research

at THOMAS JEFFERSON UNIVERSITY

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Forging Partnerships to Fight Cancer

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Thomas Jefferson University
HOME OF SIDNEY KIMMEL MEDICAL COLLEGE

***Research* at Thomas Jefferson University**
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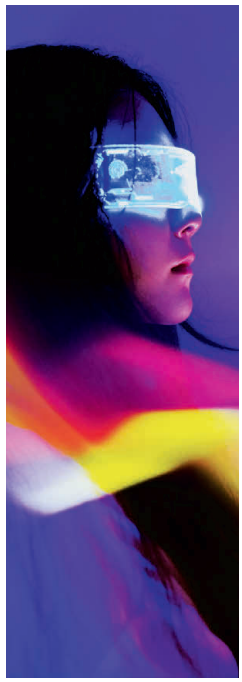

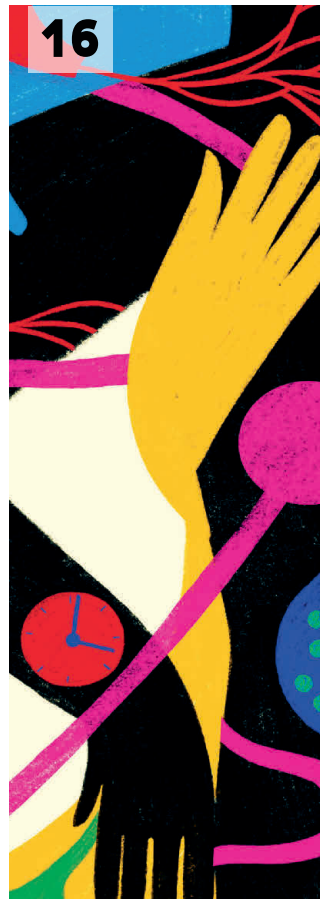

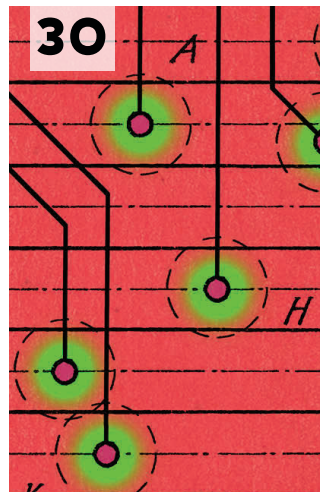

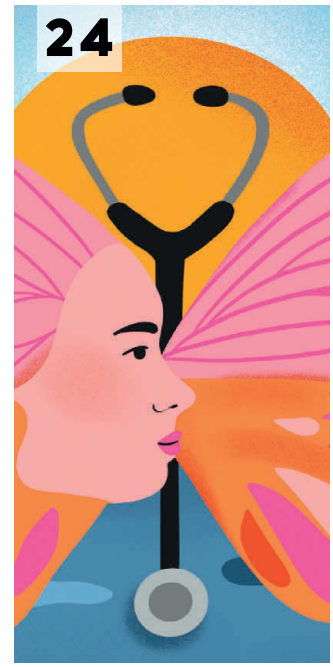

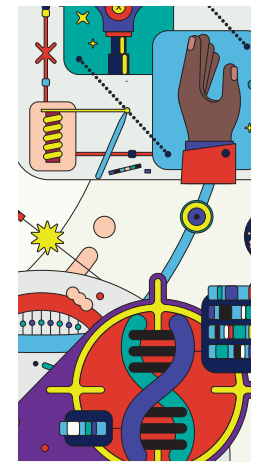

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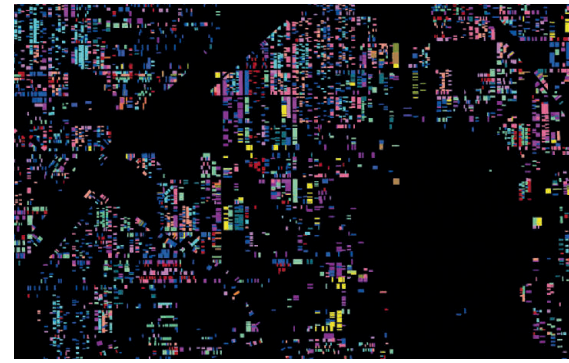


RESEARCH IN OUR THIRD CENTURY

DAVID WHELLAN, MD
JAMES C. WILSON PROFESSOR OF MEDICINE, DEPUTY PROVOST FOR RESEARCH

As Thomas Jefferson University enters its third century of education, research and care, it's inspiring to consider all that this institution has achieved since its founding in 1824. Jefferson has grown from one of the nation's first and most innovative medical colleges to a multifaceted national research university, healthcare system and nonprofit health insurance plan.

Today's Jefferson is driving major advances in biomedical research, from discovery science through translation to clinical trials and population science. Our impact in biomedical sciences was made clear this spring, when Jefferson's Sidney Kimmel Cancer Center became a National Cancer Institute-designated Comprehensive Cancer Center — an accomplishment discussed in more detail on pages 14 and 15.

You'll observe throughout this magazine, we are also creating and applying new knowledge across a broad range of disciplines and topics: from sociology and history to finance and business management; from the use of artificial intelligence in health care to the effects of art on communities; from the link between food and structural racism to advances in material sciences and the design of tomorrow's cities.

While traditionally some challenges are best addressed by working within a single discipline and within the traditional research categories of basic, translational, clinical and applied, Jefferson's way of envisioning research has evolved. In particular, as our academic range has expanded over the years — especially since our 2017 merger with Philadelphia University — we have increasingly invested in transdisciplinary, team-based studies and multifaceted projects.

We've made those investments because we know that addressing the most significant social, economic or technical challenges our society faces requires robust collaboration — across departments, disciplines, professions and institutions. And it's clear that fulfilling the potential inherent in the research discoveries we make often requires us to hasten the translation and application of new knowledge and methods.

Thus, guided by the principle of collaboration, we're leveraging current strengths and building new teams to support our research and educational mission. We're asking faculty and students to pose the question, "How might my work influence or be useful to researchers in other fields?" — and we're providing resources for cross-disciplinary pilot studies. We're building new programmatic bridges between researchers and scholars on our two campuses. And we are nurturing deeper connections with the many communities that Jefferson serves so that we can better understand and address the specific components of the most pressing challenges they face.

For example, we are investing more time and resources to tackle the problem of health inequities and disparities in care. Today, Jefferson has more than 150 funded research and service activities focusing on health inequity challenges that range from substance use disorder to food insecurity to healthcare access — and beyond. Our research and service teams are working in communities across Pennsylvania and New Jersey, collaborating with a host of local and regional organizations. Together, through multidisciplinary teamwork and multi-organization partnerships, we are striving to more fully understand how inequities and disparities develop and persist — and to create and pursue strategies that remove those barriers to health and well-being for our patients and our broader community.

In these ways and many others, Jefferson is leveraging its 200 year-old foundation of discovery and application to help define what research and scholarship will look like in coming decades — all in service of our mission to improve lives of people throughout our region and around the world.

SEEKING ARTISTRY IN RESEARCH

Jefferson's Research as Art Competition celebrates all Jefferson faculty, students and staff who have an eye for the beauty in their research or scholarship. Explore a sampling of submissions here and learn about the winning entries and judges at research.jefferson.edu/art-competition.

"Spectrumgenesis" by Pooja Bhoge

The enchanting transformation of white light into a vibrant array of colors is a captivating natural phenomenon. It's also a poignant reminder of the magic inherent in white light, its therapeutic potential and how it impacts the circadian rhythms enhancing the well-being and healing of a human brain.

HOW WILL AI CHANGE HEALTH CARE?

Doctors say AI has the potential to reshape patient care for the better, but the technology needs to be implemented responsibly. →

BY MARILYN PERKINS

As the capabilities of artificial intelligence (AI) surge, the healthcare sector is rapidly finding new ways to use algorithms and machine learning for patient care. In 2022 alone, the Food and Drug Administration (FDA) approved over 90 different medical devices using AI, including algorithms that track atrial-fibrillation history or rapidly analyze X-rays to diagnose collapsed lungs. As these new technologies multiply, it's becoming clear to doctors and patients alike that AI has the potential to reshape medicine.

"Radiology is probably one of the specialties most impacted by artificial intelligence," says Nicholas Lim, MD, a radiology resident physician.

Of the over 500 submissions of AI medical devices authorized to date by the FDA, three-quarters are for radiologists. These tools improve image quality, detect difficult-to-see features and flag the most severe patients for immediate treatment. For example, in one study, Jefferson researchers identified 22 new AI-based brain imaging tools to speed stroke diagnosis and promote post-stroke recovery.

Radiologists are also experimenting with AI tools that help patients outside of the exam room. In a recent study, Ryan Lee, MD, chair of radiology at Jefferson Einstein Philadelphia Hospital, used an algorithm that analyzed physician reports to automatically recommend follow-up appointment dates. He found patients who received those automatic reminders were more likely to return for important follow-up visits than those who did not have these reminders.

Other medical fields are employing AI to improve patient care, too. Chen Wu, MD, a professor of neurological surgery and radiology, recently published a study that used machine learning to predict quality-of-life changes in patients with Parkinson's disease to help guide treatment. Based on clinical symptoms alone, the algorithm flagged patients who were likely to experience a drop in quality of life in the upcoming year for further testing and medical attention.

Dr. Wu imagines AI can help patients with Parkinson's even more in the future. One of his areas of expertise is deep brain stimulation (DBS), a method that helps restore function to damaged motor circuits in Parkinson's patients' brains. These devices often require months of delicate calibration, and success is highly dependent on the experience of the managing physician. Dr. Wu believes AI could be leveraged to rapidly calibrate DBS devices based on a patients' individual neurological features.

"The uniform results you get from AI could help standardize outcomes and care," says Dr. Wu. "That's where the big benefit is."

But while AI has the potential to improve patient care, there are risks if it isn't used carefully. One of the biggest problems is ensuring the data an algorithm is trained on is representative of the patients it's eventually used on. "If you train your model off of biased data, you're going to generate biased results," says Dr. Wu.

Dr. Lim says it's also important to understand how the algorithm works. Many AI algorithms are "black boxes," meaning programmers may not be sure how they generate their outputs. This is important as AI tools lacking in transparency could be more likely to demonstrate biases.

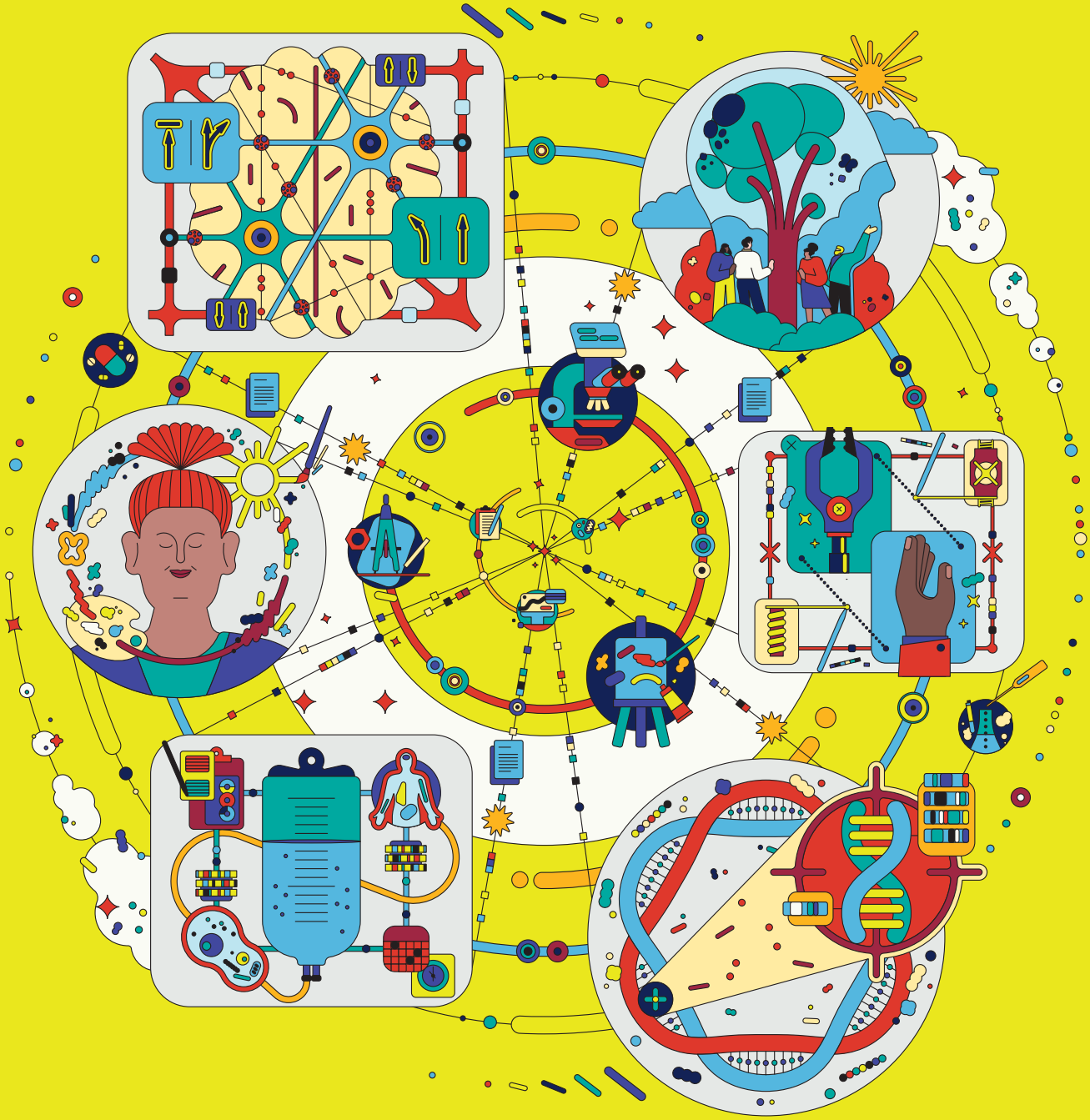
"It's important to understand the steps and calculations that the algorithm is going through to produce its output as best we can. This allows us to find potential weaknesses where health disparities may be perpetuated," says Dr. Lim.

