vosburgh explains, "The 1939 Internal Revenue Code could fit on one page of the *New York Times*. Now, it's about 4 million words, and that doesn't include all the corresponding materials." Vosburgh joined Penn Medicine at a time of "some pretty significant changes, particularly with respect to qualified plans like 401(k)s and 403(b)s. An awful lot of Americans have those, and not necessarily Americans of great wealth. Planned giving allows a broader swath of people to use their resources in a tax-efficient way to make an even bigger impact."

Vosburgh and his team help the Penn Medicine community do just that—providing stable, lasting support for causes they value deeply. "The exciting moments are when we can help folks do even more of the good that they want to do, when someone realizes that with a little bit of forethought, they can do five scholarships instead of one or actually make an outright gift and see its impact now. For those who are interested in breakthroughs, scientific discovery, quality of care, and access to care, Penn Medicine is a fantastic future steward of resources.

"Plus, it feels good," Vosburgh adds. "We can all make a difference."

► **Robert can be reached at 215-898-5341 or vosburgh@upenn.edu.**

A DIMMER SWITCH FOR ALLERGIC INFLAMMATION



New research is bolstering scientific understanding behind why some people are more prone to allergies than others.

Researchers in the Perelman School of Medicine identified how genetic differences that alter a specific protein called ETS1 can affect our body's response to allergies. They found that small changes in ETS1 in an animal model can lead to an increased likelihood for allergic reactions that cause inflammation. The findings were published recently in *Immunity*.

The United States Centers for Disease Control and Prevention reports that allergies rank as the sixth most prevalent cause of chronic illness in the U.S., resulting in an annual expenditure exceeding \$18 billion. While previous research has established a strong genetic basis for allergies and identified specific genetic sequence variations which predispose for these chronic diseases, how our DNA can affect our chances of developing an allergy remains unclear. But understanding this could lead to improved research and potential new treatments.

By using modern genomics and imaging techniques, a collaborative team of researchers co-led by Penn's Golnaz Vahedi, PhD, an associate professor of Genetics, and Jorge Henao-Mejia, MD, PhD, an associate professor of Pathology and Laboratory Medicine, found that the ETS1 protein plays a role in controlling a type of immune cell called CD4+ T helper cells, which are important in allergic reactions and help orchestrate the immune response by activating and coordinating other immune cells.

DNA interactions within the genomic segment encompassing the ETS1 gene control how much of the ETS1 protein is made.

"We discovered that these interactions work like a dimmer switch," said Vahedi. "When there are changes in the DNA in this area, it can mess up the dimmer switch, causing problems with controlling the ETS1 protein. This can lead to imbalances in our immune cells and cause allergic inflammations."

This same phenomenon may occur in other common diseases such as autoimmune disorders, Henao-Mejia added.

Many complex conditions with a genetic component, like allergies, cannot be explained by simply "turning off" one gene. Instead, they may be caused by small changes in the DNA that affect how genes work together. Researchers are still learning how these changes in DNA relate to how our genes are organized and how they affect how genes are expressed in most complex diseases.

"This work demonstrates how small differences in our DNA can disturb the balance between our immune cells, resulting in significant observable characteristics in patients," Henao-Mejia said. ▢

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Penn Medicine topped off construction this summer on seven new floors of research space atop an existing office building at 3600 Civic Center Boulevard. Three floors will be dedicated to new discoveries related to Immune Health, immunology, and autoimmune disease.

▶ **Read more about the Immune Health vision on page 12.**

