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MCB

SMALL BUT MIGHTY

Tiny organisms that make a big impact

ILLINOIS
College of Liberal Arts & Sciences

LETTER FROM THE DIRECTOR

Dr. Milan K. Bagchi, Director, Deborah Paul Endowed Professor of Molecular and Cellular Biology

Greeting friends and alumni:

Our fall issue of the MCB magazine focuses on the diverse ways in which microbes affect our health. While certain pathogenic microbes pose a serious threat to our health and wellbeing, we do host communities of microbes collectively known as the microbiome, which have potent health-promoting activities. Beginning at birth and throughout our lifetime, the microbiome shapes our health. According to Lynn Margulis, an American evolutionary theorist and biologist, "beneath our superficial differences we all are walking communities of bacteria." There is a clear need for fundamental and translational research on the very diverse beneficial and detrimental roles of microbes in influencing our health. This magazine showcases cutting-edge research performed by our faculty that focus on microbes and microbial environments in infection and its impact on human health, as well as the health of interconnected ecological systems.

In MCB, the Department of Microbiology has developed and maintained the highest national and international reputation for more than 100 years. The Department was recently designated a "Milestones in Microbiology" site by the American Society for Microbiology. MCB scientists studying microbiome and host interactions have excellent opportunities for scientific synergy and collaboration across the campus. For example, in the Carl R. Woese Institute for Genomic Biology, five research themes including Biocomplexity, Infection Genomics for One Health, Microbiome Metabolic Engineering, Mining Microbial Genomes, and the Energy Biosciences Institute are actively investigating microbial communities or applying knowledge gained from the study of the microbiome to challenges facing humanity, such as renewable fuels. The UIUC Health Sciences Strategy Task Force has identified "Microbes: Drivers of Health and Disease" as one of the five "Impact Areas" which represent opportunities in which Illinois is poised to have the greatest global influence. This magazine highlights some of the innovative and interdisciplinary research programs led by our scientists. It features undergraduate, graduate, and postdoctoral researchers who are contributing to this research.

This is an opportune time for our undergraduate students. MCB faculty continues to support student research experience in our laboratories. Alumni are supporting these research opportunities, and we now have an incredible learning center that supports advising assistance, as well as areas for collaborative and individual resources. We thank our alumni who have made this space possible.

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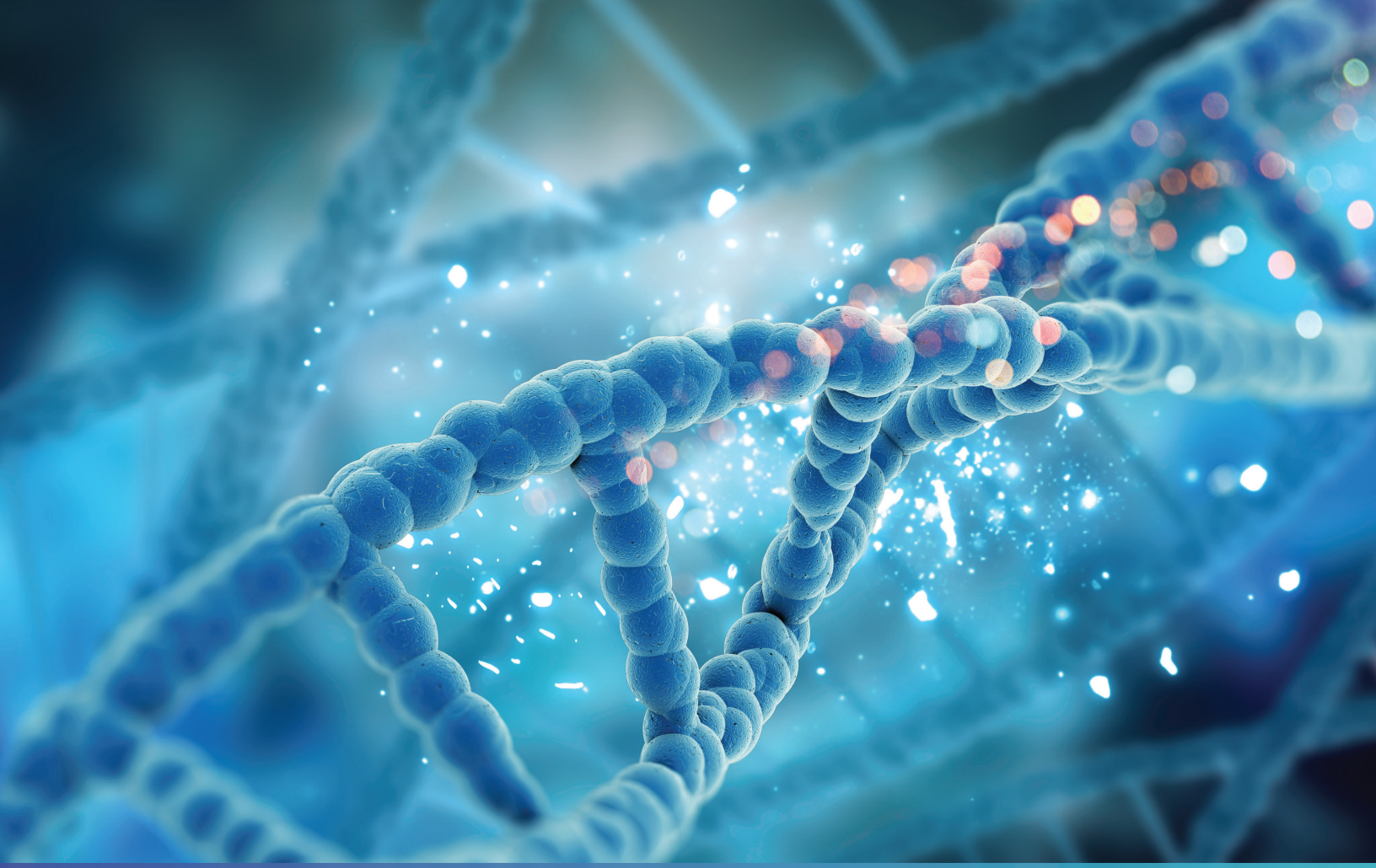


The Next Gold Rush: Mining Microbial Genomes

By Deb Aronson

"Microbes are king of the world. If human beings ceased to exist, microbes wouldn't even notice [except those in the human microbiome], but if microbes ceased to exist today, human beings would cease to exist tomorrow."

Willam Metcalf, G. William Arends Professor in Molecular & Cellular Biology, professor of microbiology.

Like the hills around San Francisco back in 1849, microbes have treasure buried deep within them. Unlike gold, this treasure can be used to cure disease, improve crop yields, improve the environment and even remove stubborn laundry stains.

Researchers in the Mining Microbial Genome (MMG) theme at the Carl Woese Institute for Genomic Biology (IGB), including several MCB researchers, are "mining" microbes to uncover their seemingly endless potential for useful natural products.

"The goal of our theme is to tap into the immense world of microbes," says William Metcalf, G. William Arends Professor of Molecular and Cellular Biology and MMG theme leader. "Their potential is incredible."

It used to be that microbes, unlike gold, were misunderstood or even abhorred. Even now —despite the fact that microbes have given us beer, bread and penicillin — the popular perception of microbes may be that they represent dirt, disease and spoiled food.

But talk to Metcalf for one minute and it quickly becomes clear that microbes hold more potential than all the gold in the world. Already, he points out, more than half of all human medicines — antibiotics, cancer treatments, anti-virals and blood pressure reducers — are natural products developed from microbes and microscopic fungi.

The Power of Microbes

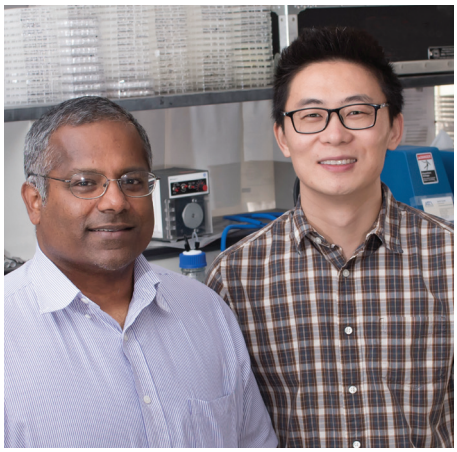
"I'll tell you something most humans don't realize," says Metcalf. "Microbes are king of the world. If human beings ceased to exist, microbes wouldn't even notice [except those in the human microbiome], but if microbes ceased to exist today human beings would cease to exist tomorrow."

Life as we know it would be impossible without microbes. It is thanks to them that we have an oxygen atmosphere, the carbon cycle, the nitrogen cycle, the sulfur cycle and other elemental cycles that make our lives on Earth possible.

Part of the power of microbes lies in their incredible numbers. Microbes —there are one million microbial cells for every star in the known universe — live in every imaginable and even unimaginable environment. And in each of these environments they've developed metabolic pathways that enable them to survive.

"There is no bit of metabolism in any higher organism that is not found in bacteria. The reverse is not true," Metcalf says.

That means there are microbes that can metabolize a given substance — fat, for example — at high temperatures and others than can do so in cold and also at room temperature. Within those metabolic pathways are molecules that can be harnessed to help humans. So far researchers have barely harvested the lowest low-hanging fruit in microbial metabolism and already we have numerous antibiotics, herbicides and other drugs people use every day.



Biochemistry Professor Satish Nair, left, and Postdoctoral Researcher Shi-Hui Dong.

Until recently, accessing these molecules and compounds was like mining gold with a pick and shovel: laborious and expensive.

Antibiotics Arms Race

One on-going goal is to develop new antibiotics. As bacteria become resistant to antibiotics, researchers are always on the lookout for a new antibiotic: weapons in the ever-present anti-bacterial arms race. By understanding how microbes make molecules to defend themselves against other bacteria, researchers can engineer them in the lab and, ultimately, use them to treat patients.

A conference titled "Outpacing Antimicrobial Resistance," co-sponsored by MCB, IGB, the Carle Illinois College of Medicine and others, was held this September 24-25 in order to raise awareness, discuss challenges and possible solutions to the problem.

In addition to discovering new treatments, MMG researchers are keeping an eye on the cost of new treatments. For example, because malaria is a particular problem of less-developed countries, the World Health Organization has decided not to support any anti-malarial therapy that costs more than $1 per dose. By identifying a microbe that creates the anti-malarial molecule and understanding how it does so, researchers can engineer other organisms to over-produce those molecules and lower the cost, enabling an affordable medicine or vaccine. For example, Huimin Zhao, Steven L. Miller Chair in Chemical Engineering and a member of the MMG theme, has taken an anti-malarial compound recently characterized by the MMG theme and engineered bacteria to overproduce it. So far, his group has lowered the cost to about $8 per dose and, as they refine their methods, the cost will continue to fall, says Metcalf.

The power of microbes extends beyond medicine. Many fungicides and herbicides are microbial products. Metcalf is particularly keen to focus on agricultural applications. After all, he points out, we eat three times a day and we go to the doctor far less often, so we must not lose sight of the importance of agriculture and the need to increase crop yields to feed growing populations.

Likewise, microbes also hold the key for green chemistry. Some chemicals, when made synthetically, create toxic by-products or require immense heat or pressure. There have been cases where microbes have been discovered that make that same chemical without needing those conditions or creating toxic by-products. Once the pathway is understood, it will be possible to engineer other organisms to overproduce that chemical. Likewise, other microbes play a big role in bioremediation by being able to metabolize toxic by-products of industrial production.

Mining for Phosphonates

Until recently, accessing these molecules and compounds was like mining gold with a pick and shovel: laborious and expensive. Isolating even a single molecule was time-consuming and risky, says Satish Nair, I.C. Gunsalus Endowed Professor of biochemistry. Medicinal chemists had to screen for a specific activity, then isolate and purify the molecule. The work was arduous and, especially by the end of the 20th century, researchers were often re-discovering molecules that had

already been discovered. Researchers might work for close to decade on a molecule only to find it was already known.

"It just sort of killed the field," he says.

One development that changed was the plummeting cost of sequencing genomes. Today the cost to sequence a bacterial genome is in the range of $100, as compared to about $500 just five years ago.

Rather than isolating and purifying small molecules one by one, researchers can now sequence a genome and be able to determine if a specific gene was there or not. If we know, for example, that any organism making a particular product (a specific herbicide, for example) must have a particular gene, then researchers can scan the available, sequenced microbial genomes for that gene.

The MMG has focused a lot of attention on a novel group of molecules known as phosphonates. Metcalf, among others, has long been interested in these molecules and their potential for antibiotic action. Previously discovered phosphonates include powerful medicines, herbicides (such as Round Up) and fungicides. A couple more hold potential for new anti-malarial and anti-TB drugs.

The nature of the phosphonate chemical group makes them particularly useful at targeting metabolism. That is because phosphonates are characterized by having a carbon-phosphorous bond, which is difficult to break. They work by mimicking molecules the microbes use for metabolism. Because they tend to be more resistant to enzymatic breakdown they, in fact, interfere with metabolism. Many microbes produce phosphonates to thwart their competitors.

Also, in the case of phosphonates, researchers knew the key gene was pepM. They had only to look for that particular gene to determine if a given microbe was producing phosphonate.

This is genome mining at its best.

Recently the team at MMG demonstrated the efficacy of this so-called genome mining. In four years — a mere blink of an eye in research — they scoured 10,000 bacterial strains, found 278 strains that had the pepM gene. This screening effort required only two

One development that changed that was the plummeting cost of sequencing genomes. Today the cost to sequence a bacterial genome is in the range of $100, as compared to about $500 just five years ago.

John Gerlt, professor of biochemistry and Gutgsell Chair.

postdoctoral researchers, a lab technician and four undergraduates.

The group identified 70-80 broad molecular classes within the phosphonates. Within those classes there are potentially hundreds of different molecules. They purified a dozen in detail as a proof of concept. One of the molecules they purified looks to be a new antibiotic in a novel class no one has seen.

By checking the genes on either side of pepM, the researchers could determine if a given pathway was a previously unknown pathway to build new phosphonates or one already known. In this process they found 19 new phosphonates.

More Than One Way to Mine the Genome

But what if you have a genome sequence but you don't know what genes code for? This is a common situation.

