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Executive Summary

The muscular dystrophies are a group of diseases that cause weakness and progressive degeneration of skeletal muscles. Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy and the translation of basic research into effective therapies has been slow. However, a number of therapeutic approaches are showing promise and the National Institutes of Health (NIH) is rigorously pursuing a broad-based research program in translational research in the muscular dystrophies. As part of this program, NIH recently funded two large-scale projects, one to develop new small molecule drugs for the treatment of muscular dystrophy and a second to improve therapeutic gene delivery to muscle.

Translational research in muscular dystrophy has been stimulated through two NIH initiatives released in November 2005, which are linked to the broader National Institute of Neurological Disorders and Stroke (NINDS) Cooperative Program in Translational Research. Projects at the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers are also focused on the development of therapies, including optimizing gene therapy and stem cell-based approaches. The recent reissue of the Request for Applications (RFA) for Wellstone Centers requires that applicants propose multi-disciplinary and collaborative studies that address one or more gaps in the therapeutic development pipeline for muscular dystrophy.

In June 2007, NIH sponsored a workshop on translational research in muscular dystrophy. The workshop brought together representatives from NIH, the Food and Drug Administration (FDA), academia, industry, and patient voluntary groups to discuss the status of different therapy development approaches and how to identify the most promising strategies. A summary of the workshop is published online (http://www.ninds.nih.gov/news_and_events/proceedings/Translational_Research_in_Muscular_Dystrophy.htm) and is also included in this report.

Translational research is also well represented in the Muscular Dystrophy Coordinating Committee’s (MDCC) Action Plan for the Muscular Dystrophies. Research objectives include several approaches to therapy development, including ones that are currently being funded by NIH. To contribute to the implementation process, MDCC members identified those components of the plan that their agency or organization is contributing toward or can contribute toward in the future. A table listing that information is included in this report. In fiscal year (FY) 2006, NIH began fiscal reporting for each of the five broad categories in the plan, and this data is presented in this report as well. Recent accomplishments related to the five broad categories of the plan will be appended to the plan within the next year, and accomplishments and initiatives by all MDCC member agencies and organizations will be tracked via the public MDCC website (http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm).
MUSCULAR DYSTROPHY TRANSLATIONAL RESEARCH

Introduction

In its report on the Fiscal Year 2008 budget for the Department of Health and Human Services, the House Committee on Appropriations stated:

The Committee is aware that NIH will be convening a conference focused on translational research opportunities for Duchenne and Becker Muscular Dystrophy (DBMD) this June. The Committee applauds NIH for taking this concrete step forward and requests that a comprehensive report summarizing the conference’s findings, identifying the most promising opportunities for a DBMD translational research initiative and establishing clear next steps to establish this initiative, be published within five months of the conclusion of the conference. The Committee requests the Muscular Dystrophy Coordinating Committee (MDCC) develop a clear action plan that includes, among all the identified goals, tracking of NIH funded grants against the identified scientific opportunities for DBMD translational research, and mapping areas of investment and areas of unmet opportunity, by February 1, 2008. (House Report 110-231, page 138)

The following report has been prepared by the National Institutes of Health (NIH) of the Department of Health and Human Services in response to this request.

Overview of Translational Research in Muscular Dystrophy

The muscular dystrophies are a group of diseases that cause weakness and progressive degeneration of skeletal muscles. There are many different forms of muscular dystrophy, including Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, myotonic dystrophy, facioscapulohumeral muscular dystrophy (FSHD), and limb-girdle muscular dystrophy. The various forms differ in their mode of inheritance, age of onset, severity, and pattern of muscles affected. Most types of muscular dystrophy are multisystem disorders with manifestations in body systems including the heart, gastrointestinal and nervous systems, endocrine glands, skin, eyes, and other organs. DMD is the most common childhood form of muscular dystrophy, and is caused by mutations in the gene for the protein dystrophin. Dystrophin is part of a complex structure involving several other protein components. This “dystrophin-glycoprotein complex” helps anchor the structural skeleton within the muscle cells, through the cell’s outer membrane, to the tissue framework that surrounds each cell. The mdx mouse, which lacks dystrophin, is a widely used animal model to study DMD.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Although research has identified genetic and pathogenic mechanisms underlying DMD, as well as several of the other muscular dystrophies, the translation of basic research into effective therapies has been slow. Translational research is the process of applying ideas, insights, and
discoveries generated through basic scientific inquiry to the treatment and prevention of human disease. Translational research includes pre-clinical studies to test potential therapies and bring them to readiness for clinical trials. Based on a better understanding of the disease mechanisms at play in the muscular dystrophies, there are now multiple potential pathways to therapeutic development for these diseases. These include:

- **Developing drug-based therapies to maintain muscle mass.** Debilitating loss of muscle is characteristic of muscular dystrophy as well as other muscle disorders. Loss of muscle mass and function is primarily responsible for reduced quality and length of life. In the absence of a cure, drug treatment strategies may be able to inhibit the breakdown of muscle proteins.

- **Developing strategies to enhance the normal regenerative process of muscle.** Many muscular dystrophies share traits of progressive depletion of skeletal muscle regeneration and repair mechanisms. Applying knowledge of regeneration mechanisms may provide new therapeutic targets to offset muscle degeneration.

- **Developing cell-based muscle therapeutic strategies.** In muscular dystrophies due to inherited mutations in the dystrophin-glycoprotein complex (such as DMD), muscle degeneration results from the absence of key membrane-associated proteins. It may be possible to use stem cells to populate diseased skeletal and cardiac muscles with muscle fibers that express the absent proteins. These newly formed muscle fibers may be protected from the progressive degeneration characteristic of the disease and potentially restore muscle function in patients.

- **Developing, testing and improving strategies for gene replacement therapy.** Many of the dystrophies result from point mutations or deletions in identified genes or genetic regions. Gene or drug therapy strategies may replace the defective gene or increase expression of functionally equivalent genes that may compensate for the defective gene.

- **Developing and testing genetic modification therapies to bypass inherited mutations.** Some muscular dystrophy patients have mutations that cause gene product synthesis to terminate early, producing either no protein or defective protein. Several strategies including molecular drug and antisense exon skipping strategies can manipulate the steps leading to protein synthesis mechanisms in order to skip or “read-through” the defect in the gene. These strategies may allow diseased muscle to produce enough functional protein from the mutated gene to decrease or reverse the degeneration process.

- **Developing combination therapies.** Combination therapies that rely upon more than one of the strategies listed above may produce a more effective treatment than any single strategy provides.
NIH Activities in Muscular Dystrophy Translational Research

The NINDS, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Child Health and Human Development (NICHD), and National Heart, Lung, and Blood Institute (NHLBI) are the primary institutes at NIH that fund research on the muscular dystrophies. Funded projects at these four institutes include basic, clinical, and translational disciplines and span studies from understanding the basic molecular and cellular mechanisms of disease to developing and testing therapies and interventions to treat the disorders and improve the quality of life of patients afflicted with them.

Recently Funded Large-Scale Translational Projects

While NIH is rigorously pursuing all pathways to therapeutic development in muscular dystrophy, NIH recently funded two large-scale projects exploring a few of the more promising approaches. The first project aims to develop new small molecule drugs for the treatment of DMD and potentially other forms of muscular dystrophy. The project will pursue a number of strategies including stimulating muscle growth by modulating growth factor pathways and upregulating proteins that may structurally and functionally substitute for dystrophin or contribute in normal muscle cells to the dystrophin protein complex. The researchers have already completed a high-throughput screening process on each of these strategies in order to identify small molecules that are candidate therapies. The project will focus on improving the properties of these small molecules as drug candidates and carry out research that will help support further clinical studies using these compounds. One exciting aspect of this project is the fact that a patient voluntary organization and a biotech company are contributing funds to this project, thereby creating a public-private partnership to leverage funds. The second project is exploring diverse strategies to correct the dystrophin gene defect which causes DMD. The project is building on recent success of intramuscular delivery of a mini-dystrophin transgene (a region of the dystrophin gene plus the gene delivery vehicle) in mice. The researchers will test the safety and efficacy of vascular delivery (via the circulatory system), which may be more effective than intramuscular injection in delivering the transgene to widespread muscle groups. The project will test vascular delivery of the transgene in primates and will also explore ways to avoid an immune response to the transgene, which is a concern with gene therapy studies.

Both of these projects were funded through the NINDS Cooperative Program in Translational Research, a program that supports milestone-driven projects focused on the identification and pre-clinical development of drugs, biologics, and devices in cells and animals, leading to new and effective interventions for any neurological disorder. This program, in combination with the NIH Translational Research Initiatives in Muscular Dystrophy has been instrumental in increasing the amount of muscular dystrophy translational research funded by NIH.
To help take advantage of the multiple opportunities for therapeutic development in the muscular dystrophies, NIH released two specialized program announcements with set-aside funds and a special grant review environment for “Translational Research in Muscular Dystrophy” in November 2005. NINDS, NIAMS, and NICHD participated in these initiatives. These initiatives support (a) exploratory/developmental grants to identify candidate therapeutics, collect initial efficacy data, and develop in vitro/in vivo assays and (b) cooperative agreements that use a milestone-driven approach to support preclinical therapy development activities up to and including an Investigational New Drug application to the FDA. As part of the cooperative agreement, NIH extramural program staff work closely with the applicant to help develop and guide the project. To ensure that grants are reviewed by individuals with the appropriate expertise, the NIH convenes a special review panel made up of scientists with the highly specific expertise necessary to review applications received through this program.