But if these factors are addressed, Dr. Lim believes AI tools could be a pathway towards health equity: the attainment of good health for everyone regardless of gender, race or socioeconomic status. If algorithms are built in a way that accounts and corrects for current biases and inequities, they could reduce health disparities by improving diagnostic accuracy and overall patient care.

Patricia Henwood, MD, executive co-sponsor of Jefferson's newly formed AI Center of Expertise and the executive vice president and James D. and Mary Jo Danella Chief Quality Officer, agrees. "There's incredible promise and potential, and I think there's much more to come."

Ultimately, the doctors say that AI still won't be replacing them any time soon — it'll just be another way for them to serve patients.

"AI is not taking over what we do," says Dr. Lee. "The take home message is that the physician in concert with these tools will ultimately result in better patient care."



SIX STEPS FORWARD

exploring recent discoveries at Jefferson

ILLUSTRATIONS BY
BRATISLAV MILENKOVIC

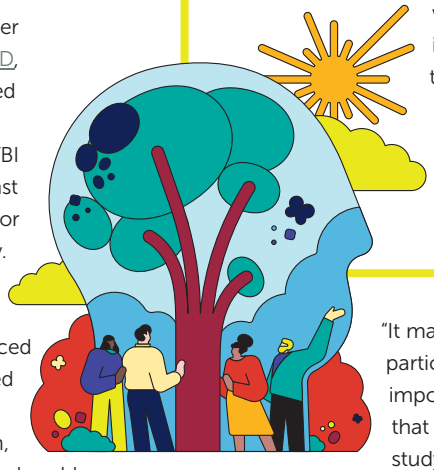
01.

DISCRIMINATION'S IMPACT ON RECOVERY

Traumatic brain injuries (TBIs) can lead to lifelong disability and require long-term medical care. While drugs and surgery can treat TBI, new research suggests that experiencing discrimination may hinder recovery.

We know that discrimination causes psychological distress, which can lead to downstream health problems. People with TBI are especially at risk for discrimination, as those from minoritized communities are more likely to sustain a TBI. What's more, TBIs can cause disabilities that are subject to discrimination.

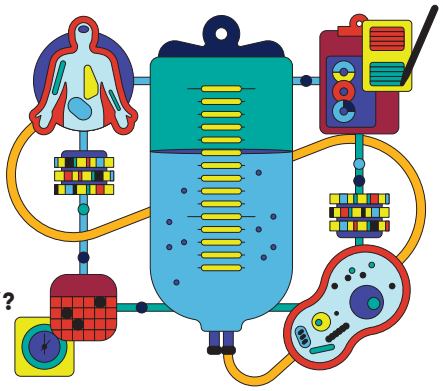
Rehabilitation researcher Umesh Venkatesan, PhD, and colleagues surveyed how often people with moderate and severe TBI felt discriminated against for any reason, related or unrelated to their injury. The study's results showed that TBI patients who experienced discrimination measured higher on scales of anxiety and depression, showed more behavioral problems like poor self-regulation and even reported worse quality of life.



"It makes it particularly important that we study these social factors and experiences in our patients," says Dr. Venkatesan. "Because social issues like discrimination may have been negatively influencing their whole lives, there's no reason to believe these factors are going to stop influencing their health after the brain injury. If anything, the injury might make tough situations worse."

BY MARILYN PERKINS

02.



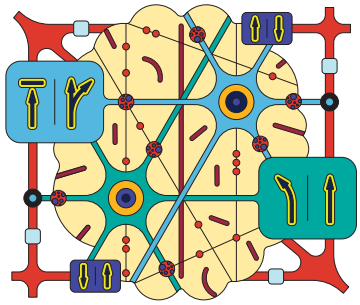
DO STEROIDS AFFECT CANCER IMMUNOTHERAPY?

Steroids are commonly given during cancer care, either to treat the disease or manage symptoms like pain or nausea. However, steroids can suppress the immune system and interfere with immunotherapy, which is why most clinical trials for immunotherapy exclude patients treated with steroids. Outside of the controlled setting of a clinical trial, though, many patients are treated with both immunotherapy and steroids, but studies specifically looking at the interaction of these two drugs have yielded mixed results.

Researchers Nikita Nikita, MD, and cancer epidemiologist Grace Lu-Yao, PhD, and colleagues at the Sidney Kimmel Comprehensive Cancer Center sought to address this question with the largest population-based real-world study to date. Through a database search, they identified 1,671 melanoma patients treated with immunotherapy, 907 of whom also received steroids within 12 months prior to their immunotherapy. "It is important to monitor cancer patients who took steroids prior to receiving immunotherapy because of the possible drug interaction," says Dr. Nikita.

The researchers found that patients who had steroids within a month prior to immunotherapy had a 126% higher risk of death than those without steroid exposure in the year before immunotherapy. "Further studies are warranted to understand the mechanism, but this research suggests a longer time interval between these two therapies may improve survival," says Dr. Lu-Yao.

BY EDYTA ZIELINSKA



03.

TRAFFICKING CONTROL IN BRAIN CELLS

A single brain cell or neuron can send signals to hundreds of others using its axon — a thin fiber that acts like a telephone cable carrying electrical messages and splitting into numerous tree-like branches. Different cellular materials need to be transported along the axon and its elaborate branches to support the development and function of brain cells, but how they do it has been a puzzle.

Neuroscientist Le Ma, PhD, and colleagues developed a simple method to tackle the question. They cultured neurons in a dish and studied transport at the junction of two branches by tagging a cellular cargo called lysosomes, small sacs that travel along branches to remove waste and recycle nutrients. They found that if the two branches were the same length, the lysosomes traveled equally to both. However, if one branch was longer than the other, more lysosomes travelled to the longer one, suggesting that branch length influenced transport.

They also looked at the growth cone — the branch tip that acts like a sensor, looking for things to grow toward or to avoid. They found that lysosomes preferred traveling to branches with more dynamic growth cones over the still ones. Interestingly, when they used a molecular tool to make a still branch more dynamic, the lysosomes swarmed to it.

"These experiments showed us how trafficking is regulated in brain cells and could give insight into how neuronal transport impacts conditions like nerve injury and memory loss," says Dr. Ma.

BY KARUNA MEDA

04.

FINDING A HIDDEN CANCER TARGET

Triple-negative breast cancer often fails to respond to treatments. But Jefferson researchers have identified a vulnerability in these cells, and designed a way to exploit it.

Their studies revolve around two genes: p53 and MDM2. When p53 functions properly, it can prevent cancer; and in healthy cells MDM2 turns off p53. One strategy for treating breast cancer has been to use drugs that block the MDM2 and reactivate p53.

However, most people with triple-negative breast cancer have a mutated and inactive p53 gene that allows cancers to grow. "For these patients, MDM2 inhibitors are ineffective and have toxic side effects," explains Clare Adams, PhD, lead author on the study. That fact led scientists to assume that MDM2 drugs would not work in any cancer with a mutated or deleted p53.

This approach could open a new chapter for many kinds of p53–mutant cancers.

"However, we discovered that deleting the MDM2 gene actually kills mouse cancer cells lacking p53," Dr. Adams says. So, the investigators designed and tested a compound called MDM2 PROTAC that causes the MDM2 protein to be "chewed up" and eliminated from cells. "Existing MDM2 inhibitors cause a toxic build-up of MDM2, but eliminating MDM2 avoids this toxicity," says Dr. Adams. The result: the cancer cells died, regardless of whether p53 was mutated or not, with no signs of toxicity.

"This approach could open a new chapter for many kinds of p53-mutant cancers," says senior author Christine Eischen, PhD, the Herbert A. Rosenthal, MD '56 Professor of Cancer Research at the Sidney Kimmel Comprehensive Cancer Center.

BY MERRILL MEADOW & LAUREN LANGEBEIN

05.

EXPLORING ART THERAPY'S BROADER BENEFITS

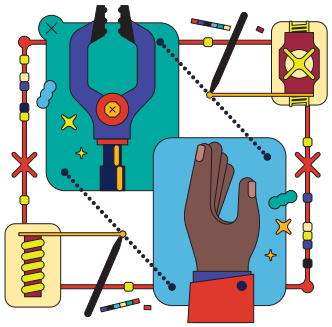
Many people might define art therapy simply as "making art as a way to feel better." Yet it has much deeper and multifaceted benefits. "It enables a person to turn inward reflection into outward creative expression of thoughts, emotions or struggles, non-verbally," says art therapy researcher Rachel Brandoff, PhD.

Much of Dr. Brandoff's clinical work and research focuses on individuals dealing with prolonged grief disorder and physical or emotional trauma. But she also explores how art therapy can enhance well-being for communities and across fields — ranging from medicine, nursing and public health to architecture and interior design.

One such initiative, a unique course she co-created called Health and the Art Experience, guides students from multiple disciplines to develop, implement and analyze projects where art is designed to address specific social, emotional or educational issues. For example, one project studied whether an economically depressed town's self-regard could change when it invited artists to adorn abandoned homes with light. Another assessed bus shelter art installations as a tool for building awareness about local resurgence in HIV/AIDS.

"I believe deeply that efforts like these can have wide-ranging benefits for individuals and communities," Dr. Brandoff explains. "In fact, I'm working with colleagues to bring art therapy principles to the design of outpatient healthcare facilities — such as Jefferson's new Honickman Center — as another way of providing care for our patients, their families and our surrounding communities."

BY MERRILL MEADOW



06.

DESIGNING FOR UNIQUE PATIENT NEEDS

Developing assistive technologies for people with disabilities is a challenge. "If something is not properly designed, our clients can't use it," says occupational therapist Kim Mollo, OTD.

