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Advances in the Treatment of Neuronal Ceroid Lipofuscinosis

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Abstract

Neuronal ceroid lipofuscinoses (NCL) represent a class of neurodegenerative disorders involving defective lysosomal processing enzymes or receptors, leading to lysosomal storage disorders, typically characterized by observation of cognitive and visual impairments, epileptic seizures, ataxia, and deterioration of motor skills. Recent success of a biologic (Brineura®) for the treatment of neurologic manifestations of the central nervous system (CNS) has led to renewed interest in therapeutics for NCL, with the goal of ablating or reversing the impact of these devastating disorders. Despite complex challenges associated with CNS therapy, many treatment modalities have been evaluated, including enzyme replacement therapy, gene therapy, stem cell therapy, and small molecule pharmacotherapy. Because the clinical endpoints for the evaluation of candidate therapies are complex and often reliant on subjective clinical scales, the development of quantitative biomarkers for NCLs has become an apparent necessity for the validation of potential treatments. We will discuss the latest findings in the search for relevant biomarkers for assessing disease progression. For this review, we will focus primarily on recent pre-clinical and clinical developments for treatments to halt or cure these NCL diseases. Continued development of current therapies and discovery of newer modalities will be essential for successful therapeutics for NCL.

Areas covered: The reader will be introduced to the NCL subtypes, natural histories, experimental animal models, and biomarkers for NCL progression; challenges and different therapeutic approaches, and the latest pre-clinical and clinical research for therapeutic development for the various NCLs. This review corresponds to the literatures covering the years from 1968 to mid-2019, but primarily addresses pre-clinical and clinical developments for the treatment of NCL disease in the last decade and as a follow-up to our 2013 review of the same topic in this journal.

Expert opinion: Much progress has been made in the treatment of neurologic diseases, such as the NCLs, including better animal models and improved therapeutics with better survival outcomes. Encouraging results are being reported at symposiums and in the literature, with multiple therapeutics reaching the clinical trial stage for the NCLs. The potential for a cure could be at hand after many years of trial and error in the preclinical studies. The clinical development of enzyme replacement therapy (Brineura® for CLN2), immunosuppression (CellCept® for CLN3), and gene therapy vectors (for CLN1, CLN2, CLN3, and CLN6) are providing encouragement to

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families that have a child afflicted with NCL. We believe that successful therapies in the future may involve the combination of two or more therapeutic modalities to provide therapeutic benefit especially as the patients grow older.

Keywords

Neuronal ceroid lipofuscinoses (NCL); ceroid lipofuscinosis, neuronal (CLN); palmitoyl protein thioesterase-1 (PPT1); tripeptidyl peptidase-1 (TPP1); enzyme replacement therapy (ERT); gene therapy; adeno-associated virus (AAV); clinical trials

1. Introduction to Neuronal Ceroid Lipofuscinoses

Neuronal ceroid lipofuscinoses (NCL) are a collection of 13 autosomal recessive and 1 autosomal dominant neurologic disorders involving defective lysosomal processing enzymes or receptors, leading to lysosomal storage disorders[1–6]. Similar to other neurologic diseases, the disruption of normal lysosomal function leads to a toxic buildup of protein aggregates within the central nervous system (CNS), and is a major contributor to NCL pathologies[7]. The unique feature of NCL is the aggregation of lipopigments (lipofuscin) in lysosomes[5,8,9], which appear in histopathology as fine yellow-brown pigment autofluorescent granules, composed of a mixture of lipids and protein, including protein subunit c of mitochondrial ATP synthase (SCMAS) and sphingolipid activator proteins (SAP) A and D, among others (Table I)[10–14]. While the CNS is dramatically affected in all NCL patients, many have additional eye pathology (retina and ganglion cells), and other NCL mutations result in systemic pathology of visceral organs such as liver, heart, spleen, adrenals, and kidney[7,15,16]. While the buildup of lipofuscin aggregates in neurons occurs slowly as a secondary consequence of the normal aging process[5,14], it is rapidly advanced in NCL patients. As the lipofuscin aggregates in the lysosomes, it alters the neuronal cytoskeleton and cellular trafficking, creating a pathologic state resulting in neuronal loss, and glial proliferation and activation[7].

As a collective group, NCL patients are typically defined by observation of cognitive and visual impairments, epileptic seizures, and deterioration of motor skills and balance issues[12,17]. The hallmarks of these diseases are similar to other cognitive disorders and therefore, families encounter difficulties and severe delays in obtaining a confirmed diagnosis of NCL from local pediatricians and neurologists, unless there is an older sibling with the same diagnosis[18]. Children with NCL, who initially exhibit normal development, suffer a regression in their ability to talk or walk and develop cognitive or learning disability. Each NCL type has a different age of onset and rate of decline of the observational hallmarks of language and motor skill development, with many becoming lethal as the children age[14,19,20]. The severity of progressive neuronal degeneration in the CNS leads to the overt neurologic phenotypic changes typically observed in NCL-affected children[6]. NCL is the most common cause of dementia in children[1,3,6,21]. Other than Brineura® therapy for CLN2, there are no effective therapies for NCL[22]. However, the last 5 years have seen significant progress in development of therapeutics to halt and/or reverse the progression of these diseases. There are new therapeutics on the horizon and some that have already gained approval. We will review these advances in this article.

Presently, the NCL family of disorders includes 14 separate subtypes. The majority are inherited as autosomal recessive disorders with a combined incidence worldwide of 1:12,500 to 1:100,000 (Table I)[14,23,24]. The NCL database maintained by University College in London, UK (https://www.ucl.ac.uk/ncl/mutation.shtml) lists 515 known genetic mutations from 1436 NCL patients, including missense, nonsense, deletions, and splicing defects, assigned to genes encoding the 14 ceroid lipofuscinosis neuronal (CLN) lysosomal proteins[4]. From this database, the 4 most common NCL types are CLN1 (also known as "Infantile NCL", with 220 patients), CLN2 ("Late Infantile NCL", 369 patients), CLN3 ("Juvenile NCL", 423 patients), and CLN6 ("variant LINCL", 132 patients). Although the disorders all dramatically affect the CNS, some NCL children are also afflicted by blindness (typical in CLN2, CLN3, CLN11, CLN14), sleep disorders, and language delay or language regression[12,25,26]. The natural history of each NCL subtype is reviewed in section 2. Similar to other lysosomal storage disorders, NCL disorders affect the lysosomal processing of cellular waste products, and include defects involving secreted lysosomal proteins (CLN1, CLN2, CLN5, CLN10, and CLN13) and lysosomal transmembrane proteins (CLN3, CLN4, CLN6, CLN7, CLN8, CLN12, and CLN14)[27–29]. Over the past decade, investigators have deciphered the functions of many of the CLN proteins; however, several remain unknown with regards to function/activity (Table I)[29–32].

Since our 2013 review of the NCL family of diseases in this journal[33], there have been several reviews focusing on the biology of various forms of NCL and the potential of different therapeutic interventions[3–5,14,26,29,34–40]. Hence for this review, we will focus primarily on pre-clinical and clinical developments for the treatment of NCL disease since 2013, and demonstrate the exponential growth in the interest of academicians and industry to put forward resources to halt or cure these devastating rare diseases. This review will focus on the natural history for the different NCL subtypes (section 2); experimental animal models for development of NCL therapeutics (section 3); biomarkers reported for NCLs (section 4); challenges for development of NCL therapies (section 5); the different therapeutic approaches to NCL (section 6); the latest pre-clinical and clinical research for therapeutic development for the various NCLs (section 7); how all the promising academic preclinical work has resulted in many partnerships with foundation/industry (Section 8); and will end with conclusions (section 9) and our opinion on what we see as the breakthroughs and challenges in the field of therapeutic development for NCL (section 10). The sections on natural history, animal models, biomarkers and therapeutic approaches are subdivided by NCL subtype with the corresponding current findings.

2. Natural History of the NCLs

The natural history or progression of the various NCL types is of vital importance for identifying ideal treatment windows and milestones for assessment of improvements or of rate of decline. There have been many natural history studies to track the progression of NCL as the patients age (Table II)[25,26]. These observational studies did not involve therapy or treatments, and many of the early studies enrolled subjects with NCL of all subtypes. More recent observational studies have been completed for single NCL subtypes: CLN2, CLN3, and CLN6 (Table II).

2.1. CLN1.

CLN1 disease, also known as infantile Batten disease or infantile neuronal ceroid lipofuscinosis (INCL), is caused by mutations in the *CLN1* gene, which encodes the secreted lysosomal protein palmitoyl-protein thioesterase 1 (PPT1)[41]. Early development appears normal in affected patients, but by 18 months of age, they typically begin to show signs of developmental regression[42]. Rapidly developing psychomotor issues include decreased muscle tone, ataxia, myoclonus, epilepsy, and loss of vision, mobility, and vocal abilities[42]. There is progressive brain atrophy, and microcephaly can result. As the condition progresses, a feeding tube is often required. Children with the disease do not usually survive past early childhood[25,26,42]. There are some *CLN1* mutations that cause later-onset forms of the disease, but all forms are associated with severely reduced life expectancy[43–45].

2.2. CLN2.

CLN2 disease, also known as late infantile neuronal ceroid lipofuscinosis (LINCL), is caused by mutations in the *CLN2* gene, which encodes the lysosomal protein tripeptidyl peptidase 1 (TPP1)[46]. Affected children usually display symptoms of the disease by ages 2 to 4, typically starting with recurrent seizures and difficulty in coordinating movements[47,48]. The disease progresses with developmental regression, affecting speech and motor skills. Actions such as sitting and walking become more difficult, as does swallowing. Affected children also develop myoclonus, vision loss, and intellectual disabilities, and typically do not survive past 8 to 12 years[47]. Natural history observational studies have linked genotype and the severity of the phenotype, and the rate of neurologic decline has also been determined[47,49,50]. In an MRI study analyzing CLN2 children (n=38) compared to healthy controls (n=52), global thinning of the cortical regions was noted across the brain[49]. In newer observational studies for the same set of CLN2 subjects and healthy controls, MRI was used to measure the regional cortical thickness in the brain, which appears to be 2X thicker in controls *vs* CLN2 subjects, demonstrating the overall declining neurologic health of the CLN2 children[50]. In a recent study, which used the same methods of assessment for patient cohorts in the US and Europe, the natural history of children afflicted with CLN2 was defined, characterizing a predictable time frame of decline of language and motor skills[51].

2.3. CLN3.

CLN3 disease, also known as juvenile neuronal ceroid lipofuscinosis (JNCL), is the juvenile-onset form of the disease. It is caused by mutations to the *CLN3* gene that encodes a lysosomal transmembrane protein, the function of which is unknown[52]. It is theorized to be involved with the modulation of vesicular trafficking and fusion, or alternatively with regulation of lysosomal pH or osmoregulation[16,53–56]. Disease onset usually occurs between 4 and 10 years of age, starting with visual failure from rapidly progressing retinal degeneration, followed by progressive cognitive decline and motor dysfunction[57–59]. Behavioral problems and seizures then develop. Life expectancy is in the early 20s[14,59]. A small scale natural history trial is currently recruiting CLN3 patients (Table II), with no results reported to date.

2.4. CLN4.

CLN4 disease, also referred to as Parry disease, is an adult NCL, with signs and symptoms typically appearing around age 30[60–63]. Affected individuals develop general seizures and myoclonic jerks, along with decline in intellectual and physical function. Dementia, ataxia, tremors, and speech problems worsen over time, leading to death about 15 years after the symptoms first appear[25]. Contrary to the previously described forms of the disease, CLN4 patients do not have deterioration of vision, and it is the only NCL with an autosomal dominant inheritance pattern[61,63]. CLN4 disease is caused by a mutations in the *DNAJC5* gene, which encodes the pre-synaptic co-chaperone cysteine string protein (CSP)[61,63]. CLN4 disease is closely linked to CLN1 disease, and it has been theorized that CSP and PPT1 have a substrate-enzyme relationship[63].

2.5. CLN5.

CLN5 disease is also known as the Finnish variant of late infantile NCL[64]. It is caused by mutations in the *CLN5* gene, which produces a soluble lysosomal glycoprotein of unknown function. The age of onset is typically between 4 and 7 years of age[65]. Affected children usually have normal growth and development until the disease manifests with motor impairment or psychomotor regression. As the disease progresses, patients exhibit clumsiness, seizures, loss of vision, ataxia, and myoclonus. Life expectancy ranges from 13 to 30 years of age, with some individuals having a slower progressing form of the disease[65].

