Vestigo

ISSUE 1
SUMMER 2020

VANDERBILT UNIVERSITY **SCHOOL OF MEDICINE | BASIC SCIENCES**

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This research and art piece is called "Power Outage: A human cardiomyocyte derived from induced pluripotent stem cells with dysfunctional mitochondria." It was taken by Megan Rasmussen, a Ph.D. candidate in the lab of Vivian Gama.

Along with two more images [shown on the bottom of the opposite page], Megan's was chosen through a contest to decorate the Basic Sciences conference room in MRBIII.

Faculty in Basic Sciences published over

360 **research papers in 2019**

with 280 collaborators

spread out over 34 states and 28 countries

In this issue

EDITOR-IN-CHIEF
Lorena Infante Lara

EDITOR
Carol Rouzer

CONTRIBUTING WRITERS
Cayetana Arnaiz Yépez, Stephen Doster, Alexandra Fuller, Sydnie Hochstein, Lorena Infante Lara, Danielle Kopke, Leigh MacMillan, Alexandria Oviatt, Laura Powell, Seth Robertson, Linda Sealy, Suneethi Sivakumaran, Eric Skaar, Bill Snyder, Matthew Tyska, Ryan Underwood, Kathy Whitney, Allison Whitten

DESIGN AND ART DIRECTION
Mary Alice Bernal/Corporate Design

PHOTOGRAPHY
Caroline Cencer, Andrea Cuentas-Condori, Stephen Doster, Joseph Howell, Anne Rayner, Daniel Dubois, John Russell, Linda Sealy, Erin Smith, Nilay Taneja, James J. Thweatt , Matthew Tyska

BASIC SCIENCES WEBMASTER
Stephen Doster

ILLUSTRATIONS
Kendra H. Oliver

Vanderbilt School of Medicine | Basic Sciences
465 21st Avenue South
Nashville, Tennessee 37203
Tel: 615-322-0907 | Fax: 615-875-2441
alumni@vanderbilt.edu
medschool.vanderbilt.edu/basic-sciences

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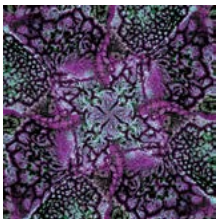

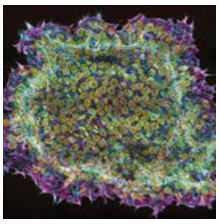

Kaleidoscope. (above left) This kaleidoscopic image is a single immuno-fluorescence slide that has been rotated three times about a corner. The artist and researcher, **Caroline Cencer**, is a Ph.D. candidate in the lab of of Matt Tyska who uses enterocytes to study the maturation of the intestinal brush border. In this image, the microvilli, shown in magenta, are coming out of the page toward the reader.

Stem Cell Colony. (above right) This image was taken by **Nilay Taneja**, a Ph.D. candidate in the Dylan Burnette lab. It shows a colony of human embryonic stem cells with its actin cytoskeleton in magenta, myosin motors in cyan, and DNA in yellow. Embryonic stem cells give rise to all tissues in the body and hold great potential in designing cell-based therapies for multiple diseases.

Cover: an artist's rendering of AMPA receptor, focus of study for Terunaga Nakagawa (page 13).

IN EVERY ISSUE

Vestigo, (ves-TEE-go) the name for our new magazine, comes from the Latin "vestigare": to discover, search after, seek out, inquire, investigate. It encapsulates the spirit of discovery and dedication to research we strive to embody at Vanderbilt University Basic Sciences. We hope you enjoy reading our first issue.

Every month we email a newsletter, *Basically Speaking*, summarizing recent achievements, awards, and discoveries of our trainees, staff, and faculty. Sign up to get it in your inbox: bit.ly/2BcKY6L

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COVER STORY

DISCOVERY

INNOVATION

IMPACT

SPECIAL FEATURE

Dear alumni and friends:

JOHN RUSSELL

Welcome to *Vestigo* – the chronicle of biomedical research in the School of Medicine Basic Sciences at Vanderbilt. We plan to publish regularly, highlighting the talented people in the Basic Sciences and the exciting discoveries they are making.

I've been at Vanderbilt for over 30 years and have witnessed tremendous growth in the research enterprise. A lot of things have changed during that time, but our collaborative environment and collegial culture have not changed, nor has our commitment to discovery science. I joined the faculty in the Department of Biochemistry a few years after Stanley Cohen, also a Biochemistry faculty member, shared the Nobel Prize in Physiology or Medicine with Rita Levi-Montalcini for their discovery of growth factors. Earl Sutherland from the Department of Physiology had won the Nobel Prize in Physiology or Medicine 15 years earlier for his discovery of cyclic-AMP. Their accomplishments created a deep appreciation for the power of fundamental discovery that remains today.

Basic scientists study the function of molecules in native cellular and organismal environments to determine their contribution to cell identity, cell growth, intercellular communication, firing of neural circuits, and more. In addition to shining a light on how complex biological systems work, basic science discoveries provide critical insights that define the origin of diseases and identify targets for their treatment.

The linkage of basic research to clinical medicine that occurred in the early twentieth century has paid massive dividends in improvements in human health. Today, we occasionally hear that we don't need to invest in basic research anymore because we've got all the knowledge we need to treat diseases. It only takes an example such as the ongoing coronavirus pandemic or the virtual absence of treatments for genetic diseases to remind us that we will always need state-of-the-art basic research.

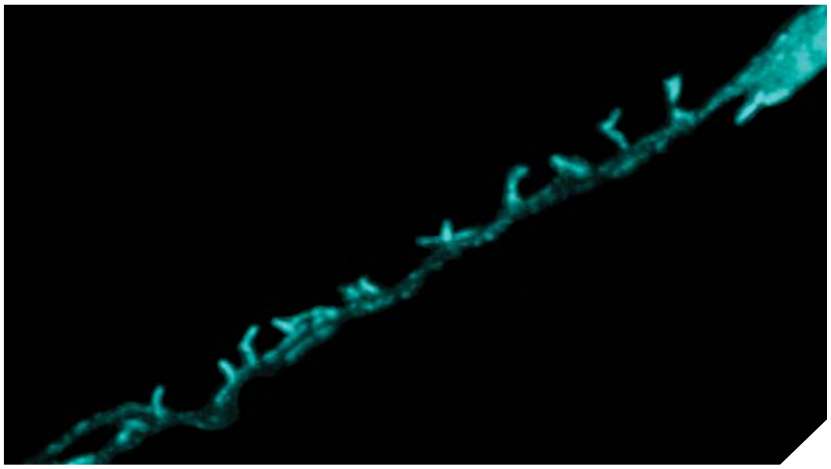
The COVID-19 pandemic has shaken the world to its foundation and focused society's attention on biomedical research like never before. It has also illustrated that discovery, innovation, and impact—the three pillars of Basic Sciences—need to be pursued aggressively on a continuing basis. They cannot be kept on a shelf or in a freezer to be dusted off or thawed out when they are needed to solve a major health crisis. The fundamental research performed in basic science departments all over the world is essential to understanding the basis of life and developing strategies to protect and enhance it. The following pages provide snapshots of the exciting research that our trainees, staff, and faculty are conducting and supporting in the Vanderbilt School of Medicine Basic Sciences.

Sincerely yours,

Lawrence Marnett
Dean of Basic Sciences

Basic Sciences focuses on the fundamentals of biomedical research, and comprises a group of 4 departments; 9 research centers, institutes, and programs; and 19 specialized cores.

DANIEL DUBOIS



ANDREA CUENTAS-CONDORI

Worms show some (dendritic) spine

Neurons share information with one another through two kinds of projections—axons, which release information, and dendrites, which receive information. In vertebrate neurons, dendrites are decorated with short protrusions called spines, which are specialized functional components of neural circuits. The shape and density of spines, which are regulated by neural activity, have strong ties to learning and memory.

Trainee first author: Andrea Cuentas-Condori, Ph.D. candidate

For a long time, scientists thought that dendritic spines were a side-effect of the way neuroscientists prepared brain tissue for microscopic examination. This belief changed rapidly when legendary neuroscientist Santiago Ramón y Cajal showed that the spines actually have a physiological function. Since this discovery, researchers have generally believed that dendritic spines are only a feature of the more evolved nervous systems of vertebrates or higher invertebrates, such as flies, and that lower invertebrates do not possess them.

Now, however, new research from **Andrea Cuentas-Condori,** a graduate student in the lab of **David Miller, III**, professor emeritus of cell and developmental biology, challenges this notion by demonstrating that two motor neurons in the roundworm *Caenorhabditis elegans* exhibit the hallmarks of dendritic spines.

The study, published in the journal *eLIFE,* is the first to rigorously show that *C. elegans* dendritic spines share similar shapes and functions to those of mammalian neurons. Thus, these findings could establish the roundworm—noted for its transparency and ease of handling—as a new model system to study spines in live, intact animals. As proper spine formation and maintenance are crucial for a well-functioning nervous system and avoidance of neurodegenerative diseases, the availability of a robust and practical in vivo model system is an important contribution to the neuroscientist's armamentarium. **— Danielle Kopke**

The study, published in the journal *eLIFE,* is the first to rigorously show that *C. elegans* dendritic spines share similar shapes and functions to those of mammalian neurons.

A new partner for maternal embryonic leucine-zipper kinase

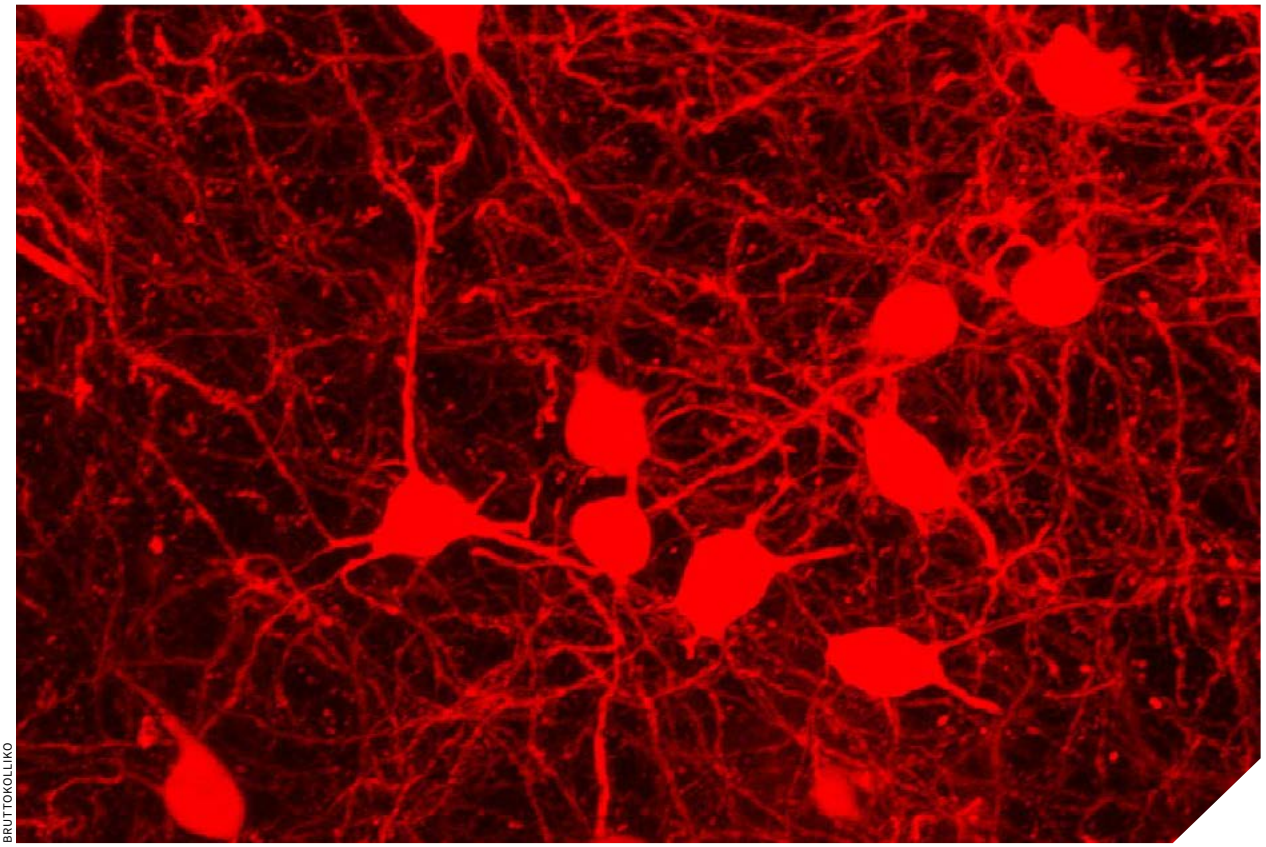
Proteins exert a wide range of functions in our body, ranging from structural support to regulation of biochemical reactions and more. In particular, enzymes—proteins that catalyze or speed up chemical reactions—often activate other enzymes to create chain reactions or signaling cascades that modulate a cell's response to its internal and external environment.

Maternal embryonic leucine-zipper kinase or MELK plays important roles in the control of the cell cycle; cell proliferation, renewal, and death; cell migration; and embryogenesis. It exerts these functions both in normal and cancer cells through interactions with other proteins. Although previous studies have identified many functions and interacting proteins of MELK, there is much yet to be learned, particularly regarding how abnormal levels or regulation of MELK contribute to the growth and survival of some kinds of cancer cells.

Trainee first author: Nicole Perry, Ph.D.

A research group under the direction of Professors of Pharmacology **Tina Iverson** and **Vsevolod Gurevich** used biophysical techniques and in-cell assays to identify how MELK binds to one of its interacting partners, arrestin-3, a protein involved in the action of multiple hormones and related signaling molecules. They showed that arrestin-3 binds to multiple sites of MELK with varying degrees of strength, the strongest binding of which occurred at a region of MELK known as a kinase domain; this interaction decreased the number of cells in the S-phase of the cell cycle—the phase in which cells synthesize new DNA in preparation for cell division. These findings indicate that this MELK-arrestin-3 interaction may affect cell fate.

The research, published in the journal *Cellular Signaling*, implicates the binding interaction of both proteins in the regulation of the cell cycle. These findings provide a potentially important new clue to our understanding of how MELK functions in healthy cells, as well as how abnormalities in MELK function could lead to excess proliferation of cancer cells. **— By Suneethi Sivakumaran**



BRUTTOKOLLIKO

Medium spiny neurons and "sticking" to bad habits

By the time March rolls around, New Year's resolutions to ditch the expensive lattes and spend less time (and money) shopping online are often far behind us. Activity within the nucleus accumbens, a region of the brain implicated in motivation and addiction, may be at play.

Recent work published in the *Journal of Neuroscience* by the labs of **Brad Grueter**, associate professor of pharmacology and molecular physiology and biophysics, and **Heidi Hamm**, Aileen M. Lange and Annie Mary Lyle Chair in Cardiovascular Research and professor of pharmacology, reveals processes that may disrupt communication between the NA and other areas of the brain.

Trainee first author: Kevin Manz, Ph.D.

When you experience an event, chemical messages released throughout the brain are gathered by neurons in the NA and interpreted as pleasant or unpleasant, which may ultimately impact how you respond to similar events in the future.

When you experience an event, chemical messages released throughout the brain are gathered by neurons in the nucleus accumbens and interpreted as pleasant or unpleasant, which may ultimately impact how you respond to similar events in the future.

The researchers set out to better understand how responses in the NA are fine-tuned by studying interactions between medium spiny neurons of the NA and other neuron types. They discovered that inhibitory neurons impair the release of incoming chemical messages from other areas of the brain, making medium spiny neurons less likely to activate; this happens through activation of receptor called $GABA_BR$. The researchers found that some neuron pairings were more sensitive to interference by inhibitory neurons than others.

Molecular studies that characterize interactions between neurons help to form a bigger picture of how our brains interpret events and drive us to seek the habits that we wish to avoid. This knowledge may advance our understanding (and treatment options) for addiction and other psychiatric disorders, or may help us come up with resolutions we can actually stick to.

— Alexandra Fuller

Fight, flight—or freezing?

When faced with a threatening stimulus, an organism's brain only has fractions of a second to choose a life-saving response: fight, flee, or freeze. Research published in *Nature Neuroscience*, from the molecular physiology and biophysics labs of **Dr. Sachin Patel**, associate professor and James G. Blakemore Chair in Psychiatry, and **Danny Winder**, professor and Bixler-Johnson-Mayes Chair in Basic Sciences, reveals new insight into the neurobiology behind the selection of appropriate behaviors based on previous experiences.

