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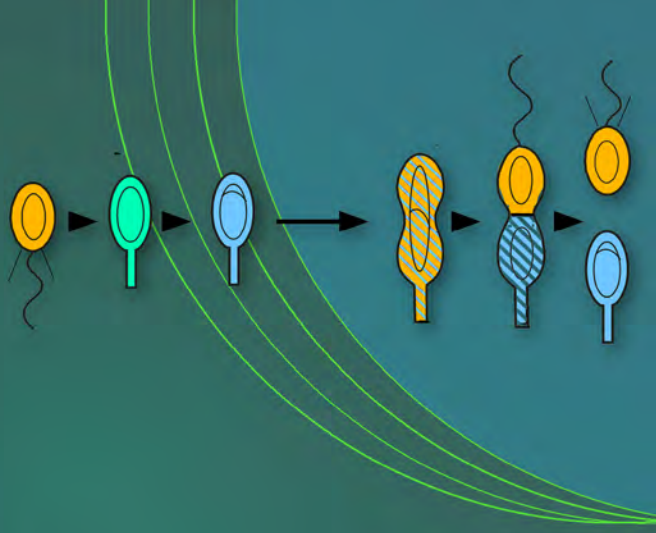

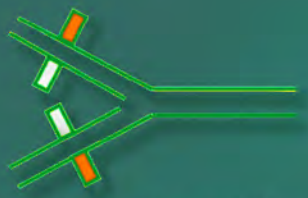

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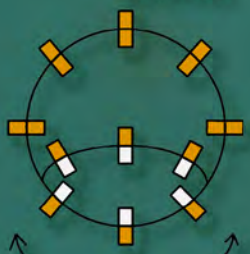

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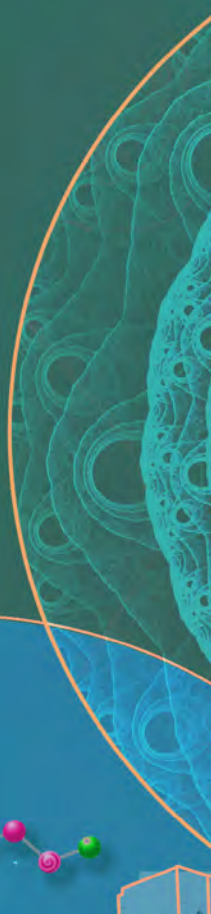

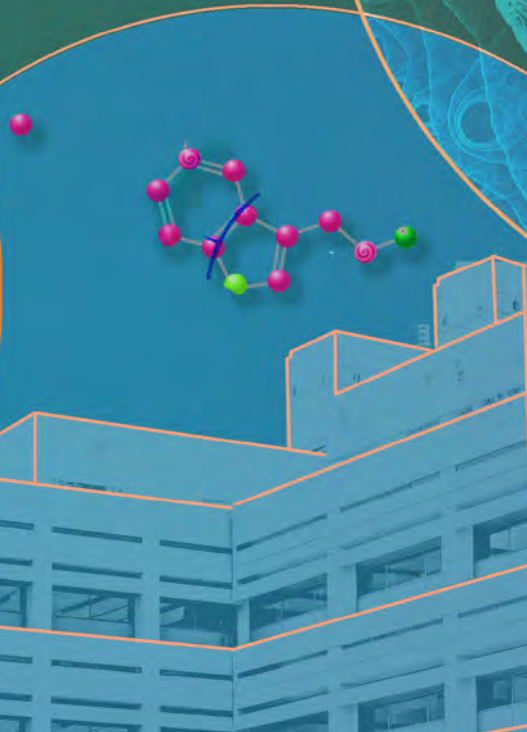

New Faculty Members Bring New Ideas to the Beckman Center

By Sarah C.P. Williams

> We are excited to welcome our extraordinary and diverse group of new faculty members, who are opening new areas of exploration and collaboration. They exemplify the interdisciplinary science and state-of-the-art technology that is the central focus of Stanford's Beckman Center.
>
> — Lucy Shapiro, Ph.D.

Scientists are the lifeblood of the Beckman Center for Molecular and Genetic Medicine. Their ideas, ingenuity, and curiosity fuel innovative research that helps to fulfill the mission of the Beckman Center: to promote discovery and innovation in the basic sciences, encourage interdisciplinary collaboration, and accelerate connections between the research bench and clinical medicine.

