

A GOAL FOR LIFE

For Friends and Supporters of the Ara Parseghian Medical Research Foundation



When the Ara Parseghian Medical Research Foundation was launched in 1994 by the Parseghian family and an army of dedicated volunteers, their first and foremost goal was to raise money to fund research to find a treatment and cure for Niemann-Pick Type C disease (NP-C).

Since that time great strides have been made and so much has been learned. Thanks to the generous support of thousands of individuals, corporations, foundations and other NP-C families more than \$40 million dollars has been raised for research. The number of labs studying NP-C has grown from 2 to more than 50, with 14 currently being funded by the Parseghian Foundation.

Inside this newsletter you will read about the notable progress that has recently been made about Niemann-Pick Type C disease.

Clinical Trial Updates for Niemann-Pick Type C Disease

Cyclodextrin Phase 1 Trial

A Phase I Clinical Trial using Cyclodextrin is nearing completion and has gathered significant research data to determine the drug's safety, dosing levels and effectiveness. The trial, which began in January 2013, has enrolled twelve children and young adults with NP-C. The trial using lumbar intrathecal injections (spinal taps) to administer the cyclodextrin has tested doses between 50 and 400 mg. Researchers who are part of the Therapeutics For Rare And Neglected Diseases (TRND) team at the National Institutes of Health are studying the initial biomarker results which are deemed promising in slowing the disease process. The TRND team will continue to obtain and analyze biomarker data over the next few months. There are some safety concerns with patients who have experienced hearing loss and the researchers are working to better understand this issue.

Work is being done to move Cyclodextrin into a Phase II/III trial. The next trial will concentrate on the clinical benefits of the drug. This phase of testing will require more patients and thus will be conducted at multiple sites and most likely will be conducted internationally.

APMRF funded researchers Steve Walkley, Albert Einstein College of Medicine and Benny Liu, UT Southwestern Medical Center, first recognized the potential therapeutic benefits for its therapeutic potential for NP-C. Since then the APMRF has continued to support the research efforts to determine the mechanism of action, safety and dosing levels, including extensive animal testing necessary leading up to the NP-C patient trials. The APMRF also supported the NP-C Natural History Study at the NIH, which garnered valuable data in developing biomarkers for the Cyclodextrin trials and for other drug trials in the future. We commend the TRND team for their efforts in moving the trials forward. We are thankful for Dr. Forbes D. Porter lead investigator on the Cyclodextrin trial for his continued devotion to NP-C patients.

HDACi Proof of Concept Trial

A Phase I proof of concept trial will likely begin in the fall of 2014 with a histone deacetylase inhibitor (HDACi) to help determine if this group of drugs can be used to treat NP-C1. The initial HDACi drug to be tested will be vorinostat. Vorinostat has already been approved by the FDA for the treatment of cutaneous T-cell lymphoma. A NIH Institutional Review Board (IRB) has approved a protocol to test the safety and efficacy of vorinostat in a cohort of 12 adult NPC1 patients. This trial will focus on the safety of HDACi in NPC1 patients and determine if HDAC inhibition has a desirable biochemical effect in white blood cells of NP-C patients.

Since this is a proof of concept trial and the safety of this drug in NP-C subjects is not likely to differ significantly from patients with cutaneous T-cell lymphoma, the APMRF was able to obtain a waiver of the requirement for an Investigational New Drug application for the testing of vorinostat in adult subjects with NP-C1. Merck Pharmaceuticals has graciously agreed to donate the vorinostat for the trial.

Paul Helquist and Olaf Wiest at the University of Notre Dame, along with Norb Weich, first recognized the potential therapeutic affects of HDACi. The Maxfield and Sturley research groups showed that HDACi are able to reduce cholesterol storage in cells that have been cultured from NPC1 patients. Drs. Maxfield, Ory and Porter were awarded a National Institutes of Health (NIH) UO1 grant to evaluate HDACi in NP-C1. This was one of the first grants of this nature awarded by the NIH to promote extramural utilization of the NIH Clinical Center. An "HDACi Working Group" has been collaborating over the past year to establish a proof of concept clinical trial of HDAC inhibition in NPC1. This intramural/extramural collaboration has now been expanded to include investigators from Notre Dame (Drs. Helquist and Wiest), Broad Institute (Dr. Holson), TD2 (Dr. Steven Gately), Mayo Clinic (Dr. Patterson) and Cindy Parseghian, President of the APMRF. The Notre Dame College of Science and the Ara Parseghian Medical Research Foundation are supporting this effort.