These initiatives, in conjunction with the broader NINDS Cooperative Program in Translational Research, have already resulted in a dramatic increase in the number of applications received and funded by the NIH for development of novel therapies for muscular dystrophy. Successful applications have focused on both DMD and myotonic dystrophy, and use a range of strategies from small molecule drugs through gene therapy. For example, a cooperative agreement funded through the initiative is utilizing a vascular delivery (via the circulatory system) approach to allow for better access of the vector (gene delivery vehicle) to muscle and testing this approach in a canine model of DMD. Exploratory grants funded through the initiative are focused on finding compounds that upregulate genes that encode protein components of the dystrophin-glycoprotein complex. Another project is developing optimal vectors with enhanced gene delivery efficiency in dystrophic skeletal muscle using the mdx mouse. One project focuses on delivery of a protein that can act to compensate for the lack of dystrophin in DMD. Two projects focus on targeting mechanisms involved in myotonic dystrophy to develop therapies for that form of muscular dystrophy.

Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers

NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (www.wellstonemdcenters.nih.gov) which have been designed to accelerate the translation of fundamental scientific advances to the clinic through close interaction between basic researchers and clinicians. NINDS, NIAMS, and NICHD each fund two Wellstone Centers. Translational research projects at the Wellstone Centers are focused on optimizing gene therapy and stem cell-based therapeutic approaches as well as identifying therapeutic strategies to enhance muscle regeneration mechanisms. The research cores at a number of the Wellstone Centers support translational research efforts as well. Research cores are shared resources that are available to the entire muscular dystrophy research
community. In August 2007, NIH re-issued the request for applications (RFA) for Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers to solicit applications for new and competitive renewal applications for centers. NHLBI recently joined NINDS, NIAMS, and NICHD in the reissue of the RFA. The re-issue of the RFA requires that applicants propose multi-disciplinary and collaborative studies that address one or more gaps in the therapeutic development pipeline for muscular dystrophy. NIH anticipates awarding grants in response to the RFA in 2008.

Through the Wellstone workshop program, NIH provides supplements to Wellstone Centers to host conferences on important topics in muscular dystrophy research. An October 2007 conference focused on the use of animal models in therapy development.

Government Performance and Results Act (GPRA) Goal on Muscular Dystrophy Therapies

Under the 1993 Government Performance and Results Act (GPRA), federal agencies must set goals, measure performance, and report on their accomplishments. Each year, NIH Institutes develop new goals and propose strategies for achieving annual targets associated these goals. The White House Office of Management and Budget (OMB) grades each agency annually according to its success in achieving its GPRA goals. Because of the scientific promise in the area of muscular dystrophy therapy development, NIH proposed the following goal in FY 2007: “By 2013, advance two emerging new strategies for treating muscular dystrophy to the point of preparedness for clinical trials.” The GPRA goal demonstrates NIH’s commitment to this area of research and belief that research in a number of the therapeutic development pathways is poised to make significant advances toward testing therapies in patients in the next 5 years.

NIH Workshop on Translational Research in Muscular Dystrophy

In June 2007, NIH sponsored a workshop on translational research in muscular dystrophy. The workshop was held following a number of previous meetings organized by the muscular dystrophy community related to translational research and following the release of muscular dystrophy translational research initiatives by NIH as well as other organizations. This represented an ideal time to discuss the status of different therapy development approaches and how to identify the most promising strategies to move forward. The goals of the conference included: to summarize and evaluate the current state of translational research in muscular dystrophy; to identify obstacles to ongoing translational research; and to identify ways (processes, collaborations, and strategies) to facilitate the rapid progression of therapies in the muscular dystrophies based on experiences in these and other diseases. Participants at the meeting included representatives from NIH, FDA, academia, the pharmaceutical and biotechnology sectors, and patient voluntary groups. Key discussion points from the meeting are summarized
Participants reviewed the state of the science for multiple approaches to therapy development and discussed roadblocks for each of these approaches. They agreed with a broad-based approach for therapy development and supported pursuing multiple approaches to therapy development in parallel. This is particularly important since it is not clear which strategies will be successful and since combination therapy is likely to be necessary in treating the muscular dystrophies. Workshop participants noted the increase in recent years in the level of collaboration among the key partners in the muscular dystrophy field and remarked that the maturation of such partnerships is essential to achieving new therapies. They discussed obstacles to therapy development including recognizing the limitations of available animal models, but still moving forward with existing models rather than delaying the testing of therapies until the ‘perfect’ model is developed. Workshop participants also discussed the need to study mechanisms common to the different forms of muscular dystrophy and to take advantage of these similarities to expedite therapy development. They stressed the importance of looking ahead to clinical trials and beginning to define and validate endpoint measures. They emphasized that early consensus on preclinical and clinical measures would enhance the ability to compare different therapeutic strategies. The workshop concluded that a number of therapeutic strategies are showing promise and have a strong likelihood of leading to clinical trials in the next few years. Collectively, the muscular dystrophy field needs to take a broad view of therapy development and begin to identify and focus on the key ‘solvable’ issues in the field that may lead to effective drugs and biologics in a shorter timeframe.

Translational Research in the MDCC’s Action Plan for the Muscular Dystrophies

As part of its charge in the MD-CARE Act, the Muscular Dystrophy Coordinating Committee (MDCC), with input from scientific experts in the field, developed the Action Plan for the Muscular Dystrophies, which includes over 70 research objectives to accelerate progress toward the effective detection, diagnosis, treatment, and prevention of all types of muscular dystrophies. Following approval by the MDCC in November 2005, the Action Plan was sent to Congress and posted on the public MDCC website (http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm).

Research objectives in the Action Plan are divided into five broad categories: Mechanisms of Muscular Dystrophy; Diagnosis and Screening of Muscular Dystrophy; Therapy of Muscular Dystrophy; Living with Muscular Dystrophy; and Research Infrastructure Needs for Muscular Dystrophy. A number of the objectives are relevant to muscular dystrophy translational research. For example, understanding pathogenic mechanisms of muscular dystrophy will help identify
targets for therapy development. In addition, research objectives include several approaches to therapy development, including some that are currently being funded by NIH. For example, preclinical studies using growth factors, preclinical testing of myostatin inhibition, development of cell-based therapies, gene therapy (including the development of optimal vectors and delivery techniques and minimizing the immune response) and gene repair techniques are all discussed in the plan. One objective in the plan stresses the need to identify new strategies to implement translational research projects for muscular dystrophy. Several of the objectives related to research infrastructure also apply to translational research. These include the need for repositories of patient samples, the development of better animal models and other model systems, and the need for better distribution and availability of large and small animal models.

Implementation and Tracking of Action Plan Objectives

In its report on the fiscal year 2007 budget for the Department of Health and Human Services, the House and Senate Committees on Appropriations requested that the Muscular Dystrophy Coordinating Committee (MDCC) designate the agencies and organizations with responsibility for the goals in the Action Plan. To address the Committees’ requests, NIH asked the MDCC members to identify those components of the Plan that their agency or organization is contributing toward or can contribute toward in the future. Compiled responses, organized by thematic groupings of the Plan, were included in a February 2007 report to Congress, and were discussed further at the most recent MDCC meeting in June 2007. A table listing the thematic groupings and the responses from MDCC member organizations and agencies can be found in conjunction with the minutes from the June 2007 MDCC meeting at: http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm. The table is also included in Appendix 2 of this report.

While it is not feasible to track the amount of money spent specifically on each of the objectives in the Action Plan, NIH began fiscal reporting for each of the five broad categories in the Plan beginning in FY 2006. Funding data for FY 2006 is presented below. Note that since many grants fall into more than one of these categories, combining the dollar figures below will exceed overall NIH funding for muscular dystrophy ($40 million in FY 2006). These numbers should therefore be used as a guide representing relative amounts of research funded by NIH in these areas.

Mechanisms of Muscular Dystrophy: $22.1 million
Diagnosis and Screening of Muscular Dystrophy: $2.3 million
Therapy of Muscular Dystrophy: $19.2 million
Living with Muscular Dystrophy: $0.4 million
Research Infrastructure Needs for Muscular Dystrophy: $4.1 million

Recent accomplishments related to the five broad categories of the Plan, including those applicable to translational research, will be appended to the plan within the next fiscal year. These and future accomplishments and initiatives by all MDCC
member agencies and organizations relative to the Action Plan will be tracked by means of the MDCC public website (http://www.ninds.nih.gov/find_people/groups/mdcc/index.htm). A record of key publications, conferences and workshops, and initiatives that are relevant to specific research objectives will be maintained on the MDCC website as well. In addition, MDCC members will present reports on activities relevant to the goals of the Action Plan at the regularly scheduled MDCC meetings.

Conclusion
Over the past few years, NIH has significantly increased its portfolio in translational research in muscular dystrophy and currently funds research on multiple pathways to therapy development. As highlighted at the recent NIH Workshop on Muscular Dystrophy Translational Research, such a broad based program is the most appropriate way to approach therapy development at the current time. NIH is committed to furthering progress toward therapies and hopes to see strategies for treating muscular dystrophy to the point of readiness for clinical trials in the next few years.
Appendix 1: Workshop Report: NIH Workshop on Translational Research in Muscular Dystrophy

NIH Workshop on Translational Research in Muscular Dystrophy
Crowne Plaza Hotel, Silver Spring, MD
June 25-27, 2007

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1. Organization

Sponsored by the National Institutes of Health (NIH): National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Child Health and Human Development (NICHD), and NIH Office of Rare Diseases (ORD)

Chair: Katherine Mathews, M.D. (University of Iowa Children’s Hospital)

Organizing Committee: Katherine Mathews (University of Iowa Children’s Hospital), Cristina Csimma, Pharm.D. (Clarus Ventures, LLC), Sharon Hesterlee, Ph.D. (Muscular Dystrophy Association), Jerry Mendell, M.D. (Columbus Children’s Research Institute), Daniel Perez (FSH Society, Inc.), Lee Sweeney, Ph.D. (University of Pennsylvania), and Peter Wald, M.D., M.P.H. (USAA)
2. Goals

1. To summarize and evaluate the current state of translational research in muscular dystrophy;
2. To identify obstacles to ongoing translational research;
3. To identify ways (processes, collaborations, and strategies) to facilitate the rapid progression of therapies in muscular dystrophy based on experiences in this and other diseases;
4. To produce a summary document for peer-reviewed journal publication and a more thorough summary for the Muscular Dystrophy Coordinating Committee website.

