NNPDF-Funded Research Grant # 41

TITLE: Therapeutic Monitoring of Glycolipid Storage Diseases in the Clinic Using Cell Biological Assays and Proteomics
PROJECT INVESTIGATOR: Frances M. Platt, Ph.D.

PERIOD: 5/1/2006 - 11/30/2006

PROJECT DESCRIPTION

Glycosphingolipid (GSL) storage diseases are severe diseases that typically afflict infants and young children, but can also develop in adulthood. They are caused by inheriting mutations in a gene that codes for an enzyme needed to break down GSLs within the cells of the body. GSLs therefore accumulate over time and this is termed “storage”. Most storage diseases involve the brain and as a consequence these disorders typically have a neurodegenerative clinical course, resulting in premature death in infancy or childhood. We currently cannot treat any storage disease with brain involvement.

For the past decade we have been developing a drug based therapy for these diseases called substrate reduction therapy (SRT). The drug slows the rate at which GSLs are manufactured in the body and so they are stored more slowly. This approach is approved for use in a storage disease that lacks brain involvement, type 1 Gaucher disease, and we know a great deal about the safety and side effect profile of this drug. We have shown in mice that get the same diseases as humans, that the drug also works in storage diseases that affect the brain. Based upon these findings, clinical trials are in progress in three diseases (type 3 Gaucher disease, Niemann-Pick disease type C1 and late onset Tay-Sachs disease). In a previous study we showed that monitoring the peripheral blood of an NPC patient on SRT using multiple carefully controlled tests was helpful in demonstrating that SRT was making the diseased cells of the patient more normal.<BR
We now aim to determine the degree to which the changes we observe in the peripheral blood assays correlates with clinical response in a larger group of patients. We will focus on one classical GSL storage disease (Sandhoff) and one disorder with secondary GSL storage (NPC1). We will also investigate the relationship between the therapeutic levels of the SRT drug, miglustat, in the plasma and CSF of patients undergoing therapy and the clinical and cell biological responses. The study will include juvenile Sandhoff patients (n=5-10) and adolescents and adults with NPC1 (n=10-15). The aim is also to identify the most robust assay that correlates optimally with clinical changes. The focus will be on the development of a single simple and cheap assay that can be employed for monitoring patients with CNS disease receiving SRT in the future. In addition, we will use proteomic analysis, on defined populations of peripheral blood cells from patients, to determine to what degree lipid raft associated proteins are mislocalised in these diseases and whether SRT corrects their distribution. The functional implications of mislocalisation on disease pathogenesis will be explored. Together, these approaches will provide us with new methods for monitoring therapeutic efficacy and provide new insights into disease

pathogenesis. These latter studies could lead to new therapeutic approaches and/or identify new surrogate markers of disease.

FINAL STATUS REPORT
Dated 11/24/2006

Glycosphingolipid (GSL) storage diseases are severe diseases that typically afflict infants and young children, but can also develop in adulthood. They are caused by inheriting mutations in a gene that codes for an enzyme needed to break down GSLs within the cells of the body. GSLs therefore accumulate over time and this is termed "storage". Most storage diseases involve the brain and as a consequence these disorders typically have a neurodegenerative clinical course, resulting in premature death in infancy or childhood. We currently cannot treat any storage disease with brain involvement.

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Over the past year we have been determining the degree to which the changes we observe in the peripheral blood assays correlates with clinical response in a larger group of patients. We are focussing on one classical GSL storage disease (Sandhoff) and one disorder with secondary GSL storage (NPC1). We are investigating the relationship between the therapeutic levels of the SRT drug, miglustat, in the plasma and CSF of patients undergoing therapy and the clinical and cell biological responses. The study includes juvenile Sandhoff patients (5-10 patients) and adolescents and adults with NPC1 (10-15 patients). We are also analysing an additional group of NPC patients who are taking part in the NIH natural history study (25 patients). We are identifying the most robust assay that correlates optimally with clinical changes. The focus is on the development of simple and cheap assay that can be employed for monitoring patients with CNS disease receiving SRT in the future. These studies are providing us with new methods for monitoring therapeutic efficacy and provide new insights into disease pathogenesis. Within the remit of the grant support from NNPDF, we have made considerable progress on all these objectives. Most significantly, we have proven that one particular assay (lysotracker) is a very robust way of monitoring NPC disease. We are pleased that we have now secured funding in the UK from Action Medical Research for a further three years of funding on this project that will expand to include other storage diseases.

PUBLICATIONS:
No Publications on this Work To Date