AG10 potently and selectively stabilizes transthyretin in vitro and upon oral dosing in dogs: Potential for treating transthyretin amyloidosis

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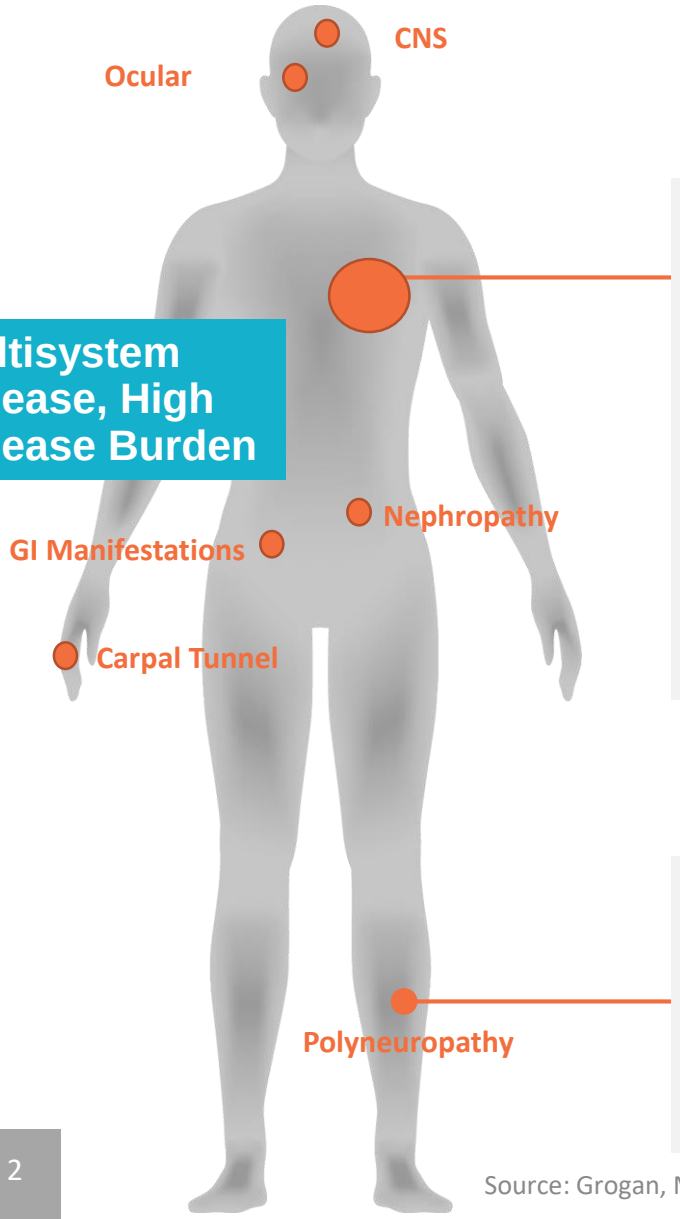
High unmet medical need



ATTR cardiomyopathy (ATTR-CM)

- Deposition of mutant (e.g., V122I) or wild-type TTR amyloid in the heart
  - Leads to predominantly diastolic heart failure
  - Afib/stroke and heart block frequently seen
- Affects 200K+ worldwide, likely underdiagnosed
- Late onset (50-60+), death within 4-6 years
- No FDA-approved treatments

ATTR polyneuropathy (ATTR-PN)

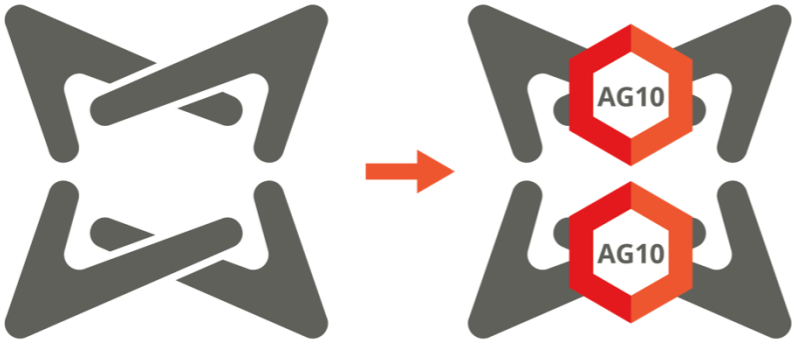
- Affects ~10K worldwide, primarily in EU and JP
- Exclusively caused by mutant TTR (e.g., V30M)
- No FDA-approved treatments