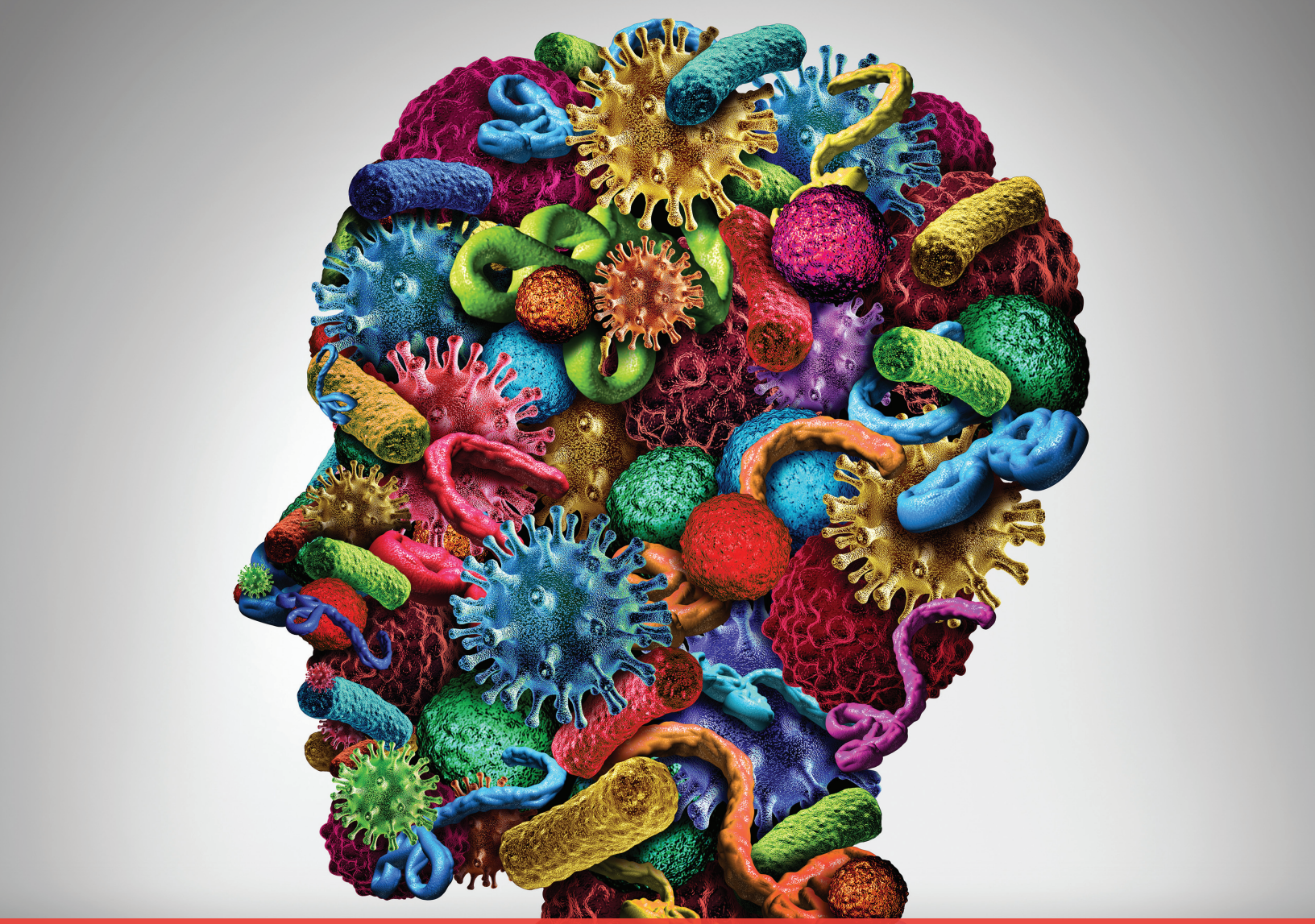
"We discover genes today faster than we can determine function," says Metcalf.

Researchers must crack the "black box" of the microbial genome in order to understand what each gene does before it can determine which gene to pursue. One way to do that is to focus on an enzyme and its substrate, the molecule to which the enzyme "docks" in order to begin a reaction. This helps determine an enzyme's function. Understanding an enzyme's function will elucidate what genes are needed in that pathway and, thus, what role the gene plays.

The key is to figure out a way to do this more efficiently. The Enzyme Function Initiative, a program project grant led by John Gerlt, professor of biochemistry and Gutgsell Chair, and part of MMG, has developed a way to do this on a large and efficient scale. This multi-investigator grant has sub-projects that go together to make a whole that is larger than the sum of the parts. Some of the steps include determining an enzyme's structure, another step involves using that information to computationally determine a list of possible substrates, and ultimately to determine the function of the gene or genes involved in that pathway.

Miracle of Microbes

As microbes continue to be harnessed in ways that improve human lives, perhaps their reputation will improve. But whether or not that happens, marvelous microbes and the almost miraculous metabolic pathways that they have developed will continue to evolve. It is the way of microbes. Researchers like those at MCB and MMG continue to delve into their workings, making discovery after discovery, many of which will help others. Microbes may be unsung heroes, but they are appreciated where it matters, in the hallways and labs of places like MCB and the IGB. n



Infection Genomics for One Health: Where Research Realms Collide

By Serina Taluja, undergraduate researcher, Whitaker Lab

Natural, industrial, and agricultural ecosystems all make an impact on human health and vice versa. Studying these impacts is the focus of the Infection Genomics for One Health (IGOH) theme at the Carl R. Woese Institute for Genomic Biology (IGB). This theme comprises researchers from across disciplines, and is led by Dr. Rachel J. Whitaker, professor of microbiology.

"We're all connected. That is an undeniable truth," said Whitaker.

"Between the realms of agriculture, nature, and humans, the unifying factor is the microbes that exist in each and the specific genes those microbes carry. The IGOH theme at the IGB allows research to be contextualized, and to exist in a space where lab work becomes immediately relevant and applicable to the rest of the world," she said.

IGOH: From an Idea to a Theme

The idea for this theme started with three professors: Dr. Rachel Whitaker, Dr. Rebecca Stumpf, and Dr. Carla Cáceres. Each of these three scientists were from different departments, and they shared a desire to understand organismal interactions throughout the course of natural history. Dr. Whitaker saw the theme through its application to the IGB, to its trial phase, to expanding across the nine departments it encompasses today. There are currently ten professors who conduct research within this theme, and only two of them are from the same department.

"We started this theme because we wanted to create a type of hub for information to flow through, to allow people from different departments to work on infection genomics together," Dr. Whitaker explained.

Prior to the creation of this theme, researchers across the University of Illinois were working on a variety of infection studies, mostly within their own discipline.

Whitaker and others knew that the research would become stronger if they could work together.

"Studying them as a whole makes more sense," said Whitaker. "For instance, an infectious microbe may travel from a water system into humans, or from the soil, into plants, into livestock. The combinations of transmission go on, and in order to study these pathways, we needed this informational hub for cross-departmental collaboration."

"Luckily the IGB director, Gene Robinson, thought it was a great idea from the very beginning, and provided us with a space to meet in and lots of encouragement as we got the theme started," Whitaker said.

This theme was unique compared to anything else the IGB had seen before because it brought evolutionary biology to a modern light, and it allowed infection biology to be examined in a novel way: the studies would be more about the dynamics of infection and how these dynamics impacted evolutionary trajectories.

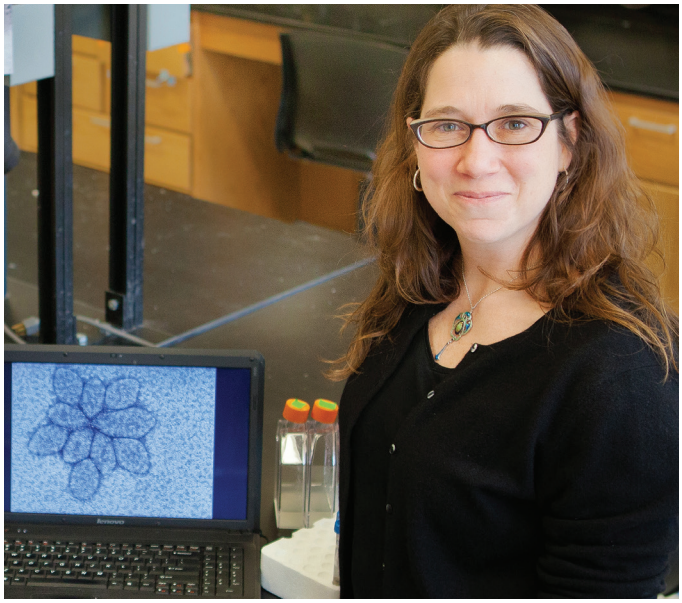
It's also established a system of communication between people working in different departments, just as Whitaker had hoped from the start. Between microbiology studies of estrogen levels in humans, to civil engineering projects about drinking water treatment, to anthropology investigations of ancient human interactions, this theme houses a wide variety of projects and disciplines.

For instance, the work Dr. Whitaker is currently pursuing under this theme focuses on multi-level infection genomics in patients with cystic fibrosis. In these patients, *Pseudomonas* bacteria, a genus that includes several well known species such as *P. aeruginosa*, *P. syringae*, and *P. putida*, can establish a chronic infection in patients, and these bacteria are subsequently infected by bacteriophages. Bacteriophages are viruses that specifically infect bacteria, as opposed to other hosts such as plants or humans. These bacteriophages would normally enter a human body and have no effect on the overall health of the individual. However, in the presence of the bacteria these viruses have an affinity for, they infect the *Pseudomonas* which have already infected the lungs of a human.

These infection patterns and mechanisms then impact the way the bacteria affect the human who's serving as their host. Specifically, viral infections of *Pseudomonas* in cystic fibrosis patients can alter the bacteria's production of virulence factors. These factors are what make the disease more or less severe in humans, and include any molecules that make the bacteria biofilms that *Pseudomonas* form more structurally or functionally sound. Depending on the way that mobile genetic elements are transferred between the bacteria and virus during the viral infection, the severity of the disease in the human host can fluctuate.

"This project focuses on the within-host dynamics of infections," said Dr. Whitaker. "The bacteria are the hosts to the viruses, and their interaction is happening within the human ecosystem. The human microbiome is like a mobile landscape within which the evolution of this chronic infection is taking place."

These studies will allow scientists to better understand how the environment of a human host will impact the internal evolution of *Pseudomonas* bacteria themselves. Whitaker says that the results of this work to have been quite interesting, especially after antibiotic treatment of this infection. While the research that has been done is preliminary so far, it suggests that antibiotic exposure in general may trigger evolutionary mechanisms in *Pseudomonas*.



Rachel Whitaker, professor of microbiology

"It seems as though all the bacteria emerge from one colonization event, which makes them genetically similar. But after antibiotic treatment, they start to evolve within the patients' lung over time, and we can track that evolution through deep population analysis," said Whitaker.

By sequencing several hundred samples from different time points throughout an infection, the lab will be able to discern if population variation is predictable, and ultimately that will become a model to predict intra-host dynamics. This will become a piece in the broad and predictive framework that the IGOH theme seeks to develop.

Infection as a Means of Interaction

The word infection tends to be interpreted to mean illness or sickness, but this is not always the case. Infection genomics can include commensal relationships as well as parasitic relationships. Any interaction between two or more organisms can be considered a form of infection genomics, since most interactions involve not only organisms themselves, but their microbiomes as well.

"As humans interact with plants, animals, and the environment, we exchange microbes with one another," said Whitaker. "These microbes can interact amongst themselves through their mobile genetic elements, small pieces of DNA that allow microbes to communicate and exchange information about survival tactics depending on environmental conditions," she said.

Microbial communication depends on the microbes that are interacting, the genetic elements they each possess, and the environment in which the interaction is taking place. This high number of variables leads to a huge variety in microbial interactions, and is the way those interactions make an impact on their hosts.

However, among these variables, patterns emerge where interactions become similar.

"As these patterns begin emerging across systems studied in different departments, it's possible to overlay these patterns with mathematical models, which will allow these findings to develop into a broad and predictive framework, which scientists can base future evolutionary theories off of," said Whitaker. "Building this framework has been one of the main goals of this theme since the beginning."

"We're trying to describe an evolutionary framework within real life systems based on evolution and transmission. We're working towards creating predictive models that fit within the physical structure of what people are seeing in the lab," Dr. Whitaker explained.

The IGOH theme encompasses this micro-lab work all the way to work done on a macro-scale, such as work currently being done by theme affiliate Dr. Rebecca Stumpf in the Department of Anthropology at the University of Illinois. The Stumpf group has been doing studies examining primate population interactions in Uganda since 2007, and they are presently examining how these interactions affect each population's internal microbiomes.

"Our more recent studies are focused on examining microbial presence, prevalence and inter-species dynamics among primates, livestock and the environment to identify and hopefully limit pathways for pathogen and antibiotic resistance transmission," Stumpf said.

"The work Dr. Stumpf's group is doing is important because this is on-the-ground-type work. It teaches you about real-life connections, and these connections are so important. Knowing how these species interact, when do they interact, and where do they interact, it all makes a difference in the way you would study those dynamics," Whitaker explained. "You won't know all that sitting and reading about it in the lab, this work involves going out and seeing the world so your work can replicate the reality that you're studying."

Dr. Stumpf's newest project has recently been funded by the National Institutes of Health (NIH), and will employ metagenomics experts as well as veterinarians, computational biologists, and microbiologists to discover how microbial interactions affect primate health and evolution. This work will be able to help scientists understand what the key factors are in microbiome diversity within interacting populations, whether it's diet, physiology, mating patterns, or habitat. Again, this work will add to the predictive model that IGOH strives to create surrounding evolution and transmission.

One Health as a Concept

One Health is an initiative at many institutions with the goal of bringing together the health of all living things under one roof. In this case, One Health represents a concept. "It's the realization that we are all connected in a way that makes the study of health stronger if we examine the health of the natural world as a whole, rather than in component parts," she said.

"There have been institutional barriers that have kept groups of people from working together in the past, and One Health is an initiative to allow all of these people to study our connectedness together."

Whitaker says that it is challenging to study antibiotic resistance in human systems alone, without the context of the rest of the living world. The same type of resistance may have developed in plants or animals, and the resistance found in humans strains may have originated in one of these other areas and been transferred. As long as humans interact with the rest of the world, our health depends on the health of everything else around us.

IGOH and the World

Whitaker: "This theme works helps move lab work from *in vitro* to *in vivo*."

"Rather than learning about life through microscopes or agar plates or line graphs, it's learning about life in the context of the whole world throughout all of time," said Whitaker. "One Health is the idea that you cannot study life without knowing where the life you study comes from naturally."

Of course in order to study infection at the microscopic level, which is where many of the studies within this theme find their roots, it takes a lot of skill in microbiology to attain and interpret data that lead to the findings.

"MCB's microbiology department has helped us, since the thing that connects us is our microbes. The basic mechanistic understanding comes from microbiology principles. The biology is a piece that you need to build the larger framework we're trying to build up. We couldn't do this without the supporters we have in the microbiology department," Dr. Whitaker said.

The current work that is being done under this theme has endless possibilities for the future of evolution and transmission, finding common ground in research that will allow us to understand life more fully. By allowing infection genomics to encompass all the realms of life, it is possible to create a more broad understanding of humans' place on the planet. n

"HIV has ways to either hide from the immune system or to trick the immune system into mounting a response that is ineffective. That way, over time, the virus can evade your responses."

The Changing Shape of HIV

By Daniel F. Le Ray

The Procko lab applies big data tools to molecular biochemistry. Their goal: a better understanding of how we might fight HIV-1.

According to Erik Procko, HIV is "a tricky little beast."

Research into this potentially deadly virus, which has infected nearly 38 million people worldwide, accounts for half of the Procko lab's work at the School of Molecular and Cellular Biology.

"What's clever about it," explained Procko, assistant professor of biochemistry, biophysics and quantitative biology, "is that it has ways to either hide from the immune system or to trick the immune system into mounting a response that is ineffective. That way, over time, the virus can evade your responses."

At the core of the lab's research: understanding how changes in the shape (or conformation) of proteins on the surface of the virus and proteins on the surface of host cells affect the virus' behavior. Greater insight on a molecular level could play a role in developing more effective vaccines.

One way that HIV eludes the immune system is by presenting multiple conformations of the HIV envelope protein to the body's cells. The envelope protein enables the HIV viral membrane—which surrounds the viral genetic material within—to fuse with a host cell. Once fusion is complete, the viral material is released, allowing the virus to infect the host cell and begin to replicate.

"The envelope protein is conformationally heterogeneous—there are many different shapes that it presents," Procko explained. "The problem is that not all of those conformations are necessary for HIV infection. Antibodies may bind to a certain shape of the envelope protein but then fail to neutralize the virus and fail to prevent the virus from infecting the cell."

To study this protein's shape-changing ability, Procko's team alters its genetic make-up.

"We can mutate everything—every possible single amino acid substitution can be put in our experiments," Procko said. They then look at "how these mutations affect shape changes and how that might affect presentation, for example, of the envelope protein to the immune system."

