research

at THOMAS JEFFERSON UNIVERSITY

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***Research* at Thomas Jefferson University**
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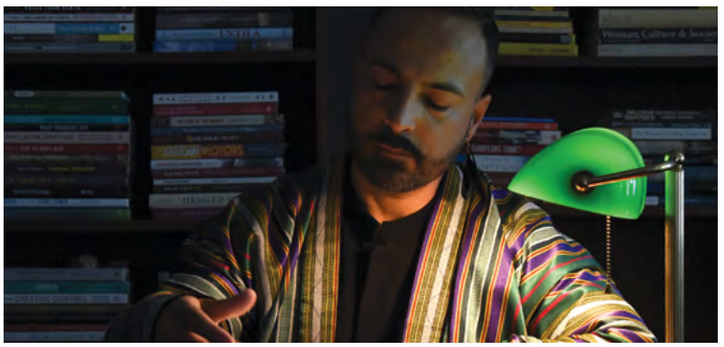

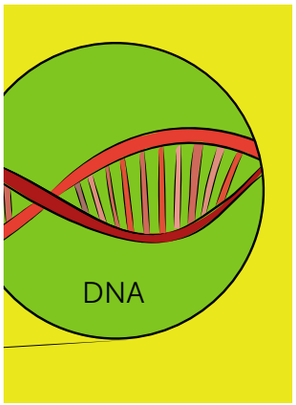

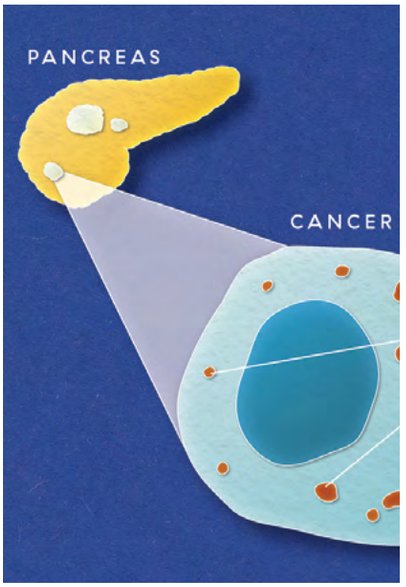

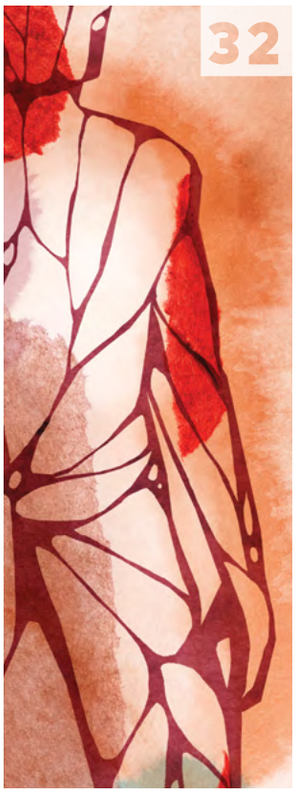

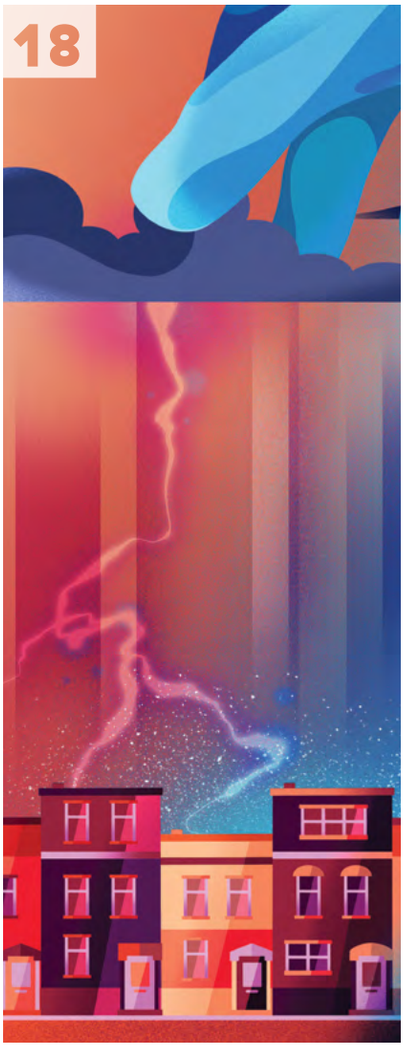

CONTENTS

photograph by Robert Carter

LOOKING FORWARD, PURSUING IMPACT

A message from Mark L. Tykocinski, MD
Anthony F. and Gertrude M. DePalma Dean, Sidney Kimmel Medical College
President of Thomas Jefferson University

Next year will mark Jefferson's bicentennial: two centuries of leadership in education and research since the 1824 founding of Jefferson Medical College (now Sidney Kimmel Medical College) and 140 years since the founding of the Philadelphia Textile School. As proud as we are of our history, we are laser focused on the future, asking ourselves this fundamental question: How best can we increase the beneficial impact that our faculty and students have as builders, creators and healers of society — particularly given the unique merger of Thomas Jefferson University and Philadelphia University in 2017?

The goal of having a positive, meaningful impact for communities here and across the globe is at the heart of our new strategic plan for research. That plan builds on the strong foundation the Jefferson research enterprise has established during the past decade: We have expanded research infrastructure and resources, nurtured new transdisciplinary and multi-institutional partnerships, and begun pursuing a range of new opportunities for discovery, translation and application addressing major societal needs. As a result — to cite just two significant metrics — external funding for Jefferson research was over $200 million with a 55% increase in NIH funding since 2016.

Today, we are engaging concretely across disciplines, professions and geographies. Jefferson researchers are, for example, helping drive economic development in Pennsylvania and preserving artisanal textile processes in Burkina Faso in West Africa; translating basic science discoveries into new cancer treatments (p. 32); creating efficient methods to track changes in ocean flows (p. 9); and conceiving ways to reverse cognitive deficits caused by lead exposure (p. 7).

Over the next five years, the Jefferson research enterprise will grow in both magnitude and impact. We are providing more support for the broad array of research and scholarship undertaken by our faculty, students and postdocs — adding new facilities and technical capabilities; creating more flexible laboratory spaces; increasing intramural funding; and expanding research faculty and support staff. (We are also bolstering the team leading the Jefferson research enterprise, and I encourage you to read the Research Perspective on page 4, written by Dr. David Whellan, who was recently inaugurated deputy provost for research.)

Looking forward, a focal point for our research vision is our centers of research excellence concept: developing selected areas of research strength into larger scale, multidisciplinary centers capable of garnering meaningful philanthropic support and corporate investment. This is the logical next stage for our team science journey, and the core of some of these are already in place. Those up-and-running programs include the Center for Computational Medicine, the Center for Vaccines & Pandemic Preparedness, the Annesley Eye Brain Center and the Institute for Smart and Healthy Cities. Others are poised for formal launch, such as the Institute for Global Health Security, the Center for Primary Care Research, the Rehabilitation Institute, and the Convergence Institute. All of these centers of research excellence will continue to build interdisciplinary collaborations designed to tackle complex problems that cannot be solved without deep, multifaceted expertise.

While our major research programs are diverse in focus, they share three fundamental characteristics. First, they each address a future state — a vision of society's concrete needs through the 21st century. Second, they each leverage specific Jefferson strengths in order to have meaningful, measurable impact. Third, they each prioritize courageous, paradigm-breaking work — striving for major leaps forward, not merely incremental progress.

These characteristics are woven into Jefferson's robust, forward-looking culture. And they reflect a research environment that sparkles with excitement, engagement and achievement.

Please read on to learn more about the people who make the Jefferson research enterprise so extraordinary, and about the impact they are having on the world around us.

A NEW WAY TO HAVE IMPACT

A message from David Whellan, MD
James C. Wilson Professor of Medicine
Deputy Provost for Research

Since 2017, Thomas Jefferson University has risen in the Carnegie Classification to become a national doctoral research university, and extended both the range and impact of its research programs. During the next five years, the Jefferson research enterprise will continue to grow. To guide that growth, the University is expanding its leadership team — beginning with the creation of the role of Deputy Provost for Research. Dr. David Whellan has been appointed to that position, in which he leads the implementation and ongoing refinement of the University's strategic plan for research. He also stewards clinical research at Jefferson and directs the Jefferson Clinical Research Institute, which he helped create in 2015. Here, Dr. Whellan offers a perspective on the professional changes this new role brings.

For much of the past three decades, I've had two primary professional roles: practicing cardiologist with a specialty in heart failure and systolic dysfunction, and clinical researcher on new and more effective ways of diagnosing and treating people with serious cardiac disease. My efforts in both roles have been motivated by the desire to help my patients have longer and better-quality lives. The joy I've felt in seeing these individuals become stronger, physically and emotionally, is powerful.

I've experienced a deep sense of professional accomplishment and excitement from a source that I'd not anticipated when I first left medical school: undertaking clinical trials of new treatments, devices and approaches. Relatively early in my career I came to understand the extraordinary potential that clinical research holds for helping thousands of patients regain their well-being. I first undertook a leading role in clinical research projects in 1997, as a cardiology fellow, and remained directly engaged for the past 26 years. Perhaps the most rewarding clinical research project has been one that I helped initiate in 2002; it focused on exercise for patients with "weak hearts." While it took more than a decade to obtain funding and complete the study, its results led to changes in practice guidelines and to cardiac rehabilitation being covered by insurance for this patient population. Now, I am part of a leadership team for another physical therapy intervention study. This one focuses on older adults with "stiff hearts," a condition that limits their function and increases their risk of being in the hospital or dying. The seeds of this large multi-center study started with a Jefferson-funded pilot study in 2011.

That experience helped solidify the belief that I could help other clinician-researchers launch their own investigations at Jefferson. With the help of an incredible team, I launched the Jefferson Clinical Research Institute in 2015. The Institute's goal is to provide clinicians with the technical support they need to balance their clinical responsibilities with research that aims to improve treatment for the patients they serve every day.

However, for the foreseeable future, I won't be serving on the front line for clinical trials. Becoming deputy provost has meant taking on new responsibilities that, I believe, will enable me to have far greater impact across a broader range of research at Jefferson. But it also means that I have stepped back from patient care and from direct patient engagement in clinical research. While I will miss my patients, I'm excited about helping Jefferson pursue its potential for improving human well-being and advancing knowledge.

Yes, in the next few years, we will continue to grow our clinical research program (which now has more than 2,000 active grant-supported studies) and increase Jefferson's support for the translation of research into real interventions. But we will also be elevating basic, translational and applied research and scholarship across the University, ranging from life sciences to humanities and social sciences to design, engineering and business. We will launch new regional partnerships to access high-end technologies, and catalyze national consortia to pursue targeted high-priority research goals. And, we'll continue building transdisciplinary collaborations that enable our researchers to approach complex problems from multiple technical and professional perspectives — better positioning them to address multifaceted challenges ranging from the effects of climate change to racial disparities in health and economics.

I believe the faculty at Jefferson will continue to have tremendous beneficial impact on our communities, our nation and the world.

It won't be easy: It will require hard work, resilience and flexibility in the face of unyielding technical, social and economic changes. And, for me, it will mean adapting to a new sense of my professional role and goals.

But I'm all in, for the long run.

photograph ©Thomas Jefferson University Photography Services

SIX STEPS FORWARD

exploring recent discoveries at Jefferson

by
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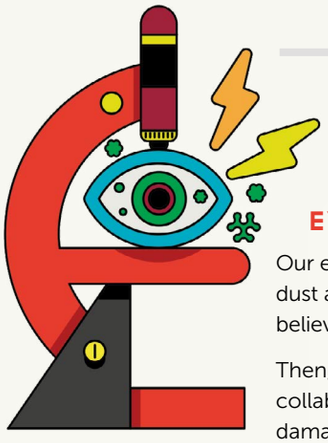
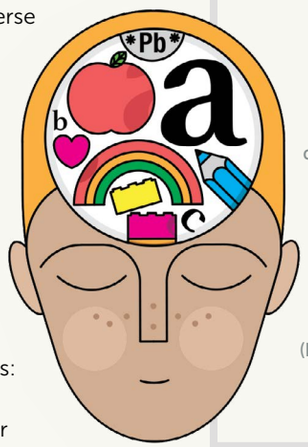


01.

REVERSING LEAD POISONING'S EFFECTS

It's estimated that more than 500,000 U.S. children have so much lead in their blood that they are at risk of developing severe cognitive and behavioral impairments. But a major preclinical study offers hope that most of the genetic changes associated with those impairments could be reversed.

"Our new research shows that lead poisoning in children affects a wide array of genes in the part of the brain involved in learning and memory," explains neuroscientist Jay Schneider, PhD. "However, our data suggest that enriched early-childhood environments and access to stimulating activities could minimize or potentially reverse those effects."



Dr. Schneider's team studied rats exposed to lead in a way that replicated conditions and developmental timing of children exposed to lead in early childhood. After the lead exposure, the rats were separated into two different housing conditions: "enriched" cages, with substantial opportunities for interaction with other rats and with a variety of toys, climbing and nesting materials, and tunnels that were changed regularly; and cages offering much less stimulation and social interaction. Then the team assessed gene expression in the brains of both groups.

The researchers found that lead exposure affected the expression of more than 3,500 genes. As much as 80% of these lead-induced gene expression changes were reversed in rats in the enriched or high-stimulation environment.

The researchers agree that their study clearly points to the neurological benefit of providing at-risk children and children known to be exposed to lead with stimulating environments and rich social interactions. *EZ, MM*

02.

EYE-DISEASE DEFENSES

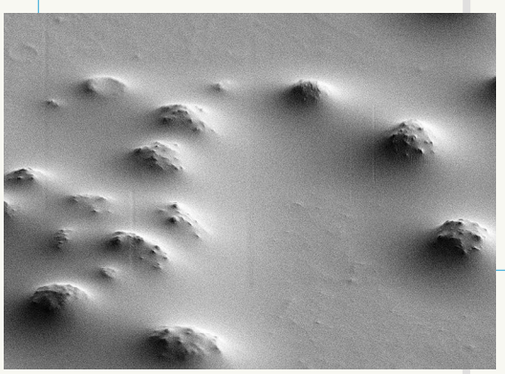
Our eyes need to protect themselves from many things — ranging from dust and chemicals to bacteria and ultraviolet light. Yet scientists long believed that key parts of the eye lack protection by immune cells.

Then, a few years ago, cell biologist Sue Menko, PhD, and collaborating researchers observed immune cells trying to fix the damaged lens of mice they were studying. They found that when mouse corneas were wounded, immune cells travelled to the surface of the lens to repair the eye and protect from further damage.

The researchers wondered whether they would see the same kind of responses in uveitis, an auto-immune inflammatory disease of the eye. Even though, in humans, uveitis can lead to retinal scarring, glaucoma and cataracts of the lens, the role of immune cells in uveitis-associated cataracts had never been explored. "That's why, when our team used high-resolution microscopy to observe the uveitis-model mice, what we saw amazed us: a robust response comprising dozens of immune cells of different types, including T-cells and macrophages," says Dr. Menko.

Moreover, they found that the lens capsule — a thick protein-rich layer surrounding the lens — had deep pits or divots. "These formations are evidence that the immune cells are actually integrating into the lens capsule," explains JodiRae DeDreu, a PhD student researcher in the Menko lab. In fact, they observed the number of divots increasing and becoming deeper, indicating further invasion of immune cells into the lens capsule as the disease progressed.

"There is much work still to be done," says Dr. Menko. "But we believe that uncovering these processes — which had never been shown before — could lead to wholly new pathways for understanding and treating eye disease." *KM, MM*



The researchers used a scanning electron microscope to capture detailed changes on the surface of the lens capsule of the eye. They found many bumps, indicating regions where immune cells had become integrated within the lens capsule in response to damage and inflammation. (Image credit: Mary Ann Stepp, PhD, George Washington University.)

03.

HYPERTENSION DRUGS AND PANCREATIC CANCER

Pancreatic cancer remains extremely difficult to treat, with only about 11% of patients surviving five years past diagnosis. But new research suggests that common anti-hypertension medications might significantly improve those survival rates.

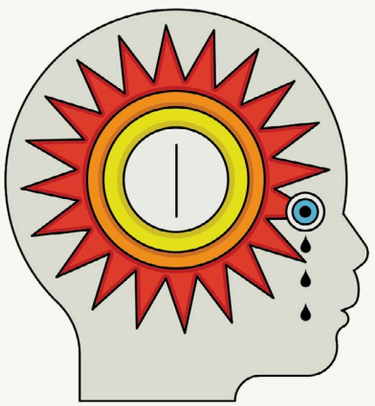
The investigators — led by biostatistician Scott W. Keith, PhD, and population health professor Vittorio Maio, PharmD — used data on 3.7 million adults in Italy to perform the largest retrospective study of anti-hypertensive drugs' impact on pancreatic cancer survival. "The associations we found in our results suggest that a randomized clinical trial is warranted," says Dr. Keith, "especially because these are inexpensive therapeutics with relatively few side effects."

In their study, the team constructed statistical models to predict and compare mortality risks for pancreatic cancer patients who had been prescribed either of two common types of blood-pressure medications — angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors — versus patients who had not been prescribed those medications.

These medications interact with the angiotensin system, which is normally responsible for narrowing blood vessels but has also been shown to interact with cancer-growth pathways.

The study found that patients prescribed ARBs after their pancreatic cancer diagnosis had a 20% lower mortality risk; and those prescribed ACE inhibitors had a 13% lower mortality risk within three years after diagnosis.

