Selective Nonpeptide Somatostatin Receptor Subtype 5 (sst5) Agonists Suppress Glucose- and Sulfonylurea-induced Insulin Secretion in Rats

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Cognitive hyperinflammation (CHI) results from mutations within the insulin secretion pathway and is characterized by excessive and inappropriate insulin secretion by pancreatic β-cells. CHI is the most common cause of persistent hyperglycemia in newborns and infants and is estimated to affect 120,000 to 150,000 live births. Prompt recognition and treatment are vital to prevent long-term neurological complications, and even death. If medical control of CHI is unsuccessful, near-total pancreatectomy may be required. The nonpeptide somatostatin is an important mediator of pancreatic hormone signaling and plays a critical role in the suppression of insulin and glucagon. Glucagon secretion from a-cells is inhibited by somatostatin, and CHI is associated with hyperexpression of sst2, sst3, and sst5. The inactivated peptide drugs of sst2 and sst3 are potential agonists at sst5 and are often deployed as an off-label medical intervention to prevent or delay pancreatic expression. These peptide sst5 activity leads to inhibition of glucagon secretion, potentially reducing their effectiveness and compromising a key defense mechanism against hyperglycemia. We hypothesize that antagonists targeting sst5 but lacking sst2 activity will possess an optimal efficacy/safety profile for patients with hyperglycemic hyperinsulinemia.

Using in vivo models, Crinetis has discovered several classes of highly potent, orally bioavailable, small molecule sst5-selective antagonists with drug-like pharmaceutical properties. Our discovery efforts aimed at finding a compound to treat CHI have yielded potent and selective nonpeptide sst5 agonists with sub-nanomolar EC50 in rat-based assays of receptor activation. These compounds also typically possess arterial potential for the rat articular receptor. To probe their physiological consequences and to gain insight into mechanisms, we compared the in vivo pharmacokinetic and chronic effects of the peptide antagonistic, a pan-agonist that is most potent at sst5, on glucagon control in several rat models, which generally demonstrated a high drug translation to humans. This study demonstrates that the sst5-selective antagonists inhibit sulfonylurea-induced hyperglycemia, and on blood glucose levels in both the fed and fasted states. In each model, selective nonpeptide sst5 agonists suppressed insulin secretion and raised blood glucose levels while having minimal effects on glucagon secretion, as predicted by their in vitro pharmacology. These results support our efforts to develop potent nonpeptide selective sst5 agonists with pharmaceutical and safety profiles suitable for evaluation in human clinical trials. This work was supported in part by an SBIR grant from the NIH awarded to Dr. Betz (R42DK083871).

**Hypothesis:** targeting sst5 to treat CHI

Glucose

Figure 1. Depiction of blood glucose regulation by pancreatic α and β-cells.

**CRN24061 is a selective & orally bioavailable sst5 agonist**

**CRN24061 does not inhibit glucagon secretion during an IP-pyruvate tolerance test**

**CRN24061 increases glucose levels and prevents sulfonylurea-induced hypoglycemia in PND10 rats**

![Graphs and figures showing biological effects of CRN24061](https://example.com)

**Figure 3.** Effect of subcutaneous injection of vehicle (gray), CRN24061 (5 mg/kg, green), or exendin-3 (10 mg/kg, red) on blood glucose levels in fasted male Sprague Dawley rats (n=8/group) following IP pyruvate challenge.

**Figure 5.** Effect of CRN24061 and the sulfonylurea glyburide on glucose and insulin in juvenile rats. Male Sprague Dawley rats (age PND10) were administered vehicle or 1 mg/kg (SC) CRN24061. Parallel experiments were done with and without glyburide (5 mg/kg, IP) which mimics the hyperglycemia observed in many CHI patients. (n=8/group)

**Figure 7.** Effect of CRN24061 on the glucose and insulin levels in juvenile rats. Male Sprague Dawley rats (age PND10) were administered vehicle or 1 mg/kg (SC) CRN24061. Parallel experiments were done with and without glyburide (5 mg/kg, IP) which mimics the hyperglycemia observed in many CHI patients. (n=8/group)

**Figure 9.** Effect of CRN24061 on the glucose and insulin levels in juvenile rats. Male Sprague Dawley rats (age PND10) were administered vehicle or 1 mg/kg (SC) CRN24061. Parallel experiments were done with and without glyburide (5 mg/kg, IP) which mimics the hyperglycemia observed in many CHI patients. (n=8/group)

**CRN24061 raises glucose in both the fed and fasted states in rats**

**Conclusions**

CRN24061 represents a proof of concept molecule in our oral nonpeptide sst5 agonist program:

- Potent and selective sst5 agonist
- Exhibits good pharmacokinetics in the rat
- Increases and extends glucose excursion across different metabolic states
- Suppresses insulin but not glucagon secretion
- Rescues sulfonylurea-induced hypoglycemia in juvenile rats

Small molecule agonists selectively targeting sst5 represent a promising strategy to treat CHI