#297

Next Generation TED Therapy in Clinical Development

VRDN-001, a Full Antagonist Antibody to IGF-1R in Development for Thyroid Eye Disease (TED), Binds to a Distinct Epitope from Teprotumumab

Yang Zhao, Jordan Tsai, Rachel Newell, Vahe Bedian | Viridian Therapeutics Inc, Waltham, MA

KEY TAKEAWAYS

Results from in vitro assays demonstrate the unique binding epitope and functional characteristics of **VRDN-001**:

- Similar binding site to teprotumumab, but does not exhibit sensitivity to certain mutations in IGF-1 binding region, while teprotumumab does
- More completely inhibits IGF-1 binding and IGF-1R signaling (phosphorylation of IGF-1R and AKT) than teprotumumab

These findings may explain the favorable results of **VRDN-001** in the phase 1/2 TED proof-of-concept trial (NANOS Platform Session II) and support the ongoing THRIVE phase 3 trial (NCT05176639, Poster #296).

INTRODUCTION

- Clinical and preclinical studies have confirmed IGF-1R antagonism reduces the inflammation and proptosis that occur in TED.[1-3]
- **VRDN-001**, a full antagonist antibody to IGF-1R, is under development for the treatment of TED.
- As different anti-IGF-1R antibodies may have distinct characteristics, we compared the binding epitope and in vitro antagonist properties of the IGF-1R antibody **VRDN-001** with teprotumumab.

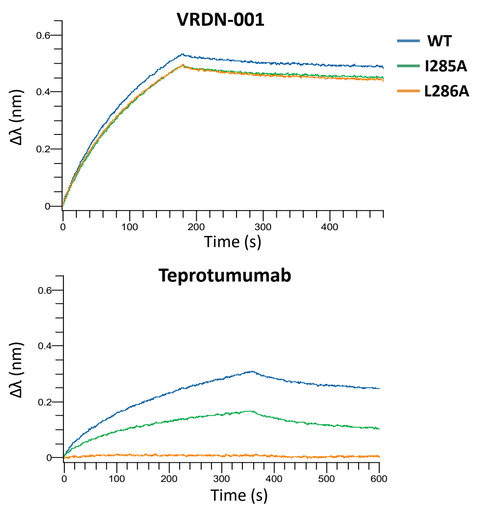
STUDY DESIGN

- **Mutational scan:** A panel of 40 IGF-1R ECD point mutants at potential IGF-1 binding residues or human/rodent differences* and 3 N-terminal truncations (L1, L1+CR, L1+CR+L2) were generated. Binding was assessed by BLI (Octet).
- **Inhibition of ligand binding:** Dose-responses of inhibition of biotinylated IGF-1 binding to IGF-1R expressing FreeStyle™ 293-F cells were assessed by flow cytometry.
- **Antagonist properties:** Dose-responses of inhibition of IGF-1R and AKT phosphorylation (endpoints of IGF-1 mediated signaling) were assessed in human ocular choroidal fibroblasts (HOCFs).

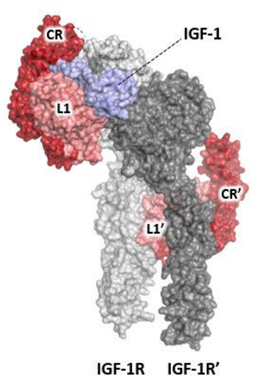
*Since both VRDN-001 and teprotumumab bind human IGF-1R but not rodent IGF-1R, human-specific residues were considered more likely to be part of binding epitope.