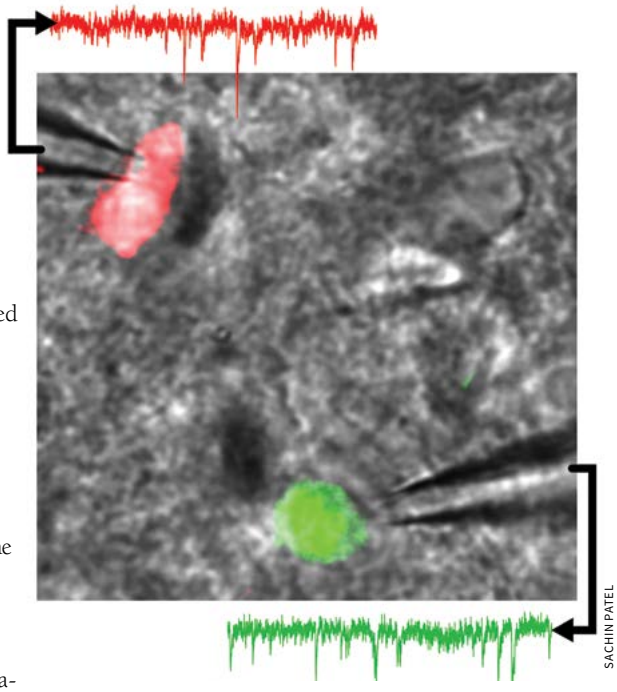
The researchers used electrophysiology, which measures the activity of individual neurons, and optogenetics, a technique that uses light to activate neurons, to map neuronal circuits in mice. They compared the neural activity of naïve mice and mice that had been conditioned to freeze in response to a tone paired with a foot shock.

Trainee first author: Nolan Hartley, Ph.D.

The team found that, in the fear-conditioned mice, the neural activity in a region of the brain called the amygdala decreased specifically in neurons that expressed corticotropin releasing-factor—a hormone involved in stress. In contrast, the neural activity increased in neurons that did not express this hormone, as well as in neurons that expressed somatostatin, a hormone that regulates the endocrine system.

When mice underwent training to extinguish the freezing response, this pattern was reversed: the circuit shifted neural activity back to neurons that did express corticotropin releasing-factor. The research team was able to track the location of these changes specifically to the basolateral amygdala.

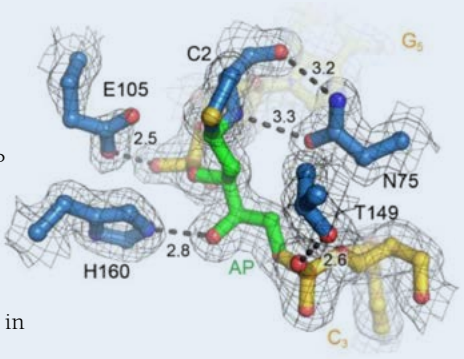
Through their research, the investigators identified key neurons that play a role in acquiring and losing conditioned fear responses, a finding that may have important implications for understanding mental illnesses that are associated with excessive fear and anxiety. This work could be used to help identify why people with post-traumatic stress disorder continue to neurologically "select" a fearful response to a stimulus that is no longer threatening. **— Allison Whitten**



SACHIN PATEL

A cover-up: HMCES protects DNA from error-prone repair

DNA is under constant threat of physical and chemical damage from agents both within and outside of cells. A common form of DNA damage occurs when a base—either adenine, guanine, cytosine, or thymine—is removed from the sugar backbone of a DNA nucleotide to generate an abasic or AP site. If an AP site occurs in double-stranded DNA, repair is fairly straightforward because the undamaged strand can serve as a template that indicates which base should be added back. However, repair of AP sites in single-stranded DNA is, unfortunately, error prone.



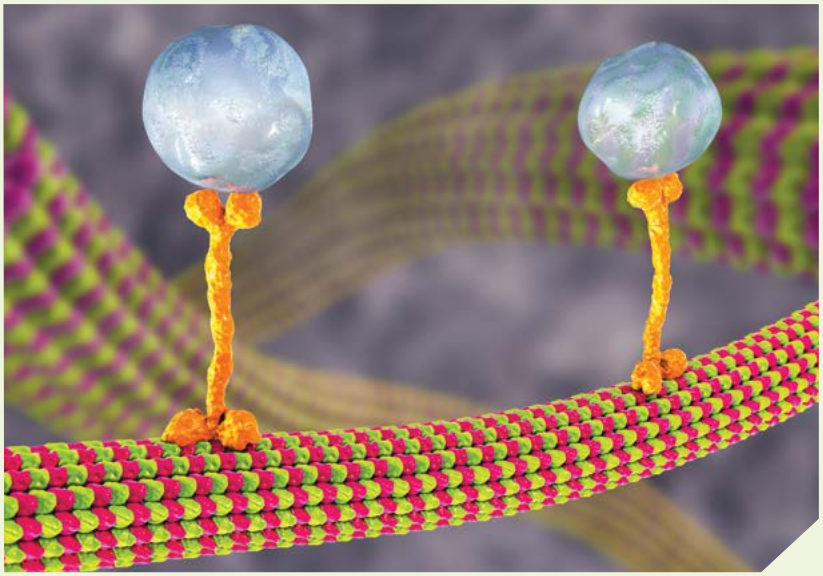
Work from the labs of **David Cortez,** Richard N. Armstrong, Ph.D. Chair for Innovation in Biochemistry, and **Brandt Eichman**, William R. Kenan, Jr. Chair of Biological Sciences and professor of biochemistry, published in *Nature Structural and Molecular Biology,* suggests that the protein HMCES can bind to and stabilize AP sites in single-stranded DNA, ultimately leading to more accurate repair.

Trainee first author: Petria Thompson, Ph.D.

Initial studies revealed that HMCES binds tightly to AP sites in single-stranded DNA and the bond remains untouched even if the protein is completely degraded. Using a crystal structure of the protein bound to an AP site, computer modeling, and various experimental designs, the researchers found that the binding site of HMCES can also accommodate a second strand of DNA on one side of the AP site. This suggests that HMCES can perfectly accommodate a DNA structure in which single- and double-stranded DNA flanks an AP site, such as at replication forks.

The Cortez lab previously found HMCES at sites of DNA replication and showed that it protects cells from toxic agents that induce the formation of AP sites. The current work expands our knowledge of DNA repair and the mechanisms by which cells maintain genomic stability, especially in the context of damage encountered during DNA replication.
— Alexandria Oviatt

ADOBE STOCK



A tale of two ends

Microtubules are hollow, fibrous tubes that support and give shape to a cell. They are made up of α– and β-tubulin proteins, which bind together to form pairs that are then arranged in a head-to-tail manner. Thus, microtubules have two structurally distinct ends: the fast-growing "plus" end and the slow-growing "minus" end.

Minus ends tend to be anchored to microtubule-organizing centers, making it challenging to study their assembly and disassembly. As a result, studies of minus-end dynamics had always lived in the plus end's shadow, until **Claire Strothman,** a Ph.D. candidate in the lab of **Marija Zanic**, assistant professor of cell and developmental biology and biochemistry, and colleagues shared their recent findings in the *Journal of Cell Biology*.

Trainee first author: Claire Strothman, Ph.D. candidate

Using purified proteins and microscopy, the researchers explored the differences between the dynamics at the two microtubule ends and discovered that tubulin dimers likely bind more tightly at minus ends than at plus ends. This may help minus ends evade "catastrophe," which occurs when an end becomes unstable and the microtubule rapidly shrinks, a phenomenon that is much more common at plus ends than minus ends. To probe the observed differences in end stability, the research group also studied the effects of two different "motor proteins", kinesin-14 HSET and kinesin-13 MCAK, that were known to be involved in microtubule assembly and disassembly. They found that kinesin-14 HSET stabilizes minus ends by suppressing tubulin disassembly and protecting them from the action of kinesin-13 MCAK, which breaks down microtubules.

The study results have addressed an important knowledge gap in the microtubule field and serve as a new basis for understanding microtubule dynamics, with important implications for multiple cellular processes such as cell division, shape, and motility. — **Cayetana Arnaiz Yépez**

A new angiogenesis pathway

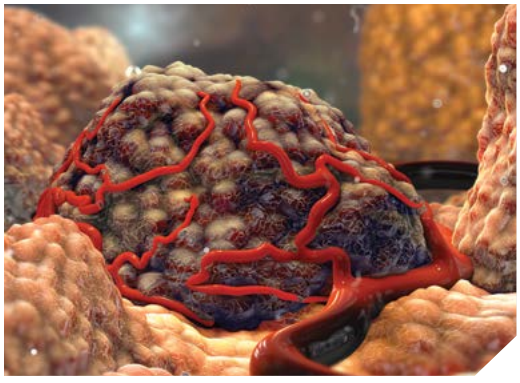
Over 65,000 people develop head and neck squamous cell carcinoma each year in the United States alone, and the 5-year survival rate is less than 50%. Angiogenesis, or the formation of new blood vessels, fuels tumor growth and promotes metastasis, thus contributing to cancer-associated mortality. Current therapies intended to block well-known angiogenesis pathways are limited and often ineffective, highlighting the need for identification of novel angiogenesis-related drug targets.

Alissa Weaver, Cornelius Vanderbilt Chair and professor of cell and developmental biology, and colleagues investigated the role of extracellular vesicles in promoting angiogenesis. EVs are small, secreted particles that mediate myriad cellular functions. Previously, cancer-derived EVs were shown to contribute to tumor growth, but the mechanism was not well understood.

Trainee first author: Shinya Sato, Ph.D.

The research team took stock of the proteins within EVs purified from head and neck squamous cell carcinoma cells and identified a cell surface protein, ephrin type B receptor 2, or EPHB2, that promotes blood vessel recruitment into tumors. Their work, published in *JCI Insight*, revealed that the presence of EPHB2 on cancer-derived EVs enables them to bind to endothelial cells through an interaction between EPHB2 and its partner, ephrin-B2. The result of this interaction is an increase in angiogenesis in the tumor.

The angiogenesis-promoting pathway identified in this study is a promising target for a drug therapy. Such a drug could be particularly effective when used in combination with pre-existing treatments. **— Laura Powell**



ADOBE STOCK

Giving in action:
Endowed chair and Armstrong Family Funds

By Kathy Whitney, Seth Robertson, Sydnie Hochstein

Richard Armstrong died in 2015, but funds in his name ensure his legacy lives on.

The story of Richard Armstrong is a shining example of how one person's life and legacy can have a powerful ripple effect on the people and places dear to them.

Armstrong served as a member of the Vanderbilt University School of Medicine Basic Sciences faculty from 1995 until his death in 2015. He was known for his groundbreaking research aimed at understanding the enzymatic foundation of antibiotic resistance and was a respected scientist and teacher. During his tenure in the Department of Biochemistry, he was a tireless advocate for the school and for the wider biochemical research community.

"He was dedicated to the idea that asking new questions could yield very important discoveries," said his daughter, Katie Armstrong.

Armstrong was an elected fellow of both the American Association for the Advancement of Science and the American Chemical Society. Other honors included the ACS's Repligen Award in Chemistry of Biological Processes and Arthur C. Cope Scholar Award, as well as the Stanley Cohen Award for Outstanding Contributions to Research given by the faculty of Vanderbilt's School of Medicine. Armstrong also served as editor-in-chief of the influential journal Biochemistry, and held a foreign adjunct professorship at the famed Karolinska Institute in Stockholm.

It was his love for biochemical research that prompted Armstrong's family to give back to Vanderbilt in his honor. A $1-million donation helped establish the new Richard N. Armstrong, Ph.D. Chair for Innovation in Biochemistry, which will support a faculty researcher in the Department of Biochemistry within Basic Sciences.

"This is the first major gift for Basic Sciences and the first donor-supported chair during my tenure," said Basic Sciences Associate Dean for Research **Charles Sanders**. "Endowed chairs provide the necessary funding to advance research and discovery, and are critical for retaining and attracting the best faculty. I'm very grateful to the Armstrong family for this impactful gift."

In addition to the new named chair, the Armstrong family also created the Vanderbilt Biochemistry-Armstrong Fund, which provides unrestricted, immediate-use funding for the Department of Biochemistry.

The Armstrong Fund supports departmental activities such as lecture series and student awards, and it enables faculty members to pursue high-impact, high-risk research projects prior to applying for grants from outside sources.

For example, in 2017, the Armstrong Fund helped biochemistry researchers purchase a new mass spectrometer that has empowered many Vanderbilt investigators. Housed in the Mass Spectrometry Research Center Proteomics Core, the instrument supplements an older model that suffered from a high volume of users and frequent maintenance downtime.

Among the heaviest users of the new instrument is **David Cortez**, professor of biochemistry and Ingram Professor of Cancer Research. Much of his work depends on mass spectrometry, which he and his team uses to analyze proteins that play a role in DNA damage repair—allowing them to see in detail the key players and how they change over time.

The new mass spectrometer has made a world of difference for the team in their quest to discover the basic biological processes that govern cell growth and genome stability. Since acquiring the new instrument, Cortez estimates the turnaround time for receiving his analyzed data has dropped from six weeks to two. In the competitive research world, that difference in turnaround time is crucial to making new discoveries.

"Discoveries happen rapidly, or they don't happen at all," Cortez said. "This infrastructure is critical; it has been a launching point for everything happening in my lab in the last few years."

In fact, preliminary data gathered using the instrument has been essential for the Cortez lab's success in securing three National Institutes of Health grants and publishing numerous papers. With the help of the new mass spectrometer, Cortez and his team discovered a protein, RADX, that plays a role in the development of resistance to cancer chemotherapy in cells.

Thanks to these early basic science studies on RADX, the Cortez group established a collaboration with others on campus who are now working to translate the findings into improvements in the clinic. Assistant Professors of Medicine Drs. Vandana Abramson and Satya Das are now seeking approval for a clinical trial that will test a combination of two drugs, which target DNA repair, to see whether the combination can help overcome drug resistance and improve patient outcomes.

"The gift from the Armstrong family was essential to making this discovery possible and driving potentially better therapies in the clinic," Cortez said.

Richard Armstrong in his lab in the Robinson Research Building in 2015.

"Endowed chairs provide the necessary funding to advance research and discovery, and are critical for retaining and attracting the best faculty. I'm very grateful to the Armstrong family for this impactful gift."

– Charles Sanders, associate dean for research

Leadership in a COVID-19 world

Biomedical scientist Susan Wente, Vanderbilt interim chancellor and provost

by Leigh MacMillan

JOHN RUSSELL

When the first reports of an unusual new respiratory disease made news in January, **Susan Wente** leaned on her years of experience as a biomedical scientist and academic leader. She gathered data, listened to diverse experts and made sure the right teams were in place.

"Vanderbilt has a very robust emergency response management plan that covers everything from tornadoes to active shooters to floods to pandemics," says Wente, interim chancellor and provost. "As we watched the situation in China evolve, our team was meeting to update our pandemic matrix plans in response to what we were learning about COVID-19."

Wente describes a near-constant series of meetings, conference calls, and conversations that became particularly intense in early March when the first patients with COVID-19 were reported in Tennessee.

"There were so many unknowns about how the disease was spreading," she says. "Our priority was always the safety and well-being of Vanderbilt students, staff, and faculty. We were taking into account the best information we had at the time and moving as quickly as we could to protect everyone as best as possible."

Being a biomedical scientist has served Wente well as she's led the university through "a rapid succession of significant decisions," she says.

"In both science and in leadership, you need to gather as much data as you can and consider all the options, approaches, and potential consequences. And you also have to feel comfortable making the call, even when you may not have all the data at hand.

"Scientists do that every single day—they draw the best conclusions, make the best hypotheses, and design the next experiments based on the data they have at the time."

Trust, transparency, teamwork

The March 9 decision to suspend in-person classes at Vanderbilt and move to online instruction—what many people think of as the "big decision"—Wente says, was part of the plan. "We knew

"I always gravitated towards mentoring others, and it was one of the things that drew me to being on the faculty doing research, that opportunity to teach others how to make discoveries."

— **Susan Wente**

we would take that step when we had a triggering event or set of events."

Several students who had returned to campus following spring break reported being exposed to an individual who tested positive for COVID-19 that day. Although no one on campus was known to have tested positive for the disease, university leaders "felt the threat was high that the coronavirus could potentially spread to members of our community," Wente says.

The suspension of in-person classes was one of the first decisions of its type in the region, and it proved to be prescient for the Nashville stay-at-home orders to come.

In the days following March 9, online learning was extended from weeks to the rest of the semester, students were instructed to move off campus, all athletics events were suspended, and staff and faculty members were directed to work remotely.

Wente and the leadership team swiftly put additional working groups into place to help guide the university through the pandemic crisis. They made the painful yet necessary decision to postpone in-person Commencement for the Class of 2020 until May 2021 and have launched a comprehensive, strategic Return to Campus plan. Extensive communications and answers to frequently asked questions about all aspects of the university's response populate a dedicated website.

Wente, who has served as a Vanderbilt leader for 18 years, believes that her efforts to build a culture of trust, teamwork, and collaboration helped prepare the university for this time of crisis.

