SIGNAL
News from the Center for Rare and Neglected Diseases

Fall & Winter Double Issue

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Strengthening International Ties
CRND forum on international collaborations for rare diseases

Patients & Families at the Niemann-Pick Disease Conference in Baltimore
On Friday September 27th, Karen Quandt visited with Notre Dame students enrolled in the BIOS 60565 class “Clinical Research in Rare Diseases”. Ms. Quandt is an active member of the National Niemann-Pick Disease Foundation (NNPDF) and the International Niemann-Pick Disease Alliance (INPDA). She is also the mother of Ty Quandt, who has been living with Niemann-Pick Type C (NPC).

During her visit, Ms. Quandt gave an overview of the mission of the NNPDF and the INPDA and highlighted the importance of collaborations with Notre Dame faculty and students to help find a cure for the disease.

Committed to a Cure!

During her visit, Ms. Quandt shared some photos of Notre Dame’s own Dean Greg Crawford at the end of his cross-country bike ride as he reached the finish line at the annual Niemann-Pick Disease conference in Baltimore. CRND was represented at the conference by Dr. Kasturi Haldar, Dr. Shahir Rizk and Marisa Truong (CRND Program Coordinator). This year’s conference featured a strong representation by the international participants from the UK and many other countries through the INPDA.

CRND is thankful to the commitment of Dean Crawford and the Notre Dame community for their efforts to raise awareness for rare disease research.
clinical trials in India. They also spoke of the challenges in changing the misconceptions that rare diseases do not deserve attention and in making existing pharmaceuticals and diagnostics available in India.

The group gave an overview of the work of the Notre Dame Center for Rare and Neglected Diseases carried out on NPC research and the commitment of the CRND faculty to rare diseases. Dr. Shaun Lee (Biology) and Dr. Anthony Serianni (Chem/Biochem), who collaborate on work to discover drugs for the lysosomal storage disorder MPSIIIA, joined the discussion.

Additionally, Yuan Gao (ESTEEM student) provided an overview of the Rare Health Exchange (RHE) database developed and maintained by Notre Dame faculty and students.

The Ara Parseghian Foundation (APMRF) has recently announced on its website (www.parseghian.org) that a clinical trial is expected to begin to test a class of drugs known as HDAC-inhibitors as potential therapies for NPC. The phase I trial may take place as early as summer 2014.
The idea was to develop an educational and service program to help the National Organization for Rare Diseases (NORD) continuously update its vast library of rare disease summaries. These summaries are an invaluable resource for families afflicted with a rare disease, where they can learn about its genetic basis and progression, physicians and centers that treat and study the disease, as well as well peer groups and funding opportunities that support patients. Almost 30 million Americans suffer from rare diseases, so the summaries address an important healthcare problem.

**Coffin-Siris syndrome** (CSS) is a rare genetic disorder, caused by a mutation in one of the five following genes - ARID1A, ARID1B, SMARCA4, SMARCB1, and SMARCE1. These genes help regulate the folding and packaging of DNA, so a mutation in them subsequently affects a variety of systems throughout the body. Most cases of CSS are not inherited, resulting from a new genetic mutation. About 80 cases of CSS worldwide have been reported, with females affected about four times more frequently than males.

**Nonketotic hyperglycinemia**, also known as glycine encephalopathy, is an autosomal recessive hereditary disorder. The disorder is characterized by mutations in proteins in the “Glycine cleavage system,” which prevents the efficient breakdown of the amino acid glycine. This causes large amounts of glycine to build up in the blood, urine and, particularly, the cerebrospinal fluid (CSF).
I am senior majoring in biological sciences and minoring in Catholic social teaching. After graduation I hope to go to medical school and pursue a career as a physician. In my time at Notre Dame, studying rare diseases has helped to shape my outlook on medicine and imparted on me the importance spreading awareness to researchers, medical professionals and the general public about rare disease. In the future I hope to be an active participant in rare disease research and activism.

**Hereditary Hemorrhagic Telangiectasia** (HHT) is a rare autosomal dominant disorder of the blood vessels that occurs in about 1 in 5,000 people. It is characterized by blood vessel malformations, known as telangiectases or arteriovenous malformations (AVMs) resulting in bleeding in areas like the nose, lungs, gastrointestinal tract, brain, liver, and spinal cord. HHT is caused by a number of different genetic mutations in the genes associated with controlling cell survival and replication in blood vessels. Five different genes have been discovered as potential causes for HHT. Often presenting with mild symptoms, HHT is under-diagnosed, makes its frequency difficult to determine.

**Jackie Picache**

Jackie is a senior Science Preprofessional Studies major and a Science, Technology, and Values minor. She intends on going to medical school with the hopes of helping underserved populations – especially those of the rare disease community.

**Holt-Oram syndrome** is a disorder that affects proper heart development and/or upper limb bones. The symptoms and physical findings associated with Holt-Oram syndrome vary greatly from case to case, even within the same family. Seventy-five percent of those affected have a congenital heart malformation. The most common heart malformations are atrial septal defect and ventricular septal defect. The size and location of the defect determine the severity of the symptoms.

