

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.

Alglucerase Injection (Ceredase[®]) for Gaucher Disease

Overview

Lysosomes are compartments in cells that dispose and recycle waste, using specific enzymes to break down cellular debris into components that can be reused or discarded. People with lysosomal storage disorders lack one or more of these enzymes, causing certain waste products to accumulate in cells and resulting in a variety of symptoms. In Gaucher disease, the deficient enzyme is glucocerebrosidase, which degrades the fatty molecule glucocerebroside (also called glucosylceramide). Type 1 Gaucher disease primarily affects macrophages, a type of white blood cell that devours other worn-out cells. Symptoms range from mild to severe and include liver and spleen enlargement, severe anemia, easy bruising, and painful skeletal deformities. Two other forms of Gaucher disease affect cells in the brain as well, leading to neurological symptoms. These neuronopathic forms include Type 2

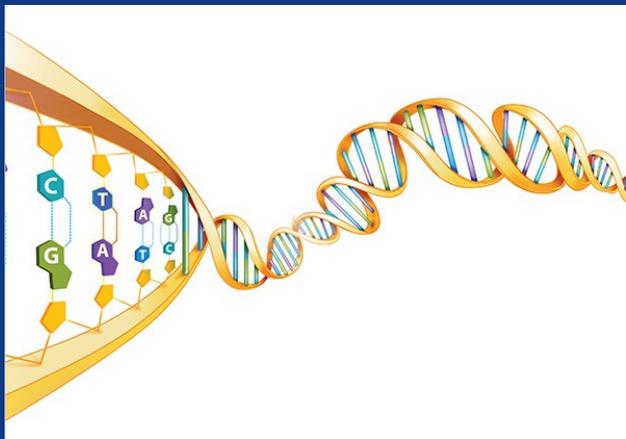
Gaucher disease, a severe disorder with onset in infancy or before birth, and Type 3 Gaucher disease, a milder form with later childhood or adult onset.

Physician-scientist Roscoe O. Brady (1923-2016) was an intramural investigator at NINDS who dedicated much of his career to research on lysosomal storage disorders. His work to identify the missing enzyme in Gaucher disease and determine how to restore it ultimately led to the development of alglucerase injection (Ceredase[®], Genzyme) for the treatment of Type 1 Gaucher disease, the first enzyme replacement therapy approved in the U.S. Brady's career at NINDS exemplifies the ingenuity and long-term commitment necessary to develop promising approaches into safe and effective treatments.



National Institutes of Health

Alglucerase Injection (Ceredase®) for Gaucher Disease Development Timeline



Researchers clone and sequence the human glucocerebrosidase gene, *GBA*.

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1964

Belgian scientist Christian DeDuve introduces the concept of enzyme replacement therapy (ERT). He will later receive the Nobel Prize for his discovery of the lysosome.

1965-1966

NINDS intramural investigator Roscoe Brady discovers the biochemical defect in Gaucher disease and proposes ERT as a treatment.

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1968

Brady and colleagues purify a small sample of the enzyme from human placenta and conduct initial tests in patients.

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1973-1974

1977

Larger-scale purification allows further trials in patients, but with inconsistent results, likely because the purified enzyme is not well suited for uptake into macrophages where it is needed.

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1981

Based on growing understanding of lysosomal enzyme uptake into different cell types, the enzyme is modified for improved targeting to macrophages.

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1985

1990-1991

Brady and his team conduct pivotal clinical trials using the modified enzyme and report dramatic improvement in disease symptoms, first in 1 child and next in 12 individuals with moderate-to-severe Type 1 Gaucher disease.

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1991

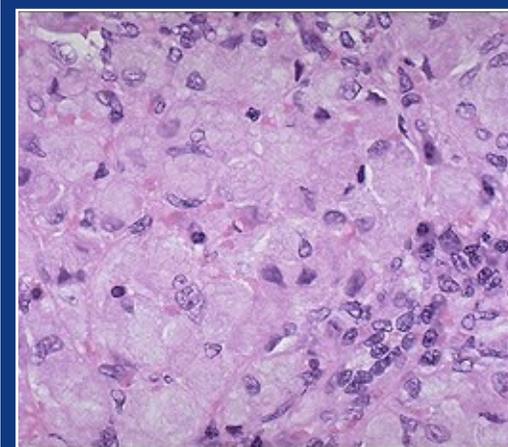
The FDA approves the orphan drug alglucerase (Ceredase®), an enzyme derived from human placenta, to treat Type 1 Gaucher disease.

1994

The FDA approves imiglucerase (Cerezyme®), a form of the enzyme produced using recombinant DNA technology.

2007

President George W. Bush awards Brady the National Medal of Technology and Innovation, one of many accolades he received for his research.



Brady and colleagues show that the enzyme glucocerebrosidase is localized to lysosomes.

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