Vestigo

ISSUE 3
SUMMER 2021

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

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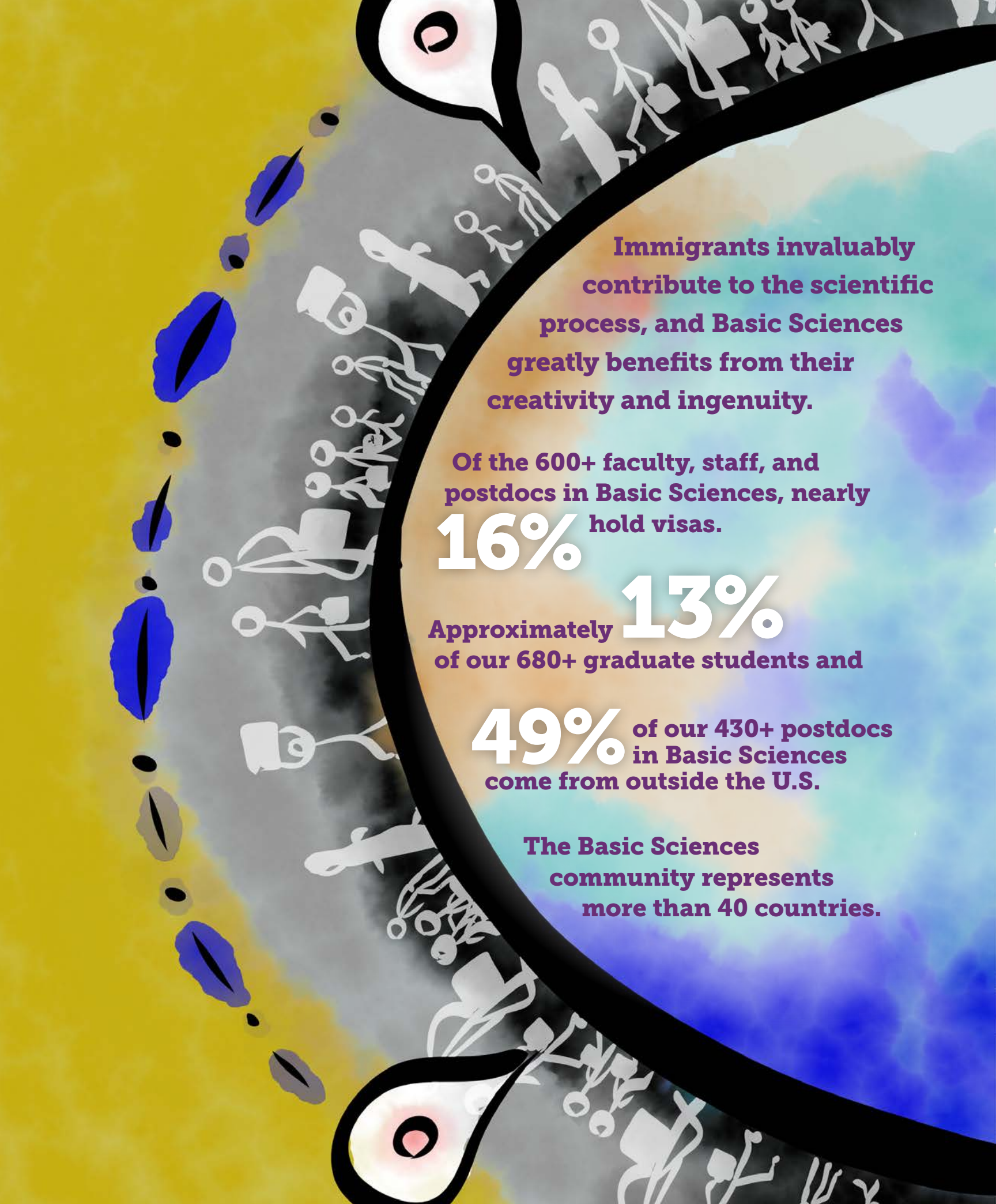

Immigrants invaluably contribute to the scientific process, and Basic Sciences greatly benefits from their creativity and ingenuity.

Of the 600+ faculty, staff, and postdocs in Basic Sciences, nearly 16% hold visas.

Approximately 13% of our 680+ graduate students and

49% of our 430+ postdocs in Basic Sciences come from outside the U.S.

The Basic Sciences community represents more than 40 countries.

In this issue

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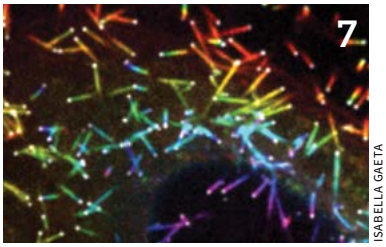
Vestigo is published semi-annually by the Vanderbilt University School of Medicine Basic Sciences in cooperation with Vanderbilt University Division of Communications and Marketing, 2100 West End Ave., Suite 1100, Nashville, TN 37203, which also provides online support. Articles appearing in *Vestigo* do not necessarily reflect the opinions of the basic sciences or the university. Vanderbilt University is committed to principles of equal opportunity and affirmative action. Please recycle.

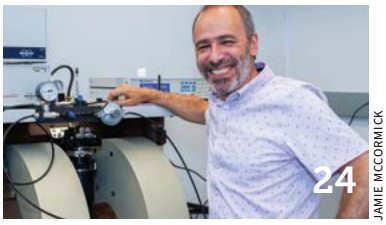
Cover: An artistic interpretation of a two-dimensional brain representation generated by José Maldonado through whole-brain imaging conducted in the new Vanderbilt Neurovisualization Lab at Vanderbilt University. Illustration by Kendra H. Oliver.

Left: Science is a global endeavor, and here in Basic Sciences we welcome researchers from all over the world. In this issue, we highlight immigrant scientists and their contributions in honor of Immigrant Heritage Month (June). Read the story on page 32 and make sure to check out a new video celebrating an immigrant scientist on our social media channels each month! Illustration by Kendra H. Oliver. #CelebrateImmigrants

JOE HOWELL



ISABELLA GAETA



JAMIE MCCORMICK

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 School of Medicine Basic Sciences.

If you just can't wait for the nest issue of *Vestigo* to keep up with Basic Sciences, we can send you news straight to your inbox. We have weekly and monthly newsletters — sign up at http://vanderbi.lt/BasicSciencesNewsSignUp

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Correction: In the last issue, we incorrectly listed the dissertation mentor of Tomas Bermudez, a graduate student in the Microbe-Host Interactions program. He is mentored by Maria Hadjifrangiskou and Mariana Byndloss.

COVER STORY

DISCOVERY

INNOVATION

IMPACT

SPECIAL FEATURE

Dear alumni and friends:

JOHN RUSSELL

Welcome back to *Vestigo*! We are pleased to share more stories about the people and programs of the School of Medicine Basic Sciences. Our third issue highlights more great science as well as the behind-the-scenes structures and activities that make it possible.

The stereotype of the lone scientist working diligently on a lifelong pursuit is fading, as science is increasingly done by teams of students, postdocs, staff, and faculty. The collection of scientific advances highlighted in this issue reflects that reality, underscored by national efforts to map all human tissues at the molecular level (page 14).

Multi-investigator collaborations can be fostered by centers focused on exciting research areas that span various disciplines. Our newest is the Center for Extracellular Vesicle Research, which brings together researchers from across the university and the Vanderbilt University Medical Center (page 34).

Our research core facilities provide frontier techniques and instrumentation and are an integral part of our research efforts. The Molecular Design and Synthesis Core, for instance, makes drugs and chemical probes and recently celebrated its tenth anniversary (page 8). Our cover article (page 10) highlights the origin story and recent work of our newest core, the Vanderbilt Neurovisualization Laboratory, which has expanded the frontier of microscopy through visually stunning techniques that make tissue transparent.

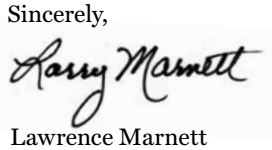
Grants managers help faculty manage the complex life cycles of research grants and contracts. The exceptional individuals interviewed on page 30 are true unsung heroes of the Basic Sciences.

Most of the research in the School of Medicine and the medical center is performed by talented and passionate Ph.D. students and postdocs. Our Office of Biomedical Research Education and Training provides a support system for them and is legendary throughout the international biomedical community for its efficiency and impact (page 27).

Many of our researchers come from countries outside the U.S. In honor of Immigrant Heritage Month, we highlight on page 32 some of the incredibly talented international scientists who enrich our campus.

Vestigo brings to life the people and programs of Basic Sciences, but it's not the only way we communicate the impact of our work to the community. Earlier this year, we established a Lab-to-Table Conversations event series that brings scientists and celebrities together for panel discussions of compelling contemporary topics (page 22). Don't hesitate to let us know of ideas for stimulating discussions! Email us at basicsciences@vanderbilt.edu.

Sincerely,



Lawrence Marnett
Dean of Basic Sciences

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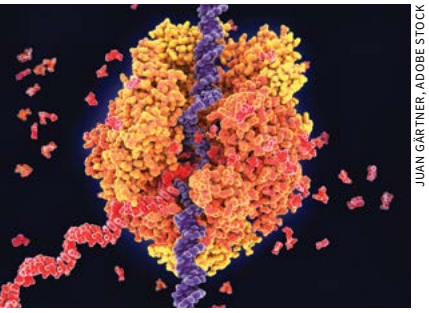
Error-prone or adaptive?

The role of topoisomerases during DNA replication and transcription conflicts

Replication—copying a cell's DNA—and transcription—making RNA from DNA—are not separated spatially or temporally in a cell and can happen simultaneously. That means that the protein complexes (also called "machineries") responsible for replication and those responsible for transcription sometimes have conflicts with one another. Such conflicts can be harmful to the cell, leading to mutations in the DNA or even cell death.



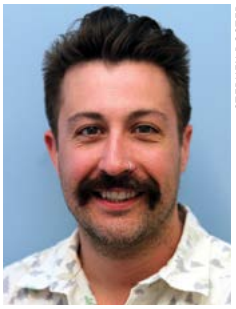
JUAN GÄRTNER, ADOBE STOCK

One type of conflict is the head-on conflict, which happens when the two sets of machineries approach each other from opposite directions. **Kevin Lang**, a postdoctoral fellow in the lab of **Houra Merrikh**, professor of biochemistry, recently described a critical cause of the deleterious effects of head-on conflicts—and a surprising benefit—through the use of a bacterial model.

Separation of the DNA strands during replication and transcription results in overwinding, or tight coiling, of the DNA double helix ahead of the two sets of machineries. When the two approach each other, there is a buildup of overwound DNA; the tight coils in the DNA must be removed or the cell cannot complete its replication and transcription tasks.

The researchers found that the enzymes gyrase and topoisomerase IV are needed to unwind the tight DNA coils that accumulate at regions of head-on conflicts. When both of those enzymes were inhibited, the DNA at the head-on conflict remained overwound and replication stalled. Inhibiting one or both enzymes resulted in much lower bacterial cell survival, suggesting that both enzymes are necessary to resolve head-on conflicts.

Previous work by the team had shown that R-loops, or regions where RNA and DNA hybridize to each other during transcription, contribute to the negative effects of head-on conflicts if they are not resolved at conflict regions. Thus, they tested whether the presence of gyrase and topoisomerase IV could influence formation of R-loops. They found that the enzymes, particularly gyrase, can promote R-loop formation and, consequently, stalling at head-on conflicts.



STEPHEN DOSTER

First author: Kevin Lang, postdoctoral fellow

Lang and Merrikh's work adds to our understanding of the dynamics of DNA replication and transcription, which are central to the functioning of cells. At first glance, this mechanism seems counterintuitive: Why would a process exist that results in potentially harmful conflicts? A large body of work from the Merrikh lab has shown that head-on conflicts increase mutation rates, and, although increased mutagenesis is often detrimental to cells, it can help bacteria rapidly adapt to changes in their environment. **— By Alexandria Oviatt**

***Lang, K.S.**, Merrikh, H. (2021). Topological stress is responsible for the detrimental outcomes of head-on replication-transcription conflicts.* Cell Reports *34, 108797. https://doi.org/10.1016/j.celrep.2021.108797*

The case against rapid change

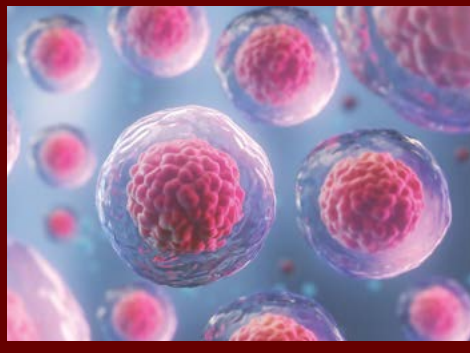
Pioneering research led by **Alexander Thiemicke**, former graduate student in chemical and physical biology, and **Gregor Neuert**, assistant professor of molecular physiology and biophysics, reveals that cells respond differently to environments in which conditions change gradually as opposed to rapidly. The investigators developed a cell culture environment that more closely mimics incremental physiological changes—such as in hormone or nutrient levels—as opposed to conventional approaches in which sudden alterations are made. Their goal is to provide researchers with a more relevant context to inform both basic research and drug discovery efforts.

GREGOR NEUERT

First author: Alexander Thiemicke, recent Ph.D. graduate

In their most recent study, the researchers changed—first gradually and then suddenly—the amount of salt surrounding immune cells that typically exist in the kidney and intestine. This alteration causes osmosis, the movement of water across the cell membrane. Neuert and Thiemicke then monitored deviations in 25 markers of cell stress and death. They determined that 60 percent of cells died when exposed to gradual stress, whereas 90 percent of cells acutely exposed to the same change died.

Cells exposed to a gradual salt increase took up protective amino acids to defend themselves against the extracellular stress. Upon acute stress, however, a cell death program was triggered before the cells had time to protect themselves. The researchers also found that, if acutely stressed cells were given those protective amino acids, they survived at rates similar to those of the gradually stressed cells.



ANUSORN, ADOBE STOCK.

"Looking at how cells respond to perturbations in their environments in this way is an entirely new approach in biomedical research," said Neuert, also a Dean's Faculty Fellow and an NIH New Innovator Awardee. "This has serious implications as we unravel fundamental biological questions and for how drug development is pursued." **— By Marissa Shapiro**

***Thiemicke, A.**, Neuert, G. (2021). Kinetics of osmotic stress regulate a cell fate switch of cell survival.* Science Advances *7, eabe1122. https://doi.org/10.1126/sciadv.abe1122*

How a key antidepressant works

The recent discovery of ketamine's remarkable antidepressant activity has led to considerable excitement among neuroscientists. Used as an anesthetic for more than 50 years, ketamine can provide, in as little as two hours, up to weeks of antidepressant relief for individuals resistant to typical antidepressants. In contrast, typical antidepressants take four to five weeks to work, if they work at all. However, along with the excitement comes a mystery—how does ketamine work as a rapid-acting antidepressant in the brain?

Lisa Monteggia, professor of pharmacology and Barlow Family Director of the Vanderbilt Brain Institute, along with her collaborators, is addressing that question.

COURTESY OF JI-WOON KIM

First author: Ji-Woon Kim, postdoctoral fellow

Synapses are structures within the nervous system by which two neurons communicate with one another. Communication occurs when one neuron releases a chemical neuro-transmitter that travels across the synapse and binds to a protein receptor on the other, thereby triggering a physiological response in that neuron. Monteggia's work supports the current understanding that ketamine blocks glutamate N-methyl-D-aspartate—or NMDA—receptors, triggering a neural biochemical pathway that elicits the rapid antidepressant effect.

Monteggia's team, which included **Joachim Herz**, a professor of molecular genetics, neurology, and neuroscience at UT Southwestern, also looked into how reelin—a protein that controls cells' interactions in the brain—is involved in ketamine's action. They found that mutations or impairments to reelin could result in a patient not experiencing ketamine's antidepressant activity.

Understanding why ketamine works in some patients but not others is important for everyone. "Depression is a heterogenous disorder; it is rather remarkable that antidepressants and ketamine work in as many patients as they do," Monteggia said. "By understanding the target and how mutations or impairments affect the drug's mechanism, we can develop fast-acting antidepressants that target other populations." **— By Marissa Shapiro**

***Kim, J.-W.**, Herz, J., Kavalali, E.T., Monteggia, L.M. (2021). A key requirement for synaptic Reelin signaling in ketamine-mediated behavioral and synaptic action.* Proceedings of the National Academy of Sciences *118, e2103079118. https://doi.org/10.1073/pnas.2103079118.*

Single-cell data curation with machine learning

Single-cell RNA sequencing, or scRNA-seq, allows researchers to explore cell-to-cell variability in healthy and diseased tissues—and even entire organisms—lending insight into normal development and complex pathologies such as cancer.

The lab of **Ken Lau**, associate professor of cell and developmental biology, in collaboration with **Jake Hughey**, assistant professor of biomedical informatics, recently developed a fully automated machine learning tool to help researchers maintain high quality in scRNA-seq experiments. The work, published in *Genome Research*, will help biologists better extract information from the large amount of data generated by this method.

Recent advances in single-cell technologies have made such data accessible to researchers working on diverse biological problems. The most common platforms make use of small, liquid-flow channels that capture individual cells in a water-oil emulsion from which RNA molecules can be isolated and sequenced. Because of the large number of cell-free droplets generated to ensure the isolation and capture of single cells, a major challenge is distinguishing cells from "empty droplets" based on the detected RNA alone.

The automated tool, called "dropkick," performs quality control and cell identification on scRNA-seq data. After determining batch-specific metrics that describe droplet quality, dropkick learns a gene-based representation of real cells and background noise, calculating a cellular probability score for each droplet. Thanks to dropkick, researchers can interpret the biological significance of background RNA expression and fine-tune the filtering cutoff and downstream analysis accordingly.

