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Q1 # Exon skipping therapy for Duchenne muscular dystrophy

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ABSTRACT

Duchenne muscular dystrophy (DMD) is caused mostly by internal deletions in the gene for dystrophin, a protein 17 essential for maintaining muscle cell membrane integrity. These deletions abrogate the reading frame and the 18 lack of dystrophin results in progressive muscle deterioration. DMD patients experience progressive loss of 19 ambulation, followed by a need for assisted ventilation, and eventual death in mid-twenties. By the method of 20 exon skipping in dystrophin pre-mRNA the reading frame is restored and the internally deleted but functional 21 dystrophin is produced. Two oligonucleotide drugs that induce desired exon skipping are currently in advanced 22 clinical trials. 23

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Q3 ## 1. Introduction

30 Duchenne muscular dystrophy (DMD) is a rare, degenerative, 31 X-chromosome-linked muscle wasting disease that affects approxi- 32 mately 1:3500 newborn boys [1]. The disease is caused by various mu- 33 tations, most commonly internal deletions, in the gene coding for 34 dystrophin protein. This 2.4 Mb long gene is the largest known human 35 gene and includes 79 exons and 78 introns [2]. Dystrophin protein, a 36 component of the sarcolemmal complex, connects the complex to 37 actin filaments (Fig. 1) and is essential for maintenance of muscle cell 38 integrity. Mutations in the dystrophin gene that cause DMD lead to a 39 lack of dystrophin, resulting in muscle cell membrane destabilization 40 that leads to muscle deterioration and loss. Although the age at which 41 patients with DMD experience specific disease milestones varies, the 42 disease progresses in a predictable and relentless course. Initially, 43 DMD patients experience delayed walking and other developmental 44 milestones but continue to improve on clinical examination with 45 growth, albeit at a slower rate than non-affected peers. Typically after 46 age seven, muscle deterioration overtakes muscle growth and patients 47 begin to experience declines on functional tests. Boys with DMD usually 48 lose ambulation in their early teens, require assisted ventilation and 49 with intensive care usually survive to their mid-twenties [3].

50 Mutations in the DMD gene are known to result in two forms 51 of muscular dystrophy: Duchenne Muscular Dystrophy (DMD) and 52 Becker Muscular Dystrophy (BMD). DMD is characterized by a lack of dystrophin, which is caused by mutations that shift the reading frame, 53 most commonly from deletion of one or more exons. As a result of 54 this frame shift, the mRNA following the deletion does not code for a 55 functional protein and any protein produced from the transcript is 56 presumably degraded by the proteasome. BMD, a milder form of 57 muscular dystrophy, is characterized by production of a shortened 58 dystrophin protein, most commonly from deletion of one or more 59 exons that do not result in a shift of the mRNA reading frame [3]. 60 Fig. 2 illustrates the DMD exon map and the mechanism underlying 61 these differences. 62

All 79 dystrophin mRNA exons are represented as rectangles, which 63 comprise full codons, parallelograms, in which codons are split between 64 exons but deletion will maintain an open reading frame, and trapezoids, 65 in which first, last or both codons are split between the two adjacent 66 exons. That is, one or two nucleotides of the terminal codon reside on 67 an upstream exon and the remainder of the codon triplet resides on 68 the downstream exon. In dystrophin mRNA that carries an internal de- 69 letion and the codons remain in frame, translation continues, generating 70 an internally deleted but still functional dystrophin protein. If the read- 71 ing frame is disrupted, because part of a codon on the terminal exon 72 remains, translation is usually terminated downstream from the incor- 73 rect splice junction. 74

It was discovered over 20 years ago that pre-mRNA splicing could be 75 manipulated to restore a disrupted reading frame by targeting an oligo- 76 nucleotide to the splicing elements in the exon or intron. First shown in 77 thalassemia, a blood genetic disorder, and later in DMD [5–7] splicing 78 manipulation and exon skipping has been explored in a number of 79 disorders [3,8] but the most advanced work is for treatment of DMD 80 by two different oligonucleotide drug candidates (see below). 81