Over the past few months, we have been thrilled to welcome six outstanding new scientists to the Beckman Center community: Alex Gao, Ph.D., assistant professor of biochemistry; Lauren Goins, Ph.D., assistant professor of developmental biology; Ruth Huttenhain, Ph.D., assistant professor of molecular and cellular physiology; Nicole Martinez, Ph.D., assistant professor of developmental biology and of chemical and systems biology; Tino Pleiner, Ph.D., assistant professor of molecular and cellular physiology; and Florentine Rutaganira, Ph.D., assistant professor of biochemistry and developmental biology.

“We are excited to welcome our extraordinary and diverse group of new faculty members, who are opening new areas of exploration and collaboration,” says Lucy Shapiro, Ph.D., director of the Beckman Center. “They exemplify the interdisciplinary science and state-of-the-art technology that is the central focus of Stanford’s Beckman Center.”

Read on to learn more about our new colleagues and their fascinating areas of research.

FEATURE ARTICLE

> There are fascinating questions about why microbes have this amazing system. Where did it come from? What other systems might be out there? I think there's a lot of interesting molecular biology waiting to be discovered.
>
> — Alex Gao, Ph.D.

Alex Gao, Ph.D.

Assistant Professor of Biochemistry

If you were to count all the genes that exist on our planet, only a minuscule percentage would come from humans. Researchers have estimated that just across the species of bacteria that live in the human gut, there may be twenty million genes—about 1,000 times the number of genes humans have.

Alex Gao, Ph.D., a new assistant professor of biochemistry, thinks these millions of microbial genes—from the human microbiome, as well as other sources—likely hold secrets to developing new drugs and research tools.

"An enormous number of genes exist in nature, particularly in microbes," says Dr. Gao, who launched his Beckman Center lab in December 2022. "It's only in recent years that we've started to tap into the bulk of this diversity, and I think there's a lot of interesting molecular biology waiting to be discovered."

Dr. Gao grew up in a small town in Idaho, fascinated by math and science as a child. He found both beauty and mystery in the intricacies of biology and chemistry, and came to Stanford University as an undergraduate chemistry major. As part of the Bio-X Undergraduate Summer Research Program, he studied new methods for imaging proteins using fluorescent labels that were inspired by molecules found in fireflies—perhaps the first hint that Dr. Gao would devote his career to seeking out biological tools from nonhuman organisms.

But Dr. Gao also had other interests; he stayed at Stanford after his undergraduate degree to earn a co-terminal master's in electrical engineering.

"It was a complementary skill set that I wanted to learn," says Dr. Gao. "It helped expand my knowledge base in new directions, and I'm glad I had the opportunity to do that."

Dr. Gao then began to combine his engineering and life sciences skills in the Department of Biological Engineering at MIT. There, he pursued his graduate degree in the lab of Feng Zhang, Ph.D. The lab focused on the CRISPR/Cas gene editing system that researchers had co-opted from bacteria. In bacteria, the system helps fight off viruses by cutting up their genetic material; scientists had learned how to use this to specifically edit genes in the lab.

"There are fascinating questions about why microbes have this amazing system to begin with," says Dr. Gao. "Where did it come from? What other systems might be out there? I started to really look at the basic microbiology."

In 2015, Dr. Gao and his colleagues reported ways to improve the Cas9 enzyme often used in gene editing, work that was published in *Science*. Over the next few years, Dr. Gao pondered ways to systematically discover and harness genes from microbes, while continuing to develop CRISPR genome editing tools, including Cas12a. The latter part of his time at MIT—including time spent as a Junior Fellow at Harvard University, after earning his Ph.D.—was then devoted to finding new interactions between bacteria and the viruses that infect them, called bacteriophages.

"The majority of bacteria actually don't have CRISPR, so the thought was that they must have other interesting ways to defend themselves against viruses," he says.

