Drugs of the Future 2009, 34(12): 1001-1004

CCC: 0377-8282/2009
DOI: 10.1358/dof.2009.34.12.1444443

THERAPEUTIC TARGETS FOR GAUCHER'S DISEASE

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ABSTRACT

Gaucher's disease is an autosomal recessive lysosomal storage disorder caused by mutations in the gene encoding the enzyme glucosylceramidase. The physiological result is a deficiency in this enzyme and a consequent accumulation of the lipid substrate glucosylceramide in lysosomes of the monocyte–macrophage system. Glucosylceramide accumulation in macrophages induces an increase in serum levels of proinflammatory cytokines, while accumulation in other cell types can cause the breakdown or production of additional complex glycolipids, consequently leading to anemia, skeletal abnormalities, organ dysfunction, bone pain and neurological dysfunction. The therapeutic goal in Gaucher's disease is to achieve equilibrium within the cell so that degradatory activity can maintain homeostasis and prevent the accumulation of undegraded macromolecules. To date, therapeutic strategies include enzyme replacement, substrate reduction and chemical chaperone therapies. The search continues for more effective treatment strategies for Gaucher's disease, with the investigative focus aimed at identifying novel targets for therapeutic intervention. This article presents those drug targets that are currently under active investigation for the treatment of Gaucher's disease.

INTRODUCTION

Gaucher's disease is an autosomal recessive lysosomal storage disorder that is caused by a deficiency in the enzyme glucosylceramidase. This deficiency is due to mutations in the gene (*GBA*) encoding glucosylceramidase, which result in protein misfolding and consequent accumulation of the lipid substrate glucosylceramide (also called glucocerebroside) in lysosomes of the monocyte–macrophage system. These lipid-engorged cells (Gaucher cells) accumulate and gradually replace healthy normal cells in the bone marrow and visceral organs. The abnormal accumulation and storage of undegraded material in bone marrow interferes with normal functions, such as the production of platelets and red blood cells, and may also trigger the loss of bone mineralization. Moreover, glucosylceramide accumulation in macrophages induces an increase in serum levels of proinflammatory cytokines (e.g., interleukins IL-1β and IL-6, TNF-α, IL-10 and granulocyte–macrophage colony-stimulating factor [GM-CSF]), while accumulation in cell types other than lysosomes may culminate in the breakdown or production of additional complex glycolipids, leading to potentially detrimental effects, such as anemia, skeletal abnormalities, organ dysfunction, bone pain and, in some cases, neurological dysfunction (1-3).

Gaucher's disease is classified into three subtypes based on the presence and severity of neurological involvement. Type 1 (non-neuronopathic) is the most common type of Gaucher's disease. It can affect children as well as adults, and is most prevalent in the Ashkenazi Jewish population. Type 1 is heterogeneous in its presentation, varying widely in severity, progression and symptomatology. Type 2 (acute neuronopathic) Gaucher's disease is a rapidly progressive form of the disorder characterized by severe central nervous system (CNS) involvement. Symptoms emerge in the first year of life, and patients rarely live beyond the age of 2 years. Type 3 (chronic neuronopathic) Gaucher's disease has its onset in childhood or adolescence. It is characterized by variable (moderate to severe) neurological involvement and a slowly progressive disease course (1-3).

The National Gaucher Foundation states that Gaucher's disease is the most prevalent of the lysosomal storage disorders. It is estimated that approximately 1 infant out of every 20,000 live births is afflicted with the disorder; this incidence is increased in the Ashkenazi Jewish population in particular, where type 1 Gaucher's disease occurs in 1 of 450 live births. Type 2 and type 3 Gaucher's disease are much rarer, occurring in 1 of 100,000 and 1 of 50,000 live births, respectively (1, 4).

The goal of treatment in Gaucher's disease, as with other lysosomal storage diseases, is to achieve a state of equilibrium within the cell such that the degradatory activity within the endosomal/lysosomal system is sufficient to maintain homeostasis and prevent the accumulation of undegraded macromolecules. Three therapeutic strategies are currently available. These include enzyme replacement therapy, in which the missing or defective lysosomal enzyme is replaced, and substrate reduction therapy, which suppresses the synthesis of macromolecules to the point where the residual activity of the mutant enzyme is able to prevent storage. In addition, a novel class of agents known as chemical chaperones has been identified.

