NATIONAL NIEMANN-PICK DISEASE FOUNDATION, INC.

Volume 1, Issue 3

Spring 2003

Inside this issue:

FAMILY SUPPORT SUPPLEMENT

~ ~ ~ NNPDF Families ~ ~ ~
Meeting The Challenge!

We decided to take a break from the usual updates in the Family Support Supplement so that we could focus on two extremely integral parts of the structure and success of the foundation.

*****Fundraising campaigns and the research that these monies support.***

The most urgent reason to raise funds is, of course, to further research into NPD for the understanding and knowledge required to find a cure for NPD. We have also found that with raised awareness into NPD, earlier and more frequent diagnosis of NPD is taking place. As the foundation continues to grow, both in the number of services offered and to the number of families that we support, the need for more families to hold and sponsor a fundraising event or awareness campaign in increasingly important.

In the first section of this supplement you will find research updates as reported by the foundation's director of research, Janet Ward Pease. The second section of this supplement is a fundraising packet which was developed specifically for families of the NNPDF. We want to encourage and support ALL of your efforts towards raising monies and awareness into Niemann-Pick Disease.

I wanted to share two different comments from members of our foundation with respect to their view of fundraising for the foundation. Stephanie and her family joined the foundation earlier this year after they received word that their son, Tristen, had NPB. Melissa is our current director of fund raising and has been on the board of directors for a number of years. Her son, Lee has NPC. I hope that these messages will inspire all families to "take the challenge" to host a fundraising event or awareness campaign this year. Please contact the foundation office if you require any assistance or have any questions.

Stephanie:

"To be honest with you, I don't know the first thing about fundraising either! But after we received our diagnosis and I found the NNPDF and began receiving their support and encouragement, I began racking my brain as to what I could do to raise money. The one thing that I found so completely amazing is how much support we received and how many donations & services you will receive when you just ask. We were not tuned down one time. For me, this experience has been incredibly emotional, but also very healing and I can't wait until next year to have our 2nd Annual Spinathon for Tristen!

Melissa:

"I recently realized something. I know I had realized it before, but suddenly it became TRUTH to me. I began fundraising in a desperate need to save Lee. But now it's not only him I am desperate to save. I want to be a part of something huge. I don't want another family to have to be told their child is dying with NP. I don't want another family to have to plan their child's funeral. The only way these things WON'T happen is, if we continue to fund research. The only way a cure will ever be found is for us to pay for it. We must continue to work together as a foundation with one common goal…..A CURE."

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United Kingdom - Niemann-Pick Disease Group (UK)
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~ ~ ~ OGT—918—007 Drug Protocol Update ~ ~ ~

NPC Coordinator, Lori Seidman, MSN, CPNP

On January 26, 2003 the first subject for the OGT-918-007 drug trial was screened at Columbia University. This same subject will be the first randomized person in the trial on Feb. 11th, 2003. As of now, the first six subjects out of the nineteen waiting to be evaluated are scheduled for screening visits. The following statement was posted to the NNPDF web site on January 22, 2003 to update families on the progression of the study.

"Dr. Patterson and I are pleased to announce that we have begun scheduling patients for the OGT-918 for Niemann Pick, Type C screening. As many of you know, the screening involves two visits to Columbia University over the period of one month. The two visits must be at least eight days apart and must be completed within thirty days. Each visit will last approximately 3 days. During each screening visit, the family and subject will meet with Dr. Patterson to complete the informed consent and then have a physical and neurological exam. I will then assist the subject with doing a swallowing exam, peg board exam, quality of life questionnaire, and spiral drawings. Each subject will see the dietician for a nutritional evaluation and have their blood drawn at both screening visits. The following exams will be scheduled one time over the course of the screening visits: tremor assessment, psychometric testing, Cat Scan of the abdomen, and nerve conduction testing. These tests will be repeated twelve months after each subject is randomized into the study.

During the last day of the second screening visit each subject will be randomized to the drug or non-drug group. Ten subjects will receive OGT-918 and five will not. Each family will know if their child will receive the drug or not prior to their departure from Columbia. There is no placebo. If the subject does receive the drug they will take home three months worth of OGT-918. All subjects will be followed up by phone one week after they leave Columbia and the again one month later and two months later. During month three they will return to Columbia to be re-assessed.