2.6. CLN6.

CLN6 disease, also known as variant late-infantile/early juvenile NCL, is caused by a mutation in a transmembrane protein[66,67]. The disease manifests between 18 months and 8 years of age, and is highly variable. Affected children experience loss of vision and motor skills, epilepsy, dysarthria, and ataxia[68]. Deterioration is rapid and death usually occurs before the teenage years. Mutations in the *CLN6* gene have also been shown to be responsible for Kufs disease Type A, which was formerly classified as CLN4 disease[62]. Kufs Type A disease presents with symptoms very similar to those of CLN4 disease, but it has an autosomal recessive pattern of inheritance[62]. A small-scale natural history trial is currently recruiting CLN6 patients (Table II), with no results reported yet.

2.7. CLN7.

CLN7 disease is caused by a mutation in a lysosomal membrane protein of unknown function[69]. Onset is typically detected between ages 2 and 7, with symptoms including epilepsy, developmental regression, myoclonus, ataxia, loss of vision, and speech impairment[70]. Motor function and cognitive ability progressively worsen until death in the teenage years.

2.8. CLN8.

CLN8 disease is caused by mutations in a gene encoding a transmembrane endoplasmic reticulum protein, which regulates lysosome biogenesis[12,71,72]. The disease presents in 2 different ways: the Turkish variant late-infantile NCL or Northern epilepsy. The severity of the *CLN8* gene mutation is responsible for the differences. The Turkish variant is the more-

severe form of the disease, with onset typically between ages 2 and 7[73]. Affected patients develop myoclonic epilepsy and ataxia, along with developmental regression, which causes loss of the ability to walk and speak. Cognitive ability also declines progressively, and affected individuals rarely survive past late childhood or early adolescence. Northern epilepsy is the less-severe form of the disease and is characterized by recurrent seizures[74]. Age of onset is typically between ages 5 and 10. As the disease progresses, affected individuals develop ataxia and other motor dysfunctions, and experience a slow decline in cognitive abilities. In the less severe Northern variant, affected individuals develop vision problems later in life, and life expectancy is reduced, although most survive into their 50s[74].

2.9. CLN9.

CLN9 disease was identified recently[75], and is not well characterized. The underlying genetic cause remains unknown, but it is theorized to be a regulator of dihydroceramide synthase[76]. Symptoms typically appear in early childhood (average age 4 years) and include declining vision, seizures, ataxia, and myoclonus[75]. Cerebral atrophy and developmental regression also occur, with death usually between ages 15 and 20 years[75].

2.10. CLN10.

CLN10 is very rare, and it is likely that most cases go undiagnosed[77–81]. The disease can present in neonates with microencephaly, absence of reflexes, epilepsy, and respiratory problems[77–81]. Seizures can start before birth. CLN10 has the earliest onset for the NCLs, with expected survival measured in days, and cardiac failure being the most common cause of death[77–81]. There are also late infantile and juvenile variants of the disease, with later onset of symptoms and a slower disease progression[82,83]. These patients may have normal early psychomotor development, but then begin to exhibit neurodegenerative symptoms including ataxia, and cognitive decline, with loss of vision, speech and mobility[82,83]. CLN10 disease is caused by mutations in the gene encoding for the lysosomal aspartic protease cathepsin D (*CTSD*). Different mutations cause varying levels of cathepsin D functionality, leading to the differences in disease progression[81].

2.11. CLN11.

Similar to CLN4, CLN11 disease has a relatively late onset of early- to mid-20s. The disease is characterized by rapidly progressive visual failure due to retinal dystrophy, seizures, myoclonus, cerebellar ataxia, and cerebellar atrophy[84]. To date, it has only been reported in two members of an Italian family[84]. It is caused by a homozygous mutation in the granulin precursor (*GRN*) gene[84].

2.12. CLN12.

CLN12 disease, also known as Juvenile parkinsonism-neuronal ceroid lipofuscinosis, has an onset between ages 13 to 16[85]. This Parkinson-like disorder is caused by mutations in the *ATP13A2* gene, which encodes an enzyme that is thought to regulate ion homeostasis[86]. First characterized in a canine model[87,88], CLN12 disease has also been identified in four members of a Belgian family[85]. For these 4 subjects, learning difficulties were evident around the age of 8 years, followed by unsteady gait, myoclonus, and mood disturbance in

the pre-teen years. As the disease progresses, the affected individuals lose speech and develop mobility issues. Over time, they exhibit a combination of progressive spinocerebellar ataxia, bulbar syndrome, extrapyramidal and pyramidal involvement, and intellectual deterioration[85].

2.13. CLN13.

CLN13 disease, also known as Kufs disease type B, is characterized by adult onset dementia, often associated with movement and behavioral abnormalities[89,90]. The disease is caused by mutations in the gene encoding cathepsin-F, a lysosomal cysteine protease[89,90]. Symptoms usually present around 30 years of age, starting with memory deficits and behavioral disturbances. As the disease progresses, motor function deteriorates and brain function decreases. Affected individuals develop tremors, bradykinesia, and extrapyramidal type rigidity. CLN13 is rare among the NCL family of diseases, and unlike most NCLs there is no loss of vision[89,90].

2.14. CLN14.

CLN14 disease, also known as progressive myoclonic epilepsy (EPM3), is caused by mutations in the *KCTD7* gene, which codes for the potassium channel tetramerization domain-containing protein 7[91,92]. The disease is infantile-onset, usually manifesting between 8 to 24 months of age. Patients present with myoclonic seizures, followed by neurodegeneration, developmental regression, and visual failure as they age. Intracellular accumulation of autofluorescent lipopigment storage material is evident in fibroblasts, neurons, and eccrine secretory epithelial cells obtained through skin biopsy[93,94]

3. Experimental Animal Models Used for Testing Therapeutics for NCLs

Over the course of the last decade, many animal species and strains have been identified, with naturally occurring neurologic deficits relevant to the NCLs, while other experimental animals have been genetically engineered to knock out or knock-in NCL specific genes[34,95–98]. Breeders and farmers have identified quite a few mammals with NCL-like deficits and investigators have mapped the genomic mutations responsible for NCL subtypes and variants in mice, dogs, pigs, and sheep (Table III)[97,99,100]. While most of these mutations are not the same as the major human NCL mutations, the hallmarks of the specific NCL subtypes are present, such as neuronal apoptosis, gliosis, and autofluorescent lipofuscin aggregates, allowing investigations of the function of the NCL proteins *in situ*[34,98,101]. Animal disease models are a useful tool for the development of novel new therapeutics for the human NCL. Since pre-clinical studies involve delivering candidate drugs/viral vectors to complex organs such as the brain or liver, where most NCL variants have pathology, an animal model is helpful to evaluate proof of concept. Large animal models (dogs, pigs, and sheep) provide a surrogate for the therapeutic target with similar size and complexity closer to the human brain[34,35,39,98]. These experimental animals also allow for multiple assessments of safety along with comparative studies for drug distribution as a function of administration routes to the CNS. The following summarizes the current animal models available for each NCL with particular emphasis of those added to the literature since 2013 (Table III). While there are non-mammalian models (zebra fish, *C.*

elegans, and yeast) being created for NCL drug development, they are not included here as they have been previously reviewed by Faller et al[34].

3.1. CLN1.

There are two different mouse models commonly used for CLN1 research. These have been genetically created by homozygous deletion of either the entire exon 4 ($Ppt1^{\Delta ex4}$) or the exon 9 ($Ppt1^{\Delta ex9}$) of the *PPT1* genome[102]. These deletion mutations are not genetically analogous to human CLN1 mutations. Miller et al created the R151x mouse model, with a knock-in for the C>T genomic point mutation in exon 5 of the *Cln1* gene, which mimics the human p.R151x mutation, the most common nonsense mutation in *Cln1* (52.3%) based on genetic surveys[31,103,104]. The $Cln1^{R151X}$ mouse model was used to demonstrate that read-through drugs gentamicin and Ataluren (Translarna™) increased PPT1 enzyme activity, a measure of therapeutic efficacy[103]. In addition to the engineered mouse models, a Dachshund and a Cane Corso dog have each been found to have CLN1 phenotype and genotype, with efforts underway to establish colonies[105,106].

3.2. CLN2.

Pre-clinical studies with TPP1 deficient mice ($Tpp1^{-/-}$), a model of CLN2 disease, were used to evaluate the potential for enzyme replacement and gene therapies[107–109]. Two newly developed mouse models have been characterized. (1) $CLN2^{R208X}$ which carries a nonsense mutation that, unlike the original $Cln2^{-/-}$ mouse model, allows for mutation-guided therapies such as antisense oligonucleotides (ASO) and nonsense suppression which would be relevant to the human p.R208X mutation[110]. (2) A mouse model based on an inducible *TPP1* transgene is still in development, which uses a stop cassette inserted ahead of the $Tg^{LSL\text{-}TPP1}$ transgene, thus disrupting TPP1 expression. The stop cassette is removable by tamoxifen-induced cre-mediated recombination; however, none of the four tested transgenes worked in the mice as hoped[111]. In addition, similar to CLN1, a Dachshund dog model has also been found with CLN2 phenotype and genotype[101].

3.3. CLN3.

Multiple mouse models of CLN3 have been developed, each with large gene deletions ($Cln3^{-/-}$, $Cln3^{\Delta ex1-6}$, $Cln3^{\Delta ex7-8}$) to mimic the human mutation. These mice display similar progression of CLN3 pathology including early glial activation followed by neuronal loss[112]. These mouse models have been used to develop anti-inflammatory and candidate gene therapies[113–118]. Some phenotypes observed in CLN3 patients are not recapitulated in these mouse models[6]. A novel porcine model of CLN3 disease ($CLN3^{\Delta ex7-8/\Delta ex7-8}$) is currently under development by Exemplar Genetics (ExeGen minipig)[6], but no detailed publications are available. These CLN3 minipigs had decline in behavioral, pathological, and visual deficits similar to CLN3 children[6]. In contrast to mice, pigs are good animal models as they share with humans similar brain development and structure, anatomy, and physiology[6]. In addition, these pigs have a macula–like structure, area centralis, that has been shown to be valuable for studying macular-associated retinal diseases, a critical phenotype of the human disease which is missing in CLN3 mice[6].

3.4. CLN4.

There are no animal models created to model CLN4 disease, and no naturally occurring CLN4 animals have been reported[34,39,101].

3.5. CLN5.

In addition to the exon 3 deleted mouse model of CLN5 (*Cln5*$^{\Delta ex3}$), there are bovine, canine, and ovine large animal models with naturally occurring mutations homologous to that of human CLN5[106,119–124].

3.6. CLN6.

Unlike the other CLN mouse models created via homologous recombination, there is a naturally occurring mouse model of CLN6 disease (*Cln6*^{nclf}), with a 1 bp insertion frameshift mutation similar to that detected in CLN6 patients of Pakistani origin[68]. The *Cln6*^{nclf} mice present hallmarks of the CLN6 phenotype, including early loss of vision followed by severe CNS and behavioral deficits[68]. Recent developments for CLN6 gene therapy of the eye using CLN6 mice revealed that the retinal disease in *Cln6*^{nclf} mice is predominantly characterized by photoreceptor degeneration[125]. There are also two breeds of sheep (South Hampshire and Merino) and one dog model of CLN6[126,127].

3.7. CLN7.

A mouse model of CLN7 disease was created by inserting a *lacZ* gene-trap cassette and disrupting the murine *CLN7* gene[128], *MFSD8*. These Cln7-deficient mice (*Mfsd8*$^{tm1a/tm1a}$) resemble the NCL-phenotype of human CLN7, including the accumulation of autofluorescent material in the brain and peripheral tissues, rapid progressive deterioration of photoreceptor cells in the retina, and generalized neuroinflammation[128]. Mutant CLN7 mice lose more than 70% of their rod photoreceptors by 4 months of age, and have accumulation of SCMAS and saposin D in the retinas[129]. The lifespan of these mice is shortened, and lysosomal dysfunction was shown by the storage of autofluorescent lipofuscin-like lipopigments: subunit c of mitochondrial ATP synthase, and saposin D in the CNS and peripheral organs; and increased expression of lysosomal cathepsins B, D, and Z in the brains of Cln7 knockout mice[130]. Neurodegeneration occurs in the olfactory bulb, cerebral cortex, and cerebellum[130]. A family of Chihuahua dogs has also been diagnosed with a naturally-occurring mutation in the *MFSD8* gene, resulting in CLN7 disease[131]. The symptoms also match human cases[131]. There is also a suspected case of the same mutation in a Chinese crested dog, but there were no family ancestries available to confirm the genetic trait[131]. A naturally occurring primate model has been identified in Japanese macaques[132] with a homozygous frame shift mutation in the *MFSD8* gene. The affected monkeys display progressive neurological deficits and visual impairment over a disease course of 5 to 6 years. While the mutation is not homologous to any previously identified *CLN7* mutations in humans, it is believed to result in the formation of a truncated, non-functional lysosomal protein[132]. The disease manifestations closely mirror those of human *CLN7*, as well as those of the *MFSD8* dogs[132].