In a 2020 *Science* paper, Dr. Gao reported 29 new types of genes important for protecting bacteria from viruses. He went on to reveal the details of how some of these genes play a role in defense. In a 2022 *Science* paper, he showed how bacteria recognize a unique section of the bacteriophage structure by wrapping around the virus; he likens it to a glove fitting onto a hand. That study was the first to reveal this kind of direct recognition of viral proteins by prokaryotes; most known bacterial defense systems detect viral DNA or RNA.

When it came time to start his own lab, returning to Stanford was an easy decision, Dr. Gao says. "I loved being here as a student and was really thrilled at the opportunity to come back."

The goal of his lab, he says, is to harness the genetic diversity of Earth's microbiome. That means developing new ways to screen countless species of bacteria and viruses for genes that could be useful. Already, bacteria have been the source of biological tools, such as restriction enzymes, recombinant DNA, and CRISPR gene editing. Dr. Gao thinks that's only the beginning.

"I'd like to understand more about the really interesting genes that are hidden out there in all these weird microbes," says Dr. Gao. "I'm excited by the potential to develop new technologies that let us study and manipulate human cells in new and better ways."

Dr. Gao's lab has deep expertise in genetics, bioinformatics, and biochemistry, all helpful in designing experiments that can pull useful information from massive sets of bacterial genomes. He thinks that with the help of emerging data mining techniques, the ability to comprehensively sequence and understand all bacterial genes will be within reach in the future. And he wants to be a part of that.

If you can't find Dr. Gao in his lab, you might follow the sounds of music; Dr. Gao is an accomplished piano player and has already drawn attention playing in White Memorial Plaza. "It's very relaxing," he says.

> It was my first taste of live microscopy and I just completely fell in love with it. I've tried lots of other things, but I always come back to microscopy.
>
> — Lauren Goins, Ph.D.

Lauren Goins, Ph.D.

Assistant Professor of Developmental Biology

When developmental biologist Lauren Goins, Ph.D., gives a seminar about her research, she often shows a cartoon of two personified stem cells: a small babyish cell and an old, wise-looking cell. "How do I decide what I'm going to be when I grow up?" the smaller cell is asking the older one.

That question is the crux of Dr. Goins' research; she wants to know how blood stem cells chose their fates—a complex process that is mediated by both their genetic identity and external molecular factors. Her research has implications for understanding how to treat infections, cancer, and other diseases.

Like the stem cells she studies, Dr. Goins' scientific career has been shaped by an amalgam of influences. She grew up in New Orleans in a struggling family. In elementary school, her father died from liver cancer; not long after, her mother became disabled with multiple chronic diseases.

"Seeing my parents face these medical predicaments really drove my passion for research and science," says Dr. Goins. "I realized, even as an elementary school student, that doctors often didn't have the tools to help people, because the research wasn't there. I wanted to become someone that helped change this."

Dr. Goins attended summer research programs in high school, excelled in her classes, and secured a spot studying biochemistry at Harvard University. The summer after her freshman year, she participated in the Stanford Summer Research Program in the Biomedical Sciences, working in the lab of Julie Theriot, Ph.D., then at the Beckman Center. Dr. Theriot was studying actin, a dynamic molecule with both structural and functional roles in cells. That summer, Dr. Goins helped image how actin in fish skin cells moved around.

"It was my first taste of live microscopy and I just completely fell in love with it," recalls Dr. Goins. "I've tried lots of other things, but I always come back to microscopy. For me, seeing something happen is believing."

During the rest of her undergraduate education, Dr. Goins took advantage of every chance to both study science and see the world—she spent summers in labs in Italy and Ireland. Back at Harvard, she worked in the lab of Ruth Ruprecht, M.D., Ph.D., studying how HIV mutations increased the ability of the virus to replicate, and working toward an HIV vaccine.

When it came time to pick a graduate school, though, Dr. Goins says she wanted to focus on what she'd first discovered at Stanford: the actin cytoskeleton. She pursued her Ph.D. at the University of California, San Francisco, working with Dyche Mullins, Ph.D., to study tropomyosin, a protein that binds to actin to regulate its organization.

"Actin is like a brick that is this simple, fundamental unit, but can be used in all kinds of elaborate structures and buildings," says Dr. Goins. "Tropomyosin helps dictate those designs."