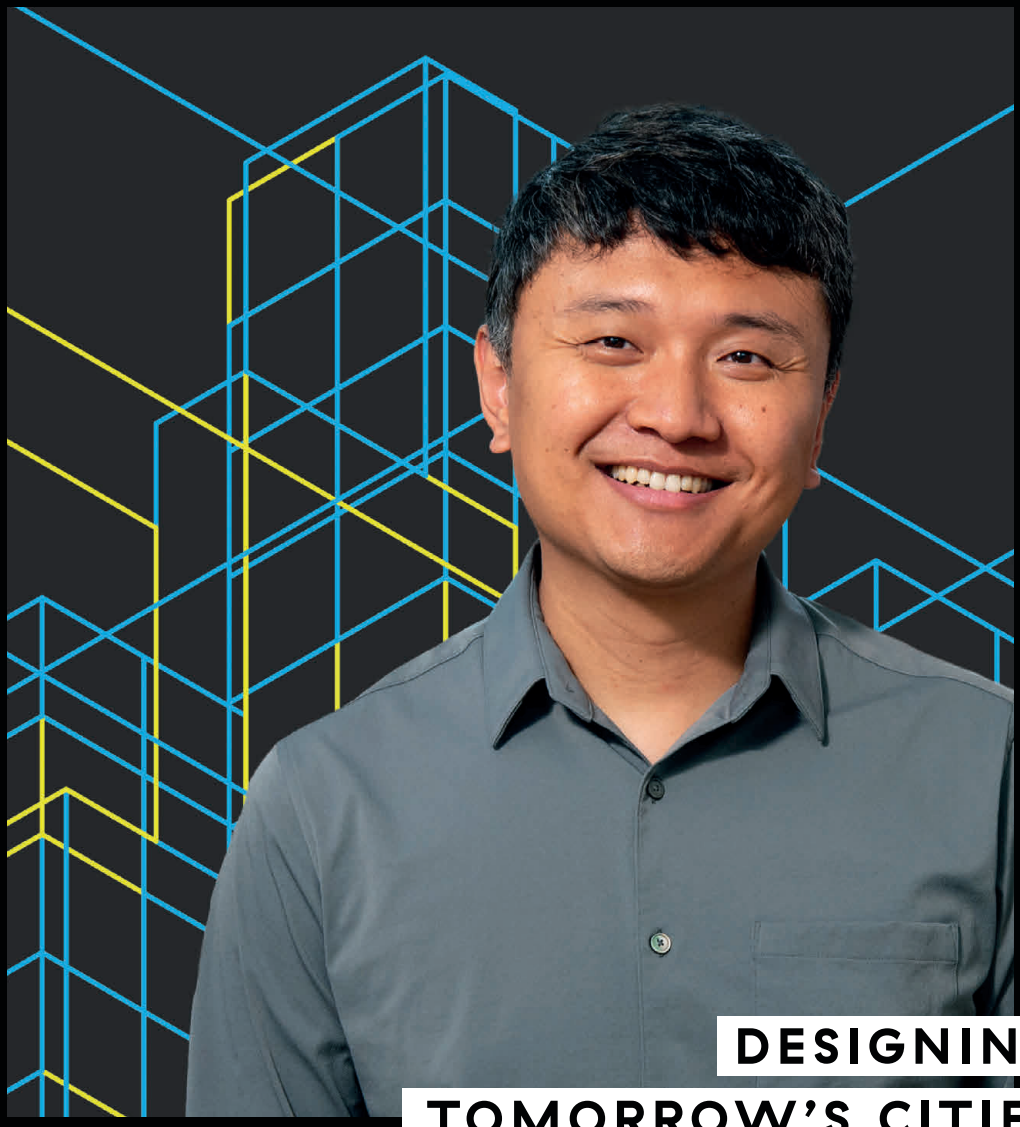
To develop better designs, Dr. Mollo, along with industrial designers Eric Schneider and Tod Corlett, invited students studying occupational therapy or industrial design to develop devices for those with fibrodysplasia ossificans progressiva (FOP). FOP is a rare, genetic condition that causes mobility loss as muscles and tendons turn to bone.

> ***The students' innovative design has the potential to help all people who are dealing with mobility and strength issues, not just those with FOP.***
>
> —PROFESSOR SCHNEIDER

For their clinical capstone course, occupational therapy students interviewed people with FOP about their needs and desired improvements to their current assistive devices. Then, industrial design students developed, prototyped and tested devices to meet those needs.

The student groups designed four devices, the most developed of which is an improved reacher or grabber. Traditional reachers have a pistol grip that requires considerable hand strength and is impossible to adjust. With the students' new design, FOP patients with limited arm mobility can use a tunable electro-mechanical gripper with a telescoping and pivoting handle to reach objects. The dial-controlled claw is accurate enough to "pick up a potato chip without crushing it, and strong enough to lift a full water bottle," says Schneider. "This innovative design has the potential to help all people who are dealing with mobility and strength issues, not just those with FOP."

BY MARILYN PERKINS



PENG DU, PHD

DESIGNING TOMORROW'S CITIES WITH DATA

Employing sophisticated analytics and computer modeling to create healthy, sustainable cities that can accommodate the growing global population.

BY PATRICK MONAGHAN AND MERRILL MEADOW
PHOTOGRAPH © THOMAS JEFFERSON UNIVERSITY PHOTOGRAPHY SERVICES

By 2050, nearly 2.5 billion more people will live in urban areas than do today. How can global society accommodate that growth without putting quality of life at risk, harming local environments and worsening global climate change?

"We must examine urban environments holistically and reimagine how cities are built and function," says Peng Du, PhD, an architecture researcher. "That deep, comprehensive rethinking is essential if we want future generations of urban residents to have healthy, sustainable and equitable lives." Dr. Du, who directs the master's programs in urban design, urban analytics and geodesign at the College of Architecture and the Built Environment (CABE), studies how to use data-driven and simulation-based tools to address climate change, population shifts, public health and resource depletion in urban areas. He is also a collaborator on the Smart & Healthy Cities Institute, which forges collaborations between design, engineering, health and science to build more resilient urban environments.

Dr. Du has lived in and loved big cities most of his life. From a young age he viewed architects as great contributors to culture and human well-being. "So it was natural," he observes, "that I became an architect focusing on creating urban environments that make people's lives better." To do that effectively, he came to believe, "Architects and designers need to stay on the leading edge of technology — not just in how we construct individual buildings, but also in how we design cities."

Today, he pursues those goals by teaching future architects and conducting urban design-focused research. In parallel, he is a program leader for the Council on Tall Buildings and Urban Habitat, a global research and education organization dedicated to helping create smart, sustainable cities.

"My particular passion is helping develop net-zero carbon buildings and cities by using large data sets and quantifiable measurements to produce scenarios that help envision how best to manage urban growth," he explains. "Together, my students and I explore how to use data-driven simulations to assess the trade-offs among urban design goals such as solar energy potential, outdoor thermal comfort, availability of green space, pleasant visual aesthetics and ease of mobility."

But the overarching objective under which all those goals fit is ensuring the well-being of urban residents as both population and climate-change effects grow. "If we do not significantly reduce the amount of carbon emitted when buildings are constructed and when they're in use," Dr. Du states, "urban residents will find themselves increasingly vulnerable to climate change's most dire effects."

While firmly convinced that technology-driven urban design can help build more livable, equitable, resilient and efficient cities for our futures, Dr. Du believes that design must start with understanding people's lived experience of cities. "One of my most important goals is helping my students understand how to balance what we learn from data analysis and computer modeling with what people tell us," he says.

"Dr. Du believes that design must start with understanding people's lived experience of cities."

That's why, for example, Dr. Du and his research collaborators are working with Jefferson students to develop a digital method of visualizing and analyzing the trade-off between ease of transportation and potential negative effects (for example, increased air pollution and atmospheric carbon) on the health of people living in Center City Philadelphia. "This project will give residents, designers and policymakers a new way of viewing and evaluating the practical costs and impacts on people's day-to-day lives," Dr. Du explains.

And in another research and education project, he is developing technology that more directly connects students with the lived experience in the center of a big city. It's a system for using mixed reality (MR) technology — integrating both virtual and augmented reality imaging — to give designers an opportunity to experience a variety of scenarios. "Currently, we're using MR to think about the future of downtown Philadelphia," he says. "The students are really energized by the whole experience."

MARILISA NAVARRO, PHD

STRUCTURAL RACISM THROUGH FOOD

Exploring how racial inequities are reinforced, as well as how acts of resistance are empowered, through food.

BY KARUNA MEDA
PHOTOGRAPH © THOMAS JEFFERSON UNIVERSITY PHOTOGRAPHY SERVICES

On February 15, 2010, an event dubbed "The Compton Cookout" took place on the campus of University of California, San Diego (UCSD). Hosted by several fraternities, it used the guise of Black History Month to celebrate Black culture — but in reality, it was steeped in belittling racist tropes and stereotypes. Attendees were invited to experience "life in the ghetto;" women were told to dress as "ghetto chicks;" "purple drank" would be served. The party sparked protests and sit-ins by students and faculty. Among those protesting was Marilisa Navarro, who at the time was a doctoral student in the Ethnic Studies program at UCSD.

"It was devastating," recalls Dr. Navarro, now an assistant professor of African American Studies at the College of Humanities and Sciences. "However, it also wasn't totally surprising. There was such a small percentage of Black faculty and students on campus, it wasn't the most welcoming place."

With both her parents being activists in social justice movements of the 1960's-70's, the importance of racial representation was central to Dr. Navarro's upbringing. As an African American and Puerto Rican, she had also often encountered being a minority in predominantly white spaces. In fact, as the drama of "The Compton Cookout" unfolded, Dr. Navarro noticed feeling marginalized beyond UCSD's campus.

"At the time, San Diego had these massive farmer's markets that would go for several blocks," she remembers. "Whenever I went, I noticed how both the vendors and consumers were primarily white. I was usually one of the few people of color there."

She began to think about how a food space like a farmer's market, touted as being equal access, could shape ideas about race. She wondered if communities of color had similar access to nutritious, fresh food and soon became involved with an organization that started a farmer's market in a predominantly Black and LatinX neighborhood. It was much smaller compared to the markets in majority white neighborhoods, and not easily accessible by public transit. This inequity became a driving topic of Dr. Navarro's doctoral research, examining how food is connected to social, political and economic issues, including segregation and gentrification.She also began exploring how these same communities were also engaging in self-empowerment. "These systemic imbalances were not necessarily novel," she says, "but we knew less about how communities were resisting them."

> **"Food is not just about choice, but is a cultural artifact linked to so many other factors."**
>
> —DR. NAVARRO

She analyzed food events and cookbooks, and found that culturally appropriate foods had been in these communities for hundreds of years: dandelion greens, certain types of legumes and grains. But these foods had largely been rejected by historically Eurocentric, white diets. She found examples of chefs and home cooks resisting those ideals. One such person was African American gourmet, vegan chef Bryant Terry who is part of the slow food movement, which promotes local and traditional cooking as an alternative to fast food. Through his work, Dr. Navarro explored how Black culinary traditions have been excluded from what has been considered "slow food" despite the fact that Black communities have been cooking "slowly" for centuries. Based on this work, she developed a concept called "Black culinary epistemologies" which she defines as the "culinary knowledge produced by Black chefs, cooks and food preparers that build upon the Black radical tradition, reframe Black foods and consumption, and participate in life-making practices in death-producing spaces."

In a full circle of sorts, Dr. Navarro is now reexamining "The Compton Cookout" and its flattened interpretation of Black femininity through the "Ghetto Chick" and the parallels to the iconic "Aunt Jemima" brand. "These two figures seemingly have nothing to do with each other," she explains, "but they're both examples of ways in which Black women are being constructed through food as inferior to white womanhood." Food is not just about individual choice, says Dr. Navarro, but is a cultural artifact linked to so many other factors.

A CENTER BUILT AROUND PARTNERSHIPS

Dr. Andrew Chapman, Director
Sidney Kimmel Comprehensive Cancer Center

Research shows that patients of comprehensive cancer centers have better outcomes. This fact results from many factors, but I believe three are paramount. First, our commitment to cancer prevention and early diagnosis. Second, our expertise in testing and delivering leading-edge treatments. Third, our dedication to engaging a diverse array of people to guide our research and turn discoveries into effective ways of diagnosing and treating the disease.

At Sidney Kimmel Comprehensive Cancer Center, partnerships are at the heart of each of those factors: partnerships with the communities we serve, among disciplinary experts, between researchers and clinicians, and with other universities.

The expanding number of individuals, neighborhoods and organizations who comprise our community-based partners are the engines for the cancer education and research "dialogue" that is essential to our mission. The accompanying article, Forging Partnerships to Fight Cancer, wonderfully captures the benefits of this dialogue for both the people we serve and the Cancer Center's researchers.

The dialogue enables us to learn more about a community's needs and concerns regarding cancer screening and treatment. It helps community members gain a better understanding of how they might prevent cancer and why early diagnosis is so important. It provides researchers with concrete direction to improve prevention, diagnosis and treatment. And it creates trusted pathways for individuals, families and communities to participate in clinical trials of new diagnostic methods and treatments — participation that's necessary to ensure they are broadly effective.

Our communities fuel our research partnerships as well. For example, the Sidney Kimmel Comprehensive Cancer Center Research Consortium is a longstanding collaboration between Thomas Jefferson University and Drexel University focusing on basic research and population health. The researchers involved are constantly searching for new and more effective ways to combat cancer in the lab and through community dialogue. We believe that the Consortium is a national model for comprehensive cancer center institutional collaborations.

Our partnerships are central to all that we hope to achieve. And we're working hard to build on them.

Forging Partnerships to Fight Cancer

Cancer researchers and community members come together to address racial disparities in prostate cancer at the molecular and patient level. →

BY KARUNA MEDA
ILLUSTRATIONS BY DIANA EJAITA

Sunlight streams through the windows

at the New Covenant Church in Germantown, Philadelphia. It's the church that Moriah Cunningham grew up in. As she surveys the crowd filled with her family, friends and people who raised her, she's filled with gratitude. But she also sees a community that faces an insidious, yet profound, threat — cancer. For Moriah, the threat hits close to home.

