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Review

Experimental gene therapies for the NCLs

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ABSTRACT

The neuronal ceroid lipofuscinoses (NCLs), also known as Batten disease, are a group of rare monogenic neurodegenerative diseases predominantly affecting children. All NCLs are lethal and incurable and only one has an approved treatment available. To date, 13 NCL subtypes (CLN1-8, CLN10-14) have been identified, based on the particular disease-causing defective gene. The exact functions of NCL proteins and the pathological mechanisms underlying the diseases are still unclear. However, gene therapy has emerged as an attractive therapeutic strategy for this group of conditions. Here we provide a short review discussing updates on the current gene therapy studies for the NCLs.

1. Introduction

The past 15 years has seen huge advances in viral vector gene delivery technology allowing for more efficient transfer of nucleic acids to cells. This has led to life-saving or life-changing gene therapy clinical trials for immunological (severe combined immunodeficiency due to adenosine deaminase deficiency [1–4] (reviewed by [5]), Wiskott–Aldrich syndrome [6–9], X-linked severe combined immunodeficiency [10–12]), haematological (haemophilia [13–16]), myeloid leukaemia [17], Sickle cell disease (reviewed by [18–20]), ophthalmic (reviewed by [21]) (RPE65-associated Leber congenital amaurosis [22–25], Choroideremia [26,27]) and neurological (spinal muscular atrophy type 1 [28–30]), Parkinson's disease [31,32] (reviewed by [33]) conditions. There are now a growing number of gene therapies being commercialised and licensed for clinical use.

The application of gene therapy for neurological conditions is technically challenging. The brain is arguably the most complex organ of the body, and identifying and characterising the discrete regions that are affected and how the disease progresses in such an anatomically diverse organ is difficult. Both the skull and the selective blood-brain barrier (BBB) represent physical hurdles that any therapy will need to traverse to gain access to the brain and at sufficient quantities to have a therapeutic effect. Advances in paediatric and adult neurosurgery have meant that the brain can be accessed through the skull and the therapeutic modality can be administered directly into the brain parenchyma or ventricles. Indeed, we discuss in the 'CLN2 Disease' section how multiple injections may be required. Furthermore, the identification of vectors such as adeno-associated virus serotype 9 (AAV9) that have the ability to cross the blood-brain barrier have opened up the possibility of systemic administrations that could treat both neurological and accompanying visceral pathology. In addition, applying a haematopoietic stem cell (HSC) gene therapy approach offers potential systemic benefits using integrating vectors such as those based on lentiviruses (LVs). An example of this is the preclinical studies of lentiviral based HSC gene therapy using a mouse model of the neurological disorder metachromatic leukodystrophy [34,35] that led to clinical trials in patients [36,37]. These advances in gene delivery technology in combination with different routes of administration to the brain have led to gene therapy clinical trials for a wide range of neurological disorders. These include the more common conditions such as Parkinson's Disease and Alzheimer's Disease but now also rare paediatric neurodegenerative diseases such as the neuronal ceroid lipofuscinoses (NCLs).

The NCLs (subtypes and affected proteins summarized in Table 1) have become a popular group of candidate diseases among the rare neurological disorders for pre-clinical and clinical gene therapy studies.

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Table 1
NCL subtypes and their affected proteins.

Subtype/gene	Protein	Location	Function	Clinical phenotype	Pre-clinical AAV gene therapy study
CLN1	Palmitoyl protein thioesterase (PPT1)	Lysosomal matrix	Regulation of synaptic vesicle *endo*- and exocytosis, endosomal trafficking and lipid metabolism	Infantile, juvenile and adult onset	✓
CLN2	Tripeptidyl peptidase 1 (TPP1)	Lysosomal matrix	Linked to macroautophagy and endocytosis	Late infantile onset	✓
CLN3	CLN3	Golgi and lysosomal membrane	Unknown function	Juvenile onset	✓
CLN4	DnaJ homolog subfamily C member 5 (DNAJC5)	Cytosol, associated with vesicular membrane	Involved in presynaptic endo/exocytosis	Adult (Parry disease)	x
CLN5	CLN5	Lysosomal matrix	Unknown function	Late infantile onset	✓
CLN6	CLN6	Endoplasmic reticulum membrane	Unknown function	Late infantile onset	✓
CLN7	CLN7	Lysosomal membrane	Unknown function	Late infantile and juvenile onset	x
CLN8	CLN8	Endoplasmic reticulum membrane	Unknown function	Late infantile onset	x
CLN10	Cathepsin D (CTSD)	Lysosomal matrix	Involved in apoptosis and autophagy	Congenital	✓
CLN11	Granulin	Extracellular	Unknown function	Adult (Kufs disease)	✓
CLN12	CLN12	Lysosomal membrane	Unknown function	Juvenile onset	x
CLN13	Cathepsin F (CTSF)	Lysosomal matrix	Associated to proteasome degradation and autophagy	Adult (Kufs disease)	x
CLN14	BTB/POZ Domain-Containing Protein KCTD7	Partially associated with plasma membrane	Unknown function	Infantile and late infantile onset	x