Depending on the availability of the staff at NIH, the subjects will travel to Bethesda for their eye exam either during screening visit one or two. The eye assessment involves two tests. Each test is one hour in duration. Each test will be done in the morning and than repeated in the afternoon.

All travel arrangements will be made through an agency here in New York City. Once I contact you to schedule the screening visits, the agent will call you to arrange the airline tickets, ground transportation and hotel for New York and Bethesda. A car service has been arranged in both cities to bring families to and from airports and to and from the hospital. There will be provisions for meals only for the subject for the duration of the visit. Each subject will receive $10.00 for breakfast, $14.00 for Lunch, and $30.00 for dinner.

I will be scheduling approximately two patients per month to be screened for a total of four visits per month. I would ask each family to be patient with the scheduling process as it takes many hours and sometimes days to coordinate the eight departments involved in the study. I can be contacted preferably by e-mail or by phone at 212-305-4136 for any further questions".

OGT-918-007 Pediatric Patients

Children with NPC who are less than 12 years of age (the lower age will be around age 6 years as of now) will have the opportunity to participate in the current drug trial after the IND (investigational new drug) application is approved by the FDA. The application was submitted in March. The FDA is obligated to approve the application or request additional information within four weeks of the request. If the approval is received than a protocol amendment will be submitted to the Columbia IRB (ethics committee) in April to include the younger children in the current drug protocol. The number of younger children to be included has not yet been decided by Oxford GlycoSciences. The drug formulation will be one that dissolves in the mouth.

NNPDF Spring 2003 Newsletter – Research Update

by Director of Research, Janet Ward Pease

DIRECTIONS

Type B: Paul L. Kaplan, Ph.D., M.B.A., Senior Director of Program Management for Genzyme Corporation, had this to say about the ongoing survey of NPB patients and the upcoming enzyme replacement therapy clinical trial :

"Genzyme expects to complete the formal analysis of data collected in the multi-national survey study of Niemann-Pick disease patients with sphingomyelinase deficiency in the next few weeks. This study included a significant effort by Dr. Ed Schuchman and Dr. Robert Desnick at the Mount Sinai School of Medicine in New York and was designed to collect baseline data on the disease and its impact on patient's lives, but not to evaluate a particular therapy. No new patients will be enrolled in the survey; however the study has now been extended in order to learn more about disease progression in patients with sphingomyelinase deficiency. Some patients have now returned for annual follow-up evaluations. It is expected that these long-term data will be valuable in understanding the course of the disease and the impact of therapy. The extension of the survey study will be conducted in parallel with other clinical trials that evaluate potential therapeutic treatment. Participation in the survey study or its extension is neither a requirement for nor a guarantee of inclusion in future clinical trials and patients will not be excluded from a clinical trial in order to continue gathering data for the survey study.

The information gathered in the survey study is now being used to design the initial clinical study of enzyme replacement therapy (ERT) for patients with sphingomyelinase deficiency. The details of the initial study and the inclusion criteria are expected to be finalized by the middle of this year following meetings with US and European regulatory authorities. The study, which is expected to start in the second half of this year, will eventually form part of the package of clinical data necessary to support international approval of a product. The primary goal of the initial study will be to establish the safety of ERT in patients with a spectrum of manifestations of NPD. Other goals are to select an optimal dose for future studies and determine what disease parameters must be measured to prove the effectiveness of the drug to regulatory authorities in future trials. Genzyme's goal is to obtain international regulatory approval of a safe and effective therapy and make it available to all patients with Niemann-Pick disease due to sphingomyelinase deficiency as quickly as possible."

Type C: While the OGT-918 clinical trial continues in the U.S. and U.K., basic research into the structure and function of the NPC1 and NPC2 proteins remains important in identifying therapeutic options. Dr. Steven Walkley, whose research on mice led to the OGT-918 trial, said recently "The bottom line for all ... advances in therapy is, I believe, that the more we truly understand about every detail of these diseases the more likely it is that we will come up with some way to correct them. ... Just knowing the identity of the gene and protein are not enough, we also need to know precisely what the protein does and how, and how its actions fit into the larger puzzle of cell and organ function. Still, progress in understanding rare diseases [like NPC] today is substantial on many fronts."