3.8. CLN8.

In addition to a known English Setter model[133], novel mutations in the *CLN8* gene have been discovered in two other breeds of dogs. One mutation, observed in Alpenländische Dachsbracke dogs, consists of the entire deletion of the *CLN8* gene[134]. Another novel mutation in the *CLN8* gene was observed in the Salukis breed, consisting of a single base pair insertion in exon 2, producing a stop codon[135]. In affected dogs of both breeds, the clinical signs and histological findings mirrored those of human *CLN8* patients.

3.9. CLN9.

No animal models have been reported for CLN9[34,39,101].

3.10. CLN10.

Mouse models are available to study the cathepsin D (CTSD) defect found in CLN10 patients, with knockouts of the gene by neomycin inactivation of exon 4 have been created[136]. Naturally occurring defects have also been found in sheep[137] and in American bulldogs[138].

3.11. CLN11.

For CLN11 mouse models, two strains of progranulin (PGRN)-deficient mice have been created. One strain ($Grn^{-/-}$) consists of 129/SvJ mice that have the *Pgrn* gene knocked out through targeted disruption[139], while the other is a conditional knockout created by crossing *pgrn* floxed mice with CAG-Cre transgenic mice[140]. The first strain was created to investigate male sexual behavior, aggression, and anxiety in mice, while the second strain was created to investigate frontotemporal dementia (FTD). Little is known about the function of progranulin in the CNS, but the available data supports its involvement in embryonic development, cell growth modulation, wound healing, inflammation, and tumorigenesis[140]. The $Grn^{-/-}$ mice were observed to have elevated aggression and anxiety levels compared to wild-type mice, as well as lower levels of mRNA expression of the serotonergic receptor 5-HT1A in the hippocampus[139]. The PGRN-deficient mice were observed to have an exaggerated inflammatory response to bacterial infection, and the brains showed greater activation of microglia and astrocytes[140]. When subjected to behavioral testing, PGRN-deficient mice demonstrated increased depression- and disinhibition-like behavior, as well as social recognition deficits[141]. Progressive development of neuropathology started at 12 months of age, and older mice demonstrated impaired spatial learning and memory in the Morris water maze[141].

3.12. CLN12.

There is an mouse model for CLN12 (Atp13a2-deficient) available which was created by gene disruption, and a CLN12-like phenotype has been found in Tibetan terriers due to a deletion mutation in *ATP13A2* gene[87,101,142].

3.13. CLN13.

No new animal models since our 2013 review[34,39,101].

3.14. CLN14.

No new animal models since our 2013 review[34,39,101].

4. Biomarkers

Although there are many common clinical pathologies among the NCLs, the subset corresponding to any one NCL as well as the age of onset varies significantly between the NCLs and this may or may not correlate with genotype. Therefore, the determination of endpoints for the evaluation of candidate therapies is complex and often relies on complicated clinical scales. The development of quantitative biomarkers for the NCLs is thus an important component in the validation of potential treatments. Biomarkers that are specific biochemical and/or structural changes that represent a unique “fingerprint” of a particular NCL would be ideal as surrogates for assessing disease progression, particularly if the assessed clinical phenotypes, which are often non-quantitative and subjective, are highly variable among the affected population. The use of clinical grading scores of a patient’s performance on a language/motor based rating scale or on quality-of-life questionnaires is subjective by the nature of the observational assessments. Alternatively, the use of clinical imaging by MRI or CT to monitor the progression of the disease may be quantitative, providing a measure of structural changes that correspond to disease progression. Discovery of a validated biomarker in the blood or CSF would enable investigators to track the improvement or decline of their patients with a biochemical assay without subjective appraisals of the subject’s condition.

Recent investigations of NCL subjects and animal models have resulted in several potential clinical biomarkers. In the Hersrud et al[143] study, plasma biomarkers were assessed in subjects exhibiting CLN3 (n=13) and other NCLs, 3 with CLN1, 1 with CLN2 and 2 with Finnish variant, CLN5. These investigations identified 7 potential biomarkers associated with neurodegenerative and inflammatory diseases that were significantly elevated in CLN3 plasma samples compared to normal controls, including: brain-derived neurotrophic factor (BDNF), cell adhesion molecules (NrCAM and VCAM1), clusterin, adiponectin, Apolipoprotein E (ApoE), and myoglobin. A subset of these biomarkers (BDNF, ApoE, and VCAM1) were significantly elevated in all NCL serum samples. These findings suggest that these potential biomarkers denote cellular decay in the CNS during late-stages of NCL, especially the neurotrophin BDNF, which is a compensatory response to brain injury and neuroinflammation[143].

The study by Sleat et al., was the first biomarker study comparing NCL patients (CLN1, CLN2, CLN3) and healthy controls with mass spectrometry and proteomics[144]. Whereas the earlier Hersrud study tested plasma from NCL patients with immunoassays[143], the Sleat study[144] assessed biomarkers from NCL patient brain tissue and CSF derived from autopsy. Unfortunately neither study assessed more than a single time point in the same patient, leaving missing the critical time-dependent change in biomarkers. For example a promising candidate biomarker is myoglobin, where the levels of myoglobin were elevated in the CSF in CLN1, CLN2, and CLN3, and in plasma for CLN3[143]. As might be expected in the brain samples of those affected with an NCL, abnormal storage material components were significantly elevated, such as: (1) ATP5G1 (one of three human paralogs that encode

membrane subunit c of the mitochondrial ATP synthase) in CLN2; and (2) PSAP (prosaposin, precursor of lysosomal saposin proteins, A, B, C and D) in CLN1 (Table I). Glial cell activation of GFAP (glial fibrillary acidic protein) in CLN1/CLN2 and STXBP1 and STX1B (syntaxin-binding proteins, both associated with recurrent seizures (epilepsy), abnormal brain function (encephalopathy), and neurodevelopmental disorders) in CLN1 were all decreased[144,145]. This study identified 18 potential CSF biomarkers in common for 3 NCLs that were significantly altered compared to the normal control. Specifically, proteins elevated in all NCL CSF included: cellular retinoic acid binding protein 1 (CRABP1), aldehyde dehydrogenase 1-A2 (ALDH1A2), and collagen type XIV α1 chain (COL14A1). Proteins consistently down-regulated proteins in all NCLs tested were myelin-associated glycoprotein (MAG) and carnosine dipeptidase 1[144]. Proteins that appear to be NCL-specific included REG3A (regenerating family member 3 alpha; elevated in CLN1 CSF), STXBP1 (reduced in CLN1 CSF and brain), and calbindin1 (elevated in CLN2 CSF)[144].

A study published last year using mass spectrometry for untargeted metabolite profiling focused on identifying potential biomarkers from CSF samples from CLN2 patients (n=11) *vs* healthy controls (n=10)[146]. Among the CSF metabolites evaluated, potential biomarkers for tracking the progression of CLN2 disease included a dozen acetylated amino acids, such as N-acetylaspartylglutamic acid (NAAG), the most abundant excitatory peptide neurotransmitter in the CNS, glycerol-3-phosphoinositol, N-acetylneuraminic acid, N-acetylneuraminic acid dimer, N-acetylalanine, N-acetylserine and N-acetylthreonine, as well as glycero-3-phosphoinositol and sulfoacetic acid. All of the metabolites were significantly reduced in CSF samples from CLN2 affected subjects[146]. It is not known if this panel of metabolites is observed in other NCLs, or may offer a unique biomarker signature for CLN2 disease prognosis and the monitoring of efficacy for treatment modalities[146].

There have been several studies evaluating serum biomarkers for CLN3 disease in affected individuals and mouse models. A clinical study of CLN3 analyzed 25 subjects (11 male and 14 females) by genome-wide expression profiling (GWAS), and found dysregulation of the dual specificity phosphatase 2 (DUSP2) gene in all CLN3 individuals, while 13 other genes including guanine nucleotide exchange factor 1 for small GTPases of the Ras family (RAPGEF1) and transcription factor Spi-B (SPIB) were found to be possible disease-modifier genes[147]. Validity of these potential biomarkers would be likely if these genes were found to play a critical role in CLN3 biosynthesis. There have been two studies in CLN3-deficient mice. An analysis of homozygous CLN3-deficient mice (*Cln3*$^{\Delta ex7/8}$) for hematological biomarkers found changes as early as 15 weeks of age in serum ferritin concentrations, mean corpuscular volume (MCV) of red blood cells, and reticulocyte counts compared to wild-type mice. Also, T-cell deficiencies were found in the male *Cln3*$^{\Delta ex7/8}$ mice[100]. In contrast, another recent hematological biomarker study in CLN3 knockout mice (*Cln3*$^{\Delta ex7/8}$) found no consistent changes[148].

5. Challenges for Development of Therapies for Treatment of NCLs

Since the manifestations of the NCL family of diseases affect the CNS directly, a successful therapy must overcome a host of issues to become an approved therapeutic. The blood-brain barrier (BBB) is a major barrier to the systemic administration of most CNS

therapeutics[39,149]. Only selective compounds like lipids are transported across the tight junctions forming the barrier[149]. Some research has focused on direct administration of therapeutics to the CNS to bypass this anatomical barrier. The challenges for effective CNS therapy include: (1) the short half-life of proteins used in enzyme replacement modalities, necessitating a repeated infusion of the recombinant proteins to be efficacious; (2) the need for widespread distribution of the therapeutic across the CNS; (3) avoiding immune response against the therapeutics; and (4) identifying the disease and treating early due to the rapid decline of NCL patients. In addition to these challenges, delivery of recombinant functional proteins or viral vectors to the CNS also have to overcome the dense cellular environment of specialized cell types in order to target the appropriate cell type. This is important, since different NCL subtypes affect different regions of the brain, ranging from widespread neurons across the cortex regions to focal cerebellar deficits[3,39]. When successful therapy requires the spread of therapeutics to cover the breadth of the CNS, the challenge is to assure that local administration of the therapeutic is sufficient. For example, while a reservoir of constitutive production of secreted proteins may cure CLN1 and CLN2, transmembrane NCL proteins like CLN3 that are not secreted and hence do not undergo receptor-mediated uptake by neighboring cells. For the NCLs with non-secreted gene products, larger numbers of transduced cells will be obligatory for a cure. A significant issue is the immune response against the therapeutic[150]. Antibody response evoked against the therapeutic protein or, in the case of gene therapy, the delivery vehicle, can lead to clearance of infused proteins and/or gene therapy vector. Finally, due to the rapid decline in health of NCL patients from the disease manifestations, it may not be possible to reverse or halt disease progression once the NCL is identified. This is especially critical in early onset NCL for infants. Successful modalities may require a combination of the therapies. Therapies like enzyme replacement therapy may provide coverage in the short term, while long-term therapies like gene therapy take time to develop in multiple regions of the CNS and body.

6. Therapeutic Approaches to the NCLs

There have been major advances in the treatment of NCLs, including identification of the genetic mutations and resulting protein defects, creation of animal models, enzyme replacement therapies, and the initiation of clinical trials for novel treatment modalities. Unlike other lysosomal storage disorders, the proteins involved in some of the NCLs are not secreted, making therapeutic attempts more difficult. Despite numerous challenges ranging from therapeutic strategy, to early identification of afflicted subjects and measurable endpoints, new research has been carried out in 2 categories: (1) Disease-specific therapies that are unique to a given subtype; and (2) therapies that target downstream pathology, which may be applicable to more than a single NCL[2,6,33,37,151,152]. The first category includes: enzyme replacement therapy, stem cell *ex vivo* therapy and gene therapy, and the second category includes pharmaceutical treatments involving small molecule drugs. The following describes each of these treatment options and the associated pros and cons. The current treatment modalities in development for each NCL type are discussed in section 7.

6.1. Enzyme replacement therapy (ERT)

Using ERT as a strategy to augment the decreased levels and/or non-functioning protein with a functional protein, treatment of many lysosomal storage disorders have been evaluated by systemic protein infusion[7,153–155]. While this works for lysosomal storage disorders (LSD) that are non-neuropathic, they have limited success due to the blood-brain barrier (BBB) in disorders like the NCLs that have CNS involvement[156]. To circumvent the BBB, it is necessary to use extremely high doses of systemically-delivered enzyme during the neonatal period in order to get some penetrance into the CNS. An alternative is to use fusion proteins in which enzyme molecules are attached to a peptide moiety that is able to assist in delivery across the BBB by receptor-mediated endocytosis. Finally, another approach could be by direct infusion of the recombinant protein into the CSF via an intrathecal, intracerebroventricular, or intracisternal route[149,154,156]. Studies have shown that ERT products have varying degrees of success in treating lysosomal storage disorders, and are dependent on initiating therapy at an early stage of disease development as well as achieving widespread distribution. Early intervention is key to halting or slowing disease progression prior to irreversible pathology. Since several of the NCL defects arise in proteins that are secreted (CLN1, CLN2, CLN5, CLN10, CLN13), ERT could potentially provide functional versions of the relevant protein to the site of need in the CNS. The advantage of treatment of a disease in which the gene codes for a secreted protein is that the ERT protein uses the natural mechanism by which receptor-mediated uptake provides an efficient pathway for trafficking to the lysosome[157,158]. Importantly, only low amounts of the enzyme (~5–10% of the endogenous levels) are typically needed for therapeutic effects[7,154,155]. However, there are several disadvantages of ERT to treat the NCL[7,154,155]. First, the short half-lives of the NCL enzymes (days to weeks) require repeat administration of the therapeutic protein to the CNS. This requires frequent, specialized treatment. There may be the development of humoral immunity against repeat administered proteins that could limit efficacy, induce inflammatory responses, and reduce cost effectiveness. There are also the potential complications resulting from the use of delivery devices such as catheters or long-term placement of implanted reservoirs[154]. Finally, the manufacturing of the protein product requires extensive methods development and processes that include qualified host cell lines and validated purification schemes. Despite these challenges, one of the first successes in NCL therapeutic development is Brineura®, an FDA-approved intracerebroventricular administration of ERT for CLN2[159].