"We can't reliably predict how long these medications might extend survival," says Dr. Maio. "We urge academic, advocacy and pharmaceutical organizations to establish a collaborative, well-resourced prospective study to determine the potential benefits of ARBs and ACE inhibitors for pancreatic cancer patients." *EZ, MM*



04.

ANTI-NAUSEA DRUGS COULD HELP INFANTS WITH OPIOID WITHDRAWAL SYNDROME

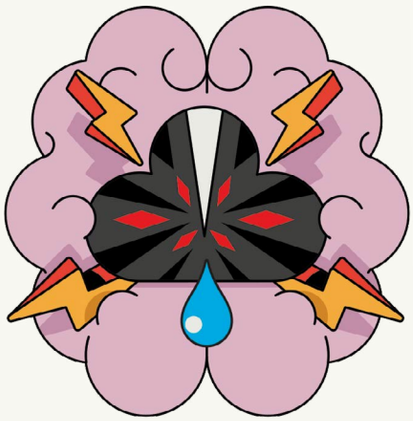
As the opioid epidemic has mounted over the past two decades, so too have cases of neonatal opioid withdrawal syndrome (NOWS). NOWS is a condition in which infants born to people who have used opioids during pregnancy experience withdrawal symptoms after birth. Treatment for NOWS includes therapies like morphine to alleviate the potentially life-threatening withdrawal.

A study co-authored by clinical pharmacologist Walter Kraft, MD, and neonatalogist Susan Adeniyi-Jones, MD, suggests that a common anti-nausea medication called ondansetron may help ease the symptoms of NOWS. Previous research revealed that administration of ondansetron relieved opioid withdrawal symptoms in both mice and adult humans.

To determine if the drug would also help infants with NOWS, the researchers administered ondansetron or a placebo to mothers with opioid use disorder during labor and to their infants for five days after birth. The research team measured the efficacy of ondansetron by the severity of the infants' withdrawal symptoms and number of infants in each treatment group who required morphine.

The researchers found that infants treated with ondansetron experienced significantly less severe NOWS symptoms, supporting the drug as a potential treatment. In addition, fewer of the ondansetron-treated infants required morphine compared to the placebo group; however, this difference was not statistically significant. Ondansetron does not easily enter the brain, so the researchers are planning to test higher doses or different routes of administration.

"If we could get the levels high enough," says Dr. Kraft, "I think we could determine an endpoint that would demonstrate fewer babies requiring opioid treatment, which would be a major development in NOWS treatment." *MP*



05.

ESTROGEN'S IMPACT ON POST-TRAUMATIC EMOTIONAL EXPERIENCES

Stress is common in many people's lives and it can make straightforward tasks challenging. In fact, stress can affect both the way we think and how our bodies function.

Psychology researcher Jenna Rieder, PhD, studies how chronic stress and trauma interact with physiology. "I am particularly interested in how stress-related changes in the body connect with outcomes like risk for mental illness," she says.

In one recent study, she and colleagues at the University of Nevada assessed how the hormone estradiol impacts everyday emotions of women who have experienced trauma. Fluctuations in estradiol have been linked to mood, cognition and the body's stress response. "But it's unclear if estradiol levels can affect the emotions of women who have experienced traumatic events," says Dr. Rieder.

Her team showed that among women exposed to trauma, daily emotional experiences — including symptoms of post-traumatic stress disorder (PTSD) — differed by menstrual cycle phase. They found that participants experienced more PTSD symptoms and greater mood changes during days of lower estradiol levels.

These results might help clinicians anticipate when symptoms increase in their trauma-exposed patients who menstruate, and could also guide patients' own responses to stress.

"Stress is often viewed as purely psychological," says Dr. Rieder. "I hope that our studies help people recognize how stress is linked to our natural biology and physical health." *KM, MM*

06.

THE INNER LIFE OF OCEAN WAVES

For many, watching ocean waves roll to shore provides fascination and joy. Others, however, are absorbed by ocean waves that flow underneath, transferring heat, energy and nutrients throughout the ocean.

"The ocean is stratified, with heavy cold water below and light warm water above," says physicist Edward Santilli, PhD. "But there are lots of interactions between these layers, which spur 'internal waves' that can flow many kilometers before they become turbulent and dissipate."

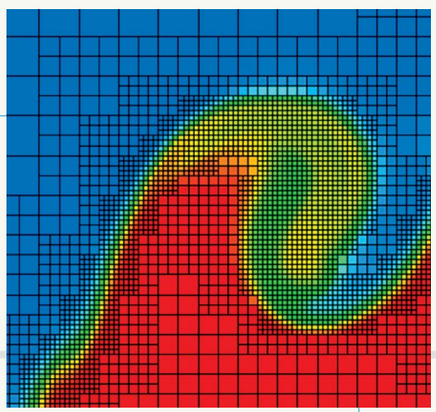
That turbulence affects the ocean, the atmosphere — and, ultimately, us.

About two hundred feet down, a change in the water's density blocks anything from traveling up from the abyss or down from the shallow ocean. "But turbulent mixing breaks through that wall, allowing nutrients to rise into shallow waters and carbon dioxide absorbed from the atmosphere to descend into the abyss," Dr. Santilli explains.

Just how many nutrients and how much carbon dioxide do internal waves exchange? That is challenging for researchers to quantify. "In the actual ocean, that process would require plenty of equipment," Dr. Santilli says. "So, we look to computer simulations. Unfortunately, no modern computer is powerful enough to capture the enormous range of scales of internal waves."

So, Dr. Santilli created the Stratified Ocean Model with Adaptive Refinement (SOMAR), which works on a simple principle: At any given time most of the ocean is not turbulent, therefore an efficient model rarely needs to capture very small-scale motions. SOMAR models large-scale motions only, at least until it detects turbulence. Then it triggers a data-intensive small-scale model that feeds information back to the large-scale model. Once that data has been incorporated, the turbulence model ceases and the large-scale model resumes — until new turbulence is detected.

Dr. Santilli and his collaborators hope to use SOMAR to develop a model of internal wave mixing. Such a model would facilitate more accurate investigations of microbial lifecycles and global weather patterns. *KM, MM*



The SOMAR model uses adaptive grids to calculate mixing at the interface of two water densities. As the heavy (red) fluid moves to the left and the light (blue) fluid moves to the right, the fluid in between overturns and mixes (yellows and greens).

Ahmad Qais-Munhazim, PhD

WAR AND IDENTITY

How war complicates gender and sexuality in Afghanistan and its diaspora.

by Karuna Meda
photographs ©Thomas Jefferson University Photography Services

In the summer of 2021, while the world watched in horror the images of the Taliban takeover and the international community's sudden withdrawal from Afghanistan, Dr. Ahmad Qais-Munhazim was frantically doing whatever they could from Philadelphia to get Afghans to safety. As a scholar of international relations and Muslim diasporas, they were also being contacted by the media to shed insight on the displacement and violence faced by Afghans, particularly women and the LGBTQ+ community.

Identifying as a genderqueer, Afghan, Muslim, immigrant, this was not the first time Dr. Munhazim encountered the overlap of their lived experience and professional work. Here we talk to them about their interdisciplinary research that challenges Western narratives about Afghanistan and queerness in Muslim diasporas.

KM: How would you describe your work?

AQM: I study the intersection of migration and war, gender, and sexuality, with a specific focus on Afghanistan and its diaspora.

War is tumultuous and yet there's so much we don't understand about how it changes everyday lives of those who experience it and are displaced by it. They carry memories of violence and trauma, which impact how they identify with concepts of home and self.

How does war disrupt the performances of gender and sexuality, specifically in Muslim diasporas?

Gender and sexuality are critical elements of our identities, but they're also performances of social constructs. We all perform them differently — the way we dress, speak, move, and relationships we form with social and political structures including borders, states and communities.

War is an inherently masculine phenomenon. Femininity is therefore seen as vulnerable. Growing up in Afghanistan, I was used to seeing men wear eyeliner and henna on their hands. I remember when the U.S. invaded Afghanistan, these behaviors seemed feminine to the white military and humanitarian gaze. As a result, Afghan men felt pressured to assert and even outperform their masculinity.

I theorize this behavior to be "vigilant masculinities." It refers to the state of caution in response to direct and indirect violence. It comes from a place of subordination, powerlessness and loss. It's also apparent in refugees of war. When my family fled to Pakistan during the war in the mid-90s, I worked in vegetable markets to support our income. I had to act hyper-masculine as I was navigating my everyday life in masculine spaces in a foreign country.

How are women impacted?

Afghan women have often been caught between war and its masculine forces. They are used as pawns to justify both the Taliban's extremist rules and the West's rhetoric of 'liberating' oppressed Muslim women to rationalize military invasions.

As refugees and diasporic people in their new homes, Afghan women continue to battle this stereotype of oppression. Like many Asian women, they are hypersexualized in Western societies, which compromises their safety. They also have to confront gender inequity, especially as immigrant women of color. I hope my research shows that while women in Afghanistan and Afghan diasporas are portrayed to perform conventional roles as roles as caregivers and homemakers, they take on other roles as breadwinners, leaders and activists.

What about minoritized gender and sexual identities?

For minoritized gender and sexual identities, there is threat of violence and stigma both at home and abroad. When the Taliban took over, many of my friends in the LGBTQ+ community in Afghanistan were caught in a dilemma — stay and risk their lives or try to escape — but to where? In the West, LGBTQ+ individuals in Muslim diasporas still face racialized systems in majority white LGBTQ+ spaces, and have to hide parts of their identity. It is a survival mechanism, but I want to celebrate the sense of agency it takes to move between identities like that.

What is your approach to studying these complex questions?

My work is informed by many disciplines with a focus on ethnography, which involves engaged observations and historical interviews to collect and listen to stories of war and displacement. I also bring in my own experiences — autoethnography — because I have lived and continue to live many of the phenomena I study.

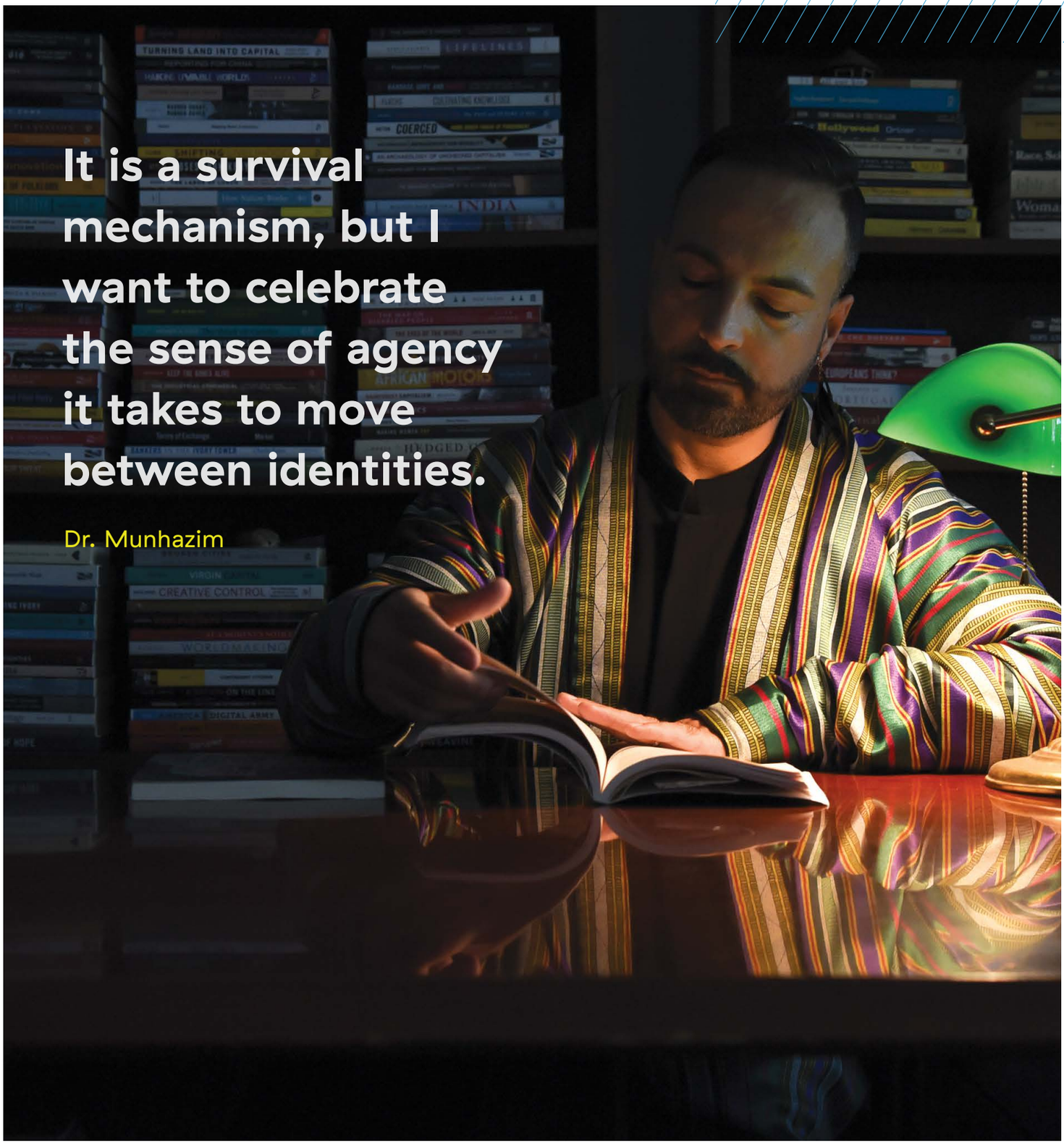
I also use a de/colonial approach. As someone who grew up in Afghanistan and Pakistan, my native language is not English. It's not a language I dream in or understand war, violence, love and everyday life in. But my research and the people whose stories I tell are in so many ways a reflection of colonial forces. I am trying to challenge not only conventional narratives, but also the notion of who produces this knowledge and for whom. My aim is to center Afghans as resilient protagonists of their own stories.

What was your journey into this field?

I knew who I was from very early on. I was an unapologetically feminine kid. I grew up reading the famous Afghan poet Rumi, who wrote openly about love for another man. I started writing my own poems to navigate my gender and sexuality, and learned the power of autobiographical storytelling.

When I returned to Afghanistan from Pakistan, I worked for the United Nations High Commission for Refugees for five years, honing my interest in refugee regimes. In 2008, I landed in Minneapolis to pursue my undergraduate studies in political science and global studies.

At that time, the 9/11 attacks and the "War on Terror" was the dominant discourse on Afghanistan. People were fascinated by my experiences, but in a very orientalist way that romanticized my trauma and queerness. There was little knowledge of what was happening in Afghanistan, and any information available was produced mainly by Western scholars. I didn't want that to be the only reference. I also felt a personal responsibility towards other queer, Muslim immigrants who have not had a voice for so long. I don't see the people I interview as my study subjects, but rather as my co-travelers in collectively trying to understand our experiences and the world around us.


It is a survival mechanism, but I want to celebrate the sense of agency it takes to move between identities.
Dr. Munhazim

Ruth Jeminiwa, PhD

DIGITAL TOOLS AND SHARED DECISION-MAKING

How technology can improve collaborative treatment approaches for patients with opioid use disorder.

by Makhari Dysart
photographs ©Thomas Jefferson University Photography Services

Effective health care is shaped around good communication between a doctor and their patient. However, historically this relationship has been dominated by the physician rather than mutual participation. This often left little consideration for the structural barriers facing patients outside the doctor's office.

The 1980s began a shift in medical culture to a model of shared decision-making, where a patient and their provider discuss risks and benefits of different treatment options, and jointly make decisions. The model has gained support for empowering patients and improving outcomes.

This approach is especially important for patients with opioid use disorder, who often face stigma and rigid treatment plans, leading to low patient retention rates. Despite the availability of effective treatments, the U.S. has over 100,000 overdose deaths annually. Pharmacy researcher Dr. Ruth Jeminiwa, is hoping to empower this patient population through digital heath tools that can promote more collaborative interventions.

MD: Tell us about your research.

RJ: My research focuses on understanding preferences of people living with opioid use disorder to promote shared decision-making and other patient-centric treatment approaches. I am particularly focused on pregnant women with opioid use disorder, a patient population that has quadrupled since 1999. These women often face added stigma and punitive measures from child welfare and criminal justice systems, including having their child removed from their care. This has a cascading effect on the mental and physical health of mother and child. It is also important to consider that not all patients have agency in their treatment decisions. Some patients may be seeking to escape a violent situation, or may have a court order for treatment.

What led you to your current research path?

Prior to becoming a researcher, my background was in web development and pharmacy. As a pharmacist I provided care to people with all types of conditions, including those with substance use disorder. I observed that these patients face misconceptions around substance use, which leads to shaming and judgement. Even clinicians can hold bias that can hinder their attitude towards patients and their communication about treatment.

Getting a glimpse of patients' lived experiences, I just felt like I could do something to help. I also wondered if my experience in technology and pharmacy could be blended to improve patient care.

Tell us more about that transition, and your early research findings.

I began to study the doctor-patient relationship and the imbalances that can hamper the transparent exchange of information. For instance, I studied asthma patients, a population in which treatment adherence is generally low. We found that patients did not hold the same beliefs as their healthcare providers around their asthma or medication use, which contributed to intentionally skipping doses. This highlighted the role of shared decision-making in educating patients and understanding their preferences. I learned that when patients are more engaged with care and have shared decisions with their clinicians, they're more likely to stick with their treatment plan.

We also found that digital health interventions can improve treatment adherence by encouraging patients to track their medication use and by providing them "push" reminders. It showed how digital tools can give patients more agency and promote shared decision-making.

