

MMI NEWS



SPRING 2025



WELCOME TO THE SPRING 2025 NEWSLETTER!

As we begin this new year, we're thrilled to share some fantastic highlights from our current faculty and esteemed department alumni. Their recent achievements and ongoing contributions continue to inspire and shape our community, and we are proud to showcase their incredible work.

We hope this newsletter serves as a reminder of the strength and vitality of our department, and we wish all of you a wonderful start to 2025. Whether you're embarking on new projects, pursuing personal goals, or continuing your journey with us, we look forward to what lies ahead and the continued success of our collective efforts.

Vanessa Sperandio, Department Chair

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Department of Medical
Microbiology and Immunology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

MMI ALUM WINS PRESTIGIOUS NAT. L STERNBERG THESIS PRIZE

Mary Ellen Gabriel | HONORS & AWARD

Ruth Isenberg, a first-generation college student who earned her PhD in microbiology from the UW–Madison Microbiology Doctoral Training Program in 2023, was awarded the 2024 Nat L. Sternberg Thesis Prize in August for outstanding doctoral research in the field of bacterial molecular biology. In the 29-year history of the international prize, Isenberg is the first recipient to have completed her dissertation in the UW School of Medicine and Public Health. Her thesis advisor was Mark Mandel, professor of medical microbiology and immunology. Isenberg received her Bachelor of Science degree in molecular and cellular biology from the University of Puget Sound.

Your dissertation research focused on the associations between beneficial bacteria and their animal hosts. What bacteria-animal system did you study?

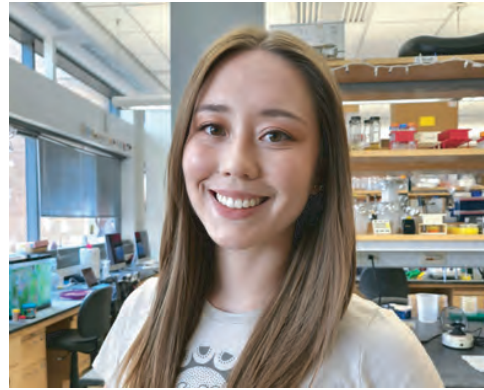
The Mandel lab uses the naturally occurring association between the Hawaiian bobtail squid and a bacterium that glows in the dark called *Vibrio fischeri* to study beneficial host-bacteria interactions. It's a valuable study system because *Vibrio fischeri* is the only bacteria that colonizes the specialized light organ of the squid. It's uncommon to find a naturally occurring host-bacteria association involving only one host and one species of bacteria. The *Vibrio*-squid system is a natural simplified microbiome, which is useful as a study system because researchers can more easily determine specific bacterial and host factors required for the association, as compared to studying a complex association such as the human gut microbiome.

What were you looking for, specifically?

I was focused on the role of a small molecule, cyclic diguanylate, in establishing associations between beneficial bacteria and their hosts. That role is not well studied, and my dissertation work aimed to help fill that knowledge gap.

What did you discover, and how does it impact the field of microbiology?

My work determined that *Vibrio fischeri* has a large and complex cyclic diguanylate signaling network – a system that bacteria use to sense and respond to various environmental changes. High levels of cyclic diguanylate prevent host colonization through a mechanism that researchers have yet to fully



Dr. Ruth Isenberg

understand. I originally thought that cyclic diguanylate in *Vibrio fischeri* would impact squid colonization by influencing biofilm formation (how bacteria stick to each other and to surfaces) and/or motility (how bacteria move around in their environment). Both behaviors are required for *Vibrio fischeri* to colonize squid, and both behaviors are also regulated by cyclic diguanylate. However, my work shows that while cyclic diguanylate does impact squid colonization, it is not through regulating either biofilms or motility. This means that other mechanisms contribute to *Vibrio fischeri*'s ability to successfully colonize squid. Uncovering those mechanisms and how cyclic diguanylate influences them would give us new information on how bacteria form beneficial associations with their hosts.

How could your research be translated to advance human health?

