# Less may be more for TTR in ATTR: model-predicted outcomes of TTR reductions

*Bill, living with transthyretin amyloidosis, and his wife, Maura*

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*QSP Summit*
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[2]Applied BioMath, Concord, MA
[3]QuanTx Consulting, Mountain View, CA

# Outline

- **Background**
  - A primer on transthyretin (ATTR) amyloidosis, transthyretin (TTR) protein, and amyloid deposits
  - NTLA-2001: a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy being investigated in ATTR amyloidosis

- **Less may be more for TTR**
  - Greater TTR knockdown is expected to achieve greater improvements in certain clinical outcomes

- **Totality of the evidence: correlation and causation**
  - Correlative analyses suggesting the importance of TTR knockdown on clinical outcomes
  - Causation with quantitative systems pharmacology (QSP) to capture the determinants of NTLA-2001 PK/PD and provide mechanistic corroboration

# Transthyretin (ATTR) amyloidosis is caused by accumulation of amyloid deposits composed of misfolded TTR protein

## Rare, progressive, fatal disease

- ATTR amyloidosis consists of two forms of the disease: hereditary and wild type
- Rate of new diagnoses is increasing

### Hereditary ATTR amyloidosis (ATTRv)

**~50,000** patients worldwide

#### Variable phenotype

- Peripheral and autonomic neuropathy (ATTRv-PN)
- Amyloid cardiomyopathy (ATTRv-CM)
- May occur as mixed phenotype

### Wild-type ATTR amyloidosis (ATTRwt)

**~200,000 - 500,000** patients worldwide

#### Cardiomyopathy phenotype

- Increasingly recognized cause of heart failure in patients aged >50 years
- Progressive and fatal within 3 - 10 years
- Majority of cases never diagnosed

TTR, transthyretin

Donnelly JP, Hanna M. Cleve Clin J Med 2017; 84:12–26 Lane T et al. Circulation 2019; 140:16–26
Pinney JH et al. J Am Heart Assoc 2013; 2:e000098 Rowczenio D et al. Orphanet J Rare Dis 2017; 12(Suppl 1):165; Abstract P1



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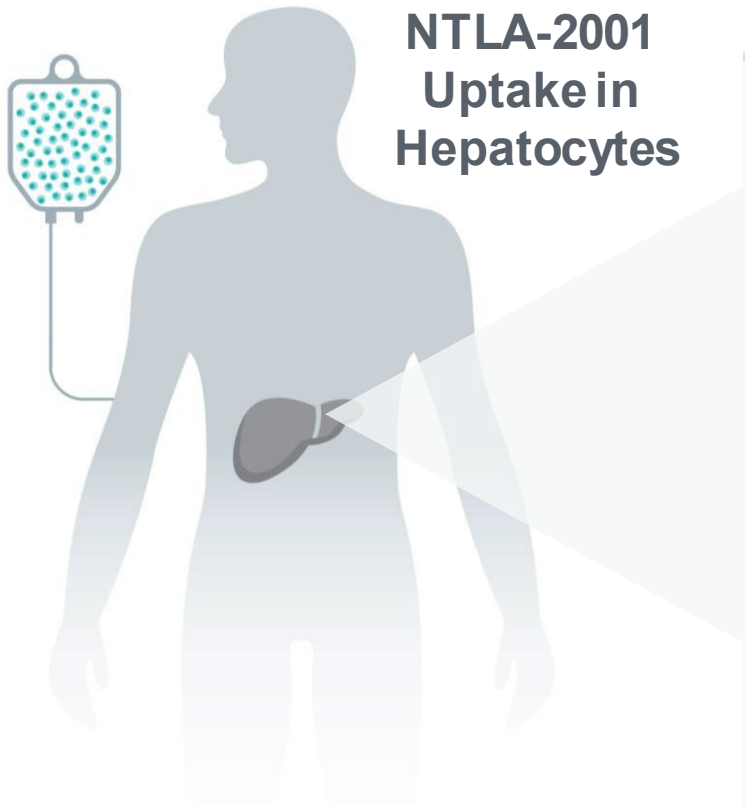
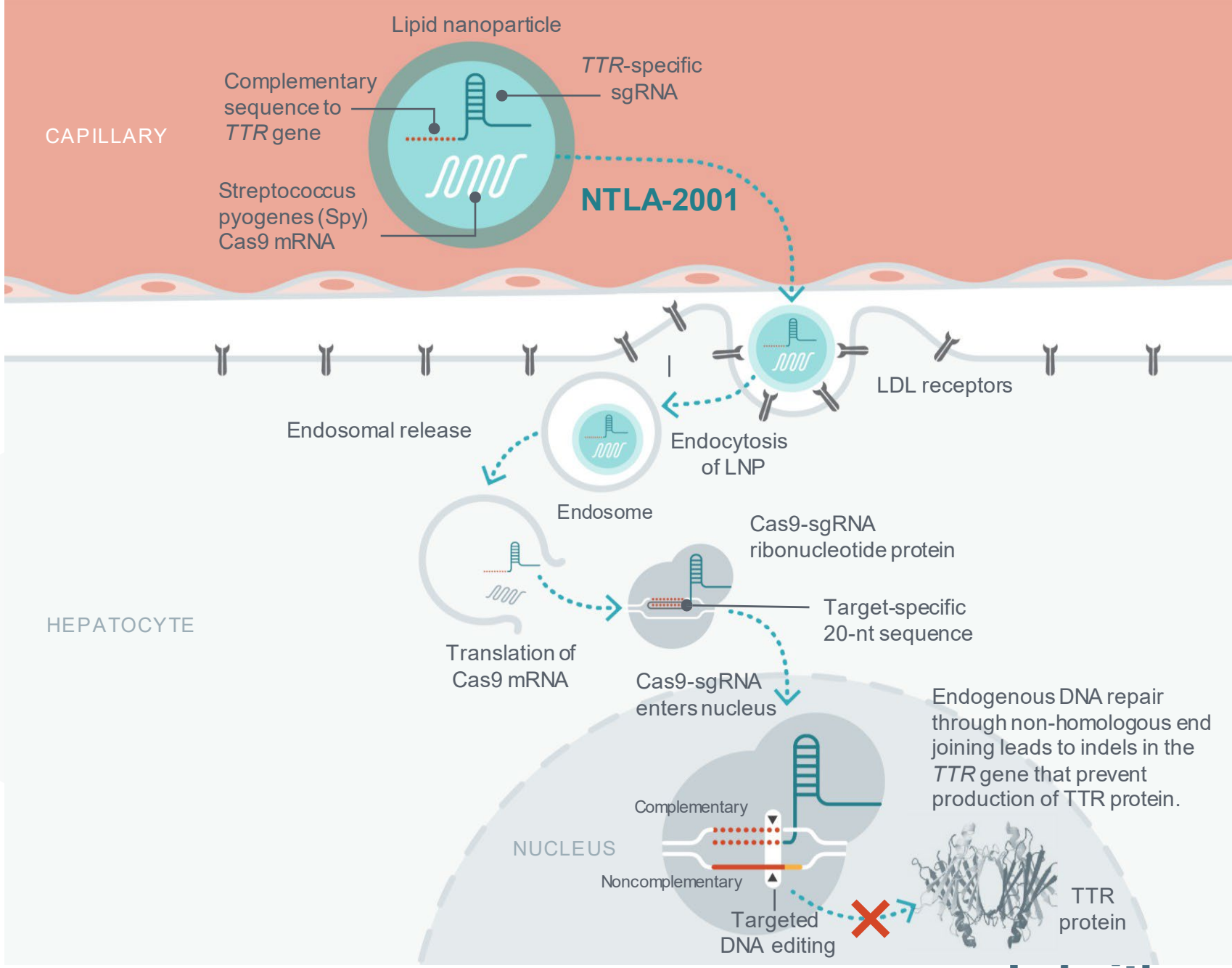
# NTLA-2001 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy



