NCL
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"Action for Therapy" Conference
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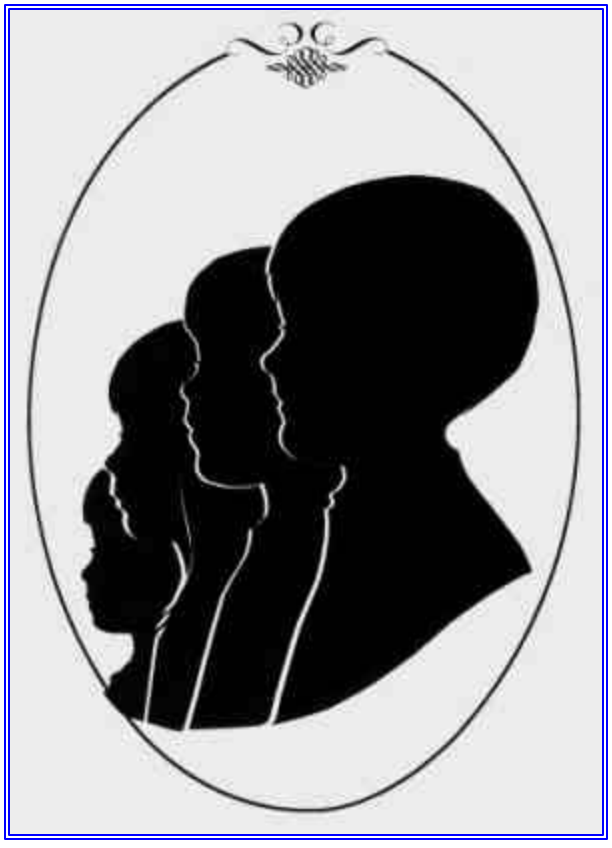

Conference Summary and Recommendations

DRAFT - NCLRA Conference Summary

Contents

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Introduction

The information that is contained in this document is to be used for reference only and should not be construed as absolute information. The information has been compiled from various sources and represents opinions of those who attended the conference. All information should be used in a constructive nature.

The aim of this document is to attempt to understand the "Have's", the "Needs" and the "Where to next" for the three major forms of NCL (CLN1, CLN2 and CLN3).

The use of this information is at the user's own discretion and is meant to be produced as a guide for those new to the field of NCL research, better understanding for the current investigators, and for highlighting guidance and help from government bodies.

Conference Goals and objectives

The goals of this conference were to discuss the future of NCL therapy and foster collaboration and communication between private charities and scientists. This symposium has provided a forum for scientists with expertise in gene transfer technology, neuronal stem cell biology, neurotrophic factors and enzyme replacement, who are not necessarily directly involved in NCL research, to share their knowledge with scientists actively studying this disease. Several of these therapeutic approaches are currently being used clinically or are in the initial phases of FDA approval. In addition, small animal models for the various forms of NCL are being developed which will allow experimentation to proceed rapidly. Therefore, an interdisciplinary symposium of this nature is both timely and necessary to discuss the current potential therapies and to determine which are viable to pursue for clinical trial.

Objectives:

1) Determine the applicability of various therapeutic approaches to NCL.

2) Establish a working relationship among the scientists and between the NCLRA.

3) Determine the availability of reagents to study NCL.

4) Gain better understanding of regulatory issues with regards to clinical trials for rare disease.

5) Identify the needs for the three major forms of NCL's and develop an action plan.

"Quick Glance" Summaries

CLN1

Have	Needs	Comments
Enzyme type and functionality (PPT)		
Comparable enzyme expression data from other similar Lysosomal Storage Disorders i.e. MPS V11, Krabbes		
	Clinical grade AAV sources for pre-clinical trials.	
Test for INCL (PPT deficiency).		Currently, strictly as research and not for diagnosis. Although results can go to physician/family under a consent form. A lab at Harvard will be soon set up for this commercially.
	Mouse Models	Peltonen (6 months), Hofmann (12months)
	Biotech for mass manufacture of clinical grade PPT	For use in pre-clinical and clinical trials.
	Marker and endpoints defined for clinical trials	Is clinical response good enough due to the nature of the disease. Imaging fMRI's
	Clinical trials planned	"Creative" model to move to human trials fast. Someone needs to put planning together NOW.
	Monoclonals	