Highlights of the 2014 Michael, Marcia, and Christa Parseghian Scientific Conference for Niemann-Pick Type C Research

The University of Notre Dame hosted the 20th NP-C Science Conference in June, bringing researchers from around the world to discuss the progress in NP-C research. This conference was made possible by an endowment the APMRF established to ensure the continuation of this very important meeting. It is the only large meeting specifically held for NP-C researchers so they can focus their attention on conquering the disease. The attendees also help formulate the plans for the direction of the research, highlighting special areas to be investigated.

The conference started with a series of talks summarizing the progress on identifying improved biomarkers for NPC1 disease. Biomarkers are measurable characteristics that doctors and researchers can use to assess the progression of a disease. This research is highly relevant to the goal of developing drugs to fight NPC: only with good biomarkers can doctors ascertain objectively whether a potential therapy is helping children with the disease. The challenge to identifying good biomarkers is knowing where to look, what to look for, and when a particular biomarker can and cannot be relied upon to provide an accurate assessment of disease progression. Stephanie Cologna from the lab of Forbes (Denny) Porter at NIH discussed their progress towards identifying protein-based biomarkers in human cerebrospinal fluid, while the Halder lab presented work on their efforts to develop inflammation-related proteins in blood plasma as biomarkers for progression of NPC disease.

The next series of talks discussed the important topic of attempts to develop the compound cyclodextrin as an NPC1 therapy. As many readers will be aware, cyclodextrin has been reported in some preliminary research to improve or at least slow down the progress of NPC disease in animal models, and also in very limited human tests. However, while this information is hopeful, this research is still in its infancy, and much work remains to be done before cyclodextrin can be considered a safe, appropriate, and effective treatment. In particular, it is very difficult to safely administer cyclodextrin so that it can be delivered to the most affected tissues (the brain), and little is known even from animal studies about basic questions such as the

timing of administration and the relationship between dose and effect (good or bad).

Two of the most significant talks on this topic were those of Charles Vite and Forbes (Denny) Porter. Charles Vite presented the results of a large collaborative group that has been studying the effects of cyclodextrin in NPC1 cats, and reported among other observations that intracisternal administration of cyclodextrin to cats that had already started becoming symptomatic did help ameliorate the symptoms relative to untreated NPC1 cats. This work built upon previous work showing that pre-symptomatic cyclodextrin administration could improve symptoms. Forbes (Denny) Porter presented the preliminary results of the TRND Team's ongoing human clinical trial of 2-hydroxypropyl- β -cyclodextrin (HP β CD) in NPC1. (See page 1) In addition to these and other talks discussing administration of cyclodextrin to animal models and humans, Chris Collins of the Thompson lab discussed their lab's efforts to chemically modify cyclodextrin to improve its water solubility and circulation time.

While there is a great deal of interest and even some hope surrounding cyclodextrin as a therapy, it was clear from this meeting that it is not the only potential therapy in the pipeline. One of the best developed (though still preliminary) is a class of compounds called histone deacetylase inhibitors, which have been shown to improve NPC1 disease characteristics in tissue culture cells by increasing the production of functional NPC1 protein. Importantly, some HDAC



Researcher Stephen Sturley, Ph.D., Columbia University Medical Center

(cont'd. on page 3)

Scientific Conference Update (cont'd. from page 2)

inhibitors have already been approved as drugs for other human diseases, so it is hoped that human testing for NPC1 disease could be accelerated. There was a series of talks focused on using tissue culture cells to determine for which NPC1 mutations the HDAC inhibitors are effective, and why these drugs are not equally effective for all mutations. It turns out that these drugs are most effective against the set of mutations that produce proteins that have partial function, and this is because the drugs work by altering the expression or folding of the genetically encoded NPC1 proteins. Although it is unfortunate that the drugs will not work for all mutations, the effective group does include the most common mutation (I1061T). Importantly, a clinical trial testing HDAC inhibitors for NPC1 disease is planned and should be underway soon.

In addition to these and other talks focused on development and testing of potential NPC1 therapies, there were also talks on basic science that help improve understanding of the disease and lay the foundation for development of future therapies. One project with immediate potential to impact drug discovery was presented by Maria Praggastis, who discussed the collaborative efforts of a team that has finally succeeded in creating a transgenic mouse that carries the most common human NPC1 mutation (I1061T). Because this protein has some partial function, it is hoped that this mouse will be a much better model for studying the human disease and testing potential therapies than is the commonly used “null” mouse, which does not make any protein at all. Another exciting talk was by Paulina Ordonez-Naranjo of the Goldstein lab, who discussed her efforts to develop the use of human-induced-pluripotent stem cells as models for NPC disease.