Knowing how bacteria form beneficial associations with an animal host could potentially be applied to other bacteria-animal interactions, including those that occur in humans. Also, the human gut microbiome contains bacteria that produce and break down cyclic diguanylate, one of the most common signaling molecules in bacteria. Understanding how bacteria use cyclic diguanylate to contribute to the assembly of a healthy gut microbiome could be useful in the treatment of conditions related to the gut microbiome and development of effective probiotics.

What was most interesting and fulfilling about working on your dissertation in the Mandel laboratory?

The most fulfilling aspect was the mentorship, both received and given. I had a lot to learn when I started in the lab, and during the first few years of my PhD, Mark was patient and supportive while I grew as a scientist. I felt comfortable making mistakes and learning from them under Mark's guidance, which helped me become independent. I was surrounded by other people in the lab I could go to for support. I also became passionate about



V. fischeri bacteria make light for their squid host, camouflaging the squid's shadow as it forages in the moonlight.

teaching and mentoring while I was in the Mandel lab. I started mentoring undergraduate students, and it was my greatest joy to watch them develop into independent scientists. Much of my dissertation would not exist if it were not for these undergraduate students, and I have seen two of them go off to pursue PhDs of their own. During the last couple years of my PhD, Mark basically let me run my own mini lab within his lab with the people I was mentoring, and it instilled in me the desire to continue teaching and mentoring after my PhD. Through the Delta Program in Research, Teaching, and Learning at UW–Madison, I took classes on teaching and mentoring and completed a teaching internship at Madison's Edgewood College. I am so fortunate to have completed my PhD in a program that allowed me to develop my professional interests.

When did you first know that you wanted to pursue a PhD in medical microbiology?

I'm a first-generation college student, so I knew nothing about the world of research or how getting a PhD worked. It wasn't until my last semester of my undergraduate degree that I did any sort of research. Once I did, I was hooked and knew that I wanted to pursue a PhD in microbiology. I have my undergraduate advisor and research mentor, Mark O. Martin, PhD, at the University of Puget Sound, to thank for instilling a love for bacteria and microbiology research and supporting me throughout my journey.

Where are you working now, and what are you studying?

I am now a National Institutes of Health (NIH) K12 Institutional Research and Academic Career Development Award (IRACDA) postdoctoral associate at the University of Minnesota, in the lab of Julia Willett, PhD. My work now focuses on how bacteria interact with other bacteria that live in the same niche, and my current research project investigates interactions between the opportunistic pathogen *Enterococcus faecalis* and the oral cavity pathogen *Streptococcus mutans*. As a part of my

IRACDA fellowship, I am also involved in undergraduate research mentorship and teaching. A major goal of mine is to become a professor and run my own research program while continuing to mentor and teach.

What did you love about Madison, when you were here?

I loved the sense of community in Madison, both within the university and the city as a whole. The research community is collaborative and rigorous without being competitive against each other. The people of Madison are friendly and there are a lot of groups with different interests throughout the city. For example, I am an avid knitter/crocheter and there were several local yarn shops in the area where I could go and find other people with the same interests. I also loved the Terrace at Memorial Union and the collective understanding that summer afternoons are for the Terrace!



FACULTY AWARDS AND RECOGNITION

Dr. Mark Mandel won the Vilas Associates Competition.

Dr. Andy Mehle was elected to the American Academy of Microbiology

ANNOUNCING THE 2025 PERLMAN SYMPOSIUM ON ANTIBIOTIC DISCOVERY AND DEVELOPMENT



Registration is now open for the 2025 Perlman Symposium on Antibiotic Discovery and Development!

Mark your calendars and join us on **Friday, April 25, 2025, from 9:00 AM to 5:00 PM** for an exciting day of scientific exchange, innovative research presentations, and networking opportunities. This year's Symposium offers attendees the choice of virtual or in-person attendance, ensuring accessibility and engagement for all.

The Symposium will take place at Ebling Auditorium and Atrium at the University of Wisconsin-Madison for in-person attendees, with virtual participants able to join via live-stream. The program will feature four outstanding keynote speakers, two dynamic poster sessions showcasing research from trainees and early-career scientists, and networking opportunities. Additionally, four poster presenters will be selected to give lightning talks on the main stage, adding an interactive highlight to the day's agenda.