Within the endoplasmic reticulum (ER), these agents bind to the active site of and stabilize those variant enzymes that otherwise would have the tendency to unfold, be retained within the ER and subsequently degraded by proteasomes. Chemical chaperones thus increase trafficking of variant enzymes out of the ER, through the Golgi and onward to their target environment, the lysosome. In short, if the enzyme proves stable, it may exert sufficient catalytic activity to perform its normal degradative function (1, 2, 5-9).

The search for effective treatment strategies for Gaucher's disease continues, with research focusing on the identification of novel targets for drug development. Those targets which are currently under active investigation are discussed below (see Figure 1). Table I provides a selection of products under active development for each target and Table II includes selected patents.

TARGETS

Ceramide glucosyltransferase (glucosylceramide synthase, GLCT-1)

Ceramide glucosyltransferase, also known as glucosylceramide synthase (GLCT-1; EC 2.4.1.80), is a member of the glycosyltransferase family 2 and is involved in glycosphingolipid and glucosylceramide

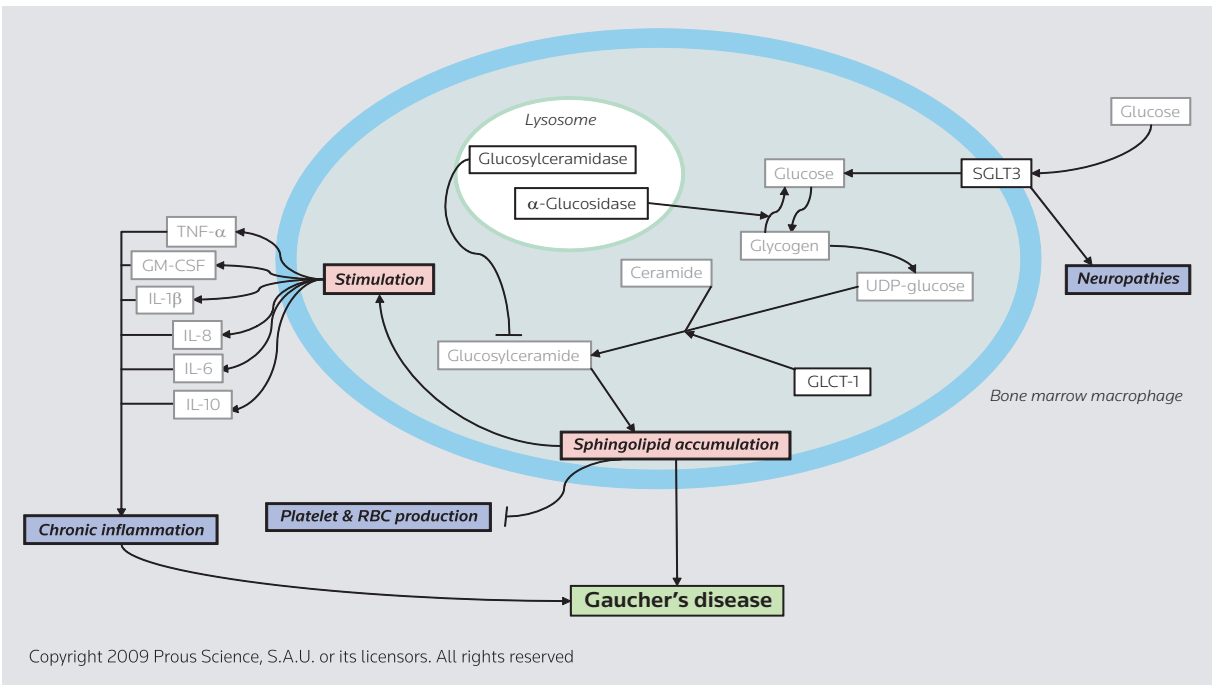

Figure 1. Gaucher's disease targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of Gaucher's disease and their biological actions. Arrow: positive effect; dash: negative effect. Gray or lighter symbols are targets that are not validated (i.e., targets not associated with a product that is currently under active development for Gaucher's disease). Abbreviations: GLCT-1: ceramide glucosyltransferase (glucosylceramide synthase); α-glucosidase: lysosomal α-glucosidase; GM-CSF: granulocyte–macrophage colony-stimulating factor; RBC: red blood cell; SGLT3: sodium/glucose cotransporter 3.

