

WINTER 2010

# A GOAL FOR LIFE

For Friends and Supporters of the Ara Parseghian Medical Research Foundation



*Gratitude unlocks the fullness of life. It turns what we have into enough, and more.*

*It turns denial into acceptance, chaos to order, confusion to clarity.*

*It can turn a meal into a feast, a house into a home, a stranger into a friend.*

*Gratitude makes sense of our past, brings peace for today and creates a vision for tomorrow.*

*Melody Beattie*

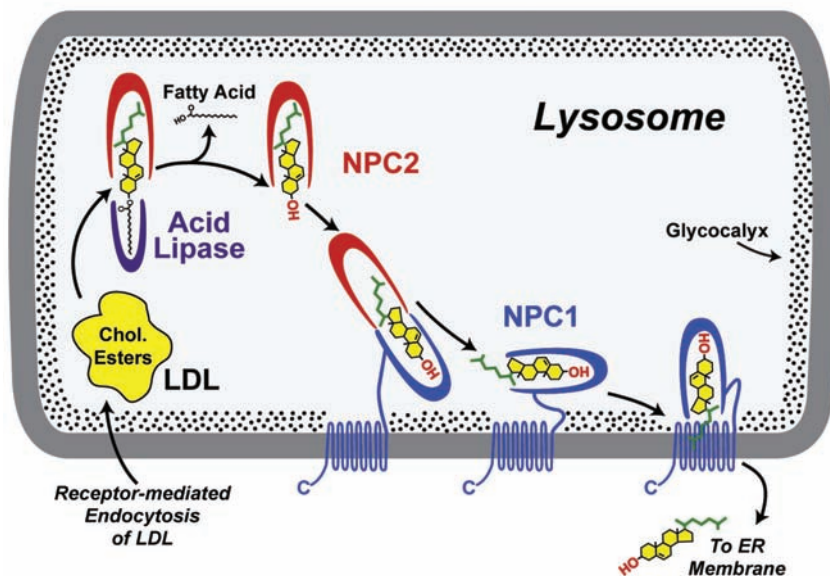


# NP-C Scientific Conference Overview by Dr. Suzanne Pfeffer

*The annual Scientific Conference on NP-C Disease was held at the Westin La Paloma Resort & Spa, Tucson, AZ on September 24-25, 2010. Over 65 researchers were in attendance for two very full days of presentations of the latest research developments, discussions and collaborations.*

*Next year's conference will be held at the University of Notre Dame on June 10 – 11, 2011.*

*We wish to thank Dr. Suzanne Pfeffer for the following highlights of this year's conference.*



Niemann Pick Type C disease is caused by mutations in the genes encoding NPC1 or NPC2; when the functions of these proteins are compromised, cholesterol and sphingolipids accumulate in a cellular compartment called the lysosome. Lysosomes are especially important for brain function, and the hope is that knowledge about the roles of NPC1 and NPC2 proteins will give scientists additional tools to treat NPC disease. The talks ranged from the most fundamental studies of NPC1 protein and its interactions with NPC2 protein to the latest results obtained from initial

trials of cyclodextrin in cats and in children.

The University of Texas Southwestern (UTSW) Medical School laboratory of the Nobel laureates, Mike Brown and Joe Goldstein continues to provide fundamental information regarding how NPC1 and NPC2 proteins bind cholesterol in lysosomes for delivery to the cell's cytoplasm (see figure from Kwon et al. (2009) Cell 137, 1213).

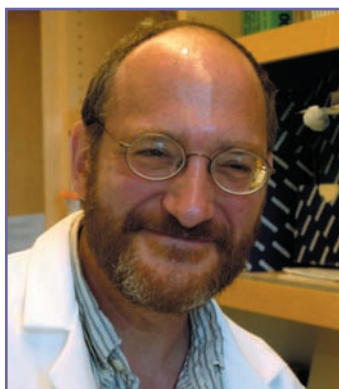
Cholesterol is delivered to cells from the plasma in the form of low density lipoproteins (LDL). Cholesterol esters are hydrolyzed in the lysosome, releasing free cholesterol. This cholesterol is proposed to bind to NPC2, which may transfer it to NPC1 for delivery (by an as yet unknown mechanism) across the lysosome membrane.

Normally, cholesterol released from lysosomes is delivered to another cellular compartment called the endoplasmic reticulum (ER) where an enzyme called ACAT re-esterifies the cholesterol for storage, and signals to a regulatory cascade to decrease new cholesterol synthesis. Lina Abi-Mosleh (UTSW) showed that cyclodextrin relieves the NPC1 or NPC2 block in lysosomes, enabling the ACAT reaction to take place. This allows for cholesterol ester storage in the cytoplasm where it is much less toxic than in lysosomes. NPC1 protein is believed to span the membrane 13 times; it also contains three large luminal domains that face the inside of the lysosome.

