Public-Private Partnerships (PPP) represent a collaborative business model for pharmaceutical companies, academic researchers, and the government to form partnerships. The goal is to strengthen research and the development of drugs and vaccines for rare and neglected diseases. When many partners form an alliance, not one sole organization incurs all expenses when undertaking a risky project. Additionally, partners reap the benefits of sharing intellectual property, innovative technologies, and expertise on specific diseases.

Collaboration on Malaria: CRND-Lilly/CRND-MMV
CRND has forged a collaboration with Eli Lilly and

Company with regard to the discovery of new antimalarial compounds. With the additional contributions of Medicines for Malaria Venture, a global pharmaceutical cooperative committed to the eradication of malaria, we have screened a select Lilly chemical library to develop potential new medicines. From over 110,000 compounds tested, nearly 300 are potentially promising in that they are potent and selectively inhibit malaria parasite growth but not that of human cells. Now that the first round of testing is complete, we will run confirmatory assays of the active compounds

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and cross-reference this with information from the Lilly chemical database. With this added knowledge, we at CRND aim to identify the best candidates to put into pre-clinical development.

In parallel to the antimalarial drug studies, CRND is setting up a high throughput screening facility on-campus so that ND investigators can rapidly screen the Lilly chemical library for activity against their chosen pathogen. We are working with Lilly scientists to ensure that our biological tests meet the highest quality standards and have started quality testing using the Acumen high-content microscope. Other key pieces of equipment, such as liquid handlers, bar code readers, and automated sample processors, are being evaluated to integrate with the microscope. Our aim is to mirror the industrial discovery phase but at a smaller, academic scale.

Additional partnership building CRND is forging new alliances with many organizations. We are building partnerships with Amicus Therapeutics, a leading rare disease pharmaceutical company, with other biotech companies, and with the NIH therapeutics translational programs. We would like to further develop PPPs with pharma partners. The overall goal is to harness the power of public-private partnerships to move therapies forward and strengthen research in rare and neglected diseases.

CRND Research Incubator Awards … a step up

Part of the CRND mission is to develop scientific collaborations in clinical medicine, engineering, physical sciences and the life sciences. The aim of the Research Incubator Program is to seed interdepartmental and interdisciplinary research that promises to lead to external funding. All funded projects also develop intellectual property. Our goal is to stimulate development of therapeutics and diagnostics in rare and neglected diseases by supporting early discovery and translational projects.

We are pleased to announce the 2011-2012 awardees. Congratulations to…

Dr. Rob Stahelin, Assistant Professor at the Indiana University School of Medicine and adjunct Assistant Professor in the Department Chemistry and Biochemistry, University of Notre Dame, for his proposal, “New Drug Targets of Viral Hemorrhagic Fever.” Stahelin studies a group of viruses that cause Viral Hemorrhagic Fevers, which are classified as both rare and neglected diseases. His aim is to first find commonalities in the lipid envelope that encapsulates these viruses and then second discover one drug that targets that common feature. Stahelin proposes using one drug to kill the group of viruses.

Dr. Paul Helquist, Professor in the Department of Chemistry and Biochemistry, for his proposal, “Molecular Probes for Lipid Trafficking Disorders.” Helquist will use chemical probes to capture a key enzymatic event between two proteins known to play important roles in Niemann Pick Type C disease, a fatal neurodegenerative disease. This step may aid biologists to study this disease.

Dr. Zachary Schafer, the Coleman Assistant Professor in Cancer Biology in the Department of Biological Sciences, for his proposal, “The Examination of the Molecular Mechanisms Underlying the Survival of Inflammatory Breast Cancer Cells.” Schafer studies Inflammatory Breast Cancer. He hypothesizes that by understanding specific changes in cellular metabolism, he can design better therapies that will specifically target these cancer cells without affecting normal, non-diseased cells.
CRND hosted the 1st Annual Midwest Neglected Infectious Diseases Meeting (MNID) held in McKenna Hall at the University of Notre Dame on Aug 26-27th 2011. It was made possible through the support of the Burroughs Wellcome Fund.

This meeting has its origins from one held in Chicago semiannually beginning in the early 2000s. Although the Chicago meetings were smaller, they drew a core of 10 investigators to discuss research advances in the broader field of eukaryotic pathogens. The overarching goal for the MNID remains the same, namely to create a Midwest network that serves as a platform for regional activities, collaborations and increased exposure for trainees.