6.2. Stem Cell Therapy

As an alternative to the requirement for a lifelong repeated dosing for ERT, *ex vivo* cell therapy could provide an *in vivo* source of the therapeutic protein via transplanting heterologous bone marrow or isolated hematopoietic stem cells with the normal gene coding for the functional protein, or alternatively, autologous marrow or stem cells that have been genetically modified with the normal gene.

6.2.1. Bone marrow transplant - unmodified.—One source of a therapeutic stem cell population for NCL therapy is the delivery of hematopoietic marrow cells from a donor to the affected patient. While this has been only modestly effective in clinical studies for several CNS disorders, such as cerebral adrenoleukodystrophy[160], it may work for some of

the NCLs. There are many disadvantages to using marrow transplants including the requirement of an HLA-matched donor to prevent graft rejection and the need for a lifelong immunosuppression regimen[161]. In addition, providing unprocessed marrow cells may fail to provide sufficient amounts of wild-type enzyme to the whole body; and critical for NCLs, the likelihood of impact on the CNS manifestations is low due to the BBB.

6.2.2. Stem cell transplant – local or systemic delivery.—To improve the potency of transplanted cells, most research has targeted the use of a subpopulation of the blood, marrow, or umbilical cord blood – hematopoietic stem cells (HSC)[161]. Isolation of HSC from blood or bone marrow or umbilical cord blood can be easily accomplished with antibody sorting columns or with fluorescent antibody cell sorting (FACS)[162,163]. Isolated processed HSC can be obtained from the donor's blood or marrow following cytokine immobilization to boost the HSC populations. Infusion of the stem cells can be either systemic or localized to the CNS. Use of systemic delivery of cells may correct the disease in peripheral organs, but the BBB presents a challenge to effective CNS therapy[36]. Clinical trials for metachromatic leukodystrophy (MLD), unrelated to the NCLs, have shown that some of the transplanted stem cells do manage to migrate into the CNS, becoming glial cells[164–169]. Other clinical studies have looked at direct localized delivery of cells to CNS to correct neurodegeneration[170,171]. There are several stem cell types (hematopoietic, mesenchymal, neurogenic) available for transplant trials[168,171]. Several clinical trials with HSC have been completed for CNS disorders unrelated to NCLs (globoid cell leukodystrophy, adrenoleukodystrophy, MLD, and Hurler syndrome) and show safety and limited efficacy[165,172], suggesting that this approach could offer a solution. But, there are distinct disadvantages to using HSC for NCL therapy. The requirement of a matched donor to avoid graft rejection, and the continued immunosuppression remain as significant challenges. While systemic cell therapy involves intravenous infusions, direct delivery to the CNS involves an invasive procedure with safety risks. In addition, use of HSC therapy requires log expansion of stem cells in culture prior to stem cell transplant, requiring a wait period before the administration procedure. Based on previous human clinical data, the human stem cell transplant may correct only a small subset of the CNS, and thus fail to provide sufficient amounts of functional enzyme to the target CNS cells[173]. A critical hurdle here is the extent to which transplanted cells can safely and effectively repopulate the CNS.

6.3. Gene Therapy

In contrast to transplanting unmodified cells, gene therapy involves use of viral vectors (e.g., AAV, lentivirus) to deliver genes that encode functional proteins *in vivo*. If safe and efficacious, gene therapy has the potential for lifelong cure[150]. Gene therapy applications have been evaluated by direct administration of the viral vectors to the patient or by augmenting pre-treated isolated cells *ex vivo* for autologous transplant to patients. The HSC isolated from patients can be grown in culture and reinfused back into the patients (*ex vivo*) following viral transduction and sorting for the optimal producing cells. The advantages and disadvantages of these strategies are described below.

The NCL family of diseases have features that facilitate a gene therapy strategy. First, each of the diseases is caused by mutations in a single gene, they are primarily autosomal

recessive disorders, and the missing/deficient protein has been well characterized for most of the 14 NCLs[13,15,16]. For instance, with CLN2, comparisons of genotype and phenotype suggest that only 5 to 10% of normal levels of the functional protein are associated with a less severe form of the disease with delayed age of onset and mortality. Thus, the severe phenotype should be ameliorated if the functional TPP1 protein is at levels that are 5 to 10% that of normal. Second, several of the NCL proteins are secreted and are capable of cross-correcting neighboring cells. This precludes the need to transfer the therapeutic gene to all of the cells in the CNS. Cross-correction occurs by the uptake of the TPP1 protein precursor (the "pro" form secreted by the gene therapy-corrected cells) is mediated by mannose 6-phosphate (M6P) receptors[174–176]. The M6P moiety, added to the TPP1 protein precursor during post-translational processing, binds to cell membrane receptors followed by internalization and sorting of the TPP1 precursor to the lysosomal compartment. The implication of this biology for gene therapy is that the cells transduced by the viral vector become factories for the corrective enzyme, decreasing the challenge of extensive cell transduction and enhancing the potential for successful therapy[177].

6.3.1. *Ex vivo* gene therapy, systemic.—The use of gene therapy vectors to modify stem cells has an extensive history and has been optimized over time to ensure a high rate of recovery of transduced cells[162,178]. Transplanting these modified cells to a patient with NCL has several potential advantages. Systemic delivery via an intravenous infusion catheter would spare the need for invasive surgical administration into the CNS and would simultaneously treat non-CNS disease manifestations[162]. Transduced stem cell progenitors are expected to replicate for the long term, thereby requiring a single dose for life-long therapy. If autologous patient cells are used, then immunosuppression regimens may not be required[179]. The disadvantages of *ex vivo* therapies for NCL include the challenge of assuring the appropriate trafficking of progenitor cells to the brain (if inadequate, direct administration to the CNS may be necessary) and the need to select for efficiently transduced HSC *in vitro* prior to re-administration[162,167].

6.3.2. *Ex vivo* gene therapy, CNS.—As with systemically-delivered genetically-modified cells, local delivery to the CNS of an NCL patient would have several advantages: (1) a single dose of treated cells may be sufficient to stem or ablate the disease progression and no immunosuppression may be required if autologous cells are used; (2) there are neurogenic stem cells which have been approved for clinical transplant trials[171]; and (3) the expressed therapeutic protein would likely be translationally modified in an identical fashion to the normal protein. The disadvantages are similar to the systemic infusion route: manipulations of the HSC requiring complex *ex vivo* culture processing, and a potential lack of a selective advantage mechanism for efficiently transduced stem cells. The likely requirement for intraparenchymal or intrathecal administration of the genetically-modified stem cells is potentially risky with a need to carefully monitor safety for possible rogue differentiation or tumor formation. Further, an inflammatory response and/or cell-mediated immunity directed toward the administered cells may result in loss of therapy.

6.3.3. *In vivo* gene therapy, AAV vectors.—The most commonly used gene therapy transfer vector for therapeutic development for NCLs is the adeno-associated virus

(AAV)[152,180]. It has the advantage of high efficiency *in vivo* cell transduction and persistent transgene expression. There are many AAV serotypes with tropism for cells in the CNS and the retina, thus providing numerous options with some selectivity for specific cell type[180–183]. There is extensive safety data for the use of AAV for CNS gene transfer as a therapeutic modality to address Parkinson's disease, Alzheimer's disease, Canavan's disease, Pompe, MPS IIIA, MLD, and LINCL (CLN2) in human clinical trials[89,184–196]. There remain several challenges for AAV gene therapy to the CNS. Although systemic AAV therapy has been shown to be efficacious in mouse models of NCL, the blood-brain barrier appears to be a greater hurdle in humans and therefore direct CNS administration may be required[180]. Pre-existing anti-AAV seropositivity in humans may lead to complications of inflammatory response, and/or cellular immunity-mediated loss of transgene-expressing cells[197,198]. Careful choice of AAV serotype can reduce this concern, but it is not practical for selecting specific serotypes to address the needs of individual subjects[197,199].

6.3.4. *In vivo* gene therapy, lentivirus vectors.—While the majority of the gene therapy investigations have tested AAV vectors, one group has been testing lentiviruses to deliver the genes for CLN5 and CLN6 to cell cultures and large animal models (NCL-afflicted sheep)[200,201]. While lentivirus vectors can support larger transgenes and can insert the payload into the host cell genome to ensure passage of the therapeutic genes to daughter cells, neither of these advantages are particularly relevant to NCLs, where genes are not large and cells are mostly non-(or slowly-) dividing cells. However, most of the lentiviral vectors have been used with *ex vivo* stem cells and there is limited safety and clinical data on the use of lentiviruses for direct CNS gene therapy.

6.4. Pharmacological Treatments

Various small molecule treatments have been evaluated for treating neurological disorders such as the NCLs. These small molecules include lysosomotropic agents, glutamate receptor antagonists, anti-apoptotic drugs, and immunosuppressants[21,202]. A number of these agents have been evaluated in clinical trials for NCLs, as described below and separately for each NCL in section 7. The advantages of small molecule therapies include the ability to manufacture large and easy-to-characterize batches of the drugs for clinical testing of safety and efficacy. Disadvantages include the potential of the drugs to have numerous off-target effects, toxicology related to unanticipated reactions, and unpredictable outcomes of metabolites. Importantly, these drugs represent an orthogonal approach and can be used either with existing therapies or may be combined with other genetic-based therapies. It is important to note though, that the disadvantages of combining treatments would be that it makes it difficult to discern individual degrees of efficacy. The small populations of those afflicted with an NCL would preclude carefully controlled comparative studies with individual and combined drugs. Finally, animal studies for other diseases have shown that doses in small animal models may not be scalable for human usage.

6.4.1. Lysosomotropic agents.—The first class of drugs being tested as NCL therapeutics are termed lysosomotropic drugs (includes cysteamine, phosphocysteamine, cysteamine bitartrate (Cystagon) and N-acetylcysteine). These compounds are transported to lysosomes where they function by inhibiting formation of cysteine thioesters and blocking

ceroid accumulation, thereby reducing storage material and improving lifespan of treated animals[203]. Investigational drugs that mimic the thioesterase activity of PPT1 may have therapeutic potential for CLN1 by providing an alternative enzymatic means to hydrolyze the thioester bonds in the lysosomal ceroids[203,204].

6.4.2. AMPA receptor antagonists.—These novel candidate therapeutics are antagonists designed to bind the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor; AMPAR), a CNS transmembrane receptor for glutamate and the glutamate analog, AMPA[36]. AMPA receptors are continuously being trafficked into and out of the neuronal plasma membranes[205]. The noncompetitive AMPA receptor antagonists (talampanel and perampanel) have been demonstrated to have activity in the treatment of adults with partial seizures, suggesting a potential target for the treatment of NCLs with epilepsy[205,206]. These drugs treat the symptoms rather than the underlying disease. Several mouse studies have indicated potential usage for AMPA receptor attenuator in NCLs[36,207–209].

6.4.3. Anti-apoptotic drugs.—Anti-apoptotic drugs, such as flupirtine (ethyl-2 amino-6 (fluorobenzyl)-amino-3-pyridine carbate), which is a non-steroidal analgesic, are being tested to arrest neurodegenerative progression in CNS neurons prominent in some NCLs[210,211]. Another example is anti-caspase-4 inhibitor (such as Z-LEVD-FMK), which has also been shown to inhibit the apoptotic effects[212].

6.4.4. Other interventions.—There are multiple small molecule drugs being tested for NCLs that have shown promising results in other neurologic disorders. Immunosuppressive drugs such as CellCept® (mycophenolic mofetil) and lipid regulating agents such as LOPID® (gemfibrozil) are currently being tested in clinical trials. Gemfibrozil, which has been shown to reduce inflammation, glial activation, lipofuscin in the brain, and apoptosis, is being studied for delay of motor deficits in mouse models[116,213]. Finally, immunomodulatory drugs (such as fingolimod and teriflunomide) have been shown to reverse neurodegeneration in a mouse model[116]. Some of these drugs have been combined with diet modifications to improve the current therapies, which will be discussed in the individual subtype sections.