TRACY HEISER

First author: Cody Heiser, Ph.D. student

The dropkick tool was benchmarked against existing filtering approaches on simulated and real-world data and was shown to reproducibly recover rare cell types and exclude empty droplets, especially in high-background datasets. These characteristics make dropkick extremely valuable for biologists by protecting downstream analyses from noise that may skew interpretations and rescuing rare cell populations, contributing to robust biological discovery. **— By Cody Heiser**

***Heiser, C. N.**, Wang, V. M, Chen, B., Hughey, J. J., & Lau, K.S. (2021). Automated quality control and cell identification of droplet-based single-cell data using dropkick.* Genome Research, *Article gr.271908.120. https://doi.org/10.1101/gr.271908.120*

RNA-protein interactions mediate an innate immune response

The innate immune system is made up of receptors that, upon detection of a potential pathogen, trigger a robust transcriptional response in cells. This means that hundreds of mRNAs are made that encode for pro-inflammatory and anti-viral proteins that protect cells from infection. However, dysregulation of the mRNAs can lead to improper levels of those pro-inflammatory proteins, which can be detrimental to cells and tissues. To prevent damage, cells have evolved mechanisms to carefully balance the levels of immune-relevant mRNAs to promote a strong immune response but avoid rampant overstimulation.

MANUEL ASCANO

First author: Katherine Rothamel, recent Ph.D. graduate

Overactivation of the immune system among patients is a primary concern of health care workers who treat infections such as COVID-19. A better understanding of the mechanisms that prevent immune overstimulation could lead to better treatments for patients with autoimmune disorders or for those who develop hyperactive reactions to bacterial or viral infections, and even vaccinations.

One way the cell regulates gene expression is through the control of mRNAs by RNA-binding proteins, or RBPs. RBPs can target specific mRNAs to alter their stability, location inside the cell, and ability to be translated into proteins. RBPs that bind to mRNAs that get made into innate immune proteins influence the duration and intensity of the immune response.

Researchers from groups of **Manuel Ascano**, assistant professor of biochemistry, and **Neelanjan Mukherjee**, assistant professor of biochemistry and molecular genetics at the University of Colorado School of Medicine, showed that the RBP ELAVL1 binds to a specific region within mRNAs that stabilizes them during an innate immune response.

Before a cell receives a signal from the innate immune system, ELAVL1 is located in the nucleus, where it binds to introns, or non-coding sections of mRNA. Upon receiving a signal, ELAVL1 moves to the cytoplasm, where it binds to a set of innate immunity-related mRNAs at a very specific location called the 3' untranslated region. This transition is required to stabilize the mRNAs that encode for the innate immune proteins.

Overall, this study provides a novel example of how the activation status of an immune cell affects not only the identity of the mRNAs that RBPs bind, but also the function of those RBPs on their targets. The redistribution of ELAVL1 stabilizes certain mRNAs, switching immune cells from a resting to an activated state, and demonstrates how an RBP targeting specific mRNAs can positively regulate the immune response and can significantly influence a cell's resilience to infection. **— By Nicole Kendrick**

***Rothamel, K.**, Arcos, S., Kim, B., Reasoner, C., Lisy, S., Mukherjee, N., Ascano, M. (2021). ELAVL1 primarily couples mRNA stability with the 3' UTRs of interferon-stimulated genes.* Cell Reports *35, 109178. https://doi.org/10.1016/j.celrep.2021.109178.*

Finding better structures

Proteins carry out vital functions throughout the cell, and many of them need to undergo structural changes to accomplish their tasks. Bacterial drug exporters, for example, adopt several distinct structural poses to grab and eject toxic drugs from within the cell. Knowing the detailed structures of these poses can help researchers design drugs that can, for example, circumvent bacterial drug resistance mechanisms. Unfortunately, proteins are rarely captured in the full breadth of structural states they adopt.

SELENA CHACÓN SIMON

First author: Diego del Alamo, Ph.D. student

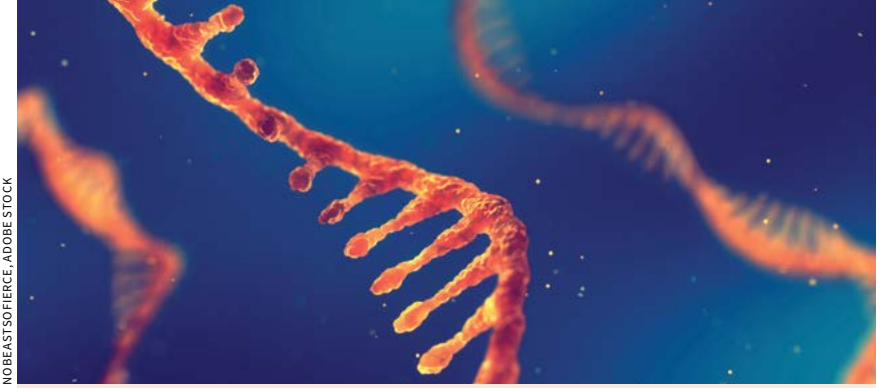
The labs of **Hassane Mchaourab**, professor of molecular physiology and biophysics, and **Jens Meiler**, professor of chemistry, recently teamed up and tackled this challenge by integrating experimental spectroscopy and computational modeling. Our research, published in *PLOS Computational Biology*, adapted a technique called multilateration. Multilateration is used in everyday life for things such as positioning cellphones using GPS distance data.

The central idea of the research is that specific structural states that may be poorly understood can be detected and monitored using an experimental technique called electron paramagnetic resonance—or EPR—spectroscopy, which measures distances between pairs of probes attached to a protein. Although these probes are quite flexible, we showed that a multilateration algorithm can calculate their precise positions.

We combined this algorithm with Rosetta, a modeling platform, to model structural rearrangements in a well-studied bacterial multidrug exporter. We found substantial improvements in the accuracy and precision of the model, allowing us to recapitulate the change in the structure of the transporter that leads to bacteria ejecting a drug.

This algorithm promises to address fundamental challenges to modeling protein structures using data obtained through EPR, which has previously been restricted to monitoring low-resolution structural movements. The work also opens the door to improved knowledge of the relationship between protein structure and function. **— By Diego del Alamo**

***del Alamo, D.**, Jagessar, K.L., Meiler, J., Mchaourab, H.S. (2021). Methodology for rigorous modeling of protein conformational changes by Rosetta using DEER distance restraints.* PLOS Computational Biology *17, e1009107. https://doi.org/10.1371/journal.pcbi.1009107.*



NOBEASTSOFIERCE, ADOBE STOCK

RNA editing enzymes as internal pH sensors

Cells have to regulate gene expression to function properly, and they have many tools to do this. Many of these tools are dependent on the DNA or RNA sequences or have to do with controlling whether the RNA is made in the first place. However, one cellular tool called "RNA editing" is employed after the RNA is produced but before it is used to make a protein. The regulation of RNA editing is not yet well understood, but recent findings from the lab of Professor of Pharmacology **Ron Emeson** show that it is dependent on the pH of the cell.

RNA is made up of four bases: adenosine (A), guanosine (G), thymidine (T), and uracil (U). One common RNA editing event occurs when a cell replaces an A with inosine (I), a rare base that looks and acts like a G; this change is called "A-to-I editing." It can be present in any cell but is particularly important and occurs frequently in the nervous system. Alterations in A-to-I editing are associated with a variety of neurological disorders, such as epilepsy, amyotrophic lateral sclerosis, and schizophrenia.

A recent paper from the Emeson lab identified intracellular acidification as an important regulator of RNA editing. They found that the enzymes responsible for A-to-I editing, called ADARs (adenosine deaminases acting on RNA), are pH sensitive and become more active at a lower, or more acidic, pH than is normally found in the cell. This is due to a structural change that occurs at acidic pH that makes ADARs better at stabilizing the RNA.

Based on these results, Emeson and colleagues suggest that ADARs might act like pH sensors, allowing cells to modulate their RNA editing to respond to environmental changes. For instance, stressors such as hypoxia or stroke disturb the pH balance in neurons, leading to acidification of their internal environments. Acidification can cause hyperexcitability in neurons, which can damage or kill cells if unchecked. Higher levels of ADARs have been shown to decrease neuron excitability, and the RNA of many proteins that help control membrane excitability in neurons is a target of A-to-I editing. Therefore, the authors speculate that RNA editing may provide a pH-dependent protective mechanism for neurons by facilitating the rapid editing of RNAs that encode membrane proteins to correct hyperexcited states and thereby limit damage.

KAYLA SHUMATE

First author: Turnee Malik, recent Ph.D. graduate.

Currently, RNA editing is an attractive way to try to repair mutations associated with some genetic diseases. Careful study of the regulation of RNA editing, such as that carried out by the Emeson lab, is necessary to develop safe and effective strategies for precisely targeting RNA editing enzymes to the specific sequences that need repair. **— By Wendy Bindeman**

***Malik, T.N.**, Doherty, E.E., Gaded, V.M., Hill, T.M., Beal, P.A., Emeson, R.B. (2021). Regulation of RNA editing by intracellular acidification.* Nucleic Acids Research *49, 4020–4036. https://doi.org/10.1093/nar/gkab157.*

Unveiling the life cycle of a microvillus

The surface of the intestinal tract is the sole site of nutrient absorption—a life-sustaining process—and disturbances to this tissue have the potential for deadly consequences. The small intestine has evolved a variety of structures that maximize the surface area available for nutrient uptake, including microvilli, fingerlike projections that protrude from the cell. The collection of microvilli on the surface of intestinal cells forms a larger structure known as the brush border, which resembles the bristles on a toothbrush.

MATT TYSKA

First author: Isabella Gaeta, Ph.D. student

In a recent *Current Biology* paper, graduate student **Isabella Gaeta**, from the lab of Professor of Cell and Developmental Biology **Matt Tyska**, reveals how microvilli are born and begin to grow. The assembly of new microvilli is critical for the function of the intestine, but until now little was known about how cells build these structures.

The intestine is different from most other tissues because of its high rate of cell turnover—old cells constantly die off and are replaced by new, robust cells. Each new cell, however, also must build brand-new microvilli. This process is driven by the end-to-end assembly of a cellular protein known as actin, and the resulting actin "filaments" are in turn bundled together to form a strong support for the cell membrane. Using live-cell microscopy, Gaeta observed the various proteins that come to the cell surface to "birth" a microvillus and revealed that EPS8, a protein known to help form actin structures, is required for microvilli to continue to grow.

Gaeta also showed that a "mother microvillus" is capable of birthing a "daughter" by creating a new branch off an existing projection that in turn splits into an independent structure. This exciting new finding illuminates a novel pathway for microvilli formation, and additional studies along these lines will lead to a better understanding of the birth and growth of microvilli. This work will also allow researchers to understand how the complex structures of the intestine may be disrupted in diseases characterized by loss of microvilli, such as enteric (intestinal) infections with pathogenic *Escherichia coli*. **— By Colbie Chinowsky**

***Gaeta, I.M.**, Meenderink, L.M., Postema, M.M., Cencer, C.S., Tyska, M.J. (2021). Direct visualization of epithelial microvilli biogenesis.* Current Biology *31, 2561–2575.e6. https://doi.org/10.1016/j.cub.2021.04.012.*

Meet Vanderbilt's molecular architects

By Stephen Doster and Carol Rouzer

The Molecular Design and Synthesis Center is staffed by talented researchers. From left, Gary Sulikowski, Kwangho Kim, Alex Waterson, Plamen Christov, Benjamin Guttentag, LaToya Scaggs, Ian Romaine, KyuOk Jeon, and Somnath Jana.

Vanderbilt's Chemical Synthesis Core, recently renamed the Molecular Design and Synthesis Center, celebrated a decade of work this year. To commemorate the anniversary, we sat down with **Gary Sulikowski**, Stevenson Chair of Chemistry and faculty director of the center since 2008, who shared insights into synthetic chemistry and discussed the center's history and involvement in drug discovery at Vanderbilt.

JOHN RUSSELL

What is the purpose of the MDSC?

The main purpose of the core has always been to support the synthetic chemistry needs of Vanderbilt investigators across campus. As synthetic chemists, we can describe ourselves as molecular architects. We first design a molecular structure on paper, and then, using the tools of organic chemistry, we build the molecular structure in our lab and place it a bottle for study by the investigator's lab.

We focus on two main goals. The first is to support preclinical lead optimization in drug discovery. This is the process where we make structural changes to an active hit compound—a molecule that looks like it has a biological activity of interest—to improve its physical and biological properties. The goal is to make the compound more drug-like so that it can be used in animal models.

Our second main goal is to help researchers who are not necessarily interested in drug discovery acquire or develop chemical tools that will help them better understand biological processes from a basic science perspective. For example, some projects require that we create synthetic processes to provide investigators with large amounts of natural metabolites or drug-like compounds in the quantities needed for animal studies.

> "The Molecular Design and Synthesis Center has had a big impact on my lab's work. They have certainly helped us expand our own capacity and move our projects forward faster."
>
> **Stephen Fesik,** Orrin H. Ingram II Professor of Cancer Research and professor of biochemistry and pharmacology

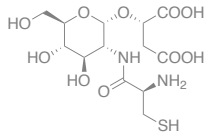
What's one of the center's proudest successes?

One notable success was making a compound called bacillithiol, a member of the wider class of thiols, which are compounds that often play an important role in cells by destroying certain types of toxic metabolites.

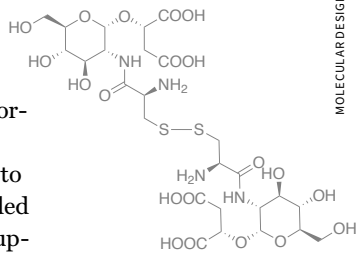
At the time of bacillithiol's discovery, the late Professor of Biochemistry **Richard Armstrong** was interested in the role of thiol compounds in the ability of bacteria to develop resistance to the antibiotic fosfomycin. He thought the bacteria that make bacillithiol might have been using it for this purpose. He could not test this hypothesis, however, because bacillithiol was only available in minute quantities. There was no known lab-based synthesis of the compound then, but we developed a method to do it in large quantities.

To this date, I think we're one of only two groups that have ever prepared this compound, and it's not uncommon for us to get requests from investigators outside of Vanderbilt—from Switzerland and Israel, for instance—for bacillithiol to support their studies of pathogenesis or other functions in bacteria.

Chemical structures of bacillithiol and bacillithiol disulfide.



bacillithiol (BSH)



bacillithiol disulfide (BSSB)

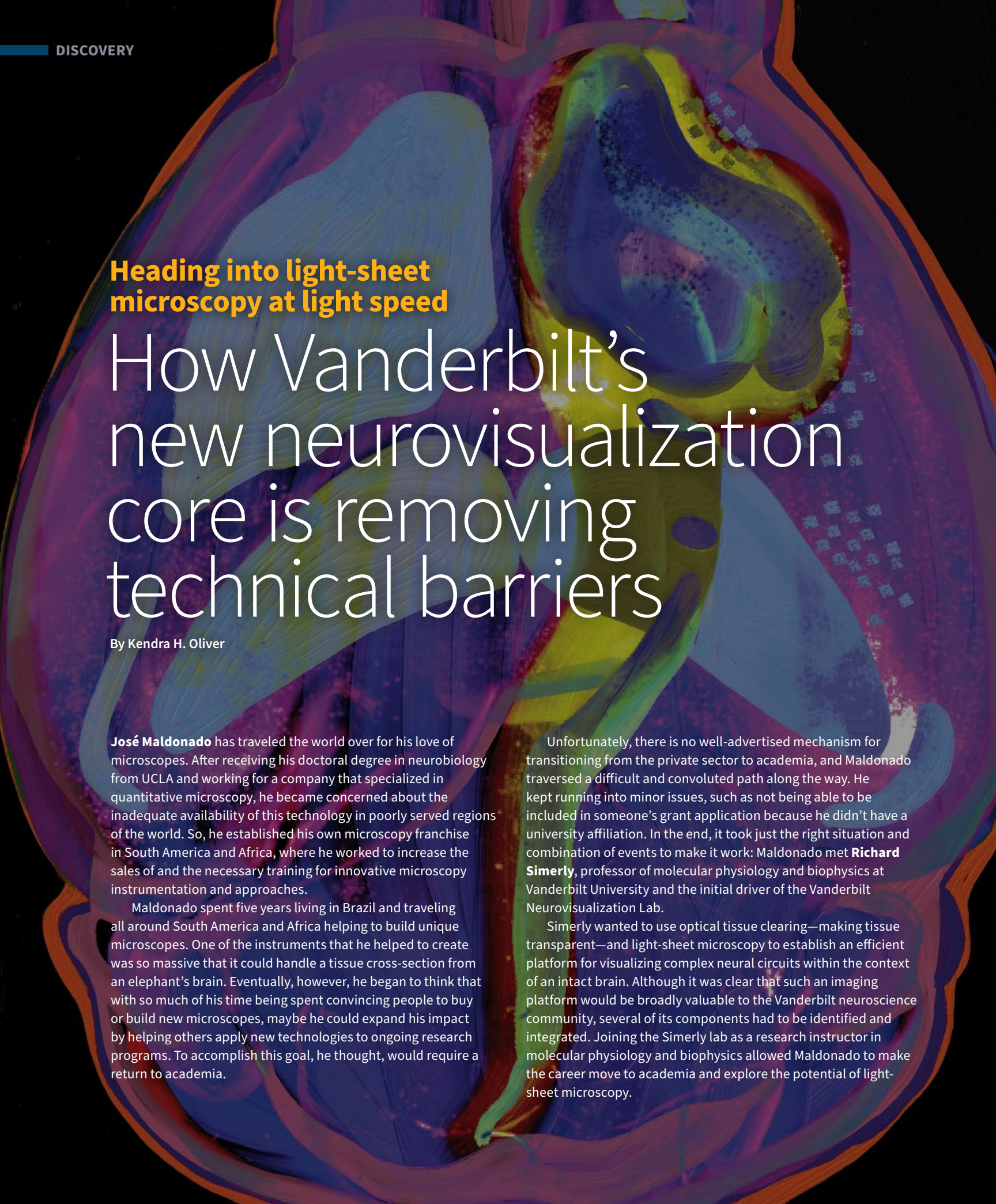
MOLECULAR DESIGN AND SYNTHESIS CORE

Has COVID-19 affected perceptions about chemical synthesis and drug discovery?

Oh, yeah. One silver lining about the pandemic is that it has highlighted the importance of drug discovery and is advancing our understanding of infectious diseases. Early on during the pandemic, Professor Steve Fesik had an idea for a possible drug to target SARS-CoV-2, the virus that causes COVID-19. To test his hypothesis, he needed material quickly, and we were able to ramp up and give him some initial synthetic support, providing early lead molecules designed by his team.

This example illustrates why we're also sometimes referred to as a SWAT team. We are known for our ability to mobilize and help support researchers quickly. Typically, our seven talented investigators work on over 20 ongoing projects in the core at any one time.