**Abe Yu**

Abe Yu is a senior studying biology and plans to attend medical school following college. His interest in rare diseases began his junior year of college when he took the clinical research in rare diseases course that focused on NPC and Congenital Hypothyroidism. He hopes to one day become a physician and better assist those who suffer from sickness and disease.

**Mucolipidosis Type IV** is a rare inherited metabolic disorder that affects males and females equally. It is caused by a deficiency in a certain protein that prevents fatty substances and complex carbohydrates from accumulating within cells of many tissues of the body. People with Mucolipidosis Type IV usually have learning disabilities, poor coordination, weak muscles, and visual impairment. The disorder usually presents with symptoms three to eight months following birth. Most affected infants show diminished muscle tone, delays in reaching developmental milestones like walking and talking, and have trouble coordinating muscular and mental activities.
My name is Jing Wang, and I’m a senior Science Pre-Professional Studies major at the University of Notre Dame. I became involved in the Center for Rare and Neglected Diseases my sophomore year as an undergraduate research assistant. After engaging in malaria research for a school year and nine weeks over the summer, I enrolled in the Rare and Neglected Diseases course for the past two semesters to learn more about rare diseases and gain exposure to clinical research. I believe that there is no disease out there so rare that it does not deserve attention. I plan to enroll in medical school within the next two years and become a physician to help ease the pain and suffering of others.

Hypohidrotic ectodermal dysplasia (HED) is a rare inherited multisystem disorder that belongs to the group of diseases known as ectodermal dysplasias. Ectodermal dysplasias typically affect the hair, teeth, nails, sweat glands, and/or skin. HED is thought to occur in approximately one in every 100,000 births and one in every 50,000 male births. Thus, approximately one in every 17,000 people worldwide is affected. Several hundred cases have been reported in the medical literature since the disorder was originally described in 1848.

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**Test your Rare Disease Knowledge**

1. **True or False:** Rare Diseases can result from new genetic mutations or from infections.

2. NKH results in accumulation of which of the following metabolites in affected individuals?
   - a. Glycerin
   - b. Glycine
   - c. Glycerol
   - d. Glycogen
   - e. Glyphosate

3. HHT cases occur in less than ____ individuals
   - a. 1 in 10
   - b. 1 in 100
   - c. 1 in 1,000
   - d. 1 in 10,000
   - e. 1 in 100,000

4. Holt-Oram Syndrome affects mainly which of the following organs?
   - a. Heart
   - b. Lungs
   - c. Kidneys
   - d. Eyes
   - e. Feet

5. **True or False:** Males are 4 times more likely to be affected by Mucolipidosis Type IV.

6. Hypohidrotic ectodermal dysplasia was first described in:
   - a. 1948
   - b. 1884
   - c. 1776
   - d. 2014
   - e. 1848
CRND Hosts the 3rd Annual MNID Conference

On August 23-24th, the Midwest Neglected Infectious Diseases meeting was held for the 3rd consecutive year as the major venue for researchers in the fields of pathogenic parasites and fungi in the region. The meeting is supported and organized by CRND and the MNID steering committee, and is sponsored for the 3rd consecutive year by the Burroughs-Wellcome fund. This year, two additional sponsors were also added; the Indiana CTSi and the University of Michigan Medical School research fund. The meeting was attended by roughly 120 researchers and students from the 6 states surrounding Notre Dame (Indiana, Michigan, Ohio, Illinois, Wisconsin and Missouri). The conference also featured a talk by Dr. M. John Rogers (NIH, NIAID), via videoconference, who spoke to the group about federal resources and funding opportunities in drug discovery and development.

This year, the meeting featured two keynote speakers, Notre Dame’s own Dr. Marvin Miller (Chem/Biochem) and Dr. Aaron Mitchell of Carnegie Mellon. Dr. Miller kicked off the meeting with an energetic presentation about the emerging threat of microbial antibiotic resistance to current drugs, and how work here at ND in collaboration with Dr. Jeff Schorey (Biology) has produced a number of potential new strategies to fight back against some of the most resistant bugs. On the second day of the meeting, Dr. Mitchell presented his lab research on C. albicans, a fungus that can cause infections in humans with compromised immune systems. Dr. Mitchell’s lab identified a gene that is responsible for the fungus’ ability to form a “biofilm”, which is a property that allows it to stick to surfaces, such as plastic. His lab also identified the genetic changes that take place when the fungus becomes infectious, and how anti-fungal drugs influence these changes.

In addition to Dr. Mitchell, Dr. Amy Hise presented her work on C. albicans, where she studied a large cellular machine known as the inflammasome, which is activated in response to an infection. Other speakers presented their work on infectious fungi and yeast. Dr. Christina Hull (Wisconsin) spoke about Cryptococcus, an infectious yeast found in pigeon droppings. She found that a specific stage in the Cryptococcus life cycle, known as the spore stage, is responsible for the infection, which can cause a form of meningitis. Dr. Tamara Doering (Washington D.C.) and Dr. John Osborn (Biology) also presented their work on infectious fungi and yeast.
University, St. Louis) followed by describing how Cryptococcus forms and maintains its cell wall. Finally, Michael Davis (Michigan) concluded with how this organism survives inside its host by living within the very immune cells that are supposed to kill it.

