**Mission Statement.** The Boler-Parseghian Center for Rare and Neglected Diseases (CRND) at the University of Notre Dame is charged with the mission of supporting research of Notre Dame faculty in developing drug and additional therapies for rare and neglected diseases.

This newsletter is a long overdue update but for the best of reasons. 2014-2016 has been a period of expansive growth. Highlights are presented. Our outstanding faculty, fellows and students are inspired to partner with deeply committed patients, clinicians and pharma collaborators and coalesce single-mindedly on galvanizing research for new therapies in diseases where they are most urgently needed. With your continued support we again look forward to many more successes in 2017. **Contact:** 574-631-3372 sbanchik@nd.edu 107 Galvin Life Sciences, Notre Dame, IN 46556
CRND: a broad remit for drugs and genetic therapies across rare and neglected diseases.

A major gift of the age of genomics is indisputable evidence that ‘Rare and Neglected diseases’ are not freak oddities of misfortune, but a massive, health problem that visits one of every ten people across the globe. Research in these diseases also provides ‘portals’ for treatments in other diseases. Founded in 2008, the Center for Rare and Neglected Diseases (CRND) received early support from the James Parson and Carrie Quinn Endowment, enabling a strong head start. Endowed in 2014 by Boler-Parseghian, CRND is honored to partner in Notre Dame’s fight, with our leading programs that reach broadly across rare cancers, neurological diseases and resistant infections.

Individual rare diseases may affect only a handful of people, but around 30 million people in the US, i.e. approaching 1 in 10, suffer from the cumulative of ~7000 rare and neglected diseases (and worldwide estimates may be higher). Drugs (both small chemical molecules and biologicals) are the mainstay of treatment. Recent new genetic technologies such as CRISPR/Cas9 also hold great promise. Yet the sobering reality is that we have yet to develop research and find treatments for the vast majority. The spirit of ND in the fight will kick off 2017 Rare and Neglected Disease Symposium & Celebrations with a fight song and hockey! Everyone is welcome, but for those who can’t be lured to the frozen Midwest on the first week end in February, sing along with us to a tune well known and loved! [https://vimeo.com/37980822](https://vimeo.com/37980822)
On Sunday October 11th, 2014, the University of Notre Dame celebrated the dedication of CRND as the “Boler-Parseghian Center for Rare and Neglected Diseases”. We thank the Parseghian family for their commitment to research in Niemann Pick Type C disease and the Boler family whose gift allows us to expand the research that ranges from developing drugs in neurological disorders and neglected infectious diseases to rare cancers.

We thank the faculty, students, fellows and staff for their hard work, the academic and alumni leadership, our community partners and patient families for their support of rare and neglected diseases research.

We also welcome Dean Mary Galvin, who took over as Dean of the College of Science in 2015. We are grateful for her deep commitment and strength in guiding our passion for rare and neglected disease research at Notre Dame.

Mary Galvin
Dean, College of Science
Undergraduate Excellence in Rare and Neglected Disease Education and Awareness.

Congratulations to the University of Notre Dame Rare Disease Team, for their prize from the National Institutes of Health (NIH)!

ND Seniors, Madeline Zupan (Captain; COS ND ’16 ESTEEM ’17) Roland Rebuyon (COS ND’16) and Katherine McIntyre (COE ND ‘16) won second prize in the rare disease Sickle Cell Challenge for Undergraduate Students competition sponsored by the Department of Health and Human Services (HHS) National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH) in Bethesda, Maryland. The team won $5,000 and expenses paid to travel to present their winning application “Snap Out of Sickle Cell: Informing and Involving America with a Targeted Social Media Campaign.” at the Annual Sickle Cell Disease Clinical Research Meetings held at the NIH on August 15 – 17, 2016. Their tool https://www.youtube.com/watch?v=iIM7GQIXyQk (also below) has been warmly received and deployed by the Sickle Cell Disease Patients and Researchers.

