SELECTED OPPORTUNITIES IN RARE DISEASES

ALLELE-SPECIFIC SILENCING THERAPY FOR DYNAMIN 2-RELATED DISEASES (BIO17148)

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Product factsheet

Stage: in vivo PoC

- **Target:**
  - Dynamin 2
- **Product:**
  - shRNA / siRNA
- **Application:**
  - Centronuclear Myopathies / Possible application in Myotubular myopathy, Duchenne muscular dystrophy, Charcot-Marie-Tooth disease, Hereditary spastic paraplegia, lymphoblastic leukemia, Prostate cancer, pancreatic cancer.
- **Rational / POC:**
  - Centronuclear myopathy is an autosomal dominant genetic disease caused by heterozygous mutations of DNM2 gene for which there is no treatment
  - DNM2 encodes dynamin 2, an ubiquitous protein belonging to the family of GTPases / scaffold protein that can deform biological membranes to induce the formation and release of vesicles especially in endocytosis
  - Twenty-six missense mutations were identified / R465W is a recurrent mutation found in 30% of patients
  - Identification of siRNAs capable of specifically reducing mutant allele expression without affecting WT allele in a knock-in mouse model
  - Allele-specific AAV-sh 3-month treatment abolishes muscle defects in young mice
  - siRNAs exhibit allele-specific silencing and functional rescue in patient-derived fibroblasts.
- **Patent and publication:**
  - PCT/EP2017/080884 «Allele-Specific Silencing Therapy For Dynamin 2-Related Diseases» Priority: 2016/11/29
  - Trochet et al. 2018. « Allele-specific silencing therapy for Dynamin 2-related dominant centronuclear myopathy ». **EMBO Mol Med.**

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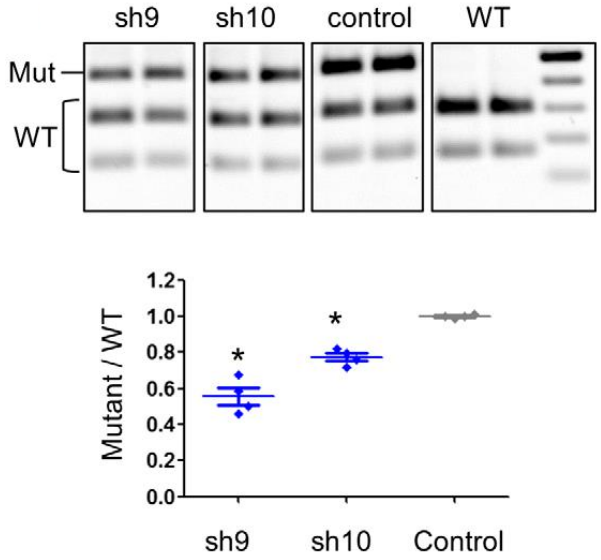
Proof of concept

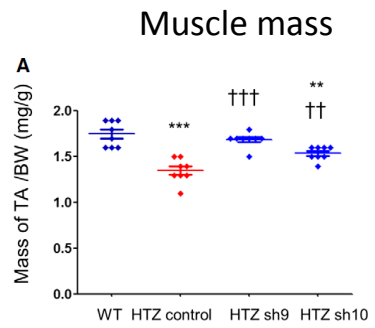
- **Allele-specific AAV-shRNA treatment abolishes muscle defects in Dnm2 Knock-in (KI) mice**

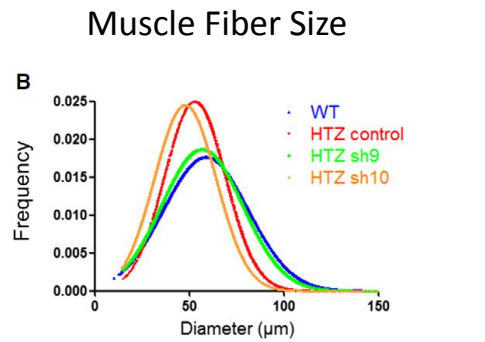
sh9 and 10 specifically reduce mutant allele in Dnm2 KI mice

