2023

Annual Report

BERTHIAUME INSTITUTE
FOR PRECISION HEALTH

UNIVERSITY OF NOTRE DAME | RESEARCH

About the Institute

The Berthiaume Institute for Precision Health (BIPH) at the University of Notre Dame seeks to prevent and treat disease, promote wellness, and reduce health disparities by developing new tools to understand human variability at the molecular and cellular levels.

The BIPH serves its community by fostering both discovery-based and hypothesis-driven research, educating and training students, and moving proven ideas out of the lab and into broader use.

To advance these goals, the Institute engages scientists, engineers, clinical practitioners, and industry partners in cross-cutting, multidisciplinary research themes. The BIPH also educates the public about the opportunities, challenges, and complexities inherent in health-related research.

BIPH researchers are investigating the factors underlying each person's health, particularly those in under served populations, and they work to ensure new discoveries, data, and technologies benefit all populations.

The BIPH is a unit of Notre Dame Research.

Research Highlights

Researchers invent trap for capturing and comparing individual bacterial cells

All hospitals battle an invisible threat: *Pseudomonas aeruginosa*. It is a type of bacteria that affects thousands of patients each year in intensive care units, where it can cause sepsis, pneumonia, and other types of infections.

"For the average healthy person, *P. aeruginosa* does not pose a serious threat," said University of Notre Dame bacteriologist Joshua Shrout. "But for those who are most vulnerable — who are immunocompromised, who are using a ventilator or catheter, or who are recovering from serious burns or surgeries — it is not just serious, but life-threatening. And that is due to the bacteria's sophisticated suite of self-defense tactics."

Shrout, a professor in the Department of Civil and Environmental Engineering and Earth Sciences, leads a research group that studies those tactics in intricate detail. He explains that in addition to being resistant to many of the most common antibiotics, *P. aeruginosa* readily sticks to surfaces where it creates its own protection by blanketing itself in a polymer-like biofilm. Under certain conditions, *P. aeruginosa* can also acquire other organisms' antibiotic strains, and it can even generate cyanide to kill off competitors.

Thinking outside the Petri dish

A decade ago, Shrout began collaborating with Paul Bohn, the Arthur J. Schmitt Professor of Chemical and Biomolecular Engineering. Bohn's lab specializes in creating new technologies for more precise analysis of cells and molecules. Together, Bohn and Shrout began searching for new ways to observe microorganisms like *P. aeruginosa*, moving beyond the traditional process of observing cell cultures grown in a Petri dish.

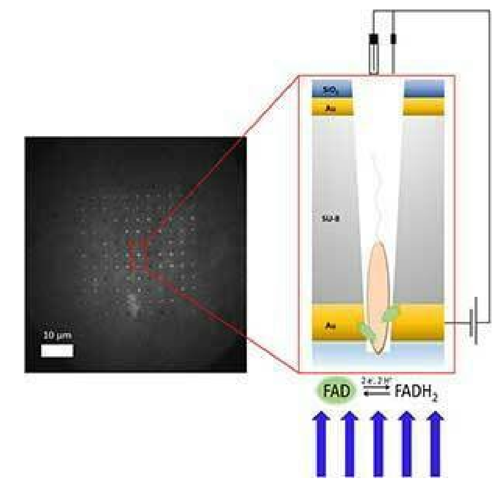
"If you grow and observe a whole culture of cells, you are seeing general behaviors, on average," Bohn said. "But we now know that the biggest effects sometimes come from the minority of a given population."

Joshua Shrout

Shrout explained this effect using an analogy with other organisms' behaviors. "Imagine you are sitting on your back porch listening to the crickets outside," he said. "There might be thousands of crickets, but the ones that affect you are the ones chirping. There can be similar types of variation in populations of bacteria, too. However, most microbiologists don't have the tools to fully appreciate the effects of minor players within a population."