(Director of NNPDF Research Report continued)

NNPDF-FUNDED RESEARCH:

Recently Completed

Melanie Dobson, Ph.D. at Dalhousie University has been using yeast to understand the function of the NPC1 gene ("A Yeast System for Analysis of Sterol Trafficking Defects in NPC"). Her lab has been investigating the effects of deleting the yeast NPC1-related gene, NCR1. They have found that loss of NCR1 reduces the efficiency of endocytosis. Endocytosis is the process by which material is moved into a cell from its extracellular environment. In related experiments they have been using a genetic screen to look for genes that work with NCR1. Their hypothesis is that in a cell lacking NCR1, an essential cellular process may function less efficiently. If these cells then acquire a mutation in another gene that participates in the same process, the efficiency of the process would be further reduced leading to cell death. Their search for this class of genes has identified GFA1, a gene which appears in both yeast and humans. GFA1 deficiency impairs addition of sugar groups to secreted proteins and in yeast, it impairs cell wall biosynthesis. Taken together these results suggest NCR1 may participate in two basic cellular processes, endocytosis and secretion. Given the similarity between the yeast and human NPC1 proteins, these findings suggest that investigating how NCR1 contributes to these evolutionarily conserved processes may help us to understand the function of NPC1.

Ongoing Projects

Studying yeast is an excellent means of doing experiments in a simple and controlled environment (because yeast are single-celled, simple and reproduce very rapidly). And genes equivalent to human NPC1 and NPC2 have been identified in yeast (called "NCR1" and "NPC2" respectively). However, NPC yeast researchers have been hampered in their efforts by the lack of functional differences observed between yeast that are missing the NCR1 or NPC2 gene and normal yeast. This is important because if a functional difference in normal vs.mutant yeast can be observed, therapeutic options can then be tested to see if they "fix" the mutant yeast and make them behave normally. But if no difference is observed, it is difficult to test therapies and get definitive results. In an extremely important finding, Dr. Anita Corbett, Ph.D. at Emory University School of Medicine ("Functional Analysis of Niemann-Pick C Protein (NPC1)") reports that her lab has successfully identified a functional difference between normal yeast and those which are missing either the NCR1 or the NPC2 gene. The mutant yeast can now be distinguished from normal yeast by their resistance to the ether lipid drug, edelfosine. Dr. Corbett is using this information to advance her genetic screen which aims to identify other genes that are functionally related to NCR1 and NPC2. Her findings should also be very useful to NPC researchers worldwide who use the yeast model for study.

Maria Ledesma, Ph.D. and her colleagues at Fundazione Cavalieri Ottolenghi at the University of Turin in Italy are analyzing neuronal development using mice that lack the acid sphingomyelinase ("ASM") enzyme and suffer the same symptoms as patients with Niemann-Pick disease type A. ("NPA: Molecular analysis of neuronal membrane maturation and synapse formation") She says "The comparison of brain extracts and cultured neurons from these [ASM-deficient] mice and wild type mice has revealed an imbalance in the lipid content of raft membrane microdomains. These microdomains are involved in neuronal signaling, correct distribution of neuronal membrane proteins and establishment of synapsis. Indeed, we find a deficiency in the sorting to the axonal membrane of one raft marker. We are currently investigating more deeply raft alterations and their implications in synaptic function. We believe these defects can be at the base of the severe neurological problems associated with Niemann Pick type A disease."

(Director of NNPDF Research Report continued)

Daniel S. Ory, M.D. at Washington University School of Medicine ("The Role of HE1 in Cholesterol Trafficking") says: "The goal of our studies is to understand the role of the NPC2 gene in cholesterol metabolism. Our initial studies focused on examining the location in the cell where NPC2 functions. We showed in cultured human skin cells that NPC2 is found both in vesicles that contain NPC1, as well as lysosomal proteins. These findings suggest that the NPC proteins may function at a similar step in the processing of cholesterol. To understand how NPC2 participates in cholesterol metabolism, we next examined the effect of absence of NPC2 protein on the regulation of cholesterol levels in the cell. We found in NPC2 mutant cells a failure to properly regulate both the synthesis of cholesterol and the uptake by the cell of lipoprotein-derived cholesterol (for example low-density lipoprotein or LDL particles). These defects were attributable to failure of the NPC2 mutants to appropriately shut down the regulatory machinery responsible for these activities, as well as stimulating pathways that help the cell eliminate excess cholesterol. We showed that the defect in cholesterol regulation in both NPC1 and NPC2 mutants correlated with the inability of these cells to produce metabolites of cholesterol termed oxysterols. Moreover, we demonstrated that treatment with oxysterols reduces cholesterol accumulation in the NPC mutants. These findings indicate that NPC2 is necessary for generation of these cholesterol metabolites, and importantly may have implications for the treatment of NPC disease."