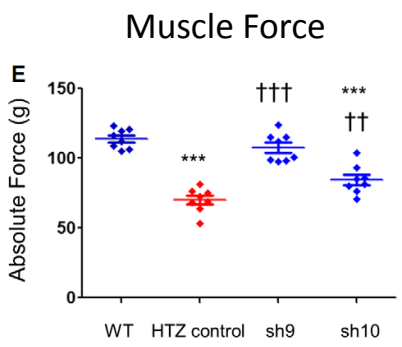


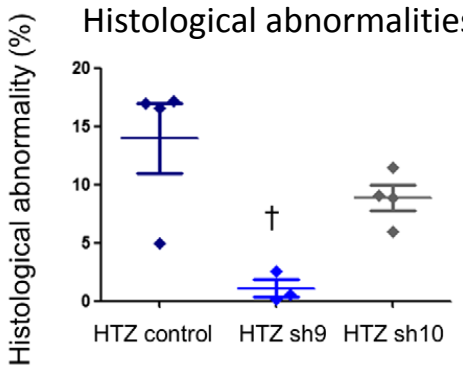
3-month old mice were injected with AAV-sh9 and 10 or control in the Tibialis. RNA expression was mesured by RT-qPCR

sh9 and 10 alleviate muscle phenotype and histological abnormalities in KI mice









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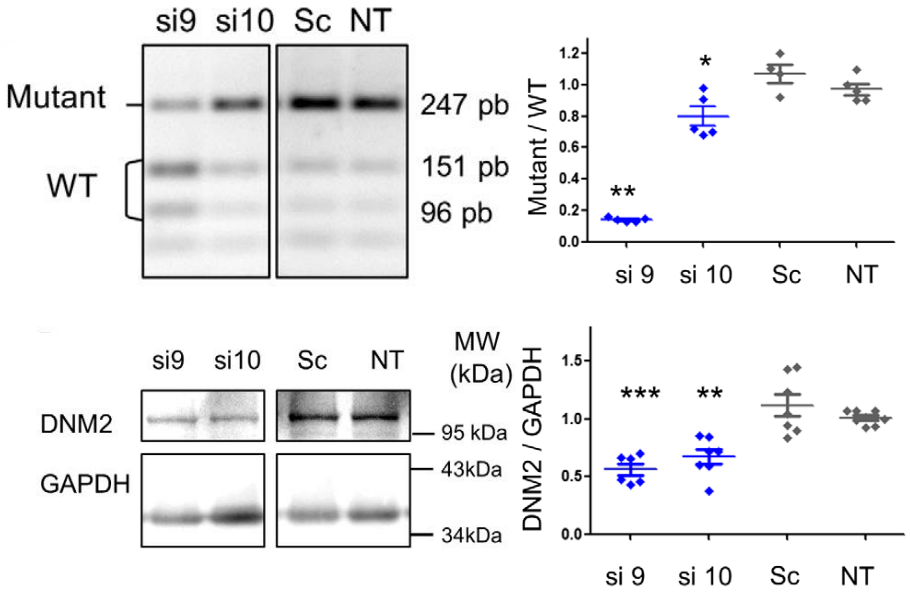
ALLELE-SPECIFIC SILENCING THERAPY FOR DYNAMIN 2-RELATED DISEASES (BIO17148)

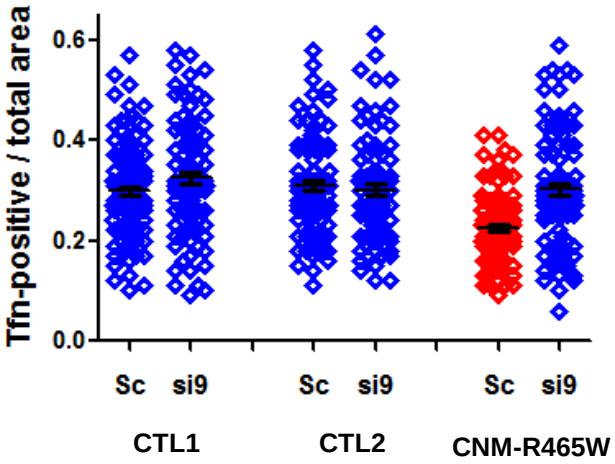
Proof of concept

- **Allele specific reduction and functional restoration of DNM2 in patient fibroblasts**