General registration is free and open from February 1 through March 30, 2025. Attendees can select between the virtual and in-person options when registering. Abstract submissions for poster presentations are due by March 21, 2025, so don't miss your chance to contribute to this vibrant scientific community.

Virtual attendees will enjoy live-stream access to all main-stage presentations and lightning talks taking place in Ebling Auditorium. While this option provides flexibility and accessibility, it does not include meals, participation in the poster session, or access to the afternoon reception. In contrast, in-person attendees will have full access to all events in Ebling Auditorium and Atrium, complimentary meals, and the afternoon reception. They will also benefit from the opportunity to engage directly with poster presenters during the in-person poster sessions in Ebling Atrium.

Whether you choose to join us virtually or in person, the 2025 Perlman Symposium promises an engaging program packed with innovative research and collaboration opportunities. In-person attendees will enjoy enhanced networking experiences and a more immersive event atmosphere, while virtual attendees can participate from the convenience of their own location.

For registration, abstract submissions, and the full event schedule, please visit the Symposium website at <https://perlman.mmi.wisc.edu>. If you have any questions about registration or abstract submission, feel free to contact Allison Bauer at allison.bauer@wisc.edu.

We look forward to welcoming you to the 2025 Perlman Symposium!

DR. NANCY KELLER FEATURED IN THE SCIENTIST

HOW MOLDY CANTALOUPE TOOK FLEMING'S PENCILLIN FROM DISCOVERY TO MASS PRODUCTION

Article taken from The Scientist | Written by Hannah Thomasy, PhD

Alexander Fleming's 1928 discovery of a mold with antibacterial properties was only the first serendipitous event on the long road to penicillin as a life-saving drug.

Tucked away in a dusty corner of St. Mary's Hospital in London lies a tiny, one-room museum dedicated to one of the most important discoveries in the history of medicine: a mold that changed the world. Curators have recreated Alexander Fleming's laboratory as it would have looked on the day of his discovery, from the cigarettes that he smoked incessantly while working in the lab to a replica of the famous Petri dish of *Penicillium*.

While samples of the original isolate, known as *Penicillium rubens* IMI 15378, are cryopreserved in collections around the world, this strain is curiously absent from modern-day commercial penicillin production. The isolate used in mass production today didn't originate in Fleming's laboratory at all; instead, the multi-billion dollar industry uses a microbe derived from a moldy cantaloupe found at a fruit market in Peoria, Illinois in the early 1940s.

While the serendipity of Fleming's original discovery is widely known, the following lesser-known developments are equally unusual: biographer Gwyn Macfarlane described the process as "a series of chance events of almost unbelievable improbability." These scientific advancements would have immediate impact, preventing death from infection for an uncountable number of soldiers towards the end of World War II, but also long-lasting effects whose repercussions are still felt today.

"Penicillin is, I would argue, the single most important medication that's ever been introduced," said Robert Gaynes, an infectious disease physician and medical historian at Emory University. "It completely changed the way we think about drug discovery," he continued. "It transformed the pharmaceutical industry in many ways, and it completely changed the thinking about treating infectious diseases."

Penicillin's Inauspicious Beginnings

Although Fleming's discovery of *Penicillium*'s unusual properties is famous today, his 1929 publication made relatively little impact at the time. Indeed, said



Mycologist Nancy Keller explores fungal genomes for biosynthetic gene clusters that produce novel secondary metabolites.

Gaynes, when Fleming presented his study to the Medical Research Club in London, not a single question was asked.

Fleming had observed and carefully noted the effects of the mold on bacteria, but he—along with his increasingly frustrated assistant—was unable to isolate the antibacterial substance itself. Fleming enlisted the help of Harold Raistrick, a biochemist at the London School of Tropical Medicine and Hygiene. Yet Raistrick's team also abandoned the project after a few years, largely due to "the advice of medical friends that penicillin could never be of practical use in clinical medicine because of its instability."