## NTLA-2001 Uptake in Hepatocytes




LNP; lipid nanoparticle; sgRNA; single guide RNA; TTR, transthyretin



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# Potential for gene editing to address unmet need for ATTR amyloidosis

- Therapy in ATTR amyloidosis is directed at reducing the circulating amyloid-forming protein
  - Gene silencing therapy knocks serum TTR down by ~80% and benefits neuropathy in ATTRv[1]
- Greater TTR knockdown is expected to achieve better clinical outcomes and can potentially reverse progression of the disease
- Editing of the *TTR* gene is an attractive therapeutic strategy

**NTLA-2001 is being studied as a potential one-time treatment to permanently knockout the *TTR* gene**



1. Adams D, et al. N Engl J Med 2018; 379:11–21

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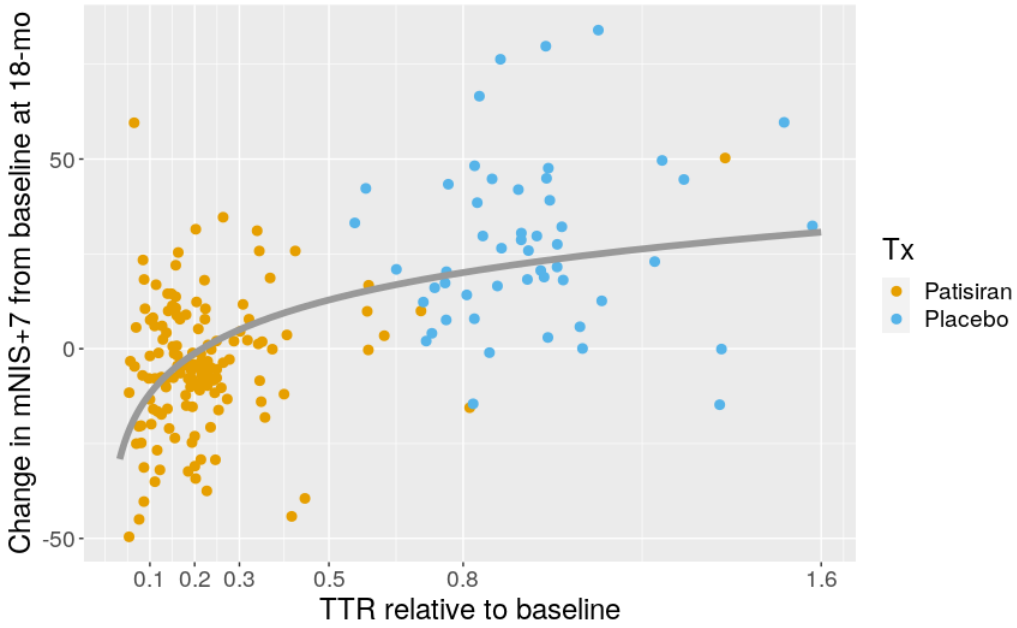
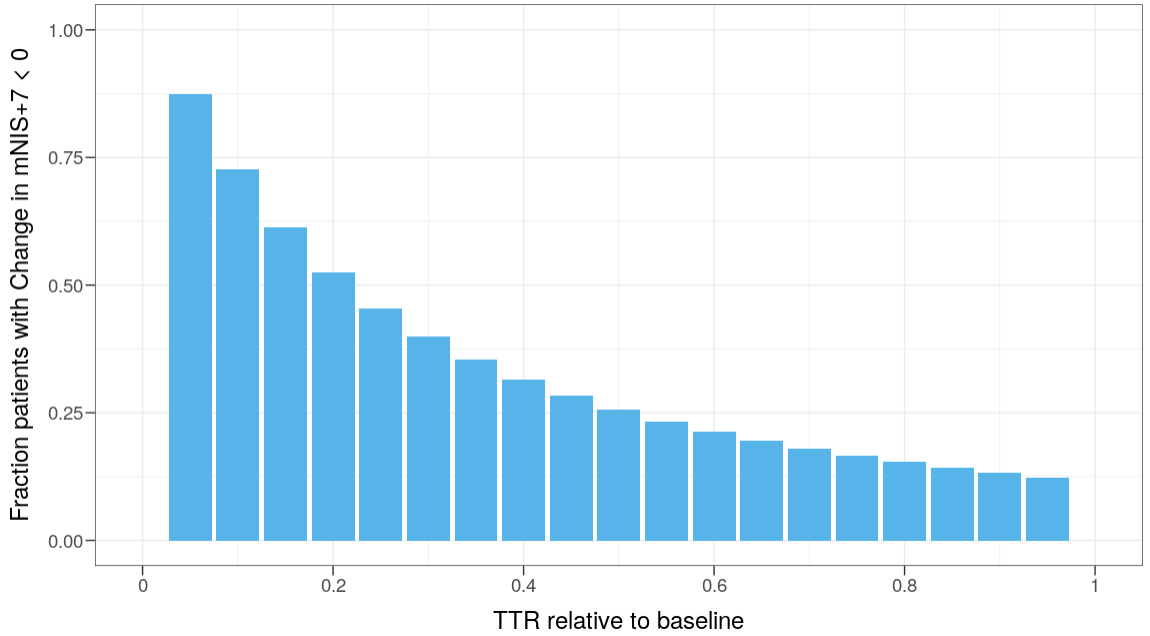
# A preliminary analysis suggests that there is a greater-than-proportional improvement in neurologic impairment in ATTRv-PN patients with decreasing TTR

