

A GOAL FOR LIFE

For Friends and Supporters of the Ara Parseghian Medical Research Foundation



Dear Friends,

Those lazy, hazy, crazy days of summer, we all wish for, are winding down as fall quickly approaches. At the Foundation, our busy summer was filled with fundraisers, science gatherings and the opportunity to connect with new Niemann Pick Type C (NP-C) families. It was a summer that saw many advances in the research, the continued support of many caring souls and the pain of meeting new families who recently had children diagnosed with NP-C.

As you'll read in this newsletter, the annual Michael, Marcia and Christa Parseghian Scientific Conference for Niemann Pick Type Research was held at the University of Notre Dame. Over three days in June, researchers from around the world gathered to report their advances in understanding NP-C and to discuss the exciting development of several promising therapies, which are moving towards trials. Several new families also attended the conference and shared with the researchers the struggles facing NP-C children.

In addition to the informative science meetings, several fundraisers were held across the country. From Virginia to Michigan, Indiana, Illinois, Arizona, Colorado and California, events were held to raise the much-needed dollars for NP-C research. Greg Crawford, the Dean of the College of Science at Notre Dame, managed to visit almost all of these states, as he once again rode his bike across the country in support of NP-C research, traveling 3,300 miles on his "Road To Discovery" journey.

As we say good-bye to summer, we extend a deep felt gratitude to all of the generous Foundation supporters who have dedicated some of their valuable summer days and resources to helping all children afflicted with NP-C.

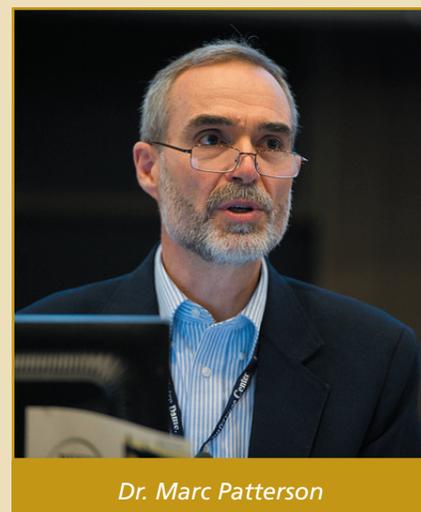
We thank you,

Cindy and Mike Parseghian

NP-C Scientific Conference Highlights

by Katerina Lichtenwalter, Dr. Holly Goodson and Dr. Richard Taylor

The 2012 Michael, Marcia, and Christa Parseghian Conference on Niemann-Pick Type C Research took place on June 7-9 at the University of Notre Dame in South Bend, Indiana, U.S.A. The conference opened with a video-call greeting by **Gregory Crawford**, dean of Notre Dame's College of Science, who was in the middle of his transcontinental bike ride, the Road to Discovery – a fundraiser for NP-C research. Following the greeting, the keynote speaker, **Dr. Marc Patterson (Mayo Clinic Children's Center)** gave an overview of the evolution of our understanding of NP-C from its first identification in the late 1940s through the cloning of the NPC1 gene in the late 1990s and up to present day efforts to find effective treatments, develop better screening, and improve the lives of children with NP-C. Dr. Patterson stressed the importance of family and patient advocate groups, which began



Dr. Marc Patterson

(cont'd. on page 2)

organizing in 1990s, on this journey. Important for all of us in 2012: focus on earlier diagnosis and prevention of neurodegeneration (since lost neurons cannot be restored with modern technology); better treatments; realistic clinical trials; education of elected officials, insurers, health authorities, as well as the general public; machine-implemented and standardized protocols for disease diagnosis and testing of potential treatments; and adaptation of the FDA drug approval process for rare diseases.

