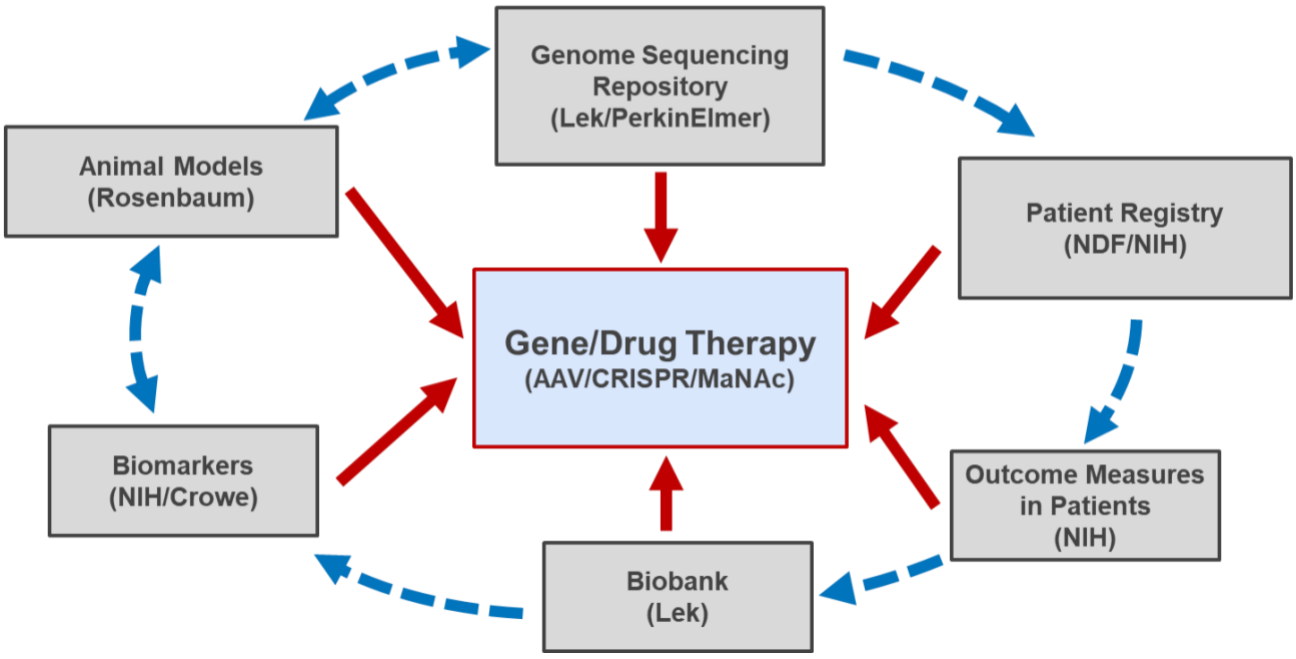
NEUROMUSCULAR DISEASE FOUNDATION
JOIN THE GLOBAL EFFORT TO CURE NEUROMUSCULAR DISEASES

Current Status of Therapy Development

Several factors contribute to the successful development of an effective therapy to HIBM

- Identification and optimization of a therapeutic approach (AAV-mediated gene therapy, gene correction strategies, drug replacement/development therapy)
- Development of outcome measures (critically important in diseases characterized by slow progression like HIBM)
- Identification of biomarkers to be used to validate efficacy as well as identify new drugs that can slow down disease progression
- Establishing a patient registry to use for clinical trials
- Generation of animal models to validate therapy efficacy
- Repositories of data and biological specimens to identify biomarkers/outcome measures



SUMMARY OF PROPOSALS SUPPORTED BY NDF IN 2019

Project 1. Development of animal models for GNE myopathy (Hadassah/Rosembaum
The goal of the project is to develop a mouse and a zebrafish model lacking expression of GNE. Progress reports submitted to the NDF show that both projects are on their way. The mouse model project appears to have stalled at the identification of 2 founders obtained early during the 2-year funded study. NDF will follow up to ask for clarifications and, if needed, subcontract this part of the project to a third party to ensure that the project stays on track and that by the end of the proposed study, we have a model to share with other institutions assessing therapeutic efficacy/possible biomarkers. The zebrafish model appears to show promising results.

Project 2. Biobank (M. Lek/ A. Lek)
The goal of this project is to establish a repository of cells from patients, family members and eventually animal models as a resource for the HIBM community of scientists and pharmaceutical companies for research purposes (including identification of biomarkers and to validate therapeutic applications). To date, the Lek lab was able to establish and bank 40 cell lines. All are available as fibroblasts (skin cells) as well as myoblasts (muscle cells). DNA and RNA have been collected and stored for upcoming sequencing and samples have been already shared with other investigators in the HIBM field (Noah Weisleder-Ohio State University, Kelly Crowe-Mount St. Joseph University). Future plans include further collection and storage of samples that contain different mutations so as to obtain a good representation of all HIBM patients worldwide.

Project 3. Whole Genome Sequencing (WGS) (M. Lek/ PerkinElmer)
Of the 100 samples originally contracted with PerkinElmer (PE), a total of 40 samples have been collected and WGS has been carried out accordingly. Samples were obtained from NIH (8 samples, 2 families), India (18 samples), Israel (27 samples), Philadelphia (26 samples). One family (5 samples) overlap with NIH samples. Sequencing of 40 samples completed and raw data was shared by PE. Raw data is currently being processed and analyzed in the Lek lab.

Project 4. Identification of Biomarker (NIH/M. Huizing)
The proposal is focused on identifying biomarkers and gene modifiers that could play a role in disease progression. Analyses could identify new players in the disease as well as new potential outcome measures to use in clinical trials to validate the efficacy of the therapy. Currently, there are 22 GNE-M patients from the Phase 1-ManNAc trial and 12 patients from the Phase 2-ManNAc trial, whose blood has been tested for differences in free Neu5Ac from baseline levels. Quantitative lectin analysis on muscle biopsy slides at baseline and
after 30 days of ManNAc therapy in 12 patients in the NIH Phase2-ManNAc trial show significant differences in hyposialylation of GNE-M muscle tissue after 30 days ManNAc therapy compared to baseline, suggesting that this assay could be used as possible outcome measure although it requires invasive procedures like collection of muscle biopsies. Current studies are now focused on identifying additional biomarkers which require less invasive procedures (Sialylated Blood Glycans, Plasma T-ST Ratios).

Project 5. CRISPR gene editing approaches to GNE (A. Lek)
The project is focused on conducting proof-of-concept studies in cells in vitro and at correcting the M743T mutation in patient fibroblasts. According to the most recent progress report, the cell lines and constructs needed to carry on the project have been successfully generated and results on the feasibility of using CRSPR-mediated gene editing approaches should be obtained by the end of the funded project.

Project 6. Lectin Staining Biomarker for GNE Myopathy (NIH/Crowe)
The goal of this proposal is to test levels of GNEM biomarkers in patient cells in vitro before and following gene therapy. A progress report was submitted showing that the project has been carried out as proposed, although it is too early to determine the success of the proposal.