The lab creates a library of every possible genetic mutation—around 20,000 in all—before introducing this collection of mutants into cell culture. The culture is screened with antibodies that recognize particular conformations.

Finally, by comparing which mutations are found in the library before and after screening, "we can determine how every mutation has either increased in frequency, which means it is beneficial, or decreased in frequency, in which case they're mutations that are deleterious."

How might understanding the body's response to conformational variations in the envelope protein play a part in creating better vaccines?

Scientists have identified a certain shape of the envelope protein that is recognized by the most effective antibodies. So "using our massive mutational profiling, we could find the mutations that, when you express the envelope protein, result in better presentation of the shape of the envelope protein that is most desirable for the vaccine."

Any successful vaccine needs "breadth—in

that you target a broad diversity of HIV strains—and potency, so that you're most effective in neutralizing the virus," Procko added.

While looking at ways to engineer the envelope protein is not unique, many of the lab's methodologies are. First and foremost, the creation of big data tools that allow them to carry out what they call "deep mutational scanning." By analyzing data on both viral proteins and their receptors—molecules in the body that the virus binds to—the team can better understand the mechanisms behind viral transmission.

According to Procko, a typical biochemistry student might look at a dozen protein mutations, "test those mutations, see what effect that has and that could be a good chunk of their thesis work. Whereas, with the methods we now have, we can look at thousands and thousands of mutations in a single experiment."

Another difference: while many labs use purified fragments of the HIV envelope protein, Procko's group does all of their research in the context of the complete envelope protein in a membrane.

"We have the full envelope protein embedded in the membrane," he explained. By using a more true-to-life context, their research findings may be more applicable to the development of certain vaccines, such as virus-like particles—essentially the HIV virus without any viral genetic material.

When Procko arrived at Illinois, his focus was on neuroscience. But soon, he added HIV to his research portfolio.

"I came and I started brand-new projects from the very beginning. That's exciting—thrilling, even," he recalled. "But it's also quite nerve-wracking, as things can take longer to get going and you're always kind of wondering how people in your new field will receive your research."

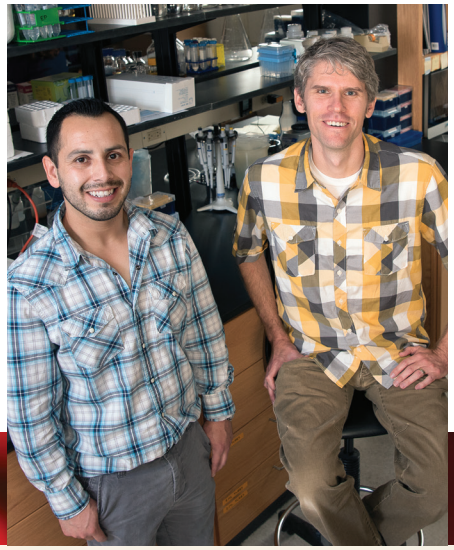
Thankfully, his peers have recognized the value of "somebody from outside of the field coming in with new ideas, new techniques to try to apply to problems in the HIV community."

Now, as well as mentoring undergraduate and graduate students in his lab, Procko collaborates with scientists around the country and at UIUC, including Blue Waters Assistant, Professor Diwakar Shukla, in the School of Chemical and Biomolecular Engineering, and Associate Professor of Molecular and Integrative Physiology, Hee Jung Chung, at MCB.

And he feels that he is doing the best research of his career.

"It's a great place to work," he said. "Everyone's very friendly and helpful, and I'm excited to do the research I do." n

Jeremiah Heredia, graduate student, and Erik Procko, assistant professor of biochemistry.



Evolving a Better Vaccine

Jeremiah Heredia was the first student to join the Procko lab three-and-a-half years ago. Now, the fourth-year biochemistry Ph.D. candidate is an integral member of the group's research team.

Heredia spends most of his time analyzing the interactions between different conformations, or shapes, of the HIV-1 envelope protein (Env) and the antibodies in the immune system.

"Env adopts multiple protein conformations, such as the open and closed conformations," Heredia explained. The closed confirmation is more successfully recognized by broadly neutralizing antibodies (bNAbs) in the body, making it a potential element in an effective HIV vaccine.

In his experiments, Heredia introduces multiple mutations into Env.

"This has provided insight into Env mutational tolerance for acquiring closed and open conformations, [which] has allowed us to engineer Env towards the closed conformation recognized by bNAbs," he elaborated.

At Heredia's disposal is deep mutational scanning, one of the big data tools pioneered at the lab.

This computer-assisted process allows the team to analyze thousands of protein mutations simultaneously—one of the unique methodologies that first attracted him to the Procko lab. As he learned more about virology, Heredia realized that "studying diseases added a tangible aspect to the science and made it far more interesting to study."

From day one, Procko has been a mentor.

"It was nice being the first student, because I was able to learn directly from Erik. I saw firsthand how he worked and it set the guidelines for me," said Heredia.

There is still a long road ahead in terms of creating a polyvalent vaccine—one that provides immunization against more than one strain of a virus.

"HIV-1 is a huge disease," Heredia said. "A true vaccine would need these Env mutations to be transferrable to several of those strains."

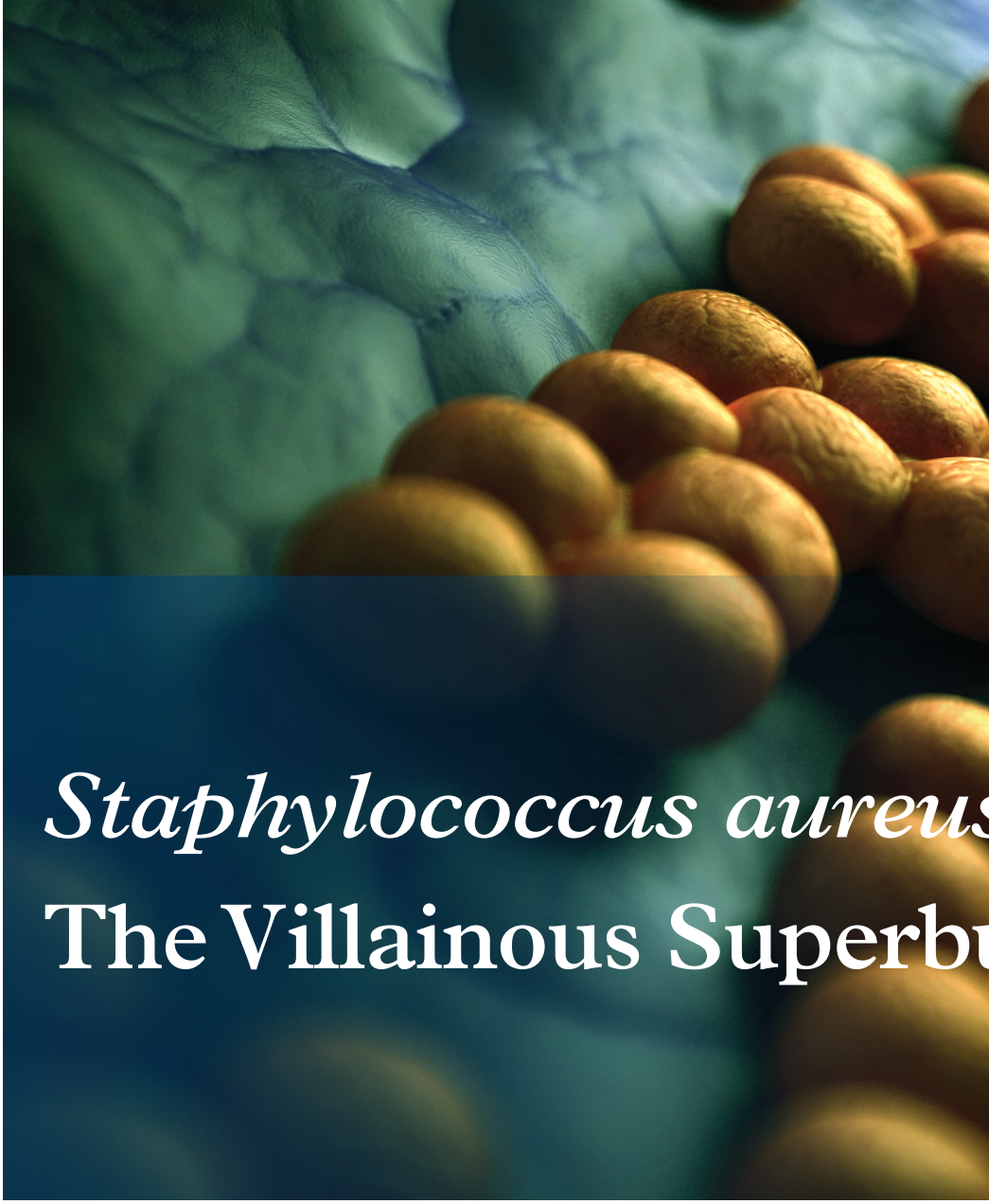
But the lab's findings are a step in the right direction: Heredia has already discovered some beneficial mutations that work across different strains of HIV.

This work on vaccine development continues to pique his interest.

"Every week, I'm either learning something new or obtaining a new result that shifts my understanding."

And in spite of how overwhelming HIV research can seem, the work is always rewarding.

"It's great to know that Erik and I are in this together," said Heredia. "Even though we are in this competitive field, I feel we are obtaining results that will benefit the HIV-1 community in (hopefully) developing an HIV-1 vaccine." n



Staphylococcus aureus: The Villainous Superbu

By Doug Peterson

Staphylococcus aureus is on the "most wanted list" for the National Institutes of Health, making it a major villain in the microbial world, said Robert B. Gennis, an MCB biochemistry professor.

S. aureus also happens to be on the most wanted list in the lab of Thomas Kehl-Fie, MCB professor of microbiology. That's why Kehl-Fie and Gennis have teamed up, along with research scientist Lici Schurig-Briccio, to probe this deadly bacterium.

Just this past June, a 22-year-old woman from Danville, Illinois, died of a *S. aureus* infection, according to the *Champaign-Urbana News-Gazette*. The woman, who had done gymnastics when she was younger, was injured doing a backflip. When she began hallucinating and experiencing a low-grade fever and numbness in her limbs, she was rushed to Carle Hospital in Champaign, eventually passing away from staphylococcus-related meningitis.

What makes *S. aureus* particularly dangerous is its ability to adapt to so many places in the body.

"Some pathogens infect only one place in the body," Kehl-Fie said, "but *S. aureus* can infect everywhere. That's why it is so hard to treat. It will infect your brain, it will infect your bones, it will infect your skin."

Gennis pointed out that *S. aureus* can even collect on an artificial hip, coating the surface and creating havoc. Sometimes, the infection is so great that surgeons have to remove the hip they just installed.

"*S. aureus* has learned to adapt to environments where there isn't much for it," he added. "It protects itself, and it keeps going. That makes it very dangerous."

"We have to understand what is going on in the bacteria before we can figure out a way to stop them," Kehl-Fie said. Specifically, his laboratory has been focusing on how bacteria eat and survive in nutrient poor environments, using *Staphylococcus aureus* as the model system.

"You might think of us humans as a smorgasboard of tasty things for the bacteria to eat, but we're actually quite nutrient poor," he said. "From bacteria's perspective, we're basically taking away the food before they can eat."

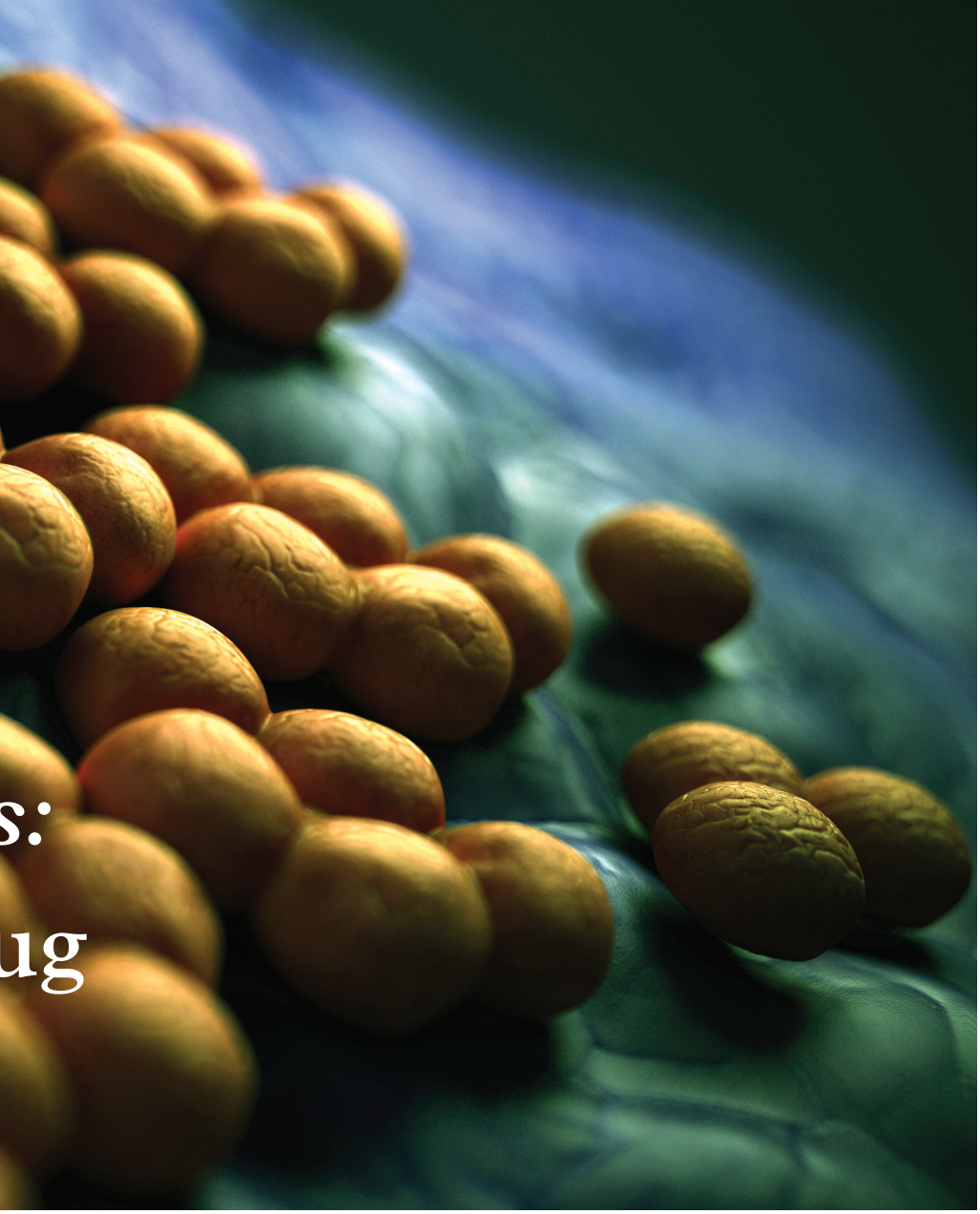
Kehl-Fie's laboratory concentrates on manganese and zinc because the human body tries to deprive bacteria of those two nutrients—a defense system known as nutritional immunity.

"We fight bacteria by taking those metals away from them, weakening them so other parts of our immune system can come in and attack them with a one-two punch," he said.

For many years, researchers focused on the deprivation of iron from bacteria, but Kehl-Fie's work showed that manganese and zinc are also being withheld. His lab mimicked the starvation of *S. aureus in vivo*, highlighting the important role of the protein, calprotectin.

"Calprotectin is a metal-binding protein that sucks up manganese and zinc at the sites of infection, starving bacteria for these metals," according to Kehl-Fie. Starving *S. aureus* of manganese breaks down its defenses against the immune system's oxidative bursts, which kill bacteria.