"This pandemic has forced a change in the way we work and live. This is now a COVID-19 world," Wente says. "As we plan for the future, our various working groups and task forces and committees are all looking to each other for guidance and strength.

"I believe this kind of camaraderie, paired with my guiding principles of trust, transparency, and teamwork, not only prepared me but prepared all of us as a 'One Vanderbilt' community. We are doing what Vanderbilt does best—collaborating, finding solutions, and moving forward, together."

A scientist from America's heartland

The eldest of three children, Wente was raised in the small town of Emmetsburg, Iowa. Her mother, a registered nurse, and her father, an educator, instilled in their children a love of education and a strong work ethic.

Wente excelled in math and science and was one of her high school class's valedictorians. Her talent in forensics and drama earned her a scholarship to the University of Iowa, where she enrolled in the fall of 1980 as a pre-dental hygiene major, a practical choice that she knew would lead to a steady job.

The major, however, required that she take freshman English, a course she had tested out of and was not interested in "re-taking." On reviewing her high school transcript and records, the pre-dental hygiene adviser suggested she change to "open major"—a designation that would allow her to choose a major later—and take courses recommended for pre-med and science majors.

It was a moment she now thinks of as one of the "zig-zags" in her career, a time when she stayed open to an unexpected opportunity. Mentors, she says, and supportive friends and family have made it possible for her to take risks and embrace changes to her path.

"That undergraduate adviser turned my life upside down by telling me to go open major, and now I'm so thankful for that guidance," Wente says.

At the University of Iowa, Wente found a scientific home in the Department of Biochemistry, where she discovered the "thrill and rigor of basic biomedical research."

She enjoyed mentoring others, even during her time as an undergraduate—an early sign that she might enjoy leadership roles.

"Mentoring others was one of the things that drew me to being on the faculty doing research, that opportunity to teach others how to make discoveries," she says.

Wente pursued graduate studies at the University of California at Berkeley, where she studied catalytic and regulatory properties of a protein enzyme—and met her future husband, Chris Hardy. Together, they moved to New York, and Wente trained as a postdoctoral fellow first at Memorial Sloan Kettering Cancer Center and then at Rockefeller University.

She launched her independent research career at Washington University in St. Louis, studying the nuclear pore complex, channel-like portals made up of hundreds of proteins that regulate the movement of cargoes into and out of the cell nucleus.

Vanderbilt comes calling

Wente was just eight years into her faculty position when she got an unexpected call from a former colleague. **Dr. Arnold Strauss**, who had worked with Wente on thesis committees, had moved to Vanderbilt and was leading the search for a chairperson for the Department of Cell Biology (now Cell and Developmental Biology). He wanted her to apply for the position.

The timing didn't seem right. Her research was continuing to accelerate with recent high-profile papers in *Nature* and *Science*. Wente and Hardy, who was also on the faculty, and their two young daughters had just moved into a new house.

"We planned to stay put for a while. I wasn't looking to become a department chair at that point in my career," Wente says. But Strauss persuaded her to visit and give a seminar.

"I had never been to Vanderbilt before, so I thought, why not."

By the end of the visit, she was intrigued. Vanderbilt had committed funding to trans-institutional centers and institutes that crossed traditional boundaries between departments, schools, and colleges, as well as shared research core facilities that were open to all investigators. The university was investing in a truly interdisciplinary graduate program in the biomedical sciences.

"These kinds of things weren't happening at every university," Wente says. "I became so impressed and excited by Vanderbilt. It seemed like a place where if you had a good idea, the leadership said, let's try it."

She also felt excited about the idea of extending her passion for mentoring. She had been heavily involved in the graduate programs at Washington University and had served as the co-director of the M.D./Ph.D. joint degree program. As a department chair, she knew she would be involved in recruiting and mentoring junior faculty, and in building a department to promote the success of faculty and trainees at all levels.

She joined the Vanderbilt faculty as chair of the Department of Cell and Developmental Biology in 2002 and quickly distinguished herself as a leader. She prioritized supporting a diverse faculty, and together with her colleagues, she grew the department dramatically and tripled the number of women on the faculty.

In 2009, she became the associate vice chancellor for research and senior associate dean for biomedical sciences, a position that combined research and graduate education under one leader for the first time. In this role, she was responsible for providing infrastructure and designing strategic planning efforts for basic biomedical science research, as well as leading trans-institutional graduate programs and overseeing the training of more than 1,000 graduate students and postdoctoral fellows.

Magnified mentoring impact

In May 2013, she got another out-of-the-blue phone call—this time from then-Chancellor **Nicholas Zeppos** requesting that she meet with him. He wanted her to co-chair the strategic planning process for the university, and he wanted the planning to be faculty driven and include all 10 schools and colleges from its inception.

With co-chair **John Geer,** now Ginny and Conner Searcy Dean of the College of Arts and Science, Wente led a planning process that gathered feedback from more than 1,500 faculty members.

"During that process, I learned so much about all the different strengths across campus. I fell in love with all 10 schools and colleges, and I got so excited about the strategic plan," Wente says.

When the provost position became available late in the strategic planning process, she applied.

"I was so grateful that Chancellor Zeppos and the search committee selected me," she says. "It's unusual for someone to come from medical center leadership to the provost position."

Wente has served as provost and vice chancellor for academic affairs since 2014. She is Vanderbilt's first female provost and has led implementation of the Academic Strategic Plan, with its key pillars of cross-disciplinary research, an immersive undergraduate residential experience, innovative educational technology, and health care solutions.

For the past year, she also served as interim chancellor—the first woman to lead the university. Daniel Diermeier became Vanderbilt's ninth chancellor in July 2020.

As provost, Wente spearheaded inclusive faculty hiring efforts and launched the Women's Advancement and Equity, or WAVE, councils with the goal of ensuring that all women are supported and positioned for success. After establishing Vanderbilt's first Office of Inclusive Excellence in 2017, she created the Interim Chancellor's Diversity Council this past year to advise on equity and inclusion across all areas of the university.

"Being a woman in two male-dominated field—university leadership and the sciences, has taught me the importance of having many different voices and perspectives at the table when decisions are made," Wente says.

A driver at each of her leadership transitions has been the opportunity to have a "magnified mentoring impact," she says, from graduate students to faculty members to department chairs to deans. "It's been an expanding purview of mentoring that still all goes back to faculty, staff, and students, and how I can best help others be successful."

She has been able to seize opportunities for new roles because of the strong support of family and friends, she says.

"I feel so fortunate to have such a close family that I knew would support me, no matter what decision I made or what opportunity I was given or not given. My husband and daughters have been my greatest cheerleaders and are a driving force and inspiration in everything I do."

Question, collaborate, discover, and solve

In her office in Vanderbilt's Kirkland Hall, Wente keeps a book that she purchased during her postdoctoral days. It is D. W. Fawcett's *The Cell*, filled with electron micrographs and drawings of cellular structures. Post-it notes peek out from some of the pages, and Wente turns to one of them, a smile lighting up her face.

"These are pictures of nuclear pore complexes and nuclear envelopes," she says, pointing to dark spots in the grainy black-and-white photos. "I've spent my career working on understanding that black box. How does it control the movement of proteins and RNA in and out of the nucleus?"

Wente has been continuously funded by the National Institutes of Health since 1994 to study "that black box." In 2010, she received a coveted Method to Extend Research In Time or MERIT award, given to "investigators with stellar records of research accomplishment," according to the NIH.

Her scientific training permeates her approach as a leader.

"People often say that biomedical graduate programs don't prepare you for all the things you are going to need to do across your career span," she says. "But I think that being a biomedical scientist and running a research lab prepared me for a ton of what I deal with on a leadership level."

Scientists must do their homework to know all the background on a given topic, be data-driven in making decisions about next experiments, work as part of teams, and have an optimistic outlook, she says.

"As a scientist, you have to be optimistic and learn to regroup when something doesn't turn out the way you expected—to tweak a variable or change a reagent and try the experiment again."

It's safe to say that Wente's year as interim chancellor didn't turn out the way she expected. But in this COVID-19 world, she continues to question, to listen, to gather data, and to design new "experiments" to move the university forward.

She is inspired by the resilience and innovation of Vanderbilt staff, faculty, students, and alumni.

"We're a community that continues to question, collaborate, discover, and solve," she says. "We're resilient and caring, and I've seen those qualities exemplified during our response to COVID-19. What we're doing now will set the stage for us to ensure that generations to come can have a Vanderbilt education and do research in the Vanderbilt way."

After wearing multiple hats this year, Wente will continue in her role as provost with a new perspective and fresh ideas to further advance the 'One Vanderbilt' culture of collaboration, creativity, and civility. She is looking forward to working with Incoming Chancellor Daniel Diermeier, who has served as a provost and has a keen understanding of the significance of the role.

"I'm also eager to find more opportunities to help others succeed," she says. "With so much uncertainty in the world at this moment, these personal connections feel especially important." ■

Brainy findings

Cryo-electron microscopy is not a new frontier, but with new technological advancements, scientists can see even the tinier details of life.

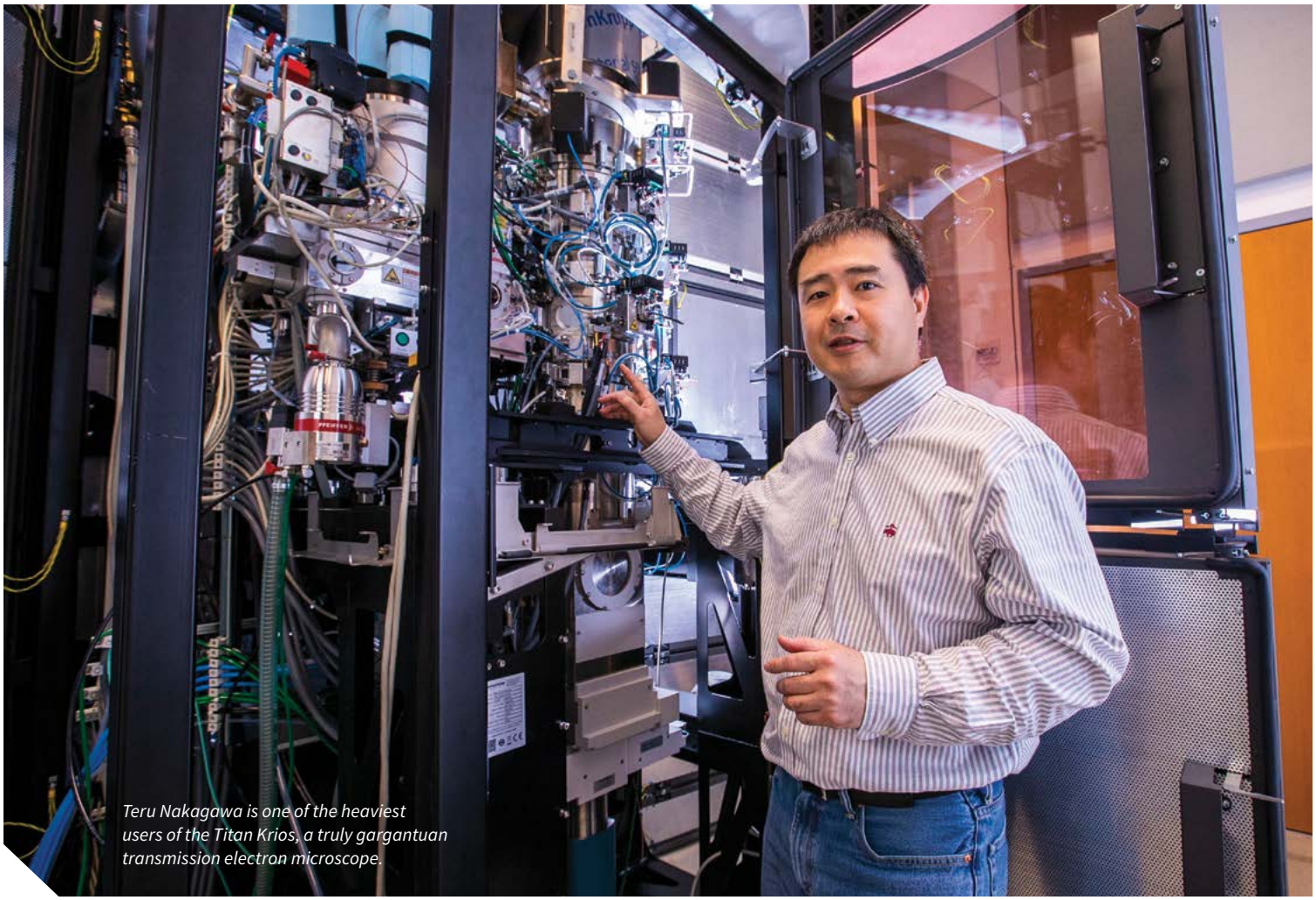
By Lorena Infante Lara

Ph.D. students who aim to stay in academia after they graduate tend to go into postdoc positions. The average academic completes one or two postdocs that last up to a couple of years apiece. Dr. Terunaga Nakagawa has been at it for two decades.

Or at least, that's how it feels.

(Continued on next page)

ANNE RAYNER



Teru Nakagawa is one of the heaviest users of the Titan Krios, a truly gargantuan transmission electron microscope.

ANNE RAYNER

Nakagawa is not actually a postdoc: he's an associate professor in molecular physiology and biophysics at Vanderbilt University. A native of Japan, he earned an M.D./Ph.D. from the University of Tokyo in 2000, then went on to start a postdoc at Harvard Medical School that he finished at MIT after his advisor moved there. Before joining VU's faculty as an expert on glutamate receptors in the brain in 2012, he worked at the University of California at San Diego as an assistant professor. Although he's had his own lab since 2005, Nakagawa is constantly learning; every research task he does adds to his training.

"In that sense, I feel like a 20th year postdoc," Nakagawa joked.

Nakagawa's ample expertise was recently showcased in his latest publication in *Science* last December. As the sole author of the paper, Nakagawa determined the near-atomic structure of the cornichon CNIH3, an auxiliary subunit of the AMPA receptor.

AMPA receptors sit on the surface of many central nervous system cells and mediate fast synaptic transmission—they help propagate signals to and from your brain and spine. These kinds of receptors respond to glutamate, an amino acid that functions as the most abundant excitatory neurotransmitter in our nervous system.

"Neurons communicate with each other the same way people communicate with each other," Nakagawa explained. "In a society, things happen because people communicate: they can either start to work together or start to fight with each other. Things are very similar in the brain. A million trillion neurons communicate with each other, but how they do it can be modified by changing the way the neurotransmitter and its receptor respond." Because glutamate receptors are so abundant and central to the communication process, understanding their molecular mechanism is key to understanding how they affect things like cognition, learning, and memory.

In addition to its role in normal physiology, deficiencies in AMPA receptor functioning have been linked to a variety of neurological and psychiatric disorders such as seizures, Alzheimer's disease, major depressive disorder, limbic encephalitis, intellectual disability, and autism spectrum disorder. To understand how AMPA receptors contribute to pathology, it is critical to determine how it relates to other proteins and to its auxiliary subunits.

"No one had seen a cornichon before," said Nakagawa, referring to the particular type of auxiliary subunit his paper focused on, "so we had no idea where it bound, what it looked like, and how it affected the global architecture of the receptor itself."

To "see" the cornichon CNIH3, Nakagawa used cryo-electron microscopy. This technique employs electrons instead of light to obtain images of a given sample; because of their relative physical properties, electrons yield images with a higher resolution. The downside of using electrons, however, is that the high-energy beam can damage samples. This is where the cryo part comes in: to protect them, researchers must freeze the samples on scaffolds called grids.

> "Everyone in the field was working on this protein assuming that it was a three-transmembrane protein, but if you have the hypothesis wrong, you get to the wrong conclusion."
>
> **– Teru Nakagawa**

Melissa Chambers, co-director of the Cryo-EM Facility.

Researchers record hundreds of thousands of images of the samples using a highly sensitive detector known as a direct electron detector, but, because they are frozen in a solution, the molecules are randomly oriented within the three-dimensional space. An algorithm is needed to parse all the images and put together a 3D representation of what a given molecule looks like. Any amount of contamination in a sample, though, can be mistaken as "input" and incorporated into the shape of the sample. To avoid that, researchers must be very careful in generating pure, uncontaminated samples.

According to **Melissa Chambers**, co-director of the Center for Structural Biology's Cryo-EM Facility, the process of preparing grids can also be difficult. "There's a lot of manual handling of the grids, which can lead to errors or mistakes," she said. "Most people will give us between four and eight grids, and maybe two of them will be good. Teru [Nakagawa], our scientific director, has given us only one or two grids before, but they always work."

