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Therapeutic landscape for Batten disease: current treatments and future prospects

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Abstract

Batten disease (also known as neuronal ceroid lipofuscinoses) constitutes a family of devastating lysosomal storage disorders that collectively represent the most common inherited paediatric neurodegenerative disorders worldwide. Batten disease can result from mutations in 1 of 13 genes. These mutations lead to a group of diseases with loosely overlapping symptoms and pathology. Phenotypically, patients with Batten disease have visual impairment and blindness, cognitive and motor decline, seizures and premature death. Pathologically, Batten disease is characterized by lysosomal accumulation of autofluorescent storage material, glial reactivity and neuronal loss. Substantial progress has been made towards the development of effective therapies and treatments for the multiple forms of Batten disease. In 2017, cerliponase alfa (Brineura), a tripeptidyl peptidase enzyme replacement therapy, became the first globally approved treatment for CLN2 Batten disease. Here, we provide an overview of the promising therapeutic avenues for Batten disease, highlighting current FDA-approved clinical trials and prospective future treatments.

Batten disease is a family of primarily autosomal recessive, progressive neuropaediatric disorders, also known as neuronal ceroid lipofuscinoses (NCLs), characterized by seizures and visual, cognitive and motor decline, ending in premature death. Batten disease is caused by mutations in 1 of 13 different genes[1,2]. The worldwide prevalence of Batten disease is ~1 in 100,000 live births[3–5], and until the past few years, no effective treatments had been available to halt progression of these diseases. Therapy development for Batten disease has been limited because the function of a number of the disease-associated proteins is only partially understood. In 2017, the FDA approved an enzyme replacement therapy (ERT)

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Author contributions

The authors contributed equally to all aspects of the article.

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called cerliponase alfa (Brineura; BioMarin Pharmaceutical), the first treatment to delay the progression of CLN2 Batten disease. In parallel with this momentous achievement, a number of research teams are using a multitude of therapeutic modalities to accelerate the development of novel treatments for other forms of Batten disease at an unprecedented pace. Here, we provide an overview of Batten disease, including the unique challenges faced by researchers studying this disease and the innovative strategies that they are pursuing to reshape the treatment landscape for these devastating diseases.

Classification of the NCLs

The first reported description of Batten disease was by Otto Christian Stengel in 1826. He described a case of progressive dementia and blindness in four siblings[6]. This initial report was followed by similar reports by Frederick Batten in 1903 (refs[7,8]). In 1969, the term NCL was coined on the basis of the ultrastructural pattern of accumulated lipofuscin or ceroid[1] — a feature that helped to distinguish this group of diseases from similar neurological disorders. Before the discovery of mutated genes in NCLs, patients were classified by a combination of age of onset and ultrastructural patterns of these deposits[9,10]. The disease was first classified as infantile onset (with granular deposits[11]), late-infantile onset (with curvilinear profiles or rectilinear complex[12]), juvenile onset (with fingerprint profiles[13]) or adult onset (with granular deposits[14]). Additionally, an ultra-rare congenital NCL (with granular deposits) was identified[15–23]. Several cases described over the past decade do not follow these classic pathology-based classifications (for example, patients with *TPP1* mutations who do not have onset until their early teens or with *CLN6* mutations that result in disease onset in the late teen years). In addition, several genes have been identified in which mutations lead to the accumulation of autofluorescent storage material (ASM), and the associated conditions have been grouped as Batten disease. Thus, the field has slowly transitioned to a nomenclature that reflects genetic mutation rather than pathology.

The first genes associated with Batten disease were discovered in 1995 through exhaustive genetic linkage methods[24,25]. These findings opened the door for genetic characterization and classification of individual forms of the disease. Improvements in genetic sequencing technologies now enable Batten disease to be delineated according to mutations in 1 of 13 different genes[26] (Table 1). In 2012, an updated classification system was proposed to provide thorough characterization of patients' genetic background, taking into account biochemical and clinical phenotypes (reviewed previously[27]). In the proposed classification, the disorder classification has been simplified and codified numerically according to the affected gene (for instance, CLN1 Batten disease).

Clinical diagnosis and disease progression

The diagnosis of Batten disease is based on a combination of clinical signs and symptoms, ophthalmological evaluations, EEG and brain MRI and is subsequently confirmed with genetic and biochemical tests[2,28,29]. In developing countries, where access to neurophysiology, imaging and genetic testing is limited, cellular pathology and electroretinograms continue to be used as diagnostic tools. The clinical features historically used to identify Batten disease were the result of a compilation of case reports, and natural

history reports have continued to inform disease characterization and clinical trial preparation[8,30–34]. In the clinical setting, age and onset of symptoms still play a key part in suspicion of Batten disease and eventually in pursuit of confirmatory genetic testing for the disease. Common clinical hallmarks of Batten disease include visual impairment, inability to achieve normal developmental milestones and/or developmental regression, behavioural problems, progressive cerebral atrophy, seizures, cognitive decline and dementia[10,19,32,35–38]. However, the order and frequency in which these symptoms present vary between the different subtypes and between the different variants for each genetic mutation. Although an extensive clinical review is out of the scope of this paper, we briefly discuss genotype–phenotype correlations of the most common neuropaediatric diseases. Clinical generalities for all subtypes of Batten disease are included in Table 1.

Common subtypes of Batten disease

CLN1.—Inheritance of CLN1 Batten disease is autosomal recessive. The disease is caused by mutations in palmitoyl protein thioesterase (encoded by *PPT1*) a lysosomal enzyme involved in the removal of palmitate residues from proteins. PPT1 is also associated with important cellular pathways, including synaptogenesis and synaptic maintenance, endosomal trafficking and lipid metabolism[39–45]. Classic onset of CLN1 disease is in the first year of life, with irritability, developmental arrest and rapid regression, deceleration of head circumference growth, hypotonia, myoclonic seizures and progressive vision loss with optic nerve atrophy. In some variants of CLN1 disease, the clinical presentation mimics CLN3 disease, with slower progression and less severe seizures than in typical CLN1 disease. This variant is probably associated with some residual activity of PPT1 that is sufficient to cause a protracted disease course but not enough to prevent disease progression. With regards to genotype–phenotype correlations, severe forms of the disease are associated with Arg151X homozygous mutations, whereas Thr75Pro substitution is associated with a later onset and more protracted clinical course than other *CLN1* mutations[46,47].

CLN2.—Inheritance of CLN2 Batten disease is autosomal recessive, and affected patients have mutations in the lysosomal enzyme tripeptidyl peptidase (encoded by *TPP1*). The proposed mechanism of action involves the removal of tripeptides from the amino terminus of small polypeptides. Classic clinical presentation includes acute onset of myoclonic seizures (usually refractory to medication), ataxia, developmental arrest and regression, central hypotonia with appendicular spasticity and rapidly progressing motor decline. Similar to CLN1 disease, residual TPP1 activity is associated with a protracted disease course, as patients who retain small amounts of active TPP1 demonstrate slow disease progression[48]. Although these protracted cases are rare globally, they occur in ~50% of affected individuals in the South American population[48,49]. Additionally, mutations in *TPP1* have been described in a subgroup of patients with spinocerebellar ataxia 7, which further suggests that residual activity is associated with less severe or atypical forms of the disease[50,51].

CLN3.—Inheritance of CLN3 Batten disease is autosomal recessive, and the disease is caused by mutations in battenin (encoded by *CLN3*), a ubiquitously expressed protein of unknown function that is associated with cellular homeostasis and neuronal survival.

Patients usually present with central vision loss followed by behavioural and cognitive problems, motor decline, parkinsonism, speech apraxia with echolalia and seizures. Most of the patients harbour a 966 bp deletion in *CLN3*, and individuals with protracted disease have been reported, all of whom were compound heterozygous, with some lacking the most common mutation[52]. As with CLN1 and CLN2 disease, additional rare cases of *CLN3* mutations have been reported that lead to late-onset (~20–40 years of age) nonsyndromic retinal degeneration[53], adding to the clear genotype–phenotype correlations of these diseases.

CLN5.—Inheritance of CLN5 disease is autosomal recessive and is caused by mutations in ceroid lipofuscinosis neuronal protein 5 (encoded by *CLN5*), a transmembrane protein of unclear function. Most cases of CLN5 disease have been described in patients of Finnish descent, but mutations have been identified in patients with diverse ethnic backgrounds[54–57]. The most common clinical features include intellectual disability, ataxia and myoclonic epilepsy, and the classic form has an age of onset between 4 and 7 years. Similarly to other Batten disease forms, variants with late onset and/or mild symptoms have been reported[58].

