Principal Investigator: Ajit Varki
Abbreviated Title of Research Proposal: **Engineering Human-like Sialic Acids in Mice with HIBM**

Section II - Research Plan Summary, Cont. (2)

Lay Summary: (Do not exceed space provided) This lay summary to be used and published as ARM sees fit.

Our laboratory has a longstanding and pioneering role in the field of sialic acid (Sia) research. Sias are sugar molecules decorate the surfaces of all cells in humans and mice. Because of their terminal position on complex sugar chains they are known to mediate or modulate many biological processes like embryonic development, normal tissue organization, tumor metastasis, and in the interactions with pathogens. HIBM is an adult onset neuromuscular disorder associated with mutations in the gene involved in the first two steps of Sia biosynthesis. Dr. Daniel Darvish recently created a mouse strain bearing the founder mutation of the Iranian-Jewish IBM2 patients. There is one major flaw in using this mouse as a model for human disease. It so happens that normal humans have another genetic defect in Sia metabolism, i.e., the absence of the common mammalian Sia called N-glycolylneuraminic acid (Neu5Gc). The CMAH mutation responsible for this metabolic difference is unique to humans, and universal to all human populations. Meanwhile, we had generated a mouse that has a CMAH defect identical to that of humans. Thus, we feel that mating the two mice would produce a Sia biology situation much more closely analogous to that of the human condition. Such mice will be characterized by multiple methods. One particular goal would be to test the hypothesis that these mice (like humans) may incorporate Neu5Gc from exogenous dietary sources. If so, it will suggest whether the human sialic acid Neu5Ac can also be used to treat mice and humans. Finally we can ask how Neu5Gc incorporation might influence the disease progression. We look forward to being involved in HIBM research, and are committed to contribute to increase the understanding of the underlying mechanisms, and with the ultimate goal of helping develop treatments for patients with HIBM-associated GNE mutations.