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COLLEGE OF COMPUTER, MATHEMATICAL, AND NATURAL SCIENCES

ODYSSEY

DECODING DISEASE, TARGETING THREATS ›

ODYSSEY

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Odyssey is published for alumni, friends, faculty, staff and students of the College of Computer, Mathematical, and Natural Sciences. Your comments and feedback are welcome. Please send them to abbyr@umd.edu.

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ON THE COVER

Brightly labeled cells in the auditory cortex display extensive dendritic trees and axons that descend to the auditory midbrain. Microscopy by Rose Ying.

Message from Dean Amitabh Varshney

Dear Science Terps,

Last year, the university published its new strategic plan, *"Fearlessly Forward: In Pursuit of Excellence and Impact for the Public Good,"* which presents a bold reimagining of what our university must be to uphold and expand our mission of service to humanity.

To improve the lives of every person on Earth, the plan identifies several goals: to reimagine teaching and learning, to accelerate solutions to the grand challenges of our time through creativity and discovery, and to forge a diverse and inclusive community where our differences are celebrated and equity is relentlessly pursued. Together, we will dedicate ourselves to advancing the public good because our individual well-being is enduringly bound to our collective well-being.

As we **take on humanity's grand challenges**, faculty, staff, students and alums from our college pursue new ideas, interests and capabilities that profoundly impact and improve the lives of individuals around the world.

This issue of *Odyssey* magazine is dedicated to experts fighting relentlessly against diseases and conditions that claim countless lives and undermine ability, function and perception. These threats to human health and well-being present unprecedented challenges, but also opportunities for breakthrough technologies and therapeutics.

Researchers in our Departments of Biology, Cell Biology & Molecular Genetics, Chemistry & Biochemistry, among others, are working hard to decode diseases and target threats. On the pages that follow, you can read about their efforts, and those of our alums, to tackle these imminent threats to health and well-being. Together, they are finding solutions that move us *Fearlessly Forward.*

Amitabh Varshney photo by John T. Consoli

DECODING DISEASE, TARGETING THREATS

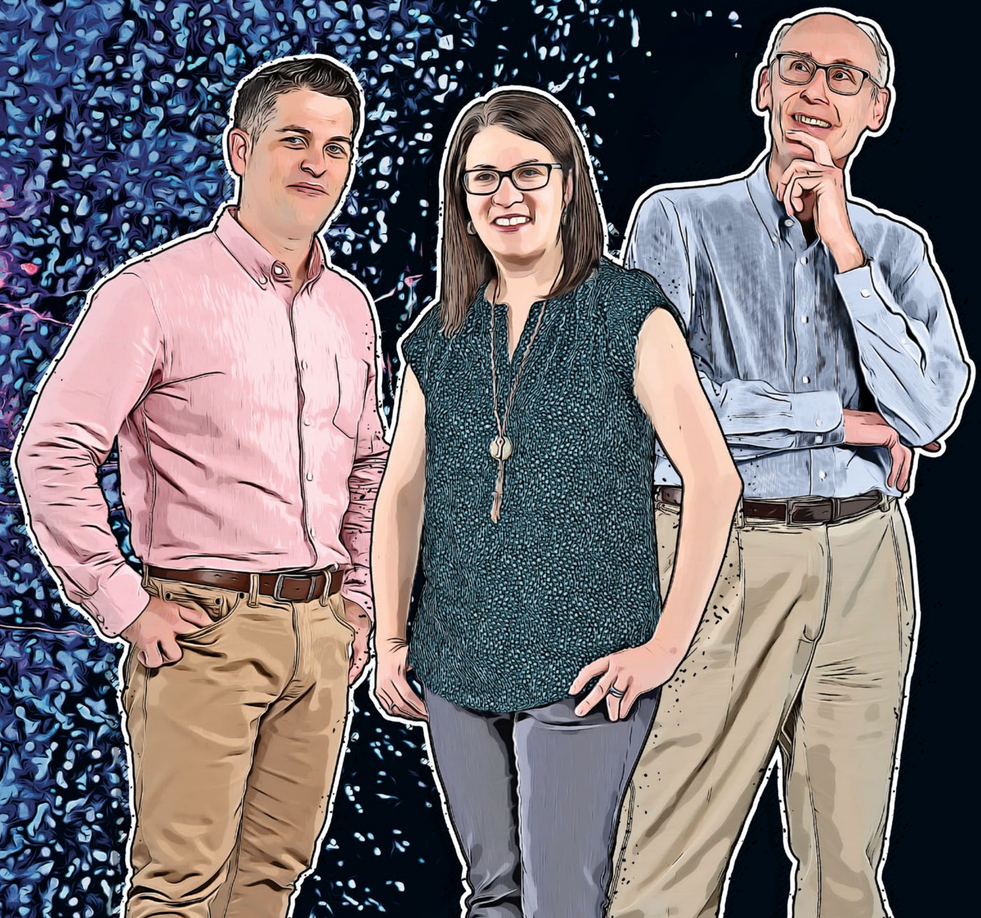
HUMAN HEALTH IS AT RISK. HOW CAN WE FIGHT BACK?