The Workshop goals directly relate to the implementation of the Muscular Dystrophy Coordinating Committee’s (MDCC) *Action Plan for the Muscular Dystrophies* ([http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf](http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf)) in assessing the current status of therapy development in muscular dystrophy and identifying the most effective and efficient ways to move forward. The Workshop was held immediately after the annual MDCC meeting (June 25, 2007), to allow Committee members to participate and better understand how their agencies and organizations can best interact with and support therapy development efforts.

The organizers and participants are committed to obtaining the most value from this Workshop. In addition to this summary, links to all of the PowerPoint presentations and posters from this Workshop (minus unpublished data slides) can be found in the Agenda section of this report.

3. Summary

*Introduction.* The NIH Workshop on Translational Research in Muscular Dystrophy was attended by 75 academic scientists and industry, regulatory agency, governmental organization, and patient organization representatives from the U.S. and Europe, as well as patients or parents of children with muscular dystrophy (see Participants).

http://www.parentprojectmd.org/site/PageServer?pagename=nws_index), and the Muscular Dystrophy Association (MDA Translational Research Advisory Committee; http://www.mdausa.org/research/trac/) have all launched therapy development funding programs in recent years, just as there has been increasing investment from biotechnology and large pharmaceutical companies for the development of new drugs with potential value for muscular dystrophy. The purpose of the meeting was to critically examine current activities in therapy development in the muscular dystrophies, and to draw on the expertise and experiences in other fields to identify ways to increase the efficiency and efficacy of these efforts.

The Workshop presentations included keynote talks, a ‘lessons learned’ case study in therapy development for a rare neuromuscular disorder, summaries by working groups that reached consensus on a topic prior to the meeting, individual talks by selected experts, and feedback by a panel of distinguished industry scientists and regulators from outside of the muscular dystrophy community. The potential for new therapeutics was evidenced by the number of companies represented at the Workshop with active muscular dystrophy programs and the innovative partnerships that have already been formed between academia, corporations, advocacy groups, and funding agencies.

**Keynote talks and case study.** Keynote presentations from Francesco Marincola and Francesco Muntoni overviewed the goals and challenges of translational research and issues specific to development of new treatments for the muscular dystrophies. The different perspectives on translational research were discussed: patients and physicians are focused on capturing the benefits of translational research, academia is focused on testing novel compounds and identifying new therapeutics for human disease, while companies exploit iterative processes designed to expedite the development of therapeutics for profit. The two keynotes touched on multiple themes that carried throughout the Workshop (see PowerPoint presentation links in the Agenda).

Edward Kaye, from Genzyme, provided a case study of the development of the Pompe disease drug, Myozyme®. As a drug for a rare genetic disorder of primarily muscle origin, this case study provided several important lessons for the muscular dystrophy field. In Pompe, the infantile-onset form has a more narrowly defined clinical phenotype, while the adult-onset disease is more prevalent but clinically heterogeneous. The decision to start initial trials on the infantile-onset disease then was based upon medical need (i.e., rapid progression of the infantile-onset form), clinical homogeneity of the infant test population (versus that in the adult), availability of clear endpoint measures (respiratory failure and death), and the existing production limitations upon drug supply. The production issues were not trivial—scale-up of Myozyme® production after completion of the early studies required changes in manufacturing processes that, in turn, resulted in increased regulatory burdens. A clear lesson is that cost/time savings can be achieved through ensuring, as much as possible, that the product to be given to patients is always identical.

Once the infant sub-group was selected for the initial trials in Pompe disease, finding the patients to do the clinical studies required a substantial reduction in the time to diagnosis. This was achieved through physician education and the
Other lessons from the Genzyme effort include the necessity of understanding the natural history of the disease (one lesson being, do not completely rely on what is in the literature), the characterization of the variability in clinically significant endpoints which are then agreed upon by the FDA (ventilator-free survival and six-minute walk test), an evaluation of the ethical considerations for placebo-controlled trials, determination of whether results seen in one patient population can be extrapolated to a general disease population, and the obligation to provide for long-term follow-up of clinical trial subjects. The retrospective natural history data in Pompe disease was sufficient to guide trials, probably because standards of care appeared to have changed little in 20 years. By contrast, clinical trials in muscular dystrophy are unlikely to enjoy this same advantage. Finally, the use of a clear endpoint measure with quality of life implications, ventilator-free survival, greatly simplified the conduct and interpretation of the Myozyme® trials. The emergence of similar clarity of endpoint measures will be important for clinical trials in the muscular dystrophies.

**NINDS milestone funding plans for translational research.** Tom Miller discussed the NINDS’ use of milestone funding plans in translational research cooperative agreements (see [http://www.ninds.nih.gov/funding/research/translational/index.htm](http://www.ninds.nih.gov/funding/research/translational/index.htm)). His talk emphasized the need for a mindset change among academic investigators when entering into translational research—from discovery-oriented studies that are hypothesis-driven to goal-oriented studies that are milestone-driven. Project decision making then becomes appropriately objective, centering upon go/no-go decision points with pre-set quantitative success criteria.

Posters were presented on the NIH, MDA, and PPMD translational research funding programs (see Agenda for links). Efforts funded by these programs are now at various stages of the therapy development pipeline, from lead optimization through Phase 2 clinical trials. Recent advances in therapy development for the muscular dystrophies called for a Workshop where the field could step back and perform self-examination, as well as obtain input from a panel of experts in drug development from other fields, in order to increase the efficiency and efficacy of these funding programs.

The remainder of the Workshop was organized into three major areas, addressing therapeutic development processes, therapeutic development collaborations, and therapeutic development strategies. Convergence of thinking across these three areas will be essential to efficient and effective therapy development in the muscular dystrophies.

**Therapy development processes.** Among the various types of muscular dystrophy, basic scientists have had variable success in the identification of disease mechanisms that can serve as novel targets for drug development. Duchenne muscular dystrophy (DMD) is target-rich (such as fibrosis, membrane repair, and dystrophin replacement)—it is unclear which targets represent the best opportunities and how the drugs and biologics that emerge will be best combined to effectively manage patients. In this target-rich environment, with limitations on time, effort, and funding, participants discussed the critical question...
as to when enough was known about a particular target and candidate therapeutic to enter into a formal therapy development program.

By contrast, the pathogenic mechanisms responsible for myotonic dystrophy (DM) and facioscapulohumeral muscular dystrophy (FSHD) are just starting to emerge and current research efforts are either on basic science focused upon understanding disease mechanisms or on drug discovery focused on general interventions that may be common to several of the muscular dystrophies (such as enhancing strength of remaining muscle fibers). There were clear reasons for optimism—as recent progress in mechanistic understanding of FSHD and DM offer hope for the initiation of targeted therapeutic development efforts for these diseases.

The Challenges of Target Identification and Development Decisions Working Group (Cristina Csimma, Kenneth Fischbeck, and Lee Sweeney) reviewed the known mechanistic targets in muscular dystrophy, potential strategies to attack these targets, and examined the question of when in the course of disease knowledge acquisition to launch a therapy development program.

A key issue early in drug development is the identification of a viable target for therapeutic development, either the primary genetic defect itself or the downstream pathophysiology. The answer to the strategic targeting question is very much dependent upon that state of mechanistic knowledge (i.e., target identification) in a specific type of muscular dystrophy. Basic and clinical studies have identified a considerable number of events between the gene defect and the muscle pathology, and between the muscle pathology and the clinical manifestations of disease. Kurt Fischbeck stressed that some of these events may be essential stages in the disease process, and represent solid targets for therapies, while others may be ancillary to disease pathogenesis, and thus interventions at these points may have little to no therapeutic value. Failure of muscle regeneration, for example, seems to be a phenomenon common to most muscular dystrophies and represents a viable therapeutic target. Examples of therapy development opportunities presented by the primary and downstream events in the pathogenesis of DMD were discussed by Lee Sweeney. The most promising targets are reviewed in depth in the Therapy Development Strategies portion of this report.

A key in any therapeutic program launch decision, one that potentially addresses many of the combined scientific, industry, and regulatory concerns, is knowing which events, if altered, would yield a meaningful (life-changing) benefit for the patient.

Cristina Csimma discussed the critical factors in the decision to launch a formal therapy development program—noting that these decisions require consideration of a range of factors that affect scientific, drug development, and funding decisions. These include:

- Is the pathology of the disease clearly defined?
- Is the target appropriate?
• Is there sufficient preclinical support to go forward to the clinic? How predictive are the preclinical models to the human disease and drug activity in the clinical setting?
• What is the degree of unmet medical need and the risk/benefit ratio (especially in the context of novel targets with higher risk, with clinical relevance not yet established, and potential exists for off-target toxicity)?
• Are there opportunities, throughout the preclinical and early clinical programs for the progressive reduction of uncertainty in both efficacy and safety (i.e., are there opportunities to make progress with a feasible development plan)?
• Is there an established regulatory path to approval (including the existence of clinical trial endpoints that industry and FDA will consider well-established)?
• Are back-ups to the development candidate compound available?
• Is this a commercially viable compound (e.g., what is the cost and scalability of the manufacturing process)?
• What is the intellectual property status?
• What is the market size that can be captured given the compound profile, the fit in the current standard of care, and the reimbursement environment? Does the compound have relevance to multiple populations/diseases? What is the competitive landscape: considering approved drugs as well as those in development?