Nakagawa developed that expert hand from his two decades' worth of accumulated knowledge within the cryo-EM field. He has been using this technique since he was a postdoc when he solved the first low-resolution structure of the brain-derived AMPA receptor, but technological developments in the early to mid-2010s led to drastic improvements in the level of detail that instruments could achieve. Where a cryo-EM microscope from the turn of the century could generate a structure at a resolution of 10 Ångströms, today's equipment can generate a structure with a near atomic resolution (~1.5–3 Å), finally surpassing even other structural biology methods such as x-ray crystallography.

Even considering the technological advances in structural biology, however, there are some proteins that stubbornly refuse to allow scientists to study their structures. Membrane proteins, for example, are notoriously challenging. Without direct observations, scientists often rely on computational models and algorithms to come up with probable structures that they can then use to make inferences about a protein's function, mechanism of action, and interaction with other proteins.

Structure prediction algorithms function by looking at the amino acid sequence of a protein and predicting how the amino acids relate to one another in a 3D space. So, certain clusters of amino acids with similar physical properties are grouped into particular structures.

In the case of CNIH3, a structure prediction algorithm suggested that the protein spanned the width of the cell membrane three times, and scientists in the field used those predictions to direct their own related research. Nakagawa's cryo-EM structure, however, challenged those assumptions: the data show that the cornichon spans the membrane four times.

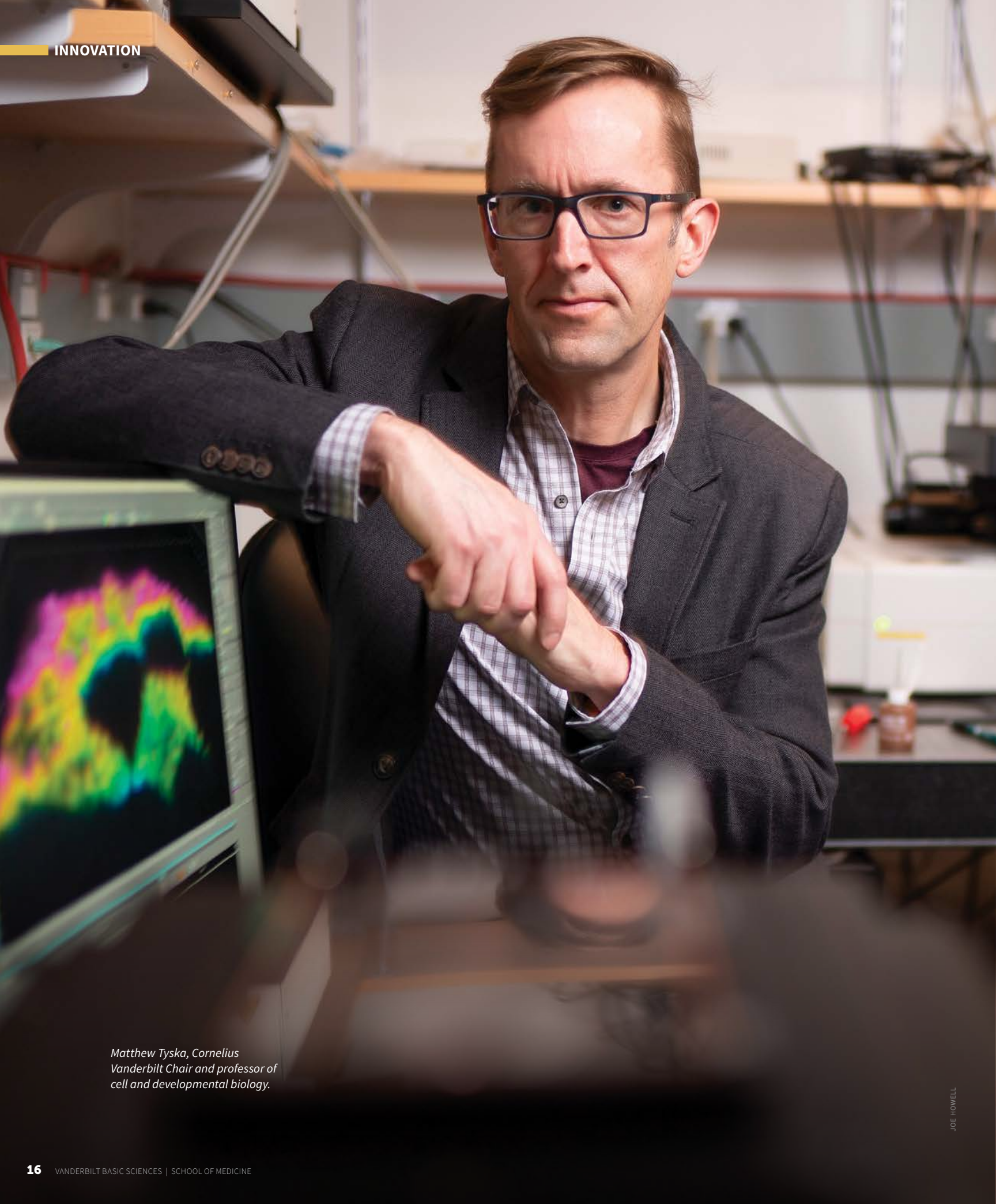
"Everyone in the field was working on this protein assuming that it was a three-transmembrane protein, but if you have the hypothesis wrong, you get to the wrong conclusion," said Nakagawa.

Another fascinating finding was that the structure of the cornichon was very similar to those of TARPs, another class of auxiliary subunits, even though their amino acid sequences are vastly different. It's as if two instruction manuals had completely different wording, but the end product was the same.

Nakagawa's findings are important not just for the structural biology field, but also for neuroscience. Thanks to his work, scientists now know that the AMPA receptor can bind two very different auxiliary subunits in the same place, which could affect how they propagate signals in the brain. Understanding how these natural modifiers of receptor function do their job can help scientists design therapeutic compounds that can change the way the receptor functions.

Although Nakagawa traveled to Japan to gain access to high-end microscopes available at the University of Tokyo, Vanderbilt is currently expanding its cryo-EM capabilities. Basic Sciences recently acquired its own highest-end microscope available on the market and hired two new assistant professors specialized in the technique, Qiangjun Zhou and William Wan, in the Departments of Cell and Developmental Biology and Biochemistry, respectively.

"In very short order, we'll be able to do the kind of workflow I used in the *Science* paper in-house," said Nakagawa. ■



Matthew Tyska, Cornelius Vanderbilt Chair and professor of cell and developmental biology.

JOE HOWELL

Multi-scale snapshots:

Imaging everything from proteins to humans

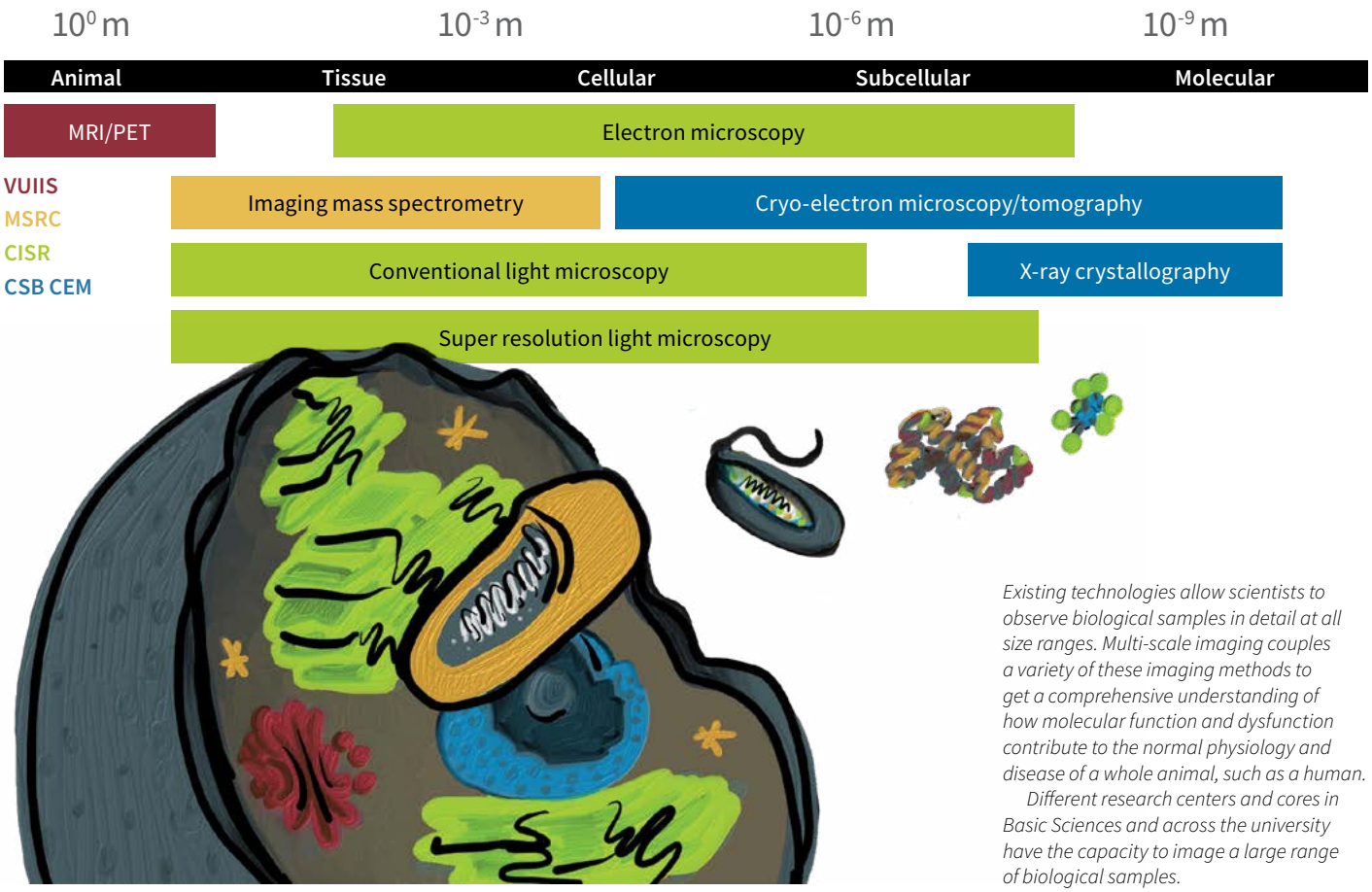
By Matthew Tyska and Eric Skaar

For millennia, humans have relied on the intuitive power of direct observation to build an understanding of nature. In the 1600s, this practice moved into the microscopic world when Antonie van Leeuwenhoek mastered the crafting of small, polished glass beads that could function as high-powered lenses. This technological leap immediately led to the development of *cell theory*—the general concept that cells represent the fundamental unit of life. In the centuries that followed, major advances in imaging technology would enable similar significant leaps forward in our understanding of the inner workings of cells, tissues, and organs, and, in turn, human development, physiology, and disease.

Since the turn of the century, the pace of technological growth in the area of biological imaging has accelerated dramatically. Driven by parallel advancements in optical technology, molecular probes, camera and detector electronics, and computing power, scientists now perform experiments that were thought impossible only a decade ago. Advancements in positron emission tomography now allow for the direct visualization of microbial infections as they develop in living animals. Newly invented light sheet microscopes now permit long-term imaging—through the course of hours or days—of organ, tissue, and cell function with minimal disturbance to their normal activity. The development of super-resolution microscopy allows real-time observation of single protein machines performing their designated functions in cells with resolutions well below the physical diffraction limit of ~200 nm. Imaging mass spectrometry allows investigators to probe the molecular composition of cells and tissues at ever-increasing resolutions. In the area of structural biology, scientists are now beginning to apply cryo electron microscopy tomography to solve nanometer-scale molecular structures *in situ*, or as they exist in living cells.

Much of the technology needed to perform these experiments exists on our campus. VUIIS, the Vanderbilt University Institute of Imaging Science, develops state-of-the-art probes and technologies (e.g., PET, functional magnetic resonance imaging, computed tomography) for imaging biological signals and processes in living animals. CISR, the Vanderbilt University Cell Imaging Shared Resource, is our campus-wide light and electron microscopy core, which provides investigators access to a wide range of technologies for visualizing both preserved and living tissues and cells with the

Multi-scale imaging at Vanderbilt



Existing technologies allow scientists to observe biological samples in detail at all size ranges. Multi-scale imaging couples a variety of these imaging methods to get a comprehensive understanding of how molecular function and dysfunction contribute to the normal physiology and disease of a whole animal, such as a human.

Different research centers and cores in Basic Sciences and across the university have the capacity to image a large range of biological samples.

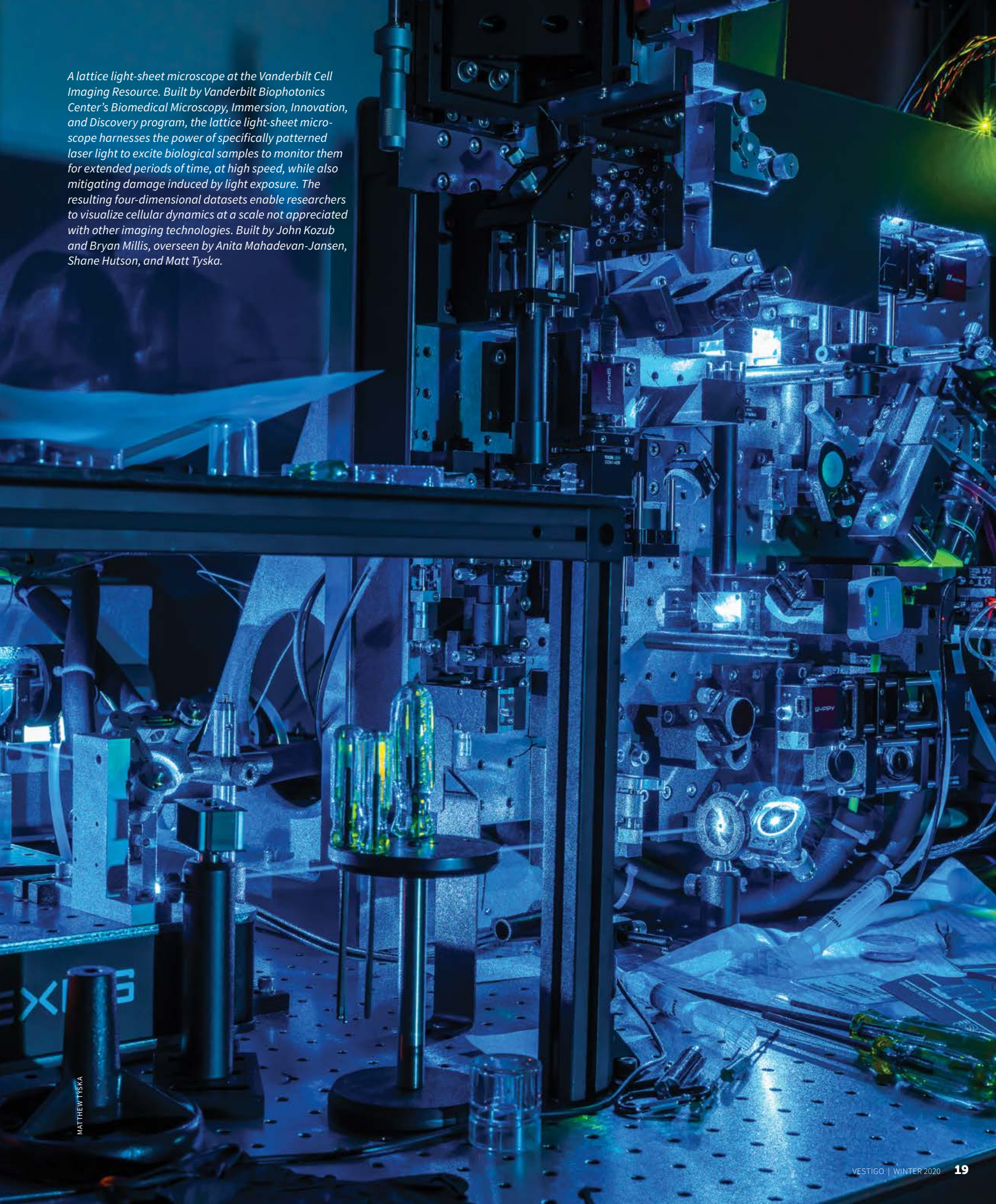
highest resolutions currently available. MSRC, the Vanderbilt Mass Spectrometry Research Center, is a National Research Resource for imaging mass spectrometry. The Vanderbilt University Center for Structural Biology and the newly formed Vanderbilt Cryo Electron Microscopy Facility, known as CSB CEM, are bringing the latest cryo-EM technology online for sub-nanometer-scale molecular structure determination in vitreous ice. The collective capabilities of these imaging resources are unique to Vanderbilt and will allow our scientists to investigate problems across the full range of biological scale—from living animals down to single molecules.