Fleming's work might have been relegated to the scrap heap of history if Ernst Chain, then a biochemist at Oxford University, had not found the 1929 paper nearly a decade later. Chain and Oxford pathologist Howard Florey were instantly intrigued by Fleming's bacteria-killing mold, and after that, their research proceeded quickly. By 1940, the Oxford research group, which also included biochemist Norman Heatley, had determined how to grow the mold and purify the penicillin, and shown that it could save mice from three different types of deadly bacteria.

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Tests in human patients began almost immediately. On February 12, 1941, researchers administered the first dose of penicillin to a man with a life-threatening *Staphylococcus aureus* infection. After just 24 hours, his condition had improved dramatically, but by February 17, the supply of penicillin had run out. The infection returned and within a month, the patient died.

Researchers knew that the discovery and isolation of this near-miraculous substance would be meaningless if they could not figure out how to scale up its production. But as World War II dragged on and German bombs devastated many major cities, Britain did not have the resources to devote to this massive undertaking.

And so, said Gaynes, "Florey was forced to turn to the United States for help."

Fleming's Mold Comes to America

In the spring of 1941, Florey met with Warren Weaver, the director of the Division of Natural Sciences at the Rockefeller Foundation, during Weaver's visit to London. Florey explained his inability to produce sufficient quantities of penicillin in war-torn Britain. Weaver determined that the Foundation would fund Florey and Heatley's travel to the US, where they could seek help from government research institutions and pharmaceutical companies to turn their dreams of mass-producing penicillin into a reality. While the US had not yet officially entered WWII, the government had been providing aid to the Allied powers for some time, so Florey gambled that US scientists would be willing to join the cause.

So, in June of that year, Florey and Heatley made their way to the US, bringing with them the precious cultures of *Penicillium*. Their first visit was to Yale University, where John Fulton, an old friend of Florey's, was working as a professor. Through Fulton's scientific connections—and subsequently through a chain of other researchers and government officials—Florey and Heatley made their way to Washington, DC and then to the Northern Regional Research Laboratory (NRRL) in Peoria, Illinois.

Robert Coghill, the head of the NRRL's Fermentation Division, would later note, "Penicillin has often been referred to as a miracle drug, but one of the least understood miracles connected with it is that Florey and Heatley were directed to our Peoria laboratory." Their time in Peoria was short but impactful: the duo



Alexander Fleming first observed the antibacterial effects of *Penicillium* mold in 1928, but the first attempts to treat humans with penicillin did not occur until more than a decade later.

shared Fleming's mold strain and everything they knew about culturing it. After the pair of Oxford researchers returned home in early 1942, the NRRL scientists worked doggedly to improve yields of the drug. Several crucial developments happened in Peoria that enabled penicillin to progress from a substance of the utmost rarity—so rare that early human trials involved harvesting and re-using the penicillin excreted in patients' urine—to a clinically useful product of global importance.

With years of expertise in fermentation, the NRRL group had developed several techniques to increase the growth of microbes of interest, which they applied to the *Penicillium* strains.

First, they used different ingredients in their culture media, developed by NRRL mycologist Andrew Moyer. The important ingredient, said Gaynes, was "a byproduct of corn starch production which was called corn steep liquor. It was a waste product. They were lousy with it in the middle of the Midwest. And it turned out that—again, there's the serendipity—it was much better for growing up the *Penicillium* than anything that Heatley had used. It was another example of just unbelievable luck."

Researchers at the time felt similarly. "[The NRRL] was, I am sure, the only laboratory in the country where the corn steep liquor medium would have been discovered," asserted Coghill. "The discovery of its key place in a penicillin medium was foreordained and inevitable once the problem was assigned to our Fermentation Division."

The NRRL researchers also increased yields using a submerged fermentation process, in which the microbes

were grown in vessels subjected to constant mixing to aerate them, instead of surface fermentation, in which microbes were grown in large, flat dishes.