On Dec 2nd 2016 a new group of ND students formed a focus group to extend the award winning social media tool in promoting awareness of a Non Ketotic Hyperglycinemia on campus. They learned firsthand from Patrick Sarb (ND ’76 ’78) and Lynda Sarb as well as John and Mary Fitzpatrick, how this devastating rare disease affected their families.
Rare Diseases in Our Community: Alumni-ND Student Case Report

Title: Aggressive Tibial Pseudarthrosis as Primary Symptom in Infant with Neurofibromatosis

Authors Mary Alice Reid\textsuperscript{a}, MD (ND ’79), Madeline Zupan \textsuperscript{b} (ND ’16), Nicole Sevison\textsuperscript{c}, et al. 2016

Affiliations: \textsuperscript{a}Beacon Health System, Bristol Street Pediatrics, Goshen, Indiana; \textsuperscript{b}Boler-Parseghian Center for Rare and Neglected Diseases, Dept. Biological Sciences, University of Notre Dame Notre Dame, Indiana; \textsuperscript{c}Memorial Hospital, South Bend, IN

Presented with permission. In 2015, Dr. Mary Alice Reid (ND ’84, above) and her patient family (above, mother Nicole Sevison with daughter Skylar) were invited to campus by RareND club. Dr. Reid is a pediatrician in Elkhart Indiana and her clinic (Bristol Street Pediatrics, BSP) sees its share of rare genetic disorders. CRND is privileged to collaborate with BSP. Skylar was diagnosed with neurofibromatosis (NF1) a rare genetic neurologic disorder. But this was an unusual case of NF1, with a delay in diagnosis because the first symptom was severe Pseudarthrosis (PA), also known as a “false joint”. PA on its own does not indicate NF1. For all known NF1 reported cases prior, PA appeared at 2 years of age or later and following NF1 characteristic café au lait spots. But Dr. Reid’s patient was a 4-month old infant who presented with severe PA as primary symptom. Detailed review of the case records by physician, patient family and students led to a case report* with the following diagnostic recommendations.

‘For primary PA without clear etiology, first-contact and consulting physicians should pay careful attention and be vigilant to timing of clinical onset and severity. Early, severe primary PA warrants accelerated NF1 exome sequencing, suggesting expansion of existing federal guidelines may be necessary to improve detection and prognosis of this rare, debilitating but readily managed condition’. Mary Alice Reid, Madeline Zupan, Nicole Sevison, Barbara Calhoun, et al. doi: http://dx.doi.org/10.1101/066316 * Supported in part by a Ganey Award from the Center for Social Concerns, UND.
**ND-NORD Editorial Internships.** The fight against rare diseases is both up close and personal as well as global. And while this often feels daunting, our students have laid paths that can be followed by others to come in their footsteps. To paraphrase John Crowley (ND Law ’89, Rare disease-biotech leader, -parent and now ND parent) from 2015 Rare Disease Day Celebrations, the fight against rare disease is both the short and long haul.

ND students have been partnering as Editorial Interns with the National Organization for Rare Diseases (NORD) to help them continuously update NORD’s publications of rare disease summaries. Student summaries are first reviewed by expert physician-scientists and subsequently added to NORD’s vast library. The 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. Twenty-five of forty summary links are below - few thousand more to go!

- **Rob Callus** - PC Deficiency- Pyruvate Carboxylase Def.
- **Billy Christy** - Nemaline Myopathy
- **John Shields** - Hepatic Fibrosis
- **Madeline Zupan** - Galactosemia
- **Sarah Toner** - Chediak Higashi
- **Joshua Banago** - Carnitine Deficiency
- **Niraja Suresh** - Hunter Syndrome, MPS II
- **Madeline Zupan** - Neurofibromatosis 2
- **Robert Power** - Friedrich’s Ataxia
- **Bianca Fox** - Coffin-Siris syndrome (CSS)
- **Allie Kress** - Nonketotic hyperglycinemia
- **Andy McAsey** - Hereditary Hemorrhagic Telangiectasia (HHT)
- **Abe Yu** - Mucolipidosis Type IV
- **Joey Kim** – L1 Syndrome
- **Joseph Lee** – Collins Syndrome
- **Jackie Picache** - Holt-Oram syndrome
- **Jing Wang** - Hypohidrotic ectodermal dysplasia (HED)
- **Theresa Lai** – Jervell and Lange-Nielsen
- **Sarah Fagan** – Cardiofaciocutaneous Syndrome
- **Michelle Yanik** – Incontinentia Pigmenti
- **Zachary Weber** – Thrombocytopenia Absent Radius
- **Lee Haruno** – Hyperekplexia
- **David Brouch** – Fanconi Anemia
- **Joey Kim (Founder)** – Brugada Syndrome
- **Joey Kim** – Kennedy Disease
Rare Cancers

Rare cancers are a major focus for CRND. They can start in an unusual place in the body, be of unusual type and are often aggressive, spreading rapidly. Diagnosis takes longer and they have to be treated differently from major cancers. These factors compound when they affect underserved populations, making them more deadly to vulnerable groups.

