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and survival. Systolic blood pressure ($p<0.05$), heart rate ($p<0.05$) and body temperature control ($p<0.05$) were also normalized. Hyperactivity, which was observed in the AAV9 treated mice, was not observed. In conclusion, we demonstrated that a systemic gene therapy could treat a neurotransmitter deficiency disease.

365. Reducing Dynamin 2 Rescues a Severe Congenital Myopathy in Mice

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Centronuclear myopathies (CNM) are congenital disorders associated with muscle weakness and abnormally located nuclei in skeletal muscle. An autosomal dominant form of CNM results from mutations in the gene encoding dynamin 2 (DNM2), and loss-of-function mutations in the gene encoding myotubularin (MTM1) result in X-linked centronuclear myopathy (XLCNM), which promotes severe neonatal hypotonia and early death. Currently, no effective treatments exist for XLCNM.

The main goal of this study was to validate a novel rescue approach for XLCNM. Recent data suggested some CNM-causing DNM2 mutations increase the dynamin oligomer stability and GTPase activity. Also, we and others showed that overexpression of wildtype DNM2 in skeletal muscle cause a CNM-like phenotype. We hypothesize myotubularin and dynamin 2 function in a common pathway, where either MTM1 loss-of-function or DNM2 gain-of-function lead to the CNM phenotype. To test this hypothesis, we reduced the expression of DNM2 in Mtm1-/y mice that reproduce a CNM phenotype with a progressive myopathy leading to death by about 12 weeks. Mtm1-/yDnm2+/- mice survived up to 2 years. Classical CNM histological features including fiber atrophy and nuclei mispositioning were prevented or strongly delayed and reduced, and muscle strength was increased. Downregulation of Dnm2 selectively in skeletal muscle during embryogenesis or in young mice after onset of the disease showed that the rescue is cell autonomous and that downregulation of Dnm2 can stop and potentially revert the progression of the phenotype.

In conclusion, we identified MTM1 and DNM2 are in a common pathway regulating muscle organization and force. We introduce the original concept of 'cross-therapy' where one form of the disease (XLCNM, MTM1) can be rescued by decreasing expression of another gene mutated in CNM (DNM2 in ADCNM). While DNM2 is a key mechanoenzyme for important cellular processes, its reduction is strongly beneficial for centronuclear myopathy and represents a novel potential therapeutic approach.

366. Combining Delivery of GLP-1 Gene Expressing Plasmid and DPP-4 Gene Silencing siRNA Using Chitosan-Based Nanoparticles for Type-2 Diabetes Treatment

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Purpose : Glucagon like peptide 1 (GLP-1), an incretin hormone that regulates blood glucose level post-prandially, is rapidly inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme, which results in a short circulating half-life of the active form of GLP-1. GLP-1 analogues and DPP-IV inhibitors are both currently used for the treatment of Type 2 Diabetes. Here we evaluated the potential of novel polymer/nucleic acid nanoparticles using the natural polysaccharide chitosan (CS) for the delivery of plasmid DNA expressing native and modified GLP-1 and of siRNA specific for DPP-IV knockdown.

Methods: Nanoparticles were prepared by mixing nucleic acid with different chitosan formulations, named [DDA-MW-N:P ratio], according to their specific molecular weight (Mn), degree of deacetylation (DDA) and ratio of chitosan amine to nucleic acid phosphate (N:P ratio). Physicochemical characterization of nanoparticles and in vitro analysis by ESEM, DLS, qRT-PCR, live imaging confocal microscope were performed in order to evaluate delivery by different chitosan formulations. Glucose metabolism in the diabetic ZDF rat model was assessed after intramuscular (IM), and subcutaneous (SC) administration of nanoparticles. ELISA, intraperitoneal glucose tolerance tests were performed to evaluate the efficacy and longevity of the treatment in ZDF rats.

Results: Chitosans formed spherical nanoparticles containing nucleic acids, with diameters of 141–283 nm and 68–129 nm for plasmid and siRNA, respectively. In vitro tests showed high cell uptake (up to 99%). Quantitative real time PCR showed nanoparticle-mediated inhibition of DPP-IV coding mRNA at levels similar to that of the positive control DharmaFECT (72% DPP-IV gene silencing) (Fig.1A) but without toxicity seen with liposomal systems. DPP-IV enzymatic activity was reduced to 56% in HepG2 and Caco-2 cell lines by CS-siRNA. Recombinant native GLP-1 protein levels in media of transfected cells reached 23 ng/L while DPP-IV resistant analogues resulted in a fivefold increase of GLP-1 levels (115 ng/L). Animals injected with CS-based nanoparticles showed GLP-1 plasma levels of about 5 fold higher versus non-treated animals (Fig. 1B). The insulinotropic effect of recombinant GLP-1 in treated animals was reflected by an increase in plasma insulin levels compared to controls. Intraperitoneal glucose tolerance tests revealed efficacious decrease of blood glucose to near-normal levels in treated versus controls for up to 24 days following treatment.

Conclusion: The versatility and efficiency of CS-based delivery of pDNA and siRNA indicates a strong potential of this delivery platform in the treatment of type 2 diabetes.

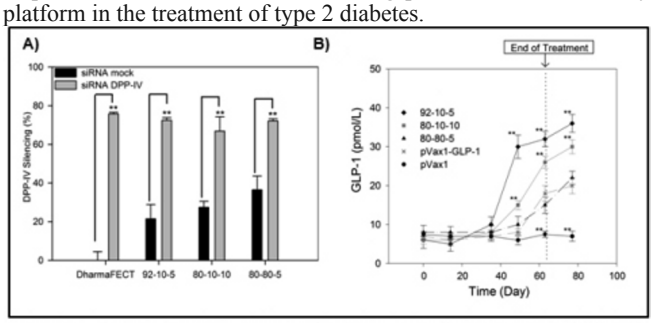

Figure 1: A) Quantitative Real-Time PCR (qRT-PCR) analysis of DPP-IV silencing using both effective and mock siRNAs in HepG2 cell line. **p < 0.01 compared with the positive control DharmaFECT. **B)** Quantification of GLP-1 (7–37) levels in blood by ELISA in ZDF rat model injected subcutaneously (SC) with different chitosan-based formulations. Values are expressed as means ±standard deviation; N=3 rats per group. *P<0.05, **P<0.01 compared with pVax1-GLP-1 alone (no chitosan).

367. Recombinant AAV-DJ Vector-Mediated FGF-21/ FGF-21-GLP-1 Long-Term Expression in db/db Mice With Type 2 Diabetes Mellitus

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Background: The type 2 Diabetes Mellitus (T2DM), featuring with insulin resistance, is prevailing all over the world, and is threatening people's life. While current treatments including oral drugs and insulin were not good enough, gene therapy offers promise. Due to their low immunogenicity, broad host-range, and efficient infection of a wide

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