How can shared decision-making help overcome barriers faced by patients with opioid use disorder?

According to 2019 estimates, less than 35% of people with opioid use disorder had received treatment in the past year. There is also usually a gap of several years between the onset of the disorder and entering treatment. This reflects significant barriers for this patient population, particularly pregnant women.

Currently, there are two FDA-approved medications for opioid use disorder for pregnant women: methadone and buprenorphine. These are highly effective treatments, but several legal and regulatory barriers make it difficult for patients to access treatment. With methadone, you have to go to the clinic every single day to get your medication. Buprenorphine is not as demanding because you can get a prescription from your doctor and take the medication at home on your own. This may be preferable for some pregnant women, for whom traveling to the clinic can pose a major barrier. However, physicians often prioritize risk of misuse and ease of prescribing over patients' preferences. This leads to patients dropping out of treatment.

Shared decision-making could help patients understand the pros and cons of different treatment options, and patients explaining their preferences could help reshape preconceived notions a clinician may hold about opioid use and the disease of addiction. Most importantly, incorporating patients' preferences in treatment decisions could lead to better medication adherence and retention in treatment programs.

What digital tools does your research explore to facilitate shared decision-making for this population?

Among other things, my research seeks to develop a checklist that prompts the physician to educate the patient about treatment options, clarify their treatment preference and make a shared decision about treatment. This program could be integrated into the electronic medical record, making it easy for clinicians to see whether they have had a discussion with the patient. These tools build on other work at Jefferson that focuses on telehealth, like the Center for Connected Care and its mission to improve access to digital health tools.

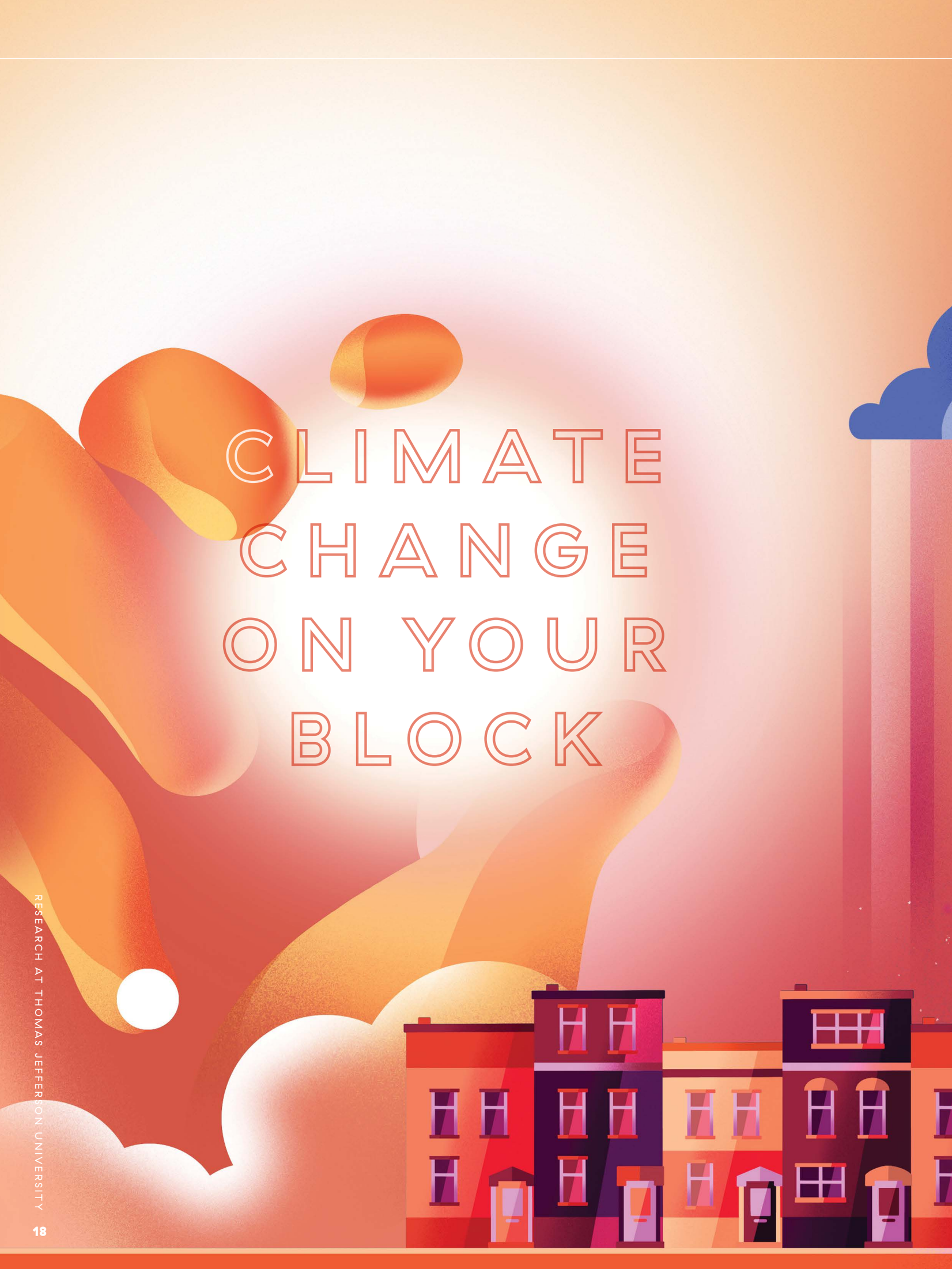
What are some of the challenges patients and/or doctors might experience with these tools?

I worry that not everybody in this patient population will have access to digital interventions, highlighting the problem around digital health equity. For physicians, there is still a problem of workload and time constraints. In my current research, I am trying to understand the barriers and facilitators of shared decision-making on the physician side and interviewing clinicians to understand how best to implement our decision-support tool. I've received positive feedback, and that makes me optimistic.

When patients are engaged with care and have shared decisions with their clinicians, they're more likely to stick with their treatment plan.

Dr. Jeminiwa

CLIMATE CHANGE ON YOUR BLOCK



In Philadelphia, summer is nearly 22 degrees warmer in some neighborhoods than others — researchers and city agencies are teaming up to address this environmental disparity.

→

by Karuna Meda

illustrations by Ollie Hirst

Wisps of pastel pink and orange tinge a dark blue sky as dusk settles on a summer's eve in the city of Philadelphia.

The soothing hues belie the intense heat that researcher Radika Bhaskar, PhD, can feel radiating off the pavement. She kneels to place a temperature sensor in the ground, moving cautiously on the hot surface. Across the street, her colleague Megan Heckert, PhD, does the same. "It's so much more bearable here under the trees," she calls out. Dr. Bhaskar nods — with a research journey traversing both ecology and environmental engineering, she knows all too well the cooling properties of plants. A beep on the sensor app catches her attention and she's taken aback by the reading — a blistering 95°F, even at sun down. She stands and surveys the surrounding houses in concern, thinking about their inhabitants who will have to sleep through this uncomfortable heat. It's a troubling snapshot of the planet's warming in our own backyard.

In just the last thirty years, Philadelphia's average summer temperatures have increased by 3°F, making it almost as hot as Atlanta, Georgia. Average annual rainfall has also increased. In 2021, Hurricane Ida was a terrifying example of the havoc wreaked by severe storms, with record flooding along the Schuylkill River that displaced hundreds and killed five.

These local patterns are reflected globally. In fact, some of the most devastating effects of climate change have happened in the past year alone — floods in Pakistan that submerged a third of the country; record-breaking drought in China that dried up dozens of rivers and reservoirs; massive wildfires in Europe that destroyed more than a million acres of land. The latest report from the Intergovernmental Panel on Climate Change, the world's leading body on climate science, indicates we are now on track to surpass acceptable limits of warming as early as 2037. We have reached a 'code red' and extreme weather events and their cascading effects will likely happen more frequently, and severely.

The rate of warming that has brought us to this precipice has indisputably been driven by humans burning fossil fuels, which emit heat-trapping gases. Yet, while all of humanity's fingerprints are present, the impact will be felt unevenly. According to the Environmental Protection Agency, Black and Latino communities in the U.S. are 40–50% more likely to live and/or work in areas with the highest projected increases in temperature and flooding compared to other demographic groups. These

populations also experience higher incidences of conditions like hypertension and asthma, symptoms of which are worsened by rising temperatures.

Understanding this environmental injustice, at least in cities, requires focusing on the urban environment. For the past four years, Dr. Bhaskar, an engineering professor at Thomas Jefferson University, has embarked on an ambitious partnership with researchers in geospatial mapping and industrial design, and Philadelphia's Water Department and Office of Sustainability, to study how climate change impacts the city's hardest hit neighborhoods. The team is combatting the local trends of a warmer, wetter planet by combining human engineering with tools from Mother Nature herself.

USING GREEN INFRASTRUCTURE TO COMBAT INCREASED STORMWATER

The approach of integrating natural systems and engineered systems has been a driving force behind Dr. Bhaskar's research, from studying how to use plants to pull pollutants from the air and soil, to measuring fluid dynamics in trees that live in drought conditions. "I'm always thinking about how we can bring ecology into our urban environments," she explains. "How do we then measure the different functions of these nature-based solutions?"

These were similar questions that Philadelphia's Water Department sought to answer in their "Green City, Clean Waters" initiative. Started in 2011, the project aims to combat stormwater overflow. Two-thirds of Philadelphia is served by an older water-drainage system called the combined sewer system, meaning a single pipe collects both household sewage and stormwater. During increasingly wetter seasons due to climate change, this system often overflows and billions of gallons of stormwater and diluted sewage pollute local waterways. This harms aquatic life and hinders recreational activities like swimming.

"The urbanization of our environment has resulted in more impervious surfaces," explains Matthew Fritch, an environmental engineer in the Water Department. "So when it rains heavily, stormwater has nowhere to go."

"Green City, Clean Waters" applies green tools or infrastructure that 1) use the natural properties of plants to both absorb rain and to physically intercept it before it hits the ground and 2) also contain the stormwater in an underground catchment area made of rocks and absorbent material, to ensure it has time to soak into the soil and release more slowly into the sewage pipes. The city has already installed nearly 3,000 structures across the city which have kept almost three billion gallons of sewage overflow out of Philadelphia's waterways over the past 10 years.

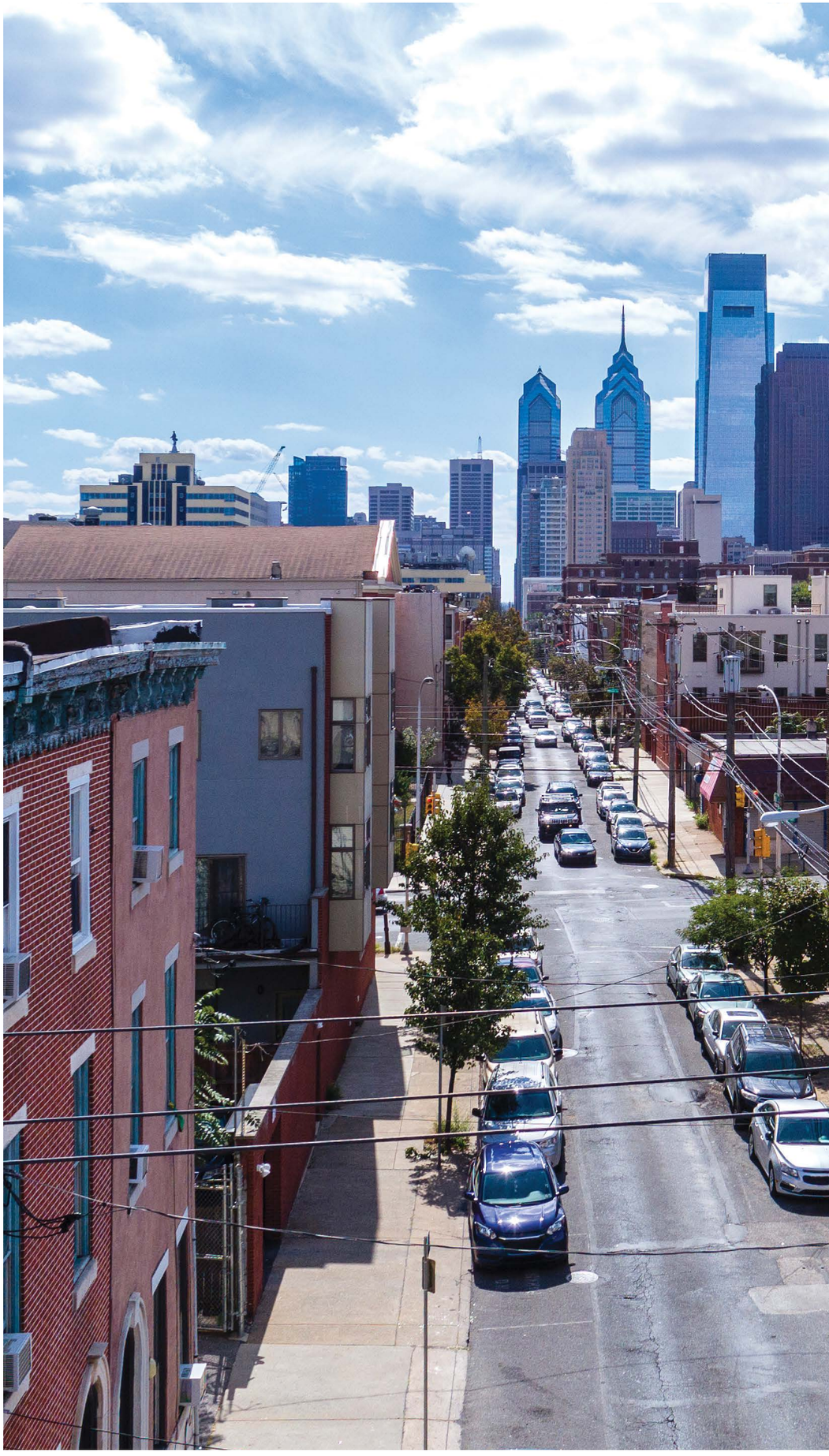
"Philadelphia is a national, if not international, leader of green stormwater infrastructure," says Fritch. "But it is challenging — we are used to dealing with pipes, not plants. It's a different world."

A world, however, very familiar to Dr. Bhaskar, whose knowledge of engineering and plants' adaptive mechanisms made her an ideal collaborator. In 2018, Fritch teamed up with her to test different materials and plants for a green roof, one of the many types of "Green City, Clean Waters" installations. They wanted to evaluate how well the roof was absorbing water, using sensors placed in the soil. They also wanted to measure a process called evapotranspiration, whereby water taken up by the plants' roots is released back into the atmosphere. This moisture-laden vapor cools the surrounding air.

"So plants not only act like sponges, soaking up the excess rainwater, but also like air conditioners," explains Dr. Bhaskar. It's not the only way plants cool — they cast shade, and reflect sun rays off their leaves, preventing paved surfaces like asphalt from heating up as much. This combined cooling means that urban green spaces can reduce surface temperatures by 1–4°F during the day.

As they collected the measurements from the roof, it occurred to Dr. Bhaskar, could these green tools be used to combat another major effect of climate change — rising temperatures?

> **As Dr. Bhaskar stands and surveys the surrounding houses in concern, she thinks about their inhabitants who will have to sleep through this uncomfortable heat. It's a troubling snapshot of the planet's warming in our own backyard.**



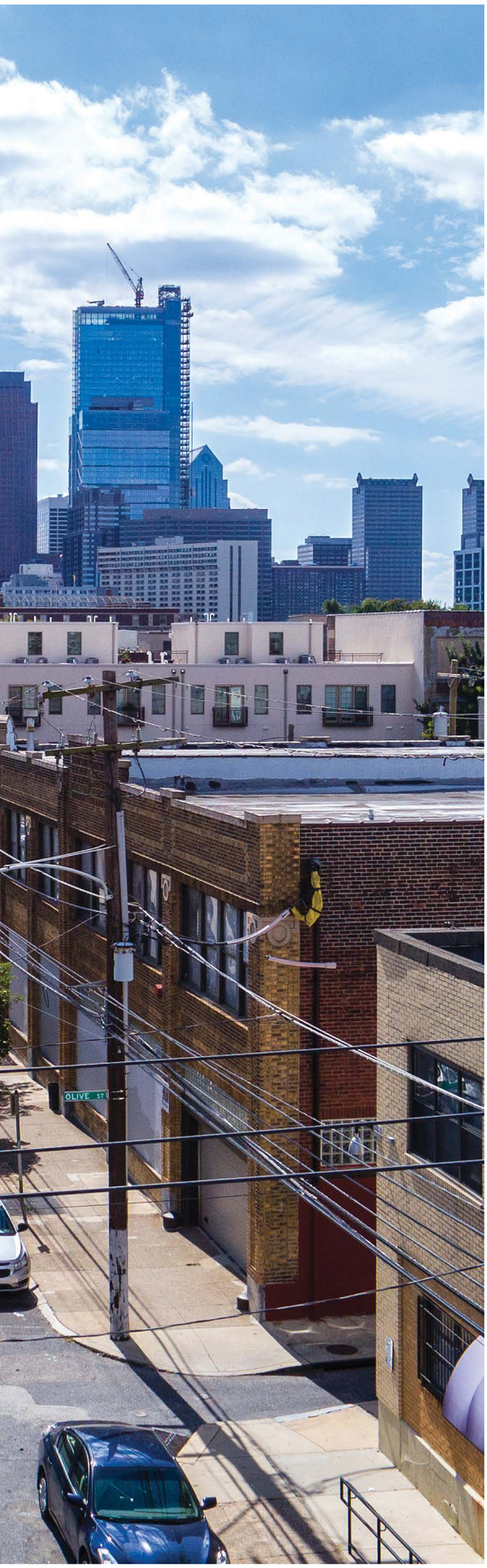
A view from North Philadelphia.