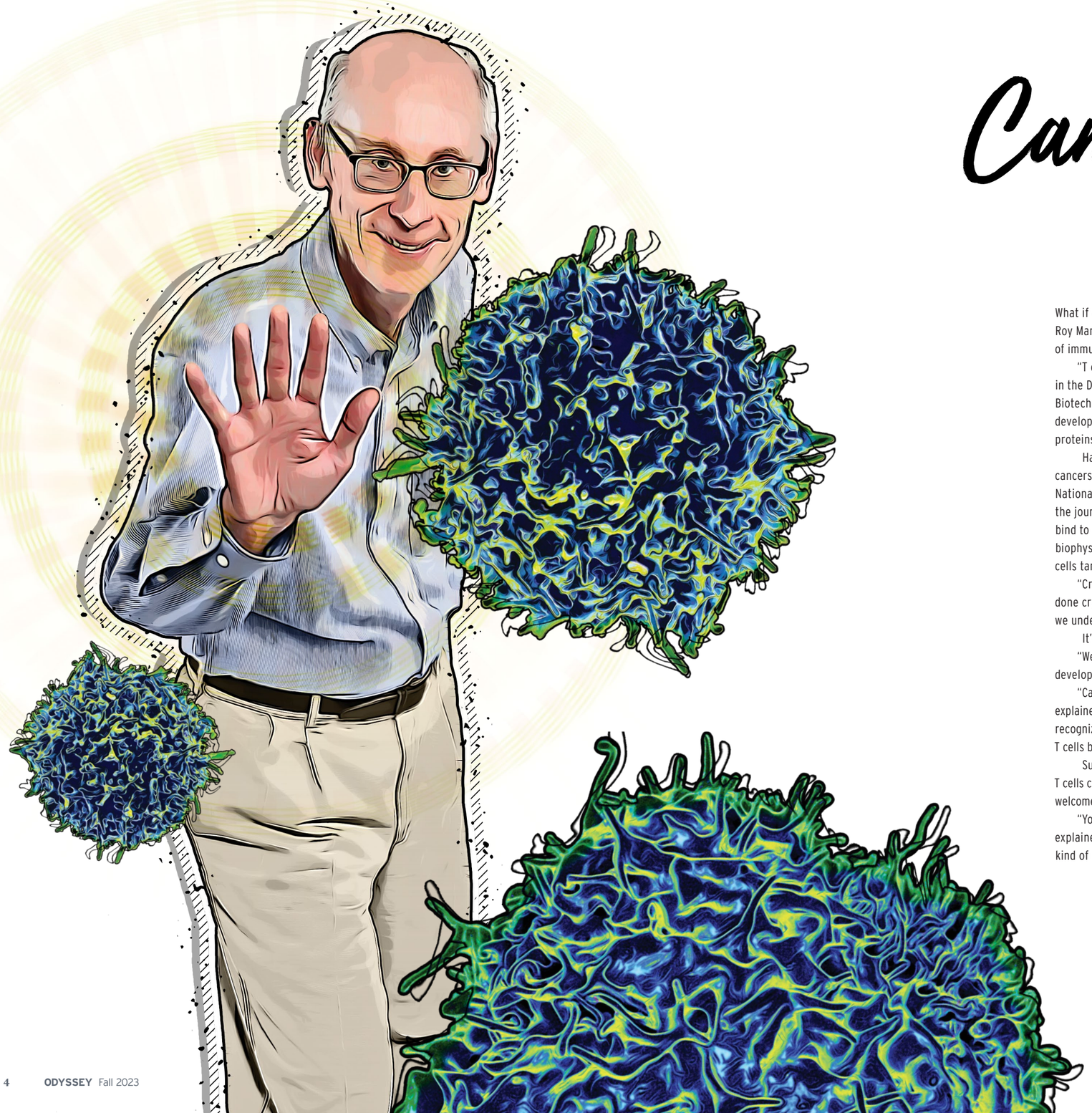
Though modern science has eradicated countless threats to human health, many other diseases and degenerative conditions continue to take a devastating toll. How can we eliminate these threats to health and well-being?

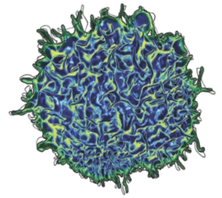
Researchers in the University of Maryland's College of Computer, Mathematical, and Natural Sciences (CMNS) fight relentlessly against diseases and conditions that claim countless lives and undermine ability, function and perception. These scientists are committed to finding answers by mapping complex neurological circuitry to better understand how the brain works and what happens when something goes wrong, tapping into the power of disease-fighting T cells to stop cancer in its tracks, and unraveling complex mechanisms to better understand and treat neurological impairments caused by aging and disease.

Grand challenges demand bold ideas and real-world solutions. In CMNS, we lead *Fearlessly Forward*.

STORY BY ***KIMBRA CUTLIP, GEORGIA JIANG*** AND ***LESLIE MILLER***
RESEARCHER PHOTOS BY ***JOHN T. CONSOLI***
COMPOSITES BY ***FAYE LEVINE***
ART EFFECTS BY ***NUWAN PANDITHA***







ROY MARIUZZA

Canceling Cancer WITH T CELLS

What if we could engineer our immune system to make the human body better at fighting cancer? Professor Roy Mariuzza is part of a major research effort aimed at doing just that. An expert in the structural biology of immune system proteins, Mariuzza studies T cells, the body's first responders against cancer.

