

Pre-clinical Development of ALN-TTR

RNAi Therapeutic for Treatment Of Transthyretin-mediated Amyloidosis

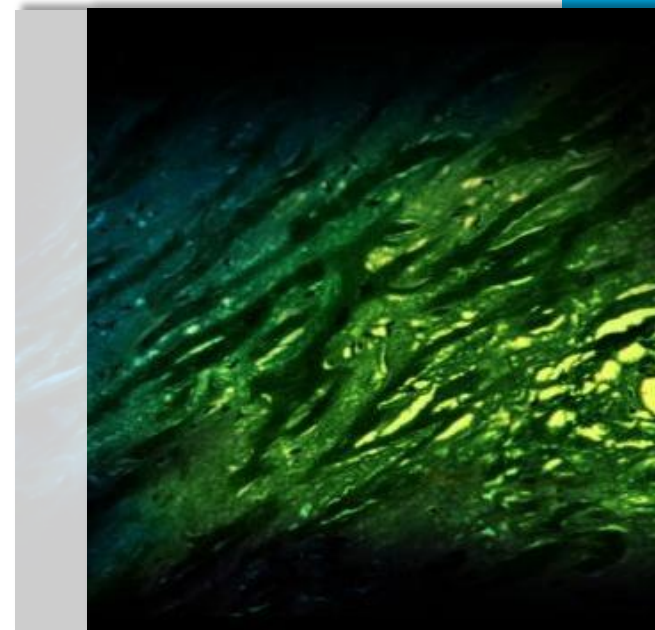
Peripheral Nerve Society
June 29, 2011

Transthyretin (TTR)-Mediated Amyloidosis (ATTR) Program

Unmet Need and Product Opportunity

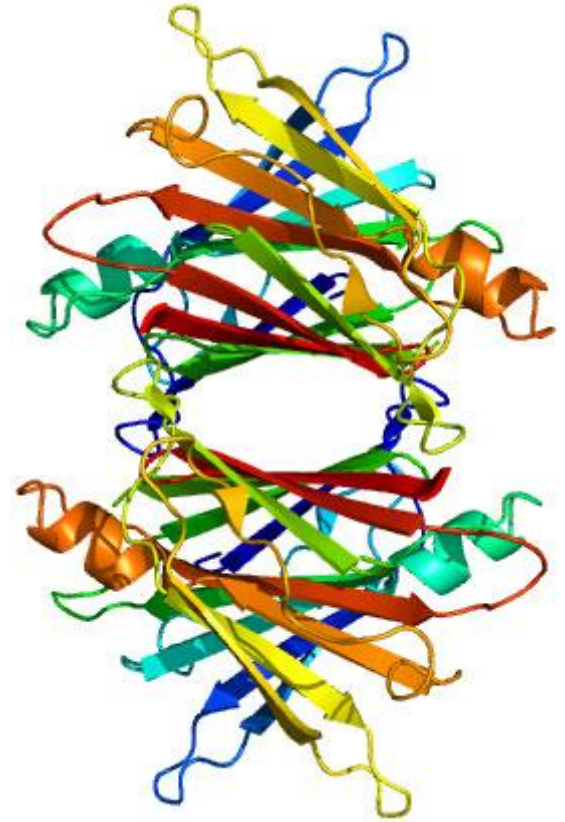
RNAi to treat genetic disease

- ATTR is significant orphan disease
 - » Caused by mutation in TTR gene
 - » ~50,000 patients worldwide
- Clinical pathology
 - » Onset ~40 to >60 yr
 - » Two predominant forms
 - Familial amyloidotic polyneuropathy (FAP)
 - Familial amyloidotic cardiomyopathy (FAC)
 - » Peripheral sensorimotor neuropathy, autonomic neuropathy, and/or cardiomyopathy
 - » Fatal within 5-15 years
- Liver transplant current standard of care
 - » <3,000 Patients eligible
- Phase I trial initiated July 2010



ATTR Program Rationale

- Effective delivery of siRNA to hepatocytes with current LNP platform
 - » Chemically modified TTR siRNA
 - » Formulated in SNALP for systemic delivery
- Hepatocytes primary site of TTR expression
 - » Mutant and wild-type TTR proteins pathogenic
 - Liver transplant can stabilize or improve V30M FAP patients
 - However, cardiac disease accelerates in other ATTR patients due to increased production of wild-type TTR
 - » Production of both wild-type and mutant TTR ideally targeted
- Target well validated with human genetics
 - » ~90% FAP caused by V30M mutation
 - » FAC caused primarily by V122I mutation

