

SIGNAL

News from the Center for Rare and Neglected Diseases



The Center for Rare and Neglected Diseases at the University of Notre Dame is charged with the mission of supporting translational research of Notre Dame faculty. The aim is to link researchers with the

finances and scientific resources needed to translate their research into technologies- drugs, vaccines, diagnostics- that will ultimately improve patient outcomes.

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Upcoming Events:

June 2011

Ara Parseghian Foundation and College of Science meeting held at Notre Dame, June 9-11

63rd Annual Midwestern Conference of Parasitologists at St. Mary's College, June 23-25th

August 2011

Midwest Neglected Diseases meeting to be hosted by CRND

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The Need for CRND

A rare disease is a disease that afflicts less than 200,000 people in the United States while neglected diseases afflict millions of people, mainly in developing nations. What these two classes of diseases have in common is a lack of investment that is necessary to take findings from basic research to

patients. Interest from the pharmaceutical industry is low in rare diseases because of restrictions imposed by the small pool of patients and in neglected diseases due to the inability of patients to

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Dr. Kasturi Haldar hosted an assembly to raise awareness on Rare Disease Day, February 28th

pay for therapies. Another barrier is the lack of a coordinated effort to apply basic research into technologies that

address clinical need. One solution is to create an alliance between academia and the pharmaceutical industry to enable scientists performing basic research to work with scientists who have drug discovery expertise in big pharmaceutical companies.

The U.S. government has two initiatives that will help accelerate development of therapies for rare and neglected diseases. The Orphan Drug Act of 1983 provides pharmaceutical companies an incentive to invest in drugs with little return on investment. The National Institutes of Health will soon launch the National Center for Advancing Translational Sciences to accelerate bringing

medicines to market. However, academic research institutions need to be poised to work together with governmental, pharmaceutical, and non-profit institutions to move their discoveries out of the lab and into the clinic.

A concerted effort by CRND to bring together the rare and neglected disease communities promises to facilitate drug development for both groups. CRND focuses on bringing together investigators, patients and clinician members of the rare and neglected diseases communities together with the pharmaceutical industry to address the problem of moving research findings to the clinic.

What CRND Does

CRND administers a seed fund to finance faculty projects, translating their bench research into the

framework of a pharmaceutical discovery-phase project.



Katrina Epperson explains the importance of creating a new social venture as part of the CRND mission.

CRND has forged an alliance with and Eli Lilly, forming a public-private partnership. We have purchased high capital equipment, not normally available to individual academic labs, to mirror the industrial discovery phase but at a smaller, academic scale. Scientists at Eli Lilly provide the know-how on implementing high throughput screens to rapidly identify active chemical entities. They also provide thousands of chemicals to test for activity. The advantage of using their chemical library is that CRND has been granted access to the Lilly database listing additional biological activity of each chemical. This knowledge will allow investigators to mine the database for chemical entities with desirable characteristics and eliminate those with adverse activities.

Who We Are

At a recent stakeholders breakfast held on 16 April 2011, several investigators outlined their projects funded by the CRND. Three major areas of study emerged: finding and making better drugs, understanding cellular processes to alleviate disease, and leveraging strengths at Notre Dame to create a social venture.

Finding and making better drugs

Dr. Olaf Wiest, a professor in the Department of Chemistry and Biochemistry, and Dr. Jesus Izaguirre, a professor Department of Computer Science and Engineering, are collaborators on a computational chemistry project. The idea is to take advantage of their computing power to screen chemicals for activity against a protein target. They use computer simulations to dock chemical entities within a protein



Dr. Olaf Wiest

whose crystal structure is known or modeled. They then determine which chemicals have the best fit, and hence most likely to be active. They propose that by analyzing these computational simulations, they will be able to decrease both time and money to find the best chemical drug leads.