The generosity of the Boler Family has empowered a broad platform of expansion of excellence in our early investment in rare cancers through new faculty hires as well as CRND’s Catalyst Program.

We are delighted to announce the appointment of Dr. Xin Lu as the John M. and Mary Joe Boler Assistant Professor in the Department of Biological Sciences. Dr. Lu completed his Ph.D. at Princeton followed by postdoctoral work at MD Anderson Cancer Center. His research as a graduate student in Professor Yibin Kang at Princeton, made fundamental impact on our understanding of how cancers spread and the development of new treatments for invasive breast cancer to bone, lung and other organs. As a post doc with Ronald DePinho (President MD Anderson) Dr. Lu specialized in developing multiple mouse cancer models and treatments for rare cancers. His research publications (to list a few in Cancer Cell, PNAS, Genes & Development, Nature Medicine, Cancer Research) show an unprecedented level of productivity at an international scale. During his training he won multiple awards, including the prestigious Paget Foundation award and the HHMI/Jane Coffin Childs Postdoctoral fellowship.

His research program at ND investigates understanding and targeting the tumor microenvironment which is at the forefront of current basic and translational cancer research. Targeting tumor microenvironment is closely related to tumor immunology and immunotherapy, one of the most exciting and rapidly evolving areas of cancer research. An intense focus of research in his lab is investigating molecular and cellular mechanisms underlying cancer – tumor microenvironment crosstalk, in particular interactions between cancer cells and the myeloid compartment, in both primary tumors and metastases to bone and other organs. Dr. Lu hypothesizes that the efficacy of immune checkpoint blockade drugs (e.g. anti-CTLA4, anti-PD1 antibodies) on refractory
metastatic cancer can be potently enhanced when combined with other therapy modalities, including targeted therapy that specifically antagonize immunosuppressive activities yet preserve T cell functions in the tumor microenvironment.

Dr. Lu will pursue these hypotheses in rare cancer types such as penile cancer and sarcoma and in other cancers as well. To achieve this goal, he will use integrated approaches centered at cancer genome mining and validation as well as sophisticated inducible transgenic mouse modeling. In addition to finding new mechanisms the work will advance preclinical work that moves drugs to patient in cancers and improve understanding of cancers where the numbers of patients are extremely small (sometime less than a few hundred).

**CRND ‘Catalyst’ Program** proposals in biomolecular medicine are directed toward critical treatment targets or processes of drug resistance in cell, tissue, organismal and human systems.

The goal is to also recognize advanced graduate students and support them through critical periods of training and research productivity. These students are also supported by the Bill and Lisa Powers family.

Congratulations to three labs and excellent graduate student awardees researching aggressive rare cancers! Three 2016-2017 Boler-Powers fellows are as follows.

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<tr>
<th>Student</th>
<th>Rare Cancer Type</th>
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<td>Josh Mason</td>
<td>Rare inflammatory breast cancer</td>
<td>Dr. Zach Schafer</td>
<td>Ye Zhang</td>
<td>Rare Invasive melanoma</td>
<td>Dr. Crislyn D'Souza-Schorey</td>
<td>Ian Guldner</td>
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**Josh Mason** in the Schafer lab investigates rare inflammatory breast cancer that appears as an infection rather than a tumor and therefore frequently misdiagnosed.

**Ye Zhang**, in the D'Souza-Schorey lab pursues rare melanoma and their invasive projections (arrows) that causes cancer spread.

**Ian Guldner** in the Zhang’ lab studies rare metastatic brain cancer that requires immune cell involvement (gliosis, shown in red).
Neurological Diseases

CRND has research interest in a wide range of neurological disorders, including Niemann Pick Type C disease. These are a wide range of diseases that remain amongst the most difficult to diagnose and treat. Our goal is to develop both broad and tailored therapies for these heartbreaking (often pediatric) disorders.