CLN2

Have	Needs	Comments
Enzyme type and functionality (TPP1)		
Comparable enzyme expression data from other similar Lysosomal Storage Disorders i.e. MPS VII, Krabbes		
	clinical grade AAV sources for pre-clinical trials.	
	Mouse Models	Lobel (6-9 months), Katz (6-9 months)
	Biotech for mass manufacture of clinical grade TPP1	For use in pre-clinical and clinical trials. Collaboration with BioMarin and Genzyme ongoing
	Marker and endpoints defined for clinical trials	Is clinical response good enough due to the nature of the disease. Imaging MRI's, other technology?
	Clinical trials planned	"Creative" model to move to human trials fast. Someone needs to put planning together NOW.
Preliminary results with Gentamicin		Lots of problems i.e. toxicity, generality, etc. Further experiments to see if viable.
Stanford for Enzyme Replacement		
Roscoe Brady doing similar trials on ERT with Gauchers		
	Monoclonals	

CLN3

Have	Needs	Comments
Two CLN3 KO Mice models (Nussbaum/Mitchison) & Katz	Move to Jackson labs for maintenance and distribution.	• Breeding pairs available, contact Bob Nussbaum in the US, Hannah Mitchison in the UK. Contact Martin Katz. • Behavioral studies complete on (Mitchison/Nussbaum) replication study underway. • Other methodology EEG, ERG, FMRI etc? • Centralized characterization?
Chloroquine trials begun in young mice	Trials in older mice in parallel.	Nussbaum feeding mice with Chloroquine based on pH findings in yeast CLN3 homolog by Dave Pearce. Measurement of success? EEG's fMRI's, pH testing etc.
	ANTIBODIES	Source investigators to construct.
	PROTEIN FUNCTION	Source investigators
	Marker and endpoints defined for clinical trials	Is clinical response good enough due to the nature of the disease. Imaging fMRI's
	Clinical trials planned	"Creative" model to move to human trials fast. Someone needs to put planning together NOW.

Directions that seem important:

1. Pursue clues that CLN3 maybe involved in endocytosis and/or in regulating pumps. in general, try to determine cellular function of CLN3 protein; sort of ties in with #4
2. (Obviously)-detailed and ongoing characterization of the mice.
3. Search for suppressor genes beginning with yeast.
4. Investigate "Intermediate" models between mice and yeast i.e. nematode or fruitfles.
5. Determine interacting proteins.

Detailed Summary

Listed below are summaries of the potential therapies that were presented and include the overviews of the scientific advisory panel. The information is laid out by session and individually in the three forms for easier viewing. For CLN1/CLN2 it is probably true to say that the resultant therapies will apply to both of them. However, due to the nature of CLN3 the therapeutic path is unclear and requires further aggressive investigation.

Reagents

Murine models & Antibodies

Overall the mice models are under way. CLN1/CLN2 mice models are being worked upon and are 6-12 months from completion without characterization. Three models for CLN3 are now available with varying degrees of characterization.

CLN1

No investigator was present to represent the CLN1 mouse models, however, this work is being conducted at two facilities.
Dr. Leena Peltonen (UCLA, CA) has begun work on a model and current status is unknown. Dr. Sandra Hofmann's (Southwestern Medical Center, TX) model is 6-12 months from completion with 1-2 year's characterization.

- Currently no outside support is deemed necessary at the moment.

CLN2

Two facilities are working on these. Dr. Katz (Mason Eye institute, University of Missouri) and Dr.'s Lobel and Sleat (Center for Advanced Biotechnology and Medicine, NJ).
They are both in a similar state of construction but are using different techniques. Dr. Katz is using the conventional gene deletion method of knocking out the relevant coding area so that there is no enzyme production. Lobel/Sleat are using a different technique (introduction of point mutations within CLN2 and loxP flanking of neo) as there is concern that a gross disruption of the CLN2 gene may have complicating positional effects on adjacent or overlapping genes.

- Both models are 6-12 months from completion.
- Currently no outside support is deemed necessary at the moment.

CLN3

Dr. Katz, CLN3 KO mice, are available but yet to have been bred on a stable background. At present these mice exhibits different phenotype within a litter and some mice exhibit a constant spinning behaviour. This is most likely due to the mice mixed on 129SV/J and C57BL6 Backgrounds. These are presently being back-crossed to transfer CLN3 knockout mutation onto a uniform C57BL background and is projected to be accomplished in 12 months.