But for every move made by the immune system, *S. aureus* has a countermove. So Kehl-Fie's and Gennis's labs are working together to explore how *S. aureus* adapts to nutritional immunity. They believe the ArlRS system, a two-component response regulator, is important in enabling *S. aureus* to resist nutritional immunity, but the labs are trying to figure out how it works.



Bacteria have a sweet tooth, Kehl-Fie noted. But his lab discovered that restricting metals can force *S. aureus* to eat other carbon sources instead.

"We think that starving *S. aureus* of manganese actually changes what these bacteria eat," he said. "They go from having a sweet tooth to preferring steak."

Gennis said these findings dovetail nicely with their research, which shows that the bacterium's response is quite different if it's presented with a sugary meal or a meal of protein.

"It's got a hierarchy of what it's attracted to," he said, "and depending on where it finds itself in the body, it adapts to make the best of it."

"*S. aureus* would love to eat sugars if it could," Kehl-Fie pointed out. "But it's not a question of what it wants to eat, but what it's forced to eat if it wants to survive."

Although the labs are working together, Gennis and Schurig-Briccio come at the problem from a different angle than Kehl-Fie. They take a biochemistry approach because Gennis's lab has a long history of work on the biochemistry of respiration—how oxygen is used to break down foods to generate energy.

"Our lab is interested in bioenergetics," Gennis said. "We've done a lot of work on the fundamentals, and we decided to focus on *S. aureus* when Lici (Schurig-Briccio) came here. We're trying to take what we learned with various enzymes from different organisms and see how it applies to *S. aureus*."

During infections, Schurig-Briccio said, bacteria need to extract energy from many different environments in the body. *S. aureus* has to figure out a different way to adapt to each organ in the body—each place that it infects.

"So we're looking at how bacteria change their feeding patterns—their metabolism—to adapt to the different environments, which have different carbon sources, nitrogen sources, and may have either high or low oxygen levels," she said.

"Metabolism matters," Gennis added.

Using information from the genome, Gennis and Schurig-Briccio have learned what enzymes are being made or can be made by *S. aureus*, and he said they have identified what "we think are vulnerable loci—places that are particularly important for *S. aureus* under certain conditions."

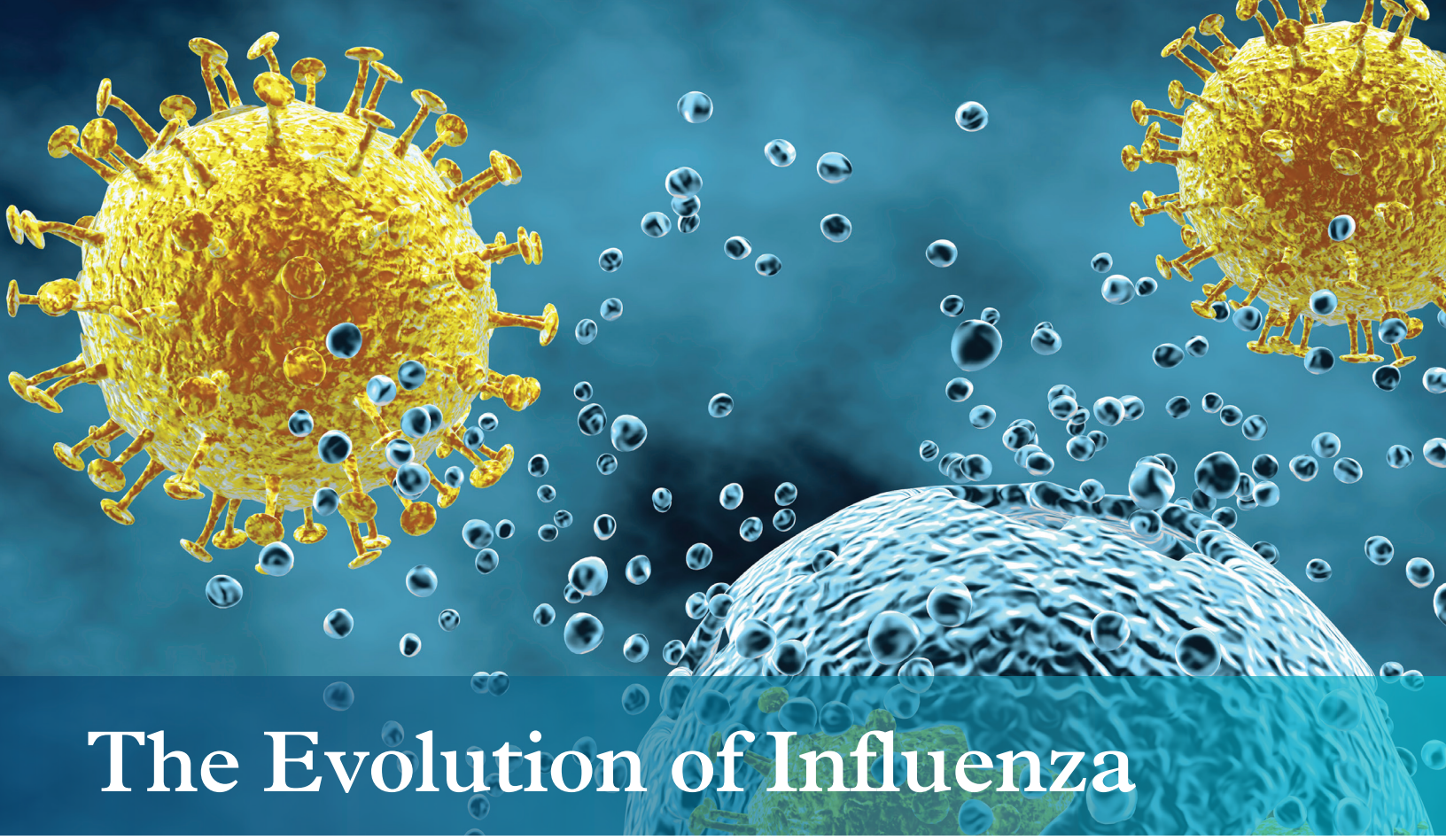
Specifically, they are looking at certain NADH-dependent enzymes, which are important for oxidation.

"What would happen if you eliminate the capacity of the bacteria to use that enzyme?" Gennis asked. "How would it adapt to that loss? That's giving us a window into how *S. aureus* adapts." And you have to learn how the bacterium adapts before you can find ways to disable it.

The human body is an extreme environment for bacteria, Kehl-Fie pointed out. Humans have entire cells dedicated to killing bacteria, and the body has elaborate systems for starving them, and yet these single-celled organisms can still kill us.

"I've always been fascinated by bacteria because they have this phenomenal ability to thrive in distinct and hostile environments," he said. "How do they do that?"

As Gennis put it, "They've got all kinds of nasty tricks." n



The Evolution of Influenza

By Daniel F. Le Ray

Influenza is one of the most adaptable viruses known to man. By tracking down flu's weak spots, Christopher Brooke's lab hopes to aid in the development of new treatments.

When Assistant Professor of Molecular and Cellular Biology Christopher Brooke was three years old, his mom bought him a book about marine creatures.

"For whatever reason—I think just because I thought the animals were really weird—I was super into it," Brooke recalled. This childhood fascination with biology turned viral at college, where he worked in a lab researching influenza and fell in love with the environment.

"People coming in and working to satisfy their own curiosity—that just seemed like a really nice way to make a living ... So I was hooked at that point."

After completing a Ph.D. focusing on how the immune system fights off viruses, Brooke turned back to flu, "because it's kind of shocking how little we know about this virus that kills so many people and costs so much money, even though we've been studying it for decades."

Now, Brooke leads his own lab at the School of Molecular and Cellular Biology. One of its goals: understanding how influenza adapts, transmits and replicates.

At its most basic, influenza is "a sort of code for propagating itself," Brooke said. The virus is made up of eight ribonucleic acid (RNA) molecules. When it infects a cell, it rewires that cell to turn it into a factory producing more RNA molecules as well as the machinery needed to turn those molecules into new flu particles. Those particles then move on to another cell and the process starts over.

What makes the virus so dangerous is its remarkable adaptability. Worldwide, there are between 300,000 and 650,000 flu fatalities each year; in the United States alone, upwards of $10 billion is spent annually on tackling influenza and its effects.

Adaptability refers to the ability of the virus to evolve to thrive in new environments or overcome selective pressures—for example, "asking [the virus] to replicate in a new species or putting it in a human that has some degree of immunity," Brooke explained.

"That selective pressure will select for variants within the starting virus population that have different genomic sequences that make them better able to handle whatever that selective pressure is."

In other words, when the virus infects people with a high level of immunity, there is selection for traits that help it escape that immunity. Thus, a new strain is born.

And non-human strains pose a graver threat.

"We typically have some degree of pre-existing immunity against human influenza strains, [but] animal (or zoonotic) strains—we have no immune protection against them," said Brooke. This means that if a new strain jumps species, it can replicate more efficiently and lead to a pandemic.

The Brooke Lab focuses on influenza A, the strain that affects humans and some other mammals, including birds and swine. By expanding our understanding of the mechanisms behind the virus' ability to adapt and transmit, Brooke hopes that his team might contribute to the creation of a universal flu shot.

"If we could develop a vaccine that actually worked in the same way that the polio vaccine or the measles vaccine works—especially if it's effective and can actually eradicate the virus—that would be a pretty significant benefit for mankind."

Findings in a forthcoming paper may provide one clue to fighting influenza on a broader scale.

The textbook image of a flu virus, Brooke explained, shows eight identical genome segments. But when he and his colleagues analyzed populations of flu virus particles, they found that they were, in fact, far from genetically identical.

Fighting the Flu

"You can really think of a population of influenza viruses as a collection of incomplete particles that carry fractions of the genome. They have to work collectively to replicate," Brooke said.

That is to say, once the virus has entered a cell, only a minority of the viral particles—from as low as one to no more than 30 percent—can replicate on their own. These semi-infectious particles (a term coined at the lab) can infect a cell but they cannot multiply without the help of other particles.

What might this mean for a potential vaccine?

"If the virus really does have to work together as a collective to replicate efficiently, [then maybe] there are certain constraints that could potentially be targeted."

Finding those constraints means detecting patterns within multiple flu strains.

"Where our vaccines and our immune system currently target the virus, it is very tolerant of mutations, so it's able to change and escape detection," said Brooke. But if researchers can identify parts of the virus that are not as adaptable, then it might be possible to develop treatments that attack those areas.

According to Brooke, "figuring out where to target the virus … and then figuring out how to instruct the immune system to target those regions are really the two breakthroughs that need to be made. I think that's the goal of the field and it might take 10 or 20 years or more, because these are really difficult problems."

Collaboration in the name of curiosity is still something Brooke enjoys.

Working with undergraduates, post-docs and graduate students in his lab is "very enjoyable, because they bring different perspectives, they have different ideas that you would never have," he said. "It's really satisfying to be able to watch [them] develop as scientists right in front of you."

And even if influenza were eradicated tomorrow, Brooke's curiosity would not be extinguished. There are, after all, plenty of other viruses that he finds just as fascinating.

"They're super weird and I'm still constantly a little bit freaked out by them," Brooke said. "I find them to be continuously surprising and strange, and that keeps me interested." n

The Brooke lab is home to post-doctoral fellows, undergraduates and graduate students who are working to understand how influenza adapts and transmits. Two of the lab's key areas of research are genomic diversity—that is, variation in flu particles on the genetic level—and collective interactions between flu particles during the process of infection.

"Every day is a new journey of discovery. There are always challenging puzzles to be solved and pieces of evidence to be put together to become knowledge," said Fadi Alnaji, a postdoctoral fellow who designs and conducts experiments using Next Generation Sequencing (NGS) that help characterize the factors affecting the virus' evolution and transmission.

Alnaji also develops bioinformatics analytical tools, including visualization and statistical examination, to correlate the NGS data to its biological relevance. Recent investigations into defective interfering particles (DIPs), a type of viral particle that loses a critical part of its genome after replication, have proven particularly intriguing.

Identifying and characterizing hundreds of DIPs will "help us and others in understanding their biological roles," Alnaji explained. "These molecules are generated by the virus itself and possess antiviral activity, which makes them a potential target for designing a new, efficient, smart vaccine."

One of the highlights of Alnaji's work is collaborating with Brooke and his other colleagues.

"There is always room for constructive discussions and suggestions, which almost always lead to planning out novel, thrilling and challenging experiments—or discovering something," he said.

Graduate student Jiayi Sun joined the lab in 2016 and has been instrumental in studying the behaviors of semi-infectious particles. These particles do not express a full set of genes when they infect a host cell, meaning that they must co-infect cells with other particles in a viral population in order to complement with each other and produce viral progeny.

Sun discovered a novel mechanism that governs the semi-infectious particles' ability to co-infect.

"I hope to explore and find more about the effects of viral heterogeneity on replication and evolution," Sun said, adding, "I think these efforts will eventually transform into discoveries and publications."

MCB and psychology major Morgan Samanic, one of the Brooke lab's undergraduate researchers, has always been fascinated by viruses.

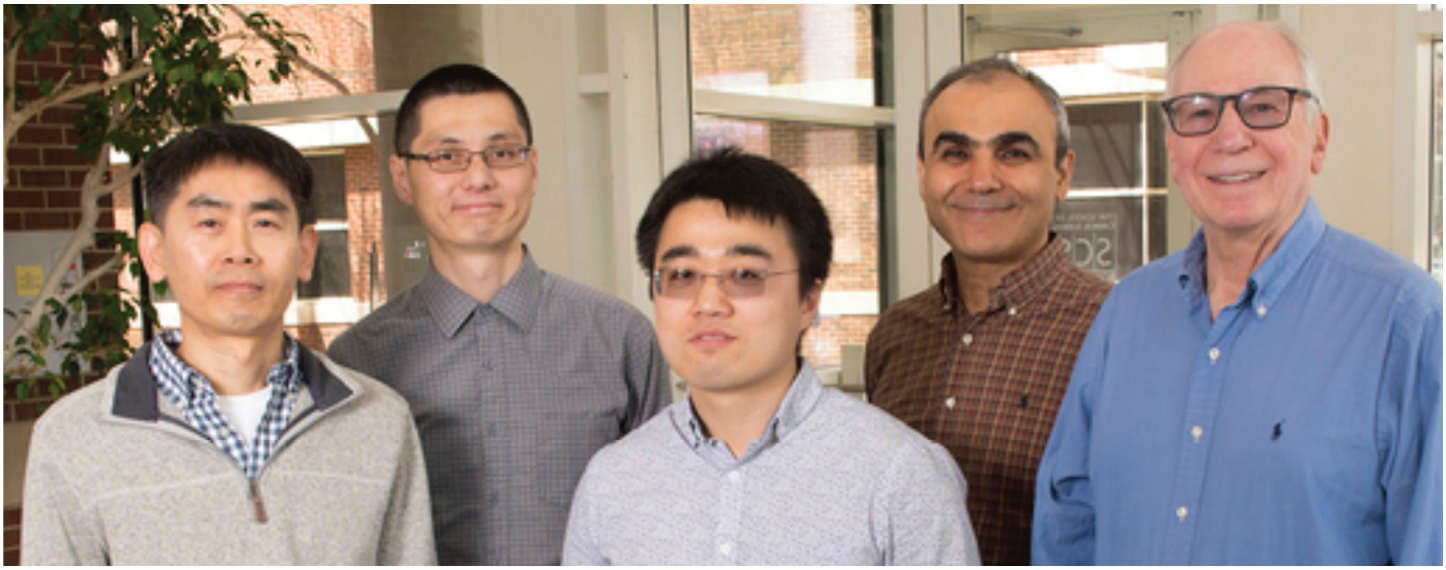
"Even though they are so small, they are very smart and they can do a lot of damage," she said.