Drs. Paul Helquist and Holly Goodson, both professors in the Department of Chemistry and Biochemistry, also take advantage of computer models of proteins. They model proteins hypothesized to be responsible for causing the rare



Dr. Paul Helquist

disease Niemann Pick Type C. NPC1 and NPC2 are proteins that work in concert to move cholesterol through different cellular compartments. When one is mutated, cholesterol becomes trapped within a specialized compartment, and this immobility causes major tissue damage, especially in the brain, liver and spleen of affected individuals. Helquist and Goodson begin with computer models of these proteins, and then they simulate how one protein transfers cholesterol to the other. The scientists are most interested in this transfer step and propose synthesizing molecules that will freeze this step in time. They hypothesize that by capturing this event, biologists will be better equipped to study this disease.

Dr. Marvin Miller, a professor in the Department of Chemistry and Biochemistry, and Dr. Rohit Tiwari, a postdoctoral researcher, use a "Trojan horse" approach for delivering anti-tuberculosis therapies. They chemically couple potential anti-TB agents to iron transport molecules. Iron is an essential nutrient for the bacteria that cause TB. Bacteria acquire iron through a transport molecule then extract the iron to use it for metabolism. Tiwari and Miller have chemically linked drugs to these iron carriers so that



Dr. Rohit Tiwari

bacteria take up both iron and the drug. Once the drug enters the cell through the transport molecule "Trojan horse", it will kill the bacteria by targeting essential cellular processes. Tiwari and Miller are synthesizing additional "Trojan horse"-like molecules to act as dual targets against both TB and malaria.

Dr. Shaun Lee (see [Faculty Spotlight](#)), an Assistant Professor in the Department of Biological Sciences, is exploiting the chemical warfare that bacteria wage against each other to produce synthetic versions of naturally occurring compounds called bacteriocins. Bacteriocins are biological peptides produced and chemically modified by bacteria. These modified peptides act as antibiotics to kill other species of bacteria or those within close proximity. Lee has identified genes that produce a large family of bacteriocins and uses genetic approaches to design novel bacteriocins that may have tremendous therapeutic potential. His aim is to produce a vast array of these toxins and determine their biological activity against TB, other medically important bacteria, cancer, and malaria.

Understanding cellular processes to alleviate disease

Dr. Jeff Schorey, a professor in the Department of Biological Sciences, and Dr. Basar Bilgicer, a professor

in the Department of Chemical and Biomolecular Engineering, have formed an interdisciplinary collaboration to design a "slow release" vaccine against tuberculosis. The vaccine that is presently available only protects against childhood disease but is not effective against adult pulmonary disease. To boost the adult immune system, Schorey proposes to use specialized vesicles that are naturally produced during tuberculosis infection. These vesicles are named exosomes and have been shown to activate immune cells. He is in the process of producing exosomes from cultured cells and has enlisted the help of Bilgicer for developing a "slow release" formulation. The "exosome boosters" need to be released in a sustained manner, and Bilgicer has expertise using polymeric scaffolds for just such a purpose. Biocompatible polymer matrices can be designed such that they are non-toxic and engineered with desirable characteristics to enable slow decomposition and sustained release of exosomes.



Dr. Basar Bilgicer

Together Schorey and Bilgicer are testing optimal size, chemistry, shape, and activity against the bacteria that cause tuberculosis.

Dr. Crislyn D'Souza-Schorey, an Associate Professor in the Department of Biological Sciences, uses a cellular model to study Niemann Pick Type C disease. She uses cells isolated from patients to understand how cholesterol becomes trapped within



Dr. Crislyn D'Souza-Schorey

specialized cellular compartments and is testing ways to move it out of these compartments and out of the cell. Because cholesterol accumulation within the cell is believed to be responsible for tissue damage and disease, D'Souza-Schorey brings her knowledge of intracellular dynamics to bear upon the problem of cholesterol mobilization. She has focused her efforts on one protein in particular (Arf6) that is responsible for moving cellular cargo from one compartment to another. By designing a cell line (isolated from a Niemann Pick Type C patient) with this protein in a constantly active state, she can move cholesterol out of the cell. She is studying this process in greater detail for its use as a therapy.