Bohn and Shrout knew that before they could find the key differences in a population of *P. aeruginosa*, they would need to solve some major technical challenges. First, they would need to capture individual cells. Then, to conduct a meaningful experiment, they would need to apply the same stimulus to the cells in the same way at the same time. And, finally, they would need a way to observe the experiment, tracking the differences between the cells as they respond to the stimulus.

With funding from the National Institute of Allergy and Infectious Diseases and the National Science Foundation, Bohn and Shrout decided to pioneer a new approach. "At the start," Bohn said, "we were captivated by a very simple question: 'What if we drill holes the same diameter of the bacterial cells? If we do, could we induce the cells to move in and stay inside?'"



Micropore electrode array (MEA)

Building a better bacteria trap

Allison Cutri, a chemistry doctoral student in Bohn's research group, took on the challenge of creating the device as part of her dissertation research. Cutri worked alongside postdoctoral research associate Vignesh Sundaresan to develop the main platform of the device inside the clean room at Notre Dame's Nanofabrication Facility. They used an additive process, building the platform layer by layer like a microchip. For the core of the device, they used a layer of epoxy, and they capped both sides with a thin veneer of gold to conduct electricity to targeted points on each bacterium, like attaching an electrode at either end of the cell.

Then Cutri worked with Notre Dame's Integrated Imaging Facility to mill more than 100 tiny holes called micropores into the device. Each micropore is drilled using a focused ion beam to a diameter of less than a micron — or about 50 times smaller than the diameter of a human hair — to allow one bacterium to slip inside.

Thanks to *P. aeruginosa*'s proclivity to stick to surfaces, Cutri was able to corral individual cells onto the device and into the micropores, where each settled into its own pore. The team was then able to apply electrical charges through the layers of gold while filming the experiment through a fluorescence microscope specially designed to look at one class of bacterial molecules.

They observed glowing from the wells, which proved the device had been properly loaded with bacteria. And as they tested regiment after regiment of cells, they noticed that patterns began to emerge. Some cells glowed along with the electrical charge. Others glowed intermittently in response to the charge, while a third set glowed independently of the charge.

"We are still not sure what other differences might exist or what the differences mean for combatting *P. aeruginosa*," Shrout said. Upon further investigation, however, they were able to see similar patterns in a different type of bacteria: *E. coli*. They were also able to determine that each cell's metabolic state — whether it was taking in or expending energy — played a key role in shaping how it behaved.

For now, the researchers said they are hopeful that the patterns they observed and the device they created, which were recently described in Cell Reports Physical Science, will inspire similar research projects.

"We have known for some time that *P. aeruginosa* exhibits fluorescent behavior in response to a charge," Cutri explained. "But to recognize that there is so much variation in the ways that cells respond, you need a device that will allow you to observe cells individually. With existing approaches, those differences would be masked."

Shrout added, "As a researcher, it is rewarding to not just be asking new questions but to also be developing the new tools and new platforms that make those questions possible. By bringing a knowledge of cell behavior together with nanofabrication and high-resolution imaging, that is what we have been able to do with this project."

Notre Dame chemist Paul Bohn honored as a fellow of the American Chemical Society

The American Chemical Society (ACS) announced that it has selected Paul Bohn, the Arthur J. Schmitt Professor of Chemical and Biomolecular Engineering at the University of Notre Dame, as a fellow.

Bohn joins a cohort of 42 new fellows selected for their "outstanding achievements in and contributions to science, the profession, and the Society."

The fellows come from leading research universities, including the University of Chicago, the University of Pennsylvania, Cornell University, Princeton University, and the Georgia Institute of Technology and from industry leaders such as Dow, Bayer, and Pfizer.

Bohn is an internationally known leader in the field of precision health. His research and innovations focus on molecular nanotechnology, personal health monitoring, and the imaging of microbial communities.

Paul Bohn

"Paul Bohn is an innovative, interdisciplinary researcher who has demonstrated exceptional leadership here at Notre Dame," said John T. McGreevy, the Charles and Jill Fischer Provost. "It is wonderful to see the American Chemical Society recognize his contributions to the field through his selection as a fellow."

