SUMMER 2009

A GOAL FOR LIFE

For Friends and Supporters of the Ara Parseghian Medical Research Foundation

Dear Friends,

With the arrival of the warm days of summer, many of us slow down and take time off to enjoy family and friends. But as the mercury rises in Tucson, work at the Ara Parseghian Medical Research Foundation continues without pause.

At the end of May, the APMRF's Scientific Advisory Board and nearly 80 researchers gathered together to collaborate on the progress of their research. This meeting of the foremost minds in cholesterol, neurobiology, genomics and protein structure was a milestone of information and inspiration. In an intense weekend of comparing notes, reviewing data and exchanging data, they chartered the course for future research.

Peg Romano, my dear friend and APMRF Associate Director, gave me a special pendant this spring. On the pendant is an angel sitting upon an anchor with the words "My hope remains even in the storm." This pendant is a reminder of all those who have come forth to help the foundation. The researchers are tremendous anchors of hope for all Niemann-Pick families. Through their dedication and perseverance in the laboratories they are unraveling the complexities of the disease. Just as an anchor is steady, firm and committed, so are our researchers. Every hour they dedicate to researching NP-C brings us closer to a therapy.

So this summer, I am filled with renewed hope. Advances in research and the enthusiasm of these dedicated scientists, paired with your continued commitment and support has made it possible to continue the battle against Niemann-Pick Type C disease.

Sincerely,

Cindy Parseghian

NP-C Annual Scientific Conference

In June, eighty researchers from around the world convened a meeting to discuss the advances in Niemann-Pick Type C (NP-C) disease research. These meetings were funded by generous grants from the Bacon Family Foundation and the C. R. Bard Foundation, Inc.

In addition to the research presentations spanning two and half days, a full day was also devoted to the first ever clinical workshop co-sponsored by the National Institutes of Health. A summary of the presentations is provided inside this newsletter.

Mark Your Calendar

July 13, 2009 – **Notre Dame Club of Milwaukee's "Ara's Outing 2009"**, Westmoor Country Club in **Brookfield, WI**. Join Notre Dame members and celebrities for golf, dinner and an auction. Contact Tom or Terry Mulcahy: (262) 240-3527.

August 5, 2009 – The third annual **"Irish Legends" Golf Tournament** will take place at the Lost Dunes Golf Club in **Bridgman, MI** to benefit the APMRF and The Lou Holtz Foundation. For information on this fun golf outing, dinner and auction contact Angela Monger: (800) 628-9922, Ext. 503.

August 15, 2009 – Hosted by the Smith Family in honor of their three children with NP-C, **"BReaK Thru Fund Golf Outing"** will be held on August 15, 2009 at Lafayette Elks Country Club in **Lafayette, IN**. Call Trent Smith for information: (765) 477-3410.

October 1-4, 2009- Tucson Originals, a group of local, independently owned restaurants presents the seventh annual **"Tucson Culinary Festival"**, Tucson's premier food and wine event with proceeds to benefit APMRF. Held at Loew's Ventana Canyon Resort in **Tucson, AZ** go to: www.tucsonculinaryfestival.com for information and to purchase tickets.

October 2009 - Stay tuned for the second Reno Gala in support of **Addi & Cassi Hempel**, 5 year old twins with NP-C from **Reno, NV**. For more information visit the website www.addiandcassi.com

ND Honorary Degree Conferred Upon Cindy Parseghian

– From the Proclamation –
At the 164th Commencement
The May Exercises
The University of Notre Dame
Confers the degree of Doctor of Science, honoris causa,
on
a loyal daughter of Notre Dame who has transformed personal tragedy into a passionate commitment to find a cure for Niemann-Pick Type C disease, the rare and fatal genetic disorder that has taken the lives of three of her four children. She and her husband, Michael, have helped raise more than $33 million to fund scientific discovery through the Ara Parseghian Medical Research Foundation, an organization named in honor of the children's grandfather and Notre Dame's legendary football coach. With the strength and heart that only a mother can possess, she has combined deep determination with unwavering faith to become an inspiration and example to all.

Cindy K. Parseghian
Tucson, Arizona

Heartfelt Thanks...

The 14th annual **"One More Victory, Ara!" Celebrity Golf and Gala** weekend presented by **University Medical Center** took place on April 17–18 in Tucson, AZ. It was a fun- filled weekend where friends, fine food, fabulous golf and superb entertainment were enjoyed. Many thanks to Amy Grant and talented friends; Jeff Hanna, Matraca Berg and Phil Madeira along with comedian Gary Mule Deer who provided Gala Guests with an evening to remember.