7. Pre-clinical and Clinical Trials for the NCLs

Even though the most prevalent and most studied NCLs are CLN1, CLN2, and CLN3, many of the other NCL subtypes have also been the target of development of novel therapeutics in the last few years. The most promising and latest efforts are discussed below. We have separate sections for natural history studies (Table II) and interventional NCL clinical trials (Table IV). Treatment of NCL subtypes that are affected via soluble secreted lysosomal proteins (such as CLN1, CLN2, and CLN10) have had the most success with ERT and gene therapy either in animal models or human clinical trials. Receptor and membrane-bound CLNs (CLN3 and CLN6) have also had some success in treating the disease phnotypes in mice and large animals. As a general principal, candidate therapies require proof-of-concept animal studies with some measure of efficacy typically in one or more of the following parameters: CNS pathology, behavior, survival, and distribution of morphological or

histological measures as a function of time. The candidate therapy also requires demonstration of general safety prior to commencing with a human study. The following sub-sections detail the progress made for the various therapeutic modalities for each NCL subtype since our last review on this topic[33]. There have been no publications for therapeutics that address CLN4, CLN9, CLN12, CLN13, and CLN14 and thus these are not included in the subheading reviews below.

7.1. Therapies for CLN1

7.1.1. ERT.—Pre-clinical studies have demonstrated recombinant PPT1 to be efficacious and safe[214,215]. Human PPT1 enzyme administered intrathecally on 3 consecutive days significantly extended the lifespan of the *Ppt1* knockout mouse model when treated at 6 wk age[215]. Motor deterioration was delayed, and neuropathology was improved based on autofluorescence (associated with lysosomal storage), CD68, and GFAP immunostaining[215].

7.1.2. Stem cell therapy.—Ppt1$^{-/-}$ mice implanted with human CNS stem cell neurospheres (hCNS-SCns) resulted in increased PPT1 production in the CNS and reduced lipofuscin storage[216]. Two Phase I clinical trials in CLN1 and CLN2 subjects, sponsored by StemCells, Inc (NCT00337636, NCT01238315, Table IV) have investigated the use of cultured human CNS stem cells implanted into the CNS for safety assessment[217]. The feasibility of neurosphere implantation and absence of transplantation-related serious adverse events warrants further study of HuCNS-SC transplantation as a potential treatment for CLN1. However, a second trial (NCT01238315) was withdrawn due to lack of patient accrual (clinicaltrial.gov).

7.1.3. Gene therapy.—Gene therapy studies in the CLN1 mouse model have demonstrated that a treatment with dual routes of administration appears to delay disease progression[218,219]. Dual intraparenchymal and intrathecal administration of an AAV9-hPPT1 vector into the CNS showed synergistic improvements in median lifespan and motor function, compared to treatment groups receiving only one route of administration[220]. The conclusion of these studies was that targeting the brain may not be sufficient and that targeting the spinal cord in addition leads to an improved outcome. A study (ABO-202), with orphan drug designation from the FDA and the European Medicines Agency (EMA), is evaluating self-complementary adeno-associated virus 9 (scAAV9) expressing the human CLN1 gene both systemically (intravenous) and to the CNS (intrathecal) in human clinical trial[221]. A third approach tested the AAV2 gene transfer vector to deliver the human PPT1 gene to the eye of *Ppt1*-deficient mice to correct CLN1-mediated vision degeneration and demonstrated a significant increase in retinal function and reduced loss of photoreceptors[218,222]. To treat both the CNS and systemic effects of CLN1 disease in the CLN1$^{-/-}$ mouse, CNS-directed AAV5-mediated gene therapy was combined with either bone marrow transplantation or systemic delivery of phosphocysteamine. Both were equally efficacious[223,224].

7.1.4. Pharmacological treatments.—Numerous investigations have been evaluated for the capacity to reduce or ablate the storage defects of CLN1[203,224–226]. Lysosomotropic drugs (such as phosphocysteamine) showed promise in blocking ceroid accumulation,

reducing storage material, and improving lifespan of treated CLN1 model mice, cultured CLN1 cells, and human CLN1 patients[203,224,226]. A pilot clinical trial in CLN1 patients using a combination of cysteamine bitartrate (Cystagon®) and N-acetylcysteine (NCT00028262) resulted in modest improvement in patients carrying severe CLN1 mutations[227]. Anti-apoptotic drugs like flupirtine, retigabine, and anti-caspase-4 inhibitor (Z-LEVD-FMK) have been tested to inhibit the apoptotic effects and arrest neurodegenerative progression in CLN1 cultured patient lymphoblasts[202,210,211].

Immunomodulatory compounds with acceptable tolerability profiles are being designed to modify the immune response of NCLs[116]. For example, Fingolimod works by sequestering lymphocytes in the lymph nodes and prevents them from being transported to the CNS, while teriflunomide works by inhibiting the production and function of activated T cells[116]. Pre-symptomatic mouse models of CLN1 disease were treated over a period of 5 months with the oral administration of one of two immunomodulatory compounds, fingolimod or teriflunomide[116]. At the end of the treatment period, both forms of immunomodulation reduced secondary neuroinflammation, the T cell count (in optic nerve and CNS), and microgliosis in the CNS. The treatments also reduced axonal damage, neuronal loss, retinal thinning, frequency of myoclonic jerks, and total brain atrophy[116]. These treatments are non-invasive, and might work in conjunction with gene therapy or ERT.

7.2. Therapies for CLN2

7.2.1. ERT.—ERT has been shown to have therapeutic effects in murine and canine CLN2 models. Weekly intrathecal injections of TPP1 recombinant protein in a TPP1-deficient mouse model resulted in a significantly improved median lifespan[228]. Even when mice were treated after the onset of disease symptoms (late-stage), ERT reversed the decline in motor function. In mice, the intrathecal route of administration resulted in an uneven distribution of TPP1 within the brains of treated animals, and repeated intrathecal administrations also became more difficult as the study progressed, due to scarring[228]. In contrast, in a canine model, direct administration of TPP1 via infusion into the CSF, repeated every other week, delayed the onset and progression of the disease without significant adverse effects[229]. Survival was prolonged, and cognitive function was preserved. The ERT approach requires a lifelong commitment of regular infusions. One issue with ERT therapy directly to the CNS is the general concern that once the CNS pathology is cured, other effects of the disease will become apparent. For instance, Katz et. al., observed elevated serum troponin levels in all ERT-treated CLN2 dogs, suggesting that the TPP1 deficiency in the heart was not corrected by the ERT administered to the CNS[229]. A related study looked at intravitreal (IVT) administration in the canine CLN2 model, with biweekly hTPP1 treatments starting at 3 months of age[230]. The treatment was well tolerated and was found to slow or prevent disease progression based on electroretinography (ERG) and post-mortem histopathology of the retinas[230].

In a recently concluded clinical trial (NCT01907087) based on canine preclinical proof of concept data, repeat intraventricular administration of Cerliponase alfa (a recombinant proenzyme form of TPP1) slowed disease progression in treated CLN2 patients compared to untreated historical controls[231]. One challenge of this therapy is that 50% of the study

participants experienced some adverse events relating to the delivery devices including device-related infections, device leakage, and needle displacement[231]. None of these adverse events were severe enough to warrant withdrawal from the trial. There was no evidence that cerliponase alfa evoked an immune response that impacted safety or efficacy[232]. Importantly, significant slowing of disease-related clinical decline was observed. Based on this study the FDA approved Brineura® (cerliponase alfa) in 2017[231]. Patients are given a 300 mg dose every other week, with drug delivery accomplished using a surgically-implanted ventricular reservoir and catheter[231].

7.2.2. Stem cell therapy.—Preclinical studies have been undertaken to examine the effects of stem cell therapy of the retina pathology in a canine model of CLN2[233]. A single dose of autologous bone marrow-derived stem cells were transduced with an AAV2 expressing TPP1 construct, and implanted intravitreally into one eye of a group of miniature long-haired Dachshunds with a frame shift mutation causing a complete absence of TPP1 enzymatic activity. The treated eyes had a significant reduction in both the prevalence of retinal detachments and rate of progression of retinal degeneration when compared to control eyes of the same dogs implanted with control GFP-expressing stem cells[233]. As mentioned for CLN1, there have been 2 clinical trials studying the use of human CNS stem cells involving CLN1 and CLN2 patients (NCT00337636, NCT01238315). However, although a safe and tolerable outcome was reported, there were no clinical improvements[217]. See 7.1.2. for details of the trials.

7.2.3. Gene therapy.—Gene therapy is less invasive than ERT as it is a one-time administration in contrast to the lifelong repeated treatments. Numerous murine pre-clinical studies addressing CLN2 deficiency by treatment with various AAV serotypes have demonstrated high levels of TPP1 enzyme and reduction of storage material[107,234–237]. Direct intraparenchymal administration of several AAV serotypes expressing CLN2 demonstrated that AAVrh.10hCLN2 gene therapy provided the best distribution in the CNS and reduction of disease phenotype in mice and widespread TPP1 distribution in nonhuman primates[236]. In a canine model of CLN2 disease, a single intracerebroventricular injection of rAAV2caTPP1 (AAV2 expressing the canine form of TPP1) was found to delay disease onset and progression, protect from cognitive decline, and extend the lifespan[238]. AAV-derived TPP1 expression in ependymal cells, which line the CSF-filled brain ventricles and the central canal of the spinal cord, was robust and widely distributed in brain parenchyma. Significantly, elevated AAV-derived TPP1 levels were also detected in peripheral organs, including the spleen and heart[238]. However, these levels of TPP1 expression were not enough to ameliorate non-neuronal pathology and the dogs still exhibited progressive cardiac, liver, and muscle pathology and impaired cardiac function, suggesting that the optimal treatment regimen may require systemic and CNS delivery of TPP1 genes[238]. Three clinical studies have assessed the potential for gene therapy for CLN2 using AAV2 (NCT00151216) and AAVrh.10 (NCT01161576, NCT01414985; Table IV). All of these studies used direct intraparenchymal delivery to the CNS[2,190,239]. Results for the AAV2 study demonstrated a statistically significant slowing of the neurologic decline in treated subjects *vs* published natural history controls[190]. The results for the AAVrh.10 study have not yet been published.

7.2.4. Pharmacological treatments.—Anti-apoptotic drugs like flupirtine have been tested to arrest neurodegenerative progression in CLN2-cultured lymphoblasts and neurons[210]. Retigabine, analogous to flupirtine, was shown to rescue CLN2 patient-derived lymphoblasts from accelerated apoptosis, and decreased ceramide accumulation[211]. Gemfibrozil has been shown to reduce inflammation and increase survival in treated Cln2 knockout mouse models[213], and has been shown to be safe in children[240].

7.3. Therapies for CLN3

7.3.1. ERT.—No published studies to date.

7.3.2. Stem cell therapy.—No published studies to date.

7.3.3. Gene therapy.—Preclinical testing of gene therapy using AAV vectors to treat CLN3 disease have shown efficacy in both cell culture and mouse models. AAV2-CLN3 was successful in restoring full-length CLN3 transcript and protein in iPSC-derived retinal neurons[115], and CRISPR-Cas9 plasmids have been used to correct CLN3 patient-derived iPSCs[241]. Preclinical studies with intraparenchymally-administered AAVrh.10 or intravenously-administered scAAV9 vectors expressing the CLN3 gene partially correct mouse models of the disease[113,114]. These results have prompted a clinical trial with AAV9 for CLN3 patients (Amicus Therapeutics, NCT03770572), which is recruiting at Nationwide Children's Hospital (Columbus, OH, USA) (Table IV). This non-randomized, open-label, dose-escalation clinical trial for efficacy and safety of a single administration of AAV9-CLN3 via the intrathecal route in CLN3 subjects (3 to 10 yr old children), will begin with a low-dose derived from the minimum effective dose (MED) as determined in non-clinical studies (NCT03770572). Upon demonstration of safety in this first cohort, dose escalation to a high-dose (2x MED) will proceed. Publications do not provide the starting dose.

