

U.S. NATIONAL INSTITUTES OF HEALTH WORKSHOP ON TRANSLATIONAL RESEARCH IN MUSCULAR DYSTROPHY

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Report for the TREAT-NMD Meeting on Outcome Measures in Early DMD Trials
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This Workshop, organized by the U.S. National Institutes of Health, was attended by over 60 scientists and regulatory agency, governmental organization, and industry representatives from the U.S. and Europe and representatives of 5 patient organizations. The motivation for the meeting was the progress and potential for new therapeutic development in muscular dystrophy and the need for changing mindsets on R&D models among both academia and corporations, the need for changing collaborative models, to ensure that appropriate expertise is brought to bear, and changing funding strategies, given that high development costs preclude any one party from fully funding a novel therapeutic program in rare diseases such as DMD. A variety of mechanisms were incorporated into the Workshop, including keynote talks, a 'lessons learned' case study in therapy development for rare neuromuscular disorders, working groups that reached consensus on a topic prior to the Workshop and presented findings, individual talks from selected experts, and an outside panel of distinguished industry scientists and regulators, seeking to examine the processes and collaborative models used in developing new therapies and to assess the current state of the various therapy development strategies in muscular dystrophy. Particularly at the program launch stage, it was viewed as essential that academia, biotech, and large pharma understand the strengths, weaknesses, and motivations of one another and to begin to formulate partnerships early in the process.

The goals of the Workshop were to: (a) summarize and evaluate the current status of translational research in muscular dystrophy, (b) identify obstacles to ongoing translational research, (c) identify ways to facilitate the rapid progression of therapies in muscular dystrophy based upon experience in this and other diseases, and (d) to produce a summary document for a peer-reviewed journal publication and a summary of the meeting for the U.S. Muscular Dystrophy Coordinating Committee website. The NIH (NIH Translational Research Program in the Muscular Dystrophies), Parent Project Muscular Dystrophy (Project Catalyst), and Muscular Dystrophy Association (MDA Translational Research Advisory Committee) have all launched therapy development funding programs in recent years, just as there has been increasing investment from biotechnology and large pharmaceutical companies in drug development efforts with potential value for muscular dystrophy. This environment called for a Workshop where the field could step back and perform a 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 efforts.

Therapeutic development processes

Muscular dystrophy is a target-rich environment—there are numerous potential targets, and it is unclear which of these represent the best therapy development 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, presenters and participants discussed the critical question as to when enough was known about a target and a candidate therapeutic to enter into a formal therapy development program. This decision involves science considerations (pathology clearly defined, target appropriate, availability of preclinical support to go to the clinic?), drug industry considerations (risk/benefit, regulatory barriers—a clear path to approval, established clinical endpoints, back-up compounds, potential performance of the candidate therapeutic, relevance to multiple populations/diseases, ease, cost, and scalability of the manufacturing?), and issues of the governmental, corporate, and venture capital funders of early stage R&D programs ('experts' comfortable with the target, addresses an unmet medical need, applicability of animal model data to human disease?). A careful overview 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. But it was recognized that we do not yet know enough about the relationship of pathogenesis in dog and mouse models of the human disease, and about the predictability of endpoints in animal models for human efficacy, to yet reach a consensus on models and endpoints. Key principals discussed at the Workshop included the observations that no animal model is perfect (accept what's available, but carefully optimize the experimental design, and recognize that some very good drugs have come from very bad animal models of other diseases), no in vitro/in vivo assay should be used in isolation to avoid misleading results, and quantitative, go/no-go criteria should be used in a milestone-driven research design in order to reach unambiguous decision points in therapy development programs. Emergence of a best practice for preclinical development likely will require successes and failures in clinical trials to validate a specific subset of animal models and endpoints. It was noted that investigators conducting efficacy studies should also be focusing on development of the surrogate endpoints/biomarkers in animals that will facilitate shorter duration clinical trials. Finally, discussions of regulatory and ethics issues that have or will emerge in this field included the need to harmonize local (IRB) and national (EMA/FDA) human studies approval requirements, including coordination between funding and regulatory agencies, the streamlining of bureaucracy at academic institutions, the restoration of common sense into human subject data protection regulations (HIPAA), and eliminating the 'we're here to help you, no matter how long it takes' regulatory burdens.

