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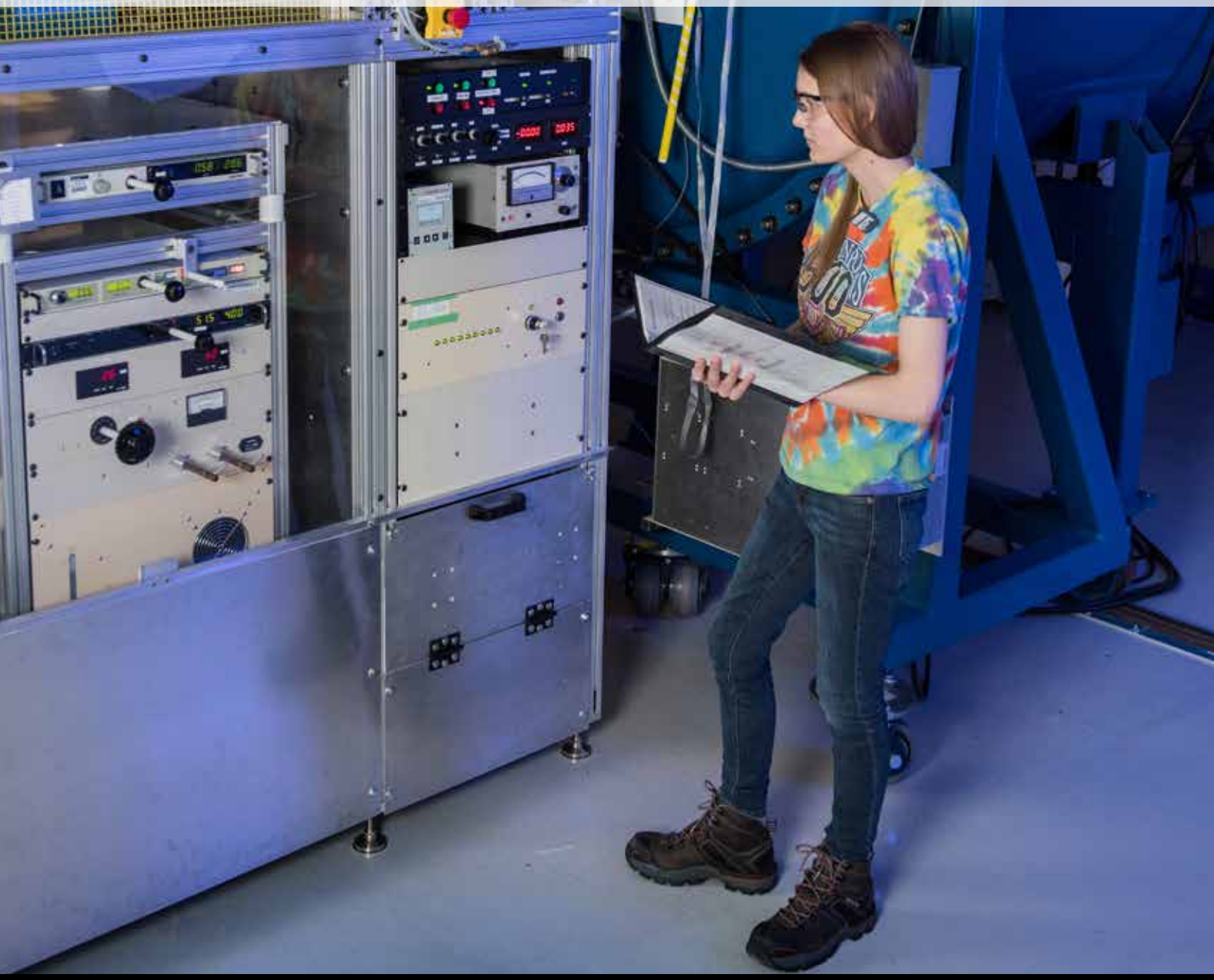
SCIENTIA

Undergraduate Journal of Scientific Research
University of Notre Dame



UNIVERSITY OF NOTRE DAME
College of Science

CHARLES EDISON FUND

A Letter From Dean Galvin

Research is essential to scientific understanding and discovery. Conducting research as an undergraduate prepares today's students to become tomorrow's scientific leaders. Whether students plan to attend graduate school or medical school after graduation, research they participate in at Notre Dame prepares them for that next step.

We are grateful for the support our generous donors provide that allows so many of our undergraduate students to immerse themselves in summer research. Through research in a working laboratory environment, undergraduates experience what it's like to be a scientist. They benefit from working alongside lab professionals and they experience the joy and wonder inherent in scientific discovery.

Research also affords students the opportunity to author scientific papers, travel to scientific conferences, and present their findings to other scientists. Through the scientific research process and presentation of research results, students begin to develop critical skills like writing and communicating their research—critical skills that will serve them throughout life.

Scientia is a student run journal that fosters research communications across disciplines, helping undergraduates to think about how to communicate their science in an accessible way to non-experts. This ninth volume of *Scientia* is a particular source of pride for the College of Science because the work included encapsulates the mission of the University of Notre Dame. Stories range from working on the problem of lead in homes right here in our community to witnessing through a telescope in Chile a star explosion 143 million light years away. They include progress in drug discovery and examining chemicals in fast food wrappers. Together, these stories and the research published in *Scientia* speak to the dedication and quality of scholarship of our students and faculty.

It is my great honor to be part of this college and to support *Scientia*.

Yours in Notre Dame,

Mary E. Galvin

Mary Galvin, Ph.D.
William K. Warren Foundation Dean of the College of Science
Professor of Chemistry and Biochemistry

Editorial Board 2017-2018

Acknowledgments: *Scientia*, comprised exclusively of undergraduate work, is sincerely thankful to the students who have submitted their research. Additionally, the editorial board expresses its gratitude for the dedication and guidance of Xuemin Lu, Ph.D., our faculty advisor; Dean Mary Galvin, Ph.D., for her inspiration, enthusiasm, and support for our mission; Tammi Freehling, Lotta Barnes, and Deanna McCool, for helping guide us through the publication process; and the College of Science and the Charles Edison Fund for their financial support.

From the Editors

Scientia is, at its core, undergraduates supporting the research efforts of other undergraduates. From ensuring that students of all backgrounds are able to engage more fully in research opportunities through the Charles Edison Foundation Fellowship to promoting the dissemination and discussion of scientific endeavors through platforms such as "Talk Science" seminars, *Scientia* is committed to recognizing the importance of undergraduate research here at the University of Notre Dame. In our annual publication, we endeavor to highlight the talented students and faculty who make up this strong community of scientists. We ask that you view this publication of student research not as the conclusion of various projects, but rather as the beginning of a new dialogue. Be inspired, ask questions, critique. After all, the late Stephen Hawking once said, "Mankind's greatest achievements have come about by talking, and its greatest failures by not talking."

Over the course of the 2017-2018 academic year, we have been pleased to see *Scientia* grow and continue to develop. At our monthly "Talk Science" lectures, we have brought together professors and students across a wide variety of disciplines in the College of Science. These presentations have allowed students and faculty to engage in conversation about exciting research that is going on at Our Lady's University. We are extremely grateful for the participation of several passionate faculty and student researchers, who have undoubtedly contributed to the success of these events. At two of our seminars, we were excited to recognize David Shaw and Sarah Herzog, the 2017-2018 Charles Edison Foundation Fellows. With the ongoing support of the Charles Edison Foundation and the College of Science, *Scientia* is pleased to continue to offer this award in its second year.

We are proud to introduce the 2018 edition of *Scientia*, now in its ninth year. This year's journal offers a diverse collection of high-caliber research, highlighting three diverse topics in physics alongside stimulating research in areas of biology and health. This publication is the culmination of the dedication and time that our editorial staff and reviewers have invested in the journal. The success of this journal would not be possible without the undergraduates who submitted their research and their faculty advisers, and we are grateful for their engagement with *Scientia*.

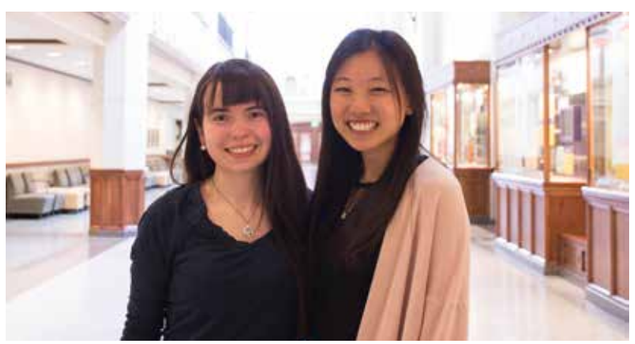
In celebrating the publication of this journal, we wish to formally acknowledge the tremendous support that *Scientia* has received from Dean Galvin and the College of Science. Furthermore, we are thankful for the guidance of our new faculty advisor, Dr. Xuemin Lu. As a mentor, Dr. Lu has modeled dedication to promoting an enthusiastic culture that recognizes the importance of undergraduate research by organizing annual student research conferences for the College of Science. Her input and experience have been invaluable.

As we look ahead to the 2018-2019 academic year, we are pleased to leave *Scientia* in the capable hands of Ruby Hollinger and Eric Sah as Co-Editors in Chief. With combined backgrounds in neuroscience, mathematics, and fine arts, Ruby and Eric have demonstrated tremendous leadership and dedication to this journal. We are excited to see *Scientia* excel under their guidance and continue to promote undergraduate research.

In Notre Dame,

Elizabeth McGough

Candice Park
Scientia Editors in Chief



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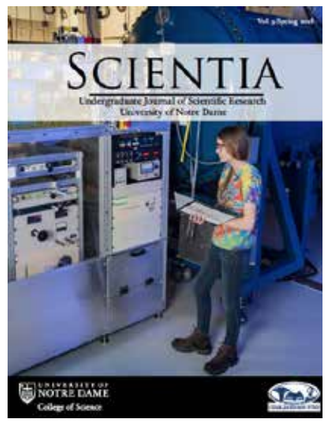
On the Front and Back Covers

A researcher in Notre Dame's Nuclear Science Laboratory prepares the newest particle accelerator for a data collection run by starting the accelerator's ion source. Samples are placed on a target wheel where they will be hit with a particle beam, and detectors will measure the subsequent interactions. To read more about the exciting research that the new particle accelerator is being used for, turn to page 10. Photos courtesy of Barbara Johnston.

Biology

Physics

Health



College of Science New Faculty Spotlight

SARAH CATE BAKER, BRYCE DZBURA, MADELENE MCKENZIE, ZHEFAN ZHANG

Brian Blagg, Ph.D., Charles Huisking Professor of Chemistry and Biochemistry, is Notre Dame's first director of the Warren Family Research Center for Drug Discovery and Development. After earning his B.A. in both chemistry and environmental studies at Sonoma State University, his Ph.D. in organic chemistry at the University of Utah, and completing an NIH postdoctoral fellowship from The Scripps Research Institute, Blagg started a medicinal chemistry lab at the University of Kansas in 2002. Now at Notre Dame, his lab continues its focus on the biochemical nature of chaperone proteins and protein folding in relation to cancer. Cancers are inherently more dependent on chaperone proteins because of their constant division, and Blagg's team works to selectively inhibit particular chaperone proteins to halt cancer growth. His lab also studies the possibility of using chaperone proteins to effectively re-fold malfunctioning proteins to treat and prevent diseases, such as Alzheimer's. Blagg was attracted to Notre Dame because of the University's ambitious commitment to elevate its graduate programs. Since becoming a faculty member, he has found Notre Dame's unique atmosphere—one that includes a caring and personable administration, a strong alumni base, and a passion for knowledge—to be liberating and intellectually exciting. When not at work, Blagg enjoys watching the Irish football team and spending time with his children.

Stefano Castruccio, Ph.D., assistant professor in the Department of Applied and Computational Mathematics and Statistics (ACMS), received his B.S. in 2005 and M.S. in 2007 in mathematical engineering with a concentration in statistics from Politecnico di Milano. Shortly after, he obtained his Ph.D. in statistics from the University of Chicago in 2013. Castruccio has worked as a postdoctoral fellow at King Abdullah University of Science and Technology (KAUST) in Saudi Arabia, and then prior to joining as a faculty member at Notre Dame, he was appointed an assistant professor in Newcastle University in the United Kingdom. Having had the opportunity to start a new program in statistics during his time in Saudi Arabia, Castruccio was excited to join a similarly new and expanding program of ACMS in Notre Dame. His excitement is sustained by the possibilities of developing new ideas, courses, and collaborations that are relevant to ACMS. His own career exemplifies the wide variety of collaborations that can exist in this field: from ongoing research assessing wind energy in Saudi Arabia, to research projects in neuroscience, air pollution in developing countries, and visualization of space-time data with virtual reality. Given the University's unique merging of faith with science, Castruccio believes that Notre Dame is an ideal place to explore the ethical principles of interdisciplinary data science research, which he believes could be ascribed to the moral teachings of the Catholic Church.

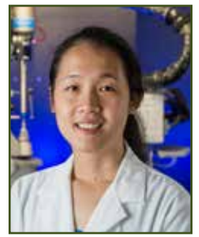
Jeffery Chilcote, Ph.D., assistant professor in the Department of Physics, received his B.S. in physics and astronomy at Northwestern University and his Ph.D. in astronomy at UCLA. Before coming to Notre Dame, he completed his postdoctoral at the University of Toronto and Stanford University. Chilcote's research concerns the direct imaging of extrasolar planets, which involves examining light directly emitted from planets rather than the conventional method of measuring light by examining a host star. Chilcote hopes that this research will allow for the examination of other solar systems so more can be learned about our solar system. At Notre Dame, Chilcote plans to establish additional interdisciplinary opportunities for undergraduate students that will allow them to be more involved with projects from beginning to end. His favorite aspects of Notre Dame are its intelligent and motivated students and the investment the University puts into all fields of science.

Steven Heilman, Ph.D., assistant professor in the Department of Mathematics, received his B.A. in mathematics from Cornell University before earning his Ph.D. from the Courant Institute of Mathematical Sciences at NYU, where he wrote a thesis on Gaussian soperimetry for multiple sets. Before coming to Notre Dame, Heilman spent four years teaching various math subjects, from game theory to calculus. His current research at Notre Dame involves applying analytic techniques to study problems in probability. These problems are sometimes motivated by hardness results in theoretical computer science or by social choice theory. Heilman is teaching a graduate probability class this semester, and his favorite parts of Notre Dame are the friendly students and faculty. His love of math stems from both its intrinsic beauty and its applicability. Though he has not been at Notre Dame long, his favorite place on campus is the globe in Hurley Hall. Outside of math, one of his hobbies is playing piano. As an undergraduate, he was honored with the Harry S. Kieval Prize in Mathematics, and he has received a Graduate Research Fellowship and a grant from the National Science Foundation.

Lance Hellman, Ph.D., research assistant professor of chemistry and biochemistry, earned his first B.S. degree in biology from the University of South Carolina and his second B.S. degree in cytotechnology from the Medical University of South Carolina. He then went on to earn his Ph.D. in biochemistry at the University of Kentucky. Hellman first came to Notre Dame in 2011 as a postdoctoral researcher in the lab of Brian Baker. After two years as a postdoctoral researcher, he became a research scientist in the Baker lab, and he now joins the faculty of the College of Science as a research assistant professor. Within the Baker lab, Hellman's research focuses on understanding the interaction between T-cell receptors and the specific antigenic peptides they recognize. His particular interest is in trying to redistribute the binding energies within the interface between the T-cell receptor and the antigen to reduce cross reactivity of the receptor toward other antigens. He employs a variety of methods in his research, such as X-ray crystallography, surface plasmon resonance, and fluorescence anisotropy. Hellman's favorite aspect of Notre Dame is the high caliber of research conducted here.

Michael Pruitt, Ph.D., assistant teaching professor in the Department of Applied and Computational Mathematics and Statistics, earned his B.S. in mathematics from the University of Maryland, Baltimore County. After completing both his M.A. and Ph.D. in mathematics at Duke University, Pruitt held a postdoctoral fellowship in the mathematics department of the University of Connecticut. Wanting to continue his teaching at a university that has an emphasis on research, he became a visiting professor at the University of Notre Dame in 2016. Since then, Pruitt has shifted his focus from mathematical proofs toward applications of mathematical theorems. He is currently teaching three courses, including Scientific Computing, Statistics for Life Sciences, and Mathematical and Computational Modelling. While Pruitt initially did research on the numerical solutions of differential equations, he is currently focusing on the qualitative properties of finite difference and finite element solutions to parabolic and elliptic differential equations. He is looking forward to having more student participation in his research once he finds computational avenues that can be undertaken by undergraduates. Along with his awe of advanced research, Pruitt is also impressed by the intellectual strength and dedication of Notre Dame students.

Arnaldo Serrano, Ph.D., assistant professor of chemistry and biochemistry, joined the Notre Dame College of Science faculty in 2017. Serrano received a B.A. in chemistry from Rutgers-Newark University and went on to pursue a Ph.D. in chemistry at the University of Pennsylvania. He then worked as a postdoctoral researcher at the University of Wisconsin, Madison. Serrano's research is in protein folding, which he describes as the way in which proteins achieve their proper three-dimensional shape as well as what happens when this process goes wrong. Now at Notre Dame, Serrano hopes to develop ways to use high-resolution microscopy to study protein folding, which could allow researchers to visualize the folding process as it occurs inside cells. Serrano looks forward to teaching undergraduate courses in physical chemistry in the near future, and his lab is currently accepting undergraduate researchers. His favorite things about Notre Dame include the beauty of the campus and the strong sense of identity among its faculty, staff, and students. When not studying proteins, Serrano enjoys being outside, and if there are any slow-pitch softball teams in the area that could use an infielder, his door is open.



Emily Tsui, Ph.D., assistant professor of chemistry and biochemistry, joined Notre Dame in the fall of 2017. Tsui received her B.S. in chemistry from Massachusetts Institute of Technology, and her Ph.D. in chemistry from California Institute of Technology. She then completed a postdoctoral fellowship at the University of Washington. Most recently, Tsui has been studying the chemistry of colloidal semiconductor nanocrystals, or quantum dots, used in television displays. Prior to this work, Tsui synthesized a series of molecular clusters that structurally and compositionally model the Oxygen-Evolving Complex of Photosystem II, the site at which plants convert water to oxygen during photosynthesis. This specific reaction of water splitting receives a lot of attention due to its potential use in solar fuels and renewable energy technology. Tsui's great work was recognized in 2014 when she received the ACS Division of Inorganic Chemistry Young Investigator Award. Now at Notre Dame, Tsui is excited to tackle ongoing challenges in the field of renewable energy through the perspective of inorganic chemistry and catalysis. Tsui hopes her studies will lead to a greater understanding of how challenging but important transformations, such as water splitting and small molecule activation, can be achieved. When she is not busy conducting innovative research, Tsui enjoys haunted houses and is a haunted corn maze enthusiast.