7.3.4. Pharmacological treatments.—Three phosphodiesterase-4 (PDE4) inhibitors (rolipram, roflumilast, and PF-06266047) have been tested in *Cln3*$^{\Delta ex7/8}$ knockout mice to determine whether the resulting increase in cyclic adenosine monophosphate (cAMP) levels would have a beneficial neurological effect[242]. *Cln3*$^{\Delta ex7/8}$ mice have reduced brain cAMP levels, which could be corrected by inhibiting phosphodiesterases, which mediate cAMP degradation, and PDE4 is most prominently expressed in the CNS[242]. The use of PDE inhibitors limits neuronal apoptosis and neuroinflammation, as well as augment glutamate transporter expression[242]. Treatment with PDE4 inhibitors resulted in significant improvements in motor function; decreased neuroinflammation, glial activation, and lysosomal pathology; and restored glutamate transporter expression to levels comparable to wild-type animals[242]. These results support their potential use in treating CLN3. In another study, AMPA receptor antagonists/attenuators (EGIS-8332) delivered in low doses significantly improved motor skills of CLN3 mice[207]. Retigabine, was observed to be neuroprotective in CLN3-defective cultured cells[225] and rescued CLN3 patient-derived lymphoblasts from accelerated apoptosis as well as decreasing ceramide accumulation, demonstrating potential for anti-apoptotic drugs as treatment of NCL disease[211]. A survey was conducted among parents of CLN3 patients undergoing treatment with the anti-apoptotic drug flupirtine. However, the statistical analysis of the reported beneficial effect

from the treatment, based on the Unified Batten disease rating scale, showed no difference between treatment and control groups[243].

Another suitable target for pharmaceutical treatment is the transcription factor EB (TFEB) which serves to regulate cellular clearance by enhancing processes such as lysosomal proliferation, expression of degradative enzymes, autophagy, lysosomal exocytosis and lysosomal proteostasis[21,244]. Both trehalose, the non-reducing disaccharide of glucose, and the drug MK2206 have been shown to inhibit the serine/threonine kinase Akt (protein kinase B), which has in turn been shown to control TFEB activity through phosphorylation[21,244]. *Cln3*$^{\Delta ex7/8}$ mice that were given oral trehalose treatments had extended lifespans, clearance of lysosomal storage, and reduced neuroinflammation and neurodegeneration[244]. Intraperitoneal administration of MK2206 resulted in nuclear translocation of TFEB and upregulation of lysosomal and autophagy genes in the brains of *Cln3*$^{\Delta ex7/8}$ mice[244]. When tested on fibroblasts derived from patients with CLN1, CLN2, CLN3, and CLN7 disease, MK2206 enhanced cellular clearance of ceroid lipopigment deposits[244].

CLN3-affected individuals have increased autoantibody formation against CNS antigens[245]. Preclinical studies in the CLN3-deficient mice have found elevated autoantibody titers[246,247], leading to studies to test immunosuppressive agents in these mice[248]. Immunosuppression with mycophenolate mofetil administered by gavage for 30, 70, or 150 consecutive days was found to alter the disease severity in CLN3 mice with a significant improvement in motor skills[248]. Further treatment with the immunomodulators (section 7.1.4) fingolimod and teriflunomide on a CLN3 mouse model were found to have similar outcomes in pre-symptomatic mice[116]. The results suggest that secondary neuroinflammation is a relevant mechanism for CLN3 disease progression. Additional pharmacological experiments with an *in vitro* cell culture model of CLN3 disease found that treatment with lithium improved defective autophagy[249]. Autofluorescence and accumulation of mitochondrial ATP synthase subunit c were both reduced, and the lithium-treated cells were more resistant to autophagic stress-triggered cell death[250]. The mechanism of action of the neuroprotective effect of lithium was proposed to be through inhibition of inositol monophosphatase, which improves the defective autophagy[250].

The immunosuppressant mycophenolate mofetil (CellCept®), approved by the FDA as an anti-rejection medication following organ transplantation, was tested in CLN3 patients for controlling secondary autoimmunity and neuroinflammation (NCT01399047)[251]. The trial (double-blind, placebo-controlled), though limited to the short-term (8 wk), found that mycophenolate was well-tolerated. The next step is to examine clinical impact with a longer-term treatment regimen. A similar therapeutic strategy tested a regimen of prednisolone eye drops, triamcinolone (intravitreal), mycophenolate mofetil (oral), along with brinzolamide and nepafenac anti-inflammatory medications over a 2 yr period to a CLN3 patient (7.5 yo) with decreased visual acuity[252]. The patient retained ambulatory vision after 2 yr, which is normally absent in CLN3 subjects of comparable age, suggesting that inflammation of the retina plays a role in vision loss in CLN3 subjects[252].

7.4. Therapies for CLN5

7.4.1. ERT.—

No published studies to date.

7.4.2. Stem cell therapy.—No published studies to date.

7.4.3. Gene therapy.—Neural cells cultured from prenatal CLN5-deficient sheep brains rapidly accumulate storage bodies in culture, mainly in microglial cells and also in neurons and astrocytes[200]. Transduction of these cells with a recombinant lentiviral vector expressing ovine CLN5 rapidly reversed accumulation of storage material with a 50% reduction of cell-contained storage bodies 6 days after treatment[200]. Direct intraparenchymal and intracerebroventricular injections of lentiviral vectors in juvenile CLN5 sheep successfully delivered the transgene, but the doses appeared to be too low for therapeutic effect as there was no improvement in disease progression[201]. Juvenile CLN5 sheep (2–3 months of age before the onset of clinical symptoms) receiving higher doses of lentiviral vectors as well as AAV9 vectors have remained disease-free 4 to 5 months beyond the typical age of end-stage clinical disease[122]. All AAV9-CLN5 or lentivirus-CLN5 treated animals appeared phenotypically normal, with delayed-onset visual loss being the only clinical symptom[122]. In a cohort of the same study in which a self-complementary AAV9 vector was administered to older CLN5 sheep (at 7 months, the early stage of clinical disease), there was attenuation of disease progression and extension of lifespan but visual loss remained[122].

7.4.4. Pharmacological treatments.—No published studies to date.

7.5. Therapies for CLN6

7.5.1. ERT.—No published studies to date.

7.5.2. Stem cell therapy.—No published studies to date.

7.5.3. Gene therapy.—One of the hallmarks of CLN6 disease is the rapid loss of vision which provides a relatively good phenotype for evaluating efficacy[253]. Early studies with AAV8-CLN6 failed to modulate vision loss[40], but a current study of AAV2–7m8 to target the inner retina bipolar cells significantly slowed loss of photoreceptor cells and function in *Cln6*^{nclf} mice[125]. Combination gene therapy targeting the CNS and the eye may be necessary to treat all aspects of the CLN6 disease.

Using the self-complementary AAV9 (scAAV9), significant reversal of phenotypic defect in *Cln6*^{nclf} mice has been achieved[40]. Cain et al[254] delivered scAAV9-hCLN6 to the cerebral ventricles of *Cln6*^{nclf} mice resulting in improved behavioral motor skills and decreased autofluorescent lysosomal storage material at up to 3 months of age[254]. Longer-term studies with the same vector and route resulted in reduction of autofluorescent substrate material throughout the brain and spinal cord, and improved motor performance and cognitive behavior out to 22 months with median survival extended to 22 months, significantly greater than the 12 to 14 months for untreated mice[255]. There were significant reductions in astrocyte and microglial activation in the same model at 18 months[256]. A follow-up safety study looked at 3 Cynomolgus macaques treated with scAAV9-hCLN6 by intrathecal lumbar injection. Over the 6 month course of the study, there were no adverse events or apparent pathology observed. High levels of transgene expression were observed in both the brain and the spinal cord[255]. The successful proof of concept in the mouse and the distribution and safety data from the non-human primate has been used to support a clinical phase I/II trial

for CLN6 patients[21,40]. Using 1.5×10^{13} vector genomes (vg) of a self-complementary AAV serotype 9 vector to deliver CLN6 cDNA (scAAV9.CB.CLN6) intrathecally (lumbar puncture) to patients (n=12 proposed, 10 treated currently), an open-label, single-dose clinical trial is in progress at Nationwide Children's Hospital (NCT02725580, Table IV)[257,258]. No results have been published for this trial, but Amicus Therapeutics, who has licensed this product, has shown encouraging interim data on 2 treated subjects at NCL meetings[259,260]. Two siblings with the same genotype were treated with a single intrathecal administration of AAV9-CLN6, at ages 2.8 and 5.3 years of age. Two years post-treatment, the younger sibling's motor and language scores showed no evidence of disease progression, while the older sibling's scores indicated stabilization of disease progression[259].

In studies in a large animal model, CLN6$^{-/-}$ South Hampshire sheep were treated with either lentiviral or AAV9 viral vectors expressing CLN6. The ongoing trial seeks to assess improvements via CT scans and behavioral analyses (including vision, cognitive score, and maze navigation) to determine if the expression is sufficient to delay or halt disease progression[261]. Direct intraparenchymal and intracerebroventricular injections of lentiviral vectors in juvenile CLN6 sheep successfully delivered the transgene, but the doses appeared to be too low and there was no improvement in disease progression[201]. Higher doses of lentiviral vectors as well as AAV9 vectors in juvenile CLN6 sheep demonstrated only one of six treated animals with clinical benefit. This is in contrast to the CLN5 study in sheep in which all treated animals showed great improvement comparable to normal controls[201]. An *in vitro* study with mixed neural cultures isolated from the CLN6 sheep, found treatment with a lentiviral vector delivering the wild-type CLN6 gene was able to repair disease-related changes in lysosomal acidity, autophagic flux, and synaptic endocytosis[121].

7.5.4. Pharmacological treatments.—Anti-apoptotic drugs like flupirtine have been tested to prevent apoptosis in CLN6-deficient lymphoblast cultured cells[210,225]. Retigabine, was observed to be neuroprotective and rescued CLN6 patient-derived lymphoblasts from accelerated apoptosis, and decreased ceramide accumulation[211]. Dietary supplementation of CLN6^{nclf} mice with naturally-occurring immunomodulators curcumin and docosahexaenoic acid (DHA) was found to result in significantly higher visual acuity and higher ERG amplitudes compared to untreated control CLN6^{nclf} mice. Retinal morphology in DHA-supplemented mice was significantly preserved compared to wild-type mice, curcumin-treated CLN6^{nclf} mice, and untreated CLN6^{nclf253}. Oral administration of the anti-inflammatory drug minocycline was evaluated in CLN6 NCL South Hampshire lambs, but chronic drug administration over the course of 3 to 14 months did not change disease progression[201,262]

7.6. Therapies for CLN7

7.6.1. ERT.—No published studies to date.

7.6.2. Stem cell therapy.—No published studies to date.

7.6.3. Gene therapy.—While no traditional gene therapy studies have been published for CLN7, a study with an antisense oligonucleotide therapy was used to treat one individual

with CLN7 disease. The antisense oligonucleotide drug was specially tailored for this individual's mutation, and preliminary results suggest that the treatment has appeared to halt further deterioration, with reduced seizure intensity and frequency[263].

7.6.4. Pharmacological treatments.—No published studies to date.

7.7. Therapies for CLN8

7.7.1. ERT.—No published studies to date.

7.7.2. Stem cell therapy.—Bone marrow transplants in CLN8 mouse and dog models led to CLN8 expression in marrow but not in CNS[264].

7.7.3. Gene therapy.—No published studies to date.

7.7.4. Pharmacological treatments.—Several early studies in CLN8-deficient mice showed improvements with AMPA receptor attenuator (ZK-187638) therapy, including improvements in motor coordination; however, nothing new has been published since the 2006 study[265]. Retigabine, was observed to be neuroprotective and rescued CLN8 patient-derived lymphoblasts from accelerated apoptosis, and decreased ceramide accumulation[211]. Other interventions tested for CLN8 include mice administered IGF-1 (insulin-like growth factor 1) by infusion into brain ventricles, resulting in neuroprotection[266]. β2-adrenergic agonists have mediated motor neuron improvements in CLN8 mice[267].

7.8. Therapies for CLN10

7.8.1. ERT.—No published studies to date.

7.8.2. Stem cell therapy.—No published studies to date.

7.8.3. Gene therapy.—In a studies published in 2010 and 2011, AAV therapy with mCathD transgene administered intraparenchymally or intraventricularly in CLN10 mice demonstrated cathepsin D expression and enhanced lifespan[268,269]. No further studies have been reported.

7.8.4. Pharmacological treatments.—No published studies to date.

7.9 Therapies for CLN11

7.9.1. ERT.—No published studies to date.

7.9.2. Stem cell therapy.—No published studies to date.

7.9.3. Gene therapy.—AAV1 vectors that mediate progranulin were administered to the medial prefrontal cortex (mPFC) in *Grn*$^{-/-}$ mice with a resulting reduction in lipofuscinosis and microgliosis, even in regions where progranulin expression was low, suggesting that only a small number of cells needs to be transduced for efficacy. Progranulin expression was detectable in neurons but not in microglia, suggesting that microgliosis is partly due to neuronal dysfunction and this can be at least partially repaired[270]. Intracerebroventricular

delivery of AAV9-GRN mediated high levels of broad and sustained GRN expression, but GRN overexpression led to cell toxicity and hippocampal neurodegeneration preceded by T cell infiltration[271]. When repeated with an AAV4 vector, severe ependymal and choroidal hypertrophy was observed with corresponding T cell infiltration[271]. Control mice injected with EGFP-expressing vectors did not experience the same issues, suggesting that the overexpression of GRN, not the AAV vector, may be harmful. While a localized immune response was seen in the AAV1 study, the AAV9 and AAV4 study used higher doses and followed the treatment for a longer study period. The higher expression levels may have caused toxicity or the earlier study was not long enough to observe toxicity[271]. Before clinical translation of the therapy can occur, a safe level of expression has to be determined which maintains efficacy.

