# NNPDF-Funded Research Grant # 48

## TITLE: Construction & Characterization of New Mouse Models for Types A & B Niemann-Pick

**PROJECT INVESTIGATOR: Edward H. Schuchman, PhD**

## PERIOD: 4/1/2008 - 3/31/2009

**PROJECT DESCRIPTION**

Our laboratory has been studying the biology and treatment of Types A and B Niemann-Pick disease (NPD) for nearly 20 years. Among our accomplishments is the creation of a mouse that completely lacks acid sphingomyelinase (ASM) protein and enzymatic activity, i.e., the ASMKO mouse. We have used these mice for many purposes, including the development of enzyme replacement therapy (ERT) for Type B NPD, which is currently being evaluated in clinical trials. However, despite the considerable value of these animals, they have several important limitations. Among these is the fact that they completely lack the ASM protein. In contrast, all Type B NPD patients, and most Type A patients, have normal levels of mutant ASM protein (albeit very low functional enzymatic activity). Thus, the ASMKO mouse is a very poor biochemical model for the human disease. Also, because these animals completely lack the ASM protein, they cannot be used to evaluate chaperone and other enzyme enhancement therapies (which may be needed to treat brain disease in Type A NPD). Furthermore, when we administer ERT to the ASMKO animals they develop a profound immune response to the recombinant ASM, which limits the effectiveness of therapy. In addition, the ERT studies could only be monitored for relatively short periods of time since the animals died at 6-7 months of neurological disease.

For these reasons we believe that it is extremely important to develop new mouse models of Types A and B NPD that more closely resemble the human disease. In this application we are proposing such an endeavor. ASMKO mice will be produced that express three specific mutations: R496L, the most prevalent Type A NPD mutation in Ashkenazi Jewish individuals, deltaR608, the most common Type B NPD mutation in North America and Western Europe, and H421Y, a common mutation that accounts for ~95% of all patients in Saudi Arabia (a “hot-spot” for Type B NPD). Since this is only a two-year grant application, the project is limited to the production and initial characterization of mice expressing each of these three mutations. We are also proposing one therapeutic experiment; i.e., to repeat the ERT studies in mice expressing the deltaR608 mutation. This is an important priority since ~40% of the patients enrolled in the phase 1 Type B NPD ERT study express this mutation, and it is crucial that we evaluate ERT in more clinically relevant animals. Indeed, we predict an even better outcome in the deltaR608 mice as compared to the complete “knock-out” ASMKO mice due the lack of immune response and neurological disease.

**Interim STATUS REPORT**
**Dated 10/1/2008**

The goal of our research is to create a new mouse model of Type A NPD. This mouse will make an abnormal (or mutant) form of acid sphingomyelinase in all of its cells and tissues. The specific mutant form of acid sphingomyelinase (designated R496L) is the same as one frequently found in human Type A NPD patients. This new mouse will be different from the available mouse model of this disease (referred to as ASMKO) in that these latter animals do not make any mutant acid sphingomyelinase protein. These animals can be used for a wide range of research purposes. For example, there is a new and promising treatment strategy for lysosomal diseases based on "reactivation" of mutant proteins. This is referred to as "chaperone therapy". With the currently available ASMKO mouse this treatment strategy cannot be evaluated since no mutant protein is being made. In addition, by comparing mice expressing different amounts of the R496L mutant acid sphingomyelinase, we will be able to estimate how much "reactivation" is necessary to prevent or reverse the specific organ abnormalities in the brain, liver, spleen, lungs, etc. To date we have produced the first of these mice, and are now in the process of studying their disease. In the future we will use these mice to evaluate chaperone therapies for Type A NPD.

**PUBLICATIONS:**
No Publications on this Work To Date