7th Translational Research Conference for the Management of NCLs
3-4/11/2022, Chicago

The purpose of this meeting is to create a forum to bring together scientists, clinicians and patients advocates to explore new and innovative approaches for treating Batten Disease.

The meeting was divided into the following themes:

Clinical Trial Updates and Lessons Learned
Natural History Studies, Biomarker Discovery and EMR Mining/AI in Drug Discovery
Non-traditional and Pathological Changes
Small Molecules, ERTs, Chaperones and Biologicals
Viral Mediated Gene Correction
Emerging Nucleic Acid Therapeutic Approaches

Clinical Trial Updates and Lessons Learned

There are more than 7000 molecular diseases but just 600 therapies. Many diseases are rare, caused by loss of function or gain of function mutations but have the same underlying molecular cause so, in theory, lessons from one disease can be applied to another.

An example of this is gene therapy using viruses to deliver replacement genes. Most gene therapy uses a virus called Adeno Associated Virus (AAV) and this technology has 2 approvals in the USA which can speed up progress for other trials using AAVs. This is because they use the same virus, the same production and purification method and the same route of administration, the only thing that differs is the gene which is specific for each disease. This should also apply as the gene editing technologies, such as CRISPR, develops.

It is hopeful that this degree of similarity will allow collaborative work to streamline pre-clinical testing, regulatory pathways and minimal set of acceptable pre-clinical testing for toxicology and thus speed up getting new potential treatments into clinical trials.

Gene therapy in clinical trials
CLN1

- Preclinical trials in mice showed “rescue” compared to controls.
- An increase in the gene product was seen in the blood for the lifetime of the animal.
- No way of determining whether this reaches the brain.
- There is still progression.

CLN5

- CLN5 has been tested in animal models by administering into the brain and the eye.
- After brain administration there is a relative stabilisation of clinical disease and brain volume
    - Still decline possibly due to loss of eyesight.
- Injection of the vector into the eye stabilises retina.
- Studies are now ongoing to determine benefit of treating brain and eye together
- January 2022 clinical trial NCT 05228145 opened.

CLN7

- research financed by non-profit organisations has resulted in getting into clinical trial faster
- 4 children have received the treatment (NCT 04737460)
- insufficient funds for more.

CLN2
Brineura

- Observational studies of children on ERT show there is a slowing of progression.
- Eyesight loss is an issue as Brineura does not reach the eye.
- hTPP (the protein missing in CLN2) tested in dogs showed preservation of retinal structure and function.
- BDFA funded trial showed that Brineura could be safely injected into the eyes
    - Further data is required to determine the effectiveness of this treatment.

CLN3
Miglustat

- Isolated from natural sources.
- Used to treat mild to moderate Gaucher's disease type I and Niemann Pick disease type C.
- Functions by reducing the build-up of molecules that damage cells.
- Can cross the blood brain barrier (slowly).
- Similar products build up in Batten Disease
    - Miglustat normalises the response of cultured neurons to a neurotransmitter (chemical messengers used to carry signals from one nerve to another)
    - Currently an open-label safety, pharmacokinetic and efficacy study in progress (NCT05174039) sponsored by Beyond Batten Disease Foundation in collaboration with Theranexus.

Trehalose

- Treatment increases CLN3 mouse life span.
    - Decreases neurodegeneration by promoting clearance and through decreasing neuroinflammation.
- It works through a signalling pathway called Akt and prevents transcription of target genes.
- There is NO current evidence in humans

Other studies offer insights into the difficulties of developing new therapies. Initial animal data suggested that mGluR signalling was relevant in Fragile X. However, clinical trials showed no benefit to adolescents or adults demonstrating that data in animals does not always translate to humans. Furthermore, rare patients are heterogeneous behaving as N of 1. Therefore, it is suggested their decline should be assessed from birth and any treatment compared to this rather than many individuals.

Natural History Studies, Biomarker Discovery and EMR Mining/AI in Drug Discovery

What are Natural History Studies and what data is collected?

To identify demographic, genetic, environmental and other variables that can have an impact on disease progression and severity.
Draft guidelines from the FDA: https://www.fda.gov/media/122425/download

This information is needed in preparation for clinical trials.

What decisions need to be made about the study?

How often to collect data?
Duration of the study? (this is disease dependent, e.g. CLN3 – 20-30 year progression)
Biomarkers?
Retrospective or prospective?