A major consideration is the ease of conducting clinical trials—key factors here are centralized access to patients, agreement on disease diagnoses and outcomes, understanding of natural history of disease and correlation with regulatory endpoints, sufficient number of clinical sites with infrastructure for conducting registration-driven trials, etc. Therapy development programs will have the best opportunities for success if this full range of scientific, drug development, and funding considerations are evaluated at the time of the initial program launch decision, even when the launch decision is being made by a purely academic group.

Relative to other disease areas, the muscular dystrophy field enjoys the benefits of high unmet need, very little competition within industry, chronic diseases requiring long term treatment, and the potential that one therapeutic could affect several diseases. Limitations of the field include novel targets that present an elevated risk of identifying therapeutics, limitations in the animal models, limited likelihood that activity of drugs could be detected before Phase III trials, and the need to assess multiple biomarkers. The balance between these benefits and limitations will determine the success/failure of therapy development efforts in muscular dystrophy.

The Animal Models and Preclinical Endpoints Working Group (Joe Kornegay, Jill Rafael-Fortney, Maury Swanson, and Kathryn Wagner) assessed the basic tools necessary for preclinical therapy development. The dual roles of animal models were discussed by Kathryn Wagner in (a) providing an opportunity to study disease pathogenesis (i.e., exploration) and (b) serving as a feasible system to determine efficacy and toxicity of novel therapeutics (i.e., applied therapy development). In the second role, positive efficacy data would trigger expensive preclinical toxicology studies, an IND application, and a clinical trial, thus
extrapolating animal results to therapy development program launch must be done with caution. The Working Group stressed the importance of level-of-scientific-evidence considerations when using animal models in the exploratory versus applied therapy development roles.

Available animal models for various muscular dystrophies were contrasted in the Workshop—for example, the dystrophin mutations in the mdx mouse, the utrophin null/mdx (dko) mouse, and Golden Retriever Muscular Dystrophy (GRMD) dog, where the molecular biology is disease-appropriate for DMD, even if the disease progression is not identical to human. The various animal models of DM, where the pathophysiology involves perturbations in the splicing of gene transcripts due to triplet repeat expansion or splicing factor loss of function, appear to be reasonable disease models. By contrast, the Frg1 over-expressing mouse is still evolving as one of several models of FSHD. Daniel Perez asked whether there was an established algorithm for selection of animal disease models for translational research; whether there was certification of specific disease models by professional or regulatory organizations. It was noted that advocacy group-commissioned recommendations have been made on animal models, for example, in the case of hemophilia, but that establishment of such standards has not been common practice. Overall mechanistic knowledge is not fully developed for any of the muscular dystrophies and better understanding of pathogenesis will help define the relevance (or lack thereof) of specific animal models and might lead to the identification of novel therapeutic targets. This clear need for continuation of mechanistic studies should not, however, impede the launch of therapy development programs, as it is not practical to wait for full disease understanding. Furthermore, mechanistic studies may, in turn, be better informed by the success/failure of early stage clinical trials.

A careful review of animal models and preclinical endpoint measures was motivated by a desire to achieve a ‘best practices’ consensus to facilitate efficiency and comparability of diverse preclinical development efforts. Answers to key questions such as when to invoke the scarce resource of large animal models, and whether large animals are appropriate for preclinical trials or simply for the more limited purpose of proof-of-concept studies, are currently unclear. Jill Rafael-Fortney provided an overview of the major classes of preclinical endpoint measures for use in therapy development. It was recognized that we do not yet know enough about the ability of specific endpoint measures in animals to reliably predict efficacy in human subjects. Ultimately, the predictive value of the various animal models and preclinical endpoints will be validated only when more therapeutics have been found to succeed or fail in clinical trials. It is as yet unclear, for example, what threshold of force improvement in the mdx mouse (or GRMD dog) would translate into time of ambulation in the DMD patient. Moreover, it was recognized that while the common animal model endpoints (typically biochemical or functional) cannot easily be used to compare different treatment strategies, the most acceptable endpoint measures in patients (typically mobility, respiratory function, and quality of life (activities of daily living, etc.)) may be used to directly compare different treatment strategies. A relevant workshop that will continue the animal models and endpoint theme, “Pre-Clinical Testing for Duchenne Dystrophy: End-Points in the mdx Mouse,” has been scheduled for October 27-28, 2007, in Washington, DC.
Drawing on an example from best practices developed for hemophilia drug development, Joe Kornegay noted that inbred strains of mice have generally not predicted immunological complications later seen in dogs, while the dog data has provided a basis for successful translation to clinical practice. The high costs, breeding limitations, and phenotypic variability of large animal models currently limits their utility for therapy development in the muscular dystrophies.

Several key principles in preclinical therapy development processes were discussed at the Workshop. No animal model is perfect and researchers should understand the degree to which the animal phenotype mirrors human disease and move forward with available models. The point was made that some very good drugs have come from very bad animal models in other diseases. Since animal efficacy data serve as a trigger for expensive, IND-enabling activities and clinical trials, care should be taken to design animal experiments with appropriate statistical rigor. Potentially problematic are preclinical efficacy studies that may label results as positive, but do so in isolation without comparing the candidate therapeutic to other available drugs or treatments. In the same vein, investigators should try to avoid using any single in vitro/in vivo assay in isolation. In the case of the muscular dystrophies resulting from single gene defects, animal models and endpoint measures may be reasonable predictors of the efficacy of gene function restoration strategies. However, when moving away from restoration of the main mechanical properties of, for example, dystrophin-deficient muscle, it becomes much more complex to select experimental endpoint measures and to weigh the evidence of a possible effect. Finally, in contrast to basic science studies, preclinical translational work should develop a candidate therapeutic profile at the onset, with quantitative, go/no-go criteria in a milestone-driven research design, in order to reach the unambiguous decision points essential for therapy development programs.

It was noted that investigators should be focusing on development of surrogate measures (or biomarkers) in animals now, as these have a prolonged qualification and validation process and will be essential for human efficacy trials and to the development of more informative clinical trials. Also critical to the development of new therapeutic strategies is designing trials that utilize more informative outcome measures and more creative study designs that can help understand why the compounds fail (e.g., missed effect due to sample size/design, vs. a true lack of biological effect on the target tissue or a non-clinically relevant target, etc.). This approach should help focus efforts on relevant targets and, in the process, further advance study methodologies and novel biomarkers. While a significant effect is unlikely to be detected in early stage exploratory trials, the incorporation of multiple biomarkers and outcome measures can help evaluate a candidate if the measures are directionally consistent and support the biological plausibility of the observations.

During discussion, Ronald Cohn raised the notion of whether a protein fingerprint could be characterized for the various types of muscular dystrophy, with the resulting disease and stage-specific fingerprints serving as robust biomarkers for therapeutic trials. Elucidation of such a fingerprint could aid diagnostics, natural history studies, subject stratification for clinical trials, and serve as an endpoint measure for clinical trials.
The **Regulatory Issues and Ethics Working Group** (Diana Escolar, Berch Griggs, Langdon Miller, and Robert Nelson) addressed issues essential to clinical trials in muscular dystrophy, with the recognition that these can represent substantive obstacles and need to be considered at rather early stages of therapy development. Berch Griggs discussed regulatory and ethical issues that either have or will soon emerge for therapy development in the muscular dystrophies, including: (a) the need to harmonize local (IRB) and national (EMEA/FDA) human studies approval requirements, including coordination between funding and regulatory agencies, (b) the streamlining of bureaucracy at academic institutions, (c) the restoration of common sense into human subject data protection regulations, and (d) minimizing bureaucratic obstacles, as much as possible. The emergence of a global registry to inform those conducting clinical trials was viewed as essential in development of Genzyme’s Pompe disease drug and is necessary infrastructure for therapeutic development in the muscular dystrophies. Despite the frequent perception that the patient population is readily available for clinical trials, due to the weaknesses in accurate diagnosis and practical problems with subject participation (e.g., lack of therapies and high unmet medical need), recruitment is nearly always a problem. Mechanisms that build confidence among academic and corporate trialists that adequate numbers of research subjects are readily available will facilitate decisions to initiate therapy development programs.

Langdon Miller discussed potential solutions to overcoming regulatory impediments, based upon recent muscular dystrophy drug experience at PTC Therapeutics. There must be an acknowledgement of the necessity of safety/regulatory activities, and researchers must acquire the resources, including appropriate expert review and funding support, to meet regulatory requirements. Early and regular involvement of those with necessary expertise is encouraged, whether obtained through academic-industry collaborations or via consultants or contract research organizations (CROs). Finally, engaging the FDA is essential to provide a scientific and disease context for drug candidate risks and to push for a resolution of problems on the path forward.

The new Translational Research in Europe—Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD; [http://www.treat-nmd.eu/](http://www.treat-nmd.eu/)) effort provides a single, clear point of entry into infrastructure that is essential for clinical trials (e.g., dissemination and access to best practices, matching patients with available trials, etc.) for DMD. The NIH-funded National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members ([http://www.urmc.rochester.edu/nihregistry/](http://www.urmc.rochester.edu/nihregistry/)) is already providing a patient resource for clinical studies and trials in two other types of muscular dystrophy. Such infrastructure efforts are often difficult to fund when competing with research projects. As efforts are made to put key infrastructure into place, they must avoid geographic boundaries in order to provide sufficient resources that can facilitate the clinical stages of therapy development in muscular dystrophy.