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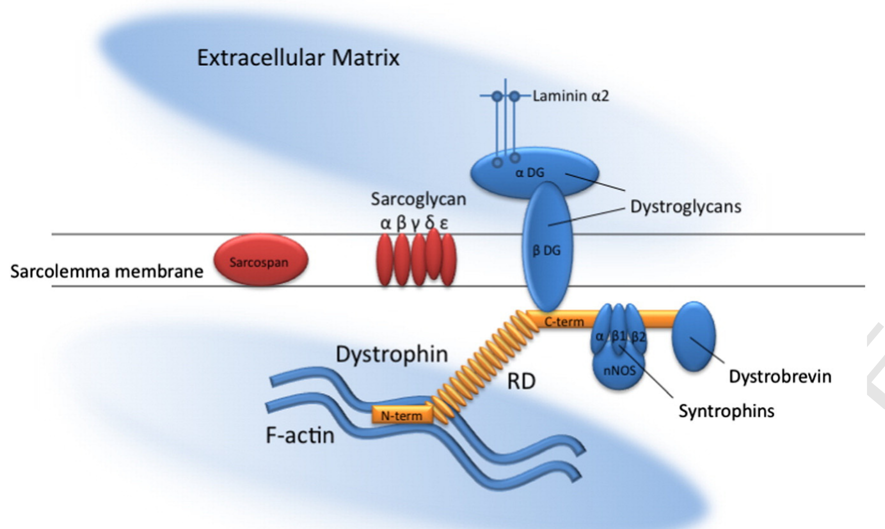

Fig. 1. Dystrophin connects the dystroglycan complex in the muscle cell membrane with intracellular actin filaments, providing a flexible link that prevents cell membrane damage during muscle contraction and maintains muscle integrity. Adapted from [4].

The most frequent deletions that cause DMD end at exon 50 and encompass exons 49–50, 48–50, 47–50, and 45–50 and a deletion of exon 52. Any of these defects disrupt the translational reading frame and prevent translation of dystrophin. As illustrated in Fig. 2, additional skipping of exon 51, induced by an exon-51-targeted oligonucleotide, restores the reading frame. Exon 51 skipping is expected to benefit a total of 14.0% of DMD patients. Additional sequence specific oligonucleotide drug candidates will be needed to treat patients with other deletions. For example, skipping of exons 45, 53, and 44 should benefit an additional 9.0%, 8.1%, and 7.6% of patients respectively. In all these cases exon skipping restores the translational reading frame and is expected to produce an internally deleted yet functional dystrophin protein [9].

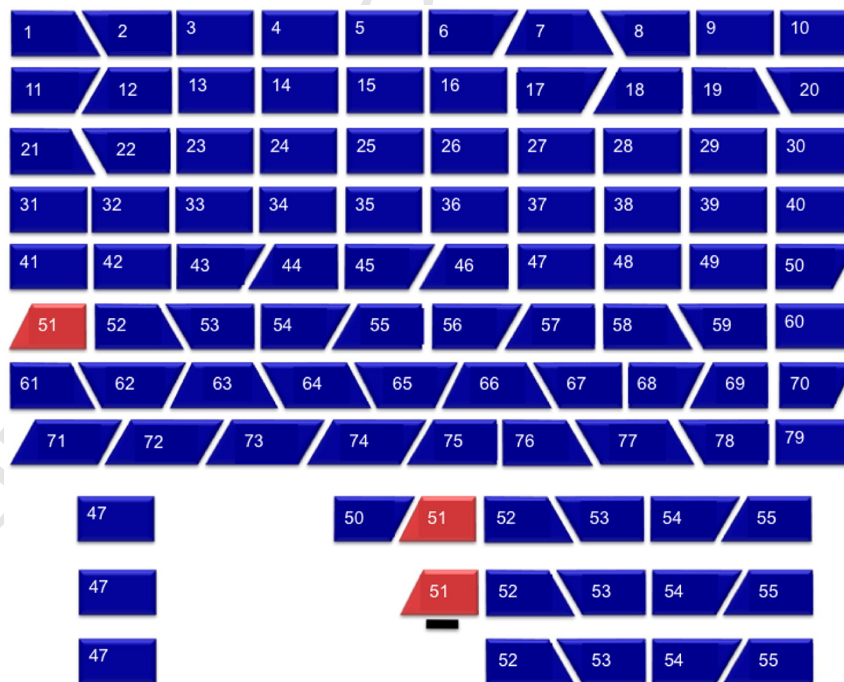

Fig. 2. Oligonucleotide-induced exon skipping in DMD. Top panel. Exon arrangement in dystrophin mRNA. Rectangles represent exons with a full complement of codons, trapezoids represent exons in which first, last or both codons are split between the two adjacent exons. Exon 51 is marked in red. Bottom panel. The three lines show exons in: a BMD patient with a deletion 48–49, which does not disrupt the reading frame, allowing translation of internally truncated but functional dystrophin. Second line: a DMD patient with deletion 48–50, which disrupts the reading frame and prevents expression of dystrophin protein. Third line: the oligonucleotides (heavy black line), such as eteplirsen or drisapersen discussed here, targeted to exon 51 in pre-mRNA are designed to prevent exon 51 inclusion and generate mRNA with a 49–51 deletion. The reading frame in this RNA is restored and an internally deleted, functional dystrophin protein could now be translated (bottom line). Adapted from [4]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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