Catalyst Biosciences

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Anti-Complement (C3) for Dry AMD

OIS@ASRS

8 August 2016

Anti-C3 Proteases for Dry AMD (GA)

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- Advantages of Protease versus Antibody or small molecule drugs
  - Catalytic versus Stoichiometric Mechanism of Action
    - Unlike stoichiometric drugs, proteases will maintain effective regulation at concentrations significantly below the target concentration
    - Enhanced duration of action expected to allow decreased dosing frequency
- Advantages of C3 as Target
  - C3 inhibition blocks all arms of the complement cascade and prevents formation of anaphylotoxins and other pro-inflammatory mediators as well as the membrane attack complex (MAC)

Catalyst Dry AMD (GA) Program

- Use proprietary selection/counter-selection technologies to create orthogonal anti-C3 leads based on two distinct human proteases (u-PA & MTSP-1)
- Target Product Profile
  - ≤ 6 mutations
  - C3 knockdown in vitreous ≥95% at 10 days and ≥75% at 20 days (equivalent to every two months in man) after single dose in cynomolgus monkeys
  - No ocular toxicity at efficacious dose (therapeutic index testing limit is 6-8 with current formulation)

Anti-C3 Dry AMD Program: Toxicity Study

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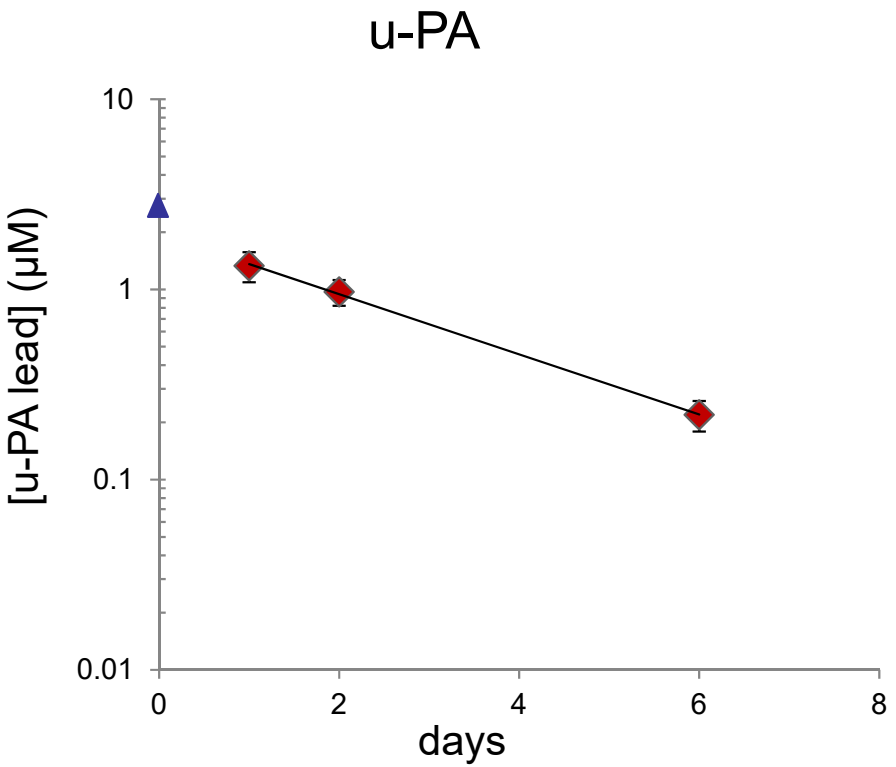
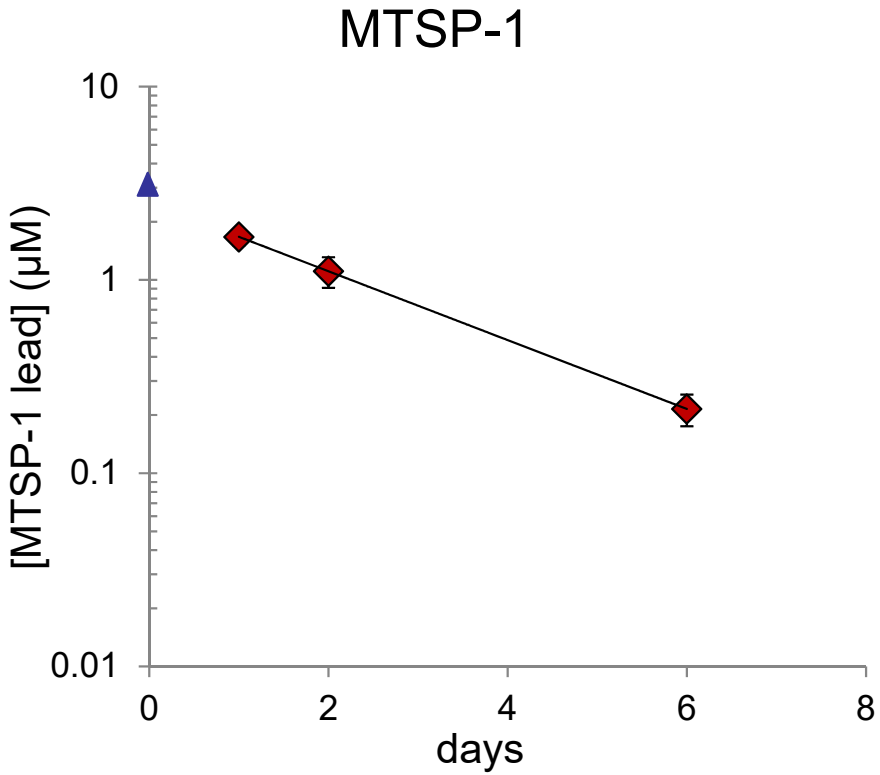
- Comprehensive, non-human primate single dose escalation ocular safety/toxicity study completed for advanced MTSP-1 & u-PA based leads
  - Three intravitreal doses (12.5, 37.5, or 125 µg/eye)
  - Right eye received test article; left eye injected with vehicle control
  - "Clinical observations", food consumption, *etc*.
  - Ophthalmic examinations: slit-lamp biomicroscopy and indirect ophthalmoscope observations, followed by color fundus photography or optical coherence tomography (OCT) prior to dosing and on days 2, 8, and 15 post-dosing
- No observations for one of two molecules tested for both u-PA and MTSP-1 based leads

