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Although muscular dystrophy and other diseases of muscle are well suited to treatments using antisense oligonucleotides or siRNAs, efficient delivery remains the key challenge for oligonucleotide-based therapies to fulfill their full potential. Targeting oligonucleotides to an endocytosing liver-specific receptor (ASGPR) through conjugation to its ligand GalNAc enhanced delivery of oligonucleotides into hepatocytes and led to various therapies for diseases involving the liver.

Here we demonstrate that conjugation of oligonucleotide payloads to antibodies specific for the transferrin receptor (TfR1) facilitates efficient delivery of siRNAs and single stranded morpholino oligonucleotides to muscle and other organs. A single IV administration of 3 mg/kg of a TfR1 mAb-myostatin siRNA conjugate produced significant (>70%) reductions in levels of myostatin mRNA/protein in vivo. The knockdown of myostatin lasted for more than 5 weeks and resulted in increased muscle size and grip strength in wild-type mice. An RISC loading assay demonstrated that these phenotypic effects were mediated through an RNAi mechanism. A single dose (5 mg/kg) of a TfR1 mAb-morpholino conjugate enabled exon skipping of exon 23 in dystrophin pre-mRNA in wild-type mouse skeletal muscle, demonstrating the ability of antibody oligonucleotide conjugates (AOCs) to support delivery of diverse oligonucleotide payloads.

The ability to recruit antibodies and other protein-based scaffolds to deliver oligonucleotides to specific cell surface receptors for internalization broadens the number of tissues and diseases that can be targeted with oligonucleotide therapeutics. The specificity of these therapies can be enhanced through careful selection of the targeted receptor and/or the oligonucleotide payload. In addition, delivery of multiple oligonucleotide payloads and/or the use of therapeutic antibodies enables potentially greater potency and the regulation of multiple cellular targets. Studies are ongoing to identify additional receptors suitable for oligonucleotide delivery and therapeutic oligonucleotides for the treatment of muscle dystrophies, sarcopenia, cachexia, and other muscle disorders.

8-06
Mechanisms involved in the cross-talk between humoral and mechanical cues underlying muscle wasting in cachexia

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Introduction: Exercise training improves quality of life and survival of cancer patients. In an animal model of cancer cachexia we demonstrated that wheel running counteracts cachexia by releasing the autophagic flux. Exercise pleitropic effects include the alteration of circulating factors in favour of an anti-inflammatory environment and the activation of mechanotransduction pathways in muscle cells. Our goal is to assess whether mechanostransduciton *per se* is sufficient to elicit exercise effects in the presence of pro-cachectic factors of tumor origin. Serum response factor (SRF) is a transcription factor of pivotal importance for muscle homeostasis, which is activated with its co-factor MRTF by mechanostranduction in a way dependent on actin polymerisation.
Methods: We use C26 tumor-bearing mice, in the absence or presence of wheel running, and mixed cultures of C2C12 myotubes and myoblasts treated with C26 conditioned medium (CM) in the absence or presence of cyclic stretch to mimic the mechanical stimulation occurring upon exercise.
Results: *In vivo* both SRF expression and activity are differentially modulated by the C26 tumor, i.e. by humoral factors, and by exercise. *In vitro* we showed that CM had a negative effect on muscle cell cultures, both in terms of myotube atrophy and of myoblast recruitment and fusion, and that these effects were counteracted by cyclic stretch. We showed that CM repressed SRF-MRTF transcriptional activity, while mechanical stretch rescued their transcriptional activity; in addition, loss of function experiments demonstrated that SRF was necessary to mediate the beneficial effects of mechanical stimulation on muscle cells. At least part of the observed effects were mediated by the balance of pro- and anti-myogenic factor of the TGFbeta superfamily.
Conclusions: We propose that the positive effects of exercise on cancer patients and mice may be specifically due to a mechanical response of muscle fibers affecting the secretion of myokines.

8-07
Efficacy of a novel selective androgen receptor modulator (TEI-SARM2) with once weekly dosing in rat unloaded muscle atrophy and Duchenne muscular dystrophy models

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Introduction: TEI-SARM2, a non-steroidal selective androgen receptor modulator (SARM), induces strong anabolism in muscle with minimal effects on reproductive tissues with once-weekly dosing regimen. In cancer cachexia models, TEI-SARM2 prevented body weight loss and improved survival rate. In this study, effects of TEI-SARM2 in animal models of unloaded muscle atrophy (tail-suspension) and Duchenne muscular dystrophy (DMD) were examined.