We thank our title sponsor, UMC, as well as co-sponsors Precision Toyota, Bon Voyage Travel, Cox Communications, Wells Fargo, La Encantada/Westcor and The Westin La Paloma Resort and Spa.

Cynnie Ochoa with Event Co-Chairs Susan Campisano and Kathy Orr.

Michael Parmacek, Scientific Advisory Board Director, Honored

Thank you for this award, I truly appreciate it. The sculpture will always remind me of the team effort that lays at the foundation of the APMRF. It has been my pleasure to serve as the Director of the APMRF SAB for the past fifteen years. While we have made great progress in understanding the cause of NPC disease, I recognize that progress can never come fast enough for children afflicted with NPC disease and their families. Nevertheless, I am confident that the APMRF has explored every reasonable avenue of investigation and someday these efforts will lead to successful therapies, and ultimately a cure, for NPC disease. The APMRF SAB has tried to balance fundamental basic research into understanding the molecular and genetic basis of NPC1 and NPC2 protein function with applied research screening for drugs and compounds that may be therapeutically beneficial. Our greatest success has been attracting world-class medical researchers to focus their efforts on NPC disease research. When the foundation was established, I never dreamed that we would attract this quality of scientist to work on an orphan disease. On multiple occasions, internationally recognized scientists attending the APMRF Scientific Meeting have commented on the remarkable quality of science and research presented at our meetings. This is testament to the quality of the APMRF, members of the APMRF SAB who have reached out to friends and colleagues, and the medical research community at large who have rallied behind this cause.

I owe a personal debt of gratitude to all of the SAB members who have volunteered their time over the past fifteen years. Our original scientific advisory board included Mark Keating, John Lowe, David Ginsburg, Jeff Leiden and Marc Patterson. This group with special expertise in human genetics accelerated discovery of the NPC1 gene, began to elucidate the pathogenesis of NPC disease and oversaw the first drug screen. After it became clear that the molecular defect in NPC disease emanated from a block in lysosomal-endosomal trafficking, we shifted the expertise of the SAB to include Matt Scott, Bill Pavin, Bill Balch, Konrad Sandhoff, Marie Vanier, Jon Epstein, Marlene Haffner and Marc Patterson. Over the course of fifteen years, each SAB member has selflessly volunteered their time and effort, reviewing grant applications generally within 2-3 weeks of receipt and attending our annual meeting in Tucson. I have never worked with a more talented or dedicated group.

At the same time it has been humbling to learn details of the foe we are combating. We believe that to cure NPC disease we must overcome, or bypass, a block in endosomal trafficking which somehow triggers neuronal cell death. Due to the successful fund raising efforts of the foundation, the only criteria the SAB has used to determine if a proposal will be funded is what is the likelihood that this could increase our understanding of NPC disease and/or accelerate progress toward a treatment or cure. However, I've learned that simply throwing money at a problem doesn't get you to the answer any faster. What matters is the quality and creativity of the research scientists that you attract to any given field of research. The APMRF has raised approximately $34,000,000 over the past fifteen years. While this sounds like a lot of money in the grand scheme of medical research and drug discovery, it is not. I am proud of the progress, APMRF-funded scientists have made (though still it is not enough). Ultimately, I believe that the studies performed in APMRF-funded labs will lead to new therapies for NPC disease. Moreover, I am confident, that APMRF-funded research studies will impact on other diseases in ways we cannot anticipate. I also anticipate that research in another field will fundamentally impact on NPC disease.

I'd like to personally thank Cindy and Mike Parseghian and other members of the APMRF Board. It has been my pleasure to work with a board composed of family and friends, who while personally involved in battling NPC disease, never lost sight of how to accelerate and catalyze NPC research. It is a pleasure representing a foundation that spends close to 90% of dollars raised on medical research. This speaks volumes about the dedication of the many volunteers who have contributed to the foundation. Thank you for the sculpture, for the opportunity of working with this group of volunteers, staff and research scientists and for hosting this important meeting.

