News from the Center for Rare and Neglected Diseases

World Rare Disease Day 2012

The Center for Rare and Neglected Diseases observed World Rare Disease Day on February 29, 2012. This year marked the fifth annual observance. The theme for this year’s day was “Solidarity” with the slogan “Rare But Strong Together.”

The purpose is to raise awareness of rare diseases to improve patients’ access to treatment and inform policies affecting rare disease communities. The official sponsors of World Rare Disease Day are EURORDIS, an alliance of 510 patient organizations in over 48 countries, and the U.S.-based National Organization for Rare Disorders, a non-profit which offers programs of education, advocacy, research and service for the 30 million American with rare diseases. Along with 26 partners, NORD and EURORDIS hosted a website (www.rarediseaseday.org) that acted as a nucleating center for bringing supporters together, disseminating information about events, and brainstorming on ideas to raise awareness on February 29.

The Center for Rare and Neglected Diseases participated as one of over 700 supporters from the U.S. It hosted an informational dinner to launch the

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The agenda for the evening was informative, engaging, and provided a little entertainment. Dr. Kasturi Haldar began by explaining the evolution of the class “Developing Health Networks in Rare and Neglected Diseases,” which has provided a mechanism of introducing clinical research to Notre Dame undergraduates. It required the participation of many people both within and outside of Notre Dame. Ms. Marisa Truong, Program Coordinator for the class, introduced the audience to Rare Health Exchange and illustrated some of its key features. Ms. Natalie Bott, a student of the class, administered a quiz to expose the audience to different rare diseases and how they manifest. Even with teams of 8 people answering the questions, most received a failing grade. The questions were very challenging and were meant to highlight how little the general public knows about rare diseases. As a way to engage the audience and share the correct answers, Dr. Pamela Tamez, Director of External Programs for the CRND, used an on-line polling system so that respondents could text their answers and the entire audience can see the responses in real-time. When the grades came in, the highest scoring team correctly answered 12 out of 20 questions.

The Notre Dame Glee Club, an all male collegiate choral group, closed the evening. They sang traditional songs and spirituals. They also premiered the ND “Rare Disease Fight Song” (see RHE website).

Over 80 students and faculty attended the assembly. Because half are engaged in research, teaching or learning about rare diseases, the CRND was able to reach another 40 people to raise awareness on rare diseases.
Malaria is a blood disease that kills nearly 1 million people each year. It is caused by a parasite that infects red cells in the blood. Once inside the cell, the parasite exports proteins beyond its own plasma membrane border into the blood cell (see image). These proteins function as adhesins that help the infected red blood cells stick to the walls of blood vessels in the brain and cause cerebral malaria, a deadly form of the disease that kills over half a million children each year.

A team of scientists led by Dr. Kasturi Haldar and Dr. Souvik Bhattacharjee at CRND, has made a fundamental discovery in understanding how malaria parasites cause deadly disease. Their results were published in the January 20th issue of the journal Cell, the number one journal in the life sciences and a Cell Press Publication (DOI 10.1016/j.cell.2011.10.051). They show how parasites target proteins to the surface of the red blood cell that enables sticking to and blocking blood vessels. Strategies that prevent this host-targeting process will block disease. The study was supported by the National Institutes of Health.

In all cells, proteins are made in a specialized cell compartment called the endoplasmic reticulum (ER) and subsequently delivered to other parts of the cell. Haldar and Bhattacharjee collaborated with Dr. Robert Stahelin at the Indiana University School of Medicine-South Bend/adjunct faculty, Department of Chemistry and Biochemistry, University of Notre Dame, and with Drs. David and Kaye Speicher at the Wistar Institute, University of Pennsylvania to discover that for host-targeted malaria proteins the very first step is binding to the lipid phosphatidylinositol 3-phosphate, PI(3)P, in the ER. This was surprising for two reasons. Previous studies suggested the enzyme Plasmepsin V released proteins into the ER and controlled export. However, Haldar, Bhattacharjee and colleagues discovered that binding to PI(3)P lipid that occurs first, is the gatekeeper to control export and that export can occur without Plasmepsin V action. Further in higher eukaryotic cells (such as in humans), the lipid PI(3)P is not usually found within the ER membrane but rather is exposed to the cellular cytoplasm.