Source: Grogan, M et al. JACC 2016, 68:1014-20; Planté-Bordeneuve, V. and Said, G. Lancet Neurol 2011, 10:1086-97

Disease mechanism and therapeutic approach

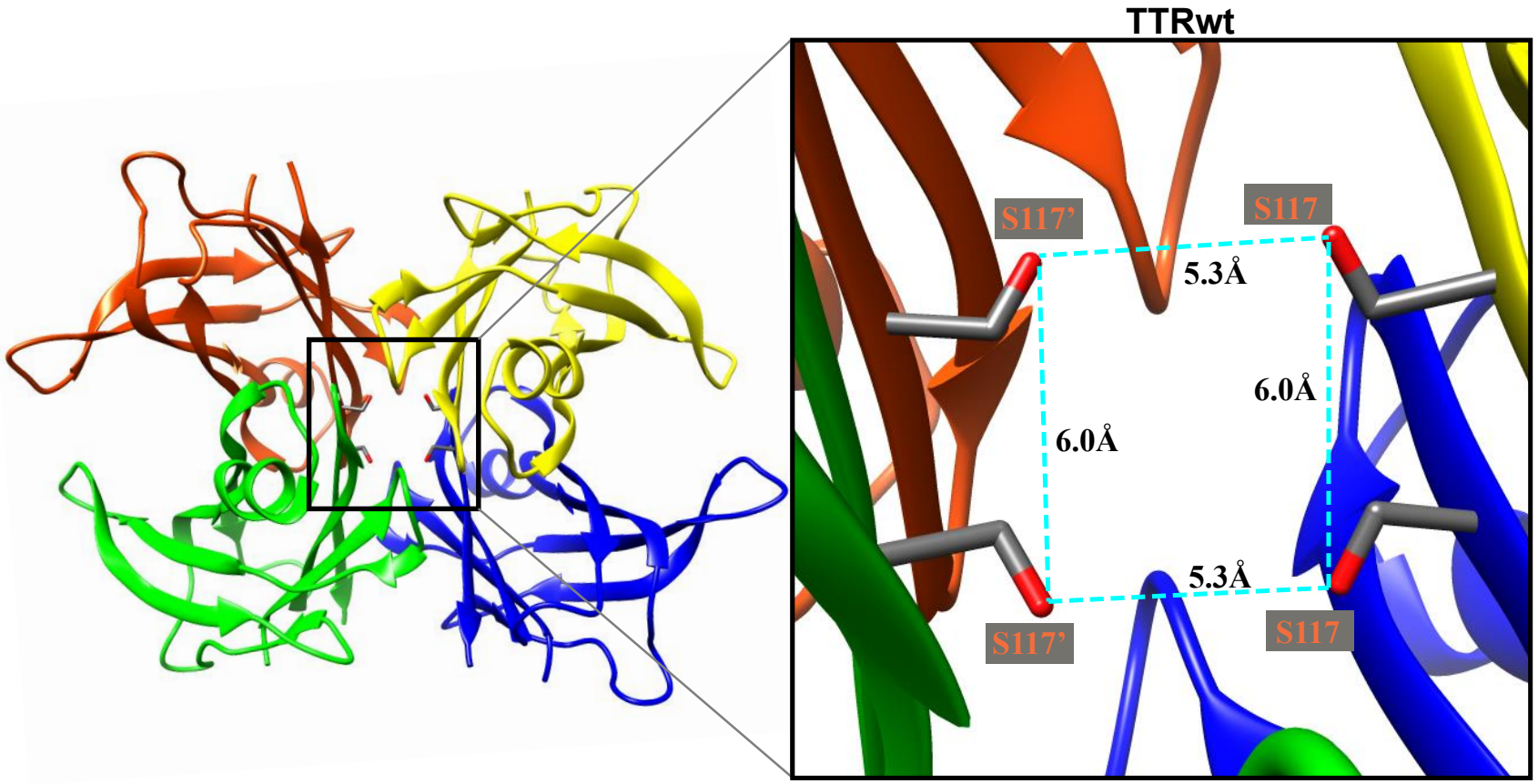
Disease mechanism

Therapeutic hypothesis

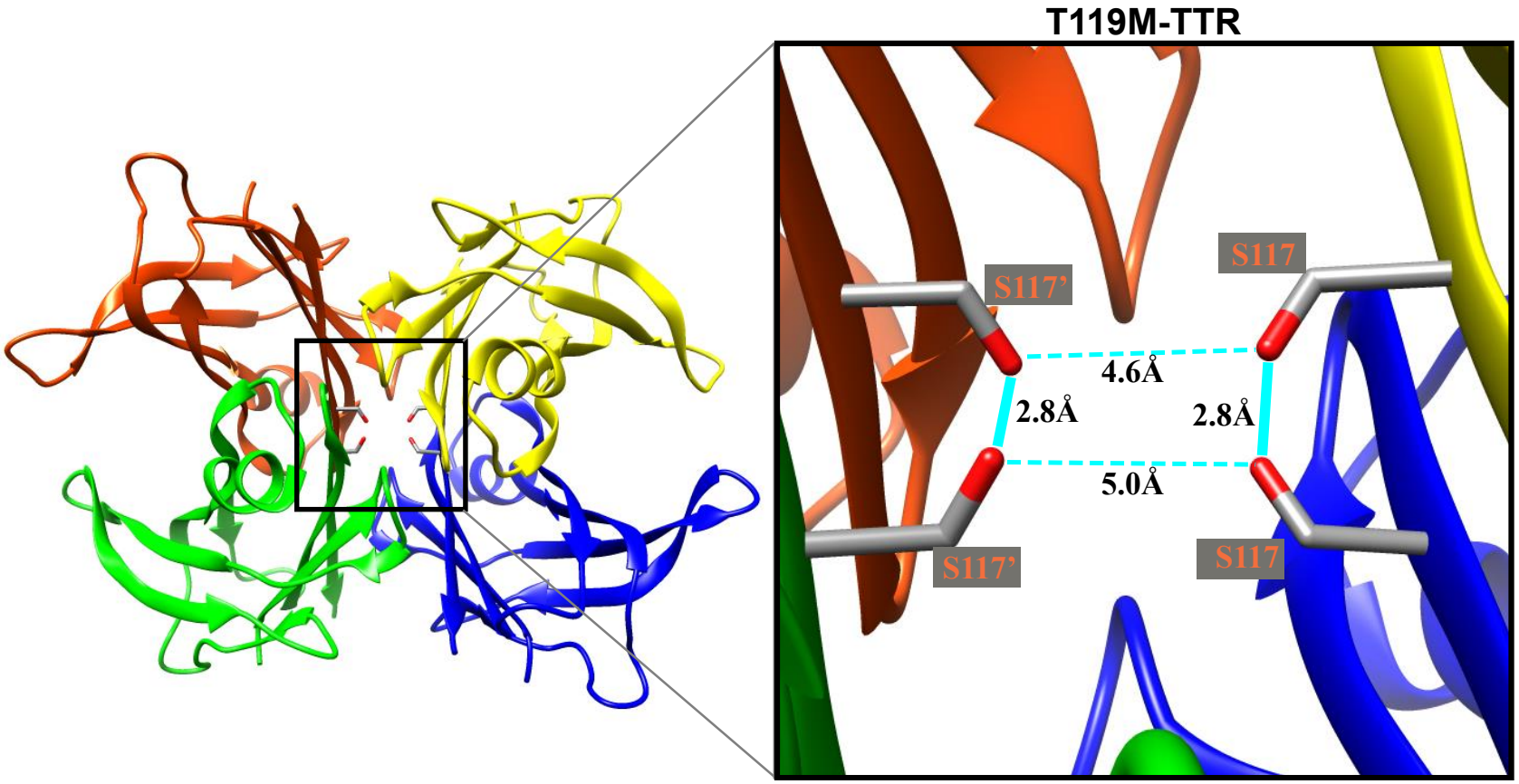


Stable tetramer
