3rd Annual Complement-based Drug Development Summit 2019

CB 2782-PEG: a Complement Factor C3-Inactivating Protease and Potential Long-Acting Treatment for Dry AMD

Complement-based Drug Development Summit 2019

November 15th 2019

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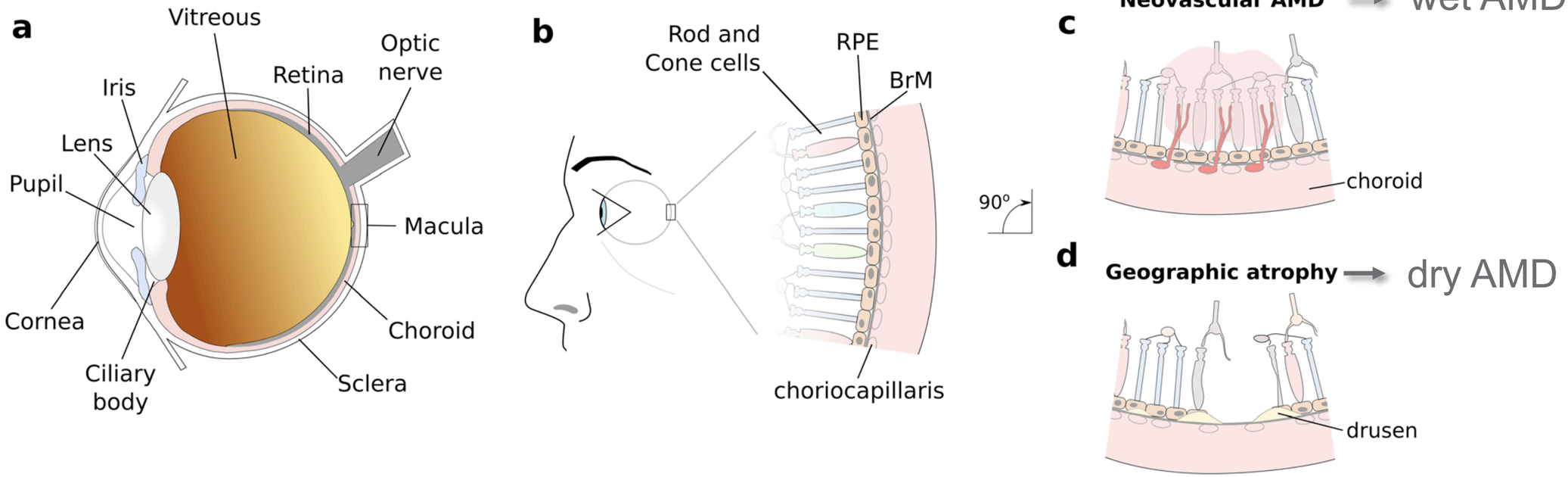
VP Translational Research

CATALYST BIOSCIENCES

Age-Related Macular Degeneration (AMD)

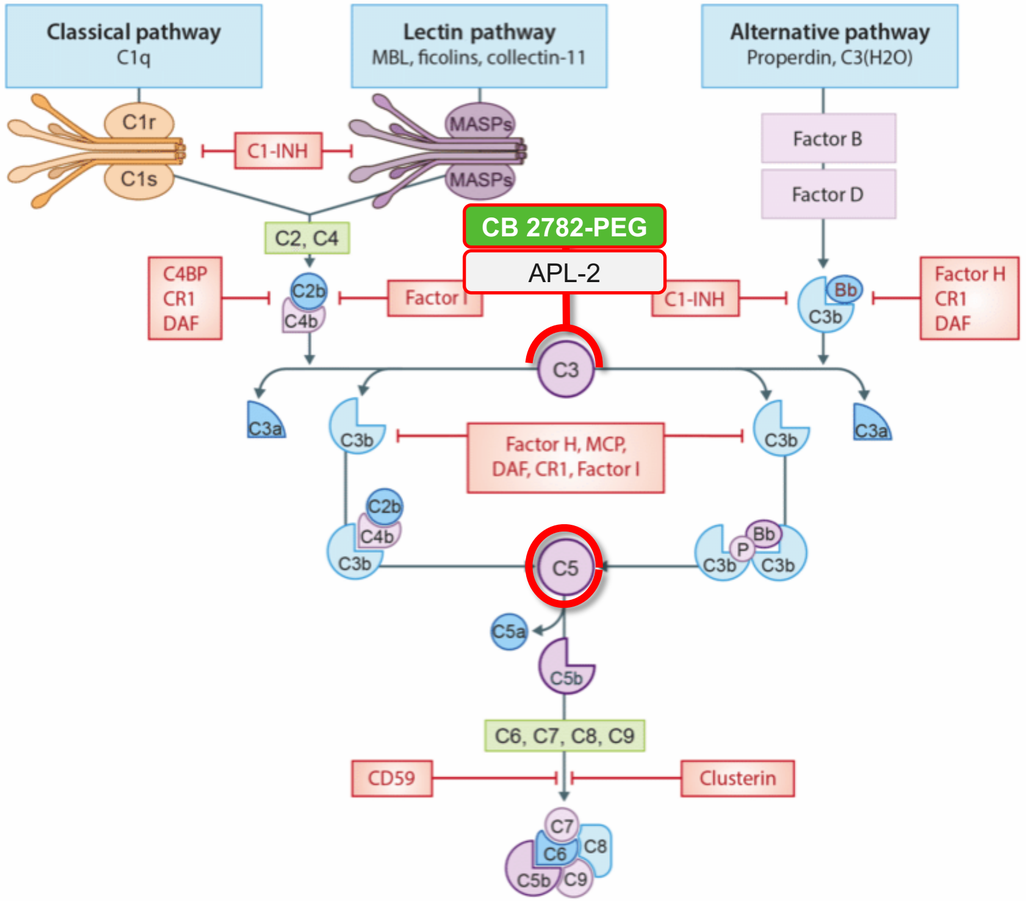


Clark and Bishop "The eye as a complement dysregulation hotspot" Semin Immunopathol (2018) 40:65–74

+ Wet and dry AMD are distinct diseases of which both **lead to vision loss and blindness**
+ Geographic atrophy (GA) results in progressive loss of photoreceptors and irreversible central vision loss
+ Unlike wet AMD, **no marketed treatment is available for dry AMD**

