Targeting glycosphingolipids for human therapy

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Profile

Professor Fran Platt received a BSc degree in Zoology from Imperial College, University of London and a PhD in Animal Physiology from the University of Bath, UK. She was a post-doctoral fellow at Washington University Medical School (St. Louis, USA) and returned to the UK in 1989 to The Glycobiology Institute, Department of Biochemistry, University of Oxford. She was awarded a Lister Institute Senior Research Fellowship in 1996. In 2006 she moved to the Department of Pharmacology, University of Oxford.
Her research interests are in glycosphingolipids (GSL) and in particular glycosphingolipid (GSL) lysosomal storage diseases. She and her colleagues (Terry Butters and Raymond Dwek) pioneered a novel approach to treat these inherited metabolic diseases (substrate reduction therapy, SRT) that has led directly to the development of an approved drug (miglustat) for treating type 1 Gaucher disease and Niemann-Pick disease type C.
She was awarded The Alan Gordon Memorial award from the UK Gaucher association and the Horst-Bickel Award in recognition of her role in developing substrate reduction therapy for lysosomal disorders. Prof. Platt has presented plenary talks at multiple scientific and clinical meetings and is currently an Editor for the Journal of Biological Chemistry and serves on the advisory board of multiple lysosomal storage disease charities (UK and USA). She has published over 130 papers in peer-reviewed journals and co-edited the book Lysosomal Disorders of the Brain with Steve Walkley.
She was elected Fellow of the Academy of Medical Sciences in 2011.

Our understanding of the functional roles played by glycosphingolipids (GSLs) remains incomplete[1]. However, when these molecules cannot be degraded fully in the lysosome severe diseases result, termed GSL lysosomal storage disorders[2] (Figure 1). The majority of these diseases result from inherited defects in the genes that encode lysosomal enzymes involved in GSL catabolism.

While studying inhibitors of N-glycan processing, determining how they disrupt the life cycle of HIV[3] we made the serendipitous discovery that the drug we were studying, *N*-butyldeoxynojirmicin/miglustat, had a novel and very unexpected enzyme target, glucosylceramide synthase[4] (Figure 2). This drug could therefore be used to pharmacologically inhibit the biosynthesis of GSLs to probe their physiological functions, but also had the potential to treat GSL lysosomal storage diseases. We therefore tested whether this orally available drug would show efficacy in mouse models of Tay-Sachs and Sandhoff disease. It was found that the drug delayed disease progression, reduced neuroinflammation and prolonged life expectancy[5)6)]. Clinical collaborators and a commercial partner tested this drug in type 1 Gaucher disease patients and efficacy was demonstrated[7)]. The drug was approved by the EMEA in 2002 and by the FDA in 2003. We called this pharmacological approach substrate reduction therapy (SRT). The drug reduces the number of GSL molecules synthesised by cells so fewer require degrading in the lysosome, allowing the rate of biosynthesis to better match the impaired rate of catabolism. As the drug crosses the blood-brain barrier it also has the potential to treat CNS manifestations of these disorders. It was recently approved by the EMEA for treating Niemann-Pick disease type C (NPC), following efficacy being demonstrated in an international clinical trial[8)].

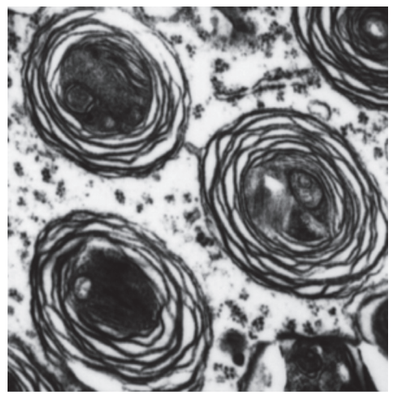

Figure 1. Electron microscopy showing the ultrastructure of lipid storage bodies in Tay-Sachs disease cells.

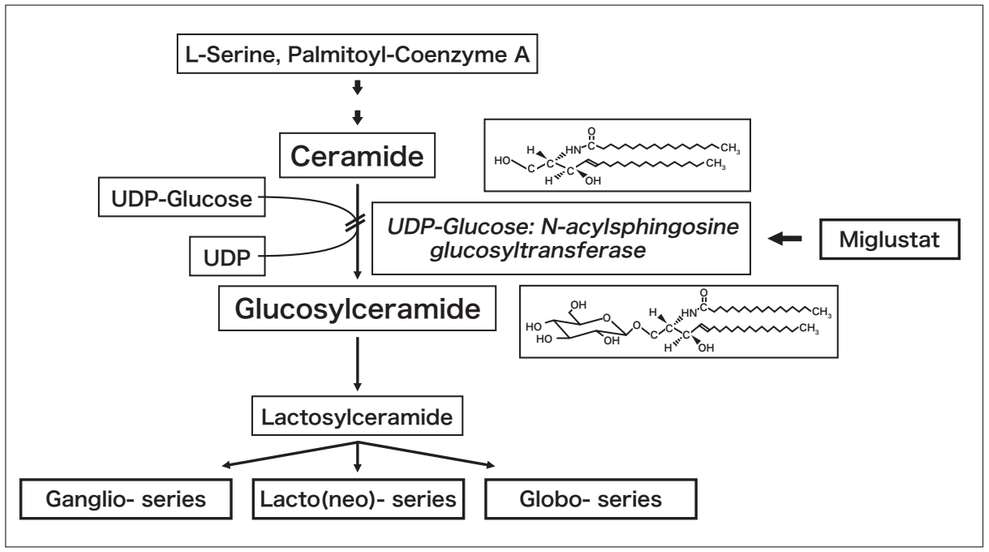

Figure 2. Glycosphingolipid biosynthesis highlighting the step in the pathway inhibited by miglustat

Having developed miglustat as a therapeutic agent we have now turned our attention to investigating pathogenic mechanisms in lysosomal disorders to identify novel clinical intervention points. For example, a major current focus of the laboratory is Niemann-Pick disease type C (NPC) disease, a disorder involving the storage of myltiple classes of lipids including GSLs. We have discovered that this disease involves the primary storage of the ceramide degradation product sphingosine[9)]. Sphingosine storage in turn causes dysregulation of acidic storage calcium, preventing the fusion of late endosomes with lysosomes, explaining the cellular hallmarks of this disorder and explaining why all GSL species are stored in this disease[9)10)]. Furthermore, elevating cytosolic calcium compensated for the novel calcium defect in NPC disease and was of therapeutic benefit in a mouse model of NPC disease[9)]. Very recently, we have made a mechanistic link between the cellular pathway affected in NPC disease and more common human disorders suggesting SRT targeting GSLs may have utility beyond lysosomal storage diseases.

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