"T cells can actually recognize and kill tumor cells," explained Mariuzza, who has appointments in the Department of Cell Biology and Molecular Genetics (CBMG) and the Institute for Bioscience and Biotechnology Research (IBBR). "And this is going on all the time in our bodies because we're constantly developing potential cancers. These T cells recognize cancerous cells using T cell receptors, which are proteins on the surface of T cells that can bind to proteins on tumor cells called tumor antigens."

Harnessing the tumor-fighting power of T cells means first determining how they recognize certain cancers. In 2020, Mariuzza and his IBBR research colleagues—CBMG Associate Professor Brian Pierce and National Institute of Standards and Technology Research Chemist D. Travis Gallagher—published a study in the journal *Nature Communications* in which they identified key structural features of T cell receptors that bind to the tumor-specific proteins on cancer cells. In this research, Mariuzza's team used state-of the-art biophysical methods including a complex process called X-ray crystallography to zero in on exactly how T cells target cancer.

"Crystallography is a way of determining the shape and atomic detail of proteins," Mariuzza said. "We've done crystal structures of these anti-tumor T cell receptors in complex or bound to their tumor targets. So, we understand exactly at the molecular level how recognition is occurring."

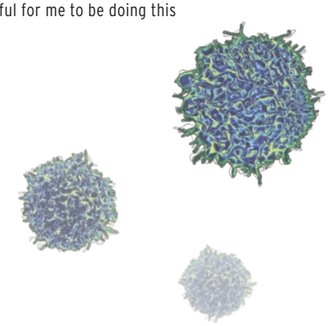
It's critical information for the therapeutic challenges ahead.

"We're laying the foundation—a database or a knowledge base—for clinical immunologists who are developing therapies that we hope will benefit from our work," Mariuzza said.

"Cancers grow very rapidly and that's one reason they can escape the immune system," Mariuzza explained. "In these clinical trials, they take T cells from a patient with a cancer, isolate the T cells which are recognizing this cancer and they grow up these T cells in large amounts. Then they put large amounts of these T cells back into the patient which are numerous enough to target cancer cells and beat back the cancer."

Supported by a $3.6 million grant from the National Institutes of Health, Mariuzza's study of cancer-killing T cells continues. After more than 15 years in cancer research, he knows there's much more work ahead, but he welcomes the challenge.

"You feel like you're part of this gigantic enterprise attacking this major human problem," Mariuzza explained. "Cancer immunotherapy will only improve going forward. It's meaningful for me to be doing this kind of research."



T cells by NIAID-NIH

MELISSA CARAS

Training THE BRAIN

People rely on their ability to improve their senses with practice—a concept called perceptual learning—for essential skills like speech recognition, language acquisition and musicality. But over time, people can slowly lose their ability to interpret and respond to what they experience through their senses. Often, this decline in sensory ability is influenced by aging, neurocognitive disorders like dementia, and sensory impairments like hearing loss. When people lose their ability to hear, they often struggle with developing or retaining the skills needed to stay connected to the world as they know it.

To find ways to help people maintain or improve their perceptual skills even as they age or encounter disease, Biology Assistant Professor Melissa Caras is trying to uncover the basic mechanistic principles of perceptual learning in freely moving animals.

"Even the weakest sensory cues can help a person get crucial information about the world around them. A dim light or a soft whisper—those all carry important messages to the person who senses these things," Caras said. "I'm interested in understanding neuroplasticity in sensory systems, which means changes in the brain that give rise to changes in sensory perception. These changes happen in both animal and human brains, impacting how we develop certain skills that are important in everyday life."

Along with her team, Caras works to uncover the mechanisms responsible for how animals can refine or improve their sensory abilities and learn to hear subtle differences between sounds that they couldn't hear before. In her research, Caras uses tools like electrophysiology (measuring the electrical activity of neurons) and optogenetics (using light to control the activity of neurons) to monitor and manipulate neural activity in the brains of animal models. By pinpointing certain brain pathways activated by perceptual learning, the team can further investigate whether these pathways can be stimulated to improve or rejuvenate the process.

"Our perception of the world isn't stable; in fact, our sense of reality is dynamic. Perceptions are malleable and based on things like our attention, expectations of upcoming events and training," Caras explained. "We get better at sensing stimuli with practice and transform from 'perceptual novices' to 'perceptual experts' during that process. For example, native Japanese speakers may initially struggle to hear the difference between the spoken letters of 'L' and 'R' in English, but with practice, they can learn to distinguish between the sounds."

According to Caras, her research could be the key to understanding how people can 'train' their brains to become skilled in perceptually demanding tasks like learning a second language.

In January 2023, she received funding from the National Institutes of Health to continue her research into the relationship between sensory perception and neuroplasticity. Caras believes that understanding how exactly expertise arises in the brain will also eventually allow researchers to facilitate expertise—or speed up the process—in individuals with age- or disease-related sensory impairments, greatly improving their quality of life.