"My father was diagnosed with cancer when I was seven," she recalls. "I didn't even know it at the time. It wasn't until I was older that my mom told us that he is a cancer survivor."

Moriah's father was one of several family members who would be struck by the disease. Particularly, many of her uncles have had prostate cancer. It's a microcosm of the disproportionate impact that the disease has: Black men are 1.76 times more likely to be diagnosed and 2.14 times more likely to die from prostate cancer compared to white men. The personal impact has driven Moriah to research the biological underpinnings of this racial disparity as a PhD student at Thomas Jefferson University.

But the biggest challenge she has encountered is the pronounced scarcity of data on Black prostate cancer patients in clinical and basic science research.

She soon realized the science was just one aspect — to increase participation in cancer screenings and clinical trials in order to improve representation in the data, she had to engage her community. The gathering at the New Covenant Church, whose congregation is historically African American, was an outreach event she had organized to raise awareness about prostate cancer and provide access to free screenings.

Community engagement is central to decreasing cancer disparities and health disparities in general. Indeed, comprehensive cancer centers, which have the highest designation given by the National Cancer Institute (NCI), must demonstrate a commitment to the communities they serve through outreach. When Thomas Jefferson University's Sidney Kimmel Comprehensive Cancer Center applied for "comprehensive" status, outreach programs like Moriah's were noted as an area of strength, along with leading-edge and transdisciplinary research.

The Cancer Center is now one of 57 centers in the country with comprehensive status. With this comes an ever-clear responsibility and ability to connect Philadelphia's most at-risk populations to cancer research and care in a mutually beneficial way, whereby the science and the community support each other.

UNDERSTANDING THE RACIAL DISPARITY IN PROSTATE CANCER

"The reasons why African American men are more likely to develop and die from prostate cancer compared to white men continue to baffle us," says researcher and clinician Leonard Gomella, MD, the Bernard W. Godwin, Jr. Professor of Prostate Cancer, who chairs the department of urology and is a senior director for clinical affairs at the Cancer Center. "While we've come a long way, we haven't been able to definitively identify the root of this disparity."

The drivers of this phenomenon are complex and wide-ranging: Evidence points to healthcare access problems, comorbidities, social inequities that result in lifestyle and dietary issues, as well as differences in genetic and molecular pathways that can impact tumor biology in different patient populations. Which of these factors is the most significant has been hotly debated.

This discussion is further complicated by the fact that "race" is a social construct rather than a biological definition. African American communities have diverse and genetically heterogeneous ancestry, and so the biological properties of their cancer as well as their response to cancer treatment is likely to be equally diverse.

"We know that mutations in certain genes can make prostate cancer more aggressive," says Moriah. "These genetic mutations may vary across and within different populations. The problem is we simply don't have robust data to make comparisons." The lack of representation makes it difficult to parse out biological factors from socioeconomic factors that drive disparities.

"One of the ways we can start to overcome this gap in data is to be more targeted with our screening and awareness programs and reach out to communities who are going to benefit the most, like African American men," says Dr. Gomella. Over the last year, the Cancer Center has worked with community organizations like the Prostate Conditions Education Council and corporate partners such as Dietz & Watson and Janssen to conduct screening in their catchment area. Of the 322 participants, 43% identified as African American. "This data is important for us to know we're reaching communities with the highest burden of prostate cancer," says Dr. Gomella. "Moriah's connection with the New Covenant Church and her project there expands these efforts."

Compared to white men, black men are:

1.76 times
more likely to be diagnosed with prostate cancer

2.14 times
more likely to die from prostate cancer

HOW CAN COMMUNITY ENGAGEMENT BRIDGE CANCER DISPARITIES?

An important part of that connection is Deacon Albert Blackstock, who has been a church leader for the past 40 years and helped Moriah in her efforts. In fact, he has been at the helm of organizing numerous health-related events for the church's multicultural community, with particular outreach to Black men. "It was a realization that we are dying at a higher rate."

When asked why Black men seem particularly reluctant to go to the doctor, Deacon Blackstock points to multiple observations from his community. "So many men would more readily fix their car than fix themselves. But there is also a level of mistrust of the medical community."

There is a legacy of mistreatment of Black people by scientists and doctors, most notably the Tuskegee syphilis study, which took place between 1930-70, in which life-saving medication was withheld from Black men. Race continues to play a role in health care, through implicit bias and "race correcting" clinical algorithms that have been shown to systematically disadvantage Black patients. Consequently, a 2022 survey by the Pew Research Center found that 61% of Black adults say that research misconduct is just as likely to occur today; and only 35% say there are measures in place today that will prevent serious cases of misconduct.

This mistrust is a major barrier to Black people participating in research, particularly in clinical trials that could be life-saving. Clinical trials involve the testing of a novel, more targeted therapy, before it's available on the market.

"Our designation as a Comprehensive Cancer Center means that patients will have even greater access to the latest clinical trials, and potentially earlier in their treatment journey," says the Center's director Dr. Andrew Chapman. The benefits of this are reflected in research that has shown that cancer patients treated at comprehensive cancer centers generally lived longer than those treated elsewhere.

But the benefits of clinical trials are largely dependent on patient participation. Numerous studies have shown that minority populations are often underrepresented in clinical trials in the U.S., which can lead to research findings being generalized across populations.

This is problematic in the face of disparities, particularly Black Americans having the highest overall cancer death rate of any racial or ethnic group in the U.S. for more than four decades.

In order to improve clinical trial participation, the NCI made a call to action to cancer centers to engage their catchment areas to build trust and respond to the needs of underserved communities. In fact, in 2016, the NCI added community outreach and engagement as an evaluation criterion for a center to be NCI-designated, a status that the Cancer Center earned again in 2017.

ESTABLISHING COMMUNITY ENGAGEMENT ACROSS THE CANCER RESEARCH CONTINUUM

"While every NCI-designated cancer center has a community outreach component, what you do with that can set you apart," says Amy Leader, PhD, director of the Cancer Center's office of community outreach and engagement, which was established three years ago.

Since its inception, the Cancer Center's outreach office has gradually built an infrastructure to sustain a bidirectional relationship between the Cancer Center and the community. These include mobile cancer screenings, bringing clinical trial advocates to communities, and inviting community members to work with scientists at the Cancer Center so they can experience research behind-the-scenes. These approaches have the capacity to improve health outcomes and empower community members.

However, there are challenges. A study found that only 5% of cancer survivors reported participating in research, even though 26% expressed interest in participating. One barrier is the disconnect between laboratory scientists and the community. Historically, patients are more likely to interact with clinicians and population science researchers like Dr. Leader. But basic science researchers are far more removed, and lack formal training in communicating to the general public.

To bridge this gap, the Center's outreach office and the office of cancer research training and education coordination collaborated to create a unique program in which cancer research trainees like Moriah design, implement and evaluate a community engagement project. This is an opportunity for early-career scientists to build communication skills and an appreciation for the community's needs, and in turn for community members to voice their personal experiences to scientists. This dialogue can generate research that is useful to and trusted by patients.

When Moriah's mentor at the time Matthew Schiewer, PhD, learned about the program, he knew it was right up Moriah's alley and encouraged her to apply. "I already had a strong interest in science communication and outreach," says Moriah, "but when I realized how the lack of community engagement directly impacts my research, it became a passion." She became one of four trainees in the program's inaugural cohort.

BRINGING THE SCIENCE TO THE COMMUNITY

As Moriah thought about how her project could address the burden of prostate cancer among Black men, her childhood church seemed like a great place to start. When she reached out to Deacon Blackstock with the idea, he jumped at the opportunity.

"We are keenly aware of the burden of prostate cancer in our community," he says. "Moreover, Moriah represents a voice at the table."

The impact of her community seeing themselves represented in the scientific arena was not lost on Moriah. Black people are historically underrepresented in science: a recent report found that just 9% of the STEM workforce in the U.S. identifies as Black. "Many men we're trying to reach remember things like the Tuskegee experiments," says Moriah. "Knowing that research that might help them is being done by someone from their community helps to build trust."

The groundwork for this trust involved educating the community about the disease and offering transparency around related research findings. Moriah put together a short presentation on important prostate cancer facts. She also gave insight into the scientific process, using her own work as an example: She focuses on a protein called Poly (ADP-ribose) polymerase-1 or PARP-1, which plays a role in DNA damage. Drugs that inhibit PARP-1 activity are sometimes used to treat prostate cancer.

Moriah also invited Jefferson urologist Whitney Smith, MD, and Fox Chase Cancer Center epidemiologist Charnita Ziegler-Johnson, PhD, to speak — they both identify as Black. For some in the audience, it was their first time encountering researchers and clinicians who looked like them. Even the event volunteers from nearby West Chester University's student organization called "Empowering Communities Around You" identified as Black. "I really wanted this event to be by the community, for the community," says Moriah.

Free prostate cancer screening for prostate specific antigen (PSA) was offered on-site during the event to emphasize the importance of early detection. Of the 47 attendees, all who identified as Black men, more than half received screening - for some it was their first time. Five men ended up having an elevated PSA level and were referred to a urologist at the Cancer Center for follow-up care.

"I'm really thankful I got screened. It turns out I had a recurrence of prostate cancer that I had developed decades ago," says one individual, who has been a key figure in Moriah's life at the church. "But because I caught it at an early stage, my prognosis is good, despite being older."

> **You're not only going to be surrounded by the brightest minds in cancer research, you are also going to be supported in every way.**
>
> **— DR. CHAPMAN**

For Moriah, it was deep and personal validation of the project. "It was so rewarding to learn that the event changed someone's life," she says. And it changed hers too – she went back to the laboratory with ideas that would influence her research trajectory.

BRINGING THE COMMUNITY TO THE SCIENCE

When Moriah presented her work on PARP-1 at the event and how targeting its activity can affect prostate cancer, someone in the audience asked: Do Black men respond differently to PARP inhibitors?

It's something that had already been percolating in Moriah's mind and was unexplored in the field. But hearing her community express interest spurred her to make this a focus of her thesis research. She first had to understand whether there were differences in PARP-1 between Black and white prostate cancer patients. Normally, PARP-1 helps recruit repair proteins to a site of damaged DNA, moving away once the repair protein is in place. However, in prostate cancer, PARP-1 becomes overactive, allowing the cancer cells to grow with abnormal DNA. A few years ago, Dr. Schiewer had collected important data to describe the mechanisms of how overactive PARP-1 influences the availability of repair proteins in prostate cancer.

Moriah decided to reanalyze this data and separate the tissue samples by race. There were around 50 European American samples and only 12 African American samples with prostate cancer. She compared PARP-1 activity between the two groups and her preliminary analysis indicated that PARP-1 activity is higher in African American patients. This could, in turn, make prostate cancer more aggressive in African American patients vs. European American patients. It could also mean that PARP inhibitors might be differentially effective in African American patients.

While the preliminary results are promising, Moriah is collecting more evidence. Using tissue explants derived from patients that retain all the salient features of the original tumor, she plans to explore if there are any other genetic differences in PARP-1 and response to PARP-1 inhibitors between different racial backgrounds.

"I hope this work shows why representation of different patient populations, especially high-risk ones, is so important in clinical research," says Moriah.

EXPANDING THE PERSONAL CONNECTION

Moriah would go on to organize a second event for prostate cancer at the New Covenant church — she was one of two trainees who continued their work beyond the scope of the Cancer Center's outreach program. She brought in more Black scientific experts and an advocate from Prostate Cancer Zero, the leading national nonprofit that provides education and support to communities impacted by the disease.

Dr. Leader and the outreach office are rigorously collecting data on their programming, including the projects of Moriah and the three other trainees in her cohort. "This data allows us to evaluate the effectiveness of our initiatives so we can improve them in the future," says Dr. Leader.

The Cancer Center will continue to build on their outreach to at-risk communities, providing evidence-based solutions for community engagement in research. "Moriah stepping out of the laboratory and into the community sends a powerful message," says Dr. Gomella. "Anytime we can make that personal connection, it resonates more with people. The information becomes more meaningful and they're more likely to be proactive about screening and participating in research."

"We want our patients to know we envelop you with care," says Dr. Chapman. "You're not only going to be surrounded by the brightest minds in cancer research, but you are also going to be supported in every way."

For Moriah, community engagement will continue to be a central part of her scientific career. "I feel like you have to have a certain amount of love for your community to do research that is going to change lives," she says. "This work is a labor of love."