During the session “Molecular and Cellular Biology,” **Dr. Suzanne Pfeffer (Stanford University School of Medicine)** presented her lab’s continued work to understand the interactions between NPC1 and NPC2 proteins, and she described the results of recent experiments in which she found that modification of the lysosome’s inner membrane may allow more cholesterol to exit the lysosome in the absence of functioning NPC1 protein. After the formal presentation, there was discussion of the possibility that this mechanism might contribute to the effectiveness of miglustat against NP-C. **Dr. Yang (University of New South Wales)** presented his group’s efforts to use yeast cells (which contain proteins related to NPC1 and NPC2) to identify the molecular mechanisms that regulate cholesterol efflux from the late endosome/lysosome compartment into the endoplasmic reticulum. **Ting Yu** from **Dr. Andrew Lieberman’s** lab at the **University of Michigan Medical School** discussed his work showing that compounds known as ryanodine receptor antagonists can reduce the destruction of several different mutants of NPC1, and that the resulting increases in the levels of the mutant NPC1 proteins correlate with reduced accumulation of cholesterol and sphingolipids. These observations suggest that compounds that regulate protein degradation might have utility as NP-C therapies. **Dr. Paulina Ordonez** (a member of the lab of **Larry Goldstein** at **University of California San Diego**) talked about the Goldstein lab’s success in generating neurons from induced pluripotent stem cells derived from patient fibroblasts. The Goldstein lab hopes to use these human induced pluripotent stem cells to study the effects of different NPC1 defects in neurons and develop a platform for high-throughput screening of potential therapeutics for

NP-C and other neurodegenerative diseases. **Dr. Dorothea Maetzel** in Rudolf Jaenisch’s lab at the **Whitehead Institute for Biomedical Research** is also generating human induced pluripotent stem cells from patient fibroblasts for the study of the effects of NPC1 in both neurons and liver cells.

Opening the session on “Developing Diagnostics,” **Anne-Katrin Giese (University of Rostock, Germany)** presented preliminary clinical trial data on two newly-identified biomarkers, NPC-509 and NPC-465, which show high sensitivity and specificity for NP-C and allow for discrimination between Niemann-Pick Type C and Types A and B as well as between phenotypes from carriers, who do not exhibit elevated levels of these compounds. **Dr. Daniel Ory’s** lab at the **Washington University School of Medicine** continues to work on blood screening for oxysterols, also a highly-specific and sensitive method, which he expects will replace filipin staining as the diagnostic standard and which can be used to measure treatment efficacy. His group is also working on an analytical assay for dried blood spots from newborn screening cards, which would allow for an earlier diagnosis. **Dr. Suhail Alam** from the lab of **Dr. Kasturi Haldar** at the **University of Notre Dame** reported on comparing whole-genome expression and cellular analyses to determine which genes were upregulated in NP-C mice so that their products could be evaluated as potential biomarkers or targets for therapeutic agents. Dr. Alam and his colleagues found that elevation in an immune system protein known as lysozyme correlates with disease severity.

In the session on “Approaching New Treatments in Patients,” **Dr. Denny Porter (NIH)**, reported on the results of his team’s ongoing study of 68 patients ranging from 3 months to 54 years old, 42% of whom are already on miglustat. One important goal of



Dr. Denny Porter

this study is to establish a set of biomarkers that can be used to assess disease progression and the efficacy of potential therapies. In this study, the patients' disease progression is being evaluated according to a number of criteria, including eye movement, speech, fine motor skills, hearing, seizures, ambulation, swallowing, cognition, and memory; additional markers in serum and cerebral spinal fluid are also being examined. Dr. Porter also discussed how the Therapeutics for Rare and Neglected Diseases Program (TRND) at the NIH is collaborating with the NIH's new National Center for Advancing of Translational Sciences (NCATS) to launch a Phase I trial directed toward establishing a safe and effective dose of cyclodextrin. **Dr. Camilo Vieira (Federal University of Bahia – Brazil)** reported on the progress of two Brazilian sisters who have been receiving cyclodextrin treatment for two years via a combination of intravenous and intrathecal injections. The girls were reported to show marked improvement as evaluated by subjective criteria such as ambulation and as seen in brain metabolism on PET-scans. While these observations were viewed as being very hopeful, some attendees also expressed caution in interpreting these results because the trial was not controlled, and so the improvements could be due to changes in other medications, etc. **Dr. Norbert Wiech (Lysomics, LLC)** presented a talk on the repurposing of vorinostat – a histone deacetylase inhibitor (HDACi) already approved in 2006 for the treatment of cutaneous T-cell lymphoma and studied in more than 1000 cancer patients – for the treatment of NP-C. HDACi do cross the blood-brain-barrier (unlike cyclodextrin) and have demonstrated anti-inflammatory activity in humans. Dr. Wiech's company – Lysomics, LLC – is working with Merck Research Labs, which markets vorinostat, to set up clinical trials to test the therapeutic potential of HDACi for NP-C. **Lisa Peintinger**, from the **Clinic and Policlinic for Psychiatry and Psychotherapy in Regensburg, Germany**, presented her work on a psychiatric profile for NP-C patients, which would serve to enable earlier diagnoses of NP-C and provide a clearer picture to the caregivers about the patients' psychological state. This is a previously untouched area in NP-C research.

