Application Title: The efficacy of pharmaceuticals in the treatment of adult polyglucosan body disease

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Abnormal accumulation of glycogen or polyglucosan (PG) causes diseases that can affect multiple organ systems, such as muscular, nervous and/or cardiac. Lafora disease and APBD are typical examples of PG storage. PG also accumulates in other genetic diseases like; phosphofructokinase deficiency (GSD VII) and a newly described myopathy/cardiopathy due to mutations in the ubiquitin ligase RBCK1. PG also forms in the aging brain known as corpora amylacea. Dr. Minassian and his group (Toronto, ON Canada) have shown that elimination of PG in Lafora mouse models by reducing glycogen synthase activity has ameliorated symptoms. Developing methods that clear PG will help us understand the mechanism and pathogenicity of this inert molecule and design treatments for glycogen-storage diseases (GSD).

We have developed a mouse model of polyglucosan body disease which accumulates PG in brain, muscle liver and heart. We have also shown that embryonic fibroblasts of this mouse model accumulates detectable amount of PG. We used this cell line for high throughput screening (HTS). Out of 1700 pharmaceutical compounds, HTS analysis showed that two compounds (A and B) decrease glycogen accumulation. Because compound A is available and used for clinical treatments, we propose to test the effectiveness of this compound in our mouse model of APBD. We will study A by exploiting the fact that our disease model shows generalized glycogen storage, affecting especially the central nervous system and skeletal muscle. We will test two originally accepted doses, and monitor the effect of compound A on glycogen content and synthesis in brain, heart, liver, and muscle. This research will open not only a new door for the treatment of GSDs but also teach us about the mechanism of GSDs.