In the lab, Samanic learns something new every day, "whether that be a new concept of how the influenza virus works, how to analyze next generation sequencing data or how results never seem to turn out as expected."

In the future, she hopes to learn more about DIPs and how they interact with the virus' genome, so that, "hopefully, this information can guide us as to how we can potentially fight the flu."

Samanic, too, appreciates Brooke's mentorship.

"Whenever I meet with him, he always pushes me to look for things I can improve on while also recognizing my accomplishments. I appreciate that he pushes me like he does the other members of the lab." n



Researchers, from left, Sangjin Hong, Yuhang Wang, Chang Sun, Emad Tajkhorshid and Robert Gennis

Bacteria's Energy Efficient Supercomplex

By Steph Adams

Gennis Lab: Researchers determined the structure of a supercomplex of enzymes many bacteria use to generate energy.

Biochemists at the University of Illinois have isolated a protein supercomplex from a bacterial membrane that, like a battery, generates a voltage across the bacterial membrane. The voltage is used to make ATP, a key energy currency of life.

The new findings, reported in the journal Nature, will inform future efforts to obtain the atomic structures of large membrane protein supercomplexes.

"With billions of years of evolutionary experience, bacteria are adept at surviving in changing environments," said Robert Gennis, a University of Illinois professor emeritus of biochemistry who led the new research with biochemistry professor Emad Tajkhorshid. "Most have the ability to modify, replace or combine molecular tools to suit the new demands – sometimes within a single cell's lifetime," Gennis said. These tools include enzymes, which catalyze chemical reactions to perform specific tasks.

The energy required by the bacterium is obtained by transporting electrons from high energy food molecules to oxygen, similar to what occurs in plant or animal cells, Gennis said. Electrons pass from one enzyme to another until finally reaching oxygen.

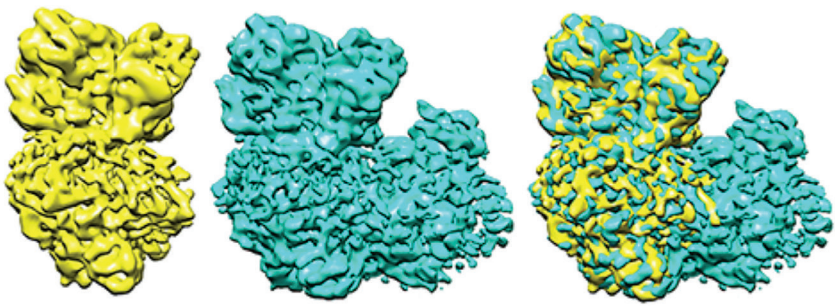
Typically, an enzyme passes an electron on during a random collision with another enzyme. The researchers showed that in some conditions, nature eliminates the need for random collisions by sticking the enzymes together to form a "supercomplex." Each part of the supercomplex can generate a voltage, but all parts must function in sequence, Gennis said.

"It makes sense that they will function as a single unit to make sure the electron transport is rapid and the electrons end up where they belong," he said. "Supercomplexes are probably important in all electron transport chains, but in most cases, attempts to isolate them fail because they fall apart. We were lucky to be studying an organism called a Flavobacterium, in which the supercomplex is stable."

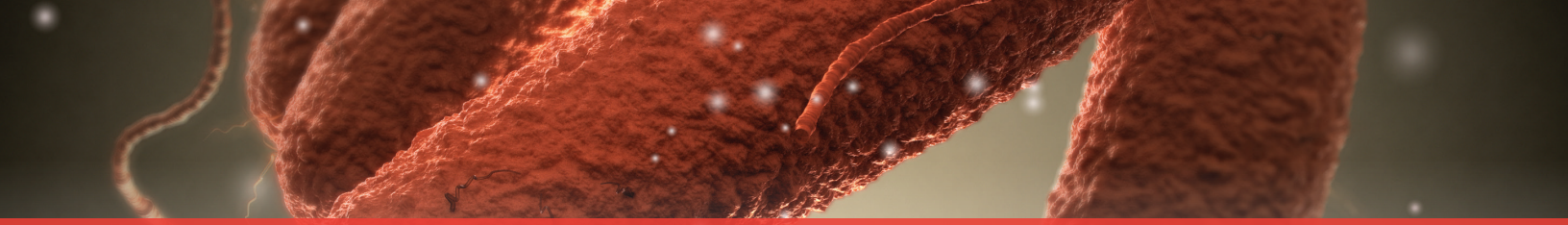
Rather than relying on detergents to extract the proteins from the membrane, as is typically done in such experiments, the team tried an industrial polymer – a kind that plastics are made from. Using this polymer, they extracted and isolated the supercomplex in a single, rapid step. The process embedded the supercomplex in a small disc of membrane shaped like a coin.

With the help of their collaborators at the University of Toronto and the New York Structural Biology Center, the team used cryo-electron microscopy to determine the configuration of the supercomplex components.

"Evolution has resulted in a very efficient 'nano-machine' that is also beautiful to look at. Seeing how this works gives one a great appreciation of nature and is one of the joys of doing science," Gennis said.n



One of the enzymes, in yellow, that is part of the supercomplex, blue, fits nicely into the ankle and heel of the boot-shaped supercomplex.



Salmonella's Sweet Spot

MCB Collaboration Unravels Bacteria's Virulence Regulation System

By Doug Peterson

For *Salmonella*, it's all about being in the right place at the right time—although for a human victim, it's more like the wrong place at the wrong time.

"*Salmonella* is designed to sense a variety of environmental parameters that tell the bacterium where it is in the intestine, allowing it to turn on virulence systems at the appropriate time and place," explained James M. Slauch, head of microbiology in MCB. "It's like a switch, turning it on, turning it off."

For the person on the receiving end of the infection, the result can be a severe bout of stomach cramps, fever, and diarrhea.

Slauch has studied complicated *Salmonella* systems for 30 years, and for the past two years he has collaborated in some of his research with fellow MCB microbiologist, Cari Vanderpool. They are studying regulation of the primary virulence system required for *Salmonella* to invade and colonize the small intestine.

For instance, they recently identified two small RNAs that play a role in regulating *Salmonella*, but how they work depends on oxygen levels. If the environment in a person's small intestine is too anaerobic—if there is not enough oxygen—then the first of these small RNAs shuts off activation of *Salmonella*. And if the intestinal environment has too much oxygen, the second small RNA also shuts off S*almonella* virulence.

However, if oxygen levels are at a sweet spot for the bacteria—not too much or too little—then it is conducive to infection, Slauch and Vanderpool discovered.

But oxygen is only one of many factors that influence a *Salmonella* infection. Salt content and fatty acids also play a role in activating the virulence system, and once again, it's all about bacteria finding the sweet spot.

"*Salmonella* is a major food-borne disease throughout the world, with over a million infections in the United States each year," Slauch pointed out. "Over 500 people per year die from the infection, and in the rest of the world the death rate is much higher."

In many cases, people don't even realize they have been infected, as the ailment runs its course over four to seven days.

In 2018, there have been several multi-state outbreaks of *Salmonella*, according to the U.S. Food and Drug Administration. For instance, one outbreak may have started with tainted, pre-cut melons in fruit salad mixes, with *Salmonella* cases popping up across seven states, including Illinois. In this outbreak, *Salmonella* struck 70 people between April and June, and over half of them were hospitalized, reported the FDA.

Slauch and Vanderpool concentrate on *Salmonella Typhimurium*, one of the serovars most responsible for infections worldwide. *Salmonella* invades the cells of the small intestine, and this is required for disease, Vanderpool said. If the bacteria simply move through the middle of the intestine, they do no harm. But if they invade the epithelial cells lining the surface of the small intestine, they can wreak havoc.

What's more, the target epithelial cells are located in the final stretch known as the distal small intestine. Once *Salmonella* bacteria invade the surface cells of this region, they induce an inflammatory response. It was once thought that the inflammatory response was the immune system's way of battling the infection. But Slauch said they now know that *Salmonella* induces the inflammation because it helps the bacteria propagate.

"The inflammatory response gives rise to new sources of carbon and terminal electron acceptors that only *Salmonella* can use," he pointed out. "The vast majority of other bacteria in the intestine cannot use these terminal electron acceptors. So *Salmonella* intentionally induces diarrhea to create an environment where it can propagate and outcompete the other organisms."

Nevertheless, the inflammatory response is a two-edged sword for the bacteria. Although it helps *Salmonella* propagate, it is also the body's way of flushing out the gut, "and that's a good thing," Slauch said. That is why doctors recommend that those suffering from Salmonella use oral rehydration as a treatment. Drink lots of water.

The collaboration between the two MCB labs can be traced back to the doctoral work of PhD student Kyungsub Kim, which began five years ago. His research in Slauch's lab generated the preliminary data used to obtain a grant from the National Institutes of Health, and Kim continues to play a key role in the work.

Vanderpool's laboratory has a long history of research on small RNAs, such as the ones that can influence *Salmonella*. But small RNAs are relative newcomers in biology. "We knew virtually nothing about small RNAs and small RNA regulation until the early 2000s," she said.

Small RNAs, which can be as short as 100 nucleotides in length, were once called non-coding RNAs because it was believed they did not code for proteins. Although it's true that most of them do not code for proteins, some do, as it turns out.

"It used to be that life was simple," Slauch said. The Central Dogma of Molecular Biology was that DNA makes RNA, and RNA makes protein. But as researchers such as Vanderpool and Slauch dig deeper, it gets more complicated.

Small RNAs can base pair with messenger RNA (mRNA), which carry genetic information from the DNA to the ribosomes. However, when some small RNAs bind to regions of the mRNA, they *inhibit* the creation of proteins by ribosomes. Some small RNAs can even regulate the virulence response in *Salmonella* bacteria.

Slauch and Vanderpool have identified roughly eight small RNAs that control the *Salmonella* invasion system through base pairing.

"Our idea is to get a comprehensive view of the virulence signals at the molecular level," Slauch said. "Small RNAs are a big part of that, but not the only part by any means."

According to Slauch, so many conditions have to be just right for a Salmonella infection to occur. As he put it, "You have to have a, b, c, d, e, f, and g, and they all have to be on at the same time."

"But if we can interfere with any one of those conditions, we can have an impact because all of those conditions are required," Vanderpool said. "If we can stop the cells from sensing these signals—if we block the system from turning on—we block the *Salmonella* infection." n

H. Pylori's Survival Strategy: Shut off the Energy

By Steph Adams

Researchers report in a new study that the bacterium Helicobacter pylori – a major contributor to gastritis, ulcers and stomach cancer – resists the body's immune defenses by shutting down energy production within the cells of the stomach lining that serve as a barrier to infection.

The new findings, reported in the journal *Cell Microbe & Host*, will aid efforts to better understand and combat *H. pylori* infections, the researchers said.

"*H. pylori* infects and causes gastritis in half the world's population. It is transmitted from person to person, usually during the first two years of life," said University of Illinois microbiology professor Steven Blanke, who led the new research. "Long-term infection can extend over decades, and most people never experience any symptoms of infection until the disease has progressed to an advanced state."

The human stomach is the only known environment where *H. pylori* exists, Blanke said.

"When any barrier in the human body is colonized by a pathogen, the immune system sets off a series of predictable counterattacks to reclaim the infected space," he said. "*H. pylor*i cripples these immune counterattacks by going straight to the source of a host cell's power to shut down energy production."

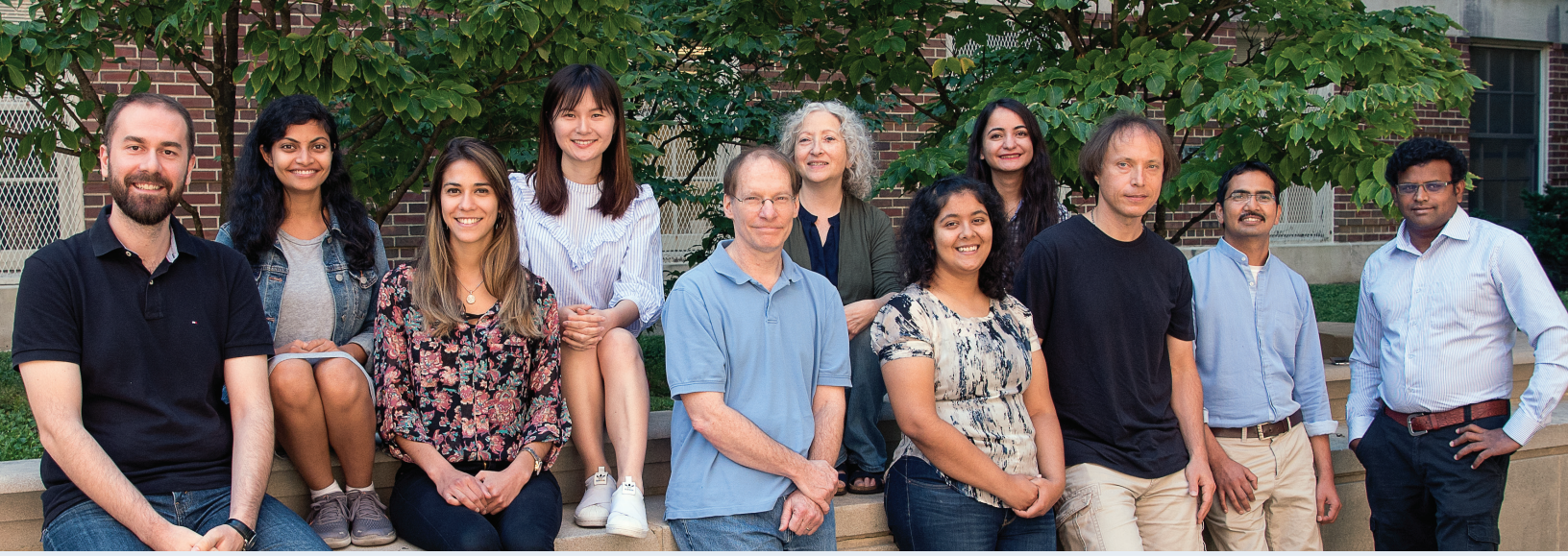
Using stomach cells and tissues, the team found that *H. pylori* manipulates the cell from the outside by sending in a toxin to directly target the mitochondria, which serves as the powerhouse where the cell's energy is produced.

"The toxin disables the mitochondria, resulting in a loss of energy production," Blanke said. "When the cell tries to compensate by reallocating resources from other parts of the cell, a signal is triggered directing the cell to stop production and start breaking things down."

Disabled but still alive, the cell eventually loses its ability to fend off infection.

"The results of these studies provide an important example of how pathogens effectively target host metabolism in an effort to establish an enduring foothold within the host," Blanke said.n

Microbiology professor Steven Blanke, graduate student Ik-Jung Kim and their colleagues discovered how a disease-causing bacterium, Helicobacter pylori, undermines the body's immune defenses. Photo by L. Brian Stauffer.



The lab members (from left to right): Stefanos Giannakis, Anshika Gupta, Victoria Arias, Yidan Zhou, James Imlay, Karin Imlay, Ananya Sen, Maryam Khademian, Sergey Korshunov, Sanjay Rohaun, and Ramakrishnan Sethu.

How Oxygen Actually Damages Our Cells

By Ananya Sen, microbiology graduate student, Imlay Lab

Life evolved four billion years ago in a world that was fundamentally different from the world we live in today. The main difference: there was no oxygen. However, the lack of oxygen did not deter the growth of ancient bacteria. They thrived and built their chemical processes around iron, a metal that can catalyze diverse chemical reactions. Two billion years later the subsequent evolution of photosynthesis generated oxygen, which was a double-edged sword.