Bohn earned his bachelor's degree in chemistry from Notre Dame in 1977 and a doctorate in chemistry from the University of Wisconsin-Madison. He was named one of the world's top 20 analytical scientists in 2019. He has authored or co-authored over 300 publications and owns nine patents in technologies related to his work.

Successfully preventing peanut allergic reactions in mice, blocking onset in its tracks

An allergen-specific inhibitor devised by researchers at the University of Notre Dame and the Indiana University School of Medicine has successfully prevented potentially life-threatening allergic responses to peanuts. The results of the new study were published in Science Translational Medicine.

"Our approach is unique because our inhibitor starts working before the allergen has a chance to trigger an allergic reaction," said Başar Bilgiçer, professor of chemical and biomolecular engineering at the University of Notre Dame. "Our collaboration with Dr. Mark Kaplan at Indiana University School of Medicine and Dr. Scott Smith at Vanderbilt University Medical Center made the development of these inhibitors possible. With their help, we were able to demonstrate the potency of our approach in animal studies."

Başar Bilgiçer

Using a cHBI inhibitor that they designed in their previous work, the researchers prevented allergic reactions in mice with human immune cells. A single administration provided protection against peanut allergic reaction for over two weeks. Moreover, when given shortly after the onset of symptoms, the inhibitor stopped the progression of the allergic reaction in its tracks.

When IgE antibodies and peanut allergens interact in an allergic person's bloodstream, inflammatory mediators such as histamine are released in large quantities throughout the body.

"The release of histamines is meant to fight against invading pathogens, but, in the case of peanut allergy, there is no pathogen, just peanut proteins," said Bilgiçer.

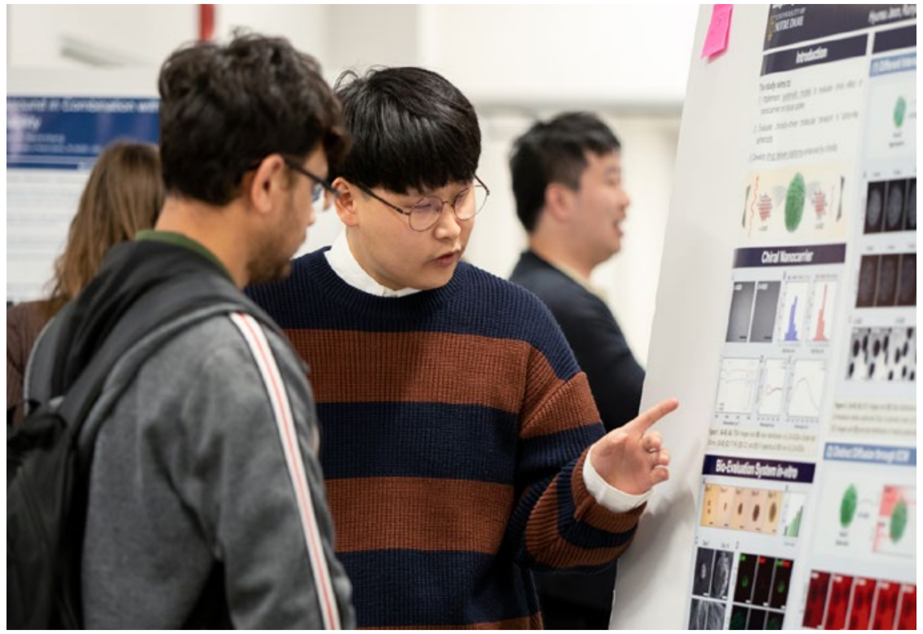
The new inhibitor effectively masks the immune system's ability to recognize the allergen, allowing it to fly under the immune system's radar without initiating a dangerous response or compromising its ability to fight real pathogens.

