***Specific Aims***

Gaucher Disease (GD) is the most common lysosomal storage disease and can produce a broad range of symptoms affecting the nervous system, blood, spleen, liver, and bone marrow. [1].  The disease is caused by the accumulation of glucocerebrosides, which are components of animal muscle and nervous tissue [2]. Glucocerebroside accumulation causes cell death, but they are normally hydrolyzed in the lysosome by glucocerebrosidase (Gcase) [3]. GD is most commonly caused by mutations in the gene that encodes for Gcase, *GBA.* However, in a small number of patients, glucocerebrosides accumulate due to a lack of saposin C, an essential activator of Gcase [4].  Saposin C is encoded by the *PSAP* gene, which will be the focus of this study.

Patients with an identical homozygous *GBA* mutation can exhibit variability in their symptoms [5]. It has also been demonstrated that mice with mutations in both *GBA* and *PSAP* have more severe phenotypes than mice with only *GBA* mutations [6]. In humans, however, it is unknown how variations in *PSAP* expression and activityinfluence the phenotypes of patients who already have GD. **Here we will test the hypothesis that variations in *PSAP* expression and activity contribute to the phenotypic variability in GD patients with the same *GBA* mutation.**

Our **long-term goal** is to identify how variations in *PSAP* expression and activity contribute to different phenotypes of GD patients.

We will pursue the following specific aims:

1. **Aim:** Identify regions of the genome that may contribute to the variability of symptoms seen in GD patients with the same *GBA* mutation.

**Approach**: GD patients with the same *GBA* mutation and variability in their symptoms will have their genomes sequenced. These patients will be divided into two groups: those with severe symptoms and those with mild symptoms. The groups will be compared in order to identify variable regions in the genome.

**Hypothesis:** If mutations exist in the genome that are contributing to the variability of phenotypes, then the region(s) responsible would be polymorphic between the two groups.

**Rational:** If region(s) are identified, it is possible they contribute to symptom variability via altering the expression or activity of *PSAP*.

2. **Aim:** Identify the phosphorylated amino acids in PSAP of GD patients with the same *GBA* mutation.

**Approach**: Using mass spectrometry, we will determine the location of the phosphorylation sites on PSAP in GD patients with the same *GBA* mutation.

**Hypothesis:** If there are differences between the phosphorylation sites of patients containing the same *GBA* mutations, it may alter the activity of the PSAP protein.

**Rational:** If differences in PSAP phosphorylation are identified, it is likely that these will affect the activity of the protein and may contribute to varying phenotypes.

3. **Aim:** Compare tissue specific levels of *PSAP* expression in GD patients.

**Approach**: Using RNA sequencing, the level of *PSAP* mRNA will be measured in GD patient tissues that exhibit variability in symptoms. The amount of expression will be compared to a control group of people without GD.

**Hypothesis:** If different *PSAP* expression levels play a factor in the symptom variability, then different expression levels in the same tissue that also exhibits variability in symptoms will be observed.

**Rational:** Correct stoichiometric amounts of the PSAP protein are likely to be essential in proper cell maintenance and any deviation from the wild type expression might lead to symptom variability.

The discovery that *PSAP* plays a role in the symptoms of GD patients with the same *GBA* mutation would illuminate one of the mysteries of the disease. This may eventually lead to the clinical improvements via the development of therapies to modify PSAP levels in patients.

Sources Cited

[[1]](http://www.archivesofpathology.org/doi/full/10.1043/1543-2165%282008%29132%5B851%3AGDROTL%5D2.0.CO;2) Chen, M and Wang, J. (*2008*) Gaucher Disease: Review of the Literature. *Archives of Pathology & Laboratory Medicine,*132, 851-853.

[[2]](http://www.ncbi.nlm.nih.gov/pubmed/17996473) Guggenbuhl P, Grosbois B, Gerard C. (2007). Gaucher DIsease. *Joint Bone Spine*, 75, 116-24. [doi:10.1016/j.jbspin.2007.06.006](http://dx.doi.org/10.1016/j.jbspin.2007.06.006%22%20%5Co%20%22%22%20%5Ct%20%22doilink)

[[3]](http://archneur.jamanetwork.com/article.aspx?articleid=592621) Tamargo TJ,*et al.*(2012).The role of saposin C in Gaucher disease *Mol Gent Metab*, 106(3), 257-63.

[[4](http://archneur.jamanetwork.com/article.aspx?articleid=592621)]Brady RO,  Barton NW, Grabowski GA. (1993). The Role of Neurogenetics in Gaucher Disease. *Archives of Neurology,*50, 1212-1224. [doi:10.1001/archneur.1993.00540110088009](http://archneur.jamanetwork.com/article.aspx?articleid=592621).

[[5](http://www.ncbi.nlm.nih.gov/pubmed/12489486)] Beutler E, West C. Polymorphisms in glucosylceramide (glucocerebroside) synthase and the Gaucher disease phenotype. Isr Med Assoc J, 4: 986–988, 2002

[[6]](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2830832/) Sun Y, *et al.*(2010). Neuronopathic Gaucher disease in the mouse: viable combined selective saposin C deficiency and mutant glucocerebrosidase (V394L) mice with glucosylsphingosine and glucosylceramide accumulation and progressive neurological deficits. *Mol Gent Metab, 19(6), 1088-1097.*