

Discovery and Identification of Late Stage, Selective Nonpeptide Somatostatin Subtype 5 (SST5) Agonists for the Treatment of Hyperinsulinemic Hypoglycemia

Melissa A. Fowler, Jian Zhao, Emmanuel Sturchler, Elizabeth Rico-Bautista, Rosalia de Necochea-Campion, Jon Athanacio, Taylor A. Kredel, Agnes Antwan, Michael Johns, Oleg Tsivkoski, Shimiao Wang, Rosa Luo, Ana K. Kusnetzow, Ajay Madan, R. Scott Struthers, Stacy Markison, Yun Fei Zhu, Stephen F. Betz

Crinetics Pharmaceuticals, San Diego, CA.

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Congenital hyperinsulinism (CHI) results from mutations within the insulin secretion pathway and is characterized by excessive and/or inappropriate insulin secretion by pancreatic islet β -cells. CHI is the most common cause of persistent hypoglycemia in newborns and infants and is estimated to affect 1:2,500 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, a near-total pancreatectomy may be required, but hypoglycemia often persists. 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. The injectable peptide drugs octreotide and lanreotide are potent SST2 agonists used to treat CHI, but in addition to suppressing insulin, the SST2 activity of these peptides may also inhibit glucagon secretion, potentially reducing effectiveness and compromising a key defense mechanism against hypoglycemia. Glucagon secretion from α -cells is inhibited through activation of SST2 receptors, while insulin secretion from β -cells is inhibited through activation of SST2 and SST5. We therefore hypothesize that agonists selectively targeting SST5 and lacking SST2 activity will offer an improved efficacy/safety profile for patients with hyperinsulinemic hypoglycemia.

Using iterative medicinal chemistry and pharmacology, 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. Insulin secretion from isolated human and rat islets was suppressed upon exposure to SST5 agonists. Potent and selective SST5 agonists were then evaluated in a number of acute and repeat dose in vivo animal models (e.g., OGTT, fed/fasted conditions, sulfonylurea-induced hypoglycemia) to assess physiological effects and to gain mechanistic insights. As predicted by in vitro pharmacology, selective nonpeptide SST5 agonists suppressed insulin secretion and raised blood glucose levels in each model, while having minimal effects on glucagon secretion. Leading SST5 agonists were also evaluated for drug like characteristics, including stability in liver microsomes, lack of inhibition of cytochromes P450 and the hERG ion channel, and were shown to exhibit good exposure upon oral dosing in both rats and dogs. The culmination of these studies has led to a subset of candidate molecules that are being evaluated in genotoxicity, safety pharmacology, and general toxicity studies to determine the molecule most suitable for evaluation in human clinical trials.

