

The Warren Roundup

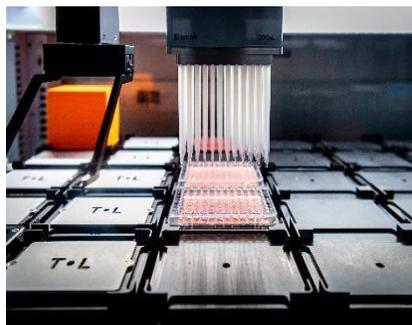
Warren Family Research Center for Drug Discovery

Director's Note~

As the 2018 academic year comes to an end, a summary of this year's accomplishments is provided in the annual Warren Roundup. First of all, several lead compounds have been identified by Notre Dame researchers and are undergoing preclinical evaluation, in hopes of identifying investigational new drugs (IND) for clinical evaluation. In fact, multiple companies have been started by Notre Dame Researchers to accelerate the drug discovery process, and in several cases, collaboration with the pharmaceutical industry has taken place to further accelerate the discovery of new drugs. New instruments have been acquired via grants and financial support from the Scholl's Foundation, which can be used by members of the Warren Center and are listed on the last page of this newsletter. All three cores (computational, synthesis, and biological) are available to researchers at Notre Dame. Finally, the Warren Center recently received an endowment from the Filipi Family to support a graduate

student fellowship in the area of neuroscience research, with a focus on drug discovery. An RFA for this fellowship will be announced in the summer and a fellowship will be awarded during the next academic year.

Drugs in the Pipeline



Professors Mobashery and Chang continue to develop a drug for the treatment of diabetic wound healing and it is hoped that a molecule will enter clinical trials within the next two years (see SalvePeds article). Koren and Blagg are working with a venture capitalist firm and pharmaceutical company to develop a new treatment for glaucoma, which is hoped to enter clinical evaluation within the next 1–2 years. Hsiri Therapeutics (Miller and coworkers) signed a licensing agreement with Shionogi and

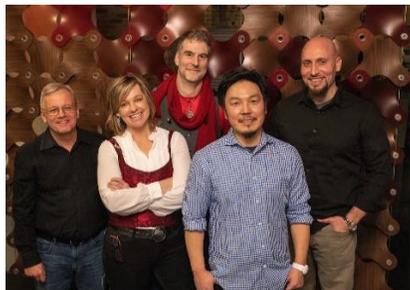
hope to develop a new antibiotic through this collaboration (see New License article). Mishra and Blagg are spinning off Grannus Therapeutics, which aims to develop new anti-cancer agents. Structured Immunity (Baker and colleagues) was launched in 2017 with the goal of partnering with established immunotherapy companies to help improve and optimize therapeutic pipelines via structural and computational biology. Having had initial success, the company is currently pivoting, with the aim of using its technology to develop immunological therapeutics for rare cancers. An investigational new drug, developed by the Blagg Lab, continues to undergo clinical evaluation for the treatment of neuropathy.

By the Numbers

Warren Center Researchers include 26 principal investigators, 40 postdoctoral researchers, 99 graduate researchers, 20 research scientists, and 98 undergraduate researchers, which when combined published 128 scientific articles

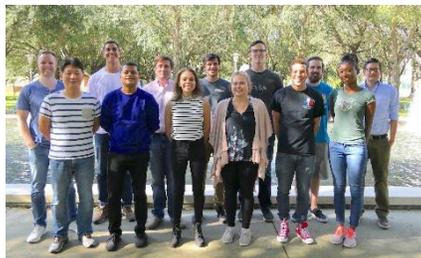
in 2018, have spun off at least 5 start-up companies, and have requested more than \$40 million dollars in federal grant support.

Celebration



The first annual Warren Center Christmas Party was held in McCourtney Hall on December 15th to celebrate recent successes and to promote additional interactions. All PI's and their group members were invited to "Eat Drink and be Merry". Approximately 130 people attended. Entertainment was provided by The Standard Deviants (pictured above), featuring our very own Dr. Brian Baker and Dr. Shaun Lee. Great fun was had by all, and we look forward to celebrating new accomplishments this next December.

