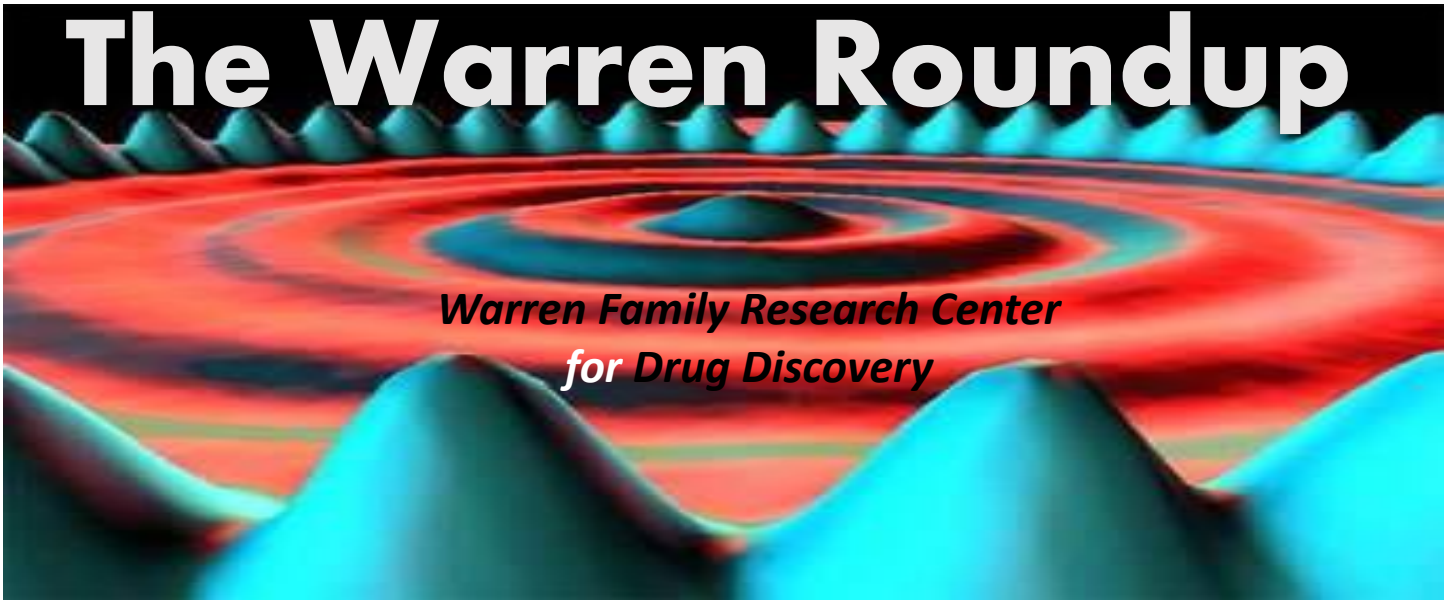
The Warren Roundup



Director's Note– Welcome to the first edition of the Warren Roundup, wherein an attempt is made to summarize accomplishments by members of the Warren Family Research Center for Drug Discovery. In addition, you will find below a succinct summary of the services provided by each of the three scientific cores (synthesis, computational, and biological). Not only do I invite you to provide updates for inclusion in upcoming issues, but I also encourage you to learn more about the Warren Center cores and how they can help expedite your research.

New Drugs in the Pipeline

Research in Mayland Chang's and Shahriar Mobashery's laboratories on the molecular basis for why diabetic foot ulcers (DFUs) do not heal and what can accelerate wound healing has led to the discovery of a new target, matrix metalloproteinase (MMP)-9 and a first-in-class small molecule inhibitor, referred to as ND-336. The technology was licensed to Well Zeus for the Chinese market and is being negotiated by SalvePeds for the US, Europe, and Japan markets. DFUs affect 1 million diabetic patients in the US alone every year. Current treatment options are few and ineffective, resulting in 100,000 annual lower-limb amputations in the US. Prognosis after a lower-limb amputation is poor, with a one-year mortality rate of 50%. There is a single FDA-approved drug, Regranex™, a recombinant growth factor, but it is not standard-of-care due to increased risk of cancer and death. ND-336 is more efficacious than Regranex™ at accelerating wound healing in diabetic mice. Investigational New Drug (IND)-enabling studies are underway with the goal of starting phase I clinical trials in July 2019.

Structured Immunity

Immunotherapy has rapidly become the "4th pillar" of cancer therapy, leading to new drugs and entirely new approaches to treatment. In the newest form of immunotherapy, termed adoptive T cell therapy, a patient's own cytotoxic T cells are genetically engineered to express immune receptors that target cancer antigens. These genetically engineered T cells are then delivered back to the patient where they mount a personalized, cancer-specific immune response. Although adoptive T cell therapy is highly promising, and is in fact the first FDA-approved gene therapy, immune receptors possess intrinsically low specificity. Thus T cell therapy carries significant risks of off-target immune toxicity. Structured Immunity is a new startup company that utilizes structural biology and protein engineering to develop immune receptors with enhanced target specificity while delivering optimum cytotoxic potency. Structured Immunity partners with cell

therapy companies to improve their early stage candidates, and is developing its own pipeline of tumor antigen specific immune receptors for adoptive T cell therapy–by Brian Baker

