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Duchenne Muscular Dystrophy Research Projects
Prepared for the Fighting Duchenne Foundation
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Research Focus Update:
The ongoing support from the Fighting Duchenne Foundation has continued to promote a collaborative Duchenne focused research environment here at Vanderbilt. As outlined below, we have included additional research labs on campus that have proposals related to muscular dystrophy that they are moving forward. The gifts from the Fighting Duchenne Foundation have been investments in like-minded individuals who are committed to DMD care and research advancement. Similar to the way Dr. Soslow utilized Fight DMD funds to support his successful grant applications (American Heart Association and NIH/NHLBI K23), there has been additional grant applications which have resulted from current support.

Dr. Markham (M.D. Cardiology) We are participating in a multi-center international project entitled, "Sudden Cardiac Death in Pediatric Duchenne Muscular Dystrophy: What is the Incidence, and How do We Prevent it?" To date, the proposal includes 12 centers (9 within North America and 3 international). This study is an international registry to collect data related to cardiac care required for advanced Duchenne Muscular Dystrophy (DMD) and the incidence of Sudden Cardiac Death in this population. The goal would be to identify 5000 DMD boys to follow over time. We have utilized Fighting Duchenne Foundation Gift funds to support our involvement in this study. This is an ongoing project that has been supported 1 year. **Total: $15,000** ($5,000 per year x 3 years total).

Our research nurse has been instrumental for the research program to be successful enrolling patients in study activities. The RN has been responsible for assisting Dr. Soslow and Dr. Markham in collecting the necessary data and meeting regulatory requirements. Ongoing support is needed given the increased research effort. This is an ongoing and increasing need. **Total: $15,000** ($5,000 per year x 3 years).

Dr. Soslow (M.D. Cardiology) Fat accumulation in heart muscle can lead to abnormal heart function, and our preliminary data suggest this may be a significant issue in boys with DMD. We are starting to utilize Magnetic Resonance Spectroscopy to evaluate the accumulation of fat in heart muscle. Depending on the initial data, the plan would be to proceed with a small human clinical trial evaluating a therapy such as metformin, then pursue additional grant funding. Initial funding of the pilot data for 10 magnetic resonance spectroscopy studies has been provided. We are currently enrolling healthy control subjects and performing cardiac MRIs for comparison to boys with DMD. There is potential to require more MRIs for comparison.

Dr. Galindo (Ph.D. Cardiology) was instrumental in performing the studies in a collaborative research project with Texas A&M evaluating the differences in gene expression between skeletal and cardiac muscle in the dog model of DMD. This work which was part of our previous Wellstone grant application (did not get funded) has been accepted for publication in the journal Pediatric Research (*Translating golden retriever muscular dystrophy microarray findings to novel biomarkers for cardiac/skeletal muscle function in Duchenne Muscular Dystrophy*). This work is the preliminary data for additional grant applications as follows: a. *Mechanisms and Assessment of Brain-Derived Neurotrophic Factor (BDNF) as a Treatment for Duchenne Cardiomyopathy* which is a Department of Defense Investigator Initiated Research (Budget $575K total, maximum of 3yrs). The application has passed the pre-review stage; b. *A three-dimensional , patient-specific culture system for testing current and new therapies for Duchenne cardiomyopathy* which is an American Heart Association, NCRP Innovative Research Grant (Budget $150K total, maximum of 2yrs) in addition to a Parent Project Muscular Dystrophy Exploratory Grant ($50K total).

Dr. Schoenecker (M.D., Ph.D. Orthopedics) and his laboratory are working on mechanisms of muscle regeneration. His lab has done extensive work to demonstrate that plasmin is essential for muscle regeneration, and that in the process, it is consumed. Hence, the hypothesis, that restoring the tank will enhance healing, and reduce scar in the injured muscle. They have already performed the analysis of the MDX mice in regards to their degenerative phenotype. With the original $20,000 gift from Fight DMD, work has been completed as the preliminary data for additional grant applications as follows: Department of Defense Therapeutic award (Budget $471K total, maximum of 3yrs). The application has passed the pre-review stage; b. American Heart Association (Budget $900K). The purpose of this proposal is to test the idea that improving the activity of plasmin in DMD has the unique potential to directly improve the healing of the limbs, lungs, and heart, thereby extending the lifespan. To accomplish this, the investigators have developed a new drug that can be injected one time every three weeks and allows plasmin to work at a much greater level, thus making up for the lower levels of plasmin seen in children. The investigators will test this drug first in mouse models of Duchenne Muscular

Dystrophy and monitor the function of the limbs, lungs, and heart, and overall survival of the animal. Given that the human version of the drug being tested in mice is already available, the immediate next step would be to conduct similar studies in humans.

Dr. Carrier (Ph. D; working with Drs. James West and Anna Hemnes in the Pulmonary Division) recently completed studies of a drug that dramatically decreases cardiac fibrosis in a pulmonary artery banding model of pulmonary hypertension. As they are moving toward clinical trials in patients with secondary pulmonary hypertension, we suggested that they also look into muscular dystrophy models, because so many DMD patients experience cardiac fibrosis as part of their cardiomyopathy. With the original $20,000 gift from Fight DMD, they have purchased and are breeding genetically modified mice (a double knock out mdx which has more severe cardiac disease and the delta-sarcoglycan knock out). They are moving forward with testing of the animals to see if this drug can impact cardiac fibrosis/function with skeletal muscle fibrosis and function as secondary endpoints. The drug is already being used in adult humans so safety data will be known to make a determination if this would be an option for DMD. Preliminary data is expected in the next 3-6 months.

Publications (First author and status):

1. Increased myocardial native T1 and extracellular volume in patients with Duchenne muscular dystrophy (Soslow submitted and accepted pending revisions)
2. The correlation of skeletal and cardiac muscle dysfunction in Duchenne muscular dystrophy (Soslow submitted and accepted pending revisions)
3. Translating golden retriever muscular dystrophy microarray findings to novel biomarkers for cardiac/skeletal muscle function in Duchenne Muscular Dystrophy (Galindo accepted)
4. Body mass index does not predict premature cardiomyopathy onset for Duchenne muscular dystrophy (McKane submitted)