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GENSCI098-A POTENT TSHR ANTAGONISTIC ANTIBODY FOR THE TREATMENT OF TED

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Objective:

The stimulation of TSHR by TSHR-stimulating antibody (TSAb) is key to the induction of orbital phenotypes seen in Thyroid eye disease (TED). TSHR, due to its limited tissue distribution and its role in TED, serves as a promising target for developing therapeutics against TED. Here, we aim to develop a potent TSHR antagonistic antibody that might possess advantages over existing therapeutic options for the treatment of TED.

Methods:

In *in vitro* studies, receptor binding and cAMP assays were used to investigate the binding and antagonistic activities of GenSci098 across species. The blocking effects of GenSci098 on hyaluronic acid (HA), IL-6 and IL-8 secretion were evaluated in TSAbs-stimulated primary human orbital fibroblasts (OFs) isolated from active and inactive TED patients. In *in vivo* efficacy studies, we have adopted an acute M22-induced hyperthyroidism mouse model to test the inhibitory effects of GenSci098 on T4 production. We also conducted pre-clinical studies to evaluate the toxicity and pharmacokinetics of GenSci098.

Results:

In the receptor binding assay, GenSci098 showed great binding activity to TSHR in receptor-overexpressing HEK293 cells (EC_{50}=1.11nM (human), 1.31nM (mouse), 5.81nM (rat), 1.66nM (cyno)). In the cAMP assay, GenSci098 showed excellent blocking activities on M22-stimulated human TSHR-expressing HEK293 cells (IC_{50}=2.3nM). In addition, GenSci098 exhibited comparable blocking efficacy as teprotumumab on HA, IL-6, and IL-8 production in TED-Igs treated OFs from both active (IC_{50} (GenSci098, Tepezza), HA: 0.64nM, 0.79nM; IL-6: 2.93nM, 1.97nM; IL-8: 5.72nM, 1.57nM) and inactive patients (HA: 0.44nM, 0.60nM; IL-6: 1.98nM, 1.23nM; IL-8: 3.65nM, 0.99nM). The antagonistic activity of GenSci098 on TSHR *in vivo* was confirmed in a M22-induced hyperthyroidism mouse model, with minimum and maximum effective doses at 0.5 mg/kg (40.8% inhibition) and 3mg/kg (99.7% inhibition) respectively. The half-lives of GenSci098 in mice (327h) and monkeys (462h) support a potential once-monthly dosing frequency in human. Finally, GenSci098 was proved to be safe and well-tolerated in the mouse and monkey tox studies, with no signs of hypothyroidism.

Conclusion:

In our studies, GenSci098 has demonstrated comparable efficacy as teprotumumab in improving HA secretion from retro-orbital fibroblasts of TED patients and alleviated the thyroid hormone secretion in acute GD mouse model with low safety risks. More importantly, no hypothyroidism was observed with GenSci098 in mouse and monkey tox studies. Therefore, GenSci098 might be a promising drug for further development in the treatment of TED and Grave's disease.