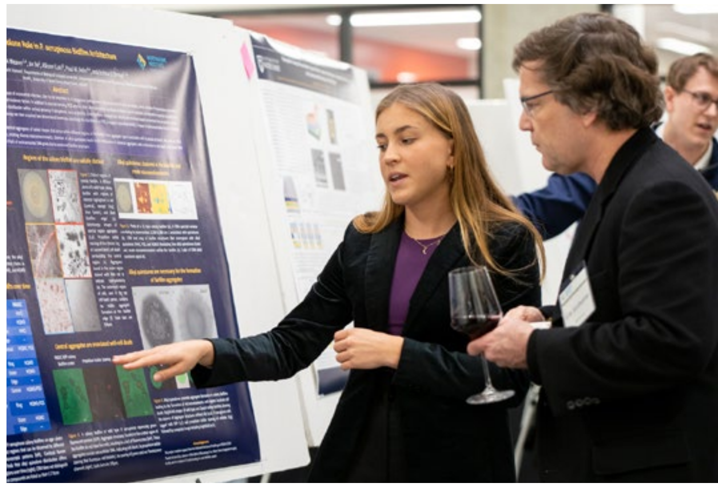
The researchers developed inhibitors specifically for peanut allergy because it is the most common food allergy, with high prevalence especially in children. Nevertheless, the success of cHBI in this study paves the way for the development of other allergen-specific inhibitors.

"What we've developed is a platform technology," said Bilgiçer. "The same design and engineering principles used in this paper can be applied in developing inhibitors to treat a range of other allergies such as shellfish and penicillin."

The research will now advance to preclinical studies.

BIPH Symposium 2023





Campus Expansion

Notre Dame's McCourtney Hall has been home to the Berthiaume Institute for Precision Health since 2016.

In the summer of 2022, Notre Dame broke ground on a second research building that will be attached to McCourtney Hall. The 200,000 square foot building is expected to be completed in the winter of 2025.

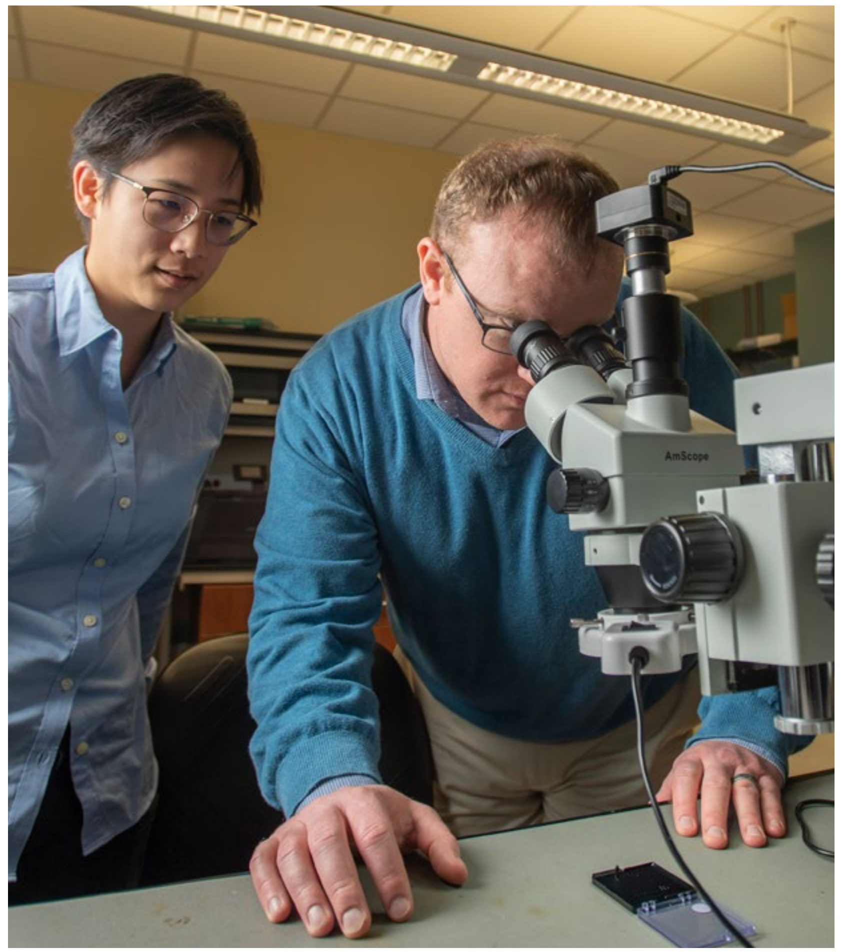
Research Translation and Entrepreneurship