CLN6.—The CLN6 disease subtype was initially described in a large cohort of patients from Costa Rica, where this form is one of the most common causes of Batten disease in the country. Nevertheless, patients with CLN6 disease have been identified from across a broad range of ethnic backgrounds[52,59]. CLN6 disease is caused by mutations in ceroid lipofuscinosis neuronal protein 6 (encoded by *CLN6*), a transmembrane protein of unknown function, and is inherited in an autosomal recessive manner. Symptoms include early-onset seizures, motor decline and ataxia, halt in developmental milestones and, subsequently, developmental regression and progressive cognitive decline and speech problems. Classic forms of CLN6 disease have an onset of symptoms between 3 and 5 years of age, and some variants are associated with a protracted disease course with slow progression. Additionally, a rare form of adult-onset CLN6 disease, known as Kufs disease, exists in both autosomal recessive and dominant forms and manifests at around age 30 years. This variant might have therapeutic implications, as it might be amenable to pre-symptomatic treatments that would be otherwise impossible in paediatric-onset forms of the disease without prenatal genetic diagnosis[14,60].

Diagnosis

Many neurodegenerative diseases of childhood share similar symptoms, so delayed diagnosis of Batten disease is not uncommon[61]. Definitive diagnosis can be challenging in infants and toddlers, in whom thorough neurological and ophthalmological evaluations require a skilled and knowledgeable professional. Batten disease presents after a period of apparently normal development, despite the lack of a functional protein that is important for brain function, and so one must conclude that a small therapeutic window exists where successful interventions can halt and/or prevent the progression of the disease. Consequently, early diagnosis is crucial for optimal therapeutic results, and prospective trials must include patients who are only mildly affected by disease. In this respect, the clinician must be familiar with the clinical features of the disease and suspect the diagnosis in order to pursue confirmatory testing as quickly as possible.

Microscopic, biochemical and genetic assays

Conventional diagnosis of Batten disease phenotypes had been based on microscopic analysis of storage deposits. However, genetic testing and enzyme activity assays are now standard of care. These approaches are readily available in most developed countries and can be conducted reliably prenatally with amniotic fluid or fetal cells[23,24,38,62–65]. In countries where genetic and biochemical testing is not readily available, skin biopsy samples can be collected, and accumulation of lipopigments, a pathological hallmark of these disorders, can be evaluated[38,66–70]. Electron microscopic analysis of the ultrastructural patterns of cellular deposits helps to delineate patients into possible subtypes of Batten disease. Lipopigment morphotypes tend to correlate strongly with genotype[37], but genotype does not always align with the clinical presentation of the disease. Thus, storage deposits can be used as confirmation of Batten disease subtype rather than as a strictly diagnostic tool, with different morphotypes indicative of different forms of the disease[38,71] (summarized in Table 1). Additionally, patients with CLN3 Batten disease have vacuolated lymphocytes; this feature can be assessed by regular blood smear and can aid differential diagnosis of patients[72,73].

Biochemical enzyme activity assays of three lysosomal enzymes that are mutated in various forms of the disease (PPT1, TPP1 and cathepsin D (encoded by *CTSD*)) are conclusive methods for diagnosis of CLN1, CLN2 and CLN10 Batten disease, respectively[23,74–77]. For PPT1 assays, patient samples — including fibroblasts, leukocytes, amniocytes, dried blood spots and chorionic villi — are mixed with a synthetic substrate that is hydrolysed by active PPT1 enzyme to release a detectable fluorophore[76,77]. Absence of the fluorophore confirms CLN1 disease. Similarly, TPP1 and CTSD activity assays use fluorogenic Ala–Ala–Phe-coupled and haemoglobin-coupled synthetic substrates, respectively, in which the active enzyme of interest cleaves the substrate for fluorophore activation[78–80]. Each of these assays provides a rapid and reliable tool to aid clinicians in delineation between prospective disorders during initial diagnosis.

Technological advances in genomic sequencing make whole-exome, whole-genome or direct Sanger sequencing the most definitive analytical tools to precisely identify patient mutations[29,81,82]. These methods are particularly helpful in patients with clinical variants and/or patients with atypical or novel mutations. The vast differences in age of onset, clinical presentations, severity and disease course of Batten disease mean that genetic testing remains one of the most informative tools that clinicians and scientists can use to determine specific genetic mutations that might result in protein dysfunction. Currently, clinicians are primarily using commercially available gene panels or whole-exome sequencing to diagnose patients with Batten disease. A mutation database now exists that catalogues all the known variant mutations of Batten disease genes, consisting of ~446 disease-causing mutations[81]. Continual collaboration between clinicians and investigators is essential to reach prompt diagnoses for patients affected with these devastating diseases.

Neuropathology

Several pathological hallmarks exist for Batten disease, and these changes are well characterized in human tissues and animal models (Tables 1,2). Massive neuronal loss and accumulation of intracellular ASM are predominant features in all patients with Batten

disease. Cortical, subcortical, cerebellar, brainstem and spinal cord neurons are affected by pathology to varying degrees depending on the disease variant. Cortical layer-specific loss of neurons has been described in layers II and V in CLN2, CLN3 and CLN5 disease[83–85], layers II and III in CLN4 disease[85], the occipital lobe and layer V in CLN6 disease[85] and complete disorganization of neurons in CLN10 disease[15,20]. Hippocampal neuron degeneration and microglial activation occur selectively in the CA2–CA4 regions, whereas the CA1 region is seemingly spared[85–87]. Cortical and hippocampal neuron loss is accompanied by loss of Purkinje and granular cells in the cerebellum and dentate nucleus, extreme glial activation, severe astrocytosis and demyelination of white matter[1,15,17,20,21,85,88]. Visual problems generally comprise one or more of the following: retinal atrophy, photoreceptor death, gliosis, bull's eye maculopathy, disc atrophy, peripheral pigmentary changes and attenuation of retinal vasculature[12,85,89–92].

Advances in therapy development

Although little is known about the cellular function of many of the CLN proteins (reviewed previously[93]), robust animal models that effectively recapitulate features of human disease (Table 2) have provided an improved understanding of the pathology and disease hallmarks of Batten disease that has accelerated therapeutic development. Many different tailored mouse models have been engineered to match individual, uncommon mutations from patients to enable specific therapies to be tested. Large, multi-laboratory collaborations among the Batten disease research community have also substantially increased the rate at which novel treatments that slow or halt the rapid progression of Batten disease are being developed and tested. Additionally, researchers and clinicians have teamed up to develop a number of much needed tools to monitor patients as the clinical phase of drug discovery is initiated (box 1). Together with cerliponase alfa, these advances have enabled numerous promising therapies to rapidly enter preclinical and clinical testing phases for multiple Batten disease subtypes. We highlight a number of these studies here and consider their limitations and therapeutic challenges.

Use of animal models in Batten disease

Animal models of Batten disease enable the genetic, molecular, biochemical and metabolic mechanisms that lead to the rapid neurodegeneration observed in patients to be studied on a substantially abbreviated timescale. Animal models now exist for nearly every form of Batten disease (a comprehensive list of these models is reviewed elsewhere[94]). In the past few years, these models have been key contributors to preclinical testing of the safety and efficacy of prospective therapies and, in some cases, have helped researchers to tailor therapies to individual mutations (Table 2). In this respect, mouse models have been an integral part of Batten disease research. However, neurodevelopmental, neuroanatomical and mechanistic differences between mice and humans present challenges for translation and are apparent in the phenotypic presentation of Batten disease mouse models (reviewed previously[95,96]). Specifically, disease presentation varies depending on strain in several Batten disease mouse models, retinal degeneration does not occur or is limited in several models, and most models show delayed or reduced mortality compared with their human counterparts[97] (reviewed previously[98]). Perhaps as a consequence of these differences,

several clinical trials have shown that therapies that showed promise in these mouse models lacked efficacy in patients (although they have generally been safe and well tolerated)[99–101].