Table 2
Clinical trials of NCL gene therapy (www.clinicaltrials.gov).

NCL type	Title	NCT number	Viral vector	Status	No. of participants
CLN2	Genotype - phenotype correlations of late infantile neuronal ceroid lipofuscinosis	NCT 00151268	AAV2.CUhCLN2	Completed	18
CLN2	Safety study of a gene transfer vector for children with late infantile neuronal ceroid lipofuscinosis	NCT00151216	AAV2.CUhCLN2	Phase 1; Active, not recruiting	10
CLN2	Safety study of a gene transfer vector (rh.10) for children with late infantile neuronal ceroid lipofuscinosis	NCT01161576	AAVrh.10.CUhCLN2	Phase 1; Active, not recruiting	25
CLN2	AAVrh.10 administered to children with late infantile neuronal ceroid lipofuscinosis	NCT01414985	AAVrh.10.CUhCLN2	Phase 1/2; Active, not recruiting	8
CLN3	Phase I/IIa gene transfer clinical trial for juvenile neuronal ceroid lipofuscinosis, delivering the CLN3 gene by self-complementary AAV9	NCT03770572	AAV9-CLN3	Phase 1/2; Recruiting	7
CLN6	Phase I/IIa gene transfer clinical trial for variant late infantile neuronal ceroid lipofuscinosis, delivering the CLN6 gene by self-complementary AAV9	NCT02725580	AAV9.CB.CLN6	Phase 1/2; Active, not recruiting	12

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Table 3
Pre-clinical gene therapy studies for NCLs.

NCL type	Animal model	Viral vector	Promoter	Delivery route	Time of intervention	Reference
CLN1	*Ppt1* knockout mouse	AAV2	CAG	Intra-brain-parenchymal injection	Neonate	[47,49]
		AAV2	CAG	Intra-vitreal injection	P18-21 or 8 weeks	[48]
		AAV5	CAG	Intra-brain-parenchymal injection + PPT1 mimetic	Neonate	[52]
		AAV5	CAG	Intra-brain-parenchymal injection + BMT	Neonate	[50]
		AAV5	CAG	Intra-brain-parenchymal injection + MW151	Neonate	[51]
		AAV9	CAG	Intra-brain-parenchymal and/or intrathecal injection	Neonate	[53]
CLN2	*Tpp1* knockout mouse	AAV2 or AAV5	CMV/CBA	Intra-brain-parenchymal injection	6 weeks	[56]
		AAV1	CMV/CBA	Intra-brain-parenchymal injection	4 or 11 weeks	[55]
		AAVrh.10	CMV/β-actin	Intra-brain-parenchymal injection	Neonate, 3 weeks or 7 weeks	[57,58]
		Epitope-modified AAV2	–	Intravenous injection	6–8 weeks	[61]
	CLN2 deficient Dachshund dog (CLN2: c.325delC)	AAV2	CMV/CBA	Intracerebroventricular injection	11–14 weeks	[62–64]
		AAV2	CAG	Intravitreal transplantation of autologous mesenchymal stem cells transduced with the viral vector	14 weeks	[65]
CLN3	*Cln3*$^{\Delta ex7/8}$ knock-in mouse	AAVrh.10	CAG	Intra-brain-parenchymal injection	Neonate	[72]
		AAV9	MeCP2 or CMV/CBA	Intravenous injection	1 month	[73]
CLN5	*CLN5* deficient Borderdale sheep (CLN5: c.571 + 1G > A)	AAV9 or Lentivirus	MNDU3	Intracerebroventricular + intra-brain-parenchymal injection	2–3 months	[91]
		AAV9	CBA	ICV injection	7 months	[91]
CLN6	Naturally occurring *Cln6*^{nclf} mouse	AAV7m8	CMV, PCP2 or Grm6	Intravitreal injection	P5–6	[97]
		AAV9	CMV	Intracerebroventricular injection	Neonate	[99]
		AAV9	CBA	Intracerebroventricular injection	Neonate	[98]
CLN10	*Ctsd* knockout mouse	AAV2	CMV/HBA	Intra-brain-parenchymal injection and/or liver/stomach injection	P3	[100]
CLN11	*Grn* knockout mouse	AAV1	CBA	Intra-brain-parenchymal injection	10–12 months	[108]
		AAV9	CMV	Intracerebroventricular injection	6–8 months	[109]

