

# **NNPDF-Funded Research Grant # 36**

**TITLE: Organization of Synapses in Niemann-Pick Disease Type A**  
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**PERIOD: 9/15/2004 - 9/14/2005**

## **PROJECT DESCRIPTION**

Niemann Pick disease Type A (NPA) is a neurodegenerative disorder of early childhood accompanied by mental retardation. It results from the inherited deficiency of the acid sphingomyelinase activity (ASM) that is responsible for the turnover of sphingomyelin (SM). Recently, sphingolipids and SMcholesterol rich membrane domains, the so-called rafts, have been related with the formation and maintenance of synapses. We postulate that defects in SM turnover may alter an essential neuronal function: the ability to make synapses to propagate information. This could explain, at least in part, the severe neurological problems observed in NPA patients. Using mice that lack ASM and show the same symptoms of the human disease we will analyze, in vitro and in vivo, the morphology and composition of synapses. We expect to find anomalies in the lipid composition of the synapses that may lead also to altered protein pattern and therefore deficient synaptic function. If this is the case, we plan to manipulate by pharmacological means the levels of lipids found to be changed in primary neurons in culture of these mice. With this approach we aim to rescue the aberrant phenotypes observed. We hope the results obtained will help to understand the contribution of lipids to synaptic activity. This could be relevant not only for NPA but also for other lipidosis that also lead to cognitive impairment.

## **FINAL STATUS REPORT**

**Dated 9/15/2005**

Our working hypothesis proposed that the deficiency in the sphingomyelin (SM) turnover in Niemann Pick disease type A (NPA) would lead to altered composition and function of synapses. This would explain, at least in part, the severe cognitive impairment of NPA patients. The results obtained strongly support this hypothesis. Thus, analyses of synapses in the brains and in primary neurons in culture of wild type mice and mice that mimic the human NPA disease have revealed the accumulation of SM and altered protein composition in the latter. This is accompanied by reduced number of synaptic contacts, reduced size of the presynaptic terminals and low number of synaptic vesicles at least in the hippocampus, the area analyzed so far. We have also detected functional consequences as the synaptic response to certain stimuli is altered in these mice. Our results not only confirm our hypothesis but also provide with targets and read out systems, at least in vitro, for possible therapeutical strategies.

## **PUBLICATIONS:**

<http://www.molbiolcell.org/cgi/content/full/19/2/509>