From this perspective, Vanderbilt University is positioned to become an international leader in the nascent but potentially transformative field of multi-scale imaging, the powerful integration of multiple imaging methods at different scales of biology to generate a comprehensive understanding of how molecular function and dysfunction contribute to the normal physiology and disease of a whole animal.

As an example, the CSB and the CSB CEM could determine the molecular structure of a protein implicated in cancer using cryo-EM, and CISR could localize it in an image of cancer cells from a tumor using light sheet microscopy. The tumor, in turn, could be interrogated with imaging mass spectrometry at the MSRC to reveal the molecular composition of the microenvironment, and, finally, whole-body images could be used to determine tumor distribution in specific tissues using magnetic resonance imaging at the VUIIS. Such an unprecedented view across scales will facilitate detection and treatment of cancer, offer a comprehensive and fundamental understanding of the disease in its native context, and uncover new factors involved in cancer metastasis. A similar approach could be applied to any physiologically relevant process from any organism.

Leadership in multi-scale imaging will require that Vanderbilt continue to acquire state-of-the-art imaging resources at all scales and develop next-generation imaging technologies that do not yet exist in the commercial realm. To maintain and further these efforts, we must keep recruiting new faculty who leverage these advanced imaging approaches to answer biological questions, such as recent hires Qiangjun Zhou and William Wan. We must also recruit new faculty who have the computational expertise to approach the complex co-registration problem that must be solved to generate meaningful multi-scale datasets. Finally, we must hire new staff with high-level expertise in the operation and management of our state-of-the-art imaging instrumentation.

If Vanderbilt can sustain a significant investment in these areas, it will enable our investigators to approach biological questions of tremendous breadth—across scales ranging from molecules to humans—and will provide an unprecedented view into biology, health, and disease. Vanderbilt is poised to become a leading institution for imaging sciences worldwide. ■



A lattice light-sheet microscope at the Vanderbilt Cell Imaging Resource. Built by Vanderbilt Biophotonics Center's Biomedical Microscopy, Immersion, Innovation, and Discovery program, the lattice light-sheet microscope harnesses the power of specifically patterned laser light to excite biological samples to monitor them for extended periods of time, at high speed, while also mitigating damage induced by light exposure. The resulting four-dimensional datasets enable researchers to visualize cellular dynamics at a scale not appreciated with other imaging technologies. Built by John Kozub and Bryan Millis, overseen by Anita Mahadevan-Jansen, Shane Hutson, and Matt Tyska.

MATTHEW TYSKA

ERIN SMITH

VU319: The academic difference

By Bill Snyder

Earlier this year, researchers at Vanderbilt University reported tantalizing results from a Phase 1 trial in humans of a potential new drug—called VU319—that could transform the treatment of Alzheimer's disease and schizophrenia.

The story of VU319 is one of collaboration. Three of the principal players can be seen on the opposite page: Craig Lindsley (left), P. Jeffrey Conn, (center), and Carrie Jones.

Results of the study were reported this summer at the Alzheimer's Association International Conference, a virtual event this year due to COVID-19. This is an important step toward confirming that VU319 may improve cognitive functioning, including learning, memory and attention, in people who suffer from these devastating diseases.

The findings also represent a tour de force for an academic medical center, a collaboration between Vanderbilt's Warren Center for Neuroscience Drug Discovery, where the compound was discovered and optimized for activity in preclinical studies, and the Vanderbilt University Medical Center, where the compound was evaluated for safety in human testing.

"While there are other academic drug discovery groups, there's nothing like what's happening here, with the combination of deep basic science and a large team of people focused on one endgame—to continue to develop and deliver [potential new drugs] on a pipeline," said **Craig Lindsley**, William K. Warren, Jr. Chair in Medicine and professor of pharmacology and WCNDD's director of medicinal chemistry.

"There have been some bumps in the road but we've always managed to get over those bumps," added **Paul Newhouse**, the Jim Turner Chair in Cognitive Disorders, who led the clinical trial. "I remain very optimistic that this treatment approach could have a real impact on patients."

The Phase I study, which began in the summer of 2017, was designed primarily to evaluate VU319's safety, but it also incorporated a battery of cognitive and electroencephalography tests of brain function, which monitor and record electrical activity in the brain. Safety was excellent in individuals who received VU319, and, at the highest doses, the healthy participants showed evidence of enhancement on EEG measures of memory and attentional performance over levels at lower doses or while on placebo.

"I want to make my contribution to science," said one of the participants in the Phase I trial, Rhea-Anne Pendley, who is from Springfield, Tennessee. Pendley's mother died from dementia-related complications in 2017. "If I can help someone or even help myself along the way," she said, "that's worth it all."

The next step is to conduct extensive Phase II trials of VU319 in patients with Alzheimer's disease. As significant resources are required for such studies, Vanderbilt recently licensed VU319 to San Diego-based Acadia Pharmaceuticals for further clinical development.

Solving the puzzle

This model of drug discovery and development is the brainchild of the center's founder, **P. Jeffrey Conn**, who holds the Lee E. Limbird Chair in Pharmacology. "For me, brain disease has always been a passion, to see if systematically developing new approaches, each of which could be a breakthrough, could fundamentally impact patient care and patients' lives," he said.

Conn's passion began early. After watching his grandmother lose her memory to dementia, and after a close childhood friend was hospitalized for early-onset schizophrenia, this young man from Cleveland, Tennessee, resolved to try to do something to improve the treatment of brain disease.

Conn earned a doctorate from Vanderbilt in 1986, then joined the faculty at Emory University, where he began studying how the neurotransmitter glutamate affects brain function.

Neurotransmitters are molecules that carry signals between neurons. Most act by binding to protein receptors on the surface of the cell that will receive the signal. When something goes wrong with neurotransmitter binding or signaling, that's when disordered thinking, behavior, and function—brain disease—can occur. Many drugs that act to modulate brain function do so by modulating the function of neurotransmitter receptors.

Paul Newhouse

Conn became interested in Parkinson's disease, a movement disorder characterized by tremors, difficulty walking, and muscle weakness caused by the progressive loss of nerve cells that produce the neurotransmitter dopamine.

Current dopamine replacement therapy for Parkinson's disease improves normal motor function, but prolonged use of the drugs can cause significant side effects, and they become less effective as the disease progresses. This led Conn to wonder if it was

possible to treat the disease by "tweaking" pathways involving other neurotransmitters, notably glutamate.

In 2000, Conn accepted a position as senior director and head of the Department of Neuroscience at Merck Research Laboratories in West Point, Pennsylvania. There, he and his colleagues found that by activating $mGlu_4$, a specific glutamate receptor, they could relieve symptoms of Parkinson's disease in animals. However, there are multiple different types of glutamate receptors in the brain, and they could not find a compound that would bind only to $mGlu_4$ without activating these other receptors and causing unwanted effects.

That's when they hit upon "allosteric modulation" as a possible solution. This tongue twister refers to the ability of some compounds to bind to a secondary site on a receptor in a way that modulates its activation by the neurotransmitter. Think of the neurotransmitter as the key that unlocks the receptor's activity through their main binding sites, and of allosteric modulators as a dial that adjusts the intensity of the receptor's activation. Since secondary sites differ more widely that primary sites among different receptors for a single neurotransmitter, it is easier to find an allosteric modulator that is selective for only one type of receptor, such as $mGlu_4$.

Within a couple of years, Conn and his team had discovered an allosteric potentiator—a modulator that increases a receptor's activity—that was specific for $mGlu_4$. But Conn knew it would be difficult to secure the time and resources needed to validate—through laboratory and animal testing—the therapeutic potential of his "high-risk" idea in a corporate environment.

Building a winning team

At about the same time, Vanderbilt was making a significant investment in early-stage drug discovery by creating the Vanderbilt Institute of Chemical Biology. Seeing an opportunity to advance his research, Conn moved his lab to Vanderbilt in 2003.

"As drug discovery has become more automated and technology driven, it's really a matter of being able to afford the technology and having a culture of collaboration," Conn said at the time. "This is not out of range for a university like Vanderbilt that has a tradition of investing in big science."

In 2006, Lindsley, who'd worked with Conn at Merck and was a pioneer in discovery of the early allosteric modulators of neurotransmitter receptors, came aboard as director of medicinal chemistry. "The ability to recruit someone of Craig's caliber to Vanderbilt represented a real milestone that allowed us to begin to execute full industry-standard drug discovery efforts", said Conn.

Others who joined Conn's team and the Vanderbilt faculty during this period included **Colleen Niswender**, a research professor of pharmacology and now the WCNDD director of molecular pharmacology, and **Carrie Jones**, associate professor of pharmacology and WCNDD director of behavioral pharmacology.

By early 2008, the researchers had reported the discovery of highly selective allosteric modulators that could independently ramp up the activity of two receptors for the neurotransmitter acetylcholine—M_1 and M_4. Based on animal studies, the discovery raised hopes that new, more specific and more effective treatments for brain diseases like schizophrenia and Alzheimer's disease were now within reach. This work led to the discovery of VU319, an allosteric modulator of M_1.

The academic difference

Through the Vanderbilt Center for Neuroscience Drug Discovery, which was established in 2011, the researchers received substantial support from the NIH; AstraZeneca, a global biopharmaceutical company; Janssen Pharmaeutica, a Johnson & Johnson company; and the Michael J. Fox Foundation for Parkinson's Research.

The center also got a big boost from the William K. Warren Foundation of Tulsa, Oklahoma, which supports research aimed at improving the treatment of schizophrenia and other forms of serious mental illness. Thanks to continued support and a sustained partnership, in May of this year it was reestablished as the Warren Center for Neuroscience Drug Discovery.

The size of a small biotechnology company, the Warren Center receives approximately $20 million in corporate and government funding each year to support the work of 100 full-time faculty and staff scientists, postdoctoral fellows, and graduate students.

Close behind VU319 are several more potential drugs in various stages of testing and development for the treatment of Parkinson's disease, schizophrenia, depression, Rett syndrome, and other brain disorders.

"It's really unprecedented for an academic group to have a pipeline with multiple targets that are moving forward," Conn added. Because researchers in academia can spend more time studying the effect of their compounds on brain function, "we hope

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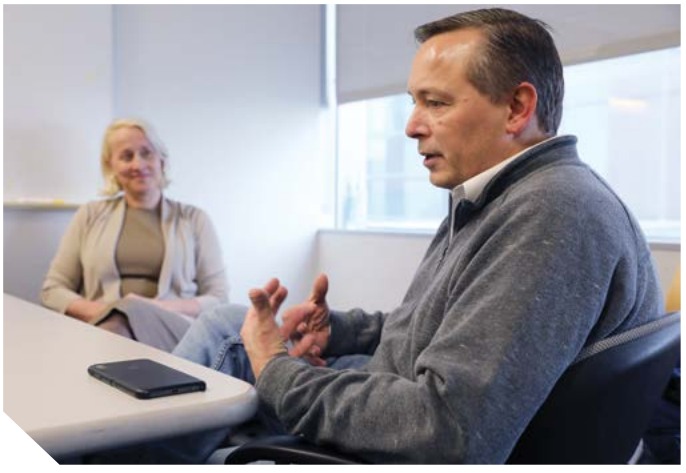


ERIN SMITH

we're developing better drugs…with a higher chance of going the distance," he said.

"In industry you'd have 18 months to 2 years to start a program from scratch and get a candidate and move on," Lindsley explained. "And time and time again we'd see those [programs] fail because you didn't have the time to understand the compound well enough to design a target for it.

"Here we can spend five to six years doing the basic science, understanding what a candidate compound should look like, and developing the candidate that really is going to be ideal for that target with the right efficacy and safety," he said. "It's the ideal situation."

That doesn't mean road to the Phase 1 trial of VU319 was an easy one to travel.

Clinical trials are highly regulated by the US Food and Drug Administration. "Universities aren't necessarily set up to handle all of the regulatory burden and they don't necessarily have all the systems in place for making sure…that all that data and all those processes pass FDA muster," Newhouse said.

Fortunately, the Warren Center had a lot of help, including from:

- The **Center for Cognitive Medicine** at VUMC, which ran the Phase 1 trial;
- The **Vanderbilt Coordinating Center**, which supports clinical and translational research throughout the medical center;
- The **Investigational Drug Service**, a team of specially trained pharmacists and certified pharmacy technicians within the VUMC Department of Pharmaceutical Services that supports human clinical research involving investigational products;
- The **Vanderbilt Clinical Research Center**, an inpatient and outpatient research facility dedicated to conducting clinical research patient care; and
- The **Vanderbilt Institute for Clinical and Translational Research**, a comprehensive resource for researchers and clinicians supported by VUMC's Office of Research and by a Clinical and Translational Science Award from the NIH.

"We couldn't have done this without everyone pitching in," Newhouse said. "It's very much a cross-institutional effort."

Support from the Warren Foundation enabled the researchers to conduct safety studies of VU319, as required by the U.S. Food and Drug Administration before granting an investigational new drug application to conduct human trials.

The Phase 1 trial received substantial support from the Alzheimer's Association and its Part the Cloud program, which aims to accelerate critically needed Alzheimer's disease research, and from the Alzheimer's Drug Discovery Foundation in New York.

"That's what you need for this kind of work in academics," Lindsley said. "You've got to have some philanthropy."

That, and passion.

"We're realizing a lifelong quest," said Conn. "Many of us come into science because we want to make an impact on human health…We're not satisfied would with the status quo…We want to change things in a positive way."

$20M gift establishes new Warren Center for Neuroscience Drug Discovery

Vanderbilt University received $20 million from The William K. Warren Foundation in Tulsa, Oklahoma, to establish the Warren Center for Neuroscience Drug Discovery, formerly known as the Vanderbilt Center for Neuroscience Drug Discovery.

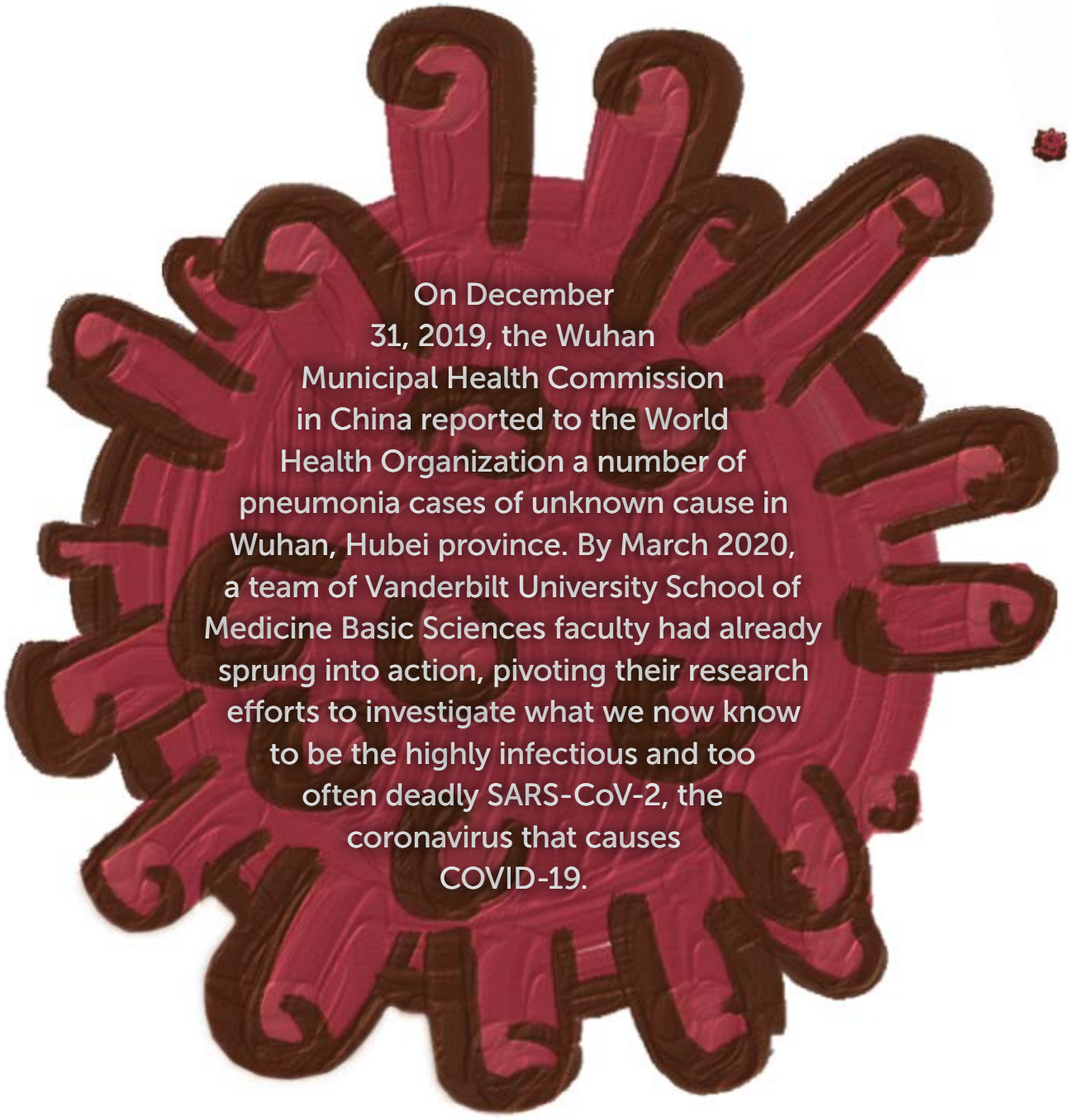
The William K. Warren Foundation was founded in 1945 by oilman William Kelly Warren and his wife, Natalie Overall Warren, who graduated from Vanderbilt (1920) and shares that distinction with her father (1885) and her four siblings. The Warren Foundation established Oklahoma's largest health care provider, the Saint Francis Health System, and the Laureate Institute for Brain Research in Tulsa. The Foundation supports health care innovation, medical research, Catholic initiatives, education, and Tulsa-specific causes.