The session titled "From Molecules to Drugs" opened

with a presentation by **Dr. Kanagaraj Subramanian (lab of William Balch at the Scripps Research Institute)**. He has assembled a large set of NPC1 mutant genes that have been engineered to produce mutant NPC1 proteins in human cells, and he is studying how potential therapeutic compounds known as proteostasis regulators and HDAC inhibitors (HDACi) can be used to restore the folding, trafficking, and function of different classes of these mutant proteins in tissue culture cells. **Dr. Fred Maxfield** and **Dr. Shu Mao (Weill Cornell Medical College)** also reported on their efforts to study how HDACi compounds affect the activity of various mutant NPC1 proteins in tissue culture cells. In combination, their observations suggest proteostasis regulators and HDAC inhibitors might have therapeutic value, but not for the subset of people bearing mutations that are insensitive to these compounds. **Dr. Andrew Munkacs**i and **Dr. Stephen Sturley of Columbia University Medical Center** reported on their efforts to use yeast cells to identify genes other than NPC1 and NPC2 that could modify NP-C disease onset and progression and would therefore be good therapeutic targets. **Dr. Richard Taylor (University of Notre Dame)** presented his work, still in its early stages, on herboxidiene – a natural, bacteria-derived compound. Herboxidiene upregulates gene expression and may correct NPC1 deficiency, like HDACi, although via a different method – by inhibiting pre-RNA splicing. **Dr. Holly Goodson (University of Notre Dame)** presented on the quantitative comparison of several compounds in treating the cholesterol accumulation in NP-C fibroblasts: HDACi, cyclodextrin, rapamycin, decitabine, chloroquine, and chlorpromazine. While some of these decreased cellular cholesterol levels and others increased them, a combination of some of these compounds with cyclodextrin proved beneficial.

Opening the session on "Cyclodextrin - Drug Development and Molecular Basis", **Dr. Cesar Lopez (University of Groningen, The Netherlands)** presented work from his lab on computer molecular dynamics simulations of cyclodextrin-mediated cholesterol efflux from the late endosome/lysosome. Since the pathway by which cyclodextrin aids in cholesterol clearance is not yet established, Dr. Lopez and his colleagues propose that an understanding of

how it works will allow for the design of more effective derivatives of this compound. **Cristin Davidson** in the lab of **Dr. Steven Walkley** at the **Albert Einstein College of Medicine** presented the results of their comparison of the efficiency of ten different cyclodextrins in treating the symptoms of NP-C disease in NPC1 mutant mice. This analysis confirmed that hydroxypropyl- β -cyclodextrin, which will be used in the upcoming NIH clinical trial, is the most effective version of the compound. **Dr. Leslie McCauliff** in the lab of **Judith Storch** at **Rutgers University** reported on their studies of NPC2, which provide evidence that NPC2 has at least two membrane-interacting domains that are necessary for cholesterol transport. They also performed tests on a group of novel cyclodextrin polymers developed by the Thompson laboratory at Purdue. They reported that these polymers (which might be expected to have longer circulation times in vivo) were effective at reducing cholesterol accumulation in NPC2^{-/-} tissue culture cells, suggesting that these cyclodextrin polymers might have therapeutic applications in NP-C disease.