Reduced amyloid formation and deposition

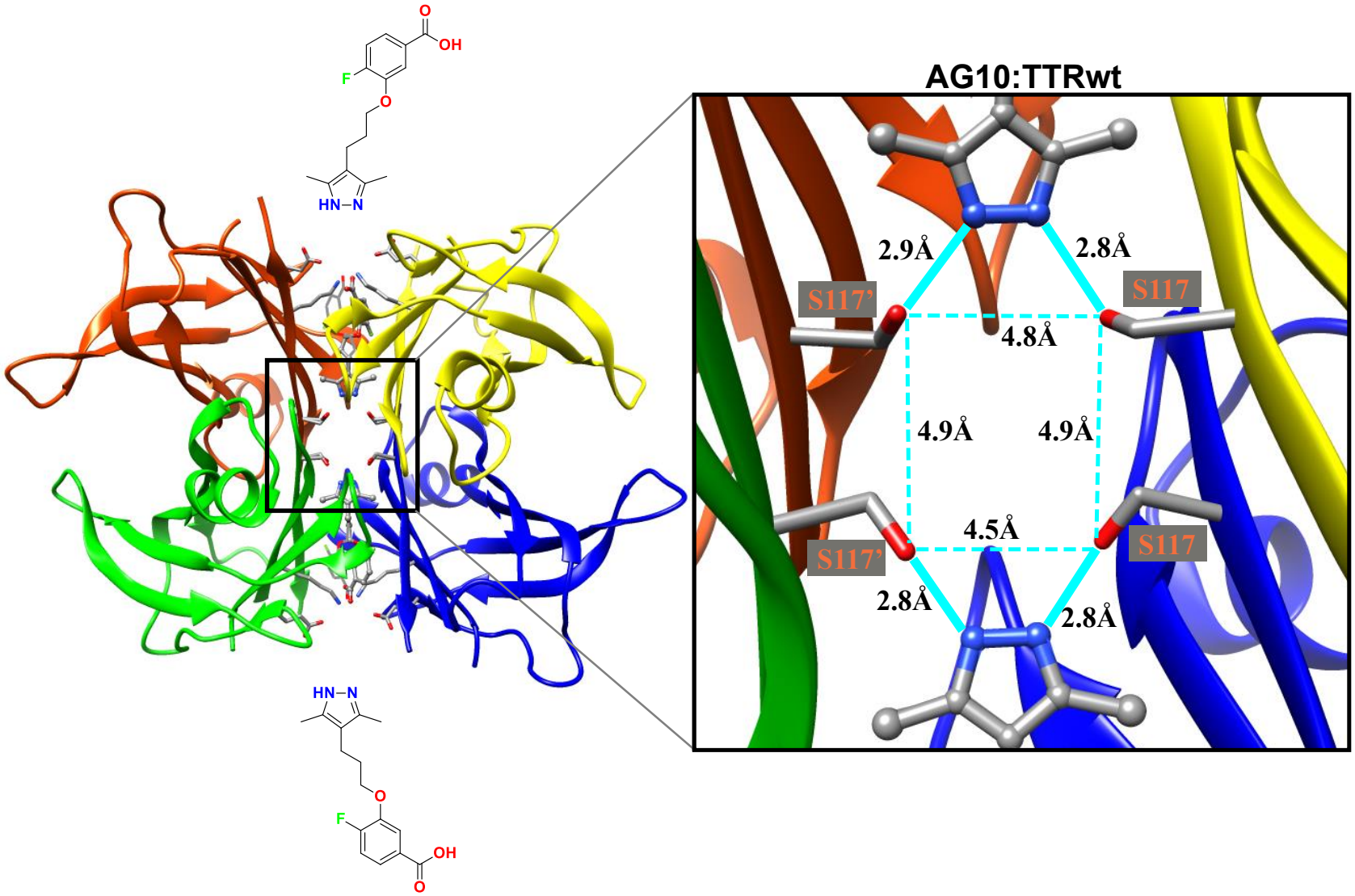
AG10 stabilizes TTR by mimicking the disease suppressing T119M variant



