NINDS Contributions to Approved Therapies

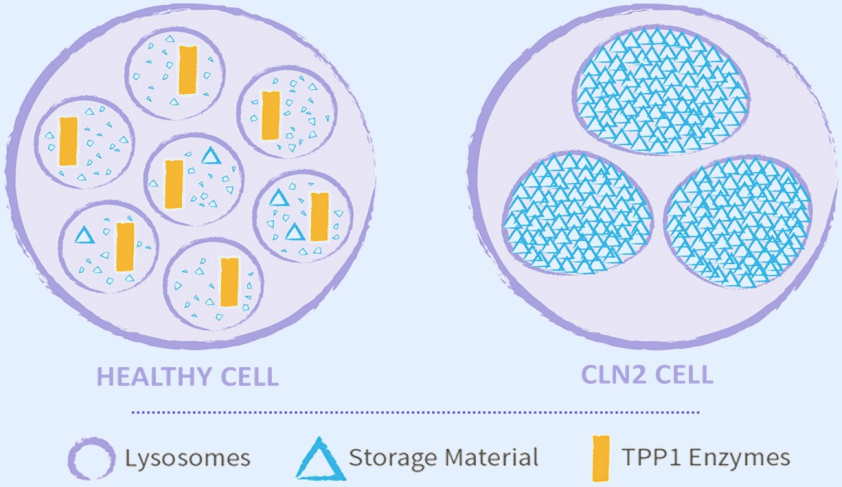
NINDS invests in and conducts research across the spectrum of neuroscience and neurology research, from basic studies on fundamental biological mechanisms, to clinical trials to test new treatments in patients. Here, we describe the path leading to the development and approval of one therapy for a neurological disorder, and we highlight contributions enabled by NINDS and NIH support.

Cerliponase Alfa (Brineura®) for Ceroid Lipofuscinosis 2 (CLN2 Disease)

Overview

Ceroid lipofuscinosis 2 (CLN2 disease) is a form of Batten disease, one of a group of rare genetic disorders called neuronal ceroid lipofuscinoses (NCLs) that together occur in two to four of every 100,000 children in the U.S. More broadly, CLN2 is a type of lysosomal storage disorder, in which affected individuals lack a specific enzyme that breaks down molecules such as lipids (fats) and proteins in cellular compartments called lysosomes. Individuals with CLN2 disease lack the protein-cleaving enzyme tripeptidyl peptidase1 (TPP1). As a result, undegraded material accumulates in neurons and other cells, leading to impaired cell function and neurodegeneration. Symptoms of CLN2 disease typically appear between the ages of two and four years and include recurrent seizures, poor coordination, involuntary muscle jerks or twitches, and progressive vision loss, as well as developmental regression and worsening intellectual disability. Children with CLN2 disease rarely survive beyond their teenage years.

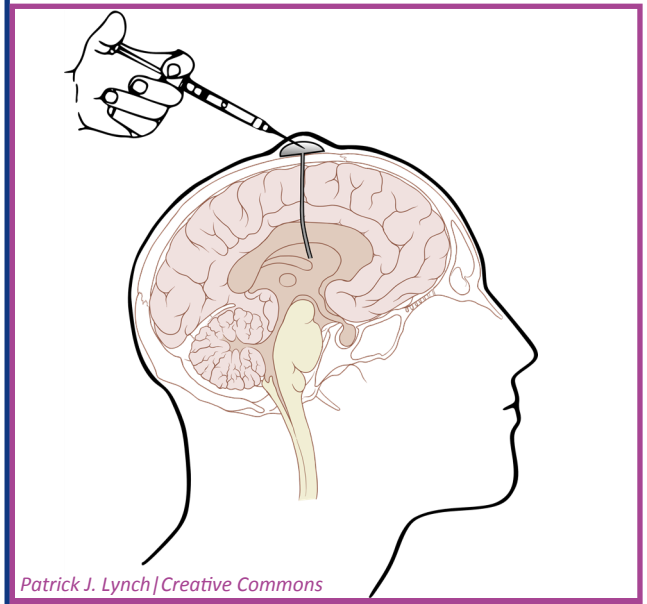
Cerliponase alfa, marketed in the U.S. as Brineura® (BioMarin), is an enzyme replacement therapy (ERT) that delivers TPP1 to the brain. It is approved to slow the loss of walking or crawling ability in children with CLN2 disease who are three years of age and older. Cerliponase alfa is the first ERT approved for direct delivery to the brain and the first treatment approved for any form of NCL. NINDS and other NIH institutes contributed to the development of cerliponase alfa, from finding the genetic cause of CLN2 disease, to producing the deficient enzyme, and conducting initial tests of treatment efficacy in animal models. Additional partners in this success were non-profit organizations including the Batten Disease Support and Research Association and others in the U.S. and abroad.



Courtesy of BioMarin

Learn more at: https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies

Cerliponase Alfa (Brineura®) for CLN2 Disease
Development Timeline



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1997

- Researchers isolate the missing enzyme in CLN2 disease. NIH
- A study maps the causal gene in CLN2 disease to a region on human chromosome 11. NIH NINDS

1999

The researchers who first isolated TPP1 successfully produce recombinant TPP1 in a cell culture system. NIH NINDS

2001

BioMarin begins the first clinical trial of intraventricular delivery of TPP1 in children with CLN2 disease.

2004

These same researchers develop a mouse model of CLN2 disease. NIH NINDS

2006

A study describes a canine model of CLN2 disease, providing a large animal model necessary for research on brain-targeted ERT. NIH

2008

- Researchers report effective delivery of recombinant TPP1 via the brain's ventricles in CLN2 mice. NIH NINDS
- Using mice engineered to produce different levels of TPP1, researchers find that restoring 6% of normal levels could have therapeutic benefit. NIH NINDS

2011-2015

BioMarin conducts further preclinical studies in larger animal models to assess brain distribution of delivered enzyme, as well as safety and efficacy.

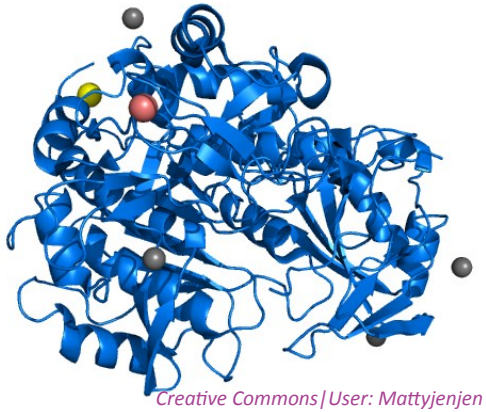
2013

2016

BioMarin completes pivotal clinical trial to compare disease progression in TPP1-treated patients with natural history data from an international CLN2 disease registry. NIH NINDS

2017

The FDA approves TPP1 (as cerliponase alfa; brand name Brineura®) to slow the loss of walking or crawling ability in children with CLN2 disease who are three years of age and older.



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Studies confirm the missing enzyme in CLN2 disease is the lysosomal protease TPP1.