## Digitized change in mNIS+7 versus TTR relative to baseline from Adams et al. along with log-linear model fit




## Model-estimated fraction of ATTRv-PN patients who would be expected to achieve change in mNIS+7 < 0 at 18 mos




ATTRv-PN, Hereditary Transthyretin Amyloidosis with Polyneuropathy;
mNIS+7, Pairwise modified Neuropathy Impairment Score+7
mNIS+7 and TTR change from baseline data digitized from
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and subsequently fit to assumed log-linear relationship



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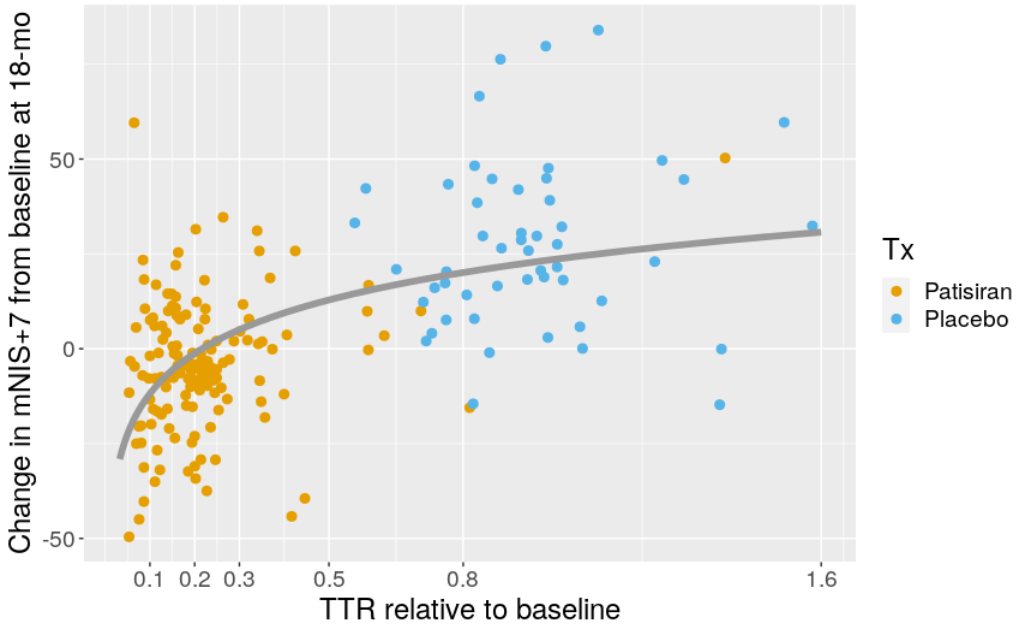


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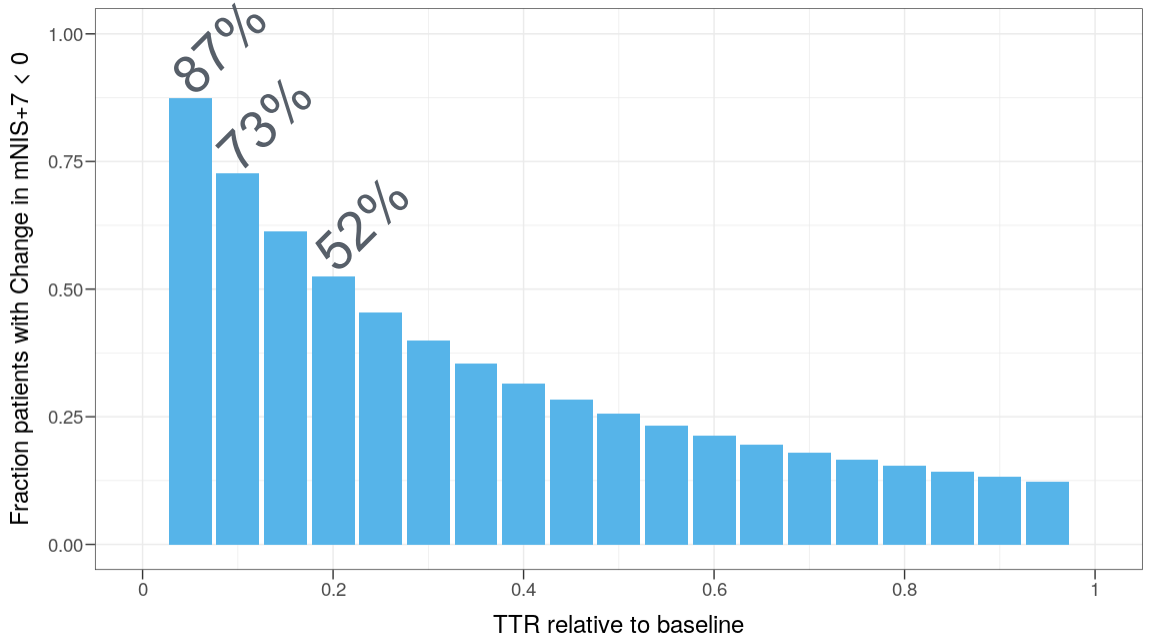