On one hand, cells learned to use oxygen to generate energy for cellular processes. On the other hand, since oxygen is a reactive chemical, it can cause aberrant reactions that give rise to dangerous chemicals such as superoxide and hydrogen peroxide, collectively referred to as reactive oxygen species (ROS). These species react with to the intracellular iron, resulting in the damage of iron-containing proteins.

This crisis with oxygen occurred before life diversified to form multicellular organisms. Subsequently higher organisms, including us, are inherently dependent on oxygen, but remain vulnerable to the effects of ROS. This vulnerability has several consequences. White blood cells in our body exploit it to kill invading microbes by spraying them with ROS thereby preventing infections. Researchers use chemotherapy and gamma radiation to generate ROS to kill tumor cells by overwhelming them with oxidative damage.

"My interest in oxidative stress started during graduate school. I chose the lab because they attacked scientific questions with rigor and the problems they were looking at dealt with oxidative stress. Fundamentally oxidative stress is a chemistry problem. Therefore, my background in chemistry enables me to ask mechanistic questions that are slightly different from those of a conventional biologist," said Jim Imlay, a Professor in the Department of Microbiology.

Although oxidative stress is a chronic problem, life endures. To understand how oxidative stress damages cells and what their defense mechanisms are, the Imlay lab uses *E. coli* as a model organism. There are several advantages to this approach. *E. coli* can be easily manipulated to gain insights into cellular function. Unlike human cells which have an absolute requirement for oxygen, E. coli can grow both in the presence and absence of oxygen. Therefore, it is easier to identify the components that are required to defend cells in the presence of oxygen.

E. coli uses several defense mechanisms to counter oxidative stress. One of the current projects in the lab looks at how *E. coli* uses manganese instead of iron. "When the cells sense elevated levels of ROS, they pull the iron out from proteins and replace it with manganese," Imlay explained. "Although manganese is not as efficient a catalyst as iron, it is resistant to oxidative stress."

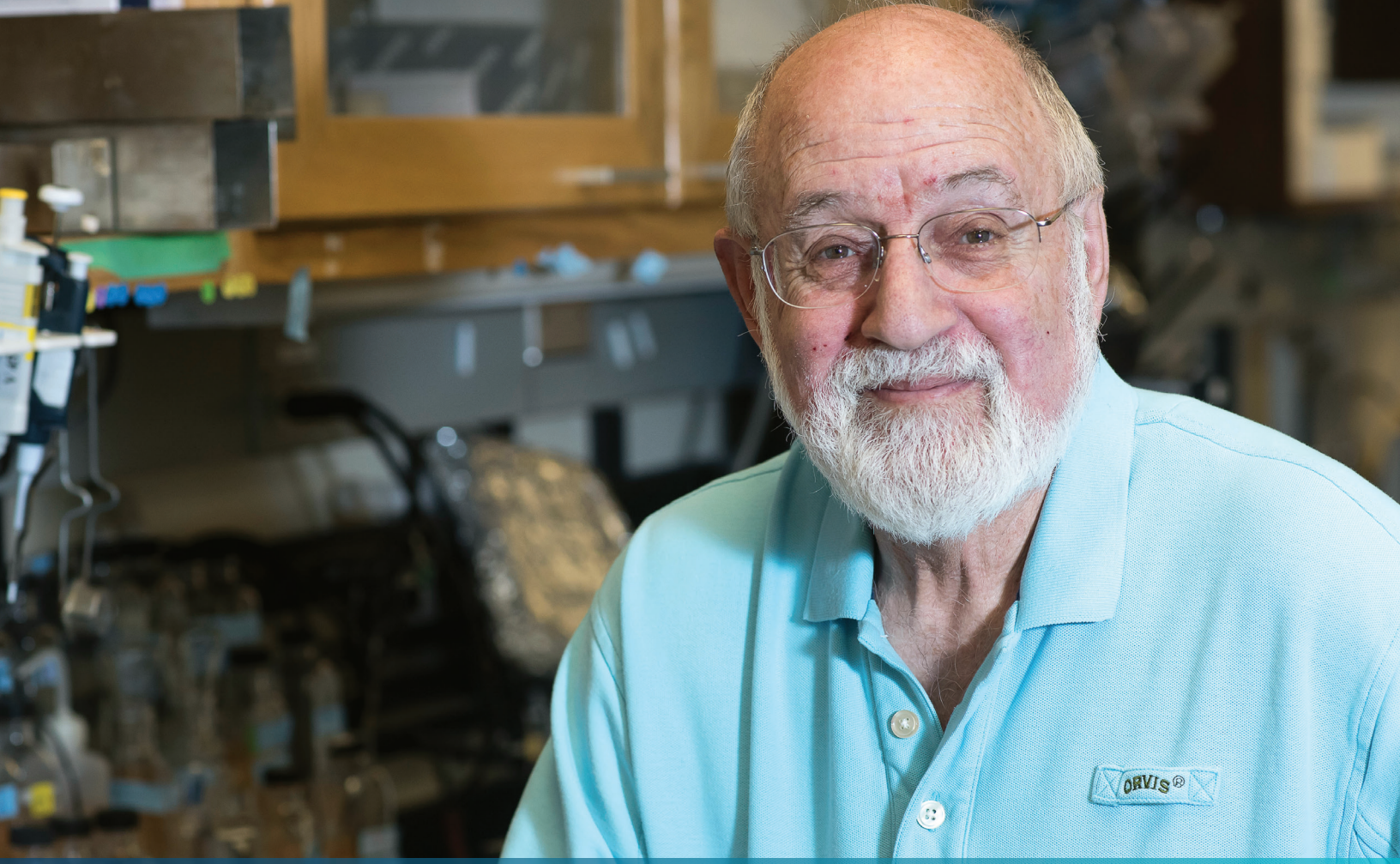
The lab also studies organisms that live on the extreme ends of the oxygen spectrum- those that cannot tolerate oxygen and those that live only in oxygen-rich environments. The former, also known as obligate anaerobes, form an integral part of several environmental niches. "The vast majority of microbes in our guts are obligate anaerobes. The gut is kept devoid of oxygen to allow these organisms to survive. This shows that there is a connection between oxidative stress and how our gut microbes are organized. You cannot understand one without the other," said Imlay.

The work with organisms that live in oxygen-rich, stressful environments further confirms the studies done with *E. coli* . The adaptations that *E. coli* makes only under duress are continuously used by these organisms. One such adaptation is the use of manganese instead of iron.

Surprisingly, bacteria can even exploit ROS stress. "One of the recent publications by Maryam Khademian, a graduate student in our lab, showed that that E. coli has evolved to cope with ROS so well that it can use hydrogen peroxide to grow," explains Imlay. "It is startling because we were used to thinking of hydrogen peroxide as a poison and here is an organism that uses it for its benefit."

There are several long-term questions in the field, whose answers are applicable to human health and disease. For instance, oxidative stress might be harnessed to develop antibiotic therapies which would suppress the growth of microbes. Furthermore, several human disorders involve inflammation, which results in tissue damage. A large part of that damage is due to the formation of ROS. Understanding oxidative stress will help us develop therapies that can suppress the damage.

Unlike other stresses, oxidative stress is unique in its type and impact because life evolved in its absence. According to Imlay, "studying oxidative stress means understanding an evolutionary story. At the same time, its impacts can be narrowly focused and even be used for our benefit to battle infections and tumors." n



A Lifetime of Lipid Research

John E. Cronan, PhD '68, Biochemistry

By Ananya Sen

It is rare to fall in love with a field during college, pursue it, and build a stellar career. Yet, that's what John Cronan's life has always been about- fatty acids. Cronan's interest in lipids began when he was undergraduate student. "I did an NSF summer internship at UCLA where I studied how green algae made unsaturated fatty acids," said Cronan. At the time John worked with Armand Fulco, an accomplished lipid metabolism investigator. "My experience with Armand encouraged me to go to graduate school at the University of California, Irvine."

"At the time most studies that were being carried out focused on brain lipids, which were polyunsaturated and were therefore could react with oxygen," he said. "I wanted to investigate whether the same was true for *E. coli*." He discovered that *E. coli* contained monounsaturated fatty acids, which were not susceptible to oxidation and thus much easier to work with. He went on to study the fatty acid and phospholipid contents of *E. coli* and investigated the changes that occur during different growth phases.

What makes Cronan's studies even more impressive, other than publishing seven papers in three years, is that he carried out his work largely single-handedly. "At the time, UC Irvine was just getting started and had only a few faculty, no one worked on lipids, so I had to solve problems by teaching myself how to do the analyses."

Unsurprisingly, when it was time to look for a post-doctoral position, Cronan was immediately recruited by Roy Vagelos. Vagelos, a renowned scientist in the field of lipid biochemistry, was impressed by Cronan's ability to do independent research and use different investigative approaches, a trait that was encouraged at Irvine by having open labs that allowed the sharing of resources. After a productive 2 years, Cronan moved to the Department of Molecular Biophysics and Biochemistry at Yale, where he remained for 8 years before finding his permanent home in Urbana-Champaign.

"Ralph Wolfe was the head of the search committee when I was hired at the U of I. He's my hero- an unassuming man who was always above politics and produced a staggering body of work," said Cronan. Quite a compliment, considering Cronan himself has trained over 40 Ph.D. students, published 300+ papers, is a member of the National Academy of Sciences, was the head of the microbiology department for 21 years, and has been awarded the same grant for 48 years.

How did Cronan build a career in microbiology given his biochemistry

background? "I learned by osmosis in seminars. My only experience prior to UIUC was a microbiology course I took as an undergraduate. I learned how to take apart a microscope and put it back together really quickly."

For today's researchers, John believes that the walls that separate each field are very thin. The fields have become more molecular, and it is imperative to continue learning new concepts. "The next big thing will be to study the microbiome, how bacteria communicate with each other, and what signals they send to the hosts. My favorite joke is that the human body was designed by bacteria in order to carry them around."

Interestingly, John still works in the lab, which is unusual for a faculty member. "I enjoy it, it's my hobby. Also, I understand the technology because I've actually done it," he quips. To put that into perspective, in order to carry out his early work, John had to buy frozen *E. coli* cells from Grain Processing in Muscatine, Iowa, which came in giant Chinese food take-out containers. The cells had to be thawed, thrown into a homogenizer, and then processed through several steps to extract proteins. Now with the development of sophisticated techniques all these steps have been reduced to a day's work. "When I was in Yale we also made our own restriction enzymes and would swap with other labs. Now you can go down to the storeroom and pick them up." Of all his accomplishments what does John take pride in? Without skipping a beat, he says "My graduate students, they've done all their work from scratch".

Outside lab John has several interests, the biggest ones being tennis and travel. "I got into California State University, Northridge on a tennis scholarship. It covered my books, fees, and a meal card in the cafeteria." He also has traveled extensively with sabbaticals in Australia and New Zealand and the UK as well as several trips to Africa. John is also the proud holder of the "Rwanda Gorilla Trekking Certificate", where he got to observe silver-backed gorillas in their habitat. "I've had a young gorilla bounce off my leg when it was playing, I've been attacked by an elephant and a buffalo, and I've loved it. I look forward to going back."

"The next big thing will be to study the microbiome, how bacteria communicate with each other, and what signals they send to the hosts. My favorite joke is that the human body was designed by bacteria in order to carry them around."

When asked about his experience as Department Head John points to his office which is an assortment of papers and lab equipment and jokes "My wife said that having looked at my office, she didn't think that I would ever get anything straight!"

For most of his time here John says that the department has been a "bug department", focusing on fundamental bacterial metabolism. "This type of department, while being uncommon in the U.S., is standard in Germany where I'm treated like a minor rockstar. However, it is exciting to see that now we are becoming more diverse and we have virologists and immunologists."

Even so, the collegial environment has remained unchanged. "We have similar personalities and values. When I first arrived I implemented the open door system of labs and this aspect surprises many of our visitors. This department has a generosity of spirit that is rarely seen." n

The Cronan Lab: Solving the Process of Lipoic Acid Assembly in Humans

The Cronan lab recently published a paper in PNAS titled "Protein moonlighting elucidates the essential human pathway catalyzing lipoic acid assembly on its cognate enzymes."

Lipoic acid is an essential cofactor for certain key metabolic enzymes. It is a helper molecule that enables enzymes to carry out their function. Human disorders in lipoic acid synthesis result in disruption of mitochondrial function, decreased energy production, toxic accumulation of certain amino acids and death generally soon after birth.

The pathways whereby lipoyl groups are assembled on enzyme proteins have been previously characterized by the Cronan lab in *E. coli* and *Bacillus subtilis* and others have shown that *Staphylococcus aureus* mimics the latter pathway. All three organisms follow similar pathways- the lipoic acid precursor is attached to a protein and then modified to form the functional lipoyl cofactor. However, the number of enzymes involved and the order of assembly differs in each organism. In *E. coli* each protein that requires the lipoyl group is individually modified. However, *B. subtilis* and *S. aureu*s the lipoyl groups are assembled on the H protein, which is also involved in the breakdown of glycine, and then transferred to the other enzymes. In humans genetic disorders identified three proteins required for lipoyl assembly - LIAS, LIPT2, and LIPT1. Of these, the function of LIPT1 was poorly understood and was thought to have a role in the uptake of dietary lipoic acid. Also the function of LIPT2 was only hypothesized. Direct biochemical assays with purified enzymes done by the Cronan lab showed that similar to *B. subtilis*, LIPT1 transfers the lipoyl group from the central H protein onto other lipoic acid-dependent enzymes whereas LIPT2 is responsible for attachment of the lipoyl precursor to the H protein. Therefore, their findings explicitly define the pathway involved in human lipoic acid assembly and fully explain the genetic disorders. n

Kidney Stones' Distinct Geological Histories

Using a suite of techniques both common and new to geology and biology, researchers, from left, M.D./Ph.D. student Jessica Saw, geologist and microbiologist Bruce Fouke, microscopy expert and plant biologist Mayandi Sivaguru and their colleagues made new discoveries about how kidney stones repeatedly grow and dissolve as they form inside the kidney. Photo by L. Brian Stauffer

By Diana Yates

A geologist, a microscopist and a doctor walk into a lab and, with their colleagues from across the nation, make a discovery that overturns centuries of thought about the nature and composition of kidney stones. The team's key insight, reported in the journal Scientific Reports, is that kidney stones are built up in calcium-rich layers that resemble other mineralizations in nature, such as those forming coral reefs or arising in hot springs, Roman aqueducts or subsurface oil fields.

Most importantly for human health, the researchers found, kidney stones partially dissolve and regrow again and again as they form.

This contradicts the widely held notion that kidney stones are homogenous rocks that never dissolve and are different from all other rocks in nature, said University of Illinois geology and microbiology professor Bruce Fouke, who led the new research with Jessica Saw, an M.D. student at the Mayo Clinic School of Medicine and Ph.D. student at the U. of I.; and Mayandi Sivaguru, an associate director of the Carl Zeiss Laboratories@ Location at the Carl R. Woese Institute for Genomic Biology at the U. of I.

"Contrary to what doctors learn in their medical training, we found that kidney stones undergo a dynamic process of growing and dissolving, growing and dissolving," Fouke said. "This means that one day we may be able to intervene to fully dissolve the stones right in the patient's kidney, something most doctors today would say is impossible.

"Instead of being worthless crystalline lumps, kidney stones are a minute-by-minute record of the health and functioning of a person's kidney," he said.

The findings were the result of looking at kidney stones much more closely and with a broader array of light and electron microscopy techniques than others had employed before, said Sivaguru, the lead author of the study who led the microscopy work. The methods included bright-field, phase-contrast, polarization, confocal, fluorescence and electron microscopy, with newly invented combinations of these tools and X-ray spectroscopy.

