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In Focus

The Action Duchenne 13th International Annual Conference, November 6–7, 2015, London, UK

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1. Identifying New Targets in Duchenne Muscular Dystrophy (DMD)

Increasing our understanding of the pathophysiological mechanisms that manifest in DMD patients offers the opportunity to identify new pharmacological targets. Dominic Wells and Thomas Voit, University of London, provided insights into the most promising drug targets currently under investigation to treat DMD. Increasing muscle mass by inhibiting myostatin, has produced promising results with Pfizer's, PF-06252616 in phase II and Bristol Myers Squibb, BMS-986089, in early development. Decreasing muscle inflammation and fibrosis has been achieved by inhibiting the protein complex NFκB, and multiple compounds are being tested in clinical trials. Improving mitochondrial function is another strategy and stimulating PGC1a, which regulates genes involved in energy metabolism, has shown therapeutic promise. Progress is also being made in repurposing existing drugs. Tadalafil (also used to treat erectile dysfunction), is in phase III studies and increases blood flow to cardiac and skeletal muscle, while Simvastatin (a lipid lowering drug), has been shown to effectively reverse dystrophic pathology in preclinical trials (Whitehead et al., 2015). Identification of new druggable targets offers additional options to the healthcare community and renewed hope for those living with this progressive condition.

2. Gene Therapy to Restore Dystrophin

Gene therapy applications to restore dystrophin expression is widely considered one of the most promising approaches for the treatment of DMD. Recombinant adeno-associated virus vectors (rAAV) have been well characterized over the past few years to deliver the functional dystrophin gene, as they are very efficient in the transduction of skeletal and cardiac muscle. However, full-length dystrophin cDNA exceeds the packaging capacity for a single rAAV gene-delivery cassette. Therefore, truncated versions, namely microdystophins, have been designed and optimized to include a few clinically important regions of the dystrophin protein. Two groups recently published data, a single-dose intravascular delivery of rAAV2/8-Spc512-μDys (Le Guiner et al., 2015) and AAV-9 reporter or micro-dystrophin (μDys) vector at doses of $1.92–6.24 \times 10^{14}$ viral genome particles/kg (Yue et al., 2015) in Golden Retriever Muscular Dystrophy Dogs, the canine model of DMD. Overall, the improvement of multiple muscle parameters was observed with no reported severe adverse events. Whilst the DMD community are at a precipice in bridging the gap between late pre-clinical and early clinical work on AAV gene-therapy, a few very important safety concerns associated with route of delivery, immunogenicity of vectors and transgenes remain to be addressed.

3. Gene Editing to Correct Dystrophin Mutations That Cause DMD

Various genome editing technologies have attempted to restore expression of the dystrophin gene in cells carrying dystrophin mutations. Principal Investigator, Charles Gersbach from Duke University, USA, presented data showing how his lab has applied the CRISPR/Cas9 gene editing system to restore the dystrophin reading frame in DMD patient myoblasts (Gersbach, n.d.). Using single or multiplexed guide RNAs (sgRNAs), a variety of mutations could be corrected by introducing small targeted deletions, or removal of whole or even multiple exons. Dystrophin protein was restored in correctly-targeted cells and could be detected when these cells were transplanted into mice (Ousterout et al., 2015). Theoretically, this approach can correct >60% of DMD mutations, offering an exciting therapeutic avenue. Gersbach was clear to point out that despite cautious optimism, the CRISPR/Cas9 system needs refining to improve its targeting efficiency and minimize off-target activity. However, if these challenges can be addressed, gene editing might be the molecular tool to enable treatment of individual DMD mutations by precision medicine.

4. Combination Therapy to Treat DMD

In the absence of dystrophin, many negative pathway cycles get activated in an attempt to compensate for the lack of dystrophin. Each of the downstream aspects of the pathology associated with DMD is being investigated as separate drug targets. Leading experts are starting to consider the potential of combination treatment, as they feel it is likely that a few of these targets could have additive benefit (Wells). Corticosteroid use is often a baseline inclusion criteria for most trials, but this has not been extensively tested in

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preclinical models. Another dimension is repurposed compounds from other therapeutic areas; depending on whether this has been well-studied in the pediatric setting, may have a faster-track to the clinic. There needs to be a clear strategic and collaborative approach on what potential poly-therapy (Ricotti et al., 2015) would be synergistic based on the patients' genotype and/or stage of the condition with a complementary robust safety pharmacology package for any potential combination.

5. Magnetic Resonance Imaging (MRI) in DMD Management

Magnetic resonance imaging (MRI) is sensitive to alterations in muscle composition and structure and can quantify measures related to inflammation and skeletal muscle fat; it is used to assess inflammation, fibrosis, and fatty infiltration of skeletal muscle. At a recent European Neuromuscular Centre workshop, natural history data was presented in which fatty tissue deposition within one year in the soleus and vastus lateralis muscles were observed in all DMD age groups (5–12 years old), but not in the unaffected controls (Ferlini et al., 2015). Other recent groups have used this quantitative muscle composition (fat fraction) to assess the effect of treatment and its potential reduction correlated with functional outcome measures. An ongoing observational Imaging DMD study (Clinical trials.gov website, n.d.), at five US sites is comparing the muscles of ambulatory boys with Duchenne with muscles of healthy children of the same age to monitor disease progression over a five year period. Considering the advances made in MRI and MR spectroscopy, key multi-national experts feel that this could be strongly considered as a future potential non-invasive prognostic and pharmacodynamics biomarker (Fig. 1).

Fig. 1. The Conference Dinner.

6. Developing Better Outcome Measures in DMD

Progress in preclinical strategies to tackle DMD has underscored the need to rethink outcome measures for gauging therapeutic response in clinical trials. Historically, clinical outcome measures comprised assessment of walking skills, such as the 6-minute walk test and the North Star Ambulatory Assessment. Whilst reliable, these tests are only applicable to ambulatory boys, thereby precluding the involvement of non-ambulatory DMD patients in clinical trials. Annemieke Aartsma-Rus, coordinator of the EU-funded TREAT-NMD network (TREAT-NMD website, n.d.), spoke passionately about international efforts from patients, clinicians, physiotherapists, scientists, advocacy groups and industrial partners to devise a roadmap to improve clinical outcome measures, making them applicable to all DMD patients. One strategy, is the development of functional tests that measure the progressive decline in upper limb movement that deteriorates in a proximal-distal direction, during the course of the disease. The introduction of MyoTools (to measure hand strength) and MRI modalities (to non-invasively measure disease characteristics) can complement assessment, enabling treatment response to be quantified. The hope is that tailoring the most accurate clinical outcome measures for a specific clinical trial cohort will aid therapeutic assessment and facilitate regulatory approval of the most promising candidates.

Declaration of Interests

DR is Director of Research at Action Duchenne and organized The Action Duchenne 13th International Annual Conference.

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