For more information about the center and its successes, read "Ten-Year Retrospective of the Vanderbilt Institute of Chemical Biology Chemical Synthesis Core," published in ACS Chemical Biology, *May 21, 2021, or visit the center's website: vanderbi.lt/syncore* ■



Heading into light-sheet microscopy at light speed

How Vanderbilt's new neurovisualization core is removing technical barriers

By Kendra H. Oliver

José Maldonado has traveled the world over for his love of microscopes. After receiving his doctoral degree in neurobiology from UCLA and working for a company that specialized in quantitative microscopy, he became concerned about the inadequate availability of this technology in poorly served regions of the world. So, he established his own microscopy franchise in South America and Africa, where he worked to increase the sales of and the necessary training for innovative microscopy instrumentation and approaches.

Maldonado spent five years living in Brazil and traveling all around South America and Africa helping to build unique microscopes. One of the instruments that he helped to create was so massive that it could handle a tissue cross-section from an elephant's brain. Eventually, however, he began to think that with so much of his time being spent convincing people to buy or build new microscopes, maybe he could expand his impact by helping others apply new technologies to ongoing research programs. To accomplish this goal, he thought, would require a return to academia.

Unfortunately, there is no well-advertised mechanism for transitioning from the private sector to academia, and Maldonado traversed a difficult and convoluted path along the way. He kept running into minor issues, such as not being able to be included in someone's grant application because he didn't have a university affiliation. In the end, it took just the right situation and combination of events to make it work: Maldonado met **Richard Simerly**, professor of molecular physiology and biophysics at Vanderbilt University and the initial driver of the Vanderbilt Neurovisualization Lab.

Simerly wanted to use optical tissue clearing—making tissue transparent—and light-sheet microscopy to establish an efficient platform for visualizing complex neural circuits within the context of an intact brain. Although it was clear that such an imaging platform would be broadly valuable to the Vanderbilt neuroscience community, several of its components had to be identified and integrated. Joining the Simerly lab as a research instructor in molecular physiology and biophysics allowed Maldonado to make the career move to academia and explore the potential of light-sheet microscopy.

Light sheets ahead

Researchers using traditional microscopy to study cellular or tissue morphology slice up the organ of interest like pieces of deli meat, prepare and image them separately, and then reconstruct them digitally. This process can come with a few issues, such as the potential for damage to the tissue, the requirement of extensive labor for the preparation of many samples, and the challenge of accurately assembling the whole from the many parts.

"When you image a tissue section in a conventional microscope, it really is like looking down at the world through a straw," Maldonado explained. "You're looking down at one little piece, and you're taking all these little pictures through that straw. And then you have to stitch it all together in your head."

However, a whole new world emerges with the application of light-sheet microscopy, which allows researchers to keep the tissue intact so that they can view an entire organ without having to reconstruct structures from sections. "A particularly powerful application of single-plane illumination microscopy, a form of light-sheet technology, is to visualize the brainwide organization of neural circuits. Instead of using a knife to cut sections through the brain, we use light to create virtual slices in order to construct 3D renderings of neurons and their connections, while maintaining their in vivo orientation. It's a potent tool for looking at whole-organ anatomy."

The origin story

Simerly, Louise B. McGavock Chair in Molecular Physiology and Biophysics, studies how environmental factors, such as nutrition and hormones, impact the development of neural circuits that control behavior and metabolism to better understand how early events in an individual's life influence traits like feeding and overall physiology. Goal-directed behavioral decisions—such as feeding, a primary focus in the Simerly lab—result from the neural integration of signals from the external environment with sensory information—sight, taste, and smell, for instance—that reveals the internal state to the brain. The Simerly lab explores how all of this information is conveyed to key circuit nodes responsible for goal-directed behaviors, and how the complex neural connections develop under the influence of environmental factors such as nutrition.

In particular, the lab studies the hypothalamus, a part of the brain that has a vital role in controlling many bodily functions, which has long been known for its dominant role in feeding regulation. "The neural circuits that control feeding extend from the cerebral cortex to the brainstem, so gaining a brainwide understanding of how these circuits are organized requires a new way of visualizing their architecture and development," Simerly said.

With critical support from **Larry Marnett**, dean of basic sciences, Simerly and Maldonado began working together three years ago to assemble an effective platform for visualizing brain circuitry. At this point, light-sheet microscopes were available, but they were not widely adopted and resolution was somewhat limited.

"José brought a unique blend of expertise in optics, microscopy, and digital technologies to this project, as well as a fanatical pursuit of the enhancement of the signal-to-noise ratio," Simerly said. "Working closely with members of my lab, José assembled and optimized tissue visualization and data capture technology to reveal a variety of interconnected neural systems."

Another development was the emergence of novel tissue-clearing technologies and a new commercially available light-sheet microscope developed by Life Canvas Technologies, a Boston-based company that grew out of an academic lab. Maldonado forged a powerful collaboration with Life Canvas to accelerate the adaptation of their new tools for a whole-brain analysis platform. "This is a great example of a public-private partnership. José's expertise and knowledge of their world was a perfect match," Simerly said.

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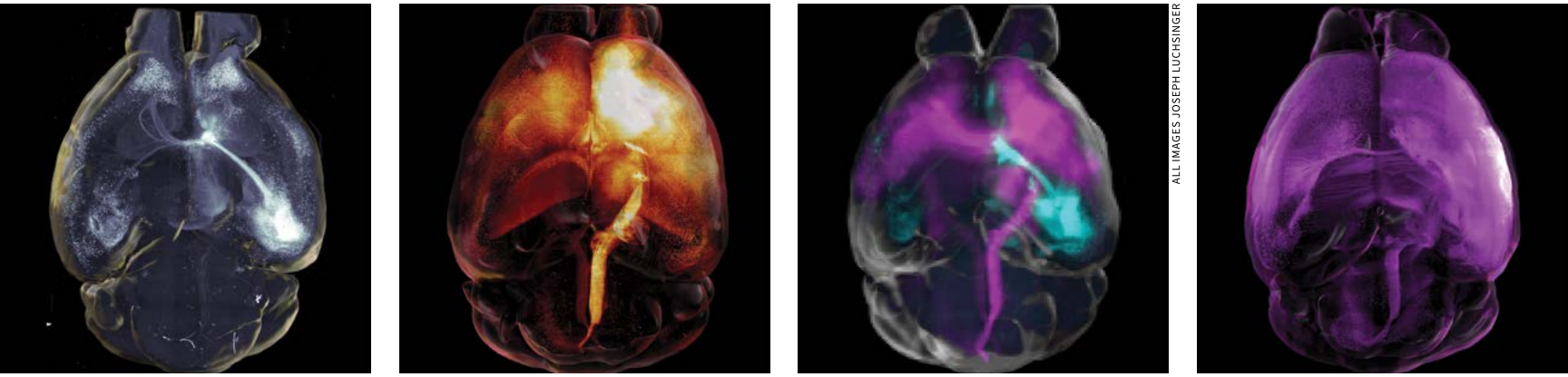

ALL IMAGES JOSEPH LUCHSINGER

Opposite: An artistic interpretation of a two-dimensional brain representation generated by José Maldonado through whole-brain imaging carried out at the Vanderbilt Neurovisualization Lab. The illustration was made by the author of the article, Kendra H. Oliver.

Above: Cleared mouse brains light up at sites of reporter protein expression, illuminating the tracts of neurons that make up distinct circuits. Whole-mouse brain projections are "stitched" together from thousands of images.

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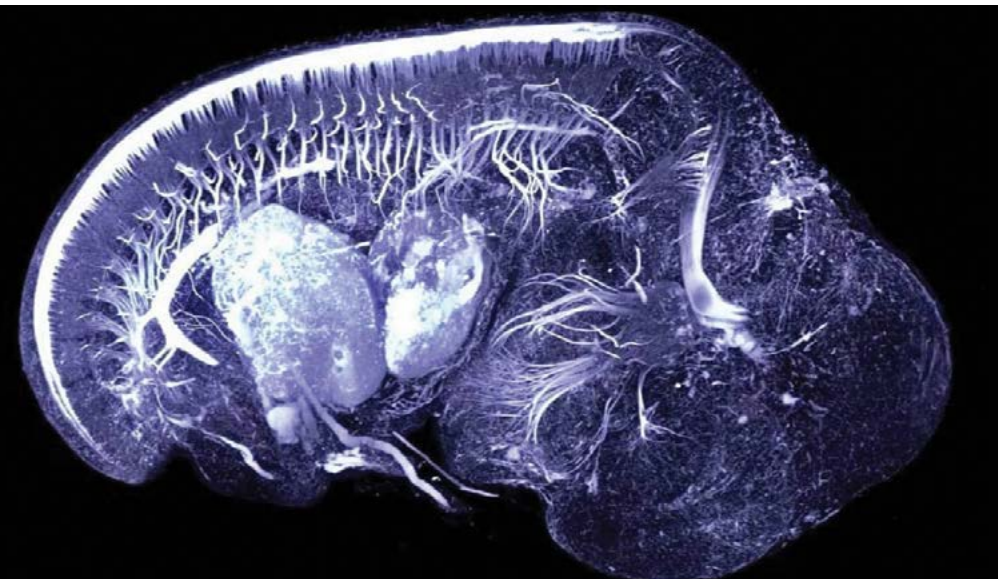
The new light-sheet imaging platform is beginning to bear fruit. In work that was recently published in the journal *Science Translational Medicine*, **Michelle Bedenbaugh**, a postdoctoral fellow in the Simerly lab, and Maldonado showed that the melanocortin-3 receptor is much more widely expressed in hypothalamic circuits than previously thought. MC3R is a receptor that sits on the surface of neurons and has a role in energy homeostasis. The research, conducted in collaboration with **Roger Cone**, director of the Life Science Institute at the University of Michigan, showed that MC3R is expressed differently in males and females and may be an important target for novel drugs to treat both anorexia and obesity.

Although powerful, these complex and costly technologies are challenging for labs to integrate into their research programs in isolation. "I am certainly not the first person to use light-sheet microscopy," Maldonado said, but he did have to overcome a few barriers when he first began working in the field. "I found the use of the light-sheet microscope to be highly artisanal. It required a lot of attention, technical knowledge, and a lot of time to work with the machine to get a good result." He made it his goal to guarantee that this technology was accessible to researchers to use without having to put in all of the preparatory work.



LAURA GEBEN, SERENA SWEET

Researchers in the lab of Richard Simerly are working to expand the reach of the VNL. Serena Sweet of the Simerly lab taught fellow graduate student Laura Geben, of the Rebecca Ihrie lab in the Department of Cell and Developmental Biology, the VNL ropes. As part of Geben's training, they used a tissue-clearing technique called iDISCO+, combined with light-sheet fluorescence microscopy, to visualize a protein that marks the developing nervous system of a mouse embryo.

Thus, the Vanderbilt Neurovisualization Laboratory was born.

Getting the word out

Early supporters of the core were **Danny Winder**, professor of molecular physiology and biophysics, and lab members **Joseph Luchsinger** and **Samuel Centanni**, who worked with Maldonado and other members of the Simerly lab to identify a neuronal circuit in the brain that plays a role in the response to restraint-induced stress.

Their work, published in the journal *Nature Communications*, revealed the location of the circuit and outlined other connections that provide input to and receive information from it. They showed how input from the motor cortex activates the circuit before a restrained animal begins to struggle, and their results also suggest that the circuit plays a role in the affective (emotional) behavior displayed in response to the stress.

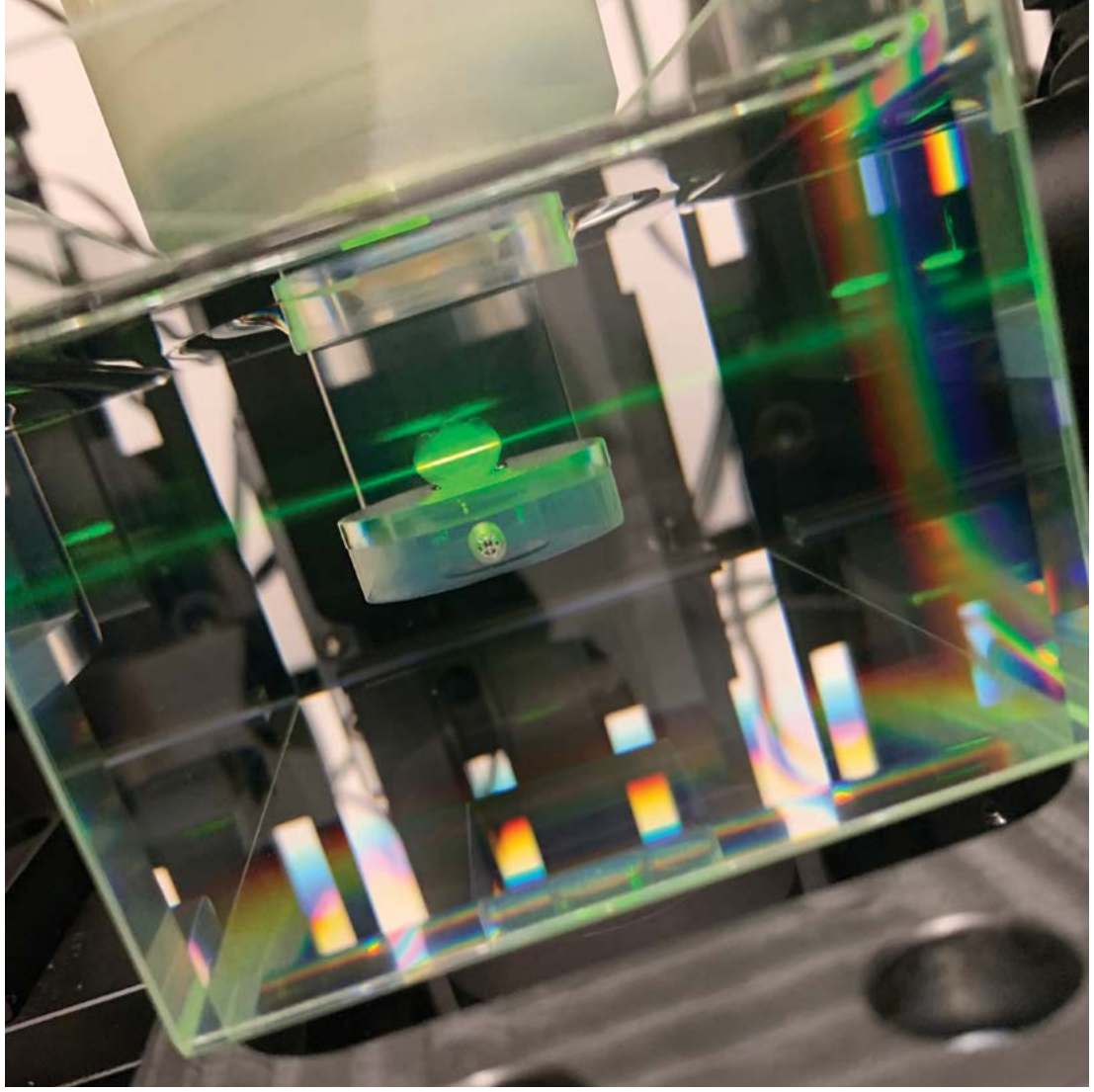
"This paper was the result of a shared interest of the Winder and Simerly labs in how forebrain circuits coordinate key aspects of motivated behavior and provided a perfect test case for the light-sheet imaging approach José developed," explained Simerly. "The results illustrate how taking a brainwide approach to neural circuit architecture uncovers new functional targets and focuses attention on the most important pathways. This capability will be important to a wide variety of Vanderbilt research programs and documents the utility and opportunities created by the VNL," he said, referring to the Vanderbilt Neurovisualization Lab.

Maldonado and the new VNL, often called the NeuroViz core, are hoping to expand their success further within the Vanderbilt research community. Maldonado described his drive: "If I were going to produce a product for the private sector, how would I make this as streamlined and easy to use for a customer as possible? Except that, instead of selling a product, what I am really trying to do is enable people to look beyond the pretty picture and think about quantifying things."

To this end, Maldonado continues to integrate resources and establish partnerships across the academic and private sectors to offer a set of readily accessible analytical tools for researchers. The goal is to make it easy for someone to both generate images and do the associated quantitative analysis. But this has not been a simple task.

Everything has been customized to increase usability. Maldonado scoured GitHub—a cloud-based repository for software development projects—for existing code to use for automatic quantification. "There were a couple of them that were failures," Maldonado explained. Over the last few years, Maldonado has been augmenting the existing system, using the expertise of commercial partners and implementing various tools to get his turnkey quantitative software set up.

"*The Nature Communications* paper demonstrates the power of what we've been able to establish: the ability to image cleared tissue and quantify cell



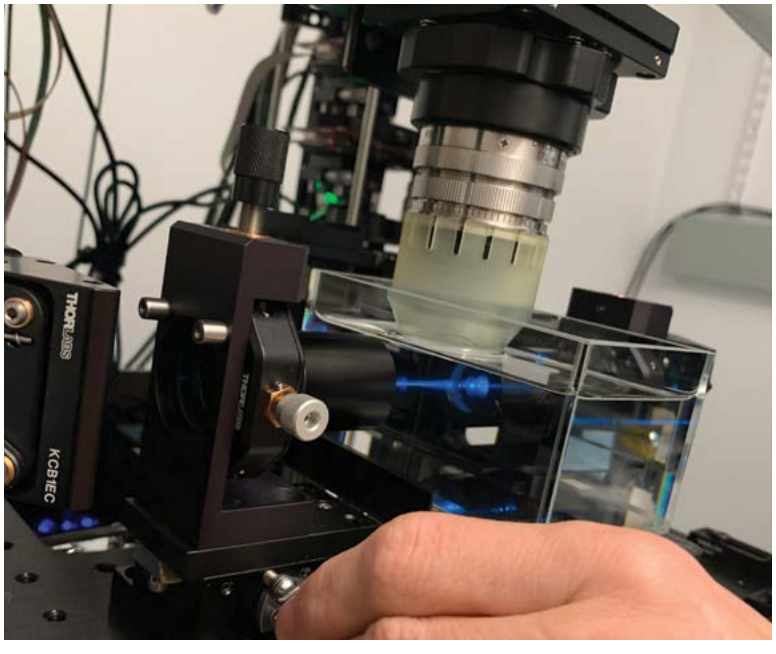
A cleared mouse brain is secured to a sample holder (below) in preparation for imaging. Laser light is formed into a sheet and passed through the sample, which is now immersed in a liquid-filled chamber (left). A specialized lens is carefully calibrated into place for the three-dimensional imaging of the sample (bottom).

numbers based on anatomical brain regions through the application of unbiased computational methods," he said. Even though this sort of quantitation and mapping has been published, it was not previously possible to do that sort of analysis easily or to that scale.