- These mice are available and Dr. Katz should be contacted directly.
- Symptoms - uncontrolled hyperactivity, retinal degeneration.
- Pathology - MRI's, ERG, EEG etc. ??
- On-going work - breed on to stable background, behavioural studies.

A CLN3 KO mouse model was made jointly by the groups of Dr. Mitchison (UCL, England) and Dr. Nussbaum (NIH/NHGRI) at the NIH. Mice show a lysosomal storage disease, details of which are published in Mitchison et. al., Neurobiol. Dis 6:321-334 (1999), including details of neurodegeneration as analyzed by Jonathon Cooper (Stanford).
One set of behavioral studies has been completed at Baylor College of Medicine, and confirmatory studies are in progress. By 16 months certain knockout mice are clearly different from wild type littermates, being smaller and moving more slowly.

CLN3 Continued…

There is a suggestion of a distinctive gait of the rear legs which is possibly indicative of muscle wasting. These observations must be recorded in larger numbers of animals to confirm.
Preliminary results have been obtained by brain imaging using MRI, which is being performed in collaboration with the group of Dr DG Gadian, Institute of Child Health, UCL, London. The retinal phenotoype is currently being characterized by ERG and histological examination of variously aged mice, in collaboration. EEG will be performed by Dr Jeff Noebels, Baylor College of Medicine.

- Availability - mice are available directly from Mitchison in the UK and Nussbaum in the US.
- Symptoms - visual failure 4-9 weeks, photoreceptor degeneration 6-14 weeks, dementia 6-9 weeks, seizures 14-16 weeks.
- On-going work - behavioural study replicated, Understand why Katz v Mitchison mutants are so different in severity i.e. is it environmental or genetic?
  Analysis of gene expression changes in mutants.
  Pathology – Further phenotype in aged mice, concentrating on characterization of neurodegeneration.

- *Despite differences in genetic background and phenotype of disease, both CLN3 KO mice models are deemed suitable for gene therapy experiments.*
- *As with all mice models having them centralised for distribution such as Jackson Labs would be advantageous for new and existing investigators to acquire them.*
- *Since there is evidence for <u>wide</u> genetic heterogeneity in mice and humans, investigate potential "suppressor genes"; for example AKR strain.*

mnd/nclf

Dr. Faust (Tufts University School of Medicine, MA) presented the working hypothesis that murine NCL neurodegeneration is due to impaired mitochondrial metabolism brought about by defects in phospholipid metabolism.
The two spontaneously occurring mouse models of NCL are mnd (equivalent to human CLN8) and nclf (CLN6). It was also stated that the AKR genetic background is a strain modifier for mnd, and that he has narrowed down the mouse CLN6 (nclf) region to a 450kb sequence containing ~20 genes.

Breeding the mnd onto an AKR background modulated the mnd disease. This phenomenon would be worth investigating and may hold some clues as to the relevancy, previously highlighted, between the different mouse phenotypes of CLN3 which are bred on different backgrounds. It is thought that with the difference in phenotype of the disease of children, even within the same family, that this line of investigation may aid in identification of potential CLN3 modifier genes. This may provide valuable insights into the normal function of the CLN3 protein, possibly leading to alternative approaches to therapy.

- breed CLN3 to AKR

Antibodies

Reliable monoclonals are required against human CLN1-3 proteins. Good polyclonals are needed for CLN3.

Potential Therapeutics

Chloroquine - CLN3

There is evidence in yeast (by Dr. Pearce of University of Rochester Medical Center, NY) that chloroquine can overcome changes in vacuolar pH caused by a deficiency in the non-essential CLN3-homologue. It remains to be demonstrated that the CLN3 protein plays a role in human lysosomal pH; if not, then chloroquine would not be predicted to help JNCL patients. Mouse experiments could circumvent the requirement for such data by directly showing whether chloroquine helps.

Chloroquine experiments are underway in young mice models in Dr. Nussbaum's lab. 8 mice are fed chloroquine in their drinking water while 8 are not treated. This experiment was started approximately 3½ months before this conference.

- The need remains to determine the function of CLN3p.

Anti-Apoptotic - CLN2-CLN3

Dr. Boustany (Duke University Medical Center) presented a basis for anti-apoptotic therapy in the juvenile and late infantile forms of NCL.
This is a new scientific avenue for the field of NCL and more is known about apoptosis in other research fields.

In the absence of CLN3, neuronal cells die, apparently by an apoptotic mechanism. However, generally the term anti-apoptotic is reserved for genes that encode proteins actively involved in suppressing endogenous death pathways. This is not clear for CLN3.