Dr. Goins turned to isolated fruit fly cells—which have fewer kinds of tropomyosin than do human cells—to understand the details of the molecule. She discovered some surprises about how tropomyosin variants moved through cells and helped cells keep their shape. Certain mutations in tropomyosin, she found, made blebs start bubbling off the sides of cells. At the same time, Dr. Goins discovered how supportive and fun the fruit fly research community was; she knew she wanted to continue working with the model organism.

As a postdoctoral fellow in the lab of Utpal Banerjee, Ph.D., at the University of California, Los Angeles, Dr. Goins aimed to perfect live imaging of fruit fly internal organs. The lab studied how organs work together to coordinate development, immune and stress responses, and cancer. Following organs over time in living fruit flies was critical to this research. Dr. Goins had never seen a living fruit fly before, she says (she'd worked only with isolated cells in graduate school), but leapt at the opportunity to work on microscopy methods.

"People had tried so many different ways of making this kind of microscopy work, but I came up with something different," she says. "It worked incredibly quickly; within a few weeks or months of joining the lab, we were seeing things."

Dr. Goins' method for seeing inside fruit fly larva let her track stem cells in real time during development. That led to another observation: blood stem cells have a never-before-described intermediate progenitor state in between their immature and mature forms.

Now, her lab at Stanford is aiming to better understand that intermediate state. She wants to know how the balance of different intermediate stem cells dictates their eventual fate as mature blood and immune cells. Those intermediate stem cells, she hypothesizes, also could play a role in some blood cancers, like acute myeloid leukemia.

Dr. Goins' expertise in visualizing actin—which plays roles in the physical separation of cells into mother and daughter cells—will also help her probe the asymmetrical division of stem cells and how that division might impact the cells' mature states.

While her research asks basic questions, Dr. Goins says it also fulfills her desire to contribute to medical advances.

"I think with fruit flies, we can really get at the basic mechanisms of these cellular processes," she says. "Once we know what genes are involved, we can delve into how those players are implicated in disease."

> My hope is that using our quantitative proteomics approach, we can understand better what is happening inside a cell. If we understand that biology, we can use it to guide drug design.
>
> — Ruth Huttenhain, Ph.D.

Ruth Huttenhain, Ph.D.

Assistant Professor of Molecular and Cellular Physiology

The first time Ruth Huttenhain, Ph.D., ran a mass spectrometry experiment, she was hooked. At the time, she was a student in her native Germany but had flown to the United States for a short research experience at the National Institutes of Health (NIH). She was studying variants of hemoglobin—the protein in red blood cells that carries oxygen. At the NIH, she learned how mass spectrometry could differentiate these variants and help shed light on how they were modified in people with sickle cell anemia.

"I got really fascinated with the capability of the technology," recalls Dr. Huttenhain, who joined the Department of Molecular and Cellular Physiology this spring. "I realized this was a rapidly growing field and that mass spec was incredibly more powerful than most people gave it credit for."

Today, her passion for mass spectrometry hasn't faded. In her new lab, she is using the technology—coupled with other proteomics methods—to better understand a class of molecules known as G-protein-coupled receptors (GPCRs). Those receptors are the biggest class of targets for human drugs, but questions abound on how to better target them to treat conditions as wide-ranging as pain, high blood pressure, obesity, depression, cancer, and Alzheimer's disease.

"My hope is that using our quantitative proteomics approach, we can understand better what is actually happening inside a cell when these receptors become activated," says Dr. Huttenhain. "If we understand that biology, we can use it to guide drug design in the future."

The fact that her mass spectrometry work has steered her toward drug targets, she says, brings her career full circle. As an undergraduate at the University of Bonn, Dr. Huttenhain studied to be a pharmacist; through an internship program she began working in a pharmacy.

But when an advisor mentioned the possibility of studying abroad while receiving a master's degree, Dr. Huttenhain jumped at the opportunity—leading her to the NIH and mass spec. Despite her interest in pharmacology, she decided she wanted to pursue more basic research.

Back in Europe, Dr. Huttenhain began a Ph.D. program at ETH Zurich, where she joined the lab of Ruedi Aebersold, Ph.D., one of the world leaders in proteomics technology development. There—as a graduate student and later as a postdoctoral research fellow—she worked on improving methods and workflows that researchers were using to identify cancer-related proteins.