The Vanderbilt Neurovisualization Lab represents a fine-tuning of the application of light-sheet microscopy for neuroscience, and Maldonado now feels that he knows how to make an impact as the core director.

"A lot of the things that I am faced with in academia mirror the kind of things that I helped people do in the private sector," Maldonado said. "Basically, I am trying to make microscopy technology a little bit more accessible."

However, in contrast to being in the private sector, Maldonado now gets to drive every aspect of the work that he does and distribute his expertise across multiple research programs. "When you see a scientist look at one of their images for the first time, that's the payoff," Maldonado said. "When they see the brain this way, the look on people's faces is the most impactful part for me. So, right now, I want to get this in front of as many eyes as possible. But more importantly, I want to get the point across that this is something that is accessible to every researcher's lab." ■



Molecular maps lead the way to

By Bill Snyder

Researchers at Vanderbilt University and Vanderbilt University Medical Center are creating high-resolution, single-cell "atlases" of human tissues that promise to lead to more precise ways to prevent and treat everything from diabetes-related blindness to colorectal cancer.

Human cell atlases are complete and multi-dimensional catalogs that encompass information on cell location, function, gene expression, and more. But they're not mere lists of biological components. They're more akin to the interactive maps that can call up an address with a tap in a cellphone application.

Thanks to cutting-edge tissue-mapping technologies, researchers can generate images of specific cells, proteins, lipid molecules, and genetic material that shimmer across tissues and organs like constellations of stars in the night sky.

While cellular mapping projects are underway around the world, Vanderbilt scientists are uniquely positioned to make their mark in the field. They have pioneered technologies such as imaging mass spectrometry and multiplex immunofluorescence that can bring individual proteins and other biomolecules into sharp focus.

VU and VUMC also have a long tradition of collaboration and cross-fertilization between the basic and clinical sciences. Biochemists and cell biologists routinely team up with specialists in cancer, digestive diseases, diabetes, lung disease, and blindness. Out of that synergy have come some astonishing discoveries.

Major mapping projects currently underway at Vanderbilt include:

- Creating atlases of the kidney, pancreas, and eye
- Tracking lung development and revealing why COVID-19 is much worse in people with chronic lung disease
- Searching for clues to the chronic intestinal inflammatory disorder known as Crohn's disease
- Identifying the key first steps to colorectal cancer

The Human Biomolecular Atlas Program

One of the key technologies that enables human cell mapping at Vanderbilt is imaging mass spectrometry.

Developed in the late 1990s by **Richard Caprioli**, the Stanford Moore Professor of Biochemistry and director of the Mass Spectrometry Research Center, IMS is essentially a "molecular microscope" that can visualize the distribution, spatial rearrangement, and alterations in expression levels of proteins, lipids, and other biomolecules in cells and tissues.

In 2015, Caprioli and his colleagues achieved the first "image fusion" of mass spectrometry and microscopy—a technological tour de force that revealed the molecular makeup of tissues in high resolution.

Three years later they received a four-year, $5.5-million grant from the Common Fund of the National Institutes of Health to establish the Vanderbilt Biomolecular Multimodal Imaging Center, or BIOMIC—one of 18 tissue-mapping centers in the NIH Human Biomolecular Atlas Program consortium.

> "The ability to generate and integrate imaging data across broad spatial and molecular scales is what makes BIOMIC so unique."
>
> — **Jeffrey Spraggins**

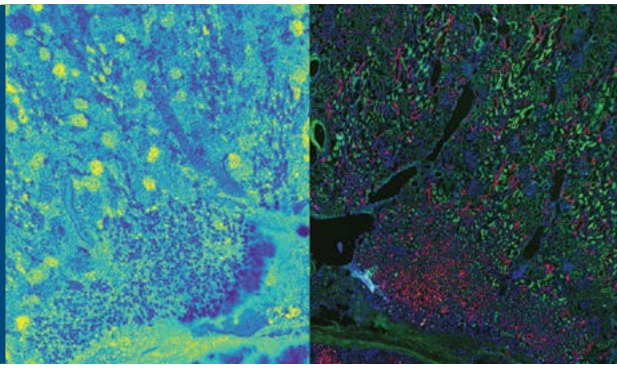


IMAGE COURTESY OF JEFFREY SPRAGGINS

Jeffrey Spraggins, research assistant professor of biochemistry and chemistry, and Caprioli are the principal investigators of BIOMIC, which initially was charged with creating an atlas of the human kidney. Its mission has since been expanded with an additional $4.4 million in HuBMAP consortium funding to include atlases of the pancreas and eye.

"It's early days, but I'm quite excited about it," said **Ken Lau**, an associate professor of cell and developmental biology who is a member of the BIOMIC team and two other Vanderbilt mapping projects.

By applying computational and systems biology tools to single-cell analysis, Lau investigates interacting networks of cells, metabolites, and gene expression patterns. "We now can look at human tissues with a different lens, a finer resolution," he said.

better medicine

JOHN RUSSELL

Opposite: Side-by-side images of human kidney tissue, snapped using imaging mass spectrometry, or IMS (left), and multiplexed immunofluorescence, or MxIF (right). IMS allows researchers to discover the localization of hundreds to thousands of molecules in situ and MxIF provides a way to label specific cell types within tissue microenvironments. By connecting these multimodal data, researchers can uncover the molecular characteristics and cellular architecture of human tissues.

Above: Molecular atlas projects incorporate work from the university and the medical center sides. From left, Ken Lau, Robert Coffey, and Martha Shrubsole.

Another team member, **Bennett Landman**, develops applications for integrating image processing, artificial intelligence, and informatics to combine data across scales from microscopic tissue studies with RNA and protein expression data to whole-body imaging.

He develops three-dimensional averages of anatomical images from hundreds of clinical computerized tomography and magnetic resonance scans that the entire HuBMAP consortium is using as a common framework to help with atlas construction.

Landman is a professor of electrical and computer engineering and started the Center for Computational Imaging in the Vanderbilt University Institute of Imaging Science. He now chairs the Department of Electrical and Computer Engineering.

"The ability to generate and integrate imaging data across broad spatial and molecular scales is what makes BIOMIC so unique," Spraggins said.

Leading efforts to create atlases of the pancreas and eye, respectively, are **Dr. Alvin Powers**, the Joe C. Davis Professor of Medical Science and director of the Vanderbilt Diabetes Center, and **Kevin Schey**, professor of biochemistry and chemistry.

Caprioli noted that a multidisciplinary approach is crucial for meeting such a complex challenge. "It's an absolutely great melding together of clinicians and basic scientists that is done so well at Vanderbilt," he said.

Other HuBMAP centers are mapping the heart, bone, spleen, lymph nodes, intestines, urinary tract, and the female reproductive system. The hope is that atlases of normal, healthy tissues will lead the way to understanding how abnormalities—diseases—occur.

One such disease is diabetes, the leading cause of end-stage renal disease and a leading cause of blindness. High blood glucose levels, the hallmark of type 1 diabetes, can damage the glomeruli, the kidney's filtration units, as well as the retina in the back of the eye.

HuBMAP's rationale is that to decipher the molecular basis for disease, researchers first must know what each cell type normally does in its tissue environment. Only then can we fully appreciate changes that, for example, block insulin production by pancreatic beta cells and that consequently damage the eye and kidney.

Ultimately this knowledge may lead to treatments precisely tailored to individual patients—the ultimate "precision medicine," Spraggins said.

Pulmonary pathways

Single-cell RNA-sequencing, or scRNA-seq, is one of the most important tools for building human cell atlases. By measuring RNA, a marker of the expression of specific genes, the technique can distinguish between different populations of cells.

Using scRNA-seq, **Dr. Jennifer Sucre** and her colleagues earlier this year reported the creation of a single-cell atlas that tracked the lineages of major cell types during the later stages of lung development.

Dr. Jonathan Kropski and colleagues who participate in the international Human Cell Atlas Lung Biological Network are using scRNA-seq to study the molecular mechanisms and gene regulatory architecture underlying lung diseases like idiopathic pulmonary fibrosis.

Pulmonary fibrosis is a condition in which the lungs become progressively scarred over time. Idiopathic pulmonary fibrosis, a subset of the disease with no known cause, kills up to 40,000 Americans each year.

Sucre, an assistant professor of pediatrics, and Kropski, an assistant professor of medicine, both have secondary appointments in the Department of Cell and Developmental Biology.

Last year, Sucre and Kropski teamed up with **Dr. Bryce Schuler**, a resident physician in pediatrics and genetics at VUMC, to determine why SARS-CoV-2, the virus that causes COVID-19, causes such severe illness in older patients and those with chronic lung diseases.

Using the scRNA-seq technology, they discovered that older patients have increased expression of a cellular enzyme called TMPRSS2. The enzyme enables SARS-CoV-2 to enter certain lung cells, where it hijacks their genetic machinery to copy itself.

In patients with chronic lung diseases, the researchers also found an increased expression of inflammatory and immune-response genes, which may increase the risk for severe reactions to COVID-19.

Although vaccination against SARS-CoV-2 has proven to lessen the severity of or even prevent COVID-19 illness in most people, it may not protect patients whose immune systems are suppressed, such as those undergoing cancer treatment.

In this vulnerable population, targeting TMPRSS2 and turning down the inflammatory response potentially could help avoid severe illness and adverse outcomes from COVID-19, the researchers concluded.

Fire in the gut

Inflammation also plays a prominent role in Crohn's disease, a debilitating chronic disorder of the upper and lower intestines. The challenge to improving treatment is that the disease is highly variable and presents with a wide range of phenotypes and clinical characteristics, including patient history, symptoms, and response to medications.

Thus the need for the Gut Cell Atlas: an initiative of the New York City-based Leona M. and Harry B. Helmsley Charitable Trust.

VUMC is among several institutions participating in the Gut Cell Atlas, which is part of a larger international effort called the Human Cell Atlas. In turn, the Human Cell Atlas is collaborating with the NIH HuBMAP consortium to map all of the cells in the human body.

The Vanderbilt project, led by **Dr. Keith Wilson**, the Thomas F. Frist Sr. Professor of Medicine, and **Dr. Lori Coburn**, assistant professor of medicine, is funded for more than $3.6 million and applies scRNA-seq and bioinformatics analyses to cells isolated from biopsies and surgical resections obtained from patients seen in the Vanderbilt Inflammatory Bowel Disease Center.

By comparing samples from patients at different stages of disease, as well as from healthy controls, the researchers hope to identify key cell types and patterns of gene and protein expression that will enable them to correlate inflammation at the cellular level with clinical presentations of the disease.

"Each patient is different—that's what makes it difficult," Coburn said. "Determining what's going on at the cellular level will aid the search for new therapies and help physicians choose treatments that are most likely to work in their patients."

Gut Cell Atlas team members include Ken Lau and Bennett Landman, as well as **Gregor Neuert**, assistant professor of molecular physiology and biophysics and pharmacology, and **Qi Liu**, associate professor of biostatistics and biomedical informatics.

Liu and her colleagues have developed techniques for analyzing the scRNA-seq data, while Neuert is an expert in RNA-FISH, a method for detecting and localizing RNA in cells. When combined with multiplex immunofluorescence, which allows up to 40 proteins to be examined on a single tissue section, this technology can quantify RNA and protein expression at the single-cell level.

JOE HOWELL

Keith Wilson, far right, is leading a research team funded by a major grant from the Leona and Harry Helmsley Charitable Trust to find new ways to treat Crohn's disease. His colleagues are, from left, Ken Lau, Qi Liu, Gregor Neuert, Lori Coburn, and Bennett Landman.

Malignant neighborhood

One of Vanderbilt's most ambitious mapping projects, funded by a five-year, $11-million Cancer Moonshot Grant, is to build a single-cell-resolution atlas that tracks the routes that polyps in the colon take to progress to colorectal cancer, the second leading cause of cancer death in the United States.

Leading the Colon Molecular Atlas Project are **Dr. Robert Coffey**, Ingram Professor of Cancer Research and director of the Epithelial Biology Center at VUMC; **Martha Shrubsole**, research professor of medicine in the Division of Epidemiology; and Ken Lau. Qi Liu is also contributing to this project.

Vanderbilt, one of five institutions to be designated as a Pre-Cancer Atlas Research Center (and grant recipient) by the National Cancer Institute in 2018, has been a powerhouse of colorectal cancer research for decades. In 2002 it gained NCI recognition as a Gastrointestinal Specialized Program of Research Excellence.

Coffey and his colleagues in the Epithelial Biology Center have pioneered single-cell technologies such as multiplex immunofluorescence.

Complementing the protein analysis, Lau's lab uses a microfluidic approach—handling liquids in channels that are less than a sixteenth of an inch wide—to isolate thousands of cells encapsulated in an oil-liquid emulsion and analyze their gene expression patterns.

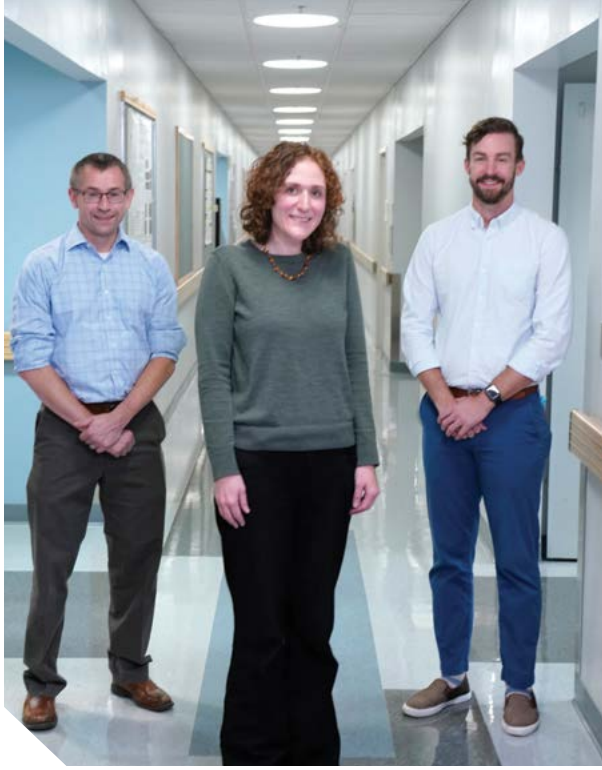
"We know that within a tumor there is a highly heterogeneous ecosystem," Lau said. "You have tumor cells, you have immune cells, you have microbes—all of them coexisting." Single-cell technologies are revealing how "behavior of the ecosystem" may drive the development of cancer, he said.

Most colorectal cancers arise from adenomas, a type of polyp or small clump of cells that forms in the epithelium, the lining of the colon.

Neoplastic adenomas, those that progress to cancer, are characterized by loss of the tumor suppressor gene *APC*, which normally keeps a tight rein on the Wnt signaling pathway that regulates cell growth and proliferation in the epithelium. Without the *APC* "brake," Wnt signaling accelerates in an out-of-control manner.

About a third of colorectal cancers arise from another type of polyp, called a sessile serrated lesion or SSL, which is characterized by its flattened (sessile) appearance. Surprisingly, these lesions, at least in their early stages, don't exhibit a loss of *APC* or overactivation of the Wnt pathway.

Rather, the Vanderbilt researchers have found SSLs in a setting of metaplasia, a precancerous transformation of the epithelium that is suggestive of inflammation and potentially a microbial insult. In much the same way, infection by the bacterium *Helicobacter pylori* triggers metaplastic changes that lead to stomach cancer.



From left, Jonathan Kropski, Jennifer Sucre, and Bryce Schuler.

DONN JONES

"It's a very new perspective on the origin of a not-uncommon type of colon cancer," Coffey said. "To me that is fascinating and offers perhaps new diagnostic and therapeutic opportunities."

"We will have a couple more years of work to go," Shrubsole added, "but we're very hopeful that we'll have some potential targets that can then move onto the next phase of testing."

Over at the Gut Cell Atlas, researchers are collecting as many tissue samples from patients with Crohn's disease as they can. The deeper they get into their investigations, the more questions about the biology of the disease arise.

"This is a really hard project," Wilson said. Given the disruptions caused by the COVID-19 pandemic, "it's pretty miraculous that we are where we are." ■

Other contributors to Vanderbilt's single-cell atlas projects

Biomolecular Multimodal Imaging Center

- **Dr. Mark de Caestecker**, professor of medicine in the Division of Nephrology and professor of cell and developmental biology
- **Dr. Agnes Fogo**, the John L. Shapiro Professor of Pathology and director of the Division of Renal Pathology in the Department of Pathology, Microbiology and Immunology
- **Dr. Raymond Harris Jr.**, the Ann and Roscoe R. Robinson Professor of Nephrology in the Department of Medicine and professor of molecular physiology and biophysics
- From the Mass Spectrometry Research Center: **Danielle Gutierrez**, research assistant professor of biochemistry, **Heath Patterson**, research instructor in biochemistry, **Elizabeth Neumann** and **Angela Kruse**, postdoctoral fellows, and **David Anderson**, staff scientist
- From outside of Vanderbilt: former postdoctoral fellow **Raf Van de Plas**, now at Delft University of Technology in the Netherlands (Kidney Atlas), and **Christine Curcio**, at the University of Alabama at Birmingham (Eye Atlas)

Gut Cell Atlas and Colon MAP

- **Dr. Kay Washington**, professor of pathology, microbiology and immunology
- **Yu Shyr**, the Harold L. Moses Professor of Cancer Research and chair of the Department of Biostatistics
- **Dr. Timothy Geiger**, associate professor of surgery (Colon MAP)
- **Dr. Reid Ness**, associate professor of medicine (Colon MAP)
- From outside of Vanderbilt: **Dr. Cindy Sears**, Johns Hopkins University School of Medicine (Colon MAP)

JOHN RUSSELL

Chancellor sees Vanderbilt's Basic Sciences as 'crown jewel' with great potential

By Lorena Infante Lara

Transformational research does not happen in a vacuum. It requires more than just the talent and grit that engenders innovation, more than just long hours staring at code or through a microscope. It requires institutional support, and the Vanderbilt University School of Medicine Basic Sciences has that in abundance.