"Vacancy" by Craig Griffen

Image created from a GIS (Geographic Information System) map of Lower North Philadelphia (generated by Research Assistant Trisha Kawa) to explore potential sites for sustainable, urban infill housing. Each different color indicates the depth of the building lot and thereby how many housing units it can hold.

BREAKING THROUGH

Jefferson researchers inform evidence-based guidelines for transgender patients

BY KARUNA MEDA | ILLUSTRATIONS BY SOL COTTI

Lilly McBride was twenty-six years old when she came out as transgender, though she had known for years that something felt different. When she was younger, she observed the changes happening in her male body and longed for them to be more like her female peers. "It's painful to think that for more than half my life, I was never me."

Her journey of transitioning involved many components — building a supportive social network; seeking out counseling; and using fashion and makeup to express her identity outside of the gender binary. She also sought out gender-affirming hormone therapy to achieve desirable physical characteristics.

Throughout this experience, she became aware of the challenges that both transgender patients and health providers face in having open dialogue about care. She's taken part in clinical trials, including here at Jefferson Health, as well as education efforts in her own community to further the understanding of gender-affirming care.

But Lilly makes the caveat that not all transgender people seek hormone therapy or gender-affirming surgery, and that routine health care is just as important. In a report from the Center for American Progress, nearly half of transgender people — and 68% of transgender people of color — described having experienced discrimination from a medical provider.

At the heart of inclusive care is that an individual is truly seen —

This dissuades many transgender people from going to the doctor, jeopardizing essential screenings and follow-ups. On the provider side, a lack of training means that many doctors, nurses and administrative staff don't feel adequately prepared to provide culturally sensitive care for transgender patients.

RESEARCH INTO IMPROVING GENDER-AFFIRMING CARE

Several researchers at Thomas Jefferson University and Jefferson Health are working to bolster evidence-based approaches and provide education for patients and providers in two central areas of concern for the transgender community: HIV therapy and cancer care. The approaches used in these studies all fall under the umbrella of gender-affirming care.

Gender-affirming care, as defined by the World Health Organization, is a range of social, psychological, behavioral and medical services "designed to support and affirm an individual's gender identity." The World Professional Association for Transgender Health (WPATH) outlines well-established, evidence-based guidelines on who can access what form of gender-affirming care, and when they are eligible to receive it. The WPATH, along with every major medical and mental health organization in the U.S. — including the American Medical Association and the American Psychological Association — recognizes that gender-affirming care is medically necessary.

This care is embodied in Jefferson Pride Care — Haddonfield, a multidisciplinary LGBTQIA+ affirming practice and the first of its kind in South Jersey. It joins Jefferson Einstein Philadelphia Hospital's Pride Care at Community Practice Center, which has been providing care for over a decade. Many patients who have sought care at these clinics identify as transgender, and the stories from patients and doctors alike reflect the impact of inclusive care. In a recent article on Jefferson Health's Living Well blog, Dr. Baligh Yehia, president of Jefferson Health, explains that, "At the heart of inclusive care is that an individual is truly seen — seen by their

seen by their doctor, care team and the community.

— DR. YEHIA

LILLY MCBRIDE

doctor, care team and the community. Inclusivity is about feeling welcomed, valued and respected, no matter where you're from or who you are. This is a core value of Jefferson:
putting people first."

Research has shown that gender-affirming care can improve well-being in transgender individuals. Last year, a multicenter U.S. study funded by the National Institutes of Health and published in the New England Journal of Medicine found that 315 transgender and non-binary individuals experienced significant improvement in gender dysphoria, and sustained improvements in depression and anxiety over two years after starting gender-affirming hormones. It was the largest study of its kind, with the longest follow-up, and it supported previous evidence from numerous studies in transgender individuals.

"If I could wave a magic wand and feel safe in my body, I would do it in a second. But it doesn't work like that," says Lilly.

The work of Jefferson researchers is critical in addressing knowledge gaps, because they define what gender-affirming care is, and provide clarity on the range of approaches it includes, and their benefits.

> "If I could wave a magic wand and feel safe in my body, I would do it in a second."
>
> — Lilly McBride

A LIFE-THREATENING CHOICE

"I am considered an "elder" in the transgender community. There aren't that many of us because so many perished during the AIDS epidemic," says Lilly, who came out as transgender in 2010. According to the World Health Organization, transgender women are 49 times more likely to be living with HIV-1 than the general population, and have a higher prevalence than transgender men. This reflects factors like stigma, discrimination, negative healthcare encounters and limited access to health care.

Antiretroviral drugs help keep HIV-1 from developing into AIDS. However, transgender women living with HIV-1 infection often worry that antiretroviral drugs will interfere with their hormone therapy.

In one study, 57% of transgender women with HIV-1 reported this concern to their healthcare provider, with 40% citingit as a reason to not use antiretroviral drugs, hormone therapy, or both.

"It's hard to pinpoint the exact origin of this belief," says clinical pharmacologist Walter Kraft, MD. "But it means that some transgender women are skipping their HIV meds. Even one missed dose can drastically reduce the level of drug in the body needed to keep the virus in check."

"There are so few studies that have examined this interaction specifically in transgender women," says Edwin Lam, PharmD, who worked with Dr. Kraft to study this topic during his research fellowship. "This lack of robust data means we don't have clear guidelines to offer to our transgender patients."

Her role as an activist in the Philadelphia LGBTQ+ community was critical in recruiting more volunteers for the study. "She gave us so many great suggestions for reaching the transgender community," says Courtenay Fulmor, the research nurse coordinator for the study who was responsible for patient screening and education, "including cultural and community service events and support groups." But, even with these efforts, there was one major aspect of the study that gave potential volunteers pause.

"To participate, women had to agree to a drug wash-out," says Kevin Lam, PharmD, another research fellow who continued the project after Dr. Edwin Lam (unrelated) took up a new position. "This means that volunteers had to stop whatever hormone therapy they were on so they could get a uniform dose of hormones while in the clinic, along with the antiretrovirals."

> So few studies have examined this drug interaction, specifically in trans women.
>
> — DR. EDWIN LAM

To address this gap, Dr. Lam and Dr. Kraft embarked on a clinical trial to assess how the two types of drug interact. They assessed two antiretroviral drugs (doravirine and tenofovir disoproxil fumarate) with feminizing hormone therapies (17ß-estradiol and spironolactone), which had not yet been studied together in transgender women.

The goal of the Phase 1 trial was to study this interaction in healthy transgender women, so as not to put those living with HIV-1 at any risk for drug resistance. Recruiting volunteers was impeded by the COVID-19 pandemic, and the team had to try several outreach approaches – social media, targeted marketing campaigns and apps like Grindr. It was through these channels that Lilly learned about the trial and volunteered as a participant.

"For someone to stop the medication that was helping them in their transition — it's a lot to ask for," says Lilly. "It was not a pleasant experience. I started to feel this incongruent connection between myself and my body. Masculine features started to reappear, which was very dysphoric and distressing."

The trial managed to recruit eight healthy volunteers, including Lilly, which was adequate for a drug interaction study. By comparing the levels of each drug in each participant's blood throughout the study, the researchers could see that there were no changes in the effectiveness of any of the drugs. Most importantly, they saw no clinically significant interaction between the antiretrovirals and feminizing hormones."

This data gives transgender women the confidence to stay on their HIV medication," says Dr. Kraft.

For Lilly, participating in the trial was all worth it. "No one should have to make the choice between two life-saving drugs."

TRAINING CANCER CARE DOCTORS IN INCLUSIVE CARE

Another area where education can have a life-changing impact on patient outcomes is cancer care. The combination of increased risk factors (like HIV, smoking and alcohol use), lack of access to health care and mistrust of providers contributes to poorer outcomes in LGBTQ+ cancer patients. In fact, one study showed that transgender people may be diagnosed at later stages, be less likely to receive treatment and have worse survival for several cancer types, compared to cisgender patients.

A critical step in improving outcomes is cancer screening. However, there are no guidelines specific to the LGBTQ+ population, which leads to uncertainty for both providers and community members. A 2022 study led by Nicole Simone, MD, the Margaret Q. Landenberger Professor and a researcher at the Sidney Kimmel Comprehensive Cancer Center, surveyed over 400 LGBTQ+ community members and found that over half of the respondents were not certain what cancer screenings should be done and at what age they should begin. Half of the respondents also reported that emotional distress prevented them from seeking cancer screening, citing fear of discrimination and lack of training among physicians and nurses. These concerns are not unfounded. In fact, a subsequent study in 2023 by Dr. Simone and colleagues surveyed 355 providers nationwide and found that only 28% reported previous LGBTQ-related training and 71% agreed their clinics would benefit from training.

"Better training and education have the potential to improve consensus among physicians about cancer screening for this population," says Dr. Simone. "It would take out a lot of guesswork."

Ana Maria Lopez, MD, another cancer physician and researcher the Cancer Center, was part of a research team that recently created and tested the Together-Equitable-Accessible-Meaningful (TEAM) training program to educate cancer teams across the country to improve culturally competent care for sexual and gender minorities. Healthcare providers spent approximately a year participating with the TEAM training, learning about inclusive care and understanding the facilitators and barriers to

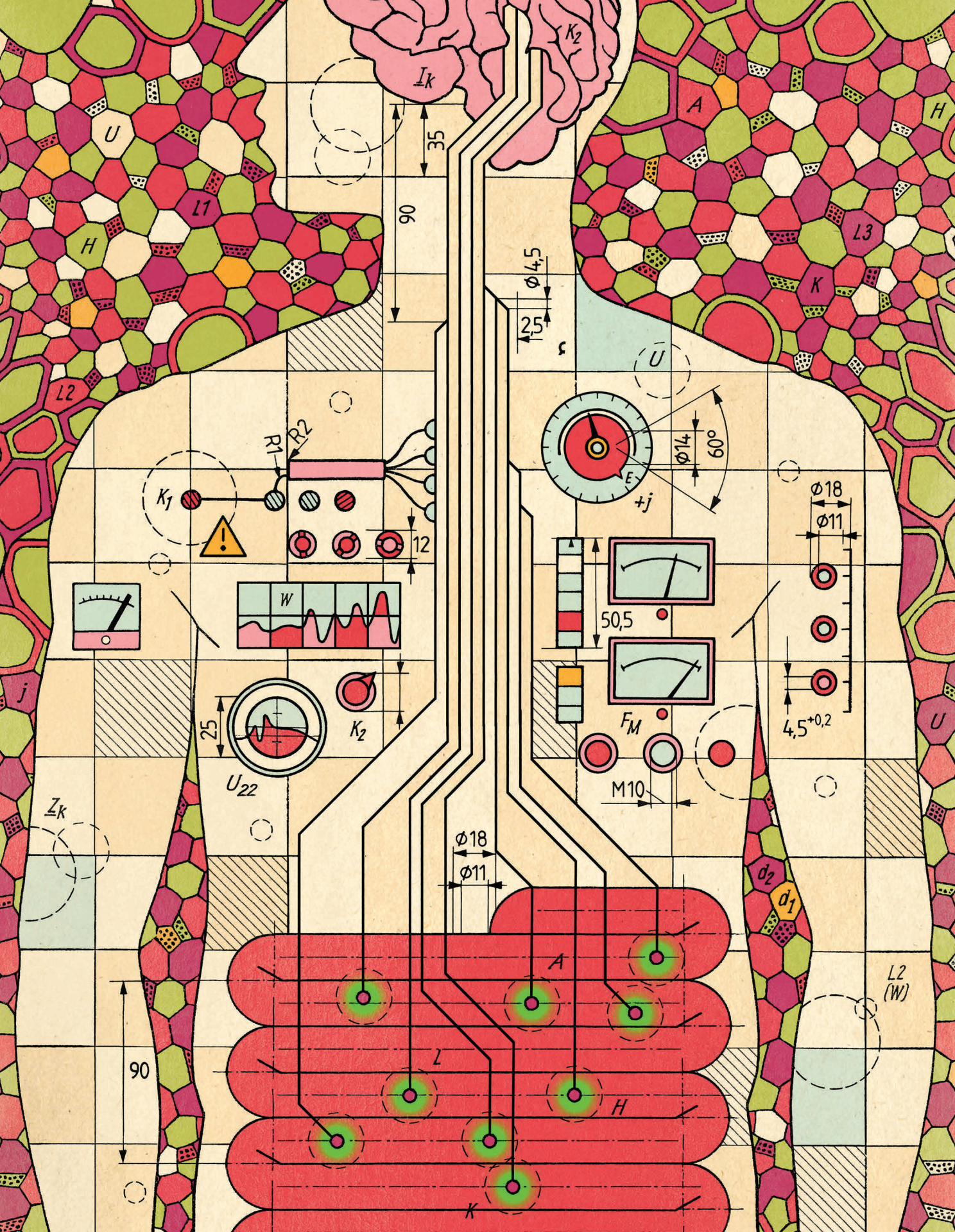
implementing initiatives for equitable care. These initiatives ranged from creating inclusive signage in clinics to asking patients their preferred pronouns.