Their lucky streak continued. Coghill, along with Kenneth Raper and Dorothy Alexander, his colleagues in the NRRL Fermentation Division, tested hundreds of *Penicillium* strains to determine whether any of these had higher penicillin yields than the Fleming strain. They gathered an enormous variety of samples, collecting microbes from moldy breads, cheeses, fruits, and vegetables, as well as enlisting the help of the Army Transportation Corps to acquire soil samples from countries around the world, including England, Brazil, Australia, and India. They needn't have looked so far afield, for, as Coghill noted, "the travesty of this worldwide hunt was that the best producer of all was cultured from a moldy cantaloupe picked up in a Peoria fruit market.

There is some controversy over who exactly found the "cantaloupe strain," or *Penicillium rubens* NRRL 1951, which is now the state microbe of Illinois. In the decades following the discovery, local newspapers reported that the cantaloupe had been found by NRRL technician Mary Hunt, nicknamed "Moldy Mary," and indeed, Hunt is listed in the acknowledgments of the 1944 paper on the microbe's identification. Coghill, Raper, and Alexander wrote that "We are likewise indebted to Miss Mary K. Hunt for collecting samples of moldy materials and for assisting in the isolation and preliminary testing of many strains." Years later, however, Raper told a reporter that the cantaloupe had simply been dropped off by a local housewife.

Regardless of who initially found it, the cantaloupe strain gained great importance as the "parent" from which today's commercial strains are derived. The significance of these developments in hastening the mass production of penicillin cannot be overstated: "At the beginning of 1942 they didn't have any [penicillin], and by the end of '42 they had enough for the first clinical trial," said Gaynes. "And by the end of '43 they had enough penicillin to treat all of the Allied armed forces... it really was a remarkable transformation."

Yet the work of the NRRL researchers went largely unrecognized on the world stage; Fleming, Chain, and Florey, on the other hand, were awarded the Nobel Prize in Physiology or Medicine in 1945.

Antimicrobials: The Golden Age and the Rise of Resistance

The following few decades came to be known as the Golden Age of antibiotic discovery. Selman Waksman's work on soil microbiology at Rutgers University led to the isolation of streptomycin, the first antibiotic that was effective against *Mycobacterium tuberculosis*, in 1943. Nine years later, this discovery won him the Nobel Prize. Between 1940 and 1970, researchers discovered more than 20 new classes of antibiotics, most of which were derived from bacteria and fungi.

But the pace of discovery soon slowed dramatically. Despite major technological advancements, relatively few new antibiotics or antifungals have been introduced in the present century. And while these drugs have largely remained the same, pathogenic microbes—and the planet—are undergoing rapid and profound change.

The pace of microbial evolution should come as no surprise: In the very same 1941 paper in which the Oxford researchers published the miraculous recoveries of patients treated with penicillin, they experimentally demonstrated the alarmingly fast development of antibiotic resistance. They cultured bacteria in gradually increasing concentrations of penicillin and in just a few months noted that "the microbe was able to multiply in a concentration of penicillin a thousand times greater than that which inhibited the parent strain in a parallel test." Today, antibiotic-resistant bacteria kill more than one million people each year; researchers estimate that the annual death toll will nearly double by 2050.

Although less well-known, antifungal resistance is also becoming a major threat. Many of the organisms classified as fungal priority pathogens by the World Health Organization are naturally resistant, or have acquired resistance, to at least one of the four classes of antifungals currently in use and researchers have described the rise of pan-drug resistant *Candida auris* as "alarming." Paralleling the development of resistance, and perhaps spurred along by fungal adaptations to a warming climate, global mortality from fungal infections is rising sharply.

As with Fleming's *Penicillium*, many researchers are once again turning to fungi for novel antibacterial and antifungal agents. Among them is Nancy Keller, a medical microbiologist at the University of Wisconsin–Madison and cofounder of Terra BioForge. Keller and her team comb through fungal genomes for groups of genes, called biosynthetic gene clusters (BGCs), that

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could produce useful secondary metabolites, including those that could function as antimicrobials. Given the nature of her work, it is fitting that Keller's official title is the Robert L. Metzenberg and Kenneth B. Raper Professor of Mycology—the latter being one of the NRRL researchers who was instrumental in the development of penicillin more than half a century ago.