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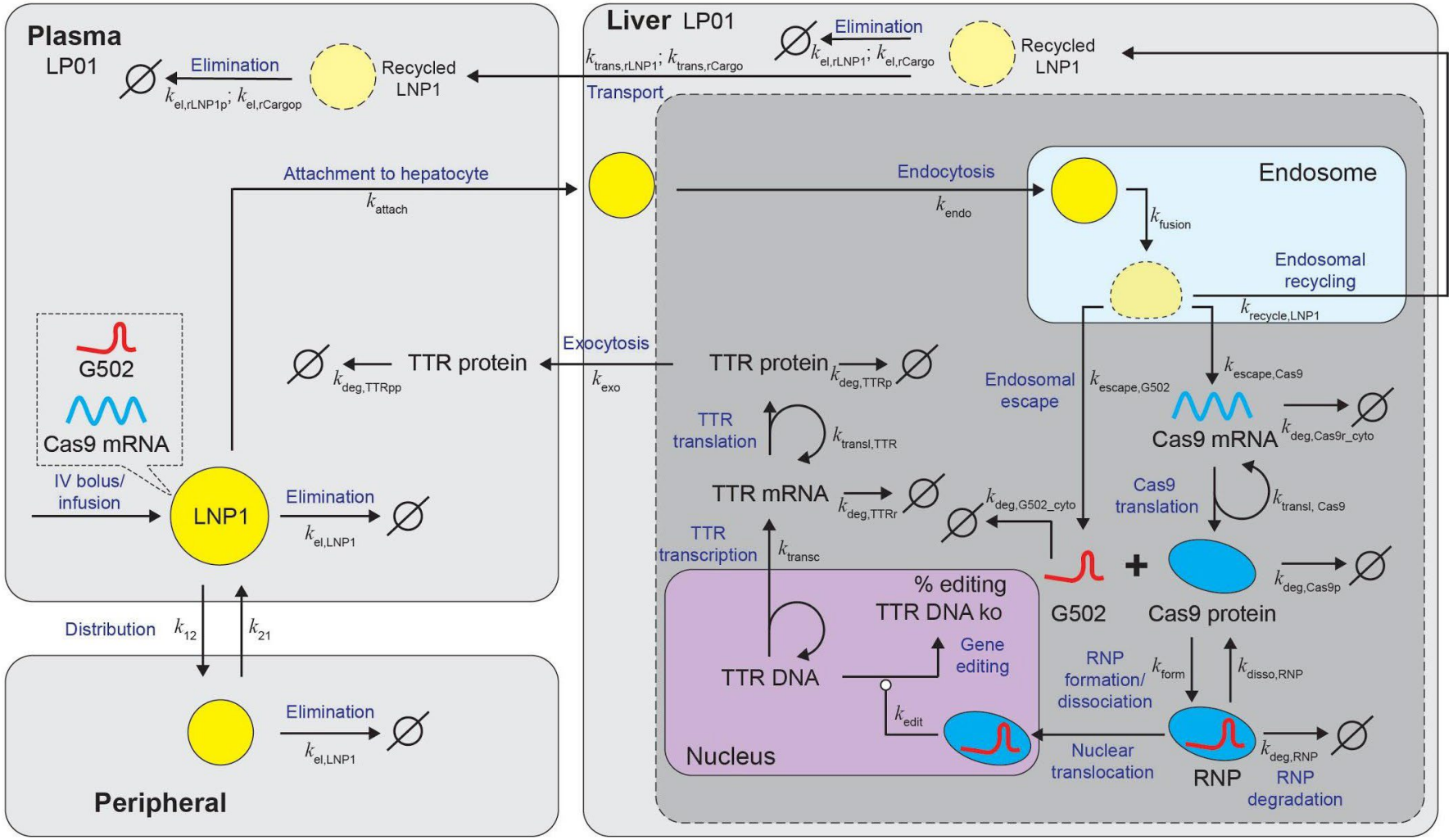
# A mechanistic QSP model was developed to capture the determinants of NTLA-2001 PK/PD

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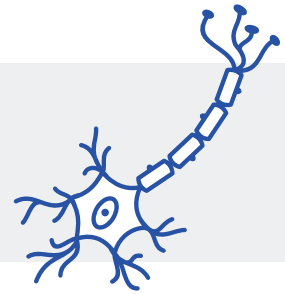
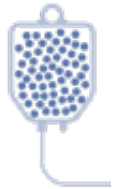
# NTLA-2001 Phase 1 Study: Polyneuropathy Arm

## Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN)



**Intervention:**
Single dose administered via an intravenous (IV) infusion



**PART I – DOSING COMPLETE**
**Single-Ascending Dose**

- 1.0 mg/kg (n=6)
- 0.7 mg/kg (n=3)
- 0.3 mg/kg (n=3)
- 0.1 mg/kg (n=3)

**PART II – ONGOING**
**Dose Expansion**

- 80 mg fixed dose
- Additional Dose Expansion Cohort*

### PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

### SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of neurologic function

- *Neuropathic impairment endpoints include NIS (Part 1 and 2) and mNIS+7 (Part 2 only)*

Clinicaltrials.gov ID: NCT04601051
**NIS**: Neuropathy Impairment Score **mNIS+7:** modified NIS+7 **PK:** Pharmacokinetics **PD:** Pharmacodynamics
* Announced on August 4, 2022: Plan to add a second dose expansion cohort to study at or near the fixed dose equivalent to 0.7 mg/kg, subject to regulatory feedback. Growing body of clinical data from Phase 1 study indicated similar serum TTR reduction at 0.7 mg/kg and 1.0 mg/kg. Additionally, a significant elevation in liver enzymes was observed in a patient dosed with 80 mg (the fixed dose corresponding to 1.0 mg/kg) of NTLA-2001 in the dose-expansion portion of the polyneuropathy arm at day 28. Elevated LFTs normalized without any medical intervention. Patient was asymptomatic and the event was deemed nonserious by the investigator.



