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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Graves' disease is an autoimmune condition that affects approximately 1 in 100 people in the United States and 2-3% of the population worldwide. It is characterized by the production of autoantibodies against TSHR, and the pathology of Graves' disease is driven by TSHR stimulatory antibodies (TSAb) that result in heightened activation of TSHR. This overstimulation results in hyperthyroidism due to an increased production of thyroid hormones. Approximately 30-50% of patients with Graves' disease also develop thyroid eye disease (TED or Graves' orbitopathy) due to overactivation of TSHR in orbital fibroblasts, leading to excessive production of hyaluronic acid (HA), adipogenesis, cytokine (e.g. IL-6) production, and fibrosis. This can cause a myriad of debilitating symptoms including pain, swelling, blurry vision, diplopia, and proptosis. Several treatments for Graves' hyperthyroidism are available including anti-thyroid drugs, radioactive iodine (RAI), and surgery. RAI and surgery are definitive treatments for Graves' hyperthyroidism but often associated with unwanted side effects and long-term complications. In addition, none of the current treatments for Graves' hyperthyroidism are effective in preventing or treating TED and, in some cases, such as with RAI, worsen the condition. Blocking TSHR activation directly via a TSHR antagonist may provide an important new therapeutic mechanism for patients that would effectively treat both the hyperthyroidism and TED, and prevent the onset of TED.

Crinetics has identified CRN12755, an orally bioavailable, nonpeptide TSHR antagonist, which has shown promising efficacy in a preclinical in vivo model of Graves' hyperthyroidism and a human ex vivo model of TED. In vitro, CRN12755 demonstrates potent activity at the human TSHR (K_B= 19 nM), and rat TSHR (K_B= 78 nM), significantly reducing agonist efficacy (>300-fold at human, >200-fold at rat). It also exhibits good oral exposure in preclinical species (rat F = 40%, dog F = 80%) and overall has good drug-like properties. In a rat model of hyperthyroidism in which a TSHR stimulatory antibody is administered to induce elevated thyroxine (T4) levels, oral administration of CRN12755 effectively suppressed T4 levels in a dose-dependent manner. To probe the potential efficacy of CRN12755 for TED, we examined its effects ex vivo in orbital fibroblasts obtained from Graves' disease patients (GOFs). CRN12755 suppressed agonist induced HA and IL-6 production in GOFs stimulated with either M22, TSH, or plasma from TED patients.

Together, these results provide evidence that a nonpeptide TSHR antagonist may serve as an effective treatment for Graves' disease and associated TED. Currently, CRN12755 is in IND-enabling studies in preclinical species to support first-in-human clinical studies.