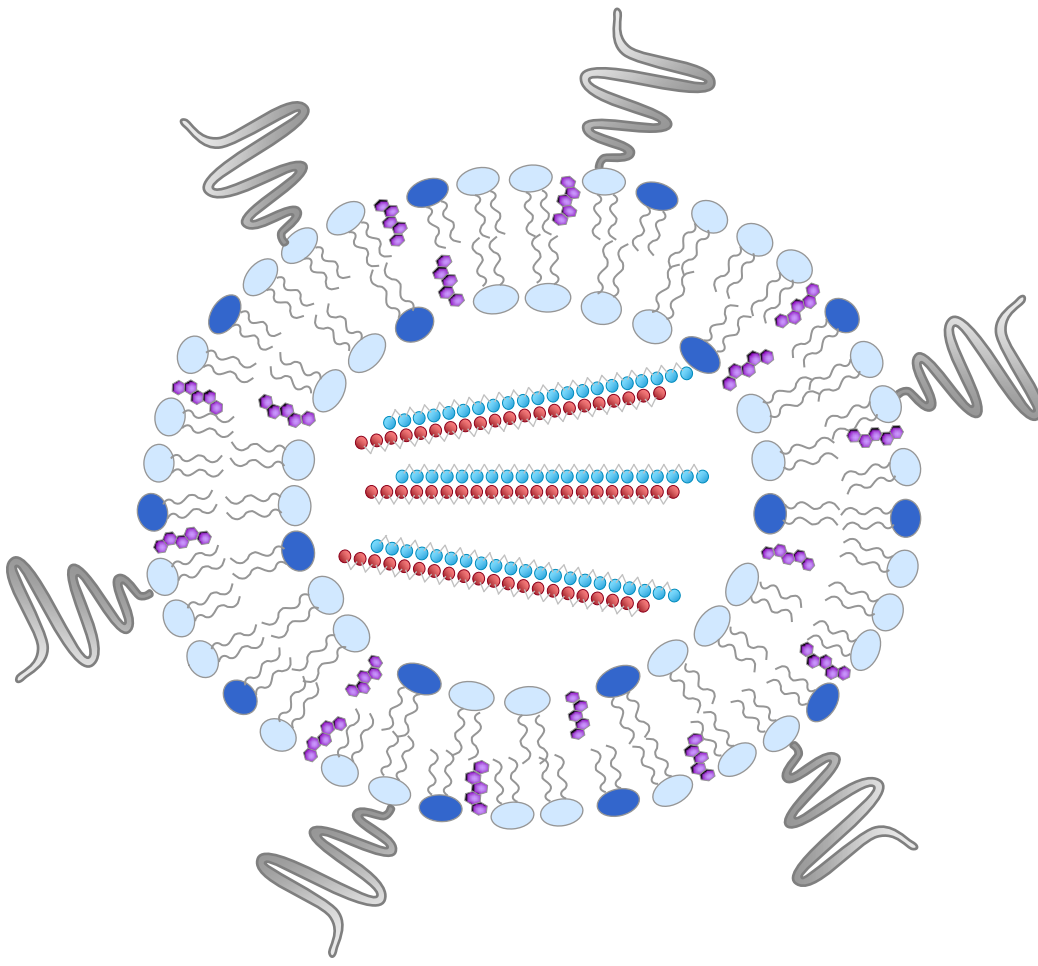


Transthyretin crystal structure

Systemic RNAi Delivery

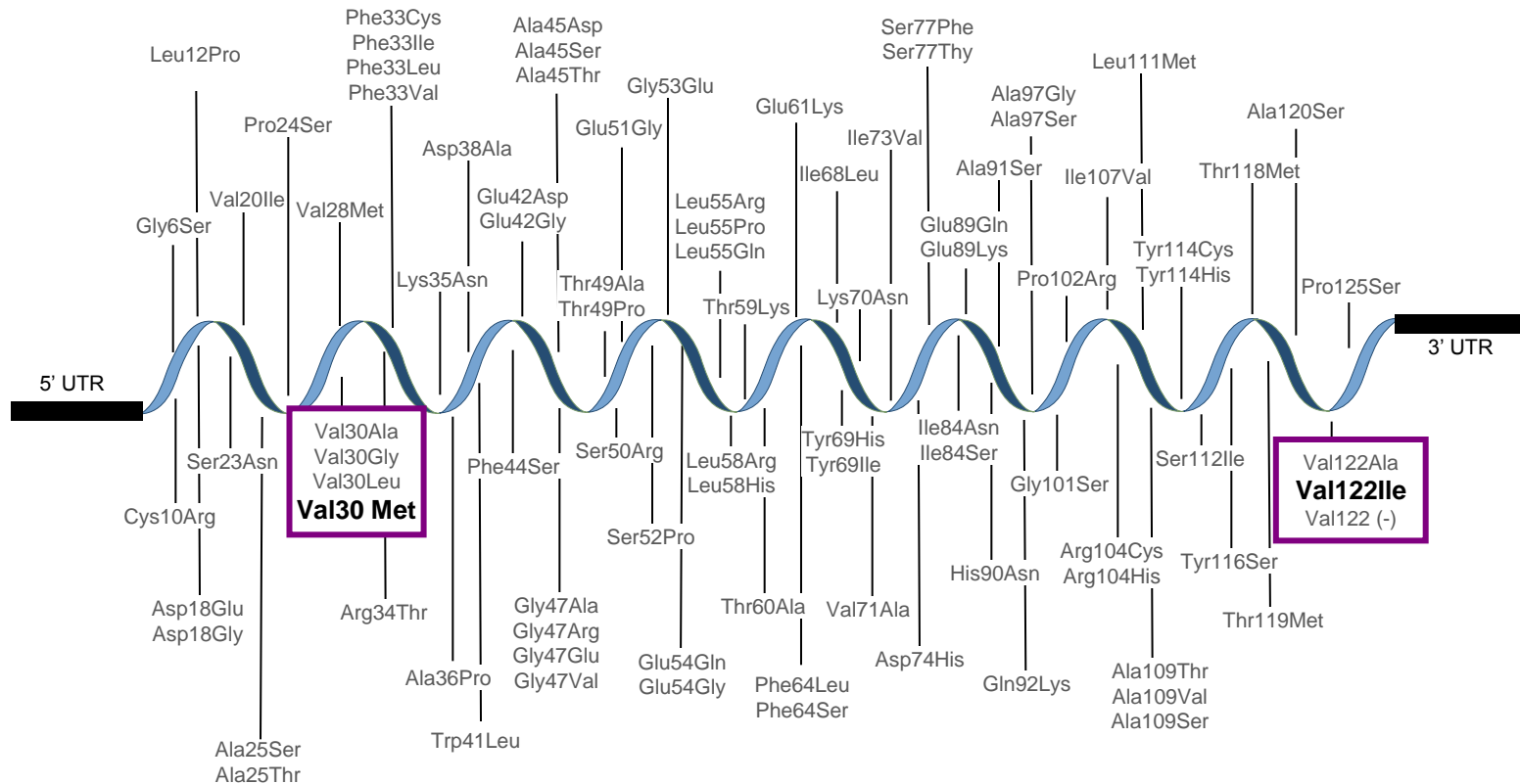
LNP

- Unformulated siRNAs are rapidly cleared from circulation
- Lipid nanoparticle formulations (SNALP) of siRNAs prolong half-life and enable hepatic delivery
- Systemic administration of SNALP-formulated siRNAs results in
 - » Dose-dependent mRNA and protein suppression of
 - » hepatocyte-expressed disease targets
 - » Suppression maintained for 2 to 4 weeks
 - » Has been demonstrated in multiple species (rodents, non-human primate) for multiple targets (apoB, TTR, Factor VII, PCSK9)*