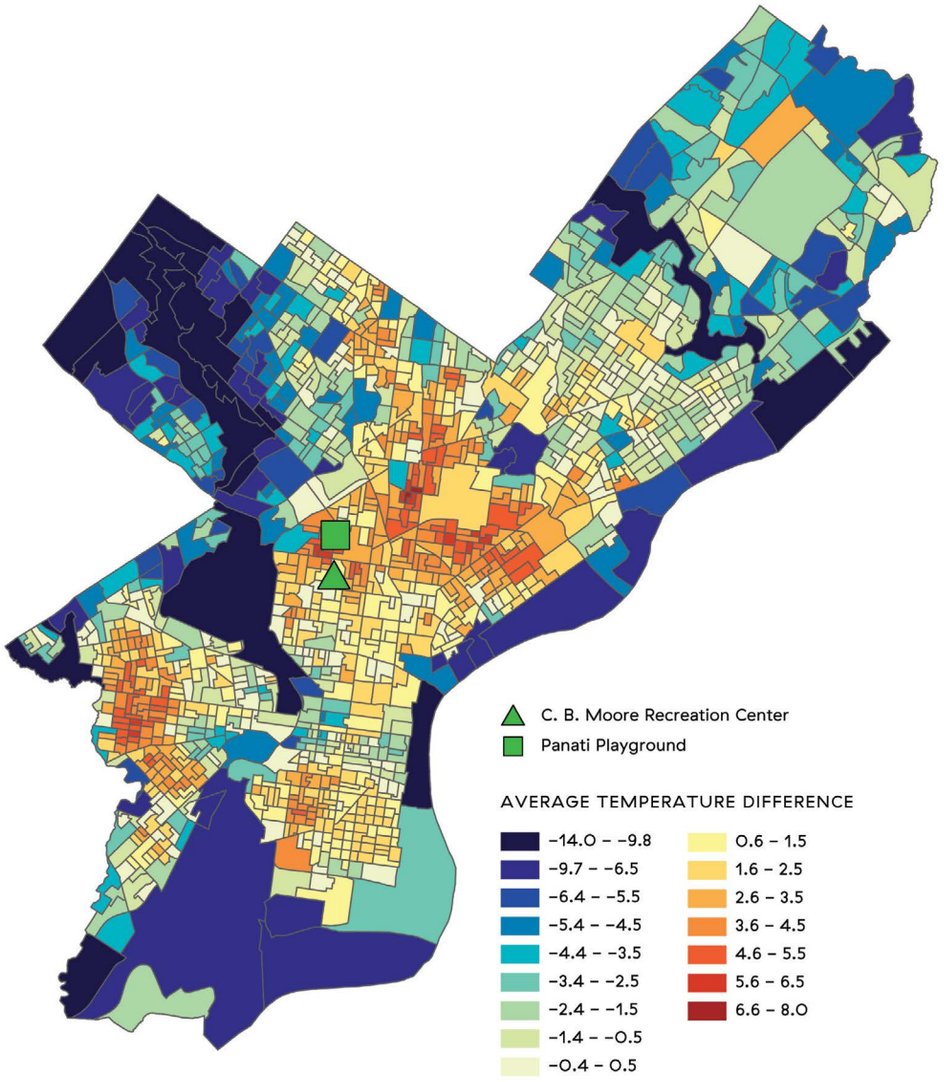
THE URBAN HEAT ISLAND EFFECT AND ENVIRONMENTAL INJUSTICE

While this question percolated in her mind, Dr. Bhaskar serendipitously met Saleem Chapman at a panel on climate change in early 2019. At the time he was the chief resilience officer in the Office of Sustainability and recently became its director. The conversation quickly turned to warming in Philadelphia.

Local climate projections predict that by 2030, the number of days with temperatures reaching 95°F or higher is expected to double in Philadelphia, from 21 to 42, which would be nearly half of the summer season. But warming is not distributed evenly across the city — neighborhoods that have more buildings, pavement and black rooftops are warmer than those with more trees and parks. Because of deep-seated inequities and discriminatory practices like red-lining, tree cover or canopy is not equitably distributed in Philadelphia, with 40% in some areas and 3% in others. The latter experience an intense "urban heat island" effect, and on a peak summer's day, they can be nearly 22°F warmer than the coolest neighborhood. It's like living in two different climates.

These heat islands face other stressors. In 2018, Chapman's office and the Department of Public Health created a Heat Vulnerability Index that combines data on daytime temperature, availability of resources like pools and cooling centers and socioeconomic factors like income, age and incidence of disease. It's a tool that several cities across the world have used to pinpoint hotspots to keep residents safe during the summer.





VISUALIZING HEAT ACROSS PHILADELPHIA

The researchers created a map of temperature variation across Philadelphia using data provided by the Water Department. Each shape represents a census block group and those in orange and red are the hottest neighborhoods of the city. The researchers chose study sites within these areas (in green) to measure the cooling effect of green infrastructure. Many of these blocks overlap with the areas identified as most vulnerable to heat by the city's Heat Vulnerability Index, due to the prevalence of conditions exacerbated by heat like diabetes and hypertension, and lack of cooling resources. Many of the darkest blue or coolest areas correspond to the presence of big parks and/or water bodies. The cooling effect of these spaces spread to adjacent areas, in lighter shades of blue.

> **A significant aspect is that the heat effects health. During the day, extreme heat can lead to dehydration and cardiovascular stress. Higher nighttime temps disrupt the ability to sleep, increasing the risk for hypertension, disease and worsening existing conditions.**

An area is more vulnerable if it is both very hot and the people who live there are more sensitive to the effects of high heat (see map on p. 23) — for instance, older citizens, people with pre-existing medical conditions and those who don't have access to or cannot afford air conditioning. The index indicates that regions in North and West Philadelphia are the hottest, and that Black and Latino communities and people experiencing poverty are disproportionately vulnerable to that increased heat.

As Dr. Bhaskar and Chapman discussed the injustices of these urban hotspots and the sensors on the green roof, they arrived at the same questions — could they use similar sensors to measure the temperature at green infrastructure sites and identify a possible cooling effect? And if so, how could this encourage the placement of future green infrastructure in areas that are vulnerable to both increased heat and stormwater?

"Heat mitigation was not a primary consideration of the Water Department's green stormwater infrastructure program," says Chapman "But it is a potential co-benefit that could promote collaboration between city agencies, exactly the kind of approach we need to confront multiple environmental stressors."

They started a research partnership to explore tackling two climate change birds with one green stone. After more discussions and successfully acquiring funding from the William Penn Foundation, they began assembling a team.

ZOOMING IN ON HEAT, AT NIGHT

Dr. Bhaskar brought in the expertise of Dr. Megan Heckert, an urban geography researcher at West Chester University who uses geographic information systems and spatial analysis to explore issues like sustainability and tree equity. They shared the goal of collecting information on small scales, more relevant to the experience of urban warming.

"Much of the research on urban heat relies on satellite data, which while informative, is not at the resolution we need to understand temperature differences across short distances," explains Dr. Heckert. "What is it like to live on a shady street or city block, compared to one with fewer trees?"

Many green stormwater infrastructure installations are considerably smaller than city parks, the types of urban green spaces typically studied for mitigating urban heat. So their potential cooling effect might be limited, both in magnitude and geographic reach. This also motivated the researchers to take a finer scale approach to understand what level of cooling can meaningfully impact the on-the-ground experience of heat.

A significant aspect of that experience is the effect on health. During the day, extreme heat can lead to dehydration, cardiovascular stress and increased risk of heatstroke. But the danger lasts into the night. Surfaces like concrete and asphalt can bake up to 140°F degrees on a hot day and radiate that stored heat back into the air at night. It forces residents to incur higher energy costs by running air conditioning or fans through the night, which is prohibitive for some. Without the ability to cool down sufficiently, higher nighttime temperatures disrupt sleep, thereby increasing susceptibility to disease and worsening existing conditions like hypertension. In fact, one analysis showed that elevated nighttime temperatures were a major factor in heat-related mortalities in Philadelphia from 1983–2008.

"Residents living in these urban hotspots can maybe escape the heat of the day by being in an air-conditioned place of work or cooling center," says Dr. Bhaskar. "But at night, they're literally trapped."

Average summer-night temperatures in Philadelphia have increased by nearly 4°F since 1970. But unlike daytime temperatures, less is known about how this increase is distributed across the city, let alone a city block. The researchers therefore decided to gather their temperature measurements after sun down, hypothesizing that the effects of shading and evaporative cooling provided by the green infrastructure persist into the night. The next step was to determine how and where.

Heat sensor installed on a street sign.

CAMOUFLAGING SENSORS ON A CITY BLOCK

During the summer of 2020, Dr. Bhaskar's team and Philadelphia Water Department engineer, Matthew Fritch, rigorously tested low-cost sensors against high-end ones used by Philadelphia's Air Management Services Laboratory to compare accuracy and repeatability of measurements. Once a reliable sensor was identified, the next challenge was to camouflage it into the urban environment. The sensors needed to be placed where people are actively living, working, playing, etc. in order to capture the on-the-ground experience of heat. This proved to be challenging — some sensors were stolen, others succumbed to the elements. Dr. Bhaskar turned to Eric Schneider, an industrial design professor at Jefferson, and his students to help create a casing that would easily disguise the sensor in areas of high foot-traffic, but not hinder its accuracy.

"The students had to design for a hybrid environment, incorporating features that could blend in with concrete as well as soil and trees," says Schneider. Ultimately, two designs were chosen — one that looked like a rusty, utility box and another that could double as a plant label or mounting stake. Both held up well in the field – the sensors logged data accurately and remained undisturbed.

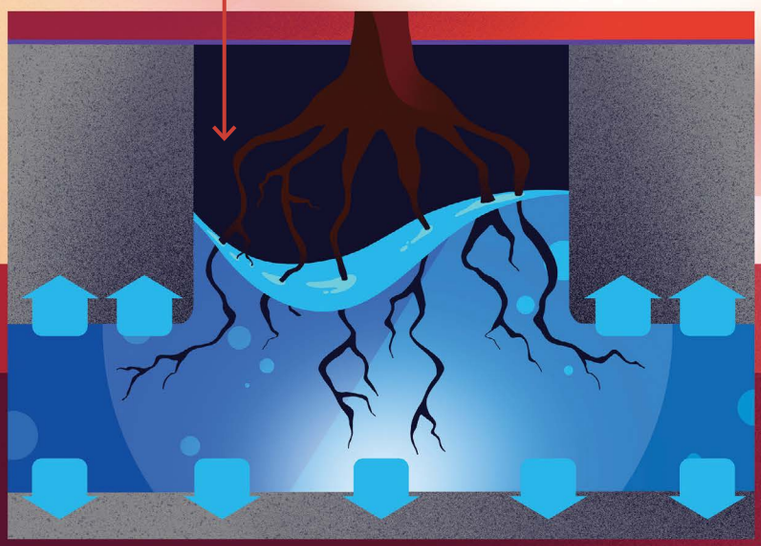
MEASURING CLIMATE CHANGE ON A CITY BLOCK

With reliable sensors ready to be deployed (see sidebar), Dr. Heckert mapped out potential locations, prioritizing green infrastructure sites in neighborhoods with high heat vulnerability, low surrounding tree cover and high energy costs. The team decided on two sites with green infrastructure built by the Water Department in Upper North Philadelphia, one of the hottest parts of the city: the Panati Playground, which has a rain garden with trees, and the Cecil B. Moore Recreation Center, which has tree trenches incorporated into the sidewalk.

In the summer of 2021, Dr. Bhaskar and researchers in her lab, including rising senior Cianna Quintana, installed the sensors in and around the study sites. Quintana, who grew up and still lives fifteen minutes away from the study sites, was shocked at the stark temperature differences from block to block. "We have lots of trees where I live, so even on a really hot day, the shade provides relief," she says. "But as I commuted to the study sites, I would see fewer trees, and not even a strip of grass in some places. There's no escape from the heat." The experience has inspired her to develop a pavement material that will release less heat at night for her senior team project, and seek a career path in climate resilience.

HOW TREES CAN MANAGE RAIN AND INFLUENCE HEAT

Green stormwater infrastructure combines plants' natural properties with man-made engineering. In tree trench structures, water coming from a storm grate infiltrates an underground storage area or reservoir made of rocks and other material. This stored water soaks into the soil where it is taken up by the roots of the tree, ensuring that stormwater is released more slowly into the sewage pipes and prevents overflow.



Trees have multiple benefits: Water taken up by the tree roots is released as moisture-rich vapors by the leaves, cooling the surroundings like an air conditioner. Trees also act like a sponge, with their canopy absorbing rain and thereby reducing the amount of water entering storm grates. They also intercept the sun's powerful rays and provide shade.

A sidewalk with fewer trees gets uninterrupted heat from the sun and is much hotter than a shady sidewalk. The heat absorbed by the sidewalk during the day is then radiated back into the air at night, dangerously increasing nighttime temperatures.

One of the first things they noticed was a difference in nighttime temperatures based on geography: At night, the temperatures of their study sites in Upper North Philadelphia were nearly 10°F warmer than Chestnut Hill, one of the coolest neighborhoods in the city. While this is less than the daytime disparity (22°F), it provides evidence that nighttime heat should be factored into existing health disparities. It could also account for the six-fold increase in heat-related mortality expected to hit Philadelphia by the end of the century.

They then compared surface temperatures of the green infrastructure sites to their surroundings. On average, the temperatures within both sites were approximately 4°F cooler compared to the adjacent sidewalk at night. The Panati Playground rain garden was more than

> **The magnitutude of cooling was surprising, considering how small these green spaces are and how hot the study locations are.**
>
> — **Dr. Bhaskar**

10°F cooler than the sidewalk across the street. In fact, the spatial analysis showed that this cooling effect reached the paved surfaces at the corner of the playground, which were also cooler than the sidewalk across the street. "It suggests that a green stormwater infrastructure's cooling could have a reach at the level of a city block, but more needs to be done to determine the precise geographic reach," says Dr. Heckert.

"This magnitude of cooling was quite surprising, especially considering how small these green spaces are and how hot the study locations are," says Dr. Bhaskar. "It shows us that, at least on a short time scale, these green tools have a measurable cooling effect at night."

> **It is urgent that we take action now, or the most vulnerable will continue to pay the price. Drawing on different areas of expertise and experiences, we can strive to build equitable climate resilience.**
>
> **— Dr. Bhaskar**

ENGAGING CITY, COMMUNITY AND HEALTH STAKEHOLDERS

Much more needs to be done to build on this work — the team hopes to replicate their findings at other green infrastructure sites in the city, and determine their geographic reach of cooling. But it was an important proof-of-concept for how to approach climate change. "We're dealing with moving targets, so we have to be nimble and action-focused," says Elaine Montes, who recently joined as a program manager of infrastructure resilience in Philadelphia's Office of Sustainability. "This means maximizing our resources, and getting buy-in from the agencies that manage those resources."

The cost of building green stormwater infrastructure can run into the six-figure range, then requires continuous maintenance by grounds crews. It also relies on coordination with the departments of Parks and Recreation and Streets. Because of silos among government agencies, communication is key. Montes has been working with Dr. Bhaskar on developing messaging around their pilot study for key city stakeholders.

For Dr. Bhaskar, it has underscored the complexities and roadblocks of government work around climate. But she has appreciated the urgency with which the city has approached this project. "It's made me realize how vital it is to have civic collaborators for research like this," she says. "I'm excited to co-design more studies with those who shape climate policy, in the hopes that it translates into action."

An equally important priority is starting dialogues with the public. "When we were out in the field, nearby residents would sometimes stop and ask what we were doing," recalls Quintana. Some people were curious, others were mistrustful and worried the green infrastructure would pose a nuisance. But many didn't even know the city had installed these tools. "Without engaging community members, it's hard to convince them that a tree is going to have a positive impact. Especially when they are facing so many other stressors."