It is important to consider whether apoptosis as a consequence of CLN3 deficiency, is a primary or secondary effect of the disease, before deciding that this is an appropriate target. Furthermore, at present, we do not have a good handle on how to stop neuronal cell death in all the various types of neurons that degenerate in CLN3 using anti-apoptotic approaches. It assumes that we can permanently block death by anti-apoptotic treatment. In KO mice of the pro-apoptotic gene Bax, it is not known how to do this. In the Bax-deleted mice the rescued cells are not structurally and functionally normal. Can this therapy be targeted specifically to the CNS regions where neurons die in the disease and not affect the normal, ongoing beneficial cell death that occurs in many other tissues in the body (e.g. the skin, intestine, taste and smell sensory receptors, etc.).

- Work on going - Dr. Boustany is continuing to pursue a drug not available in the U.S. to experiment to see effects. Experiments using the available transgenic mouse models should rapidly evaluate the value of this approach.

Gentamicin – CLN2

Aminoglycoside antibiotics that cause read-through of nonsense mutations have demonstrated potential for the therapy of cystic fibrosis and muscular dystrophy. In preliminary experiments (Dr. Sleat/Dr. Lobel), gentamicin-mediated restoration of ~4% of the normal activity of CLN2 protease was shown in an LINCL cell-line that was compound heterozygous for two different CLN2 nonsense mutations.

- Further studies are underway to determine the general applicability and practicality of this approach.

Neurotrophic Factors – CLN1-3

Trophic factors have been previously studied as they seemed to offer huge potential in meeting therapies for neurologic disease. To date, after many studies, this has not yet been borne out. The study presented (Dr. Cooper of Stanford CA), was certainly encouraging and interesting but critically, an effect of neurotrophic factors on disease phenotype in a mouse model of one of the major forms of the disorder remains to be demonstrated. At the present time, it seems unlikely that neurotrophic factors, by themselves could treat CLN1-3. Perhaps combinations of trophic factors and other treatments may prove feasible in the long run.

- On going work - Identification of additional, and potentially more potent neurotrophic factors by screening compounds in established in vitro systems. Appropriate delivery systems, assay for functional efficiency, IGF treatment of younger mnd/mnd and other mutants.

Enzyme Replacement - CLN1/CLN2

It is well documented that replacement of enzyme has been shown to be successful in other diseases, such as Gauchers.
Enzyme replacement may be suited to both INCL and LINCL and the potential and problems were well covered by Dr. Mobley.

General considerations for enzyme replacement therapy

1) *Can the recombinant enzyme be produced in sufficient quantities?*
An estimate for levels of PPT in human brain is 1µg enzyme / g brain tissue. Therefore, to reintroduce 100% of the normal amount, ~1mg/day would be needed. Less than 100% may (probably will ?) be sufficient to have beneficial therapeutic effects though.

2) *Can the recombinant enzyme be delivered to the brain?*
Problems with the blood brain barrier suggest that IV introduction is not likely to work, though there are ways of temporarily allowing movement across the BBB by for example osmotic shock. This is not likely to be useful for a continuous dosing so direct intraventricular introduction is probably necessary.

3) *Can intraventricular introduction of a recombinant enzyme be achieved without brain injury?*

4) *Will the recombinant enzyme diffuse throughout the brain?*
There is evidence for reasonable diffusion of ß-glucocerebrosidase in mice brain.

5) *Will the recombinant enzyme be interalised by neurons?*
Experiments with PPT and CLN2 protease, as well as other lysosomal enzymes suggest that they will if they contain mannose 6-phosphate. (both mannose-6 phosphorylated CLN1 and CLN2 have been shown to be taken up by patient cell lines and correct enzymatic deficiency)

6) *Will the recombinant enzyme be delivered to the lysosomes?*
Yes, if uptake is mediated by mannose 6-phosphate receptors.

7) *Will enzyme therapy result in a clearance of excessive substrate?*
It does in the MPSVII mice.

8) *Will enzyme therapy enhance the function and viability of neurons?*
Need to test this in specific animal models.

9) *Can enzyme therapy be carried out without serious complications?*

- Begin ASAP to find a company willing and able to make high-grade ("manufacturing grade") enzyme.
- Pursue efficiency trials in vitro and in vivo as soon as animal models are available.
- Delivery and diffusion issues can begin to be addressed now (Talk to R. Brady, neurosurgeons and pharmacologists) these will be critical later.