C3 is the best validated target for GA in dry AMD

Nasdaq: CBIO



Advanced dAMD, or geographic atrophy (GA), has a devastating impact on vision and leads to blindness

+ No currently approved therapies

C3 is the best clinically validated target in GA

+ Apellis - APL-2 (anti-C3 PEGylated peptide) completed P2

C5 targeting has shown 2 failures and 1 success in dAMD

+ Iveric - Zimura (avacincaptad pegol) - met primary endpoint
+ Novartis – LFG316 (IVT) – failed primary endpoint
+ Alexion – Soliris (IV) – failed primary endpoint

Proteases provide superiority to peptides or antibodies

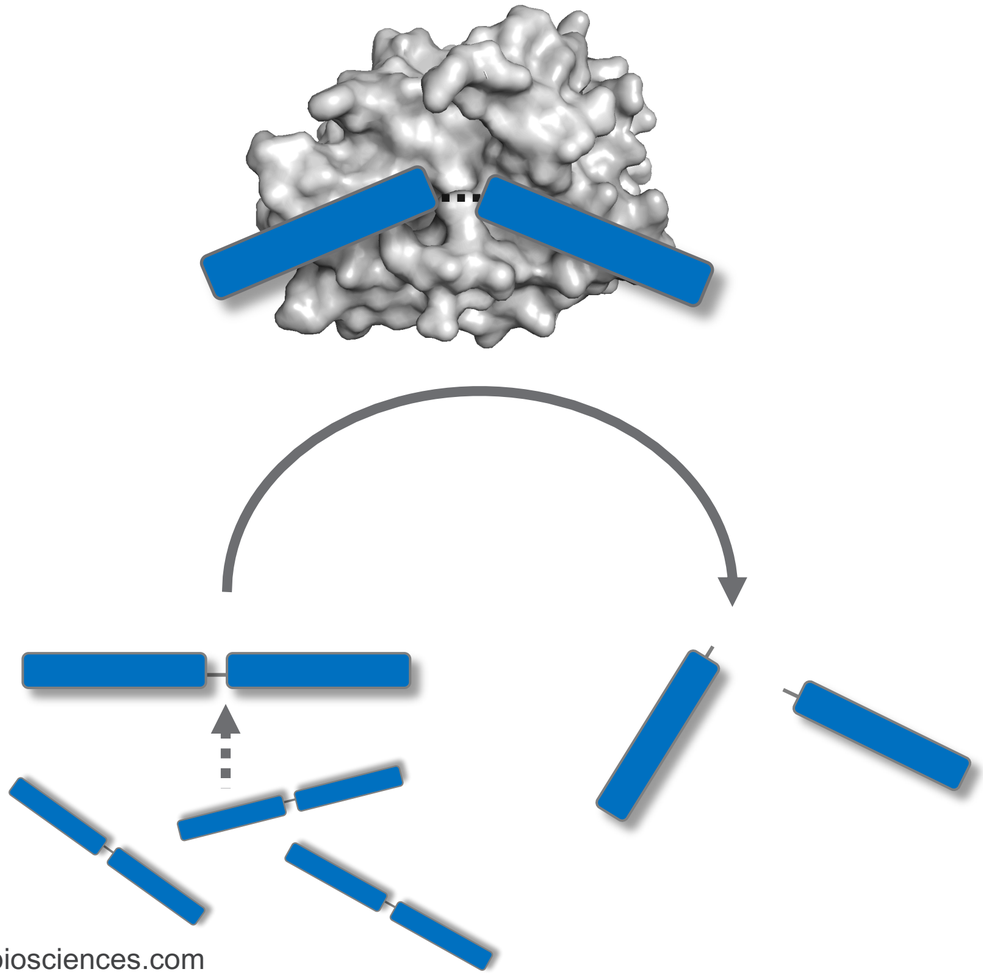
+ Sub-stoichiometric dosing and a catalytic mechanism
+ **Potential best-in-class anti-C3 therapeutic**
+ **Q3mo or Q4mo dosing**