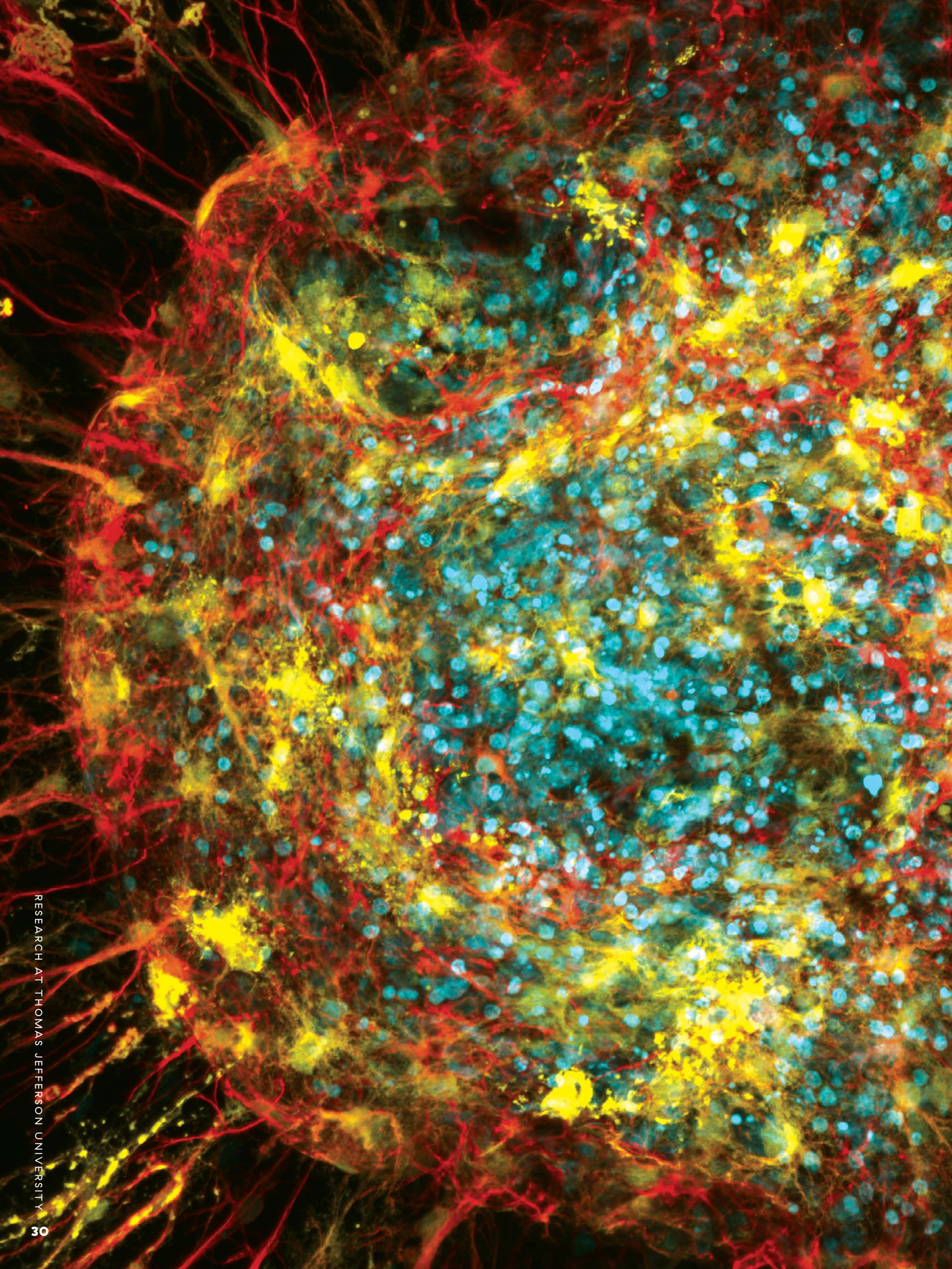
Community outreach is one of the main goals of the city's first Environmental Justice Advisory Committee, announced in February 2022. Dr. Bhaskar is one of 17 members who will make recommendations to the mayor's office and be ambassadors for climate equity. Through the committee, Dr. Bhaskar met Mariel Featherstone, DPM, a student in the master of public health program at the University of Pennsylvania. There she's done work with Dr. Eugenia South, showing that urban green spaces significantly improve mental health. She and Dr. Bhaskar aim to have conversations out in the community to see if green infrastructure has influenced well-being. "There is a direct link between a person's surrounding and their mood," says Dr. Featherstone. Violent crime increases on hotter days, and people who face climate-related natural disasters frequently struggle with mental health problems. "Climate change is no longer just an environmental issue, it's a public health issue."

LEARNING FROM ECOLOGICAL RESILIENCE

Dr. Bhaskar hopes involving other health experts, students and community members will bring varied perspectives to a multi-layered challenge. Her approach is inspired by an ecological concept she studied in her postdoctoral work called response diversity.

The theory describes how diversity can confer resilience: an ecosystem is made up of various species with different properties — some that tolerate drought, some that withstand high temperatures, and others that handle extremely wet conditions. Any one of them might struggle in one of these extreme conditions, but as long as the others thrive, the ecosystem as a whole can still function. "We can learn from how living systems with diverse responses can withstand a changing climate and apply it to engineered systems like green infrastructure."

But Dr. Bhaskar fears we are dangerously close to a tipping point, a permanent shift that even the most resilient ecosystem will not be able to prevent. "It is urgent that we take action now, or the most vulnerable will continue to pay the price," she says. "Drawing on different areas of expertise and experiences, we can strive to build equitable climate resilience."



SEEKING ARTISTRY IN RESEARCH

This year, Jefferson launched its first enterprise-wide Research-Art Competition that celebrated researchers with an eye for the beauty in their work. From capturing cellular landscapes to exploring expressions of grief and growth through art therapy, this year's submissions cover a wide swath of research interests. Enjoy a sampling of submissions here, and learn about the winning entries and the judges at research.jefferson.edu/art-competition.

← **"Astrosun" by Karthik Krishnamurthy**
Fluorescent micrograph of cells called astrocytes (red) from mouse spinal cord were experimentally manipulated to express amyotrophic lateral sclerosis (ALS) aka Lou Gehrig's disease linked toxic protein SOD1-G93A (yellow). Astrocytes expressing this protein kill motor neurons in ALS patients.

CANCER AND BUTTERFLY DISEASE

Years of research point to a therapy to treat the life-threatening cancer of patients with a rare disorder known as butterfly disease.

by Roni Dengler

illustrations by Greg Betza

Surgery, chemotherapy even cutting-edge immunotherapy — all failures. →

The cancer growing along the surface of the patient's skin was overpowering their body's last defenses. Traditional treatments for a typically curable skin cancer had all been unsuccessful. A clinical trial about 300 miles away and across an international border from the patient's home in Germany was a last hope.

Across the globe in Philadelphia, researcher Andrew South, PhD, sat glued to video conference calls with collaborators at all hours, coordinating the trial and tracking the patient's progress. This patient would be the first to enroll in a study that the team hoped could halt the cancer's progress.

For most people, a type of skin cancer called squamous cell carcinoma is treatable, and survivable when caught early. But for this patient and thousands of others living with a condition known as recessive dystrophic epidermolysis bullosa (RDEB), commonly referred to as "butterfly disease," the cancer is a death sentence.

RDEB is a rare genetic condition that makes the skin incredibly fragile. Patients with RDEB do not make enough, or any, of a protein called collagen 7, that helps to hold layers of the skin together, due to mutations in a single gene. Without collagen 7, the skin cannot make anchoring fibrils, which act as the glue between the upper and lower layers of skin. As a result, the skin is so delicate the slightest touch makes these layers separate and blister. Because anchoring fibrils also help hold together layers of mucosal surfaces in the mouth, esophagus and anal sphincter, blisters in the mouth and along the esophagus make swallowing difficult. Eating may require a feeding tube and laxatives and stool softeners are helpful, and sometimes necessary, for defecation.

It is the almost constant inflammation and chronic scarring from the blisters that lead to the nearly inevitable development of skin cancer. Chronic inflammation, or persistent infection anywhere in the body can lead to cancer because inflammation damages DNA, causes cells to multiply faster and stimulates the growth of blood vessels that bring oxygen and other nutrients to the area — all factors that support cancer development. Individuals with RDEB live with chronic inflammation and often develop skin cancer within the second or third decade of life. The majority of patients do not live to celebrate their 35th birthdays.

"This disease is diabolical in its cruelty," says Sharmila Collins, founder of Cure EB, a patient advocacy and funding organization, and mother to Sohana who lives with the disease. "A treatment would be a massive relief, the lifting of a death sentence."

While progress has been made for many other cancer types, a treatment for the skin cancer in RDEB patients has evaded scientists. Many molecules can look promising in laboratory experiments, but few actually make it through clinical trials with patients, and far fewer of those become approved drugs. A decade ago, Dr. South discovered a molecule that appeared to drive skin cancer in cells derived from patients with RDEB. He didn't know it then, but that discovery would be the first of many leading to a treatment for the disease.

FROM THE LAB BENCH: IN SEARCH OF A TARGET

Dr. South became interested in RDEB cancer as a newly-minted doctoral graduate in 1999. He investigated the cancer from many angles over several years, looking for something unique to RDEB that would expose a weak link in the cancer that researchers and clinicians could attack with treatment.

Dr. South and colleagues made a pivotal discovery when they studied gene expression in a type of skin cell called keratinocytes. This cell type makes up most of the outer layer of the skin and produces keratin, a protein that helps to keep hair, nails and skin strong. It is also where skin cancer takes root and begins to grow.

The researchers made four sets of comparisons: healthy and cancerous skin keratinocytes from RDEB patients, versus healthy and cancerous keratinocytes from patients with typical skin cancer induced by ultraviolet (UV) light. They were expecting to find something unique about the cancerous RDEB cells, something that would explain why the cancer is so aggressive in these patients.

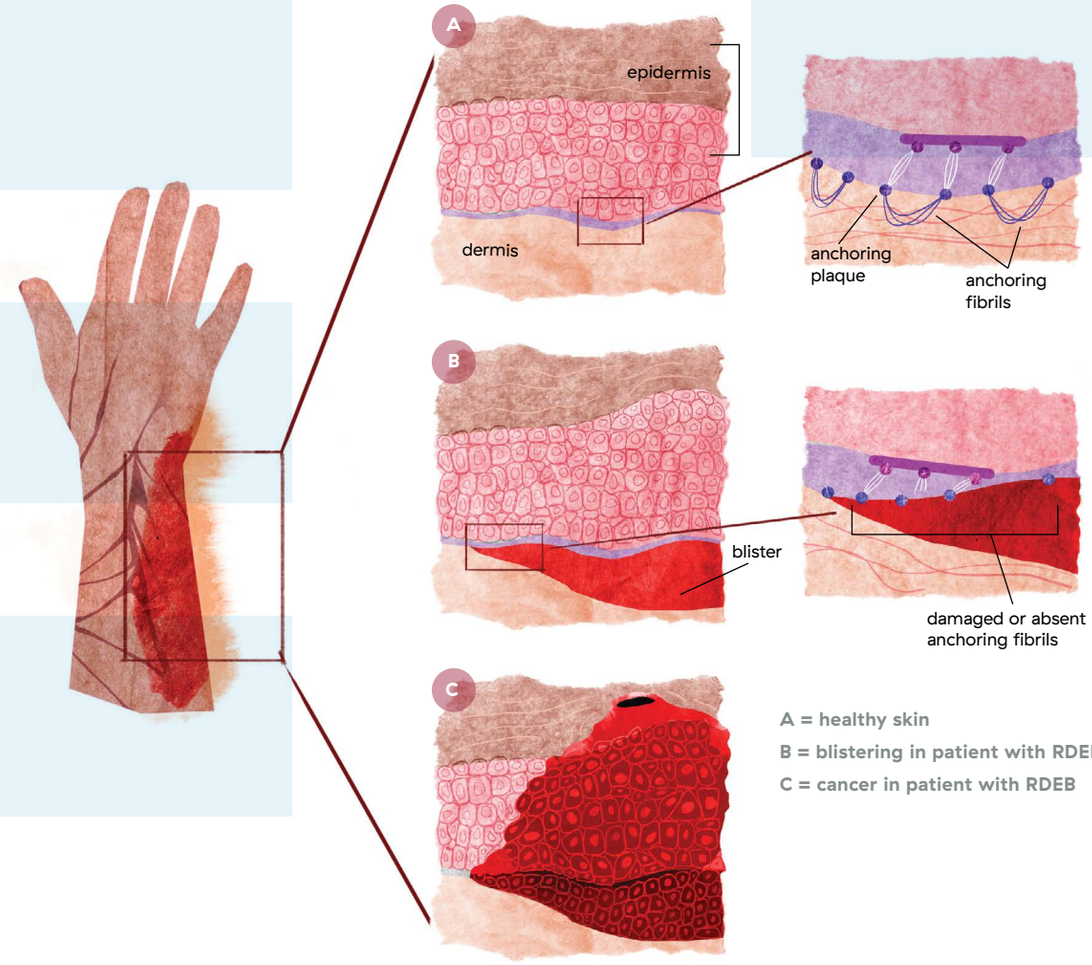
But the experiment didn't give them the results they were expecting. Cancerous keratinocytes from RDEB patients weren't all that different than cancerous keratinocytes from patients with UV-induced skin cancer. Although surprising, the findings meant that the results could apply to any type of squamous cell carcinoma, whether or not it developed from sun exposure or RDEB.

The comparison, however, did reveal big differences between healthy keratinocytes and cancerous ones, whether or not they came from patients with RDEB or UV-induced skin cancer. There were much higher levels of about 20 genes in the cancerous cells than the healthy cells. These became his potential targets.

To pare down the list further, Dr. South and colleagues silenced the expression of each of these genes one at a time using a technology called short interfering RNA, or siRNA, to learn which ones were essential for tumor growth. siRNAs interrupt the protein-production of a gene, effectively rendering the gene non-functional, or silenced. When the researchers looked at how many cancer cells were still alive after each siRNA treatment, they saw that knocking down expression of only two of the genes they tested consistently killed a large proportion of the cancerous cells.

Recessive dystrophic epidermolysis bullosa (RDEB), sometimes called butterfly disease, is caused by mutations in the gene for collagen 7. Without collagen 7, the skin cannot make enough anchoring fibrils (A), which are essential for keeping the top layers of skin (the epidermis) securely fastened to the lower layers (the dermis). Without these fibrils, any rubbing on the skin can lead to separation and blistering (B) that is difficult to heal. The inflammation and scarring that accompanies these blisters creates an environment for skin cancer formation (C) that is often deadly for RDEB patients.

GENETICS AND CANCER IN RDEB →



A = healthy skin
B = blistering in patient with RDEB
C = cancer in patient with RDEB

One of the genes, called polo-like kinase 1 (PLK1), plays a central role in helping cells multiply. Cancer cells multiply much faster than healthy cells, making PLK1 an ideal target. (Explore the infographic on p. 37 to learn how blocking PLK1 kills cancer cells.)

Dr. South and colleagues then searched for a chemical that could do the same job as the siRNA, and would be more suitable for use in humans. One chemical they found was able to kill nearly all of the cancerous cells within three days while only slowing the growth of the healthy cells. Treating cancerous growths in mice with the chemical decreased the number of cancerous cells in as little as two weeks and dramatically shrunk the size of the tumors. Dr. South and colleagues had found their target. Now they needed to find a drug that would disable PLK1 in human patients' cancers.

FROM THE LAB BENCH: DRUG DISCOVERY

As PLK1 plays a role in many cancers, a number of drugs that block the enzyme, also called inhibitors, were already available and in development for other diseases. In a preclinical study, Dr. South and colleagues tested six of these inhibitors in a dish on healthy and cancerous cells isolated from RDEB patients during routine diagnostic and surgical procedures. Of the six drugs they tested, one called rigosertib stood out from the rest.

Although all of the drugs that the researchers tested were good at killing cancerous cells, most of them also killed healthy cells, which might create serious side-effects for patients. That is, all of the drugs except rigosertib. "It really did nothing to the normal cells," says Dr. South. Rigosertib was only capable of slowing the growth of healthy cells at much higher doses than required to kill the cancer cells, suggesting that if used to treat patients with RDEB cancers, rigosertib might produce fewer side effects than the other drugs.

What was more surprising, however, was how effective the drug was. Dr. South and colleagues tested rigosertib on cancerous cells isolated from 10 patients. In all 10 cases, the cancer cells died. "An efficacy of 60% is something one might think about taking into clinical trials," says Dr. South. "Rigosertib was 100% effective."

The researchers went on to bolster their in vitro findings in mouse models of the disease. When administered throughout the whole body, or systemically, rigosertib was very effective at stopping the cancer growth and shrinking tumors. This was another key factor in rigosertib becoming a potential treatment. RDEB patients' cancers can spread to other parts of the body very quickly, creating metastases that can be even more difficult to treat. A drug that can be administered systemically, intravenously or with a pill for example, will target all of the cancer cells in the patient.

FROM BENCH TO PATIENT BEDSIDE

With this promising evidence in hand, Dr. South began to secure funding to run a clinical trial. Grants from patient advocacy organizations helped to get things going, but the trial had a rocky start. The success rate for potential therapies to go from discovery to approved treatment is low. Less than 10% of potential drug treatments become approved therapies that patients can actually use. For cancer drugs, the success rate is about half that. Most drugs don't make it past Phase I trials, where researchers assess the safety of a drug and identify side effects.

To complicate matters, rigosertib is an experimental drug that is not yet approved by the U.S. Food and Drug Administration (FDA) for any treatment. Establishing a clinical trial in the U.S. would require a complicated and long logistical process. While working to overcome these obstacles, Dr. South initially set the trial to be conducted in Europe, virtually managing the paper-work and red tape from Philadelphia. "All of that took about a year and a half just to get the contracts finished," says Dr. South.

The trial became open to recruiting patients in Europe, at long last, in 2019. Before any patients were able to enroll, however, the novel coronavirus shut the world down. The first patient was finally able to enroll in the spring of 2021. She traveled from her home in Germany to Austria to participate in the trial. There, she checked into a hospital for a three-month stay. Clinicians administered rigosertib via an intravenous line over three days every three weeks, a task made exponentially more difficult in a patient with such delicate skin. Doctors and nurses were on constant watch for the looming threats of infection and sepsis.

Over the next months, a medical team monitored three of the primary skin-cancer lesions scarring the patient's body. Within six months, two of the lesions showed complete remission and the third was no longer growing. Nine months after beginning treatment, all three lesions had disappeared.

"This is the outcome we'd been hoping for, after so many years," says Dr. South.

A year and a half after treatment with rigosertib, the patient remains cancer-free.

Until now, no therapy has successfully treated this cancer in patients with RDEB. But, a year and a half after treatment with rigosertib, the patient remains cancer-free. It is an unprecedented outcome for RDEB patients with advanced skin cancer.