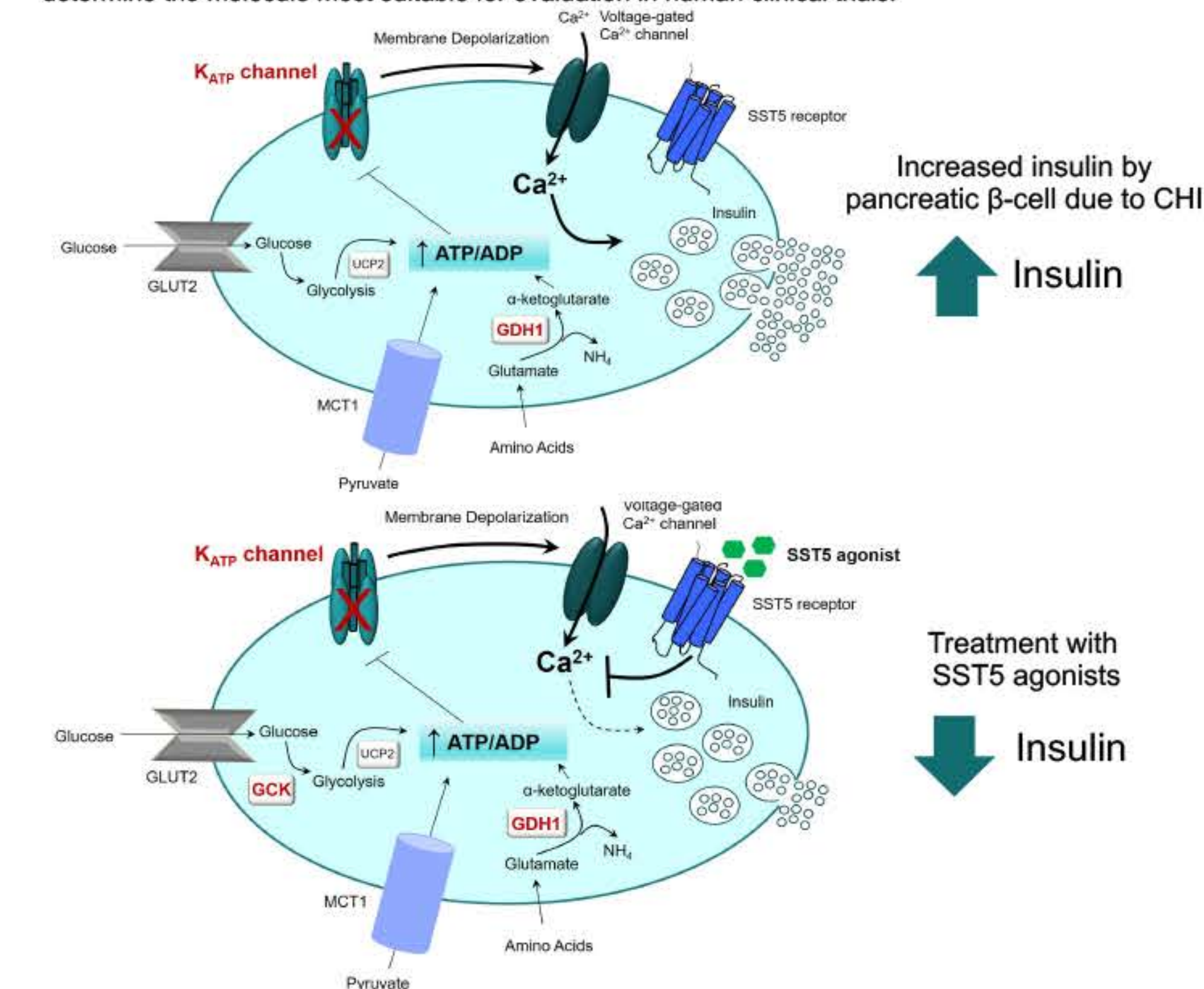


Figure 1. Treatment with SST5 agonists inhibits abnormal insulin secretion from CHI pancreatic β -cells. The most common mutations in CHI are highlighted in red (GSK, GDH1, K_{ATP} channel- SUR1 & Kir6.2).