Sound waves by Melissa Caras

FEATURE

COLENSO SPEER

Mapping Molecules IN THE BRAIN

It's hard to fix a machine you don't understand. That means medical practitioners fighting brain disease and injury are at a disadvantage, because no one really knows how a human brain works. They don't know how many cells it contains or how each cell connects with hundreds or thousands of others to form thoughts and control actions.

Biology Assistant Professor Colenso Speer has a plan to answer those questions. He creates innovative ways to map the physical layout of brain cells, known as neurons. And he uses sophisticated new techniques to identify the complex chemical signals between neurons that form the intricate circuitry in our brains.

"This research could help identify where and how things go wrong in the brain," Speer said. "It could possibly lead us to genetic candidates for treating neuropsychiatric disorders, neurodevelopmental disorders, aging and memory disorders, and many other cognitive functions that are directly impacted by changes in the connections between neurons."

Those connection points are called synapses, and they are extremely complex environments where thousands of different proteins create signals that flow from one neuron to another. These signals enable the brain to think and build memories.

"But proteins degrade very quickly, within hours to days," Speer said. "So, how do our memories last for years? How do the neurons constantly produce new proteins to rebuild and maintain synaptic connections and keep our memories and capacity for learning alive?"

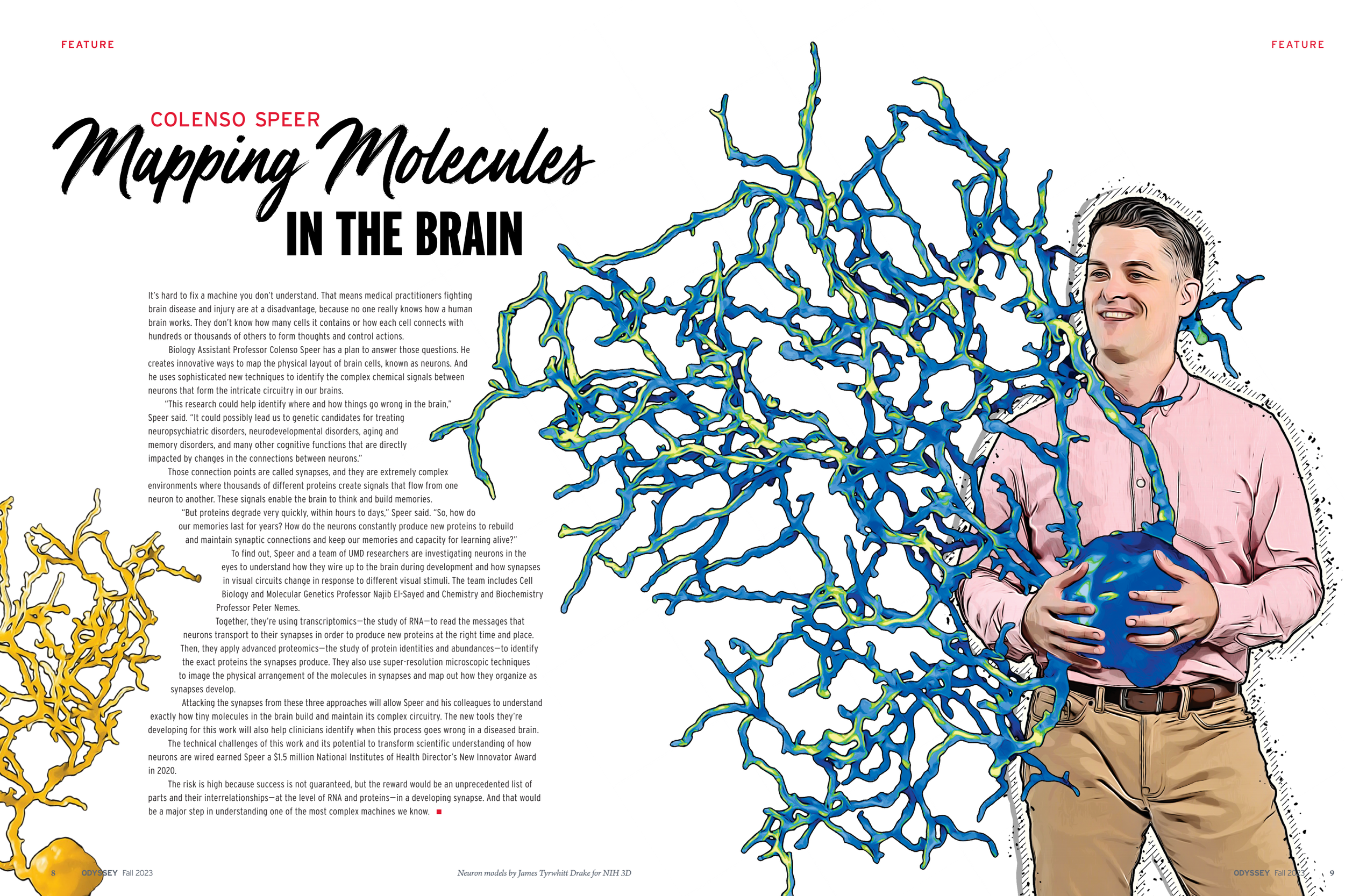
To find out, Speer and a team of UMD researchers are investigating neurons in the eyes to understand how they wire up to the brain during development and how synapses in visual circuits change in response to different visual stimuli. The team includes Cell Biology and Molecular Genetics Professor Najib El-Sayed and Chemistry and Biochemistry Professor Peter Nemes.