MUTATIONAL SCAN: UNIQUE IGF-1R Ab SIGNATURES

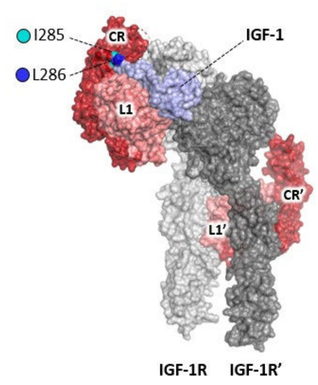
BLI screening data for point mutants



Impact on VRDN-001 binding



Impact on teprotumumab binding



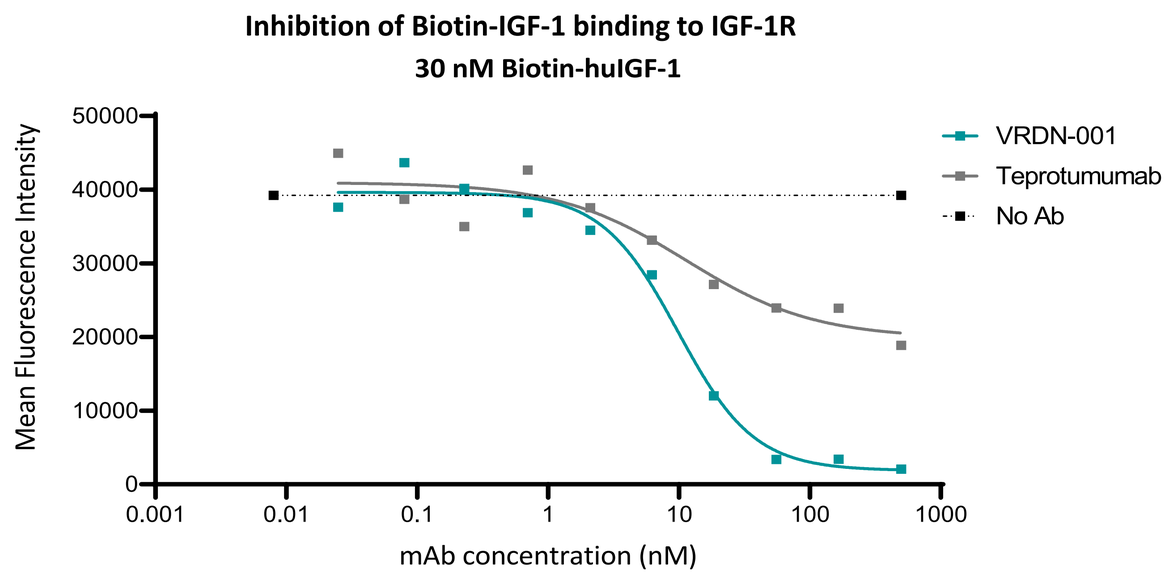
PDB 6PYH: mIGF-1R dimer in complex with hIGF-1[4] (mIGF-1R 96% identical to hIGF-1R)

Point mutations: no binding; reduced binding

Domain deletion: no binding; reduced binding

- Deletion of L1 reduced binding, while deletion of L1+CR (or L1+CR+L2, not marked in image) eliminated binding for both antibodies (data not shown).
- None of the 40 point mutations impacted **VRDN-001** binding; 2 mutations impacted teprotumumab binding: I285A reduced binding while L286A abrogated binding by teprotumumab.
- **VRDN-001** was sensitive to the same domain deletions as teprotumumab but was not sensitive to the same point mutations, consistent with overlapping binding sites but distinct receptor interactions.

ANTIBODY INHIBITION OF LIGAND BINDING TO IGF-1R

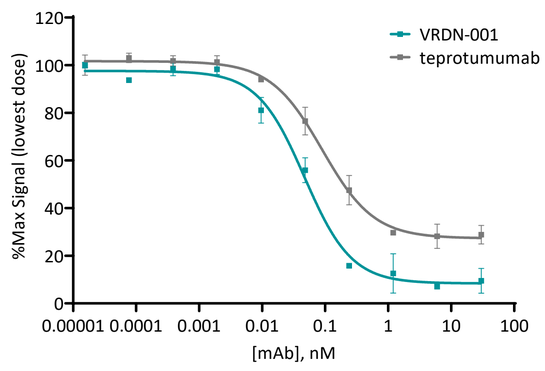


Methods: FreeStyle™ 293-F cells preincubated with antibody on ice. Incubation with 30 nM biotin-IGF-1; detection with streptavidin-APC.

