Nathan's Battle Foundation's focus is therapy development for LINCL. NBF's goal is to pursue every and all therapeutic approaches as aggressively and effectively as possible.

The potential therapeutic options for Late Infantile Batten Disease and the NBF's current directions toward these therapies are:

Gene Transfer, Small Molecule Pharmaceuticals, Cell mediated therapies, and Enzyme Replacement Therapy. The following is NBF's progress in each area:

NBF's Research Value

- Established collaborations with NCL scientists for knowledge transfer
- Facilitate the obtainment of necessary CLN2 tools: data, model access, cDNA, enzymatic assays, cell lines, antibodies, stains, and other reagents.
- Advocate voice to regulatory bodies
- Patient population representation
- Leverage clinical program experience:
  pre-clinical study design, protocol development, tox. study design, regulatory requirements, detailed feasibility study...
- Strong relationships politically and with governmental agencies (NIH and FDA)

The LINCL disease target advantage:

- Good model disorder to pilot therapy technologies.
- "Easy" rare disease to solve given that it is truly an enzyme deficient disorder.
- ·Risk/benefit ratio is in favor of therapy.
- Orphan disease status.
- Well-funded foundation to readily support therapy development projects.
- LINCL can benefit from an increase enzyme levels and CNS regeneration.

Gene Transfer Therapy - This therapy would introduce a functioning gene into the Central Nervous System (CNS) of a LINCL patient. This functioning gene would

produce the necessary enzyme that is required by the CNS to remove the harmful storage material. In principle this would be a long-term cure for the disease.

Nathan's Battle Foundation entered into a formal agreement with Cornell University's Institute of Genetic Medicine to perform a feasibility study verifying gene therapy is a viable treatment option for this disease and then mount a gene transfer clinical study. The feasibility study began in October 2000 and concluded that gene therapy is a promising and viable option to treat LINCL. On March 15, 2001, the pre-clinical studies and drug development process began. This project has produced more LINCL data than any other known research project. Over 350 rodent studies, countless in-vitro studies, several new analytical methods, and 45 non human primate studies have been performed verifying this therapy. The project has achieved numerous milestones all of which continue to support gene therapy as a treatment for LINCL. Some highlights are:

- Successfully manufactured the drug in clinical grade form for human use.
- Consistently performed successful gene transfer in rodents.
- Demonstrated long term expression of TPP-1 rodents.
- Performed toxicology studies in rodents.
- Received favorable reviews from the FDA to move forward and defined criteria to move to humans.
- Performed primate distribution and dosage studies meeting the FDA's criteria to move to humans.
- Designed and developed NHP toxicology studies.
- Developed clinical protocols including evaluation methods.
- Performed primate toxicology studies
- Received regulatory approvals from all levels
- Begun human clinical trials.

We are treating children but we lack the total necessary FUNDING to cover the clinical trial expenses. Our foundation entered into a pledge agreement with the University to raise the required funds to pay to treat the children. We need help in identifying and approaching philanthropist and foundations that want to help save

children's lives by contributing funding to our gene therapy clinical trial. The generosity of these types of individual donors can make the difference.

The feasibility study is published by scientific journal. The Journal of the American Medical Association (JAMA) CLICK TO REVIEW

The clinical trial protocol has also been published

Project Overview - This is a high level overview of our project. This can be given to potential funders.

Small Molecule Pharmaceuticals- This therapy would introduce a drug compound into the body that could cross the blood brain barrier into the CNS of a patient to either enhance residual enzyme activity or remove the storage material that is harmful the the patient. This therapy is thought to be viable but more research needs to be performed on the CLN2 gene with high through put screening of drug compounds. Since the CLN2 gene has not been identified for very long, not a lot of research has been performed in this area. The Nathan's Battle Foundation would like to pursue high through put screening on Nathan and P.J.'s mutations to identify possible beneficial compounds. The Nathan's Battle Foundation is investigating projects to perform high through put screening for CLN2.

In February 2002, NBF entered into an agreement with a biotech company in Massachusetts to greatly expand our drug screening program. This is a major project to screen several compound libraries (libraries include the FDA-2000 and the GNC libraries). NBF is the first and currently the only organization performing drug screening for CLN2. This screening will use CLN2 cell-lines to screen drugs against. This project identified some potential compounds that had affects on the enzyme level. Validation studies are currently being performed. If positive these compounds can be move to the clinic quickly.

