Lay Summary

The objective of this research proposal is to develop a new class of therapeutics that could rescue the folding and trafficking defect of most NPC1 variants found in the clinical population.

A paradigm shift is emerging in terms our understanding of how a protein like NPC1 folds and functions in the cell, and what goes wrong in human inherited disease. Inherited diseases create a problem that is not only devastating to the family, but an almost incomprehensible challenge to clinicians. What is different about our approach than that of the current approaches used for drug development is that we use emerging, evolutionarily conserved protein folding homeostasis or simply 'proteostasis' concepts that nature has applied for 3.5 billion years to make us who we are at this moment in time and space. Proteostasis operates by optimizing survival on a daily basis and fitness in the long-term- rules that now need to be applied to rare diseases such as Niemann-Pick, a disease that challenges these rules from the day you are born.

Fundamentally, we take advantage of these 3.5 billion years 'preliminary results' that tell us how biology uses misfolding prevention systems to ensure normal function*. In other words, we are not trying to dictate to biology how to fix a problem, rather we gently nudge biology to adapt a slightly altered way of 'thinking' to adjust the physiology problem associated with NPC1 disease back into the realm of healthy activity to provide benefit to the patient. We know this strategy works based on recent successes in other diseases in the clinic, particularly Cystic Fibrosis.

Our first-in-class approach will now apply a class of newly developed therapeutics we call 'folding regulators" that we have recently found to restore NPC1 variant trafficking and normalize cholesterol homeostasis, as a new approach to treat the disease in the clinic. In our initial efforts, we have identified two novel proteostasis regulators (referred to as NPC1-C1 and NPC1-C2) that correct the folding and trafficking of the highly divergent disease-causing I1061T and G1240R mutants- thereby leading to a reduction in cholesterol accumulation in LE/LY compartments. The ability to correct the function of divergent variants raises the hope that many variants may also be accessible to the same therapeutic and therefore robust for a clinical development program. These folding regulators exploit the properties of key cellular 'chaperones' and their 'cochaperones' (proteins that function like parents to keep their kids out of trouble!) to favor function over the inherited dysfunction that occurs at birth. Given our discoveries to date, the first goal of our therapeutic approach will be to optimize the activity of our newly discovered compounds. The second goal will be to get the optimized corrective compounds into disease models (both mouse and cat models of NPC1 disease) that allow us to test efficacy in the context of the physiology of the mammalian environment. The third goal will be to understand exactly how these compounds work- with the hope of identifying even better second-generation compounds.

In general, we think this new approach, an approach that uses 'biology to correct biology' through pathways that are operational on daily basis in each and every person, whether healthy or sick, provides an opportunity to not only rethink what is Niemann-Pick disease, but how to manipulate the folding environment to make a NPC1 variant triggering disease more functional during a patients lifespan and thereby alleviate disease symptoms. Of course, many challenges remain, but this first-in-class approach is really not new- as I mentioned, nature has been doing it for 3.5 billion years- we just need to learn how to adapt its rules to challenges faced by all NPC1 patients that have the common problem of a protein that fails to do the job it should be doing!

Kanagaraj Subramanian