Drs. Haldar and Bhattacharjee are experts in malaria parasite biology and pathogenesis. Dr. Stahelin is an expert in PI(3)P lipid biology, and Drs. David and Kaye Speicher are experts in proteomics and a method called mass spectrometry. This interdisciplinary collaboration reveals a fundamental, novel cellular function, disruption of which can provide new therapies that are urgently needed for malaria.
Dr. Jeff Schorey receives funding from the Bill and Melinda Gates Foundation*

As part of the Grand Challenges in Global Health initiative, the Bill and Melinda Gates Foundation has created a new grant program to identify biomarkers for diagnosing tuberculosis. Dr. Jeff Schorey along with Dr. Karen Dobos at Colorado State University and collaborators at the University of California at San Francisco received one of only ten funded projects.

The team has been funded to develop exosomes for TB diagnostics. Exosomes are vesicles or sacs that contain protein and other cellular material and function in intercellular communication. They make attractive targets for diagnostics because they can be found in many different bodily fluids (so samples can easily be taken) and when isolated from TB patients, contain specific components from the pathogen. In related work, Schorey and colleagues also found that exosomes make good vaccine candidates as they contain specific TB proteins that stimulate the human immune system.

Tuberculosis is caused by the pathogen *Mycobacterium tuberculosis* and although there are antibiotics that can treat most cases of TB, many patients still go untreated. This is due in part to the limited sensitivity of the current diagnostic test. Surprisingly, nearly half of all TB cases go undiagnosed.

In 2007 through a serendipitous discovery, Schorey and his team detected bio-signatures from the TB pathogen that were released from infected cells on exosomes. Through a collaboration with Dr. Karen Dobos the team identified pathogen-associated signatures from TB-infected patients.

The purpose of the grant awarded through the Biomarkers for the Diagnosis of Tuberculosis is to define biomarkers that can identify active TB patients and to begin developing a detection platform that can be used as a point-of-care diagnostic test for TB.

CRND Data Club

CRND hosts a Data Club bi-monthly to showcase research supported by CRND seed money. CRND faculty as well as their lab members attend the monthly meetings.

In the past months, Dr. Marvin Miller described his program for synthesizing and testing molecules to act as targets against TB and malaria. He and his team have devised a creative, “Trojan horse”-like strategy for delivering anti-tuberculosis therapies.

Dr. Crislyn D’Souza-Schorey described her program for using a protein named ARF6 to answer important biological questions that impinge upon diseases such as cancer, Huntington’s Disease and Niemann Pick Type C.

Dr. Robert Stahelin described his program for understanding the lipid code that underlies protein targeting, membrane biogenesis, and lipid sorting. Among other resources, Stahelin listed MeTaDoR (Membrane Targeting Domains Resource), which serves as a centralized resource for learning about membrane targeting domains.

Dr. Jeff Schorey described his program for characterizing exosomes as diagnostics and vaccines for tuberculosis. He highlighted the lab’s latest results using an apparatus that the CRND funded. The apparatus allows for *in vivo* testing using physiologically relevant conditions.

Be on the lookout for up-coming seminars from Dr. Zachary Schafer in April and Dr. Edwin Michael in June.

*Visit CRND’s YouTube channel “rareandneglected” for more.*
CRND was pleased and honored to host the White-Richardson, White and Simon family on March 23rd. The visit was the culmination of a continuing conversation between the family and students Natalie Bott and Aaron Patzwahl (see RAREhealth Exchange on page 6).