Large animal models resemble humans more closely than mouse models do in terms of anatomy, physiology, size, lifespan, biochemistry and genetics, and bridge the substantial gap between the current Batten disease mouse models and the clinic (reviewed previously[102]). A variety of models have been developed or discovered in sheep, dogs and pigs, and a naturally occurring nonhuman primate model of CLN7 Batten disease was also reported in the past year[103–108]. Although each of these models has clear limitations with regards to translation to the clinic — including size, cost and unavoidable anatomical and physiological differences — each of these species has the potential to improve the accuracy of not only models of Batten disease but also models of therapeutic delivery mechanisms, pharmacodynamics and toxicology[109–112]. Swine models of Batten disease might prove particularly insightful, given the similarities in pig and human brain development, structure and size[113,114]. Indeed, swine models of human diseases such as ataxia telangiectasia[115], cystic fibrosis[116,117] and neurofibromatosis type 1 (ref.[118]) have been very useful in recapitulating disease hallmarks in instances where mouse models have failed.

Enzyme replacement therapy

ERT is a treatment strategy for enzyme deficiencies that introduces purified recombinant enzymes via intravenous, intracerebroventricular or intrathecal injection. The injected enzyme is then delivered to the correct cellular compartment via receptor-mediated uptake. Four of the Batten disease subtypes result from deficiencies in soluble lysosomal enzymes: CLN1 (PPT1), CLN2 (TPP1), CLN10 (CTSD) and CLN13 (cathepsin F (CTSF))[81,119]. Preclinical studies on the efficacy of recombinant human PPT1 ERT indicated that both intravenous and intrathecal delivery systems were well tolerated in *Ppt1*$^{-/-}$ mice and reduced many of the pathological hallmarks of the disease, including ASM, astrocytosis and glial activation[120–123]. In vitro experiments have also tested potential ERT of a recombinant human TPP1 (rhTPP1) proenzyme in human TPP1-deficient fibroblasts. The proenzyme is not enzymatically active until acidification autocatalytically converts it to the mature form[124]. This process requires efficient trafficking and targeting of the enzyme to the lysosomal compartment of recipient cells. Trafficking of lysosomal hydrolases, including TPP1, requires mannose-6-phosphate post-translational modification for proper endocytosis and targeting of the proteins to the lysosome[124,125] (fig. 1). rhTPP1 retains mannose-6-phosphate post-translational modifications, which results in receptor-mediated endocytosis of the enzyme by the mannose-6-phosphate receptor, trafficking to the lysosomal compartment, restoration of TPP1 activity and reduction in ASM accumulation in fibroblasts[124]. Successful treatment of patients with Batten disease would require efficient targeting of ERTs to the CNS, which necessitates that the protein bypasses the blood–brain barrier (BBB). Consequently, intravenous administration of rhTPP1 is unlikely to be efficacious. Permeabilization of the BBB is possible[126–128], but this process can further exacerbate neuronal damage[129,130] and therefore is not ideal for treatment in all patients. In initial safety and efficacy tests of rhTPP1 delivery in mouse and dog models of CLN2 disease, recombinant enzyme was delivered through catheters implanted in the lateral ventricle (intracerebroventricular) or subarachnoid space (intrathecal) that remained intact

during the duration of the studies[125,131]. This delivery method resulted in widespread diffusion of rhTPP1 in both hemispheres of the brain and significant reduction in the region-specific neuronal loss, ASM, reactive astrocytosis and tremors associated with CLN2 Batten disease progression[125,131]. Additionally, rhTPP1 treatment preserved cognitive function and significantly extended the lifespan of CLN2 model animals in a dose-dependent manner.

On the basis of these preclinical results, BioMarin Pharmaceutical manufactured an rhTPP1 enzyme, cerliponase alfa (also known as BMN 190 or Brineura), and evaluated its safety and efficacy for treatment of patients with CLN2 Batten disease in a phase I/II study[132], the results of which were published in 2018. In the initial trial, 24 patients between the ages of 3 and 16 years with CLN2 Batten disease were enrolled[133]. Three multicentre, multi-national trials are currently underway[134–136]. Patient inclusion criteria for the initial 48-week open-label dose-escalation study were as follows: ≥3 years of age at enrolment; diagnosis of CLN2 Batten disease by TPP1 enzyme activity in leukocytes or by molecular analysis identifying two known pathogenic mutations; and a two-domain score of 3–6 on the motor–gait and language domains of the Hamburg Scale[133]. Exclusion criteria included previous receipt of stem cell therapy, gene therapy or ERT for CLN2 disease; diagnosis of additional neurological disease; contraindications for neurosurgery or MRI; an episode of generalized motor status epilepticus or severe infection within 4 weeks of the first infusion; presence of ventricular abnormality or shunt; and known hypersensitivity to any components of cerliponase alfa.

Baseline clinical scores (including both the Weill Cornell CNS scale[137] and the Hamburg CLN2 scale[30] (NCL-2 rating scales), which quantify seizures, loss of language, motor and visual function), vital signs and EEG, electrocardiography and MRI findings were recorded before surgical implantation of the intracerebroventricular reservoir and cannula in the lateral ventricle of the right hemisphere. Implantation was confirmed by MRI. Blood and cerebrospinal fluid (CSF) were also sampled to monitor potential biomarkers, immunogenicity and pharmacokinetics during the study. All patients received cerliponase alfa at the time of surgery or within 14 days after surgery and every other week thereafter. Infusions were administered at 2.5 ml/h over 4 h, followed by electrolyte infusion. Patients 1–9 were assigned to three cohorts of three patients, who each received an initial dose of 30, 100 or 300 mg. For the dose-escalation period, each initial dose was administered for 4 weeks before increasing to the subsequent dosing schedule. After the escalation period, all participants received a stable dose of 300 mg cerliponase alfa every other week for at least 48 weeks. Of the 24 patients enrolled in the initial trial, 23 are enrolled in the ongoing long-term extension study[135] for continued treatment and monitoring for 240 weeks.

Efficacy of the ERT in patients was monitored with the NCL-2 rating scales for motor–language scores and total scores in four domains — motor skills, language, vision and seizures[133] — and compared with natural history data from 42 patients from two CLN2 Batten disease registries (Weill Cornell CNS scale[137] and Hamburg CLN2 scale[30]). Rates of decline from baseline in the motor–language score were calculated over the 48-week and 96-week periods[133]. The scoring for motor and language function consisted of a score of 0–3 for each domain, for a total score of 6. A score of 3 represented normal gait and intelligible language with no decline noted. A 1-point decline in the motor score indicated the ability to

walk with obvious instability and possible falls. A 2-point decline corresponded to the requirement for assistance to walk or having the ability to only crawl, and a score of 0 represented loss of the ability to walk or crawl. A 1-point decline in the language domain score indicated recognizable abnormalities in speech, a 2-point decline represented language that was difficult to understand with little ability to formulate intelligible words, and a score of 0 corresponded to loss of vocalizations and no intelligible words. Secondary efficacy parameters were based on brain atrophy (grey matter volumes), as measured with high-resolution T1-weighted MRI, and changes after treatment were descriptively summarized. Primary efficacy changes in treated patients were compared with matched patients in the historical control group that had the closest values in baseline scores, age and genotype. Safety analysis consisted of reporting of any adverse events, summarized by system organ class, preferred medical term, relationship to treatment and severity.

ERT resulted in substantial delay of motor, language and visual decline, as evidenced by stabilization of NCL-2 rating scores and substantial reduction in cortical volume loss. Historical control patients experienced a mean (± s.d.) adjusted rate of decline in motor–language scores of 2.06 ± 0.15 points per 48-week period, whereas the treated patients never reached a 2-point drop in motor–language scores and averaged declines of 0.38 ± 0.10 points over the same period[133]. Direct comparison of 1:1 matched pairs among the treated and historical groups revealed a mean motor–language score decrease of 0.20 ± 0.67 and 0.50 ± 0.71 points for the treated group compared with 1.90 ± 1.23 and 2.80 ± 1.10 points for historical controls at 48 weeks and 96 weeks of treatment, respectively[133]. Additionally, two treated patients who had perfect motor–language scores at the start of the study did not experience a single-point decline at the conclusion of 96 weeks. Total four-domain score declines for treated patients were 0.30 ± 1.70 and 0.40 ± 2.08 compared with 2.80 ± 2.04 and 4.30 ± 2.26 for historical controls after 48 weeks and 96 weeks of treatment, respectively[133]. The importance of this finding is emphasized if one considers that small declines on the NCL-2 rating scale (a simple 0–3 score system) can represent the difference between walking or being wheelchair bound. Grey matter volumes of treated patients decreased by 6.7% on average; however, volumetric changes were not recorded for historical controls. Nevertheless, this value is much lower than that reported from separate studies, which indicate an average loss of cortical volume of ~15–20% annually for patients with untreated CLN2 Batten disease[138].

