Discovery and Characterization of an Orally Bioavailable Nonpeptide Thyroid Stimulating Hormone Receptor (TSHR) Antagonist for the Treatment of Graves' Disease and Thyroid Eye Disease

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BACKGROUND

- **Graves' disease (GD) hyperthyroidism** is an autoimmune disorder affecting ~1% of the U.S. population and 2–3% globally. It is caused by autoantibodies that stimulate the thyroid stimulating hormone receptor (TSHR) - TSAbs, which lead to thyroid gland overstimulation and elevated thyroid hormone levels.
- **Thyroid eye disease (TED)** occurs in 30–50% of GD patients and is driven by TSHR activation in orbital fibroblasts causing increases in hyaluronic acid, cytokines, adipogenesis, and fibrosis, which result in eye pain, swelling, double vision, and proptosis.
- **Current treatments** (antithyroid drugs, RAI, thyroidectomy) often induce hypothyroidism and do not address the autoimmune cause or TED.
- **Crinetics has developed CRN12755**, a selective, potent, oral TSHR antagonist that directly inhibits TSHR signaling at the thyroid gland and eye, thereby reducing thyroid hormones, hyaluronic acid, and IL-6 production, and providing benefits for both GD and TED.

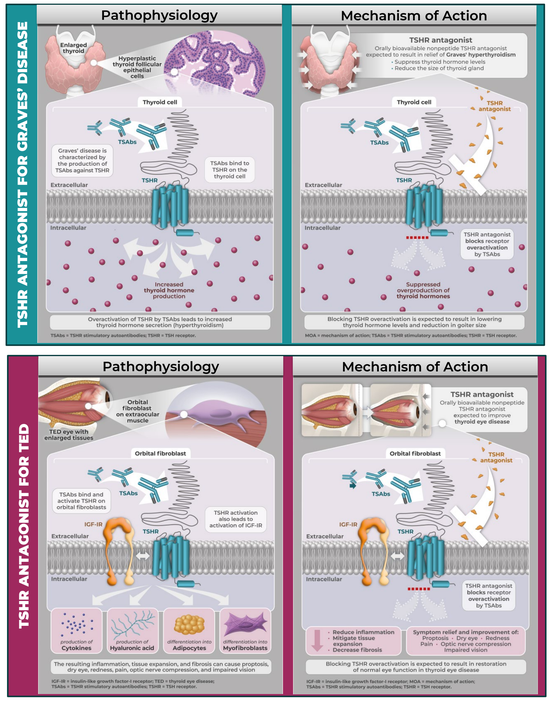


Figure 1. Pathophysiology and mechanism of action (MOA) for a TSHR antagonist for Graves' Disease (Top Panel) and Thyroid Eye Disease (TED) (Bottom Panel).

In Vitro

CRN12755 Is Potent in Functional Antagonist Assays Targeting Human and Rat TSHR

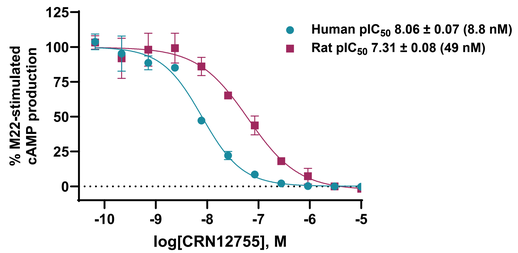


Figure 2. Functional antagonist concentration-response activity at human and rat TSHR. CHO-K1 cells heterologously expressing human or rat TSHR were treated with 11 concentrations of CRN12755 in the presence of an EC_{80} concentration of the TSHR-stimulating antibody, M22.. Data points are the mean with SEM error bars of duplicate wells. Curves are representative of ≥6 independent experiments.

CRN12755 Is an Allosteric Modulator that Decreases Signaling Efficacy of TSHR-Stimulating Antibody M22

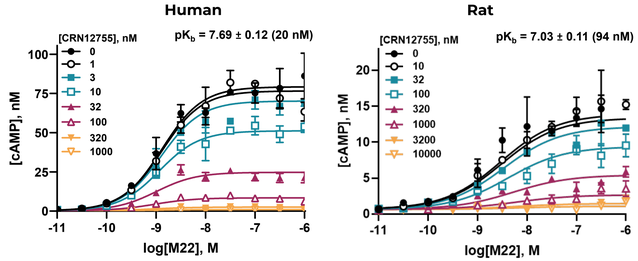


Figure 3. Matrixed-titration data for CRN12755 using M22 in human TSHR (left) and rat TSHR (right) expressing cell lines. CRN12755 greatly lowers the signaling efficacy of M22, consistent with a β-modulation allosteric mechanism. Data points are the mean with SEM error bars of duplicate wells. Graphs are representative of 3 independent experiments.