Catalytic inhibition is superior to stoichiometric inhibition

Nasdaq: CBIO

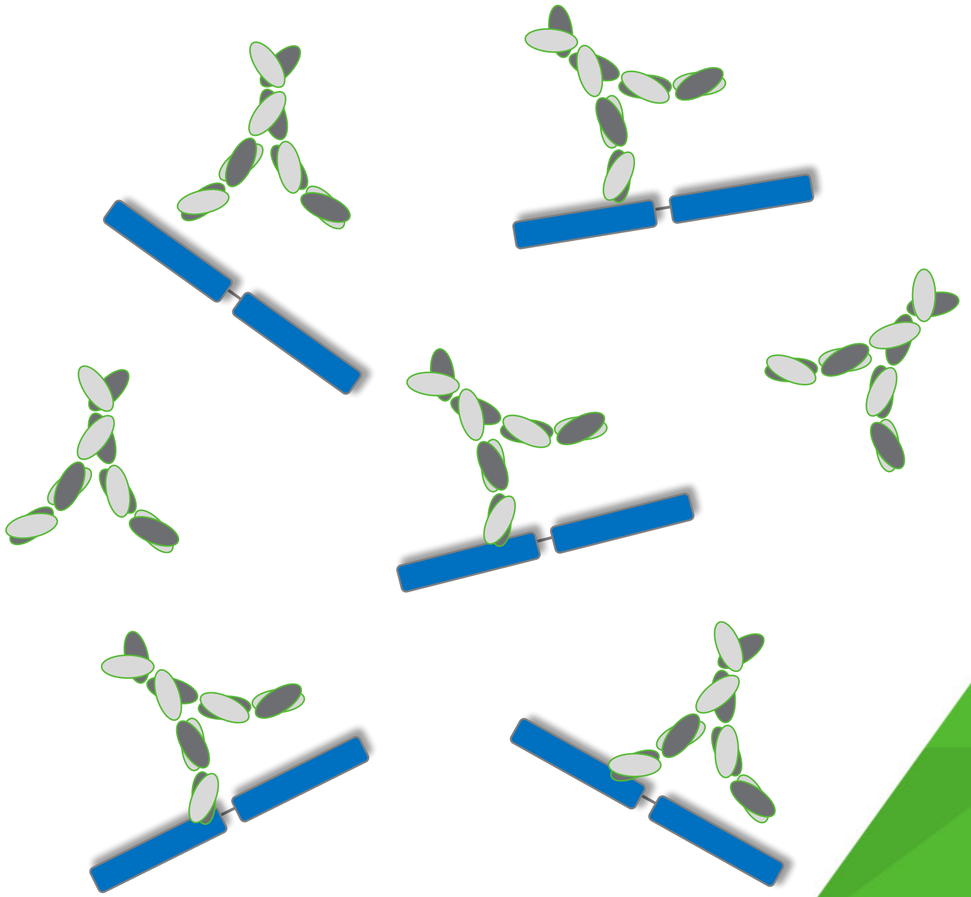
Catalytic Inhibition

1 protease inhibits 1000s of target molecules



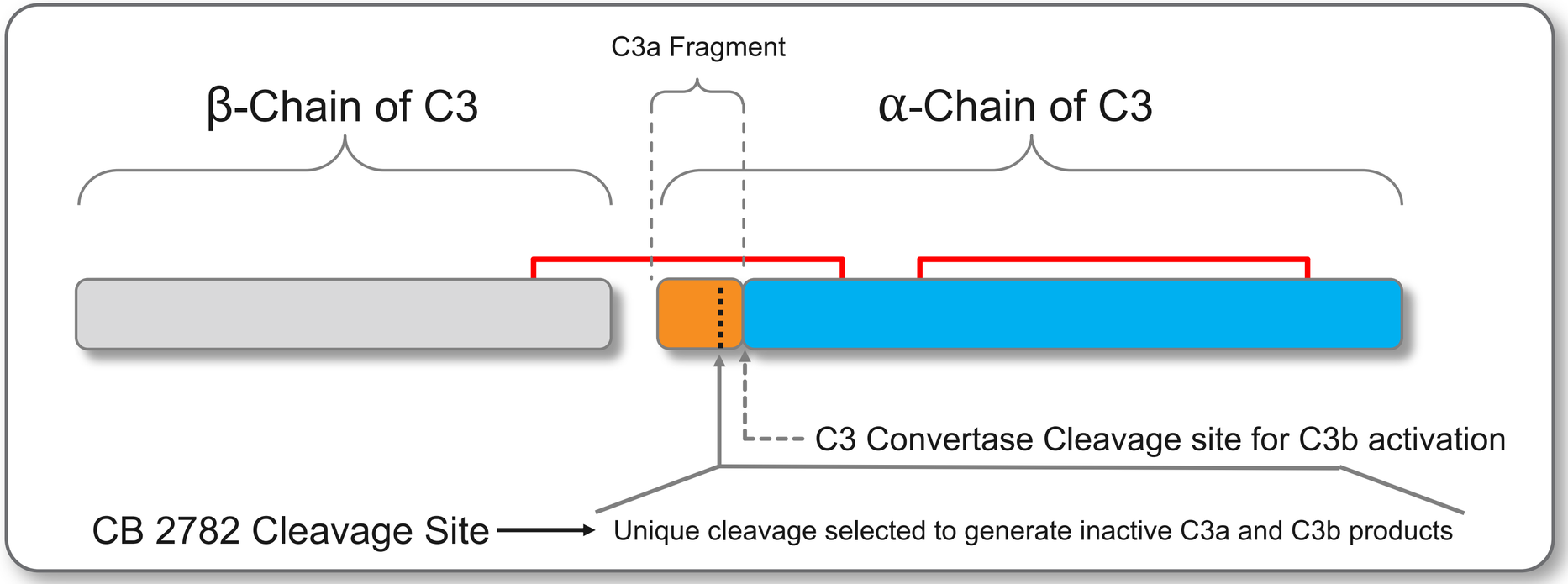
Stoichiometric Inhibition

≥ 1000s binders inhibits 1000s of target molecules



Selection of a specific “inactivating” cleavage site

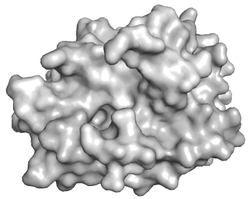
Schematic of C3 structure and the C3 convertase cleavage site



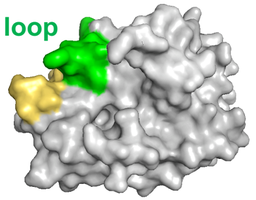
- CB 2782 was engineered to specifically cleave a single site in C3
  - Divergent from that which is cleaved by the C3 convertases
- Cleavage of C3 results in an inactive C3a and C3b-related species
  - Cannot be further activated by the C3 convertases

Molecular evolution of CB 2782 for C3-specific cleavage

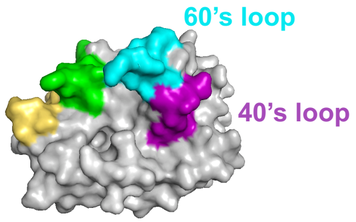
Nasdaq: CBIO



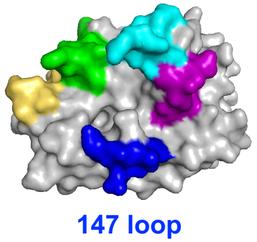
MTSP-1



CB 2013



CB 2426



CB 2470

CB 2782
(lead candidate)

