National Niemann-Pick Disease Foundation Grant #48
Six-Month Progress: *Lay Summary* – Edward H. Schuchman, PhD

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.