Roger Woodard, Ph.D., director of the online program in data science, received his B.A. in mathematics from Culver-Stockton College in Canton, Missouri, and his Ph.D. in statistics from the University of Missouri. Prior to joining the faculty at Notre Dame, Woodard held positions at Washington University in St. Louis, The Ohio State University, and, most recently, North Carolina State University. Woodard joins Notre Dame as the inaugural director of the new online M.S.-ACMS Data Science graduate program. His current research focuses on student learning of statistics coupled with technology. Noticing that introductory statistics students often find it difficult to grasp why the calculations they are learning actually work, Woodard's research focuses on student learning styles, methods to develop statistical thinking, and the use of technology to find ways to help students develop a deeper understanding of the discipline. As someone who enjoys employing data science to answer questions about the real world and working with people in different fields, Woodard looks forward to participating in the development of a cohort-style program that fosters a deep understanding of statistics towards which his research is directed. In his spare time, he likes to build furniture.

College of Science Faculty Continue International Collaboration

MADELENE MCKENZIE

Since 2013, Notre Dame has been strengthening ties with Pontificia Universidad Católica de Chile (PUC) through various international collaborations between the faculty of both institutions. These programs aim to foster the natural connections between international Catholic institutions, and are made possible through the Luksburg Foundation Collaboration Grants presented in conjunction with the Kellogg Institute for International Studies and Notre Dame International. Faculty members from the Notre Dame College of Science have been instrumental in the formation of these collaborative programs and fostering the relationship between the two universities.

In October 2016, several faculty members in the Department of Chemistry and Biochemistry traveled to Santiago to give talks on their research and meet with chemistry faculty at PUC. The two departments were able to identify natural and overlapping research interests. Many faculty found that they were working on similar projects from a different perspective or using different techniques. Professor Brandon Ashfeld of Notre Dame's Department of Chemistry and Biochemistry attended the October visit and enjoyed the chance to collaborate in person. "It's one thing to read what they are doing in the literature, and another to hear about it firsthand," Ashfeld said.

In addition to giving talks and finding faculty collaborations, a second aim of the October 2016 visit was to begin a researcher exchange program in which graduate students could come from PUC and spend time working in labs at Notre Dame. According to Ashfeld, the ultimate goal would be to create a dual-degree program in which graduate students from PUC could receive a Ph.D. from both PUC and Notre Dame.

The physics department has also undertaken extensive collaborations with PUC through the QuarkNet program. QuarkNet is an NSF-funded program run jointly by Notre Dame and Fermilab, that is dedicated to bringing the methods of particle physics to high school classrooms. According to Kenneth Cecire, a National Staff Teacher for the program, "the idea [of QuarkNet] is to put the data out there in such a way that the students can use it, learn from it, and get a sense of what it is physicists really do." Through the Luksburg Grant, QuarkNet has been able to expand its operations to Chile in what they call the Masterclass Institutes Collaborating in the Americas and beyond (MICAb) program. Now in the fourth year of the MICAb project, Cecire and his colleagues are looking to expand. This May, QuarkNet staff plan to conduct an experiment in which they will travel through Chile taking cosmic ray measurements to study an anomaly in the magnetic field of the southern hemisphere. This is feasible as one of the QuarkNet cosmic ray detectors is already at PUC. Their team of researchers, high school physics teachers, and graduate students will stop at rural schools to conduct masterclasses along the way.

Collaboration with PUC has also opened up valuable research opportunities in astronomy. Chris Howk, a professor of physics here at Notre Dame, recently returned from a sabbatical at Instituto de Astrofísica at PUC, where he researched how stars form in unusual, less-dense environments. Howk explained that Chile is a much better location than South Bend to study astronomy, due to the clear skies and very tall, dry mountains. "By the mid-2020s, there will be more collecting area for optical telescopes in Chile than in all the rest of the world combined," Howk said. Chile is of great importance to the future of astronomy and PUC has one of the best astronomy programs in the region. Howk hopes to return to Chile to continue to collaborate with his colleagues at PUC, saying, "[the Chilean faculty] have a nice perspective on science and beautiful telescopes that yield some of the best data in the world."

The future of the program looks bright: in March 2017, it was announced that $100,000 would be contributed annually for the next five years for the purpose of continued expansion of the relationship between the two universities. Thanks to the generosity of the Luksburg Foundation Grants, the ties between Notre Dame and PUC will hopefully continue to develop long into the future. According to Ashfeld, "There's a lot of enthusiasm on both ends to build up the collaboration and see where it can go."

Notre Dame Professors Receive Patent for NP-C Drug

MATTHEW GUGGENBILLER

When Mike and Cindy Parseghian, son and daughter-in-law of former coach Ara Parseghian, discovered that three of their four children had been diagnosed with Niemann-Pick type C disease (NP-C), they knew they needed to take action. NP-C is a rare, progressive, genetic disorder characterized by the inability of the body to transport cholesterol and other lipids inside the cell, subsequently leading to abnormal accumulation and damage in the affected areas. NP-C is usually detected during childhood and progresses to cause life-threatening complications by young adulthood. Paul Helquist, professor of chemistry and biochemistry, explains that NP-C can be caused by more than 300 genetic mutations, all of which have varying effects. The most common form of NP-C is diagnosed when a child is 2 or 3 years old. Clinical symptoms, such as subtle losses in coordination, are not immediately obvious. However, some time after the onset of the disease, symptoms such as loss of focus and ambulatory function, difficulty in swallowing, and degradation of speech begin to manifest. The disease affects every organ of the body, but most importantly the lungs, spleen, liver, and brain.

In 1994, the Ara Parseghian Foundation began to fund medical research aimed at finding a treatment for NP-C. The funding originally was used to study the mechanisms and structures which NP-C affected, but it shifted toward the development of drug treatments when Cindy Parseghian met with Notre Dame professors Paul Helquist and Olaf Wiest. Together they discussed the development of the NP-C drug. Helquist, an expert in unique chemical synthesis, and Wiest, a computational chemist with a focus on reaction mechanisms, agreed to delve into treatment options for NP-C. In collaboration with Fredrick Maxwell, a colleague from Cornell University, they proposed a treatment modeled on a method for the treatment of various cancers: the use of histone deacetylase (HDAC) inhibitors. By removing an acetyl group from DNA molecules, histone deacetylase permits DNA to wrap more tightly, subsequently downregulating the expression of genes. The HDAC inhibitors disrupt this regulation of genes, releasing DNA from the histones and activating gene expression.

Focusing on cholesterol alone is problematic during drug development. Targeting cholesterol is detrimental as it is required for hormone synthesis and the maintenance of cell membranes. However, Helquist and Wiest saw a loophole in targeting this cholesterol-related disease. In about 95% of NP-C patients, the mutation and subsequent downregulation in the *NPC1* gene causes cholesterol accumulation. Similar to their use in treating cancer, Helquist and Wiest believed that HDAC inhibitors could be used to up-regulate *NPC1* expression, thereby reducing cholesterol accumulation. Helquist and Wiest sent HDAC inhibitors to their colleague Maxwell, and results looked promising: cholesterol levels in NP-C cells showed no significant variation from those in healthy cells.

Helquist and his collaborators have two clinical trials underway. The first targets the improper protein transportation of cholesterol by using HDAC inhibitors. This clinical trial proved successful, and Helquist and his collaborators are now determining which particular HDAC inhibitor will bring about the best clinical effects for NP-C patients. The second clinical trial uses a synthetic protein to transport cholesterol rather than attempting to fix the mutated protein. According to Helquist, the treatment from the second clinical trial "has more promise for specifically NP-C disease," but the treatment from the first clinical trial has greater applicability to other diseases similar to NP-C. Helquist and Wiest are currently focusing on the development of different treatment options for NP-C; they hope to find the treatment with the best clinical effects.

For Helquist, the focus on rare diseases such as NP-C is of utmost importance. "The marketplaces are very hard for a pharmaceutical company to jump in and create a drug," Helquist says, "It's just too expensive. So, they will invest their assets in cancer, heart disease, and so on." Since no one seems to be fighting for the survival of patients with rare diseases, Helquist feels an immense connection and duty to use his talents to pursue treatment options. He believes his efforts will be rewarded by the support and relief it will provide to the families like the Parseghians.

Professor Paul Helquist explains NP-C research to an undergraduate student.

Life Sciences Symposium Highlights Graduate Research and Addresses Big Questions

MATTHEW WANG

The morning of October 11, 2017, was bound to be busy for the Morris Inn. The building would soon be swarming with graduate students, as well as distinguished researchers and academics, all of whom were ready to showcase their research. This was the morning of Notre Dame's first Life Sciences Symposium.

The Life Sciences Symposium, "Biomedical Sciences: Bridging the Gap from Bench to Bedside," was originally conceived as an event to help showcase graduate research at the University of Notre Dame, as well as to give graduate students the ability to reach beyond Notre Dame's boundaries. According to Mark Hawk, a graduate student in the Department of Biological Sciences and head of the fall 2017 Life Sciences Planning Committee, the conference came out of conversations with his fellow graduate students who expressed considerable interest in conducting "outreach with other faculty members outside of Notre Dame." More significantly, however, was the collective feeling that "[the students] should be doing something at Notre Dame that is showcasing [their] research," Hawk said. This focus on graduate student research was also emphasized by Cody Smith, assistant professor of biological sciences, who served as a faculty advisor to the Planning Committee along with professors Rebecca Wingert and Zachary Schafer.

As easy as it may have been to conceptualize the event, extensive planning and organizing were necessary to make it a reality. Hawk and his fellow graduate students first gained faculty support. Then, the team secured outside funding from a private family foundation. Subsequently, the group entered the planning phase, which fittingly utilized a "graduate student and faculty hybrid committee," Hawk recalled. Although the faculty advisors provided crucial guidance, "the students were the ones who were actually [doing] most of this," Smith said. "They took the initiative."

As suggested by its title, the symposium sought to discuss topics important in biomedical science, such as those regarding cancer and stem cells. More importantly, however, the "Bench to Bedside" phrasing alludes to the desire to bring more biomedical research into medical practice. "Many researchers at Notre Dame are…doing some kind of biomedical-based research that can eventually…be used in some way in the clinic," Smith said. Hawk also noted that biomedical researchers are growing closer to "taking the research that [they are] doing in basic research labs and...helping improve clinical trials and/or helping improve disease treatments."

However, such medical and scientific transitions require time, leading to the present gap between biomedical research and its clinical use. Smith emphasized that, although biomedical researchers are making a greater push toward clinical application, it doesn't "necessarily [mean] that the clinical impact has to be tomorrow." In order to achieve these sorts of medical improvements, Hawk noted, communication and collaboration are necessary. Hawk said that biomedical research increasingly needs experts in research laboratories and clinical centers to work together in order to reach feasible and effective medical treatments, adding "that's why collaborations are huge."

At the end of the day, the first Life Sciences Symposium was a tremendous success. "This was the single most exciting and impactful event in the life sciences that has taken place at Notre Dame in my nearly nine years on the faculty," Schafer said. Hawk added that many of the visiting guests expressed surprise at the rigor of Notre Dame science, saying "I knew you had an undergraduate program. I knew you had a football team. I didn't know you had a research program." Thus, the event was seen as an effective portrayal of Notre Dame's graduate research program.

As for the next symposium? The topic has not yet been decided, although Hawk did speculate that it may focus on big data science and related areas, such as "data mining and mathematical modeling." Regardless, the Life Sciences Symposium has established itself as an outlet for graduate research, a statement about Notre Dame science, and an event that is here to stay.

Getting the Lead Out

KARA MIECZNIKOWSKI

Notre Dame faculty and students are working together to help South Bend households live lead-safe, an effort that hinges on community awareness and citizen science. Graham Peaslee, a physics professor at the University of Notre Dame, is a faculty member participating in the effort. "Lead became a huge environmental issue when we started putting it in paint and gasoline in the late 1800s and 1930s, respectively," Peaslee said. "Using lead was convenient and presented a cost savings." Lead was used in paint to increase durability and prevent peeling, and in gas to prevent knocking (a detrimental, uneven burning of fuel) in engines. The harmful effects of lead exposure on human health, however, far outweigh its commercial benefits. Exposure to lead has been linked to attention disorders and antisocial behaviors, as well as a decrease in IQ, academic achievement, and socioeconomic status. Lead exposure is particularly detrimental to babies and young children, as their brains are in critical development stages.

Lead in paint was eventually banned in 1978 and phased out of gasoline around 1980 in the United States. "But lead does not biodegrade," Heidi Beidinger-Burnett, a faculty member of the Department of Biological Sciences and Eck Institute for Global Health also involved with the project, explained. "Lead is a heavy, toxic metal that is inert, so once it drops where it is, it won't move until it's disturbed. It persists in our environment." Lead exposure remains an issue across the nation—particularly in areas of lower socioeconomic status, where homes were built before the ban and have not been torn down or renovated.

A study published by Reuters in December of 2016 (in response to the Flint, Michigan water crisis) examined lead levels in inner cities across the U.S. and found that 15 cities exhibited levels higher than those found in Flint. South Bend was one of them. The CDC threshold for an elevated blood lead level is five micrograms per deciliter and above, which is considered 'lead poisoning.' "One census tract in St. Joseph county has 36.4 percent of the children testing above that level," Peaslee said. "Flint, at its peak, had six percent. So we are five times higher than Flint was at its peak, and that's where we are every day." Residual lead is often hiding in plain sight: it is found in paint chips, keys, varnish, soils, and even Mardi Gras beads. "We will never get to a place where we say we can live lead free; we need to live lead-safe," Beidinger-Burnett said.

Notre Dame's Lead Innovation Team (ND LIT), a collaboration of faculty and both graduate and undergraduate research students, has been making an effort to help people do just that. Beidinger-Burnett said they are addressing the problem on several fronts. "We are involved at the organization level—on organizing the community around this issue and raising awareness. We are involved at the policy level, the research level, and the teaching level. We are firing on all pistons to attack this complex public health problem," Beidinger-Burnett said. "We are a research institute, but we can do a lot more than that."

These efforts include the organization of community-based coalitions, addressing ordinances such as those that include loopholes allowing landlords to rent homes without disclosing that they contain lead, and conducting research with an interdisciplinary team of faculty from the Eck Institute for Global Health, the Center for Digital Scholarship, and the Colleges of Science and Engineering. One of the most important components of these efforts is what Peaslee refers to as "reversing the paradigm," which involves identifying homes with lead in them before identifying children with lead poisoning and then tracing them back to their homes. "Traditionally we've used our children as sort of a divining rod to find lead, which is immoral and unethical," Beidinger-Burnett said. "So how do we help parents to identify sources of lead in their home so that we don't wait to use children's bodies to find the lead?"

ND LIT is working to reverse the paradigm by utilizing citizen science to collect samples from homes sent in by citizens themselves. Last fall, the team distributed over 1,000 lead sample kits to students at Adams High School in South Bend; the kits, which consist of nine plastic pre-labeled sample bags and instructions on how to collect soil, dust, and paint samples, allowed students to collect and send in samples from their homes for free lead testing. Samples from households are quickly tested using x-ray fluorescence, and households with positive lead results are sent safety tips, such as suggestions to put mulch down over leaded soil and to wash horizontal surfaces once a week. The samples also provide aggregate data for mapping areas of varying lead exposure in the city of South Bend.

The team hopes to extend the sample kit program to South Bend's Clay, Riley, and Washington high schools in the near future, and Peaslee is optimistic about the results that reversing the paradigm may have. "We think this is a model that will scale to all urban developments. So if it works in South Bend to lower children's blood lead levels, we should go try it in Indianapolis and Fort Wayne. If it works there, it should work all over the country."

Professor Marya Lieberman is a member of the integrative team of Notre Dame faculty and undergraduates working to get the lead out.

Astronomy Students Witness Never-Before-Seen Star Collision

KRISTINA WHITE

Last August, third-year physics graduate students Kaitlin Rasmussen and Devin Whitten were working at the Irénée du Pont Telescope in Las Campañas, Chile. The graduate students were looking for signs of heavy elements, or r-process elements, in old stars. What they saw instead was a never-before-seen astronomical event: a neutron-star collision.

Lucky enough to be in the right place at the right time, the two students were present when a brief flash of gamma rays

was detected in the constellation Hydra in the galaxy NGC 4993, 143 million light years away. Gravitational waves detected by the Advanced Laser Interferometer Gravitational-Wave Observatory (LIGO) indicated the event was indeed a neutron-star merger.

The heaviest elements in the universe come from these collisions, as well as from collisions of neutron stars with black holes. Astrophysicists had theorized that these elements, which are heavier than iron, form in neutron capture reactions, but they did not have an explanation for where these reactions occurred in the universe. Over the past few decades, scientists have derived models suggesting that collisions of extremely dense objects like neutron stars and black holes could be a source of these reactions. The August observation confirmed that neutron-star mergers are in fact a site where r-process elements are synthesized.

Although there is still an open question about the frequency of neutron-star mergers, this event was a good opportunity to test some of the developed models. For a long time, these mergers were thought to be associated with short gamma ray bursts. With the accompanying gravitational wave detection confirming this connection, it is likely more mergers will be detected in the future. Whitten described the significance of a triple system of detection and verification going forward: the photometric brightening and light curves, the gamma ray bursts, and the use of LIGO to pinpoint the gravitational wave signature, which is crucial for identifying cosmic events as neutron-star mergers, black-hole mergers, or related events.

During Rasmussen and Whitten's observation period, they were able to see the electromagnetic signature of the collision's resulting ejecta and cool-down as it happened, asking questions and learning what they could about the event. Trained in scientific skepticism, Whitten described their initial reaction: "We were trying to keep a level head, but it was almost eerie because you try to suspend belief that it is going to be an amazing event, but then as the data comes in, it turns out well, it has the magnitude, it's behaving the way it should if it's a neutron-star merger." As news of an important transient event and the accompanying gravitational waves spread among astronomers at the observatory, excitement grew. Rasmussen said, "I was really excited as an astronomer in my field, I finally get to watch this thing that's happening that I've been studying for a while. But then time went on and we realized there is even more impact than just r-process, confirming that gamma rays come from these events."

Rasmussen and Whitten are listed among almost fifty co-authors on a paper about the event published last October in *Science*. Their own research focuses on r-process elements in old stars and neutron-star mergers in the early universe. They are working on a National Science Foundation project called the R-Process Alliance along with scientists and research groups from other universities, including MIT and the University of Texas. Project members travel to telescopes looking for some of the universe's oldest stars. They take short-exposure spectroscopic images of them in order to determine signs of r-process elements before moving on to larger telescopes to take long-exposure images. Astronomers then compare the data to get a better idea of the heavy element patterns that are produced and the specific mechanisms that are responsible for producing more of one element and less of another. The group is especially interested in galactic chemical evolution, or how the chemical elements in the Milky Way formed. They are concerned with satellites to the Milky Way and are hoping neutron-star mergers happen in the nearby environment of our galaxy.

Rasmussen and Whitten are currently considering futures in academia. Both became involved in astrophysics after having been interested in space as children. Whitten describes astrophysics as a "dream come true," and Rasmussen calls it a "wild leap" she made in college after deciding not to pursue her initial major, music education. Rasmussen holds a B.S. in astrophysics from Florida State University, and Whitten earned his B.S. at a regional campus of Purdue University.