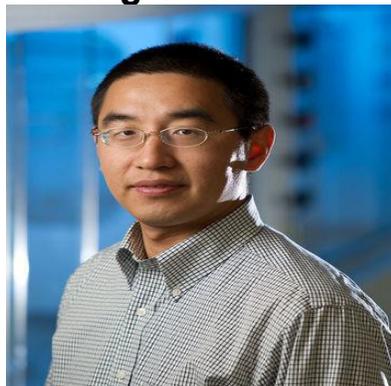
Juan Del Valle Joins Notre Dame



Juan received a B.S. in Chemistry from Carleton College in 1999 and a Ph.D. in Organic Chemistry from the University of California San Diego in 2004. After

postdoctoral studies at the University of Montreal (2004-2006), he joined the faculty of the Department of Chemistry & Biochemistry at New Mexico State University. In 2009 he moved his laboratory to the Moffitt Cancer Center at the University of South Florida and was promoted to Associate Professor of Chemistry at the University of South Florida in 2014. Juan's research program lies at the intersection of organic synthesis, chemical biology, and drug discovery. His laboratory is particularly interested in the structure-based design of peptide mimics and small molecules that target signaling pathways implicated in various diseases. At Notre Dame, Juan's group will continue their efforts to synthesize and develop (1) disruptors of protein-protein interactions for the treatment of cancer and neurodegenerative disorders, (2) small molecules to inhibit stress response mechanisms critical to malignant progression, and (3) biologically active peptide natural products with untapped drug development potential.

Featured Faculty – Haifeng Gao



Haifeng Gao received his B.S. degree in 2000 and M.S. degree in 2003 both in Polymer Science from Fudan University, China. He came to the United States in 2004 and received his Ph.D. degree in Chemistry from the Matyjaszewski group at Carnegie Mellon University in 2008. After two-years of postdoctoral experience (2009-2011) with the Frechet group at the University of California Berkeley, Haifeng joined the University of Notre Dame as an Assistant Professor and was promoted to Associate Professor with tenure in 2017 within the Department of Chemistry & Biochemistry. Haifeng's research interest is primarily focused on the design and synthesis of functional polymers with controlled nanostructures and determining their fundamental structure-property relationships. These nanostructured polymers can be used as materials for polymer catalysts, polymer membranes, and delivery nanocontainers for therapeutic drug molecules and diagnostic imaging probes. Haifeng has co-authored more than 80 peer-reviewed papers, 7 book chapters and co-edited two books. Haifeng was the recent recipient of 2010 AkzoNobel Award for Outstanding Graduate Research in Polymer Chemistry from the ACS, 2014 Army Young Investigator Program (YIP) award, and a 2016 NSF CAREER award.

New Hope



At Notre Dame, SalvePeds—which translates to “saving feet” in Latin—is a new startup company founded by two Notre Dame faculty members and an alumnus, researching the disease in search of clinical options to treat diabetic foot ulcers and to help mitigate some 100,000 annual amputations in the United States alone, 50% of which prove fatal. The Center for Disease Control and Prevention predicts that one in three American adults will suffer from diabetes by 2050. SalvePeds is founded by Drs. Mayland Chang, Shahriar Mobashery, and Trung Nguyen. Dr. Mayland Chang is a research professor of chemistry and biochemistry, with extensive drug discovery and development experience in big pharma. Dr. Shahriar Mobashery is the Navari Professor of Life Sciences, and Dr. Trung Nguyen worked for five years side by side with Drs. Chang and Mobashery to develop this drug. ND-336 was developed in the laboratories of Drs. Chang and Mobashery, to counteract the underlying condition of the ulcer, inhibiting the sustained inflammation and promoting the body’s biochemical response in healing of the wound. ND-336 shows superior efficacy in diabetic mice than the only presently approved drug that is not standard-of-care. With a recently awarded \$4.6 million Therapeutic Development Award from the Department of the Army, ND-336 is currently going through Investigational

New Drug testing with the goal of starting phase I clinical trials in 2021. Dr. Chang has a personal investment in studying diabetic foot ulcers. Her mother and aunt both had diabetes and died prematurely. Her sister is diabetic and Dr. Chang is prediabetic. Studies have shown that an estimated one in four diabetic patients develop foot ulcers throughout their life, which are notoriously difficult to heal and can result in lower-limb amputations. SalvePeds offers a solution to the current ineffective methods in addressing this condition.