There are a number of reasons for this: (i) taken together, the NCLs represent the most frequent neurodegenerative condition in children; (ii) they are monogenic conditions where the defective gene has been identified and characterised; (iii) the development and availability of animal models of disease has furthered our understanding of disease pathology and progression and also provided invaluable tools for pre-clinical testing of new therapies; (iv) there is no major disease modifying treatments available in the clinic for the NCLs (with the recent exception of CLN2 disease) and palliative care remains the main option; (v) some of the NCL proteins (*e.g.* CLN2 and CLN5) are secreted by cells, which allows for cross-correction that could facilitate efficiency of gene therapy. The purpose of this review is to provide an update on the current status of efforts to develop gene therapies for the NCLs. All the preclinical studies and clinical trials are also summarized in Tables 2 and 3, to allow comparison and future study design.

2. CLN1 disease

CLN1 disease is caused by homozygous or compound heterozygous mutations in the *PPT1* gene, which leads to a deficiency in the lysosomal enzyme palmitoyl protein thioesterase-1 (PPT1) (Table 1). Disease of onset is typically in infancy but some patients show later onsets varying from late infancy to adulthood [38]. Affected infants usually present with progressive development retardation, seizures and jerks, vision deterioration and motor difficulties, leading to premature death occurring in early and mid-childhood. To model CLN1 disease, *Ppt1* knockout or knock-in mouse models have been developed [39–42] and currently the most commonly used is the *Ppt1* knockout mouse generated by the disruption of exon 9 of the mouse *Ppt1* gene [40]. This model recapitulates many pathological and clinical aspects of the human disease including accumulation of lysosomal storage material, gliosis, neuronal and retinal degeneration, motor defects and shortened lifespan of approximately 8 months [40,43–49].

Pre-clinical studies using mouse models to investigate gene therapy for CLN1 disease (for an overview see Table 3) were initiated by utilising a recombinant AAV2 vector harbouring human *PPT1* driven by the CAG promoter [47–49]. Brain-targeted delivery of the vector *via* multi-regional injections resulted in significantly increased PPT1 activity in regions of the brain surrounding injection sites, albeit still lower than that measured in wild type mice [47,49]. Autofluorescent lysosomal inclusions, neurodegeneration and performance in motor coordination tests (the rotarod, pole and ledge tests) were significantly improved but the lifespan of the mice was not increased. Follow up studies using AAV2 pseudotyped with the AAV5 capsid protein led to a better therapeutic efficacy and significantly improved the mouse survival by around 2–5 months [50–52]. Furthermore, brain-targeted AAV2/5 gene therapy in combination with other therapies such as bone marrow transplantation [50], or systemic delivery of PPT1 mimetic (phosphocysteamine) [52] or anti-neuroinflammatory (MW151) [51] have been investigated pre-clinically with the *Ppt1* knockout mice. Gene therapy combined with systemic delivery of PPT1 mimetic [52] or anti-neuroinflammatory drug [51] did not produce dramatic synergistic effects. However, combining with bone marrow transplantation (BMT) largely improved the therapeutic effects of gene therapy, which is particularly noteworthy considering that BMT alone did not show any beneficial effects [50]. The mice treated with AAV + BMT presented with greatly slowed disease progression and prolonged lifespan to around 18 months of age. The authors found that the vector transduction was much higher in the mice treated with AAV + BMT, which might be associated with the gamma radiation accompanying BMT and might directly contribute to the synergy between gene therapy and BMT. More recently, Shyng et al. found that dual intracranial and intrathecal administration of AAV9.PPT1 improved the disease pathology in both the forebrain and the spinal cord, leading to a significant delay in the motor function decline and an increase in lifespan to around 19 months, whereas intracranial or intrathecal treatment alone had only a moderate effect [53], indicating that spinal cord pathology is of critical importance and will need to be taken into consideration to optimise a gene therapy strategy for CLN1 disease. Collectively, CNS-targeted gene therapy appears promising as a potential strategy for

CLN1 disease, but still needs further optimisation with respect to achieving widespread vector transduction and PPT1 correction across the CNS.