The emergence of a global registry that facilitates 'one-stop-shopping' for those conducting clinical trials was viewed as essential in the development of Genzyme's Pompe disease drug and represents necessary infrastructure for therapeutic development in the muscular dystrophies. In the case of clinical trials for DMD, where the subjects are minor children, a balance must be sought among the regulatory and ethical concepts of scientific necessity, parental permission, child assent, enrolment of healthy children controls, and an appropriate balance of risk and benefit for the subject. The inability to reach consensus on clinically meaningful outcome measures in the muscular dystrophy

field also might be a consequence of the need to first learn from success/failures in more early stage trials. While there is broad international agreement on the core ethical principles to guide pediatric research, there has been resistance in moving from an academic to an industry model in the design and conduct of clinical research. Such a shift has been critical for fields with more experience in drug development and likely would aid the muscular dystrophy field.

Therapy development collaborations

Participants in the Workshop heard advice from an academic director of corporate alliances who is responsible for facilitating academic-corporate drug development partnerships at a major U.S. medical school. The need to build strong relationships between academic and corporate partners was viewed as essential in helping overcome the variety of barriers to collaboration (time, space, cultural, access, attention, priorities, long-term plans, etc.). Emphasis was placed on the need to broker relationships, not simply 'deals,' and to base academic-corporate relationships on both science and project management. 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 a well-honed process for facilitating academic-corporate partnerships in therapeutic development. The TREAT-NMD partnership model also was presented and praised as essential infrastructure to facilitate new treatments for muscular dystrophy.

Therapy development strategies

The major strategies currently being pursued in muscular dystrophy were evaluated by working groups of 3- to 4-members, with their findings presented at the Workshop. Separate panels looked at Gene Therapy & Repair/RNA Targeted Therapies, Cell Based Therapies, Muscle Regeneration Therapies, Anti-Inflammation/Fibrosis Therapies, and Membrane Repair/Compensatory Membrane Proteins Therapies. Summaries of these discussions are too lengthy to present here but will be made available on the Muscular Dystrophy Coordinating Committee website and in a peer-reviewed publication.

Overall assessment

An expert with experience from both large pharma and a venture capital firm commented that there has been a palpable increase in collaboration and respect among the key partners in the muscular dystrophy field and that maturation of such partnerships is essential to the achievement of effective new therapies for muscular dystrophy. The field has a clear recognition of the value and limitations of available animal models and can best move forward by understanding the caveats and designing careful, statistically rigorous studies to identify not just any candidate, but the best candidates to move forward into the clinic. Again, tendencies to promote personal favourite candidates need to be replaced by pragmatic decision making. An outside industry representative pointed to data that as many as 50 projects need to be launched to produce a drug. The notion was raised that a critical mass of efforts needs to be initiated for muscular dystrophy with a fail early/fail often and move on philosophy. Put another way, muscular dystrophy researchers need to learn how to objectively and dispassionately triage candidates both at the preclinical and clinical trial launch stages—while bets have to be placed on a wide array of targets and therapeutic candidates, available resources are not without limit at any stage of the therapy development pipeline making triage critical. Although potentially 'curative' strategies such as antisense-mediated exon skipping are attractive,

and require attention, focusing on common downstream pathways that may be conserved among the different muscular dystrophies allows marshalling of knowledge and resources that might lead to more timely development of new therapeutics.

A regulatory agency participant emphasized the need to understand why a therapeutic candidate fails and, conversely, to appreciate the problems that arise from 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, tempered 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). While there was recognition that agreement on preclinical and clinical endpoints is critical, and that earlier consensus would enhance comparability of different therapeutic strategies, there was an appreciation that the predictive value of endpoints will be validated only by experiences in clinical trials that complete the bench to bedside and back loop. Finally, it was noted that both the pharmaceutical industry and venture capital firms are shifting support toward late-stage therapy development, where risk/benefit ratios are more favourable, and thereby are creating a gap in the earlier stages of drug development that needs to be addressed by alternative funding paradigms. 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.

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