

**Grant #45
Frances M. Platt
University of Oxford**

**Evaluation of anti-inflammatory intervention (NSAIDS)
as an adjunctive therapy in Niemann-Pick type C1 disease**

Lysosomal storage diseases are severe disorders that typically afflict infants and young children, but can also develop in adulthood. They are caused by inherited mutations in a gene that is involved in the specialized part of the cell called a lysosome. This is where molecules go to be broken down but can also be sent elsewhere from the lysosome for recycling. In these diseases molecules fail to be broken down properly and accumulate over time. This is termed “storage”. Most lysosomal storage diseases involve the brain and typically have a neurodegenerative clinical course, resulting in premature death in infancy or childhood. We currently cannot treat any storage disease with brain involvement.

We have had a long-term interest in understanding and treating storage diseases that involve the storage of specialized fatty molecules called glycosphingolipids (GSLs). One of the responses that the brain and other organs of the body makes to the storage of GSLs is to mount an inflammatory response that involves specialized cells of the immune system, called microglia and macrophages. This response also occurs in more common neurodegenerative diseases such as Alzheimer’s and Parkinson’s.

We have studied the inflammatory process in some detail in a mouse model of Sandhoff disease. The storage of GSLs in this disease (called gangliosides) activates resident microglia and causes the recruitment of macrophages to the brain. The inflammation in the brain gets more aggressive and destructive as the level of storage lipids increases. This inflammatory process directly contributes to the development and severity of symptoms as treating a mouse model of Sandhoff disease with over the counter anti-inflammatory drugs (such as aspirin and ibuprofen) delays the onset of symptoms, slows disease progression, and the mice live significantly longer than untreated mice. In Niemann-Pick type C disease the storage of many different types of lipids occurs, including the same GSLs that are stored in Sandhoff disease.

The storage of these lipids causes a very similar inflammatory response in the brain in the NPC mice that we have observed in the GSL storage diseases such as Sandhoff disease. In this proposal, we aim to test whether anti-inflammatory drugs may be a beneficial adjunctive therapy in NPC disease. We will do this by studying how the NPC mouse model responds to anti-inflammatory drugs, either alone or in combination with the substrate lowering drug miglustat. This drug is currently undergoing clinical trials in NPC disease. We hypothesize that reducing inflammation will be of benefit in NPC disease and will be additive or synergistic when combined with miglustat. These findings could be rapidly translated into carefully controlled clinical studies in the future.

Specific Aims

1. To determine whether anti-inflammatory drugs show benefit in the NPC1 mouse and at what stage of disease.
2. To determine whether combining NSAIDS with miglustat leads to greater benefit than either therapy alone.
3. Brain tissue sections (from 1 & 2) will be evaluated to determine the histopathological consequences of NSAID therapy. ELISAs on brain tissue will be used to evaluate changes in cytokine levels.
4. To recommend to clinical colleagues an optimal experimental protocol for rapid translation into clinical trials.

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In this proposal, we have therefore tested whether anti-inflammatory drugs may be a beneficial adjunctive therapy in NPC disease. In the first six months of the grant, we verified that Non Steroidal Anti-inflammatory Drugs (NSAIDs) such as ibuprofen and aspirin are of benefit in NPC (increased survival and less severe tremor). However, when we treated NPC mice using vitamin C, that is an anti-oxidant, this was only of minimal benefit. These findings suggest NSAIDs but not antioxidants may be helpful in managing NPC disease.

The second phase of the project will address the clinical outcome in the mouse when we combine NSAIDs with the substrate lowering drug miglustat. These studies are in progress.

Bascunan-Castillo E. C., Erickson R. P., Howison C. M., Hunter R. J., Heidenreich R. H., Hicks C., Trouard T. P. and Gillies R. J. (2004) Tamoxifen and vitamin E treatments delay symptoms in the mouse model of Niemann-Pick C. *J Appl Genet* 45, 461-467.

Jeyakumar M., Smith D. A., Williams I. M., Borja M. C., Neville D. C., Butters T. D., Dwek R. A. and Platt F. M. (2004) NSAIDs increase survival in the Sandhoff disease mouse: Synergy with N-butyldoxynojirimycin. *Ann Neurol* 56, 642-649.