In addition to CNS-targeted gene therapy, ocular gene therapy has also been pre-clinically studied. Intravitreal administration of AAV2.CAG.hPTT1 significantly increased the retinal function and reduced the photoreceptor loss in the *Ppt1* knockout mice [48], suggesting a potential addition to the CNS-directed gene therapy with the aim to improve the quality of life of the patients.

Recently, the U.S. Food and Drug Administration (FDA) has granted an AAV9 gene therapy clinical trial for CLN1 disease, which is currently at the preparation stage (https://battendiseasenews.com).

3. CLN2 disease

CLN2 disease is caused by homozygous or compound heterozygous mutations in the *CLN2* gene, which leads to a deficiency in the lysosomal enzyme tripeptidyl-peptidase I (TPP1) (Table 1). The disease has a late-infantile onset around 3 years of age, while some patients may show a later onset [38] or a distinct clinical phenotype [54]. Typical symptoms include development retardation, seizures, motor difficulties and vision loss, leading to premature death that usually occurs around 6–12 years of age [38]. Gene therapy has been extensively studied for CLN2 disease using both small and large animal models (for an overview see Table 3) and subsequent clinical trials have already been initiated (Table 2).

Gene therapy mediated by various AAV serotypes, such as AAV1 [55], AAV2 [56], AAV5 [56] and AAVrh10 [57,58], have been investigated using the *Cln2* knockout mice, a model for CLN2 disease devoid of Tpp1 enzyme activity [59]. The mice present with progressive tremor, motor impairments and shortened longevity to around 3–6 months of age. Histologically, they show progressive lipofuscin accumulation in various brain regions and neurodegeneration [59]. Brain-targeted (bilateral administration in four brain locations per hemisphere) AAVrh10-mediated gene therapy in 7-week old *Cln2* knockout mice produced wide distribution and high levels of TPP1 in the brain, resulting in significant improvements of the pathology and the phenotype [57]. AAV1 carrying a codon-optimised version of the human *CLN2* gene delivered bilaterally into multiple brain locations also showed dramatic therapeutic efficacy in the *Cln2* deficient mice [55]. Notably, timing of intervention appears to be an important factor in the therapeutic outcomes. Pre-symptomatic administration of gene therapy produced significantly better pathology and phenotype improvements and further extended the lifespan compared with post-symptomatic treatment, highlighting the importance of early intervention before disease onset [55,58]. These studies highlight the need of multiple intra-parenchymal injections in order to transduce sufficient area of the brain even in small animal models. This does highlight potential difficulties in translation to a brain size of human. An alternative is to investigate systemic delivery of viral vectors with respect to CNS transduction efficiency. Up to date, two studies provide potential systemic AAV delivery strategies with significant CNS TPP1 biodistribution when injected to the adult mice [60,61] (Table 3). Foley et al. tested intra-arterial injection of the AAVrh10.CLN2 vector in combination with mannitol treatment (a blood-brain barrier permeabilizer), which resulted in widespread TPP1 activity in the brain of the wild type mice [60]. In addition, Chen et al. tested a novel strategy to increase the CNS biodistribution of intravenously delivered AAV in the CLN2 mice. They identified a specific epitope binding to the brain vascular endothelia of the diseased mice and inserted the epitope into the AAV2 capsid; they showed that intravenous injection of the modified AAV2.TPP1 into adult CLN2 mice resulted in significant TPP1 activity across the CNS and improvement of the neurological pathology and phenotype [61]. The underlying mechanism for this epitope-modified vector is that the viral transduction in the brain endothelia is promoted through the capsid modification and the overexpressed TPP1 is secreted from the endothelia and then taken up by neurons and glia. Together, these two studies provide more options for the gene therapy delivery approaches that can reach the CNS, and hopefully could help to overcome the difficulties arising from multiple intra-cranial injections.