APMRF Annual Scientific Conference Highlights

Matt Scott, Ph.D., Professor of Genetics, Cell and Developmental Biology at Stanford and a member of the APMRF SAB, chaired the Thursday morning session examining NPC1 protein structure and function. **Rodney Infante, M.D., Ph.D.**, an APMRF Fellow in the laboratory of Nobel Prize laureates Michael Brown and Joe Goldstein at UT Southwestern presented a molecular model that explains how the NPC2 protein transfers cholesterol from within the lysosome to the NPC1 protein which resides in the limiting membrane. In collaboration with other scientists at UTSW the Brown and Goldstein group crystallized NPC1 N-terminal domain bound to cholesterol providing fundamental insights into the molecular basis of NPC1 structure and function. A manuscript describing these important contributions is in press. **Guosheng Liang, Ph.D.**, who is also from UT Southwestern, created a genetically engineered mouse in which the NPC1 gene is conditionally targeted and can be ablated in specific cell types. This valuable reagent will be made available to the NPC research community. **Suzanne Pfeffer, Ph.D.**, Professor of Biochemistry at Stanford, generated a series of tethered NPC1 domain mutants harboring mutations observed in human NPC1 patients. By expressing these mutant proteins she examined which human mutations block the function of NPC1 protein versus which proteins are simply mis-folded and inappropriately trafficked in the cell. These findings may provide a basis for determining which human NPC1 mutations may be amenable to molecular chaperone therapies. Dr. Pfeffer used a novel native gel electrophoresis methodology to identify proteins that physically associate with an NPC1-containing protein complex.

Kangaraj Subramanian, Ph.D., a post-doctoral fellow in the laboratory of Scripps Investigator and SAB member Bill Balch tested a series of NPC1 mutant proteins to distinguish which human mutations functionally disable the protein and which mutations lead to protein mis-folding. Similarly, **Dan Ory, M.D., Ph.D.**, Professor of Medicine at Washington University tested a series of NPC-1 mutant proteins harboring human mutations in the cysteine-rich domain. Like Dr. Pfeffer's studies above, these experiments which were performed with recombinant full length NPC1 protein should provide insights into which human mutations may be amenable to molecular chaperone therapies.

Peter Lobel, Ph.D. (Robert Wood Johnson Medical School) led a session on NPC2, which is mutated in less than 5% of NPC cases and appears to function in the same biochemical pathway as NPC1. He described progress made in creating new mouse models that can be used to study the biological function of the NPC1 and NPC2 proteins. **Judith Storch, Ph.D.** (Rutgers University) presented her work on the mechanism by which NPC2 catalyzes transfer between membranes, and on the relationship between the NPC2 structure and its cholesterol transport properties. She also showed that cyclodextrin may be working by accelerating the rate of cholesterol transfer between membranes.

Dr. Peter Lobel, Ph.D.

John Dietschy, M.D., Professor of Medicine at UT Southwestern chaired an evening session on the cyclodextrin and NPC disease. **Drs. Dietschy, Benny Liu, M.D.** and **Charina Ramirez, M.D.** from UT Southwestern extended the findings described in their recent PNAS manuscript demonstrating that administration of cyclodextrin prolongs the life of NPC1 mutant mice. It also delays the onset of symptoms and, at least initially, improves the observed block in cholesterol storage within the cell. However, cyclodextrin did not cure NPC disease in mice; the longest surviving mice live approximately 6 months. **Steven Walkley, D.V.M., Ph.D**, and **Cristin Davidson, Ph.D.**, from Albert Einstein College of Medicine, using more frequent injections of cyclodextrin (every-other-day) showed that longevity of mice with NPC1 disease could be more than doubled. They also showed that injections started after disease was in progress were also beneficial in prolonging life and in substantially reducing storage of both cholesterol and gangliosides. Importantly, their studies also revealed that cyclodextrin was effective in NPC2 disease but not in other lysosomal diseases exhibiting cholesterol storage in neurons, suggesting a mechanism of action of cyclodextrin linked specifically to the NPC1-NPC2 metabolic defect. **Anton Rosenbaum** and **Fred Maxfield, Ph.D.** from Weill-Cornell Medical Center, examined the mechanisms of action of cyclodextrin in NPC1 mutant cells. **Charles Vite, Ph.D., D.V.M.**, from the University of Pennsylvania, reported that he has begun to test the efficacy of cyclodextrin and miglustat alone and in combination in NPC1 mutant cats. The studies have just begun and very little data is available. While this is potentially an important advance, many questions remain to be addressed including: i) whether cyclodexrin

continued...

APMRF Annual Scientific Conference Highlights (cont'd. from page 4)

Dr. Lawrence Goldstein, Ph.D.

crosses the blood-brain barrier, ii) what form(s) of cyclodextrin possess potentially therapeutic actions, and iii) what toxicity is associated with short and long term administration of cyclodextrin?

