Technology Offer

DMD Gene Therapy Approach

Reference Number 01-00987

Challenge
Duchenne muscular dystrophy (DMD) represents the most frequent hereditary childhood myopathy, leading to progressive muscle degeneration and weakness, and to premature death due to respiratory and cardiac impairment.
Genetic approaches such as antisense oligonucleotide (AON)-mediated exon skipping, aimed at reframing dystrophin transcripts, has been translated into clinical trials. However, AONs offer only temporary and limited efficacy of dystrophin expression. In contrast, genome editing strategies provide a more efficient and permanent genomic correction.
Recently, intravenous application of AAV9 delivering CRISPR/Cas9 components in a beagle model of DMD (exon 50 deficiency) proved successful in restoring expression of a shortened dystrophin in various muscles, including the heart. However, functional data have not been reported yet. Consequently, there still is a further need for efficient and sustained DMD therapies.

Technology
The novel therapeutic approach is an exon skipping strategy based on a split-intein-Cas9-mediated exon 51 excision which results in expression of a shortened but functional dystrophin protein (dysD51-52). Proof of concept experiments have been performed in a proprietary porcine model of DMD lacking exon 52 resulting in an out-of-frame mutation with a premature stop codon and complete loss of dystrophin expression.
It has been demonstrated that intramuscular application of an adeno-associated vector of serotype 9 (AAV9) carrying split-intein-Cas9 and a pair of guide RNAs targeting exon 51 induces expression of a shortened dystrophin (dysD51-52) which is leading to a major structural and functional improvement of skeletal muscles. Systemic application of the AAV9-construct led to widespread muscular dystrophin expression in Delta52-pigs, including diaphragm and heart in addition to skeletal muscles. Such animals showed an enhanced survival and reduced arrhythmogenic vulnerability.
Substantially improved delivery of the AAV9-vector has been achieved by a coating with dendrimer-nanoparticles without influencing the myotropism of the AAVs.

Commercial Opportunity
The technology is available for in-licensing or further co-development.

Patent Situation
A European patent application has been filed in 2019.

Further Reading
Moretti et al., Somatic gene editing ameliorates skeletal and cardiac muscle failure in pig and human models of Duchenne muscular dystrophy. *Nat. Med.* (2020). doi.org/10.1038/s41591-019-0738-2ti et al., Somatic gene editing ameliorates skeletal and cardiac muscle failure in pig and human models of Duchenne muscular dystrophy. *Nat. Med.* (2020). doi.org/10.1038/s41591-019-0738-2

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