- **VRDN-001** gives near complete inhibition of IGF-1 binding at ≥50 nM.
- Teprotumumab only partially inhibits IGF-1 binding, plateauing at ~50% inhibition at ≥50 nM.

ANTIBODY ANTAGONISM OF IGF-1R SIGNALING

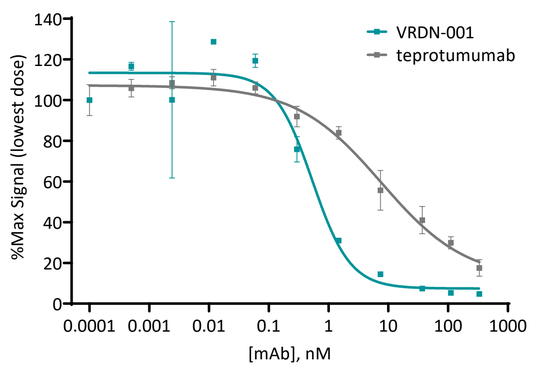
Inhibition of IGF-1R phosphorylation (proximal signaling)



Methods: Serum-starved HOCF cells preincubated with antibody titration, then stimulated with 26 nM IGF-1 for 10 min. Phospho-IGF-1R was measured in cell lysates using an ELISA from R&D Systems.

- **VRDN-001** provides more complete inhibition of IGF-1–induced IGF-1R phosphorylation than teprotumumab.
- By 10 nM, **VRDN-001** nearly fully inhibits IGF-1–induced proximal signaling, while teprotumumab plateaus at only partial inhibition.

Inhibition of AKT phosphorylation (distal signaling)



Methods: Serum-starved HOCF cells preincubated with antibody titration, then stimulated with 23.5 nM IGF-1 for 40 minutes. Phospho-AKT was measured in cell lysates using an ECL immunoassay from Mesoscale Discovery.

- **VRDN-001** provides more complete inhibition of IGF-1–induced AKT phosphorylation than teprotumumab in dose range tested.
- By 50 nM, **VRDN-001** fully inhibits IGF-1–induced distal signaling, while teprotumumab only partially inhibits distal signaling through 300 nM.

THERAPEUTIC IMPLICATIONS

- In healthy volunteers and TED patients, **VRDN-001** elicited rapid and sustained increases in IGF-1 serum levels (target engagement biomarker) that were similar across groups, indicating maximal target engagement at even the lowest dose (Poster #298).

Poster #298

- In a phase 2 proof of concept trial in TED patients, rapid and clinically meaningful reductions in proptosis, inflammation, and diplopia were observed at 6 weeks, following only 2 infusions of **VRDN-001** at all doses tested (NANOS Platform Session II).

Disclosures: This study was sponsored by Viridian Therapeutics Inc. **VRDN-001** is an investigational treatment. Formatting and editorial assistance was provided by Keira Kim and funded by Viridian Therapeutics Inc. All authors met the ICMJE authorship criteria and had full access to relevant data. All authors are employees of Viridian Therapeutics Inc. The authors would like to thank the study investigators and research teams who make this research possible. **References:** **1.** Pritchard J et al. *J Immunol*; 170:6348–6354 (2003); **2.** Krieger CC et al. *J Clin Endocrinol Metab;* 100:1071–1077 (2015); **3.** Smith TJ et al. *NEJM;* 376:1748–1761 (2017); **4.** Li J et al. *Nat Commun*; 10(1):4567 (2019).

PDF of poster and additional information: Scan QR code

Abbreviations used in poster: IGF-1R, insulin-like growth factor-1 receptor; ECD, extracellular domain; BLI, biolayer interferometry; HOCF, human ocular choroidal fibroblast; Ab, antibody; mAb, monoclonal antibody; ECL, electrochemiluminescence; APC, allophycocyanin

Contact Information: info@viridiantherapeutics.com

Poster #297

VIRIDIAN

North American Neuro-Ophthalmology Society (NANOS)
Orlando, FL; March 11-16, 2023