AAV-mediated gene therapy has also been investigated using a large animal model of CLN2 disease - the *TPP1*-deficient canine Dachshund model [62–64]. Pre-symptomatic intracerebroventricular (ICV) administration of AAV2 vectors harbouring canine *CLN2* resulted in ependymal transduction and TPP1 distribution throughout the CNS, leading to dramatically slowed disease onset and improved survival of the mutant dogs [63]. Notably, the retinal degeneration and visual impairment were not prevented by ICV delivered gene therapy, underlining the necessity of direct ocular treatments [63,64]. Tracy et al. attempted to treat the retinal degeneration in the mutant dogs by intravitreal implantation of autologous mesenchymal stem cells that were transduced *ex vivo* with an AAV2.*CLN2* vector prior to the surgery. Treated dog eyes had a reduced number of retinal lesions and the loss of retinal function was slowed, although retinal function was not fully preserved long-term. Of note is that the size of the implanted cell mass decreased over time, which may explain why the therapeutic effect was not maintained [65]. Furthermore, the researchers found clear evidence of peripheral (especially the heart) pathology in the *TPP1*-deficient dogs, which became more obvious as the life span increased after CNS-targeted gene therapy [62]. Blood biomarkers of tissue damage (*i.e.* cardiac troponin, alanine aminotransferase and creatine kinase) increased over time, and the electrocardiography parameters also showed significant changes, none of which was improved by the CNS-targeted gene therapy [62]. Therefore, the systemic manifestations of CLN2 disease do support a gene therapy strategy that would ideally target multiple body systems.

On the basis of the above pre-clinical studies, clinical trials of CLN2 gene therapy have been initiated (Table 2). In 2008, data from the first clinical trial of CLN2 gene therapy (ClinicalTrials.gov Identifier: NCT00151268; NCT00151216) was reported [66]. Ten CLN2 patients (3–10 years of age) received injections of AAV2 vectors carrying human *CLN2* driven by the CAG promoter to 12 cortical locations through 3 burr holes per hemisphere. Safety and efficacy were then monitored for 18 months. With respect to safety, severe adverse effects such as seizures were observed post-surgery, but none could be definitely attributed to the vectors; it was unclear whether the adverse effects were due to disease progression, the surgical procedures or the vector administration. Importantly, assessment using the modified Hamburg late infantile neuronal ceroid lipofuscinosis clinical rating scale showed significantly slowed disease progression in the treated patients compared to a combined control group consisting of four untreated patients and historical data. Although the study was small in size and the controls were not matched, randomized or blinded, the data still provided valuable support for more AAV-mediated gene therapy tests for CLN2 disease and possibly other CNS disorders. Recently, the AAVrh10 vector (ClinicalTrials.gov Identifier: NCT01414985; NCT01161576) has also been proposed to be tested on CLN2 patients, with the estimated primary completion in late 2020.

4. CLN3 disease

CLN3 disease is caused by homozygous or compound heterozygous mutations in the *CLN3* gene, which encodes for a transmembrane protein of unknown function (Table 1). *In vitro* study shows that CLN3 is localized to the late endosome-lysosomal compartments of neurons, in both the soma and neurites [67]. Classic juvenile CLN3 disease patients usually show an onset of disease around 4–8 years of age, mainly with vision loss as the first symptom followed by memory and learning difficulties, seizures, motor and speech dysfunctions [38]. The course of disease is variable between patients, and death usually occurs in the second or third decade [38].

There are four genetically modified mouse models for CLN3 disease,

with two being *Cln3* knockout mouse lines and two *Cln3* knock-in lines [68–71], allowing for evaluation of potential therapeutic approaches using AAV vectors. To date, AAV gene therapy has only been studied with the $Cln3^{\Delta ex7/8}$ knock-in mice developed by Cotman et al. [68] (Table 3). Intracranial injection of AAVrh10 vectors harbouring *CLN3* into newborn $Cln3^{\Delta ex7/8}$ knock-in mice resulted in widespread *CLN3* expression in the brain up to 18 months post vector administration [72]. Neuronal lysosomal storage material accumulation and astrocytosis were decreased, but the microglia-mediated inflammatory response remained unchanged [72]. Notably, the authors did not perform motor function tests to evaluate efficacy, as no difference was found between wildtype and untreated mutant mice in the balance beam and grip strength test at 18 months. Bosch et al. [73] conducted a study using an approach that utilises AAV9's ability to cross the blood-brain barrier when administered intravenously [74–76]. 1-Month old $Cln3^{\Delta ex7/8}$ knock-in mice received intravenous injection of scAAV9 vectors carrying the human *CLN3* gene driven by either the ubiquitous CAG promoter or the weaker neuronal MeCP2 promoter [73]. A widespread transgene expression was detected throughout the CNS with lower expression levels in MeCP2-treated brains than CAG-treated brains. Interestingly, the authors found that treatment with the MeCP2 promoter, but not the CAG promoter, resulted in decreased lysosomal accumulations and gliosis and a better performance in the rotarod test in mutant mice up to 5 months after vector administration. Long-term data have not been published so far. Moreover, the early, non-progressive rotarod phenotype described in this study has not been reported consistently in other studies using $Cln3^{\Delta ex7/8}$ mice [77,78].