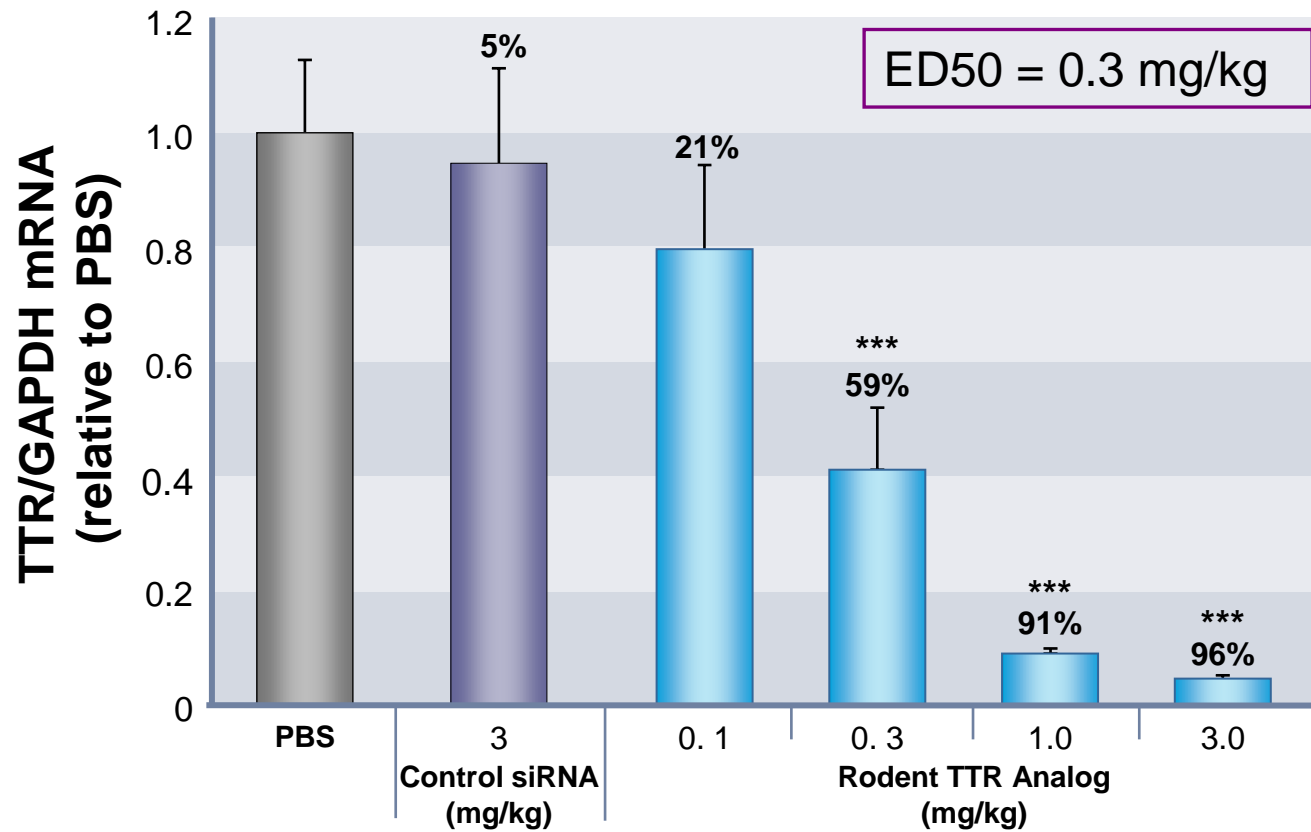
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- Low surface charge
 - Small uniform size particle < 100 nm

ALN-TTR siRNA Selection

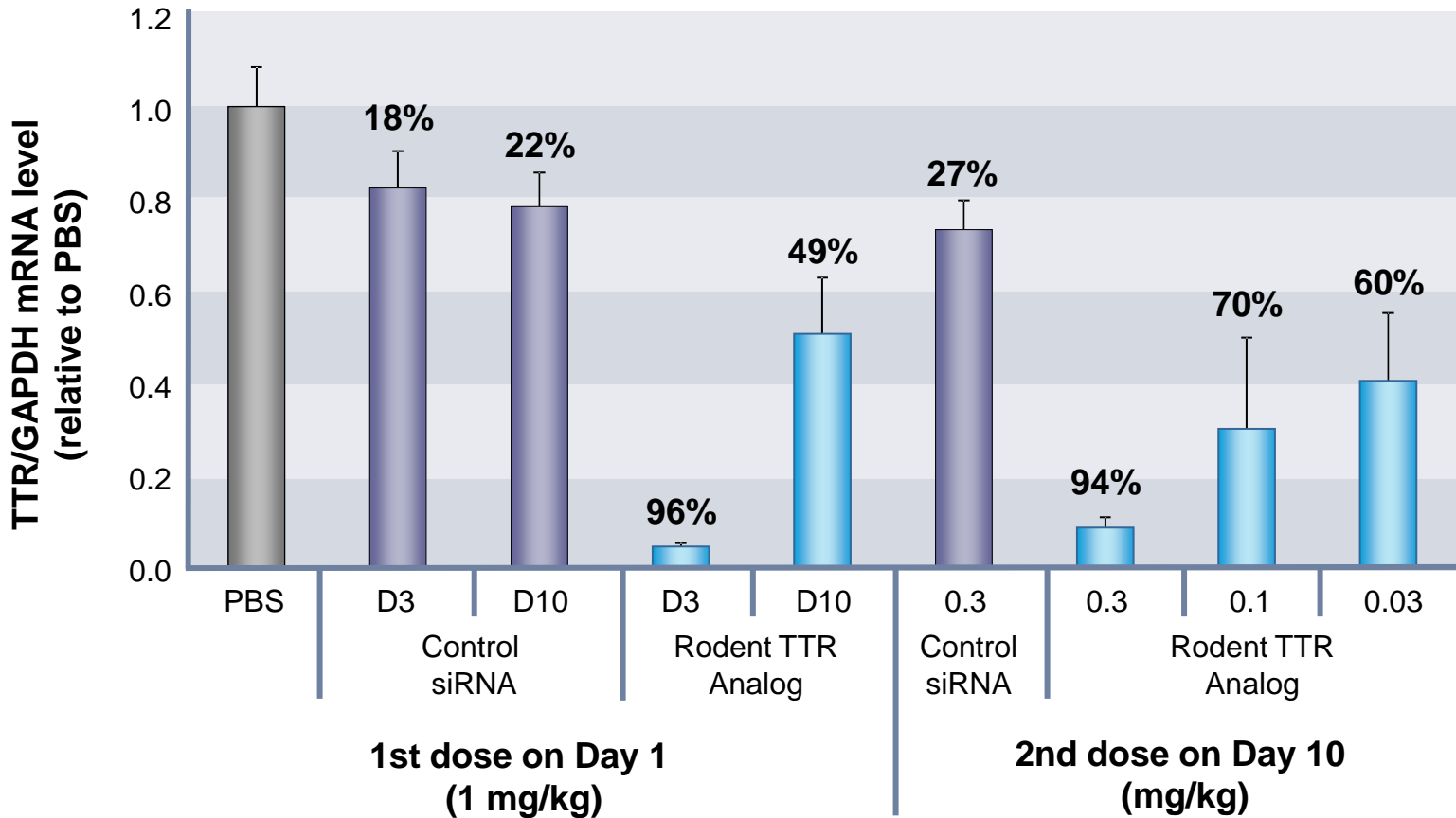
- >100 Mutations identified in TTR gene
- ALN-TTR targets region of TTR mRNA common to wild-type and all known mutant forms of TTR