Newly-Funded Research

In February, 2003, the NNPDF Board awarded its first post-doctoral fellowships to Amit Kumar Choudhury, Ph.D. and Heng-Ling Liou, Ph.D.

Dr. Choudhury will be working at the Mayo Clinic and Foundation in the lab of Richard E. Pagano, Ph.D. His project ("Reduction of lipid accumulation in Niemann Pick fibroblasts by modulation of membrane trafficking") continues work he has done on the use of rab proteins to correct lipid trafficking in Niemann-Pick C cells. Of this work, Peter Pentchev, Ph.D. (retired Chief of Cellular and Molecular Pathophysiology, Developmental and Metabolic Neurology Branch, NINDS, NIH) says
"the reversal of cholesterol accumulation in NP-C cells by way of rab protein modulation is in my opinion the single most important new experimental finding to come out in the NP-C field in the last couple of years".

Dr. Liou is at the Robert Wood Johnson Medical School, University of Medicine & Dentistry of New Jersey, working in the lab of Peter Lobel, Ph.D. who identified the NPC2 gene. Dr. Liou did her doctoral work in the lab of Judith Storch, Ph.D., one of the world's leading experts on the fatty acid binding proteins. Dr. Liou's project ("The role of NPC2 (Niemann-Pick disease type C2) protein in lysosomal cholesterol trafficking") takes advantage of her abundant experience in studying lipid-binding proteins to investigate the structure and biochemical properties of NPC2 and its interactions with other proteins and compounds in the cell. Basic research of this type is fundamental to identifying options for therapeutic intervention.

The NNPDF Board also voted to provide $40,000 in transitional funding to Robin Henry Lachmann, MA, MB, BChir, PhD at the University of Cambridge, U.K. Dr. Lachmann's gene therapy project ("Therapeutic gene delivery to the cerebellum in Niemann-Pick Type C") has been funded by the Niemann-Pick Disease Group–UK for the last 2 1/2 years. Unfortunately the work was critically delayed when the mice colony being used in the research was wiped out by a virus. At present, the colony has been rebuilt and progress is good but funding from the NPDG-UK will run out at the end of June. The transitional funding being provided by the NNPDF should allow the project to continue for several more months while Dr. Lachmann looks for other funding sources to allow him to finish his work.

(Director of NNPDF Research Report continued)

OTHER RESEARCH NEWS

Center for Disorders of Lysosomal Metabolism

In December of 2002, we were advised by Dr. Stephen Walkley that an NIH planning grant was awarded to the Albert Einstein College of Medicine in Brox, New York for establishment of a Center for Disorders of Lysosomal Metabolism.

The aims of the center are:

- to foster research collaboration among labs working on lysosomal diseases affecting the brain;
- to encourage lysosomal disease research by providing equipment use and expertise to labs doing this research and by facilitating exchange of personnel and resources between the CDLM and collaborating labs
- to disseminate up-to-date information on relevant research advances to parent organizations and other groups dedicated to human lysosomal disorders.

We are talking to Dr. Walkley about how this center can benefit NP research and the NP disease community.

Rare Diseases Clinical Research Network

NIH recently issued a Request for Applications (RFA) to set up a Rare Diseases Clinical Research Network. The RFA says that NIH expects to fund four centers as well as a a data and technology coordinating center to begin the network in 2003. Each center can receive up to $1.25 million for their proposed program. Quoting the RFA, "Each Rare Disease Clinical Research Center will consist of a consortium of clinical investigators, institutions, and relevant organizations, including patient support organizations, focused on a subgroup of rare diseases." Dr. Marc Patterson of Columbia is investigating to see how the NNPDF can participate and have Niemann-Pick disease included in the research done by this network.

CoQ10 Study - Preliminary Results

According to the University of California, San Diego's Healthcare website ("health.ucsd.edu"), "... coenzyme Q_{10} (ubiquinone) is a compound naturally made in the body. A coenzyme is a small molecule that, by itself, does not catalyze a reaction. Rather, a coenzyme enhances an enzyme, which is a protein that speeds up a chemical reaction...In addition to its role in the metabolic process, coenzyme Q_{10} is known to act as an antioxidant that helps neutralize cell-damaging molecules known as free radicals."