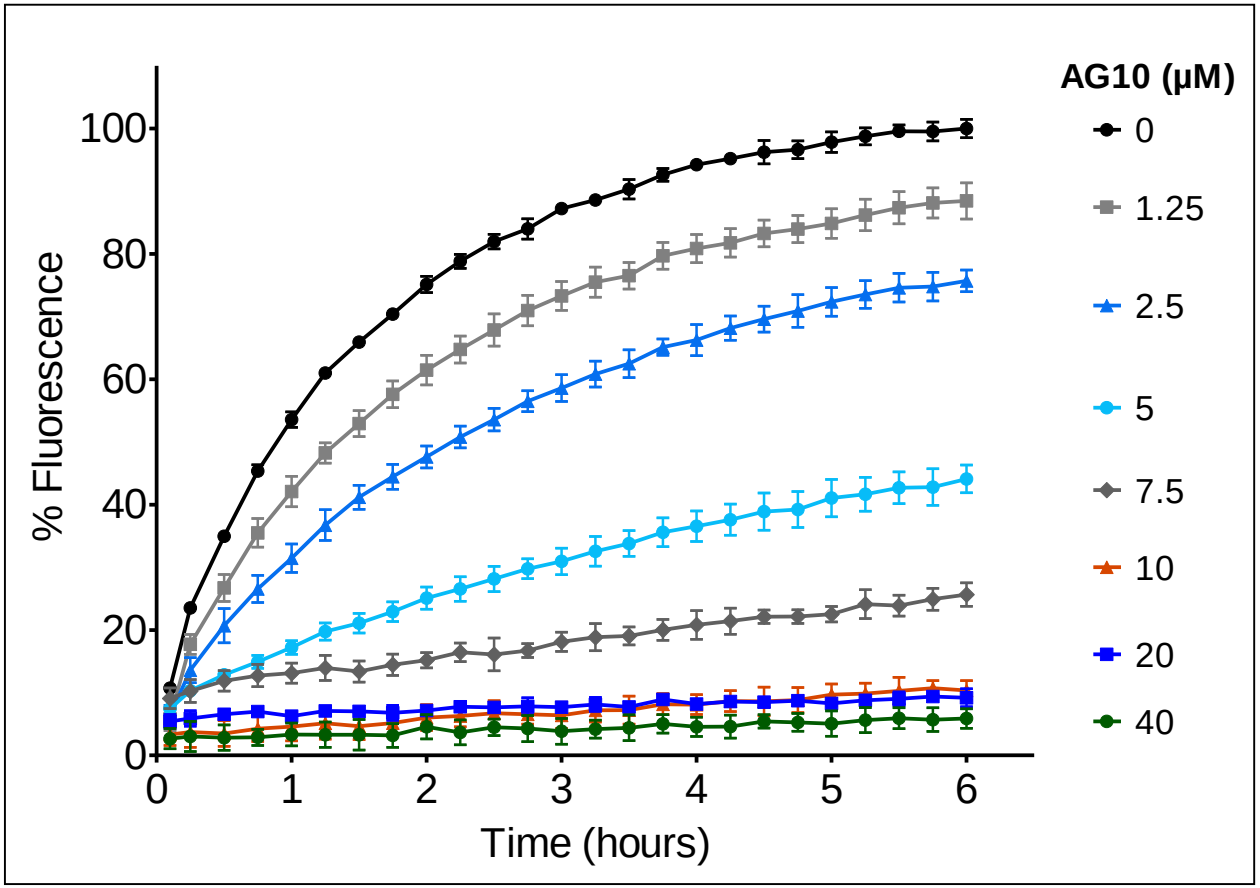
AG10 stabilizes TTR by mimicking the disease suppressing T119M variant