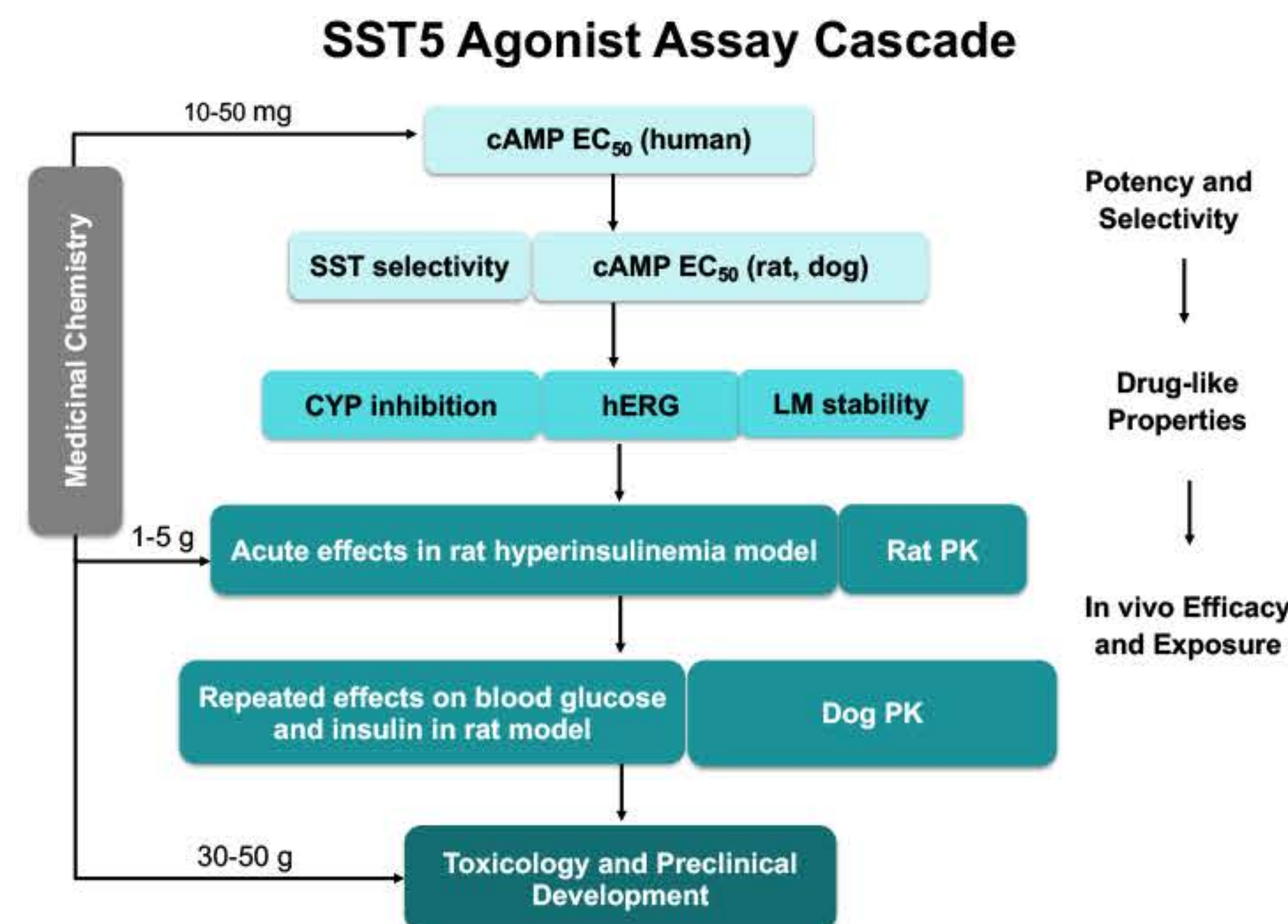


Figure 2. Assay cascade to identify SST5 agonists. Compounds were screened in cAMP assays to identify potent SST5 agonists, which were then counter-screened against the other SST receptors. Drug-like properties were assessed by screening for hERG channel and CYP enzyme inhibition, as well as liver microsomal stability. Suitable molecules were assessed in rat models of efficacy and pharmacokinetics. A subset of those compounds were advanced to dose range finding toxicology studies and preclinical development.