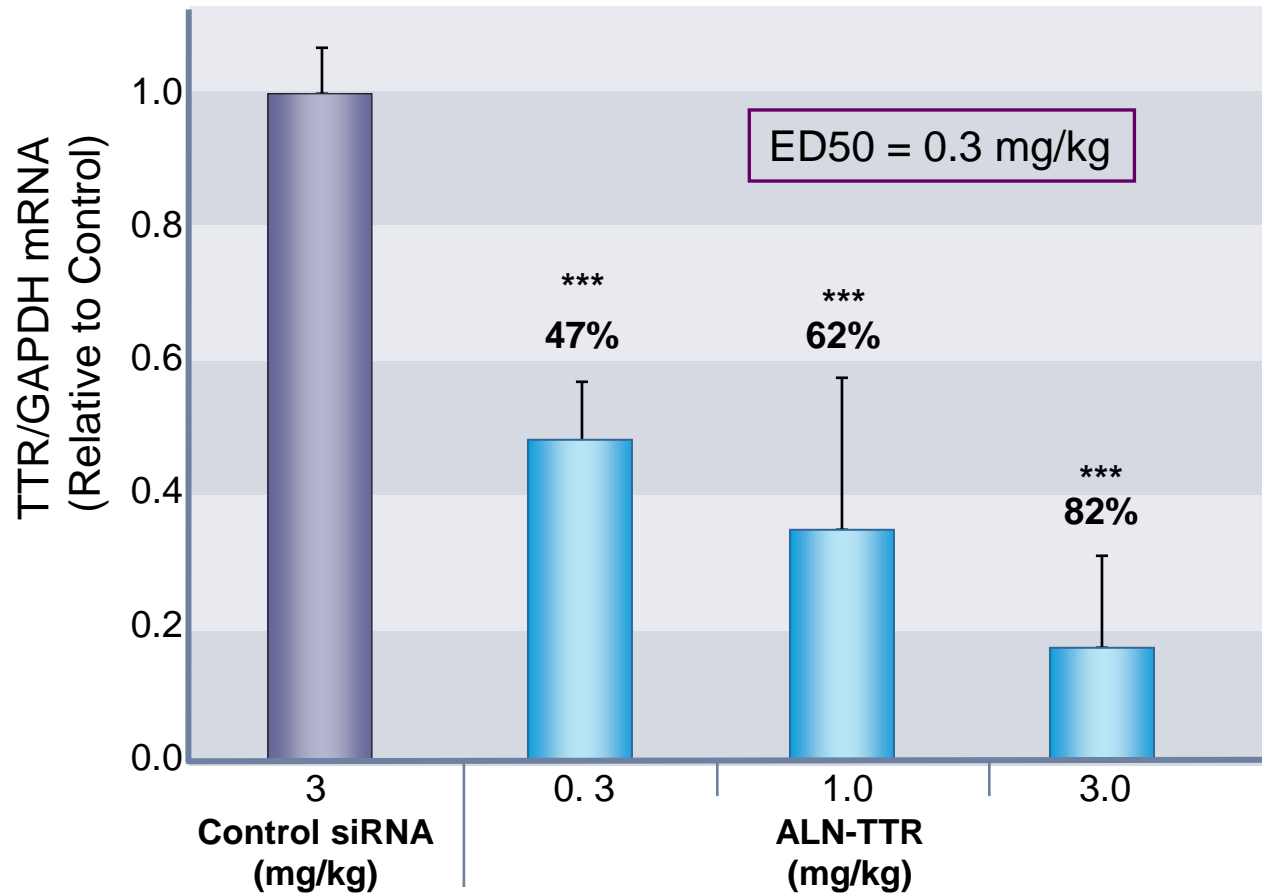
Rodent TTR siRNA Reduces TTR Levels in Rats



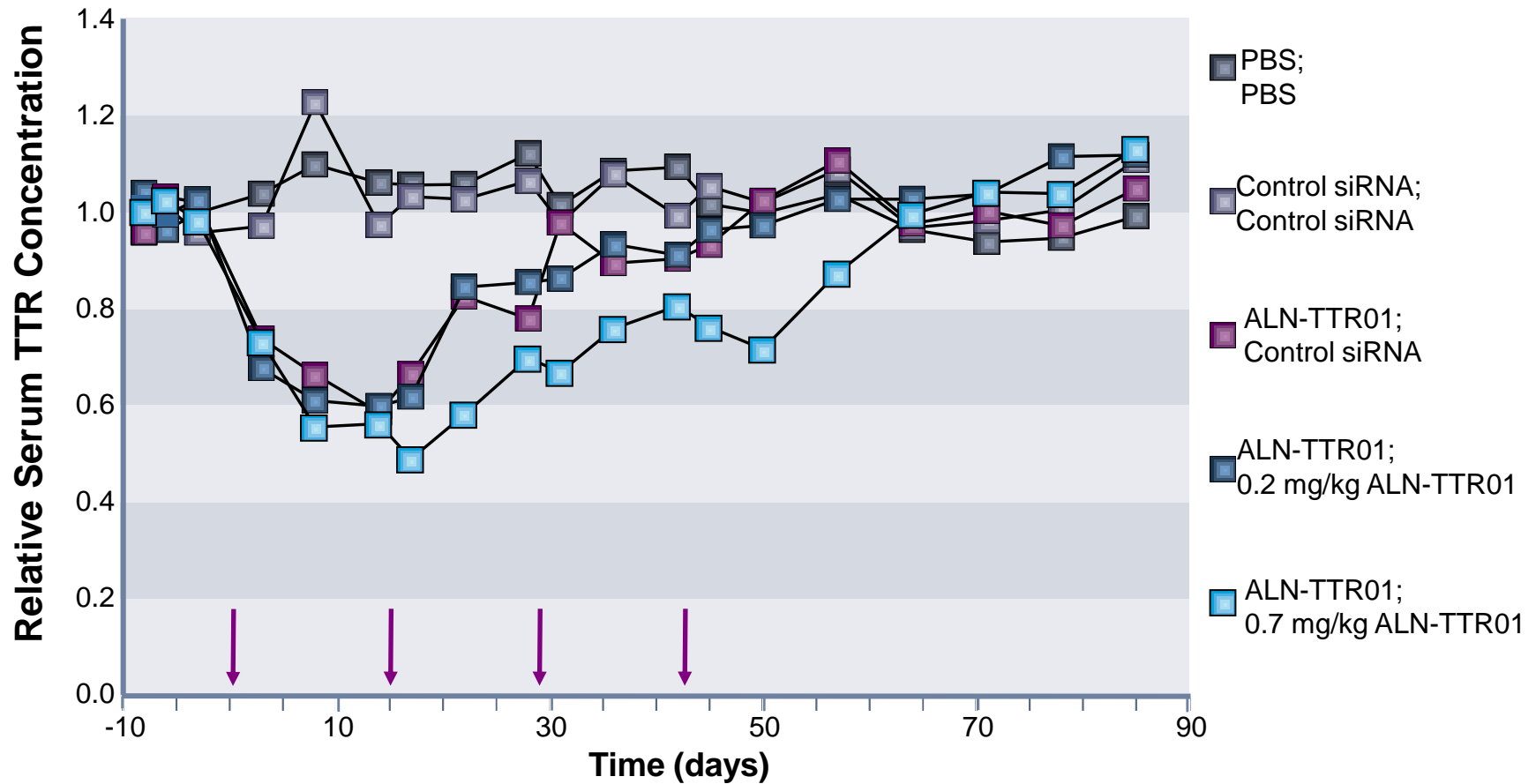
Rodent TTR siRNA Exhibits More Potent ED₅₀ When Redosed