Other talks that were focused on basic science included those by Suzanne Pfeffer, who discussed her lab’s research into the basic cell biology of the lysosome (the organelle in which the NPC1 and NPC2 proteins reside), and Leslie McCauliff, who is investigating how the NPC2 protein works. In addition, Luis Milla and Steve Sturley presented their talks on how genetic screens in invertebrate model organisms (fruit flies and yeast) can provide insight into the basic cell biological and biochemical pathways involved in NPC disease. The hope is that learning more about these

pathways will help researchers devise detours around the roadblock that is presented by defective NPC1 protein.

In summary, this was a very exciting meeting that was similar to previous AMPRF meetings in the common sense of urgency, shared goals, and community spirit. However, it was different in one profound way: new drugs that have the potential to at least ameliorate NPC1 disease are on the horizon, and human clinical trials are finally under way. In football terms, the ball has been moved closer to the end-zone with the goal line in sight, thanks to the hard work and dedication of countless researchers and fundraisers. Anyone interested in finding out more details about the research presented can find the full abstract book at <http://niemannpick.nd.edu/assets/135126/2014abstractbooklet.pdf>.

We extend our gratitude to the Notre Dame College of Science for organizing the conference. Richard Taylor, Holly Goodson, Paul Helquist, Jenna Rangel, Allen Utterback and Dean Greg Crawford worked diligently behind the scenes to provide a well run, informative meeting.



Researcher Dan Ory, M.D., Washington University School of Medicine

Currently Funded Research – July 1, 2014

Cathleen R. Carlin, Ph.D., Professor, Case Western Reserve University – TITLE: “High Throughput Screen for Allosteric Modulators of ORP1L Function”

Lawrence S.B. Goldstein, Ph.D., Distinguished Professor of Cellular & Molecular Medicine and Neurosciences, University of California, San Diego – TITLE: “Rational drug discovery using patient-derived human-induced pluripotent stem cell models of Niemann-Pick Type C1”

Paul Helquist, Ph.D., Professor & Associate Chair for Research, The University of Notre Dame, **Richard Taylor, Ph.D.**, Professor & Associate Vice President for Research, Director of the Warren Family Center, The University of Notre Dame, **Olaf Wiest, Ph.D.**, Professor, The University of Notre Dame – TITLE: “Design and Synthesis of Small Molecule Agents for Studies and Treatment of NP-C Disease”

Guosheng Liang, Ph.D., Associate Professor, University of Texas Southwestern Medical Center – TITLE: “Use CRISPR/Cas9 Technology to Generate Mouse Models of NPC Disease Carrying Common Clinical NPC1 Mutations of Human Patients”

Frederick R. Maxfield, Ph.D., Professor and Chairman, Biochemistry, Weill Medical College of Cornell University – TITLE: “In vitro and in vivo tests of the efficacy of therapies for NP-C disease”

Daniel S. Ory, M.D., Alan A. and Edith L. Wolff Distinguished Professor of Medicine at Washington University School of Medicine – TITLE: “Histone Deacetylase Inhibitors for Treatment for NPC1 Disease”

Suzanne Pfeffer, Ph.D., Professor and Chairman of Biochemistry, Stanford University School of Medicine – TITLE: “NPC1-mediated export of cholesterol from lysosomes”

Joyce Repa, Ph.D., Associate Professor, University of Texas Southwestern Medical Center – TITLE: “Novel therapies to target energy metabolism in NPC disease”

Sarah Spiegel, Ph.D., Professor and Chair, Virginia Commonwealth University – TITLE: “FTY720 – A Novel Approach for Treatment of Human Niemann-Pick Type C Disease”

Judith Storch Ph.D., Professor, Rutgers University and **Fatima Bosch, Ph.D.**, Professor & Center Director, Universitat Autònoma de Barcelona – TITLE: “Gene therapy for Niemann-Pick type C2 disease in a mouse model”

Stephen L. Sturley, Ph.D., Associate Professor, Columbia University Medical Center – TITLE: “Modifying NP-C disease: A unifying hypothesis”

David H. Thompson, Ph.D., Professor, Purdue University, **Kasturi Haldar**, Professor, University of Notre Dame – TITLE: “Impact of 2-Hydroxypropyl- β -Cyclodextrin: Pluronic Polyrotaxanes on Inflammation in the NPC Mouse”

Mark Your Calendar

June 11–13, 2015

The annual “Michael, Marcia & Christa Parseghian Scientific Conference” for Niemann Pick Type C research will be held on June 11 -13, 2015 at the University of Notre Dame. Researchers will gather for three days to discuss the advances in NP-C research. This yearly meeting helps to form collaborations and determine the future direction of NP-C research.