Dr. Zach Schafer, the Coleman Assistant Professor in Cancer Biology in the Department of



Dr. Zach Schafer

Biological Sciences (B.S. Class of 2001), has recently acquired two cell lines isolated from patients with Inflammatory Breast Cancer. This disease is rare but aggressive and accounts for 1-5% of all breast cancer cases. Schafer is investigating cell death and metabolism in these cell lines to understand how they survive in the circulation, where these cells are typically found. He hypothesizes that by understanding changes in metabolism, he can design better therapies that will specifically target these cancer cells without affecting normal, non-diseased cells.

Leveraging strengths at Notre Dame to create a social venture

Katrina Epperson, CRND Program Coordinator (B.S. Class of 2010), has spearheaded an effort to realize a social venture promoting outreach to patients with rare diseases. She has been working as part of a team with Mary Claire Sullivan (M.B.A. Class of 2012), Aldo Leal (M.B.A. Class of 2012), Valerie Champoux (M.B.A. Class of 2012), Brendan Maher (B.B.A. Class of 1994), Dr. Nitesh Chawla (Professor in Department of Computer Science and Engineering), and Dr. Kasturi Haldar (Director of CRND). Their aim is to overcome the barrier of finding patients with rare diseases by creating a repository of medical records to accelerate the time to bring new therapies to market. They propose to populate the repository with medical records from patients who have volunteered their information. Because the information is centralized, it is a convenient means for doctors to easily access the repository to learn how to diagnose and treat their patients with rare diseases. Thus, this venture, by improving physician awareness of rare diseases, may help reduce the time required for diagnosing a rare disease, a major problem for people suffering from these maladies. The repository can also be accessed by companies interested in conducting clinical trials and will serve as a control arm by outlining the natural history of disease progression. The team has constructed a business plan that has been vetted by the Fellow Irish Social Hub. They are now working on a pilot of the social venture for Summer 2011.

Faculty Spotlight on Dr. Shaun Lee

As an undergraduate at UC Berkeley, Dr. Shaun Lee practically lived on campus. He was busy constructing models for architecture projects then running across campus to spend many hours in biology lab. His dual major was in Architecture and Molecular Biology, but his attention shifted away from architecture after an eventful Physiology lab.

Lee needed to measure neuronal activity from a frog sciatic nerve for a Neurophysiology class. He attempted to keep his hands very steady for an entire hour to guide a micropipette into the nerve bundle without poking through. After many failed attempts of trying, he got it! "I think I screamed out loud... and was totally hooked".

It was that moment of elation that spurred Lee to pursue a path in scientific research. After graduation, Lee wanted more research experience. Without any prior contact, he walked into

the office of Dr. W. Ian Lipkin and asked for a job. These were formative years that exposed Lee to Lipkin's groundbreaking work as a modern-day pathogen hunter. Lee learned the tools and techniques to study microbes and witnessed first-hand the events that led Lipkin's team to first identify West Nile Virus in the United States. Lee then joined the lab of Dr. Maggie So at the Oregon Health Sciences University where he studied how bacteria that cause gonorrhea and meningitis use hair-like fibers called pili to infect human cells. He mapped the host responses that mediate the initial contact and invasion by the bacteria. Following his graduate work, he pursued postdoctoral studies with Dr. Jack Dixon at UC San Diego, where he first identified how bacteria make a highly conserved class of bacteriocins (see "What We Do: Dr. Shaun Lee").

"Don't be afraid of failure [because]...success is definitely not the absence of failure." Science



"Don't be afraid of failure!"

is an iterative process that requires failure to find success. Lee reminds budding scientists of Edison's many failed attempts at perfecting the light bulb. It is often the puzzling, unexpected results that lead to the most insightful observations that can shift scientific paradigms.

Please visit the CRND website for video of the full interview (<http://www.nd.edu/~crnd/>).

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