Featured Faculty— Matthew Webber



Matthew Webber is an Assistant Professor in the Department of Chemical & Biomolecular Engineering and holds a concurrent position in the Department of Chemistry & Biochemistry. Matt received his B.S. in Chemical Engineering in 2006 from the University of

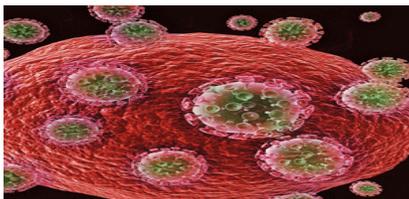
Notre Dame and a PhD in Biomedical Engineering in 2011 from Northwestern University. From 2012-2016 he was a NIH-NRSA postdoctoral fellow at Massachusetts Institute of Technology within the Koch Institute for Integrative Cancer Research. He joined the faculty at Notre Dame in 2016. His research group, based in McCourtney Hall, applies materials chemistry and supramolecular recognition to develop new strategies for drug delivery. He is especially interested in leveraging high-affinity interactions between host and guest molecules to facilitate recognition in the body for minimally invasive routes of spatiotemporal therapeutic control. He is also interested in engineering the thermodynamic pathway of self-assembly under directive cues from biological metabolites or disease indicators, as a means of accessing responsive therapeutics and life-mimicking synthetic materials.

New License



Hsiri Therapeutics, Inc., located in Media, PA, has entered into a license agreement with Shionogi & Co., Ltd. Hsiri Therapeutics, Inc., which was founded by two Notre Dame

graduates, works on the treatment of mycobacterial diseases, drug resistant gram-negative bacterial infections, and drug-resistant anaerobic bacterial infections. Shionogi is a leader in small molecule drug discovery and advancement in the antibacterial area. Terms of the agreement allow Shionogi the right to develop, manufacture, and commercialize the compounds worldwide. Through this license agreement, they are working to discover and develop novel therapeutics for non-tuberculous mycobacterial (NTM) diseases and tuberculosis (TB). The compounds are expected to be more effective than the present therapies for mycobacterial infections. These compounds originated in the lab of Marvin J. Miller, the George and Winifred Clark Professor of Chemistry and Biochemistry Emeritus at Notre Dame.



New Collaborations



Warren Family Research Center has established a number of partnerships in an effort to

identify potential treatments for glycogen storage diseases (GSDs) such as Cori (GSD III) and Pompe disease (GSD II). GSDs are inherited errors in metabolism due to irregular production or failure of the breakdown of energy stored as glycogen of which there is no current cure. Professor Rich Taylor initiated the effort by identifying potential similarities between Cori disease and Lafora disease and researchers on Lafora at Indiana University School of Medicine (IUSM). A collaboration between the Warren Center and IUSM has now developed a mouse model of Cori disease. However, mouse model systems are not ideal for high-throughput screening. Thus, the Warren Center began working with Perlara, a rare disease drug discovery company. Perlara's approach utilizes simple animal models such as worms and flies that have parallel genetics to humans. Over the past few months, Perlara created two worm models of Cori disease and a fly model applicable to Cori and Pompe diseases. Modelis, another rare disease drug company, has been added to the GSD collaboration, who will utilize the worm models and develop an additional zebrafish model of Cori disease. Compounds identified by Modelis' screens will be optimized for proper pharmacological properties in the core facilities of the Warren Center and be further evaluated in the mouse models.

The Filipi Family Graduate Fellowship to be Awarded Fall 2019

When it comes to the support of their favorite football team, Rev. Jody Leahy Filipi and Dr. David H. Filipi have a "mixed-marriage" as she is a Notre Dame fan and he roots for the Nebraska Cornhuskers. However, they are one when it comes to their efforts in philanthropy, international mission, and other aspects of their life together. Jody Leahy Filipi grew up in a large Catholic family. Her father, James J. Leahy MD '42, passed his love of Notre Dame to his children. One of her brothers, Kevin B. Leahy PhD, graduated from Notre Dame in 1974. Jody has two master's degrees. She has an MS in Speech-Language Pathology from the University of Nebraska – Omaha and her Certificate of Clinical Competence in that field. Over the years, Jody has been a speech-language therapist, stay-at-home mom, president of a children's' chorus, an executive director of a physicians' organization, and an editor of a monthly magazine and a weekly e-zine, a pastor and a volunteer in mission. In 2001, she earned her second master's degree, an M. Div. from Bethel Seminary in St Paul, MN and was ordained as a minister of word and sacrament in the Presbyterian Church-USA. As a pastor, she served several congregations and developed a passion for mission in partnership. In retirement, she continues to be involved in mission, serving as the chair of a non-profit working internationally in partnership