Gene therapy

Adeno-associated virus (AAV)-mediated gene therapy is a promising option for the treatment of neurodegenerative diseases and lysosomal storage disorders and is effective in several models of Batten disease. AAV-mediated gene therapy has been shown to be safe and effective in several clinical trials for lysosomal storage disorders, including Pompe disease and mucopolysaccharidoses[139–142] (reviewed previously[143]). Previous studies have also shown that reintroduction of a lysosomal enzyme via gene therapy can rescue enzyme activity systemically and in the CNS. In 2018, Abeona Therapeutics reported that, in patients with mucopolysaccharidosis type IIIA (a lysosomal storage disorder associated with mutations in the lysosomal enzyme SGSH), a single intravenous dose of self-complementary AAV9 (scAAV9) containing human SGSH (hSGSH) was well tolerated, crossed the BBB,

increased SGSH enzyme activity, reduced accumulation of heparin sulfate in CSF and urine and improved cognition[143]. To date, nearly 40 clinical trials have been listed on the NIH online clinical trial registry that are using various serotypes of AAV to treat a variety of neurodegenerative diseases and lysosomal storage disorders, including Parkinson disease (PD), Leber hereditary optic neuropathy, Pompe disease, mucopolysaccharidosis types I, II, IIIa, IIIb and VI, CLN6 Batten disease, CLN2 Batten disease, spinal muscular atrophy, Alzheimer disease (AD) and Charcot–Marie–Tooth neuropathy type 1a.

AAV carries single-stranded DNA and naturally infects humans. Twelve AAV serotypes and >108 serovars exist, each differing in its antigenicity and tropism (reviewed previously[144,145]). Successful infection, transduction and biodistribution of the AAV for therapy depend on a number of factors, including the route of administration and the specific tropism of the different serotypes. Efficiency of gene cassette expression can be increased by using scAAV vectors, which eliminates the need for double-stranded DNA synthesis at the cost of a reduction in the capacity of the gene expression cassette. When targeting AAVs to the CNS, it is important to consider not only the dose, route, tropism and targeting of cells outside the CNS but also the potential for immune response to the viral capsid or transgene product. AAV exposure in humans is a common occurrence and results in production of neutralizing antibodies that can negatively affect AAV transduction and gene transfer. Thus, patients need to be monitored for the presence of antibodies against AAV or the transgene, and in cases where they are present, alternative approaches need to be explored.

Several preclinical studies have focused on the use of various AAV serotypes in treatment of various forms of Batten disease. Multiple intracranial injections of AAV2 encoding human PPT1 (hPPT1) have been used to successfully treat a mouse model of CLN1 Batten disease (*Ppt1*$^{-/-}$). AAV2–hPPT1 increased PPT1 enzyme activity and rescued many of the classic Batten disease pathological features, but only in areas near the injection site, probably owing to limited viral spread throughout the CNS[146]. In addition, a greater number of viral injections was associated with a greater rescue of the Batten disease pathology, including a correction of motor and learning behaviours. However, injection number had no effect on median survival[147].

Studies in a canine model of CLN2 Batten disease showed that intraventricular delivery of AAV2 encoding canine TPP1 (caTPP1) into the circulating CSF led to widespread transduction of AAV2–caTPP1 to the ependymal lining of the third and fourth ventricles. TPP1, secreted from the ependymal cells, was subsequently detected in the cortex and cerebellum. This increase in the levels of TPP1 delayed the onset of Batten disease symptoms, reduced glial activation, rescued behavioural phenotypes and increased longevity. Coadministration of mycophenolate mofetil, an inhibitor of B and T lymphocyte proliferation, starting 5 days before AAV2–caTPP1 administration to reduce the number of neutralizing antibodies led to even greater increases in longevity. Although secreted caTPP1 was taken up by neurons, the virus was only able to transduce the ependymal cells rather than spreading throughout the CNS[148].

Although AAV2 has displayed strong local levels of transduction, distribution of AAV2 from the local site of administration has been hindered by its strong heparin sulfate proteoglycan

binding[149]. To rectify this issue, the AAV2 gene expression cassette was combined with capsids from other AAV serotypes. One study used a recombinant AAV1 capsid expressing hTPP1 in an AAV2 gene expression cassette. AAV1–hTTP1 was injected into the striatum, hippocampus deep cerebellar nucleus, motor cortex, thalamus and medulla of 4-week-old pre-symptomatic or 11-week-old post-symptomatic *Cln2* mutant mice. Treatment at both time points restored TPP1 activity to wild-type levels, and mice treated presymptomatically had better pathological outcomes, including reduction in ASM, decreased axon degeneration, improved motor function and increased median lifespan. These data indicate that gene therapy has the potential to delay and prevent Batten disease pathology but not reverse it[150]. Delivery of hTTP1 using AAVrh.10, an AAV serotype derived from rhesus macaques, yielded a higher level of TPP1 activity than AAV2 and had a broader distribution in a mouse model[151,152]. AAVrh.10 carrying human *CLN3* also rescued several phenotypes associated with CLN3 Batten disease in mice, including astrocyte activation but not microglial activation[153].

An AAV2 cassette with an AAV5 capsid (AAV2/5) expressing hPPT1 has been used to rescue phenotypes in *Ppt1*$^{-/-}$ mice. A bilateral intracranial injection into the anterior cortex at postnatal day 1 restored PPT1 enzyme activity to wild-type levels, increased lifespan by 10 weeks, reduced activation of microglia and astrocytes and ameliorated motor deficits for 7 months[154]. In a subsequent study, AAV2/9–hPPT1 was used in the same mouse model and administered via intrathecal injection to the lumbar spinal cord, an intracranial injection to the anterior cortex, hippocampus and cerebellum or a combination of both at postnatal day 1 or 2. Both intrathecal and intracranial injections yielded many improvements in Batten disease pathology, including reduction of ASM, improved motor function, reduced microglial and astrocyte activation and increased median survival. As might be expected, the spinal intrathecal injection had greater local effects in the spinal cord, whereas the intracranial injection had greater effects in the cortex; however, the greatest overall benefits were observed in the animals that received combined intrathecal and intracranial injections, which increased median survival by 6–8 months compared with either injection alone[155].

The population of cells targeted for transduction might also influence the efficacy of viral treatments. One study compared the efficacy of two AAV serotypes to correct Batten disease-related pathologies in the eye. An AAV2/8 virus carrying human *CLN6* delivered intravitreally to *Cln6*^{nclf} mice (an established model of CLN6 disease) was unable to correct photoreceptor loss. However, bipolar cell-specific expression of a modified AAV2/2 serotype 7m8 successfully prevented photoreceptor loss[156].

In other studies, an AAV9 capsid has been combined with the AAV2 inverted terminal repeat (ITR) gene cassette to generate a scAAV9–hCLN3 vector driven by one of two promoters, a *Mecp2* promoter driving low expression or a chicken β-actin (CB) promoter driving high expression. The scAAV9–hCLN3 vector was delivered intravenously into 1-month-old *Cln3*$^{\Delta ex7/8}$ mice (knock-in mice with exons 7 and 8 removed)[157]. The high-expression CB promoter virus resulted in a threefold to eightfold increase in *Cln3* expression compared with the *Mecp2* promoter; however, the increase in levels of CLN3 did not correlate with increased benefit. The low-expression promoter actually corrected more disease pathologies, including motor coordination, reduced astrocytosis, microglial activation and lysosomal

pathology, whereas the CB promoter increased glial activation in the thalamus and failed to rescue motor deficit. However, whether these differing outcomes were due to change in gene expression or the types of cells expressing the scAAV9–hCLN3 was unclear[158].

Preclinical studies show that a single intracerebroventricular injection of scAAV9.cb.hCLN6 in the *Cln6*^{nclf} mouse model and intrathecal injection in non-human primates result in widespread CNS expression of the *CLN6* transcript, including in the eye and optic nerve, and result in substantial reduction of ASM and reactive gliosis[159,160]. On the basis of these data, a phase I/II clinical trial of scAAV9.cb.hCLN6 for treatment of CLN6 Batten disease was initiated[161], and is currently underway. The study involves use of an AAV9 capsid carrying the AAV2 gene cassette with hCLN6 injected intrathecally into the subarachnoid space of the lumbar spine of patients. Using a similar paradigm with a modified lower expression promoter, the same group conducted preclinical studies of scAAV9.hCLN3 in the *Cln3*$^{\Delta ex7/8}$ mouse model and nonhuman primates and reported similar widespread CNS expression and reduction of pathological hallmarks[162]. These observations formed the basis of a recently initiated phase I/IIa clinical trial[163].