Although Basic Sciences is barely five years old—founded as part of the legal separation of Vanderbilt University and the Vanderbilt University Medical Center—its departments of Biochemistry, Cell and Developmental Biology, Molecular Physiology and Biophysics, and Pharmacology have existed within the university for nearly a hundred years.

Vanderbilt Chancellor **Daniel Diermeier** recently discussed the role of Basic Sciences with *Vestigo*.

The university's ninth chancellor, Diermeier is an internationally renowned political scientist and management scholar. He has published four books and more than 100 research articles, mostly in the fields of political science, economics, and management, but also in other areas ranging from linguistics, sociology, and psychology to computer science, operations research, and applied mathematics. From 2016 to 2020, Diermeier served as the provost of the University of Chicago, and he has held leadership and faculty positions at the Stanford Graduate School of Business and the Kellogg School of Management at Northwestern University.

> "We're very proud of the work that's going on in Basic Sciences—one of the crown jewels of Vanderbilt."
>
> – Daniel Deirmeier, chancellor

Most basic sciences departments across the country are part of their associated schools of medicine and report to the schools' deans, but the dean and the school often sit under the larger umbrella of academic medical centers. What can you tell me about the organizational structure we have at Vanderbilt?

We have a unique structure in which Basic Sciences collaborates with the clinical faculty in the medical center but actually reports up to the university provost. In this innovative reporting structure, the dean of Basic Sciences, **Larry Marnett**, connects with the dean of the School of Medicine, **Jeff Balser**—as well as with Vanderbilt's new provost, **Cybele Raver**.

This structure has been enormously successful for us. Biomedical research is moving at an enormous speed. The more we can connect with other parts of the university, foster relationships, and take full advantage of the work done in other parts of the university, the better. It's going to be essential for our forward progress.

What makes Basic Sciences at Vanderbilt successful?

One of the things that has struck me the most about Vanderbilt since I arrived last year is just how collaborative this place is—how much it thinks about itself as one community and how much people look out for each other. The culture of collaboration is evident in Basic Sciences as it works with partners from across the university, whether within its own departments or with other areas across campus, such as the College of Arts and Science, the School of Engineering, or even clinicians at VUMC.

Basic Sciences is particularly important because of the fundamental, cross-disciplinary nature of its work, and its departments are among our most distinguished on campus. We're very proud of that. They add tremendously to the reputation and eminence of the university.

What role do you see for the biomedical sciences on campus and in our society?

The work these researchers are engaged in has a tremendous impact on the world in a variety of positive and tangible ways. We see this, of course, in the context of the COVID-19 pandemic. So much of the foundational work that is leading to therapeutics happens in basic sciences departments. Some of the fundamental work on vaccines dates all the way back to **Dr. Ernest Goodpasture**, a Vanderbilt faculty member who revolutionized virology by devising a sterile way to grow viruses in fertilized chicken eggs.

The basic sciences are often foundational to finding cures and treatments, and so, broadly speaking, the biomedical sciences are one of the most exciting areas of research—and have tremendous potential to make a societal impact. They're also an incredibly important partner for the work that's going on at the medical center in the clinical departments, so having a strong presence here at Vanderbilt is essential.

What can you and the university do to help raise the profile of Basic Sciences internally and externally?

There are a couple of dimensions to this. The first and most important one for us is the work itself. We need to make sure that this is a place that is a destination for the very best faculty and for the very best graduate students. Our Destination Vanderbilt initiative is an important pillar of that strategy because it allows us—in an environment where many other universities have scaled back their hiring, including in the basic sciences—to actively and aggressively recruit the brightest faculty we can find.

The second dimension is the need to further establish our global reputation. The international awareness of the great work that's happening at Vanderbilt could be stronger. We don't want that to be a limiting factor for doctoral students to come here. Vanderbilt might be a perfect fit for some of these researchers, but they may not even have us on their radar. We need to work on Vanderbilt's story not just in the United States, but also in Europe, Asia, Latin America, Africa, Australia—everywhere.

Having Provost Raver onboard will be a great opportunity for us. She has deep expertise working with the sciences, as well as in designing global strategies for top universities. She brings a valuable perspective that will be very helpful.

Where do you see Vanderbilt's Basic Sciences going from here?

We have the opportunity and the potential to be the very best in the world. That's a strong statement, but I don't think it's an overstatement. We're very proud of the work that's going on in Basic Sciences—it's one of the crown jewels of Vanderbilt. I'm very optimistic about its direction and couldn't be more pleased with the work and the breakthroughs that are happening here. ■

From left, Emily Hodges, Carlos F. Lopez, Jonathan Irish, Vito Quaranta, Ken Lau, and Gregor Neuert.

The next frontier:

Systems biology, big data, and advanced analytics

By Aaron Conley

Traditionally, biological research was done in a wet laboratory and involved a series of individual experiments that each revealed a fragment of a larger picture. However, scientists are now at a crossroad. Technology has advanced to allow the collection of data of previously unimaginable size and complexity. Researchers can then harness new computational tools to analyze them, addressing complicated questions about unified biological systems. This burgeoning field at the intersection of big data, advanced analytics, physics, chemistry, and biology, is called systems biology.

Systems biology research at Vanderbilt University benefits from world-class facilities and groups, including the Quantitative Systems Biology Center, the Vanderbilt Institute of Chemical Biology, various departments from the Vanderbilt University School of Medicine Basic Sciences, state-of-the-art imaging technologies, and a strong multidisciplinary and collaborative environment.

The QSBC, housed within the School of Medicine Basic Sciences, is a point of convergence for systems biology at Vanderbilt. "The QSBC's objective," said **Dr. Vito Quaranta**, director of the QSBC, "is to amplify systems biology into a sustainable program of excellence in basic and translational science." The center designs mathematically rigorous yet flexible advanced analytics through partnerships with the Department of Biomedical Informatics and Vanderbilt's Data Science Institute. Together, they create data analysis tools that facilitate novel and impactful research across fields. This article describes recent work by QSCB members.

Single-cell technologies

Jonathan Irish, associate professor of cell and developmental biology, uses single-cell mass cytometry and phospho-specific flow cytometry tools—techniques that allow researchers to label, visualize, and measure molecules of interest on cells—to search through billions of human cells to precisely find rare, abnormal cells or to identify beneficial immune cells. Irish's current work includes collaborative projects on glioblastoma, lung cancer, viral infections—including with rhinovirus and SARS-CoV-2—and drug discovery. This research could help scientists program immune cells to become therapeutic agents or target malignant signaling events to specifically kill cancer cells.

The Irish lab has created several computational tools and machine learning algorithms. Irish previously developed cloud-based analysis software for single-cell cytometry data, co-founding and becoming the chief scientific officer of Cytobank until it was acquired by Beckman Coulter Life Sciences in 2019. Most recently, the Irish lab created two algorithms—RAPID and T-REX—that identified a new type of aggressive brain tumor cell and pinpointed the virus-specific T cells responding to SARS-CoV-2 RNA vaccines, respectively.

Ken Lau, associate professor of cell and developmental biology, studies the cell-microbiome ecosystem in inflammatory bowel disease and the origins of colon cancer stem cells. He uses big data modeling with state-of-the-art technologies to profile tissues at single-cell resolution with thousands of data points and dimensions. Lau has developed unique software and protocols for single-cell and spatial transcriptomics. Spatial transcriptomics allow scientists to visualize and conduct quantitative analysis on the collection of expressed mRNA molecules in a cell, with spatial resolution in individual tissue sections. Additionally, Lau has developed software and protocols for the removal of ambient RNAs in single-cell data (page 4) and contributes to the Human Biomolecular Atlas Program profiled on page 14.

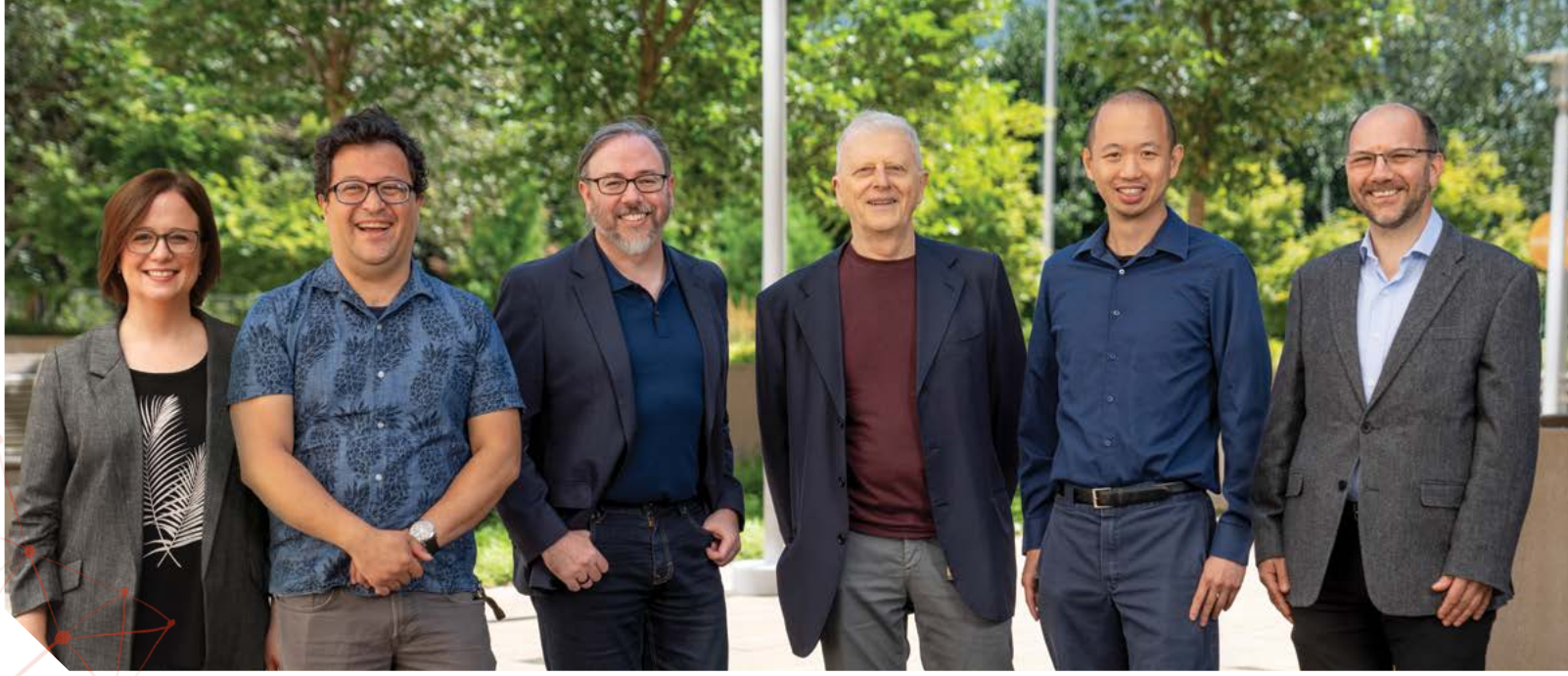
Mechanistic models

The lab of **Carlos F. Lopez**, associate professor of biochemistry, employs biochemical concepts, physicochemical methods, computational or data science approaches, and applied mathematics to explain and predict cell behaviors in health and disease, focusing on basic cellular processes and their mechanisms of dysregulation in cancer. The lab also develops new tools for systems biology research.

"Just like when you're building a house," he said, "you are restricted by the available tools." The same is true in biology—new or improved theories and tools can expand the possibilities of research.

One such tool recently developed by the Lopez lab and collaborators is Thunor, an open-source software that organizes, analyzes, and visualizes cell responses to drug treatment from large-scale screens. The ability to visualize and analyze cell proliferation—the balance between cell division and cell death—which increases in cancer, allows researchers to pinpoint drugs with the best reduction in cancer cell proliferation.

Gregor Neuert, assistant professor of molecular physiology and biophysics, studies



JOHN RUSSELL

"The QSBC's objective is to amplify systems biology into a sustainable program of excellence in basic and translational science."

— **Dr. Vito Quaranta**

how an individual cell perceives and responds to its environment. His work combines a variety of methods, including quantitative single-cell and single-molecule experiments, evaluations of cell behavior in vitro, genetics, and computational biology to explore the fundamental mechanisms that enable cells to perceive and respond to environmental changes.

Pioneering research led by Neuert and **Alexander Thiemicke**, a recent Ph.D. graduate and a former Neuert lab student, shows that cells respond differently to acute stress than to gradual stress (page 4). The findings established an entirely new way to look at cell-to-cell communication and may fundamentally change how biomedical researchers study cells.

Epigenetics

Emily Hodges, assistant professor of biochemistry, studies the epigenetic programming of human genomes. Epigenetic markers on the DNA can change how genes are expressed without changing the sequence of the DNA itself. As such, the Hodges lab focuses on two main things: 1) how these epigenetic or chemical modifications—such as methylation—are established for the functional specialization of cells during development and 2) how variation in DNA methylation is connected to disease susceptibility.

Hodges recently developed a cutting-edge approach, called ATAC-Me, to profile multiple epigenetic features simultaneously from a single DNA source. Her recent work using this new method challenges the textbook role of DNA methylation in gene regulation and may fundamentally change how we view its function.

In addition, Hodges uses BioVU, Vanderbilt's repository of patient blood samples that are connected to anonymized electronic medical records, to investigate specific functional relationships between genetic variation, the "epigenome," and disease risk.

Lung cancer

Quaranta is a cancer systems biologist who focuses on the role of transcription factors—proteins that help regulate gene expression—in tumor heterogeneity and drug resistance. His work is part of the National Cancer Institute's Cancer Systems Biology Consortium at Vanderbilt. He has developed systems-level modeling tools for studying small cell lung cancer, mathematical models to predict tumor aggressiveness, and single-cell techniques to quantify the rate of cell proliferation in response to drugs.

Drug combinations

In collaboration, Lopez and Quaranta have built a unique algorithm called MuSyC, named in homage to Vanderbilt's Music City home, to simplify the analysis that determines how efficacious and potent certain drug combinations are against cancers.

Christian Meyer and **David Wooten**, two talented graduate students, imagined the MuSyC project and, in an initial publication in *Cell Systems*, passionately explained that MuSyC has the "potential to transform the enterprise of drug-combination screens." MuSyC acts by identifying combinations of drugs that can be prescribed to patients at lower doses, with improved efficacy, or both. Further, in their most recent publication in *Nature Communications*, Lopez and Quaranta provide additional metrics for "a consistent, unbiased interpretation of drug synergy" to apply the results of synergy studies to therapeutics faster.

The software, tools, and expertise at Vanderbilt are accessible to researchers all over the world and enable scientists to rigorously sift through huge, complicated datasets to help reduce bias and drive discoveries. ■

From our labs to your dinner table

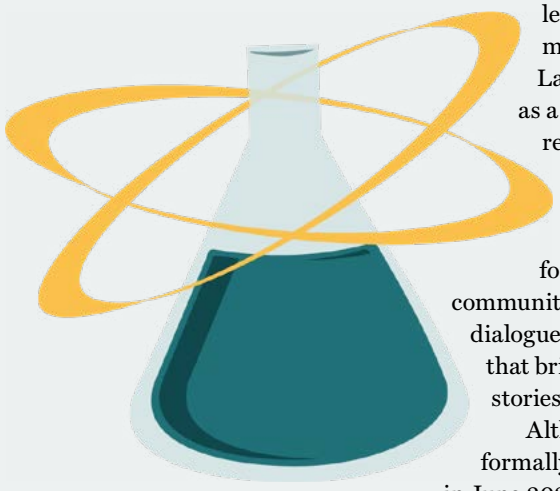
A monthly event series connecting fundamental science to everyday life

By Aaron Conley

How does fundamental biomedical discovery and its applications connect with your day-to-day life? How does research impact and inform society? Through a new monthly event series called Lab-to-Table Conversations, the Vanderbilt University School of Medicine Basic Sciences looks to explore these questions.

Basic science discoveries are the key building blocks for advancements in technology, human health, and our economy, but many people do not understand what curiosity-driven science is—or its importance. As one stark example, the National Institutes of Health's Human Genome Project, which largely funded basic research, "has resulted in nearly $1 trillion of economic growth—a 178-fold return on investment," according to the NIH. The HGP alone resulted in entire new industries and types of personalized medicine and targeted therapies that have transformed patient care and outcomes since its completion in 2003.

In 2020 the apparent disconnect between basic research and the community led the Basic Sciences communications team to create Lab-to-Table Conversations as a bridge between our research labs and our community. The events provide educational outreach and engagement for our local and national communities through captivating dialogue about basic research that brings unique personalities, stories and expertise together.



The Lab-to-Table logo was designed by an intern on the Basic Sciences communications team, Stephanie Castillo. Castillo is currently completing a Ph.D. in science communication at Vanderbilt.

Although the event series was formally named "Lab-to-Table" in June 2021, the first event of the series took place the previous February. The inaugural event, "Inclusion and Equity in Biomedical Research," was held in recognition of Black History Month and featured three faculty members and a university administrator who discussed their experiences in their careers as Black members of academe, historical impacts of prominent Black scientists, and key issues to tackle in the future.

Lab-to-Table Conversations consist of interviews and discussions between Vanderbilt researchers and well-known external experts who specialize in a relevant scientific area, bringing together fresh perspectives. The chosen topics represent areas of intersection between scientific research and current societal concerns or interests.

Events thus far have included discussions of addiction, sobriety, and art during the pandemic with **Will Welch**, the global editorial director of the magazine *GQ*; a highlight of memory and how it works with **Lisa Genova**, a neuroscientist and author of the *New York Times* bestseller *Remember: The Science of Memory and the Art of Forgetting*; a discussion with Vanderbilt University and Vanderbilt University Medical Center cancer researchers about the latest research on colorectal cancer and what it means for patients; and more.

Organic dialogue

The format of our Lab-to-Table Conversations allows for wide-ranging conversations that take off from an initial question and often veer into unexpected territory. The discussion with Welch, "Addiction, Sobriety and Art in the Time of COVID-19," was led by the Vanderbilt Center for Addiction Research Director **Danny Winder** and VCAR member **Erin Calipari** and covered topics ranging from Welch's editorial direction of *GQ* to changing stereotypical perceptions of masculinity, rapper DMX to actor Brad Pitt, addiction stigma to biomedical research, and Ernest Hemingway to jazz.