Select ⇧ Catalysis

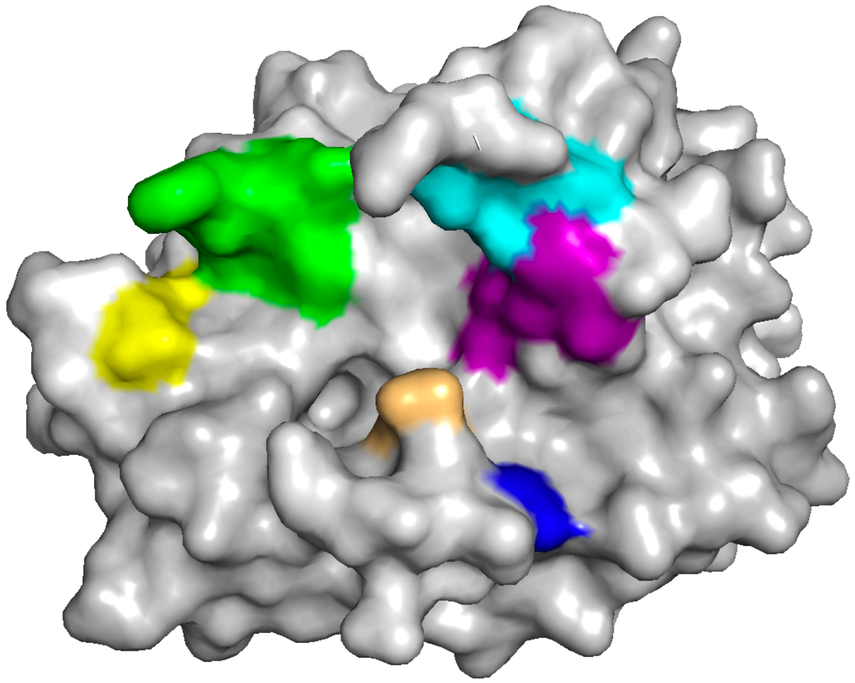
Human Plasma
(counter selection)

Antithrombin (AT)
(counterselection)

Directed Engineering

α_2-Macroglobulin
(counterselection)

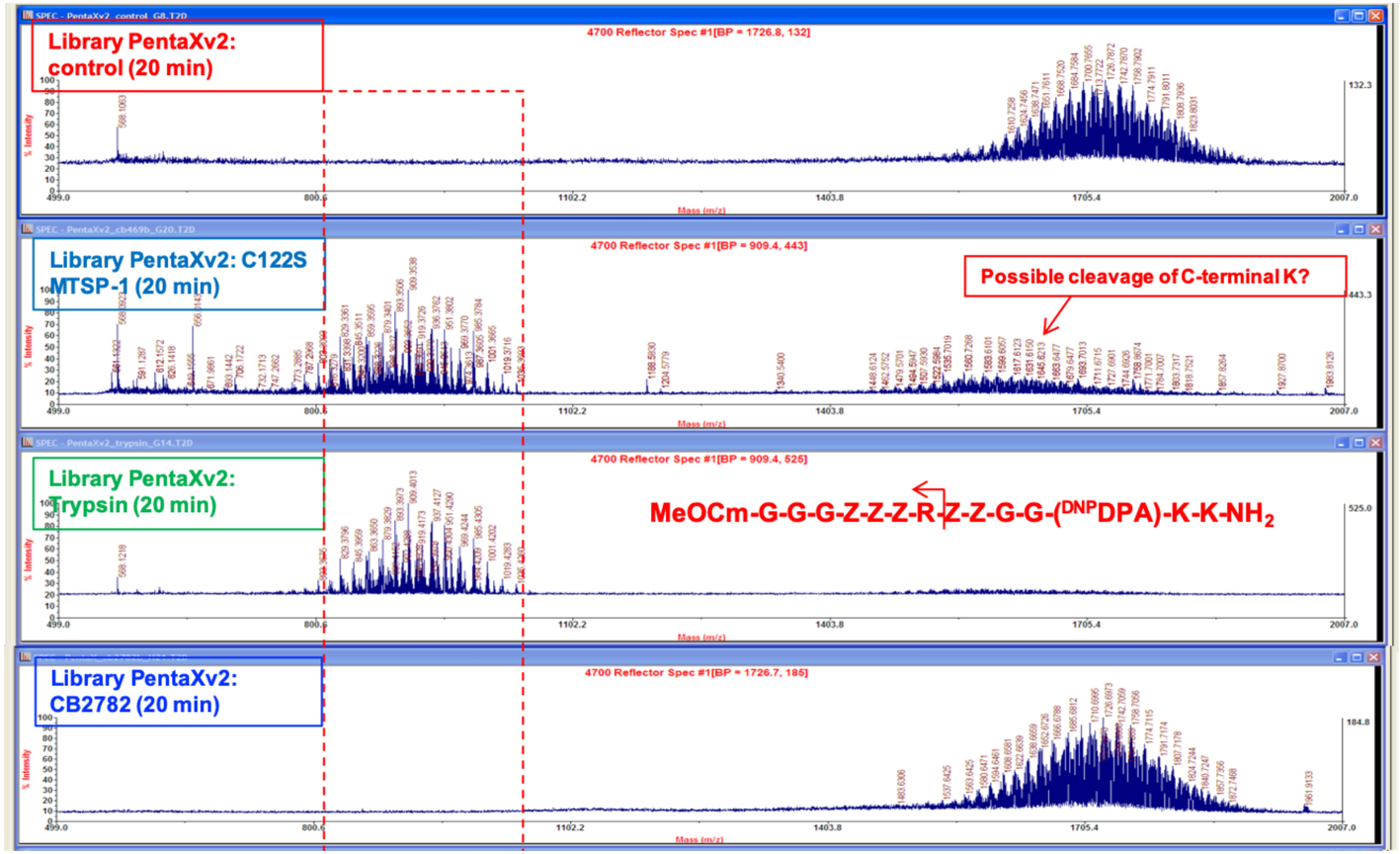
Evolved Candidate



CB 2782

CB 2782 shows high specificity

Nasdaq: CBIO



Cleavage of PentaXv2 Library

P_4 P_3 P_2 P_1 $P_{1'}$ $P_{2'}$

▲-G - G - G - Y – Y – Y – R – Y – Y - G - G - ■ - K - K - NH_2

Y Any of 18 AAs (excluding R, C)