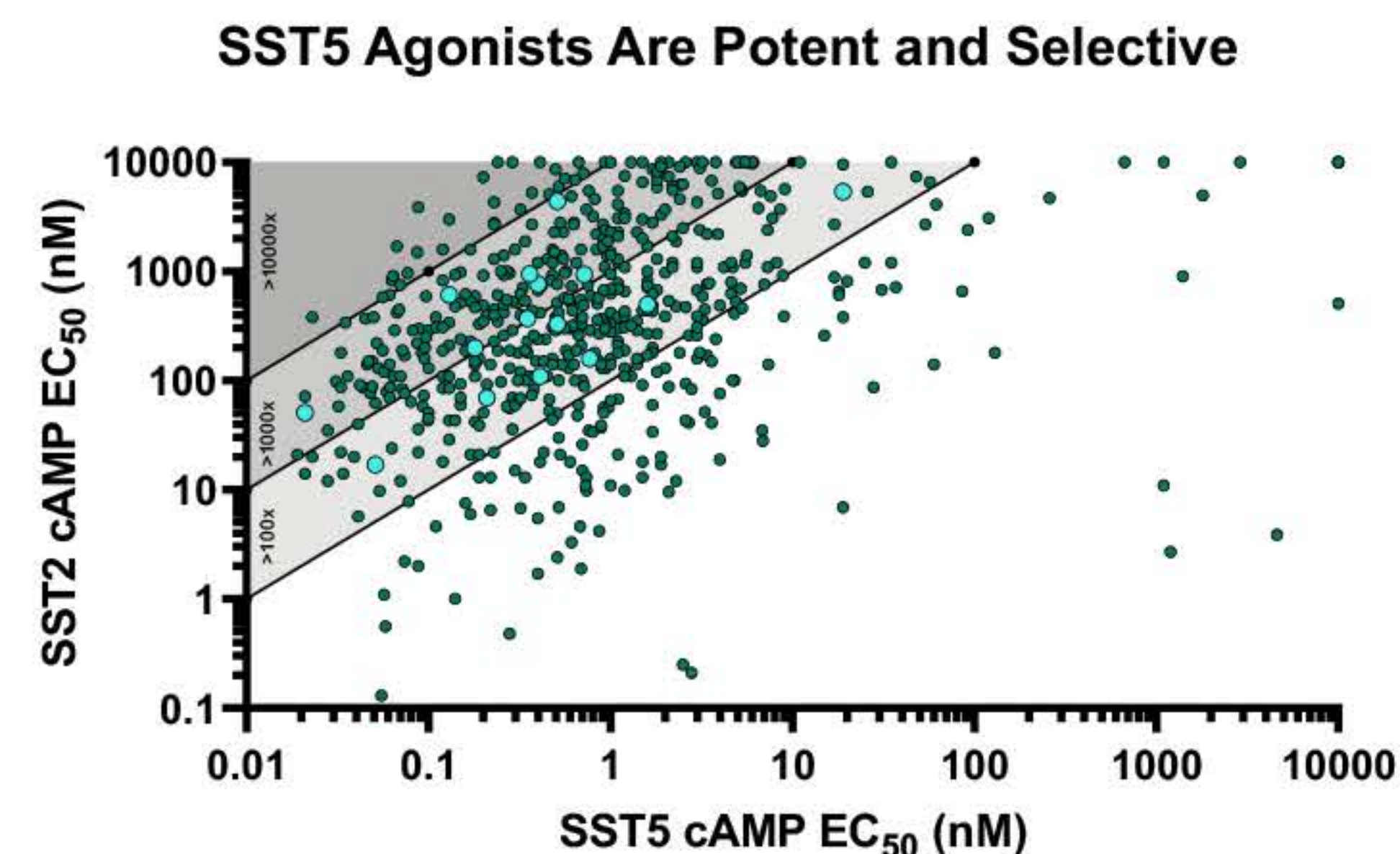


Figure 3. Potency and selectivity of SST5 agonists. Crinetics has generated a library of ~1450 compounds targeting SST5 receptors. The subset of agonists tested at both SST5 and SST2 are shown. Compounds described in Table 1 are shown in teal. Shading indicates increasing selectivity for SST5.