After a break, the session on basic research into cyclodextrin continued when **Anna Taylor** in the lab of **Dr. Joyce Repa** at the **University of Texas Southwestern Medical Center** reported her group's investigations into whether combinations of cyclodextrin and LXR agonists are more effective than cyclodextrin alone in treating Npc1^{-/-} mice. LXR agonists are compounds that have been previously shown to cause a modest increase in the lifespan of Npc1^{-/-} mice. They found that providing these treatments in combination provided no additional benefit, suggesting that the two agents might be working through a common mechanism. **Dr. Joyce Repa** continued by reporting on studies with LBH589, an HDAC inhibitor, which was found not to prolong lifespan in Npc1^{-/-} (null) mice but did appear to affect cholesterol levels in wild type mice. While initially disappointing, these observations are consistent with results in fibroblasts presented earlier in the meeting showing that HDACi have no effect on null mutants of NPC1. **Dr. David Thompson's** lab at **Purdue University** is working on synthesizing cyclodextrin polymers – long chains of cyclodextrin molecules – which would improve delivery of cyclodextrin to the

target and prevent its premature clearance from the body. The goal is to design a polymer that would release unmodified hydroxypropyl- β -cyclodextrin monomers under lysosomal conditions. Dr. Thompson and his colleagues have prepared Pluronic-based polyrotaxanes that are effective in clearing cholesterol as shown by filipin staining of NPC2-deficient fibroblasts. **Dr. Jean Vance (University of Alberta)** presented on cyclodextrin dosing of brain cells – glia and neurons. She has found that cyclodextrin administered at a concentration of .1 mM is both non-toxic and effective at clearing cholesterol from the late endosomal/lysosomal compartment.

The last session of the meeting (“Pathological models of NP-C”) focused on research that uses model organisms (animals with NP-C disease) to understand human NP-C disease and test possible treatments. First, **Dr. Charles Vite (University of Pennsylvania)** reported on an ongoing cyclodextrin trial (to be completed by Fall 2012) that is being performed on NPC1 deficient cats. He and his colleagues have found that cats who were started on intrathecal cyclodextrin treatment at 3 weeks of age showed nearly complete improvement of clinical signs (at least up to 24 weeks of age, when untreated cats die) but had a dose-dependent hearing loss. Cats who started therapy at 16 weeks of age – when they exhibit considerable neurological dysfunction – survived longer than untreated cats. A question was raised as to whether pre-loading of the cyclodextrin with cholesterol might reduce the impact on auditory function. **Dr. Benny Liu (University of Texas Southwestern Medical Center)** reported the results of cyclodextrin treatment administered both subcutaneously and intrathecally to mice at various ages. He reported that mice who received early (presymptomatic) treatments had dramatic improvements relative to control NP-C animals when measured at 100 days of age. He also tested the effect of treatments that started at 49 days of age (when the mice have begun to manifest symptoms) in order to gain insight into whether neurodegeneration might be halted in children who would start receiving treatment only after their symptoms become apparent. These mice did live longer than NP-C untreated mice, but still suffered consequences of the disease and did

not achieve a normal life span. These observations highlight the importance of early (preferably presymptomatic) diagnosis and treatment. **Dr. Barbara Karten** of **Dalhousie University** reported on her lab's analysis of energy metabolism in the mouse brain, which revealed that there are differences – sometimes apparent presymptomatically – in metabolism and gene expression between NPC1 deficient mice and wild type mice. **Dr. Frank Pfrieder** (**University of Strasbourg**) presented his group's work on mouse retinal cells, which vary in their dependency on NPC1 protein. Continued study of the underlying molecular framework should reveal new drug targets and aid in test design for potential treatments.

A special note of gratitude to **Michael, Sabine, and Lili Fornfeist** for making a transatlantic trip from Germany to attend this year's conference and share their story with us. Thank you, likewise, to **Jim Green**



Sabine, Michael & Lili Fornfeist

and the Niemann-Pick Disease Group (UK) for sending a warm greeting to the conference attendees via the Fornfeists. ■

Recently Funded Grants

Ara Parseghian Medical Research Foundation - Currently Funded Grants as of 7/01/2012

Lawrence S. B. Goldstein, Ph.D. – Distinguished Professor, Investigator, and Director of the UCSD Stem Cell Program
TITLE: “Using human induced pluripotent adult stem cell derived neurons to accelerate drug development in NPC1”.

Paul Helquist, Ph.D. – Professor, Dept of Chemistry and Biochemistry, University of Notre Dame
TITLE: “Selective Epigenetic Therapy for NP-C Disease”.

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 Niemann-Pick C disease”.