Together, they're using transcriptomics—the study of RNA—to read the messages that neurons transport to their synapses in order to produce new proteins at the right time and place. Then, they apply advanced proteomics—the study of protein identities and abundances—to identify the exact proteins the synapses produce. They also use super-resolution microscopic techniques to image the physical arrangement of the molecules in synapses and map out how they organize as synapses develop.

Attacking the synapses from these three approaches will allow Speer and his colleagues to understand exactly how tiny molecules in the brain build and maintain its complex circuitry. The new tools they're developing for this work will also help clinicians identify when this process goes wrong in a diseased brain.

The technical challenges of this work and its potential to transform scientific understanding of how neurons are wired earned Speer a $1.5 million National Institutes of Health Director's New Innovator Award in 2020.

The risk is high because success is not guaranteed, but the reward would be an unprecedented list of parts and their interrelationships—at the level of RNA and proteins—in a developing synapse. And that would be a major step in understanding one of the most complex machines we know. ■



Neuron models by James Tyrwhitt Drake for NIH 3D

Alums Fighting HUMAN **DISEASES**

CHALLENGED TO FIND A CURE

Pavel Khrimian (B.S. '00, biochemistry) and his Maryland-based startup Deka Biosciences are on an ambitious mission.

"We want to find a cure for cancer," explained Khrimian, who spent years as a scientist and business development expert in biopharma. "We know we can generate different therapeutics that can help a lot of patients."

Deka's research focuses on cytokines, which are small proteins secreted by the immune system that can be combined to create novel therapeutics for cancer as well as inflammatory diseases.

"We are the first in the world to generate targeted dual-cytokine therapeutics with an aim to stimulate a patient's immune system to find and kill tumors," Khrimian noted.

In January 2023, Deka received notification from the FDA that it may proceed with launching a phase one dose escalation clinical trial of its novel cancer molecule. Now, with plans underway to expand clinical trials and collaborate with biopharma partners, Khrimian believes Deka is on the right path.

"The early data from patients looks very encouraging and we are very excited," Khrimian said. "Our mission is challenging, but we remained focused on helping the patients. It's amazing work to be on this journey."

STOPPING BREAST CANCER METASTASIS

Patricia Steeg (Ph.D. '82, zoology) began her research career studying cellular immunology at the National Institutes of Health more than 40 years ago when she was a graduate student at UMD.

Now, as deputy chief of the Women's Malignancies Branch in the Center for Cancer Research, Steeg investigates why breast cancer cells migrate to the brain and grow and metastasize there—and how to stop them.

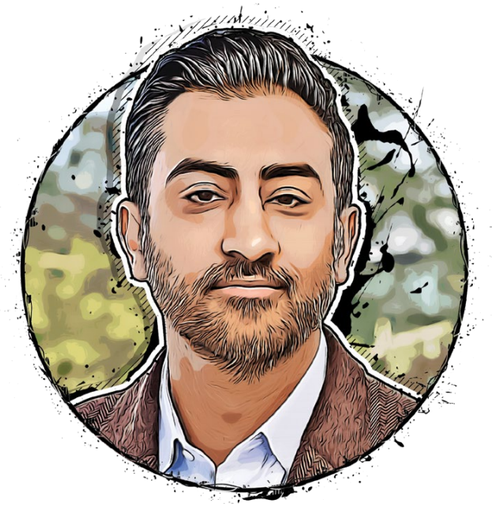
Last year, Steeg found that Temozolomide, a medication primarily used for brain tumors, prevents metastasis in breast cancer.

"We were very surprised," she said. "This prevention of brain metastasis was unheard of in breast cancer."

With the phase one clinical trial for Temozolomide now complete, the treatment will go into a phase two trial to look at whether the drug provides metastatic breast cancer patients with a year of freedom from brain metastasis, and if their overall survival rate increases compared with no treatment.

"Brain metastases are so devastating because they negatively affect your neurocognition," she said. "With this research, we hope to preserve their cognition and quality of life for longer."

Photos courtesy of Pavel Khrimian and Patricia Steeg



RARE DISEASES, NEXT-GENERATION THERAPIES

Sanjay Shukla (B.S. '93, microbiology) is committed to finding new treatments for rare and often deadly diseases that most people have never even heard of. As president and CEO of aTyr Pharma, his latest target for drug development is pulmonary sarcoidosis, an inflammatory—and devastating—lung disease that has no cure.

"Patients live with persistent cough and shortness of breath," Shukla explained. "Your lungs can become fibrotic, that's when really bad things happen. You need a lung transplant or you might die."

In early trials, aTyr recently provided the first clinical proof-of-concept for efzofitimod, a novel treatment based on a new class of protein therapeutics using enzymes called tRNA synthetases.