SST5 Agonists Have Drug-like Characteristics and Are Orally Bioavailable

Compound ^a	SST5 Potency (EC_{50} , nM)		SST Selectivity (EC_{50} , nM)				CYP450 Inhibition (μ M)				hERG Inhibition (μ M)	LM Stability $t_{1/2}$ (min)			PK (F%)		
	human	rat	SST1	SST2	SST3	SST4	3A4	2D6	2C9	2C19	hu	rat	dog	rat	dog		
AG-1	120									>10	116	\geq 693					
AG-2	19		>5400	400	>10000												
AG-3	0.35		370	85	300	>10	3.2			8.5	18	10					
AG-4	0.51	3.7	330	85	>10000	>10	2.4			>10	22	9					
AG-5	0.72	6.9	>10000	940	81	>8500	>10	3.5		>10	\geq 693	231				45	
AG-6	1.6	2.2	500	73	14000												
AG-7	0.77	17	>10000	160	19	1200	>10	TDP ^b	>10	>10	>30	346	\geq 693	\geq 693	16	37	
AG-8	0.21	3.4	>10000	70	35	86	>10	2.8	>10	>10	7.5	231	87			39	80
AG-9	0.41	2.3	>10000	110	26	200	>10	3.2	>10	>10	>30	\geq 693	346	139	35	41	
AG-10	0.13	1.8	>7900	610	230	1000			>10	>10	>10	139	173			33	21
AG-11	0.40	6.2	>10000	770	540	4700	>10	>10	>10	>10	231	\geq 693	\geq 693	30	24		
AG-12	0.36	2.0	>9000	950	640	>7500			>10	>10	>10	116	116	\geq 693	20	24	
AG-13	0.021	5.9	>5000	51	38	980	>10	>10	>10	>10	>30	173	346	\geq 693	31	48	
AG-14	0.51	11	>10000	4400	>8700	>10000	>10	>10	>10	>10	8.2	\geq 693	\geq 693			44	
AG-15	0.051	21	>10000	17	530	4500	>10	>10	>10	>10	\geq 693	\geq 693	\geq 693	39			
AG-16	0.18	3.7	>10000	200	310	830	>10	>10	>10	>10	116	\geq 693	173	44			

^a compounds have molecular weights ranging from 390-470 ^b time dependent inhibition
Table 1. Drug-like characteristics of selected SST5 agonists. Compounds were screened for SST5 receptor activity and selectivity, CYP and hERG inhibition, liver microsomal (LM) stability, and oral bioavailability (%F) in pharmacokinetic studies.

