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Link between malignant hyperthermia susceptibility (MHS) and exertion/environmental heat stroke (EHS): Is it just a hypothesis?

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Background: Mutations in the gene encoding for ryanodine receptor type-1 (RYR1), the SR Ca2+ release channel, underlie debilitating, life-threatening muscle disorders such as central core disease (CCD) and malignant hyperthermia (MH) susceptibility. To date, MH is only seen as a clinical syndrome in which genetically predisposed individuals respond to volatile anesthetics in the operating room with potentially lethal episodes characterized by elevations in body temperature and rhabdomyolysis of muscle skeletal fibers. However, virtually identical over-heating episodes have been reported in individuals also after exposure to environmental heat and physical exertion.

Specific Gaps of Knowledge: Mutations in RYR1 have been found in many, but not all, MH cases suggesting the potential involvement of additional genes; the relationship between classic MH and over-heating episodes caused by heat/exertion is not yet widely recognized; and the molecular mechanisms underlying MH episodes needs to be fully elucidated.

Recent Breakthroughs: In the last years, the field has significantly advanced: MH episodes can result not only from mutations in RYR1, but also from mutations in other proteins (i.e., Calsequestrin-1); the mechanisms underlying hyper-thermic episodes triggered by anesthetics and by heat/exertion are virtually identical, suggesting that these syndromes could be possibly treated/prevented the same drugs; during MH/EHS crises Ca2+ leak from intracellular stores results in a feed-forward mechanism mediated by excessive production of oxidative species of oxygen and nitrogen (ROS and RNS), which seems to play a central role in the cascade of events leading to rhabdomyolysis of skeletal fibers.

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Value creation and transformative opportunities in the rare diseases space: Lessons learned & what lies ahead

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Rare diseases have been a source of value creation for the Biopharma industry in the last 10 years. The transformational journey of NPS Pharma from a failing company to a $5.2 billion exit is a vivid example of a success story with significant value delivered to patients, shareholders and employees. The presentation will share the lessons learned along the way as they are continue to be applicable to public and private companies that are in the space. Yet, the winds could be turning when it comes to pricing and reimbursement of orphan drugs, especially within the context of the US presidential elections and the shift in the public opinion regarding drug costs. If not addressed, they could put significant damp on this vertical. However, innovation and patients can still win the battle through understanding cost-containment and cost-cutting approaches that are currently in play and proactively developing and executing the necessary strategies to address them. Part two of the presentation will details these challenges and offer practical options to dealing with them.

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