Development of therapeutic leads for the treatment of Duchenne muscular Dystrophy (DMD) Patients

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Duchenne muscular dystrophy (DMD) is an X-linked recessive muscular dystrophy affecting roughly 1 in 3500 boys, which is caused by mutations in the dystrophin gene (DMD) on the short arm of chromosome committed to encode “Dystrophin” protein, the key connector between cytoskeleton of a muscle fiber to the surrounding extracellular matrix through cell membrane, causing gradual loss of muscle tissue and function, which eventually leads to wheelchair dependency at approximately the age of 12 years, requirement for assisted ventilation at approximately the age of 20 years and eventually premature death. Currently, there is no cure for DMD, but improvements in integrative treatment can slow down the disease progression and thereby extend the life expectancy of DMD patients. Patients with DMD have different forms of mutations at varying positions of the protein, resulting in the production of functionally compromised dystrophin protein. The hallmark of DMD is the lack of presence of cellular dystrophin, the cementing protein linking actin cytoskeleton to muscle cell membrane. However, the selective absence of dystrophin can be reversed by the overexpression of utrophin, a close homolog of dystrophin. Mutations in the gene causing a disruption of the open reading frame or introduction of a premature stop codon lead to a complete absence of a functional dystrophin protein. One of the main strategies of the current research towards the treatment of DMD is to restore the expression and function of the dystrophin gene. Despite its severity in terms of systemic muscle impairment culminating into multi-organ failure and death, this disease is so far neglected due to lack of proper theranostic tools for in-time diagnosis and treatment.

Antisense oligonucleotide-mediated exon-skipping is currently the most promising approach, which involves the systemic delivery of specifically designed AONs to DMD patients to induce de novo protein expression in muscle. Targeted exon skipping is the front runner in the therapeutic management of DMD. Antisense Oligonucleotides (AON) based exon skipping works like a molecular patch so that the DMD gene can produce the dystrophin protein, at a lower than normal but working level, to help protect and maintain the strength of muscle fibers. The idea behind exon skipping is to hide, or mask, specific exons in a gene sequence. In DMD patients, one or more exons can be masked with specific molecules called AON or “molecular patches,” near the place in the DMD gene where one or more exons are missing. Hiding select exons works to find a “fit” between remaining nearby exons, essentially resulting in a situation where a smaller but still functional dystrophin protein can be produced. Because DMD can be caused by the deletion of different exons along the length of the DMD gene, oligonucleotides or molecular patches for a given exon will not work for all patients. For example, exon 51 skipping will only work in about 13 percent of DMD patients whose disease is amenable to skipping exon 51. Others may need skipping to take place for exons 53, or 45, etc.

Considering the severity of this neglected disease and to address the above issues, team of IIT Jodhpur in collaboration with AIIMS Jodhpur and DART Bangalore initiated a multipronged strategy to deal with the issues. This initiative will address following major issues through development of small molecule agonist for elevated expression of utrophin, recovering or balancing the dystrophin function through exon skipping using novel molecule, and development of new effective therapeutic formulation for muscle cell specific delivery. Recently, Departments of Science and Technology and Science and Engineering Research Board (DST-SERB), India under Intensification of Research in High Priority Area (IRHPA) has funded a research initiative on DMD to address the fundamental problems in DMD disease and development of multiple therapeutic leads for clinical trials in DMD patients in India. This Clinical Trial will impact the patients and the families tremendously as this is the first and only meaningful personalized genetic treatment under the “Make in India” initiative.

References


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