Pre-clinical studies in rare diseases: the challenge to speed up pharmacotherapy in Duchenne muscular dystrophy

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A disorder is defined rare when it affects a low percentage of subjects in a population, i.e. less than 1 in 2000 in Europe. In spite of this, rare diseases are a hot health problem, since there are thousands of different rare pathologies affecting millions of citizen worldwide. 80% of rare diseases are of genetic origin, most of them affecting children, and many are often misdiagnosed, chronic and life-threatening. Rare disease have been a long neglected investment by Pharmaceutical Industry research, due to the poor market and the difficulty in performing appropriate clinical trials. In the last decades FDA and EMA implemented specific regulatory acts to boost the search of diagnostics and therapeutics for rare diseases, the so called orphan drugs, by mean of financial and non financial benefits.

Duchenne muscular dystrophy (DMD) is one of the most frequent forms of rare inherited diseases affecting skeletal muscle. Since the discovery of its genetic cause, a mutation in the X-linked dystrophin gene leading to the absence of the cytoskeletal protein dystrophin, a growing interest has been devoted in searching for therapeutic interventions by both private and academic researchers, also thanks to the support of patient associations and charities. Due to the low number of patients, a specific urgency is to optimize pre-clinical studies on animal models of the disease, such as the *mdx* mouse. This latter is largely used for testing drugs with innovative mechanism of action or targeting the complex pathological cascade of events. However, the large plethora of data obtained in the *mdx* mouse is often controversial, which delay data translation and/or lead to failing clinical trials. During the last 5 years, the scientific community worldwide has intensively worked, under the concerted action of NIH and TREAT-NMD (European network of excellence for the therapy of neuromuscular disorders) to find a general consensus on the Standard Operating Procedures (SOP) to perform pre-clinical studies in animal models of DMD. The SOPs, and the critical examination of the various approaches, aim at controlling possible confounders and optimizing technical investigation and statistical analysis, in the attempt to obtain more robust and reproducible results. This is of particular importance for the primary outcomes, parameters that are more predictable of potential clinical efficacy, while secondary endpoints are mostly linked to drug mechanism of action or to proof-of-concept approaches. A list of SOPs is available at the TREAT-NMD website (http://www.treat-nmd.eu/resources/research-resources/dmd-sops/) and may be downloaded to provide general guidelines to researchers. Reviews dealing with this topic have also been published.

Based on this overview, a general approach to pre-clinical research using the *mdx* mouse model and the potential pharmacotherapy in DMD can be developed. Importantly, the prioritization of the best candidate for clinical trials needs a wide concerted revision by multiple experts, as offered in the TREAT-NMD Advisory Committee of Therapeutic, which may help to minimize risk of failure in the costly process of drug development, meanwhile taking into consideration the urgent need of patients to have access to effective and safe therapies. Hopefully the increasing collaboration between pre-clinical scientists and clinicians will help to critically evaluate the balance between benefit and failure in both pre-clinical and clinical settings, in order to avoid that promising drugs are discarded or that improper drugs could raise expectation in patients and families. Similar approaches are increasingly used for other rare diseases.