7.9.4. Pharmacological treatments.—

No published studies to date.

8. Academic and Industry Partnerships

The most promising treatment modalities have been successfully translated from animal work into clinical trials for CLNs 1, 2, 3, and 6 [such as NCT00028262 (ERT, CLN1), NCT00151216 (AAV2, CLN2), NCT00337636 (stem cells, CLN1), NCT01161576 (AAVrh.10, CLN2), NCT01238315 (stem cells, CLN1), NCT01399047 (Cellcept®, CLN3), NCT01414985 (AAVrh.10, CLN2), NCT01907087 (ERT, CLN2), and NCT02725580 (AAV9, CLN6); ClinicalTrials.gov][37]. More recently, the FDA approved the first ever treatment for CLN2 disease, an enzyme replacement therapy called Brineura®[231]. The partnership between investigators and Biotech startups have resulted in numerous companies involved in NCL research and clinical trials. Based on a survey of the field, we have summarized the companies (listed alphabetically) that show an NCL disease as part of their product pipeline. This is not an exhaustive list, but provides insight to the progress that has been made in the development of therapeutics for these rare and devastating diseases.

Abeona Therapeutics (Dallas, TX, USA) – CLN1 and CLN3 gene therapy clinical trials with AAV9 (Phase 1/2) in 2019[272].

Amicus Therapeutics (Cranbury, NJ, USA) – CLN3, CLN6, and CLN8 – gene therapy applications with clinical trials (Phase 1/2) in 2019[273].

BioMarin (Novato, CA, USA) – ERT for CLN2 disease (with clinical trials NCT02485899, NCT02678689)[274].

Circumvent Pharmaceuticals (Portland, OR, USA) – CLN1, CLN3, CLN4, CLN10 – developing small molecule thioesterase mimetics[275].

Genentech (South San Francisco, CA, USA) – CLN3 with CellCept® (mycophenolic mofetil) immunosuppressive drug (with clinical trial NCT01399047).

Polaryx Therapeutics (Paramus, NJ, USA) – CLN2 and CLN3 – developing small molecule therapy (PLX-200, Gemfibrozil), an FDA-approved lipid lowering agent that

increases lysosome biogenesis, anti-inflammatory mediators, remyelination, and neurotrophins, with clinical trials expected in 3Q 2019 in the US[276].

REGENXBIO (Rockville, MD, USA) – CLN2 – developing gene therapy for the treatment of CLN2 using RGX-181 (AAV9-hTPP1) by direct CNS injections to augment TPP1 in children with CLN2[277].

Spark Therapeutics (Philadelphia, PA, USA) – developing gene therapy for CLN2 using SPK-TPP1 vector[278].

9. Conclusions

These are exciting times for treatment of NCLs, with multiple therapeutics reaching the clinical trial stage for several CLN subtypes. The potential for cures could be at hand after many years of trial and error in the preclinical studies. The clinical development of ERT for CLN2 (Brineura® by BioMarin); immunosuppression for CLN3 (CellCept® by Genentech); and gene therapy vectors for CLN1 (ABO-202 by Abeona), CLN2 (RGX-181 by REGENXBIO, SPK-1001 by Spark Therapeutics), CLN3 (ABO-201 by Abeona, AAV9-CLN3 by Amicus), CLN6 (AAV9-CLN6 by Amicus), and CLN8 (AAV9-CLN8 by Amicus) have given NCL patients and families hope that the neurodgerenative pathology can be abated or reversed and clinical outcomes can yield improved quality of life[152,279]. With the milestone approval of the two gene therapy drugs, Luxturna™ (AAV2-RPE65) by both the FDA and European Commission and Zolgensma™ (AAV9-SMN) by the FDA[280,281], gene therapy is finally becoming a reality for other orphan diseases such as the NCLs. However, much work remains to be done before a cure for any of the NCLs is widely available. As seen with the Luxturna™ and Zolgensma™ trials, the cost of the drug and benefits for all patients must be weighed for each treatment modality[282].

10. Expert Opinion

The NCL family of diseases, like many other lysosomal storage disorders, have neurological involvement, making them a challenging target for treatment. However, emerging therapies, especially the progress made in the last decade, are overcoming these barriers and providing hope for patients and their families. With increased interest by both academic scientists and biotechnology companies, and with support from patient advocacy groups and disease-specific foundations, progress has been made in defining the natural history of these diseases, providing a critical standard by which to compare the outcomes of candidate therapies. NCL clinical research teams from all over the world are also working together to maintain and provide access to patient registries. Also important are the newly-identified biomarkers of disease progression that are unique to a given NCL and enable in-life measures of the impact of a therapeutic modality. Well-defined natural history studies and unique biomarkers of disease progression will be increasingly important as they help identify the milestones for outcomes in clinical trials that aid in the assessment of efficaciousness and comparisons of new therapies.

When considering different therapeutic approaches, ERT may conceptually be the simplest, but the blood-brain barrier is a major hurdle to the therapeutic enzyme accessing the CNS,

the most important target in all NCLs. The recent approval for intraventricular administration of Cerliponase Alfa for the treatment of CLN2 disease is a significant step forward in the field and opens up the possibility of expanding ERT not just to other NCLs but also to other LSDs with neurological involvement[231]. While this is a huge breakthrough, it must be remembered that ERT requires lifelong repeated administrations, a significant confounding factor for reasons of cost and access to therapy.

In theory, cell therapies offer promise for the treatment of these diseases, but preclinical studies to date have been confounded by limited migration from the sites of administration to encompass all the affected areas of the brain.

Gene therapies on the other hand, could be the best solution. Once administered, a gene therapy expresses the gene of interest on a persistent bases (AAV or lentivirus vectors) with the potential to be a “one and done” treatment. In the last decade, many gene therapy studies outlined in this review have demonstrated success in animal models (small and large) of NCLs. Improved vector serotypes, and less invasive delivery methods leading to widespread distribution of the therapeutic product in the CNS, have been key to these successes. Many of these preclinical studies originating in academic labs have translated to early-phase clinical studies, and numerous industry partners facilitating clinical development projects with anticipated rapid regulatory approval.

Pharmacological approaches, in addition to providing palliative care for patients with these diseases, have the potential to target processes that have an impact on the disease. Examples of these approaches are anti-apoptotic drugs, immunosuppressants, and specific receptor antagonists, but none have yet led to definitive clinical benefits. The search for these small molecule drugs with efficacy continues as partnerships between pharmaceutical companies with access to large libraries of novel and repurposed agents, and scientists who provide the screening tools and animal models, is growing. This increased interest in the field indicates that new therapies may be on the horizon.

It is important to note that most of treatments being developed for NCLs target the CNS, but it is becoming clear that treating the peripheral manifestations will also be essential. For example, studies done in the dog model of CLN2 disease, where AAV-mediated delivery of CLN2 via intracerebroventricular administration showed the delay in onset of neurological symptoms, and increased survival was observed in the context of progressive cardiac disease as well as liver and muscle pathology[101]. Studies such as this point to the fact that when the more severe and fatal neurological pathologies are resolved, the current non-life threatening peripheral symptoms come to the forefront. Therefore, there may be a need for combinatorial approaches that deliver the same therapeutic to both the CNS and the viscera. Further, the eye disease associated with many NCLs needs to be addressed in parallel to prevent the blindness.

Finally, and critically important, is the early diagnosis of an NCL. Future newborn screening programs will enable diagnosis shortly after birth, allowing the initiation of therapy, when indicated, during asymptomatic stages. There are many therapies in the pipeline for the treatment of NCLs. Most of these may halt or slow the progression of disease but are

unlikely to completely or even partially reverse the disease, therefore early diagnosis is more important than ever. In the US, many states have included newborn screening for some lysosomal disorders in their screening panel[283], and with the new therapeutics, both approved (Brineura®) and clinical development of others, it will not be long before various NCL diseases have therapies available. In the next decade, the possibility of early diagnosis combined with effective therapies should change the outlook for patients with these fatal diseases.

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Abbreviations used:

NCL	neuronal ceroid lipofuscinoses
CLN	ceroid lipofuscinosis, neuronal
LSD	lysosomal storage disorders
CNS	central nervous system
BBB	blood-brain barrier
PPT1	palmitoyl protein thioesterase-1
TPP1	tripeptidyl peptidase-1
ERT	enzyme replacement therapy
AAV	adeno-associated virus
INCL	infantile NCL
LINCL	late infantile NCL
JNCL	juvenile NCL
SCMAS	subunit c of mitochondrial ATP synthase
SAP	sphingolipid activator proteins
BMP	bis(monoacylglycero)phosphate
HSC	hematopoietic stem cells
HuCNS-SC	human central nervous system stem cells
CTSD	cathepsin D
GRN	granulin precursor
PGRN	progranulin
BDNF	brain-derived neurotrophic factor

MLD	metachromatic leukodystrophy
M6P	mannose 6-phosphate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
FDA	Food and drug administration
MED	minimum effective dose
n.d.	not determined

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Article Highlights

- Neuronal ceroid lipofuscinoses (NCL) are a collection of neurologic disorders involving defective lysosomal processing enzymes or receptors that lead to cognitive and visual impairments, seizures, deterioration of motor/language skills, and premature death.
- Many experimental animal models (mice, dogs, pigs, and sheep) for the NCLs have been created or identified, which possess genomic mutations responsible for NCL subtypes, allowing investigations of safety and efficacy of new therapeutics in preclinical studies.
- Development of quantitative biomarkers in the blood or CSF for NCLs, enabling investigators to track biochemically the improvement or decline of disease-related phenotypes, is an important component in the validation of potential treatments.
- Review of the challenges of delivery of treatments, primarily due to CNS involvement and the blood-brain barrier, and possible therapeutic approaches for the development of treatment modalities for NCL, such as enzyme replacement therapy, cell therapy, gene therapy, and pharmacological drugs.
- Current therapies for each of the NCL subtypes are discussed with emphasis on the most promising ones being translated to clinical trials, such as clinical development of ERT for CLN2 (Brineura®), immunosuppression for CLN3 (CellCept®), and gene therapy vectors for CLN1, CLN2, CLN3 and CLN6.
- Gene therapy clinical trials using adeno-associated virus (AAV) to deliver the normal NCL-relevant gene to the CNS are underway and are being evaluated for safety and efficacy.
- A combination approach using multiple treatment modalities may be the key to developing the most promising therapeutic approaches for NCLs.

Table I.

Identifying Features of Neuronal Ceroid Lipofuscinoses (NCL) [1]

Neuronal ceroid lipofuscinoses type	Gene/protein (disease variant)	Age of onset	Symptoms	Protein localization[2]	Protein function/activity[3]	Abnormal lipid/protein composition
CLN1	PPT1 (INCL)	5 months to 2 years (infantile)	Decreased head growth, blindness, seizures, hyperexcitability, slowed motor and mental development	Lysosomal matrix, extralysosomal vesicles, extracellular	Palmitoylthioesterase	Phospholipids (lipofuscin)/SAPs
CLN2	TPP1 (LINCL)	2–4 years (late infantile)	Progressive dementia, motor dysfunction, seizures, myoclonus, ataxia, loss of vision	Lysosomal matrix	Serine protease	Unknown lipids/SCMAS
CLN3	CLN3 (JNCL)	4–10 years (juvenile)	Visual failure from retinal degeneration, progressive cognitive decline, motor dysfunction, seizures, and behavior problems	Late endosomal / lysosomal membrane, presynaptic vesicles	Modulation of vesicular trafficking/ fusion, pH regulation and osmoregulation[284], resistance to endoplasmic reticulum stress[56]; regulation of ganglioside levels[285]	BMP, phospholipids, galactosyl-ceramide/ SCMAS
CLN4	DNAJC5, CSPα, (Parry NCL)	~30 years (adult)	Slow progressing, death 10–20 years after onset	Cytosolic, associated-vesicular membranes	Hsc70 co-chaperone (exo/endocytosis)	Unknown lipids/SAPs
CLN5	CLN5 (Finnish variant)	4.5–6 years (late infantile, juvenile)	Slight motor clumsiness, seizures, ataxia, myoclonus	Lysosomal matrix	Modulation of vesicular trafficking/ fusion	Sphingolipids/SCMAS
CLN6	CLN6	2–4 years (late infantile); and adult onset	Resembles LINCL in clinical characteristics	ER-lysosomal membrane	Likely involved with degradation of post-translationally modified proteins in lysosomes[286]	Phospho- and glycosphingo-lipids, cholesterol/SCMAS
CLN7	MFSD8	2–4 years (late infantile)	Seizures, poor mobility, visual impairment	Lysosomal membrane	Transmembrane transporter function predicted, regulation of soluble lysosomal proteins[287]	Unknown lipids/SCMAS
CLN8	CLN8 (EPMR)	5–10 years (juvenile)	Increasing seizures until puberty, then decreasing frequency through adulthood	ER/ERGIC membrane	Regulation in lipid metabolism predicted, regulates lysosome biogenesis[72], Endoplasmic reticulum-export recycling receptor[71]	Ceramides, phospholipids, sphingolipids, sulfatides/ SCMAS
CLN9	Unknown	Unknown	unknown	unknown	UNK, role in ceramide synthesis postulated	Ceramides, sphingomyelin, sphingolipids, globosides/protein n.d.
CLN10	CTSD/Cathepsin D (congenital)	Congenital, neonatal, and late infantile variants[288]	Epilepsy, extreme brain atrophy, with death in a few days from cardiac failure	Lysosomal matrix, extracellular	Aspartyl endopeptidase	BMP, cholesterol, phospho- and sphingo-lipids/SAPs
CLN11	GRN/Progranulin	22–23 years (adult)	Seizures, visual deterioration, myoclonus	Extracellular	UNK, roles in inflammation, embryogenesis, cell motility and tumorigenesis postulated, non-enzyme	lipids/protein n.d.