"We have been impressed with the creative approaches and hard work demonstrated by Vanderbilt researchers, especially Craig [Lindsley] and Jeff [Conn], in the Center for Neuroscience Drug Discovery," says John-Kelly Warren, CEO of the Warren Foundation and grandson of the founders. "Supporting novel, research-based methods to combat devastating cognitive impairments and mental illnesses lies at the heart of our foundation's mission. It is also gratifying to support this research at Vanderbilt University, an institution that has made a significant impact on the lives of so many, including my family."

John-Kelly Warren

In addition to supporting research efforts, part of the Warren gift will be used to create an endowment designed to encourage mentorship and the development of a long-term pipeline of research leaders.

In addition to this latest commitment, the Warren Foundation has been a longstanding supporter of Vanderbilt and its Center for Neuroscience Drug Discovery. Seven endowed faculty chairs currently are supported by the foundation—ranging in disciplines from medicine and pediatrics to divinity—and the William K. Warren Foundation Scholarship is awarded to deserving undergraduates in the College of Arts and Science. **— Ryan Underwood**



On December 31, 2019, the Wuhan Municipal Health Commission in China reported to the World Health Organization a number of pneumonia cases of unknown cause in Wuhan, Hubei province. By March 2020, a team of Vanderbilt University School of Medicine Basic Sciences faculty had already sprung into action, pivoting their research efforts to investigate what we now know to be the highly infectious and too often deadly SARS-CoV-2, the coronavirus that causes COVID-19.

Pivoting to the pandemic

By Stephen Doster


DANIEL DUBOIS

Supporting therapy development

Among the first to become involved were **David Cortez**, Richard N. Armstrong, Ph.D. Chair for Innovation in Biochemistry; **Nancy Carrasco**, Joe C. Davis Chair in Biomedical Science and chair of the department of molecular physiology and biophysics; **Yi Ren**, assistant professor of biochemistry; and **Walter Chazin**, professor of biochemistry and Chancellor's Chair in Medicine. This team of researchers is supporting **James Crowe's** COVID-19 therapeutic antibody development efforts. Crowe, a professor of pediatrics who specializes in the immune response to viral pathogens, plays an integral role in the global effort to translate naturally occurring human antibodies into safe and effective treatments for many challenging infectious diseases.

"James's research team is working to identify, isolate, and use antibodies to treat COVID-19," Cortez said. "He is discovering and making neutralizing antibodies that would inactivate the virus. The advantage of this approach is that it is scalable, since you can make the antibodies in the lab and then give them to people like a drug. While the Crowe lab has a robust pipeline, there are bottlenecks that Basic Sciences labs like ours can alleviate."

One such bottleneck is the need for coronavirus spike protein. Located on the coronavirus membrane, the spike protein binds to a receptor on a host's target cell, allowing the virus to enter. Nearly all neutralizing antibodies—those that render the virus non-infectious—bind to the spike protein. The Cortez, Carrasco, Ren, and Chazin groups are working to optimize the expression of the SARS-CoV-2 spike protein in mammalian cell culture so they can then purify the protein for the Crowe lab. The availability of purified spike protein enables the Crowe lab to identify the antibodies that bind to it with the greatest strength.

So far, the Basic Sciences team has optimized spike protein expression and purification procedures in three cell types and provided several spike protein samples for the Crowe lab. As an effective SARS-CoV-2 antibody must recognize the virus as it exists in nature, the team has also developed methods to ensure that the protein, which is made up of three identical subunits, is expressed in high yields in its fully folded form.


VANDERBILT UNIVERSITY


MANUEL ASCANO


JOHN RUSSELL

From top to bottom: David Cortez, Nancy Carrasco, Yi Ren, Walter Chazin.

Visualizing molecular interactions

While the Crowe lab team works to find therapeutic antibodies, **Tina Iverson**, Louise McGavock Chair and professor of pharmacology, is searching for clues on how the virus interacts with human cells. "We are investigating the interactions between SARS-CoV-2 proteins and human proteins, particularly those involved in breathing," says Tina Iverson.

The Iverson lab uses several structural biology model systems to understand how proteins encode information into their structures under different biological settings. Using X-ray crystallography, Iverson can image proteins at a very high resolution in order to examine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From top to bottom: Tina Iverson, Jonathan Irish, Richard Caprioli

their structural details. "If we can understand the shape of a protein, we can estimate what it is doing in a number of disease states such as cancer, neurodegenerative disease, and bacterial infection," Iverson explains. This expertise positions her well for coronavirus research.

"We want to understand whether the severity of the COVID-19 illness in some people could be compounded by interactions at the molecular level," Iverson notes. "While we don't yet know whether this could be translatable to the clinic, there are non-tailored therapies for inherited respiratory deficiency that could be of help depending on what we find."

Parsing the immune response

Jonathan Irish, associate professor of cell and developmental biology, has two main COVID-19 research projects in progress. The first is an attempt to systematically reveal and track different types of immune cells in patients' blood to identify those that are reacting to the viral infection.

"We had already been studying human immune responses to rhinovirus, another cause of the common cold," he said, "and developed a machine learning analysis tool called Trajectory-ranked Reward Extrapolation, or T-REX, that picks out extremely rare immune cells that are specifically responding to viruses. We quickly realized that we could tailor T-REX for COVID-19 research because it can pick out the rare cells without needing to know their viral target in advance."

Irish's goal is to identify which human immune cells are specific to coronavirus infections and identify these cells within individuals' immune fingerprints. This could provide critical information about what features of the virus trigger good immune responses. "Understanding and identifying the types of immune cells that help to fight off the virus could help us optimize vaccine and treatment strategies," he explains.

In their second project, the Irish lab has begun an international collaboration with King's College London and Guy's and St Thomas' NHS Foundation Trust researchers. The British researchers have begun a clinical trial to identify immune signatures of patients with severe forms of COVID-19 that may predict their responses to specific investigational drugs. One drug they are exploring is ruxolitinib, which is currently approved for use for myeloproliferative neoplasm, a rare form of blood cancer. Ruxolitinib blocks the immune system signals that lead to an excessive inflammatory response known as a "cytokine storm." Growing evidence indicates that cytokine storm is a major contributing factor to morbidity and mortality of severely ill COVID-19 patients.

The UK trial, which began in late May, initially treated 19 patients. Irish's role will be to use T-Rex to analyze and interpret the findings. "Understanding and identifying the types of immune cells that help to fight off the virus could help us optimize vaccine and treatment strategies," notes Irish." If effective, these drugs could reduce the number of patients who require ventilation and critical care support.

Finding the weaknesses of SARS-CoV-2

Yi Ren, who is helping the Crowe lab with spike protein purification, has her own COVID-19 project. Her group is using a structural biology-based approach to provide insights into possible treatments against the COVID-19 virus.

"Studies of SARS, the closest genetic relative of SARS-CoV-2, show that the virus Orf6 protein is a virulence factor that inhibits the production of interferons," she observed. Interferons are signaling proteins that cells release in the presence of viruses. "This plays an important

> "We are investigating the molecular markers and biological pathways of COVID-19 disease progression based on untargeted proteomic, lipidomic, and metabolomic profiles."
>
> **– Richard Caprioli**

role in host antiviral responses. If we can stop Orf6 from doing harm to the host processes, the virus will conceivably be weakened." Ren believes the results from her lab's studies will shine a light on how to inhibit Orf6.

Assessing patient risk

The director of Vanderbilt's Mass Spectrometry Research Center, **Richard Caprioli**, regularly works with the Defense Advanced Research Projects Agency and other government agencies that focus on assessing the threat of various chemical and biological agents. Now, his group is working on COVID-19 research that could lead to the development of assays to identify patients with a high risk of a poor clinical outcome, an important step in prioritizing healthcare resources such as personnel, supplies, and therapies.

"The global COVID-19 pandemic presents new challenges for diagnosis, surveillance, and treatment in the general population," Caprioli explains. His expertise is in mass spectrometry, which identifies molecules, such as biomarkers, metabolites, peptides, or proteins on the basis of their molecular masses. His approach frequently employs "omics," a collection of fields that attempt to measure the complete set of items that make up a particular totality. For example, the goal of proteomics is to identify and quantify all the different proteins in a sample.

"We are investigating the molecular markers and biological pathways of COVID-19 disease progression based on untargeted proteomic, lipidomic, and metabolomic profiles," Caprioli states.

One project in his lab will use the proteomic analysis of COVID-19 patient cells to monitor SARS-CoV-2 spike protein changes or mutations. These studies will employ liquid chromatography coupled to state-of-the-art mass spectrometry for protein sequence analysis.

In addition, Caprioli's team will analyze biopsies from the organs of patients who have died from COVID-19. These studies will make use of his pioneering technology in imaging mass spectrometry to map the location of biomolecules within the tissue from each biopsy. If the differences between the profiles of patients dying from COVID-19 can be distinguished from those of patients who died from other causes, physicians might be better able to elucidate specific patient characteristics that lead to a poor prognosis.

While these are still early days of the COVID-19 pandemic, these Basic Sciences investigators are leading the vanguard of research designed to alleviate suffering caused by this coronavirus. ■

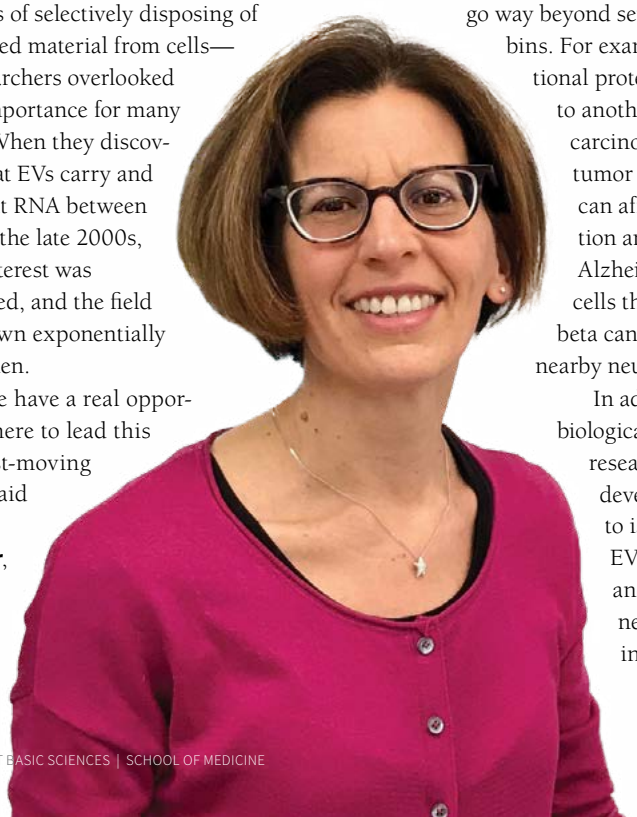
New research program seeks to understand extracellular vesicles

By Lorena Infante Lara

Extracellular vesicles, tiny pouches loaded with different kinds of molecules, roam our bodies. But what effect do they have on our normal functioning—or in disease? The Vanderbilt Program for Extracellular Vesicle Research is here to find out.

Basic Sciences has established a new research program focused on how tiny pouches that get secreted from cells act as messengers and communicators throughout the body. Extracellular vesicles, which actively get released from cells, ferry biologically active protein, lipid, and nucleic acids to themselves or to other cells to induce a change in behavior; they are messengers with instructions on how to act in certain situations.

EVs were discovered a few decades ago, but their role in normal and disease physiology has been historically underappreciated. They were initially described as "cellular garbage"—merely a means of selectively disposing of unwanted material from cells—so researchers overlooked their importance for many years. When they discovered that EVs carry and transmit RNA between cells in the late 2000s, their interest was rekindled, and the field has grown exponentially since then.



"We have a real opportunity here to lead this very fast-moving field," said **Alissa Weaver**, Cornelius Vanderbilt Chair and Professor of Cell and Developmental Biology. Weaver, who founded the program alongside Adjunct Professor of Pathology Microbiology and Immunology **Andries Zijlstra**, will direct the Vanderbilt Program for Extracellular Vesicle Research.

The field's initial belief was that EVs were secreted only from highly specialized cells, but researchers now know that all cells secrete them. "Even bacteria and plants release these vesicles," said Weaver. "They are evolutionarily conserved and are important in a variety of normal and disease events."

Researchers now know that the roles of EVs go way beyond serving as disposable garbage bins. For example, they can transfer functional proteins and RNA from one cell to another. In the case of colorectal carcinoma, when released into the tumor microenvironment, EVs can affect cell-cell communication and tumor progression. In Alzheimer's, EVs released from cells that accumulate amyloid beta can induce cell death in nearby neurons.

In addition to exploring the biological role of EVs, Vanderbilt researchers are pursuing the development of technologies to isolate, analyze, and track EVs throughout the body and in cell cultures. The new technologies will help investigators pick apart the role of EVs in different contexts, eventually leading to better detection methods or treatments for various diseases.

Vanderbilt already has a large number of investigators who are working on EVs. Formalizing the group under a single umbrella facilitates synergy among existing research efforts, fosters new collaborations, and connects Vanderbilt's EV research to the broader national and international communities.

The National Cancer Institute, for example, recently awarded a new program project grant focused on EVs and extracellular RNA to a group of 12 Basic Sciences and VUMC labs and 2 outside labs. Although the NCI-funded collaborative group is already in a position to clarify important biological questions, such as how cells choose which RNAs get secreted, how they get packaged, and how efficient exRNAs are at enabling change in other cells, the EV Research program is set to enhance the project by helping extend the program project's reach to the rest of the Vanderbilt EV community.

This new research program was established with funding from Basic Sciences, which will go toward inviting seminar speakers, supporting a works-in-progress data club, hosting events and workshops, and purchasing and maintaining shared equipment that's essential for EV purification and analysis but whose price tag would be prohibitive for individual labs.

"This program has the potential to launch Vanderbilt to the forefront of EV research," Weaver said, "and to advance our understanding of a variety of physiological and pathological states that rely on EVs for communication." ■

New Dean's Faculty Fellows program recognizes early-stage faculty

By Lorena Infante Lara

Manuel Ascano, Department of Biochemistry, and Marija Zanic, Department of Cell and Developmental Biology

The School of Medicine Basic Sciences has established a new Dean's Faculty Fellows program designed to recognize the efforts of faculty in the early stages of their career. The award targets assistant professors who have shown a strong track record of scientific accomplishment and are likely to continue producing high-quality science in their respective fields.

The inaugural recipients of this award are **Marija Zanic**, assistant professor of cell and developmental biology, chemical and biomolecular engineering, and biochemistry, and **Manuel Ascano**, assistant professor of biochemistry and pathology, microbiology and immunology. Both awardees have been members of the Basic Sciences faculty since 2014.

"Since they joined our faculty, Marija and Manny have been exemplary role models to their students and to fellow department members. They are highly creative individuals at an exciting stage of their careers. Support from the Dean's Faculty Fellows will enable them to pursue their most intriguing new ideas." said **Alyssa Hasty**, associate dean for faculty development.

Zanic, whose primary appointment is in CDB, studies microtubule dynamics. Microtubules are key biological polymers of the cytoskeleton, the structure that gives cells a defined shape. They are essential for processes such as cell motility—movement—and division. Zanic's biophysical approach to the exploration of microtubule biology is informed by her background, which includes a Ph.D. in physics from the University of Texas at Austin and a postdoctoral fellowship in biophysics at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany.

Since coming to Vanderbilt, Zanic and her team have laid bare some important aspects of microtubule regulation and determined the factors that cause microtubules to grow longer at one end than at the other. Through the use of a combined physics and biology toolkit, "Our research aims to discover the molecular mechanisms that drive dynamic remodeling of the microtubule network architecture, which is essential for its proper cellular function," Zanic said.