Fungi have been at war with bacteria—and with other species of fungi—for millennia. As such, said Keller, “The metabolites made from these BGCs, a few of them are protective against abiotic stresses like UV... most of them, though, you could think of as weapons or armor, to protect them from other microbes or to defeat other microbes.”

In terms of fungal natural products, Keller noted that most of the low-hanging fruit has already been found, but she believes that many fungal secrets remain to be discovered by looking at these organisms with fresh eyes and new technologies. “If you look at the genome of a filamentous fungus...you can predict that the fungi could make 50 or even 70 metabolites, and we only know a very few of them for each fungus,” said Keller. “So, I personally feel we can get a lot more data even from the fungi around us.”

As the cost of genome sequencing has fallen, more and more fungal genomes have been published. But sorting through reams of genomic data to identify BGCs that could produce novel metabolites is no easy task. To aid in this process, Keller's group and other research teams have been developing increasingly sophisticated bioinformatic algorithms. One way that researchers can identify BGCs, said Keller, is to look for genes that encode different types of backbone synthases, which create a “skeleton” on which the rest of the metabolite is built. Other genes in the cluster encode tailoring enzymes, which add elements onto the backbone to create the finished product. BGC atlases can help researchers assess which metabolites are dissimilar from well-characterized natural products, preventing them from wasting time “discovering” the same products over and over again.

Work by various research groups, including Keller's, has improved scientific understanding of how BGC expression is regulated, enabling researchers to tinker with fungal genomes to produce greater quantities of the metabolite of interest. If the metabolite comes from a species that is difficult to



Some *Penicillium* molds can produce the lifesaving antibiotic penicillin.

culture or genetically manipulate, researchers can use fungal artificial chromosomes, a technique developed by Keller in collaboration with scientists at Northwestern University and Intact Genomics, to express the relevant gene cluster in a more cooperative species of fungi. The list of potential natural products continues to expand: In 2023, Keller's team reported on an algorithm that could pick out BGCs with a nontraditional backbone synthase called isocyanide synthase, which revealed thousands of previously unknown BGCs, indicating a massive number of potentially novel metabolites.

The wealth of new technologies, along with the sheer number of secondary metabolites that have been unearthed so far, has reinvigorated interest in fungal drug discovery. Unlike the serendipity and secrecy that characterized the discovery and development of penicillin, new antimicrobial agents will likely depend on methodical research and sharing of genomic databases and bioinformatic tools. Similar to the events of nearly a century ago, researchers hope that fungi can once again be enlisted to protect humanity from defeat by deadly pathogens.

MEET OUR RESEARCHERS: DR. ANNA HUTTENLOCHER

Hometown: Chicago and CT

Zodiac Sign: Taurus

Research Overview

Our research focuses on characterizing the molecular mechanisms that regulate cell migration, and the implications of these mechanisms to human disease, including cancer metastasis and inflammation.

What inspired you to select your field of study?

Patients with immune deficiency and autoimmunity in clinic as a medical student and resident. I was particularly puzzled by a child I saw with fever and rash, and neutrophil migration defect. This patient was later found to have an NLRP3 mutation and autoinflammatory disease. I was hooked.

What is one piece of advice you would give to students?

Enjoy the ride, even with the ups and downs.

When you're not in the lab, how do you spend your time?

Outside. Walking in the woods with my husband and dogs. Swimming, dancing and playing music.

If you didn't become a scientist, what career would you have pursued?

I have pondered this. Being a scientist and physician has really been the right path for me. I love it. I considered becoming a musician years ago.

What is the best meal you've ever had?

Fresh greens and vegetables from the local Farmers market with grilled salmon and local strawberries and ice cream.