"It may seem like a simple question, but without asking our patients how they identify we can't screen patients for the right things or provide them with appropriate care," Dr. Lopez says.

Just last year Jefferson Health began collecting demographic information on patients' sexual orientation and gender identity in its medical records. Dr. Lopez says it's a first step to ensure transgender people are no longer invisible in research and care.

At the end of the TEAM training, the 28 participants had significantly improved clinical knowledge and behaviors around cancer care for sexual and gender minorities. However, the team is now creating a new tool to assess how meaningful the improvements are to patients. "It will need to be a mutual, ongoing education," says Dr. Lopez.

Lilly agrees. "The transgender community needs doctors and researchers as allies. We've had to fight just to be seen and heard and accepted. We just want to be cared for."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how the pain in your gut connects to your mind

An investigation into why a drug for irritable bowel syndrome had unexpected pain-relieving properties sheds new light on how the gut communicates with the brain. →

BY MARILYN PERKINS | ILLUSTRATIONS BY CHRISTIAN GRALINGEN

A faint green glow reflects in the eyes of Scott Waldman, MD, the Samuel M. V. Hamilton Family Professor of Medicine and Chair of the Department of Pharmacology, Physiology, and Cancer Biology, as he pores over his microscope. His slides are fixed with tiny slivers of intestinal tissue, each containing the molecule he's spent his career studying — guanylyl cyclase C (GCC). Marked by a fluorescent label, it acts like a tiny neon sign, pointing him in the right direction.

Dr. Waldman had spent decades tracing how GCC was key for healthy digestion. He'd connected its dysfunction to the growth of colorectal cancer, and had even begun using it to develop a cancer vaccine.

But after years of research, there was still one big question on his mind — a question that percolated as he once again examined GCC under the microscope.

In the early 2000s, researchers developed a drug called linaclotide to treat irritable bowel syndrome (IBS). Modeled on the natural gut hormones that interact with GCC to regulate digestion, the drug was designed to kick start a cascade of chemical reactions that relieved constipation.

But linaclotide also had an unexpected effect: Although nothing about its structure suggested it would have pain-relieving properties, linaclotide soothed chronic visceral pain in nearly half of the IBS patients who took it.

for years,

Dr. Waldman wondered why this was. How could a drug with a simple effect on constipation — a problem of the digestive system — have an influence on chronic pain — a problem of the nervous system?

He had a feeling that the answer had something to do with the gut-brain axis, the bidirectional communication system that connects our digestive and nervous systems. But given how little scientists knew about the molecules involved in that communication at the time, he knew this wouldn't be an easy question to answer.

"We've only scratched the surface of the gut-brain axis," he says.

But when a bright MD/PhD student named Josh Barton joined his lab with an interest in the gut-brain axis, research exploring Dr. Waldman's question began to gain momentum. Their findings show the key may be a newly-discovered cell that acts as a conduit between the brain and the gut, illuminating new ways to target visceral pain in IBS.

We've only scratched the surface of the gut–brain axis.

— DR. WALDMAN

A CORE PAIN

Visceral pain — a type of pain that originates from the body's internal organs — affects about four out of ten IBS patients, and with an estimated 10 to 15% of the population affected by IBS, chronic visceral pain is a major public health issue. The condition can present as a dull ache, cramping, or pressure, and it indicates when our internal organs are inflamed, diseased or injured.

"Generally, chronic pain is one of the major health challenges of the entire world," says Angelo Lepore, PhD, a neuroscientist and pain expert at Jefferson. "Pain is protective, it's evolutionary. But this system is hijacked such that it becomes pathological."

In people with IBS, visceral pain often presents as hypersensitivity; this means their digestive organs are more tender than usual, suggesting that the signals along the gut-brain axis that normally regulate pain have gone haywire. "These types of disorders can be intractable and devastating," says Dr. Waldman.

For IBS patients with chronic visceral hypersensitivity, there are few therapeutic options. While some doctors prescribe opioids, these can cause constipation and worsen gastrointestinal dysfunction, and they also come with serious risks of tolerance and dependence.

So linaclotide's side effect of decreasing visceral pain was good news — but it wasn't a miracle cure, either. It doesn't work for everyone, and it can only be used in patients with the constipation subtype of IBS.

This gave Dr. Waldman an idea: If he could figure out the molecular mechanism behind linaclotide's pain-relieving properties, it might be possible to harness it into a new treatment for visceral hypersensitivity in IBS. And while he wasn't sure exactly how yet, he had a hunch that the GCC receptor would be involved.

A MYSTERIOUS NEW CELL

The search to understand how linaclotide dulled visceral pain was slow at first.

"We were scratching our heads," says Dr. Waldman. "There's no obvious biological basis for this phenomenon."

Dr. Waldman thought if he could visualize precisely where GCC was in the body, it might provide a clue. He had recently obtained genetically-engineered mice whose GCC molecules were tagged with a bright green fluorescent protein. This protein didn't change anything about GCC function, but it revealed where GCC was most concentrated when examined under a microscope. He wanted to see if GCC was present anywhere else outside of the intestines, like the nervous system, which controls pain signals.

Dr. Waldman didn't anticipate finding anything out of the ordinary in the tissue from the intestines, but to be thorough, he checked anyway. He expected to see a uniform green glow representing GCC distributed evenly throughout the intestinal lining, where it normally regulates water levels during digestion.

But there was something else on the microscope slides: bright green neon dots sprinkled throughout the intestines, indicating intense concentrations of GCC in small areas.

"There was a 'starry night' appearance of the tissue where you could see sparkles against the green background," says Dr. Waldman, referencing Van Gogh's famous painting The Starry Night. There were just one or two of these beaming "starry night" cells per microscopic view among thousands of faintly glowing intestinal-lining cells where GCC was known to reside.

It was Josh Barton, the new MD/PhD student in Dr. Wadman's lab, who had the idea to zoom in on these rare "starry night" cells. "Barton was the actual brains behind this phase of this project," says Dr. Waldman.

When Barton put the sparkling cells under a high-power microscope, he noticed something unusual about their shape: They didn't look anything like the intestinal-lining cells that normally contained GCC, which resemble rectangular brick pavers along a winding garden path. The "starry night" cells instead were shaped like little pyramids, with skinny tails jutting from one side and burrowing deep into the walls of the intestine.

Though nobody in the lab had seen these cells before, Barton had an inkling about what they might be. He had been reading a paper about a newly discovered cell type called a neuropod cell, and the similarities were eerie.

Neuropod cells are a sort of hybrid: Half intestinal-lining cell, half nerve cell or neuron, these cells share characteristics of both the digestive and the nervous system. Like intestinal-lining cells, they make GCC, and like neurons, they make the cellular machinery necessary to rapidly communicate with the rest of the nervous system. They are perfectly designed to act as a middleman between the gut and the nervous system.

"It's a unique and newly described cell that was under everybody's radar," says Dr. Waldman.

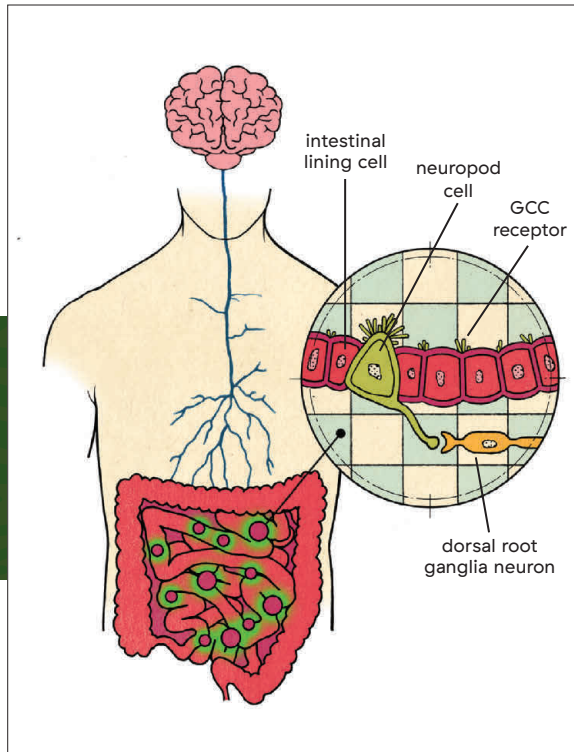
While Barton had a different topic in mind for his dissertation research at first, the puzzle of the "starry night" cells captivated him, and he changed course to focus on them. Wondering if these mysterious triangular cells might be neuropod cells, he isolated and analyzed them for the specific genetic markers that set neuropod cells apart from intestinal-lining cells. They were a match.

NEUROPOD CELLS: THE KEY TO VISCERAL PAIN?

Barton had shown that linaclotide's target, the GCC receptor, was highly concentrated in neuropod cells. This gave Barton and Dr. Waldman an idea: What if the GCC in neuropod cells was the key to understanding linaclotide's effects on visceral pain?

To find out, they needed to know what happened when GCC was removed from neuropod cells. If their theory was true, linaclotide wouldn't be able to alleviate visceral pain without GCC present.

Because it's not possible to do this sort of experiment in humans, Dr. Waldman used genetically-engineered mice as a model. "Mice have many of the same neural pathways that control pain as humans," says pain expert, Dr. Lepore, "So researchers can observe certain behaviors in mice that mimic visceral pain."

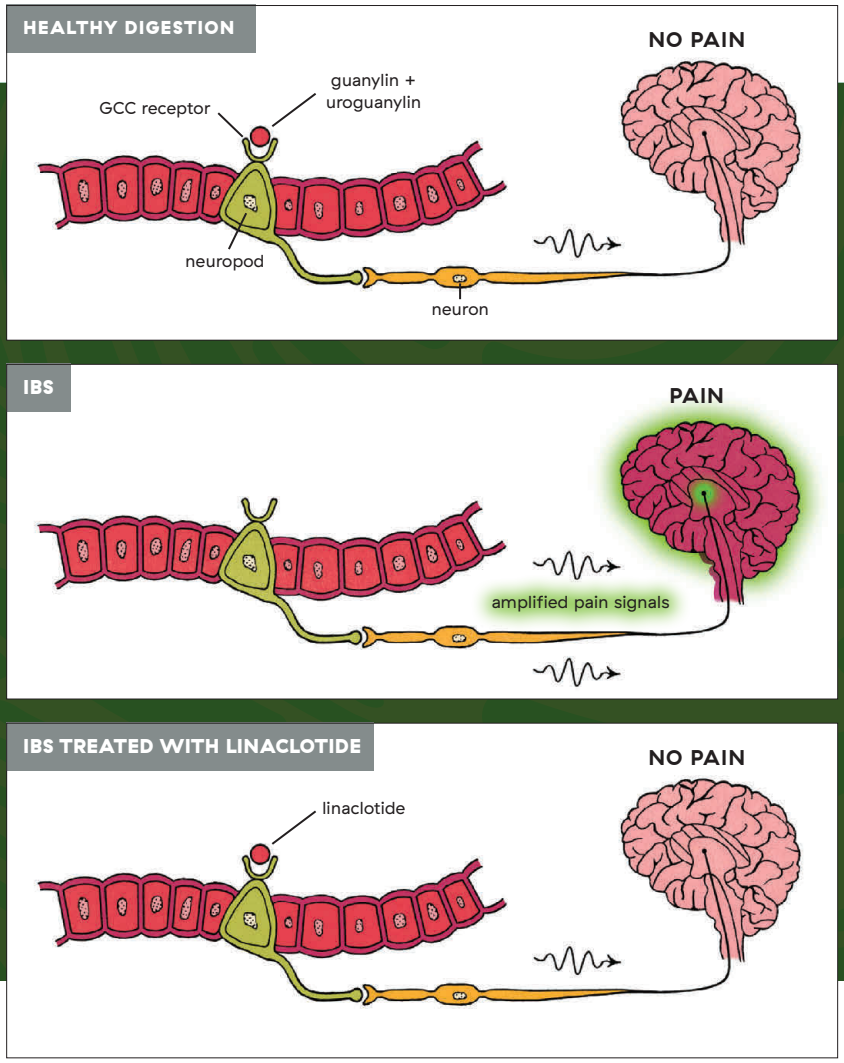


INSIDE THE INTESTINE

Neuropod cells look like a cross between intestinal lining cells and neurons. They are located along the intestinal lining, and they "reach out" to neurons that communicate with the brain.