The above screen have produced 10 drug "hits" showing potential for increasing TPP-1 enzyme level in CLN2 cells. The top 3 compounds have been further evaluated to ensure the results. The scientific group continues to receive the same positive results

from these compounds. In-vivo mouse studies or fast track human trials are potential next steps for these drugs.

In August 2001, The Nathan's Battle Foundation initiated a small molecule pharmaceutical drug screening project to screen compounds on Nathan's cell lines. Over 700 compounds are being screened by the leading CLN2 laboratory to evaluate therapeutic effects. The Nathan's Battle Foundation entered into an agreement with a pharmaceutical company and an academic university to pursue high through put screening on Nathan and P.J.'s mutations to identify possible beneficial compounds. If a compound is found that proves beneficial the compound could be administered within the year. Other drug screening proposals are being evaluated.

ADULT Stem Cell Therapy- This therapy would involve injecting adult stem cells into the CNS. These stem cells would produce the enzyme and aid the CNS to regain function. Adult stem cell therapy has tremendous promise for growing neurons in the CNS to "re-build" the brain. This therapy could also be a potential cure for the disorder with an additional advantage of having the patient regain function by stimulating CNS re-growth. Adult stem cell research is a technology that the Nathan's Battle Foundation is investigating to begin future therapy projects. Once we stop the disease we will need to regain lost function of the brain.

NBF is currently evaluating stem cell proposals for CLN2 to develop cell mediated therapies for clinical application. NBF is investigating scientists and companies interested in stem cell technologies for use as therapies for neurodegenerative disorders.

Phil hosted a dinner at the Society for Neuroscience conference in San Diego during November 01. The dinner was attended by some of the world's leading stem scientists, biotech professionals, and NIH representatives for the purpose of evaluating cell mediated therapy approaches for the NCLs. Several proposals from attendees are being reviewed.
Stem Cell Initiative Event Summary.

NBF has initiated 3 different cell mediated projects/studies. Each project is evaluating the most promising approaches / strategies for neurodegenerative

disorders. If a proof of concept is demonstrated in NCL models with any of these approaches, then a clinical program will be pursued.

Stem Cells Inc. demonstrated a proof of concept using their stem cell technology on a NCL disorder. They are now in the process of mounting a clinical program to move this technology to human clinical trials. Stem Cell's Inc.'s technologies could be in human clinical trials by Q1 2005.

Enzyme Replacement Therapy- This therapy would inject the enzyme that the patient is missing into the CNS. This therapy would work well but there are delivery issues with having to continually inject enzyme into a patients CNS. Delivery issues and continued enzyme production capabilities are being addressed before proceeding with enzyme replacement therapeutic approaches. NBF is in discussions with academic institutions to evaluate enzyme replacement possibilities. Coupled with Blood Brain Barrier technologies make this approach a more viable option and NBF is evaluating these technologies.

Blood Brain Barrier technologies. NBF is evaluating BBB technologies. New technologies are being discovered that aid compounds/enzymes to cross the BBB by altering the properties of this protective barrier. Several technologies are being evaluated to aid in delivery of TPP1 (the missing enzyme) to the brains of CLN2 patients.

Other links containing information about NBF's scientific efforts:

Business Plan/ Clinical Trial Efforts - This link contains documentation that outline specific efforts for a clinical trial for Late Infantile Batten Disease. Documents such as: a the CLN2 Business Plan, Clinical Trial Initiative Conference Summary, Action for Therapy Conference Summary, and a Non For Profit Therapy Development Model Presentation.

NCLRA - This link contains information about an organization that Phil is a member of focused on aiding in the development therapies for Batten disease. The Neuronal Ceroid Lipofuscinoses Research Alliance (NCLRA) is a united group of international foundations who's purpose is to aid in the coordination of bringing potential therapies

to clinical trials for the three major forms of NCL (INCL, LINCL and JNCL). The JNCL Research Fund is associated with the NCLRA and play a very active role in the following. creating a network of relevant research information, combined our monetary resources to achieve greater impact, project one voice for all our children

Clinical Trial Efforts

Scientific Effort | NCLRA

Efforts for a clinical trial are in process. The Nathan's Battle Foundation has an agreement with Cornell University to attempt to initiate a clinical trial using gene transfer for CLN2. A feasibility study performed by Cornell confirmed the viability of such a project and defined the necessary steps to achieve a successful clinical trial. We have funded all the the work to date but lack the necessary funding to continue the project. The development of this life saving therapy will stop without additional funding. The project will cost over $2 million to complete and we will run out of funding to support the project in a few months. If you know of anyone that can help please contact them or contact me to inform them of our cause.