As microtubules are a common target for chemotherapeutic agents, and as many of their regulating proteins are implicated in cancer and neurodegenerative diseases, designing such a tool will help provide not only fundamental insights into cell structure but also knowledge that might aid in the clinic.

Manuel Ascano

Marija Zanic

Zanic holds secondary appointments in chemical and biomolecular engineering and in biochemistry, and is involved in graduate teaching and mentoring of postdocs, graduate and undergraduate students. She is the recipient of numerous awards, including the Career Development Award from the Human Frontier Science Program, the Maximizing Investigators' Research Award from the NIH, and the 2016 Searle Scholars Award.

Ascano's main drive is to understand how cells use proteins to identify nucleic acids—DNA or RNA—as either self or non-self.

"It sounds superficially simple, but when you recognize that all RNA and DNA are variations of the same four letters, and that codons are hyper-conserved across species, you realize how remarkably difficult it really is for specialized cellular proteins to manage self gene expression in the face of a constant onslaught of pathogens such as viruses, which are ostensibly just packaged nucleic acids," said Ascano. Codons are the cipher that helps cells translate the DNA in the genome into the proteins it codes for.

Considering that over 70% of disease-causing viruses in humans are RNA viruses, and that a cell's own DNA should only be present outside of the nucleus during cell division, it is imperative for cells to monitor the cellular space—or cytoplasm—for foreign nucleic acids so that they might mount an immune response. Ascano's research, stemming from work he did as a postdoc, has resulted in the creation of two new biochemical techniques: PAR-CLIP and VIR-CLASP. The former allows researchers to identify RNA-binding proteins using UV light, and the latter, which is described in an upcoming *Molecular Cell* paper, will shed light on the first interactions between viruses and cell machinery.

Ascano, who did his Ph.D. at the University of Cincinnati College of Medicine and his postdoctoral training at Rockefeller University, has a secondary appointment in pathology, microbiology and immunology, and is involved in mentoring postdocs and graduate students, most critically in his role as the director of graduate studies of biochemistry. He holds three patents and has been recognized as a Simons Foundation Autism Research Initiative investigator and by grants such as the NIH Maximizing Investigators' Research Award.

In naming Zanic and Ascano the first two Dean's Faculty Fellows, Basic Sciences is reinvesting in their careers. They each will receive financial support for four years from funds derived from a $1-million endowment.

"I am very proud Marija and Manny were selected as inaugural Dean's Faculty Fellows," Hasty said. "They are great young faculty and exemplars to our community." ■

Stanley Cohen

A lasting source of inspiration

Stanley Cohen, Nobel Prize winner in Physiology or Medicine in 1986, was an emeritus faculty member at Vanderbilt University. In early February, 2020 he passed away at 97 years old. His memory and legacy will live on for generations.

Stanley Cohen was born in Brooklyn, New York, in 1922, the child of Russian Jewish immigrants who came to the United States in the early 1900s. Although he grew up with limited resources, his parents encouraged his academic proclivities, and he eventually attended Brooklyn College, a city college with a policy of no tuition. He graduated with a degree in biology and chemistry, motivated by his desire to understand the chemistry that drives embryo development.

To save enough money for graduate school, Cohen briefly worked as a bacteriologist at a milk processing plant. He then went on to earn a master's degree in zoology from Oberlin College and a Ph.D. in biochemistry from the University of Michigan in 1948.

After completing his doctorate, Cohen pursued postdoctoral studies focused on new radioisotope techniques at Washington University in St. Louis. While there, he worked with the new chair of the Department of Microbiology, Dr. Arthur Kornberg, who went on to earn the Nobel Prize in Physiology or Medicine in 1959. Along with Kornberg, Cohen participated in a daily journal club in which he and other scientists discussed and debated a paper's findings in depth. This experience was, in his own words, the best education he ever had.

Cohen joined the Washington University faculty in 1953, and established a fruitful collaboration with Dr. Rita Levi-Montalcini. Previously, Levi-Montalcini had discovered nerve growth factor, a small peptide that regulates the growth, maintenance, proliferation, and survival of certain neurons. Cohen and Levi-Montalcini worked together to isolate the peptide, which directs embryonic cells to develop into the vast network of neurons that make up our nervous system. The discovery and characterization of NGF led scientists to the realization that a variety of soluble factors regulates the growth and differentiation of different cell types across the body.

One such scientist was Cohen himself. While conducting experiments with mice, he noticed a peculiarity when he injected newborn pups with extracts containing adult NGF: although mice normally open their eyes ~12–14 days after birth, the injected mice were opening their eyes after only ~7 days. What seemed like a curious observation—one that his peers repeatedly discouraged him from seriously pursuing—eventually led Cohen to determine that an impurity in the extract he was using was responsible for the precocious eyelid opening in the injected mice.

Cohen came to Vanderbilt University as an Assistant Professor in the Department of Biochemistry in 1959, determined to understand what exactly was accelerating the development of the newborn mice. He set up his own research group, made up of only himself and a handful of postdocs, and was intimately involved in the experiments and interpretation of data. He eventually purified the element responsible for the increase in epidermal (skin) cell number and size: and named it EGF or, epidermal growth factor. This protein, he would find out, stimulates cell growth and differentiation by binding to its receptor, EGFR.

The discovery of EGF and EGFR was seminal, as it laid the groundwork for our understanding of both embryonic and cancer development. Furthermore, it led to the development of numerous anticancer drugs that target the EGF pathway, many of which are still used today. The importance of Cohen's work on EGF was recognized by the Nobel Committee in 1986, when he shared the Nobel Prize in Physiology or Medicine with Levi-Montalcini, who was recognized for her own work on NGF.

Cohen's passing came with great sadness to those who knew him, and at great loss to the scientific community. He—and his ubiquitous yet often waylaid pipe—are remembered fondly by current and former members of the Department of Biochemistry, and beyond. **— Lorena Infante Lara**

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"Stanley Cohen was an extraordinary scientist and a great colleague who was loved by everyone at Vanderbilt. His studies of growth factor signaling illustrate the powerful impact of basic research. Stan's work not only provided key insights into how cells divide but led to the development of many drugs that are used to treat cancer. It was a privilege to have him as a colleague and we celebrate his accomplishments and his humanity."

– Larry Marnett, dean of Basic Sciences

From biomedical Ph.D. to dream career

By Lorena Infante Lara

As a Nashville-area native, the allure of Vanderbilt University called to Renee Iacona even as a child. When it came time to apply for colleges, she applied to Vanderbilt and was admitted, but the financial aid she was offered proved to be too small. To avoid putting a financial strain on her parents, Iacona decided instead to attend the University of Tennessee at Martin on a full scholarship.

PHOTO COURTESY OF RENEE IACONA

While an undergrad, Iacona learned about oncogenes, genes that have the potential to cause cancer, and ended up falling in love with cancer research. Today, her career has not only taken her through Ph.D. and master in public health programs at Vanderbilt and to AstraZeneca, but has brought her back to Vanderbilt as part of the School of Medicine Basic Sciences's Board of Visitors.

The board supports and fosters the achievement of excellence in all aspects of research, teaching, and career development for the students and faculty members of Basic Sciences. We'd like you to meet one of its members: Renee Bailey Iacona.

Why did you choose Vanderbilt's Interdisciplinary Graduate Program?

Near the end of undergrad, I started thinking about going to graduate school. I looked at Vanderbilt first because I'd always wanted to go there, but then but then I found the Interdisciplinary Graduate Program and loved the idea because it was perfect for me. I knew I wanted to do science, but I didn't know which discipline. It was an ideal move to learn across disciplines and rotate in labs until I found the right space for me.

What was your graduate school experience like?

My situation was a little unique. During the first presentation of my thesis to my committee, they realized that I'd need a fair amount of statistics for my project. And it just so happened that the master's in public health program was starting at Vanderbilt, so they suggested that I take a few statistics courses. I entered the M.P.H. program and did it in parallel with my Ph.D. The first M.P.H. class was all M.D. students, with myself as the only Ph.D.-in-training.

I took the first of the two M.P.H. years with help from a grant, learning all the statistics I needed so I could finish my dissertation. After I finished, I got a job as a genetic analyst in the laboratory of **Jonathan Haines**, who was starting a genetics institute here at Vanderbilt, and he paid for me to complete the other half of my M.P.H.

What trajectory has your career taken post-Vanderbilt?

What I left Vanderbilt with was both a Ph.D. in pathology, which emphasized oncology, and an M.P.H., which emphasized clinical trials and statistics. Thanks to my experience, I got a job at AstraZeneca, and I've been there ever since.

I joined AstraZeneca as the lowest entry-level statistician, and I've literally developed up the ladder: I'm now the most senior statistician at the company, managing a department of approximately 500 people. My teams are made up of statisticians, programmers, informaticians, and data scientists, all of whom support oncology clinical trials at different stages, whether it be in the early phase as we're coming up with candidate drug nominations, all the way to late phase as we try to get regulatory approval to make the drugs available for patients across the globe.

As a member of the Board of Visitors, what do you hope to accomplish?

When I think about the fact that I was able to get two degrees that literally set me up for my career without it costing me a dime, I feel very much compelled to give back. I was initially approached through fundraising efforts, but I felt like the way in which Vanderbilt sent out communications was a missed opportunity since targeted mailings typically focused on undergrads or medical students. When I brought up this concern, Joe Hunter, assistant vice chancellor of development, set up a meeting where I suggested they could start focusing more on targeting Basic Sciences or other graduate students. In the end, I was invited to join the board.

Now that I'm a member, I help answer questions such as, how do you reach more alumni? What are some of the things the program should consider as the world changes? What would I suggest to someone who's trying to build up new programs in specific disciplines such as data science? What are non-alumni fundraising sources, such as venture capitalists, that Basic Sciences can tap? Through interactions with the ASPIRE program, I've also had the opportunity to meet with current students, tell them my story, and answer questions they have about joining the pharmaceutical/biotech industries.

Do you have any advice you'd like to share?

Sure. When I was in IGP, the emphasis was really on postdocs, but I never wanted to stick around and do one. Because it wasn't really thought about at that time, I had to make my own way and figure out what I would do next. Although some of what happened to me was serendipitous, I see that the future of the combination of science and quantitative analytics—the whole data science space—is really about to explode, so I really encourage students to think outside the box and look at what's coming in the future versus what they know today, because getting on the apron strings of something that's about to start and being able to ride it is pretty exciting.

To alumni who, like me, feel that they got a great education and that they should give back but don't know how, I would really suggest they come take a look into what they thought IGP was when they were here and what it is now, and perhaps even look at how they could get involved. Yes, they could help through donations, but they could also spend time with students or come and give a talk on campus. All of those are potential opportunities that I think if they looked into it or were willing to do any of them, it would be very helpful to the program and might really help them reconnect with Basic Sciences.

Exceptional graduate students honored with Dean's Award

By Leigh MacMillan

Eleven graduate students now entering their fifth year of training have received the 2019 Dean's Award for Exceptional Achievement in Graduate Studies. The award recognizes and supports outstanding graduate students who have distinguished themselves through the originality, significance and rigor of their dissertation research.

"We are delighted to recognize these exceptional students," said **Kathy Gould**, associate dean for biomedical sciences. "Their discoveries are advancing our understanding of human biology and distinguish Vanderbilt in the international scientific community. We are very proud of their accomplishments."

The Dean's Award provides each recipient $5,000 in stipend support for two years.

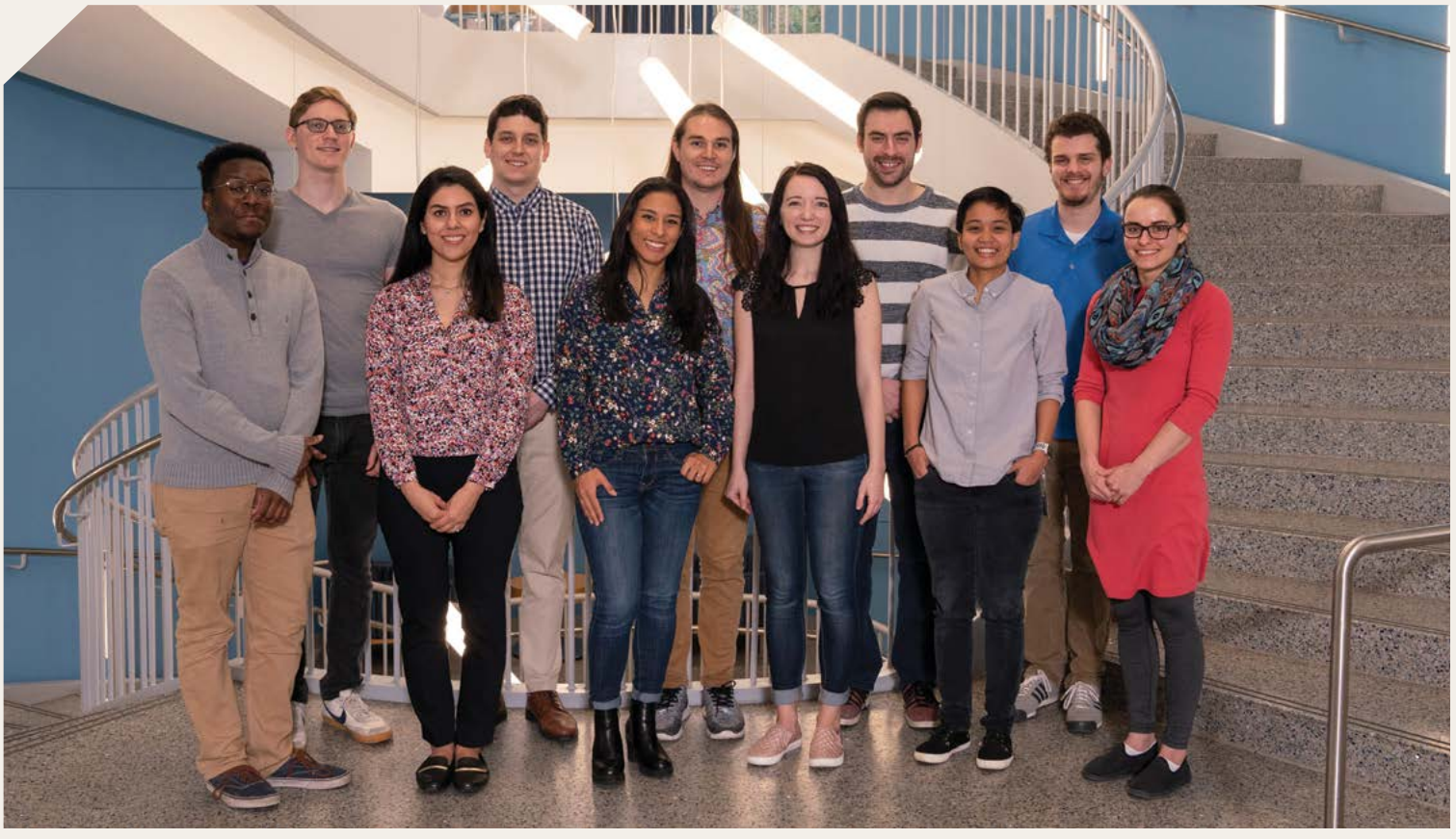
From left to right on the photograph below, the winners of the awards, their programs, and their mentors are:

- **Demond Williams,** Cancer Biology, mentored by Barbara Fingleton
- **Matthew Cottam,** Molecular Physiology and Biophysics, mentored by Alyssa Hasty
- **Azadeh Hadadianpour,** Molecular Pathology and Immunology, mentored by Dr. Scott Smith
- **Michael Doyle,** Microbe-Host Interactions, mentored by Dr. James Crowe
- **Alejandra Romero-Morales,** Cell and Developmental Biology, mentored by Vivian Gama
- **Manuel Castro,** Biochemistry, mentored by Charles Sanders
- **Abigail Neininger,** Cell and Developmental Biology, mentored by Dylan Burnette
- **Matthew Wleklinski,** Pharmacology, mentored by Dr. Bjorn Knollmann
- **Sheryl Vermudez,** Pharmacology, mentored by Colleen Niswender, and P. Jeffrey Conn
- **James O'Connor,** Cell and Developmental Biology, mentored by Andrea Page-McCaw
- **Margaret Axelrod,** Cancer Biology, mentored by Justin Balko

Students in Ph.D. programs linked to the School of Medicine are eligible for the award, as are students in the Medical Scientist Training Program the M.D./Ph.D.-granting program at Vanderbilt.

Students are put forth by faculty members, and their nominations are evaluated by a committee consisting of the directors of graduate studies for each of the Ph.D.-granting programs in the School of Medicine. The awardees are selected based on research excellence, as evidenced by fellowship awards, publications and presentations at conferences, and on mastery of a discipline as demonstrated by classwork and by the student's performances on their qualifying exam and committee meetings.

"I'm so impressed by the achievements of the awardees each year," Gould said. "I look forward to welcoming the 2020 recipients into this list of accomplished junior scientists."