Over 100 people convened from across the Midwest to attend 15 speaker presentations and nearly 40 poster presentations. Areas of interest included disease pathogenesis (malaria, toxoplasmosis, trypanosomiasis, histoplasmosis), host immunity to infection (schistosomiasis, cryptococcosis, leishmaniasis), and modeling host-pathogen interactions (dengue, filariasis, aspergillosis).

Disease Pathogenesis
Although the organisms discussed in the first two sessions of the meeting cause different diseases, several common themes emerged. Pathogens must secrete factors to neutralize host defenses, and they must infect the right kind of cell in the human body. Dr. Chad Rappleye (Ohio State University Medical Center) characterizes how the fungus that causes histoplasmosis secretes factors to neutralize host defenses. Histoplasmosis is a pulmonary disease, and resident macrophages normally kill the fungus by a reactive oxygen burst. The more virulent the fungus, the better equipped it is to deal with this burst. Dr. Hsin-Hung Huang (Rush University Medical Center) is also exploiting the effect of reactive oxygen species but in the schistosome worm. Since only one drug is available to treat the disease, Huang and colleagues have tested thousands of compounds for their ability to kill the worm. The best candidates work by disabling the worm’s limited ability to deal with reactive oxygen species. Dr. Souvik Bhattacharjee (University of Notre Dame) is characterizing how the malaria parasite secretes factors into its host, the human red blood cell. The parasite must secrete hundreds of factors into its host in order to survive, but the mechanisms of how this is governed are still being uncovered. Bhattacharjee demonstrated how the parasite sorts and determines which factors will be secreted. Dr. Christina Hull (University of Wisconsin- Madison) is studying how the Cryptococcus fungus spreads throughout the body (especially the brain) to cause disease. Hull worked out a method to isolate the pathogenic form of the fungus, a process that has taken years and eluded multiple investigators. She is
now comparing the differences between how pathogenic and non-pathogenic forms interface with macrophages, the body’s first defense.

**Modeling Host-Pathogen Interactions**

Several different approaches are being used to study how pathogens interact with their hosts. For instance, **Dr. Nancy Keller** (University of Wisconsin-Madison), uses biochemistry and cell biology to show that oxylipins can be co-opted from the plant host by the fungal pathogen *Aspergillus spp.* These are oxygenated fatty acids that control fungal sexual development and toxin production.

**Dr. Nancy Keller**

**Dr. Robert Striker** (University of Wisconsin-Madison) combines genetics and biochemistry to study the exquisite evolutionary adaptation of flaviviruses. The dengue virus is part of this family and is the only virus with a human-mosquito niche. Striker presented evidence that decreasing the amount of a mosquito protein modulates a viral protein and importantly, reduces viral load in the mosquito.

**Dr. Robert Striker**

**Dr. Edwin Michael** (University of Notre Dame) takes a broader approach with mathematical models to estimate disease burden in affected communities. His analyses help guide WHO policy decisions, and he advocates an adaptive approach rather than a command-and-control approach. With an iterative process that accounts for epidemiological changes within a community, policy makers and scientists can better monitor dynamics of infection.

**Dr. Edwin Michael**

**Host Immunobiology**

**Dr. Timothy Yoshino** (University of Wisconsin-Madison) is investigating immune factors that make snails susceptible to schistosome worm infection. Snails are the natural reservoir for schistosomiasis, and eliminating snails or snail infection can prevent disease. Yoshino is identifying the unique combination of Pattern Recognition Receptors from snail hosts and Pathogen Associated Molecular Patterns from schistosome parasites that allow for successful snail infection.

**Dr. Timothy Yoshino**

**Mr. Nicholas S. Geraci** (graduate student in Dr. Mary Ann McDowell’s lab at the University of Notre Dame) has undertaken a global approach to understand how human immune cells limit Leishmania parasite infection. The immune response has several “arms”, and depending on which arm is activated, the outcome of infection can be mild or severe. Geraci is identifying micro-regulators in immune cells that will help predict disease outcome.