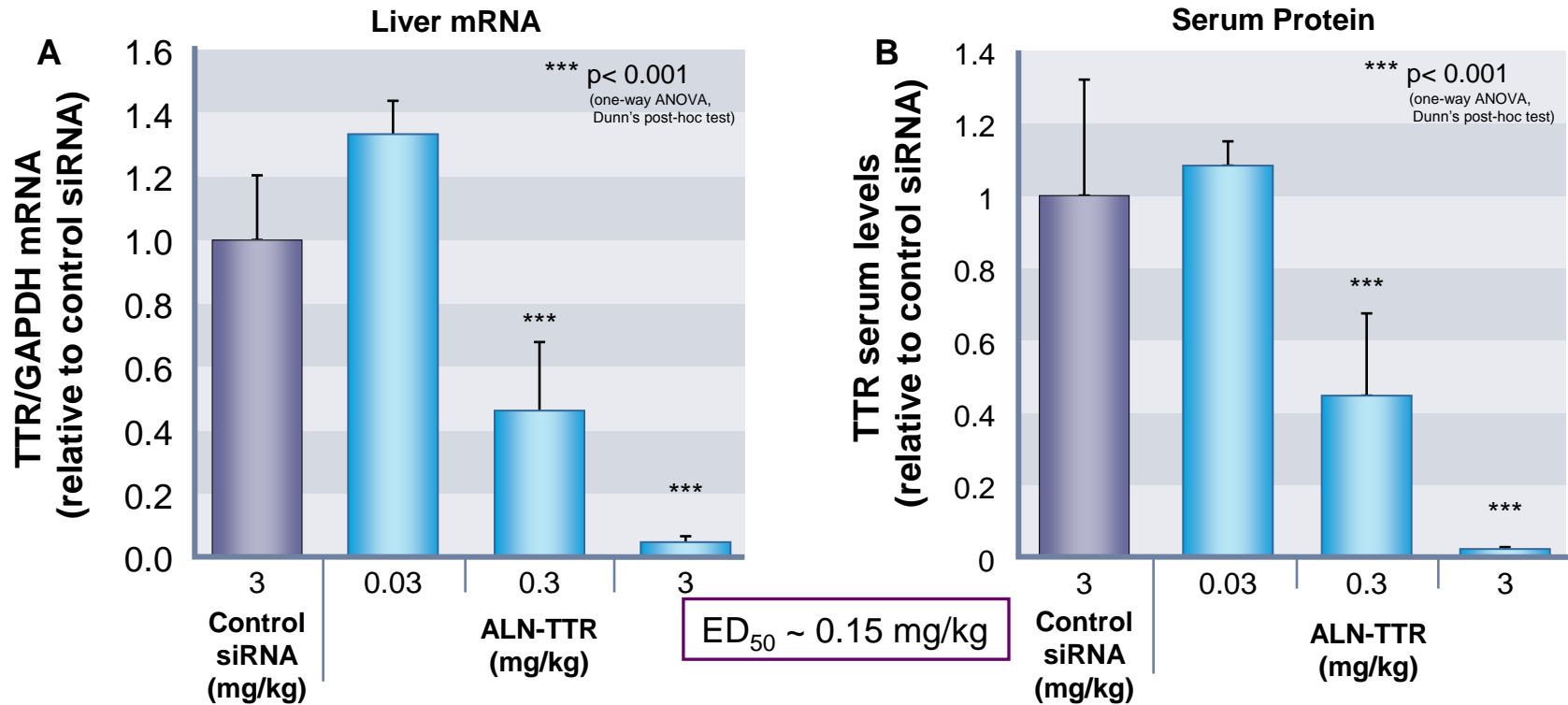
ALN-TTR Reduces Wild-type TTR mRNA Levels in NHP



