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

Emmanuel Sturchler, Melissa A. Fowler, Jon Athanacio, Taylor A. Kredel, Michael Johns, Jian Zhao, Shimiao Wang, Rosa Luo, Ana Karin Kusnetzow, Yun Fei Zhu, Ajay Madan, R. Scott Struthers, Stephen F. Betz, Stacy Markison

Crinetics Pharmaceuticals, San Diego, CA.

Congenital hyperinsulinism (CHI) results from mutations within the insulin secretion pathway and is characterized by excessive and/or inappropriate insulin secretion by pancreatic islet b -cells. CHI is the most common cause of persistent hypoglycemia in newborns and infants and is estimated to affect 1/30,000 to 1/50,000 live births. Prompt recognition and treatment are vital to prevent coma, long-term neurological complications, and even death. If medical control of CHI is unsuccessful, near-total pancreatectomy may be required. The neuropeptide somatostatin is an important modulator of pancreatic hormonal signaling and activity at different somatostatin receptor (sst) subtypes dictates the suppression of insulin and/or glucagon. Glucagon secretion from a-cells is inhibited through sst2 receptors and insulin secretion from b-cells is inhibited through activation of sst2, sst3, and sst5. The injectable peptide drugs octreotide and lanreotide are potent agonists at sst2 and are often deployed as the last medical intervention to prevent or delay pancreatectomy. These peptides' sst activity leads to inhibition of glucagon secretion, potentially reducing their effectiveness and compromising a key defense mechanism against hypoglycemia. We hypothesize that agonists targeting sst5 but lacking sst2 activity will possess an optimal efficacy/safety profile for patients with hyperinsulinemic hypoglycemia.

Using iterative medicinal chemistry, Crinetics has discovered several classes of highly potent, orally bioavailable, small molecule sst-subtype selective agonists 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 $EC_{50}$s in cell-based assays of receptor activation. These compounds also typically possess similar potency for the rat sst5 receptor. To probe their physiological consequences and to gain mechanistic insights, we compared the acute and chronic effects of these agonists to the peptide pasireotide, a pan-sst agonist that is most potent at sst5, on glycemic control in several rat models, which generally demonstrate a high degree of translation to humans. These preclinical studies evaluated the effects of the sst5 agonists during OGTT, IPGTT, sulfonylurea-induced hypoglycemia, 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 (R44DK088501)*

## Hypothesis: targeting sst5 to treat CHI

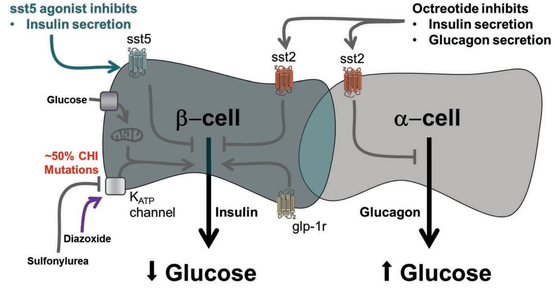


**Figure 1.** Depiction of blood glucose regulation by pancreatic α- and β-cells.

## CRN02481 is a selective & orally bioavailable sst5 agonist

| $EC_{50}$ (nM) | hsst1 | hsst2 | rsst2 | hsst3 | hsst5 | rsst5 |
|---|---|---|---|---|---|---|
| CRN02481 | >10000 | 440 | nd | 39 | 0.39 | 0.36 |
| Octreotide | > 10000 | 0.057 | 0.081 | 7.9 | 2.5 | 2.5 |
| Pasireotide | 5.7 | 0.59 | 2.5 | 0.78 | 0.076 | 0.019 |

**CRN02481 pharmacokinetic characteristics after 10 mg/kg PO dosing in male Sprague Dawley rats**

| $C_{max}$ (ng/mL) | $AUC_{0\rightarrow t}$ (ng.hr/mL) | $t_{max}$ (hr) | $t_{1/2}$ (hr) | Bioavailability, F (%) |
|---|---|---|---|---|
| 78 | 799 | 0.5 | 8.5 | 32 |