Daniel S. Ory, M.D. – Professor of Medicine, Cell Biology and Physiology, Internal Medicine, Washington University
TITLE: “Development of a Newborn Screen for Niemann-Pick C1 Disease”.

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

Forbes D. Porter, Ph.D. – Senior Investigator, Eunice Kennedy Shriver National Institute of Child Health and Human Development
TITLE: “PET Imaging of HP-B-CD in Niemann-Pick disease, type C1”.

Judith Storch, Ph.D. – Professor, Rutgers, the State University of New Jersey
TITLE: “Cholesterol transport by NPC proteins and cyclodextrins”.

Kanagaraj Subramanian, Ph.D. – Research Associate, Cell Biology, The Scripps Research Institute
TITLE: “Small Molecule Regulators Impacting the Global Correction of NPC1 Disease”.

Heartfelt Thanks

"It Comes In Pink, Pink Nic"

The 2012 "It Comes In Pink" event took on a new look and a new date. The first annual "Pink Nic" took place on May 12th at the Richmond Raceway in Richmond, VA, honoring local sweetheart, Ashton Friedl. This event provided something for the entire family with an afternoon of dancing, beach music and plenty of delicious BBQ! Thank you to all who continue to support the Friedl family and these events. With your help Ashton continues to see the "pink" side of life. The next "Pink Nic" will be held on May 4, 2013. For more information visit: www.itcomesinpink.com



Ashton Friedl



ND Class of '77 Reunion

In May, Mike and Cindy Parseghian joined classmates to celebrate their graduation from Notre Dame 35 years ago! To commemorate that era, fellow classmate, Betsy Sklena, created a CD of representative 70's tunes. The CDs were sold at the reunion and the proceeds donated to the Parseghian Foundation. Thank you Betsy and thank you to Ginger McGowan Bishop for coordinating this effort. Mike and Cindy also wish to thank the Class of '77 for the many donations that were received by the Foundation following the reunion and for the outpouring of support they have received throughout this challenging journey.

Chicago...the BAND!!! A group of Parseghian Foundation supporters were treated to an evening of great music in Tucson on July 10th at the Casino del Sol Resort. The evening kicked off with a gracious greeting back stage by the entire band and manager, Pete Schivarelli, followed by a rockin' evening of fabulous music by Chicago and the Doobie Brothers. At the evening's end, Pete was presented with a gift from the group, a statue of a young boy kicking a football, designed after the Parseghian Foundation's logo. Many thanks to Chicago for their ongoing generosity and phenomenal support. What a memorable evening! For upcoming tour information visit: www.chicagotheband.com



Pete Schivarelli with Parseghian supporters



Winning Team at Parseghian Classic

Parseghian Classic

Pebble Beach, known worldwide, for its breathtaking beauty and incredible golf courses was the setting for the inaugural Parseghian Classic, presented by the University of Notre Dame. The golf participants walked in the footsteps of the sport's legends on Pebble Beach Golf Links and the Links at Spanish Bay. The three day event culminated with a gourmet dinner at the Beach Club and a performance by comedian, Gary Mule Deer. All of the funds raised will be used to support young NP-C investigators around the world. Many thanks to the wonderful committee at UND whose tremendous efforts and organization made this event so successful.

Irish Legends

The sixth annual Irish Legends Charity Golf Classic held on June 25th was a day of great golf and grand tradition. ND Legends...Coaches Parseghian, Holtz and Kelly were on deck and in the words of Coach Holtz, "It's a great opportunity for three coaches to get together. I love Ara and we exchange ideas and visit with Brian Kelly. People come back...it's just a great time for a great cause...I really enjoy it." Thank you to Skip Strzelecki, Angela Monger and to all the participants for your unwavering commitment and support of great causes.



www.irishlegendsnd.com

Heartfelt Thanks (cont'd. from page 6)

Road to Discovery 2012....3300 miles, 13 states, 33 days!

The Dean of Science at Notre Dame, Greg Crawford has done it again! On May 21st Greg began his third epic bike ride in Boston where the ND Club of Boston provided a celebratory send off and Greg dipped the rear wheel of his bike in the Atlantic Ocean. He ended his ride on June 22nd by dipping the front wheel in the Pacific Ocean in Pebble Beach, California which provided an exciting kick-off for the first annual Parseghian Golf Classic.