Christian Melander Joins Notre Dame

Christian received a B.S. in Chemistry from UC Davis in 1994 and a Ph.D. in organic chemistry at Columbia University in 1998. After postdoctoral studies at Caltech (1998-2001) and The Scripps Research Institute (2002-2004), he joined the faculty in the Department of Chemistry at North Carolina State University in 2004, where he rose through the ranks from an Assistant Professor to his current position, the Howard J. Schaeffer Distinguished Professor of Chemistry. Christian's independent research career has focused on developing novel therapeutic approaches for the treatment of multi-drug resistant bacterial infections. He is also co-founder of Agile Sciences, a biotechnology company located in the Research Triangle Park that seeks to commercialize the antibiofilm and antibiotic potentiation activities of discoveries made in his lab at NCSU. At Notre Dame, Christian's group will continue their drug discovery efforts and focus on the identification of molecules that: 1) Repurpose Gram-positive selective antibiotics for the treatment of Gram-negative bacteria in both systemic infections and those related to cystic fibrosis patients, 2) allowed continued usage of colistin, the antibiotic of last resort for the treatment of multi-drug resistant Gram-negative bacteria, despite increased incidence of colistin resistance in the clinic, and 3) enable the use of lactam antibiotics for the treatment of multi-drug resistant tuberculosis.

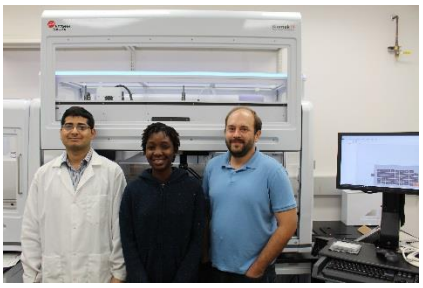
Tony Cobb Earns Safety Award

Tony Cobb received the Golden Dome award for his dedicated service to the University along with the establishment of McCourtney Hall safety tours. The McCourtney Hall Safety Group consists of faculty members and Risk Management and Safety staff whom work together not only to fix existing concerns, but to prevent future issues. The committee has established an unannounced laboratory safety walk through process as a mechanism to encourage scientists to work safely at all times. If any unsafe practices are found during the Safety Group walk, Mr. Cobb speaks with the offending labs to ensure appropriate measures are taken to remedy the situation. The committee also developed a safety enforcement flow chart to help address lab safety issues, and track issues to ensure that no unsafe practices were repeated. Tony Cobb joined Notre Dame Research in 2016 and is responsible for coordinating the day-to-day operations of Notre Dame Research facilities. His responsibilities include implementation and execution of building policies and procedures for safety, cost, and central services. Mr. Cobb is also responsible for the coordination of facilities maintenance, construction, renovations, renewal, and relocation. We are fortunate to have Tony Cobb on the Notre Dame Team.

The Biological Screening and Development Core

Dr. John Koren III is the new director of the Warren Center's Biology and AMDET/DMPK facility. John's 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. The Biology and ADMET/DMPK facility provides Notre Dame researchers with full-service high-throughput screening technology to triage libraries of compounds in pre-clinical ADMET studies including: blood-brain barrier permeability, cytotoxicity, mutagenicity, hERG inhibition, plasma and liver microsomal stability, plasma protein interactions, and CYP450 inhibition and induction. In addition to these listed assays, the core offers expertise and services in assay development, high-throughput functional assays, *in vivo* pharmacokinetics and bio-distribution, cell culture models, and recombinant protein

purification. Using our state-of-the-art Biomek i7 Dual-Arm Liquid Handling Automation Platform, our dedicated triple-quad LC-MS/MS, and AKTA FPLC we can deliver reliable data in a cost-effective manner.



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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
- Purification of complex mixtures
- Sample plating/distribution
- Project development
- Consultation

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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 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 pharmakokinetics and predictive modeling, encompassing quantitative structure-activity relationships (QSAR), cheminformatics, library and ligand-based design, and network analysis.

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Three Researchers Awarded Grants to expedite Drug Discovery

During the fall of 2017, 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 these initial grants include Professors Xin Liu, Mary Ann McDowell, and Mayland Chang. Congratulations. Another request for applications will be announced in the fall of 2018 and will encourage utilization of the Biological

Screening and Development core.

New Instruments

The Beckman-Coulter Biomek i7 will allow us to offer an unmatched level of high-throughput screening. With 45 deck positions, dual robotic arms, an integrated Cytation 5 plate-reader, and an integrated Cytomat 2 cell culture incubator, the Warren Center Biology Core will provide a vast array of biological, biophysical, and pharmacological assays. Initial assays to be integrated into this platform include: PAMPA, plasma-protein binding, microsomal stability, plasma stability, CYP inhibition and induction, solubility, and proliferation/toxicity. Due to the diverse nature of these assays, and our expertise in developing mechanistic biological assays, we will also be able to provide services in screening anti-cancer or anti-proliferative agents and screen compound libraries for efficacy in developed cell-based or recombinant protein assays. These assays represent a fraction of the capabilities the Biomek i7 Automated Liquid Handling Platform can provide, and the faculty and staff of the Warren Family Center for Drug Discovery and Development will be happy to work with you to identify how this exciting technology can benefit your research goals.

HPLC: Waters AutoPurification System includes 2465 binary solvent manager, 2767 sample manager/auto collection bed and 2489 dual channel UV/Vis detector. Users can be trained for self-service access at discounted rates.

Peptide Synthesizer: CEM Liberty Blue Microwave assisted Solid Phase Peptide Synthesizer, with reaction times at 4 minutes per amino acid monomer. Users can be trained for self-service access at discounted rates.

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.

Name the New Robot

Do you have a clever name for the new Beckman–Coulter I7? If so, please forward it to wrcadmin@nd.edu, and it will be considered.