"These enzymes—their primary job is to help create proteins but astonishingly, they break apart into fragments and migrate to different tissues to play a very non-enzymatic role, basically controlling immune environments," Shukla explained. "One of these fragments seemed to act as an immune policeman for the lungs, so we developed that into efzofitimod."

Shukla hopes this research could one day help patients battling a variety of rare, progressive lung diseases, ultimately improving outcomes and changing lives.

"You're taking something developed essentially in the petri dish to now being able to put it into patients—and hopefully you start to see some of those patients improve," Shukla said. "It's really exciting."

FROM ACADEMIC RESEARCH TO DRUG DEVELOPMENT

Sylvie Ryckebusch (B.S. '87, physics; B.S. '87, mathematics) brings an unusual mix of skills to her work—she's part scientist, part business development expert. With her experience in physics, neuroscience and business strategy, Ryckebusch has built a successful 20-year career working with pharma and biotech companies around the world.

Currently, as chief business officer for BioInvent International, Ryckebusch builds partnerships and research collaborations to support the company's efforts to develop new antibody drugs for treating cancer.

"The cost of developing a pharmaceutical product is now in the billions of dollars, so biotechs almost never take them to market on their own, you have to partner with a big pharma at some point," she explained. "There's a whole strategy around how you partner, when you partner and with whom."

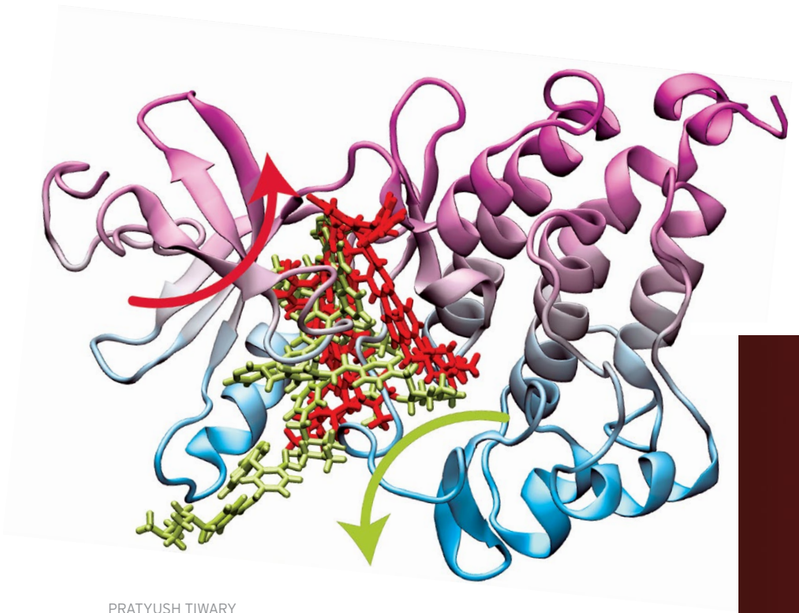
Ryckebusch takes pride in her role as part of BioInvent's drug development effort, but she's quick to note that she's just one small part of something much bigger.

"In the pharma industry, it takes 15 to 20 years to develop a drug and a lot of creative and dedicated people contribute along the way," she said. "I really hope one of BioInvent's products makes it to the market and is able to improve treatment outcomes for cancer patients. I would be proud to have contributed."

Photos courtesy of Sanjay Shukla and Sylvie Ryckebusch

RESEARCH WITH IMPACT

Our faculty members, students and alums are disease fighters. Read on to learn how Science Terps are developing next-generation diagnostic tools, advancing therapeutics and promoting human well-being.



PRATYUSH TIWARY

PETER NEMES

CHAD SMITH

GETTY IMAGES

Computer Simulation Cracks Mystery of Cancer Drug Resistance

Gleevec was hailed as a "miracle" cancer drug when it entered the market in the early 2000s. Though it has been highly successful at treating early-stage chronic myeloid leukemia, a rare cancer that forms in bone marrow cells, many late-stage patients experience drug resistance caused by mutations of vital proteins in the body. Millard and Lee Alexander Professor in Chemical Physics **PRATYUSH TIWARY** used computational chemistry to figure out what causes resistance to Gleevec at the molecular level. The simulations revealed that the N368S mutation makes a protein so flexible that a pathway opens up, allowing Gleevec to leave the protein before it can start working. A long-term goal of Tiwary's lab is to reverse this method, using computer simulations to predict changes in a drug that would make it more effective.

