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

Lay Summary: *Do not exceed space provided, and use font size of 12 point or larger. This lay summary to be used and published as ARM sees fit.*

Inclusion body myositis type II (**IBM2**) is a genetic condition that causes subjects to exhibit muscle weakness between ages of 25-35 and often progresses to severe disability. The disorder is caused by mutations on the **GNE** gene which encodes for the bi-functional enzyme UDP-N-Acetylglucosamine 2-Epimerase / N-Acetylmannosamine Kinase (GNE/MNK). Unfortunately, there is currently no treatment for the disorder. The objective of this proposal is to develop a gene therapy approach for treating this disorder.

Gene therapy hold great promise for treating disorders like IBM2. In principle, it is a simple approach to treating genetic disease. If the gene is broken, why then just fix the broken gene. In fact for genetic diseases like IBM2, which are recessive, the approach is even simpler in that one does not have the fix the broken gene but just have to add the normal working gene back into the affected cells of the patient. This is because the broken gene does not actively cause a problem but it is just not working. Giving back the normal working disease restores the ability of affected cell to work and restores health. Despite this great promise of gene therapy, it has not been possible to safely and effectively deliver the genes into patients. For IBM2, the target cells and tissue are skeletal muscle, especially in the limbs.

Wolff and colleagues have recently made a breakthrough in the ability to deliver genes into limb skeletal muscles. It is a surprisingly simple but very effective method. As an example, for delivery to arm muscles, it involves a rapid injection of a gene into a hand vein. At the same time, a tourniquet (e.g., a blood pressure cuff) is placed around the upper arm so that the injection fluid and gene remains in the arm. This procedure has been termed Pathway IV.

The gene is in the form of naked plasmid DNA which can easily be prepared in bacteria. Once a normal gene for IBM2 is obtained then one can use it in all people. This is not like transplantation where one has to keep on obtaining a gene from relatives. This is because the normal gene for IBM2 is similar among all people.

Wolff and colleague are planning to start a clinical trial within a year to test whether the Pathway IV procedure is safe and effective in people with Duchenne/Becker muscular dystrophy. If the results from this FITM (first time in man) trial indicate that the Pathway IV procedure is safe and effective, then it would be of interest to apply the procedure to treat people with IBM2. In order to be ready to begin a gene therapy clinical trial for IBM2 as soon at the first Pathway IV clinical trial has been conducted, it is necessary to conduct a number of pre-clinical studies- the focus of this grant application. The studies will involve gene expression experiments in models of the disorder. The results from these proposed studies will be critical for achieving regulatory approval to initiate a clinical trial for IBM2 as soon as possible. The aim of such a clinical trial would be to preserve hand and forearm function so as to maintain the quality of life.