The following is some background information about what we have developed and who we work with:

The Neuronal Ceroid Lipofuscinoses Research Alliance (NCLRA) is a united group of foundations whose purpose is to aid in the coordination of bringing potential therapies to clinical trials for the three major forms of NCL (CLN1, CLN2, CLN3). With our united efforts and compassionate purpose, research has rapidly advanced to a point that a therapy has evolved as a

viable treatment. The increased knowledge of the genetic defects underlying these diseases, coupled with advances in the field of gene transfer and expression, provides an opportunity to utilize gene therapy strategies in order to treat these disorders. Gene therapy using the Adeno-associated virus (AAV) has developed to be a promising therapy for two of the major forms of Nueronal Ceroid Lipofuscinoses (CLN1, CLN2).

Some of the current documentation in organizing the trial is as follows:

Business Plan

The Business Plan outlines a strong business case to pursue a clinical trial on CLN2. Given that many of the necessary components are in place to move forward with an AAV gene therapy clinical trial. From having a fast tracking IND drug application, an available and consenting patient population, years of cross correlating scientific research, a leading scientist, promising financial returns, and the NIH's and FDA's guidance and support, a CLN1 and CLN2 gene therapy trial a promising and opportunistic venture.

Stem Cell Initiative Event Summary

Phil hosted a dinner at the Society for Neuroscience conference in San Diego during November 01. The dinner was attended by some of the world's leading stem scientists, biotech professionals, and NIH representatives for the purpose of evaluating cell mediated therapy approaches for the NCLs. Several proposals from attendees are being reviewed.

May 2000, "Clinical Trial Initiative" Conference Summary

This is a summary of the "Clinical Trial Initiative" May 2000 conference. The main objectives of this conference were to generate pharmaceutical interest in pursuing a therapy for the NCLs, identify partners in a CLN1/2 clinical trial effort, and to begin defining the next steps to move forward. The summary contains: ConferenceOverview, Clinical Trial Role Definition, Next Steps, CLN1 research update, CLN2 research update, Gene Therapy Research, FDA update, Business plan overview discussion, and Bio Tech companies contributions.

November 1999 "Action for Therapy" Conference Summary

This is the conference summary from the November 1999 "Action for Therapy" NCLRA conference at the NIH. The purpose of this conference was to evaluate possible therapeutic approaches for the NCLs.

Non-For-Profit Therapy Development Model Presentation

This is a copy of the Rare Disease Non-For-Profit Therapy Development model presentation that was discussed at the Society of Neuroscience conference in New Orleans during the Advocacy Group Breakfast meeting (Nov.-00).

Business Plan Presentation (May 12, 2000)

This is a copy of the Business plan presentation that was given by Phil at the May conference, "Clinical Trial Initiative".

Business Plan Cover Letter

This is a copy of a non-specific cover letter for the Business Plan. This cover letter is sent with the

Business Plan to potential clinical trial partners. The intent is to determine the level of interest of potential partners and evaluate attendees for the upcoming clinical trial business meeting. The letter outlines the objectives and a tentative agenda.

May 2000 Conference Material (May 12, 2000)

This is a copy of the material that was handed out to each attendee. It contains the conference binder cover page, agenda, objectives, attendee contact information

NCLRA

Scientific Effort | Clinical Trial Efforts

The Neuronal Ceroid Lipofuscinoses Research Alliance (NCLRA) is a united group of foundations whose purpose is to aid in the coordination of bringing potential therapies to clinical trials for the three major forms of NCL (CLN1, CLN2, CLN3). The goal of this organization is to assist in the collaboration of researchers and aggressively assist science to develop a therapy for the NCLs. Phil Milto is a lead member of this group directing the efforts of the CLN2 research, Nathan's version of the disease, to progress to a clinical trial

