Executive Summary

Anti-Inflammatory Therapies for Duchenne Muscular Dystrophy

Parent Project Muscular Dystrophy (PPMD) convened a meeting of experts December 7-9, 2005 in Los Angeles, CA to discuss the potential opportunities for the use of anti-inflammatory therapies in the treatment of Duchenne Muscular Dystrophy (DMD). The objective of this meeting was to bring experts together to assess the state of the science in inflammation and to develop broad strategic directions for basic and applied research in this area. The meeting sought to determine whether there was any consensus on the use of anti-inflammatory therapies in DMD and to identify promising research priorities that might accelerate the development of new, effective therapies.

Priority Issues

The discussion among experts at the meeting generated the following priority issues:

Basic Science Research Priorities in DMD

- The mechanisms of inflammation in Duchenne.
  - The research community needs to study the underlying mechanisms of inflammation and fibrosis in Duchenne to examine and understand the inflammatory cell types and processes that characterized these mechanisms.
- Characterization of the differences between skeletal and cardiac muscle involvement in DMD.
- Standards of care for procedures and experiments with mice
  - Having a mouse consortium and a meeting on standards to assess disease pathology in mice would allow greater transparency in research and faster progress towards identification of potentially useful drugs.
  - Development of more “high throughput” analyses in vivo will speed drug discovery and identification.
  - Identification of biomarkers will make it easier to evaluate the severity of disease in mice and in human clinical trials.
  - Along with a mouse consortium, the idea of testing the same compounds in different mouse facilities will allow for the identification of truly promising compounds and eliminate “lab specific”, false positive results.

Anti-Inflammatory Drug Research and Development

- The systematic study of FDA approved anti-inflammatory therapies in the mdx mouse model.
  - An exhaustive literature review of anti-inflammatory therapies in other diseases could be of great use and help in expediting the study of anti-inflammatory agents.
  - Anti-inflammatory agents of interest include: Enbrel, Remicade, P188, Th1, Th2, drugs that target nitric oxide and nitric oxide synthase, L-Arginine, TGF-β as well as other anti-inflammatory and anti-fibrotic drugs.
- The pre-emptive introduction of therapies, prior to the onset of symptoms, and/or the identification of critical time points in the progression of the disease when therapies are most effective.
  - Critical time points must also drive research efforts and influence the age of animal models being used.

Clinical Care of Patients with DMD

- Uniformity in Standards of care for patients with DMD
o Standards of care need to established and disseminated.
• Biomarkers to monitor disease progression in skeletal and cardiac muscle d.
  o Osteopontin and cTnI show promise, but need additional research.
• In addition to biomarkers, standards for functional markers.
  o Echo vs. MRI; QMT vs. MET; walking vs. stair climbing.
• Identification of research and clinical endpoints...
  o Does treatment improve function and how well does therapy translate from animal models to humans?

Clinical Trials
• Establishment of a clinical trial network.
  o Clinical trials are restricted because the patient population is limited. We need clinical trials that are focused on subgroups within the DMD population and patients need to be matched with appropriate trials.
• To address the best treatment regimens in DMD, the conduct of clinical trials in parallel using different drugs and varied regimens.
  o The lack of standards is evident in the use of steroids; steroid dosage and regimen are varied and systematic research in which different steroids and regimens are studied in parallel need to occur.
• Consensus on the ethical propriety of steroid naïve trials.
  o Prior to steroid use in young children, does a six month period exist in which steroid naïve clinical trials could be conducted, or is depriving DMD children of steroids ethically wrong?
• Creation of a muscle tissue bank for use in Duchenne research, allowing for sharing of tissue samples.
  o The question of biopsy and/or autopsy must be reframed.
  o An open biopsy cannot be required and an educational campaign would be essential to teach parents and caregivers about tissue biopsy and means of collection that are less invasive and less threatening.
   Identification of the “best” outcome measures to use in clinical trials and increased communication between groups that will allow for standardization of all clinical trials. This will facilitate comparisons from group to group and speed progress.

Cardiac Care of Patients with DMD
• Early focus on cardiac involvement in DMD patients.
  o How can a standard of care for early testing and detection of cardiac myopathies be developed?
  o How do we create the necessary paradigm shift in the treatment of cardiac myopathies in DMD patients?
• Understanding cardiac involvement in inflammation and cardiac risks associated with anti-inflammatory therapies.

The DMD Community
• Reduction in the fragmentation of the DMD community needs to be addressed and
• New collaborations between the different groups of DMD care givers and patients

The Anti-Inflammatory Therapies in Duchenne Muscular Dystrophy Conference successfully identified many areas of priority in the area of inflammation and anti-inflammatory agents as well as in the larger research world of DMD. In the area of inflammation and anti-inflammatory therapies, great advances must be made. Researchers need to study the mechanism of inflammation as well as potential therapies. Progress in this area is dependent on making it a research priority, studying the underlying molecular basis of inflammation, potential therapeutics and ultimately improving the care of the boys. There was a consensus that the immune system has the potential to serve as a viable target for treatment to delay progression of DMD; however, that more research is necessary to dissect mechanisms and identify specific immune targets.