We are delighted to announce the promotion of Dr. Shaun Lee, Monahan Family Associated Professor in Rare and Neglected Diseases. Dr. Lee’s expertise is in protein mis-folding and human disease and therapy in neurological diseases. Protein folding is complex, but Dr. Lee explains it simply, in that a well folded protein is beautiful origami (health) while a badly folded protein is removed because of dysfunction (disease).

Stefan Freed a graduate student under Dr. Lee’s mentorship co-developed a multiparametric algorithm for predicting protein mis-folding. Since diseases can present in different states of severity, the predictive algorithm is very useful to understand how severe the disease will be for a given mutation in a rare genetic disorder. Stefan initiated this work in San Filippo Syndrome A (also known as Mucopolysaccharidosis IIIA, MPS3A) and has extended to the other neurological disorders, including non ketotic hyperglycinemia (NKH).

For this work, the Lee lab and Stefan were recipients of the 2016 CRND Catalyst fellowship. Congratulations to both for developing broad tools for rare neurological diseases that can be used by clinicians in understanding and treating patient disease as well as guide researchers on how cell and mouse models harboring the same mutations are also likely to be changed by (chaperone) therapies as they are moved from the lab to the clinic!

Non Ketotic Hyperglycinemia (NKH), is an inborn error of metabolism resulting from failure to break down the simplest of amino acids glycine. Increased glycine can trigger seizures in the brain (as many as a hundred a day) lead to loss of muscle tone and overall failure to thrive. However, overactive glycine cleavage promotes certain types of cancers, emphasizing how carefully metabolism must be regulated to maintain health. And remarkably, research in a neurological disorder NKH may help research in cancer. As indicated earlier, this disease affects our alumni. Unexpectedly NKH also has deep family ties in the history of Notre Dame and South Bend and high prevalence in other communities in Northern Indiana. CRND welcomes embracing and expanding the fight against NKH.
CRND News

CRND is deeply grateful for Notre Dame support that quickly emerged around NKH. We thank Dean Mary Galvin, College of Science and her team, NKH patient families, clinical care givers and other researchers, with who we look forward to continue to work in complementary and collaborative ways.

CRND’s research integrates across predictive biology, molecular and cellular assays and mouse models. Tools of computation, recent break through genetic methods like CRISPR-Cas9 are combined with expertise of pharma and clinical partners in a balanced portfolio for short term epigenetic/immunological therapies and long term chaperone, metabolic and genetic therapy. The data are combined with studies of patient cells and tissues as well natural history from patient medical records to optimize the therapeutic and diagnostic approaches. The NKH collaborative with patients, clinicians and the community is supported by our nurse practitioner Barb Calhoun, NP and Administrative and Outreach Coordinator Shaina Banchik, and well integrated into the ND education and research model.

Translating discoveries in Niemann Pick Type C (NPC) CRND has been honored to develop a drug that treats NPC, a disease which cruelly took the lives of three of Mike and Cindy Parseghian’s children (Coach Ara’s grandchildren). Dr. Suhail Alam (Research Scientist and CRND’s Director External Programs) developed a formulation of an FDA approved drug that is being developed as a patient therapy that can be administered at home weekly (or biweekly). The principle behind it is keeping the target gene in an ‘open’ state and helping by other genes (often called chaperones) to preserve and repair the damage caused by NPC disease. NKH is a very different disease from NPC but the formulation keeps NKH-associated genes ‘open’ suggesting a strategy for rapidly taking an NKH therapy to clinic.
CRND News

Resistant Infections

Even as the global burden of many infections decline, drug resistant infections are on the rise. Since its inception, CRND’s principal investment in resistant infections has been in malaria and tuberculosis (but CRND faculty work with several additional drug resistant infections that due to space restrictions are not presented). The burden of these diseases although often low in the US can be be high worldwide. But, even when rare globally, the potential to spread in vulnerable populations, urges their elimination.

An agreement with Eli Lilly & Co enables CRND to screen their vast chemical compound libraries against any rare or neglected diseases. We are pleased to report completion of that the first collaborative study with Lilly targeting resistant malaria parasites that threaten malaria elimination. The team included five postdoctoral fellows and one Research Assistant Professor mentored by Drs. Haldar, Miller and Wiest from the Departments of Biological Sciences and Chemistry and Biochemistry at Notre Dame and support from the Medicines for Malaria Venture.