Single Dose Cyno Ocular PK (vitreous)



▲ = predicted value for 100% in vivo recovery (2.5 µM)

$t_{1/2}$ = 1.9 days, 1.6 days
In vivo recovery = 78%, 73%



▲ = predicted value at 100% in vivo recovery (2.5 µM)

$t_{1/2}$ = 1.7 days, 1.7 days
In vivo recovery = 100%, 18%

Single Dose Cyno Ocular PD

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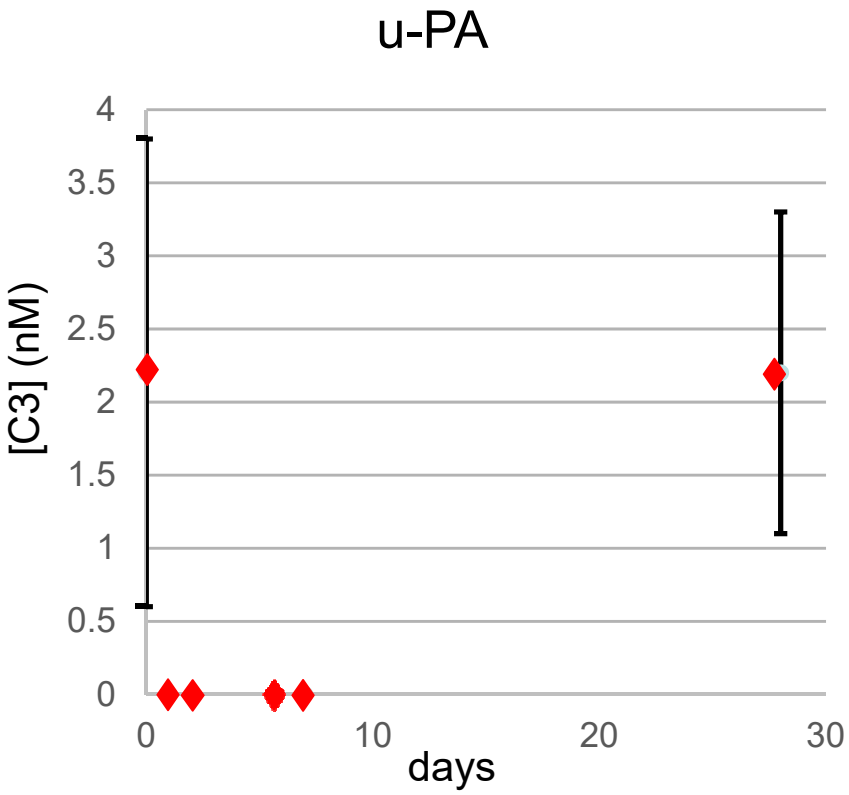
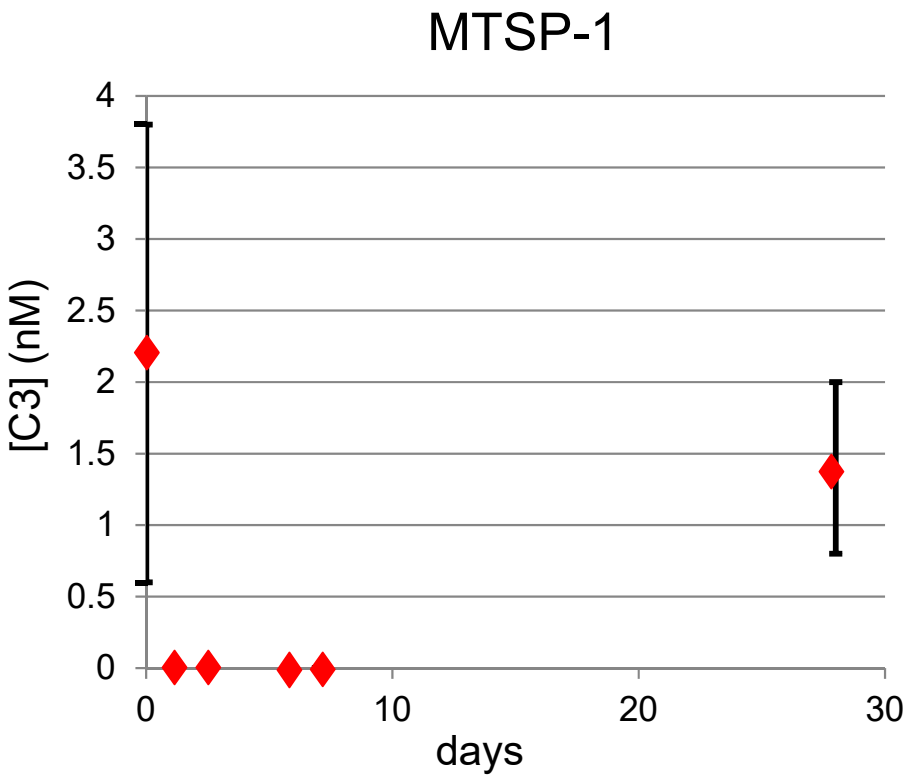
C3 levels in VH



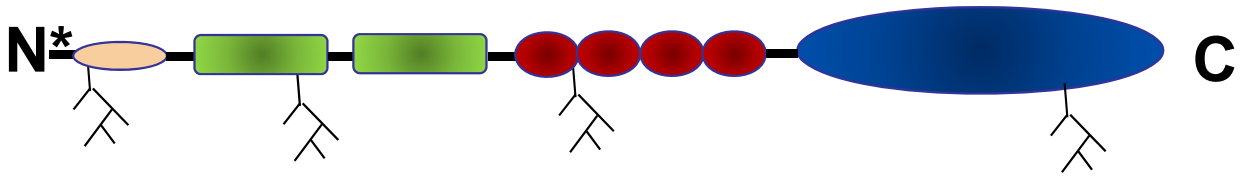


Results of two different experiments for each novel protease are plotted. Time points for experiment 1 were 0, 1, 2, and 6 days. Time points for experiment 2 were 0, 1, 7, and 28 days.

AMD Program Summary

- Catalyst anti-C3 leads are potent, stable, and well tolerated in a NHP model
  - Anti-complement leads inactivate ~5 to > 1100 human C3 molecules per hour
  - NOAEL in NHP model appears to be ≥ 125 µg for both current lead molecules (equivalent to ≥ 375 µg /eye in man)
  - 2 duration of action studies in NHP model suggest complete inhibition of C3 beyond 7 days post dosing but modest to no inhibition at 28 days (equivalent to 21 and 84 days in man)
- Catalyst anti-C3 leads expected to be differentiated from antibody and small molecule competitors
  - Catalytic turnover of target and pegylation or "full-length" protease constructs to improve PK expected to allow significantly less frequent dosing than isolated protease domains

WT MTSP-1
89kD



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