Robert Nelson discussed the obstacles and opportunities related to ethics of clinical trials in the muscular dystrophies, and, specifically, how ethics impacts trial design. In the case of clinical trials where the subjects are children (e.g., DMD and CMD), a balance must be sought between the risks and potential
benefits for the subjects, and possibly for healthy controls. With the early-onset muscular dystrophies, two key design issues must be managed: trial design in these diseases does not involve adults with the disease and, conversely, safety stage trials in healthy children are often excluded on ethical grounds. Notable are the additional FDA protections that are in place for clinical trials in children—the need for ‘minimal risk’ and the consequences this has for design of clinical trials (optimizing the prospect of a direct benefit, restricting use of non-beneficial interventions to only a minor increase over minimal risk, etc.). There is broad international agreement on the core ethical principles to guide adult and pediatric research. There is currently no curative treatment for the muscular dystrophies, so there is a strong desire on the part of affected individuals and parents of affected children to participate in treatment trials as soon as possible, even when some risk is involved.

Several clinical outcome measures have been discussed for muscular dystrophy trials—biochemical, function, strength, survival, quality of life, endurance, imaging, and others—but it still remains unclear which are adequately reliable, feasible, and sensitive. Few outcome measures have been validated as accurate indicators of disease progression. The relationship of various biomarkers to events that are clinically meaningful to the patient has not been established. What is most desirable are biomarkers that track progression of disease, as these would allow evaluation of treatment responses in clinical trials. Static markers of disease may facilitate patient stratification for clinical trials, but do not have the same value as those that track progression and, if used as the major outcome measure, could limit the patient population for which a therapy receives regulatory approval.

Conferences held on the outcome measures topic in the muscular dystrophy field have highlighted the need for additional studies (e.g., Muscle Nerve 35:8-16, 2007). In Genzyme’s Pompe trials, two endpoint measures relevant to muscular dystrophy were considered, but not used. The FDA accepted ventilator free survival as an endpoint and the six-minute walk test as an outcome measure indicative of the physical function of subjects. In contrast, forced vital capacity and quantitative muscle strength testing were not considered appropriate outcome measures for the purpose of drug approval. The six-minute walk test is under consideration for the initial Phase 3 drug trial in DMD (PTC124; PTC Therapeutics). Much of the debate over outcome measures for clinical trials in muscular dystrophy is a consequence of the need to learn from success/failures in more early stage trials. Trial efficiency for the muscular dystrophies might be improved by learning from the prior experiences of the design and conduct of trials in other rare diseases by academic and industry investigators.

Therapy development collaborations. Academic-Corporate Partnerships were discussed by Terry Fadem, an academic director of corporate alliances who is responsible for facilitating academic-corporate drug development partnerships at a major U.S. medical school. Companies are faced with a continuing stream of technology developments, ideas, and products, many of which are not pursued for a variety of reasons. A partnered relationship between academia and funding agencies may offer sufficient value to offset this information overload and attract more corporations to the muscular dystrophy field. Strong peer-to-peer relationships between academic and corporate partners are essential in
overcoming the variety of barriers to collaboration (time, space, cultures, access, attention, priorities, long-term plans, etc.). Emphasis was placed on the need to broker relationships, not simply ‘deals,’ between academia and industry, and to base these relationships on both science and project management. These relationships are optimally formed at the beginning of the research project. Just as it was viewed as important that disease registries offer ‘one-stop-shopping’ for clinical trialists, academic institutions need to minimize internal barriers and provide both a single interface point and well-honed processes for facilitating academic-corporate partnerships in therapeutic development.

The TREAT-NMD partnership model (http://www.treat-nmd.eu/), recently funded as a European Union Network of Excellence, was presented by Kate Bushby and praised as essential infrastructure to facilitate new treatments for muscular dystrophy. Part of the TREAT-NMD philosophy is that patient resources (from biopsies to subjects for clinical trials) will be rare, so the candidate therapeutics that move to trials will have to be carefully chosen and the trials that are done must utilize common endpoint measures and collect common data elements in order to be comparable. The initial focus of the TREAT-NMD network is on DMD and spinal muscular atrophy, with representative goals including developing and managing patient supranational databases, establishing standards of care, and defining clinical outcome measures for trials. Discussions of TREAT-NMD’s goals emphasized the need for global interactions in preclinical and clinical therapy development in rare disorders such as the muscular dystrophies. It was noted that the network is very much patient-driven, motivated by stakeholders working together to accelerate therapy development. The availability of infrastructure that facilitates preclinical studies and clinical trials, such as that supported by TREAT-NMD, is designed to lower the threshold on corporate decisions to enter into drug development programs for muscular dystrophy.

**Therapy development strategies.** The next section of the workshop was devoted to examining the status of the therapy development strategies that currently are active for muscular dystrophy.

The major therapy development strategies currently being pursued in muscular dystrophy were evaluated by 3-4 member working groups, with their findings presented at the Workshop. Panels looked at: (a) Gene Therapy & Repair/RNA Targeted Therapies, (b) Cell-Based Therapies, (c) Muscle Regeneration Therapies, (d) Anti-Inflammation/Fibrosis Therapies, and (e) Membrane Repair/Compensatory Membrane Proteins Therapies.

The consensus of the Gene Therapy & Repair/RNA Targeted Therapies Working Group (Eric Hoffman, Jerry Mendell, Jude Samulski, and Charles Thornton) was summarized by Eric Hoffman. He noted that considerable progress had been made in understanding the value of naturally occurring and chimeric serotypes of AAV for delivery of therapeutic gene constructs for muscular dystrophy. Capsid shuffling strategies are being explored to generate chimeric vectors that may avoid pre-existing patient antibody responses. Scale-up of vector production has, at least in part, been addressed as AAV production capacities have increased, with baculovirus facilities improving the cost profile and feasibility of a human therapeutic. Regional vascular delivery of vector now looks more feasible based upon data from recent dog and subhuman primate studies, but the next
step of systemic delivery was regarded as not yet achievable. A major remaining issue in gene therapy is retention of expression. Transient immunosuppression to block the cytotoxic T-cell response that is mounted against an AAV capsid epitope may increase efficiency of delivery and increase the duration of expression. A Phase 1 trial with local injection of AAV-mini-dystrophin in DMD will report results soon and a dose escalation trial in limb girdle muscular dystrophy type 2D is currently recruiting (http://clinicaltrials.gov/ct/show/NCT00494195;jsessionid=533AAC93089F271E4073C525A3DF7B96?order=4). Immunogenicity of the engineered, therapeutic gene products is a concern that will require further study. It will also be important to understand what structural-functional muscle types are effectively targeted by these AAV strategies. In addition to the scientific hurdles, scale up and the potential for commercialization are issues that remain to be addressed.

Antisense oligonucleotide-mediated exon skipping strategies, to convert dystrophin out-of-frame to in-frame mutations, have demonstrated the ability to restore dystrophin protein expression and function in the skeletal muscles of animal models. Considerable progress in refining the chemical properties of the oligonucleotide backbone has been important in improving efficiency of exon skipping and lowering required dosage. While 2'-O-methyl chemistry scale-up production has been good, production remains somewhat problematic for morpholino chemistry (PMO). Both chemistries are in safety and tolerability stage clinical trials in Europe, for single muscle injections. Both chemistries have also shown promise in systemic delivery studies in animals, but chemistry- and sequence-dependent differences in their in vitro versus in vivo effectiveness may complicate therapy development. Furthermore, efficiency of oligonucleotide-based exon skipping in heart muscle seems to be considerably lower than that of skeletal muscle. An alternative approach, T7 AAV gene delivery has shown promise in the mdx mouse and dystrophic dog, but no human trials have been initiated. Another unresolved issue is whether the dystrophin proteins created by exon skipping will be both stable and efficacious, and whether any of the resulting proteins will prove immunogenic. As with AAV, there are commercialization issues that have not been addressed. Intellectual property issues with oligonucleotide chemistry may be an issue and the regulatory agencies are currently regarding each combination of antisense oligonucleotide chemistry and sequence as a novel therapeutic, with each requiring the full gamut of preclinical and clinical safety testing.

Stop codon read-through strategies, to address the 10-15% of DMD patients with nonsense mutations in the rod domain of dystrophin, are currently in clinical trials (gentamicin: http://clinicaltrials.gov/ct/show/NCT00451074;jsessionid=533AAC93089F271E4073C525A3DF7B96?order=8 and PTC124). The key questions to be answered with this approach are: can sufficient dystrophin be produced to mediate functional recovery and are there substantive off-target toxicities?

Potential treatment strategies for muscular dystrophies other than DMD have also been advancing. As the molecular mechanisms of DM have been elucidated, several therapeutic strategies have emerged aimed at restoring normal splicing events. Prevention of somatic expansion of the CTG repeat in DM1 remains problematic, as it is unclear how and when expansion occurs, and
there are potential safety issues for strategies that alter DNA replication or repair. Elimination of the toxic RNA via RNA interference (RNAi) appears plausible, as specific targeting of the DMPK gene has been achieved (although biodistribution/cell access of siRNA to muscle in general and to the nuclear compartment are potential problems). Viral expression of shRNA has potential, but is not without safety concerns. Potentially more promising approaches to treatment of DM include reversal of the splicing defect by increasing expression of appropriate splicing factors (e.g., MBNL1) or by blocking binding of the splicing factors to the expanded RNA repeats.

Although the molecular mechanisms for FSHD have not yet been resolved, there appear to be some opportunities in targeted therapies that are worthy of testing in preclinical models. Reversing the deleterious chromatin conformation on 4q35 by modifying histone acetylation has potential, but genome characterization is currently unfinished in this region and the exact nature of the chromatic change is unknown. Although controversial, there are reports of over-expression of three genes in FSHD—RNAi knockdown might have potential but there is no consensus about which gene, if any, is over-expressed. Strategies designed to block muscle degeneration or promote regeneration such as protease inhibitors or myostatin inhibitors may have positive effects in FSHD (see Muscle Regeneration Therapies Working Group).