Welch shared how he was particularly touched by a tweet that was shared with him about DMX's passing.

"It gives me goosebumps to read that," Welch said. "A sentiment that was coughed up by the Internet, shared over 28,000 times because DMX on some level succumbed to a lifelong substance

abuse struggle. And I thought, 'Wow. That is pretty substantial discourse to be encountering ambiently on Twitter ... because a celebrity passed away.'"

"It also goes to show that people are ready to have this conversation," Calipari followed, "and thinking about what addiction is and who it affects and how to help them, rather than sweeping it under the rug as has been done in the past. As it impacts celebrities and people we love and know, people feel: How do we fix this?" Calipari also is an assistant professor of pharmacology.

Larry Marnett, dean of basic sciences, also was a part of the conversation with Welch and emphasized the role of basic science research in finding solutions to this pressing societal issue: "The incredible advancement of neuroscience research technologies provides hope that basic science can make fundamental discoveries in the brain that will provide new strategies for treating addiction to change the arc of this disease."

In "How the Brain Remembers," Professor of Pharmacology **Lisa Monteggia**, also Barlow Family Director of the Vanderbilt Brain Institute, spoke with Genova about her newest book, *Remember*. The discussion covered how memories are made and how we retrieve them; if forgotten memories are erased forever; why some memories are built to exist for only a few seconds while others can last a lifetime; the distinction between normal forgetting and forgetting due to Alzheimer's disease; and how to create better expectations for, and relationships with, your memory.

These first events garnered substantial interest both within and outside the Vanderbilt community, leading to their rebranding and expansion as the Lab-to-Table series.

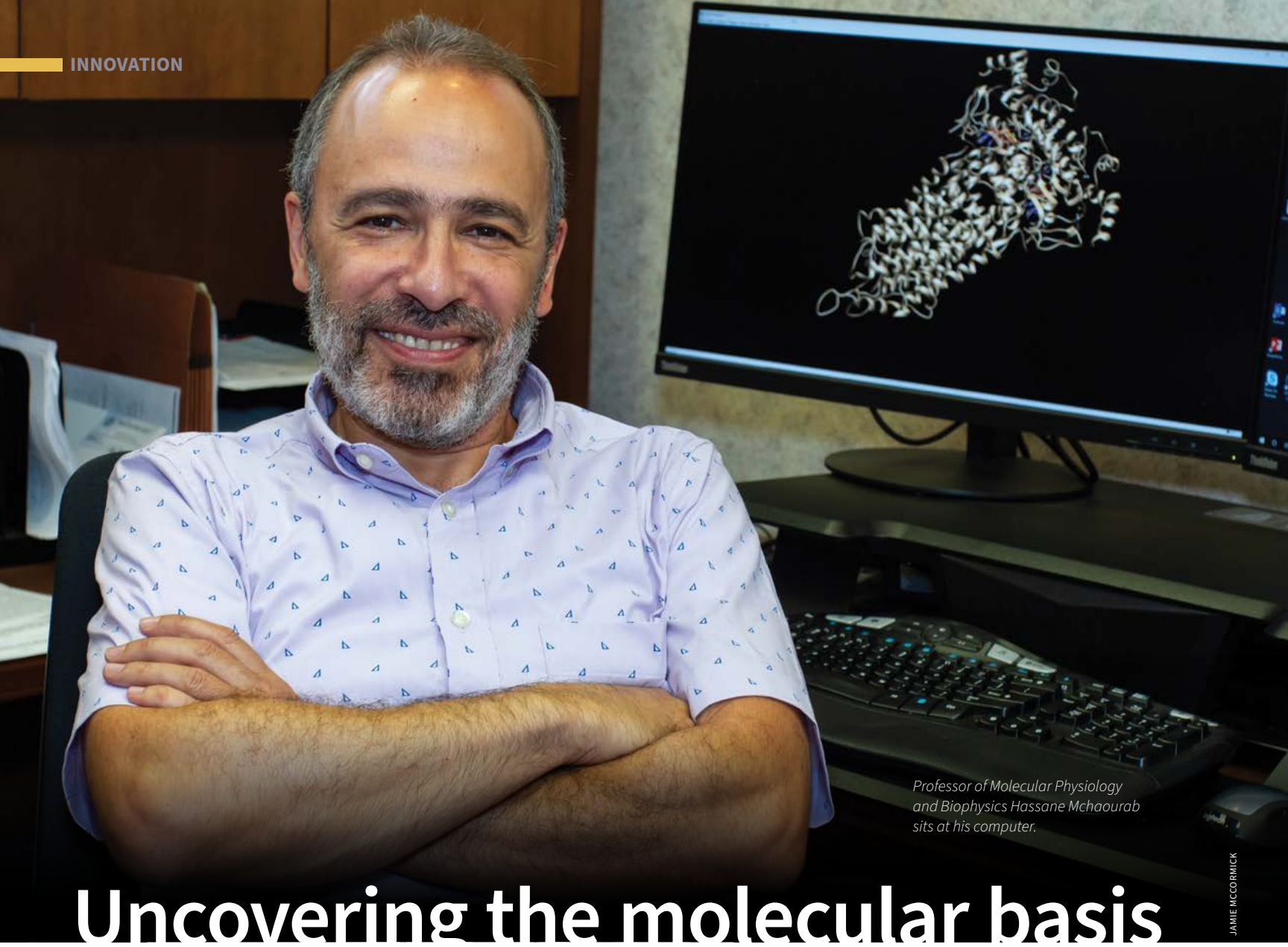
The first event of the newly branded series occurred on June 17: "Origins of Life: A Conversation Between a Biologist, a Theologian, an Astronomer, and a Philosopher." Faculty with diverse expertise discussed questions such as: is the definition of life just based on chemistry or biology, or do nonmechanistic considerations such as purpose play into it? Do science and religion conflict in this space? How common is intelligent life in the universe? How do we think about synthetic or virtual life?

What's in store for future Lab-to-Table Conversations? Our August event was "Watts, Metabolism, Data Analytics: Science's Impact on Cycling Over 25 Years," with former Tour de France competitors **George Hincapie** and **Bobby Julich** and EF Education-NIPPO Pro Cycling's head of medicine **Dr. Kevin Sprouse**; future events include a discussion on medical marijuana with a panel that will include Dean Marnett, and a chat between VCAR and country music star **Jason Isbell** about addiction and sobriety.

Through these events, we hope you'll learn something you can share at your own dinner table. What's your next table topic? ■

You can sign up to receive alerts about upcoming events and view all of our past conversations in the series on the Lab-to-Table website: https://vanderbi.lt/L2TVU. We are always looking for new event ideas! If you have an idea that you would like to share, please send it to basicsciences@vanderbilt.edu.

The chosen topics represent areas of intersection between scientific research and current societal concerns or interests.



Professor of Molecular Physiology and Biophysics Hassane Mchaourab sits at his computer.

JAMIE MCCORMICK

Uncovering the molecular basis of genetic diseases

By Wendy Bindeman

The laboratory and the doctor's office can feel like two separate worlds. Doctors run tests and observe symptoms, doing their best to treat them, but this can be difficult if the cause of the disease isn't known. Conversely, researchers identify mutations and study them extensively in model organisms but can't always determine what the consequences of a mutation are in a patient.

Vanderbilt's Program in the Molecular Basis of Genetic Diseases is one promising effort to bridge this so-called bench-to-bedside gap, focusing, as the name implies, on genetic diseases, those caused by an inherited mutation in the DNA. This initiative offers Vanderbilt researchers and clinicians a powerful opportunity for cross-disciplinary collaboration focused on investigating the links between genetic mutations of interest (the "genotype") and the way a disease presents in a patient (the "phenotype").

Hassane Mchaourab, professor of molecular physiology and biophysics and one of the founders of the MBGD program, got the idea from a collaborative research project focused on understanding a rare, non-inherited genetic mutation associated with autism spectrum disorder that was initially identified by **Jim Sutcliffe**, an associate professor in Mchaourab's department. The project grew to include Mchaourab, whose specialty is protein biochemistry and biophysics, plus **Aurelio Galli**, formerly a professor of molecular physiology and biophysics; **Jens Meiler**, research professor of chemistry and associate professor of pharmacology; and several collaborators in the School of Engineering.

The labs pooled their expertise to investigate the impact of the identified mutation—an amino acid deletion—on the structure and function of the dopamine membrane transporter encoded by that gene. They found that although the transporter, whose role it is to transport

This project had a double benefit: identifying both a genotype-phenotype link that is relevant to the treatment of a disease and yielding a basic science discovery.

the neurotransmitter dopamine across the cell membrane, was in fact produced and even correctly located at the membrane, the mutation rendered it dysfunctional. In fruit flies, a commonly used model in biomedical research, expression of the mutated protein produced behavioral phenotypes analogous to those observed in patients who carry the mutation. The collaboration resulted in a series of publications, including three in the prestigious journals *Molecular Psychiatry* and *Proceedings of the National Academy of Sciences*.

Mchaourab was particularly intrigued by the project because, he said, the mutation is an "experiment of nature." This is a reference to the fact that scientists often use mutated versions of proteins to study them; disabling part of a protein is an excellent way to find out that part's function. This naturally occurring mutation had the same effect: It "locks" the transporter in a certain conformation that is otherwise unobservable, thereby revealing a novel aspect of the molecular mechanism of the protein. This project therefore had a double benefit: identifying both a genotype-phenotype link that is relevant to the treatment of a disease and yielding a basic science discovery.

That moment of inspiration led Mchaourab, in collaboration with Meiler; **Todd Edwards**, an associate professor of medicine; and **Tony Capra**, a research associate professor of biological sciences, to propose the creation of the Molecular Basis of Genetic Diseases program. Their proposal was successful and the program was funded by the dean of the Vanderbilt University School of Medicine Basic Sciences, launching in January 2019.

A successful pilot

According to Mchaourab, the MBGD program aims to build a pipeline between geneticists, who identify rare genetic variants, and clinicians, who observe phenotypes in patients, through various collaborators who specialize in the "missing link," the molecular and cellular studies needed to determine why a particular genotype produces a phenotype of interest. There are currently eight active collaborations in various stages of development.

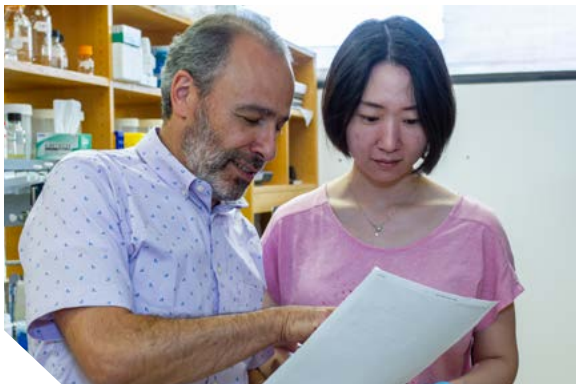
The program recently completed its pilot phase and is now "open for business" and happy to collaborate with any Vanderbilt-affiliated lab or researcher. It provides collaborators access to four central types of facilities and expertise. The first is a collaboration with the Personalized Structural Biology initiative led by Meiler and Capra, which provides expertise in computational biology and determination of protein structure. The other three include facilities for protein expression and purification, biochemical and functional analysis, and zebrafish animal models. Interested faculty, students, or postdocs can contact the program directly through its website.

When working together pays off

Already the MBGD program has produced impressive results. A collaboration with Professor of Molecular Physiology and Biophysics **Richard O'Brien**, for instance, is investigating G6PC1, a membrane-embedded enzyme that is linked to glycogen storage disorders. These disorders are characterized by abnormal storage or use of sugar that can cause a wide spectrum of health issues, most commonly affecting the liver and muscles. The Mchaourab and O'Brien labs, in an effort spearheaded by **Derek Claxton**, research assistant professor of molecular physiology and biophysics, were the first to purify G6PC1 in its functional form and are now performing experiments to figure out exactly what its function is and the impact of various mutations. They are also using cryo-electron microscopy, which uses an electron stream instead of light to visualize a frozen sample, to determine its precise structure.

A second collaboration with Galli, who is now a professor of surgery and director of the Center for Inter-systemic Networks and Enteric Medical Advances at the University of Alabama at Birmingham, is enabling study into a mutation in the dopamine transporter associated with infantile parkinsonism, which is a rare neurological condition that appears during infancy that causes tremors, movement difficulties, and global developmental delays.

JAMIE MCCORMICK



Mchaourab, left, discusses data with postdoc Ruojing Zhang, right.

Normally the dopamine transporter tightly controls the flow of ions (electrically charged atoms) in and out of the cell. Structural analyses by the researchers showed that the mutation makes the protein unable to regulate that flow, so that ions move in and out at random. When expressed in a fruit fly model, the mutation produces flies with abnormal wing function, resembling the movement difficulties caused by the disease. The researchers were even able to use that model to identify a potential treatment: chloroquine, an antimalarial drug. These findings were recently published in *eLIFE*.

According to Mchaourab, participating in these interdisciplinary projects and establishing the MBGD program has benefited his own lab by encouraging them to "think outside the box." The MBGD program is an example of a collaborative effort that brings together experts from many different points along the continuum of bench-to-bedside—and as the early results show, this can be a very powerful approach. ■

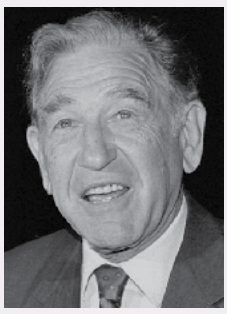
Philanthropy drives Cohen Innovation Fund

By Sarah Wolf

At first glance, it may be difficult to find links among peanut allergies, memory research and Charcot-Marie-Tooth disease, a rare inherited condition. But peering into the discovery research within the Vanderbilt School of Medicine Basic Sciences reveals one—each of these topics has received support from the Stanley Cohen Innovation Fund, an initiative supporting high-risk, high-reward research.

Established through philanthropy in 2019 and named after the late Nobel laureate Stanley Cohen, emeritus professor of biochemistry, the Cohen fund supports innovative research in perpetuity. Cohen's seminal discoveries in growth factor signaling laid the groundwork for our understanding of embryonic and cancer development and led to the development of numerous anticancer drugs that are still used today.

Over the past several years, the Cohen fund has been a fundraising priority, with gifts from donors and institutional dollars bolstering the effort. Thanks to this support, the Cohen fund is now primed to enable discovery work—innovative, early-phase proposals that are too risky to succeed through standard funding mechanisms—with the aim of advancing scientific understanding and helping researchers generate preliminary data to land larger grants.



VANDERBILT UNIVERSITY

Stanley Cohen

"We've arrived at a moment of celebration," says **Larry Marnett**, dean of basic sciences. "The Cohen fund has reached our initial goal, thanks to contributions from donors and matching institutional investment. This model of co-investment—where donors and departments come together—is propelling some very exciting work here."

James McKanna, emeritus professor of anatomy, and cell and developmental biology, was a friend, collaborator, and mentee of Cohen. Together they conducted electron microscopy studies that showed that EGF, the growth factor Cohen discovered, bound to receptors on the surface of cells and activated further signaling.

> "The Cohen Fund has reached our initial goal, thanks to contributions from donors and matching institutional investment."
>
> **– Larry Marnett, dean of basic sciences**

McKanna was among the dozens of donors who responded to the matching opportunity in support of the Cohen fund. "I am delighted that Stanley's spirit has a continuing presence on campus through this fund," McKanna said. "Stanley loved to discover something unusual and then pursue it with a great deal of enthusiasm and imagination. I hope the recipients of this fund will carry on his perspectives as a scientist, including his pragmatic approach to whittling down big problems into directed questions, and his genuine ability to lead, guide, and mentor."

As an endowment, the Cohen fund will support one compelling research project each year, chosen through a competitive selection process. Last year, the faculty selection committee evaluated 10 proposals.

Cody Siciliano, assistant professor of pharmacology, was selected to receive the Cohen fund award last year to support studies on the neural substrates of memory. Siciliano's work focuses on understanding how neural circuits in the brain orchestrate decision-making and memory, how these processes can become dysregulated due to trauma or disease, and how regulation of these circuits can be restored through various interventions.

"The Cohen fund has allowed me to think outside of the lab's usual direction and take risks on ambitious research questions. This has enabled us to quickly make progress on developing new tools and answering long-standing biological questions," Siciliano said.

"I'm thrilled that we've gotten the Cohen Innovation Fund to a level where we can support high-risk research in perpetuity," said Marnett. "The projects we've funded in our first few years offer a tantalizing look into the exciting research we will fund in the future. This is the most appropriate way I can think of to honor the legacy of our colleague, Stanley Cohen." ■

Continuing a legacy of excellence

By Wendy Bindeman

JOHN RUSSELL

The Office of Biomedical Research Education and Training is one of the centerpieces of Vanderbilt's biomedical graduate programs, and it is one of the first points of contact between prospective students and the school. Since its inception, it has been run by **Roger Chalkley**, former senior associate dean for biomedical research, education, and training and professor of molecular physiology and biophysics. With Chalkley entering a well-deserved retirement this summer and **Kathleen Gould**, professor of cell and developmental biology, taking up the mantle of senior associate dean for BRET, the BRET Office—and the biomedical graduate training it helps to manage—is entering a period of transition.

The BRET Office was founded in 1998, but it expanded over the years to include an office dedicated to postdoctoral trainees in 1999, an Office of Career Development and an Office of Outcomes Research in 2005, and, in 2011, additional career development programming that has grown into today's ASPIRE program.

Today, the BRET Office oversees and coordinates many aspects of Vanderbilt's biomedical graduate school offerings, including the IGP and QCB—that is, the Interdisciplinary Graduate Program in Biomedical Sciences and the Quantitative and Chemical Biology umbrella programs—the Initiative for Maximizing Student Diversity or IMSD, the Vanderbilt Program in Molecular Medicine, and the ASPIRE career development program.

It also runs the administrative side of graduate training, managing the training grants that provide support for graduate students and postdocs, graduate student payroll, and admissions and recruiting for the IGP and QCB.