Awards and Recognition

In 2023, members of the Notre Dame family received prestigious awards for groundbreaking research. Those receiving recognition included:

Thomas O'Sullivan, associate professor of electrical engineering, first-place winner of the 2023 **1st Source Bank Commercialization Award**, receiving a $25,000 cash prize.

- O'Sullivan co-founded NearWave, a non-invasive handheld medical device that helps physicians select the right therapy for breast cancer patients. The hand-held imaging device can tell in under a week if a treatment is working, rather than having patients wait six to 12 months and potentially suffering through toxic side effects. The NearWave device may also reduce the number of biopsies required for breast cancer by enabling imaging in OB-GYN and primary care offices.
- The concept for NearWave started in a graduate class taught by O'Sullivan. He and co-founder Roy Stillwell worked on NearWave with the O'Sullivan Research Group in the Biomedical Photonics Laboratory at Notre Dame.
- NearWave's technology has shown promising results in the ability to differentiate benign from malignant tumors non-invasively with 90 percent specificity and sensitivity. NearWave has raised $1.5 million in outside investment and has an open seed round with several investors. Currently, the device is available to researchers in oncology, women's health, traumatic brain injury research and optics-related groups.



Thomas O'Sullivan working on breast cancer research.

Indiana CTSI Navigators

The BIPH's Associate Director for Research, Prakash Nallathamby, has been appointed one of Notre Dame's Co-Navigators (along with Jessica Brookshire) to the Indiana Clinical & Translational Sciences Institute (CTSI).

Professors Brandon Ashfeld and Tengfei Luo with students in a lab at Fitzpatrick Hall of Engineering.

Tengfei Luo, the Dorini Family Professor for Energy Studies, second-place winner of the 2023 **1st Source Bank Commercialization Award**, receiving a $10,000 cash prize.

- Emerging from the Molecular/Nano-Scale Transport and Energy Research (MONSTER) Laboratory at Notre Dame, Luo's technology led to the founding of Tessellated Inc., a polymer film company that uses a patented formula to produce some of the most robust polymer materials in the world. This versatile material offers a multitude of potential uses from ballistic armor and sport gears to thermal management. It can be incorporated into composite components for both aerospace and automotive sectors.

Tengfei Luo

- Tessellated's formation was driven by Luo and his team's identification of a market opportunity leveraging the novel properties of this material. The material is being explored for protecting satellites and spacecraft from space debris and the optimization of thermal regulation in energy systems, specifically within electric vehicles. Tessellated aspires to broaden its impact across various industries that can implement its polymer thin film technology.
- Tessellated has received multiple STTR Phase I grants from the U.S. Department of Energy, the U.S. Army and the U.S. Air Force. Additionally, the company secured a Phase II grant from the Army spanning two years. Tessellated has also secured investments from an Indiana-based venture capital firm.

Alex Boomgarden, fifth-year Ph.D. candidate from the Department of Biological Sciences and 2021 BIPH Fellow, winner of the University of Notre Dame's 2023 **Shaheen Three Minute Thesis Competition (3MT®).**