Enzyme Replacement Continued…..

- Decide now how efficiency will be assessed in clinical trials.
  If the first trials only look at survival, efficiency may be disappointing as you begin with low initial doses.
- What clinical parameter, or weighted group of parameters, can be used? Parents will be in a difficult position if "historic controls" aren't available as otherwise placebo groups would be needed. [This holds true for all therapies].
- To pursue initial trials with PPT in a more time efficient manner it is probably not necessary to involve a company in order to obtain informative quantities of this enzyme. Simply provide resources to some biochemist or protein producing facility to isolate sufficient (small) quantities of it for intracerebral injection experiments to see if it is safe. There are some serious concerns about replacement trials with this enzyme since it hydrolyzes acetyl-coenzyme A as well as palmitoyl-S-proteins. Acetyl-coenzyme A is the starting material for the synthesis of lipids of the myelin sheath. Adequate quantities of it probably have to be available during myelination. Safety of PPT could be determined with approximately 100 milligrams of the purified enzyme in experiments with young rats. This could be done before trying to elicit a commitment from a biotech firm to produce clinical trial amounts of it.

AAV Gene Therapy – CLN1, CLN2, CLN3?

The data presented (Dr. Mark Sands Washington School of Medicine, MO) was very impressive and the replacement of enzyme by AAV offers one of the best strategies for potential therapy for CLN1/CLN2. It is proposed that it is likely to be more problematic with CLN3 but is worth experimenting in the available CLN3 transgenic mice.

Adeno-associated virus (AAV) is a human parvovirus that has received much attention as a potential vector for gene therapy and there are a number of reasons why this virus may be particularly suitable for neurodegenerative diseases such as NCLs; it infects non-dividing cells such as neurons; it is non-pathogenic; it is stable; it contains no viral promoters or coding sequences; and (at least for the wild type virus) it integrates in a site specific manner. Disadvantages include the fact that it can contain only small inserts (<5kb; probably not a problem for the NCLs) and it is difficult to produce in quantity.

A widely used model for testing gene therapy approaches is the MPSVII mouse which lacks ß-glucuronidase and models the corresponding human lysosomal storage disease. AAV-mediated delivery (IV??) of ß-glucuronidase resulted in 15-20% normal brain activity, decreasing storage in cortex and hippocampus but not in the cerebellum. Treated mutant mice were indistinguishable from wild type based on body weight (MPSVII mice are normally ~50% of wild type), life span, and electroretinography. The auditory evoked brain response was improved with treatment but was not completely rescued.

IV administration of AAV is not likely to be successful in humans. In view of this, MPSVII mice were treated with AAV/ß-glucuronidase by direct injection to the brain. Cognitive function in these mice, measured by the Morris water maze assay, was the same as wild type.

- Gene therapy with AAV and other viral vectors remains one of the most promising approaches to NCLs in general and CLN3 in particular. Experiments using the available CLN3 mouse models should rapidly test the potential of this approach.

- Gene therapy of autologous hematopoetic stem cells might be a viable approach. This approach did not come up at the meeting. Gene therapy of hematopoietic stem cells has not yet been achieved, but once the problem is solved for even one gene, it will be solved for this disease as well.

- On-going work – carry out experiments in mouse models when they become available.

Neuronal Stem Cell

Multipotent neural stem cells have received considerable attention as a potential therapeutic tool for neurodegenerative disease. Introduced into the central nervous system, they can exhibit a tropic response to regions of neurodegeneration and can effectively replace a number of neural cell types including neurons. In addition, these cells are genetically manipulable and can express one or more trangenes or viral vectors, thereby acting as delivery vehicles to areas of neurodegeneration.

The potential for stem cell therapy of lysosomal storage diseases has been shown in the MPSVII mouse which lacks ß-glucuronidase. Introduction of ES cells overexpressing ß-glucuronidase eliminated lysosomal storage. In demyelinating neurodegenerative mice (e.g twitcher and shiver mice), ES cell therapy was found to result in extensive oligodendrocyte replacement . In non-genetic models of brain disease (e.g. hypoxia-ischemia and tumors) ES cells were also shown to be actively tropic for regions of cell death.

Phenotype reversal in the mouse models was variable. In the hypoxia-ischemia model, cognitive based studies were difficult to interpret and studies of muscle innervation are in progress. A positive effect on disease was found in the shiverer mouse.