with organizations in post-totalitarian countries and fragile communities. Jody, also, enjoys watching their adorable grandchildren on a regular basis. Dave is a 4th generation Nebraskan. He grew up the only child of Paul and Frances Filipi. Like David, both his parents, went to the University of Nebraska in Lincoln and were strong supporters of the Cornhuskers. At Lincoln, he studied philosophy. Then David attended the University of Nebraska Medical Center to earn an MD in 1974 and completed his family medicine residency there. He joined the Physicians Clinic in Omaha in 1977 and practiced family medicine for 20 years when he moved into administration, becoming the medical director of the clinic which had grown to 150 physicians. While serving in this capacity he earned an MBA from the University of Nebraska Omaha. He retired from the clinic and almost immediately went to work for Nebraska Blue Cross-Blue Shield as its chief medical officer until 2016. Technically retired, Dave keeps busy in the medical field as a consultant and as medical director of more than one organization, including the Physicians Assistants program at the College of St. Mary's in Omaha where he also teaches. David and Jody have two grown children. Krystin and her husband, Joel Marsh, live in Omaha and are the parents of Magnolia (Noli) and Ansel. Their son, James B. Filipi PhD, lives in Portland OR. Dave and Jody love family time, traveling, reading, history, art museums, swimming and snorkeling. For

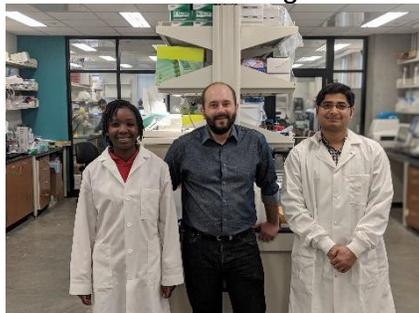
the past several years they have been adapting to changes in their life as David has a rare disease, Spinal-Cerebellar Ataxia. The doctors are unable to give them a prognosis for his disease and treatment consists of treating symptoms and figuring out how to adapt and cope with this debilitating illness. Jody is very proud of how David has adapted and learned to cope so he can continue doing what he loves. Hearing about Warren Family Center for Drug Discovery and Development at Notre Dame, the two decided to start an endowment which would help fund neuroscience research. They are excited to set up this endowment to help improve the quality of life for others with neurodegenerative diseases.

The Biological Screening and Development Core

The Biological Screening and Development (BSD) Core provides access to equipment and expertise for the biological and translational assessment of chemical compounds. The core offers many services to the Notre Dame research community; including consultation, design, development, miniaturization, and implementation of high-throughput assays to your research needs. The core can provide expertise and technologies to assist with and perform pharmacokinetic (PK), pharmacodynamic (PD), and bio-distribution studies for lead compound development using our Agilent Triple Quad LCMS – the gold standard for IND

enabling studies. We offer a full range of ADME-T services for small molecule development using high-throughput pre-clinical screenings; these assays include: Microsomal Stability, Primary Hepatocyte Toxicity, Caco-2 Permeability and Transport, Plasma Stability, Plasma Protein Binding, hERG Interaction, AMES Mutagenicity Test for frameshift and point mutations, and Blood-Brain Barrier Permeability (via PAMPA). We will be expanding our capabilities to include CYP induction and CYP inhibition in the near future. The core is capable of generating and purifying recombinant proteins for numerous in vitro assays; including Kd determinations using our new Nanotemper Microscale Thermophoresis platform. Additionally, we utilize a state-of-the-art Biomek i7 Dual-Arm Liquid Handling Automation Platform, Cytation5 plate-reader with our ALPHA capabilities, tunable fluorescence and luminescence, our dedicated Agilent 6460 triple quad LC-MS with 1290 autosampler, and GE's AKTA FPLC to deliver reliable data in a timely and cost-effective manner. Dr. John Koren III is the director of the Warren Center's Biology and AMDET/DMPK facility and runs the facility with his staff scientist Monimoy Banerjee and technician Vitumbiku Munthali. John's independent research focuses on the pathophysiology of Alzheimer's disease, combination anticancer strategies and patient profiling, developing small molecules for mental health disorders, and

studying the molecular mechanisms of glaucoma.