Additionally, one clinical trial[164] assessed the efficacy of AAV2 for treatment of CLN2 Batten disease. Twelve intracranial injections of AAV2 encoding hTPP1 were administered to patients in the moderate or severe stages of CLN2 Batten disease, according to the Steinfeld et al. neurological assessment scale[30]. Results indicated that the treatment was well tolerated and that no serious adverse events were attributable to the administration of AAV, and the rate of decline was significantly slowed when compared with natural history studies[165] according to the neurological assessment scale. Two other trials are ongoing[166,167] that use a similar paradigm to the first, with the exception of the use of an AAVrh.10 serotype with the aim to achieve a broader biodistribution of viral transduction[151,153].

Stem cell therapies

Several groups have sought to use stem cell-based therapies to address the visual deficits associated with progression of Batten disease[168]. One such study involved use of a clonal neural stem cell (NSC) line that was transduced with a lentivirus that expressed ciliary neurotrophic factor (CNTF), a cytokine that has been shown to rescue retinal degeneration in various animal models[169,170]. These CTNF-expressing NSCs were injected intravitreally into one eye, and control green fluorescent protein (GFP)-expressing NSCs were injected into the other. The NSCs subsequently attached and formed a cell layer on the lens where they stopped proliferation and preferentially differentiated into CNTF-secreting astrocytes, enabling the consistent secretion of the neuroprotective cytokine. Six weeks after the injection, the retinae injected with CTNF-expressing cells showed increased retinal thickness and increased photoreceptor numbers compared with GFP controls[171]. In another study, bone marrow-derived mesenchymal stem cells (MSCs) were transduced with AAV2–hTPP1 and injected into the eyes in a canine model of CLN2 Batten disease. The injected MSCs remained in the vitreous and could be observed for 9 weeks after injection. Eyes from *PPT1*-null dogs that were not treated with the hTPP1-expressing MSCs began to display retinal lesions at 7 months that progressively worsened, whereas hTPP1-treated dogs

developed no eye lesions and had preserved retinal function as observed by retinal histology and electroretinography[172].

In a phase I dose-escalation trial[173], human CNS-derived stem cells (HuCNS-SCs) that secreted endogenous TPP1 and PTT1 were engrafted into patients with CLN1 or CLN2 Batten disease. Patients were injected with a total of 5×10^8 cells (low dose) or 1×10^9 cells (high dose) at six subcortical sites and in both lateral ventricles. The treatment was well tolerated, with no adverse events that were associated with the course of Batten disease. Post-mortem PCR analysis of samples from two of the patients detected engrafted stem cells 357 days and 918 days after injection, indicating integration and longevity of HuCNS-SCs after engraftment[101].

Small-molecule therapies

Over the past few decades, several pharmaceutical and biological agents (referred to collectively here as small-molecule therapies) have been tested in various models of Batten disease. On the basis of the pathogenesis of Batten disease, preclinical approaches have predominately focused on small molecules that improve lysosomal or autophagic health, serve as immune modulators or neuroprotective agents, or increase transcript or protein abundance.

Pharmacological chaperones and readthrough technologies.—Lysosomal enzymes undergo a careful quality check process. Much of the quality control process is completed in the endoplasmic reticulum, where these enzymes are produced before trafficking to the lysosome, although some evidence supports a Golgi-mediated quality check that involves trafficking of the protein back to the endoplasmic reticulum for degradation[174]. Enzymes that are unstable or improperly folded might not be trafficked to the lysosome, might accumulate inappropriately in other organelles or might be prematurely degraded[175]. As many patients with Batten disease carry missense mutations that can result in enzymes that are present but only partially functional, pharmacological chaperones are a promising therapeutic agent for these individuals[176]. Pharmacological chaperones are small molecules that bind to and stabilize target proteins in the endoplasmic reticulum, enabling them to be properly trafficked to the lysosome and circumvent premature degradation[177,178]. Although a number of chaperones have been tested preclinically in a number of lysosomal storage disorders, only a few of these agents have moved forward to clinical trials[177]. In Batten disease, one study of the efficacy of chaperones in lymphoblast lines from patients with CLN1 disease showed a twofold increase in PPT1 activity[179]. Currently, no other pharmacological chaperones have been tested in Batten disease cell lines or animal models.

Nonsense mutations that yield premature stop codons and truncated protein products or nonsense-mediated decay have been reported in patients with Batten disease[180]. Compounds that increase transcript and/or protein abundance, such as readthrough compounds (compounds that override premature termination codons (PTCs) resulting from nonsense mutations) and antisense oligonucleotides, have been tested with varying success. Ataluren (also known as PTC124) is an orally administered small molecule that prevents premature translation termination at PTCs by interacting with the ribosome and promoting insertion of

near-cognate tRNAs at the nonsense site[181]. Ataluren treatment increased transcript levels in several cell lines from patients with CLN1 Batten disease and in several tissues in mouse models of CLN1 disease but was not able to cross the BBB at appropriate doses. Similarly, gentamicin, an aminoglycoside antibiotic that binds to the aminoacyl-tRNA site of the 30S subunit, successfully increased *PPT1* and *TPP1* transcript levels and enzyme activity in cell lines from patients with CLN1 or CLN2 Batten disease[182,183] but has not been tested in mouse models of Batten disease to date. Antisense oligonucleotides, small modified nucleic acids that bind to target RNA sequences to elicit a specific change in translation, have been used successfully in various genetic diseases[184] (including spinal muscular atrophy) but have yet to be applied to Batten disease.

Autophagy modulators and substrate reduction therapies.—Deficits in autophagy have been implicated in several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), AD and PD[185–187]. In several mouse models of Batten disease, membrane-bound LC3-II (a characteristic marker of autophagic membranes) was shown to be a constituent of storage material pathology, which is suggestive of immature autophagosome formation and improper autophagosome–lysosome fusion[188–190]. Additionally, CLN3 has been found to interact with the autophagic enzymes ATG3 and ATG7, which further implies a role for autophagy in Batten disease pathology[191]. Autophagy modulators have been explored as small-molecule therapeutics for Batten disease. Specifically, small-molecule PPARα agonists, such as fenofibrate, bezafibrate and gemfibrozil, were found to have beneficial effects in lymphoblast lines from patients with CLN3 Batten disease, including mitigation of autophagy deficits[192–194]. The FDA-approved agent gemfibrozil was later shown to have benefits in a mouse model of CLN2 Batten disease, in which it decreased cellular accumulates, improved motor coordination and increased longevity[195]. Mechanistically, PPARα is known to enhance levels of transcription factor EB (TFEB), which subsequently binds to promoters of genes involved in lysosome biogenesis, increasing their expression[196,197]. TFEB translocation to the nucleus can be targeted therapeutically by inhibition of protein kinase B (AKT). Transport of TFEB to the nucleus is regulated by AKT-driven phosphorylation of TFEB, and inhibition of that phosphorylation results in increased nuclear TFEB and activation of the coordinated lysosomal expression and regulation (CLEAR) signalling network. TFEB activation similarly resulted in enhanced clearance of aggregates, improved behaviour and increased longevity in multiple mouse models of Batten disease, which demonstrates the therapeutic potential of targeting this pathway[198]. The therapeutic potential of targeting autophagy and/or TFEB through other pathways such as the PI3K–mTOR pathway or AMP-activated protein kinase remains to be examined in Batten disease[199].

Substrate reduction therapies (SRTs) inhibit the enzymes required for the production of the accumulates that typically aggregate in lysosomal storage disorders. In the context of Batten disease, cysteamine bitartrate (Cystagon; Orphan Europe), an SRT currently used for cystinosis, successfully reduced cysteine thioester accumulates in patients with CLN1 Batten disease, although it did not delay disease progression in the small number of patients observed[200,201]. Further preclinical testing of SRTs is needed to determine the potential of these treatments for patients with Batten disease.

