NNPDF Grant #47 – Fran Platt

TARGETING SPHINGOSINE STORAGE AS A NEW THERAPEUTIC APPROACH FOR NIEMANN-PICK TYPE C

6 month report

Lay Summary

We have discovered that NPC cells have dramatically lower lysosomal calcium, this results in an inability to recycle lipids which ultimately results in their storage (cholesterol, sphingomyelin and glycosphingolipids). The cause of this storage is sphingosine, a lipid which accumulates in the brain and other organs of NPC patients. Storage of sphingosine is the first measurable event after prevention of NPC1 function in normal cells, and it is this storage that causes all the downstream events.

In this grant we are testing two therapeutic approaches based upon these new findings. The first is to reduce sphingosine accumulation which we are doing either with miglustat or myriocin. So far we have treated mice with miglustat and tissues are about to be analysed to measure sphingosine before and after treatment to test whether this is why miglustat is of benefit in NPC1 disease. Myriocin is quite a toxic drug that can be used experimentally in animals to test whether or not reducing the manufacture of sphingolipids is of therapeutic benefit. We are currently testing it in mice giving it either orally or by injection. These studies are ongoing.

The second therapeutic approach we are testing is to compensate for the low lysosomal calcium levels in NPC by elevating the levels of calcium in the cytoplasm of the cell, using the natural product curcumin. We have found that curcumin therapy results in benefit. In the first part of the NNPDF grant we have combined miglustat with curcumin to target two different steps of the disease process and found that the benefits of combination therapy are greater than using either drug alone. We are now doing a larger scale experiment to validate this finding and explore the effects of combination therapy in more detail.