Application Title: Drug development for treatment of glutamate dehydrogenase hyperinsulinism

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Congenital hyperinsulinism (CHI) is a disease in which the pancreatic beta-cells secrete too much insulin. Insulin is a hormone that lowers blood glucose levels. CHI is the most common cause of low blood sugar in infancy and carries a high risk of permanent brain damage. The gain of function mutations of glutamate dehydrogenase (GDH) is the second most common form of CHI. GDH is an enzyme which plays an important role in amino acid metabolism. Patients carrying the GDH mutation have a high secretion of insulin and, consequently, low blood glucose, especially after a protein rich meal. Those patients also have high ammonia levels in their blood, suggesting abnormal amino acid metabolism; they also have epilepsy, indicating the systemic impact of mutant GDH on human health. The only available long-term treatment of the GDH form of CHI is targeting beta-cells with diazoxide to inhibit insulin secretion, but this only treats the symptoms and not the cause of the disease. In addition, diazoxide has numerous side effects, including heart failure. Therefore, a new drug which can directly inhibit the mutant GDH is certainly needed. Such a GDH inhibitor would be an ideal treatment, because it could not only control the excess insulin secretion, but also benefit liver or kidney and brain function by controlling high blood ammonia levels and epilepsy.

In early investigations, we identified that EGCG, a component of green tea extract, is a potent inhibitor of GDH. In a proof of concept experiment, we confirmed that high-dose EGCG can inhibit amino acid-induced hypoglycemia in GDH transgenic mice, which is a disease mouse model of GDH-CHI. However, EGCG is not a feasible drug due to its poor bioactivity. In order to develop a better GDH inhibitor, we performed a high throughput drug screening based on a large compound library. We identified several lead GDH inhibitors which can inhibit mutant human GDH. This proposal will help us discover if those lead GDH inhibitors can inhibit amino acid stimulated insulin secretion and increase blood glucose levels in the disease mouse model. In this proposal, we will further identify the most potent candidates for clinical study. The ultimate goal of this study is identify a safe and potent GDH inhibitor to treat GDH-CHI.