Based on preliminary promising data from a clinical trial for CLN6 disease, gene therapy with AAV9 vector containing human *CLN3* (no information on the promoter) has been initiated for a Phase I/II clinical trial (ClinicalTrials.gov Identifier: NCT03770572). The vector will be delivered *via* a single intrathecal injection and two doses will be tested. The trial is still at the recruiting stage, and the estimated primary completion date is proposed to be in December 2022.

5. CLN5 disease

CLN5 disease is caused by homozygous or compound heterozygous mutations in the *CLN5* gene (Table 1). There is currently no effective treatment for CLN5 disease. CLN5 patients usually have a disease onset in late infancy, and symptoms include motor dysfunctions, vision loss, seizures and dementia, with variable rates of disease progression leading to death around 14–36 years of age [38,79]. The function of CLN5 is still unclear but it is a soluble lysosomal lumen protein and can be secreted *in vitro* by mammalian cells overexpressing *CLN5* [80–84], which allows a potential mechanism for cross-correction and makes the disease an attractive target for viral vector-mediated gene therapy. Up to date, there have been several mammalian models generated [85–90], among which the most commonly used model in pre-clinical study is the CLN5 Borderdale sheep that presents a mutation at a consensus splice site of the *CLN5* gene resulting in a truncated product [89].

Pre-clinical studies of AAV- or lentivirus (LV)- mediated gene therapy have been performed in the ovine model of CLN5 disease [91]. *CLN5*-deficient sheep treated with AAV9.ovCLN5 or LV.ovCLN5 vectors (ICV injection combined with intraparenchymal injection into the occipital and parietal cortices) at the pre-symptomatic stage showed improved longevity and were well protected from development of various disease phenotypes by 26–27 months when they were euthanized, except for a much delayed visual impairment [91]. One of the treated sheep was kept alive until 57 months at which point it exhibited blindness and mild behavioural phenotypes. Lack of ocular phenotype correction would suggest that this route of administration provides insufficient transduction of the retina. Therefore, additional ocular gene therapy may be necessary to correct retinal impairments and visual deficits. The authors also investigated AAV-mediated gene therapy in early symptomatic mutant sheep to mimic more closely the clinical scenario of treatment after diagnosis. While the existing pathology and the phenotype were not reversed, the disease progression was slowed with the exception of the visual deficits.

6. CLN6 disease

CLN6 gene encodes a membrane-bound endoplasmic reticulum (ER) protein of unknown function (Table 1). Homozygous or compound heterozygous mutations in this gene cause CLN6 disease, classically an NCL with late infantile onset. Symptoms include developmental retardation, seizures, motor dysfunction and vision loss. Premature death usually occurs between 5 and 12 years of age [92]. Rare cases of fatal, adult onset CLN6 disease without loss of vision, referred to as Kufs disease, have been reported [93].

Currently, there is only one mouse model for CLN6 disease, which is the naturally occurring $Cln6^{nclf}$ mouse [94–96]. The $Cln6^{nclf}$ mouse carries a frameshift mutation in the *Cln6* gene, resulting in a truncated, short-lived protein product. This mouse strain recapitulates CLN6 disease with severe retinal degeneration and widespread neuropathology followed by neuronal loss, behavioural abnormalities and death around 1 year of age. Pre-clinical gene therapy approaches have been tested in $Cln6^{nclf}$ mice targeting the eye and the brain. Initially, kleine Holthaus et al. [97] found that although *Cln6*-deficient mice show a predominant loss of photoreceptor cells, subretinal administration of AAV8, harbouring *CLN6* under the control of the ubiquitous CMV promoter, was not therapeutic. As *CLN6* is expressed in photoreceptors bipolar cells, retinal interneurons located in the inner retina, mutant mice were also treated intravitreally with the AAV2-derived 7m8 vector that was able to transduce bipolar cells, which preserved photoreceptor function and number of photoreceptors. By using bipolar cell-specific promoters (PCP2 or Grm6), the researchers showed that correction of the CLN6 deficiency in bipolar cells was sufficient to slow down the loss of photoreceptors. This study highlighted, for the first time, the importance of bipolar cells in CLN6 disease, but further studies are needed to determine the mechanisms underlying the association between bipolar cells and photoreceptor degeneration in CLN6 disease. It also remains to be seen if bipolar cells play an important role in the retinal degenerations of other forms of NCL.