## CRN02481 raises glucose and inhibits insulin release during both IPGTT and OGTT

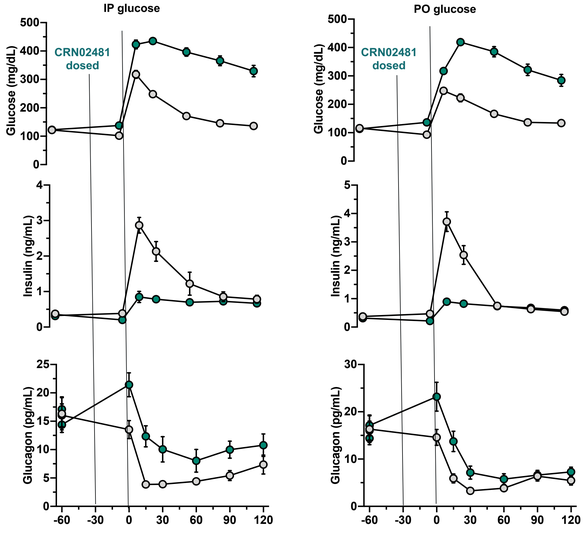


**Figure 2.** Effect of subcutaneous injection (SC) of vehicle (grey) or 5 mg/kg CRN02481 (green) on plasma glucose, insulin, and glucagon levels in fasted male Sprague Dawley rats (n=8/group) following a glucose challenge.

## CRN02481 does not inhibit gluconeogenesis during an IP-pyruvate tolerance test

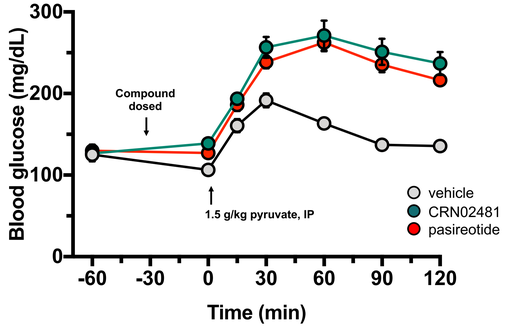


**Figure 3.** Effect of subcutaneous injection of vehicle (grey), CRN02481 (5 mg/kg, green) , or pasireotide (30 µg/kg, red) on blood glucose levels in fasted male Sprague Dawley rats (n=8/group) following IP pyruvate challenge.

## CRN02481 raises glucose in both the fed and fasted states in rats

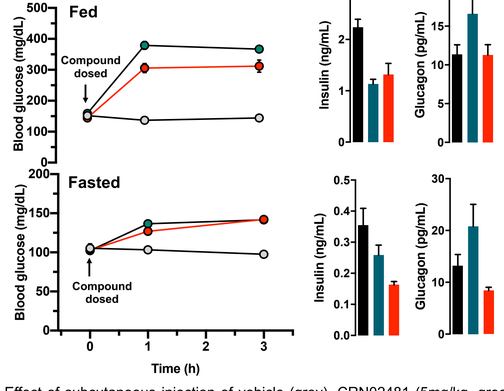


**Figure 4.** Effect of subcutaneous injection of vehicle (grey), CRN02481 (5mg/kg, green), or pasireotide (30 µg/kg, red) on blood glucose over time, insulin, and glucagon levels (at 1h) in fed and fasted male Sprague Dawley rats (n=7-8/group).

## CRN02481 increases glucose levels and prevents sulfonylurea-induced hypoglycemia in PND10 rats

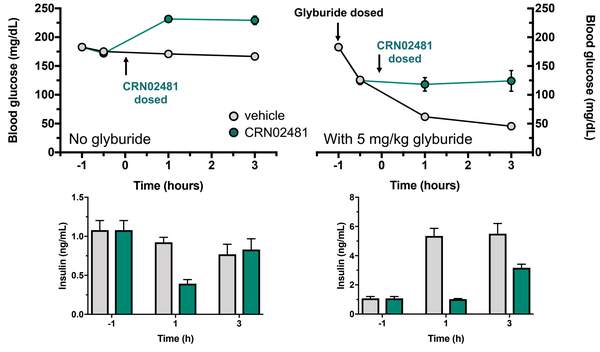


**Figure 5.** Effect of CRN02481 and the sulfonylurea glyburide on glucose and insulin in juvenile rats. Male Sprague Dawley rats (age PND10) were administrated vehicle or 15 mg/kg (SC) CRN02481. Parallel experiments were done with and without glyburide (5 mg/kg, IP) which mimics the hypoglycemia observed in many CHI patients. (n=8/group).

## Conclusions

**CRN02481 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**

Crinetics Pharmaceuticals