A long-acting anti-VEGF biologic in development for durable wet AMD treatment

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*Employees of Valitor with financial interests in Valitor, Inc.

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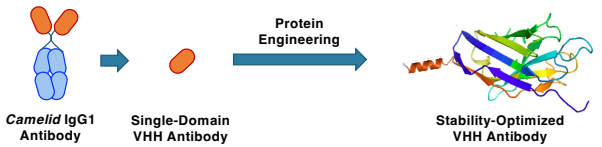
Introduction

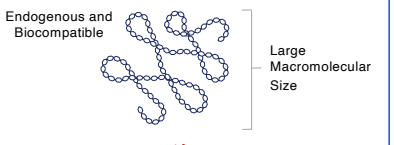
- Anti-VEGF biologics continue to be the gold standard treatment for neovascular ocular disease, including wet age-related macular degeneration (AMD)
- Current anti-VEGF biologics require frequent intravitreal (ITV) injections and/or inconsistent patient-to-patient dosing protocols, leading to poor compliance and losses in efficacy over the long-term[1]
- Valitor has developed a multivalent polymer (MVP) technology to enable sustained anti-VEGF therapy after ITV injection,[2] thereby substantially reducing the required treatment frequency compared to current treatments
- VLTR-557 is our product candidate to treat wet AMD:

We developed a proprietary anti-VEGF single-domain antibody that was engineered for *in vivo* stability

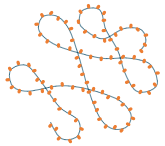


Covalent conjugation

We selected hyaluronic acid as the biopolymer for multivalent conjugation:



VLTR-557



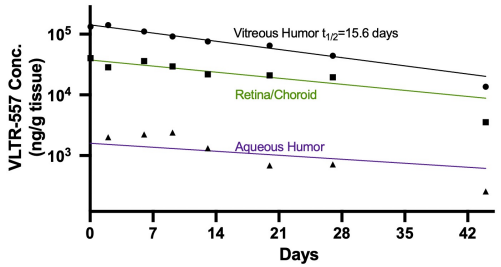
Engineered for Reliable Durability

Project Objectives:

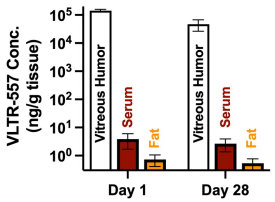
1) Verify the PK profile of VLTR-557 to provide highly-localized and sustained drug exposure to ocular tissues
2) Confirm the anti-VEGF bioactivity of VLTR-557
3) Establish an initial safety profile for VLTR-557 based on NHP subjects

VLTR-557: Pharmacokinetics Overview

The ocular and systemic tissue distribution of VLTR-557 after ITV injection was measured using ^{125}I-radiolabeling in Dutch belted rabbits:

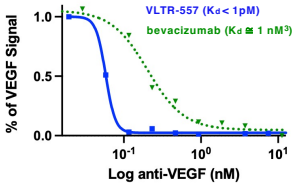


- The half-life of VLTR-557 in the vitreous humor was 15.6 days, and its half-life in the other ocular tissues was approximately the same
- The retina/choroid tissues had the second highest concentration of VLTR-557, which was approximately one third of the concentration in the vitreous humor
- The serum concentration of VLTR-557 was approximately 10,000X lower than the vitreous humor concentration
- Changes in VLTR-557 concentration in systemic tissues were similar to those in the serum-level concentrations

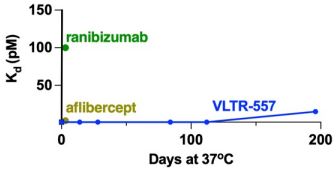


VLTR-557: Pharmacodynamics Overview

VEGF signaling inhibition by VLTR-557 was measured using the DiscoverX Pathfinder assay, and bevacizumab was included as a positive control:



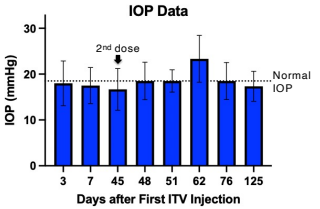
ITV stability of VLTR-557 was assessed under physiological conditions,[4] and its binding affinity (K_d) was compared to that of licensed anti-VEGF products at baseline K_d:

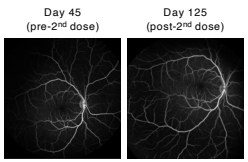


- VLTR-557 exhibited high binding affinity to VEGF-A, which has been confirmed by biolayer interferometry (BLI), surface plasmon resonance (SPR), and kinetic exclusion assay (KinExA), resulting in rapid attenuation of VEGF signaling *in vitro*
- VLTR-557 remained stable for 6 months under physiological conditions and exhibited high binding affinity