Many of the techniques are commonly employed in geology and geobiology, but have not been used to study mineralizations in living organisms, like the kidney stones and gallstones that form in the human body, Fouke said. In particular, the use of ultraviolet light, which causes some minerals and proteins to fluoresce at different wavelengths, offered a vast new treasure trove of information.

A recently developed technology, Airyscan super-resolution microscopy, allowed the team to view the samples at 140-nanometer resolution, a much higher magnification than is normally possible with light microscopy.

The effort resulted in spectacularly clear, colorful images of the interior growth history of the kidney stones, revealing that they are built up in alternating thin layers of organic matter and crystals, interrupted in places with jutting interior crystals.

In the earliest stages of kidney stone development, the researchers found, crystals of a hydrated form of calcium oxalate adhere to one another, forming a big, irregular clump. Layers of organic matter and crystals build up on top of this inner core, creating an outer shell. The stones continue to dissolve and grow. Being able to see the layers clearly for the first time made it possible to recreate this geological history, Fouke said.

"In geology, when you see layers, that means that something older is underneath something younger," he said. "One layer may be deposited over the course of very short to very long periods of time."

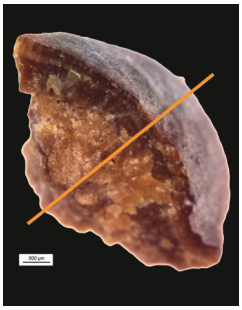
But many of the layers were disrupted, revealing that part of the stones – usually the interior dihydrate crystals – had dissolved. New crystals of a dehydrated form of calcium oxalate had begun to grow again within those voids.

"Therefore, just one rock represents a whole series of events over time that are critical to deciphering the history of kidney stone disease," Fouke said.

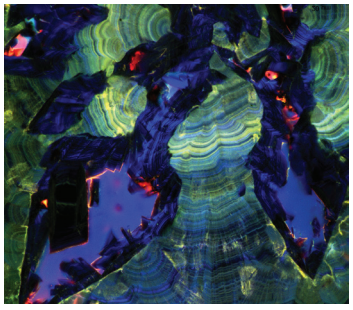
Researchers and doctors who study and treat kidney disease will now need to rethink their basic assumptions, Saw said.

"Before this study, it was thought that a kidney stone is just a simple crystal that gets bigger over time," she said. "What we're seeing here is that it's dynamic. The stone is growing and dissolving, growing and dissolving. It's very rich with many components. It's very much alive."

Fouke, Saw and Sivaguru are affiliates of the Carl R. Woese Institute for Genomic Biology. Saw is pursuing a Ph.D. in molecular and integrative physiology at Illinois. n



A human kidney stone from the Mayo Clinic. Image provided by Mayandi Sivaguru, Jessica Saw from Bruce Fouke Lab, Carl R. Woese Institute for Genomic Biology, U. of I.



Fluorescence micrograph of a human kidney stone from the Mayo Clinic. Image provided by Mayandi Sivaguru, Jessica Saw from Bruce Fouke Lab, Carl R. Woese Institute for Genomic Biology, U. of I.

Hfq's Starring Role in Gene Regulation

By Claudia Lutz

A cell's efforts to respond and adapt to its external environment rely on an elaborate yet coordinated set of molecular partnerships within. The more we learn about this complicated internal dance, the more we appreciate the flexibility of its roles. In a recent University of Illinois study, graduate student Muhammad Azam and Professor of Microbiology Cari Vanderpool have demonstrated that a protein typically assumed to support the functions of other molecules is actually able to assume a primary role itself.

The work, published in *Nucleic Acids* Research and supported by the NIH, is part of a long-term effort in the Vanderpool laboratory to understand how bacterial cells balance uptake of sugars from their surroundings with their metabolic needs. Vanderpool is also a member of the Carl R. Woese Institute for Genomic Biology, participating in the thematic research group Microbiome Metabolic Engineering, which explores the relationships between microbial communities and the environment.

"For a long time, we've been trying to understand how bacterial cells coordinate uptake of sugars with their metabolism because if these processes become unbalanced, cells get sick and stop growing," Vanderpool said. "We study a genetic regulatory system in *E. coli* and related bacteria that help them keep this balance between sugar uptake and metabolism."

One way that bacteria adapt to environmental change is by adjusting gene activity. Many genes are like recipes for proteins; machinery in the cell reads the information captured in the DNA sequence of a gene and produces a complementary strand of messenger RNA (mRNA). This information enables another piece of molecular machinery called a ribosome to construct the corresponding protein. One way bacteria can adjust the amount of protein produced is by increasing or decreasing the number of times ribosomes "read" the relevant mRNA.

For example, bacteria possess multiple genes coding for proteins that transport sugars into the cell. In an environment with an oversupply of sugar available, specialized molecules may bind to the mRNAs that produce those proteins and prevent ribosomes from reading them as easily, resulting in fewer transporters and a slower uptake of sugar. Vanderpool and her colleagues are interested in the details of how that regulation occurs.

"If we understand this process better, we might eventually be able to devise new strategies to manipulate growth of bacteria that live in us and on us—improving the growth of helpful bacteria or inhibiting the growth of harmful bacteria," she said.

In Azam and Vanderpool's study, the focus was the regulation of a gene called *manX* that codes for a protein able to transport mannose, a sugar, into the cell. They were particularly interested in how a molecule called SgrS helps control how much ManX protein is made.

SgrS is actually a short strand of RNA, the same type of molecule used to transfer the message of a gene to ribosomes during protein production. Small RNAs (sRNAs) like SgrS can play a regulatory role in this process by sticking to the part of an mRNA where a ribosome usually begins its work. Some sRNAs prevent the ribosome from grabbing the mRNA, while others help it hang on, respectively decreasing or increasing the amount of protein made.

"Prior to this study, we knew that SgrS helps cells by slowing down sugar uptake to allow metabolism to catch up," Vanderpool said. She and Azam began to examine how SgrS does this, and how it might be supported in this function by a protein called Hfq. Hfq is an RNA chaperone protein, a type of protein whose name evokes its function; Hfq helps guide and stabilize sRNAs as they bind to mRNAs.

Azam and Vanderpool were surprised to discover that SgrS does not appear to cling to the part of the ManX mRNA where a ribosome needs to attach. Instead, the Hfq protein grabs onto this area, while SgrS pairs up with a site further along the mRNA strand, reversing the roles that researchers have consistently observed in bacterial gene regulation.

"Hfq, not the sRNA, is the direct repressor," Azam said, describing the mechanism that the study revealed. "This is an unusual mode of repression . . . SgrS acts as a guide to recruit Hfq" rather than Hfq helping to guide and stabilize SgrS.

"I was very excited that we were able to define a specific mechanism for this regulation," Vanderpool said. "Our work is the first to have shown a specific and new mechanism by which small RNAs and Hfq cooperate to control translation of mRNAs."

Vanderpool and Azam suggest that this discovery of a reversed relationship between a sRNA and Hfq may lead to further documentation of similar mechanisms in bacteria—researchers may have missed other examples in the past because they didn't know to look for them. They hope that a more comprehensive understanding of gene regulation in bacteria will eventually enable scientists to reprogram bacterial behavior by affecting gene activity. n

David and Julie Mead:
The Only Two-centrifuge Family on the Block

Photo provided

By Brian Wallheimer

As a high school student, David Mead's nose could often be found inside a science fiction book. The stories told of adventures and technologies that weren't possible at the time but were plausible enough to feed a curious mind.

"They always have a kernel of science in them," Mead said. "They would do things that you might or might not be able to do in the future. I was fascinated."

When it came time to get on a career path as an undergraduate, those books drew Mead to science, medicine initially. But a stint as a hospital orderly didn't suit him. Instead, he found his way into research, working up to a doctoral program in Byron Kemper's lab at Illinois.

Kemper, emeritus professor of molecular and integrative physiology, was doing things that Mead had only dreamed about - or read about in his science fiction books.

"I was just blown away that you could manipulate DNA like that in vitro. It's amazing that you can study the invisible and figure out how to make tools to improve things like genes and proteins," Mead said. "You could modify the components of life in a test tube. I got addicted."

Mead spent his time in Kemper's lab developing a rapid method for molecular structure function analysis, eventually selling the technology. Besides the formal science, Mead also developed a skill that would serve him well over the ensuing years. Kemper insisted that his students try many different things and find ways to build synergies with the knowledge.

If there was something the students wanted to try, Kemper encouraged them to read up on it and experiment. That meant that Mead often found himself in the library, learning as much as he could about a wide variety of fields, including biology and anatomy in addition to the knowledge he gained to earn his doctorate in physiology and biophysics.

"I owe a lot to Byron's lab and his environment, his hands-off style of mentoring and training and teaching. That open-minded approach to problem solving was very helpful for a bunch of us," Mead said. "Illinois was the beginning of the training on how to do that, both in formal and informal ways. That was reinforced through my graduate career."

It was also during those years that Mead made a significant leap in his personal life. David and Julie met at Illinois State University while David was earning a master's degree and Julie a bachelor's degree in education. The two were married at Illinois, the beginning of a marriage that's in its 36th year.

After time at Illinois, David and Julie Mead set off to spend time in California and Wisconsin. In Wisconsin, David worked as a senior scientist for research and development at Promega, a biotechnology company that provides DNA identification tools, and as an associate scientist in the Department of Chemistry at the University of Wisconsin-Madison.

From there, David would build his first company, CHIMERx, which manufactures reagents and nucleic acid extraction and purification kits. By the early 1990s, Julie finished her doctorate in Madison and found a job in California. So, David followed her this time and found work as a research and development manager at Bio-Rad labs, maker of products for life sciences research and clinical diagnostics.

In just three years, the couple was back in Wisconsin, and after a brief stint with another firm, David founded another company - Lucigen Corp. David and Julie worked together, starting in their basement.

"For quite a while, we were the only two-

centrifuge family on the block," David Mead joked.

The company developed tools to advance cloning and expression and sequencing DNA. David secured some research funding and grew the company to more than 65 employees before selling it in early 2018.

Now, he's heading another company, Varigen Biosciences. The company utilizes microbes from soil and water to develop new enzymes and drugs.

"We're developing new tools to accelerate drug discovery," Mead said. "These microbes are difficult to work with. Antibiotics and other molecules require a lot of DNA. At Varigen, we are developing methods for capturing, cloning and overexpressing that DNA."

It's a different kind of company, but once again at the cutting edge. But that's ingrained in Mead after all those years of science fiction and encouragement from Kemper to try new things.

"If you're driven by or excited by the possibilities and not afraid of working hard, you're capable of so much even outside of your training and expertise," Mead said. "That's kind of the main thing that's gotten me to this point in my career."

It's an ethic he hopes more students can obtain at Illinois, and he's helping to make it happen. The Meads made a $1 million contribution this year for graduate scholarships and an endowed chair in Molecular and Integrative Physiology.

"Graduate students are major contributors to advancing science and technology in the university setting, and yet they are sometimes one of the most overlooked part of the equation. Supporting their effort through scholarships will make UI stronger and more competitive, while recognizing individuals for their contribution," Mead said. "I could not have made it through grad school without this form of assistance, and it changed my life. I hope this does the same for the next generation of young scientists." n

MCB is deeply grateful for recent gifts from alumni

Photo provided

Michael Recny: "I don't think that I would have landed my first job in a start-up biotechnology company out of Harvard in Boston had it not been for the stellar reputation of the U of I Biochemistry Department and of my thesis Advisor, Dr. Lowell Hager. I was inspired to give back to MCB because of how important and valuable my PhD degree from Illinois has been to me as I pursued a career in a field that I love for more than 30 years, and has truly has had a positive impact on a lot of people suffering from debilitating diseases. The MCB graduate programs carry the awesome responsibility of training the scientific leaders of our future. There is no better way to ensure that we will continue to drive scientific innovation than to support the graduate MCB programs that can motivate and nurture the talent pool we will need to achieve that goal."

Anonymous: "MCB would like to thank an anonymous friend and donor for supporting the new MCB Biophysics Fellowship, which provides stipends for biophysics graduate students doing research in labs within Molecular and Cellular Biology.

This gift recognizes the long history and strong ties between faculty within MCB and the Biophysics Program."

David Mead; "Over the years I have had a number of bosses, some good, many not so good. In hindsight, my PhD advisor Byron Kemper was one of only a few people who inspired me and my career. Because of that I decided it would fantastic to honor him and his mentoring by donating to UI. I also remember what it is like to struggle financially as a grad student and thought it would be helpful to support the next generation of scientists."

Dr. Brenda Wilson honored with the Dr. Larine Y. Cowen Leadership in Diversity Award

In honor of the past Office of Diversity, Equity, and Access director, Dr. Larine Y. Cowan, the Office of Diversity, Equity, and Access (ODEA) created awards consistent with Dr. Cowan's values for human rights advocacy, social justice, and diversity. The Larine Y. Cowan Make a Difference Awards recognize, and honor nominees who demonstrate exceptional dedication to and success in promoting diversity and inclusion through teaching, research, hiring practices, courses, programs, and events.

"I firmly believe that when you lead by example and with enthusiasm and when you build strong foundations by providing the enabling tools that you then empower others to engage and rise to the challenge set before them. I am delighted and honored by this recognition of my efforts to improve scientific literacy for everyone and to enhance diversity, inclusivity and equity in higher education and the community." n

The Higher Calling in a Career

From building cars to fuel cells, LAS alumna Susan Brennan takes a stand for women and sustainability

Susan Brennan, chief operations officer at Bloom Energy Corporation, has built upon her career success to introduce more women to male-dominated industries. Photo courtesy of Bloom Energy Corporation.

Susan Brennan grew up in Granite City, Illinois, and remembers crossing the Mississippi River to go from her grandmother's house to St. Louis, pinching her nose shut with her two fingers the entire time.

"It was a steel town and a wonderful place to grow up. The people and the values. The great parks, great schools, and the hard, hard working people," she said. "But it smells like hydrogen sulfide."

This is one of the reasons that Brennan (BS, '85, microbiology) has developed a passion for environmental sustainability, something she works on everyday as chief operations officer at Bloom Energy Corporation, a Silicon Valley company that creates sustainable, on-site electric power systems based on solid oxide fuel cell technology.

"From a young age, I always believed you could have jobs and a sustainable environment. So Bloom is my vision imagined," Brennan said.

At Bloom Energy, Brennan handles many duties but ultimately oversees projects from the time a sales order is made until the project is complete. She secures strategic material, runs factories, procures and secures parts, and manages business strategy.

Brennan's accomplishments were recognized this year by Achieving Women's Excellence in Supply Chain Operations, Management, and Education (AWESOME), an organization focused on advancing women's leadership in supply chain operations. Brennan was awarded the Legendary Leadership Award for her own success, as well as her commitment to bringing women into the male-dominated industry of management and supply chain. Prior to working for Bloom Energy, Brennan had a successful career in the auto-industry, another largely male-dominated field.

"I'm very honored. I've been doing this a long time. Some things change, some things don't. And the need to get more women into manufacturing and technology doesn't change," she said.

While Brennan enjoyed her microbiology degree at Illinois, and while she was aided throughout her career by the technical skills she built while earning the degree, she decided that working in research laboratories wasn't something she wanted to do for her entire life. This decision came about after some soul-searching, as family history had led Brennan to the field in the first place. Brennan's father passed away from a congenital heart issue at age 29, when Brennan was five years old, and her grandfather passed away at age 39. These tragedies led Brennan to study gene expression after graduation from U of I.

"I loved the process, I loved the challenge, and at 20, I didn't want other kids to go through what I had gone through, losing a parent tragically," Brennan said.