The potential for stem cell therapies in muscular dystrophy was discussed by the Cell-Based Therapies Working Group (Johnny Huard, Louis Kunkel, and Thomas Rando). Clinical testing of cell-based therapies in DMD originated almost 20 years with failed myoblast transfer studies. Lessons learned from these early studies include the safety of myoblast transplant procedures, the limited effectiveness—persistence of dystrophin expressing muscle fibers for no more than two-three weeks, and the role of the immune system in limiting transplanted cell dissemination and survival (98% of transplanted myoblasts do not survive). Johnny Huard discussed the return to laboratory research, the focus on identification of appropriate embryonic and adult stem cell populations, and the new potential for clinical trials. Research on cell-based therapies is the one instance in muscular dystrophy where the field has been from bench to bedside and back, and is exploiting lessons learned in clinical trials to potentiate progress at the bench. Recent strategies to characterize myogenic potential have focused upon technologies and cellular markers for cell identification and expansion. Huard reviewed lessons from his translational studies in bladder and cardiac muscle dysfunction—discussing how optimization of cell-based therapies may require distinguishing those stem cell populations that best adapt to the stressful conditions of the dystrophic muscle target. Promising findings with stem cell therapies in a cardiac infarction model clearly demonstrate the relationship between survivability in a hostile tissue environment and regeneration potential of a stem cell type. The predominate fate of the cardiac stem cell transplants was in angiogenesis, rather than in the replacement of cardiomyocytes. Taken together, stem cells have demonstrated limited efficiency in becoming cardiomyocytes, but their potential in restoration of heart function is promising nonetheless. Lessons to be learned from clinical trials using muscle-derived stem cell therapy for stress urinary incontinence—these are now at the stage of dose escalation safety studies—may help facilitate broader-scale, cell-based therapy trials in muscular dystrophy. This Working Group, as well as others
involved with the Workshop (see Anti-Inflammation/Fibrosis Therapies Working Group), emphasized the importance of the tissue environment—controlling inflammation and extracellular matrix status—for the potential success or failure of a therapy.

Recent studies using mesangioblasts in transplants with the dystrophic dog model have generated considerable controversy as to whether the positive effects could be attributed to the transplanted cells or to the immunosuppressive drugs given to the host dogs (see Neuromuscul. Disord. 17: 206-208, 2007 and Cell 127: 1304-1306, 2006).

The complex network of whole body homeostatic mechanisms and the local autocrine, paracrine, and intracellular signaling that regulates skeletal muscle protein synthesis and degradation was addressed by the Muscle Regeneration Therapies Working Group (Jennifer Lachey, Se-Jin Lee, Richard Moxley, and Lorenzo Puri). This Working Group focused on two therapeutic strategies currently under development—insulin-like growth factor I (IGF-I) delivery and myostatin inhibition. Candidate therapeutics associated with these strategies have the potential to boost muscle regeneration and may also block degeneration. These strategies could have positive effects in various muscular dystrophies and also in other muscle diseases. The broad potential applicability of drugs targeting muscle regeneration has attracted several biotechnology and large pharmaceutical companies to develop drugs for muscular dystrophy that may have broader commercialization potential. The Working Group made the key point that the genetic defect in muscular dystrophy leads to muscle wasting and loss, and that a variety of interacting events culminate in muscle loss—this constitutes the rationale for enhancing regeneration as either a stand-alone or co-treatment in muscular dystrophy.

Maturation of IGF-I as a candidate therapeutic for muscular dystrophy has been supported by advances in basic science, including characterization of its serum carrier molecules (IGF binding proteins or IGFBPs), cellular receptors, and intracellular signaling pathways. Dissection of each of these elements is yielding information to optimize IGFs drug-like properties and to identify other ligands and intervention targets in the IGF signaling cascade. Phase 1 clinical trials of IGF-I complexed to IGFBP3 (IPLEX™; INSMED, Inc.) are ongoing for DM at the University of Rochester (http://clinicaltrials.gov/ct/show/NCT00233519?order=1). Richard Moxley noted the necessity of exploring appropriate outcome measures in these early phase trials and the use of existing infrastructure to refine such instruments, such as the NIH Patient-Reported Outcomes Measurement Information System (PROMIS; http://www.nihpromis.org/default.aspx) and NINDS NeuroQual initiative.

Se-Jin Lee reviewed the extensive basic science understanding that has developed around myostatin and how its inhibition has the same potential for a broad-spectrum therapeutic for muscle wasting that was noted for IGF-I. The ongoing myostatin inhibitor clinical trials (MYO-29; Wyeth), which have enrolled adult subjects with FSHD, Becker, and limb girdle muscular dystrophy, highlight the broad applicability of this strategy. Advances in knowledge of myostatin synthesis, propeptide processing, extracellular regulators (follistatin, FLRG, and GAS-1), cell surface receptors, and intracellular signaling pathways offer multiple
avenues to optimize myostatin inhibitors for use in several types of muscular dystrophy. In addition to myostatin, other TGFβ family members contribute to muscle growth and should be evaluated as therapeutic targets. Since circulating levels of myostatin in human may be as low as 50% of the well-studied mouse levels, studies of other TGFβ ligands may be essential if the myostatin inhibition strategy is to succeed in muscular dystrophy patients. Both investment in high-throughput screening programs for muscle regeneration targets and the leveraging of resources via greater interactions between academia and companies were viewed as essential to maturation of these drug development programs.

An industry perspective on validation of myostatin as a target in muscular dystrophy was presented by Jennifer Lachey of Acceleron Pharma. While myostatin inhibition does not address the root cause of any muscular dystrophy, substantial evidence supports the exploration of this approach in order to develop therapeutics for multiple muscle diseases. Notably, the Acceleron perspective on drug development puts considerable value on the emergence of genetic tools, such as the myostatin-dystrophin double knockout and dominant negative myostatin receptor (ActR2B) transgenic mice, and pharmacologic tools, such as the myostatin neutralizing antibody and myostatin inhibitory propeptide. Studies using these tools have reinforced the notion that myostatin is not the only player, and that, while myostatin is an attractive target, there are still fundamental issues to be addressed before the potential of this therapy development strategy can be fully exploited.

Lorenzo Puri discussed the use of histone deacetylase (HDAC) inhibitors to indirectly target myostatin by influencing follistatin expression. The point was made that the rationale for HDAC inhibitor therapy arose from studies of the biochemistry of transcription and that treatment of mdx mice (with TSA, MS-27, and SAHA) has shown improvement in several features of the dystrophic phenotype. In discussion, the notion of ‘optimal muscle fiber size’ was raised and of how that concept interacts with therapeutics that function in myofiber hypertrophy and resistance to degeneration. An early stage trial of the FDA-approved HDAC inhibitor, SAHA, was suggested. The concept of combination therapies was raised here and elsewhere in the Workshop, with no clear answers as to how to best explore combining therapeutics that hit one or more targets in the pathogenic or compensatory pathways in muscular dystrophy.

Protease inhibitors as a therapeutic strategy were not discussed by this Working Group. But it was noted that the validity of calpain inhibition as a development target has been questioned in DMD.

Over-riding questions that remain for the muscle regeneration strategies include: could these approaches be deleterious in causing more rapid satellite cell depletion and can they have positive effects on the cardiomyopathy that accompanies some types of muscular dystrophy? Lee Sweeney noted that human and dog satellite cells do not maintain telomerase activity while those of mice do—these observations must be considered in development of pro-regeneration therapeutics.
In summary, the Working Group regarded the major advantages of interventions to enhance regeneration as: bioavailability to all muscle groups, immediate availability of some pre-existing drugs (e.g., HDAC inhibitors), possibility of these interventions serving to hold patients at disease stages suitable for later emerging therapies that target the primary genetic defect, broad-spectrum activity for various muscular dystrophies, and the potential for combination therapies. By contrast, the major challenges for this therapeutic strategy include achieving target selectivity, limitations on duration of activity, and potential off-target effects of these agents.

The Anti-Inflammation/Fibrosis Therapies Working Group (Ronald Cohn, Denis Guttridge, and Melissa Spencer) was tasked with addressing a broad range of therapeutic strategies that interact with the muscle regeneration group. Pathway diagrams and tables presented in the Working Groups’ PowerPoint presentations provide excellent state-of-the-science summaries and links to these are available on this website (see Agenda).

Melissa Spencer first reviewed the state of the science of inflammation and fibrosis and suggested that muscular dystrophy could be modeled as a wound-healing response, with investigators taking advantage of the wealth of information from that model. An integrated view of myofiber membrane damage, repair, inflammation, and fibrosis was presented, along with a thorough synopsis of the inflammatory cellular and gene expression events that accompany muscular dystrophy (see Agenda for links to integrative tables and pathway diagrams on inflammation in muscular dystrophy). The debate over the role of inflammation in the pathogenesis of muscular dystrophy was discussed. Of note were the positive aspects of inflammation in the repair and regeneration processes and the consequent need for carefully targeted, and titrated, therapies when addressing the immune response. In other words, hitting an anti-inflammatory pathway too hard may have deleterious consequences for the patient.

Discussion also highlighted the role of corticosteroids as the only efficacious therapy in current use. The debate was noted as to which pathways are modulated by steroids in order to achieve the positive effects seen in DMD patients. Such information could be invaluable in development more effective and less toxic drugs.

