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Therapy development for neuromuscular diseases: translating hope into promise

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Abstract

The Second Muscular Dystrophy Association Scientific Meeting was held on 21–24 April 2013 in Washington (DC, USA). The meeting provided an opportunity for research scientists, clinicians, government agencies and industry experts to highlight and discuss different aspects of therapy development for neuromuscular diseases, including novel targets, biomarkers, therapeutic approaches, animal models and clinical trials. With 500 participants, 66 presentations and 200 abstracts, the 3-day conference has become a central focus for scientists interested in translational research and moving potential therapies forward from the bench to the bedside. Key issues covered by the meeting included the need to identify new drugs to treat patients with neuromuscular diseases and the importance of establishing collaborations between government, academic and industry sectors toward an efficient and rigorous translational path for neuromuscular diseases.

As the world's leading nonprofit health organization sponsoring research on neuromuscular diseases (NMDs), the Muscular Dystrophy Association plays a central role in scientific and clinical neuromuscular communities by offering services to patients, clinicians and researchers worldwide. The scientific meeting, held in Washington (DC, USA) was intended to leverage the expertise of researchers across different NMD areas, from the academic, corporate drug development and clinical arenas, to identify barriers to therapeutic development and strategies to overcome those barriers.

The opening remarks from Kurt Fischbeck from the National Institute of Neurological Disorders and Stroke (NINDS) identified those key barriers and provided an overview of the criteria used by the NIH and pharmaceutical industries for prioritizing therapy development for NMDs. The barriers include a strong biological rationale for therapy approach, the medical need for a therapy for diseases for which no better alternatives are available and the careful assessment of the risk–benefit ratio of each clinical intervention. Diseases, such as Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), myotonic dystrophy (DM), facioscapulohumeral muscular dystrophy (FSHD) and Charcot–Marie–Tooth disease, have already received the attention of

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biopharmas as demonstrated by the presence at the meeting of numerous representatives from industries actively involved in therapeutic development for those diseases.

Various approaches are currently in the pipeline using different modalities. Adeno-associated virus vectors are being optimized in DMD mouse and canine models as well as in mouse models for SMA using gene replacement strategies. Adeno-associated virus vectors were also shown to be able to efficiently express antisense oligodeoxynucleotides (AONs) and redirect mRNA splicing of the dystrophin gene for the treatment of DMD or inhibit toxic mRNA repeats to correct the pathology associated with FSHD and DM type 1.

The updates on the clinical trials for exon-skipping therapies in DMD, presented by Francesco Muntoni (University College of London Institute of Child Health, London, UK) and Jerry Mendell (Nationwide Children's Hospital, OH, USA) on independent trials in Europe and the USA, are promising. The trials employ the phosphorodiamidate morpholino oligomer, eteplirsen, also called AVI-4658, developed by Sarepta Therapeutics (MA, USA; formerly AVI BioPharma, Inc.). The results showed low toxicity of the AON demonstrating that the drug is well tolerated in patients. Importantly, the data presented by Mendell on the 72-week Phase IIb eteplirsen trial demonstrated beneficial effects of the AON drug in all 12 DMD patients enrolled in the study. The stretch, measured in meters, that patients were able to cover in the 6-minute walk distance test remained similar to that observed at baseline, prior to entering eteplirsen regimen. Encouraging results were also reported by Thomas Voit (Université Pierre et Marie Curie VI, Paris, France) in the trial employing the 2'-O-methyl phosphorothioate AONs known as drisapersen (PRO051/GSK2402968) sponsored by Prosensa Therapeutics (Leiden, The Netherlands) in collaboration with GlaxoSmithKline (London, UK). Altogether, these outcomes meet an important milestone in therapy development for DMD by providing evidence that AON treatment can restore dystrophin expression in patients and, when administered over prolonged periods of time, can also preserve motor function or at least delay disease progression in patients.

Positive outcomes were also reported by Kathie Bishop (Isis Pharmaceuticals, Inc., CA, USA) in the Phase I trial aimed at testing the safety, tolerability and biodistribution of the experimental AON drug, ISIS-SMNRx, developed by Isis Pharmaceutical, Inc. in children with SMA. Isis Pharmaceuticals is expected to release the full neurological and toxicological test results within the next few months.

PTC Therapeutics (NJ, USA) announced the initiation of a Phase III, multicenter, randomized, double-blind, placebo-controlled study designed to determine the efficacy and safety of ataluren (PTC124) in DMD patients with nonsense mutations. Inclusion and exclusion criteria were defined based on the longitudinal data of the 6-minute walk distance test obtained in the Phase IIb trial of ataluren completed in 2009.