More recently, two groups independently investigated the efficacy of brain-directed gene therapy in $Cln6^{nclf}$ mice [98,99]. Both groups showed that neonatal ICV injections of AAV9 carrying human CLN6 driven by a ubiquitous promoter (CB [98] or CMV [99]) prevented motor deficits, many behavioural abnormalities, neurodegeneration and gliosis in mutant mice. Most notably, in both studies treated mice had a markedly improved lifespan of up to 2 years of age, restoring the natural life span of wild-type mice. Furthermore, Cain et al. administered Cynomolgus Macaques intrathecally with the same vector and demonstrated transgene expression throughout the brain without adverse effects in the CNS [98]. Both pre-clinical studies provide encouraging evidence for AAV gene therapy as a therapeutic approach for CLN6 disease. As brain-directed gene therapy is unlikely to prevent the retinal degeneration in CLN6 disease, a combined approach targeting both the brain and the eyes will be important to evaluate the feasibility to combat the loss of vision and neurodegeneration in CLN6 disease. Up to date, a phase I/II clinical trial using intrathecal administration of AAV9.CB.CLN6 is currently ongoing for CLN6 disease. Promising preliminary data have been released but have not been published in a peer-reviewed journal (ClinicalTrials.gov Identifier: NCT02725580).

7. CLN10 disease

CLN10 disease is caused by homozygous or compound heterozygous mutations of the *CTSD* gene encoding for cathepsin D (Table 1). It is a severe congenital NCL, with disease onset before or around birth, though some cases have later onset. Congenital patients present with primary microcephaly, seizures, respiratory failure and rigidity, with

death usually occurring within the first weeks after birth [38].

Gene therapy has been pre-clinically studied with a *Ctsd* knockout mouse model [100]. The *Ctsd* knockout mice develop typical NCL pathology and symptoms like seizures, and usually die around day P26 [101–103]. Profound peripheral pathology in the gut and immune organs has also been reported in these mice. Intestinal mucosa atrophy was first observed around P14 and progressed considerably towards severe intestinal necrosis by the final stage, which was suggested to be an important lethal factor of the mice [96]. Massive destruction of thymus and spleen with severe lymphocyte loss was also shown around the final stage. Such visceral pathologies have not been described in human patients. However, some of the CLN10 cases with later disease onset (infantile or juvenile) did show peripheral pathology such as cardiomyopathy [104,105]. Administration of the AAV1/2 vector harbouring mouse *Ctsd* driven by the CMV/human β-actin promoter to the brain parenchyma of the neonatal *Ctsd* knockout mice led to increased lifespan of around 2 months of age [100]. Not only was the brain pathology rescued, but also the visceral abnormalities were prevented by the brain-directed gene therapy. However, the mice then showed recurrent lethal visceral pathology at around 2 months, without development of brain pathology. The authors also combined brain and peripheral treatment, which further prolonged the lifespan by another 2–4 months [95]. This study suggests vital roles of CTSD in the periphery, and again, calls into question whether other NCL forms would affect peripheral organs especially once lifespan is prolonged.

8. CLN11 disease

CLN11 disease is an adult onset disease caused by homozygous or compound heterozygous mutations in the *GRN* gene (Table 1). Heterozygous mutations alone cause a frontotemporal lobe dementia [106,107]. CLN11 gene therapy has only been studied pre-clinically very recently on the *Grn* knockout mice (Table 3). The AAV2/1 vectors carrying mouse *Grn* gene driven by the CBA promoter were injected to the medial prefrontal cortex of the *Grn* knockout mice at 10–12 months of age (after disease onset) [108]. Improvement of pathology was observed in various brain regions, despite a very limited transduction area [108]. However, another study that used intracerebroventricular AAV9.CMV.hGRN vectors on the same mouse model reported that *GRN* overexpression caused severe hippocampal neurodegeneration, which was consistently observed over 4 time points (1, 3, 6 and 9 months post-injection) [109]. An ependymal-targeting serotype AAV4 vector carrying the *GRN* gene was also tested but caused T cell infiltration and damage of the ventricular system, suggesting that the brain toxicity was not due to the AAV serotype. The authors also suggested that the hippocampal damage was not simply caused by injection of viral vectors, as no toxicity was observed in the AAV9.*eGFP* or AAV4.*eGFP* treated mice. So, it might be a direct adverse effect of *GRN* overexpression and/or the corresponding adaptive immune response, as the hippocampal neurodegeneration was preceded by marked infiltration of T cells. Such adverse effect was not observed in the study by Arrant et al. [108], discussed above. In that study, although a strong immune response was induced post-injection in the brain parenchyma around the injection site, no adverse functional effects were observed [108]. In addition, the injection route (intra-parenchymal [108] *vs.* ICV [109]), the vector dosage (7.36e + 8 vg [108] *vs.* 5e + 10 vg [109]) and the vector (AAV2/1 [108] *vs.* AAV9 [109]) are different between these two studies. Therefore, further study is still needed to evaluate the safety of GRN overexpression and gene therapy for CLN11 disease.