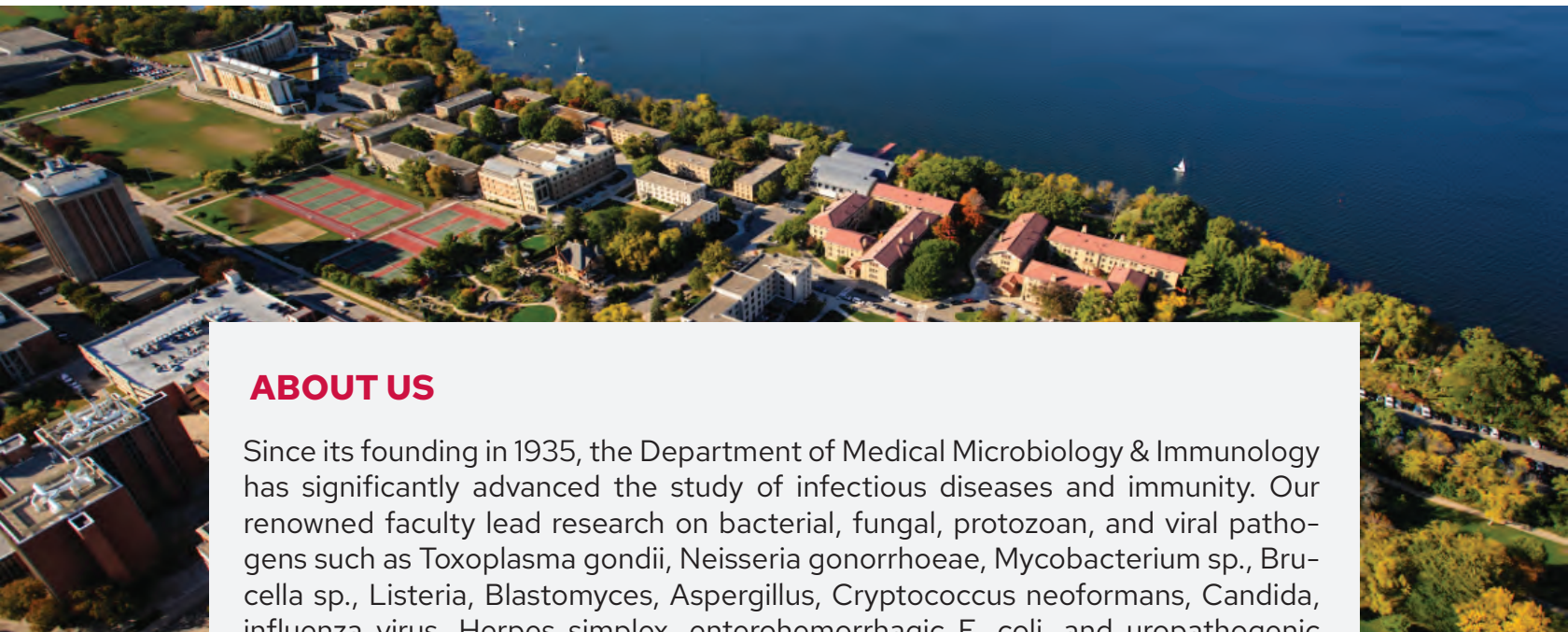
You have to sing karaoke, what song do you pick?

I think I prefer to dance.

If you had a time machine, would go back in time or into the future?

Future. As the Wisconsin motto—Forward.





ABOUT US

Since its founding in 1935, the Department of Medical Microbiology & Immunology has significantly advanced the study of infectious diseases and immunity. Our renowned faculty lead research on bacterial, fungal, protozoan, and viral pathogens such as *Toxoplasma gondii*, *Neisseria gonorrhoeae*, *Mycobacterium* sp., *Brucella* sp., *Listeria*, *Blastomyces*, *Aspergillus*, *Cryptococcus neoformans*, *Candida*, influenza virus, Herpes simplex, enterohemorrhagic *E. coli*, and uropathogenic *Escherichia coli*. They also explore immunological topics including regulatory T cell biology, leukocyte migration and vaccine development. Additionally, the department study the roles of diet, the immune system and the gut-brain-axis in the intestinal microbiome.

We offer undergraduates rigorous coursework and research opportunities, and our nationally acclaimed Microbiology Doctoral Training Program allows graduate students to earn a Ph.D.

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