Antisense-mediated exon skipping for Duchenne muscular dystrophy and other rare diseases

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Duchenne muscular dystrophy (DMD) is a severe, progressive muscle-wasting disorder, while Becker muscular dystrophy (BMD) is milder muscle disease (Emery, 2002). Both are caused by mutations in dystrophin, a protein, which stabilizes muscle fibers during contraction by linking muscle actin to the extracellular matrix. In DMD patients mutations disrupt the open reading frame, generating prematurely truncated, nonfunctional dystrophins (Monaco et al., 1988). In BMD patients, mutations maintain the reading frame allowing production of internally deleted, partly functional dystrophins.
The exon skipping approach uses antisense oligonucleotides (AONs) to induce skipping of targeted exons during pre-mRNA splicing, with the aim of reading frame restoration, converting of the severe DMD into the milder BMD phenotype (Aartsma-Rus, 2010). This approach is mutation specific. However, as mutations cluster in a few hotspots, skipping of some exons applies to larger groups of patients (e.g. exon 51 skipping applies to 13%) (Aartsma-Rus et al., 2009).
After obtaining proof-of-concept in cultured patient-derived cells, this approach was further optimized in animal models (reviewed in [3]). In each case AON treatment resulted in targeted exon skipping and dystrophin restoration. In animal models this was accompanied by improved muscle function and quality. Proof-of-concept in patients was achieved in a clinical trial where 4 patients received local injections with an AON targeting exon 51 (coordinated by Prosensa Therapeutics). Dystrophin was restored locally for each patient (van Deutekom et al., 2007).
Towards systemic application, studies in animal models revealed that dystrophic muscles facilitated uptake of 2OMePS AONs and that subcutaneous delivery was feasible (Heemskerk et al., 2010). In a subsequent clinical trial, patients were subcutaneously injected with AONS targeting exon 51. Dystrophin was restored in a dose-dependent manner at levels up to 15% (Goemans et al., 2011). All patients were enrolled in an open label extension study and have received subcutaneous AON injections at 6 mg/kg for almost 4 years. A small placebo-controlled trial in a limited group of patients has recently been completed and a pivotal, double-blind, placebo-controlled multicenter trial for exon 51 skipping is currently ongoing (coordinated by GlaxoSmithKline).
In parallel, preclinical studies to further optimize treatment regimens are in progress as well as clinical trials for additional exons for exon 44 skipping (PRO044, applicable to 6% of patients). Trials are planned for exon 45 and 53 skipping (PRO045 and PRO053, both applicable to 8% of patients).
The mutation specificity of the approach poses challenges to drug development regulations. A concerted effort of academic researchers, industry, regulators and patients is needed to adapt regulations to enable application of these personalized medicine approaches to rare diseases.

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