Peaslee Lab Integrates Undergraduates into Innovative Physics Research

REBECCA RADOMSKY

Around the world, fast food continues to feed billions of people in need of a quick and easy meal. In recent years, however, many publications and researchers have confirmed the adverse effects of fast food on human health. What many consumers do not realize is that their food wrappers might also be detrimental to their health. Per- and polyfluorinated alkyl substances (PFAS) are used to create water- and oil-proof coatings on the wrappers of many fast foods. The carbon-fluorine single bond that exists in these compounds is unusually strong, and therefore PFAS have environmental lifetimes that can last hundreds or thousands of years. Thus, PFAS found in our wrappers will end up in landfills and, subsequently, in the groundwater we drink.

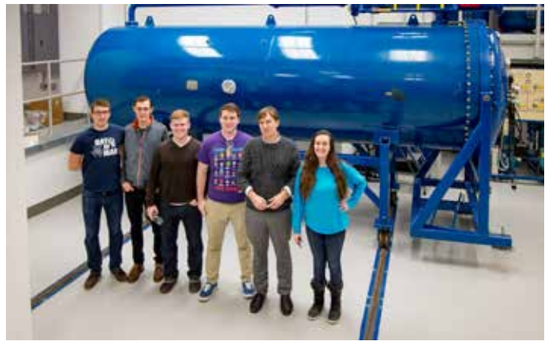
Graham Peaslee, Ph.D., and his team of researchers at the University of Notre Dame are taking a novel approach to measure PFAS. Instead of using traditional wet chemistry methods to analyze samples, which can take up valuable time and resources, the Peaslee group uses particle accelerators to excite fluorine nuclei. These nuclei emit several characteristic gamma rays when de-excited. This method is called particle-induced gamma-ray emission (PIGE) spectroscopy. PIGE allows for the rapid testing of food wrappers and textiles for the presence of fluorine, an indicator of PFAS.

When Peaslee moved to Notre Dame in the fall of 2016, he worked on the construction of the new particle accelerator facility in the physics department: the St. Andre 3MV Tandem Accelerator. Recently completed, the St. Andre facility has the ability to accelerate protons up to six million electron volts, which can measure the presence of PFAS in everyday samples, such as fast food wrappers, to measure the presence of PFAS. The Notre Dame facility will be able to test hundreds of samples per day, which is much faster than other techniques.

Peaslee's lab is unique in ways other than its scientific approaches. Although having undergraduate researchers is not uncommon, Peaslee allows these students a level of leadership and individualism quite unusual in academia. According to Peaslee, "all four of the PIGE measurements we have published so far have had multiple undergraduate co-authors, and the method paper has an undergraduate lead author." Not only have undergraduate students been part of the research in the Peaslee lab, but they have also had the opportunity to work on construction of the St. Andre 3MV Tandem Accelerator.

Patrick McGuire, a junior physics in medicine major, recalls how he first encountered Peaslee's lab. "Before Professor Peaslee came to Notre Dame, one of my physics professors told me that a professor was going to need help building a particle accelerator," McGuire said. "That sounded like the most interesting opportunity that could be presented to me." Walter McLallen, another junior physics major in Peaslee's group, agrees. McLallen explains that the new accelerator is important to undergraduate students because they helped with the assembly, and it gives undergraduates the "opportunity to start working hands-on with particle accelerators." The two current accelerators that are operated in the Notre Dame Nuclear Science Laboratory are usually reserved for graduate students, but the St. Andre will be used by undergraduates as well.

McLallen believes that his time with Peaslee has both opened him up to the world of research, and strengthened his previous scientific knowledge. "You are able to apply all of the abstract concepts that you learn as a student, and then actually see what the scientific process is like outside of the classroom." The type of undergraduate research that Peaslee fosters is what will continue to promote excellence, uniqueness, and creativity in science. Peaslee believes that undergraduates "represent a vital future for the field," and should thus be valued members of the research community. Peaslee and his team of researchers are advancing the skills of budding scientists while using innovative methods to measure PFAS, thereby helping to create a safer environment for everyone.



Professor Graham Peaslee stands with lab members in front of the newly-installed particle accelerator.

Students Contribute to the Reilly Top 10 List

ZHEFAN ZHANG

Technological developments and the ethics behind them seldom come without controversy. This relationship is now being explored by students at Notre Dame who took a one-credit course offered as part of the Science, Technology, and Values minor, titled "Men and Machine: Humanity, Technology, and the Future." One such student is Elizabeth Soller, a first-year biochemistry major who explored the relationship between pop culture and ongoing contentions in science. She then used her knowledge to contribute to the Reilly Center Top 10 List, an annual list of emerging dilemmas and ethical issues in science and technology, made by Notre Dame's John J. Reilly Center for Science, Technology, and Values.

According to the Reilly Center's website, the Reilly Top 10 List aims to "advance the understanding of the social impacts of science, technology, and their applications, to enlighten policy-making and foster sound governance." The List has been published annually since 2013, but this is the first year that students have contributed to it. During the fall semester, eight undergraduates participated in the voluntary course and were asked to select topics that they believed could spark meaningful conversations beyond the classroom. "We began with some very interesting topics," Soller said. "We went over a variety of different sites, and then narrowed down the resources to get a clear picture of specific technologies." Eventually students came up with a list that ranged from the application of technology in restructuring social systems to the interaction of technology and spirituality. Soller believes the direct student involvement allowed the List to include personal aspects of what the next generation of scientists might face.

Jessica Baron, Ph.D., the outreach and communications coordinator of the Reilly Center and the instructor of the seminar, agreed with Soller's point. "This current generation will be on the front lines of grappling with A.I., truly autonomous weapons, genetic manipulation..." Baron said. "They'll be in positions of leadership when we have to decide how to implement and regulate [these technologies]." Through collaboration with the students, Baron hopes the List will show the current generation's insights into the possibilities of the future while reflecting on the failures of the past.

Instead of beginning with novel and eye-catching headlines, the 2018 Reilly Top 10 List chose to focus on scholarship in the history and philosophy of science. Baron advised all the

participants to understand the basis of ethical frameworks and to review new research from academic journals and press releases. Those procedures were necessary to evaluate the social values and systematic impacts of futuristic technologies. To achieve this goal, students also analyzed how different media presented the information and the implications behind their words.

Along with the display of academic disciplines, the 2018 List also shows an appreciation for science fiction. Students were encouraged to watch sci-fi television shows such as "Black Mirror" and "Star Trek" for information. The television shows immersed the students in environments that made them not only anthropomorphize machines, but also sympathize with the characters who underwent emotional struggles due to the development of technology. This exercise challenged participants to re-examine their views about technological development on a theoretical level. Moreover, watching sci-fi television was indispensable to the pop culture training received by students. Soller said that using pop culture allowed the List contributors to estimate how people would respond to real as well as hypothetical technological advancements. It also made the students contemplate how technology intertwined with human existence and dignity. Both Baron and Soller considered "The Sentencing Software" to be the most compelling issue among the Top 10, as it discussed "one of the most difficult tasks a civil society faces – how to punish wrongdoing in a way that encourages rehabilitation," in a technological realm.

There are still many unsolved dilemmas in the List. As it was produced in 2017, it was difficult for the List to anticipate the technological trends of this year. Soller said that one of her greatest concerns was how far down this path of anticipation they were allowed to go. Rather than go into the details, the List aims to leave readers with a broad picture. Should people focus more on the patterns of how we invest in and monetize cutting-edge research technologies, or on the affordability of the technological changes taking place? Regardless of where the future leads, the next Reilly Top 10 List will be there to ask the difficult questions – and maybe get people thinking about solutions.

Changing the Realm of Cancer Treatment

VAISHALI NAYAK

In the last few decades, rapid developments in research have revolutionized medicine, and cancer treatment is no exception. Cancer is the second leading cause of death in the United States, and a significant amount of scientific resources has been invested in efforts to better understand and combat the disease. While research initially focused on treatments like surgery, radiation, and chemotherapy, newer research is now contributing to a fourth realm of cancer treatment: immunotherapy. Brian Baker, Zahm Professor of Structural Biology and Chair of the Department of Chemistry and Biochemistry at Notre Dame, is helping to expand this realm by exploring genetic engineering of the human immune system.

It is a natural function of the immune system to defend the body not only against pathogens like bacteria and viruses, but also against our own diseased cells and cancerous growths. Disease manifests when cancers learn to escape immune detection and destruction. Researchers in immunotherapy are interested in understanding the mechanisms that allow cancer to escape and in creating drugs that interfere with those mechanisms. However, this approach often comes with the heavy cost of inducing autoimmunity, a chronic condition that results when the immune system begins attacking the body's own healthy cells. To sidestep this often fatal result, Baker's lab at the Harper Cancer Research Institute has taken a rather novel approach – one that focuses on engineering immune systems, and can both avoid autoimmunity and potentially find explanations for it.

Conceptually, Baker bases his research on a simple idea: take advantage of the built-in diversity of the immune system in human populations to combat cancer. Such diversity exists because the molecules that make up the various components of our immune system, like T cells and their receptors, are made through random genetic recombination events. "For most cancers, particularly in their early stage, in theory there exist the perfect combination of T-cell receptors and other immune molecules that would enable the body to mount an efficient immune response against their cancer," Baker explains. "If genes encoding one of these magical T-cell receptors are inserted into immune cells of a cancer patient, for whom almost all other therapies have failed, the needed immune response can be induced." Baker believes that's where his lab comes in: examining the biochemical, biophysical, and structural aspects of cancer immune recognition and defining the best receptor to recognize a patient's cancer. This stream of research is being explored today for treating not just cancers, but also viruses (like HIV) and autoimmune diseases.

Graduate student Nishant Singh shows Professor Brian Baker promising protein crystals for structural studies in cancer immunotherapy.

While the lab is currently supported by two large grants from the NIH, grants from the Indiana Clinical and Translational Sciences Institute, American Cancer Society, and Walther Cancer Foundation have also helped foster local collaborations. One such collaboration is with renowned tumor immunology expert Michael Nishimura at the Loyola University Cardinal Bernardin Cancer Center. Given the interdisciplinary nature of the research, the Baker lab has expanded its collaborations to join forces with additional labs across the United States and abroad. "Success in this field comes from the different expertise that people in different laboratories bring to the problem," Baker explains. "We are one of those contributors: We bring in the biochemical approach to know how molecules work in the immune system, but to do real immunology, we collaborate with real immunologists." Expertise indeed comes in a variety of forms. Steven Corcelli, a professor at Notre Dame, helped to make computational simulations of molecules. Ranjan Srivastava from the University of Connecticut and a lab in Lausanne, Switzerland, also contributed their expertise. Beyond collaborations with other labs, Baker recently launched a startup company that partners with pharmaceutical companies to develop safe, potent molecules for cancer immunotherapy.

In the future, Baker is interested in teaching an undergraduate course on immunotherapy. He has already inspired interest in the army of dedicated Notre Dame undergraduates who work in his lab. Sophomore Christian Abraham believes that working in the Baker lab requires an innate dedication to the research and affords a lot of scientific liberty. Abraham explains her work as "cutting-edge science that has implications for the future of immunology" and says that this feeling of scientific novelty and relevance often inspires her to go the extra mile.

Through an extraordinary commitment to finding new answers in the crusade against cancer, the Baker lab has helped push the limits of not only its students, but also those of the field of cancer treatment.

Warren Family Research Center for Drug Discovery and Development

ROSIE CRISMAN

Established in 2014, the Warren Family Research Center for Drug Discovery and Development is the College of Science's newest collaborative hub and state-of-the-art research facility, housed in McCourtney Hall. The Warren Center caters to Notre Dame faculty with similar research interests, primarily in the fields of chemistry and biochemistry, and supports interdisciplinary projects between Notre Dame research centers, other universities, and pharmaceutical industry partners. Brian Blagg, Huisking Professor of Chemistry and Biochemistry, was appointed director of the Warren Center in the summer of 2017. Blagg, whose research focuses on protein-folding and its effects on neurodegenerative diseases and cancer, is excited for what the Warren Center has in store for Notre Dame, as well as for the burgeoning field of medicinal chemistry. "The University right now is primed to do drug discovery, and there are a lot of resources here that are not available at other universities," Blagg said. He further explained that one of the biggest benefits of the Center is the opportunity to "collaborate with other researchers, with the hope that individuals from different departments can find utility in what the center does."

The main goals of the Center are to support translational research, facilitate pre-clinical and clinical opportunities, and promote an innovative environment. In Blagg's words, drug development is "a high-risk investment with a significant reward." Launching an investigational new drug can take up to a lifetime of work, but reaps large benefits. Brandon Ashfeld, associate professor and director of graduate studies in chemistry and biochemistry at Notre Dame, is excited about utilizing research cores at the University to promote drug discovery. Cores are locations around campus with distinct research capabilities that further the drug discovery mission of the Warren Center. The Computer-Aided Molecular Design Facility "can model biological targets, which aids in the design and synthesis of small molecules and drug candidates," and the Chemistry Synthesis and Drug Discovery Facility "provides support in the development of a large compound collection," Ashfeld said. This collection is a feat of scholarship that demonstrates Notre Dame's synthetic chemistry prowess. Containing more than 20,000 unique chemicals, the collection aggregates compounds made over the past 40 years. Blagg explains, "The compound collection is a way to take advantage of the chemistry we do here. If we're looking for a new way to treat cancer, we can screen thousands of possible compounds at one time, and identify the compounds that would effectively target and kill the cancer cells."

Partnerships with other research institutions further the mission of the Warren Center and help connect Notre Dame to the wider scientific community. The Eli Lilly Faculty Fellowship promotes collaboration between Notre Dame faculty researchers and Eli Lilly and Company, a global pharmaceutical leader headquartered in Indianapolis, Indiana with a firm belief in scientific innovation. Through the fellowship, Notre Dame researchers position themselves within the chemistry program at Eli Lilly for up to three months, allowing new ideas to percolate and return to the University. The Warren Center also partners with the IDEA Center, IDEA standing for Innovation, De-Risking and Enterprise Acceleration. The IDEA Center supports both commercial and entrepreneurial activities for Notre Dame and is deeply involved with drug patents. In Blagg's words, "The IDEA Center has the resources, the expertise, and the drug patents, so a partnership will benefit both."

Most importantly, the Warren Center holds Notre Dame's mission close: caring for others and never losing sight of the human element of science. The connections between the Center and the University's mission is clear for Ashfeld: "There is philanthropy associated with the University, and designing drugs to treat prevalent and even some rare and neglected dis-

eases is quite popular. We can take on more high-risk projects, and focus on drugs that have a broader societal impact." Alumni are beginning to notice the leaps and bounds the Warren Center is taking and visit frequently for updates. Blagg is pleased by the interest of the alumni base, and that they are so well-integrated and invested in the Notre Dame community. This is only the beginning: since Blagg was recently appointed director, the Center has advanced rapidly. With new hires trickling into the Center, it has the possibility of becoming a hub for medicinal chemistry across the entire United States. All of us within the Notre Dame community and beyond would agree with Blagg when he says, "We have the opportunity to do something really special here."

A 96-well plate is loaded for an assay in the Warren Family Research Center.

International Psychoneuroendocrinolgy Conference Brings Together the Medical Community

DEAN DELP

Six members of the Notre Dame community, ranging from undergraduate students to faculty, attended the International Society for Psychoneuroendocrinology Conference held at the University of Zurich this past September. The faculty and students who traveled to the conference stayed in beautiful downtown Zurich. The location of the conference in central Europe enabled people from all over the world to attend.

The topic of the conference involved the relationship between stress and the actions of hormones, as well as how stress affects a person's long-term health. The six Notre Dame faculty members and students who embarked on this journey included undergraduates Claire Alexander and Katie Salley, graduate student Brandy Martinez, visiting professor Michelle Wirth, ESTEEM program member Marissa Koscielski, and recent graduate Natalie Pottschmidt. Koscielski, Pottschmidt, and Martinez were able to present their theses at the conference. Koscielski pointed out that the event brought together a plethora of professions and views that are not normally associated with this subject. The topic of psychoneuroendocrinology typically falls under the category of physiology, but many disciplines were present at this event. There were members of the medical and scientific communities from all across Europe and North America, representing a range of occupations in the medical industry. "These occupations ranged from anesthesiologists [to] endocrinologists [to] neurologists. The conference was very 'med' heavy and not as 'psych' heavy as you would expect," Koscielski noted. She believes that this environment cultivated an ability to grow and expand her knowledge on topics related to the field. Previously, these disconnected professions worked on a common problem but lacked communication, stalling advancements in the field. This conference was able to bridge the gap and facilitate effective communication between fields.

Koscielski presented her research at the conference in a general forum format. The research she presented focused on the extent to which age and stress factor into disorders, and which of the two has a greater effect. Specifically, her research investigates "stress-induced pathophysiology and how to tease out stress-induced versus age-induced issues over a long period of time," Koscielski said. Her project was titled, "The Longitudinal Mechanisms of Stress Dissipation on Pathophysiology," and was constructed around structural equation modeling that depicts how people feel over long periods of time. Koscielski's research was conducted through interpretation of previously collected data. This subject aligned perfectly with the topics of the conference. Elated about the opportunity, Koscielski could not say enough positive things about the entire atmosphere and experience. She believes that anyone offered the chance to attend this conference should jump at the opportunity.

Behavioral Phenotypes Associated with the Drug Manipulation of Serotonergic System in *Aedes aegypti*

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Abstract

Zika and dengue are vector-borne infectious diseases transmitted by the mosquito Aedes aegypti. *Due to the lack of universal availability of vaccinations to treat these diseases, the field has looked towards other control methods, such as insecticides. However, current insecticidal compounds are unsatisfactory due to the increased insecticide resistance of disease-carrying vectors. New techniques of vector control and disease prevention look towards G Protein-Coupled Receptors, GPCRs, as insecticide targets. Serotonin receptors are one of the identified GPCRs that are important in insect physiology. This research focuses on the role of serotonin signaling on mosquito sugar-feeding. Specific compounds that affect serotonin receptors are serotonin, an agonist, and methiothepin, an antagonist. We also looked at compounds that affect serotonin levels in the mosquito, PCPA and fluoxetine. Compounds were injected into the mosquito, after which a sugar-feeding assay was performed. These studies have shown that the sugar-feeding pathway in* Ae. aegypti *is not affected by drug manipulation of the serotonin system. Future studies will explore the role of the serotonin system in other behaviors, such as blood-feeding and flight, with the hope to discover viable compounds for insecticide development*.