AG10 stabilizes TTR by mimicking the disease suppressing T119M variant

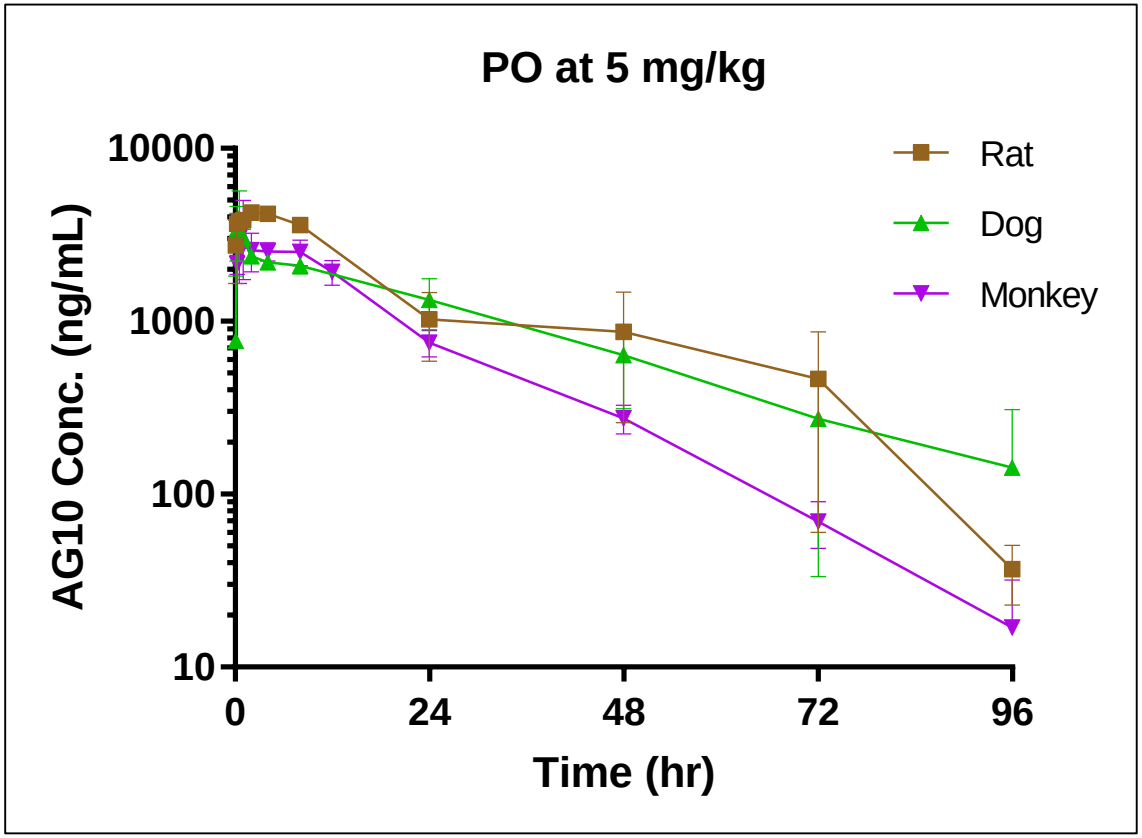


AG10 Dose Responsively stabilizes TTR in Human Serum