9. Discussion

This review presents an updated concise overview of both pre-clinical and clinical gene therapy studies for NCLs. There has been an international effort to develop gene therapy for NCLs over the past 15 years. Theoretically, the forms of NCLs, such as CLN2, that involve a soluble enzyme that can be secreted from one transduced cell and taken up and cross-correct another cell, is an easier target for gene therapy approaches. However, this has not deterred investigations into the other forms of NCLs involving integral membrane bound proteins, such as CLN6 disease and subsequent clinical trials. This has been led by promising pre-clinical studies in both small and large animal models. It is too early to objectively assess any clinical benefit from these trials in the absence of published data.

Various gene therapy studies, both within the NCL field but also more generally within neurodegenerative disorders, have highlighted the critical aspect of route of administration of the therapeutic vector and outstanding questions. Given the life-limiting neurodegeneration in the brain, the rationale taken by a number of pre-clinical and clinical studies to administer vector into the cerebrospinal fluid is understandable. This also uses the cerebrospinal fluid as a conduit through which broader biodistribution could be achieved and is important in those conditions where brain pathology is widespread and presents in anatomically distal regions. There are many unanswered questions. Do numerous intraparenchymal administrations have the ability to realistically cover the same brain volume and how many would be required? Furthermore, is there enough distribution of vector from the CSF into the periphery to address the visceral pathology that has been described in this review and numerous other studies? An example of this situation is the CLN2 canine model treated with CNS-targeting gene therapy, which developed visceral pathology once lifespan was extended [57]. The intravenous route of administration using a vector such as AAV9 that crosses the blood-brain barrier or HSC gene therapy could certainly address the peripheral pathology but do these routes provide enough vector or protein, respectively, to the brain compared to direct administration into the CNS? A dual vector administration into the periphery and CNS is a compromise that could provide a robust systemic approach but this needs to be tempered against immune responses to such high doses of vector and the ability to cost-effectively manufacture the required material. A further consideration is, when treating the brain, should we also be treating the eye? Vision impairment and retinal pathology are important features for all NCLs. This could potentially provide both life-saving and quality-of-life preserving benefits for patients.

To date, various AAV serotypes have been evaluated in pre-clinical NCL gene therapy studies (Table 3). Furthermore, AAV capsid modification to alter the viral tropism is a major area of interest in the gene therapy research field. By capsid shuffling, chemical modification, peptide inserts, *etc.*, the tropism of the AAV capsid can be changed or enhanced, which can enhance CNS-targeting gene transfer. An example of this in the gene therapy study for NCLs is the use of an epitope-modified AAV in the CLN2 mouse model, which provides promising therapeutic effects [61]. However, AAV tropism differs between species. A novel AAV capsid with specific tropism needs to be evaluated in higher species such as non-human primates before clinical use.

In conclusion, significant progress has been made in gene therapy studies for NCLs. The availability and continued improvement in animal models for NCLs provide useful tools for the pre-clinical studies of gene therapy, which has provided promising evidence for clinical trials. New questions are arising and need to be addressed with further research. However, these gene therapy clinical trials offer hope to NCL patients and have the potential to be life-saving or quality of life enhancing treatments.

CRediT authorship contribution statement

Wenfei Liu:Conceptualization, Writing - original draft, Writing - review & editing.**Sophia-Martha kleine-Holthaus**:Writing - original draft.**Saul Herranz-Martin**:Writing - original draft.**Mikel Aristorena**:Writing - original draft.**Sara E. Mole**:Writing - original draft, Writing - review & editing.**Alexander J. Smith**:Writing - original draft, Writing - review & editing.**Robin R. Ali**:Writing - original

draft, Writing - review & editing.**Ahad A. Rahim:**Project administration, Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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