New Chemical Compound Could Reverse Deadly Effects of Drug Overdoses

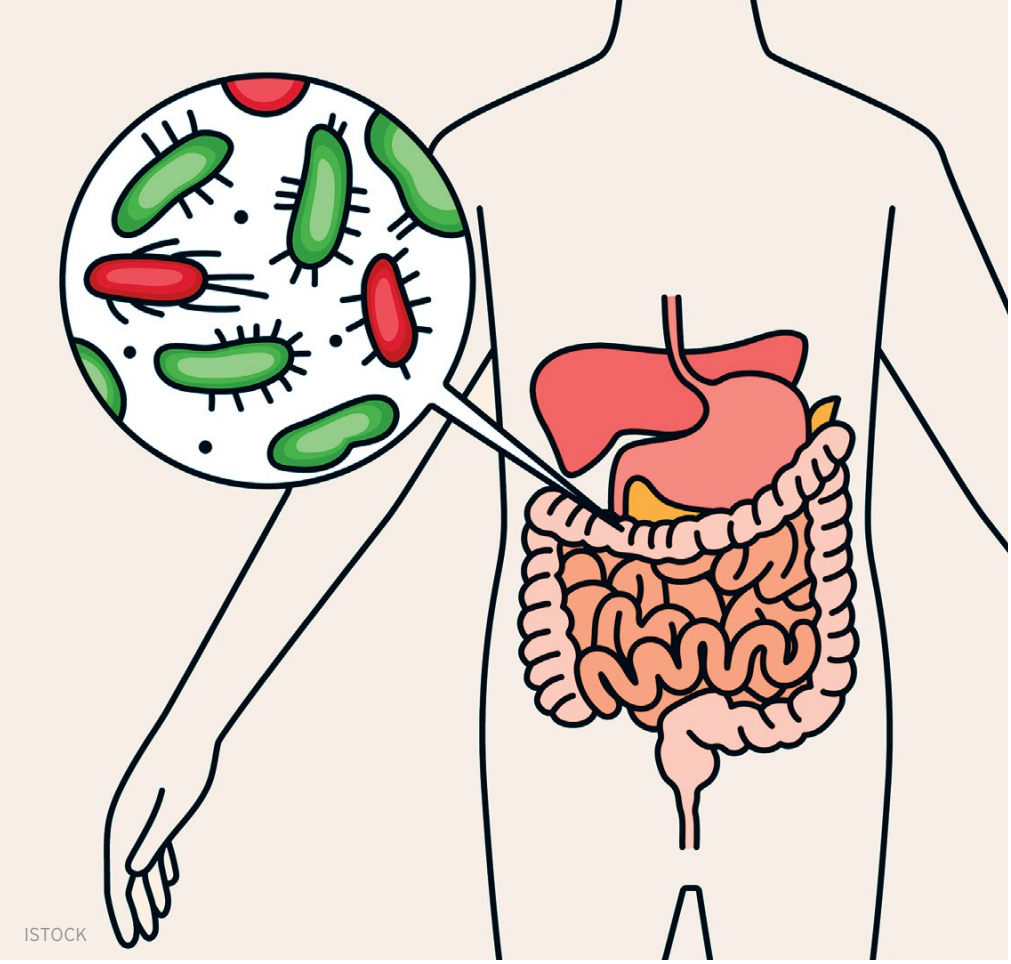
In the United States alone, nearly 92,000 people died from overdoses of illegal drugs and prescription opioids in 2020. A study led by Chemistry and Biochemistry Professor **LYLE ISAACS** identified a chemical compound, nicknamed P6AS, which could help combat this epidemic and save lives. P6AS works by binding and sequestering other molecules in its central cavity, reversing their biological effects. Laboratory tests on mice revealed that P6AS successfully mitigated the effects of fentanyl, a synthetic opioid, and methamphetamine, a non-opioid stimulant. While a reversal agent currently exists for opioid overdoses, it does not work for non-opioids and has other limitations. If approved for human use in the future, P6AS could be used to treat overdoses of a wide array of drugs that do not have an antidote, as well as particularly powerful drugs that are difficult to reverse.

A Better Way to Fight Parasites Responsible for Painful Skin Disease

Cutaneous leishmaniasis is an ulcerous skin infection caused by the *Leishmania* parasite. The World Health Organization estimates that 1 million cases of the disease arise annually, mostly in tropical or subtropical regions such as North Africa and South America. Currently, no vaccine can counter *Leishmania* and most drugs used to treat the infection are ineffective, toxic and difficult to administer. But thanks to a new $3 million grant awarded by the National Institutes of Health, Cell Biology and Molecular Genetics Professor **NAJIB EL-SAYED** and his team can directly tackle the parasite's ability to turn the disease 'on' and 'off' in an infected patient's body. Using powerful sequencing tools, the team will study the genomic and microenvironmental conditions that encourage parasite growth, ensuring that a parasite never flips the 'on' switch. This approach will help scientists develop new treatments that will be less toxic to the patient while still keeping the disease at bay.

New Instrument Expands the Analytical Toolbox of Neuroscience

Chemistry and Biochemistry Professor **PETER NEMES** developed a technological breakthrough in analytical neuroscience: the ability to profile the proteins inside of a single live neuron. For years, scientists have had the tools to detect proteins in cells but have lacked the technology to identify and quantify diverse proteins in tissue-embedded, characterized cells. The new ultrasensitive high-resolution mass spectrometer developed in Nemes' lab makes it possible to identify hundreds of different proteins in individual brain cells. The novel ability of the instrument to identify these diverse proteins will enhance our understanding of the brain's function during normal development and help advance diagnostics and therapeutics for diseases such as Alzheimer's and Parkinson's.