Introduction

Disease Transmission

Ae. aegypti are a vector for the transmission of Zika and dengue. Currently, the spread of Zika to Latin America has placed over 2 billion people in the world at risk for infection. Zika is especially detrimental to pregnant women, as it is associated with birth defects including, but not limited to, microcephaly, a condition characterized by a small head and brain size, which in turn causes mental retardation (1). Another disease caused by the same mosquito vector is dengue. Dengue affects 2.5 billion people worldwide, a population that has increased 30-fold in the last 50 years. Severe cases of dengue can result in dengue shock syndrome or dengue hemorrhagic fever (2). The virus' transmission mechanism combined with biological aspects of the mosquito vector contribute to the explosive nature of Zika and dengue epidemics. *Ae. aegypti* is an efficient vector because the mosquito performs multiple blood-feeds and has varied larval sites. Multiple blood-feeds cause the mosquito to feed on more humans, while using varied larval sites makes it harder to eradicate the problem at the larval stage (3). This, in turn, causes an increase in disease transmission. Vaccines for Zika and dengue are not yet available, which makes vector control methods the preferred way to avoid future disease outbreaks. An important preventative method is the use of insecticides. However, a recent increase in resistance to current insecticides and a lack of new modes of action for insecticides used for global health purposes in the last 30 years, have led to low efficacy of this method. This continued resistance highlights the importance of finding new insecticides with novel modes of action. With increased genetic understanding of *Ae. aegypti*, insecticide development can target specific receptors known to affect specific physiological functions in the mosquito.

G Protein-Coupled Receptors

Currently used insecticide compounds target acetylcholinesterase and voltage-gated sodium channels. Increased insecticide resistance to these compounds underscores the need to identify new potential modes of action, specifically insecticide compounds that target GPCRs, ATPases and kiFnases (4). More than 40% of human drugs on the market target GPCRs. GPCRs are "easily druggable," meaning that it is easier to develop compounds that can affect these receptors (4). Previous studies have identified GPCRs in the *Ae. aegypti* genome, including 111 non-sensory class A, B and C GPCRs and 14 atypical class D GPCRs (5). It has also been shown that *Ae. aegypti* have evolutionarily conserved GPCRs with sequence similarity to known drug targets (5). GPCRs constitute a vast family of receptors; therefore, careful selection is critical to finding which GPCRs will negatively affect physiological behaviors and decrease the mosquitoes' ability to transmit the pathogens.

Serotonin Receptors

Due to its conserved presence in invertebrates, the biogenic amine GPCR family, including octopamine, tyramine, dopamine and serotonin receptors, is a focus of targeted insecticide research (6). Specifically, serotonin (5-HT) receptors have been identified as GPCRs that are important in insect physiology. In *Ae. aegypti*, serotonin immune-reactive axons surrounded salivary glands of adult females, and after administration of 5-HT, feeding is reduced significantly (7). It can be concluded that 5-HT receptors are a potential new mode of action for insecticide compounds.

Sugar-feeding In Aedes aegypti

Sugar-feeding is a necessary physiological process for mosquitoes. Evidence indicates that mosquitoes of all ages feed on plant sugar, such as floral nectar and honeydew. Sugar is a compound that provides mosquitoes with energy needed to fly, survive and reproduce. While blood-feeding is essential for egg development, sugar-feeding is vital for survival (8). When developing an insecticide, two key physiological behaviors to knock down in the vector mosquito include flight and feeding. Both of these activities, when impaired, reduce the mosquito's

ability to transmit pathogens. Sugar-feeding and the role it plays in the mosquito's ability to survive led to the experiments performed in this study. Additionally, methiothepin, an antagonist of the 5-HT receptor, inhibits feeding pathways in the fruit fly (9). Experimental results and evolutionary sequence similarity between *Aedes aegypti* and *Drosophila* have led to the testing of different compounds that influence the serotonergic system in the mosquito. This research focused specifically on serotonin receptors as a new mode of action for insecticide compounds. Specifically, we tested serotonin (an agonist) and methiothepin (an antagonist). Also, we tested two additional compounds that affect the serotonin levels in mosquitoes: 4-chloro- DL-chlorophenylalanine ethyl ester (PCPA), which disrupts serotonin synthesis, and fluoxetine, which alters reuptake of the ligand. The compounds were injected into the mosquito, after which a sugar-feeding assay was performed to test physiological responses to the compounds. Literature demonstrates that the sugar-feeding pathway is not modulated by 5-HT receptors.

Methodology

Mosquito Rearing

Liverpool strain *Ae. aegypti* were reared in an insectary located at the University of Notre Dame. The mosquitoes' environmental conditions were held constant at 26°C with 85% relative humidity. A 16 hour light, 8 hour dark, and 1 hour dusk and dawn photoperiod cycle was used in the insectary. The larvae were fed with liver powder until they matured. The adult mosquitoes were placed in plastic cages and fed daily with 10% sucrose water.

Chemical Compounds

Sigma-Aldrich provided 5-HT, methiothepin, fluoxetine and fluorescein. PCPA was purchased from Alfa Aesar. Ultrapure water was obtained from Invitrogen and Phosphate-buffered saline (PBS) was prepared in the laboratory.

Mosquito Treatment

Five-day-old female adult mosquitoes were starved for 24 hours. Borosilicate Glass Capillary tubes were separated into 2 parts using a laser with a heat setting of 270°C, which produced a needle diameter of 150nm. The microinjection needle was then backfilled with mineral oil and attached to the Nanoject II Auto-Nanoliter Injector (Drummond Scientific Company) system. The mosquitoes were collected and placed in a 4°C refrigerator for 8 minutes prior to injections. Cooling of the mosquitoes' body temperature temporarily paralyzed them, which allowed for the injection of the compound. 69µl of 1mM methiothepin, 10mg/mL PCPA, 1mM fluoxetine, 10mM serotonin, or a combination of 1mM fluoxetine and 10mM serotonin were injected into each mosquito through their spiracle. The mosquitoes were allowed to recover for 1 hour, after which they were permitted to feed for 2 hours on a 10% sucrose, .02% fluorescein solution. Feeding was conducted by first saturating a cotton ball with 3mL of the solution and secondly placing it on the netting covering the plastic cage where the mosquitoes were kept. Following the 2 hour feed, the mosquitoes were stored in a -20°C freezer.

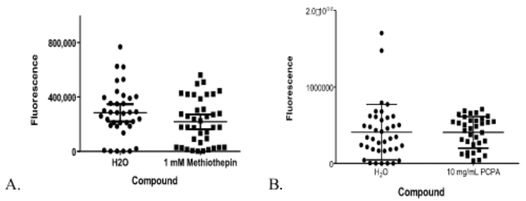
Data Processing

To determine the amount of sugar each mosquito ingested, a fluorescein assay was performed. Each mosquito was placed in a 1.5mL tube containing 250µl of 1X PBS and 3.5mm Zirconia-silicate beads. The mixture was homogenized with the FastPrep FP120 device. The homogenous solution was then centrifuged to separate solids from liquids. 100µL of the supernatant was collected and placed in one well of a 96-well white bottom plate. The fluorescence levels were quantified using the FlexStation 3 Molecular Device. Baseline fluorescein levels were determined by processing mosquitoes that were not provided with the 10% sucrose and fluorescein solution. Levels above the established baseline were measured to determine ingested sugar amounts.

Results

Post-microinjection of compounds, fluorescein levels were measured and were indicative of the amount of sugar upon which a mosquito fed. An injection of water served as the control for each experimental trial. The experiments performed aimed at identifying whether injection of the compounds would alter sugar-feeding compared to the water control.

Figure 1. **A.** Methiothepin effect on sugar-feeding showed



no significant change in the amount of sugar ingested. *Ae. aegypti* were injected with 1mM methiothepin, given a 1 hour recovery time, and a 2 hour 10% sucrose, .02% fluorescein water solution feed. An unpaired t-test at a 95% confidence interval gave a non-significant two-tailed p-value of 0.1134. **B.** PCPA effect on sugar-feeding showed no significant change in the amount of sugar ingested. *Ae. aegypti* were injected with 10mg/mL PCPA, given a 1 hour recovery time, and a 2 hour 10% sucrose, .02% fluorescein water solution feed. An unpaired t-test at a 95% confidence interval gave a non-significant two-tailed p-value of 0.1223.

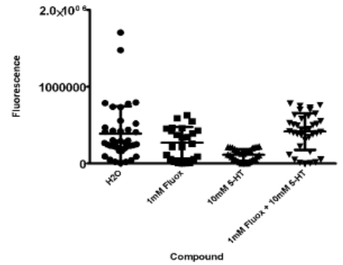


Figure 2. 1mM fluoxetine and 10mM 5-HT combined and separate effect on sugar-feeding showed no change in the amount of sugar ingested. *Ae. aegypti* were injected with 5-HT and fluoxetine at 10mM and 1mM, respectively, either independently or in combination, given a 1 hour recovery time, and a 2 hour 10% sucrose, .02% fluorescein water solution feed. An unpaired t-test comparing each compound to the water control at a 95% confidence interval gave a non-significant two-tailed p-value.

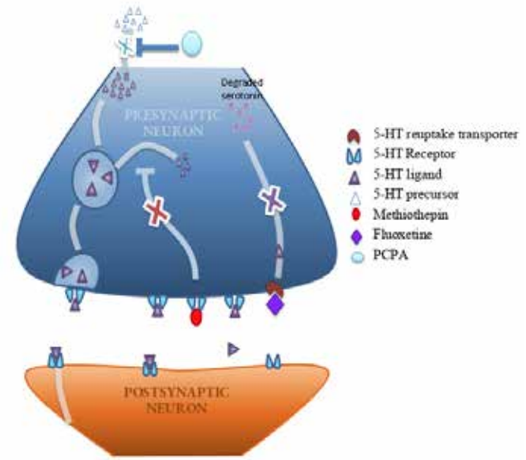


Figure 3. Various Compound Pathways in the Serotonin Synapse. PCPA prevents the production of 5-HT, fluoxetine prevents the re-uptake of 5-HT, which increases levels of 5-HT and methiothepin antagonizes the 5-HT receptor.

Antagonists

The antagonist compounds included methiothepin and PCPA. The fluorescein assay showed the comparison between mosquitoes that were injected with water (n=36) or 1mM methiothepin (n=39) (Fig. 1A), and fed with a 10% sugar, 0.02% fluorescein solution. The mean fluorescence for water was 283754 ± 31049 and for 1mM methiothepin was 218140 ± 26955. The statistical analysis produced a p-value of 0.1134 which represents that there was no significant variance. Secondly, comparison between a water control (n=39) and PCPA (n=35). The mean fluorescence for water was 408999 ± 57998 and for PCPA was 406771 ± 34813 (Fig. 1B). The p-value also showed, similar to methiothepin, no statistical significance in the data at a 95% confidence interval.

Agonists

The agonist compound used in this experiment was fluoxetine. A statistical t-test comparison was conducted between the water control (n=24), and fluoxetine 5-HT combination (n=32) (Fig. 2). The t-test showed no variance in the means, which was similar to the other two compounds. Overall, the compounds have shown to be ineffective in altering the amount of sugar-fed upon by the mosquitoes.

Discussion

Insecticide development to combat *Ae. aegypti,* has become more relevant than ever. Insects not only transmit pathogens, but are also pests to crops worldwide. Breakthroughs in genomics have allowed for sequencing of *Ae. aegypti.* The information found has led to the identification of GPCRs as potential insecticide targets. Specifically, 5-HT receptors are of interest due to their established role in vertebrate physiological activity.

The compounds that affect serotonin receptors are separated into those that act upon the 5-HT receptor, and those that influence serotonin levels in the synapse. Methiothepin and PCPA act as antagonists to 5-HT receptors, which means that they block a biological response by binding to the receptor. Methiothepin, when it acts on the 5-HT receptor, causes excess serotonin to build up in the neuronal synaptic cleft, which blocks activation of the 5-HT receptor in the post-synaptic neuron (Fig. 3). PCPA prevents the production of serotonin by inhibiting the production of tryptophan hydroxylase, which is a precursor to 5-HT (Fig. 3). Both compounds decrease serotonin levels in the neuron synapse. The reduction in serotonergic neurotransmission is theorized to affect the amount of sugar ingested by the mosquitoes.

Fluoxetine inhibits the re-uptake of 5-HT, which increases levels of 5-HT in the synapse (Fig. 3). The compound acts as an agonist to 5-HT receptors, activating them. The increased levels of 5-HT enhance serotonergic neurotransmission (10). It would be expected that this compound would cause the opposite physiological feeding response compared to the two antagonistic compounds.

The data presented in this paper did not demonstrate any changes in the amount of sugar ingested after the 5-HT receptor was targeted with various compounds. After completing an unpaired t-test with a 95% confidence interval on the data, which compared the control and the various compounds, it was concluded that the results were non-significant. This would suggest that sugar-feeding is a pathway unaffected by 5-HT receptors in *Ae. aegypti*. Previous studies have not been able to show that sugar-feeding is driven by 5-HT receptors, further supporting our data.

The global effort to find a solution to the insecticide-resistant mosquito *Ae. aegypti* is crucially important. Finding either a preventative solution or curative one is a priority. Biogenic amine receptors are the current focus for drug-targeted solutions. 5-HT GPCRs, specifically, are known to affect physiological pathways in *Ae. aegypti* and continue to be a major focus. Physiological events depend on the brain and neuronal

activity. The gap in knowledge before this paper was whether 5-HT receptors modulate sugar-feeding processes in *Ae. aegypti.* These results, while they show that sugar-feeding is most likely not modulated by 5-HT receptor pathways, open the door for new assays to identify novel drugs and pathways that 5-HT does affect. Future studies should look towards other physiological pathways that could be affected by 5-HT receptors, including blood-feeding and flight. Considering blood-feeding is necessary for reproductive means, and sugar-feeding plays an important role in energy, it is plausible that these two feeding processes are modulated through the activation of different GPCRs and pathways.

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About the Author

Zoe Loh is a senior majoring in chemistry and is from Mississauga, Ontario, Canada. She began research the summer of her sophomore year in the McDowell Lab and also with the Fraser Lab at the University of Notre Dame, and has been with both labs ever since. Zoe will be matriculating in the fall of 2018 to the Duke Pathology Ph.D. program, and is excited to begin work with brain cancer. Zoe is also part of the Notre Dame fencing team.

Gymnosperms demonstrate higher hydraulic vulnerability to drought than angiosperms in the Northern temperate deciduous forest

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Abstract

This study aimed to compare the hydraulic drought resistance capabilities of different tree species in the Northern temperate deciduous forest. Species differ in their xylem vulnerability to embolism and hydraulic failure caused by dramatic decreases in water potential during water shortages. Climate change is predicted to increase the frequency of droughts in the Northern hemisphere, so having an understanding of the ability of individual species to resist drought is essential for conservation of these forest communities. Thus, we sampled three gymnosperm species and three angiosperm species. Using a vacuum apparatus to measure embolism and a pressure chamber to measure water potential, we constructed xylem vulnerability curves. The curves allowed us to obtain the water potential at which an individual lost 50% and 88% of hydraulic conductivity (Ψ50, Ψ88), widely-used standards used to compare xylem vulnerability. We found that, contrary to our original hypotheses, the angiosperm species had more negative Ψ50 points and larger hydraulic safety margins (the difference between Ψ50 and Ψ88) than gymnosperms. This suggests that, in this ecosystem, gymnosperms could be at higher risk of drought-induced mortality caused by climate change than angiosperms. This information can be used to ensure that the Northern temperate deciduous forest is managed in a way that protects and preserves this unique forest community.

Introduction

Changes in precipitation patterns and rising temperatures attributed to climate change are likely to increase the duration and severity of droughts globally (1), which could in turn lead to widespread forest decline and mortality (2). Studies predict that temperatures will rise and precipitation will decrease, provoking more frequent and severe droughts in the northern regions of the United States which are home to unique temperate deciduous forests (3). More intense droughts can cause significant tree mortality which could alter the composition of forests (4) and their abilities to perform valuable ecosystem services, such as carbon sequestration and flood protection (5). Widespread forest mortality could also accelerate climate change by transforming forests from carbon sinks to carbon sources, changing the planet's albedo, and increasing the incidence of forest fires and insect pests (6).

The most prominent mechanism of drought-induced mortality in trees is hydraulic failure in their tree's xylem (2,7). The xylem of the tree is responsible for conducting water between the roots and leaves, and operates under negative pressures, known as water potentials, that cause water to be pulled upwards against the force of gravity (8). During times of drought and water scarcity, the soil water potential can drop significantly, causing the xylem pressures to become more negative. In such a situation, the cohesive forces between water molecules can be overcome, causing water to vaporize and form miniscule air bubbles in the xylem. This phenomenon is known as cavitation (9). Cavitation leads to large decreases in hydraulic conductivity between the roots and leaves, causing damage such as reduced growth rates and even tree mortality (10). Water stresses induce hydraulic failure, a phenomena in which water is no longer conducted from the roots to the leaves, by significantly lowering the water potential and causing the tree to develop hazardous levels of cavitation known as embolism (11). The ability of a tree to resist hydraulic embolism is strongly linked to its drought resistance capabilities (3).

The vulnerability of forests to droughts depends on the drought resistance capabilities of the tree species that make up the forest community (2). Different tree species vary in their ability to resist drought-induced embolism for several reasons. Broadly speaking, conifers tend to be more hydraulically resistant to drought than broad-leaved trees because of differences in their xylem anatomy that better enable conifers to regulate xylem water potentials (6). Stomatal control (12), wood density (13), and root depth (14) are other important factors that influence the resistance capabilities of different species. Additionally, it has been widely reported that a tree's ability to resist drought is strongly correlated to the amount of water stress the tree experiences during its ontogenetic development, with trees from wet environments that are rarely under water stress demonstrating higher hydraulic vulnerability (2).

A tree's xylem vulnerability is linked to its hydraulic safety margin, which is the range between the water potential that causes a 50% loss of hydraulic conductivity (Ψ50) and the water potential at which hydraulic failure occurs (Ψmin) (15). The hydraulic safety margin can also be approximated as the range between Ψ50 and Ψ88, because hydraulic failure in angiosperms occurs near this point (16). A wider hydraulic safety margin indicates that a tree can withstand larger drops in water potential before experiencing hydraulic failure (17). The species with more negative Ψ50 points and wider hydraulic safety margins are likely to be more resistant to drought (17).

This study aimed to compare the hydraulic resistance to drought in different tree species in the Northern temperate deciduous forest. Xylem vulnerability curves were generated for six native arboreal species in order to compare their hydraulic resistance to drought. Three gymnosperm species and three angiosperm species were studied. It was hypothesized that the gymnosperms would have more negative Ψ50 points and larger hydraulic safety margins than the angiosperms due

to the differences in their xylem anatomy that allow gymnosperms to be better able to regulate water potentials (6). The results of this study can provide insight into the potential of the forest community as a whole to resist the increasing length and severity of drought that is expected to accompany climate change. In addition, it may highlight which species are at higher risk of increased mortality from hydraulic embolism.

Materials and Methods

Study Sites and Species Choice

This study was conducted at the University of Notre Dame's Environmental Research Center in the Upper Peninsula of Michigan. This area is composed mostly of second-growth, northern mesic hardwood forests. The three gymnosperm species tested were Eastern hemlock (*Tsuga canadensis*), white cedar (*Thuja occidentalis*), and red pine (*Pinus resinosa*). The three angiosperm species tested were yellow birch (*Betula alleghaniensis*), red maple (*Acer rubrum*), and sugar maple (*Acer saccharum*). These species were chosen to accurately represent the wide taxonomic and phylogenetic diversity of trees in this forest. We chose four study sites based on previous surveys of the property detailing where each tree species was found in abundance.