June 26-29, 2015

The fourth annual “Parseghian Classic”, a 3 day golf tournament, will be held at the beautiful Pebble Beach Golf Resort. Golfers will play a round of golf at Spyglass Hill Golf Course and another at Pebble Beach Golf Links. The all-inclusive event includes a welcome reception and dinner, a putting tournament, and a final reception and dinner with a special guest performance. Full golf and non-golf packages are available. Contact promano@parseghian.org for more information.

Heartfelt Thanks...

Parseghian Classic

The third annual Parseghian Classic was an amazing weekend of wonderful weather, legendary Pebble Beach accommodations, play on award winning championship golf courses, and friends, old and new, who share the common goal of finding treatments and a cure for Niemann Pick Type C disease.

The 3-day event concluded with a delightful dinner at the Beach Club with a performance by long-time friend of the Parseghian family and foundation, the beautiful Amy Grant who was accompanied by the very talented singer/songwriter, Gene Miller.

We wish to thank the incredible team at the University of Notre Dame College of Science whose tremendous efforts and organization made this event so successful.

Ara Parseghian Cup Match

The Notre Dame Rugby Team, partnering with the Notre Dame Jordan College of Science, hosted the second "One More Victory, Ara - Parseghian Cup", a rugby series between ND and the University of Arizona, dedicated to raising money for NP-C research. Coach Ara Parseghian along with Mike and Cindy Parseghian watched as Arizona defeated the Irish for the second time with a score of 32-14. The big winners are the NP-C children and patients who will benefit from the dollars raised for research.

The "Cup" was the idea of Parseghian family friend Dave Sitton, the Coach of the Arizona Wildcats until his untimely death in August 2013. Along with ND Coach Sean O'Leary, Dave made the Cup a reality. His presence was deeply missed on the sidelines but his spirit lives on through this event and in the many other ways Dave touched people's lives.



Before this year's match began, an anonymous donor committed to giving \$25 to NPC research for every fan in attendance. Over 1,200 people attended the game – a record attendance at the Stinson Rugby Field! The entire weekend's events raised over \$42,000 for NP-C research.

We wish to extend our sincere thanks to all of the Arizona & Notre Dame Rugby players, Coaches Duffy and O'Leary, and the Notre Dame Jordan College of Science staff; Dean Greg Crawford, Sean Kassen, Marissa Gebhard, Stephanie Healey, Earl Carter, Allen Utterback and Jenna Rangel.

Next year's match will be held in March and will return to Tucson, AZ where the Arizona Wildcats will host the Irish.

Pie Throwing for NP-C

The students and staff at Lakeshore Middle School in Stevensville, MI decided to do something for NP-C disease...and organized several events with the proceeds going toward NP-C research. One of these events held this past May was... yes...you read that right.....PIE THROWING! Students were given the opportunity to purchase pies to be thrown at the teacher or staff member of their choice. There was much laughter and excitement as the pies met their mark.

Other fundraising events included an all school party with a "dj", a 3 on 3 basketball tournament and a dodge ball tournament. Over \$3,500 was raised for NP-C!

Many thanks to teacher Pam Porter and to the Lakeshore Middle School community for supporting this cause.



Former ND football players and Heisman Trophy winners, Tim Brown and John Huarte enjoying a moment at the Parseghian Classic Gala



Bill Evans, Dan Morrin, Chuck Allen and Graham Allen on the links at Pebble Beach





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Irish Legends Annual Charity Event



Coaches Lou Holtz and Ara Parseghian at the Irish Legends Gala

The fun and prestigious Irish Legends celebrated its 8th year with the addition of an elegant Gala.

Former Notre Dame Head Coaches Ara Parseghian and Lou Holtz and current Notre Dame Football Coach Brian Kelly served as hosts. Proceeds from this event support the foundations of each coach.

The event included a dozen golf teams participating in the first “Coaches Cup” at Olympia Fields Country Club with the coaches serving as captain of four teams. The weather unfortunately did not cooperate and the golf had to be cancelled but coach interviews provided lively entertainment. The evening Gala held at the Drake Hotel, Chicago was spectacular and celebrities from the sports world were in abundance. Rece Davis,

Mark May, Dave Casper, Pete Schivarelli, Johnny Lattner, Jay Harris, Jerome Bettis, Steve Beurelein, John Mosley, and Roger Valdiserri were all in attendance.

We wish to extend our sincere appreciation and thanks to Skip Strzlecki, Jim Moriarity, Greg Hughes and Scott Correira of Notre Dame Sports Properties, Lisa Klunder of the Kelly Cares Foundation, Lou & Beth Holtz, Mike Nolan, Angela Monger and St. Andrews Products.

The combined efforts of so many caring, committed friends continue to make this a premier event each and every year.



Skip Strzlecki, Rece Davis and Mark May at the Coaches Cup