"There had been an inherent problem with the consistency of quantitative proteomics," she says. "Data was not reproducible and consistent."

While a sample can contain hundreds of proteins, Dr. Huttenhain developed a way to home in on the most important proteins that a researcher is interested in, giving them high-quality data on that smaller set. She used the approach to screen blood samples from ovarian cancer patients and identify proteins that could be used to stratify patients by the severity of their disease. At the end of that project, though, Dr. Huttenhain says she wanted to know more about the biology of the biomarkers and how they functioned in cells.

"I got really interested in how proteins in large networks are working together inside cells and how we can use proteomics technologies to understand dynamic changes in these networks," she says.

That drive led her to the systems biology lab of Nevan Krogan, Ph.D., at the University of California, San Francisco (UCSF). In Dr. Krogan's lab, Dr. Huttenhain started out studying how HIV rewires the networks of proteins inside human immune cells. The research quickly immersed her in the new-to-her areas of virology and cell biology. While fine-tuning a method called proximity labeling, which lets researchers capture information about very short-lived protein interactions, a fellow postdoc mentioned to Dr. Huttenhain how useful the method could be to understand GPCRs.

"The signaling with GPCRs happens really fast, so capturing all of these events had been very difficult," explains Dr. Huttenhain. "With the proximity labeling I'd developed, we could for the first time track this very transient interaction."

Proximity labeling tags biomolecules in the vicinity of a specific "bait" protein, such as a GPCR. The tagged molecules can then be characterized using mass spectrometry.

"You label everything that's close by, like spray painting," says Dr. Huttenhain.

For GPCRs, Dr. Huttenhain used proximity labeling to discover new binding partners and piece together what happens when the receptors are activated. She gained enough new information that she and her colleagues could develop computational tools that let them predict the trajectory of a GPCR moving through a cell.

Dr. Huttenhain remained at UCSF as an adjunct professor to help lead a group of researchers in the Krogan lab, applying proteomics to understand how genetic mutations associated with autism can change the function of GPCRs.

More recently, Dr. Huttenhain is focusing her attention on a different GPCR, called the μ-opioid receptor (MOR). The drug morphine is known to bind MOR, making it incredibly important in drug development. If researchers can separate some of the side effects from the pain-killing properties of morphine, they could develop a safer opioid.

While she opens her new lab, Dr. Huttenhain is also staying passionate about mentoring younger scientists. She is the co-chair of the Early Career Researcher Committee for the Human Proteome Organization, and has helped organize efforts to increase the visibility of early career researchers in the field and pave the way for improving diversity, equity, and inclusion within proteomics.

"My science is important, but it's also important to work on things beyond my own science," she says. "This lets me have an even bigger impact."

> There's a lot we don't know about all the functions that RNA has, and all these points of regulation. There are a lot of exciting opportunities in this field right now.
>
> — Nicole Martinez, Ph.D.

Nicole Martinez, Ph.D.

Assistant Professor of Developmental Biology and of Chemical and Systems Biology

Ribonucleic acid, or RNA, is one of the most versatile, dynamic molecules in living cells—but for years, it was far less studied than DNA. While DNA contains the full set of genes that make up all the functional parts of cells, RNA molecules are transcribed from that DNA, like photocopied pages of an instruction manual. Recently, however, researchers have discovered that RNA is far more adaptable and critical than previously appreciated. Modifications to RNA can have drastic impacts on cells.

Nicole Martinez, Ph.D., who joined the Beckman Center in 2022, is among those leading new research into the role of RNA regulation in biology and medicine.

"There's a lot we don't know about all the functions that RNA has and all these points of regulation," she says. "We want to know how RNA is regulated in different situations, what the mechanisms are behind that, and how they are dysregulated in disease states. There are a lot of exciting opportunities in this field right now."

The Martinez lab is interested in how modifications to both RNA-processing enzymes and RNA itself can alter the proteins encoded by that RNA and, in turn, cause disease. It's a level of cellular regulation that goes beyond the genes contained in a cell's DNA.

Dr. Martinez did not always want to be a researcher. Growing up in Puerto Rico, she liked science but didn't know anyone who actually worked as a scientist.

"I figured after I got my undergraduate degree in biotechnology, I'd work in manufacturing or maybe the pharmaceutical industry, because those were the only science-related careers I'd had any exposure to," she recalls.