Generation of Xylem Vulnerability Curves

We identified three individuals of each species that had accessible branches, and collected three branches with fully expanded leaves from each tree. We brought the branches back to the lab immediately and hydrated them overnight to ensure the initial measurements reflected the branch's condition when it was fully hydrated.

Two apparatuses were used to generate measurements on the amount of embolism in each branch as well as the water potential of the branches' leaves. First, we built a vacuum apparatus with an Erlenmeyer flask and a vacuum sensor (Omega Engineering, PX142-015D5V) that measured the pressure of the system and reported this output to a standard multimeter (Fig. 1). This apparatus was used to measure embolism in the branches. To measure the water potential in the leaves, we used a Pressure Chamber Instrument (PMS Instruments) (Fig. 2).

To generate xylem vulnerability curves, several measurements of embolism and water potential for each branch were taken over a 24-hour period as the branches dehydrated (18). These processes were repeated for each branch until the branch was completely dehydrated. Calculations were performed to determine the percentage of air discharged from each branch for each measurement (18), and were plotted against the corresponding water potential measurements to generate xylem vulnerability curves in Excel. A sigmoidal trendline was fit to each set of data using R. Using these trendlines, the Ψ50 point and hydraulic safety margin were determined for each sample and pooled for the angiosperm and gymnosperm species.

Statistical Analysis

Two independent group t-tests were performed in R to compare the Ψ50 points and the hydraulic safety margins between the gymnosperm and angiosperm tree species.

Results

The absolute values of the Ψ50 points that were calculated for each individual species (Fig. 3) and were pooled for the gymnosperms and angiosperms in (Fig. 4). The gymnosperms had an average Ψ50 (±SE) of 1.60 (±0.13) MPa and the angiosperms had an average Ψ50 of 2.57 (±0.05) MPa (Fig. 3). An independent groups t-test demonstrated significant differences between the Ψ50 points of the gymnosperms and angiosperms (df=13, t=6.01, p<0.001, Fig. 3), with the angiosperms having significantly lower Ψ50 points.

The ranges of the hydraulic safety margins for each individual species are shown in Figure 5, and were pooled for the gymnosperms and angiosperms (Fig. 6). The gymnosperms had an average range of 1.17 (±0.06) MPa and the angiosperms had an average range of 1.68 (±0.08) MPa (Fig. 4). An independent groups t-test demonstrated significant differences between the hydraulic safety margin of the gymnosperms and angiosperms (df=13, t=4.93, p<0.001, Fig. 4), with the angiosperms having significantly wider hydraulic safety margins.

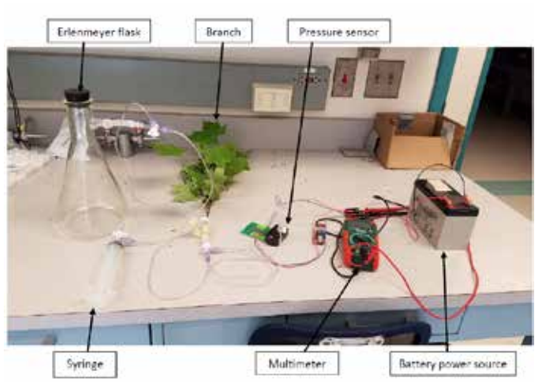

Figure 1. Experimental design. Vacuum apparatus used to measure embolism in the branches.

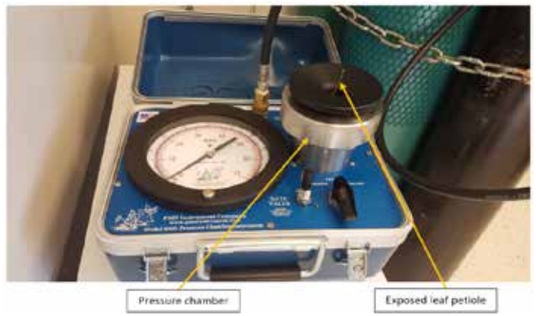

Figure 2. Experimental setup. Pressure chamber apparatus used to measure water potential in leaves.

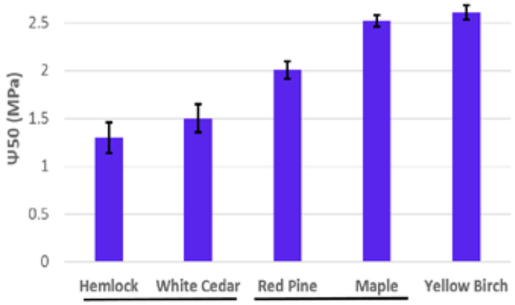

Figure 3. Absolute values of the average Ψ50 (±SE) for hemlock (n=3), white cedar (n=3), red pine (n=3), red and sugar maple (n=3), and yellow birch (n=3). Hemlock had an average Ψ50¬ of 1.30 (±0.16) MPa, white cedar had an average Ψ50 of 1.50 (±0.14) MPa, red pine had an average Ψ50 of 2.01 (±0.09) MPa, the maples had an average Ψ50 of 2.52 (±0.06) MPa, and yellow birch had an average Ψ50 of 2.61 (±0.06) MPa. A one-way ANOVA was performed comparing the Ψ50 points of each species (df=4,10, Shapiro-Wilk test p=0.627, F=26.72, p<0.001). A Tukey test was also performed, and the black lines indicate the means that are not significantly different from one another.

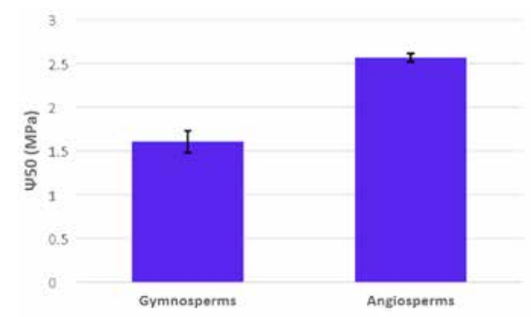

Figure 4. The average range (±SE) of the hydraulic safety margin for all gymnosperms (n=9) and angiosperms (n=6) that were sampled. The gymnosperms had an average range of 1.17 (±0.06) MPa. The angiosperms had an average range of 1.68 (±0.08) MPa. An independent groups t-test was performed comparing the hydraulic safety margin of the gymnosperms and angiosperms (df=13, t=4.93, p<0.001).

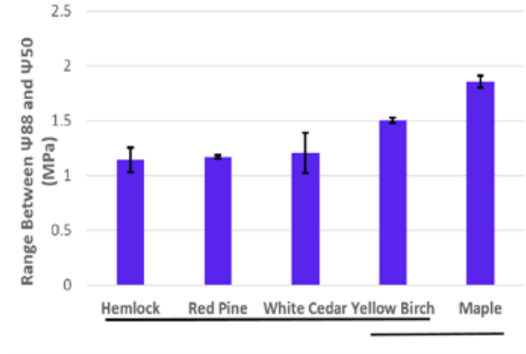

Figure 5. The average range (±SE) of the hydraulic safety margin for hemlock (n=3), red pine (n=3), white cedar (n=3), yellow birch (n=3), and red and sugar maple (n=3). Hemlock had a range of 1.14 (±0.11) MPa, red pine had a range of 1.17 (±0.02) MPa, white cedar had a range of 1.21 (±0.18) MPa, yellow birch had a range of 1.50 (±0.02) MPa, and the maples had a range of 1.86 (±0.06) MPa. A one-way ANOVA was performed comparing the hydraulic safety margins of each species (df=4,10, Shapiro-Wilk test p=0.429, F=9.29, p=0.002). A Tukey test was also performed, and the black lines indicate the means that are not statistically different from one another.

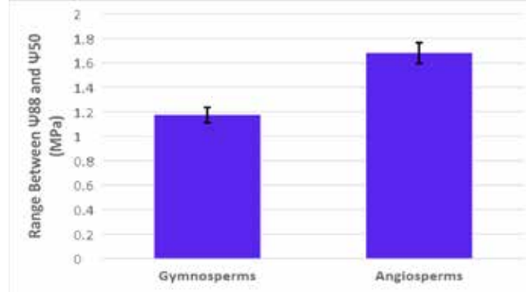

Figure 6. The average range (±SE) of the hydraulic safety margin for all gymnosperms (n=9) and angiosperms (n=6) that were sampled. The gymnosperms had an average range of 1.17 (±0.06) MPa. The angiosperms had an average range of 1.68 (±0.08) MPa. An independent groups t-test was performed comparing the hydraulic safety margin of the gymnosperms and angiosperms (df=13, t=4.93, p<0.001).

Discussion

The results of this study did not support our initial hypotheses. We had hypothesized that gymnosperms would have more negative Ψ50 points and larger hydraulic safety margins than the angiosperms, but our results demonstrated that angiosperms had more negative Ψ50 points (Fig. 3) and larger hydraulic safety margins (Fig. 4) than gymnosperms in the Northern temperate deciduous forest.

These results indicate that the angiosperms in the Northern

temperate deciduous forest are better able to hydraulically resist water shortages than the gymnosperms. This is partially contrary to previous studies that reported either no difference between angiosperms and gymnosperms (17) or that had found better hydraulic resistance capabilities in gymnosperms (2). This could be explained because angiosperm leaves feature dense reticular venation that improves the hydraulic efficiency and photosynthetic productivity of the leaves, which in turn could help prevent desiccation of the leaves and improve the ability of the plant to resist drought (19). Additionally, recent research suggests that the gymnosperm species we studied belong to a class of gymnosperms that tends to rely on tight stomatal control to reduce stomatal conductance under drought conditions (20). This suggests that these species could rely more heavily on stomatal control than on hydraulic conductivity, which would explain why these species demonstrated higher hydraulic vulnerability than the angiosperm species.

Due to the high precipitation and infrequency of water stress that is common in these regions, the trees may employ strategies such as stomatal control (closing their leaves' stomata to prevent water loss) and leaf shedding (shedding leaves that are too energetically expensive to supply with water), rather than relying on hydraulic safety. Current climatic trends as well as the age of the individuals could have strong impacts on their hydraulic properties (3). These factors, however, were not considered in this study due to time and resource constraints. There are a plethora of biotic and abiotic factors such as topography, wood density, and stomatal control that influence the hydraulic conductivity of individuals and should be examined with future research to provide a more thorough understanding of these species' hydraulic drought resistance capabilities.

Our results suggest that the gymnosperm tree species of the Northern temperate deciduous forest may be at higher risk of drought-induced mortality caused by hydraulic failure than the angiosperm tree species, especially in the face of increased droughts due to climate change. The loss of these species would be devastating for the different lifeforms that depend on them (17) and could in turn further accelerate climate change (21). As climate change progresses, these species will likely require more involved management in the future to ensure that they do not experience widespread drought-induced mortality. Understanding the hydraulic drought capabilities of the tree species in this forest is necessary to promote the most effective management and protection of this forest so that the unique communities of the Northern temperate deciduous forest are able to persist into the future and continue to provide countless benefits to both the forest and the planet.

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Analysis of Phase-Imaging Ion-Cyclotron-Resonance Mass Measurements at Argonne National Lab

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Abstract

The importance of accurate mass measurements is evident in quite possibly the most famous equation in all of physics, Einstein's Mass-Energy Equivalence equation. In the realm of nuclear physics, the well-known method of adding up the protons, neutrons, and electrons falls short of giving the true mass of the atom, neglecting the binding energy of the nucleus. Thus, further studies investigating nuclear structure are warranted, and are especially relevant for nuclear astrophysics in the study of the r-process. The primary contemporary tool for determining the mass of an ion with high precision is the Penning trap. This is a very small device that creates a quadrupole electric field that, when coupled with a homogenous magnetic field, only allows motion in the radial plane, causing ions to "orbit" the center of the trap. One of the newest methods for increasing the precision of a measured mass with the Penning trap is known as the Phase Imaging technique. Using this technique, the measurement of nuclear masses is accomplished by measuring the cyclotron frequency of the isotopes circling within the trap. To determine this frequency, a position-sensitive multichannel plate (MCP) detector is used to record the relative position of the isotope in the trap as a function of time. These time-dependent position measurements, the center of the trap, the central angles between the positions of the isotope of interest, and a measured reference spot are used to determine the cyclotron frequency and, subsequently, the nuclear mass.

Introduction

One of the grand challenges in all of physics is the identification of the site for the rapid neutron capture (r-process) nucleosynthesis. This question is difficult to solve since the nuclei that would be involved in such a process are neutron-rich and lie far from stability. While the global effort in nuclear physics is dedicated to building accelerators that can produce some of these very neutron-rich nuclei, Argonne National Laboratory is presently engaged in studying the properties of neutron-rich nuclei produced from the spontaneous fission of ^{252}Cf (Californium-252). Using a newly developed analysis method known as Phase-Imaging Ion-Cyclotron-Resonance (PI-ICR), we are able to use the Canadian Penning Trap (CPT) to measure masses in the rare-earth region to unprecedented precision.

One of the most important properties of a nucleus is its mass. As we move away from the valley of stability, it is imperative to measure the masses of nuclei with very low abundances and progressively shorter half-lives. Presently, three different techniques are used to measure masses of very short-lived nuclei: the Schottky method, the Isochronous approach, and the Penning trap mass spectrometry. Schottky mass spectrometry provides accurate measurements of nuclei with half-lives down to 10^0 s, with an approximate uncertainty of 10 keV. Isochronous mass spectrometry provides measurements of nuclei with half-lives down to 10--$^{-6}$ s, albeit with an uncertainty of around 100 keV (1). Thus, for nuclei with half-lives less than a second, Penning trap mass spectrometry (PT-MS) becomes the go-to method for obtaining nuclear mass measurements (2). Penning traps are small devices that employ the use of a quadrupole electric field and a magnetic field (Fig. 1) to confine an ion's movements to exclusively radial motion. The unique advantage of traps is that only a few nuclei are needed to make a measurement. The earliest successful Penning trap mass measurement technique was the Time-of-Flight Ion-Cyclotron-Resonance (TOF-ICR) technique, which, despite recent advances in its precision, ultimately falls short of the desired mass resolution for masses with half-lives less than 10--$^{-1}$ s (3). Thus, experimentalists have recently turned to the Phase-Imaging Ion-Cyclotron-Resonance (PI-ICR) technique, which provides significant speed and mass resolution improvements over the TOF-ICR technique (4). The PI-ICR technique relies on the determination of the cyclotron frequency (v_c), accomplished by a position-sensitive microchannel plate (MCP) detector. The cyclotron frequency itself is a combination of two radial frequency components, the modified cyclotron frequency (v_+) and the magnetron frequency (v_-). The modified cyclotron frequency, the frequence of standard cyclotron motion of an ion in a magnetic field that is weakly affected by the electric field, is greatly mass dependent, whereas the magnetron frequency, which is affected greatly in the radial direction relative to the electric field, is weakly mass dependent. Together, they relate to the cyclotron frequency as follows:

$$v_c = v_+ + v_- \qquad (1)$$

Subsequently, the cyclotron frequency is related to the nuclear mass through the following:

$$v_c = \frac{qB}{2\pi m} \qquad (2)$$

where q is the charge of the ion, B is the magnetic field, and m is the nuclear mass.

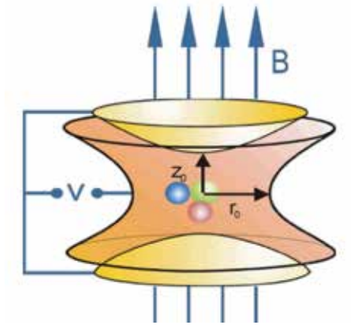

Figure 1. A model of a Penning trap, where B denotes the magnetic field direction and V is the potential difference applied to the electrodes of the trap, which create the quadrupole electric field. z_0 and r_0 are the spatial dimensions of the trap.

PI-ICR Measurements at Argonne National Lab

At the Argonne National Laboratory, the Canadian Penning Trap (CPT) is engaged in measuring masses. The source is a spontaneously fissioning ^{252}Cf source named Californium Rare Isotope Breeder Upgrade (CARIBU). The CPT measurements provide high-precision mass measurements of nuclides. Fission peaks in the A = 90 and A = 135 regions, but this research has been in the measurement and analysis of the rare-earth nuclei which are produced in much lesser quantities. The fission product ions are transferred into the CPT at a spatial range of 2ΔR (Pos. 1 in Fig. 2). By applying a dipolar radio-frequency field, the ions are moved outward an average radius, R (Pos. 2 in Fig. 2). The ions are then allowed to freely evolve for a period of time, t, such that the final phase of the ion is:

$$\phi + 2\pi n = 2\pi v \qquad (3)$$

where n is the number of turns the ion made within the trap (or the number of full revolutions around the trap it completed), and v is the "radial motion" frequency, or the frequency due to the radial motion of the ion within the trap. Other traps which have utilized the PI-ICR technique, such as SHIPTRAP in Darmstadt, Germany, measure the two components of the cyclotron frequency in succession, such that $v = v_-$ for one run and then $v = v_+$ for the next (4). However, for the CPT, $v = vc$, such that our cyclotron frequency can be measured as a function of the final phase, the number of turns, and the time of free evolution as seen below:

$$v_c = \frac{\phi + 2\pi n}{2\pi t} \qquad (4)$$

When conducting mass measurements, we regularly measure reference ions, and then analyze the final phase of the ions in question in reference to our most recent reference ion measurement. For the sake of avoiding confusion, we will refer to the ions we are interested in measuring and observing as the actual ions from here on. Thus, the final phase can be written as $\Phi = \Phi_a - \Phi_{ref}$, where Φ_a is the final phase of the actual ion and Φ_{ref} is the final phase of the reference ion. Furthermore, we measure the time t as a function of the accumulation time (t_{acc}) of the actual ion. However, this measurement is also done with respect to the most recent reference ion measurement, and thus allows us to say that $t = t_{acc,a} - t_{acc,ref}$, where $t_{acc,a}$ and $t_{acc,ref}$ are the accumulation times of the actual and reference ions, respectively.

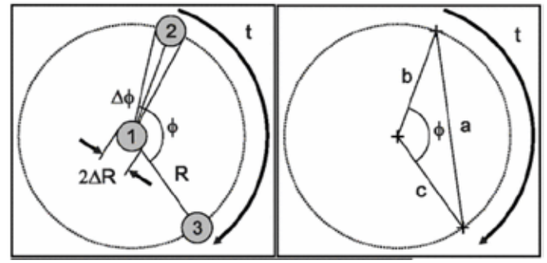

Figure 2. A diagram of the radial motion of an ion within the measurement trap.

