Cystic fibrosis (CF) remains the most lethal autosomal recessive disorder in Caucasians, affecting around 70,000 people worldwide. With over 2,000 known disease-causing mutations in the CF transmembrane regulator (CFTR), it is unsurprising that there is no current “treatment for all”. Therapeutic approaches are advancing for some of the most common disease-causing mutations in CF, but are slow for the cohort with rare mutations, largely due to lack of access to relevant cells for use in research and drug development. CF causative mutations are categorized based on their functional consequences; nonsense mutations, including Mallory’s R1158X mutation, occur in ~10% of CF cases and lead to the generation of a premature termination codon (PTC) halting production of the CFTR protein. In order to cure all CF patients, there is a critical need to develop new research strategies to generate readily expandable cells representing all rare causative mutations.

This Orphan Disease Grant for Movin’ for Mallory will fund research to develop a new model system for nonsense mutations using pluripotent stem cells (PSC) in combination with state of the art gene editing technology. In lieu of patient specific cells we will be able to generate clonal self-renewing sources of mutant cells and differentiate them to lung epithelium. Our laboratory has developed a reproducible differentiation strategy to produce airway epithelial cells and to edit the DNA at specific loci. We will generate PSC with edited genomes to represent three nonsense mutations and then differentiate into lung stem cells and mature lung epithelial cells. In collaboration with the CF foundation research laboratories, will assess CFTR activity in response to currently available therapeutics to corroborate our approach using PSC from more common mutations. After validating this proof-of-principle approach we will then establish conditions for scaling of the platform for a future industry collaboration to carry out high throughput screening for regulators of CFTR read through for our three nonsense mutant PSC and, subsequently, all known nonsense mutations.