In Vivo

CRN12755 Suppresses M22-Stimulated T4 in Rats

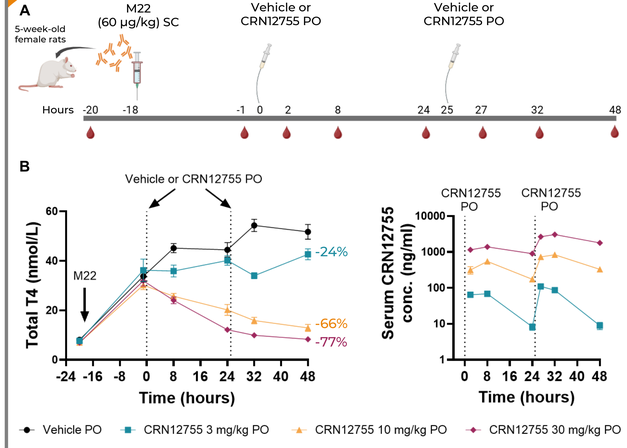


Figure 4. Effect of oral administration of CRN12755 on M22-stimulated total T4 levels in rats. Five-week-old female Sprague Dawley rats received a single subcutaneous administration of 60 µg/kg M22 to induce a rise in serum total T4. (A) Schematic showing the experimental design. Total T4 levels were measured at -20h, -1h, 8h, 24h, 32h and 48h post first dose. CRN12755 concentration was measured in the serum at 2h, 8h, 24h, 27h, 32h, and 48h post first dose. (B) Total T4 (left) and CRN12755 concentrations (right). Dotted lines indicate vehicle or test article dosing times. Percent decreases in T4 are percent changes of the AUC from the vehicle group. Points represent mean ± SEM (n=8 rats/group).

Ex Vivo

CRN12755 Suppresses M22- or TED Patients' IgG-Stimulated HA and IL-6 Production

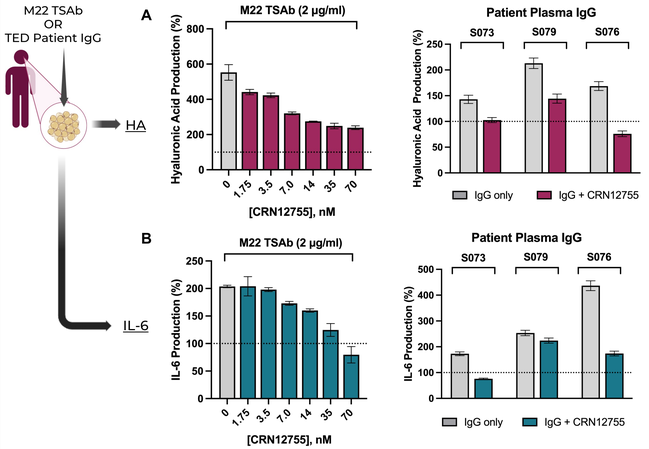
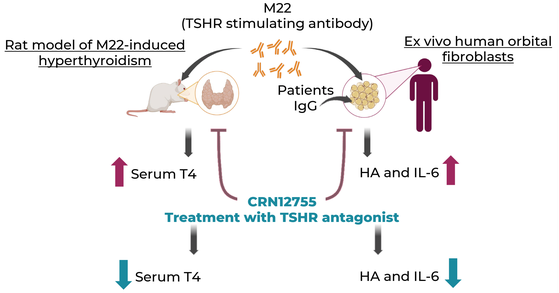


Figure 5. Effect of CRN12755 on M22- and Graves' Patients IgG- stimulated HA and IL-6 production in orbital adipocytes derived from TED patients. Orbital fibroblasts obtained from TED patients during decompression surgery were differentiated to orbital adipocytes. (A) Hyaluronic acid (HA) production and (B) Interleukin-6 (IL-6) Production after stimulation with M22 (2µg/mL; left panels) or TED patients' plasma IgG (50 µL; right panels). CRN12755 was administered at doses indicated in the left panels or at 35 nM for right panels. Dotted lines indicate basal levels when adipocytes were treated with vehicle instead of M22 or IgG and the values were set to 100%. Each bar represents mean ± SEM of 3 replicates.

CONCLUSIONS

- **CRN12755, an orally bioavailable, nonpeptide TSHR antagonist has shown promising efficacy in a preclinical in vivo model of Graves' hyperthyroidism and a human ex vivo model of TED.**



- **CRN12755 has favorable drug properties and is a promising once daily, oral treatment.**

Potency and Selectivity
Human / Rat K_b = 21 / 94 nM
High Selectivity for TSHR over FSHR

Administration
Oral
Once Daily

Safety
Favorable Profile in Early, Screening Preclinical Species

- **These findings support the development of CRN12755 as a targeted and effective treatment for Graves' hyperthyroidism and TED.**

*Illustrations in Figure 4, 5 and conclusions made using Biorender.com

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