What are the NCL challenges?

Rare
Heterogeneity
Signs and symptoms at different times
Variable rate of progression during times of developmental change
Ascertainment biases amplified by rarity
Outliers are disproportionate

There is a scale used for different motor and language skills called UBDRS.

There is the need for effective biomarkers. These are required to assess the effectiveness of a potential treatment and possibly as a diagnostic tool. Data is being gathered looking at molecules that are associated with neuronal injury to assess their suitability as biomarkers. A biomarker which is found in the blood would be the ideal especially in terms of developing a new-born screen!

Another important point raised was for the need for quality of life, not just survival. Embedded in this is when to start treatment. This is where biomarkers may have another role in determining the difference between illness and disease and guide when to start treatment.

There is a need for a central repository of patient clinical information, genotyping, biomarkers and tissue although this is a lot of work. It is very sensitive work.

Non-traditional and Pathological Changes

Immunity and treatments

- Introducing something new to the human body risks activating the immune system
- Research into peanut allergy may result in a way to reduce this risk

Sleep Function

- Approximately ⅓ - ½ of normal children to have sleep issues up to about 5 years old.
- This increases to about 90% of children with NCLs and is a real issue for parents.
- They can have fragmented irregular sleep, daytime sleepiness, parasomnia (unusual and undesirable events or experiences that disrupt sleep), decreased sleep and early rising.
- There have been 8 studies over 37 years into sleep issues in NCLs.
- However, data is hard to study and draw conclusions from due to the heterogeneous sample of children used, the lack of available genomic data from earlier studies, the variability in methods used and disease stages in addition to the fact that concurrent medication may interfere with sleep. This is being investigated further.

Digestion

- The digestive system is controlled by the enteric nervous system, a web of neurons embedded in the wall of the gastrointestinal (GI) system.
- There are between 200 and 600 million neurons and 20 different types, and its complexity means it is sometimes referred to as the "second brain."
- Issues in the digestive system can result in malnutrition.
- In mice models of CLN, KO mice had distended colons and smaller intestines than control animals.
- Investigations looked at bowel transit – how far something passes through the bowel and how long it takes.
    - In 7-month-old CLN1 mice it takes longer to passage and doesn't travel as far.
    - CLN2 mice have an earlier onset.
    - These mouse models have been treated with gene therapy into the gut and show evidence that it improves bowel transit but there is more to data to come.

Small Molecules, ERTs, Chaperones and Biologicals

One of the issues with treating Batten is getting drugs to where they are needed.

- The brain is protected by the blood brain barrier
- Many drugs are too large to pass through (Brinuera is administered through ports)
- Looking at repurposing small molecules used to treat other diseases (e.g. Tamoxifen)
- Improved drug delivery is being investigated using new and existing technologies
- Better understanding of how to deliver functional replacement proteins to lysosomes is needed, investigators are looking at chaperone molecules to help

Another issue with the development of potential treatments is the lack of cellular based models available. Currently it takes more than 60 days to induce stem cells to become neurons. Research is ongoing to improve this.

Viral Mediated Gene Correction

There are currently 13 genes involved in normal lysosome function that, when mutated, cause Batten Disease. One possible option for treatment is to introduce a normal copy of the affected gene to the cells. Getting the correct genetic code is not a problem, delivery and ensuring functionality is.

Scientists "borrow" from molecular tools nature to assist in research and as potential treatment strategies. The most widely used in gene therapy delivery currently are AAVs.

The pros and cons of AAVs:

- They exist "in the wild"
- They are unable to replicate unless they have help from a related virus (introduce genetic information into cells without causing a viral infection)
- They can infect non-replicating cells such as nerve cells and can also cross the blood brain barrier

- They don’t target all cells
- They are limited to one use only due to a response from the immune system
- They can be destroyed by the target cells

The design of AAVs is always under investigation.

In addition to gene replacement, research is ongoing into gene editing using different methods.

- CRISP-R to edit sections of genes
- Prime editing to edit single base code in DNA
- Anti-sense Oligonucleotides (ASO) (https://www.milasmiracle.org/milasen) to help copy the correct information to process into a functional protein

The important take home messages from this meeting are:

- researchers are looking into every method of treating Batten Disease and will consider and try out new drugs, techniques and ideas from other disease models to speed up their analysis
- not everything tried in the animal models will work in humans.