Immune modulators and neuroprotective compounds.—Neuroinflammation is a prominent feature of Batten disease and has been shown to exacerbate neurodegeneration[202,203]. Additionally, patients with CLN3 Batten disease produce autoantibodies against several proteins, including glutamic acid decarboxylase 2 (GAD2, also known as GAD65) and α-fetoprotein, which suggests an autoimmune component to these diseases[119,124,204,205]. Immunotherapies have been explored in a number of other neurodegenerative diseases, including PD, ALS and AD, with preclinical success[206–209]. Surprisingly, even the complete depletion of all microglia in the brain was well tolerated in AD mouse models and reduced plaque pathology and improved cognition (such as that accomplished by PLX5622, an inhibitor of colony-stimulating factor 1 receptor signalling that is required for microglial survival)[210]. Immunomodulation has been broadly studied in Batten disease. Treatment of *Cln3* mutant mice with mycophenolate mofetil improved motor coordination, reduced levels of serum autoantibodies and reduced neuroinflammation[211]. On the basis of these results, a phase II safety trial of mycophenolate mofetil was initiated in 2011 (ref.[99,212]). Although the compound was well tolerated, it was generally ineffective in preventing clinical outcomes in patients with CLN3 disease. However, as the compound was given for only a short time, further study might be warranted to determine the potential of mycophenolate mofetil in a clinical setting[99]. In CLN1 and CLN3 disease mouse models, the FDA-approved small molecules fingolimod (which impairs lymphocyte emigration into the brain via sphingosine-1-phosphate receptor modulation) and teriflunomide (which reduces the proliferation of activated immune cells via pyrimidine nucleotide synthesis inhibition) reduced neuron loss, brain atrophy and retinal thinning[213–216]. Studies of the efficacy of the steroid prednisolone showed that it reduced levels of GAD65 autoantibodies and improved motor symptoms in older patients with CLN3 Batten disease (aged 17 and 18 years) but did not improve motor symptoms or autoantibody levels in younger patients (aged 6–13 years), though the treatment did have a positive effect on these patients' IQs[217]. Additionally, prednisolone produced adverse psychiatric effects and recurrent infections in many patients. However, the efficacy of other steroids is currently being explored in other neurodegenerative diseases, including allopregnanolone in Niemann–Pick disease type C and vamorolone in Duchenne muscular dystrophy[218–220]. Several agents that modulate neuroinflammation indirectly through the regulation of cAMP levels have been screened in preclinical models of Batten disease, including a series of phosphodiesterase 4 inhibitors (rolipram, roflumilast or PF-06266047), all of which had a positive effect on Batten disease-related pathologies and behaviours[221]. Taken together, the findings suggest that immunotherapies have clinical relevance to patients with Batten disease but must be weighed carefully against adverse effects of immune modulation[222].

Lastly, the effects of neuroprotective compounds such as cannabinoids, σ1 receptor agonists, excitotoxicity and oxidative stress reducers, cytoskeletal stabilizers, c-Abl tyrosine kinase inhibitors and anti-apoptotic compounds have been studied broadly in neurodegenerative disorders[223–229]. Excitotoxicity has been of particular interest in Batten disease, as increased AMPA receptor activity has been reported in the cerebellum of *Cln3* mutant mice, and antagonist treatment substantially improved motor coordination in this model[230,231]. Other neuroprotective compounds studied in the context of Batten disease include flupirtine, an anti-apoptotic compound with multiple modes of action that was beneficial in patient cell

lines, and *N*-(tert-butyl)hydroxylamine, an antioxidant that improved motor coordination and survival in *Ppt1* mutant mice[232,233]. To date, clinical trials have not been initiated for any uniquely neuroprotective compounds specifically for any form of Batten disease, but use of these compounds in other neurodegenerative disease could pave the way for future studies.

Combinatorial treatments.—Over the past several decades, it has become increasingly common to target multiple pathologies of the same disease to maximize benefit. In diseases such as Batten disease, in which the genes of interest are expressed across several cell and tissue types, one treatment is unlikely to fend off all clinical presentations. Use of multiple therapies has been shown to improve treatment efficacy in animal models, such as use of teriflunomide with fingolimod in two CLN mouse models, ibuprofen with lamotrigine in *Cln3* mutant mice[216,234,235] and AAV2/5–5-PPT1 and bone marrow transplant in $Ppt1^{-/-}$ mice. Single molecules that target multiple pathologies or use of various routes of administration for the same therapy might also be beneficial. With gene therapy, the field has seen success with combined forebrain and cerebellar delivery of AAV2–PPT1 in $Ppt1^{-/-}$ mice[147], combined intracranial and intrathecal delivery of AAV9 in $Ppt1^{-/-}$ mice and AAV1 and AAV2 delivery across several distinct brain regions[150,155]. Taken together, use of several treatment strategies might offer additional benefits to patients with neurodegenerative disease, but the benefits of this approach must be weighed carefully against the additional adverse effects that combined treatments might bring[236].

Therapeutic challenges and considerations.—Several challenges must be overcome to design a suitable clinical trial in Batten disease, in which patient populations can be small and consequently underpowered, the therapeutic window for treatment can be small or elapsed in some patients and natural history studies can be lacking or incomplete, with the latter issue yielding a lack of reliable, non-invasive outcome measurements of therapeutic efficacy (reviewed previously[237]). Despite the focus of the Batten disease community in the past few years on biomarker discovery in a variety of subtypes, a consistent, robust, non-invasive biomarker has yet to be discovered[238,239]. Additionally, substantial practical challenges exist for patients, clinicians and researchers in that much of the expertise in Batten disease is concentrated in a few facilities, which limits access to clinical information and care[240].

Conclusion

The successful development of treatments for rare disease, including Batten disease, requires the development and validation of an arsenal of tools with which to tackle these debilitating conditions. Over the past two decades, scientists and clinicians within the Batten disease community have worked to ensure that tools are in place to enable progression towards effective treatments at an unprecedented pace. Armed with a comprehensive battery of well-characterized models of many forms of Batten disease, including large and small animal models and a vast bank of patient cell lines (including libraries of patient-induced pluripotent stem cell lines), as well as well-established pathological and behavioural strategies for monitoring disease progression in these models, the preclinical Batten disease research community sits at a turning point. Modern tools for drug discovery, including high-content and high-throughput screening and advances in medical chemistry, enable us to

move agents through (or eliminate ineffective agents from) the drug discovery pipeline much more efficiently than ever before. Growing partnerships with pharmaceutical companies have provided translational scientists with access to libraries of novel and repurposed agents for screening in Batten disease. Globally, Batten disease clinical research teams are working together to ensure that comprehensive natural history studies, patient registries and diagnostic rating scales are in place well before the launch of clinical trials rather than belatedly trying to develop these resources once a therapy is ready to enter a clinical programme. The advances in ERT, gene therapy and pharmaceuticals in Batten disease, in combination with the genomic medicine revolution that biomedical research is entering, will set an unprecedented pace for the speed of development of much needed therapies for Batten disease. Moreover, access to early patient diagnosis and the ever increasing number of clinical trials opening for patients have drawn new scientists with unique skill sets to the field, and the Batten disease research community is becoming a model of how effective, efficient rare disease research can be accomplished by working together.

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Box 1 |

Developing comprehensive tools for studying Batten disease

For >30 years, a number of patient advocacy groups have worked tirelessly with federal, academic and private partners to change the drug development system, which seemingly worked against drug discovery for rare diseases and condemned them to remain essentially orphaned. In 1983, the US Congress passed the Orphan Drug Act, which uses tax credits, grants and extended market exclusivity to incentivize development of treatments for rare diseases. Many countries worldwide followed with similar initiatives. In 2002, the US Rare Disease Act was enacted and strengthened therapy development efforts by establishing the Office of Rare Diseases and allocating increased research funding. Even with these giant strides forward, most rare diseases still have ineffective treatments and cures. In 2016, the US 21st Century Cures Act was enacted to "expedite the discovery, development and delivery of new treatment and cures and maintain America's global status as the leader in biomedical innovation." These combined efforts have enabled the development and marketing of drugs for rare diseases and have increased the number of treatments brought to market from fewer than 10 between 1973 and 1983 to well over 600 to date[241].

However, for many diseases, including Batten disease, the fight is not over. By definition, patients with rare diseases are few. Methodologies for finding patients and tracking natural history as well as standardized disease outcome tools are needed.

Standardized patient rating scale

The University of Rochester Batten Center developed a Unified Batten Disease Rating Scale (UBDRS). The UBDRS initially focused on evaluating and tracking the disease progression of patients with CLN3 Batten disease but subsequently has been developed for use in establishing patient ratings for various forms of Batten disease[8,31,242,243].

Comprehensive natural history studies

Over the past decade, efforts have been made to develop detailed natural histories of individual forms of Batten disease, an essential resource required for successful and efficacious clinical studies[8,32,34]. In the past few years, the DEM-CHILD International NCL Registry was established through a European and US-based consortium to continuously develop and refine patient assessment tools, monitor the prevalence of each form of Batten disease and develop detailed natural history studies that link genetic mutation information with clinical data for all forms of Batten disease[244].