No human trials are currently underway with ES cells, although human ES cells have been shown to be multipotent in developing monkeys. Potential approaches to human therapy include unaffected heterologous ES cell transplantation or autologous transplantation of genetically-corrected ES cells from patients.

- What are the technical issues (like how many are needed, and how feasible to expand them for use in humans)?
  They can be expanded to any amount you want.

- Replacing damaged motor neurons in motor neuron diseases, or specific populations of dopamine neurons in Parkinson's disease by stem cells, seems potentially feasible but is replacing the majority of CNS neurons of diverse phenotype also feasible?

- Will the transplanted cells function normally in place of the ones that are being lost?

- Can stem cells replace enough neural tissue in such a catastrophic neurodegenerative such has the NCL's?
  Obviously this needs to be determined empirically but, in theory, and based on some of our experimental models, we have seen pretty extensive cell replacement. Fortunately, for many problems, one does not need 100% replacement to engender functional improvement.

- Which cells are being replaced - all neurons or a specific population?
  Again, needs to be determined empirically. First, one needs to determine which cells need to be replaced in a given disease, including NCL. But, theoretically, stem cells should be able to become the necessary cells, either spontaneously or following some appropriate manipulations, to be determined.

- Which cells would be transplanted? - "Human Stem Cells", "Pig Cells", pigemented (?) epillelium that has transdifferentiated?

- How extensive a transplant would be needed to be effective? Given the <u>global</u> disease, is this possible?
  Again, can only be answered empirically. The transplants we do in mice are quick to one area and we allow the cells to distribute themselves throughout the brain -- which seems to work. Whether that is sufficient, whether administration to a few areas or over a few periods of time is needed can only be determined empirically. My goal is to give cells one to an area that allows global distribution. That was the paper we published this past summer that got all the press. However, this and all the other questions can only be answered experimentally. In theory the answer to all of them is in the affirmative.

Clinical and Regulatory Issues

This has been a misunderstood area for most and has been surrounded by some myths of the role of the FDA. Dr. Cynthia Rask (FDA, CBER) gave an overview of protocols that may be applicable to rare disease clinical trials. Several open forum questions were raised and addressed. The consensus was that the FDA is there to help us through the issues that we may be faced with in the lead up to clinical trials and is not there to block progress.

- Investigators to discuss their ideas earlier rather than later with an FDA representative.
- Start looking at clinical markers and endpoints for use in clinical trials.
- Qualitative methods should be considered for clinical trials in conjunction with valid clinical histopathology i.e. fMRI and other non-evasive measurement technology.
- Toxicity studies should be carried out with the same grade product as would be used in the human trial. Typically based over 3 months, 2 different non-specific species tested with acute higher dosage.
- Continued contact with the FDA

Recommendations

1.0 General

The following recommendations are split into several categories. The overall goal is to be able to target treatments that will slow down the disease progression, stop the disease progression or reverse the disease. The objective of this section is to open up discussions with view to future funding and to highlight where research and paths to future therapies etc. is in need of urgent attention.

2.0 Future Research Funding

The consensus is that future research should take into consideration the final outcome as being targeted towards treatment of the disease. There is a responsibility of the NIH to ensure that science is now directed at therapies for the children suffering with the three major forms of NCL.

3.0 Request for Proposals (RFP's)

At present RFP's do not exist for NCL and would encourage new and existing scientists to pursue research into pre-identified therapeutic science. i.e. CLN3 currently has no experts in Lysosomal Storage Disorders or cell biology or trafficking.

4.0 Reagents

4.1 Antibodies for CLN3 - This is a very hot tool required for CLN3 and needed urgently. Currently there are various antibodies made and each have been developed for different usage. The main issue is that they appear not to be reliable and therefore cannot be used as a freely available tool.
Antibodies need to be developed or some other method that will allow CLN3p to be measured for expression and spread etc. i.e. tracers in AAV, development of a specific color reagent for assaying expression like glucuronidase?

4.2 Mice Models - Mitchison/Nussbaum KO mice are bound for Jackson Labs. This needs to be followed through.

4.3 Centralization of Reagents - When any reagent has been developed they should be made freely available by means of centralization. These reagents include but are not limited to antibodies, cell Lines, models etc. Currently sample cell lines of all NCL mutations are being centralized at Coriell Cell Depository, NIGMS Human Genetic Cell Depository 401 Haddon Ave, Hamden NJ 08103 – Tel 1-800-752-3805 and was initiated by Dr. Sandra Hofmann

4.4 Assays to be developed for use in drug discovery and development.

4.5 Investigate suppressor genes in CLN3 using, AKR cross breeding, yeast model.
This is worth pursuing due to the success of the mnd mouse being cross bred with the AKR strain.