Denis Guttridge discussed the signaling pathways involved in inflammation and fibrosis, and drugs that have shown promise against these pathways for possible use in muscular dystrophy. A potentially problematic issue is that the signaling pathways studied in muscular dystrophy are often evaluated in an entire muscle sample, with the precise cellular origin (myofiber, vascular, lymphoid, etc.) unknown. Dissection, not only of signaling pathways, but of their precise cellular origins, will be essential to understanding their relevance to disease progression and viability as translational research targets. Recent evidence has established tumor necrosis factor (TNF) and NFκB as potentially important targets for therapy development in muscular dystrophy; noting their involvement in inflammation and/or satellite cell response in the mdx mouse.
Ronald Cohn reviewed the current status of understanding of the impact of inflammation and fibrosis on the muscle repair process. Although two separate Working Groups looked at muscle regeneration and anti-inflammatory/anti-fibrotic therapeutics, the tight linkages between these strategies were noted and it was recognized that development programs must take into account the interactive nature of these processes. The importance of fibrosis as a therapeutic target was highlighted by the observation that fibrosis interferes with muscle function and is additive with the weakness caused by loss of muscle fibers. A key question, however, is whether fibrosis is simply the endpoint of failed muscle regeneration, as the answer here will determine whether anti-fibrotic therapy is indicated and the adequacy of the therapeutic window for use of such drugs. A comment by Edward Kaye, during his case study presentation, is germane here—non-responders in the Myozyme® trials appear to have had more advanced fibrosis than those subjects that responded to the drug, suggestive of progression to an irreparable level of muscle damage in the non-responders. The greatest benefit of the drug was in the patients who had some preservation of muscle function—suggesting the benefit of early intervention in the muscular dystrophies.

In sum, the Working Group viewed optimization of the satellite cell environment as the key issue in development of therapies for downstream targets in muscular dystrophy—modulating inflammation and fibrosis and stimulating muscular precursor cell activity are all about optimizing that environment. Pro-regenerative strategies may require titration of several drugs to establish adequate tissue homeostasis to support regeneration. This Working Group also highlighted the importance of exploring combination therapies for muscular dystrophy.

The Membrane Repair/Compensatory Membrane Proteins Therapies Working Group (Kay Davies, James Ervasti, Justin Fallon, and Paul Martin) discussed (a) compensating for loss of dystrophin by upregulating expression of utrophin or delivering recombinant utrophin protein, (b) membrane repair strategies using dysferlin or a membrane sealant (poloxamer-188), and (c) compensatory mechanisms mediated through membrane protein glycosylation.

Kay Davies reviewed the background on the discovery of utrophin and the substantial proof-of-concept work in animals in support of utrophin as a compensatory protein for dystrophin in DMD. Natural sarcolemmal localization of utrophin (potentially stabilization rather than upregulation) was reported in DMD patients—a recent report linking levels of naturally occurring utrophin with time to wheelchair (Hum. Molec. Genet. 15:1623-1628, 2006). As with many of the compensatory strategies, a key question relates to the level of upregulation needed to achieve rescue—data from her lab suggests that a three- to four-fold upregulation is necessary in the mdx mouse and that systemic side effects are not apparent at these levels. Upregulation does not have to precede onset of pathology, but more effective rescue is achieved with earlier induction. A considerable amount of effort has focused on understanding the utrophin A promoter as a putative therapeutic target. Several agents have shown potential to upregulate utrophin in dystrophic muscle, including heregulin, L-arginine, okadaic acid, and interleukin-6. VASTox developed an utrophin A promoter/luciferase reporter assay in the H2K-mdx cell line to conduct high-throughput screens that have subsequently yielded candidate therapeutics...
Justin Fallon discussed the therapeutic potential of biglycan, an extracellular protein that interacts with the pericellular matrix and transmembrane proteins associated with dystrophin (alpha-dystroglycan and alpha- and gamma-sarcoglycan). Mouse studies have demonstrated that biglycan administration leads to utrophin upregulation. Fallon’s recent studies have demonstrated that human recombinant biglycan in the non-glycanated form is effective in reducing structural/functional measures of pathology in the mdx mouse and that its activity is mediated by increased utrophin transcriptional activity and protein localization to the sarcolemma (protein levels exhibited ~2.5-fold increase, roughly consistent with the efficacious levels seen in Davies’ studies). Since biglycan and utrophin are normally expressed during muscle development, any immune response to a recombinant protein therapeutic is likely to be minimal. Obstacles to development of biglycan as a therapeutic include developing routes of delivery that avoid potential adverse effects and verification of its positive effects in humans.

Direct delivery of a recombinant utrophin protein as a potential therapy for DMD was discussed by James Ervasti. Taking advantage of a fusion protein construct of utrophin and the TAT protein, which conveys the ability to travel through the muscle cell membrane, his approach established proof-of-concept with TAT-utrophin in the mdx mouse. Structural and functional measures showed improvement with dosage of full-length utrophin when delivered after onset of pathology. This work is at the early animal efficacy stage, and protein optimization (screening micro- and mini-TAT-utrophin constructs), production, dose-finding, and IND-enabling studies remain to be done. TAT protein transduction is not a tissue-targeted approach, so determination of any organ system toxicity is essential to its viability as a therapeutic.

James Ervasti also reviewed the status of targeted membrane repair strategies that are potentially useful for those muscular dystrophies with sarcolemmal integrity defects. Dysferlin, the protein defective in limb girdle muscular dystrophy type 2B, has been implicated in endogenous membrane repair processes. As a candidate therapeutic, the thinking is that the molecular mechanisms of dysferlin in membrane repair are not well resolved. Therefore, this Working Group recommended that further basic research be encouraged before its relevance as a therapeutic can be realized. Perhaps high-throughput screening, that generates probes to further explore molecular mechanisms, could accelerate basic understanding of dysferlin and its potential. A clear strength of a dysferlin-based approach is the applicability of a single therapeutic for a broad range of muscular dystrophies. Recent work on poloxamer-188, and its potential to stabilize dystrophy-weakened cardiac muscle sarcolemma, carries some of the same open questions and broad potential. The potential for poloxamers to repair skeletal muscle membranes in DMD animal models is currently being explored (http://www.abcnews.go.com/GMA/Health/story?id=1808757).

The manipulation of membrane protein (alpha-dystroglycan) glycosylation as a molecular therapeutic strategy for muscular dystrophy was discussed by Paul Martin. There are at least six forms of muscular dystrophy that directly result
from defects in glycosylation. Upregulation of the N-acetylgalactosaminyltransferase, Galgt2, inhibits the development of muscle pathology in the mdx and in a model of MDC1A, the dy" mouse. Augmentation of glycosylation in sarcolemmal-based muscular dystrophies is being pursued using a Galgt2 gene therapy strategy. This approach appears to be independent of, and potentially complementary to, utrophin upregulation or stabilization. The molecular mechanisms of a Galgt2-based therapeutic are not well understood, the potential for treating cardiomyopathy is not yet clear, and the tools and collaborations necessary for a small molecule drug development effort do not yet exist. Similarly, preclinical work on LARGE, including studies with patient fibroblasts, has demonstrated proof-of-concept for glycosylation of alpha-dystroglycan, reconstitution of binding to laminin, and rescue of muscular dystrophy phenotypes. This is the only target that has been demonstrated for dystroglycanopathies and gene therapy and small-molecule activator approaches are being undertaken. Finally, another strategy being pursued is targeting UDP-GlcNAC 2-epimerase/ManNAc 6-kinase (GNE). Mouse models have been developed and an enzyme replacement strategy is being pursued for potential use in hereditary inclusion-body myopathy.

4. Key Discussion Points

In addition to the perspectives of academic and corporate researchers involved with therapy development in muscular dystrophy, the Workshop sought input from an Expert Advisory Panel with no direct ties to emerging therapeutics in this field. Cristina Csimma also made some closing observations based upon her previous experience in the pharmaceutical and biotechnology industry and, more recently, with a biomedical venture capital firm. This section summarizes key points from both of these discussions.

There has been a palpable increase in recent years in the level of collaboration and respect among the key partners in the muscular dystrophy field. The maturation of such partnerships is essential to the achievement of effective new therapies for muscular dystrophy. We have become better at recognizing the problems facing therapy development in the muscular dystrophies and design clinical trials that are more informative to the field, independent of the outcome of the compound studied.

Participants in the Workshop have a clear recognition of the value and limitations of available animal models. The field can best move forward by understanding the caveats and designing careful, statistically rigorous studies to identify not just any candidate, but the best candidate to move forward into the clinic. Because of the limited experience with clinical trials in muscular dystrophy, it is not yet clear how much of the uncertainty about a therapeutic target and a candidate therapy the animal models will be able to remove from the table. However, progress into clinical testing should not be delayed because of an incomplete understanding of pathophysiology or lack of the ‘perfect’ animal model. Much has been made of the phenotypic differences between mdx mice and DMD patients, but Jill Rafael-Fortney noted that this may be purely a lifespan issue related to the rate of disease progression and suggested that mdx may be a very good model of early stage muscular dystrophy. Don Kirsch pointed to data that as many as 50
projects need to enter development to produce a single approved drug. The notion was raised that a critical mass of efforts need to be initiated for muscular dystrophy, with a fail early/fail often approach that objectively and dispassionately triages candidates both at the preclinical and clinical trial stages and feeds back the knowledge obtained about the animal model, the target, and the candidate therapeutic to improve early discovery efforts.

Clearly, development programs should be broadly directed across the array of primary and downstream therapeutic targets in the muscular dystrophies, in large part because (a) it is as yet unclear which strategies will be successful and (b) combination therapy is likely to be necessary in the muscular dystrophies, just as it has been in cancer and AIDS. The translational research funding programs of the NIH and advocacy groups with muscular dystrophy interests take the stance that a broad range of therapy development strategies should be supported, following a milestone-driven research model that facilitates objective decisions about continuing or stopping a particular program. Don Kirsch emphasized the theme that a corporate-style candidate therapeutic profile be established at initiation and that go/no-go decision points be applied throughout the therapy development process to ensure objective decision making. Edward Spack noted the wealth of targets in muscular dystrophy and the consequent challenge that the field faces in triaging targets and candidates. Resources are not infinite, and scientists need to be realistic as to which candidate therapeutics and preclinical models will eventually translate into clinical trials.

