***Specific Aims***

Gaucher disease (GD) is the most common lysosomal storage disease and is inherited in an autosomal recessive fashion [[1]](http://www.archivesofpathology.org/doi/full/10.1043/1543-2165%282008%29132%5B851%3AGDROTL%5D2.0.CO;2). Symptoms of the GD can produce a broad range of symptoms affecting the blood, spleen, liver, bone marrow, and neurological function [[2]](http://www.ncbi.nlm.nih.gov/pubmed/17996473).  The disease is characterized by an accumulation of glucocerebrosides, which are components of animal muscle and nervous tissues. Glucocerbrosides are normally hydrolyzed in the lysosome by glucocerebrosidase (Gcase) [[2]](http://www.ncbi.nlm.nih.gov/pubmed/17996473). GD is most commonly caused by mutations in the gene which encodes for Gcase, *GBA.* However, in a small number of patients, glucocerebroside accumulates due to a lack of saposin C (Sap C), an essential activator of Gcase [[3]](http://archneur.jamanetwork.com/article.aspx?articleid=592621).  Sap C is encoded by the *PSAP* gene, which will be the focus of this study.

It is already known that patients with the same mutation in their *GBA* can exhibit different phenotypes [7]. It has also been determined that mice with mutations in both *GBA* and *PSAP* have more severe phenotypes than mice with only mutations in *GBA* [6]. In humans, however, there is no knowledge on how variations in *PSAP* influence the phenotypes of patients who already have GD. **Here we will test the hypothesis that *PSAP* is a modifier for GD (patients with mutations in GBA locus).**

Our **Long-term goal** is to characterize the phenotypes of GD patients that result from variations in the *PSAP* gene.

We will pursue the following specific aims:

1. Sequence the *PSAP* and *GBA* gene for patients with GD.

2. Identify differences in patients with the same mutation in the *GBA* locus, but with different phenotypes and *PSAP* sequences

Payoff:

Characterization of phenotypes based off of specific genotypes in the *PSAP* gene may lead to new insights on the interactions between Sap C and Gcase. This may eventually lead to the modification of Sap C levels in patients (via enzyme replacement therapy) resulting in clinical improvements.