5.0 Centralization of information

5.1 It is quite obvious that the field of science does not allow for sharing of information that takes away credit for the work that has been put in by the investigator. So why is it important to share information. The answer is not that sharing information will progress science to therapies but rather than what type of information is required to be shared. It is known in other fields that sharing of important and up to date information is difficult to obtain and other groups are struggling to find an answer to this dilemma.
It is the view of the NCLRA that the type of information to be centralized should be based around the tools and toolkits that have been developed so that investigators can utilize them in the most productive manner to test theories etc.
The NIH should consider setting up a database and location for these tools and making competitive grants available for the development of them. This would likely be a third party company that specializes in this type of work.

6.0 Patient Controls for Clinical Trials

For clinical trials to be successful then several fundamentals should be considered.

6.1 A protocol should be established to develop markers for disease progression.
This should be non-evasive and should utilize latest technology in neuro-imaging and neuro physiology. This project should be reviewed by the NIH as to how they can be involved either intramural or extramural. This should take into consideration quantitative data combined with any appropriate and relevant histopathology.

6.2 From the NCLRA's point of view we urge that any treatment or therapy should take into consideration the three major forms of NCL regardless of their state of disease onset.

6.3 Costing for these projects should be taken into consideration by the NIH as they will be deemed too high for the patients to brunt the costs. Consider small business grants for this?

6.4 Centralization and easy access of this information should be considered by the NIH. Easy access website would be a method for consideration.

6.5 This project should be started now, as it could identify any hurdles or road blocks that would stall clinical trials.

6.6 Location for imaging and patient characterization to be considered. Is this in an intramural or extramural project.

7.0 Central Project Planning for NCL

To ensure that viable research is funded and directed toward therapies for the three major forms of NCL, a project coordinator should be put into place to oversee the projects to ensure that time and direction is adhered to. As the final goal is to ensure that therapies are made available to children who are afflicted with the NCL disease, a firm commitment that all of the appropriate resources are made available from the NIH to aid in constructing, initiating and overseeing a plan to achieve this.
Once a commitment has been established a plan could then be composed and implemented by a working group comprising of NCLRA members, scientific advisors and appropriate NIH personnel.

8.0 Drug discovery/development

Encourage NIH to pursue Drug discovery/development for the three forms of NCL. In light of recent discoveries of Chloroquine and Gentamicin as possible therapies, further aggressive research into this area would have a high potential for at least slowing down the disease progression. Investigate partnering with a commercial pharmaceutical/biotech companies to bring about for rapid discovery on a broad scale.

9.0 Continued workshop/conference grant (R13)

It has been recommended that these types of conferences focussing on therapies for the three major forms of NCL should be ongoing and subsidized or funded by the NIH. Therefore an R13 grant should be applied for.

Organization and format of the Meeting

The following comments have been included so as to highlight areas of success and improvement for future conferences.

- I want to start by congratulating you on the way the meeting went. I think it is very hard to organize a meeting that allows scientists to communicate and discuss the most recent data and provide information in a form accessible to families.
  Furthermore, scientists are used to working on their own, and following leads that they perceive as promising. Organizing and listing priorities and directions as a group is often difficult and contentious. The group was able to accomplish this in a civil and productive manner.

- I learned a lot and was impressed by the motivation and sophistication of both parents and researchers in trying to advance our understanding of Battens disease to the point where realistic therapeutic approaches can be envisioned.

- One of the main problems was the acoustics in the meeting room. Time and again, people at one end of the room would ask presenters to speak up, but it was not always effective.

- Next conference should have an individual workshop on the different NCL's i.e. one for CLN1/CLN2 as they probably would use the same course of action. Each NCL group can then select the relevant investigators and an advisor and discuss the issues and paths to clinical trials. They would then have each workshop come together and present to the whole group their working plan.

- Ensure clarity as to the role and requirements of each participant prior to the conference.

- Minimize presentation time and increase discussion. Use flip charts, whiteboards etc. agree on action plan, ownership etc. Before leaving conference publish plan.