"Therapeutic potential of adiponectin and adipoRon in Duchenne muscular dystrophy"

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Abstract
Persistent and severe inflammation exacerbates disease progression in Duchenne muscular dystrophy (DMD). Adiponectin (ApN) is a hormone abundantly secreted by adipocytes, which exhibits insulin-sensitizing, fat-burning and anti-inflammatory properties. We have previously shown that ApN potently protects muscle against inflammation and injury in mdx mice, a model of DMD. As every peptide, ApN has to be injected, while AdipoRon, a recently discovered synthetic small-molecule, which is an agonist of ApN receptors may be given orally. Here we investigated whether ApN retains its anti-inflammatory properties in DMD myotubes and whether this action may be reproduced by AdipoRon. Primary cultures of myotubes from DMD patients and age- and sex-matches controls were performed (n=7 independent cultures from 4 different patients for each group; myoblasts were obtained from the French Telethon Myobank-AFM). These myotubes were challenged by an inflammatory stimulus (to mimic the DMD inflammatory...

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G.P.248
Therapeutic potential of adiponectin and adipoRon in Duchenne muscular dystrophy
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Persistent and severe inflammation exacerbates disease progression in Duchenne muscular dystrophy (DMD). Adiponectin (ApN) is a hormone abundantly secreted by adipocytes, which exhibits insulin-sensitizing, fat-burning and anti-inflammatory properties. We have previously shown that ApN potently protects muscle against inflammation and injury in mice, a model of DMD. As every peptide, ApN has to be injected, while AdipoRon, a recently discovered synthetic small-molecule, which is an agonist of ApN receptors may be given orally. Here we investigated whether ApN retains its anti-inflammatory properties in human DMD myotubes and whether this action may be reproduced by AdipoRon. Primary cultures of myotubes from DMD patients and age- and sex-matched controls were performed (n = 7 independent cultures from 4 different patients for each group; myoblasts were obtained from the French Telethon Myobank-AFM). These myotubes were challenged by an inflammatory stimulus (to mimic the DMD inflammatory status) and treated or not by ApN/AdipoRon. ApN downregulated gene expression of TNFα, a pro-inflammatory cytokine (p < 0.01) and of IκB, an inhibitor of NF-κB (p < 0.05) while upregulating mRNA abundance of IL-6, an anti-inflammatory cytokine (p < 0.05) in control as well as in DMD myotubes. Silencing selected genes further indicated that these anti-inflammatory effects were mediated by AdipoR1, the most abundant ApN receptor in the muscle and by the AMPK–PGC-1α signalling pathway in control and DMD myotubes; PGC-1α is a transcriptional coactivator, which regulates energy metabolism and suppresses inflammation. Eventually, AdipoRon reduced TNFα mRNAs (p < 0.05) and increased IL-6 mRNAs (p < 0.001) in both DMD and control myotubes challenged by an inflammatory stimulus. ApN retains its anti-inflammatory effects in human myotubes obtained from DMD patients. AdipoRon reproduces this protection. These results could open new perspectives in the management of muscular diseases.

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G.P.249
Urotrophin modulators to treat Duchenne muscular dystrophy (DMD): Results from a Phase 1b Clinical Trial of SMT C1100
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In DMD, skeletal muscle is lost due to an inability to produce dystrophin. During foetal muscle development utrophin takes the functional role of dystrophin. Continuous muscle expression of utrophin could functionally replace dystrophin and potentially overcome the dystrophin deficit in DMD. In dystrophic animal studies, daily SMT C1100 treatment significantly reduced muscle degeneration leading to improved muscle function. Data from a recently completed Phase 1b study in DMD subjects suggest that diet is able to influence absorption of SMT C1100. This study aims to investigate this further. Twelve boys with DMD were enrolled into this Phase 1b placebo-controlled study of single and multiple oral doses of SMT C1100. Boys were randomly allocated to the three treatment sequence groups. Each patient received both doses of SMT C1100 (1250 mg twice daily (BID) and 2500 mg BID) in a dose escalating fashion, with placebo in the other study period. A minimum two week washout was included between each Treatment Period to allow for study drug washout and safety review. One of the secondary objectives of this study was to evaluate reductions in creatine phosphokinase (CPK). With 12 patients this study had 80% power of demonstrating a statistically significant reduction in CPK compared to placebo with a two-sided, 5% confidence level, if SMT C1100 reduced CPK 30% more than placebo. Data from this trial will be presented and will assist in designing future Phase 2 studies that will include functional and biomarker endpoints.

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G.P.250
Small molecule compounds that promote exon skipping in the DMD gene
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Approximately two thirds of the mutations in the dystrophin gene are deletions in the open reading frame that result in the production of C-terminus-truncated non-functional dystrophin protein. One potential therapeutic approach to address a subset of the reading frame-altering deletions, located in the central rod domain, is to cause skipping of an exon downstream of the deletion thereby restoring the reading frame. The resulting protein, containing an internal deletion, would be partially functional but expected to lead to a milder, attenuated disease phenotype. PTC Therapeutics has developed an Alternative Splicing drug discovery platform technology to identify small molecule drug candidates that target pre-mRNA splicing. This platform has been used to discover and develop orally deliverable small molecule modifiers of SMN2 alternative splicing to treat the genetic disease spinal muscular atrophy (SMA). The clinical compound is currently being investigated in human clinical trials in collaboration with Roche and the SMA Foundation. PTC is applying this drug discovery platform technology to Duchenne muscular dystrophy. We have designed high throughput screening approaches to identify compounds that induce targeted exon skipping during DMD pre-mRNA splicing of exons 44, 45, 51, and 53. For the most advanced program, exon 51 skipping, we have completed a high throughput screen of our compound library using a minigene construct. Hit molecules are undergoing structural optimization to improve biological activity and pharmacological and pharmaceutical properties.

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G.P.251
Exon 53 skipping of the dystrophin gene in patients with Duchenne muscular dystrophy by systemic administration of NS-065/NCNP-01: A phase I, dose escalation, first-in-human study
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Antisense oligonucleotide-induced exon skipping, which is being studied for the treatment of Duchenne muscular dystrophy (DMD), allows synthesis of partially functional dystrophin. Patients amenable to exon 53 skipping form the second-largest population after patients amenable to exon 51 skipping. Therefore, in 2009, the National Center of Neurology and Psychiatry and Nippon Shinyaku Company collaborated to jointly develop an exon 53-skipping drug; an investigator-initiated clinical trial was started in June 2013 (NCT02081625) to examine the efficacy of NS-065/NCNP-01, a morpholino-based antisense oligonucleotide that facilitates skipping of exon 53 of the dystrophin gene. This drug was shown to have potent efficacy and high safety, as confirmed in preclinical studies. The primary endpoint of the trial was safety, and the secondary endpoints were pharmacokinetics and dystrophin expression. A three-dose cohort design (1.25, 5, and 20 mg/kg) was adopted, and all