Analysis

Analysis of PI-ICR measurements begins by determining the x and y coordinates of the center spot at which ions have accumulated. Figure 3 shows an example of an experimentally recorded projection of ionic motion onto the MCP. Gaussian distribution curves were fit to our positional spot data, giving us the positional coordinates of the final spot center. We repeat this process for various different sets of actual ions, traditionally looking at ion sets with accumulation times within 1ms of each other, as well as for the reference measurements which the actual measurements will be referenced to. We then calculate the final phase of both the actual and reference ion sets (Φ_i) from their positional spot data, such that:

$$\phi_i = \arccos\left(\frac{b^2 + c^2 - a^2}{2bc}\right) \qquad 0 \le \phi \le \pi \qquad (5)$$

$$\phi_i = 2\pi - \arccos\left(\frac{b^2 + c^2 - a^2}{2bc}\right) \qquad \pi < \phi < 2\pi \qquad (6)$$

where a, b, and c are the distances illustrated in Figure 2. Now equipped with the phases of the ion accumulation spots, and considering that we already have the time t of free evolution, we need to determine the number of turns n that the ion went around the trap. To do so, we start by speculating the cyclotron frequency:

$$v_c = \frac{v_{c(cal)}}{m}\frac{q}{q_{cal}}(m_{cal} - q_{cal}m_e) + qm_e \qquad (7)$$

where $v_{c(cal)}$, q_{cal}, *and* m_{cal} (taken from AME2012) are the cyclotron frequency, charge, and mass of a calibrant isotope, respectively, of a traditionally well-known nuclide (5). m_e and q are the mass of an electron and the charge of the measured isotope, respectively, and also taken from AME2012.

This leaves only the mass of the measured isotope, *m*, which is simply the sum of the masses of its consistent protons and neutrons. This clearly ignores the binding energy of the nucleus, and thus is why the resulting cyclotron frequency is only a guess. Considering that the ignored mass defect is relatively small, we can use our cyclotron frequency guess in conjunction with the final phase (Φ) and time (t) in Equation 4 to calculate an approximate number of turns n. We then calculate ν_c for a range of integer values for n around our approximate guess value. From here, we traditionally choose the cyclotron frequency value closest to our guess. To find our final nuclear mass m, we traditionally eliminate the magnetic field term in Equation 2 by instead looking at cyclotron frequency ratios, and thus simply utilize a rearrangement of Equation 7, such that:

$$m = \frac{\nu_{c(cal)}}{\nu_c}\frac{q}{q_{cal}}(m_{cal} - q_{cal}m_e) + qm_e \qquad (8)$$

and use our newly chosen cyclotron frequency as ν_c.

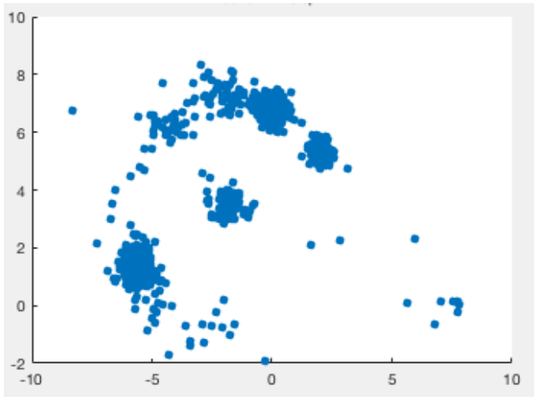

Figure 3. An experimentally recorded projection of the positions of ions within the trap, specifically for ^{159}Nd in this case. Notice the large accumulation of events around $\Phi_a = 95$, signaling that our actual measurement's final phase is most likely around that value.

Results and Sine Wave Fitting

When calculating the cyclotron frequency and nuclear mass of a measured isotope, we run analyses at various different accumulation times and thus produce different cyclotron frequencies and nuclear mass values for each measurement made at different accumulation times. Ideally, these values should be consistent. In contrast, recent analyses have suggested that cyclotron frequency seems to vary sinusoidally with respect to the accumulation time. Although not fully understood yet, we believe that the variance has to do with the magnetron frequency (*w*-), because the period of this sinusoidal variance is close to the magnetron frequency traditionally seen in the CPT. Figure 4 shows a plot of a recent analysis of C6H6 measured in May 2017, with accumulation times all approximately *234ms*. To correct for this variance, we fit a sine function ($a + b\sin(cx+d)$) to our accumulation time/cyclotron frequency data, where *a, b, c, and d* are all fitted variables. The resulting variable *a*, the "center" of the sine fit, is then taken to be our final cyclotron frequency.

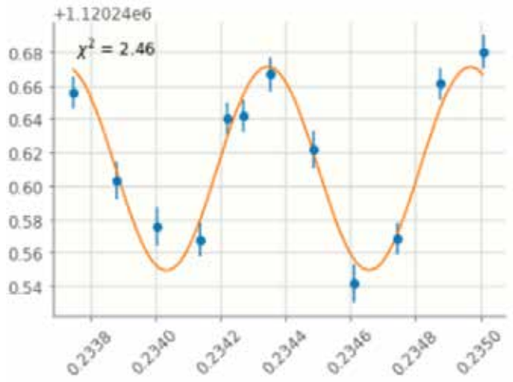

Figure 4. The accumulation time and cyclotron frequency for C6H6 measured in May 2017.

Conclusion

As more precise mass measurements are needed in nuclear physics, more precise ways of measuring short-lived nuclides have arisen, specifically the PI-ICR technique in PT-MS. Using the CPT at Argonne National Lab in combination with the PI-ICR technique, we are able to get accurate measurements of nuclides with half-lives much less than a second. Further work is most certainly warranted, as issues with cyclotron frequency variance continue to arise. Further refinement of analysis techniques will be necessary, and we must take into consideration the dependence of our measured cyclotron frequencies such that we can continue to produce reliable, accurate mass measurements farther from the valley of stability.

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About the Author

William S. Porter (Sam) is a junior physics and math major from Atlanta, Georgia, living in Siegfried Hall. He is a member of the Notre Dame Band and an active counselor for Camp Kesem Notre Dame. As a researcher, he works with Professor Ani Aprahamian's research group on projects within nuclear astrophysics. Specifically, Sam collaborates with Argonne National Lab on obtaining mass measurements of rare-earth nuclei, which are of great interest in increasing our understanding of processes that create elements heavier than iron. Sam works on a large portion of the analysis of such measurements completed at Argonne's CARIBU facility, which measures masses through use of the Canadian Penning Trap.

PHYSICS

Performance Studies for the Proposed CMS L1 Track Trigger Upgrade

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Abstract

The Large Hadron Collider (LHC) at CERN will be upgraded in the mid-2020s to produce collisions at higher rates. As a result, the Compact Muon Solenoid (CMS) detector will require an upgrade in order to handle the accompanying increase in collision data. This upgrade involves implementing a system capable of reconstructing charged particle tracks from the detector in real time, known as a Level-1 (L1) Track Trigger. In order to study the expected performance of such a trigger system, a simulation code has been developed which is capable of running the proposed reconstruction algorithm over simulated collision events. Performance is typically characterized in terms of efficiency and resolution. The efficiency is the fraction of simulated particle tracks successfully reconstructed by the L1 trigger. The resolution quantifies how well the parameters of the simulated track are measured by the Track Trigger algorithm. Measuring the efficiency and resolution in the simulation reveals problems that can be prevented in the actual trigger by solving them in the code. The focus of this research is twofold. The first part is an analysis of the performance of two distinct tracker geometries. The second examines the effects of including stricter requirements in forming reconstructed tracks. The newer tilted barrel geometry was found to perform comparably to the older flat geometry, with some expected drops in resolution. Including stricter requirements in the tracklet stage of track formation cuts down significantly on combinations that the algorithm needs to consider, without a great decrease in overall efficiency.

Introduction

With a circumference of 27 km and current center-of-mass energy of 13 TeV, the Large Hadron Collider (LHC), operated by the European Organization for Nuclear Research (CERN), is the world's largest and most energetic particle accelerator (1). By colliding particles at such high energies, scientists around the world hope to answer questions about the fundamental constituents of the universe. Already the LHC has brought about a tremendous breakthrough in particle physics with the confirmation of the existence of the Higgs Boson predicted by the standard model of particle physics. One of the greatest challenges for future discoveries is that they tend to involve the rarest of events at current energy. For example, for the energy at which the LHC was operating when the Higgs Boson was discovered, 7 TeV, the rate of Higgs production was only once per every 3 billion proton collisions (2). To increase the rate of these kinds of rare events, an upgrade of the LHC is necessary mid-2020s, the goal of the HL-LHC is to increase the integrated luminosity by a factor of ten (3).

This increase in luminosity means an increase in the rate of generated collision data, which warrants a concurrent upgrade to the detectors in order to more readily sift through this incoming data. This project focuses on the Level-1 (L1) Track Trigger upgrade of one of the four LHC detectors, the Compact Muon Solenoid (CMS) detector. The L1 Track Trigger is a system through which particle tracks from collisions in the detector are reconstructed in real time using Field-Programmable Gate Array (FPGA) technology. These reconstructed tracks are used to more quickly tell which collisions contain new, interesting physics data and should be kept, and which collisions do not and should be discarded.

An overview of the reconstruction process is shown in Figure 1. The two particle beams enter the detector along the z-axis (i.e. perpendicular to the page in the figure), and the magnetic field is also directed along this axis. This means that moving charged particles will curve in the x-y plane, as shown in the figure.

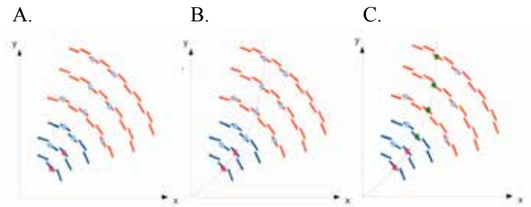


Figure 1. Track Reconstruction Steps. First, in **A.** A seeding tracklet is formed from a pair of stubs. **B.** The tracklet is projected to look for matching stubs. **C.** These stubs are used to form a track.

Only a section of the barrel part of the detector, which wraps around to form concentric circles when viewed in the x-y plane, is shown. As charged particles move through the detector, the points of intersection with the silicon tracker are recorded as pairs of hits in each layer called stubs. Pairs of stubs from adjacent layers are then considered to form seeding tracklets, for which basic tracking information is calculated. From the calculated tracklet parameters, a projection of the tracklet is made in order to search for more stubs along its path. If enough stubs are found, a track is formed by a linearized chi-squared fit. The last step is to conduct a duplicate track removal, since duplicate tracks may be formed when tracklets from different layers are projected to form the same track. In all, the algorithm takes stub information as its input and returns reconstructed tracks with four track parameters: transverse momentum (pT), initial polar angle (φ_0), pseudorapidity (η), and initial position along the beamline, (z_0).

In order to test the performance and feasibility of this algorithm, it was implemented in a simulation code written in C++ and python. By using simulated collision events in which everything about the original tracking particle is known, it is possible to quantify how well the simulation reconstructs tracks and test the algorithm thoroughly before implementation.

Tilted Barrel Performance Studies

In the studies conducted, two detector geometries were considered. The first, which had been the basis of most studies up through 2016, was the flat barrel tracker shown in Figure 2 The barrel layers mentioned above are shown as horizontal lines in the r-z plane, and the vertical lines show the positions of the disk layers, also known as the endcaps.

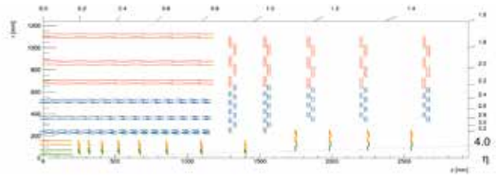


Figure 2. Flat Barrel Tracker Geometry.

Considerations of cost and material amount led to the adoption of a tilted barrel tracker, shown in Figure 3. The benefit of tilting some of the modules in the first three barrel layers was an increase in detector surface area facing the collision vertex, which meant that less material could be used to cover that region of the detector. The aim of these studies was to compare the performance of these two geometries, for single muon as well as single electron events.

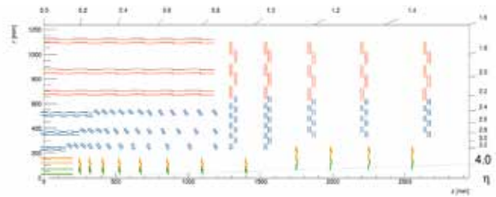


Figure 3. Tilted Barrel Tracker Geometry.

Performance is characterized in these studies by efficiency and resolution. Efficiency is a measure of how many of the "actual" particle tracks are reconstructed by the algorithm. In the simulation code, simulated particle tracks are referred to as "Tracking Particle (TP)" tracks, while reconstructed tracks are called "Level-1 (L1)" tracks. The efficiency is given by a fraction of TP tracks reconstructed as L1 tracks. To have an associated L1 track, the TP track parameters must be sufficiently close to the parameters of one of the L1 tracks. A measure of how close these parameters are is given by the resolution. For a given parameter, f, resolution is typically characterized by the width of the distribution of (fTP - fL1), or in some cases (fTP - fL1)/fTP. Thus, good resolution corresponds to a sharply peaked distribution, or a lower RMS value.

Figure 4 shows the muon efficiency vs. pseudorapidity for three versions of the simulation code, which reflect the evolution of the flat barrel geometry as well as the difference between the flat and tilted barrel geometries for the most current release of the code.

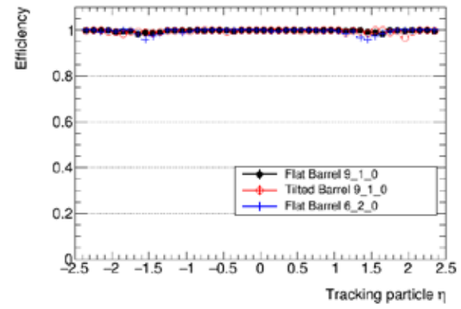
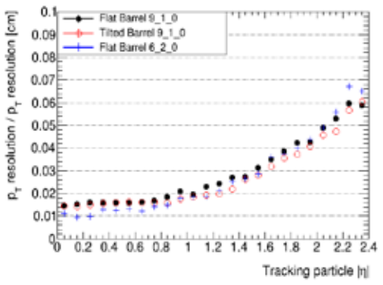


Figure 4. Muon efficiency vs. Pseudorapidity

There is good agreement between the three versions, so the tilted barrel tracker appears to be performing up to par with the flat barrel. There are some drawbacks, however, namely with respect to η and z_0 resolutions. In Figure 5, it is clear that while the resolutions for pT and φ match nicely for the most part among the three versions, those for η and z_0 are worse for the tilted tracker. This is expected due to the geometry of the tilted barrel, specifically because each tilted module has a larger η and z_0 range than a flat module would.

Single electrons were also considered in this study, and Figure 6 shows the efficiency for both flat and tilted barrel at 10 GeV and 35 GeV. It is worth noting the efficiency is significantly better for the tilted barrel in the η region that is associated with the tilted modules. This is because electrons typically radiate through bremsstrahlung upon impact with detector material, which causes them to lose energy and curve more in the magnetic field. If the energy loss is sufficient, the coordinates of the stubs left by the electron in layers following the radiation will not match the projected stub hits from the earlier layers. This could result in either the wrong track being constructed or no track being found at all. Thus, having less material due to tilted modules leads to much less radiation, and therefore higher efficiency.

A.



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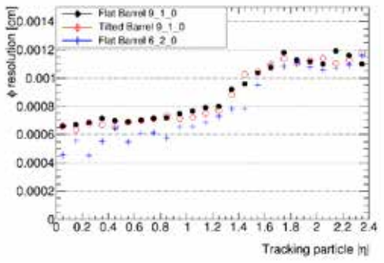

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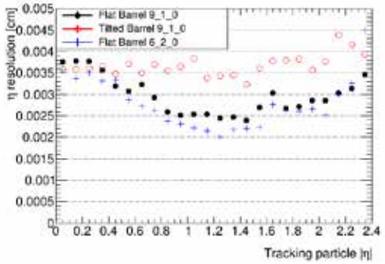

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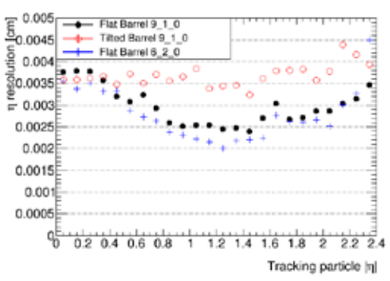

Figure 5A-D. Muon Resolutions with respect to η for the four track parameters. The higher value on the y-axis indicates worse resolution.

A. B.

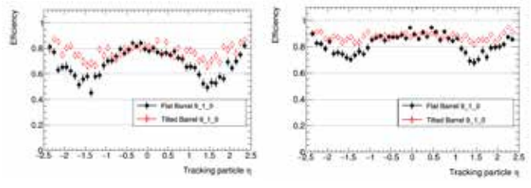

Figure 6. Electron Efficiency at **A.** 10 GeV and **B.** 35 GeV.

Stub Bend Consistency Studies

In the second step of the tracklet reconstruction diagram shown in Figure 1, pairs of stubs are used to form tracklets. Stubs themselves are pairs of hits on two sensors of a module. This means that even at the stub level, there are already two space points (three, counting the collision vertex) that can be used to calculate some relevant parameters. Ideally, one would be able to calculate a rudimentary stub pT, and this would be useful in comparing the values between two stubs to see if they are consistent enough to form a tracklet. In this case, however, rather than stub pT, we have stub bend. A stub's bend is approximately rΔφ between its two hits. In Figure 7 is a mathematical approximation of rΔφ, but in reality, bend is measured by the rφ difference between the two hits in half-integer number of "strips."

$$\varphi = \varphi_0 - \sin^{-1}\frac{r}{2\rho} \approx \varphi_0 - \frac{r}{2\rho}$$

$$\Delta\varphi \approx \frac{-\Delta r}{2\rho}$$

$$p_T = 0.3B\rho$$

$$\rho = \frac{p_T}{0.3B}$$

$$Bend \approx r\Delta\varphi \approx \frac{-0.3B\, r\Delta r}{2\ p_T}$$

Figure 7. A derivation of an approximate formula for bend.

For our purposes, the key point is that bend is approximately proportional to stub radius, but inversely proportional to track pT, as can be seen when stub bend is plotted against the pT of the associated TP track for a given layer (see Figure 8 for layer six).

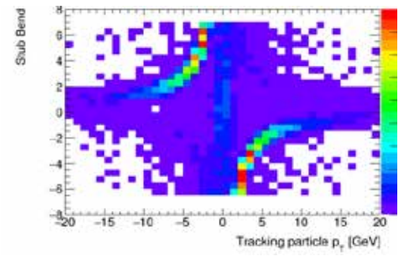

Figure 8. Stub Bend vs. TP pt for layer six (radius of ~110 cm).

One can make use of stub bend in much the same way as stub pT. By requiring some level of consistency in stub bend during tracklet formation, it is possible to eliminate many stub pairs and ultimately reduce the sheer number of combinations that the algorithm has to consider. This is one of the main challenges involved in the reconstruction algorithm. To decide how close the two stubs need to be in bend, it is useful to look at a plot of the bend difference of stubs associated with low pT tracks in the two layers being considered. Figure 9 shows layers five and six, and it is clear that a requirement of Δbend < 4 should be more than sufficient to discard stub pairs that are obviously not from the same track.