▲ N-terminal 7-methoxycoumarin-4-acetyl

■ dinitrophenyl-diaminopropyl

 # Peptides

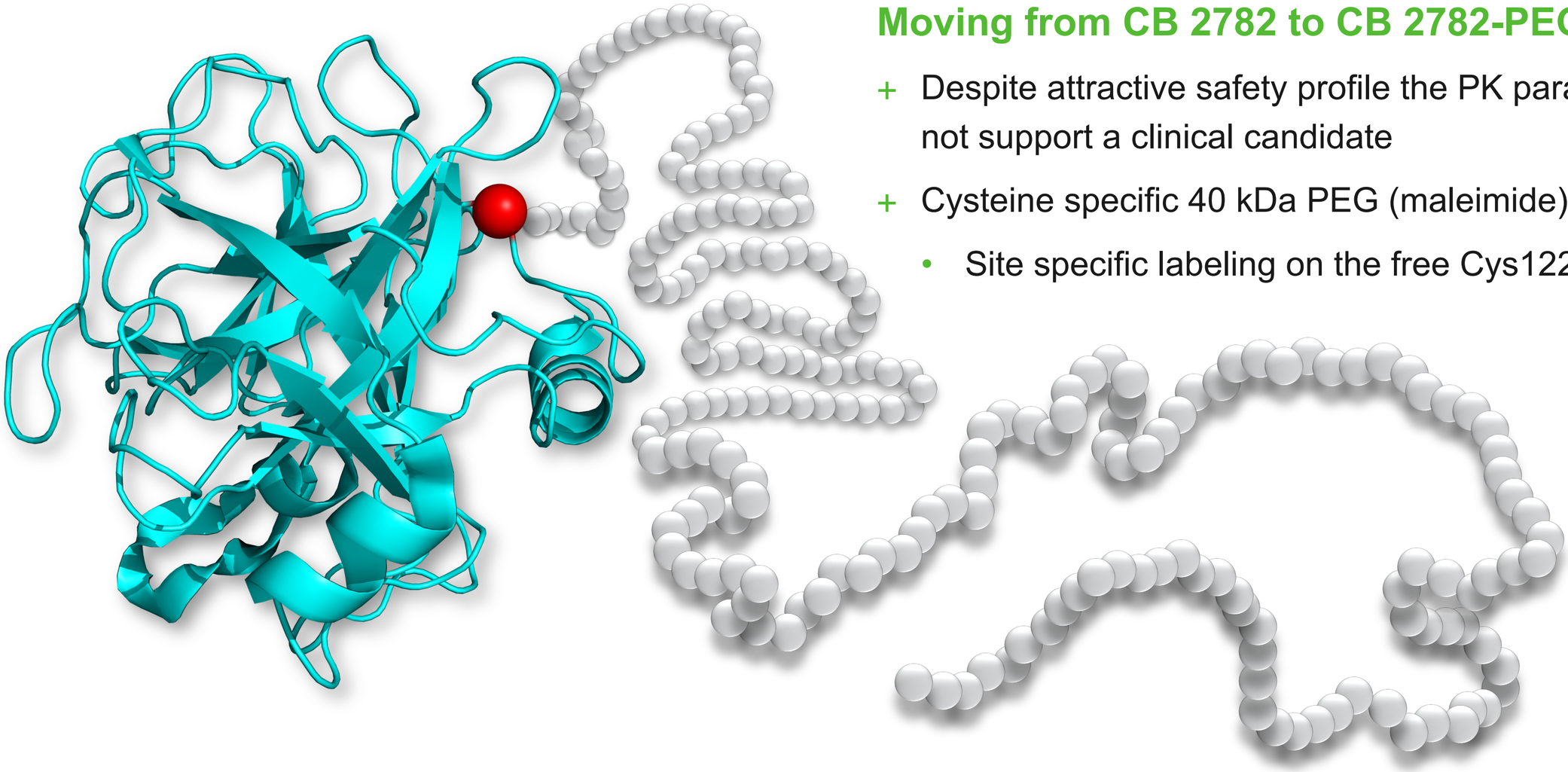
1,889,568 (18^5)

+ Essentially no detectable cleavage of the PentaXv2 library by CB 2782
+ Near complete cleavage by MTSP-1
+ Complete cleavage by trypsin

Development Candidate CB 2782-PEG

Nasdaq: CBIO

Mosaic Biosciences



Moving from CB 2782 to CB 2782-PEG

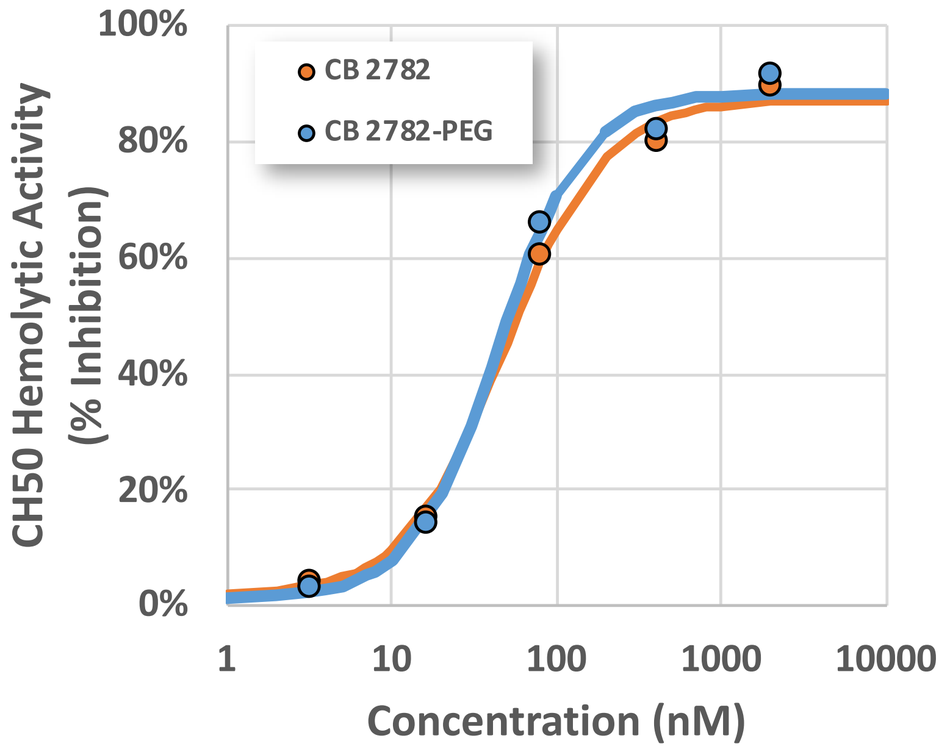
+ Despite attractive safety profile the PK parameters did not support a clinical candidate
+ Cysteine specific 40 kDa PEG (maleimide) conjugated
  - Site specific labeling on the free Cys122