Drug discovery is becoming an integral part of therapy development for NMDs. New high-throughput screening platforms and software products are being optimized to identify compounds capable of upregulating expression of therapeutic genes or able to inhibit molecular pathways that contribute to disease progression. Kay Davies (University of Oxford, Oxford, UK) presented an update on the state-of-the-art of SMTC1100, developed in partnership with Summit plc (Oxfordshire, UK), which has completed a Phase I trial. New targets within the pathway that control SMTC1100-mediated upregulation of utrophin expression have been identified, as well as new compounds that could be used to inhibit those targets to enhance the effects of SMTC1100. In addition, screening of small molecules is ongoing for other types of NMD including Charcot-Marie-Tooth disease. Also under development are new computational databases of small molecules targeting RNA motifs.

The approach was shown to successfully predict and design small molecules targeting CUG and CCUG RNA repeats that cause DM.

Several lectures were centered on describing the effects of genetic modifiers as contributors of disease pathology in NMDs [1]. The results, presented by Eric Hoffman (Children's National Medical Center, DC, USA), suggest that expression of osteopontin and LTBP4 influences functional tests in younger DMD males, response to steroid treatment and loss of ambulation supporting the use of these modifiers as predictors of disease progression. Similarly, Elizabeth McNally (University of Chicago, IL, USA) provided evidence of the implication of LTBP4 expression in disease progression and loss of ambulation in DMD patients. It is likely that the advances made in functional and comparative analyses in animal models and human patients through genomic, proteomic and metabolomic studies will enable the identification of additional modifiers implicated in NMDs and which are responsible for influencing their course or onset. Of relevance was the study presented by Stephen Tapscott (University of Washington, WA, USA) on DUX4, a double-homeobox transcription factor encoded by a retrogene in the D4Z4 macrosatellite repeat and associated with FSHD. Skeletal muscles induced with DUX4 were shown to misregulate expression of genes implicated in ubiquitin-mediated degradation pathways, as well as germline pathways. The effects on germline pathways could ultimately be responsible for the induction of specific antibodies and inflammatory responses, thus suggesting that genes involved in immunity and innate defenses are important genetic modifiers of FSHD. These studies also suggest that targeting DUX4 expression in muscle may provide a valuable therapeutic approach for FSHD patients.

Despite the progress made to date, there is still a compelling need to identify biomarkers or surrogate biomarkers to be used as primary efficacy measures of investigational drugs or therapeutic interventions in trials for NMDs [2]. Marc Walton from the Office of Translational Sciences at the Center for Drug Evaluation and Research (CDER) at the US FDA provided an overview of the qualification required to identify prognostic, predictive, pharmacodynamic or efficacy-response biomarkers. The CDER has undertaken multiple initiatives to aid the development of new tools. Among these efforts is the development of a formal process that the CDER will use to guide investigators [101]. Examples of biomarkers under development for the evaluation of diagnostic and clinical outcomes presented at the meeting included a H-reflex test and quantitative measurements of CD4⁺ Tregs, TGF⁺ or IL4⁺ T lymphocytes mRNA expression to monitor disease progression in ALS patients, a T1- and T2-weighted MRI method to monitor inflammation, muscle size and fat replacement in DMD males and a mass spectroscopy method to quantify dystrophin expression as a possible efficacy biomarker.

The meeting continued with presentations on different animal models, including several zebra fish, mouse and canine models of NMDs, identified in nature or generated in a laboratory available for genetic and preclinical studies. As highlighted by Cathleen Lutz from the Jackson Laboratory (ME, USA), the usefulness of each of these models ultimately depends on the experimental approach being implemented and their genetic background, which can vary between species and even within identical species due to genetic drift occurring naturally through intercross breeding.

Several resources have been established by the US government and made available to researchers and institutions nationally and internationally for the development of therapies for NMDs. Gurusingham Sittampalam from the Therapeutics for Rare and Neglected Diseases (TRND) program highlighted some of the resources available in the National Center for Advancing Translational Sciences Division of Pre-Clinical Innovation (NCATS-DPI) at NIH. Additional resources include the tissue bank and repositories available at the

National Cancer Institute, as reported by Jim Vaught, of the National Cancer Institute Biorepository and Biospecimen Research Branch [102] and the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database [103]. Elizabeth McNeil encouraged academic, foundation or industry investigators to take advantage of the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), instituted by the NINDS to facilitate clinical trials, and capable of providing the infrastructures necessary to validate a therapeutic intervention [104].

The concluding remarks delivered by John Porter at NINDS abridged the major topics discussed at the meeting and emphasized the importance of forming strong alliances among multidisciplinary sectors including government, private industry and academia sectors [3]. The reproducibility of results and animal efficacy data across different laboratories relies on the implementation of more standardized approaches to data analysis and data interpretation to ensure rigor in preclinical studies across institutions [4]. Porter concluded that the ultimate goal is to avoid prematurely exhausting the resources available, a goal that can be achieved by moving forward only those therapies that have been extensively optimized in the laboratory.

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