27O-ISMS19 **Development of Glycosylated Somatostatin Having Native-like Activity and Prolonged Half-life**

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Somatostatin is a peptide hormone secreted in various parts of the human body, capable of inhibiting the secretion of several hormones through the binding to five specific receptor subtypes (SSTRs 1–5). Despite its wide activity, therapeutic indications of native somatostatin are hampered due to its short plasma half-life. Although short synthetic peptide analogs with prolonged half-lives like octreotide are clinically established, these analogs are subtype-selective agonists for mainly SSTR2 and SSTR5. Therefore, it is necessary to develop somatostatin derivatives that can be used to treat octreotide-resistant diseases and adenomas/tumors in which several receptor subtypes are involved. In the present study, we developed glycosylated somatostatin analogs with a native-like binding profile and an extended lifetime in circulation. A series of glycosylated somatostatin analogs possessing a native-like agonistic activity to all five receptor subtypes were found from a glycosylated somatostatin library which was constructed using chemical glycosylation. The circulation half-life of glycan-modified somatostatin was extended by about 10-fold. One of these compounds, GT-02037, demonstrated efficient inhibition of growth hormone release in rats. In animal toxicological studies, no adverse effects were observed up to 1 mg/kg/day over two weeks. We are now performing further pre-clinical and clinical studies on GT-02037. These results indicate that glycosylated somatostatin analogs are potent therapeutic drug candidates for not only acromegaly but diseases in which several receptor subtypes other than SSTR2 and SSTR5 are involved.