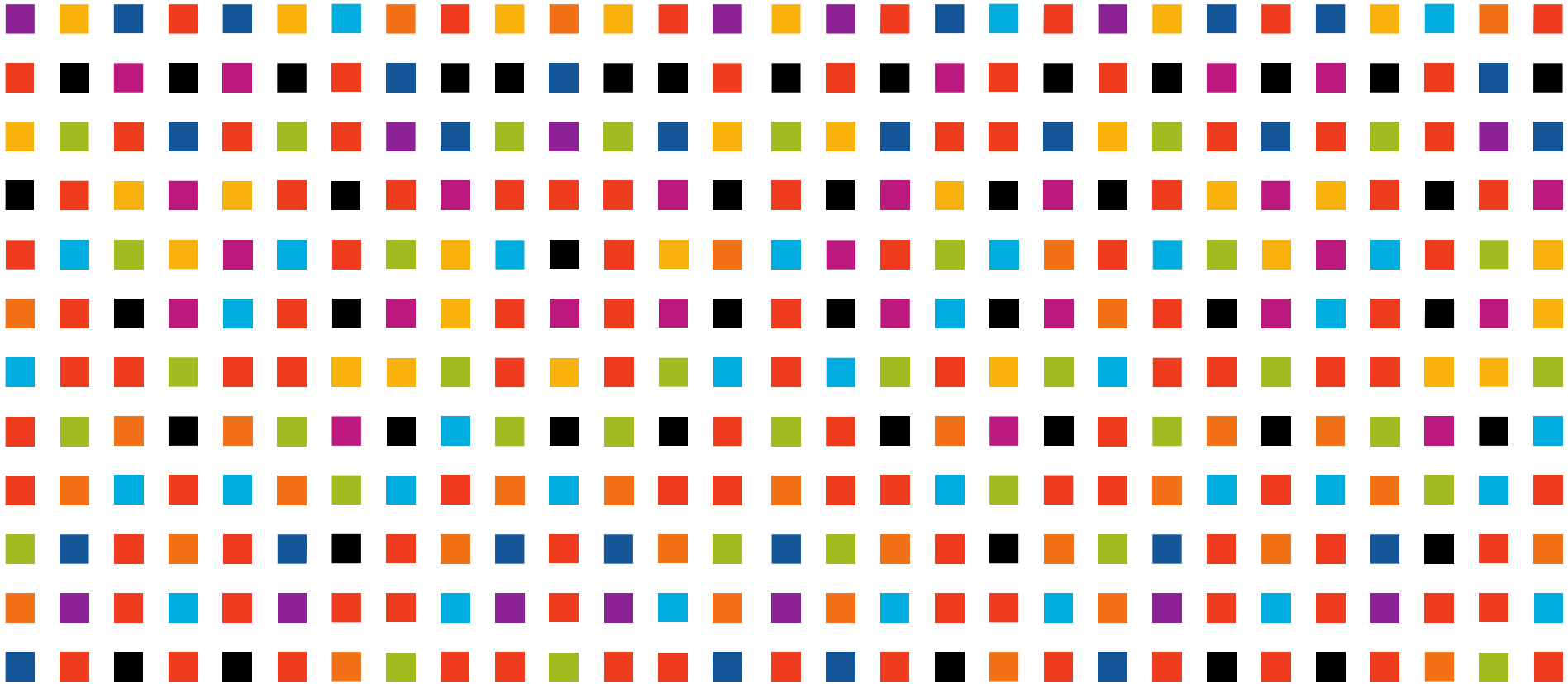
sh9 and 10 specifically reduce mutant allele in patient fibroblasts



sh9 and 10 improve DNM2 function in patient fibroblasts



15-min transferrin uptake was measured in patient-derived fibroblasts (n = 100 cells for each cell line)



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