On Friday morning, **Bill Balch, Ph.D.** a Scripps Investigator and member of the SAB, chaired a session on NPC1 Neurobiology. **Larry Goldstein, Ph.D.**, Professor of cellular and molecular medicine at UC San Diego, created a knockdown of the NPC1 gene in human ES cells and differentiated these cells into neurons. He reported that these neurons accumulate cholesterol and will be a valuable reagent to examine the pathobiology of NPC disease in the brain. **Manuel Lopez**, a graduate student in the laboratory of Matthew Scott at Stanford, demonstrated that expression of NPC1 protein in cerebellar Purkinje neurons rescues Purkinje cell death observed in NPC1 mutant mice and slowed progression of certain aspects of the disease. By contrast, expression of NPC1 protein in astroglia cells did not rescue Purkinje cell loss in NPC1 mutant mice. Manuel also demonstrated that in the cerebellum there exists immune signals that may be the trigger of autophagy within Purkinje neurons and can serve as the instructions for microglia to selectively search and destroy damaged neurons. **Joyce Repa, Ph.D.**, from UT Southwestern, is examining the interactions between neurons and glial cells in the pathogenesis of NPC disease. Her studies are focusing on the role of inflammatory cascades in the pathogenesis of NPC disease in the CNS. **Matthew Elrick**, an M.D./Ph.D student from Andy Lieberman's laboratory at the University of Michigan, generated genetically engineered mice with a conditional mutation in the NPC1 gene. He demonstrated that selectively ablating the NPC1 gene in Purkinje cells is sufficient to cause Purkinje cell death and ataxia.

Bill Pavan, Ph.D., a Senior Investigator in the NIH Human Genome Institute and SAB member, chaired the Friday afternoon session on NPC Genomics and other model systems. **Shilipi Arora** from TGen reported that she has performed an RNAi screen to identify genes that modulate cholesterol accumulation in NPC cells. "**Heiko Runz, M.D.** from the University of Heidelberg in Germany, identified a novel protein TMEM97 that physically associates with NPC1 and localizes to the lysosome". Additional studies are underway characterizing the function of this protein.

Denny Porter, M.D., Ph.D. from the NIH and **Marc Patterson, M.D.**, from the Mayo Clinic, chaired the Saturday morning sessions focusing on clinical NPC research. **Dr. Porter** and **Nicole Yanjanin, MSN** described the NPC Natural History Study which is being organized at the NIH. **Dan Ory, M.D., Ph.D.**, reported that circulating oxidized cholesterol may serve as a biomarker of NPC disease. Studies are underway to determine whether oxidized cholesterol levels correlate with disease activity or progression. **Kastruri Haldar, Ph.D.** described the newly established Rare and Neglected Diseases program at Notre Dame. **Paul Helquist, Ph.D.**, also from Notre Dame, described the combinatorial chemistry expertise of his laboratory which is being used to generate derivatives of therapeutic compounds that may be tested in NPC mutant mice and eventually NPC patients.

The Clinical workshop spanned both Saturday afternoon and Sunday morning. The workshop was unique in its primary purpose to facilitate coordination of translational and clinical aspects of NPC on an international basis. The goals of the meeting were two fold; first, to promote interactions among basic scientists involved in preclinical testing of potential therapeutic agents in mouse models of the disease and clinical scientists studying NP-C, and second the meeting helped to promote interactions and collaborations between clinical scientists studying NP-C.

Some of the topics discussed included the NIH observational trial, patient support and advocacy, and the need for a common NP-C patient registry. Further discussions were held on standardizing evaluations, including development of a severity scale, cognitive assessments and care of NP-C patients.

Manuel Lopez

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Return Service Requested

Heartfelt Thanks... (cont'd. from page 2)

We wish to thank Houston Traher and the **Catalina Foothills High School Student Council** for their continued support and great organization of the fifth annual **"One More Victory, Ara!" Walk-A-Thon** which was held on April 11 at the Rillito Park, Tucson. The students of Catalina Foothills Student Council are to be commended not only for their commitment to this cause but to making philanthropy a priority. Over the past five years more than $75,000 has been raised for NP-C research.

Run For The Angel Twins.

¡Fiesta Fantastica! and indeed it was!!! Thank you to our presenting sponsor, **Chapman Automotive** and co-sponsors **La Encantada, Tucson Lifestyle** and **Sol Casinos** for a festive evening which took place on May 8 at the beautiful La Encantada shopping center, Tucson. Guests were treated to a variety of delicious foods from some of Tucson's finest restaurants and resorts, beverages in abundance and wonderful music and dance performances.

Many thanks to Colleen Sosbee and friends of the Bouchard Family who helped to make the first **"Run for the Angel Twins"** a huge success! This event held in Frisco, Texas on March 28th raised over $9,500 for the Angel Twins Fund in support of their **"Million Dollar Mission"** and in memory of the Angel Twins, Cathryn and Corynne.