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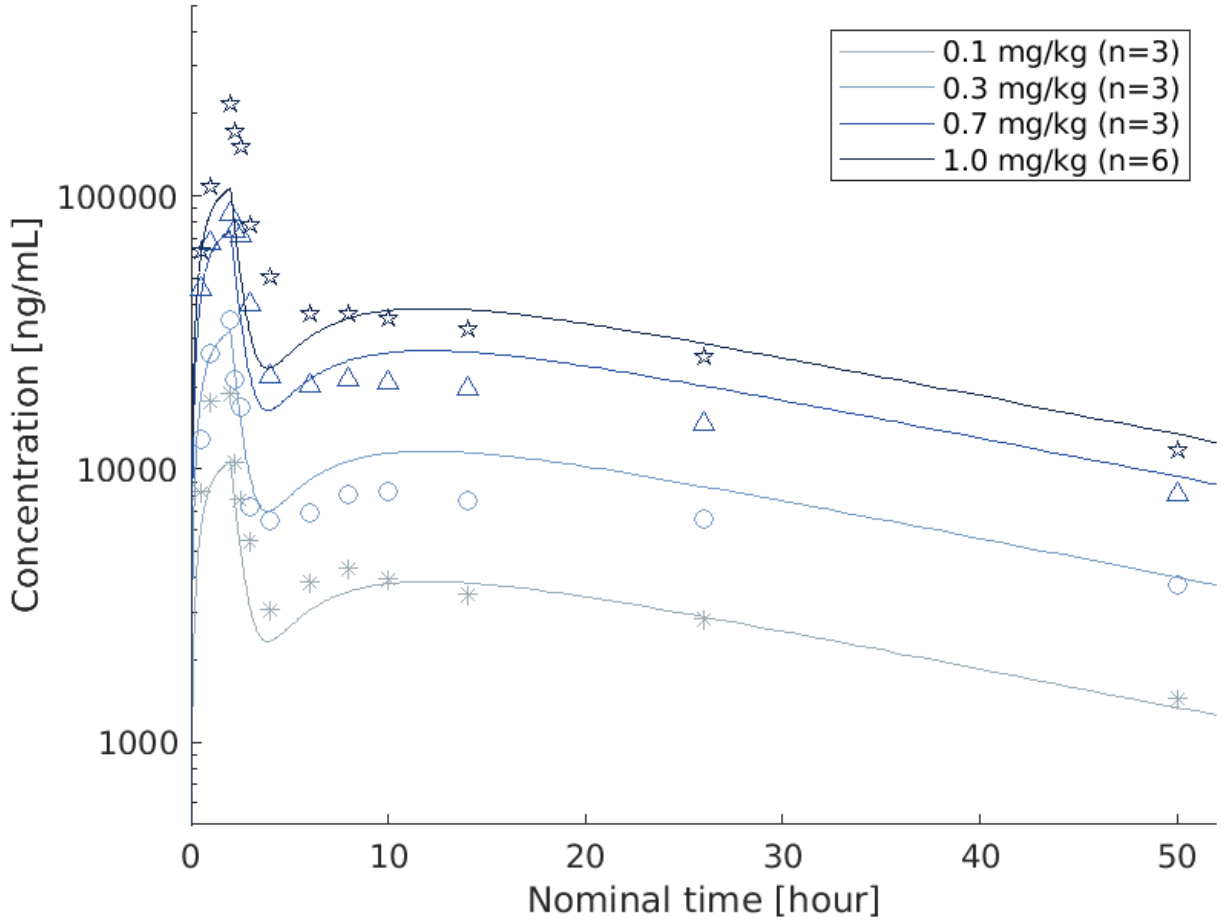
# The QSP model captures hallmark features of NTLA-2001 PK: A rapid decline from peak followed by a secondary peak and a log-linear phase

**QSP-model predicted (lines) and observed mean plasma concentration (points) of LP01 following single 0.1 - 1.0 mg/kg intravenous infusion of NTLA-2001**

**Preliminary PK/PD ITL-2001-CL-001**






NTLA-2001 comprises LP01, an ionizable lipid, additional lipids and the RNA Preliminary LP01 PK data depicted up to 48 hours post-dose

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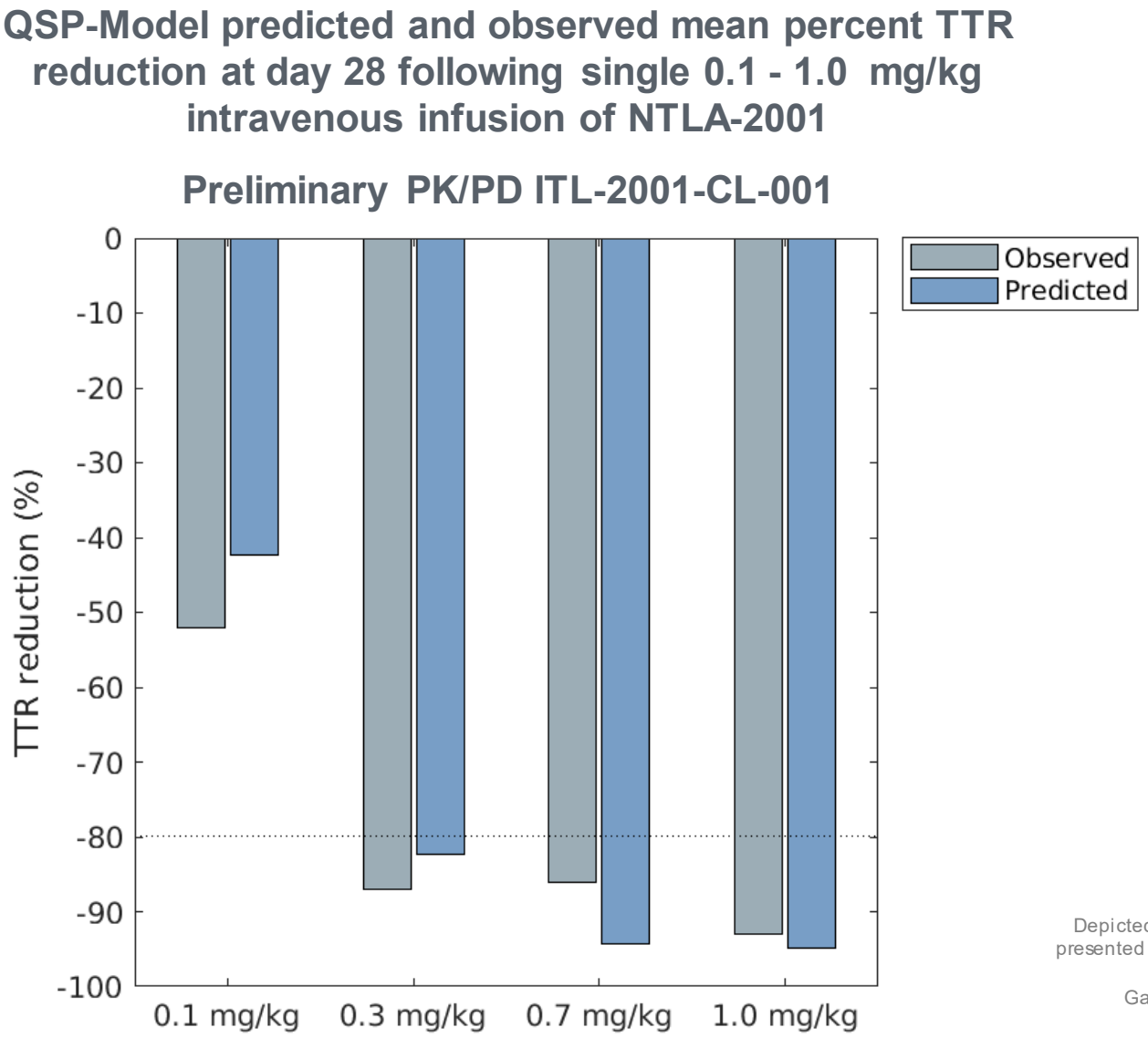
# The QSP model captures saturating dose-response for TTR