- Boomgarden, whose faculty advisor is Professor Crislyn D'Souza-Schorey, was the fourth of eight finalists to present, and his first-place finish sent him home with the top prize of $2,000. A second-place prize of $1,500 went to Mariama S. Dampha (Global Affairs), and $1,000 to the People's Choice winner, Isaac Angera (Chemistry and Biochemistry).
- Boomgarden's presentation—titled "Looking for Cancer with CAPture"—argued that cancer researchers should be shifting their focus from curative medicine to preventive and personalized medicine. In that vein, Boomgarden's research investigates microscopic calling cards in human blood known as tumor microvesicles, or TMVs. Boomgarden is working on a novel technique he refers to as the "CAPture method" to tag and separate TMVs from other elements in the blood for downstream analysis.
- His method has been used to successfully capture TMVs identifying malignant melanoma, and he is currently working to test it as a diagnostic tool for other types of cancers. Bringing the argument full circle, Boomgarden explained to the audience that, using this method, a single drop of blood at an annual physical should, in the future, be all humans need to detect — and subsequently treat — cancer at very early, non-lethal stages.

Alex Boomgarden accepting his award

Nosang Myung works with graduate student, Suporna Paul, in Myung's lab in McCourtney Hall.

Nosang Myung, the Bernard Keating-Crawford Professor of Engineering, has been elected as a **Fellow of the National Academy of Inventors (NAI)**.

- Election as an NAI Fellow is the highest professional honor awarded solely to academic inventors. The NAI Fellows Selection Committee chooses inventors who demonstrate a highly prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on the quality of life, economic development, and welfare of society.
- Myung joins a group of 1,567 Fellows who hold more than 53,000 issued U.S. patents. Their discoveries have generated over three trillion dollars in revenue and have created more than one million jobs. The 169 new Fellows are from over 110 research universities and research institutes worldwide.
- Myung and his research group are known for inventing new nanoengineered materials and applying these materials to create new spintronics, sensors, electronics, and optoelectronics, as well as devices for energy harvesting and environmental remediation. Some of Myung's recent inventions include a multi-functional water filter and a prototype of an electronic nose that mimics the capabilities of a human nose.

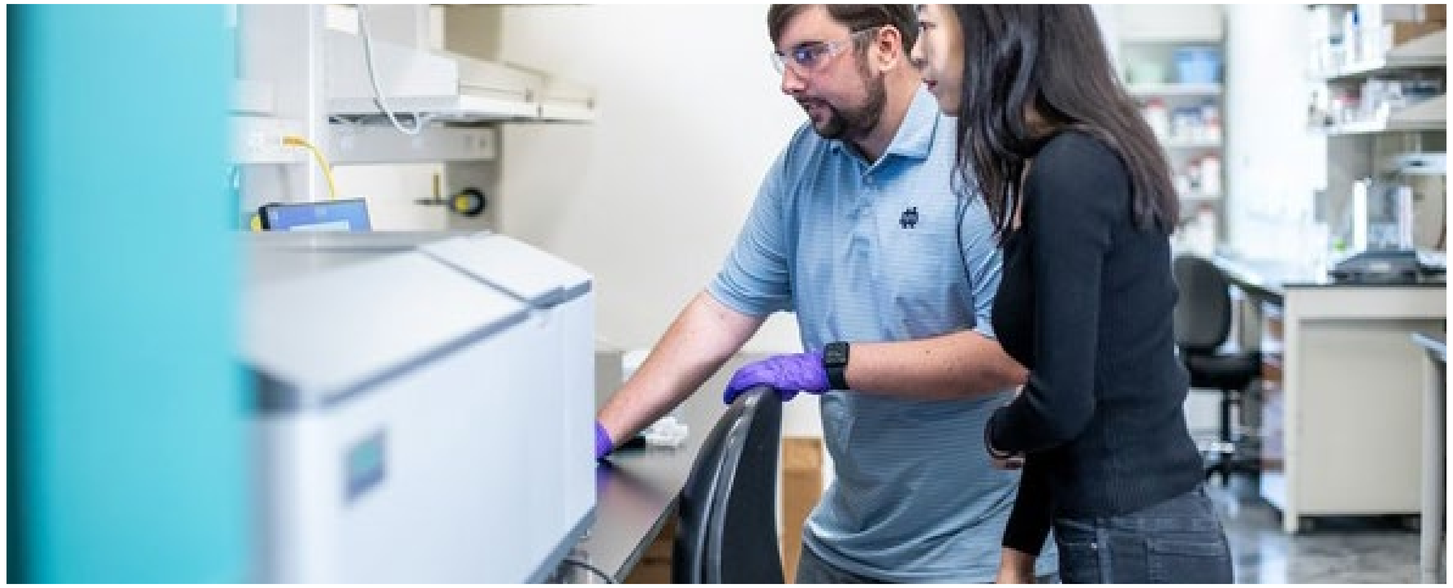
Where are they now?