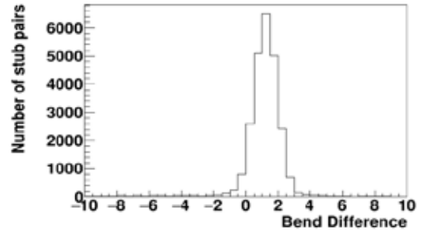

Figure 9. Stub Bend difference histogram for low pT in layers five and six.

Table 1 gives the percentage of stub pairs that are rejected by a coarse bend consistency cut for each seeding layer combination. The more stub pairs that we can reject without lowering the efficiency, the better, because it means the algorithm is not wasting time and computing power considering stub pairs that are definitely not in the same track. It is important to note that for this study, the samples considered were ttbar events with either no pileup (PU) or PU=200. Greater pileup signifies more background particle tracks, and PU=200 gets us close to the expected conditions for the HL-LHC. These events were used because of the abundance of stub pairs that are considered in each case. Layer six is again used as an example in Figure 10, this time showing the difference after applying the consistency cut (as well as filtering out pT values less than 2 GeV).

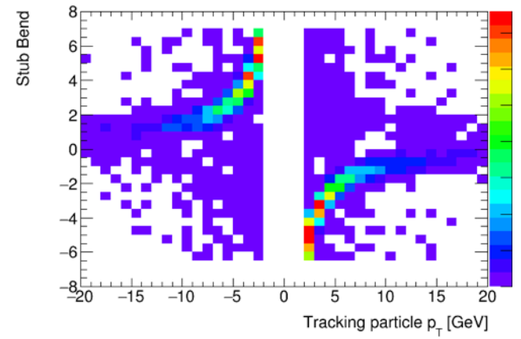

Figure 10. Stub Bend vs. TP pT for layer six after stub consistency cut.

	Layers 1 & 2	Layer 1 & Disk 1	Layer 2 & Disk 1	Layers 2 & 3	Layers 3 & 4	Layers 5 & 6	Disks 1 & 2	Disks 3 & 4	Total
PU=0	7.8%	6.6%	14.4%	11%	17%	26%	8.4%	8%	13%
PU=200	25%	24%	38%	32.6%	48%	63%	18.6%	18%	37%

Table 1. Percentage of stub pairs rejected.

Conclusion

Performance for the tilted barrel tracker approaches that of the flat barrel in general, besides some expected features for η and z_0 resolutions. In some cases, the tilted barrel geometry even offers an improvement in performance, such as the electron efficiency. Thus far, the consistency checks on stub bend are very useful for cutting down on the amount of stub pair combinations that need to be considered, even with very loose requirements. Looking forward, we are hoping that a fully realized bend consistency check will allow for greater precision in other parts of the algorithm. Overall, the results of these studies give us viable routes by which the algorithm can continue to be improved and prepared for the eventual upgrade of the CMS detector.

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About the Author

Patrick Shields is a senior physics and philosophy major at the University of Notre Dame. Patrick has been involved in the CMS Tracklet group at Notre Dame for about three years, primarily under the direction of Dr. Kevin Lannon and Dr. Michael Hildreth. He also spent his junior spring semester abroad in Geneva, Switzerland, working on-site at CERN for the same project, with Dr. Louise Skinnari. Post-graduation, he will be teaching in the Alliance for Catholic Education Teaching Fellows program for two years, after which he hopes to pursue graduate education in high-energy physics.

A Split Second in the Life of a Nucleus: Calculating Transition Probabilities Using Nuclear Lifetimes

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Abstract

Absolute transition probabilities are the cornerstone of understanding nuclear structure physics, in comparison to nuclear models. They allow one to compare the likelihood of transitions between different rotational states – larger probabilities imply more nucleons participating in the transition, and thus a greater possibility that the wave functions of those states are aligned. Transition probabilities can therefore be used to show which states are connected to each other by large matrix elements, and hence have a similar structure. These comparisons are used to draw conclusions about the overall structure of the energy levels of a nucleus. This work has focused on developing code, in Python and in Mathematica, to calculate absolute transition probabilities from measured lifetimes. Both versions of the code take parameters such as the lifetime of a given state, the energies and intensities of the gamma ray emitted in the decays from that state, and the multipolarities of the transitions to calculate the appropriate B(σλ) values. The programs account for mixing of radiation of different multipolarities and for the electron conversion of gamma rays to correct for their intensities, and yield results in absolute units or results normalized to Weisskopf units. This code has been tested against available data in a wide range of nuclei from the rare earth region, including $^{146\text{-}154}$Sm, $^{154\text{-}160}$Gd, $^{158\text{-}164}$Dy, $^{162\text{-}170}$Er, $^{168\text{-}176}$Yb, and $^{174\text{-}182}$Hf. Both versions will be available from the Notre Dame Nuclear Science Laboratory webpage for use by the community at Notre Dame and elsewhere in the world.

Introduction

For a group of radioactive nuclei, the rate at which the sample decays is proportional to a decay constant, also known as the transition probability. This constant can be expressed in terms of the mean lifetime or the half-life of a sample:

$$W = \frac{1}{\tau} = \frac{T_{1/2}}{-\ln(0.5)}$$

where τ is the mean lifetime, and $T_{1/2}$ is the half-life. One possible mode of decay for an excited nucleus is gamma decay, in which a nucleus decays from an excited state to a lower energy state through the emission of a photon. Gamma decays are labeled using "σλ" notation. In this notation, σ describes the electromagnetic character of the photon ("E" for electric or "M" for magnetic), and λ (λ = 0 for monopole, 1 for dipole, 2 for quadrupole, etc.) describes the multipole character of the radiation field produced by the emitted gamma ray (i.e. the angular distribution of the radiation, the parity of the radiation field, and the radiated power) (1).

An excited nucleus may have multiple gamma decay channels, meaning that it can decay from an initial state to multiple final states. For a nucleus with multiple gamma decay channels, the transition probability is given by the sum of all transition probabilities weighted by the branching ratio (BR_i) and the interval conversion coefficient (α_i) of each transition:

$$W = \sum_i W(i) = \sum_i \frac{BR_i}{\tau(1+\alpha_i)}$$

where the branching ratio gives the relative intensity of a particular decay compared to all other channels exiting a level, and the internal conversion coefficient accounts for the possibility of an atomic electron being ejected instead of a gamma ray being emitted from the nucleus.

Transition probabilities are proportional to the square of the nuclear matrix element that describes how a nucleus interacts with an external magnetic field in transitioning from an initial state ψ_i to a final state ψ_f. As such, the transition probability for a certain gamma decay can be used to calculate the nuclear matrix element for that transition. This can be used to understand how two states, ψ_i and ψ_f, are connected. We can extract information about the structure of excited states from both absolute and relative transition probabilities. Absolute probabilities are calculated when the lifetime of a nuclear state is known. They depend on the angular momentum dependencies of the initial and final states, represented by Clebsch-Gordon coefficients squared, and the matrix elements of those states squared. Absolute transition probabilities can be "reduced" or divided by the angular momentum dependencies (Clebsch-Gordon coefficients), to compare the matrix elements of transitions. For example, if two transitions had the same B(σλ) value, but different Clebsch-Gordon coefficients, dividing out the individual Clebsch-Gordon coefficients squared would yield different values for the matrix elements. If no lifetime exists for a level, we can still extract some information from the relative intensities of the depopulating gamma rays to determine relative transition probabilities. In contrast to absolute transition probabilities, relative transition probabilities are calculated for states with unknown lifetimes. Relative probabilities predict the likelihood that an initial state will decay to a certain final state, relative to other decays from the same initial state to different final states. Absolute probabilities extend this to calculate the probability of decay from a certain initial state to a certain final state, relative to all other decays within that nucleus.

The following equation is used to calculate absolute transition probabilities:

$$B(\sigma\lambda; J_i \to J_f) = \frac{\hbar}{8\pi}\mathcal{F}(\sigma\lambda)\frac{BR}{\tau(1+\alpha)}\frac{\lambda[(2\lambda+1)!!]^2}{(\lambda+1)}\left(\frac{\hbar c}{E_\gamma}\right)^{2\lambda+1}$$

In the equation above, the branching ratio (*BR*), the lifetime (τ), the internal conversion coefficient (α), the energy of the gamma ray ($E\gamma$), and the multipolarity of the radiation (λ) are all experimentally determined quantities. $\mathcal{F}(\sigma\lambda)$ is the multipole mixing fraction, which measures the mixing between gamma radiation of different multipolarities (e.g. electric quadrupole and magnetic dipole). For pure transitions, this factor collapses to unity. For mixed E2/M1 transitions it is given by the following equations:

$$\mathcal{F}(E2) = \frac{\delta^2}{1+\delta^2}$$
$$\mathcal{F}(M1) = \frac{1}{1+\delta^2}$$

These equations are used to calculate the probability of an E2 or M1 transition occurring, respectively. The multipole mixing fraction δ is defined as the ratio of the E2/M1 transition strengths.

Transition probabilities are dimensioned quantities, with units given by:

$$B(E\lambda): e^2\mathrm{fm}^{2\lambda}$$
$$B(M\lambda): \mu_N^2\,\mathrm{fm}^{2\lambda-2}$$

These units are known as absolute units. Another set of units, Weisskopf units (W.u.), is also commonly used to compare transition rates. The equations for determining the Weisskopf units, or single particle units, for a given nucleus are shown below for electric and magnetic transitions, respectively:

$$B_W(E\lambda) = \frac{1}{4\pi}\left(\frac{3}{\lambda+3}\right)^2 (0.12)^{2\lambda}A^{2\lambda/3}e^2\mathrm{fm}^{2\lambda}$$
$$B_W(M\lambda) = \frac{10}{\pi}\left(\frac{3}{\lambda+3}\right)^2 (0.12)^{2\lambda-2}A^{(2\lambda-2)/3}\mu_N^2\mathrm{fm}^{2\lambda-2}$$

Weisskopf units are defined as a function of the mass number *A* for each nucleus. A nucleus with *A* = 150, for example, then has a larger Weisskopf unit than a nucleus with *A* = 50. They are derived from Weisskopf estimates, estimates of the transition rates between two states (ψ_i and ψ_f) that assume that the transition is due to a single proton changing from one shell-model state to another. Dividing an experimental transition probability by the Weisskopf estimate and multiplying by a proportionality constant $(k\alpha hc/(100\mathrm{fm}^2)^2$, where $k = \lambda[(2\lambda+1)!!]^2/(\lambda+1)$ and $\alpha = e^2/4\pi\epsilon_o hc$), yields transition probabilities in terms of W.u.

Process

We have developed two programs, one written in Mathematica and the other in Python, to calculate transition probabilities for nuclei that gamma decay. Two different versions of the program have been developed to make the code accessible to a broader user base. To use either program, all that is required is the appropriate coding software, and software capable of generating a csv file (e.g. Excel or LibreOffice). Both programs read input from the csv file to calculate B(σλ) values. Figure 1 shows the necessary input parameters, and the order the parameters should take in the csv file. In Figure 1, E_γ is the energy of an emitted gamma ray (in MeV); I_γ is the intensity of the gamma ray (in arbitrary units); $I_{\gamma,\mathrm{tot}}$ is the sum of the intensities of all gamma rays exiting the level; δ_{mix} is the multipole mixing fraction for a particular transition (set to 0 if no mixing occurs); τ is the mean lifetime of the level (in fs); α_K is the internal conversion coefficient; *A* is the atomic number of the nucleus; σλ is the multipolarity of the transition; and E_{lev} is the level energy of the initial state (in keV). δE_γ, δI_γ, $\delta_{\delta\mathrm{mix}^+}$, $\delta_{\delta\mathrm{mix}^-}$, δ_τ^+ δ_τ^-, and $\delta_{\alpha K}$ are the uncertainties in their respective quantities. ($\delta_{\delta\mathrm{mix}^+}$ and $\delta_{\delta\mathrm{mix}^-}$, and δ_τ^+ and δ_τ^-, are upper and lower uncertainties in the multipole mixing fraction and the lifetimes, respectively.)

Elev (keV)	Eγ (keV)	Iγ	τ (fs)	πℓ	δ	B(πℓ) (cgs)
1049.48	960.51 (20)	138.0 (0)	$1810^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.055016^{+0.049298}_{-0.051165}$ e^2b^2
1049.48	960.51 (20)	138.0 (0)	$4750^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.020964^{+0.018781}_{-0.019502}$ e^2b^2
1129.44	1112.94 (20)	80.0 (0)	$1260^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.006144^{+0.005502}_{-0.006156}$ e^2b^2
1129.44	1112.94 (20)	80.0 (0)	$2590^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.002989^{+0.002677}_{-0.002995}$ e^2b^2
1129.44	1040.47 (20)	294.0 (0)	$1260^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.031334^{+0.028323}_{-0.031407}$ e^2b^2
1129.44	1040.47 (20)	294.0 (0)	$2590^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.015244^{+0.013779}_{-0.015279}$ e^2b^2
1129.44	841.24 (20)	119.0 (0)	$1260^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.036994^{+0.032597}_{-0.037125}$ e^2b^2
1129.44	841.24 (20)	119.0 (0)	$2590^{+0.0}_{-0.0}$	E2	$0.0^{+0.0}_{-0.0}$	$0.017997^{+0.015858}_{-0.018061}$ e^2b^2

Figure 2. Sample Output From the Python Program. The output above is calculated for ^{156}Gd transitions, and is calculated in absolute units. The LaTex-friendly tables generated by the Python script can easily be copied and pasted into a text editor.

Elev (keV)	Eγ (keV)	τ (fs)	πℓ	B(Eℓ) pure (MW.u.)	dB(Eℓ) pure (MW.u.)	dB(Eℓ) pure (MW.u.)
888.158	888.157	2830.	E2	-	-	-
888.158	807.503	2830.	E2	-	-	-
888.158	622.494	2830.	E2	-	-	-
1148.23	260.067	300 000.	E1	0.0504847	0.000789745	-0.000789745
1148.23	185.292	300 000.	E1	0.029498	0.00121694	-0.00121694
1275.77	1275.83	29.	E1	2.38548	0.402131	-0.402131
1275.77	1195.09	29.	E1	3.82255	0.722553	-0.722553
1357.92	1277.27	214.	E1	0.42655	0.00796866	-0.00796866
1357.92	1092.26	214.	E1	0.494245	0.0318184	-0.0318184
1485.67	1219.98	2910.	E1	0.0481726	0.00128821	-0.00128821
1485.67	937.144	2910.	E1	0.0399622	0.00266415	-0.00266415
1485.67	424.676	2910.	E1	0.0171904	0.00107492	-0.00107492
1485.67	302.909	2910.	E1	0.0375285	0.000987555	-0.000987555
1485.67	275.582	2910.	E1	0.0998938	0.00493333	-0.00493333

Figure 3. Sample Output From the Mathematica Program. The output above is calculated for ^{162}Dy transitions, and is calculated in W.u.

The majority of this work focused on rewriting and debugging portions of a previously existing code. The optional conversion from absolute units to Weisskopf units was added to both versions. In addition, the error propagation sections were edited to account for uncertainty on the lifetime measurements. This work also involved revising the Python version of the code

Figure 1. Required Format for an Input File. Depicts the parameters the two programs require, and the order in which the parameters should be entered in the csv input file.

Both the Mathematica notebook and Python script initially take user input to specify the location of the data file, the names of the output files, and units to be used (absolute units or W.u.). The Python script also takes user input to determine the precision to report in the calculated B(σλ) values. After reading in the input from the csv file, both programs use this input to execute transition probability calculations. The two programs are structured similarly and contain sections for calculating transition probabilities in absolute units, for converting from absolute units to W.u., and for error propagation. The Mathematica notebook yields PDF files as output (one each for transitions of each individual multipolarity and one containing all transitions) while the Python script outputs a text file, formatted in LaTex syntax. Figures 2 and 3 show sample output tables for the two programs.

to account for multipole mixing in the gamma rays emitted during decays.

This code was tested using available data from a range of rare-earth nuclei: $^{146\text{-}154}$Sm, $^{154\text{-}160}$Gd, $^{158\text{-}164}$Dy, $^{162\text{-}170}$Er, $^{168\text{-}176}$Yb, and $^{174\text{-}182}$Hf. Data for these calculations was obtained from the National Nuclear Data Center (NNDC) website, produced by Brookhaven National Laboratory (2). Output from the ^{156}Gd calculations was tested against B(σλ) values previously calculated (3), and the ^{158}Gd and ^{160}Gd output was tested against values calculated in literature (4, 5). Output from the ^{162}Dy calculations was tested against values previously found (6). The output from the two programs was tested against these known values to ensure that it reproduced the values calculated using other methods. Transition probabilities for the rest of the isotopes were calculated to verify that the code yields reasonable values for a variety of input data. The calculated transition probabilities were then used to produce schematics for selected rare-earth nuclides, as shown in Figure 4. These schematics will be used to draw conclusions about the characteristics of 0_n^+ vibrational bands and the collectivity of gamma decays in even-even rare-earth nuclei.

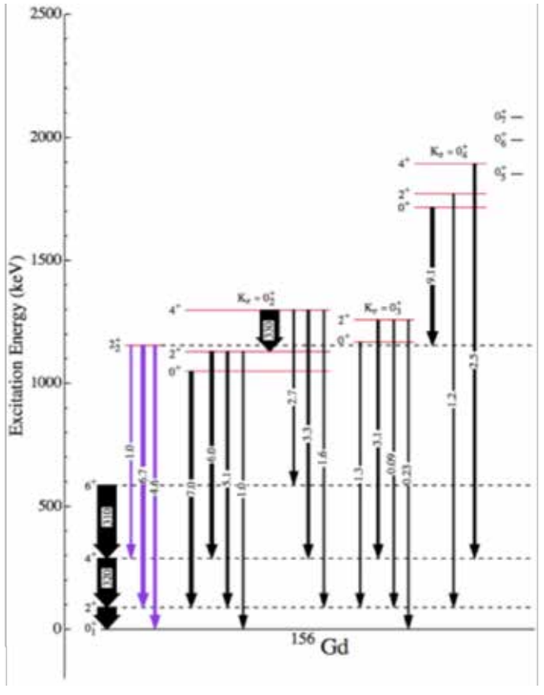

Figure 4. Level Scheme for ^{156}Gd. The Python code was used to calculate the transition probabilities (shown as the numbers on the arrows) for gamma decays from vibrational states in ^{156}Gd with recently measured lifetimes.

Conclusion

Absolute transition probabilities can be used to draw conclusions about the collectivity of nuclear transitions, which in turn provide information about the structure of vibrational states within a nucleus. As such, transition probabilities are a cornerstone of understanding in nuclear structure. The Mathematica notebook and Python script developed through this work are powerful tools for calculating absolute transition probabilities. The code requires minimal user input, can yield output in two sets of units, and accounts for multipole mixing in the emitted gamma rays. In addition, it returns uncertainties on the calculated values that account for errors in the every measured parameter in the calculations. Future work in this area will involve using the two programs to calculate B(σλ) values for newly measured excited states of nuclei and publishing the programs on the University of Notre Dame's webpage for public domain use.

