Principal Investigator:	
Abbreviated Title of Research Proposal:	

Section II - Research Plan Summary

Full Title of Research Proposal

Tissue specific evaluation of *GNE* driven sialic acid production *in vivo* using Cre/lox transgenesis.

Abstract of Research Plan: *Do not exceed the space provided (one page), and use font size of 10 point or larger. This is meant to serve as a description of the proposed work when separated from the application. If funded, this may be made public so should not include confidential information.*

Heterologous inclusion body myopathy is a neuromuscular disorder, caused by mutations in UDP–*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine (ManNAc) kinase (*GNE*), the key enzyme of sialic acid biosynthesis. Currently, it is assumed that the activity of the GNE gene is required in the muscle, which is the tissue affected in this disease. Accordingly, most therapeutic approaches focus on myoblast-based protocols, given this disorder presents primarily as progressive skeletal muscle wasting where muscle biopsies show rimmed vacuoles upon analysis. However, it is shown that whilst the target tissue for HIBM is the muscle, the expression and activity of *GNE* is much greater in the liver than in the muscle itself. We propose that GNE-dependent sialic acid produced in the liver would function in an endocrine manner to sialylate tissues throughout the body, and that the point mutations observed in HIBM may impact on the delivery of sialic acid to muscle tissue in an endocrine fashion.

In order to address this hypothesis, we will create mice carrying a GNE allele in which exon 3 is flanked by loxP sites (GNE^{flox}), so that it becomes prone to inactivation upon expression of the Cre recombinase. We will then remove GNE specifically from the liver or muscle by crossing these mice with transgenic lines that express the Cre recombinase in hepatocytes (Albumin-Cre or MX-Cre inducible) or in muscle (MEF2C-Cre or MCK-rtTA/TetOCre inducible). Phenotypic analyses of these mice over a range of developmental ages and with GNE inactivation from early development or induced at different stages during adulthood will allow a clear evaluation of the relative importance of the hepatic and muscular *GNE* activity in the physiopathology of HIBM. In addition, they will provide critical information to direct future therapeutic approaches whilst providing useful models for the evaluation of these therapeutic avenues for HIBM in the future.