CB 2782-PEG has indistinguishable activity *vs* CB 2782

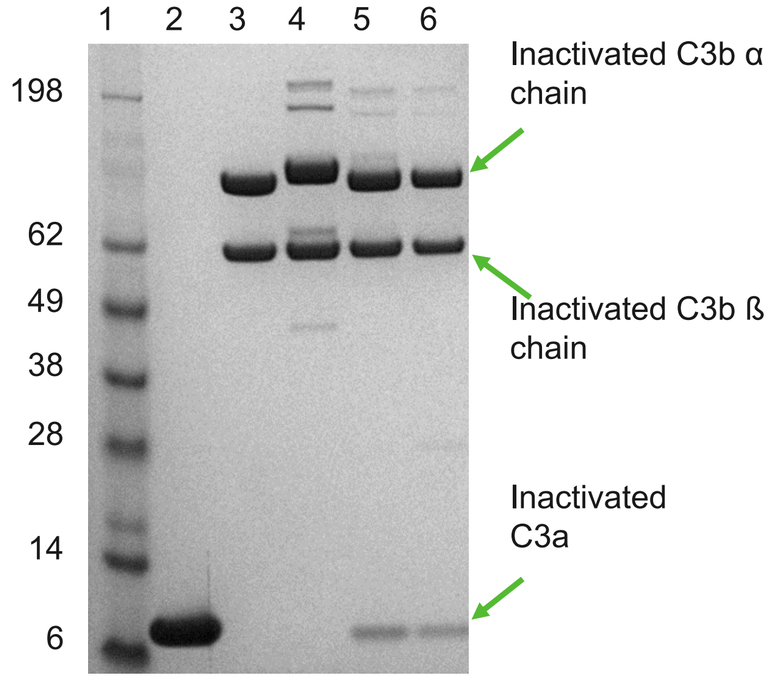
Nasdaq: CBIO

Mosaic Biosciences

CB 2782 and CB 2782-PEG inhibit complement-mediated hemolysis *in vitro*



Sub-stoichiometric CB 2782 and CB 2782-PEG specifically cleave C3 at a single site into inactive fragments

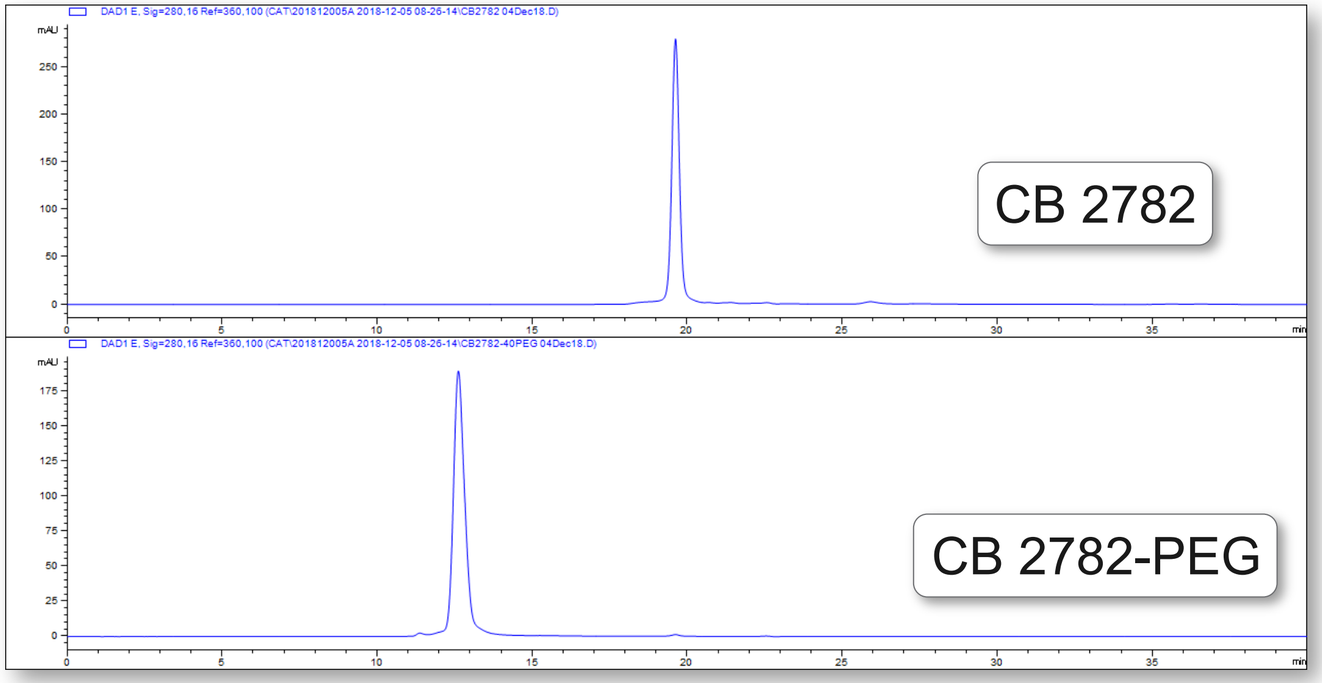


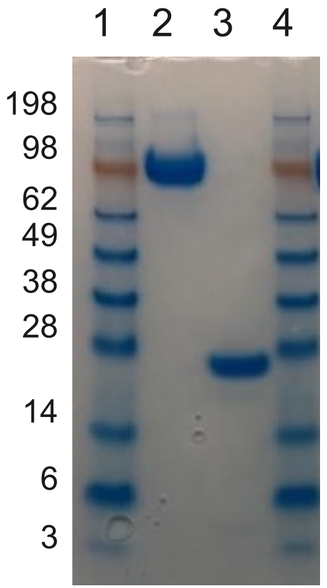
Reduced SDS-PAGE	
Lane	Sample
1	Ladder
2	C3a
3	C3b
4	C3
5	2 µM C3 treated with 0.2 µM CB 2782-PEG
6	2 µM C3 treated with 0.2 µM CB 2782

CB 2782-PEG retains full activity and is highly pure (>95%)