"We are in dire need of a treatment for cancers in these patients. We're really behind in that," says dermatologist Neda Nikbakht, MD, PhD, a physician-scientist at Sidney Kimmel Cancer Center–Jefferson Health, who is collaborating with Dr. South to open the first U.S. trial offering a new cancer treatment to patients at Jefferson's adult EB clinic, one of only a few of its kind in the country.

"With all the progress we made in many other cancer areas, for this group of patients, unfortunately, we don't have much to offer. This trial, and Dr. South's discoveries, really go a long way to address these unmet needs," she says.

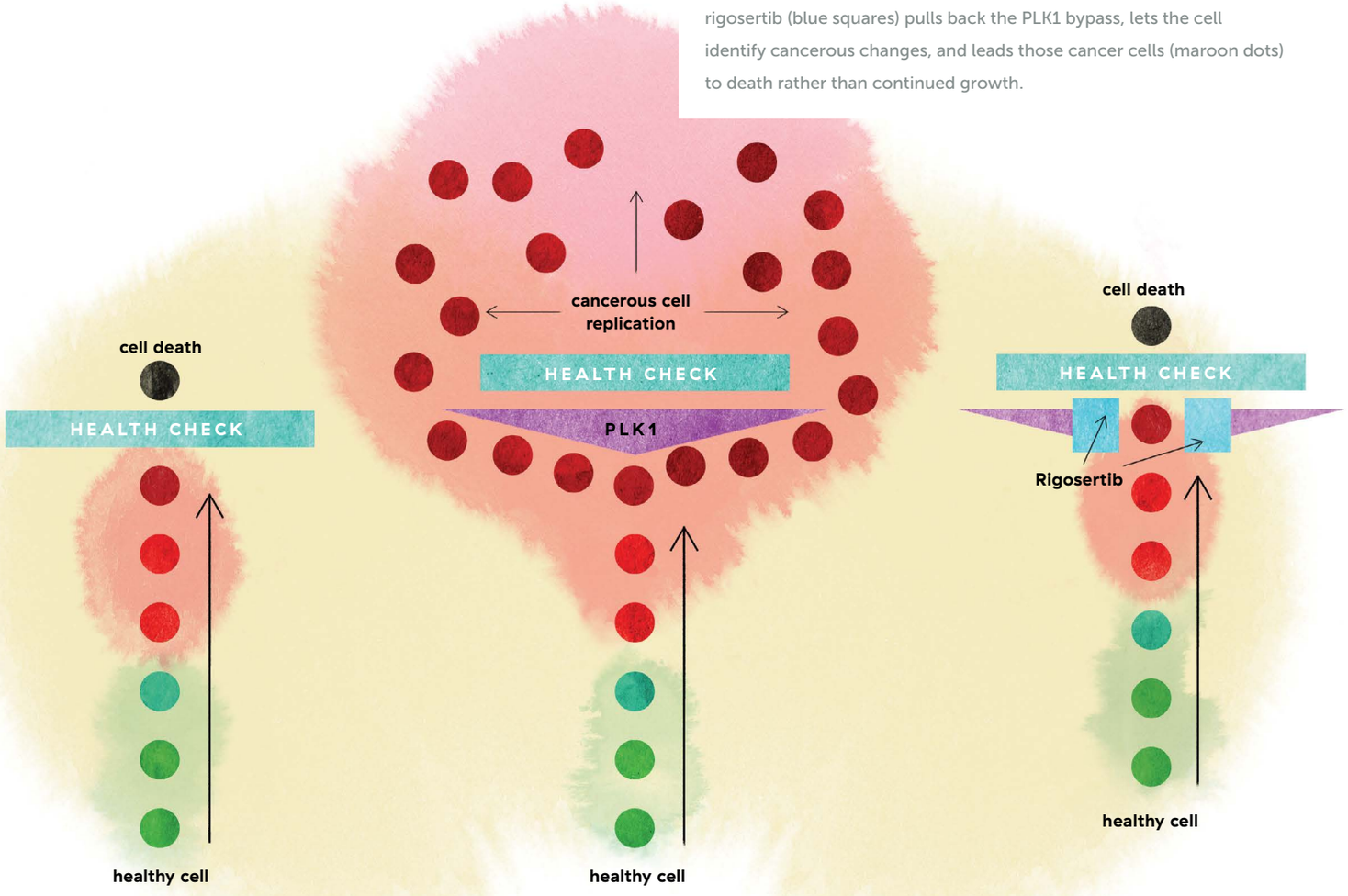
Drs. South and Nikbakht have gleaned many lessons from the trial in Europe, and have been able to improve how it will be run in the U.S. The first patient in Europe, for example, had to remain in the hospital while receiving treatment, as it must be administered over 72 hours. Now, patients seen at Jefferson's EB clinic will receive the drug as a pill. "We now have made it much easier for the patient," says Dr. Nikbakht. "Patients will be able to receive the treatment at home."

"This is the outcome we'd been hoping for, after so many years."

— Dr. South

STOPPING EB CANCER

Skin cells form a tight layer of protection and also frequently reproduce to make new layers of skin. Before a skin cell can make more of itself, it has to pass through a health check to make sure it's cleared for replication. As a healthy cell ages and accumulates damage to its DNA (progressively darker red dots), one of the first steps toward developing cancer, the cell's internal health check should prevent further replication or push the cell to self-destruct (black dots). In EB cancer (middle panel), increased amounts of a molecule called PLK1 (purple triangle) overrides the normal health check. Instead, cells with cancerous changes bypass the health check and continue to proliferate (maroon dots). Dr. South's team found that a drug called rigosertib (blue squares) pulls back the PLK1 bypass, lets the cell identify cancerous changes, and leads those cancer cells (maroon dots) to death rather than continued growth.



Within weeks of beginning treatment with rigosertib, the patient noticed a cancer lesion on her ankle had shrunk. "I'm surprised how quickly it happened," said Rachel Nasuti.

TOWARD DRUG APPROVAL

Drs. South and Nikbakht hope that this is only the beginning. For rigosertib to become a treatment available to patients beyond the clinical trial setting, other patients will need to have similar success as the patient in Europe.

"If we see another one or two patients with similar responses, then that will be the time to go to the FDA or the European Medicines Agency and apply for conditional approval of rigosertib," says Dr. South. Because RDEB is a rare disease and there are no other options for RDEB patients with squamous cell carcinoma, there is potential for the agencies to approve the treatment on compassionate grounds.

Rachel Nasuti, who has enrolled in the trial at Jefferson, may be the patient to bolster such an approval. Within weeks of beginning treatment with rigosertib, Nasuti noticed a cancer lesion on her ankle had shrunk. "The wound was indented, but it's not as much anymore," she says. "I'm surprised at how quickly it happened. I thought I wouldn't see results for three months."

Nasuti has had multiple surgeries to remove areas of skin cancer over the past eight years. She has tried chemotherapy and several immunotherapy treatments, but the cancer has always returned. When she heard about the rigosertib trial at an EB conference, she was intrigued. Rigosertib wasn't an invasive treatment and didn't appear to have the side effects of chemotherapy.

And although surgery is the quickest, most straight-forward way to remove confirmed cancer lesions, the healing process takes a while and is painful. "You also don't always know what lesions are cancer and what's not," she says. "So it's not as targeted a treatment as rigosertib."

An approved drug would have huge impacts for patients like Nasuti and their families. "If we had some effective therapy to kill the cancer, it will feel like freedom," says Sharmila Collins, the founder of Cure EB. "To have that fear lifted, it means patients can go about their lives. Life might still be difficult until we find really effective treatments for RDEB, but there might be less fear that absolutely nothing can be done. I hope more than anything that this is a successful trial and will provide us a tool with which to fight the RDEB skin cancer."

Nasuti, who lives in Michigan and drove 10 hours in each direction to enroll in the trial agrees. She is now able to continue rigosertib treatment at home between monthly visits to Jefferson. Although she is pragmatic about the possibility of the cancer returning after treatment with rigosertib, she says, "It'd be nice to live cancer free. Hopefully, rigosertib will become a treatment option for the future."

Dr. Nikbakht and her team in the clinic are hopeful. "We are thrilled to see positive results, but we will need to rigorously evaluate outcomes over time," she says.

Dr. South is cautiously optimistic as well. "Chances are that we will see similar responses to the drug in other patients," he says. "But we don't know yet, of course, and that's why we do the research."

"Patient Identity" by Savannah Patterson

The exploration of patient identity among mental health clinicians can strengthen the client-clinician relationship. This photograph explores the impact of clinician vulnerability and self-disclosure, shown by the artist's name on the sides of medication bottles that are left open.

RESTORING SMELL AND TASTE AFTER COVID

Promising results from a clinical trial provide hope to patients searching for treatment. →

by Shellie Wass and Karuna Meda
illustrations by Chiara Zarmati
photographs by ©Thomas Jefferson University Photography Services

FOR AS LONG

as Nancy Damato can remember, smell and taste have been interwoven into her very being.

These senses bring up memories of large Italian dinners with her family every Sunday, and the feast of the seven fishes every Christmas Eve. A self-professed foodie, she enjoys visits with her stepson who is a top chef in New York. She collects perfumes and as an avid yoga enthusiast, she enhances her practice with essential oils. "In what seemed like a nano-second, all of this was taken away without a trace."

Damato was one of thousands infected by the novel coronavirus during the first wave of the pandemic. She initially considered herself lucky — with mild symptoms, she continued her daily yoga routine and worked from home. But a few days into her quarantine, she realized she couldn't smell her morning coffee or taste her food. Alarmed, she called her doctor and discovered she was experiencing a phenomenon known as anosmia.

Since the beginning of the COVID-19 pandemic, over 96 million Americans have been infected with the coronavirus. With the earliest variants of the virus, loss of smell or anosmia, was one of the first signs. Although this symptom has become less common with more recent variants like omicron, it is estimated that 27 million people are still experiencing long-term anosmia.

David Rosen, MD, an otolaryngologist at Jefferson Health, has been studying and treating anosmia for over two decades, but has never seen it at this scale. "Before COVID-19 hit, I would see one or two patients with anosmia a month," he says. "Now I see three or four patients per day." He has long searched for a treatment for anosmia and other smell disorders. In 2019, he and his team began investigating a tool called platelet-rich plasma (PRP), which is thought to help regenerate the cells in the nose that enable us to smell. Little did he know that just a year later, anosmia and this treatment would be thrust into the spotlight.

Damato came across an article on Dr. Rosen's study, and it felt like a lifeline. She was told by her doctor that her senses would return after two weeks — but the time came and went, and she began desperately looking for ways to regain her senses. She reached out to Jefferson Health just in time — the clinical trial was still enrolling patients. Her and Dr. Rosen's journey offers hope to millions of patients still looking to restore the vital sense of smell and shines a light on a condition that has long been poorly understood.

THE UNDERAPPRECIATED POWER OF SMELL

The ability to smell is a complex process involving the nose and brain. It begins with odor molecules in the air passing through your nostrils and to a strip of tissue inside the nose called the olfactory epithelium. This tissue is home to millions of cells called olfactory sensory neurons, which are like taste buds of the nose. Each of these neurons has receptors that bind the odor molecules floating around. When detection happens, the neurons send an electrical signal to the brain, where it is processed into a scent that we're able to recognize.

"The sense of smell enriches our everyday lives, helps us understand our environment and form memories," says Nancy Rawson, PhD, the acting director of Monell Chemical Senses Center in Philadelphia. "But the role of smell in humans has been underappreciated because we are such visual and sound-oriented animals."

Monell is a global leader in smell and taste disorders, and a long-time collaborator with Jefferson. Their connection dates back to the late 90s, when they started the Taste and Smell Clinic located in Jefferson's Ear, Nose and Throat (ENT) Department. It was through the work of his mentor, Edmund Pribitkin, MD, with the clinic that Dr. Rosen developed a passion for smell disorders. Over the years, he has worked with Dr. Rawson and Pamela Dalton, PhD, another Monell scientist, on numerous projects to better understand how smell works at a cellular level.

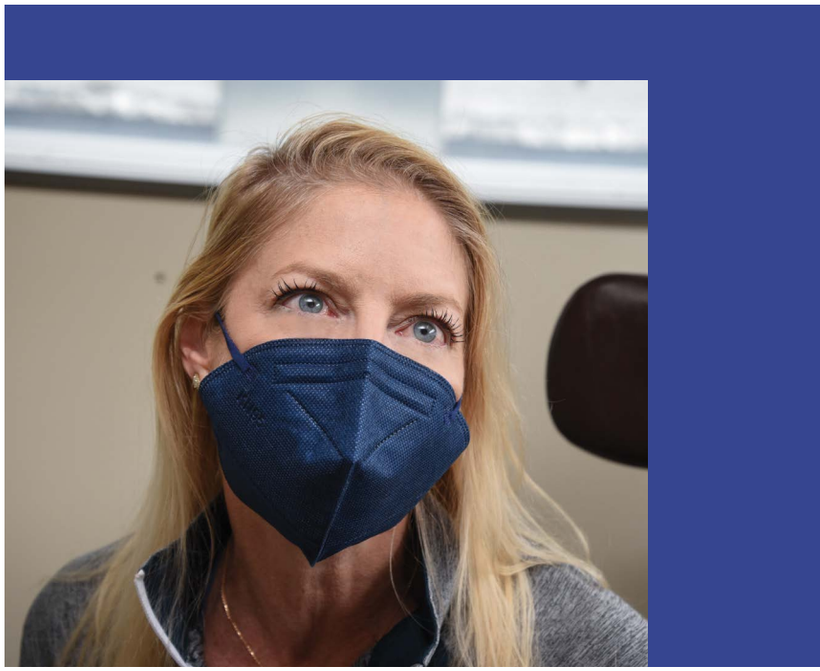
Through their work, they met hundreds of patients who had lost their sense of smell to various causes — head trauma, nasal polyps, chronic sinus disease, infection and aging. They also witnessed the impact of impaired smell through their patients' stories. Dr. Dalton remembers a flight attendant who lost her sense of smell after a car crash and struggled to navigate once familiar contexts on her travels. "She knew what the Paris metro smelled like and without that context cue, she felt like she was in a completely new environment," recalls Dr. Dalton. "It changes the way you move through the world — if you compare it to sight, colors that were once vibrant are now faded."

The description resonates with Damato, who says it goes deeper than losing her ability to taste her coffee — she feels like she's lost a part of herself. There are also long-term dangers, including not being able to smell smoke, gas or fire within your home. Anosmia patients are also at risk of developing depression and weight loss from losing the joy of tasting food, as the majority of flavor actually comes from aroma. Furthermore, an NIH-supported study involving 3,000 people above the age of 50 showed that those who could no longer detect or distinguish odors were four times more likely to die within five years than those with a normal sense of smell.

It's clear that smell is important. Furthermore, impairments in smell are actually quite prevalent. In fact, before the pandemic nearly one in four Americans over the age of 40 reported some alteration in their sense of smell. But it has been challenging for researchers like Dr. Rosen and those at Monell to convince funders to invest in their work. In 2011 the joint clinic closed because funding ran out. "And then COVID-19 changed everything," says Dr. Rosen. Suddenly, they were getting frantic calls from patients and journalists for answers — how exactly is SARS-CoV-2, the virus behind COVID-19, causing the loss of smell? And how do we treat it?

COVID-19 SABOTAGES SMELL-SENSING CELLS

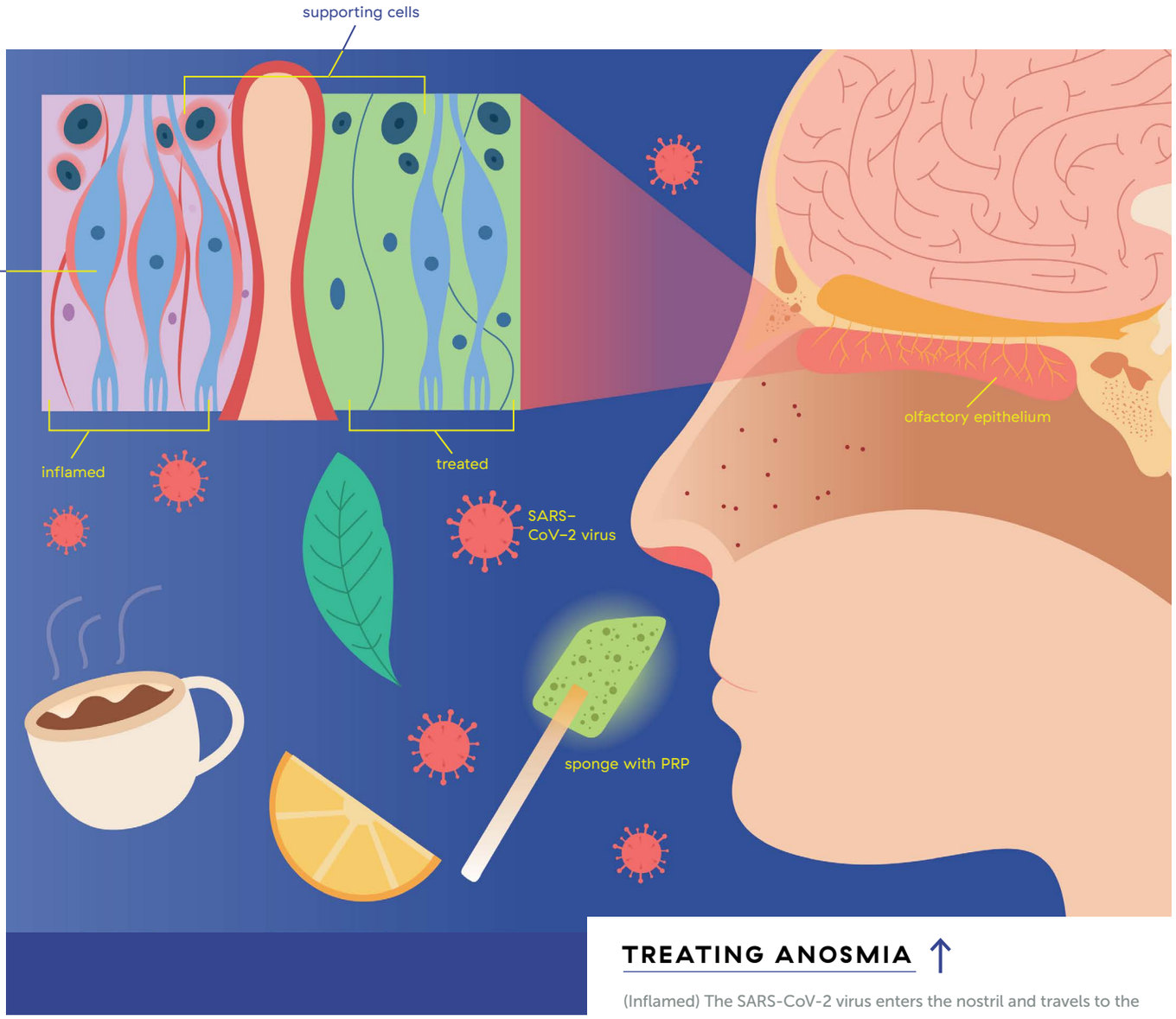
With other viral infections, the loss of smell and taste is a secondary symptom that occurs due to congestion and inflammation of the nasal passages. But with COVID-19, loss of smell is one of the first signs that precedes other cold-like symptoms. This initially baffled scientists and doctors. "If you look at the noses of COVID-19 patients with a scope, they look pristine compared to other post-viral patients whose nasal passages are clearly swollen and obstructed," says Dr. Rosen.