Ms. Jennifer White shared her experience navigating the medical system when trying to understand her son’s (Tylor White-Richardson) disease. She delved into the medical literature, joined family support groups and sought out medical experts. When the leading hospital in Iowa could not provide a diagnosis, she specifically requested a referral to the Mayo Clinic. Mr. Brian “Sy” Simon has been at Jennifer’s side and wholly supports their family.

A Mayo physician did finally provide the diagnosis of Niemann Pick Disease Type C. Dr. Marc Patterson, in particular, began an incredibly supportive relationship and continues to attend to Ty with compassion and humor. Both Jennifer and Sy appreciate Dr. Patterson’s style and told pre-professional students, “Be a person, not a clinician, and treat patients as people.”

The family handles challenges with aplomb. When Tylor required the use of a wheelchair, they found the right resources and had one custom-built. They had a wheelchair-accessible van re-fitted for Tylor and travel across the country. Jennifer, Ty and Sy maintain an active lifestyle and help mentor new families. Because the National Niemann Pick Disease Foundation has been a valuable resource, they keep strong ties.

Dr. Başar Bilgiçer and team fighting allergies

Dr. Başar Bilgiçer, an Assistant Professor in the Department of Chemical and Biomolecular Engineering, works on several different questions centered on understanding and manipulating biomolecular interactions. One project in particular has garnered much attention: inhibiting allergic reactions.

His lab designs, synthesizes and characterizes heterobivalent ligands, which are molecules that can bind antibodies at two distinct sites. One part of the molecule targets the antigen binding site, while the second part of the molecule allows for stronger interaction with the antibody. Together, they work to block allergens from binding antibodies, thus preventing an allergic reaction.
Dr. Souvik Bhattacharjee is no stranger to tough competition and hard work. After finishing his secondary education in New Delhi, India, Bhattacharjee took a National Eligibility Test in order pursue a career in research. In order to earn a doctoral degree, candidates take the test, and only 10% are granted a scholarship to undertake the research.

In 1998 he entered into the doctoral program at the Institute of Microbial Technology in Chandigarh, India, which is 90 miles from Delhi and nestled at the foot of the Himalaya Mountains. It is one of India’s premiere national labs, and graduate students become immersed in the research, as their living quarters are hostels located on-campus. While at IMTech, as the Institute is known, Bhattacharjee decided to characterize specific proteins from the rodent malaria parasite. These proteins were thought to play a role in allowing the parasite to enter red blood cells. When Bhattacharjee looked at infected cells using electron microscopy, he found that these proteins were indeed in the expected place, on the surface of daughter parasites. The surprise was that he also observed these proteins on uninfected red blood cells as well. These experiments suggested that parasite proteins bind uninfected cells, leaving them vulnerable to clearance by the human immune system. It provides one of many possible explanations for the anemia seen during malaria infection.

Bhattacharjee finished up his experiments, wrote up his thesis, and then joined the lab of Dr. Kasturi Haldar at Northwestern University. Upon his arrival, he found a flurry of activity, as the lab was busy preparing a manuscript for publication. But, electron microscopy images were required to complete the story. Bhattacharjee worked hard over the weekend and produced publication-quality images by Monday morning. After only six months in the lab, Bhattacharjee was published. He then went back to India to defend his dissertation.

Bhattacharjee’s keen insights and strong work ethic has yielded another coup. He planned out a set of experiments, and at the end of eight months wrote a manuscript that has since been published in the journal Cell (see page 3).

When talking to Souvik, you are more likely to hear one of his Indian parables than the latest round of experiments. It comes through in his excellent training of students. But, he is also quick to point out to them (and all) that one good experiment leads to 10 more questions.

**Rare Health Exchange**

RAREhealth Exchange has been launched as a website that provides information on a collaborative effort for and by undergraduate students. Students are trained to assist clinicians and patient families in creating natural histories of rare diseases.

Ms. Marisa Truong has spearheaded the effort to bring RAREhealth Exchange into existence. She along with six students (pictured) have worked together to design the site, engage the audience and reach out to patient families. Please visit the website and engage with the team.