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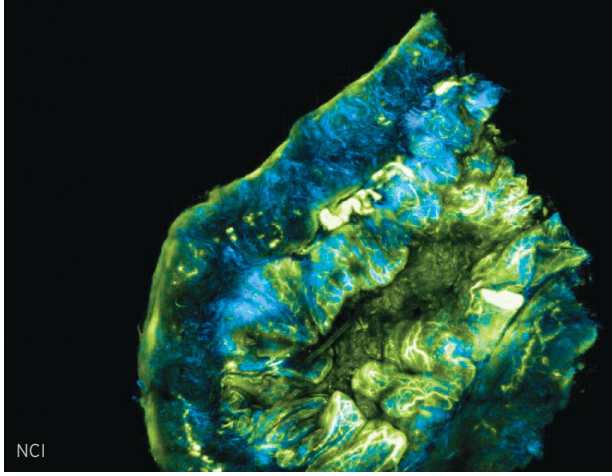

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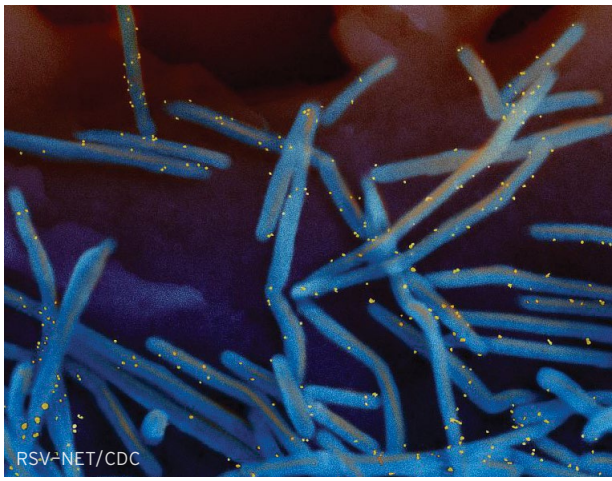

RSV-NET/CDC

New Technology Detects the 'Disease Fingerprint' of a Deadly Cancer

Early detection of ovarian cancer, which claims 184,000 lives worldwide each year, can significantly improve the chances of survival. However, few serum biomarker tests—blood tests that reveal tumor development—are highly specific yet sufficiently sensitive enough to detect early-stage disease. Chemistry and Biochemistry Professor **YUHUANG WANG** developed a new type of sensor technology to address that problem. Based on quantum defect-tailored carbon nanotubes augmented by machine learning algorithms, this new sensor technology can detect the "disease fingerprint" of ovarian cancer in serum samples, providing a much more accurate and reliable diagnosis. This technology, which has the potential to save lives by allowing doctors to catch ovarian cancer when it is most treatable, was named this year's UMD Life Sciences Invention of the Year.

Taking on the Grand Challenge of Climate Change and Microbiomes

Climate change affects the complex microbiomes that are critical to the health of humans, animals and the planet. These microbiomes inhabit the bodies of humans and animals, helping to nourish plants, degrade toxins and produce compounds that have medical or industrial uses, such as antibiotics. Computer Science Professor **MIHAI POP** and Cell Biology and Molecular Genetics Assistant Professor **BRANTLEY HALL** received a UMD Grand Challenges Impact Award to study and manipulate microbiome communities that are creating new challenges in medicine, agriculture and the environmental processes we depend on to grow crops and live. This initiative will advance cutting-edge microbiome research, train future generations of scientists in microbiome sciences and support the development of a regional innovation system that contributes to economic growth in Maryland's microbiome-related industries.

Fighting Disease by Helping the Body Clear Respiratory Infections

Mucus, the thick sticky substance produced in the nose and throat, plays an important barrier role in the human body's immune response. Depending on the molecular makeup of mucus, it can either protect from respiratory bacteria and viruses or result in thicker mucus that is difficult for the lungs to clear. Numerous diseases exhibit this buildup of mucus, from cystic fibrosis to COVID-19, and it can lead to chronic infections. Cell Biology and Molecular Genetics Associate Professor **LOUISA WU** leads a Grand Challenges Team Project aimed at helping the human body fight these infections. Wu's team will engineer a disease-fighting therapeutic that breaks the peptide bonds of the mucin proteins that are produced in excess in COVID, cystic fibrosis and other diseases–but leaves other protective mucin proteins untouched. The goal: provide a new weapon to help our bodies fight respiratory infections.

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(Left) UMD President Darryll Pines speaks to Terp alums in June 2023 about opportunities to collaborate with the IHC. (Right) Pines signs a memorandum of understanding to establish the IHC in November 2022 with Montgomery County, the University of Maryland, Baltimore, and the University of Maryland Medical System.

University of Maryland Institute for Health Computing Launches in Montgomery County

As advances in artificial intelligence and machine learning increasingly revolutionize health care, computational experts and life sciences researchers must collaborate to ensure innovation. To address this need, the University of Maryland Institute for Health Computing (IHC) was established to improve well-being and quality of life, diminish disease and enhance health outcomes for all citizens of Maryland.

Located in North Bethesda, Maryland, the IHC links university partners with the federal agencies and private life sciences companies located in Montgomery County, Maryland.

The IHC will work on projects in:

- Applied AI for Health
- Bioinformatics
- Immersive Visualization
- Population Health
- Adaptive Clinical Trials
- Real-World Data

Learn more: ihc.umd.edu

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