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Antisense Oligos for Muscular Dystrophy

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Duchenne Muscular Dystrophy (DMD) is the most common childhood genetic disease, affecting one in 3,500 newborn boys and, causing progressive muscle weakness, heart and respiratory failure and premature death. This disease is caused by the mutations in the *dmd* gene, that disrupt the open reading frame in the *dmd* gene, leading to the absence of the spectrin-like cytoskeletal protein, dystrophin. Although a number of promising new molecular therapies are being studied intensively, none of them has been established. Exon skipping by antisense oligonucleotides (AOs), a molecular manipulation of pre-mRNA splicing engineered to yield a genetic correction, is a novel method for restoring the reading frame of the mutated *dmd* gene, and for rescuing dystrophin expression. We have recently reported that the systemic delivery of AOs, targeting exons 6 and 8 of the canine *dmd* gene, efficiently recovered functional dystrophin at the sarcolemma of dystrophic dogs, CXMD_J and improved the performance of the affected dogs without serious side effects. To optimize therapeutic AOs for more frequent mutations in the *dmd* gene, we designed AOs targeting exon 51 of the

mouse *dmd* gene, and injected these separately or in combination into the muscles of *mdx52* mice, whose exon 52 was deleted. A combination of two AOs, targeting the acceptor and the donor splice sites of exon51, demonstrated excellent restoration of sarcolemmal dystrophin in injected muscle. We, therefore, injected these same two AOs into *mdx52* mice via weekly intravenous injections. Two weeks after the final injection, dystrophin was expressed throughout the body at the sarcolemma, at about 10-40% of normal levels. This was accompanied by attenuation of the dystrophic pathology, and improvement of skeletal muscle function without side effects. This study provides a proof of concept for exon51 skipping in the DMD animal model that can be applicable in up to 15% of DMD deletion patients. It is important to verify the effectiveness and side effects of AOs in experimental animal models such as dystrophic dogs or *mdx52* mice, before clinical trials in DMD patients. There has also been rapid progress in understanding how splice-correction therapy could be applied to the treatment of other neuromuscular diseases where splicing is closely related to the disease mechanism.