Nancy Damato during an appointment with Dr. David Rosen.

"The sense of smell enriches our everyday lives, helps us understand our environment and form memories. But the role of smell in humans has been underappreciated because we are such visual and sound-oriented animals."

Dr. Rawson
Monell Chemical Senses Center



TREATING ANOSMIA

(Inflamed) The SARS-CoV-2 virus enters the nostril and travels to the olfactory epithelium, where it binds to ACE-2 receptors on the supporting cells around the olfactory sensory neurons (blue), causing inflammation (in red). This in turn causes genetic changes in the neurons, hindering their ability to correctly detect smell.

(Treated) After spraying a numbing agent up the nose, a dissolvable sponge saturated with platelet rich plasma or PRP is inserted using an endoscope. The sponge dissolves over time into the olfactory epithelium, where PRP is thought to regenerate damaged supporting cells (in green) and the olfactory sensory neurons' ability to detect smell.

But a closer look at the olfactory epithelium in the nose reveals a different picture. The smell-sensing neurons are interspersed with various support cells that remove waste, provide nutrients and maintain the optimal balance of ions in the cellular environment. Researchers have found that some of these support cells are full of ACE-2 receptors, which the SARS-CoV-2 virus uses as a key to gain access into cells.

Once infected, the support cells become targets for the immune system and inflammation kicks in. Dr. Rawson says that scientists don't yet know the exact mechanism, but they think the inflammatory cascade causes the olfactory sensory neurons to drastically reorganize their genetic material. Without the correct genetic code, the neurons can't produce the receptors they need to detect odor molecules. This is another unique feature of COVID-19 — while other viruses like influenza and polio directly attack the sensory neurons involved in smell, SARS-CoV-2 hijacks the supporting cells the neurons depend on to function.

For some patients, this molecular mayhem resolves in a few weeks and their sense of smell returns. For others, like Damato, symptoms persist. Many questions remain unanswered about why some people are more susceptible to prolonged smell loss than others, and whether there are

> "The silver lining to this very dark cloud (of COVID–19) is that we've never had such a large cohort of anosmia patients at one time, and we can pinpoint the exact cause."
>
> Dr. Dalton
> Monell Chemical Senses Center

Dr. Rosen and his colleague Dr. Glen D'Souza use an endoscope to guide the placement of the dissolvable sponge saturated with PRP inside Damato's nose.

lasting changes in the brain. It will be at least another decade until we can fully understand the long-term impact of this scale of anosmia.

"The silver lining to this very dark cloud is that we've never had such a large cohort of anosmia patients at one time, and we can pinpoint the exact cause," says Dr. Dalton. It has focused some much-needed attention on not just understanding mechanisms, but also developing treatments.

THE SEARCH FOR A CURE

Dr. Rosen says the gold standard for patients with smell disorders is a technique called smell training. It is easy for patients to do at home and requires mindfully smelling different scents for a few minutes each day. Some recommended scents to start with include coffee, citrus, strongly scented soaps or shampoos and candles. A patient smells the same thing repeatedly while consciously reminding their brain what they're smelling. They would think to themselves, 'this is coffee, this is coffee…' and once they can begin to recognize that scent, they move on to another.

Damato has made smell training part of her daily routine. When she does yoga, she lines up her different essential oils and practices smelling each to help trigger her memory. Previous evidence has shown that about 30% of patients had improved smell after performing smell training for three months. But the success can vary depending on the severity, duration and cause of the smell loss. Sticking with the exercise can also be challenging.

Since inflammation can contribute to disrupted smell, steroids in the form of nasal sprays or rinses are also prescribed. But their success in COVID-19-related anosmia is limited. There have also been some early experiments with intranasal vitamin A, which has been shown to be beneficial in other forms of smell loss. Doctors also prescribe it as a supplement, along with omega-3 and alpha-lipoic acid, which are generally anti-inflammatory and have restorative properties.

"But these treatments don't have robust science behind them," says Dr. Rosen. "And they're more like band aids, so improvements, if they occur, are usually short-lived. We need something that's actually going to repair the cellular damage." This is where platelet-rich plasma comes in.

A REGENERATIVE APPROACH

Platelet-rich plasma or PRP, as its name suggests contains platelets, a blood component known for its clotting properties. They also produce growth factors that can stimulate tissue regeneration. As a treatment, PRP is generated from a patient's own blood, a sample of which is spun down rapidly in a centrifuge to separate the platelets from other blood cells and concentrate them within the plasma, the clear liquid portion of blood.

Dr. Rosen first became interested in PRP as a regenerative technique because of family members who had undergone injections of PRP into their joints to stave off invasive surgery for orthopedic conditions. Indeed, PRP has been successful in healing damaged tissue in conditions like back pain, and in regenerating healthy cells in scar removal and hair growth.

In 2018, Dr. Rosen came across a study where researchers injected PRP into the noses of patients with anosmia. While it was a small sample size, four out of five patients reported some improvement in their ability to smell. It was one of the

The results of the pilot trial are promising — among those who completed a three-month course of PRP treatments, 60% experienced improvements. "This is nearly double the improvement seen with smell training, the tried-and-true treatment for smell disorders," says Dr. Rosen. To his knowledge, it is the first and only study investigating the use of topical PRP treatment for smell loss.

first studies that had used a regenerative approach for smell disorders; Dr. Rosen wondered if he could build on this and develop a delivery system for PRP that was less invasive than an injection.

"Nasal absorption is so good that if you don't have a way to deliver something intravenously and you need to get it into the body quickly, the nose is an effective way," he says. A good example is the Narcan nasal spray that can save people experiencing opioid overdose.

Dr. Rosen and his team began developing a topical method, using dissolvable sponges saturated with PRP. After spraying a numbing agent up the nose, the sponges are inserted into the nasal cleft using an endoscope. The sponge dissolves over time into the olfactory epithelium, where the researchers hypothesize PRP gets to work to regenerate damaged cells.

They began testing their approach in 2019 with one patient, who showed improvement. She had lost her smell as a result of another viral illness almost three years prior. As they looked to enroll more patients, the pandemic hit, and they saw a massive uptick in interest. But it wasn't just from COVID-19 patients — for people who had struggled with anosmia for so long due to other causes, this treatment offered renewed hope.

THE PROMISE OF PLATELET-RICH PLASMA

Phase 1 of the clinical trial began in September 2020 with eleven patients experiencing smell loss, the majority of whom had lost their sense of smell to COVID-19. To get a baseline of their ability to smell, they underwent several types of smell tests, including the Brief Smell Identification Test™ which captures whether or not a patient was able to identify a particular scent. After this initial screening, patients had three monthly PRP treatments, and their ability to smell was tested one month after each session.

Nancy Damato joined the trial in October 2021, eight months after her initial recovery from COVID-19. She couldn't smell anything, even if it was right under her nose, and she was unable to taste any of her food. "I felt so lost," she remembers. "Dr. Rosen and his team were so empathetic."

The results of their pilot trial are promising. Among those who completed a three-month course of PRP treatments, 60% experienced improvements. "This is nearly double the improvement seen with smell training, the tried-and-true treatment for smell disorders," says Dr. Rosen. To his knowledge, it is the first and only study to date investigating the use of topical PRP treatment for smell loss.

Since ending the clinical trial, Damato has continued to see improvements. She is able to recognize scents such as lemon, rose, lavender and peppermint and can occasionally smell odors in the air. She is now able to differentiate between sweet and salty food, and can taste hints of flavors: the peppery flavor of arugula, some flavors in plain yogurt. She says her morning coffee and wine still don't taste the way she remembers. "But it's a huge improvement from when I first enrolled in the trial and I'm happy with my progress," she says. "It was also so comforting to meet other patients and to know that I am not alone."

WHAT'S NEXT?

Dr. Rosen and his team hope to expand their PRP treatments to even more patients with smell disorders, and a phase 2 placebo-controlled trial is now underway. To capture additional information of patients' baseline ability to smell, the researchers are also including the SCENTinel™ test developed by Monell. This test indicates the intensity at which patients can smell and how pleasant a scent is. "In the clinic, a patient might perform well at identifying different scents," says Dr. Rawson. "But when they're out in the real world, where scents are present at different intensities, they may not be able to smell as well. So this test paints a more accurate picture."

These studies will collect more evidence for PRP as a treatment not just for COVID-19-related anosmia, but for other types of smell loss as well. "PRP is like a soup of healing agents," says Dr. Rosen. "If it's able to regenerate the tissue in the nose, it should have the ability to reawaken smell that has long been dormant."

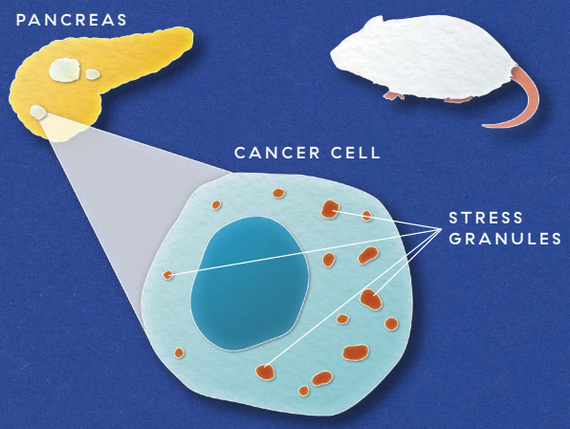
More than anything, he's relieved that he finally has a tool to offer patients and can send them home with hope.

"Conflict Zone 7" by Lyn Godley

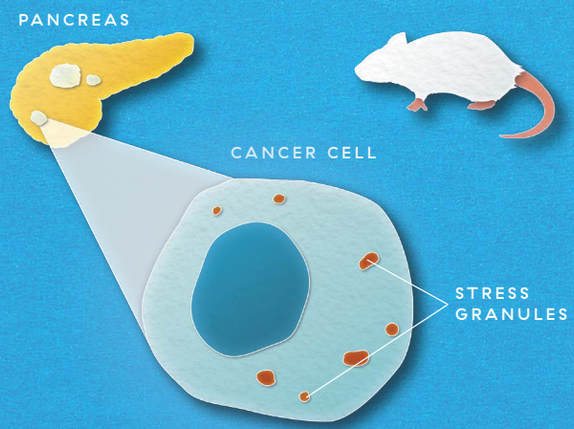
This work focuses on how the use of dynamic light merged with painted imagery can create an immersive experience, and more specifically, how that engagement could be used to beneficially impact the viewer by calming, transforming, or inspiring.

LINKING PANCREATIC CANCER AND OBESITY

OBESITY MODEL



NON-OBESITY MODEL

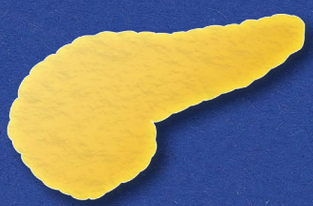


STRESS GRANULES BLOCKED

STRESS GRANULES NOT BLOCKED

OBESITY MODEL

90%
reduction in cancer growth



40% survived cancer-free

300 DAYS

NON-OBESITY MODEL

50%
reduction in cancer growth

survived

90 DAYS

NON-OBESITY MODEL

0%
reduction in cancer growth

survived

50–60 DAYS

STRESS, OBESITY AND PANCREATIC CANCER

by Edyta Zielinska
illustrations by Ava Schroedl

A common response to cellular stress may be the key to pancreatic cancer in people with obesity, pointing to new therapy for this difficult-to-treat cancer.

Early in her scientific career, as a postdoc working on pancreatic cancer, Elda Grabocka, PhD, read a review article that changed her trajectory. It discussed the importance of cellular stress in cancer formation. A few months later, she discovered that her own line of research intersected with recently discovered stress-related organelles called "stress-granules." "I had to learn more! I couldn't help but wonder whether stress granules were the missing link between cancer and obesity," says Dr. Grabocka.

Obesity, which causes stress and inflammation throughout the body, is a known risk factor for at least 13 types of cancer, but understanding this relationship well enough to block it has been challenging.

Dr. Grabocka knew that stress granules were an unusual sort of cellular compartment. The cell generates these dense globules of RNA and protein in response to cellular stresses like viral infection, neurodegeneration or starvation. In fact, they protect the cell from stress-induced self-destruction. It's a cellular reflex and defense mechanism that's present throughout the animal and plant kingdoms. Even tomato plants produce stress granules.

Dr. Grabocka started by studying the link between pancreatic cancer and stress granules, and was able to show stress granules were abundant in the tumors of patients with pancreatic cancer, proving there was a relationship worth exploring.

Indeed, after Dr. Grabocka's paper on pancreatic cancer published, other researchers showed that many cancers produce high levels of stress granules to prevent their own self-destruction.

When Dr. Grabocka came to the Sidney Kimmel Cancer Center–Jefferson Health, she began to probe the relationship further. She created a mouse model of pancreatic cancer that blocked the formation of stress granules in cancer cells. Her team saw a whopping 50% reduction in cancer growth in those mice. This was already an impressive effect, but Dr. Grabocka wondered whether it could be even bigger in obesity-related pancreatic cancer.

Obesity affects two thirds of all adults in the U.S. and 50% globally. It also doubles the risk and mortality for pancreatic cancer. About 33% of pancreatic cancer is obesity-related, a number that is only expected to rise in the coming decades.

To test the role of obesity, the researchers took two different types of mouse models of obesity and looked at pancreatic cancer in these mice. Both obesity models had five to eight times the amount of stress granules in their cancers as non-obese mice. This suggested that the cancers in obese mice might be dependent on stress-granules for their growth. "When we take away the thing a cancer depends on to live, we can kill the cancer," says Dr. Grabocka.

When the researchers blocked stress-granule formation in obese mice with pancreatic cancer, the results were really quite surprising. They either saw no cancer growth, or 1/14 and 1/20 the amount of growth they'd expect in obese mice with intact stress granules.

The most striking difference was their overall survival. Normally in models of pancreatic cancer, mice die very quickly, within 50-60 days. In obese mice whose stress granules were blocked, 40% were cancer-free after 300 days.

These experiments, published in the high-impact journal Cancer Discovery, showed that stress granules were actually driving the growth of cancer at the very start. "This is the first direct evidence linking stress granules to cancer progression," says Dr. Grabocka.

Importantly, Dr. Grabocka's lab also identified drug targets that block stress granules in obesity-related pancreatic cancer. The next step is to see if they can be translated for use in humans.

← CAPITALIZING ON STRESS

To test the role of stress granules in cancer, Dr. Grabocka and colleagues looked at pancreatic cancer in obese vs. non-obese mouse models (*top panel*), where they saw more stress granules in obese mice (*top left*). Blocking stress granules in obese and non-obese mice led to less cancer growth and increased survival (bottom left panels) compared to mice whose stress granules were not blocked (*bottom right panel*). But in obese mice, the difference was much greater, suggesting that blocking stress granules in this cancer subtype could offer a new avenue for treatment.