It is absolutely necessary to apply very rigorous definitions when reporting ‘therapeutic successes’ in preclinical models to ensure that only the best characterized and promising approaches are taken into the clinical development stage, balanced against the urgent need for therapy in this group of diseases. In the past, there has been a focus on differences across the various types of muscular dystrophy. There is real value to shifting mindset to recognizing what the diseases have in common and determining how we can build on that (e.g., myostatin inhibition strategies capable of addressing muscle regeneration in any of the muscular dystrophies). While potentially ‘curative’ strategies, such as gene therapy, are attractive, however, focusing on the common downstream pathways across the different dystrophies (as well as those pathways that may be shared with much more common diseases) allows marshalling of knowledge and resources, and increases the chances for commercialization, thereby potentially leading to more timely development of new therapeutics.

Ellen Maher noted the importance of researchers understanding why a therapeutic candidate fails, and applying that knowledge to the next generation of products, as well appreciating the problems that can arise in declaring success too early in clinical development. The regulatory perspective also included the observation that the attractiveness of repositioning existing approved drugs to muscular dystrophy (i.e., off-label use) should be, in part, mitigated by the not inconsequential issues in approval of a drug for a new indication and patient population (e.g., lack of knowledge of dosing and patient group-specific toxicity). Repositioning has, however, met with some success in other diseases and George Vella outlined the assay development and approved drug screening program run by Charlie’s Fund. The use of FDA approved drugs in screening programs does not preclude subsequent efforts to establish structure-activity
relationships and optimization of the candidate therapeutic before moving to the clinic. Given limitations on resources, and the therapeutic failure rate in Phase 2 trials, optimization of approved drugs may be desirable even in the face of the additional regulatory hurdles.

Patient resources are scarce for any muscular dystrophy. Initiation of clinical studies and trials carries with it the responsibilities that choices of therapies to test are made carefully and that trial design carry sufficient rigor to warrant the human subject risks. A recent survey of oncology clinical trials (J. Clin. Oncol. 25(18S): 6514, 2007) notes the relatively small number of ‘successful’ Phase 2 trials that moved forward into Phase 3 (13%), in part for reasons that should have been foreseen at the onset—insufficient access to patients, insufficient financial support, lack of interest in conducting the clinical trial by colleagues, and lack of support from the drug manufacturer. The question, at least in part, becomes how many therapeutic strategies do we have sufficient research manpower, funding, and patient availability to complete? Are we making the best choices as to where to invest these resources?

Participants noted that alternative clinical trial designs have not yet been applied in muscular dystrophy. Use of Phase 0 or exploratory IND models would ensure that the candidate therapeutic hits the tissue and molecular targets in humans before moving on to safety and efficacy studies in larger cohorts. Similarly, Kathryn Wagner suggested that a futility model also would be effective in triaging candidates before entering into larger Phase 1/2 trials. Given the limited patient population in muscular dystrophy, consideration of alternative trial designs, to triage candidate therapeutics at early stages, may be warranted.

As with other chronic diseases, Edward Kaye commented that clinical benefit can take years to demonstrate, well beyond the timeframe of most clinical trials, and defining and validating early surrogate endpoint measures for muscular dystrophy should be a high priority. Edward Spack stated that early consensus on preclinical and clinical measures would enhance comparability of different therapeutic strategies. This has been a difficult issue for the muscular dystrophy field and there was an appreciation that the predictive value of endpoints (preclinical and clinical) will be validated only by positive and negative experiences in clinical trials. Thus far, we do not yet know what, for example, a 10% improvement in muscle strength means in terms of clinical benefit for the patient in the short- or long-term. Participants were reminded of Francesco Muntoni's keynote remarks, where he emphasized that clinical study designs need to include, but also go beyond, traditional measurements. He noted that it would be a wasted opportunity to complete a study, where the patients have made a huge commitment and sacrifice to participate, and not generate data that can inform further studies in the field, whatever the outcome is for the candidate therapeutic.

Finally, Cristina Csimma and Edward Spack both noted that the funding gap of early development/translational research (by academia or small biotech) of high risk projects up to the time when they could be of interest to pharmaceutical industry and/or venture capital firms will require more creative paradigms and for academia to be more informed of the potential resources available for the early stages of drug development. This gap can and is being addressed by novel
funding paradigms involving government agencies and patient advocacy groups, and can include expanded use of technology transfer/licensing offices, outsourcing to experienced contract research organizations (CROs), and working more synergistically across centers. Collectively, the muscular dystrophy field needs to take a broad view of therapy development and begin to identify and focus on the key ‘solvable’ issues in the field that may lead to effective drugs and biologics in a shorter time frame.

The obstacles in translational medicine include the: (a) high costs, (b) extended time to achieve results, (c) fragmented infrastructure, (d) incompatibility of data bases, (e) shortage of qualified investigators, (f) regulatory burdens, and (g) shortage of patients. In large part, the solutions for many of these obstacles will require a closer collaboration among academia, industry, funding agencies and organizations, regulatory authorities, and patients, with the understanding that international collaborations, such as that of TREAT-NMD, may be the only way forward to new therapies for muscular dystrophy. Together, the field should be discussing the strengths and limitations of the various therapeutic development partners and strategies and together identify where we all move from here.

5. Agenda

NIH Workshop on Translational Research in Muscular Dystrophy
Crowne Plaza Hotel, Silver Spring, MD
June 25-27, 2007

June 25, 2007

7:00 pm Welcome and Introductions
John Porter, Program Director, NINDS/NIH
Stephen Katz, Director, NIAMS/NIH
Story Landis, Director, NINDS/NIH
James Hanson, Director, CDBPM, NICHD/NIH
Katherine Mathews (University of Iowa), Workshop Chair

7:20 pm Keynote: Identifying and Managing Obstacles to Translational Research
Francesco Marincola (National Cancer Institute/NIH)

8:00 pm Keynote: Specific Challenges in Therapy Development for Muscular Dystrophy
Francesco Muntoni (Imperial College)

8:40 pm Discussion and Adjourn

June 26, 2007

7:30 am Coffee and Continental Breakfast
8:00 am Welcome
John Porter (NINDS) and Katherine Mathews (University of Iowa)

**Therapeutic Development Processes**

8:15 am  Case Study in Therapeutic Development for Neuromuscular Disease
          Edward Kaye (Genzyme)

8:55 am  A Milestone-Driven Translational Research Model
          Thomas Miller (NINDS)

9:15 am  Challenges of Target Identification and Development Decisions
          Working Group
          Kenneth Fischbeck (NINDS), Lee Sweeney (University of Pennsylvania), and Cristina Csimma (Clarus Ventures)

10:05 am Break

10:35 am Animal Models and Preclinical Endpoints Working Group
          Joe Kornegay (University of North Carolina), Jill Rafael-Fortney (Ohio State University), Maury Swanson (University of Florida), and Kathryn Wagner (Johns Hopkins University)

11:25 am Regulatory Issues and Ethics Working Group
          Diana Escolar (Children’s National Medical Center), Berch Griggs (University of Rochester), Langdon Miller (PTC Therapeutics), and Robert Nelson (Children’s Hospital of Pennsylvania and FDA Office of Pediatric Therapeutics)

12:15 pm Lunch

**Therapeutic Development Collaborations**

1:15 pm  Keys to Establishing Academic-Corporate Partnerships in Drug Development
          Terry Fadem (University of Pennsylvania)

1:55 pm  Building International Collaboration in Translational Research: TREAT-NMD and Beyond
          Kate Bushby (University of Newcastle-upon-Tyne)

2:35 pm Break

**Therapeutic Development Strategies**

3:10 pm  Gene Therapy & Repair/RNA Targeted Therapies Working Group
          Eric Hoffman (Children’s National Medical Center), Jerry Mendell (Columbus Children’s Research Institute), Jude Samulski (University of North Carolina), and Charles Thornton (University of Rochester)
4:00 pm  
Cell Based Therapies Working Group  
Johnny Huard (University of Pittsburgh), Louis Kunkel (Harvard University), and Thomas Rando (Stanford University)

4:50 pm  
Poster Session: Funding and Other Resources for Translational Research in Muscular Dystrophy  
NIH, Muscular Dystrophy Association, and Parent Project Muscular Dystrophy

5:30 pm  
Adjourn

June 27, 2007

7:30 am  
Coffee and Continental Breakfast

**Therapeutic Development Strategies (continued)**

8:00 am  
Muscle Regeneration Therapies Working Group  
Jennifer Lachey (Acceleron Pharma), Se-Jin Lee (Johns Hopkins University), Richard Moxley (University of Rochester), and Lorenzo Puri (Burnham Institute)

8:50 am  
Anti-Inflammation/Fibrosis Therapies Working Group  
Ronald Cohn (Johns Hopkins University), Denis Guttridge (Ohio State University), and Melissa Spencer (University of California at Los Angeles)

9:40 am  
Break

10:10 am  
Membrane Repair/Compensatory Membrane Proteins Therapies Working Group  
Kay Davies (Oxford University), James Ervasti (University of Minnesota), Justin Fallon (Brown University), and Paul Martin (Columbus Children’s Research Institute)

11:00 am  
Panel Discussion—Status Report and the Way Forward  
External Advisory Panel: Edward Kaye (Genzyme), Donald Kirsch (Cambria Biosciences), Ellen Maher (CBER/FDA), and Edward Spack (SRI)

11:50 am  
Closing Comments and Adjourn

Other Invited Observers/Discussants: Changting Haudenschild (CBER/FDA), Stephanie Parsons (Wyeth), Jon Tinsley (VASTox), Hilary Wilkinson (Merck), and Muscular Dystrophy Coordinating Committee Members.

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NIH Workshop on Translational Research in Muscular Dystrophy
Crowne Plaza Hotel, Silver Spring, MD
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Appendix 2: Roles of Federal Agencies and Outside Organizations in MDCC’s Action Plan for the Muscular Dystrophies

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