Congrats to former BIPH graduate fellow Melinda Lake-Speers, who went on to do a postdoc with Jackie Linnes at Purdue and is now a new tenure-track assistant professor in Mechanical and Aerospace Engineering at Case Western Reserve University (CWSU). At CWSU she will continue to develop lab-on-a-chip devices for critical health challenges in cancer, global health, and biological modeling.

- Myung and his team are currently developing sensor systems to advance precision health and environmental sustainability. For example, his group developed a wearable sensor that can alert military personnel about the presence of harmful gases and other threats and a sensor that detects greenhouse gases.
- "For me, the goal behind each invention is simple: to bring new technologies into the hands of people who can benefit from them," Myung said. "I am honored that this work is receiving recognition and that others are noticing it as a step in the right direction. That gives our team a chance to spread our message about using engineering to be a force for good in the world."
- Myung is the director of the Analytical Science and Engineering (ASEND) Core Facility within Notre Dame Research as well as the micro- and nanoscale biomedical instrumentation theme leader at Notre Dame's Berthiaume Institute for Precision Health.

Advisory Board Meeting 2023

Students Success



Yichun Wang (right), assistant professor of Chemical and Biomolecular Engineering, and James Johnston (left), MERITS Fellow.

New Graduate Student BIPH Group Leaders

President
Caitlin Kerr

Secretary
Gowthami Mahendran

Co-Vice President
Hannah Marietta

Co-Vice President
Thomas Moran

Molecular Mining Theme Leader
Sayandeepa Raha

Molecular Recognition Theme Leader
Gustavo Da Silva

Microbiome and Human Health Theme Leader
Joseph Vecchio

BIPH Summer Graduate Fellows

The Berthiaume Institute for Precision Health would like to congratulate our new cohort of BIPH Summer Graduate Fellows and thank all the graduate students who submitted applications. Reviewers had a challenging time comparing so many excellent projects. Those selected for summer fellowships this year were: **Gustavo Da Silva** (adv.: Koepfli), **Eva Hall** (adv.: Hanjaya-Putra), **Hyunsu Jeon** (adv.: Wang), **Alyssa La Bella** (adv.: Flores-Mireles), **Guoqiang Liu** (adv.: Lu), and **Heather Shepherd** (adv.: Goodson).

Gustavo Da Silva

Eva Hall

Hyunsu Jeon

Alyssa La Bella

Guoqiang Liu

Heather Shepard

As part of the summer fellowships, **Sono Kumar** (adv.: Chang) was specifically selected to receive the O'Brien Endowment for Excellence Graduate Fellowship, and **Yuting Zhang** (adv.: Lu) was awarded the Leiva Graduate Fellowship in Precision Medicine.

Finally, from this same pool two students were selected to receive Berry Family Foundation Graduate Fellowships for 2023-24: **Thomas Moran** (adv.: Lee) and **Simon Weaver** (adv.: M. Champion).

Sono Kumar

Yuting Zhang

Thomas Moran

Simon Weaver

NSF Center for Bioanalytic Metrology

The Center for Bioanalytic Metrology, a Phase I National Science Foundation Industry-University Cooperative Research Center, is the Berthiaume Institute's primary mechanism for connecting and working with commercial partners. The BIPH leads and administers the Center on behalf of Notre Dame, Indiana University, and Purdue University.