Centralized patient registries

A number of patient advocacy groups, family foundations and academic research teams, including the Batten Disease Support and Research Association, have driven efforts to collate comprehensive registries of patients with Batten disease worldwide. These group registries focus on one form of the disease, for example, the Weill Cornell CNS scale[137] and the Hamburg CLN2 scale[30]. In the past few years, the Coordination of Rare Diseases at Sanford (CoRDS) programme has included development of a centralized international patient registry for all forms of Batten disease with the goal of connecting as many

patients with Batten disease with clinicians and researchers as possible to help advance treatments and cures for these rare diseases[245].

Development and continuous refinement of these tools will ensure that, when therapies do become available, the necessary resources for successful clinical programmes are in place. Moreover, rather than working separately, many of these efforts are coordinated to ensure information from one programme works in concert with that from other efforts.

Key points

- The FDA approval of the enzyme replacement therapy cerliponase alfa (Brineura) for the treatment of CLN2 Batten disease is an important milestone in Batten disease therapy.
- Promising results from preclinical research indicate that gene therapy — particularly approaches that use adeno-associated virus — represents a promising treatment option for patients in the near future.
- Many of the preclinical strategies being explored for the treatment of one form of Batten disease could have applications across multiple subtypes of Batten disease and even other lysosomal storage disorders.
- Investigators now recognize that a single treatment might not be sufficient to halt disease progression and are exploring combinatorial approaches to tackle multiple aspects of Batten disease progression.
- A battery of new preclinical and clinical tools have been developed that facilitate effective therapy development in Batten disease, enabling an unprecedented acceleration in drug discovery for these fatal disorders.

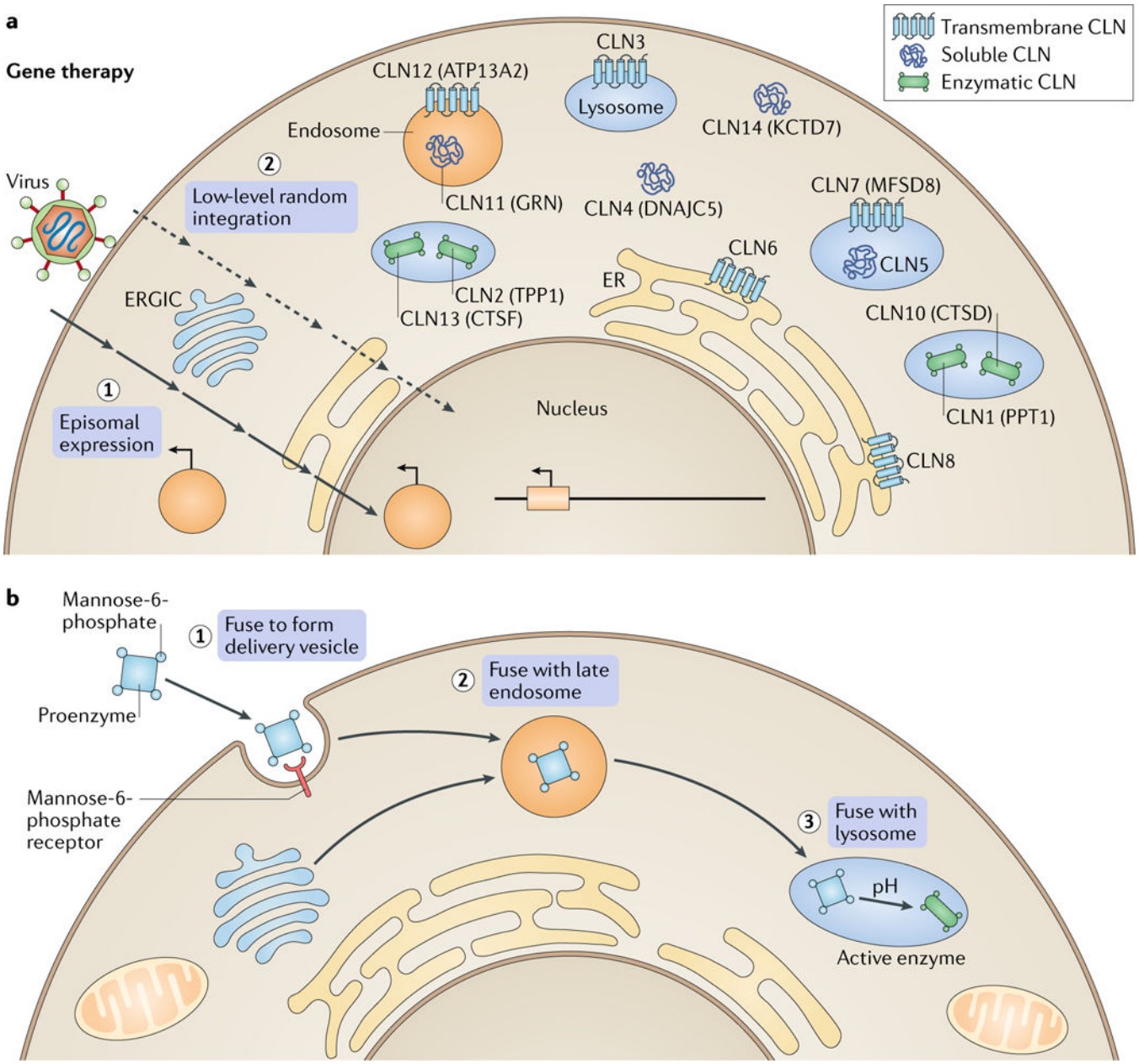

Fig. 1. Gene therapy and enzyme replacement therapy strategies in Batten disease.

a | Gene therapy as a treatment for Batten disease. Viral vectors are being explored to introduce a corrected copy of the genes mutated in Batten disease. Tropism, biodistribution and carrying capacity must be considered in selecting the type or serotype of virus to ensure the most efficient delivery. Modified adeno-associated viruses (AAVs) target expression of the CLN genes to affected cells. Once transduced into the cell, the target transgene is episomally expressed (1) (solid arrows), although limited evidence supports low-level random integration (2) (dashed arrows). The transgene is then translated, and the mature protein is trafficked to its resident location, with careful monitoring after viral transduction to ensure targeting to the correct sites. **b** | Enzyme replacement therapy (ERT) as a treatment for Batten disease. Multiple forms of Batten disease result from mutations in soluble

lysosomal enzymes and thus might be amenable to cross-correction by ERT to partially restore levels of these enzymes in the CNS. This strategy, successfully demonstrated by cerliponase alfa, is currently available for treatment of CLN2 Batten disease. Cerliponase alfa, a recombinant proenzyme containing a mannose-6-phosphate post-translational modification, is delivered intraventricularly to the patient's brain. This proenzyme is targeted to the mannose-6-phosphate receptor on the plasma membrane and endocytosed into the cell (1), where it fuses with the late endosome (2) before being delivered to the lysosome, where the acidic environment autocatalytically converts the enzyme to the mature, active form (3). CLN3, battenin; CLN5, ceroid lipofuscinosis neuronal protein 5; CLN6, ceroid lipofuscinosis neuronal protein 6; CLN8, ceroid lipofuscinosis neuronal protein 8; CTSD, cathepsin D; CTSF, cathepsin F; ER, endoplasmic reticulum; ERGIC, endoplasmic reticulum-Golgi intermediate compartment; PPT1, palmitoyl protein thioesterase; TPP1, tripeptidyl peptidase.