For more information, please contact:

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The Chemical Synthesis Core

The Chemical Synthesis and Drug Discovery (CSDD) Facility supports translational biomedical research by providing expertise that enables the preparation of small molecules for use in hit verification, lead development, and midsize scale up. In addition, the core prepares biological probes (affinity or fluorescently tagged), active pharmaceutical agents as experimental controls, and small chemical libraries for structure-activity relationships as well as the optimization of pharmacological properties. The CSDD is also charged with organizational oversight of compounds from past, current, and future chemical synthesis endeavors for establishment of the Notre Dame Chemical Compound Collection, which currently contains ~3000 unique chemical entities. The CSDD is staffed with PhD level scientists (postdoctoral associates and a research scientist) with

expertise in multi-step organic synthesis, medicinal chemistry, parallel development, and purification and isolation of small molecules and natural products. Services Offered:

- Parallel synthesis of small molecule libraries
- Single compound preparation (10 mg to 20 g)
- Synthesis of biological probe molecules
- Peptides Synthesis
- Purification of complex mixtures
- Sample plating/distribution
- Project development
- Consultation

For more information, please contact:

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The Computational Core

The Notre Dame Computer Aided Molecular Design (CAMD) Core Facility of the Warren Family Research Center for Drug Discovery and Development aims to provide a full range of computational support, from atomistic modeling to assistance in proposal writing, for drug discovery and related areas to all groups on campus. CAMD computational scientists have extensive expertise in virtual screening for inhibitor design, including docking, scoring, MM/PBSA, library selection and similarity search. CAMD expertise in molecular dynamics extends from standard MD to advanced methods, such as Long Timestep Molecular Dynamics (LTMD), Free Energy Free Energy Perturbation, and

Nudged Elastic Band simulations. CAMD expertise in electronic structure calculations encompasses density functional theory (DFT), correlated quantum mechanics (QM) and hybrid quantum/classical calculations (QM/MM). In addition to utilizing existing methodology, CAMD is actively developing new methods, such as Q2MM and Ensemble Rescoring. CAMD expertise extends to pharmacokinetics and predictive modeling, encompassing quantitative structure-activity relationships (QSAR), cheminformatics, library and ligand-based design, and network analysis.

For more information, please contact:

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Three Researchers Awarded Grants to Expedite Drug Discovery

During the fall of 2018, a request for applications was announced to assist Notre Dame researchers with the drug discovery process. Each researcher was awarded up to \$25,000 to cover the cost of research performed within the Warren Center. Researchers awarded this year grants include Professors Brandon Ashfeld, Katherine White, and Rich Taylor. Congratulations. Another request for applications will be announced in the fall of 2019 and will encourage utilization of the three cores.

New Instruments for use by Warren Center Members:



High-throughput assay development.

Dedicated technical staff and Beckman-Coulter Dual-Arm Biomek i7 Automation platform integrated with automated cell culture incubation and BioTek Cytation 5 microplate reader complete with tunable fluorescence, absorbance, luminescence, and ALPHA capabilities.

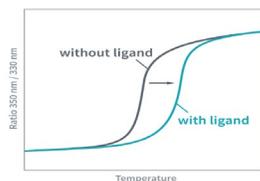


Agilent 6460 Triple Quad LC/MS

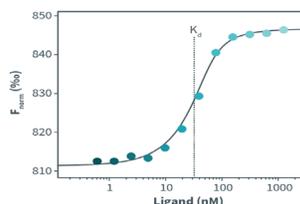
Streamlined and quantitative pharmacokinetics, bio-distribution, drug metabolism, & compound detection.



Agilent Seahorse XFe96 96-well cellular energetics, metabolism, and metabolic phenotyping



Determine functionality with a quick test of interaction between two molecules



Latest: nanoTemper Tycho and Monolith NT.115 Pico Tycho – Capillary based label-free detector of protein purity or ligand-protein interactions.

Monolith – Quantitative determination of K_d values from protein-protein or ligand-protein interactions by MicroScale thermophoresis.

Seminar Speakers?

If you would like to nominate a guest lecturer with strong expertise in drug discovery, please forward their name to wrcadmin@nd.edu, as we plan to invite 2– 4 “Warren” Lecturers during this next academic year.