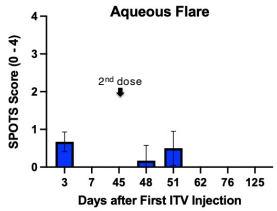
VLTR-557: Safety Overview

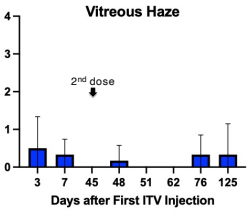
The incidence and severity of adverse events to VLTR-557 was determined using cynomolgus NHPs in a two-dose toxicity study:





Fluorescein angiography indicated normal retinal vessel architecture before and after the second dose

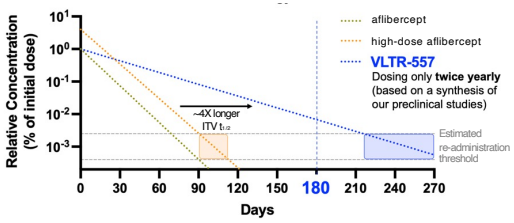




- The pilot formulations of VLTR-557 appeared to be tolerated in NHPs (n=3), with minor adverse events occurring within 7 days of dosing and well below the level that would be considered a clinical adverse event

Conclusions and Clinical Significance

Using a clinical pharmacology model and published preclinical data, we can estimate the intravitreal durability of VLTR-557:



- Based on our preclinical data, we anticipate VLTR-557 will maintain clinical efficacy for greater than 6 months with a single ITV administration
- We are continuing to develop VLTR-557 as a treatment for wet AMD with the goal of providing durable treatment and a standardized 6-month administration frequency for every patient

Acknowledgements

National Eye Institute

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R43EY027229 and R43EY032414

The clinical pharmacology model was developed with assistance from Jacques Gaudreault, PhD

References

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3. *Nat Rev.* 2004;3:391.
4. *Clin Exp Ophthalmol.* 2016;44:597

A long-acting anti-TNFα treatment for posterior chronic non-infectious uveitis (NIU)

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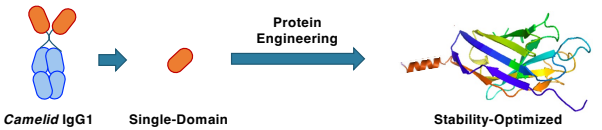
Introduction

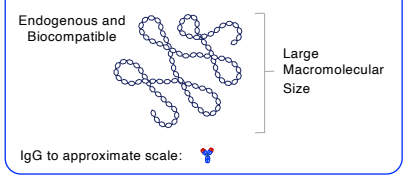
- Posterior chronic non-infectious uveitis (NIU) puts patients at high risk for vision loss. There is a clear and unmet need for an effective and durable treatment.[1]
- Intravitreal (ITV) administration of biologic TNFα inhibitors have the potential to substantially reduce the need for corticosteroids, which have serious side effects.[2]
- Valitor has developed a multivalent polymer (MVP) technology to enable sustained therapy using a biologic after ITV injection.
- We are developing a product candidate to treat NIU with a projected treatment frequency of only 2-3 times per year as a steroid-sparing treatment for NIU.[3-5]

We developed a proprietary anti-TNFα single-domain antibody that was engineered for *in vivo* stability

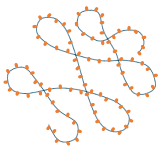


Covalent conjugation to:

We selected hyaluronic acid as the biopolymer for multivalent conjugation:



Anti-TNFα MVP:



Engineered for Reliable Durability

Project Objectives:

1) Confirm the pharmacodynamics of an anti-TNFα MVP in a rat model
2) Verify the PK profile of MVP therapeutics to provide highly-localized and sustained drug exposure to ocular tissues in a rabbit model
3) Optimize an anti-human TNFα antibody for optimal stability and conjugation compatibility

Acknowledgements

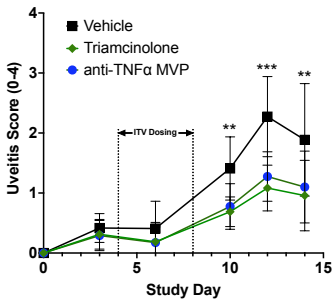
NIH National Eye Institute

R43EY027229 and R43EY032414

Research reported in this study was supported by NEI and NIAMS of the National Institutes of Health under the above listed awards. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Anti-TNFα MVP Pharmacodynamics in Rat EAU Model

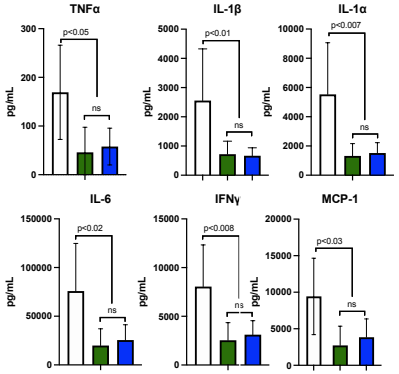
After intravitreal injection in rats, Anti-TNFα MVPs suppressed symptoms of ocular inflammation comparable to triamcinolone.