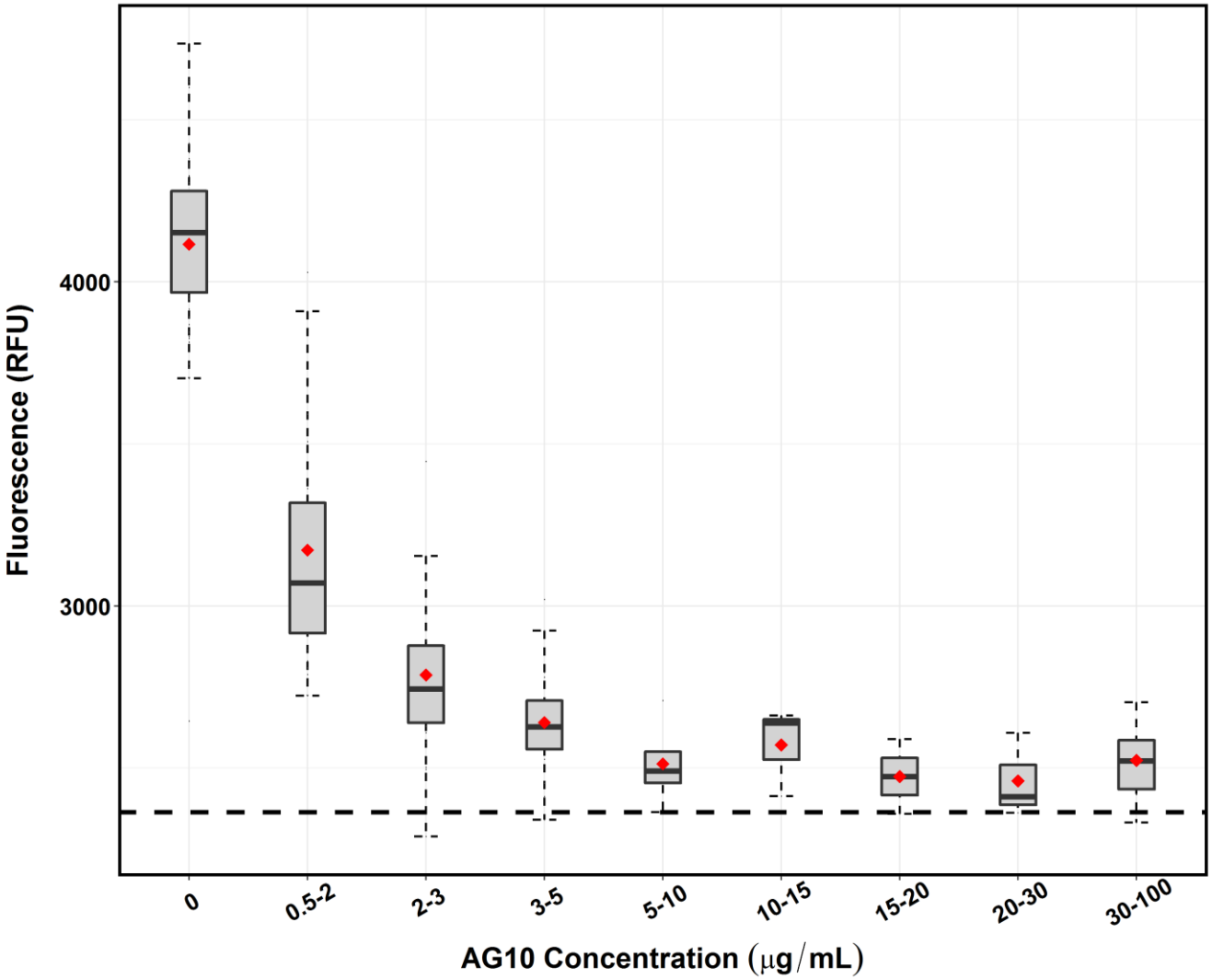
- AG10 binds to TTR at native ligand binding sites
- Fluorescence probe binding assay correlates to other measures of stabilization