But while an undergraduate at the University of Puerto Rico at Mayaguez, she attended a career fair and learned about a summer research program at the Broad Institute of MIT and Harvard. She was intrigued by the opportunity, applied, and got a spot at the Broad Institute that summer. There, she worked in a lab that was trying to find new molecules to manipulate histones—the spool-like proteins around which DNA is tightly wound inside cells.

"That was the first time I identified as a scientist," Dr. Martinez says. "I loved it. I was like 'I want to do this. I want to have my own research lab.'"

Later, while in grad school at the University of Pennsylvania, Dr. Martinez took a class in immunology. She found that topic fascinating and joined a lab studying how RNA molecules changed during immune responses. It was then that she fell in love with RNA.

"It's just a fascinating macromolecule in so many ways," she says. "It has a lot of diversity and it's regulated at so many points throughout its life cycle. RNA can serve as a carrier of genetic information like DNA, but it can also fold into complex three-dimensional structures like proteins can."

In the lab of Kristen W. Lynch, Ph.D., at UPenn, Dr. Martinez probed how RNA was cut and pasted into different combinations in immune cells—a process called alternative splicing. Dr. Martinez, Dr. Lynch, and their colleagues discovered that when T cells are activated in response to a pathogen, RNA is alternatively spliced. Dr. Martinez identified the signaling pathway that connects T cell activation to RNA splicing; that research was published in *Genes & Development* in 2015.

"Understanding the biology of this pathway can potentially lead to ways of modulating it to mediate immune responses," says Dr. Martinez.

When looking for a postdoctoral fellowship, Dr. Martinez focused on other labs studying RNA processing and modifications, and landed at Yale University, where she worked with Wendy V. Gilbert, Ph.D. Dr. Martinez's project at the Gilbert lab revolved around pseudouridine, a modified version of the RNA nucleoside uridine. Pseudouridine is the most common modified nucleoside in human cells, with pseudouridine found in about five percent of all RNA molecules. Dr. Martinez showed how the structure of RNA molecules helps determine whether a uridine is converted to a pseudouridine, work that was published in *Nature Chemical Biology* in 2019.

Today, Dr. Martinez is still interested in pseudouridine, but also RNA modifications more broadly. Some RNA-binding enzymes have been found to be present in higher levels in tumor cells; others are most highly expressed in developing neurons in the brain. In both instances, Dr. Martinez wants to know why—and how RNA modifications could be linked to cancer or developmental disorders.

"We really want to understand how RNA modifications serve as a fundamental mechanism to control gene expression and how this is dysregulated in disease," she says. "When we know that, we can develop new ways to intervene."

> There's so much creative freedom with [nanobodies]. You can control lots of things about where and when they travel in the body, or how long they're active. I think they're going to become increasingly powerful in the future.
>
> — Tino Pleiner, Ph.D.

Tino Pleiner, Ph.D.

Assistant Professor of of Molecular and Cellular Physiology

What do alpacas, antibodies, and Alzheimer's disease have in common? They all play roles in the research program of assistant professor Tino Pleiner, Ph.D., who launched his Stanford lab in June. Throughout his career, Dr. Pleiner has generated new ways to answer questions about basic cell biology using small, unique "nanobodies" generated by alpacas. Now, his new lab will apply those techniques to better understand the quality control mechanisms that cells use to ensure that membrane proteins are properly folded—a process that goes awry in normal aging as well as in diseases such as Alzheimer's, Parkinson's, and cancer.

"In aging and disease, this quality control machinery basically gets weaker and weaker, and misfolded proteins accumulate," says Dr. Pleiner. "What I think we can do with nanobodies is leverage signaling pathways to turn up protein degradation and boost folding capacity."

Dr. Pleiner was born in East Germany before the fall of the Berlin Wall; when Germany reunified early in his childhood, his parents encouraged him to take advantage of the new educational opportunities that arose. He had broad interests, enjoyed school, and liked spending time in nature wondering about the inner workings of plants and animals, so when it came time to choose his undergraduate focus at nearby Leipzig University, he picked biochemistry.