Several parents of NPC patients have given their children CoQ10 as a dietary supplement and reported improvements in alertness and, to some extent, a lessening in certain disease symptoms. Spurred on by these reports and assisted by NNPDF listserv members who supplied blood samples prior to starting NPC children on CoQ10, Columbia University has done a preliminary study of CoQ10 blood levels in human NPC patients as well as a comparison of CoQ10 levels in NPC-mutant mice and cats. The results of this study were recently provided to the NNPDF by Dr. Marc Patterson, M.D., Professor of Clinical Neurology and Clinical Pediatrics at Columbia University College of Physicians and Surgeons and Director, Child Neurology Training Program, New York Presbyterian Hospital. Dr. Patterson wrote:

Drs. Salvatore Di Mauro and Stephen Sturley have preliminary data relating to Coenzyme Q10 (CoQ 10) in Niemann-Pick disease, type C (NPC).

(Director of NNPDF Research Report continued)

Findings:

1. Blood concentrations of Coenzyme Q10 are generally lower in NPC patients than in controls, although there is a wide range of variation. The results are difficult to interpret without information regarding plasma lipid (largely cholesterol and triglyceride) levels. This should be forthcoming.

2. Concentrations of Coenzyme Q10 and Q9 in the serum of NPC mutant mice are increased.

3. Concentrations of Coenzyme Q10 and Q9 in the tissues of NPC mutant mice (i.e.. within cells) are increased.

4. Concentration of Q10 in the serum of cats lacking the NPC1 protein are also elevated.

5. Concentrations of Q9 in rodent in vitro cell models lacking the NPC1 gene are also elevated.

Interpretation:

1. CoQ10 (Q9 in mice) functions as an electron shuttle between complexes in the oxidative phosphorylation pathway in mitochondria. It also functions as an antioxidant. CoQ10 (Q9 in mice) is transported within cells and the blood with other lipids. It shares the early part of the synthetic pathway for cholesterol, thus it is likely to be regulated in the same manner as cholesterol biosynthesis. Since the NPC1 mutation upregulates the pathway, the mouse results are what would have been predicted (although it was never assessed previously).

2. Thus the human results are anomalous. One possible interpretation of the preliminary data suggest that CoQ10 is trapped within cells secondary to the trafficking defect in NPC, and that low levels in the blood in humans reflect this trapping, perhaps in an endosomal compartment. Low blood CoQ10 levels in human may also be explained, at least in part, by low serum lipid levels in some individuals.

3. Trapping of CoQ10 in other subcellular compartments may prevent its access to mitochondria, leading to functional deficiency.

4. It is unclear if administering CoQ10 orally would influence the intracellular levels of CoQ10 in the presence of a trafficking or signaling block.

5. Further studies are needed to answer the questions raised above. Particularly, the sample size for human studies needs to be increased, with careful assessment of cholesterol status.

Drs Di Mauro and Sturley and their colleagues generously performed these studies using existing resources, for which I am profoundly grateful. Specific funding would be needed to continue this work.

Marc C. Patterson, MD
March 4, 2003

(Director of NNPDF Research Report continued)

Research Opportunities

As you can see from Dr. Patterson's comments on the CoQ10 study, more research is needed to be determine what the results of that study mean in terms of a direction for therapy. The NNPDF has recently learned of some NIH funds available for clinical research and we are checking to see if we can obtain a grant for continued studies on CoQ10. However, as you know, we are always competing with many other groups for NIH support so this funding is far from certain.

This is where your donations and fundraising make such a difference. Scientists are becoming aware of the NNPDF as a funding source and this encourages more and better research on Niemann-Pick disease. Each year new findings suggest new therapeutic options which much be tested.

This year, in addition to the possibility of further studies on CoQ10, we expect to get applications in May from several scientists who are pursuing the similarities between NPC and Alzheimer's disease and from another researcher whose preliminary findings indicate a link between NPC1 and NPC2 and other important proteins.

But we will need an exceptionally successful year in terms of fundraising to be able to pursue all these opportunities. Please consider making a donation today and possibly organizing a fund-raiser for the NNPDF in your community. Your donations and fund-raising efforts are very much needed at this time and also very much appreciated.