Table I. *Selected targets and products launched or being actively investigated for Gaucher's disease (from Prous Science Integrity®).*

Target	Product	Source	Phase
Ceramide glucosyltransferase	Miglustat	Actelion	L-2003
	GENZ-112638	Genzyme	III
α-Glucosidase	Miglustat	Actelion	L-2003
Glucosylceramidase	Taliglucerase alfa	Protalix Biotherapeutics	Prereg.
	Velaglucerase alpha	Shire	Prereg.
	Isofagomine tartrate	Amicus Therapeuticus	II
	PEG-Glucocerebrosidase	National Institute of Mental Health	I
	EXR-202	ExSAR	Preclinical
Sodium/glucose cotransporter 3 (SGLT3)	Miglustat	Actelion	L-2003

Table II. *Selected patents for targets being pursued or explored for Gaucher's disease (from Prous Science Integrity®).*

Target	Patent	Source	Phase
Ceramide glucosyltransferase	EP 0782992	Seikagaku	Biological testing
	WO 2001097829	Genzyme	Preclinical/Launched
	WO 2002055498	Oxford GlycoSciences/University of Oxford	Preclinical
	WO 2004007453	Oxford GlycoSciences	Biological testing
	WO 2004007454	Oxford GlycoSciences	Biological testing
	WO 2004111001	Oxford GlycoSciences	Biological testing
	WO 2004111002	Oxford GlycoSciences	Biological testing
	WO 2005068426	UCB Celltech	Biological testing
	WO 2005039578	MacroZyme DNM	Preclinical
	WO 2005040118	Universiteit Van Amsterdam	Biological testing
	WO 2005063706	MacroZyme DNM	Preclinical
	WO 2007123403	Academisch Medisch Centrum (AMC)	Preclinical
	WO 2008150486	Genzyme	Preclinical
	US 6177447	MacroZyme DNM	Preclinical
	US 2004204379	Genzyme	Preclinical
	US 2009069375	Protia, LLC	Biological testing
Glucosylceramidase	WO 2005046611	Amicus Therapeutics	Biological testing
	WO 2006136714	CNRS (Centre National de la Recherche Scientifique)/Universite d'Orleans	Biological testing

biosynthesis. GLCT-1 is localized in the ER and is a potential therapeutic target for the treatment of Gaucher's disease. GLCT-1 is the initial enzyme in a series of reactions which results in the synthesis of most glycosphingolipids; it is involved in the transfer of glucose to ceramide. Thus, inhibition of GLCT-1 would reduce the rate of glycosphingolipid biosynthesis so that the amount of glycosphingolipid substrate is attenuated to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective (i.e., substrate reduction therapy) (9-12).

Glucosylceramidase

Glucosylceramidase (also known as acid β-glucosidase, β-glucocerebrosidase, NLGase; EC 3.2.1.45) is an enzyme responsible for the cleavage of sphingolipid glucocerebrosides (glucosylceramides). Mutations in the gene encoding this enzyme (*GBA2*) result in protein misfolding and consequent deficiencies in the enzyme, leading to the development of Gaucher's disease. Some inhibitors of this enzyme (e.g., imino sugars), bind to the active site and stabilize it for proper folding to yield the catalytic form. They act as chemical chaperones, facilitating the transport and maturation of NLGase and are therefore potentially effective in the treatment of Gaucher's disease (10, 13-16).

Lysosomal α-glucosidase

Lysosomal α-glucosidase (EC 3.2.1.20) is one of several enzymes that catalyze the release of glucose via hydrolysis of the glycosidic link in various glucosides. It is essential for the degradation of glycogen to glucose in lysosomes. Mutations in the gene (*GAA*) encoding this enzyme lead to lysosomal storage disorders such as Pompe's and Gaucher's diseases, where accumulation of large amounts of glycogen occurs in the lysosomes of skeletal muscle, heart, spinal cord and brain. Inhibition of lysosomal α-glucosidase may therefore be an effective treatment for lysosomal storage disorders such as Gaucher's disease (9, 17).

Sodium/glucose cotransporter 3 (SGLT3)

Glucose enters cells via two different types of membrane-associated carrier proteins, the SGLTs and glucose transporter facilitators (GLUT). There are three members of the SGLT family that function as glucose transporters (SGLT1 and SGLT2) or sensors (SGLT3). SGLT3 is glucose sensor that is highly selective for D-glucose. It is expressed in the plasma membrane of cholinergic neurons, skeletal muscle and other tissues, where it induces depolarization of the resting membrane potential, with an uncoupled inward sodium current in response to external glucose. Activation of this transporter may explain some of the side effects (i.e., peripheral neuropathy, tremors) associated with imino sugar therapy in Gaucher's disease, and it is thus speculated that inhibition of SGLT3 may improve adverse event profiles in imino sugar therapy (14, 18-21).

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