TTR, transthyretin

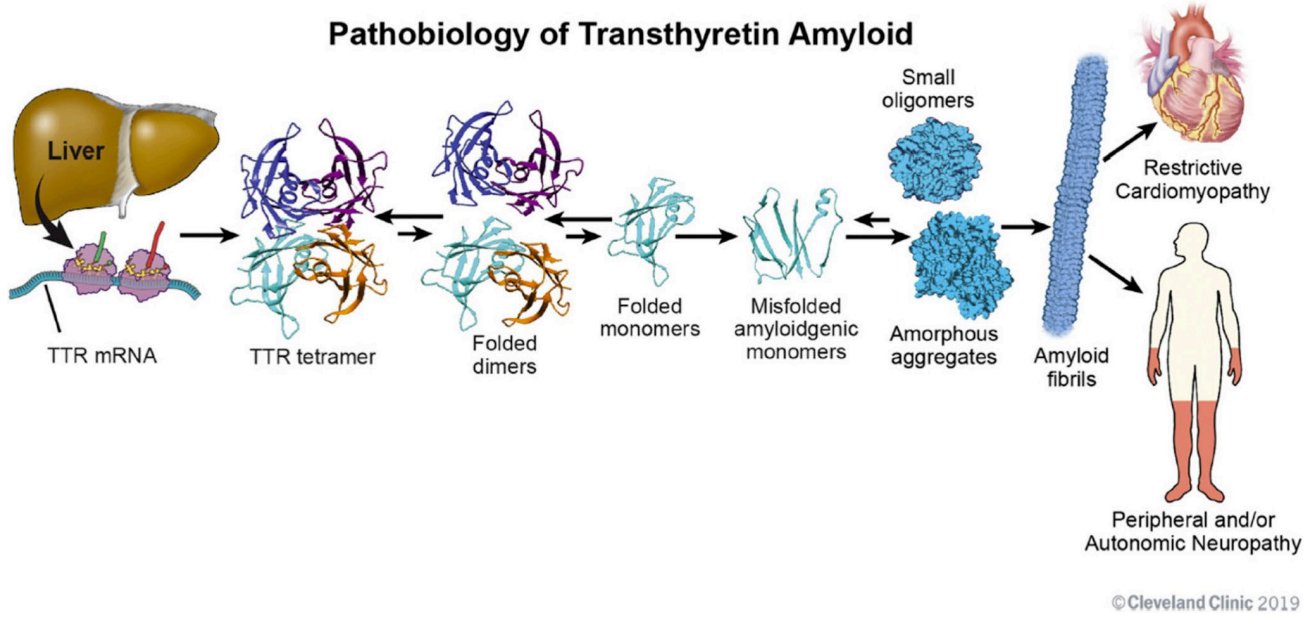
Depicted preliminary TTR reductions in ATTRv-PN patients are those presented previously at European Association for the Study of the Liver International Liver Congress 2022

Gane E J, et al. J Hepatol 2022; 77(S1):S58; Abstract OS073

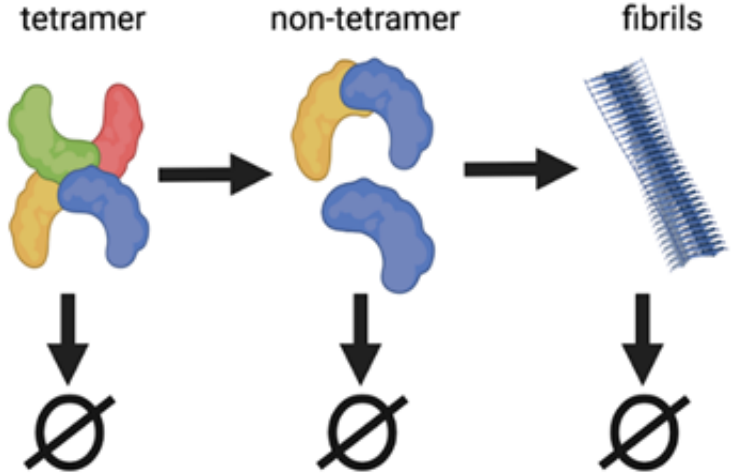
Dashed line represents the targeted minimum reduction

# The QSP model has been appended to better capture causal chain of events for ATTR amyloidosis to now include fibril formation

- The top adjacent panel is a depiction of the steps including TTR tetramer formation through to fibril and ultimately ATTR amyloidosis




- The bottom adjacent panel is a schematic of the additional reactions appended to the QSP model downstream of TTR protein



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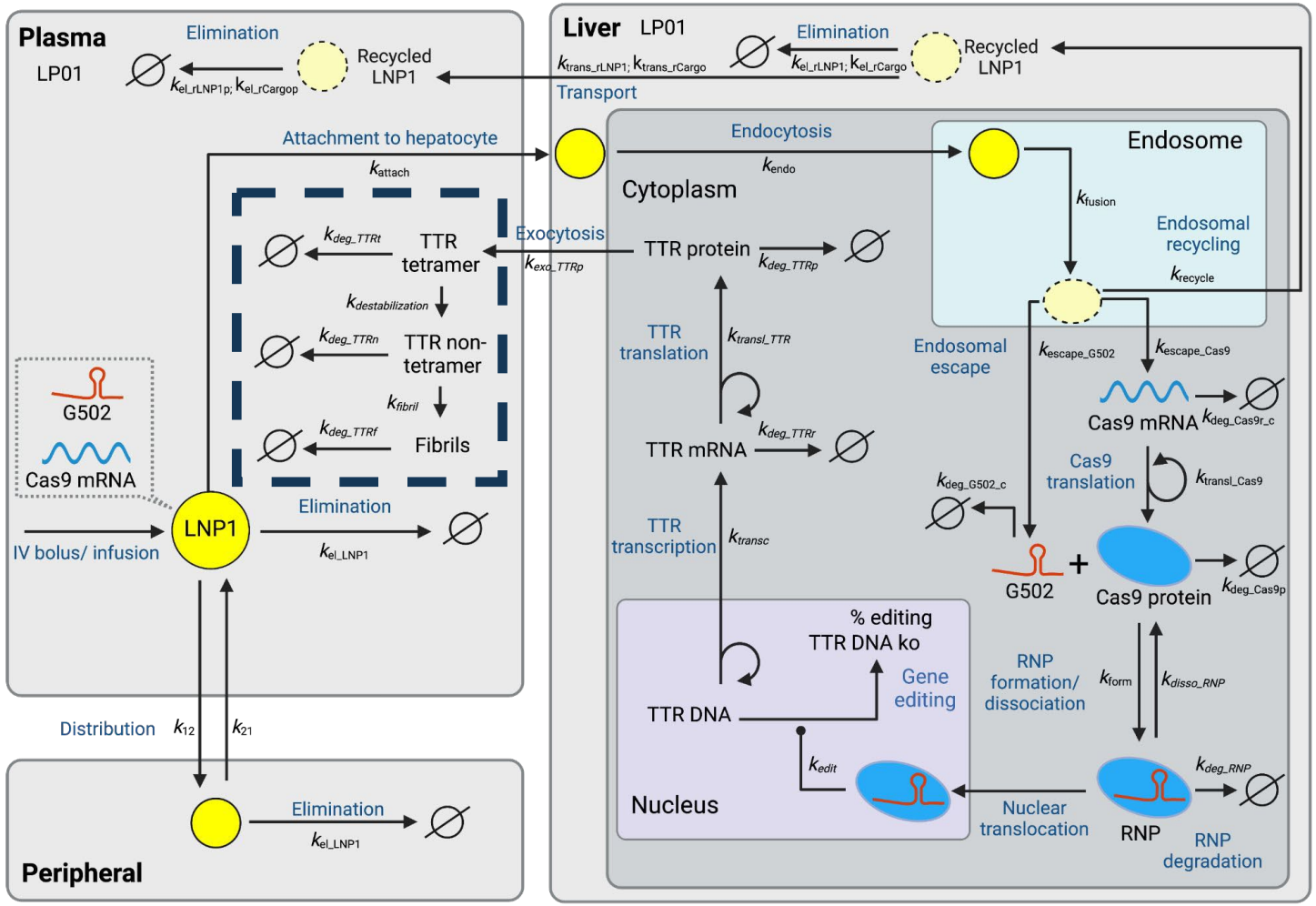
# The QSP model has been extended to capture NTLA-2001 PK/PD through fibril




