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

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Poster #132

**KEY TAKEAWAYS**

- Results from in vitro assays demonstrate the unique binding epitope and functional characteristics of VRDN-001.
- VRDN-001, a full antagonist antibody to IGF-1R, is under development for the treatment of TED.

**INTRODUCTION**

- Clinical and preclinical studies have confirmed IGF-1R antagonism can reduce the inflammation and proptosis that occur in TED.1,2
- VRDN-001, a full antagonist antibody to IGF-1R, is under development for the treatment of TED.3
- 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-1R binding residues or human/rodent differences* and three 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).
- **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; two 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**

- **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**

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

**THERAPEUTIC IMPLICATIONS**

- In healthy volunteers, VRDN-001 increased serum levels of IGF-1 (target engagement biomarker) ~5–7 fold from baseline, for all doses tested (3–20 mg/kg), indicating maximal target engagement at even the lowest dose (Poster #568).
- In a single cohort (n=8) of TED patients, rapid and clinically meaningful reductions in proptosis, inflammation, and diplopia were observed at 6 weeks, following only 2 infusions of 10 mg/kg VRDN-001 (Poster #535).
- 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.

**REFERENCES**


**DISCLOSURES**

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