Brown and Goldstein showed previously that the first luminal loop binds cholesterol in the test tube. Guosheng Liang (UTSW) reported studies that support the importance of this first luminal domain for cholesterol binding and NPC1 function in mice. His colleague from the Brown and Goldstein group, Massoud Motamed, described a rigorous study identifying the precise regions of NPC2 that bind specific sites on the first cholesterol-binding luminal domain of NPC1. Suzanne Pfeffer (Stanford) showed preliminary data that indicate that the second



William Balch, Ph.D.  
The Scripps Institute



Peter Lobel, Ph.D.  
Rutgers University



Frederick Maxfield, Ph.D., Weill  
Medical College of Cornell University



Suzanne Pfeffer, Ph.D.  
Stanford University School of Medicine

# Scientific Conference Overview (cont'd. from page 2)

luminal domain of NPC1 holds on to NPC2 to enable cholesterol transfer between the two proteins.

Kanagaraj Subramanian and Bill Balch (Scripps) generated over a hundred mutant constructs to categorize all reported disease mutants into distinct subsets. This will be important as different therapies are analyzed: some approaches may be more effective for specific classes of mutations.

Fabian Bartz and Heiko Runz (U. Heidelberg) reported their progress on a very interesting protein named TMEM97 that seems to regulate the amount of NPC1 in lysosomes. It will be interesting to learn if modulating this protein will make it possible to increase the absolute levels of NPC1 protein produced. This strategy could be beneficial for patients because in some cases, production of more mutant protein can compensate for functional defects.

Several groups have constructed mice in which NPC1 function is blocked in a tissue specific manner to try to understand the specific consequences of the disease in just the brain or the liver or other organs. Ting Yu and Andrew Lieberman (U. Michigan) knocked out NPC1 function in astrocytes of 6 week-old mice and reported that this loss of function does not recapitulate NPC1 disease. Andrés Klein and Matt Scott (Stanford) similarly showed that rescue of NPC1 function in NPC1  $-/-$  astrocytes did not alter disease course, but expression in Purkinje neurons or other neurons did.

Their data suggest that microglia and macrophages react to neuronal or hepatocyte dysfunction, and the associated inflammation is due to neuronal disease. They also found that production of NPC1 for a short period, after the disease has progressed, significantly improved liver function, showing that NPC liver pathology is reversible.

In designing new therapies, markers must be established to determine therapy effectiveness. Denny Porter (NIH) reported on his progress in identifying biomarkers in cerebrospinal fluid that have the potential to serve as surrogate markers in future therapeutic trials.

Calbindin and total tau protein levels seemed to decrease upon miglustat treatment, and may be useful markers for future studies. Magnetic resonance imaging is also being used to characterize mouse brains from several disease model strains (John Totenhagen and Theodore Trouard, U. Arizona) and may be an important means to monitor disease status in the future.

Ron Browne (Sun Valley Pharma Consult) provided an update on hydroxypropyl beta cyclodextrin (HPBCD) treatment of identical twin patients; the major take home message was the importance of drug administration to permit access of drug across the blood brain barrier. Indeed, Charles Vite (U. Penn) reported impressive results for intrathecal administration of cyclodextrin in cats. Neuronal swelling and axonal spheroid formation was markedly reduced. Nevertheless, microgliosis and astrogliosis remained, and pulmonary disease could not be avoided. Sadly, cyclodextrin led to severe loss of hearing capacity in treated cats.

Using Npc1  $-/-$  mice, several other labs also reported pulmonary pathology that was not responsive to cyclodextrin therapy (Robert Erickson, U. Arizona; Charina Ramirez and John Dietsch, UTSW). Also, Cristin Davidson and Steve Walkley (Albert Einstein) reported that HPBCD and methyl beta cyclodextrin were more effective than other substituted cyclodextrins in reducing cholesterol and glycosphingolipid storage in NPC disease in mice. Hopefully, it will be possible to design therapies that will avoid some of the toxic effects of cyclodextrin.

Fred Maxfield (Cornell Med) in collaboration with Olaf Wiest and Paul Helquist (Notre Dame) described targeted versions of cyclodextrin that should be able to pass the blood brain barrier and be concentrated by cells, so that much lower doses may be needed. In addition, their cell culture assays (and Joyce Repa's (UTSW) mouse studies) indicate that so-called HDAC inhibitors, already in clinical trials for cancer, may also have value in NPC disease. These approaches offer great promise to all of us seeking therapy for patients with this devastating illness.