SST5 Agonists Reverse Glyburide-induced Hypoglycemia

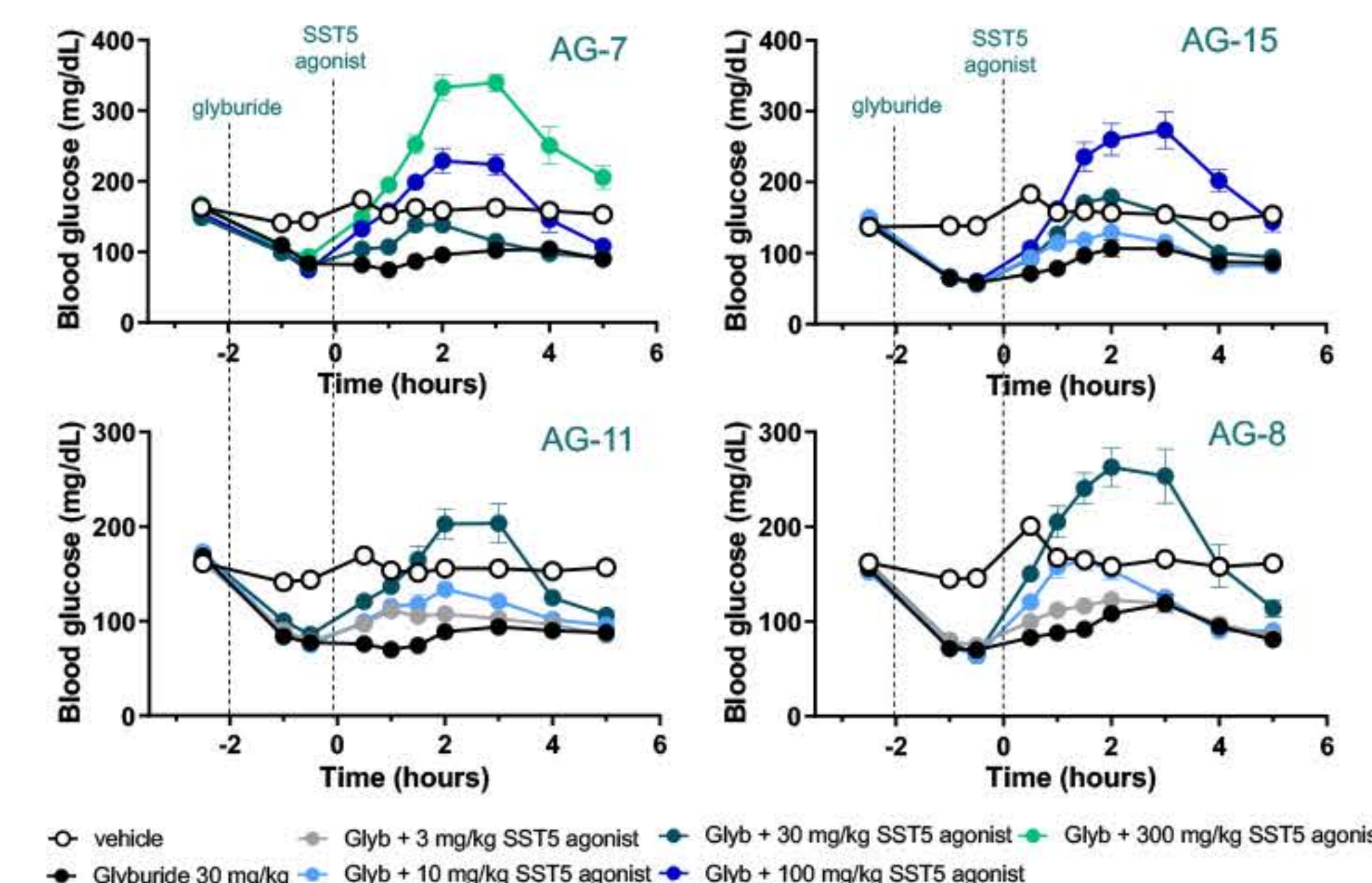


Figure 4. Effects of oral administration of SST5 agonists on blood glucose in a rat model of hyperinsulinemic hypoglycemia. Male Sprague Dawley rats were orally administered the sulfonylurea glyburide to mimic the hypoglycemia seen in CHI patients. Two hours following glyburide, rats were orally administered vehicle or SST5 agonist (3, 10, 30, 100, 300 mg/kg), and blood glucose was measured over five hours (n=8/group).