Table 1 |

Batten disease subtypes and their clinical presentation

NCL subtype (affected gene)	Neuroradiological imaging findings[a]	EEG abnormalities	Behavioural tendencies	Visual changes	Microscopic findings	Major clinical manifestations
CLN1 (*PPT1*)[38,71,246–255]	Hyperintense, periventricular high-signal rims of white matter; decreased NAA and increased choline; and severely enlarged lateral ventricles	Loss of sleep spindles at ~2 years; attenuated reaction to passive eye opening and/or closing; background activity disturbances; and reduced amplitude	Irritability and hyperexcitability	Optic atrophy; unrecordable ERG at 4 years; and blindness	GRODs	Motor coordination loss; choreoathetosis; stereotypic movements; myoclonic jerks; decelerated head growth; and death by 10 years of age
CLN2 (*TPP1*)[38,71,243,253,256–259]	Infratentorial atrophy; hypointense thalamic nuclei; reduction in NAA; increased myo-inositol and Glu:Gln ratio in the white matter; and severely enlarged lateral ventricles	Occipital spike in response to slow flash; irregular slow activity; focal spikes; absence of sleep spindles; and large VEPs and SEPs	Behavioural disturbances, Including anxiety and agitation	Progressive vision loss leading to blindness; and diminished ERG	CLPs	Myoclonus; ataxia; motor decline; spasticity; dystonic features; choreoathetosis; hypotonia; seizures; and death in early adolescence
CLN3 (*CLN3*)[35,38,71,253,260–265]	Cerebellar atrophy; enlarged third ventricle and cerebral sulci; and hypointense thalamic nuclei	Progressive background disorganization; and spike-and-slow-wave complexes	Anxiety; aggression; delayed speech; and depression	Progressive loss of vision; and pigmentary retinopathy	FPPs and vacuolated lymphocytes	Seizures; rigidity; hypokinesia; impaired balance; myoclonus; and death in second or third decade
CLN4 (*DNAJC5*)[38,71,253,266,267]	Parieto-occipital cortical atrophy; cerebellar atrophy; hyperintense periventricular areas; and corpus callosum thinning	Slow background; polyphasic spikes; and slow-wave discharges	Inappropriate laughter	No visual impairment	GRODs; CLPs; and FPPs	Myoclonus; grand mal seizures; dementia; ataxia; and facial dyskinesia
CLN5 (*CLN5*)[38,54,55,71,264,268]	Cerebellar atrophy; diminished signal intensity in thalamic nuclei; and increased signal intensity in periventricular white matter and internal capsule	Large VEPs and SEPs; and occipital spikes in response to slow flash	ND	Progressive visual decline leading to blindness; and macular degeneration	GRODs; CLPs; and FPPs	Clumsiness; seizures; dementia; motor coordination loss; myoclonus; and death between 14 and 36 years of age
CLN6 (*CLN6*)[38,71,269]	Deep cortical layer-specific neuron loss; and cerebellar atrophy	Background slowing; and high-amplitude discharges in response to photic stimulation	ND	Visual failure leading to blindness	CLPs; RLC; and FPPs	Motor decline; seizures; dysarthria; and ataxia
CLN7 (*MFSD8*)[38,71]	Cerebellar atrophy; corpus callosum thinning; and hypointense thalamic nuclei	Occipital spikes; and background slowing	Personality changes	Visual failure leading to blindness	CLPs; RLC; and FPPs	Motor decline; seizures; and myoclonus
CLN8 (*CLN8*)[38,71,270–272]	Cerebellar atrophy; corpus callosum thinning; and hyperintensity of white matter	Slow background; components of high amplitude; epileptiform discharges; and abnormal VEPs and SEPs	Irritability; restlessness; and inactivity	Retinopathy; visual decline at around 4–6 years of age; and ERG absent	GRODs; CLPs; and FPPs	Myoclonus; tonic–clonic seizures; motor decline; and progressive dementia
CLN10 (*CTSD*)[15–22,38,71,273,274]	Diminished head growth in utero; myoclonic fetal seizures; enlarged lateral ventricles; hypointense cerebral and cerebellar white matter; and decreased NAA and increase in myo-inositol	Completely depleted EEG pattern	ND	ND	GRODs	Severe respiratory distress at birth; axial and limb hypotonia; extreme microcephaly; overriding sutures; and death within hours after birth
CLN11 (*GRN*)[38,71,275]	Cerebellar atrophy	Polyspike-wave discharges with posterior emphasis; and severe attenuation of rod and cone responses	ND	Progressive vision loss; and retinal dystrophy	FPPs	Myoclonic seizures; cerebellar ataxia; and cognitive decline
CLN12 (*ATP13A2*)[38,66,271–273]	Cortical and subcortical atrophy; and decreased glucose use in grey matter, especially the thalamus and posterior association cortex	ND	Mood disturbances and dysarthric speech	No visual changes	GRODs	Loss of coordination; myoclonus; seizures; spasticity; rigidity; akinesia; and muscular atrophy
CLN13 (*CTSF*)[38,71,276,277]	Cerebellar atrophy; frontal and parietal cortical atrophy; and periventricular hyperintensities	No epileptiform activity	Behaviour and personality Abnormalities and depression	ND	FPPs	Dementia; seizures; motor coordination decline; ataxia; tremor; dysarthria; and hyperreflexia
CLN14 (*KCTD7*)[38,66,276–278]	Cortical and cerebellar atrophy; and corpus callosum thinning	Slow dysrhythmia; multifocal high-amplitude epileptiform discharges; photosensitivity; and occipital spikes	ND	Visual loss; diminished pupillary light reflex; and optic atrophy	GRODs; CLPs; RLC; and FPPs	Motor decline; myoclonic seizures; ataxia; myoclonus; and dysarthria

CLPs, curvilinear profiles; ERG, electroretinogram; FPPs, fingerprint profiles; GRODs, granular deposits; NAA, *N*-acetyl aspartate; NCL, neuronal ceroid lipofuscinose; ND, not determined; RLC, rectilinear complex; SEP, somatosensory evoked potential; VEP, visual evoked potential.

[a]Clinical hallmarks of Batten disease are a combination of retinopathy, dementia, seizures, cerebral atrophy and cognitive dysfunction[10,19,32,35]; presented here are variations depending on the subtype.

Table 2 |

Summary of mouse models of Batten disease used for therapeutic development

Mouse model	Mutation	Selective CNS pathology[a]	Visual phenotype	Behavioural phenotype	Therapeutic testing	Refs
CLN1	*Ppt1*$^{-/-}$	GABAergic neuron loss in cortex, thalamic nuclei and cerebellum; and early neuronal loss in cervical, thoracic ventral horn and lumbar dorsal horn	Vision loss	Seizures and loss of motor coordination; and death at ~6 months	ERT, AAV2, AAV2/5, AAV2/9, SCT, SMT or BMT	121,122,146,147,154,155,179,232,235,278–287
	Cln1^{R151X}	As for *Ppt1*$^{-/-}$	As for *Ppt1*$^{-/-}$	As for *Ppt1*$^{-/-}$	SMT	288,289
CLN2	*Cln2*$^{-/-}$	Disruption of myelin in white matter of corticospinal tracts; mild forebrain atrophy; and Purkinje cell degeneration	ND	Tremors, seizures and loss of motor coordination; and abnormal hunched gait	ERT, AAV1, AAV2, AAV5, AAV8, AAVrh. 10 or SMT	125,149,151,195,290–292
	Cln2^{R208X}	As for *Cln2*$^{-/-}$	ND	As for *Cln2*$^{-/-}$	SMT	293
CLN3	*Cln3*$^{\Delta ex7–8}$	Purkinje cell loss; and GABAergic interneuron loss	Retinal atrophy and altered pupillary light reflex	Motor coordination deficits	AAV2, AAV9 or SMT	157,294–300
	Cln3$^{\Delta ex1–6}$	Neuronal loss in striatum and cerebellum	Dorsal lateral geniculate nuclei degeneration; optic nerve degeneration; and retinal atrophy	Motor coordination deficits	SMT	158,211,231,299,301–305
CLN6	*Cln6*^{nclf}	Decreased cortical and cerebellar glutamine, glutamate and GABA	Retinal atrophy	Hindlimb paresis at ~8 months; memory and learning deficits; and death at 12–15 months	AAV2, AAV9 orSCT	156,171,306–308
CLN8	*Cln8*^{mnd}	Neuronal death in hippocampus and spinal cord; and GABAergic neuron loss	Retinal atrophy (photoreceptor cells)	Seizures; limb paresis at 6 months; hyperactivity; aggression; memory loss; and death at ~12 months	SMT	309–318
CLN10	*Ctsd*$^{-/-}$	ASM, astrocytosis and microglial activation in somatosensory cortex and/or thalamic nuclei; axonal degeneration; and neuronal death	ND	Congenital disease	AAV1/2	80,188,319–322

AAV, adeno-associated virus; AAV1/2, AAV1 cassette with an AAV2 capsid; AAV2/5, AAV2 cassette with an AAV5 capsid; AAV2/9, AAV2 cassette with an AAV9 capsid; ASM, autofluorescent storage material; BMT, bone marrow transplantation; ERT, enzyme replacement therapy; ND, not determined; SCT, stem cell therapy; SMT, small-molecule treatment.

[a]All models present with ASM accumulation, astrocytosis, microglial activation and neuronal loss in the cortex and thalamic nuclei; regional model-specific changes are highlighted.