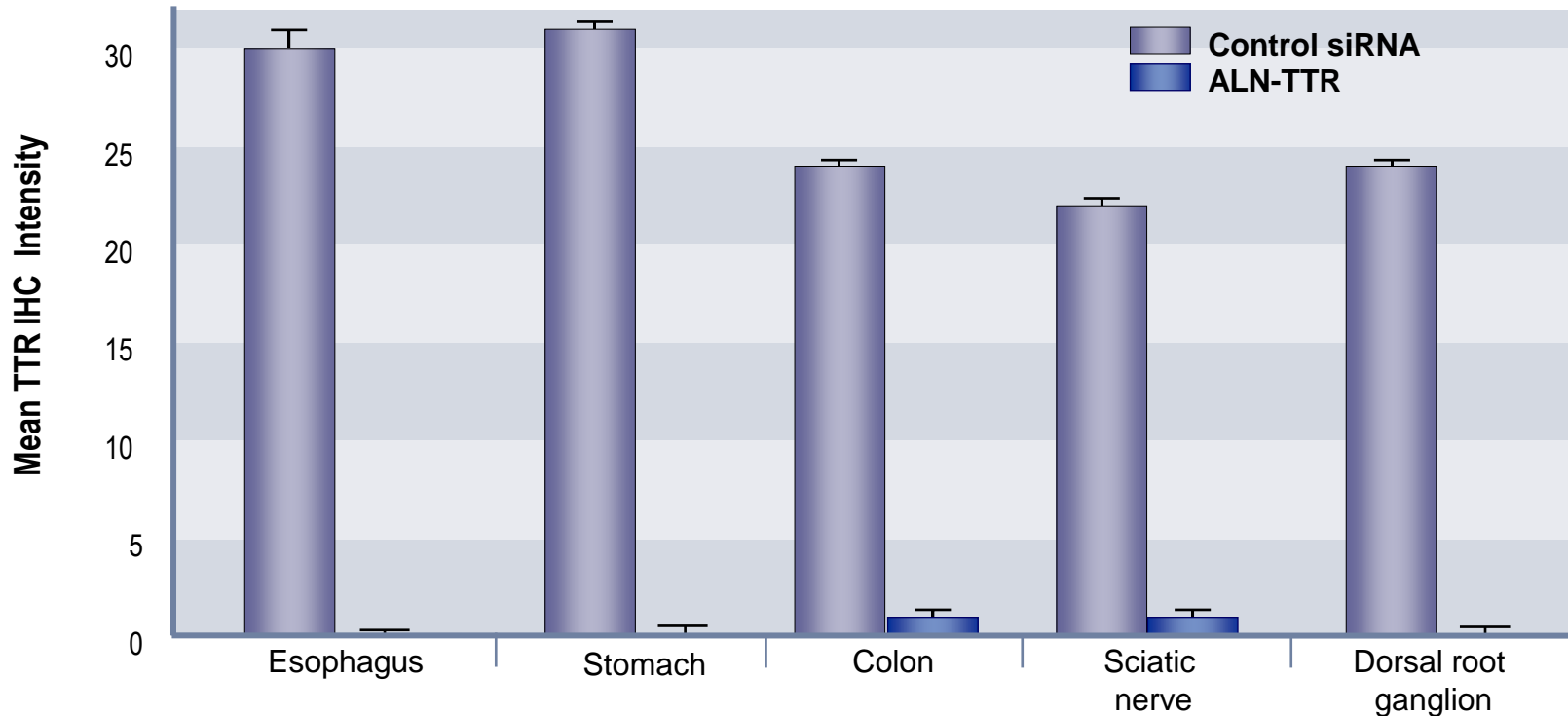
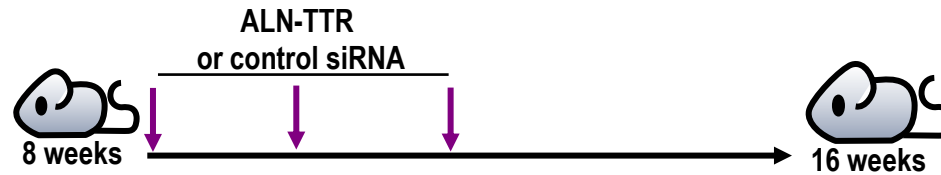
Loading-maintenance Pharmacology of ALN-TTR01 in NHP