In graduate school at the University of Göttingen, Dr. Pleiner was drawn to the lab of Dirk Görlich, Ph.D., who was studying how proteins were transported between the cytosol and the nuclei of cells.

"Dirk had a magnetic personality and this research fascinated me," recalls Dr. Pleiner. "How some proteins got this very selective access to the genetic material of a cell seemed to be this big enigma."

But once he joined the lab, which was housed at the Max Planck Institute for Multidisciplinary Sciences, Dr. Pleiner got caught up in another project: alpaca antibodies. Max Planck researchers had recently begun working with tiny nanobodies produced by alpacas, and a herd of the animals grazed in the fields outside the institute. Dr. Görlich wondered whether the small antibodies could be used to tag some of the proteins the lab was interested in, and Dr. Pleiner agreed to investigate.

"Nanobodies are about ten times smaller than conventional antibodies, and that means they can bring a fluorescent tag much closer to a protein of interest," says Dr. Pleiner. "That translates to seeing more detail inside a cell, and pictures that are much less blurry."

Dr. Pleiner spent the next few years developing new technology to add multiple fluorescent tags to the nanobodies. Once a nanobody was generated by an alpaca, Dr. Pleiner and his colleagues could isolate its gene and produce it in bacteria—a cheaper and more efficient alternative to typical secondary antibody generation in donkeys, sheep, and goats. Those approaches were described in *eLife* in 2015 and the *Journal of Cell Biology* in 2017.

To boost his ability to apply these new techniques to molecular and cellular problems, Dr. Pleiner accepted a postdoctoral research fellowship at the California Institute of Technology (Caltech), in the lab of Rebecca Vorhees, Ph.D., a new faculty member studying protein quality control. Dr. Pleiner was Dr. Vorhees' first hire—a move, he says now, that set him up well to launch his own lab.

At Caltech, Dr. Pleiner delved into the question of how cells mediate the complex process of creating new membrane proteins—proteins whose structure is embedded into any of the many membranes within a cell.

"These proteins have to be woven into the lipid bilayer as they're produced," he says. "It's a highly orchestrated and regulated process that oftentimes fails."

Dr. Pleiner studied the human endoplasmic reticulum membrane protein complex (EMC), a massive, nine-subunit cluster of proteins that, as a membrane protein is being synthesized, helps insert the growing strand of amino acids into the ER membrane in the correct orientation. Dr. Pleiner used an antibody-based approach to purify the EMC from human cells and then determined its cryo-electron microscopy structure—which was published in *Science* in 2020.

As he recruits graduate students for his new lab—and scouts out alpacas in the Bay Area—Dr. Pleiner is now thinking about how to use antibodies to uncover more about how membrane proteins fold and what happens when they become misfolded. He is aiming to use nanobodies to not only label proteins, but to also manipulate them in other ways, such as activating or blocking a protein. Antibodies can flip molecular switches inside cells much faster than genetic alterations, Dr. Pleiner says.

"Antibodies can block critical protein-protein interactions," he explains. "Then we can assess the immediate functional consequences without any delays. We might like to block the access of membrane proteins to a particular biogenesis factor, for instance, and see what happens."

Dr. Pleiner also imagines using nanobodies attached to nuclear localization signals to force signals into the nuclei of cells where they activate genes. Ultimately, he even thinks nanobodies capable of manipulating protein folding could be used therapeutically—to treat age-related diseases in which misfolded proteins accumulate, or in tumors where boosting levels of misfolded proteins could trigger cell death. For now, though, nanobodies are a valuable research tool to pinpoint and describe the pathways involved in these processes.

"There's so much creative freedom with this tool," Dr. Pleiner says. "You can control lots of things about where and when they travel in the body, or how long they're active. I think they're going to become increasingly powerful in the future."

> My work is driven by curiosity. My hope is that by pursuing these questions that are very basic in nature, we'll be able to understand biology more broadly.
>
> — Florentine Rutaganira, Ph.D.

Florentine Rutaganira, Ph.D.

Assistant Professor of Biochemistry and of Developmental Biology

Smaller than a grain of pollen, choanoflagellates measure just a few microns across. Under the microscope, they look like tiny tadpoles, and beat a single flagellum to propel themselves through the water, where they munch on bacteria. At first glance, choanoflagellates don't appear to have much in common with us humans. But these minuscule eukaryotes are among the closest living, single-celled relatives of animals.