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About the Author

Anne Stratman is a junior at Notre Dame double majoring in physics and math with a minor in the Glynn Family Honors Program. She has worked with Professor Aprahamian for nearly a year and a half and during that time has used the code described in this paper to do calculations for papers about excited states in ^{156}Gd and ^{158}Gd, and for a review of excited states of rare earth elements. Anne also participated in the National Science Foundation Research Experience for Undergraduates at Notre Dame last summer and presented the aforementioned research at the Division of Nuclear Physics Conference in October 2017. After graduation, Anne plans to pursue a Ph.D. in experimental physics and hopes to eventually work in renewable energy.

PHYSICS

Cisplatin Induced Gene Expression in Lung and Ovarian Cancer Cell Lines Reveal Specific and Shared Patterns

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Abstract

Lung and ovarian cancers will lead to over 168,000 deaths in the United States in 2018. Despite extensive research into the genetic nature of these types of cancers individually, broader relationships between the cancers are not as well understood. Cisplatin, a platinum-based drug which affects DNA replication, is used in the treatment of both lung and ovarian cancers. The goal of this research was to gain a more complete understanding of the relationship between lung and ovarian cancer treatment by examining the expression profiles of genes in cisplatin treated cell lines. Utilizing the Expression Atlas, a continually developing database of gene expression information created by the European Bioinformatics Institute, genes with significant expression changes following cisplatin treatment in ovarian cancer cells were identified. These genes were then evaluated in comparably treated lung cancer cells to identify similarities and differences. This study identified genes where expression changes were in discordant directions between treated lung and ovarian cells, where changes were in concordant directions with variable degree, and where there was little or no expression change in one of the tissues. Interestingly, this study identified three genes, MMP12, FAM9C *and* MEF2C, *which showed large expression changes in ovarian cancer cells but no detectable expression in treated lung cancer cells. These results suggest underlying gene expression relationships between lung and ovarian cancer cisplatin treatment and reveal further research directions, which could lead to more effective tissue-specific treatments of cancer with cisplatin.*

Introduction

There exists a large body of research investigating the gene expression profiles of the deadliest individual cancers, such as those of the lungs and ovaries (1, 2, 3). However, there remains a paucity of research comparing gene expression response across cancers to the same chemotherapeutic drug, such as cisplatin. Cisplatin is a widely used platinum-based drug. The drug affects dividing cells at the DNA level, crosslinking DNA and inducing cell apoptosis (4). Genetic factors have been implicated in its overall effectiveness, and the success of treatment varies widely between the host tissue of the cancer, with success rates as high as 85% in testicular cancer (5). Cisplatin is also of particular interest as it is a more cost-effective treatment option compared to many other chemotherapeutic drugs and has the potential to treat cancer in developing regions across the world.

Previous studies have investigated genes implicated in cisplatin function, such as *ERCC1* and *RRM1*, across cancer types. Examinations of these genes have not revealed major differences between cancer types due to the genes' involvement in wider cellular functions such as DNA repair (6). To identify differences in the characters of cancer types, novel genetic relationships may provide insight into more specific similarities and differences between cancers. This idea is supported by research that shows that differences in production of reactive oxygen species (ROS), which is influenced by more novel genetic differences, has been associated with success of cisplatin treatments in cervical, ovarian, and lung cancers (7, 8).

The objective of this study was to examine gene expression changes following cisplatin treatment to identify both tissue specific and more global expression patterns. Specifically, genes with significant expression changes, both upregulated and downregulated, in ovarian cancer carcinoma cells treated with cisplatin were then assessed in non-small cell lung cancer carcinoma cells following similar cisplatin treatment. The similarities and differences in gene expression were then used to compare the two cancer types, especially in the context of other observable differences in the genetic character of lung and ovarian cells.

Materials and Methods

Identification of Genes in Ovarian Cells

Genes of interest were identified using Expression Atlas, a database consolidating expression profiles from a number of bioinformatics projects including the Human Protein Atlas, GTEx, FANTOM5, ENCODE, CCLE and Genentech (9).
Genes with significant fold changes, where p<6.0 •10-6, in A2780 ovarian carcinoma cells treated with cisplatin under normal cell culture conditions were identified and prioritized for evaluation in A549 cells. Figure 1 depicts the workflow once genes were identified.

Testing Gene Expression Changes in Treated Lung Cells

A549 human non-small cell lung carcinoma epithelial cell line was grown at 37°C, 5% CO_2 in a humidified incubator. Cells were counted and treated with 5 µM cisplatin or vehicle. Cisplatin was obtained from Sigma. The cells were incubated and harvested at 3, 18, 24, and 48 hours following treatment. Cells were pelleted, and total mRNA was isolated using Illustra RNAspin mini RNA isolation kit according to manufacturer's protocol. RNA quality assessment and quantification were conducted using the optical spectrometry 260/280 nm ratio using a nanodrop. mRNA was reverse transcribed to cDNA using Applied Biosystems High Capacity Reverse Transcription Kit, to a final concentration of 25 µg/µL. cDNA was diluted to 1.25 ng/uL, and quantitative RT-PCR value was measured in triplicate using TaqMan Gene Expression Assays by Life Technology on the StepOne Plus RT-PCR system. Beta-2-microglobulin (B2M) was used as endogenous control. Fold change was independently calculated for each sample, and these values were combined.

Determining Expression in Healthy Tissues

The Genotype-Tissue Expression program (GTEx) was utilized to provide baseline expression values for each of the genes in healthy, noncancer tissues not under any drug treatment (10). Expression in tissues of interest, ovarian and lung, was evaluated as well as expression in two comparison tissues, mammary and testicular tissue, chosen due to the frequent use of cisplatin in cancers in these tissues.

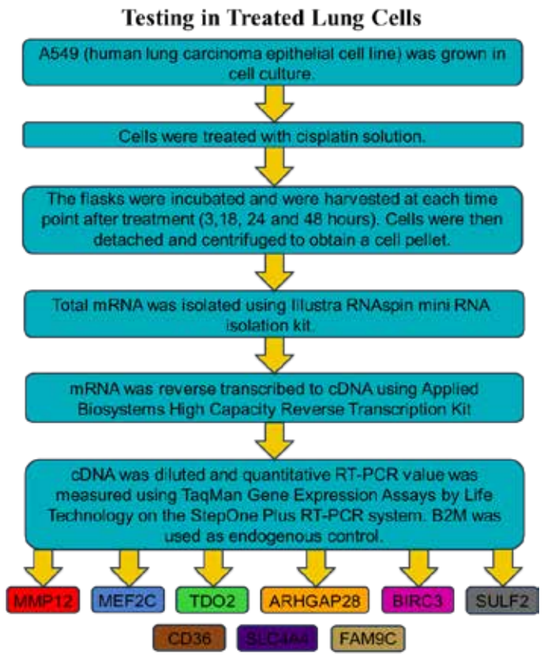

Figure 1. Outline of the process of cultivating lung cancer cells, treatment with cisplatin, and testing of gene expression in treated cells at different time points following treatment.

Results

Nine genes' expression profiles were identified with significant (p<6.0 •10-6) fold change ranging from 3.3 to 7.1 in cisplatin treated ovarian cancer A2780 cells: *MMP12*, MEF2C, *FAM9C*, *ARHGAP29*, *TDO2*, *SULF2*, *BIRC3*, *CD36* and *SLC4A4* (Fig. 2). Two of these genes, *MEF2C* and *ARHGAP29*, exhibited significant down regulation. All others exhibited significant upregulation.

Expression changes of these genes were then evaluated in cisplatin treated non-small cell lung cancer cells A549 (Fig. 3). *MMP12* (Fig. 3A) exhibited no expression in treated lung cancer cells. *MEF2C* (Fig. 3B) and *FAM9C* (Fig. 3C) exhibited so little expression in treated lung cancer cells as to be unmeasurable. Further tests with twice the amount of cDNA still did not yield measurable expression. In treated ovarian cancer, *MMP12* and *FAM9C* experienced upregulation with a fold change of 7.1 and 7, respectively, while *MEF2C* had downregulation with a fold-change of -6.9.

ARHGAP28 (Fig. 3D), *TDO2* (Fig. 3E), and *SULF2* (Fig. 3F) displayed significant expression changes in cisplatin treated non-small cell lung cancer with magnitude changes with an absolute value of less than 20% compared to respective -6.4-, 6.1- and 3.2-fold change in ovarian cells. In *ARHGAP28*, p=.02186 at hour 3; in TDO2, p=.04589 at hour 3 and p=.02476 at hour 18; in *SULF2*, p=.02722 at hour 3. *CD36* (Fig. 3G) exhibited significant negative expression change below -35% in treated lung cancer. In *CD36*, p=.01481 at hour 18. In ovarian cancer, *CD36* exhibited significant positive gene expression change. *SLC4A4* (Fig. 3H) and *BIRC3* (Fig. 3I) exhibited no significant expression changes in lung cancer. All genes were found to be expressed in healthy, untreated ovarian and lung cells by the GTEx program (Fig. 4).

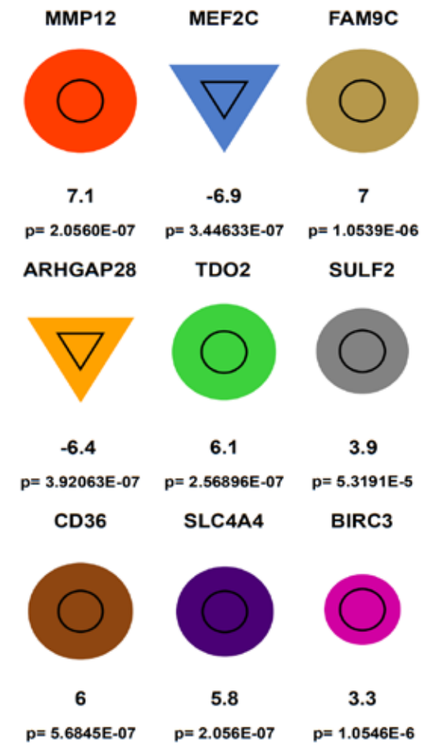

Figure 2. Gene expression fold-changes for cisplatin treated ovarian cancer cells. Circles represent genes with positive fold-change; triangles represent genes with negative fold changes. Genes were selected on a basis of absolute value of fold-change and low p-values.

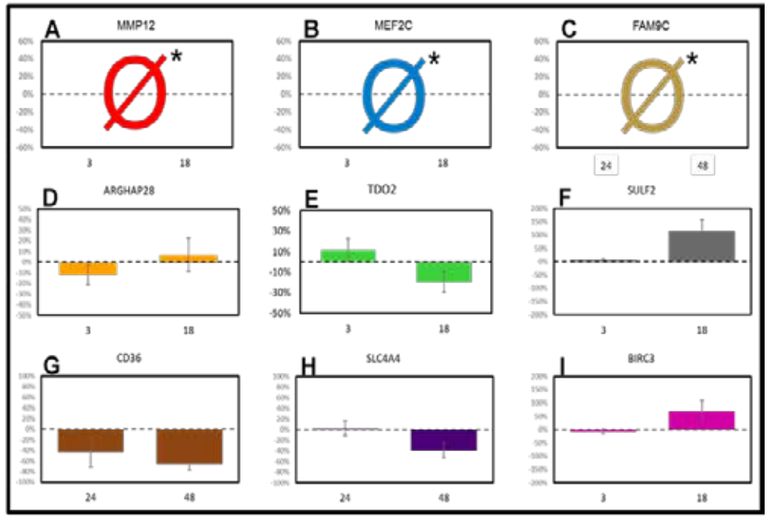

Figure 3. Results of qPCR in treated lung cancer cell lines over time. A, B, D, E, F, and I were evaluated at 3 and 18 hours. C, G, and H were evaluated at 24 and 48 hours.

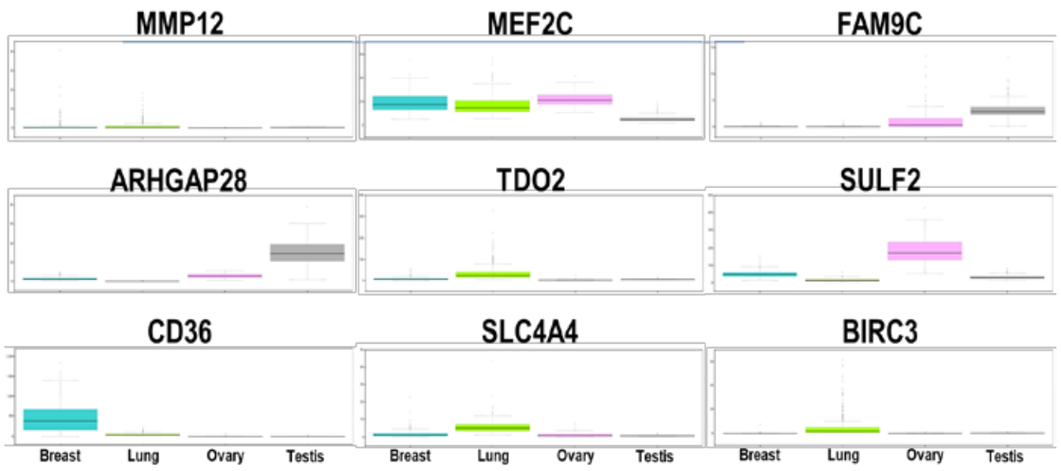

Figure 4. Gene expression levels in healthy breast, lung, ovarian and testicular tissue. GTEx provides analysis of a total of 53 tissues across 714 donors (10).

Discussion

This study suggested four major relationships in the gene expression changes induced by cisplatin in A549 (non-small cell lung cancer) and A2780 (ovarian cancer) cells. First, no measurable expression of a gene in treated lung cancer which showed significant expression change in ovarian cancer, as in *MMP12*, *MEF2C* and *FAM9C*. Second, the absence of a high magnitude gene expression change in treated lung cancer with high magnitude change in treated ovarian cancer, as in *ARHGAP28*, *TDO2*, and *SULF2*. Third, discordant expression change in treated lung cancer as in ovarian cancer, as in *CD36*, and finally the lack of any expression changes as in *BIRC3* and *SLC4A4*.

The first of these relationships, where gene expression was not measurable in treated lung cancer, was the most unexpected and potentially the most worthy of experimental follow-up. *MMP12*, *MEF2C* and *FAM9C* are expressed at an observable level in healthy lung cells, healthy ovarian cells, and cisplatin treated ovarian cancer cells. The lack of detectable expression in cisplatin treated lung cancer cells suggests that these genes may help explain fundamental differences between cancer's response to cisplatin therapy. Each gene's expression is significantly affected by cisplatin treatment in A2780, suggesting that the genes may be related to the drug's mechanism of action in ovarian cancer. Two of the tested genes, *MMP12* and *FAM9C*, showed upregulation while the third, *MEF2C*, showed downregulation, suggesting that differences occur in both regulatory directions. The lack of expression of these genes in cisplatin-treated lung cancer cells could explain major differences in the effectiveness of cisplatin in each cancer and the ability of cancers in each tissue to develop cisplatin resistance.

Of the three genes exhibiting this pattern, *MMP12* is especially noteworthy in the context of existing research. There has been relatively little study on the function of *MMP12* in lung cancer, but previous studies have implicated expression of the gene with other processes in the lung. *MMP12* has been associated with the risk of developing Chronic Obstructive Pulmonary Disease (COPD) and general lung function (11). *MMP12* was found to potentially influence pathogenesis of COPD and asthma. *MMP12* has also been implicated in the function of adenocarcinomas in lung tissue; knockdown of *MMP12* has been shown to inhibit the growth and invasion of adenocarcinoma cells in lung tissue (12). *MMP12* may play an important role in the specificity of lung tissue and affect the development of diseases within the lung ranging from asthma to cancer. The absence of expression of *MMP12* in lung cancer cells treated with cisplatin when compared to other tissues is interesting, and further research may help reveal a more complete understanding of this difference.

MEF2C and *FAM9C* also have the potential to reveal similarly interesting patterns in future studies. Neither gene has been studied specifically within the context of lung tissue or lung cancer, and further research could provide a better understanding of why these genes are not expressed in lung cancer. Understanding these changes in relation to ovarian-specific cisplatin changes remains a promising area of focus.

The second major relationship observed (treated lung cancer cells) showed absence of a high magnitude gene expression change as measured in ovarian cancer cells, in *ARGAP28*, *TDO2*, and *SULF2*, also indicates differences in tissues specificity between the two cancer types. Expression changes in ovarian cancer show that these genes experience regulation changes with the cisplatin treatment, while the lack of change in lung cancer suggests a different interaction or no interaction at all. This sort of difference may have major effects on the reaction a cancer in each tissue has to cisplatin and may help develop an understanding of the differences in response of these cancers. Further research could explore the expression changes of these genes in other cancers following cisplatin treatment, to create a more rounded understanding of the role these genes may play in cancers throughout the body. Taken with the first expression pattern, these results suggest the genes could be prioritized in ovarian cancer cells treated with cisplatin for therapy optimization.

A similar approach could be used in examining the third relationship shown in *CD36*, where gene expression change was in a discordant direction in cisplatin treated lung cancer compared to ovarian cancer. This pattern suggests an even stronger difference between the cancer types, as the gene is shown to interact with cisplatin across the cancer types but in opposite ways. Genes exhibiting such a pattern may also influence tissue specificity similar to the second relationship outlined above. A deeper understanding of these genes in specific tissues may be useful in treating cancer with cisplatin, especially when opposite direction relationships may point to major differences in how cancers of different tissues react to similar cisplatin treatments. Further testing could be undertaken to examine this pattern in the context of more varieties of cancers, if they are shared between cancers that are effectively treated with cisplatin, or if other interesting patterns are apparent between other cancer types.

Beyond the patterns of difference, this study also found lack of regulatory changes in lung cancer cells despite seeing upregulation in ovarian cancer cells as seen in *SLC4A4* and *BIRC3*. The lack of significant expression change from vehicle again suggests some underlying difference between how the two tissues respond to cisplatin treatment. This difference can be further researched and could help generate treatment optimizations in each cancer.

The possible limitations of this study are related to the concepts that also make this research compelling. The differences between the tissues could yield to dosing differences between the tissues studied and the related, potential differences in time course. Similar cisplatin treatments applied to cancers of disparate tissues may not reflect the dosages necessary to reach a fully comparable effect. Comparing time courses in this study may not full describe the relationships between the cancers. This study utilized two time points for each gene studied, though those time points varied between 3 and 48 hours. The full range of expression change across the time course was not investigated in this study, meaning some patterns of change may not have been identified.

This study identified different relationships between lung and ovarian cancers treated with cisplatin and offers a number of future research directions. These results support the idea that the comparison of gene expression induced by chemotherapy of cancer cells can reveal interesting and potentially useful patterns that may help inform an understanding of both the biology of cancers and how to more effectively treat them. In the future, comparative approaches to studying cancers will reveal information that contributes to an understanding of each type of cancer individually and broader concepts of how cancer functions across its many subtypes.

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