Fibril rate of change informed from familial amyloidosis patient data in Dubrey S et al. Transplantation 1997; 64(1):74-80

Fibril clearance rate informed from Aβ plaque turnover in Madrasi K et al. Alzheimers Dement 2021; 17(9): 1487-1498

The rates of TTR tetramer destabilization and fibril formation were selected to maintain the TTR tetramer/(TTR tetramer + TTR non-tetramer) fraction as described in Jiang X et al. Proc Natl Acad Sci USA 2021; 118(9): e2016072118

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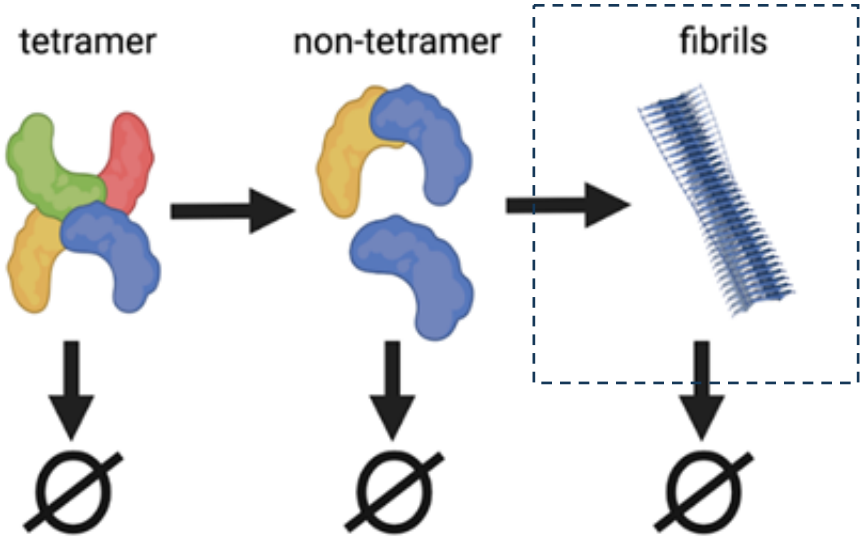
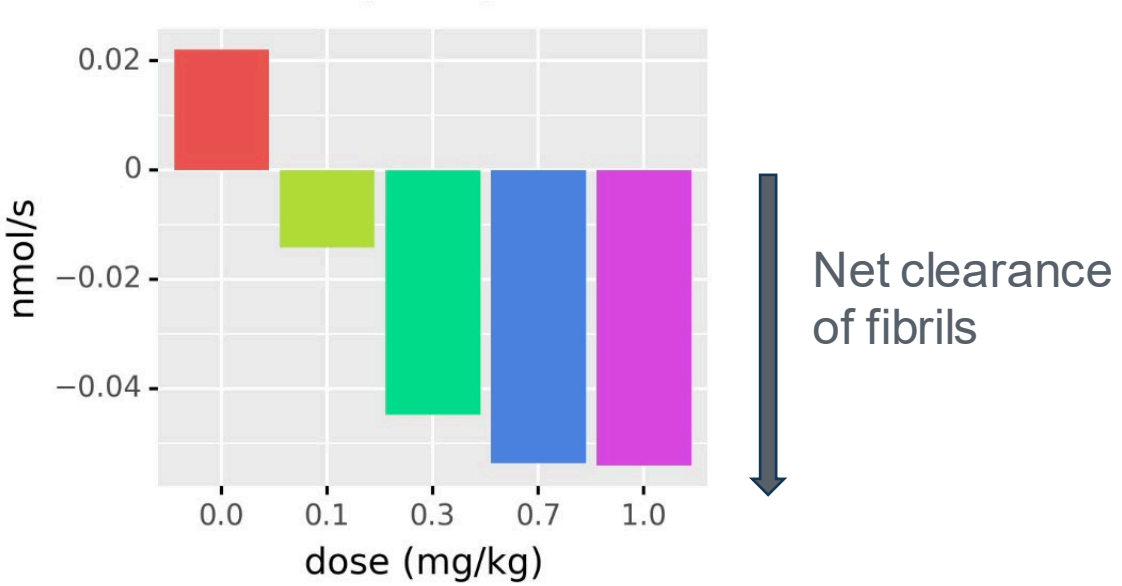
# Under the current set of model assumptions, QSP model simulations suggest that fibrils may be cleared at NTLA-2001 dose levels associated with deep TTR reductions

**Fibril accumulation as estimated by the QSP model is governed by competing first-order formation from non-tetrameric species and a saturable clearance mechanism**




**QSP-model predicted accumulation of fibrils following single 0.1 – 1.0 mg/kg intravenous infusion of NTLA-2001**




Accumulation of fibrils is based upon QSP-model predicted percent TTR reduction and is evaluated after system has reached steady state