However, after four years spent in the lab, she knew that this line of work wasn't for her and went on to get her MBA from the University of Nebraska.

"I knew there were better ways for me to contribute to the world," Brennan recalled.

It was this realization that eventually catapulted Brennan from lab work to entering management and supply chain in the auto industry.

"A philosophy I have is the worst thing you can do is fail and go back to doing what you were doing before, and the best thing you can do is be successful," she said.

Brennan found success working at Douglas & Lomason Company, an auto parts supplier. Under her leadership, Douglas & Lomason built a components plant and won the coveted Job 1 Award from Ford within six months, something that had never been done in the auto industry at the time. While at Nissan, Brennan helped launch the Nissan Leaf in 2010, an electric car that remains one of the most popular on the market today.

"We launched five vehicles within 18 months, which had never been done in the automotive industry," Brennan said. "I was able to bring the Nissan Leaf to the North American market. I was very fortunate to be able to do what most people aren't as fortunate to do."

However, her time in these work environments didn't come without challenges.

"I was excluded in an interesting way and there was clearly a lot of bias," Brennan recalled. "I had to work three times as hard to get half the amount of credit."

Brennan began a group nine years ago called the Southern Automotive Women's Forum aimed at scholarship and professional development. The group has given $250,000 in scholarships the past eight years, but it also serves as a safe place for women in the auto industry to grow, connect, and develop professionally.

Now, Brennan often speaks to young girls in middle school and high school to encourage them to go into STEM fields. Ten years ago, a popular study determined that most young girls experience an unfavorable view of women in STEM. So when speaking to young girls, Brennan does what she can to combat negative stereotypes of women in traditionally male-dominated fields.

While Brennan said that she would have enjoyed concluding her career at Nissan, the 51 year-old revamped her life to move to Silicon Valley to pursue the work in sustainability that had been in her mind ever since childhood.

"Sustainability was one of the considerations coming to Bloom, and I've been so fortunate in my career to be able to work on this passion," she said. "I've been able to bring in the skills I built in the auto industry, and the skills I have that I never used in the auto industry. I use my right brain, and my left brain. Learning is an absolute must. You can't ever stop learning." n

MCB GRADUATES

The lists are organized first by degree and then by major. Not all graduates listed are participating in today's ceremony. Because of printing deadlines, lists may be incomplete.

Doctor of Philosophy

Biochemistry
Amruta Bhate, Fall 2017
Xinyun Cao, Spring 2018
Ruchia Duggal, Fall 2017
Gregory Miner, Spring 2018
Seung Oh, Fall 2017
Nektaria Petronikolou, Spring 2018
Dennis Piehl, Spring 2018
Julian Reed, Fall 2017

Biophysics & Quantitative Biology
Kapil Dave, Summer 2017
Tao Jiang, Summer 2017
Piyush Labhsetwar, Summer 2017
Chen-Yu Li, Summer 2017
Wen Ma, Summer 2017
Marco Tijoe, Summer 2017
Yuhang Wang, Fall 2017

Cell and Developmental Biology
Li-Hsin Chang, Summer 2017
James Chu, Spring 2018
Harini Iyer, Summer 2017
Rajashekar Iyer, Spring 2018
Mahdieh Jadaliha, Summer 2018
Yating Wang, Summer 2017

Microbiology
Sunetra Biswas, Fall 2017
Sarah Henke, Fall 2017
Miglena Manandhar, Fall 2017
Michael Reno, Fall 2017
Melissa Ryerson, Spring 2018

Molecular and Integrative Physiology
Matthew Biehl, Summer 2017
Mathew Cherian, Spring 2018
Samuel Irving, Summer 2017

Neuroscience
Mariana Aparicio Betancourt, Fall 2017
Angela Bustamante, Summer 2017
Carlos Dostal, Summer 2017
Mark Fletcher, Summer 2017
Lindsey Hammerslag, Summer 2017
Kelsey Hassevoort, Spring 2018
Kevin Horecka, Spring 2018
Manoj Kumar, Summer 2017
Payel Kundu, Spring 2018
Siyuan Liu, Fall 2017
Stephanie Matt, Spring 2018
Austin Mudd, Spring 2018
James Norton, Fall 2017
Geena Skariah, Summer 2017
Marta Zamroziewicz, Summer 2017

Undergraduate Degrees—Bachelor of Sciences

Students who have completed the necessary requirements to earn one of a certificate are noted with C for Cell & Developmental Biology, M for Microbiology and N for Neuroscience.

Academic Distinction
Riley Brubaker, MCB
Bethany Bucci, MCB, Honors Conc.
Casey Bunge, MCB, Honors Conc.
Jordan Cannon M, Fall 2017
Mary Casagrande, MCB
Alex Celmer, MCB, Honors Conc.
Hannah Choi, MCB
Mohsin Dahodwala, MCB
Matthew Dungan, MCB
Ryan Emmanuel, MCB, Research Distinction
Connor Forsyth[N], MCB, Honors Conc. Highest Research Distinction
Lauren Gabra, MCB, Fall 2017
Zoe Hareng, MCB
Layna Henry, MCB, Honors Conc., Highest Research Distinction
Hunter Hicks[N], MCB, Fall 2017
Allison Hofer, MCB
William Hunter, MCB, Fall 2017
Mirjana Jovanovic, MCB
Kian Khalili[N], MCB
Mehwish Khan, MCB, Fall 2017
Samiha Khan, MCB
Terry Kim, MCB
Shalini Kumar, MCB
Jordan Marganski, MCB
William Marshall, MCB
Michael Mitchell, MCB
Luke Mittelstaedt, MCB, Honors Conc.
Travis Pflederer, MCB
John Runne, MCB
Divya Singh, MCB, Honors Conc.
Amanda Snyder[N], MCB, Fall 2017, Highest Research Distinction
Katelyn Stoker, MCB
Rongyi Sun, MCB
Ammar Ujjainwala, MCB, Fall 2017, High Research Distinction
Natalia Wojnowski, MCB, Honors Conc., Research Distinction
Emily Xiao, MCB

Highest Distinction, Research
Sneha Adusumilli, MCB Honors Conc.
Jackie Chen, Biochemistry
Jennifer Cheng, Biochemistry
Jacob Garwin, Biochemistry
Paul Kaminski, Biochemistry
Tiyaporn Tangpradabkul, Biochemistry

High Distinction, Research
Nuraini Aguse, MCB
Alondra Diaz, MCB
Sophie Gough, MCB Honors Conc., Fall 2017
Rui Huang, Biochemistry
Ozan Imir, MCB
Sai Sri Kondabattula, MCB Honors Conc.
Jeongmin Lee, Biochemistry, Fall 2017
Hannah McDowell, MCB
Amanda McKinley, MCB
Timothy Pan, Biochemistry
Lillian Scanlon, MCB
Shan Shan So, Biochemistry
Mariya Yanovskaya, MCB
Lucy YaoN, MCB

Distinction, Research
Jessica Bennett, MCB
Joshua Bertels, MCB
Rebecca Choi, MCB
Angel Ka Yan Chu, MCB
Aria Darbandi, MCB, Fall 2017
Sherri Ho, MCB
Stephanie Lozano[N], MCB, Fall 2017
Chenmin Ni, Biochemistry
Madeline Sponholtz[N], Biochemistry
Luis Tadeo Salcido, Biochemistry
Jianan Zhang, MCB

Biochemistry, Specialized Curriculum
Yiziying Chen
Madeline Doon
Annie Guo
Nina Han
Yangjing Lin
John Oh
Sunny Shah
Aleksas Valaitis

Molecular and Cellular Biology Honors Concentration
Jeannette Cullum
Navroop Gill[N]
Sana Khan, Summer 2018
Terra Scranton[N]
Shruti Srikumar
Cagla Unal[N]
Alexandra Zhang[N]

Molecular and Cellular Biology
Benjamin Abraham, Jr., Fall 2018
Amir Abusharif
Eddy Aguilar
Armaan Ahmed, Fall 2017
Anosh Akbar[N]
Abdul Quddus Akinlusi, Fall 2017
Muzammil Ali-Khan[N]
Mohammad Allauddin
Hayley Anderson
John Anderson, Fall 2017
Naomi Aspera
Seung-Hun Baek
Samiat Balogun
Ignas Baltrusaitis
Sepehr Baniassadi
Toni Banks
Bhavjot Bansi
Armando Barajas
Paul Beinhoff, Fall 2017
Brittni Belcher
Martin Beshay
Maher Bizri, Fall 2017
Jonathan BodnariucN
Kashif Bokhari
Brian Booker[N], Fall 2017
Sarah Bounab, Fall 2017
Marissa Buinickas
Paul Cacioppo
Mark Capito, Fall 2017
Shoshana Center
Marianne Chan
Michael Chaney, Fall 2017
Abbie Chang
Monish Chheda, Fall 2017
Sneha Cherukuri
Melanie Chiu
Hyun Woo Choi
Sunyoung Choi
Dane Christensen[N], Summer 2018
Natalia Ciszek
Kasandria Clark
Andrea Colin
Zaira Corral
Amanda Cowfer
Jordan Cowles
Secilia Cox
Morgan Cross
Selina Cudia, Summer 2018
Katherine Czerwinski[N]
Shoham Das
Paroma Raisa De
Julie Robin Dean
Agilda Dema
Justin DesLaurier, Fall 2017
Luke Detloff
Katie Diol
Patrick Doah, Fall 2017
Sean Doody
Brendan Du
Gabriel Dungan
Jonathan Dzielski[N]
Sabit Ejub[M]
Carol Eldeek
Fatima Eldes[N]
Willie Elliot Jr.
Donald Elmore
Thomas Emerson
Pedro Escobedo[N]
Abraham Eugenio, Summer 2018
Alessandra Fahey[N]
Noamaan Farooqui
Sarah FenimoreC, Fall 2017
Karsten FrigoM, Fall 2017
Michael Frintner
Kirollos Gabriel[N]
Alexander Gatten, Fall 2017
Nicholas Gattuso
Andrew Geiser
Matthew Gibson
Eileena Giurini, Fall 2017
Allison Goad[N]
Anthony Gomes*
Danielle Gomez
Ryan Green
Nicholas GrimesM, Summer 2018
Moshe Gross
Amarillys Guzman
Yoon Jung Han
Travis Hanson
Parnita Harsh
Sarah Hassan
Da Hye Hong
Lauren Hoover
Sean Horvath, Fall 2017
Caroline Hu
Miwei Hu
Kevin Huang
Zijing Huang
Haley Hullfish, Fall 2017
Ilham Hussaini, Fall 2017
George Ibrahim
Hundley Ignoffo[N]
Chitra Iyer, Fall 2017
Jeremy Jedwabnik, Summer 2018
Elliot Jensen[N]
Woojoong Jeong
Nalin John, Fall 2017
Varsha John, Fall 2017
Emaline Johnson, Summer 2018
Oluyemisi Joseph
O. Janet Joseph
Jeeth Joseph[N]
Lakshmi Kadkol
Chase Kangas
Andriy Kapeniak, Fall 2017
Sarah Kapolnek
Sailee Karmarkar
Nisha Karwal
Alexandra Kieffer
Sandra Kietlinska
Kyung Il Kim, Fall 2017
Michelle Kim
Richard Kim
Kathryn King, Summer 2018
Brianna Klein
Robert Knier
Joshua Koerner
Anjelica Kokinias
Christopher Kosapatti
Adriana Kraljevic
Oh Hyun Kwon
Soon Woo Kwon
Karen Lai
Eric Lamoutte[N]
Mike Lan
Kara Lane
MacKenzie Large[N]
Brenda Le, Fall 2017
Tam Le, Fall 2017
Lydia Lee
Olivia Lee
Liya Levin
Christopher Li
Alan Liu
Hanyu Liu
Shihao Liu
Evan London[N]
Jose Lopez Jr.
Tiffany Louie, Fall 2017
Tyler Maggio
Andrew Manahan
Sankara MandalikaM
Ana Manriquez Hurtado[N], Fall 2017
Naif Mansury, Fall 2017
Amer Marachli
Alexandro Martinez
Aaron Mattix-Wand[N]
Sean McCarty
Angelina Mei
Bryton Mellott
Daniel Melnikov, Fall 2017
Kaylee Mitsuuchi[N]
Eliot Mook
Eric Moore
Tyler Morgan
Noemi Muniz
Anastasia Myatt
Jacob Nachsin, Fall 2017
Gertrude Namara
Adisha Nanda
Shayaan Naseer
Anurag Nekkalapudi
Katerina Newman
Anh Nguyen
Anthony Nguyen
Hamad Niazi
Samuel Nudelman, Fall 2017
Christopher Nutley
Adebowale Olaleye
McKelvey Olson[M], Fall 2017
Amy Ou, Fall 2017
Taein Park
Youngsoo Park
Zachary Parks
Dhruv Patel, Fall 2017
Monica Patel
Neha Patel, Fall 2017
Nishal Patel
Pooja Patel, Fall 2017
Prit Patel, Fall 2017
Sonal Patel
Vishal Patel
Aeshaa Pathak[N]
Nicholas Patterson, Fall 2017
Alice Pen
Luke Peterson
Shannon Pierce, Fall 2017
Lawrence Piton
Alexandra Plezia
Alexander Pohlman, Fall 2017
Tyler Pohn, Fall 2017
Matthew Posen
Arjun Prasanna
Salma QamruddinM, Fall 2017
Sabina Raja
Rhymia Raspberry
Alexis Renee Ray
Juan Reyes[M]
Ramiz Riadi
Anita RongN, Fall 2017
Kathleen Ross
Arnab Roy
Alexia Rudofski[N]
Rosario Saldivar[N]
Steven Saletta
Benjamin Samuel
Novejot Sandhu
Lucas Sanz
Brianna Sarley
Sameera Sarma
Ashka Shah
Ryan Shaw
Omar ShennibM
Alli Shillo, Fall 2017
Samuel Shim
Aejin Shon, Fall 2017
Artemy Shumskiy
Devashish Singh[N]
Shreya Singh
Ajay Sivam
Antonios Skondras[N]
Connor Smith
Rachel Song
Anastasia Sorokina[N]
Steven Spencer
Syed Sufyan, Summer 2018
Aleksandar Surjancev[N]
Alexis Susralski
Madeline Taylor
Stephanie Teeling
Abenezer Tegegne
Camille Terry
Alexander Thomas[N]
Subeena Thomas
David Tian, Fall 2017
Alejandro Torres[N]
Kelley Tran
Anupriya Tripathi
Jamie Tse
Tiffany Tsoi, Fall 2017
Marlena Tulicki
Kevin Tun
Chelsea Tuvilla[N]
Ogorchi Ujari
James Unik, Fall 2017
Kelli Utz, Fall 2017
Alejandro Vallejo
Sarah Van Ness
Pitchaya Vichitcharoenpaisarn
Melinda Vitalis
Jarrett WadeM
Andrzej Wajda
Taylor Walker
Jessica Weislo
Collin Weintraub
Matthew Weiss, Fall 2017
Kevin Wells, Fall 2017
Claire Therese Wheaton
Joshua Whitworth
Brian Williams
Alexander Willis, Fall 2017
Ezra Winter-Nelson
Sarah Womack
Naomi Won, Fall 2017
Sally Wu
Kewei Xu
Sophia Yang
Xiaoyu Yang
Christopher Yao
Alyssa Yee
Yunsu Yu
Elana Zelden[N]
Tongyu Zhang
Zhechuan Zhang
Sara Zhukovsky
Rachel Zwilling

Notes:
This program contains an unofficial list of degree candidates for May and August 2018; as well as a list of graduates who received degrees in August 2017 and December 2017. Due to printing deadlines, names of some degree recipients may not appear while names of some degree candidates who have not yet completed degree requirements may be included.

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