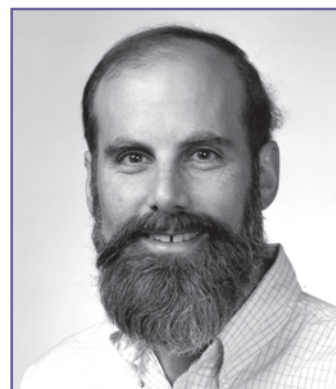
Paul Helquist, Ph.D.  
University of Notre Dame



Judith Storch, Ph.D.  
Rutgers University



Charles Vite, D.V.M., Ph.D.  
University of Pennsylvania School of  
Veterinary Medicine



Matthew Scott, Ph.D., Stanford  
University School of Medicine



## Heartfelt Thanks



*Bookstore Basketball players ready to hit the courts.*



*Thank you to the volunteers who make it happen!*



*"Team Brennan"*

The Notre Dame Club of New York under the enthusiastic direction of Maggie Dowd (ND '02) hosted the **"2010 Bookstore Basketball"** event benefitting the APMRF. This 3-on-3 basketball tournament followed by a post party at the Three Monkeys Bar was held on October 15th in Manhattan and had 17 teams compete. This event was generously supported by many "Domers" including Mike Brennan, ND lineman on the '89 Championship Team along with many non "Domers". We wish to thank the many financial sponsors, participants, donors and volunteers who helped to make this event such a great success. In the words of Maggie Dowd, "I'm so proud of what we were able to do, and am honored to have been a part of your efforts – I have so much admiration for what the Parseghian family has done, turning their loss into hope."



*Coach Ara, ESPN's Mark May and Coach Lou at the Irish Legends Golf Tournament*



*Thank you Angela, Anne, Skip and Kathy!*

On August 4th the fourth annual **"Irish Legends Golf Tournament"** took place at the Lost Dunes Golf Club in Bridgman, Michigan. With legends, Lou Holtz, Ara Parseghian, Johnny Lujack and Johnny Lattner in attendance, not even the rain could put a damper on this fun event. Many thanks again to the gracious hosts and originators, Skip Strezlecki, Jim Moriarity, Mike Leep, Mike Nolan and Angela Monger. Plans are in the works for a fifth annual tournament!!

The Notre Dame Club of Milwaukee held the 10th annual **"Ara's Outing"** on July 12, 2010 and was held at the Westmoor Country Club in Brookfield, Wisconsin. We wish to thank Tom & Terry Mulcahy for the many years of support and tireless enthusiasm for organizing and hosting this event. In the course of these ten years more than \$180,000 has been raised for NP-C research.

## Mark Your Calendar

**January 22, 2011** – Every January the local community of family, friends, benefactors, and businesses in Las Vegas, NV come together to honor and support 13 year old Ty Quandt through a benefit concert and silent auction called **"Touchdown for TY"**. Under the energetic direction of Verna Burrows, grandmother to Ty, this year marks the sixth year of this great event. For more information go to: [www.touchdown4ty.com](http://www.touchdown4ty.com) or call Verna Burrows at 702.363.5443.

# Heartfelt Thanks... (cont'd. from page 4)



*Trent Smith and friends at the "BReaK Thru Golf Outing".*



*Chandler and Keaton Smith enjoying a moment at this year's event.*

The Smith Family along with the support of many friends and businesses in Lafayette continue to raise funds for NP-C research at Purdue University through various events throughout the year.

The third annual **BReaK Thru Golf Outing**, hosted by the Smith Family in honor of their three children, Braden, Keaton and Riley, was held on August 21st at Lafayette Elks Country Club, Lafayette, IN.

Another fundraiser in honor of the Smith Family took place in August at the Monticello Family Aquatic Center and was aptly named "**Splash for Niemann Pick**". Fourteen year-old Elizabeth Miller took it upon herself to organize this event by rallying friends to enjoy a cool dip in the pool while helping a very important cause. Thank you to all who attended!



*Elizabeth Miller presents a check for \$3000 to Julie and Trent Smith for NP-C research.*



*Ashton Friedl takes the stage at "It Comes In Pink".*

The second annual "**It Comes In Pink**" event on October 1st at the Children's Museum of Richmond, VA was held in honor of eight year old Ashton Friedl. Klaxton Brown, "the smoothest sound in town" provided the music. Combined with a great dinner and auction the evening was enjoyed by over 180 attendees. We wish to thank Ashton's uncle, Kevin Currie for the many hours he spent in planning and organizing another wonderful, fun-filled evening.

Ashton's grandfather, Chuck Friedl is also working hard to raise funds and awareness for NP-C through the Ocran United Methodist Church and other churches in the Sutherland, VA area. There has been a wonderful outpouring of support through various events; a Chicken Barbeque, Youth Car Wash and Yard Sale to name a few, with all the proceeds coming to the APMRF. Thank you Chuck and thank you to all who advance the research by supporting these events.



*The Sutherland, Virginia community embraces the NP-C cause.*





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## Return Service Requested

## Desert to Dome

The University of Notre Dame Dean of the College of Science Greg Crawford and his wife Renate completed their ambitious “Desert to Dome” journey this summer by riding over 2,300 miles from Tucson to South Bend raising awareness and funds for NP-C disease and in celebration of the newly strengthened partnership between the Parseghian Foundation and the University of Notre Dame.



### DESERT to DOME

Along the way the Crawfords were cheered on by hundreds of ND alumni and hosted by many ND Clubs. Upon their return to South Bend on August 23rd, they were treated to a spirited Pep-Rally Welcome in true ND tradition! The hope and partnership that this journey created provides inspiration and motivation to continue the fight to cure this devastating disease.

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