THE MISSING PIECE →

When linaclotide (or the natural hormones it mimics) is not present to bind to GCC, neuropod cells act like a "megaphone" for visceral pain, amplifying slight feelings of sensitivity into intense signals of pain. When linaclotide is present to bind to GCC, it "quiets" or "turns off" the megaphone.



Without GCC in their neuropod cells, "the mice behavior mirrored symptoms of people with IBS," says Dr. Waldman. "In the absence of any external stimulation, they had pain."

And when the genetically engineered mice were given linaclotide to quell their visceral pain, it did little to help. Without GCC in neuropod cells, linaclotide no longer worked.

But what were the neuropod cells doing at the cellular level to relieve pain? To answer that question, Dr. Waldman recruited the help of neuroscientist Manuel Covarrubias, MD, PhD and MD/PhD student Tyler Alexander to examine the electrical activity of neuropod cells up close.

If neuropod cells really were the middlemen that relayed pain in the digestive system back to the brain, then they needed to directly communicate with the nervous system. To see if they did, Alexander grew neuropod cells in a petri dish alongside dorsal root ganglion cells, a type of neuron that transmits pain sensations from the body to the brain.

He found that when neuropod cells and dorsal root ganglia were placed next to each other, they naturally began to form synapses, or connection points, like tiny bridges between buildings. But just observing physical connections between the two cells wasn't enough to prove they were communicating; Dr. Covarrubias and Alexander also needed to observe electrical activity, the language of the nervous system.

With this knowledge, we can identify new therapies to silence the pain signals traveling from the gut to the brain, and potentially bring relief to patients.

— DR. WALDMAN

Using a tiny electrode to measure the electrical activity in a single cell, Alexander found that as the neuropod cells reached out and formed synapses, the dorsal root ganglia went from quiet and calm to buzzing with electrical activity.

"When these gut cells were making contact with the neurons," says Dr. Covarrubias, "the neurons actually started to generate multiple impulses." In the body, repeated electrical impulses would represent a pain signal being sent back up to the brain.

When Alexander sprinkled linaclotide over the neuropod cell, the pain signals from the dorsal root ganglion went quiet again. Whatever communication was naturally occurring between neuropod cells and the nervous system was blocked by the drug.

"Putting all of these pieces together," says Dr. Waldman, "We believe that the neuropod cell is the missing link between linaclotide's ability to fix visceral pain and its connection to the nervous system."

DIALING DOWN THE PAIN "AMPLIFIER"

Barton says that when he conceptualizes the role of the gut-brain axis in visceral pain, he imagines an amplifier.

When you plug in an electric guitar, explains Barton, a dial on the amplifier controls how much louder the guitar gets as it comes out of the speakers. Visceral pain, he believes, works the same way. If the volume of the music coming from the speaker represents the intensity of pain, the GCC molecules in neuropod cells control the dial. When linaclotide — or the natural hormones it's based on — is plentiful, the dial turns down, quieting or even muting visceral pain. When linaclotide isn't present, or natural gut hormone levels are too low, the dial turns up and the neuropod cells fire repeatedly, amplifying loud signals of pain back to the brain.

Dr. Waldman believes these findings suggest that IBS isn't just a disorder of digestion; it's also a dysregulation of the hormones that bridge the gap between the gut and the brain. Because linaclotide is modeled on natural digestive hormones, this research implies that if these hormones run low, it may lead to the excessive pain experienced by those with IBS.

Barton agrees. "IBS is really this black box for us right now," he says.

Dr. Waldman says continuing to untangle the complexities of the gut-brain axis will be key to treating diseases like IBS.

"We're still understanding the molecular components of neuropod cells," says Dr. Waldman. "With this knowledge, we can identify new therapies to silence the pain signals traveling from the gut to the brain, and potentially bring relief to patients with these intractable pain syndromes."

BOOSTS AND BLOCKS FOR BETTER ASTHMA MEDS

An asthma attack constricts the muscles around the airways of the lungs. Within seconds of a rescue inhaler puff, the medication (beta agonists) binds to its receptor on the surface of cells (A) and sends signals that relax the muscle, so air can pass freely. A side effect (B) of these drugs is that they attract arrestin, a molecule that in turn, blocks the signal to relax, which can put people with asthma at risk. Now, two teams discovered molecules that could (C) block arrestin, so that the receptors stay at the surface, available to relax again in case of a second asthma attack and (D) make the signal to relax stronger by holding the medicine in the receptor longer.

ATTACKING ASTHMA WITH A ONE-TWO PUNCH

Rescue inhalers can stop working in some people. Two teams discover molecules that could make puffs work better, longer.

BY EDYTA ZIELINSKA
ILLUSTRATION BY SAYO STUDIO

For many people with asthma, rescue inhalers are a sort of miracle drug. From gasping for air one minute, heart racing, mind foggy, to near immediate relief and calmer breath the next. And yet, roughly ten people die each day from asthma in the U.S. One reason for these largely preventable deaths is that rescue inhalers — this emergency tool, a powerful and effective medicine — can actually stop working, putting people at risk.

To understand why they stop working, researchers zoomed into what was happening on the surface of the cells that line our airways. These cells are covered with little antenna-like molecules sticking through the surface of the cell. These antennae, or receptors, look for signals that tell the cell to change its behavior. In asthma, that antenna is called the beta-adrenergic receptor. When it detects the main ingredient of rescue inhalers, called a beta agonist, it sends two signals: One that's positive and one that's a negative side-effect at the crux of rescue-inhaler failure.

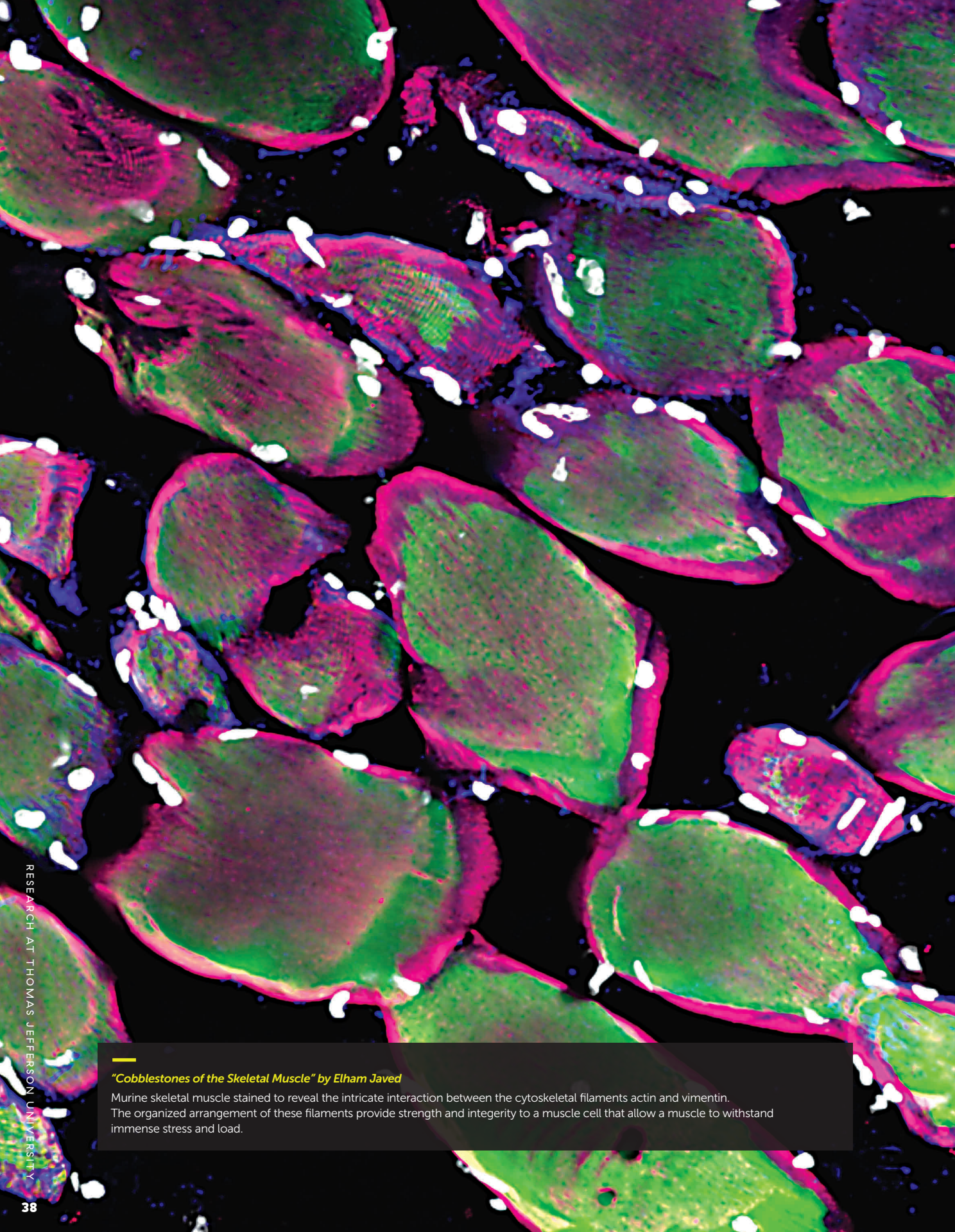
The positive signal triggers the cell to relax the smooth muscles of the airway and makes breathing easier. The negative signal turns on a cellular molecule called arrestin, which halts the positive signal, reducing muscle relaxation. With arrestin in place, the beta-agonist can no longer signal muscle relaxation, leaving that lung tissue unresponsive to the next puff from the rescue inhaler, if a need arises too soon.

Two research teams have been working on both sides of the beta-adrenergic receptor's signals — the positive and the negative — finding ways to tamp down the negative and boost the positive. If these approaches continue to show promise in further tests, they could help reduce death from asthma due to rescue inhaler failure.

For the last decade, biochemist Jeffrey Benovic, PhD, and team have been looking for a way to block the negative arrestin-mediated signal without suppressing the beneficial signals. In a recent study, co-first authors Michael Ippolito, a graduate student, and Francesco De Pascali, PhD, a postdoctoral fellow working with Dr. Benovic and colleague Charles Scott, PhD, found a molecule that did just that in airway smooth muscle cells in mice. After the receptor binds the rescue inhaler's beta-agonist, Dr. Benovic's drug would jump in and block arrestin, keeping the antennae ready to receive the next dose of medicine.

In the meantime, another team of researchers were looking at boosting the positive signals that quickly relieve airway constriction. Deepak Deshpande, PhD, and team at the Center for Translational Medicine were looking for a way to make the positive signal and smooth muscle relaxation stronger and active a little bit longer. Most receptors interact with their target briefly, then let it go, essentially halting the signal to relax. But Dr. Deshpande's group designed a second chemical that would come in and bind another part of the receptor, causing it to change shape slightly and clamp down on the beta-agonist so that the positive signal stays on longer. They were able to show that when their compound was delivered to human cells and in mice along with the beta-agonist, the strength of the drug improved 60-70%, without a comparable increase in arrestin or receptor degradation.

Although it's unclear whether Dr. Benovic and Dr. Deshpande's chemicals could be used together, both could potentially improve how rescue inhalers work for people with asthma, when they need them most. The researchers are looking into additional preclinical tests that would make the case even stronger to take these compounds into clinical trials.



"Cobblestones of the Skeletal Muscle" by Elham Javed

Murine skeletal muscle stained to reveal the intricate interaction between the cytoskeletal filaments actin and vimentin. The organized arrangement of these filaments provide strength and integerity to a muscle cell that allow a muscle to withstand immense stress and load.

STRIVING TO IMPROVE REPRESENTATION IN SCIENCE

BY KARUNA MEDA | ILLUSTRATION BY SOL COTTI

Brittany Ruiz loved biology in high school, but she didn't know it could be a career path. "Growing up in an under-resourced area like Camden, NJ, there wasn't a lot of exposure to STEM careers," she says. Moreover, her science professors in school and college were mostly white men, and she had never met anyone who shared her Latina heritage.

Now, as a second year PhD candidate in the laboratory of Dr. Hien Dang studying cancer-causing genes in the liver and pancreas, Brittany wants to change that experience for others from underrepresented backgrounds in science. "Representation matters. If I can inspire even one person who thinks science isn't meant for them, then it's all worth it."

Read more at Jefferson.edu/BeyondtheBench2024.

For 200 years, Jefferson researchers have applied expertise in medicine, textiles and design to serve society's health and well-being.

