Research Report for Families

7th Meeting
Translational Research Conference for the
Management of NCLs

Chicago, November 2022

Held every two years, this meeting brings together leading NCL researchers, clinicians, industry and advocacy partners from around the world, alongside experts from outside the NCL field who bring fresh perspectives and novel insights from other technical disciplines and therapeutic areas.

This year, program sessions covered the following areas:

1) Clinical Trial Updates and Lessons Learned
2) Natural History Studies, Biomarker Discovery & EMR Mining/AI Drug Discovery
3) Nontraditional Clinical and Pathological Changes
4) Small Molecules, Chaperones and Biologicals
5) Viral Mediated Gene Correction
6) Emerging Nucleic Acid Therapeutic Approaches

This report describes some of the major themes and key take-outs from the meeting.

- **GENE-BASED THERAPEUTICS**

We are currently living in what some have termed the 'genomic revolution' - a golden age of personalized precision medicine and advanced gene-based therapeutics. Indeed, as monogenic (single gene) conditions, the NCLs are prime candidates for the growing list of emerging gene technologies, and significant research and development (R&D) resources have been directed toward these for more than a decade. This focus was strongly reflected in the lineup of presentations at the NCL meeting with 14 of the 31 presentations related to gene-based therapeutic approaches for NCLs.

There have been significant learnings from a remarkable *six* NCL gene therapies (GT) that have journeyed the translational research road from preclinical to in-human clinical studies in recent years. Delivered directly into the central nervous system, viral vector-mediated gene therapies utilizing the adeno-associated virus (AAV) have been investigated for treatment of **CLN2 disease** (Clinical Trial ID NCT01161576; completed, now being further developed by LEXEO Therapeutics), **CLN3 disease** (NCT03770572; completed; ongoing preclinical studies; Amicus Therapeutics), **CLN6 disease** (NCT02725580; completed; discontinued; Amicus), **CLN5 disease** (NCT05228145 - CNS and eye-directed GT; recruiting; Neurogene Inc), **CLN7 disease** (NCT04737460; ongoing, UT Southwestern/Taysha Gene Therapies) and **CLN1 disease** (regulatory approval; Taysha). Although the latter has received regulatory approval (FDA and CTA) to proceed, Ph1/2 studies have not commenced to date.

Broadly speaking, so far we know that AAV9-mediated gene therapies (or AAVrh.10 in the case of the CLN2 disease) appear to have favorable safety profiles and have demonstrated early signs of disease stabilization – keeping in mind that such small studies do not have sufficient power to show whether these treatment effects are *statistically significant*. Unfortunately, the stabilization effects observed

in the CLN3 and CLN6 studies have not endured beyond two years and the respective programs have since been discontinued (CLN6) or moved back to preclinical phase for further R&D studies (CLN3).

More recently, preliminary data from the ongoing CLN7 disease GT study also indicate a stabilization effect in four patients treated so far. Patients will continue to be followed, but whether this program will expand to include additional patients remains to be seen. With the CLN5 disease GT study having only commenced in early 2022, safety and efficacy data is yet to be reported.

Addressing limitations of current gene therapy

Despite this recent progress, gene therapy poses one of the greatest technical challenges in modern medicine and faces numerous hurdles on the path to wider clinical use. One of the greatest challenges is **drug delivery**, that is, how to efficiently deliver healthy copies of the target gene to very specific cells and tissues (eg. neurons/brain) while avoiding unwanted 'off-target' effects, including unintended modifications at other gene sites or in different cells. In addition, **immunogenicity** – or switching on of the host (patient)'s immune response against the viral vector - can be very problematic in the short and longer term. In particular, this immune response prevents patients from being re-dosed if the efficacy of the gene therapy tapers off over time. These were topics keenly addressed by several conference speakers.

NCLs affect more than just neurons! To date, the AAV vectors employed in NCL clinical studies specifically target only neurons of the CNS. There is a growing body of literature however, demonstrating the critical involvement of other CNS **'support' cells known as glia**, including microglia and astrocytes, which are involved in pathogenic inflammation of the brain in NCL. Current gene therapy approaches do not target this key subset of CNS cells, yet it is likely that for a treatment to have meaningful clinical benefit, reduction in glial activation and inflammation through other therapeutic approaches will be necessary.

Furthermore, we are learning that other cell types and organs *beyond* the CNS may be implicated in the pathological effects of NCLs, including the **heart, peripheral nervous system** and **enteric nervous system** (gut). As gene therapy currently stands, there is not likely to be one 'silver bullet' or 'one-size-fits-all' therapy for Batten disease, but rather a combination approach (for example, GT and a pharmacological drug) that will be required to effectively manage the spectrum of NCL pathologies and symptoms. To this end, ongoing pursuits to develop effective biologics, small molecule and pharmacological therapeutics for the treatment of NCLs remains important and well-directed.

