The following broad challenges in GNE Myopathy research are interlinked with developing safe and effective gene therapy options.

Comprehensive understanding of mutations in GNE Myopathy patients

GNE Myopathy is a recessive disease caused by two pathogenic mutations in the gene called GNE. The GNE gene contains the instructions to make a protein that has two known enzymatic functions required to eventually produce sialic acid. Currently there are over 160 different mutations across GNE associated with this disease, where there are no patients with complete absence of GNE protein suggesting that some functional GNE is required for survival.

Knowing the biological products (i.e. ManNAc and sialic acid) that GNE is solely responsible for producing provides a rational approach to therapy, through dietary supplementation. This supplementation strategy has shown some promise but the results have not been significant or are inconclusive and thus require more clinical trials with different study designs. However, this result may suggest that GNE has additional function that supplementation cannot entirely mitigate the disease pathogenesis. Also, there is variability in age of onset, severity and progression in patients carrying the same GNE mutations between carriers in the same family and also between unrelated carriers.

We are currently in the planning stages of performing genome sequencing in a strategic cohort of patients carrying particular GNE mutations, which aims to (1) identify genetic variants within GNE and elsewhere that may be contributing to this variability and further our general understanding of GNE genetics and function (2) identify other genes that may be contributing to the disease (3) correlate outcomes measured from clinical trials to better plan future cohorts.

The lack of ideal pre-clinical models for testing therapies

Pre-clinical models are routinely used to test therapies and are typically patient cells and/or mouse models that have overlapping features of the corresponding human disease. In GNE Myopathy there is no ideal model for either of these. In human samples there is no difference in GNE protein levels between patients and healthy individuals. In addition, there is high variability in measuring both GNE enzymatic function and sialic acid levels within samples from patients and healthy individuals. Therefore, there currently exist no reliable measurement (i.e. biomarker) that can differentiate patient cells from healthy cells.

There are a few mouse models of GNE Myopathy but only one that has some reduced muscle function that is reproducible but none have the rimmed vacuoles and other degenerative muscle features typical of the human disease. This suggests the disease process in mice lacking functional GNE may be different to humans and hence not entirely ideal to test therapies. Furthermore, it highlights our incomplete understanding on how mutations in GNE cause a myopathy.

Progress of gene therapy and current challenges

In GNE Myopathy the goal of gene therapy is to provide a functional copy of the GNE gene to halt or delay the progression of the associated muscle wasting. Gene therapy has been applied to a GNE mouse model demonstrating safety and some improvement in muscle function. Although these initial results appear promising and has demonstrated safety, it's unclear how this can be translated to maximize benefits to patients. The remaining challenges are related to optimizing the effective delivery of gene therapy and include but are not limited to (1) What dosage should be used to ensure that a sufficient amount of cells express GNE to show benefits in halting the progression and improvement in everyday life activities (2) the effects of unregulated expression of GNE (3) Should other tissue/cells be targeted beyond muscle? (4) How long lasting a single dose and whether multiple future doses are required (5) Lastly, if being involved in earlier gene therapy trials will preclude patients from receiving future gene therapy approaches.