In 2023, CBM welcomed two new dues-paying members to the Center, pharmaceutical company Bristol Myers Squibb and consumer goods corporation Procter & Gamble. This brought the total number of CBM members to 13:

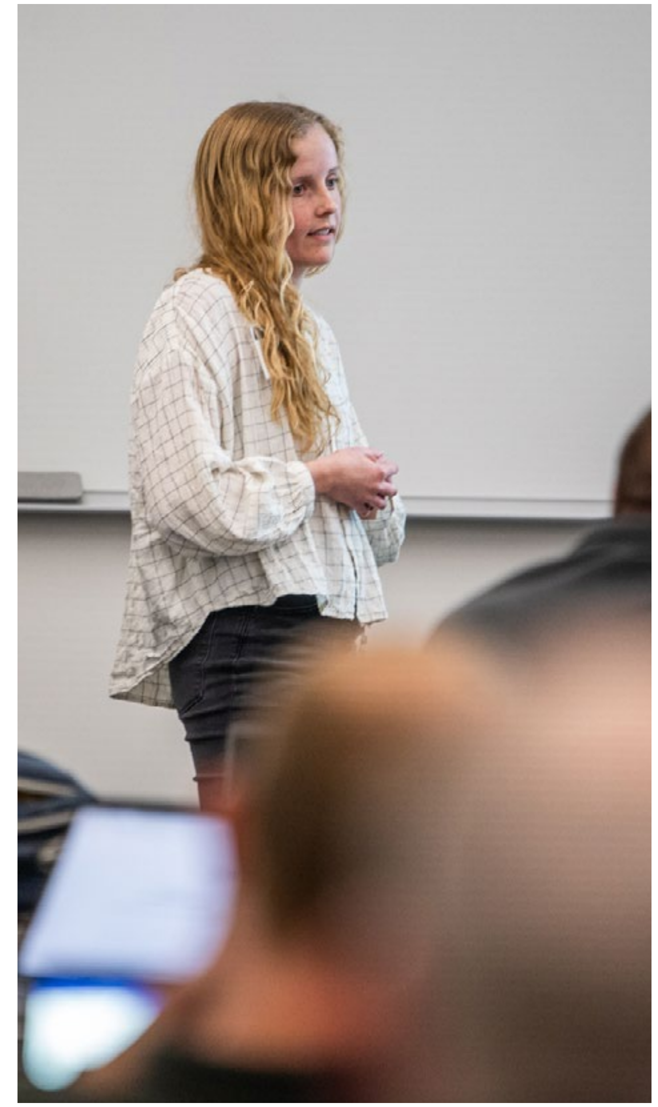
abbvie
Agilent Technologies
Bristol Myers Squibb
CORTEVA agriscience
EVONIK INDUSTRIES
ExxonMobil
Genentech
Lilly
MERCK
moderna
Pfizer
P&G
Takeda

Through the Center, these companies funded a wide range of research projects addressing their priorities, including two at Notre Dame:

- Smart miniature cell culture platform with PAT for suspension cells, led by Yichun Wang and Nosang Myung
- 3D molecular imaging of plant tissue by fluorescence lifetime imaging microscopy, led by Scott Howard, associate professor in the Department of Electrical Engineering

Another goal of CBM is to foster productive interactions between graduate students and company personnel, both to enhance the students' training and introduce the companies to potential new hires. In 2023, these interactions included a series of workshops on life as a scientist working in industry and a 3-Minute Thesis competition that gave students the opportunity to introduce their research projects and hone their presentation skills.

CBM Meeting



End of the Year Social

Looking Ahead

BIPH leaders are pursuing many avenues to expand the Institute's impact in research, education, and translational science. Four near-term areas of emphasis are:

1. **Support and enhance Notre Dame research expertise in areas of biosecurity technologies to promote health, enable early detection, and inform novel treatments in civilian and military use**
2. **Expand research efforts at the intersection of precision health, data, and artificial intelligence**
3. **Build a network of national and international collaborators to extend the impact of BIPH research through collaboration and access to new resources**
4. **Leverage existing expertise and technologies at Notre Dame to combat the ongoing epidemic of opioid abuse**

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