Antisense oligonucleotide (ASO) treatment

Rather than replacing or correcting existing genes, this therapeutic approach uses short sequences of nucleic acids, known as oligonucleotides, to influence how the cell's machinery translates genes into proteins. **Antisense oligonucleotides, or ASOs**, can be thought of as '**tiny genetic patches**' that work on highly specific segments of incorrect DNA sequences (ie. mutations), helping to restore production of the correct, healthy gene product. In a CLN3 mouse model, a single ASO treatment induced robust rescue of the 'faulty' CLN3 gene for over a year, leading to improved neuron function and maintenance of gross and fine motor skills in treated mice. ASOs overcome some of the challenges associated with viral vector-mediated gene therapy discussed above, and have demonstrated some success in an NCL

'N-of-1' clinical trial for a single patient with CLN7 disease[1]. Currently attracting substantial industry R&D support, ASO-based therapeutics appear to be within reasonable reach of further NCL clinical trials and will be one to closely watch in future.

- **REPURPOSING DRUGS FOR USE IN NCLS**

A number of presentations discussed the utility of repurposing drugs already approved for treatment of other conditions. The drug **tamoxifen** which is approved for treatment of breast cancer, is shown to activate the gene known as the 'lysosomal master controller' (transcriptional factor EB, or 'TFEB') in cell models of CLN3 and CLN7 disease. In these models, tamoxifen treatment reduced lysosomal accumulation of 'Gb3' (globotriaosylceramide), a type of **glycosphingolipid** (GSL) that can be thought of as 'building blocks' that make up the membrane surrounding the lysosome. Gb3 appears to be a component of the toxic aggregated storage material observed in CLN3- and CLN7 disease-affected neurons, and its clearance results in improvements in the function of those cells. Tamoxifen treatment also led to rescue of motor deficits in CLN7-affected mice. Preclinical studies in CLN7 and CLN3 cell and animal models are ongoing.

Miglustat is a small sugar-like molecule also known to exert effects on pathways involved in the production of lysosomal membrane **glycosphingolipids**. Approved for the treatment of the lysosomal storage disorders Gaucher disease and Niemann Pick C disease, miglustat acts by reducing precursor molecules to GSLs (so called 'substrate reduction therapy'), thereby reducing accumulation of GSLs within cells and restoring normal neuron function. Similarly, data presented at the meeting demonstrated that GSL accumulation observed in cell models of CLN3 disease were reduced when treated with miglustat. This reduction in GSL accumulation was associated with restored cellular function. Two presentations discussed the data and scientific rationale that led to a Ph1/2 clinical trial of Batten-1 (**miglustat**) now underway for the treatment of CLN3 disease.

- **BUILDING 'CLINICAL TRIAL READINESS' FOR NCLs**

Discussions also focused on the importance of curating reliable natural history data and identifying and characterizing biomarkers of disease progression. The importance of both types of studies cannot be understated. Presentations discussed optimal study design, parameters and current NHS and biomarker studies.

- **QUALITY OF LIFE CONSIDERATIONS**

Sleep disturbance and bowel dysfunction are reportedly two of the most common and burdensome symptoms for patients living with Batten disease. Despite being key contributors to poor quality of life, both domains remain poorly understood and, to date, have been grossly under-researched. It was encouraging to see highly regarded and experienced research teams now turning their attention to these important areas. In future, as our understanding of the origin and pathology of these clinical symptoms improves, opportunities for developing *adjunct* therapeutic interventions are likely to arise – for example, a combined approach may be required, with both CNS-directed gene therapy *and*

[1] The drug 'milasen' was a patient-customized ASO therapy used in the 'N-of-1' study in CLN7 disease (Kim et al, 2019).

pharmacological (or other gene-based?) treatment to target enteric nervous system and cardiac pathologies.

- **OTHER KEY TAKE-OUTS**

We heard about the Platform Vector Gene Therapy (PaVe-GT) Pilot Project, an NIH initiative led by National Centre for Advancing Translational Sciences (NCATS). The project aims to overcome operational and financial hurdles in GT development by streamlining technical processes and the path to clinical testing for multiple rare diseases in parallel. PaVE-GT will pilot GT development for four rare diseases, using the same gene delivery system (AAVs) and manufacturing methods for each - but containing disease-specific genetic constructs - therefore circumventing the need for safety and toxicity testing in Ph 1 studies, and streamlining the path to efficacy-focused Ph 2 studies. Indeed, there may be potential to leverage this model for multiple NCL subtypes in future.

We continue to follow the research developments outlined in this report, and look forward to communicating further updates in the future.

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