Nasdaq: CBIO

Mosaic Biosciences





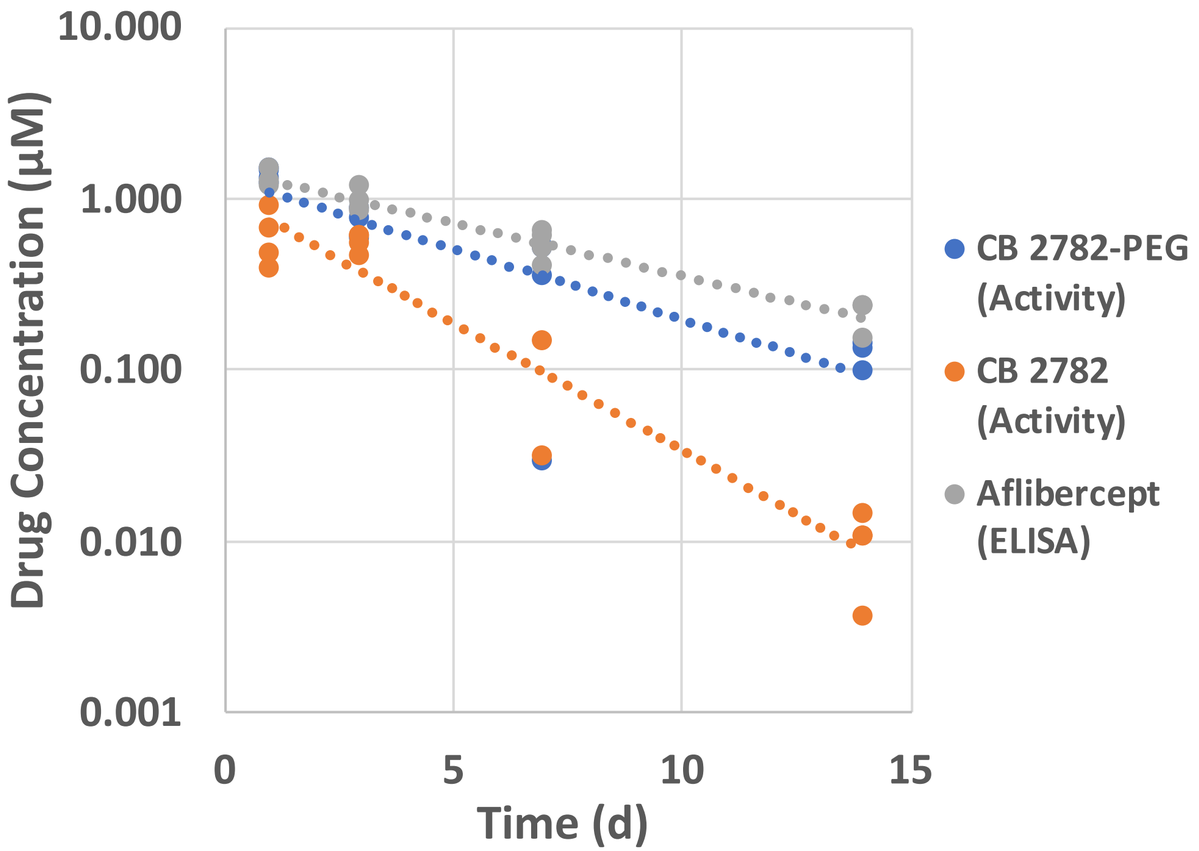
Lane	Sample
1	Ladder
2	CB 2782-PEG
3	CB 2782
4	Ladder

CB 2782-PEG has ~2x increased half-life in rabbits

Nasdaq: CBIO

Mosaic Biosciences

Rabbit IVT Pharmacokinetics



Parameter	CB 2782-PEG	CB 2782	Aflibercept
t-half-terminal (d)	3.85	1.90	4.82
Mean residence time (d)	5.63	3.21	7.24
Cmax (µM)	1.52	0.90	1.52
Tmax (d)	1	1	1
AUC 0-inf (µM-d)	7.79	3.14	9.66
AUC 0-t (µM-d)	7.07	3.12	8.06

CB 2782-PEG eliminates vitreous C3 in NHPs

Nasdaq: CBIO

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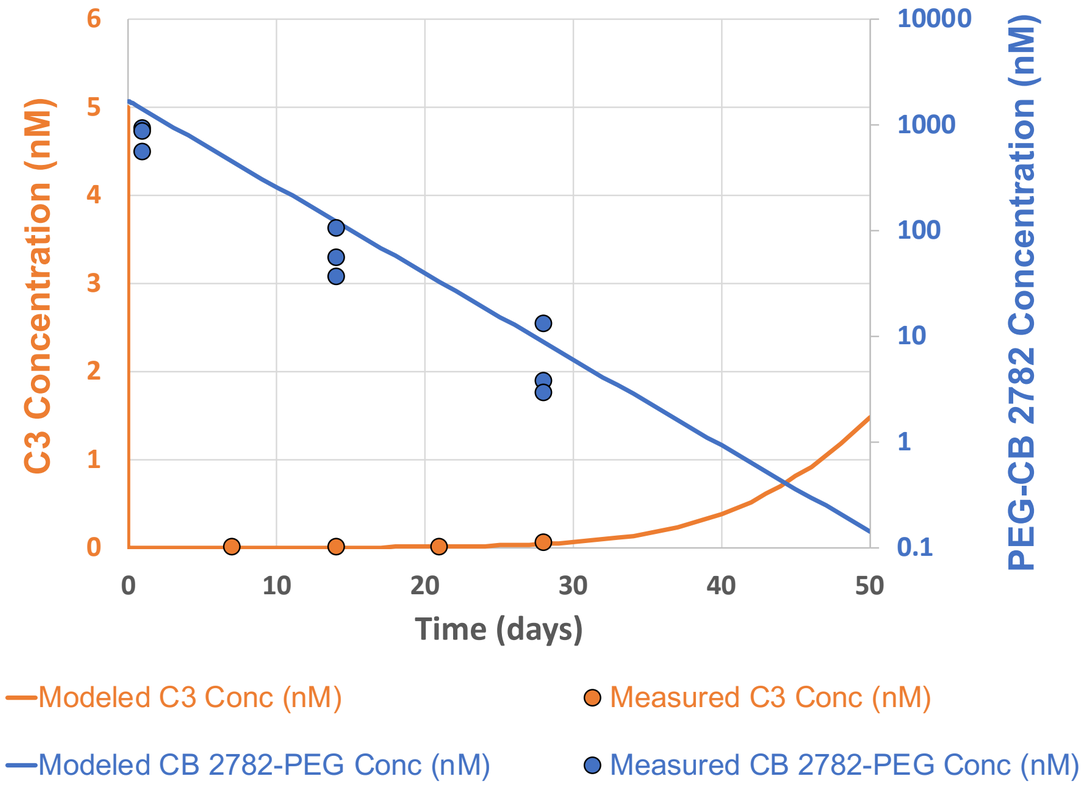
Intravitreal CB 2782-PEG has a half-life of 3.7 days and eliminates at least 99% of C3 in vitreous humor of African green monkeys for at least 28 days