Kathleen Gould

Under the training umbrella

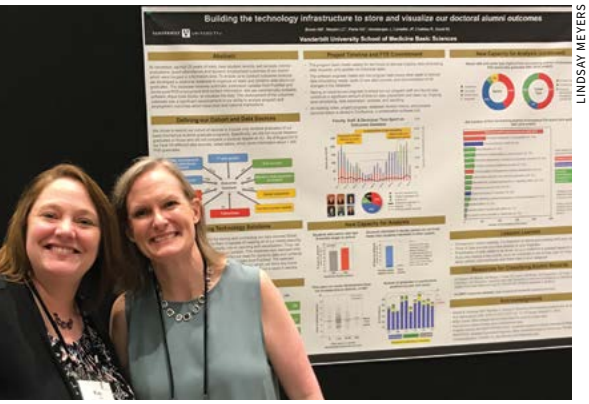
Most biomedical graduate students at Vanderbilt begin their training in one of the two "umbrella" programs. Students are initially admitted to a broad, interdisciplinary cohort, and they spend their first year working in different wet or computational labs and completing general coursework. At the end of that year, they join a lab and a corresponding program or department.

Although such programs are common now across the country, Vanderbilt was a pioneer of this graduate training structure in the 1990s, thanks to the work of Chalkley and **John Perkins**, who was then dean of the UT Southwestern Graduate School of Biomedical Sciences.

Most biomedical Ph.D. students join Vanderbilt through the IGP, which was founded in 1992 and was, at the time, only the second umbrella program in the United States. All other students matriculate through Vanderbilt's other umbrella program, the QCB, or, less commonly, directly through several individual departments.

The QCB was started in 2000 by **Albert Beth**, now emeritus professor of molecular physiology and biophysics, and **Dave Piston**, then a faculty member in the same department and now a professor of cell biology and physiology at Washington University in St. Louis. Initially called CPB-A (for Chemical and Physical Biology – Admissions), it was renamed "QCB" in 2012.

The QCB is targeted toward students with backgrounds in chemistry, physics, computer science, engineering, or mathematics, and its first-year coursework and programming are structured to provide a bridge into the biological and biomedical realm. Currently, Professor of Pharmacology **Tina Iverson** serves as the director and Professor of Biochemistry **Dr. Vito Quaranta** serves as associate director.



LINDSAY MEYERS

Kim Petrie poses with Abigail Brown, director of the Office of Outcomes Research, in front of a poster they presented at a conference.

James Patton, a professor of biological sciences who has been the director of the IGP since 1999, stepped down from the role earlier this year.

"It has been a pleasure and a privilege to lead the IGP," Patton said. He is being succeeded by Associate Professor of Pharmacology **Barbara Fingleton**, who began her tenure as director in July 2021.

Thanks in large part to stellar leadership, both umbrella programs have excellent track records of setting students up for successful completion of their Ph.D. training.

A period of transitions

Vanderbilt's approach to graduate education constantly evolves to best serve its students. The latest round of curriculum revision for IGP has been in the works since April 2020, and the changes are rolling out beginning with this year's incoming IGP class.

Previously, IGP students began rotations during which they "tried out" various thesis lab "candidates" within weeks of beginning the program. Each of four rotations lasted eight weeks, spanning the entire first year. Concurrently, students completed their first-year coursework, which comprised a survey course during the first semester and a mix of four-week modules and semester-long courses of the students' choice during the second semester.

Under the revised curriculum, students who matriculated in August for the 2021–22 academic year will focus exclusively on coursework until October before beginning their rotations. Although the number of rotations will stay the same, each one will only be four weeks long. Additionally, the new curriculum will shift away from didactic lectures to include more primary literature and subsequent discussion, enhanced training in computational techniques, additional sessions in scientific rigor and reproducibility, and general professional development.

JAN VARADARAJAN

BRET Office team members Kim Petrie, Kate Stuart, Ashley Brady, and Angela Zito present the branding for four regularly scheduled seminars introduced in 2019.

According to Gould, these changes make Vanderbilt's curriculum more competency-based, in line with current best practices for graduate education. The new curriculum is designed to prepare the students with the skills they are likely to need after graduating, such as familiarity with coding and programing.

Additionally, by removing the multitasking stress at the beginning of the year and giving students more time to identify potential rotation labs, these adjustments address some of the recommendations made by the Dean's Advisory Council for Mental Health and Wellness, which was established in 2020, for reducing student stress and improving overall wellness.

IMSD

The BRET Office also coordinates and administers the Initiative for Maximizing Student Diversity, which was founded by Chalkley and **Linda Sealy** in 1998 with the aim of recruiting and retaining talented biomedical graduate students from underrepresented backgrounds. Like Chalkley, Sealy, who was until her recent retirement an associate dean for diversity, equity, and inclusion and a research professor of molecular physiology and biophysics, was instrumental in the development of strong training programs at Vanderbilt, especially for students from backgrounds historically underrepresented in biomedical science.

The IMSD began as a postbaccalaureate program for students from diverse races, ethnicities, genders, and socioeconomic statuses, and it quickly expanded into comprehensive support for Ph.D. students. The program provides funding and resources for students during their first year, as well as programming and social activities throughout their graduate careers. It is one of the most successful graduate school diversity programs in the United States, and to date it has led to the graduation of nearly 200 Ph.D. students from backgrounds underrepresented in science.

ASPIRE to a diversity of careers

The BRET Office is also the home of a variety of career development resources for biomedical Ph.D. students and postdocs. Its flagship program is ASPIRE—Augmenting Scholar Preparation and Integration with Research-Related Endeavors—which is directed by Gould and managed by a team of dedicated staff.

Gould joined Vanderbilt in 1991 and became the director of graduate studies for the Department of Cell and Developmental Biology in 2006. In 2012 she joined the BRET Office of Career Development, where she has been instrumental in the creation and expansion of ASPIRE.

Gould describes the decision to create the ASPIRE program as "data driven." A 2012 report by the National Institutes of Health showed that many Ph.D. graduates took positions either entirely outside of academia, or within academia but outside of the traditional tenure-track path. Vanderbilt recognized the importance of preparing students for those positions, and Gould and the BRET staff began developing a suite of resources to do so.

Along with **Kim Petrie**, another early staff member in the Office of Career Development and currently the assistant dean for biomedical career development, Gould wrote a grant proposal for the Broadening Experiences in Scientific Training program that fully funded the first five years of the ASPIRE program, beginning in 2014.

BEST was an NIH-funded initiative to support enhanced career resources for biomedical graduate students and postdoctoral fellows. A total of 17 institutions were awarded one-time BEST grants, Vanderbilt included. Since its creation, ASPIRE has continued to develop and expand, and it has become a nationally recognized career resource for biomedical research trainees.

The ASPIRE program offers an array of resources for graduate students and postdocs to explore and prepare for their future careers. It focuses on six main areas of career development: career exploration and decision-making; professional development; national career development research and best practices; alumni relations, outcomes, and development; employer relations and workforce development; and campus partnerships and faculty outreach.

STEPHEN DOSTER

The staff of the BRET Office poses with Dean Larry Marnett, who is holding the 2018-2019 ASPIRE Annual Report. From left, Angela Zito, Kim Petrie, Kathleen Gould, Larry Marnett, Ashley Brady, and Kate Stuart.

Among its offerings are an annual career symposium that focuses on a different field open to biomedical Ph.D.'s each year. This year, for example, focused on "Careers for the Citizen Scientist," which, according to the Oxford Dictionary, refers to "a scientist whose work is characterized by a sense of responsibility to serve the best interests of the wider community." The event highlighted careers for students interested in science communication; other symposia have focused on industry positions and academic-track opportunities.

ASPIRE coordinates internal and external internships to help trainees build skills and try out potential future paths, provides CV editing and interview preparation services for trainees, facilitates a variety of mechanisms for trainees to connect with alumni who work in their desired fields, provides an array of professional development seminars and courses, and much more. One popular event series is the "Ph.D. Career Stories," a monthly seminar that brings in Vanderbilt alumni and other Ph.D.-level professionals to talk with current biomedical trainees about their career paths and current positions.

The newest offering of the ASPIRE program is the "ASPIRE to Innovate" fellowship, which accepted its first fellow, **Karrie Dudek**, this year. Open to graduating students and postdocs, the program provides an opportunity for interns to collaborate with the BRET Office and the Center for Technology Transfer and Commercialization for two years to commercialize an existing technology developed at Vanderbilt and to receive training in entrepreneurship and commercialization.

Looking forward

Thanks to the breadth of services it offers and its cadre of devoted staff, the BRET Office frequently receives rave reviews from graduate students.

"BRET has been extremely valuable for my career goals in a variety of ways," said **Sam Dooyema**, a graduate student in the Microbe-Host Interactions program. "Ph.D. Career Stories and the annual career symposium exposed me to potential jobs I had no idea existed and got me excited to research similar opportunities. However, the most valuable resource of the BRET Office is probably the people. They truly want to see me succeed!"

A recent graduate in pharmacology, **Francis Prael**, added that the plethora of networking opportunities provided by the office was "essential" for getting a job after graduate school.

As the BRET Office and Vanderbilt's graduate programs evolve, Gould emphasized that a main priority will be to "continue Roger Chalkley's legacy of innovation and service to students, postdocs, and faculty." ■

GRANTS MANAGERS: Don't take them

By Stephen Doster

Welcome to our first support staff shoutout! The Vanderbilt University School of Medicine Basic Sciences is a premier research institution, and the research and daily functioning of the school could not happen without the work of dedicated support staff. Each issue, we'll be introducing you to a different group of staff members who help enable our research and keep everything running smoothly behind the scenes.

Research grants don't just exist in a vacuum: grants managers assist faculty, staff, postdocs, and students with managing the often-complicated life cycle of sponsored research grants and contracts. They help researchers find funding opportunities and navigate the application process, and ensure that Vanderbilt remains compliant with funding agencies' requirements.

So, who are the people behind the grants management curtain?

Beth Rivas

Beth Rivas also derives satisfaction from submitting grants and seeing them get awarded. "It makes me feel like I am a small but essential piece of the huge overall research process," she said. Rivas appreciates that Basic Sciences faculty are patient and understanding as they try to work through any new guideline and process changes that come up.

The pre-award team she manages has submitted more than 1,900 grants, contracts, and subcontracts in the past five years. In addition to her evident dedication to her work, Rivas is a world traveler who has visited 30 countries. Her favorite destinations include Buenos Aires, Argentina; Istanbul, Turkey; Madrid, Spain; Athens, Greece; Dubrovnik, Croatia; Budapest, Hungary; and Venice and the Amalfi Coast, Italy.

STEPHEN DOSTER

Robert Dortch

The lifelong Nashvillian is the fourth male in his family to be named Robert E. Dortch, but he's the first whose hair color matches his initials. He enjoys training new faculty, postdocs or students on the grants submission and management processes and concepts.

And he's seen technology advance over the years. "When I first arrived at Vanderbilt, most, if not all, applications were done on paper and often involved last-minute trips to a FedEx location to meet deadlines. Now, basically every application is submitted via websites. We quite literally no longer need a copier as a tool for a grant application!"

Susan Hotaling

Susan Hotaling came to Nashville via Louisville, Kentucky, and has worked at Vanderbilt for 22 years. "It's very satisfying when the applications that you work so hard on are funded," Hotaling said. "But it can be frustrating when you learn about a grant application and have very little time to prepare it." Thankfully, it doesn't happen too often, and, so far, everything has always worked out.

When she's not working, Hotaling spends her downtime at the Williamson County Animal Shelter walking and working with dogs. She also helps a dog and cat transport organization, picking up animals from rural shelters and transporting them to northern and eastern parts of the country.

Images courtesy of the featured grant managers

for granted

Alicia Davis

Alicia Davis was born in Nashville but has lived in Washington, D.C., Pennsylvania, and Germany. Davis finds it very gratifying to help faculty get funding. Filing paperwork with outside institutions can make the job challenging, especially when deadlines are tight, but living in Music City provides outlets for venting those frustrations.

"I like going to Musician's Corner in Centennial Park and to Live on the Green," she said. "I don't usually know who the bands are, but there's nothing like a free outdoor concert."

Daniel Quimby

Daniel Quimby, a transplant from Long Island, New York, has been at Vanderbilt for five years. The "dreaded" deadline days are the downside to his work. Once, he said, he submitted a grant at "literally 5:00 p.m." on the deadline day. "That was wild and incredibly stressful."

It's all worth it for Quimby, thanks to the relationships he develops with faculty and his coworkers. Additionally, he has some canine companions to help him de-stress. Like Hotaling, dogs play a significant role in Quimby's life, but in his case, it's through the dog boarding business he runs with his wife.

Stephanie Clapper

Stephanie Clapper came to Nashville seven years ago by way of San Antonio, Texas, transitioning from evaluating clinical trial participants for drug side effects to grants management. "It's the best feeling when someone receives their first grant, or a grant they have been really working to get funded," Clapper said.

Clapper enjoys spending time at home with Mac, her 12-year-old, 27-pound cat.

Tracya Humphreys

For Tracya Humphreys, knowing that she is instrumental in the beginning processes that lead to a faculty member receiving funding for a grant makes her job worthwhile.

Humphreys, who moved from Memphis five years ago, loves live music—and it's all about the bass.

"I've always wanted to play the bass guitar," she said. "When I listen to music, I tend to focus more on the bass sound if I can hear it."

"We are fortunate to have a dedicated, super-talented group of grants managers who facilitate every step of the submission process right up to funding. They routinely go above and beyond the call to make sure grants are submitted on time and that they adhere to all agencies' requirements. We literally couldn't function without them. I am really proud of all of them."

Larry Marnett
Dean of the School of Medicine Basic Sciences

Vanderbilt's Immigrant Scientists

By Jan Read

DELPHOTOSTOCK, ADOBE STOCK

June 2021 marked the nation's eighth annual Immigrant Heritage Month, celebrating the accomplishments and contributions that immigrants and their children have made in shaping the history, strengthening the economy, and enriching the culture of the United States. At the Vanderbilt University School of Medicine Basic Sciences, we are proud to highlight just a few of our many scholars who came to the U.S. to advance research that serves humankind.

Rafael Arrojo e Drigo

Position: *Assistant Professor, Molecular Physiology and Biophysics*
Country of origin: *Brazil*

The Arrojo e Drigo lab uses different types of microscopes to study the biology of remarkably long-lived cells in the islet, a region of the pancreas, and other somatic organs. In his research, Arrojo e Drigo investigates how post-mitotic cells are maintained for long periods of time and how these cells are affected by aging and disease.

KrassiMira A. Garbett

Position: *Drug Discovery Scientist II, Pharmacology*
Country of origin: *Bulgaria*

Garbett's research in the lab of **Rick Sando**, assistant professor of pharmacology, aims to better understand the mechanisms of neuronal connections in the brain by visualizing the proteins interacting at the neuronal cell surface, which can help identify the partners required for establishing proper connections between these cells. Understanding how these circuits form during human development will shed light on disorders such as ADHD, autism, and schizophrenia.

Guoqiang Gu

Position: *Associate Professor, Cell and Developmental Biology*
Country of origin: *China*

The Gu lab uses mouse and human pancreatic islet cell models to establish diabetes-associated risk factors. They focus on the beta cell, which secretes insulin to lower blood glucose, and whose death and/or dysfunction causes diabetes. Gu's group recently found epigenetic factors during embryogenesis and fetal growth that could predetermine the beta cell's function after birth, a finding that has implications for a person's risk for diabetes later in life.

Marina R. Hanna

Position: *Graduate Student, Neuroscience*
Country of origin: *Egypt*

In the lab of Associate Professor of Cell and Developmental Biology **Vivian Gama**, Hanna's research focuses on myeloid cell leukemia-1, or MCL-1, a protein that stops the outer membrane of the mitochondria from becoming permeable upon receiving a signal that leads to apoptosis, or programmed cell death. She is currently working with induced pluripotent stem cells and will eventually move to a brain organoid system—a miniaturized, simplified, 3D version of a brain—to model MCL-1 activity and determine its noncanonical function in and contribution to early human brain development.

Hossein Jashnsaz

Position: *Postdoctoral Fellow, Molecular Physiology and Biophysics*
Country of origin: *Iran*

Jashnsaz, who works in the lab of **Gregor Neuert**, assistant professor of molecular physiology and biophysics, developed an integrated framework to expose cells to gradual environmental changes over time and monitor their signaling activities to build mathematical signaling models. The resulting predictive models enable investigators to determine the impact of protein interactions and mutations on cellular response and functions that are relevant in many human diseases.

Ege T. Kavalali

Position: *William Stokes Professor of Experimental Therapeutics; Professor and Acting Chair, Pharmacology*
Country of origin: *Turkey*

Kavalali's work bridges fundamental neurobiology and development of novel treatments for intractable neuropsychiatric and neurological disorders, such as major depressive disorder and developmental and epileptic encephalopathies. Communication between neurons often occurs when a nerve impulse evokes the release of communication chemicals called neurotransmitters. The Kavalali lab demonstrated that when neurotransmitter release occurs spontaneously, it operates independently of nerve impulse–evoked neurotransmission, and that this spontaneous release of neurotransmitters represents a largely autonomous mode of interneuronal communication that can be targeted to treat neurological and neuropsychiatric disorders.

Slavina "Slavi" Goleva

Position: *Graduate Student, Molecular Physiology and Biophysics*
Country of origin: *Bulgaria*

Goleva's research within the lab of Professor of Medicine **Lea Davis** is in the field of statistical genomics, and her focus is on functional seizures. This phenotype doesn't have a known organic cause, although the prevailing thought in the field is that, in a small portion of people, trauma or stress unconsciously manifest as seizures. Goleva has developed an automated algorithm to identify functional seizure patients through electronic health records at the Vanderbilt University Medical Center and has identified the first significant heritable component for this type of seizure.

Armelle Le Guelte

Position: *Postdoctoral Fellow, Cell and Developmental Biology*
Country of origin: *France*

In mammary glands, the destiny of a potential stem cell population called cap cells is unclear. Cap cells are present during major changes in the breast, such as puberty, pregnancy, and lactation, but it is unknown if can cap cells give rise to other mammary cell populations such as basal cells or luminal cells. Le Guelte, working in the lab of Professor and Chair of Cell and Developmental Biology **Ian Macara**, developed a novel lineage-tracing mouse that tracks cap cell progeny, finding that, in vivo, basal cells are normally generated. Luminal cell death triggers cap cell differentiation, which begin to express luminal cell markers in culture. Le Guelte also identified TGF-β as a key regulator of cap cell multipotency.