Neuronal ceroid lipofuscinoses type	Gene/protein (disease variant)	Age of onset	Symptoms	Protein localization[2]	Protein function/activity[3]	Abnormal lipid/protein composition
CLN12	ATPase 13A2,	13–16 years (adult)	Poor mobility, myoclonus, deteriorated speech	Lysosomal membrane, multivesicular bodies	UNK, regulation of ion homeostasis postulated, secretion of exosomes and α-synuclein[86], non-enzyme	lipids/protein n.d.
CLN13	CTSF/Cathepsin F (Adult Kufs type B)	20–32 years (adult)	Dementia, personality changes	Lysosomal matrix	Cysteine protease	lipids/protein n.d.
CLN14	K+ channel protein (KCTD7)	8–24 months (infantile)	Seizures, visual and verbal deterioration, brain atrophy	Cytostolic, associated to membrane	Transmembrane protein voltage-gate potasium channel complex, potassium and glutamine transport[92], autophagy[93]	lipids/protein n.d.

[1]Abbreviations: NCL (neuronal ceroid lipofuscinoses), CLN (ceroid lipofuscinosis neuronal), INCL (infantile NCL), LINCL (late infantile NCL), JNCL (juvenile NCL), PPT1 (palmitoyl protein thioesterase1), TTP1 (tripeptidyl peptidase1), MFSD8 (major facilitator superfamily domain-containing protein 8), EPMR (progressive epilepsy with mental retardation), KCTD7 (potassium channel tetramerization domain containing protein 7), SCMAS (subunit c of mitochondrial ATP synthase), SAPs (sphingolipid activator proteins), BMP (bis(monoacylglycerol)phosphate), and n.d. (not determined).

[2]Soluble proteins (CLN1, CLN2, CLN5, CLN10, CLN13); transmembrane proteins (CLN3, CLN6, CLN7, CLN8, CLN12, CLN14).

[3]Functions are unknown (UNK) for most of the CLNs; however, investigations have determined possible function/activity.

Table II.

Human Clinical Trials for Neuronal Ceroid Lipofuscinoses (Observational clinical studies)[1]

NCL/Study Title	Treatment	Phase	Number Enrolled	Status	NCT Number[2]
All CLN types					
Clinical and Neuropsychological Investigations in Batten Disease	Natural history only, no treatment	none (observational)	400	Recruiting	NCT01873924
Neuronal Ceroid Lipofuscinosis and Associated Sleep Abnormalities	Natural history only, no treatment	none (observational)	57	Completed	NCT01966757
Genetic Characterization of Movement Disorders and Dementias	Natural history only, no treatment	none (observational)	12,000	Recruiting	NCT02014246
Inherited Retinal Degenerative Disease Registry	Natural history only, no treatment	none (observational)	20,000	Recruiting	NCT02435940
Longitudinal Study of Neurodegenerative Disorders	Hematopoietic Stem Cell Transplantation	none (observational)	1,500	Recruiting	NCT03333200
CLN2					
Genotype - Phenotype Correlations of LINCL	Natural history only, no treatment	none (observational)	18	Completed	NCT00151268
Genotype-Phenotype Correlations of Late Infantile Neuronal Ceroid Lipofuscinosis	Natural history only, no treatment	none (observational)	75	Active, not recruiting	NCT01035424
Collection of Cerebrospinal Fluid in Healthy Children	none (normal controls)	none (observational)	32	Terminated	NCT01698229
CLN3					
Investigations of Juvenile Neuronal Ceroid Lipofuscinosis	Natural history only, no treatment	none (observational)	50	Recruiting	NCT03307304
CLN6					
Natural History of Neuronal Ceroid Lipofuscinosis, Batten's CLN6 Disease	Natural history only, no treatment	none (observational)	15	Recruiting	NCT03285425

[1] Abbreviations: neuronal ceroid lipofuscinosis (NCL); late infantile neuronal ceroid lipofuscinosis (LINCL)

[2] Clinical identifier numbers obtained from clinicaltrials.gov website

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Table III.

Neuronal Ceroid Lipofuscinoses Animal Models

Neuronal ceroid lipofuscinoses type[1]	Gene/protein (variant)	Mouse models	Large animal models with neuronal ceroid lipofuscinoses defects[2]
CLN1	PPT1 (INCL)	*Cln1*$^{-/-}$, *Ppt1*$^{\Delta ex4}$, *Ppt1*$^{\Delta ex9}$, *Cln1*^{R151X103}	Miniature Dachshund
CLN2	TPP1 (LINCL)	*Tpp1*$^{-/-}$, *Arg446His*, *Cln2*$^{R207X/R207X110}$, *Tg*$^{LSL\text{-}TPP1111}$	Long-haired Dachshund[2]
CLN3	CLN3 (JNCL)	*Cln3*$^{-/-}$, *Cln3*$^{\Delta ex1-6}$, *Cln3*$^{\Delta ex7-8}$	ExeGen mini pig
CLN4	DNAJC5, CSPα, (ANCL)	None	None
CLN5	CLN5	*Cln5*$^{\Delta ex3}$	Borderdale sheep[119,120], Devon cattle, Border collie
CLN6	CLN6	*nclf* (c.307insC)	South Hampshire sheep[2], Merino sheep[127], Australian shepherd
CLN7	MFSD8	*Mfsd8*$^{tm1a/tm1128a}$	Chihuahua[131], Japanese Macaque[132]
CLN8	CLN8	*Cln8/mnd* (c.267–268insC)	English setter[2], Alpine Dachsbracke[134], Saluki[135]
CLN9	unknown	None	None
CLN10	Cathepsin D (CTSD)	CTSD −/−[136]	Swedish Landrace sheep, American bulldog
CLN11	Progranulin	*Grn*$^{-/-}$[139], PGRN-deficient[140]	
CLN12	ATPase 13A2,	None	Tibetan terrier
CLN13	Cathepsin F (CTSF)	*Ctsf*$^{-/-}$	None
CLN14	K+ channel protein (KCTD7)	None	None
Unknown NCL genetic defect	unknown		Rambouillet sheep, Beefmaster & Holstein cattle, domestic ferret, short-haired Siamese & Japanese cats, Aegidienberger horse, Nubian goat, Vietnamese pot-bellied pig, Lovebird parrot, Cynomologous monkey, Mallet duck, and dogs such as the American Staffordshire terrier, Australian terrier, Polish lowland sheepdog, Miniature schnauzer, Cocker spaniel, Dalmatian, Japanese retriever, Welsh corgi, Labrador retriever, Australian cattle dog

[1] Soluble proteins (CLN1, CLN2, CLN5, CLN10, CLN13); transmembrane proteins (CLN3, CLN6, CLN7, CLN8, CLN12, CLN14).

[2] Active experimental populations available for study.

Table IV.

Human Clinical Trials for Neuronal Ceroid Lipofuscinoses (Clinical studies, Phases 1–4)[1]

NCL/Study Title	Treatment	Phase	Number enrolled	Status	Number[2]
All CLN types					
Stem Cell Transplant for Inborn Errors of Metabolism	Stem Cell Transplant	Phase 2/3	135	Completed (Has Results)	NCT00176904
Human Placental-Derived Stem Cell Transplantation	Human Placental Derived Stem Cell	Phase 1	43	Active, not recruiting	NCT01586455
UCB Transplant of Inherited Metabolic Diseases With Administration of Intrathecal UCB Derived Oligodendrocyte-Like Cells	UCB-derived oligodendrocyte-like cells	Phase 1	12	Recruiting	NCT02254863
CLN1					
Cystagon to Treat Infantile Neuronal Ceroid Lipofuscinosis	Cystagon and N-acetylcysteine (oral, daily)	Phase 4	10	Completed[227]	NCT00028262
Study of HuCNS-SC Cells in Patients With Infantile or Late Infantile Neuronal Ceroid Lipofuscinosis (NCL)	Human CNS stem cells (HuCNS-SC)	Phase 1	6	Completed	NCT00337636
Safety and Efficacy Study of HuCNS-SC in Subjects With Neuronal Ceroid Lipofuscinosis	Human CNS stem cells (HuCNS-SC)	Phase 1b	0	Withdrawn	NCT01238315
CLN2					
Safety Study of a Gene Transfer Vector for Children With Late Infantile Neuronal Ceroid Lipofuscinosis	AAV2CUhCLN2 (3×10^{12} particle units)	Phase 1	10	Active, not recruiting	NCT00151216
Study of HuCNS-SC Cells in Patients With Infantile or Late Infantile Neuronal Ceroid Lipofuscinosis (NCL)	Human CNS stem cells (HuCNS-SC)	Phase 1	6	Completed	NCT00337636
Safety Study of a Gene Transfer Vector (Rh.10) for Children With Late Infantile Neuronal Ceroid Lipofuscinosis (LINCL)	AAVrh.10CUhCLN2 (9.0×10^{11} or 2.85×10^{11} genome copies)	Phase 1	25	Active, not recruiting	NCT01161576
Safety and Efficacy Study of HuCNS-SC in Subjects With Neuronal Ceroid Lipofuscinosis	Human CNS stem cells (HuCNS-SC)	Phase 1b	0	Withdrawn	NCT01238315
AAVRh.10 Administered to Children With Late Infantile Neuronal Ceroid Lipofuscinosis	AAVrh.10CUhCLN2	Phase 1/2	8	Active, not recruiting	NCT01414985
A Phase 1/2 Open-Label Dose-Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of Intracerebroventricular BMN 190 in Patients With Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2) Disease	BMN 190 (rhTPP1); ERT via ICV infusion	Phase 1/2	24	Completed (Has Results)	NCT01907087
A Multicenter, Multinational, Extension Study to Evaluate the Long-Term Efficacy and Safety of BMN 190 in Patients With CLN2 Disease	BMN 190 (rhTPP1); ERT via ICV infusion	Phase 1/2	23	Active, not recruiting	NCT02485899
A Safety, Tolerability, and Efficacy Study of Intracerebroventricular BMN 190 in Pediatric Patients < 18 Years of Age With CLN2 Disease	BMN 190 (rhTPP1); ERT via ICV infusion	Phase 2	15	Enrolling by invitation	NCT02678689
CLN3					
CellCept® for Treatment of Juvenile Neuronal Ceroid Lipofuscinosis	Mycophenolate mofetil (CellCept®)	Phase 2	19	Completed	NCT01399047

NCL/Study Title	Treatment	Phase	Number enrolled	Status	Number[2]
Phase I/IIa Gene Transfer Clinical Trial for Juvenile Neuronal Ceroid Lipofuscinosis, Delivering the CLN3 Gene by Self-Complementary AAV9	scAAV9-CLN3	Phase 1/2	7	Recruiting	NCT03770572
CLN6					
Batten CLN6 Gene Therapy	scAAV9.CB.CLN6	Phase 1/2	12	Recruiting	NCT02725580

[1]Abbreviations: enzyme replacement therapy (ERT); recombinant human tripeptidyl peptidase-1 (rhTPP1); adeno-associated virus (AAV); umbilical cord blood (UCB); neuronal ceroid lipofuscinosis (NCL); late infantile neuronal ceroid lipofuscinosis (LINCL).

[2]Clinical identifier numbers obtained from ClinicalTrials.gov website.

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