Along the way....Greg's trip took him through the varied terrain of 13 states covering 3300 miles as he visited with NP-C families and was cheered on by ND Clubs. Arriving in South Bend, he joined with Coach Parseghian for a well attended Mass and reception. Coach Ara gave an inspirational talk and expressed his gratitude for the determi-

nation and dedication that Greg has shown in his mission to end this disease.

Another stop included a warm welcome by the ND Club of Denver at a gathering that took place at Little Man Ice Cream. Guests were treated to ice cream and invited to bid on a few choice raffle items. Many thanks to Marcia Mueller, Bob Kelley and the ND Club of Denver for organizing this fun event. Dean Crawford comments on the impact of the Parseghian family's story - "It's part of our mission, our passion, and it has affected our Notre Dame family. Everyone's fighting, from the kids, the families, the professors, the administrators, the alums, the coach, all the researchers. It's atypical. This is one of those things where we're all in this together."

We thank Greg for his inspirational vision and his ability to increase visibility, promote research and provide hope for all who are affected by this terrible disease.

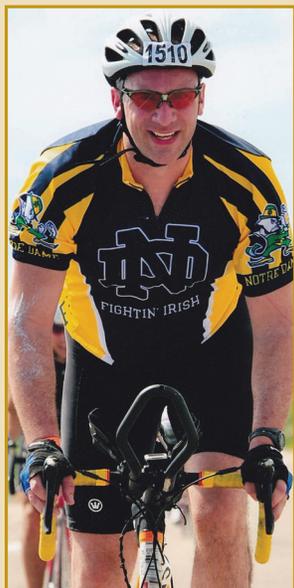


Dean Greg Crawford on the Road to Discovery



Coach Ara Parseghian

Mark Your Calendar



Bill Keen

November 25, 2012

Bill Keen, a dedicated and accomplished athlete, is putting his passion for triathlons into supporting the Irish Legends coaches: Coach Parseghian, Coach Holtz and Coach Kelly and their respective foundations. As he prepares for his 11th Ironman Competition to be held on Thanksgiving weekend, his goal is to raise significant dollars to be shared by all 3 foundations. Please consider supporting Bill Keen in this ambitious endeavor. Bill can be reached at (219) 381-6852.

June 13-15, 2013

The annual Michael, Marcia and Christa Parseghian Scientific Conference for Niemann Pick Type C Research will be held on the campus of the University of Notre Dame from June 13-15. Researchers and NP-C family members will attend 2 full days of presentations, discussions and collaborations on the latest developments of NP-C research. For information contact Stephanie Purcell at Stephanie.Purcell.27@nd.edu.

June 21-24, 2013

The second annual Parseghian Golf Classic will take place at the magnificent Pebble Beach Golf Resort. Full golf and non-golf packages will be available. For information visit www.niemannpick.nd.edu or contact Cristi Ganyard at (574) 631-3070 or cganyard@nd.edu.



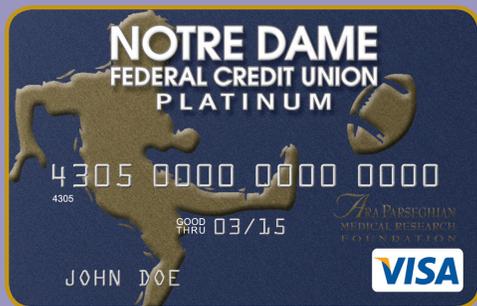
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Notre Dame Federal Credit Union...supporting APMRF since 2000



We wish to express our sincere gratitude to Notre Dame Federal Credit Union for their long time support. They have supported the foundation for 12 years, and generously sponsored Dean Greg Crawford's Road to Discovery 2012 bike ride.

We are very excited about their new venture: Notre Dame FCU has developed a credit card which will donate a percentage of the amount charged on the card towards NP-C research. Notre Dame FCU's philosophy of "people helping people" is evidenced by their continued commitment to helping in the fight against NP-C disease.

If you are interested in learning more about this program, please see the enclosed brochure.



Tom Gryp, President & CEO of Notre Dame Federal Credit Union and Jonathan Crawford, Alumni Relations Officer with University of Notre Dame, Dean of Science, Greg Crawford, at the beginning of the Road to Discovery Ride 2012.