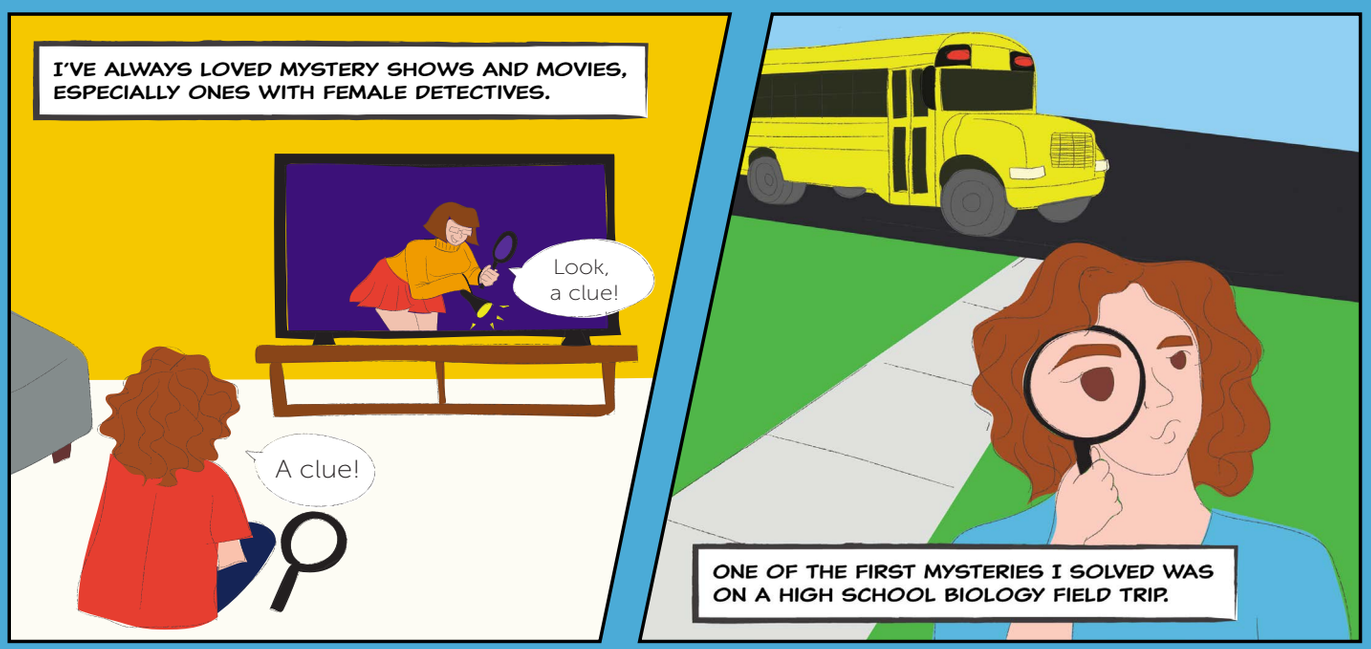
A JOURNEY THROUGH SCIENCE MYSTERIES

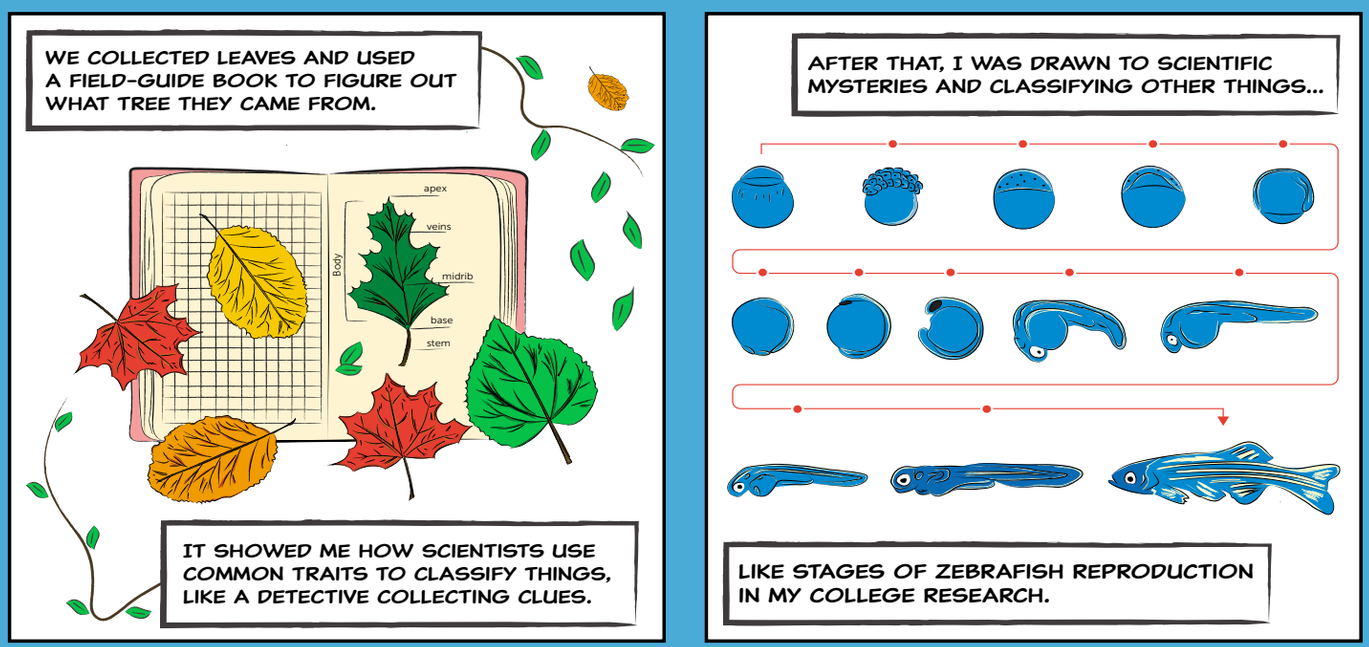
by Karuna Meda
illustrations by JKX Comics

"As a kid, I was always asking my parents about how things worked," says Tess Cherlin, PhD. "I felt like a detective digging around for clues." This curiosity for real-world mystery drew Tess to the sciences. She recently finished her doctorate in Computational Cancer Biology in the laboratory of Isidore Rigoutsos, PhD, the Richard W. Hevner Professor of Computational Medicine, where she studied a class of genetic material called ribosomal RNA fragments, or rRF's.

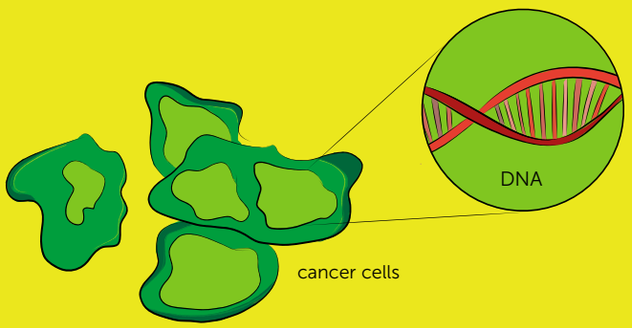
As president of Jefferson's Graduate Student Association, Dr. Cherlin spearheaded several science communication initiatives including Jefferson's first-ever Three Minute Thesis Competition where junior researchers prepare TED-style talks about their work for a lay audience.

Dr. Cherlin is continuing her computational work with a focus on women's health as a postdoctoral researcher and teaches coding workshops in Philadelphia with R-Ladies. Learn more about her journey below!



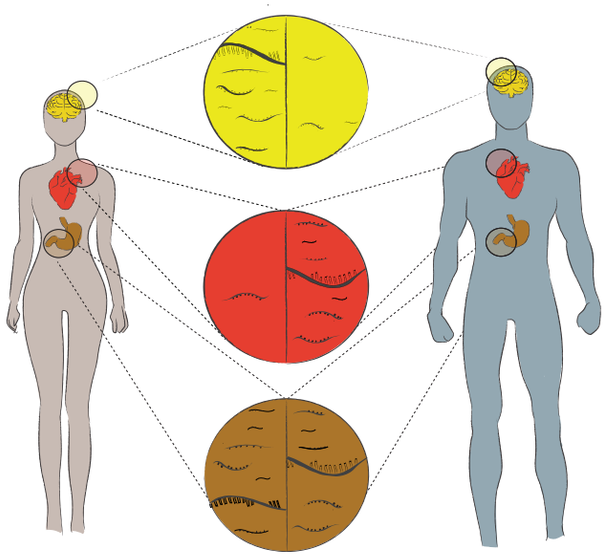


AND GENETIC CHANGES IN CANCER CELLS AS A LAB TECH.



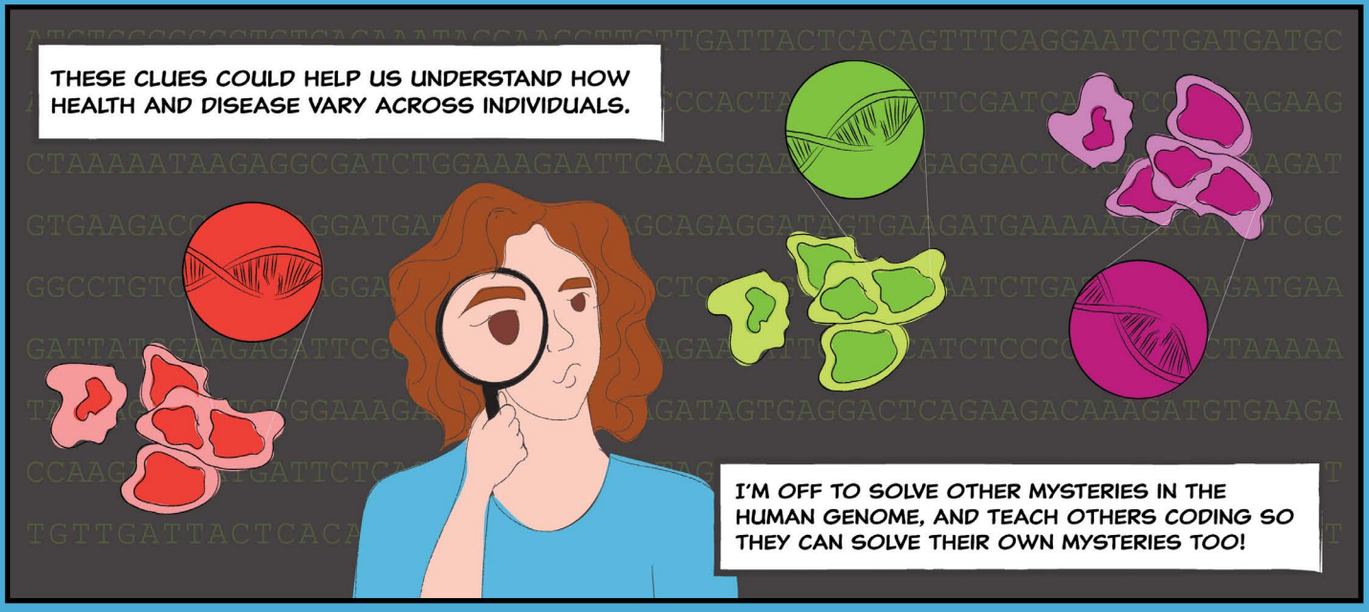
I TAUGHT MYSELF HOW TO CODE TO QUICKLY PICK OUT PATTERNS IN MASSIVE SPREADSHEETS OF GENETIC DATA. MY DETECTIVE TOOLKIT WAS THEN READY TO TACKLE "MY BIGGEST CASE YET"

THE HUMAN GENOME. DURING MY PH.D, I CLASSIFIED A NEW TYPE OF GENETIC MATERIAL CALLED RIBOSOMAL RNA FRAGMENTS OR rRFs.



I FOUND THAT THEIR PRESENCE IN OUR CELLS DEPENDS ON OUR SEX AND GENETIC ANCESTRY.

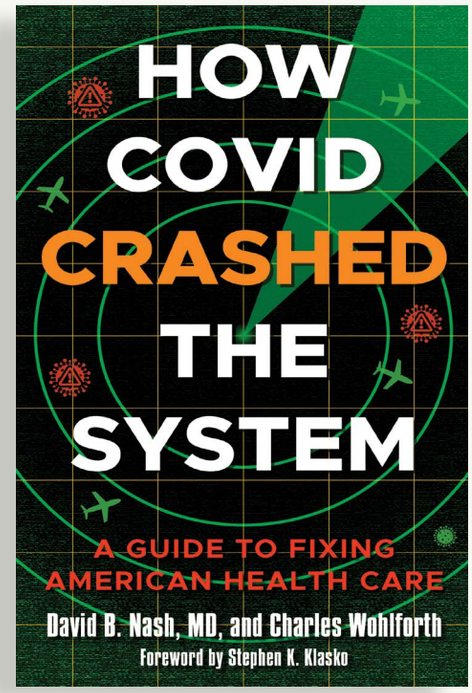
THESE CLUES COULD HELP US UNDERSTAND HOW HEALTH AND DISEASE VARY ACROSS INDIVIDUALS.

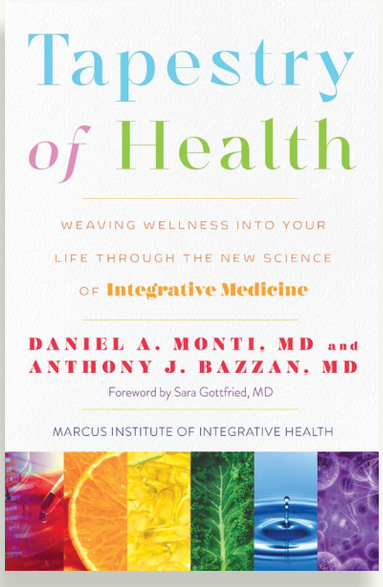


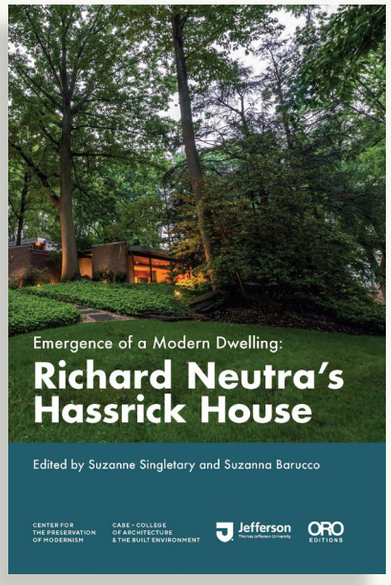
I'M OFF TO SOLVE OTHER MYSTERIES IN THE HUMAN GENOME, AND TEACH OTHERS CODING SO THEY CAN SOLVE THEIR OWN MYSTERIES TOO!

RESEARCH READS

by Makhari Dysart







How COVID Crashed the System: A Guide to Fixing American Health Care

Rowman and Littlefield Publishers, October 2022

David B. Nash, MD, founding Dean Emeritus and Dr. Raymond C. and Doris N. Grandon Professor of Health Policy at the Jefferson College of Population Health and Charles Wohlforth, science writer.

Despite being the most expensive in the world, the U.S. healthcare system crashed during the COVID-19 pandemic leading to more patient deaths than any other country. This book uncovers the story of this failure — diagnosing the systemic problems that weakened our response, from racism and poverty to under-funded public health agencies and for-profit hospitals. Stories of hope and change are also revealed, showing that while the pandemic exposed numerous healthcare problems, it also was a catalyst for the change needed to reform our system. Through extensively researched systemic analysis and impactful stories, Dr. David Nash outlines the failures that led to our system crash and offers a blueprint for how to battle the next crisis.

Tapestry of Health: Weaving Wellness into Your Life through the New Science of Integrative Medicine

Kales Press, August 2020

Daniel Monti, MD, MBA, Ellen and Ron Caplan Professor and Chair of Integrative Medicine and Nutritional Sciences and founder and CEO of the Marcus Institute of Integrative Health and Anthony Bazzan, MD, medical director of the Marcus Institute of Integrative Health.

The U.S. healthcare system is made up of highly specialized disciplines whose care is often sought out after an illness has already presented itself. While our current system has saved many lives, Americans are still getting sick with otherwise preventable illnesses. Many of the leading causes of death, such as heart disease and cancer, are exacerbated by changing lifestyles and diets. In their new book, Dr. Daniel Monti and Dr. Anthony Bazzan provide a different perspective on wellness, shifting the focus from isolated disease treatment to disease prevention through a holistic model of health. They have combined evidenced-based restorative treatments, nutritional science and healthy lifestyle practices to create a step-by-step plan for a new curative, preventive and transformative version of health care.

Emergence of a Modern Dwelling: Richard Neutra's Hassrick House

ORO Editions, January 2022

Suzanne Singletary, PhD, director of the MS in Historic Preservation, Suzanna Barucco, MS, adjunct professor in Jefferson's College of Architecture and the Built Environment.

Featuring seven years of student research and documentation, Dr. Suzanne Singletary and Suzanna Barucco chronicle a tale of the design, dwelling, neglect, restoration and reinvention of the Hassrick House. Bringing the California style to the East Falls area of Philadelphia, Pennsylvania, the house is one of only three homes in the city designed by Richard Neutra, an internationally acclaimed architect of mid-century modernism. This book contains never-before-published information from seventy letters exchanged between the Hassrick family and Neutra, along with oral histories and archival research from subsequent owners. This house highlights the emerging field of preserving modernism as the buildings of this design period reach the fifty-year mark. Preservation is often misunderstood as freezing a building in time, but the Hassrick House reveals the importance of preservation in celebrating cultural heritage and creating sustainable built environments.

JEFFERSON RESEARCH
BY THE NUMBERS, FY22 →

1,281

active studies across
Thomas Jefferson University
and Jefferson Health, including:

$201,754,645

from funding organizations such as, but not limited to:
NIH, DOD, HRSA, Genentech and COVID-related funding
from the PA Department of Health.

326

clinical research personnel

$86,135,132

IN NIH FUNDING
AN APPROXIMATE **55.74%** INCREASE IN
FUNDING SINCE 2016

45

clinical departments
performing research

250% increase

in team-science grants
from NIH over 5 years

externally funded PIs

407

8,200+ students

THOMAS JEFFERSON
← UNIVERSITY

1,828

full- and part-time faculty

200+ graduate and undergraduate programs across

10 COLLEGES AND **3** SCHOOLS

more than **1,000** patents

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HEALTH
MEDICINE
NURSING
SCIENCE
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