The NCLRA conducted a conference hosted at the National Institutes of Health, Bethesda, Maryland on May 11, 2000 and May 12, 2000. This

conference was tremendously productive in fostering collaboration and propelling research toward a clinical trial for CLN1/CLN2. The "Clinical Trial Initiative Conference" was the first of its kind. Never before had a group been assembled that contained competing biotech companies, research scientist, clinicians, a neuro-surgeon, universities, clinical centers, the FDA, the NIH, and a parent group (the NCLRA). The success of the meeting was mainly due to the open collaboration between each party interested in achieving a common goal, a treatment for CLN1/CLN2 children. This meeting was organized and conducted by the NCLRA

Conference Accomplishments and Notable information:

- Informed that a biotech company is pro-actively pursuing developing therapies for metabolic diseases of the nervous system.
- Information presented that displayed the reversal of damage in the CNS after receiving gene transfer in a LSD. Recovery of functional deficits presented.
- Informed moderately to severely effected patients should be included in NCL clinical trials in order to more easily determine therapeutic benefit of a treatment. This is especially relevant with NCL disorders due to the markers for the trial will be heavily weighted on clinical review.
- Confirmed that a mouse model is not necessary or required by the FDA to proceed.
- Generated pharmaceutical interest in therapeutic approaches to treat CLN1 and CLN2 through open collaboration with researchers in the field.
- Established open lines of communications between attendees

- Key attendees: Avigen, Cell Genesys, Genzyme, Iowa University, Targeted Genetics, University of Minnesota, Peter Lobel, Jon Cooper, Mark Sands, FDA, NIH, NCLRA, and BDSRA.
- Confirmed the need to identify markers and endpoints (gather clinical histories, imaging technology, obtain quantitative measures).
- Confirmed need to quickly establish a clinical center.
- Obtained an understanding from the FDA to keep them involved as early and as often as possible in the IND development process.
- Obtained scientific updates from NCL researchers, providing disease specific information and data to company representatives.
- Obtained research and development updates from leaders in the fields of ERT and gene therapy.
- Confirmed need to lobby government to show support of gene and stem cell therapy.
- Identified potential roles of attendees in the strategic development of initiating a clinical trial.

* A conference summary is available "Clinical Trial Initiative".

In November 1999 the "Action For Therapy" conference was held with the leading researchers on Batten disease at the National Institute for Health (Conference Summary) . The objective of the conference was to get viable therapies to clinical trials as quickly as possible. Each researcher presented their latest findings. By getting the researchers to work together and understanding what obstacles that they are facing, hopefully we can get their obstacles addressed so a

treatment can be developed. A representative from the FDA was also present to assist us in understanding the steps necessary for us to get a treatment to clinical trial. The most viable option for Nathan is Gene therapy.

Gene therapy is a cure for Nathan. A virus (AAV virus) is injected into the brain that infects the neurons. This virus will have corrected genes attached to them to produce the enzyme in which Nathan is deficient. We believe that we have all the components necessary to go forward with a clinical trial and have begun compiling the proper paper work for submission to the FDA. We potentially have the cure for Nathan. We just have to get it through to a clinical trial. The non-science factors currently stand in our way. We have some obstacles in our way, the current known obstacles for a gene therapy clinical trial are:

We do not have sponsor for our trial. A sponsor is typically a biotech company who ensures that the clinical trial is being performed according to the protocols defined in the Investigational New Drug application. By definition, a sponsor is an individual, partnership, corporation, scientific institution, or governmental agency. The FDA would rather have a company be the sponsor of the drug. It doesn't mean that we cannot be creative. I have developed a business plan (Business Plan) outlining the tremendous financial returns that could potentially be gained to try to attract companies to be the sponsor for this clinical trial. So if you know anyone interested please have them contact me.

We need a "Good Manufacturing Practices" facility to produce clinical grade virus vector for us to be used in the toxicity testing and in the clinical trial.

We need to get a hospital to host our clinical trial as the center for the inter cranial injections and clinical evaluations. Stanford has tentatively committed to be a potential site but the FDA would like for us to have at least two sites to eliminate any bias in the test results.

We will also need clinicians to participate in our trial. This would typically be a neurologist with preferably, but not necessarily, Batten's experience.

Again if you know anyone involved in these fields (enzyme replacement, gene therapy, stem cell therapy, Neurotrophic factors) or a biotech company that will sponsor our clinical trial or produce clinical grade virus forward Nathan's story to them and their name to me. Any connections we have will help push research forward. At this point who you know makes a huge difference. Remember we are all just six people from everyone.

Ask for files if links are not working.