ALN-TTR Reduces Mutant Human TTR in Transgenic Mice

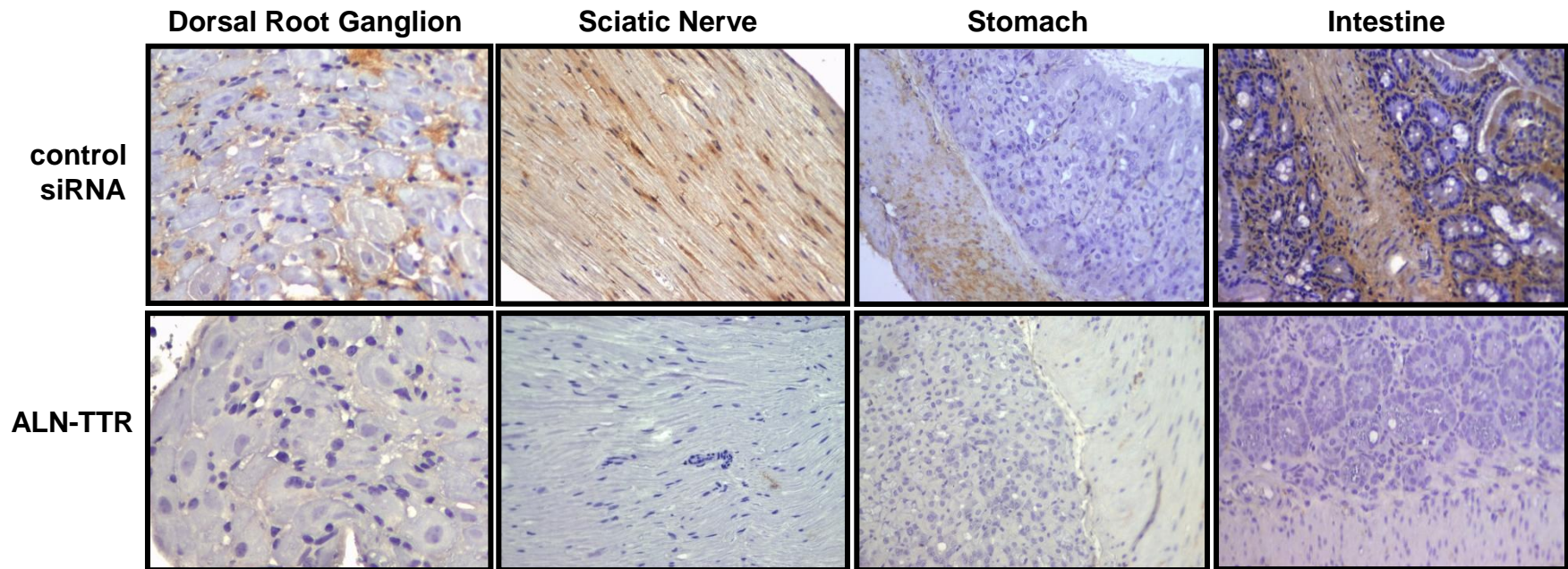


ALN-TTR Blocks Pathogenic Accumulation of Mutant Human TTR in Peripheral Tissues

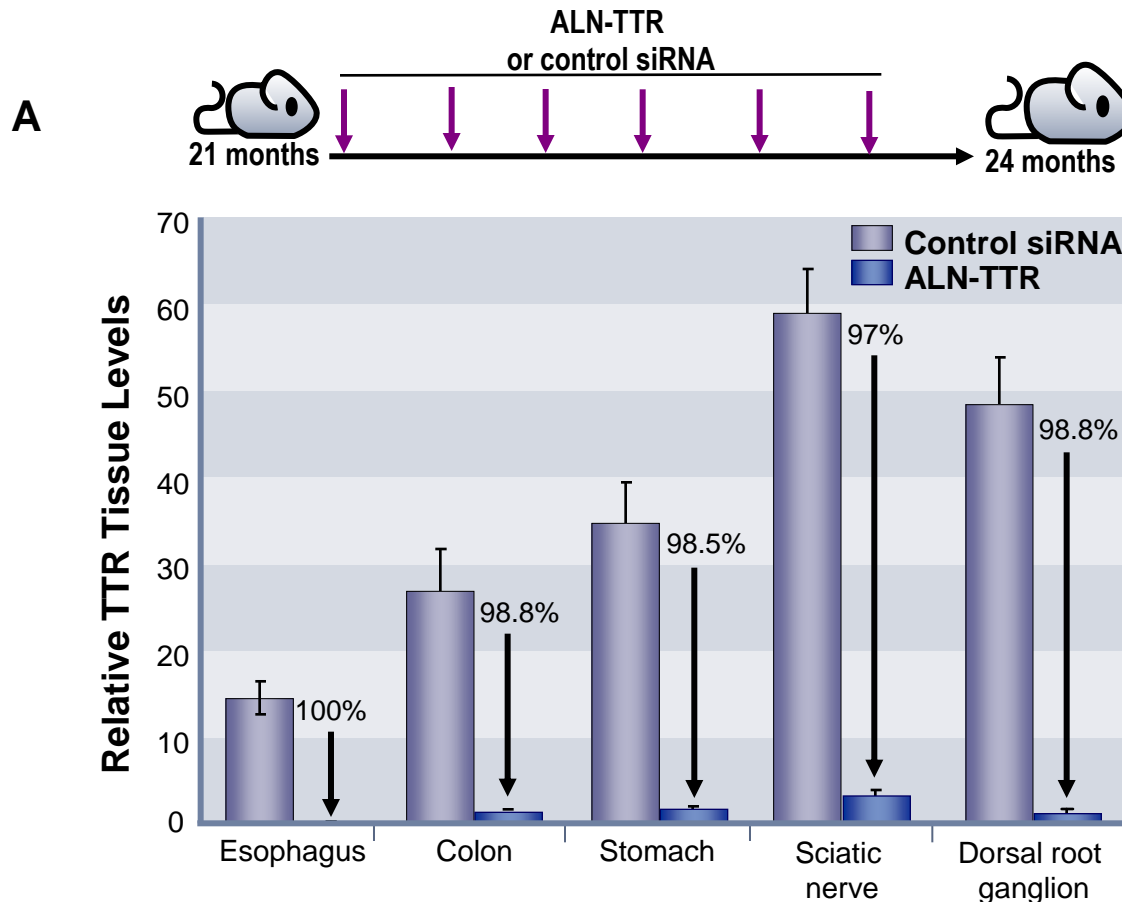


Keystone: RNA Silencing., Jan 2010

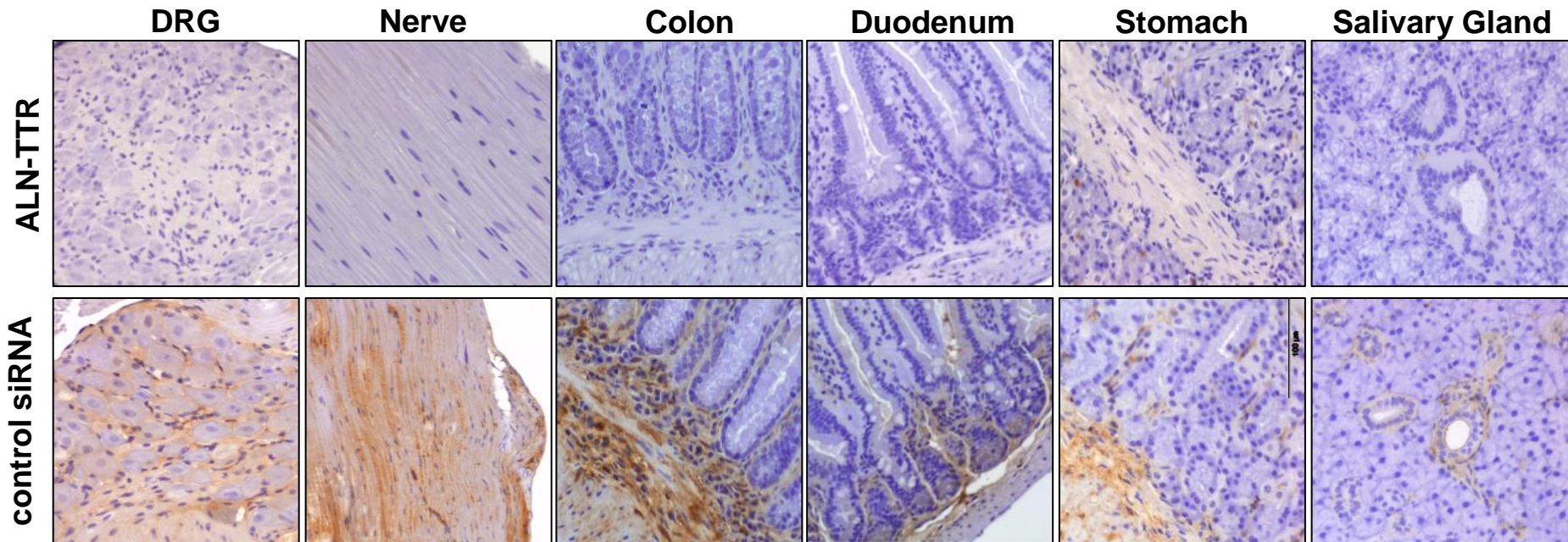
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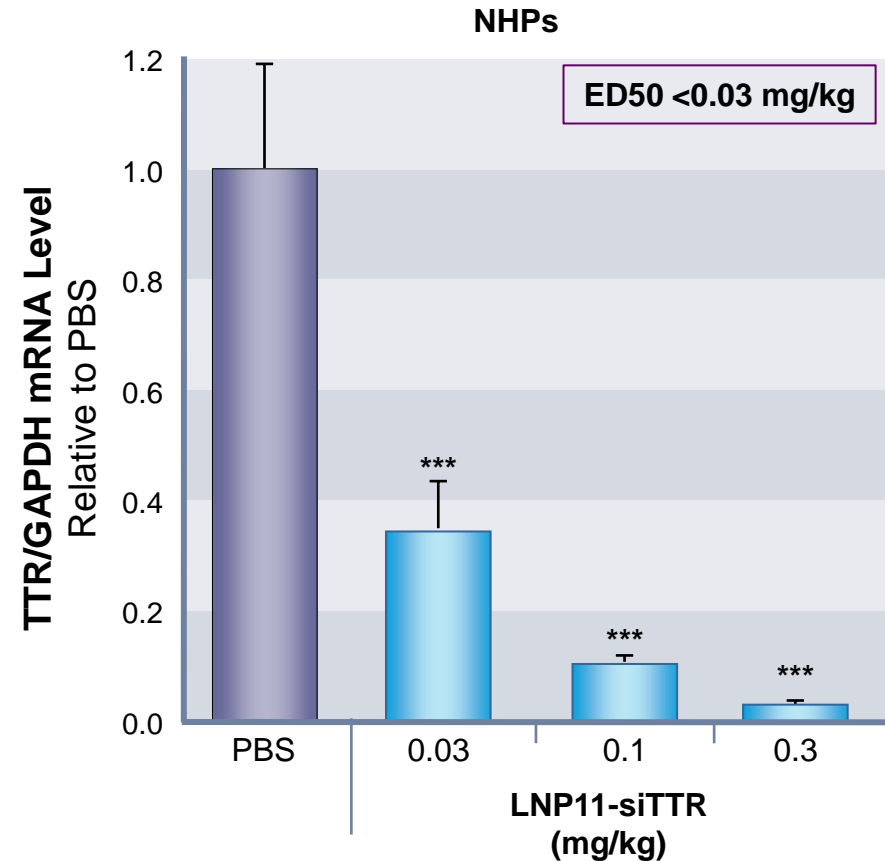
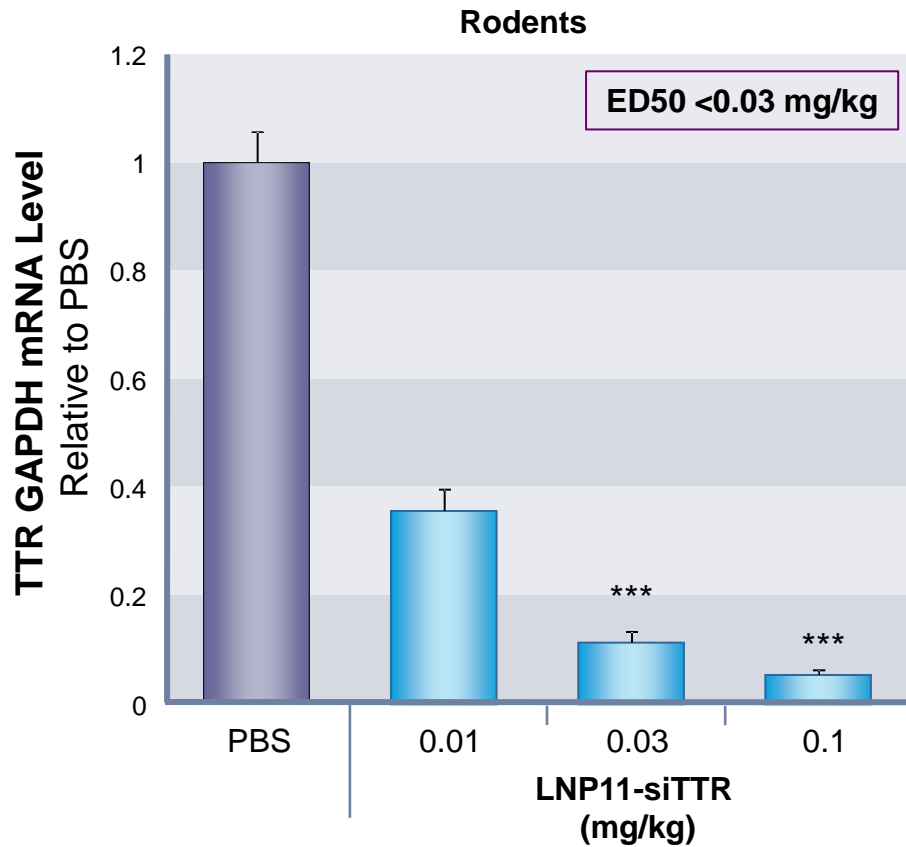
ALN-TTR Promotes Regression Of Pathogenic Mutant Human TTR Deposits In Key Target Tissues



ALN-TTR Promotes Regression Of Pathogenic Mutant Human TTR Deposits In Key Target Tissues



New Generation LNP Demonstrates Highly Potent Silencing Of TTR mRNA In Rodents and NHPs



Conclusions

- SNALP-formulated TTR-siRNA targeting rodent TTR reduced TTR mRNA levels (ED50 ~ 0.3 mg/kg) in rats, with significant reduction of TTR serum protein levels at 48 hours post-single administration
- After 1st dose at 1 mg/kg, the 2nd dose given 9 days later shows an ED50 ~ 0.03 mg/kg, suggesting that after the initial dose, a maintenance dose(s) needed to sustain TTR lowering could be ~10X lower than the initial dose in rat
- SNALP-formulated ALN-TTR01 reduced TTR mRNA levels (ED50 ~ 0.3 mg/kg) in non-human primate, with significant reduction of TTR serum protein levels and durability of suppression >14 days post-single administration
- After 1st dose at 2 mg/kg, 2nd, 3rd and 4th doses given every 2 weeks at 0.7 but not 0.2 mg/kg prolong serum TTR protein suppression in NHP
- ALN-TTR01 reduced mutant TTR mRNA and serum protein levels (ED50 ~ 0.3 mg/kg) in the hTTR V30M transgenic mouse model
- ALN-TTR01, when administered to hTTR V30M transgenic mice, prevents TTR deposition (young mice) and leads to regression (old mice) of pre-existing TTR deposits in key target tissues, including: dorsal root ganglia, sciatic nerve, stomach, and intestines
- New generation liposomal formulation demonstrates further improvements in potency, resulting in ED50 for TTR mRNA reduction of less than 0.01 and 0.03 mg/kg in rats and non-human primates, respectively
- Findings demonstrate potential therapeutic benefit of RNAi therapeutic targeting TTR for treatment of TTR-mediated amyloidosis (ATTR)