Galina I. Lepesheva

Position: *Research Professor, Biochemistry*
Country of origin: *Belarus*

The Lepesheva lab focuses on CYP51, the enzyme essential for the biosynthesis of sterols, a class of organic molecules that are a hallmark of eukaryotic organisms. While studying CYP51 from pathogenic protozoa, her group identified an inhibitory scaffold—a base drug that can be further modified—that is curative in mouse models of Chagas disease, and then explored structure-based design for its development as an antifungal/anticancer agent.

Geoffrey Li

Position: *Postdoctoral Fellow, Biochemistry*
Country of origin: *Philippines*

Li's research in the lab of Professor of Biochemistry **Chuck Sanders** focuses on determining the structure of peripheral myelin protein 22, a cell membrane protein, in model membranes using NMR spectroscopy. PMP22 is highly expressed in the Schwann cells of the peripheral nervous system, and genetic aberrations have been associated with a hereditary neuropathy known as Charcot-Marie-Tooth disease.

Jorge Rúa-Fernández

Position: *Graduate Student, Biochemistry*
Country of origin: *Peru*

Rúa-Fernández's research in the lab of **David Cortez**, Richard N. Armstrong, Ph.D. Chair for Innovation in Biochemistry and professor and chair of biochemistry, focuses on the HMCES protein. HMCES covalently binds to AP sites, a common DNA lesion, and creates a DNA-HMCES protein crosslink—a DPC. DPCs coordinate an error-free repair pathway in single-stranded DNA, but they must then be removed. Rúa-Fernández focuses on the mechanisms that resolve the HMCES DPC as part of the repair pathway.

Brinda Selvaraj

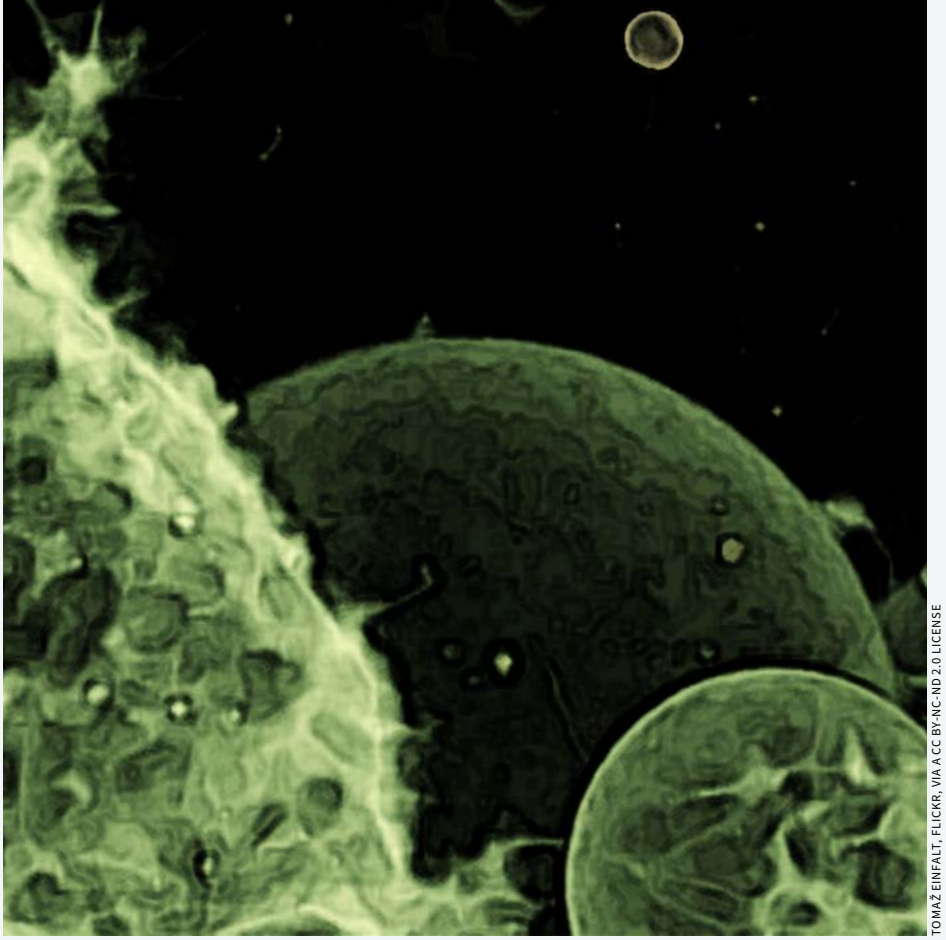
Position: *Research Instructor, Molecular Biology and Biophysics*
Country of origin: *India*

As the program manager in the Molecular Basis of Genetic Diseases program, housed in the lab of Professor of Molecular Physiology and Biophysics **Hassane Mchaourab**, Selvaraj focuses her research on catalyzing connections, collaborations, and crosstalk among clinicians, geneticists, basic scientists, and researchers to create teams focused on understanding the relationships between genes and phenotypes and identifying therapeutic targets and strategies.

Images courtesy of the featured scientists

In a tiny package:
New center explores means of cell-to-cell communication

By Lorena Infante Lara



TOMAŽ EINFALT, FLICKR, VIA A CC BY-NC-ND 2.0 LICENSE

One of the most rapidly expanding fields of basic sciences research is the study of extracellular vesicles—tiny membrane-bound particles that are actively released by cells into their environment. Originally thought to be a means of eliminating unwanted waste from cells, EVs were overlooked by researchers for many years.

This changed dramatically in the late 2000s, when the discovery that EVs carry and transmit RNA between cells rekindled interest in the field and led to its exponential growth. We now know that EVs include diverse types of vesicles and that many of them carry biologically active protein, lipid, and nucleic acid cargoes, thereby serving as a critical means of cell-to-cell communication.

Alissa Weaver, Cornelius Vanderbilt Chair and professor of cell and developmental biology, is at the forefront of EV research and propelled interest in the field at Vanderbilt by establishing the Program for Extracellular Vesicle Research in 2019. This highly successful program is getting an upgrade to become one of the nine official centers and institutes associated with the School of Medicine Basic Sciences.

As described by Weaver, who remains at the helm, the new Center for Extracellular Vesicle Research "includes 21 program faculty and covers diverse areas of extracellular vesicle research, ranging from basic functions of extracellular vesicles to applications in disease, including cancer, biomarkers, therapeutics, and regenerative medicine."

Despite sitting within the Basic Sciences, the center welcomes researchers from across the university, enabling collaborations among labs in Basic Sciences, the School of Medicine, the School of Engineering, the College of Arts and Science, and Vanderbilt University Medical Center.

EV Center faculty members have already published together and written grant proposals for shared projects, but Weaver hopes to foster additional collaborative large grants across the center.

"An early success is a National Science Foundation grant focused on therapeutic extracellular vesicles. That project came about because of the Program in EV Research," said Weaver, referencing a project led by Professor of Chemical and Biomolecular Engineering **Jamey Young** that also includes Weaver and departmental colleagues Associate Professor **John Wilson** and Assistant Professor **Ethan Lippmann**. "That brought in new faculty to the program and a new focus on therapeutic EVs that we didn't have before."

Affiliated faculty and trainees can tap center funds that may be applied to travel or toward the use of a core facility to further a particular research project. They also have access to key equipment used for purifying and analyzing EVs. Formalizing the program as an institutional center will allow Weaver to access additional funds to support new EV pilot projects or to purchase the sophisticated equipment that is needed to explore highly nuanced aspects of EV biology.

Weaver also hopes to continue and even expand the center's offerings to include a larger portfolio of workshops, seminars, and retreats. Following a successful inaugural (virtual) retreat, the center will hold its first in-person retreat in October at the Scarritt Bennett Center.

Even before becoming a center, the Vanderbilt Program for EV Research drew nationwide attention as a model for other institutions. Although other research centers have EV seminar series, host city-wide data clubs, or provide core-type services, no other program brings together an entire community like Vanderbilt's Center for EV Research.

"There's nothing really quite like this yet," Weaver said. ■

From pharmacology to neuroscience: Building from a Vanderbilt foundation

By Brett Nabit and Nick Petersen

The career of **Andrew Tapper**, PhD'01, after graduating from the Department of Pharmacology at Vanderbilt, exemplifies how modern, collaborative and interdisciplinary basic science research benefits society and trainees alike. Now serving as director of the Brudnick Neuropsychiatric Research Institute at the University of Massachusetts Medical School, Tapper reflects on how starting his scientific training at Vanderbilt guides his mentoring styles for young faculty and trainees.

Tell us about your position at the University of Massachusetts Medical School.

I'm a professor in the neurobiology department and I'm the director of the BNRI. I run a basic neuroscience lab that is working to understand the neurobiology of addiction. My lab uses mouse models to study the neuronal circuits and molecular mechanisms that underlie addiction and addiction-associated behaviors, including anxiety, depression, and novelty seeking.

How do you balance your time between your roles?

I spend more time running my lab than anything else. My position as the BNRI director involves helping other faculty in any way I can, whether it be giving advice about navigating promotion, providing feedback on grant applications, or editing manuscripts. It takes up some time, and it's very different from running a lab but it's also very rewarding. I really enjoy helping junior faculty try to achieve their goals.

How did your graduate training at Vanderbilt through the IGP and the Department of Pharmacology set the tone for your career?

My time at Vanderbilt set the foundation for everything. What I loved about the pharmacology department was that they ensure that you not only are an expert on your project in the lab, but also that you acquire comprehensive foundational knowledge in general pharmacology and physiology, which is something I use to this day. It was and is a very unique training environment. As a PI, I use Vanderbilt's model of combining interdisciplinary research methods and cutting-edge technologies to answer complex scientific questions. My mentoring approach is no different; I encourage students to find their own unique niche of interests with regards to research strategies, and, importantly, what they want to do after their graduate training. I have found that keeping an open-door policy in the lab facilitates development of graduate trainees and young faculty alike.

Tell us about your career path so far.

I've had a very traditional academic path. I defended my thesis and then went straight into an academic postdoc at [the California Institute of Technology]. Caltech was where I was exposed to neuroscience and also really got into the idea of trying to understand addiction and the effects of chronic drug use on circuits that drive addiction-related behavior. That focus led into my current position at UMass.

I was fortunate enough in my graduate career and also my postdoc career to have really great mentors. At Vanderbilt, I worked with **Al George**. As a postdoc, I worked with **Henry Lester**. Both were incredible mentors. They were very different, but also very complementary in how they approached science. I think that really helped shape my path when I started my own lab.

What are some of your areas of focus as director of the BNRI?

One of the initiatives that I am helping to advance is incorporating modern neuroscience approaches into the BNRI. Especially over the last few decades, there has been constant, rapid development of new tools for neuroscience research that can help you answer questions in the most direct way possible. I bring in and pilot state-of-the-art technologies that could benefit the group, and then also help others incorporate those tools into their research. Beyond that, I strive to support the faculty. It always helps to have people read your grant application, read your manuscripts, provide feedback, and so on, to foster an environment of collaboration and open science—things I learned first at Vanderbilt.

COURTESY OF ANDREW TAPPER

Do you have any advice for trainees?

There are a lot of career paths now for trainees that do not follow the traditional academic career path. My primary advice is to take that into account and do something that you truly love—something that makes you happy. Also, if you want to do a postdoc, take the time to find a lab environment that fits your needs and do not be afraid to change fields from your graduate work to broaden your horizons. That will set the stage for your career—just as starting my training at Vanderbilt set the stage for mine! ■

Accolade corner

By Wendy Bindeman

The hard work of our faculty, staff, postdocs, and graduate students in the Vanderbilt University School of Medicine Basic Sciences continues to be recognized on the local and national level. Here we list a few of the researchers whose work has been recognized so far in 2021.

Alyssa Hasty, associate dean for faculty and Cornelius Vanderbilt Chair and professor of molecular physiology and biophysics, recently received the Veterans Affairs Research Career Scientist Award. This award provides established, independent, non-clinician researchers with five years of funding.

Nicolas Shealy, a graduate student in the Microbe-Host Interactions program who works in the lab of Mariana Byndloss, was one of 50 students nationwide to receive the 2021 Gilliam Fellowship Grant for Advanced Studies from the Howard Hughes Medical Institute. Through its Gilliam Fellows program, HHMI aims to support graduate trainees from underrepresented backgrounds with the goal of equipping them to become leaders in biomedical research.

In February 2021, **Valeria Reyes Ruiz**, a postdoc in the lab of Eric Skaar, was named a 2020 Hanna H. Gray Fellow by HHMI. The Hanna H. Gray Fellows Program supports exceptional early-career scientists with the goal of increasing the diversity of the biomedical research community.

Catie Shelton, a graduate student in the Microbe-Host Interactions program who is mentored by Mariana Byndloss, was one of two students nationally to receive the Gut Microbiome, Yogurt and Probiotics Fellowship grant from Danone North America. Established in 2010, this program provides research grants to support graduate students conducting novel research in yogurt, probiotics, and the gut microbiome.

Marija Zanic, associate professor of cell and developmental biology, received the 2020 Early Career Award from the Motility & Cytoskeleton subgroup of the Biophysical Society. She accepted the award and presented at the 2021 Annual Meeting of the Biophysical Society in February of this year.

Bruce Carter, professor of biochemistry, has been appointed to the scientific advisory board of the CMT Research Foundation. As a member, he will help guide funding and research strategies for treatment of Charcot-Marie-Tooth disease, one of a type of disorder that causes damage to peripheral nerves.

Samuel Centanni, a postdoc, and his mentor, PI Professor of Molecular Physiology and Biophysics **Danny Winder**, received the 2020 *Neuropsychopharmacology* Editors' Award for a Transformative Original Report for their research on negative affect behavior associated with alcohol abstinence.

Professor of Biochemistry **Stephen Fesik** received the C. Chester Stock Award Lectureship from the Gerstner Sloan Kettering Graduate School of Biomedical Sciences. Fesik presented at the Stock Award ceremony in May 2021.

Three biomedical Ph.D. students received the National Science Foundation Graduate Research Fellowship Program award. The NSF GRFP is a nationally competitive program that provides three years of funding for exceptional graduate students. This year's Basic Sciences awardees were **Ebony Hargrove-Wiley** (Cancer Biology, Barbara Fingleton lab), **Kathleen McClanahan** (Molecular Pathology and Immunology, Danyvid Olivares-Villagómez and Hendrik Weitkamp labs), and **McKenzie Windham** (first-year Quantitative & Chemical Biology student).

Recent graduate **James Hutchison** (Chemical and Physical Biology program, Chuck Sanders lab) received the 2021 Karpay Award. This honor, sponsored by the Center for Structural Biology, recognizes a senior graduate student for excellence in both research and collaboration in the field of structural biology. Hutchison presented his research "We're All in This Together: Choosing the Right RAFTing Partners" at an award ceremony in early 2021.

Fred Guengerich, professor of biochemistry, and **Heidi Hamm**, professor of pharmacology, were among those inducted into the inaugural class of American Society for Biochemistry and Molecular Biology fellows. This newly established award recognizes the most accomplished members of ASBMB.

JOHN RUSSELL

Manuel Ascano, assistant professor of biochemistry, received the Richard M. Caprioli Award at the 2021 Vanderbilt University School of Medicine Faculty Awards. This award recognizes faculty who have developed, implemented, or created technology that has elevated the work of multiple researchers.

Recent Medical Scientist Training Program graduates **Petria Thompson** (Biochemistry, David Cortez lab) and **Andrew Hale** (Biochemistry, John York lab) were recognized with the John G. Coniglio Prize for Excellence in Biochemistry, which is awarded each year to exceptional biochemistry graduate students.

Rebecca Ihrie, associate professor of cell and developmental biology, received the Ivy Foundation's Emerging Leader Grant Award 2021. This grant supports early- or mid-career researchers conducting highly impactful translational research in glioblastoma, an aggressive type of cancer that can occur in the brain or spinal cord.

Craig Lindsley, professor of pharmacology, was inducted in 2021 as a member of the Medicinal Chemistry division of the American Chemical Society Hall of Fame for his work in medicinal chemistry. He is the youngest-ever inductee to the Hall of Fame.

Two Vanderbilt researchers have been recently recognized by the Burroughs Wellcome Fund: postdoc **Alberto J. López** (Erin Calipari lab) and Assistant Professor of Molecular Physiology and Biophysics **Antentor Othrell Hinton Jr.** Lopez received the 2021 Postdoctoral Enrichment Program Fellows grant and Hinton was one of the recipients of the 2021 Career Awards at the Scientific Interface, a "bridge award" that supports researchers during the postdoctoral fellow-to-faculty transition.

Kendra H. Oliver, assistant professor of pharmacology and director and founder of ArtLab and Drug Discovery Online, was recently inducted into the Academy for Excellence in Education. The academy is a collective of outstanding faculty at the School of Medicine who have made significant contributions to education.

The Dean's Award for Exceptional Achievement for Advanced Students is awarded each year to Ph.D. students and recognizes them for the originality, rigor, and significance of their dissertation research. This year's recipients (above, from left to right) are as follows:

Mary Chalkley, Cell and Developmental Biology. Advised by Rebecca Ihrie and Dr. Kevin Ess.

Jennifer Zachry, Pharmacology. Advised by Erin Calipari.

Cody Heiser, Chemical and Physical Biology. Advised by Ken Lau.

Gabriella Robertson, Cell and Developmental Biology. Advised by Vivian Gama.

Catherine Shelton, Microbe-Host Interactions. Advised by Mariana Byndloss.

Kritika Singh, Human Genetics. Advised by Lea Davis.

Ivette Perez, Biochemistry. Advised by Tina Iverson.

Melissa Wolf, Cancer Biology. Advised by Dr. Kimryn Rathmell.

Wendy Bindeman, Cancer Biology. Advised by Barbara Fingleton.

Elaine Chen, Microbe-Host Interactions. Advised by Dr. James Crowe.

Patrick Melugin, Neuroscience. Advised by Cody Siciliano.

VANDERBILT
School of Medicine
Basic Sciences

131 21st Avenue South
Nashville, TN 37203

Support Ph.D. Students Through the Simple Beginnings Fund

The annual Simple Beginnings ceremony welcomes new doctoral candidates into the School of Medicine Basic Sciences at Vanderbilt. To commemorate this educational milestone, students are presented with a personalized lab coat signifying their membership in our scientific research community.

The generous support from alumni, faculty, parents and friends makes the Simple Beginnings ceremony and additional student support efforts possible. Join us in honoring these scholars as they begin their research careers.

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