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Challenges of clinical trials in rare diseases: The learning experience of Duchenne muscular dystrophy

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Research and patient communities are united in the opinion that rare diseases require new and better therapies. Drug development programs for rare diseases have many challenges, including the limited numbers of patients and lack of clinical and research-savvy experts. International, multi-center studies in rare diseases provide added value by promoting global standards of care and by expanding market for new treatments but also represent a challenge to set-up in view of the lack of harmonization in the regulatory process between US and EU and within different EU countries. Efforts have been made in both EU and US to reduce bureaucratic delays in setting up multi-center clinical trials, to increase the efficiency of clinical trials and expand the ability to promptly deliver new therapies to patients with rare diseases. The approval system remains slow and will need to adapt to the recent development of new therapies for rare diseases which will hopefully increase the demand for prompt evaluations by the competent authorities. More recently, drug development costs have been raised as a further obstacle in developing new therapies for rare diseases. The high costs associated with drug development programs from pre-clinical to phase-I studies, to pre-marketing trials lead to often unaffordable drugs and non-sustainable drug development. Duchenne muscular dystrophy has seen a large investment in terms of new treatments entering clinical research over the past 10 years. It represents a good example where different strategies have been developed to overstep many of the challenges of drug development, which include the set up of patient registries, care and clinical trial site registries, networking, interaction with regulatory authorities and venture philanthropy models for drug development. Also the experience gained from the translational research in DMD over the past 10 years can be shared to learn about existing obstacles, to anticipate them and planned around them to ensure a realistic delivery of research.

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Temperature, pH and calcium: Arrhythmogenic triggers in mixed long QT3 and Brugada syndrome

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Sudden cardiac death (SCD) is a major cause of mortality, afflicting more than a quarter million people annually in the United States. Although there are a number of causes for SCD, inherited genetic mutations account for a substantial proportion of deaths in victims under the age of 40 years. Rare forms of inheritable cardiac disease underlying SCD include Long-QT3 (LQT3) and Brugada syndromes (BrS1), both of which arise as a consequence of mutations in the SCN5a gene that encodes the cardiac voltage-gated sodium channel, NaV1.5. A particularly rare NaV1.5 mutant, E1784K, is one of several mutants that cause mixed or overlap syndrome, which has the characteristics of both LQT3 and BrS1. We studied E1784K channels expressed in *Xenopus* oocytes and mammalian cells and found that several physiological factors, all of which are normal byproducts of intense exercise, exacerbate the biophysical defects caused by the mutation itself. Voltage clamp recordings of ionic and gating currents show changes in a range of biophysical properties in E1784K, compared to wild-type NaV1.5 channels, when temperature is raised, extracellular pH is reduced or cytosolic Ca++ is elevated. These biophysical changes are predicted to be arrhythmogenic. We incorporated our biophysical results into a ventricular action potential model and found that, at high heart rates, the effects of temperature, pH, or calcium are individually arrhythmogenic. These results lead us to the conclusion that catastrophic arrhythmias may be triggered by intense exercise in individuals carrying the SCN5a mutation underlying the E1784K form of mixed syndrome.

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