Effects of Efficacious Doses of SST5 Agonists Are Sustained Over Seven Days

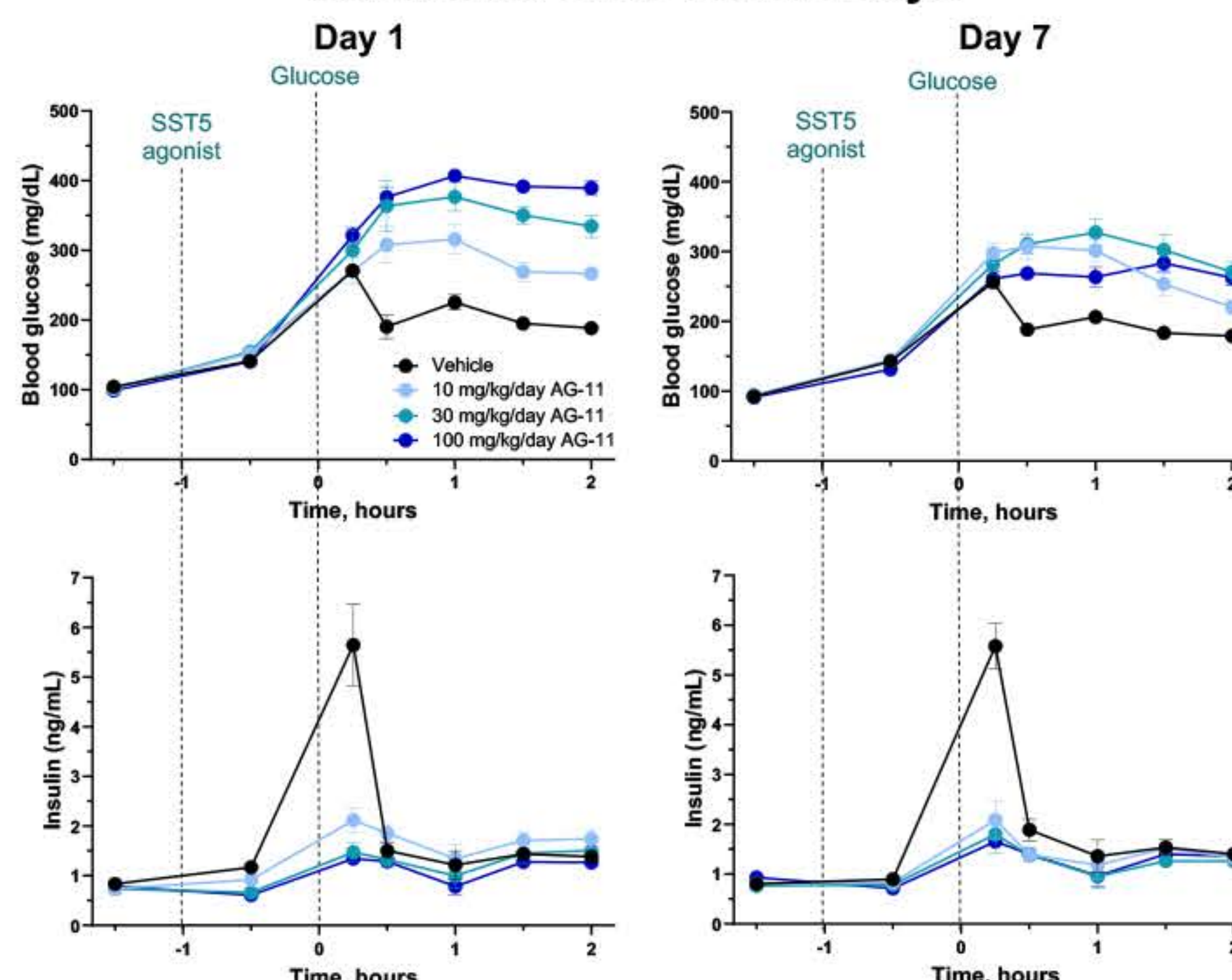


Figure 5. Effect of repeated oral administration of SST5 agonists on oral glucose tolerance. Male Sprague Dawley rats were orally administered vehicle or SST5 agonist (10, 30, or 100 mg/kg/day; n=8/group) over 7 days. An oral glucose tolerance test measuring blood glucose and insulin in response to an oral glucose load (1.5 g/kg) was performed in fasted rats on Day 1 and Day 7.

Conclusions

Crinetics has discovered potent, selective, and drug-like SST5 agonists. We describe several agonists that:

- are potent and selective for SST5 receptors over other SST subtypes
- have desirable drug-like characteristics
- show good oral exposure in rats and dogs
- reverse glyburide-induced hypoglycemia in rats
- show sustained efficacy in increasing blood glucose and decreasing insulin after repeated administration in rats

We have nominated one agonist for development and are pursuing first-in-human clinical trial GLP toxicity enabling studies.

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