In addition to infectious fungi, several parasites were featured. Dr. Vernon Carruthers (Michigan) and Dr. Gustavo Arrizabalaga (Indiana University) presented their work on *Toxoplasma gondii*, an opportunistic infectious parasite. Dr. David Engman gave a presentation about the importance of protein modification in the function of the flagellum, which is responsible for motility in the Trypanosome parasites.

A number of other talks featured research in malaria. Dr. Douglas LaCount (Purdue) gave an overview of some important proteins involved in the way the parasite interacts with red blood cells. Dr. Niraj Tolia (Washington University, St. Louis) showed results from his work on similar proteins. Using a technique known as “x-ray crystallography”, Dr. Tolia was able to provide a molecular picture of how the proteins on the surface of the malaria parasite are able to bind and infect the red blood cells. In a complementary talk, Dr. Stefan Kanzok (Loyola, Chicago) discussed
his work on the malaria parasite stage that inhabits the mosquito, and how the parasite ensures its own survival.

This year’s MNID meeting was designed with a new format that featured shorter talks (20 min) than in previous years, allowing for more speakers to discuss a wider range of topics. Also a new addition to this year’s format, a number of talks were selected from submitted abstracts, which allowed a few outstanding students and postdocs the opportunity to present their work. These included Shuang Liang (Case Western), Victoria Jeffers (Indiana University), Michael Davis (Michigan), Jim Collins (Illinois, Urbana-Champaign) and Richard Pinapati (Notre Dame). All of the work presented emphasized translational approached to combat neglected infectious diseases.

Over 3 years, MNID has continued to provide a platform for Midwest researchers in neglected infectious diseases, and has been a valuable tool for these scientists to form and maintain contacts that have resulted in collaborations. We anticipate that the meeting will continue to be a success in bridging basic science with drug development.
CTSS connects ND students with top researchers

The Clinical & Translational Seminar Series (CTSS) is part of the “Topics in Pathobiology” Course taught by a team of ND faculty including Dr. Patricia Champion, Dr. Shaun Lee, and Dr. Shahir Rizk. Through the CTSS, the students had the opportunity to discuss the latest research in infectious diseases. In addition, invited speakers presented their work to the ND community.

This Year, CTSS featured Dr. Michael Federle (University of Illinois, Chicago) who presented his work on how bacteria respond to their environment and communicate with each other. He explained how this type of communication helps bacteria become resistant to current drugs and how his work in understanding the underlying mechanisms can result in new strategies for fighting some of the most threatening infections.

The CTSS also featured an invited talk by Dr. Jeremy Burrows, Head of Discovery at the Medicines for Malaria Venture (MMV). Dr. Burrows’ talk focused on the drug discovery and development efforts by MMV to fight and eradicate malaria, a disease that kills nearly 1 million worldwide, mostly children.

Dr. Burrows also had the opportunity to participate in a visit by the CRND team to Eli Lilly & Co in Indianapolis to discuss the ongoing partnership between ND, MMV and Lilly to develop anti-malaria drugs.
Faculty Spotlight: Dr. Patricia Champion
Finding support for funding

Dr. Patricia Champion (Biology) described her experience with applying and receiving federal funding for her research. Dr. Champion is an active member of CRND who studies the bacteria that causes tuberculosis.

“I wrote that [grant] every day for seven months. I was very lucky to have several people, both at Notre Dame and outside, read the grant (more than once) and provide me with honest and useful feedback. I even held it a cycle on the advice of one of my outside readers. I was advised, given the tight funding environment, not to submit anything less than my best. The people that read the grant included colleagues in my field. The support and the mentoring was amazing, and without the opinions of several people I would not have been able to put together the grant.

It was thrilling to get the grant, and having the opportunity to continue the line of work that I spent so many months thinking about and developing is amazing. I am really enjoying it so far.”

Congratulations to Dr. Champion on receiving R01 funding for her research!

Infectious News

A $5B Pledge to Fight HIV, TB & Malaria

Renewed pledges: Encouraged by a decade of global progress, world agencies are digging in against the big three HIV, TB and malaria and renewing commitment against additional neglected diseases. Drugs have been critical for reducing disease burdens worldwide. CRND applauds these commitments and is honored to build partnerships with pharma to develop better drugs for control and eradication.

New TB Publication

A recent article in the European Journal of Immunology, describes groundbreaking research from Dr. Jeff Schorey’s lab. The article shows that proteins released from the bacteria that cause TB can be used to protect mice from infection by boosting their immune system. This work has great implications in developing vaccines for TB, which is a devastating disease that affects millions worldwide and poses a major global threat. The work comes in a critical time when current drugs to fight TB are failing due to emerging antibiotic resistance.
SAVE THE DATE!
World Rare Disease Day

Join us in Celebrating
World Rare Disease Day
On Saturday February 15th, 2014

Details will be Posted at:
www.nd.edu/~crnd

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