JOE HOWELL

Achieving true diversity

By Linda Sealy

At Basic Sciences, diversity and inclusion are a core aspect of our identity: we talk the talk but also walk the walk. We are committed to providing an inclusive environment so that every member of our community feels supported, is comfortable being their authentic self, and can do their best work. As associate dean for diversity, equity, and inclusion in the Basic Sciences, I have led these efforts for nearly 4 years, but I have been involved in promoting diversity in some form or fashion for the entirety of my 34-year career at Vanderbilt.

Our biomedical graduate training programs have three decades' worth of a track record of ensuring that the very broadest group of students—reflecting diversity of racial, ethnic, gender, and socio-economic status—is able to fully participate in the educational and training opportunities we support. Since 1998, we have awarded over 135 Ph.D.'s to students from historically underrepresented groups. In 2014–2015, we awarded the highest number of biomedical Ph.D.'s to African Americans than anyone else in the country.

A key program contributing to this success has been the Vanderbilt Initiative for Maximizing Student Diversity, funded by the National Institutes of Health in 2007 to support Ph.D. trainees. **Roger Chalkley**, senior associate dean for biomedical research education and training, and I have led the program since its inception.

As of the 2019–2020 school year, 95 Ph.D. students were affiliated with IMSD; these students are distributed among Vanderbilt's first-year umbrella graduate programs, such as the Interdisciplinary Graduate Program in the Biological and Biomedical Sciences and the Quantitative and Chemical Biology program, and our 11 different Ph.D.-granting programs. Most IMSD programming focuses on first years, but graduate students remain associated with IMSD until they finish their degree. Keeping them involved throughout their graduate career, especially through cohort-building activities like social events and peer mentoring, is essential to help our community of scholars thrive.

Beyond establishing a feeling of community, however, the IMSD also supports the development of a range of important skills such as writing grants or manuscripts and developing effective presentation skills. Not only does the IMSD cultivate scholars who approach discovery science in a rigorous way, but it also offers opportunities to develop leadership skills through outreach activities and leadership development workshops. Thanks to a partnership with the Vanderbilt Owen School of Graduate Management, IMSD students have access to an executive leadership certificate, which can be earned by attending classes where they learn from nationally recognized business faculty and rub elbows with professionals and leaders from all industries from across the country.

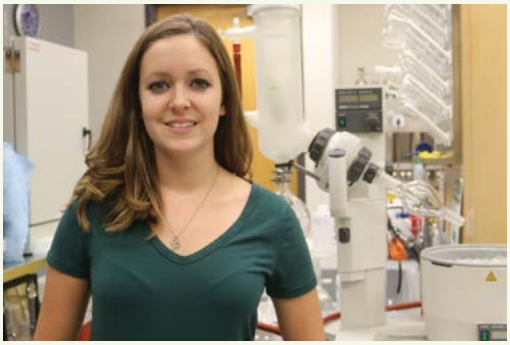
But as much as we strive to support our students through trainee-oriented programs, we cannot realize the benefits of diversity without an inclusive training environment. For this reason, Basic Sciences has implemented a customized Culturally Aware Mentoring curriculum for faculty. Led by facilitators from the NIH-funded National Research Mentoring Network, the two-day workshop covers the fundamentals of best mentoring practices interwoven with self-reflective dialogue about race and ethnicity and their influence on training experiences. Because training programs are nothing without outcomes, we are actively collecting data to see how good the workshop is for increasing the inclusiveness of our culture and climate. Hopefully, these efforts will lay the groundwork for the broader adoption of this training in the future.

Another way we're encouraging an inclusive and diverse training environment is by increasing the diversity of the faculty itself. Although we have made some progress, reflected in the hiring of eight women and five faculty of color since Basic Sciences was founded in 2016, more is needed. Because lack of inclusion is frequently cited as a barrier to having a more diverse professoriate, we believe that our culturally competent mentoring trainings will serve two purposes: they will better the support that our students get from current faculty members and they will improve our ability to attract faculty of color, resulting in a two-pronged approach to improve diversity and inclusion within our corner of science and academia.

Our Discovery Science Emerging Scholars seminar series brings outstanding, early-career investigators of color to Vanderbilt. While these high-achieving postdocs or junior faculty provide phenomenal role models to our IMSD trainees, they also have a chance to learn about the kind of home they could have at Vanderbilt if they applied for faculty jobs here down the line. During their visits, they meet with our faculty to identify possible research opportunities that could facilitate a move to Vanderbilt when they're ready to take that step.

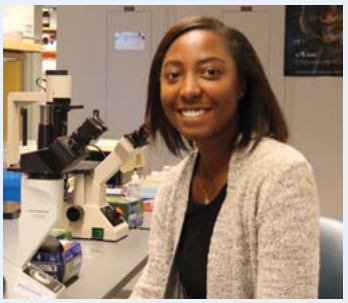
The importance of diversity, equity and inclusion has never been more apparent than in this time when the consequences of racial injustice have galvanized a much-needed focus on addressing structural racism in STEM and in this country. Not only do we stand in solidarity with those impacted by racism, but we are taking actions to widen the conversation and find additional ways we can enhance the support of Black, Indigenous, and people of color in the basic sciences.

The incredible research potential that Vanderbilt's investments in the latest research technologies create will be diminished unless we have the most talented individuals of all cultures and identities using them. Our goal at Basic Sciences is to continue to be at the forefront in terms of the number of Ph.D.'s awarded to underrepresented students in the biomedical sciences and to provide an exceptional learning environment that is inclusive and that supports the contributions of everyone in our community. ■



"The relationships that I have formed with other students, especially those who have similar backgrounds or experiences has helped me get through difficult times. As a multi-ethnic individual I have struggled with the concept of identity, and by interacting with a diverse community, I have found out that I am not alone as many people struggle with the same issues."

— Lindsay Redman, Quantitative and Chemical Biology program and IMSD class of 2016



"Vanderbilt University has served as a place in which both scholarly and personal diversity are appreciated. I appreciate the various groups on campus such as the Initiative for Maximizing Student Diversity program that allows for community building, recognition, and respect of my racial and cultural backgrounds, and supplemental programming to advance my studies. Vanderbilt acknowledges that it can always grow in its diversity and puts programming in place to do so."

— Tiffany Richardson, Interdisciplinary Graduate Program and IMSD class of 2017

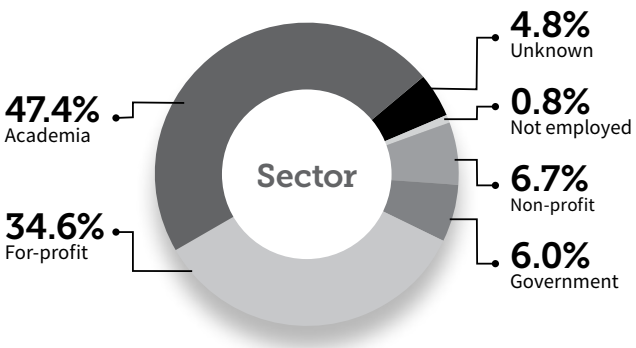
"Vanderbilt is a U.S. and world leader in graduating minority biomedical Ph.D. students. That status comes not only from the university's commitment to excellent scholarship, but also its support of the individual needs of each student as those needs are manifested."

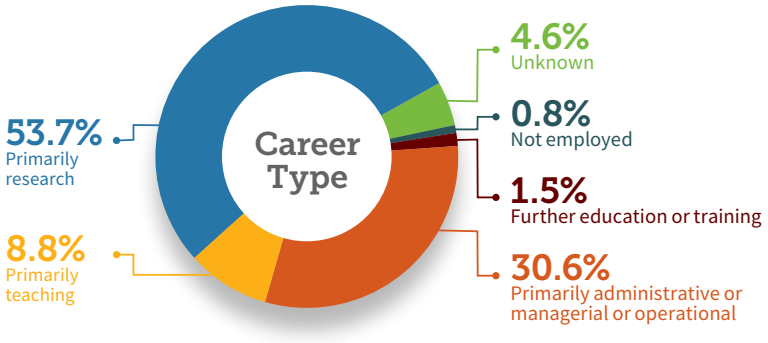
— Mark Crowder, IGP and IMSD class of 2015

"There can be some very stressful, intimidating, and lonely times, and it can be worse being the only African American in some of my classes or events. I don't think I would have made it as far as I did without them [the IMSD and BRET Office leadership] checking on me and making sure that whatever I needed, whether that was help with an assignment or a motivational speech, was taken care of. My first year has definitely been better with the support of everyone around me, and I really appreciate them for it."

—Jade Stanley, QCB and IMSD class of 2019

Student outcomes





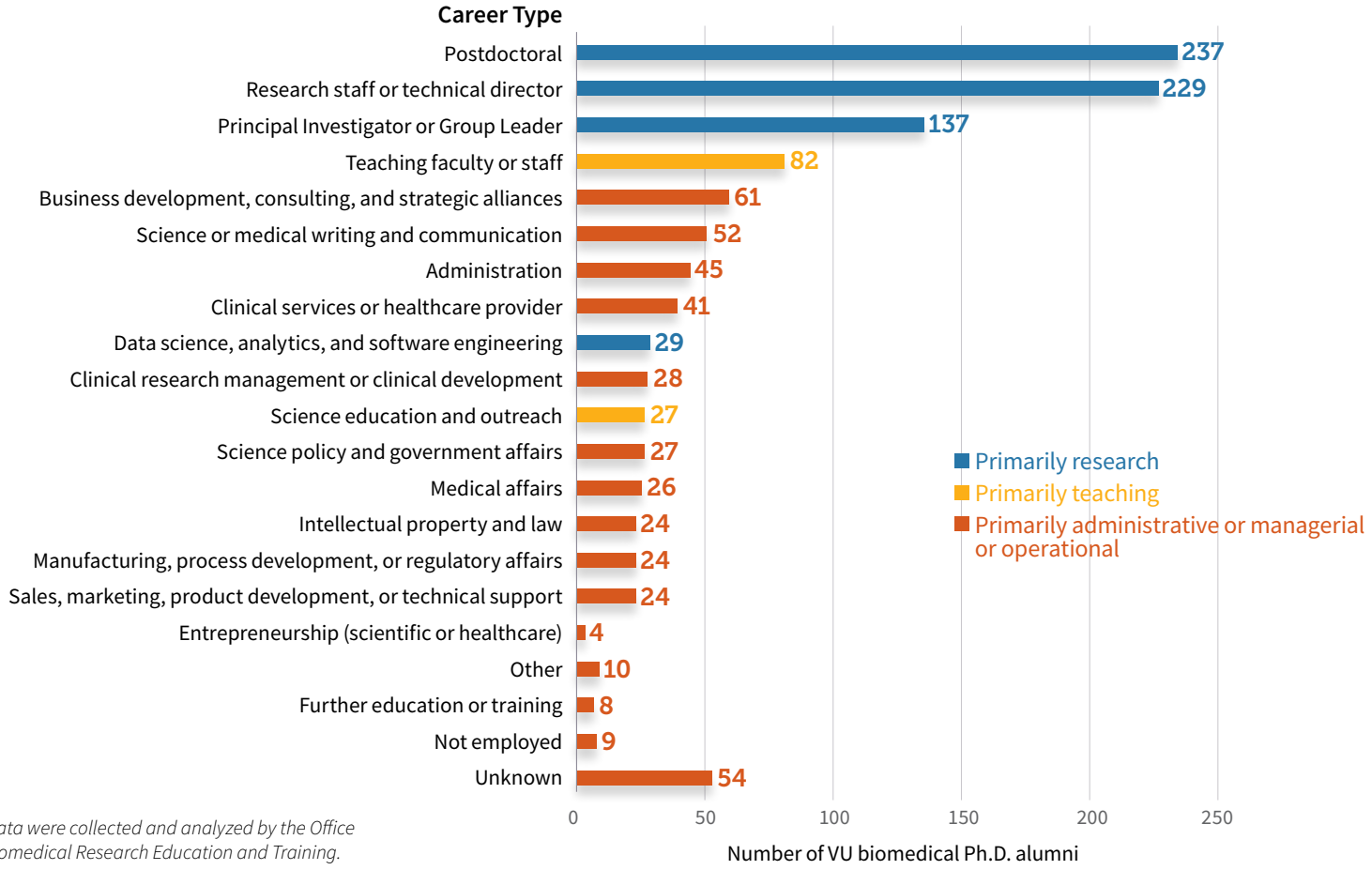
Sector and career type of the current position of all 1,178 biomedical Ph.D. alumni who graduated from our umbrella programs between 1992-2019

5.7
Average number of years it takes students to defend

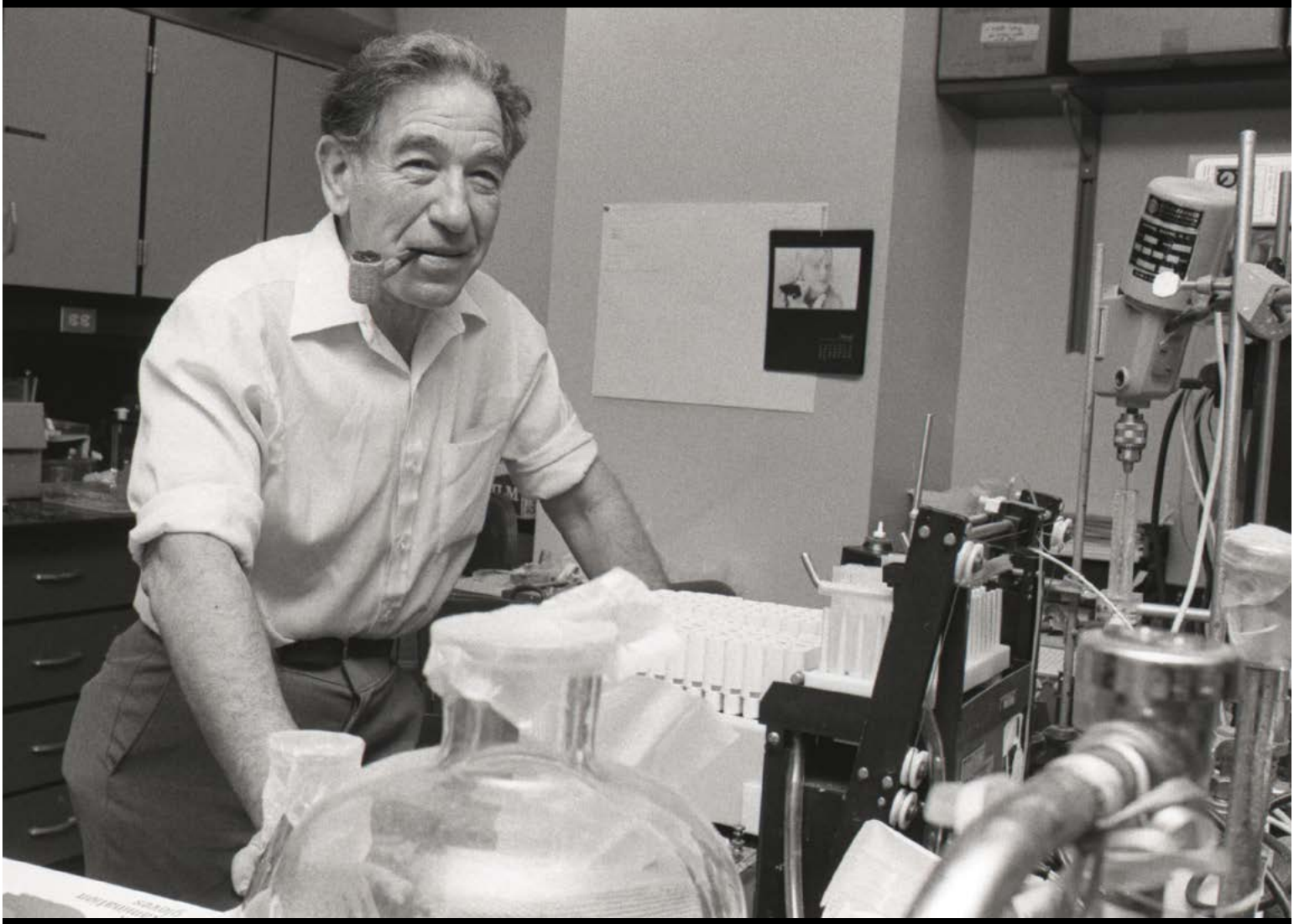
4.6
Average number of primary research papers our students publish before graduation

5.1
Average number of total papers published before graduation

Current positions, divided by job function, of all 1,178 biomedical Ph.D. alumni who graduated from our umbrella programs between 1992-2019



All data were collected and analyzed by the Office of Biomedical Research Education and Training.



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Vanderbilt Basic Sciences has pledged to double the impact of our generous partners by matching all eligible gifts of $50,000 or more through June 2021. For more information, email basicsciencesgiving@vanderbilt.edu or call (615) 343-1635.

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