- We evaluated Anti-TNFα MVPs using an experimental rat model of autoimmune uveitis[6] (EAU).
- 19 µg of Anti-TNFα MVP, 40 µg of triamcinolone and vehicle were delivered via ITV injections on study days 4 and 8.
- Anti-TNFα MVP and triamcinolone were both effective to significantly suppress ocular inflammation compared to vehicle treated eyes (ANOVA with n=24 eyes/group).

Anti-TNFα MVP Cytokine Regulation in Rat EAU Model

Inflammatory cytokine expression was suppressed after intravitreal administration of Anti-TNFα MVPs and triamcinolone

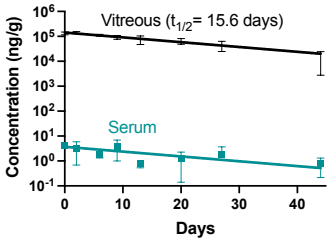


- The rat vitreous humor was analyzed using a Milliplex® cytokine magnetic bead panel.
- Both Anti-TNFα MVPs and triamcinolone significantly decreased the protein-level expression of inflammatory cytokines compared to the vehicle treated eyes (ANOVA with n=12 eyes/group).

Vehicle
Triamcinolone
Anti-TNFα MVP

MVP Pharmacokinetics Overview

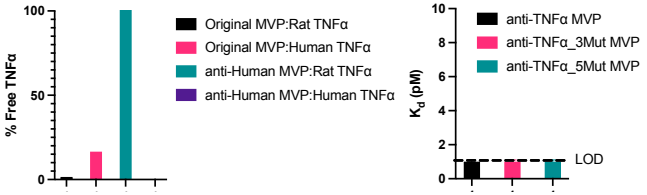
After intravitreal injection in rabbits, MVP conjugates have extended ocular durability and limited systemic exposure



- The half-life of MVPs in vitreous humor was 15.6 days (n=6 eyes/time point). The serum concentration was approximately 10,000X lower than in vitreous humor.
- The anticipated serum concentration of Anti-TNFα MVPs would be approximately 1,000X lower than adalimumab when it is administered systemically to treat uveitis.[7]

Anti-TNFα Antibody Optimization

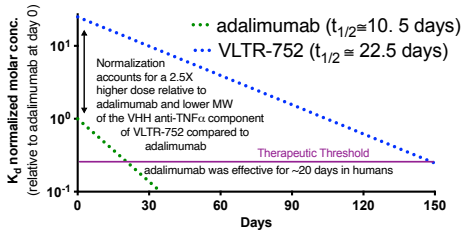
We optimized an anti-TNFα VHH antibody that was reactive to human TNFα for the development of a clinical therapy



- Based on biolayer interferometry (BLI), our original Anti-TNFα MVP effectively blocked rat TNFα from binding TNFR1.
- The anti-human TNFα MVP effectively blocked human TNFα binding to TNFR1 but is not effective against rat TNFα.
- The anti-Human TNFα MVP and optimized mutants exhibited high binding affinity to human TNFα via BLI, resulting in rapid attenuation of TNF signaling *in vitro*.

Conclusions and Clinical Significance

Using a clinical pharmacology model and published preclinical data, we can estimate the intravitreal durability of Anti-TNFα MVPs:



- We are preparing to advance an IND-candidate (VLTR-752) as a treatment for posterior uveitis as strategy to minimize the side-effects of systemic steroids/anti-TNFα therapies or adverse effects due to intravitreal steroid therapy.[2]
- The lower serum concentration of anti-TNFα from intravitreal VLTR-752 will likely lead to a better safety profile compared to current systemic or intravitreal therapeutics that have been approved to treat uveitis.
- Based on our preclinical PD and PK data, optimized anti-TNFα MVP conjugates could enable sustained efficacy after ITV injection with a projected treatment frequency of only 2-3 times per year as a steroid-sparing treatment for NIU.
- A study to assess the durable efficacy of VLTR-752 will be starting May 2023.

References

The EAU study was performed with support from Natalie Finch, Dr. Laura Belen and other personnel at Biomere Biomedical.
The cytokine analysis was performed with support from David Gerard and Dr. Jeffery Borgia at Rush University.
The PK study was performed with support from Nathan Nicholas and other personnel at Charles River Laboratories.

1. *Acta Ophthalmol.* 2018;96(6):e665-e675
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