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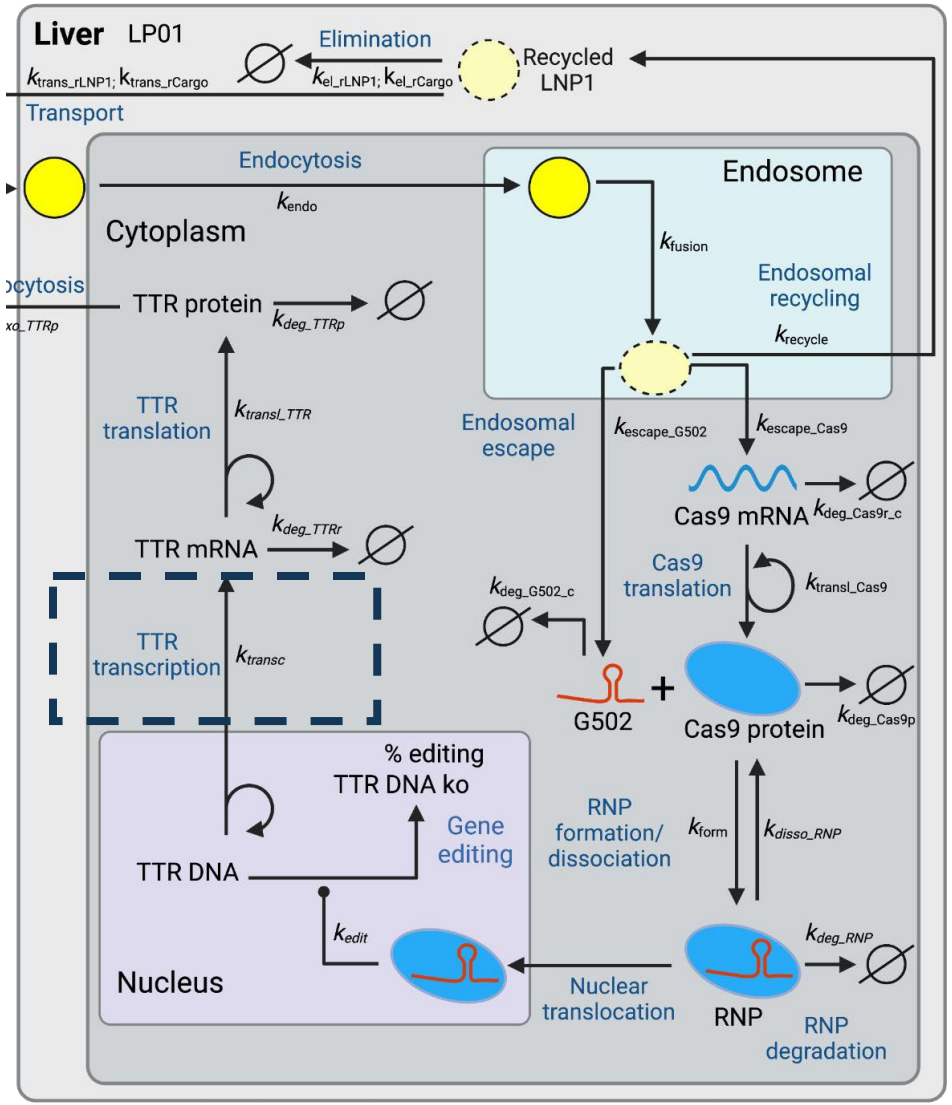
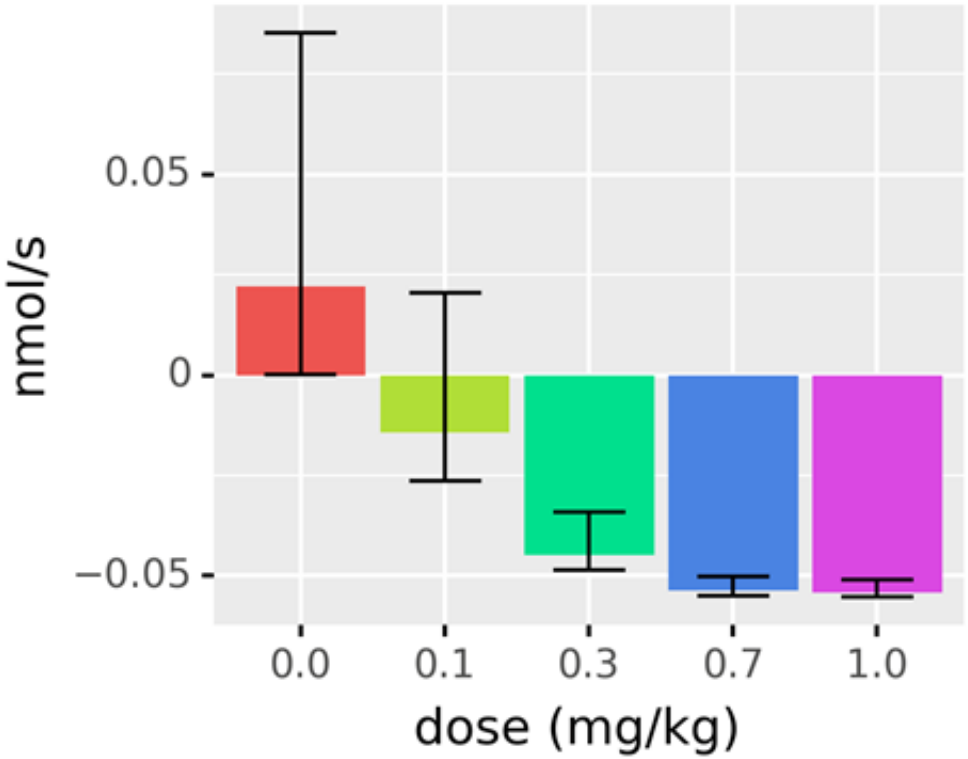
# QSP model simulations suggest that fibrils may be cleared at NTLA-2001 dose levels associated with deep TTR reductions, even when sensitive parameters (e.g. TTR transcription rate constant, $k_{transc}$) are varied




**Sensitivity of QSP-model predicted accumulation of fibrils to $k_{transc}$ (varied from 0.7 – 1.4 fold of base-case; error bars) following single 0.1 – 1.0 mg/kg intravenous infusion of NTLA-2001**



# Summary and conclusions

- ATTR amyloidosis is caused by accumulation of amyloid deposits composed of misfolded TTR protein
- NTLA-2001 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy being investigated in ATTR amyloidosis
- Correlative analyses suggest greater TTR knockdown is expected to achieve greater improvements in certain clinical outcomes
- A QSP model captures the determinants of NTLA-2001 PK/PD, and provides mechanistic corroboration to the correlative analysis suggesting greater improvements in certain outcomes with greater TTR knockdown

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