Assistant professor Florentine Rutaganira, Ph.D., who joined the departments of Biochemistry and Developmental Biology in September 2022, probes how choanoflagellates use tyrosine kinases to communicate and coordinate activity across a colony. That comparatively simple signaling, she says, can shed light on how cells organized into multicellular organisms in the first place—and even how some kinases contribute to human disease.

"My work is driven by curiosity," says Dr. Rutaganira. "But I think that fundamental science so often leads to unexpected discovery, and my hope is that by pursuing these questions that are very basic in nature, we'll be able to understand biology more broadly."

Dr. Rutaganira grew up in California's San Joaquin Valley in a scientific household; her mom was a lab manager and her dad a mathematician. She started college intending to become a pharmacist, but as an undergraduate dabbled in research—working in labs studying topics as diverse as peaches, heart failure, infectious disease, and organic chemistry synthesis. After shadowing a pharmacist at the University of California, Los Angeles, one summer, she decided she found research—especially chemistry research—more exciting than the hospital.

"I realized I was a lab rat at heart," Dr. Rutaganira says.

In grad school—at the University of California, San Francisco, Chemistry and Chemical Biology Graduate Program—Dr. Rutaganira joined the lab of Kevan M. Shokat, Ph.D., studying how to inhibit kinases that triggered human disease. For her thesis, she focused on blocking calcium-dependent protein kinase 1 (CDPK1), a kinase used by the pathogen *Toxoplasma gondii* to infect human cells and replicate. Some of the most serious symptoms of toxoplasmosis—most often spread to humans through undercooked meat—involve inflammation of the brain, so Dr. Rutaganira screened compounds not only for their ability to block CDPK1, and therefore inhibit *Toxoplasma gondii,* but also for their ability to cross the blood-brain barrier. The compound she discovered was described in the *Journal of Medicinal Chemistry* in 2017; it is now being moved toward clinical testing by a commercial venture.

As she studied the parasitic kinase, though, Dr. Rutaganira had begun to wonder about the wider diversity of kinases across different organisms.

"I was starting to think more broadly about what kinases look like in organisms outside animals," she recalls. "And I became especially interested in this question of whether a tyrosine kinase was relevant for the origin of multicellularity in animals."

For years, researchers had thought that only animals had tyrosine kinases. But in 2008, Nicole King, Ph.D., of the University of California, Berkeley, sequenced the first choanoflagellate genome and discovered evidence of kinases in the single-celled organisms. The finding suggested that the enzymes might be responsible for the coordination between cells, even in single-celled organisms.

Intrigued, Dr. Rutaganira joined Dr. King's lab. Funded by a Howard Hughes Medical Institute Hanna H. Gray fellowship that gave her support to follow her own interests, Dr. Rutaganira began screening through tyrosine kinase inhibitors that had been developed in animal models, to see which ones could also inhibit choanoflagellate tyrosine kinases.

"We thought that the chemistry of these inhibitors should transfer, but nobody had tried it before," explains Dr. Rutaganira. "So it was a lot of troubleshooting and setting up new assays and probing whether these inhibitors were impacting the choanoflagellate biology at all."

As she thought about continuing this work in her own lab, Dr. Rutaganira was drawn to Stanford's Beckman Center for its convergence of cell biology, biochemistry, and developmental biology, which all come into play for studying choanoflagellate signaling.

In her new lab at Stanford, Dr. Rutaganira is continuing to develop specific inhibitors for choanoflagellate kinases and use those as tools to probe how the kinases impact cell-cell communication, colony formation, and the way choanoflagellates coordinate processes like nutrient gathering or responding to nearby bacteria.

"Better understanding this symbiotic relationship between choanoflagellates and bacteria could shed light on the human gut microbiome," she says.

Because of this kind of potential link, Dr. Rutaganira is also excited about the Beckman Center's proximity to Stanford Medicine—the biology she uncovers about tyrosine kinases could have implications for human disease.

"I like knowing that there's a trajectory and support if my projects do lead to discoveries that impact human health," she says. "We know that these molecules we're studying are really important, because in animals when tyrosine kinases are misregulated, it leads to diseases, including cancer."