TWO CENTURIES OF

BY MERRILL MEADOW AND F. MICHAEL ANGELO, UNIVERSITY ARCHIVIST

1862

Jonathan Letterman, MD, (JMC 1849) **designs the modern military ambulance service**.

Ninian A. Pinckney, MD, (JMC 1833) **designs the first U.S. Navy hospital ship**, USS Red Rover.

1874

John N. Farrar, MD, **invented the first embossing typewriter** for the blind.

1881

Carlos Juan Finlay, MD 1855, publishes **proof of the mosquito as the vector for yellow fever** transmission.

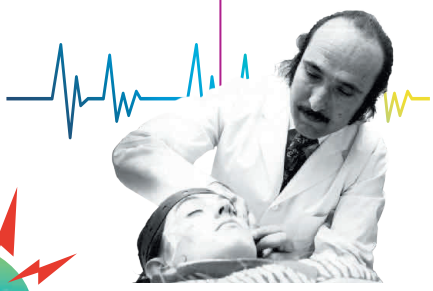
1932

Samuel M. Dodek, MD '27, **invents the hysterograph**, or tocodynamometer, the first device to accurately measure uterine contractions during labor.

1953

John H. Gibbon, MD, (JMC 1927) conceives of and **develops** — but refuses patent rights for — **the world's first successful heart-lung machine**.

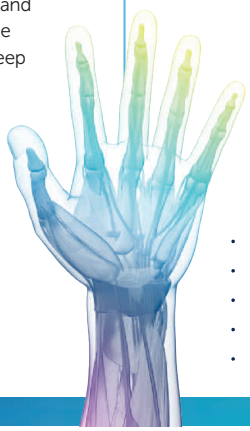
Eugene Aserinsky, PhD, **discovered REM sleep** and is considered one of the founders of modern sleep research.



1958

Thomas Edman, '48 and then-chair of the knitting department, **produces the first bifurcated aortal graft** using seamless tubes of knit fibers.

1965



Founded in 1824, Jefferson Medical College has long been at the forefront of medical education and research. Today, Jefferson's legacy also includes the fundamental discoveries and pioneering research that grew from Philadelphia University — founded in 1884 as the Philadelphia Textile School — and now part of Thomas Jefferson University. For 200 years Jefferson's faculty, students and graduates have driven advancements across the research spectrum — from basic science discovery to practical application — in fields ranging from surgical innovation to material sciences, and from RNA biology to infectious disease.

Among the many areas in which Jefferson has introduced fundamentally important discoveries and advancements — stretching from cancer biology to sustainable reuse of industrial waste — one stands out: Its ability to facilitate R&D synergies by capitalizing on its expertise in biomedicine, textile sciences and design.

RESEARCH SYNERGY

1976

James M. Hunter, MD '53, collaborates with faculty at Philadelphia College of Textiles and Science to **invent the artificial tendon for hand rehabilitation**.

Robert C. Gallo, MD '63, **co-discovers interleukin-2**, which is essential for regulating T-cells and plays a key role in human retroviruses such as HIV.

1990

Darwin J. Prockop, MD, and colleagues **discover a gene that causes osteoarthritis**.

Other Jefferson researchers **identify the defective gene that causes aortic aneurysms**.

2002

Marion Siegman, PhD, of physiology, becomes **the first woman to chair a department in the basic sciences**.

Vijay Rao, MD, of radiology becomes **the first woman to chair a clinical department**.

2014

A student team **develops the winning design** for NASA's new Z-2 series spacesuit.

2016

Jefferson is one of the **first universities in the U.S.** to establish a center **for evidence-based education and research of medical cannabis**.

2018

Sunday Shoyele, PhD, **develops a nanotechnology-based treatment approach for non-small cell lung cancer**, employing microRNA to silence disease-causing processes in cancer cells.

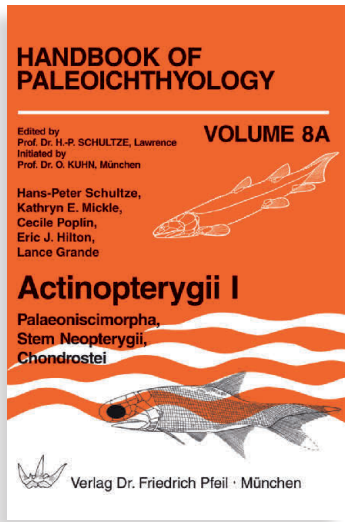
2020

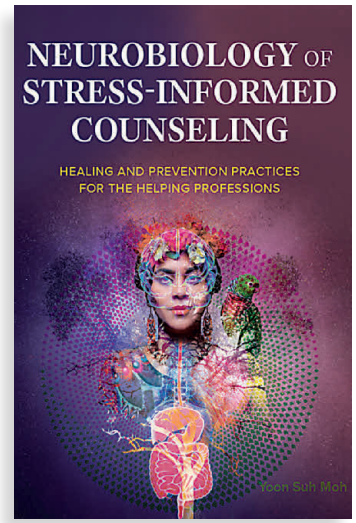
Matthias Schnell **develops a COVID-19 vaccine** based on a rabies vector that proves promising in preclinical testing.

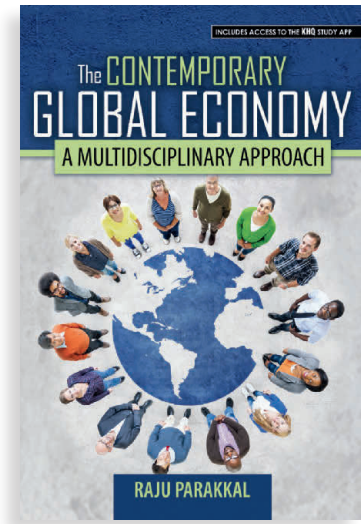
Creating Our Third Century
Jefferson200.org

RESEARCH READS

BY MARILYN PERKINS







Ancient Fish: Handbook of Paleoichthyology Vol 8A: Actinopterygii

Verlag Dr. Friedrich Pfeil Publishers, January 2022

Kathryn E. Mickle, PhD, Associate Program Director of Pre-Medical Studies and Associate Professor of Biology at the Jefferson College of Life Sciences

Actinopterygians, or ray-finned fishes, have bony skeletons and fins supported by thin rays. Actinopterygians account for the majority of today's living fishes and are among the most diverse vertebrates on the planet. They include familiar fishes such as salmon, anglerfish, and seahorses, but their long history dates back 400 million years. In a new installment of the *Handbook of Paleoichthyology*, biology professor Dr. Mickle, and co-authors Hans-Peter Schultze, Cecile Poplin, Eric J. Hilton and Lance Grande chronicle the fossil record of a large group of fossil ray-finned fishes referred to as palaeoniscoids. In addition, living polypterids and chondrosteans and their fossil relatives are examined. This volume of the Handbook of Paleoichthyology is a valuable resource for scientists, offering detailed illustrations and insight into how the diverse aquatic life of the modern age came to be.

The Contemporary Global Economy: A Multidisciplinary Approach

Kendall Hunt Publishing Company, 2023

Raju Parakkal, MA, PhD, Associate Professor of International Relations at the Jefferson College of Humanities and Sciences

The last decade has seen societal shifts on a myriad of fronts, and the economy is no exception, with the coronavirus pandemic, cryptocurrency and Brexit all making their profound marks. In *The Contemporary Global Economy: A Multidisciplinary Approach*, Dr. Parakkal comprehensively explores global markets by analyzing these recent economic events and their underlying theoretical perspectives. Dr. Parakkal, an international political economist, integrates historical events, political influences and cultural factors to provide readers with a multidisciplinary understanding of the subject. Through critical analysis of policies and practices, this book offers tools to navigate the complexities of the contemporary global economy.

Neurobiology of Stress-Informed Counseling: Healing and Prevention Practices for the Helping Professions

Cognella Academic Publishing, November 2022

Yoon Suh Moh, PhD, LPC, NCC, CRC, BC-TMH, BCN, Assistant Director of the Community and Trauma Counseling program and Associate Professor at the Jefferson College of Health Professions

Stress can be a powerful motivator or a crippling burden, and managing it is a fundamental fact of being human. In *Neurobiology of Stress-Informed Counseling: Healing and Prevention Practices for the Helping Professions,* Dr. Moh examines stress from a neurobiological, developmental perspective, exploring its positive and negative aspects and offering practical strategies for preventing and healing from stress. Dr. Moh, a licensed professional counselor and neurofeedback specialist, provides culturally responsive approaches to wellness, emphasizing self-care and holistic practices. This resource equips helping professionals with the knowledge and tools needed to support clients in managing stress and promoting well-being.

1,202
ACTIVE STUDIES
across Thomas Jefferson University and Jefferson Health in FY23

$203,226,328
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35% increase
in team-science grants from NIH over 5 years

45
clinical departments performing research

$86,135,132 IN NIH FUNDING

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50% approximate increase in funding since 2016

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graduate and undergraduate programs across

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MORE THAN **1,000**
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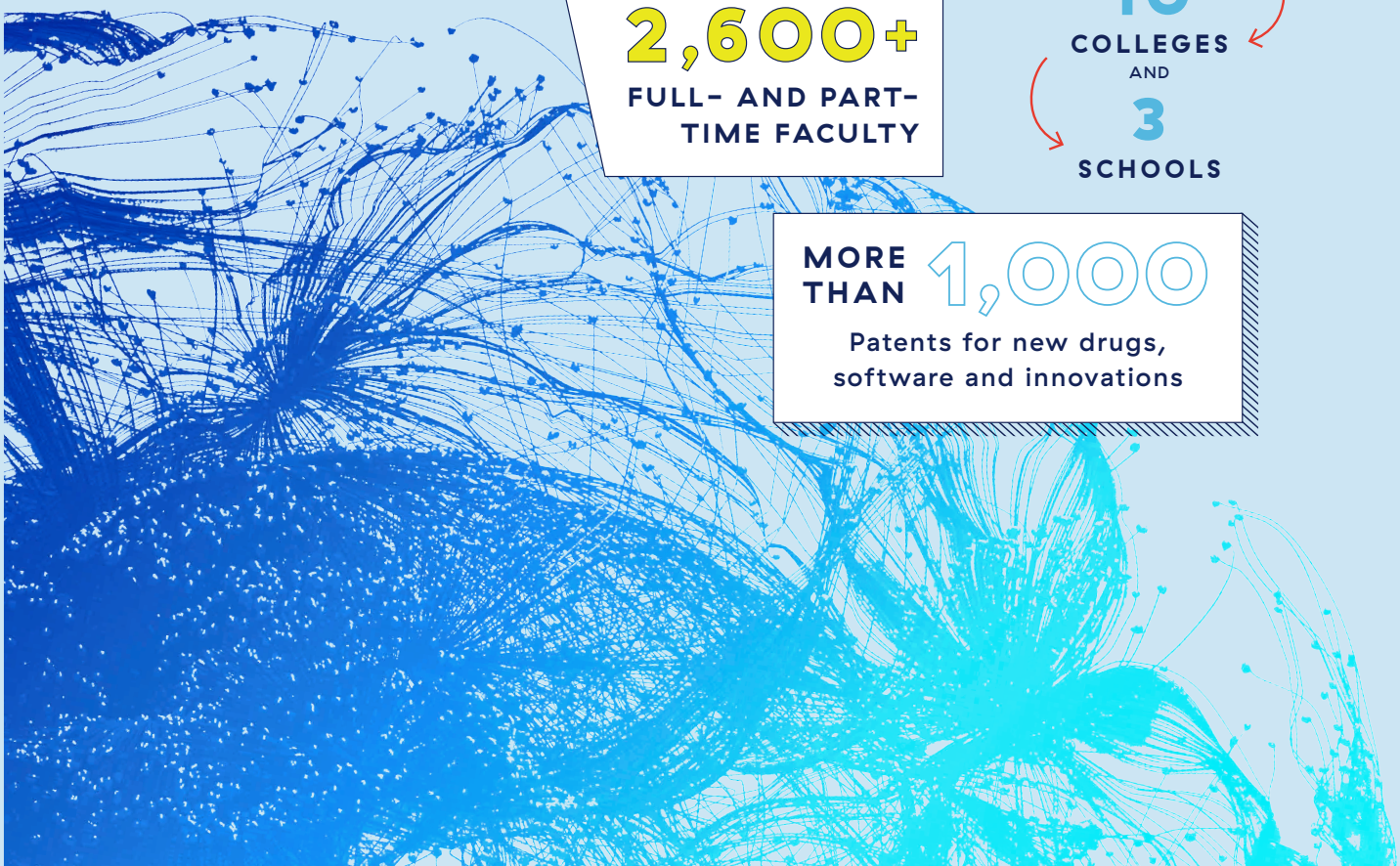

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