Pharmacokinetics of Orally Dosed AG10



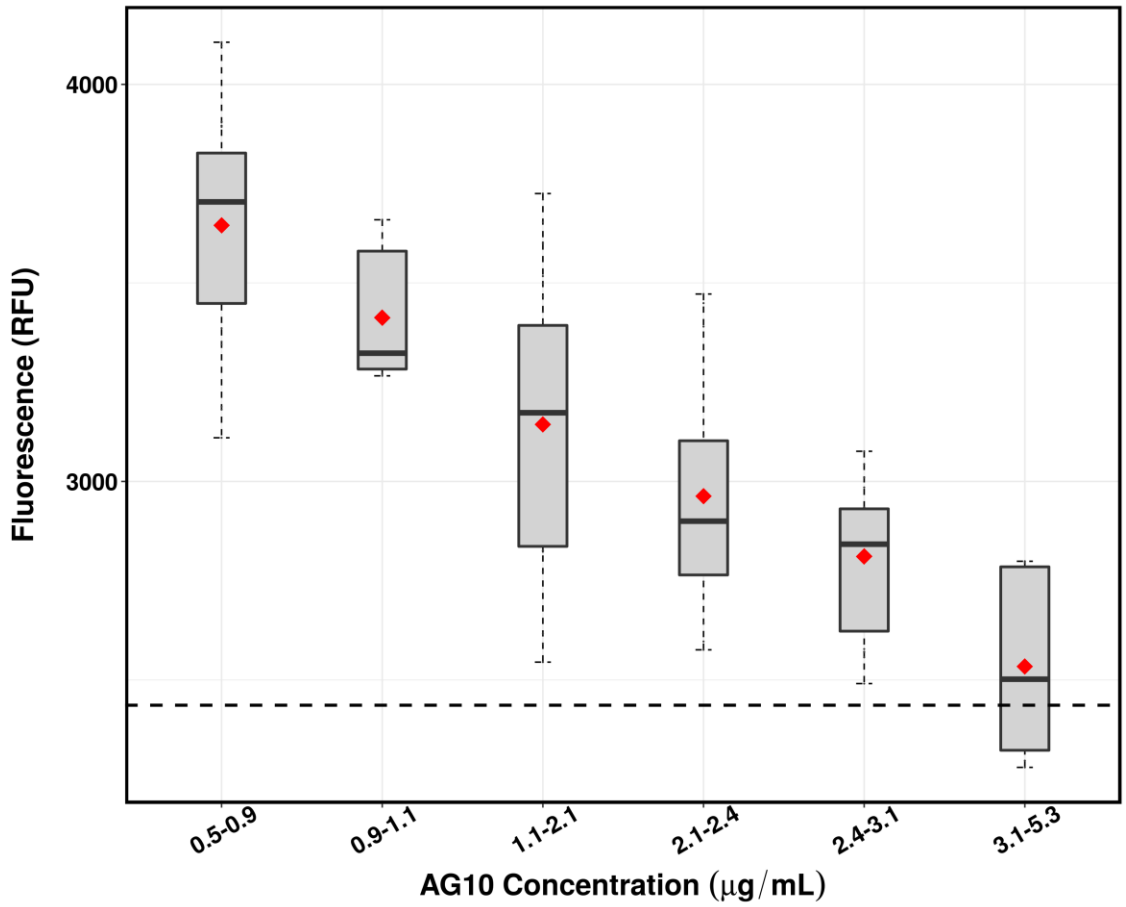
- Low systemic clearance and volume of distribution in all species tested
- Absolute oral bioavailability = 31% – 60 %

Orally administered AG10 effectively stabilizes TTR in Dogs



Dashed line = Background RFU
Line = Median, ♦ = Mean

AG10 effectively stabilizes TTR in Monkeys



Dashed line = Background RFU
Line = Median, ♦ = Mean

Summary

- AG10, a small molecule transthyretin stabilizer, targets disease at its source
  - TTR mutants with decreased stability predisposes patients to disease, whereas T119M TTR is stabilizing and protective
  - AG10 binding to TTR mimics structure of T119M variant
  - Animal PK shows consistent exposure across species
  - Dog and monkey PD measurements show dose-dependent TTR stabilization

- Phase 1 trial in healthy volunteers is in progress
  - Establish tolerability and PK profile
  - Measure TTR stabilization

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