Collaborative Agreement with Eli Lilly & Co to screen their libraries against any rare or neglected disease.

High throughput screen of the entire chemical compound collection of Eli Lilly & Co

Chemical space of ~half million compounds

Followed by SAR to optimize ‘hits’ to ‘leads’ to drugs

First study submitted for publication

Answers That Matter.
CRND and the Community

Celebration of rare & neglected disease research and stakeholders. Here, CRND’s principal mechanisms are through regional conferences, Clinical Translational Seminar Series, CRND Data Club, the RareND student club and annual Rare Disease Day Celebrations. The pictures at the end provide a vignette of the energy and activities captured in 2015-2016.

We invite you to take our quiz (see end) and win a mug! We also invite you to Rare Disease Day celebrations next year Feb 3-4, 2017, taking in dinner and the action-filled ND-Vermont Hockey Game on Feb 3.

As this year draws to an end, we see how much we have learned on our journey with you. Our successes could not have been possible without your partnership, commitment and support. We thank you. Every step, even small ones, enables us to envision future possibilities.

We encounter many requests for assistance from rare disease families. Your financial contribution will help us to give them a chance.

If you believe in research and education that can transform a child’s life, now would be a perfect time to give.

For NKH donations: www.supporting.nd.edu/nkhresearchfund or www.supporting.nd.edu/fionafund
For other CRND Donations: crnd@nd.edu
Or mail check to CRND, 107 Galvin Life Sciences, Notre Dame, IN 46556
2015-2016 RareND Club, Clinical Translational Seminar Series and Rare Disease Day

Sarb Family, Rare Disease Day
Hope, Shprintzen-Goldberg Syndrome
Rare Disease Day, Dr. Haldar with Maeve
ND-DAY 2016
Fitzpatrick, Nohelty Molina Family
NKH
Posters, Rare Disease Day
RareND Club
MNID Poster
Mary Alice Reid, MD, Ganey Project
NKH: Dr. Van Hove’s visit
Hope, Shprintzen-Goldberg Syndrome
Gaucher’s Dr. Krainc
RareND Club Fundraiser
Gary Gibson, CTSS
Gerard Berry, MD, CTSS
Zineb Ammous, MD, CTSS
MNID
Rare Disease Day 2016
1. Rare cancers are considered the frontline of the Precision Medicine Initiative because:
   a. Every patient is unique
   b. Treatments can be tailored to the patient genetic mutation causing the cancer
   c. A broad range of symptoms are seen across a given cancer
   d. None of the above
2. Non-ketotic hyperglycinemia (NKH) is an inborn error of metabolism and glycine encephalopathy (or brain disease) thought to prevalent at 1:250,000, but recent studies suggest higher levels at 1:76,000. Further, current assessments suggest that the highest prevalence of NKH lies in:
   a. A 10-20 mile area of Northern Indiana
   b. Finland
   c. British Columbia
   d. None of the above
3. Mutations in ‘P’ protein that cause NKH may protect against
   a. Propionic acidemia (PA, which causes ketotic hyperglycinemia)
   b. Certain cancers
   c. Infection
   d. Niemann Pick type C disease (also a neurological disease)
4. Chaperone therapy designed to treat a broad range of rare disease should be optimized for:
   a. A single protein target defective in a monogenetic disorder
   b. Broad action against multiple targets defective in multiple monogenetic disorders
   c. Eliminate the co-morbid infection associated with a subset of genetic infections
   d. None of the above
5. ND Professor Dr. Zach Schafer’s research has shown that rare inflammatory breast cancer:
   a. Progresses rapidly
   b. Causes the breast to look inflamed
   c. Survives by a unique mechanism that can be target of new therapy
   d. Occurs in men but at an older age than women
6. CRISPR-Cas9 is a new technology that has infused new feasibility into gene therapy in a wide range of genetic disorders and their response to injury (infectious or otherwise). CRISPR-Cas9 is
   a. A mechanism of immunity in bacteria
   b. A human genetic mechanism
   c. Derived from viruses (like oncogenes that cause cancer)
   d. None of the above
7. We should invest in discovery and development of rare and neglected disease drugs and genetic therapies because:
   a. ND is Catholic and committed to social justice
   b. These diseases provide major mechanistic portals and therapeutics for other diseases
   c. Rare disease patients are willing to do their part, by participating in emerging research
   d. All of the above