**Mr. Nicholas S. Geraci**
The National Niemann Pick Disease Foundation held its 19th Annual Family Support & Medical Conference, welcoming more than 50 families affected by Niemann Pick Disease Types A, B, or C. Joining the families were the top medical and research scientists in the field, including Dr. Kasturi Haldar, Dr. Dan Ory, Dr. Forbes D. Porter, Dr. Marc Patterson, Dr. Marie Vanier, Dr. Steve Walkley. The conference offers families the opportunity to consult with experts in the field. They can ask questions and learn about the disease and potential new therapies. The meeting also acts as a retreat, where families can bond together and share important experiences.

The National Niemann-Pick Disease Foundation was formed in 1992, and Ms. Karen Quandt currently serves as the Board Chair. Its mission is to provide families with resources for coping with the disease. In addition to organizing annual family meetings, the foundation provides advocacy services, educational resources, and service referrals. Please visit their website (www.nnpdf.org/) for more information.

Ara Parseghian Medical Research Foundation Meeting

The Annual Parseghian Scientific Conference for Niemann-Pick Type C Research was held at the University of Notre Dame on June 9-11, 2011. Ms. Cindy Parseghian announced that Notre Dame will continue to host the annual meeting since it has been endowed. The 2012 meeting will be held June 7-9.

Niemann-Pick Disease, type C (NPC) is a fatal, complex, neurodegenerative disease. Disease is due to defects in genes npc1 (associated with 95% of clinical cases) and npc2 (associated with 5% of clinical cases). Natural history studies have yielded quantifiable measures of disease severity in patients. Dr. Denny Porter and co-workers at the NIH developed a disease severity scale from natural histories. One of the highlights of the meeting was discussing the potential of using this scale to evaluate emerging therapeutics.

The meeting brought together stakeholders from the U.S., Brazil and Europe to discuss research advances and included physicians, academic scientists and representatives from industry. We would like to acknowledge the contributions of NPC parents and children to this meeting. Trent Smith, Jim Greene and other families shared their unique understanding of this disease with the NPC research community. Please visit their website (www.parseghian.org/) for more information.
NIH Innovator Awardees

Dr. Shaun Lee is a 2011 recipient of the prestigious NIH Director’s New Innovator Award. The Innovator Award recognizes unusually creative investigators who propose innovative research ideas and are at early stages of their career. It is a highly competitive award as only 49 people are selected nationwide. Dr. Lee will develop his idea to produce bacteriocins as novel anti-infective agents. His initial studies were funded by a CRND Incubator Program grant. Notre Dame is especially delighted that Dr. Rebecca Wingert is also a recipient of the NIH Director’s New Innovator Award. Typically schools with research-intensive programs, such as Harvard and Stanford, can boast multiple recipients.

Congratulations to Dr. Lee and Dr. Wingert!

New Director of External Programs

CRND welcomes Dr. Pamela Tamez, who has been appointed as the Director of External Programs. Dr. Tamez will oversee and facilitate strategic partnerships between CRND and pharmaceutical companies, federal agencies, academic stakeholders and foundations. With eight years in academic research, she laid important groundwork in establishing a new malaria infection model using adult, blood-derived stem cells. Tamez looks forward to achieving the goals of CRND and to promoting research at Notre Dame.

Undergraduates publish

ND undergraduate students are publishing their clinical research on a rare disease. Sixty-four undergraduate students were expertly trained to decipher medical records for assessing and summarizing clinical disease severity. Their work will appear in the scientific journal PLoS One.

Spotlight

Investing in tuberculosis research

Imagine that 1 in 3 people worldwide are infected with the bacterium that causes tuberculosis. Current therapies are losing effectiveness as bacteria are increasingly drug-resistant.

The CRND helped assemble a team at Notre Dame to address the issue of finding new drugs. Dr. Marvin Miller and his group have designed a method to easily and cheaply synthesize potential anti-tuberculosis agents. In only three steps, they can make enough of each chemical agent to test for activity. Using this streamlined method, they have overcome several obstacles that usually throw projects off-track, namely sufficient quantity of chemical agents, ease of synthesis, and low cost. Dr. Miller knew these agents were effective in in vitro and cellular models but required expertise on campus to help him move the project to the next logical step, testing in animal models. CRND facilitated discussions with Drs. Jeff Schorey and Patricia Champion, both of whom have expertise characterizing the molecular mechanisms of tuberculosis pathogenesis in cellular and animal models. CRND will also purchase a key piece of equipment that will allow testing these agents in a highly relevant physiological context. With these pieces in place, the team will begin testing by early next year.