Parameter	CB 2782-PEG
t-half-terminal (d)	3.7
Mean residence time (d)	3.37
Cmax (µM)	0.90
Tmax (d)	1
AUC 0-inf (µM-d)	6.94
AUC 0-t (µM-d)	6.92

Predicted 2.0 mg human dose three to four times a year

Nasdaq: CBIO

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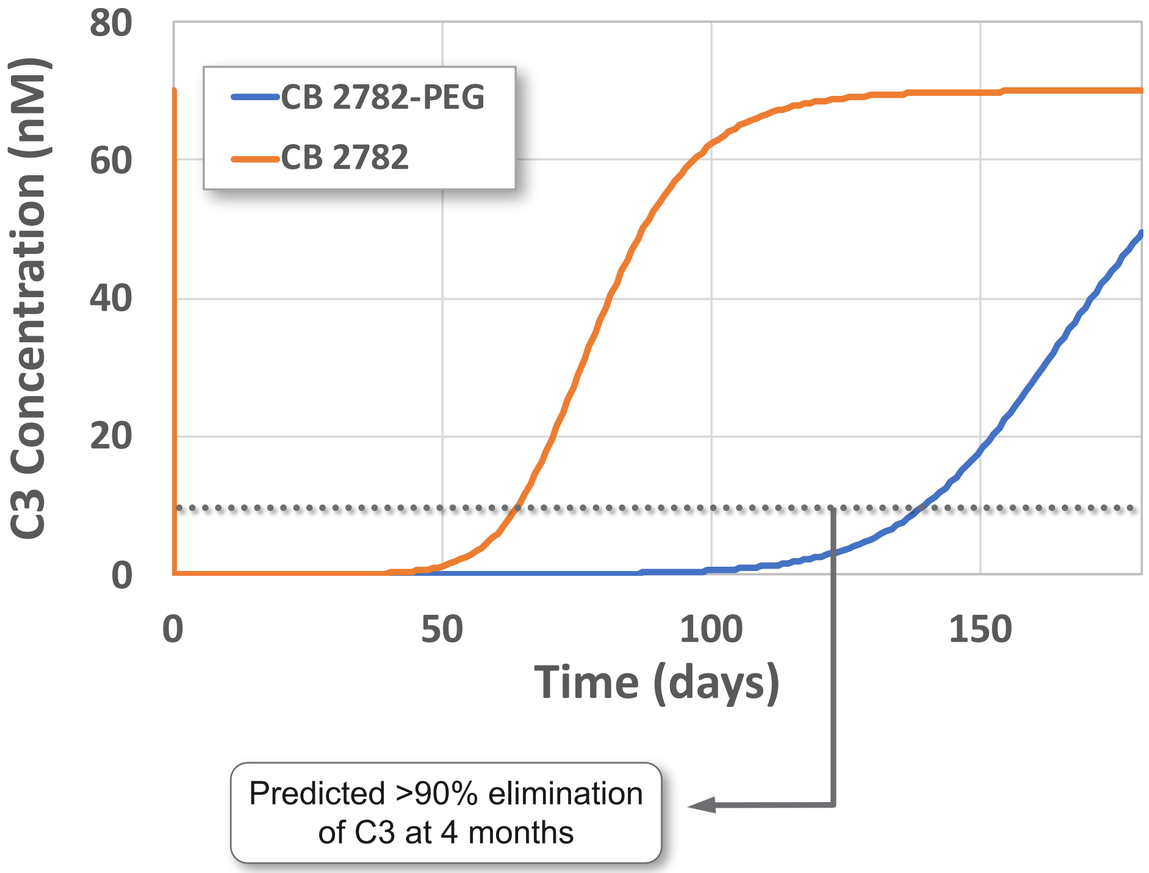
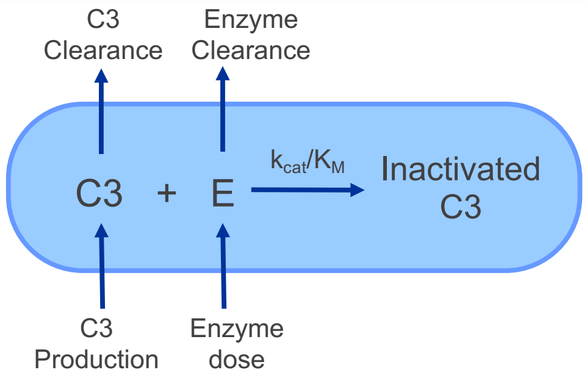
Enzyme Model: Fit to observed primate PK/PD data and scaled to the human condition



Model Parameter	African Green Monkey		Human	
	Value	Source	Value	Source
Vitreous Volume (mL)	3.0	Measured	4.4	Literature
C3 Steady State Conc (nM)	5.0	Measured	70	Literature
C3 Vitreous Half-Life (d)	4.4	Literature	8.2	Literature
Enzyme Dose (mg)	0.125	Known	2.0	Known
Enzyme Half-Life (d)	3.7	Measured	8.5	2.3X scaling from AGM to human
Enzyme k_{cat}/K_M ($nM^{-1}d^{-1}$)	1.88	Fit	1.88	AGM Model



Summary & conclusions

- Engineered novel specificity through molecular evolution and rational design
- Significantly improved catalysis and stability in a biological milieu
- Intravitreal injection resulted in at least 99% elimination of C3 for at least 28 days in monkeys that translates to >90 days in humans
- CB 2782-PEG has potential for best-in-class efficacy and convenience in dry AMD

Acknowledgements

CATALYST BIOSCIENCES

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