Investigating GPR119 agonist efficacy in a systems pharmacology model of diabetes

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Introduction

- GPR119 receptor agonists are a potential treatment for type 2 diabetes (T2D) that are reported to
  - increase the secretion of incretins with or without food intake
  - increase either glucose-stimulated insulin secretion or glucagon secretion, depending on the glucose level
- However, GPR119 receptor agonists have shown mixed results in clinical settings[1]

Objectives

The objectives of this work were to

a) integrate GPR119 mechanisms into a quantitative systems pharmacology (QSP) model of T2D
b) compare the efficacy of a new GPR119 receptor agonist with other compounds in the same class
c) increase the mechanistic understanding of the potential efficacy of oral GPR119 receptor agonists to evaluate if GPR119 is an effective target for treating T2D

Methods: Model Qualification

- The GPR119 Research Platform was implemented into a previously-developed diabetes QSP model with the tissues and functions necessary to model metabolism of glucose, amino acids and lipids
- Indirect and direct mechanisms of GPR119 receptor agonism (such as incretin release and enhanced sensitivity on insulin and glucagon secretion), PK, EC50, and Emax for the agonists were incorporated into the Platform
- Platform behavior was calibrated using public and proprietary pre-clinical and clinical data
- The Platform was qualified in accordance with Rosa's Model Qualification Method[2]

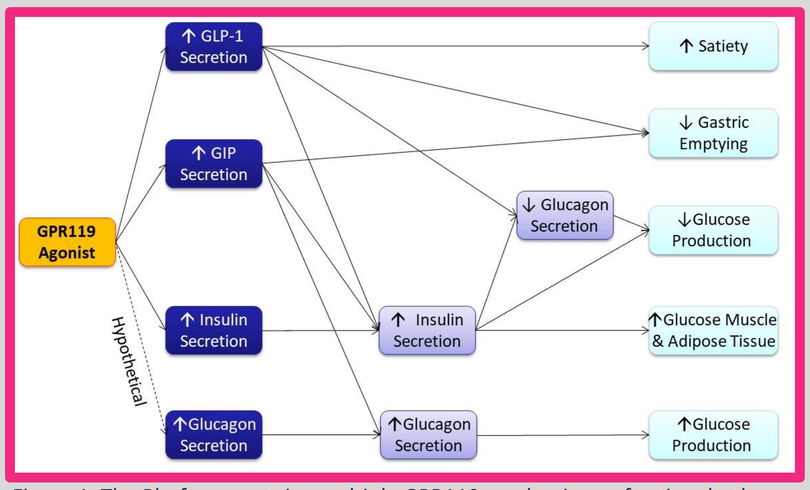


Figure 1. The Platform contains multiple GPR119 mechanisms of action, both direct and indirect

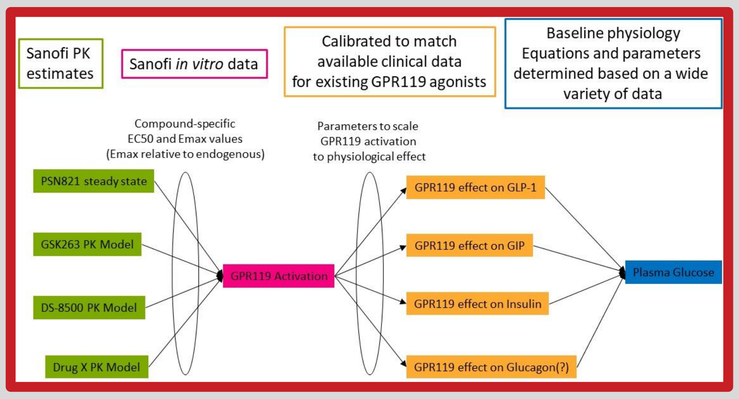


Figure 2. GPR119 receptor agonists were integrated into the Platform using drug specific PK, EC50, and Emax data developed internally as well as published in the literature

References

1. Yang 2018 PMID: 28722242; Ritter 2016 PMID: 26512410
2. Friedrich (2016) PMID 26933515
3. Wu 2014 PMID: 24647737; Vardarli 2014 PMID: 24186866; Ahren 2009 PMID: 19748066; Bock 2010 PMID: 20039889

Results: Diabetic Virtual Patient

- Obese, T2D, sedentary, diabetic virtual patient (DVP) (HbA1c = 7.2%, fasting glucose = 155 mg/dL) treated with metformin but with low response, mild pancreatic beta cell dysfunction, insulin hypersecretion, and moderate response to sitagliptin (Table 1)

Table 1. Diabetic Virtual Patient (DVP) responds appropriately to sitagliptin

	Simulation			
	No Treatment	Sitagliptin 100 mg q.d.	Change from Placebo	Literature[3]
FPG (mg/dL)	155	134	-21	-18
FPI (pM)	151	146	-5	-0-30%
GLP-1 (pM)	5.7	11.7	2.1 fold	2 fold
Ave. 24 hr. glucose (mg/dL)	157	126	-31	-36
Ave. 24 hr. insulin (pM)	352	446	+25%	+20-50%
Ave. 24 hr. GLP-1 (pM)	10.6	23.8	2.2 fold	2 fold

- Additional testing of DVP showed appropriate response to metformin monotherapy (results not shown)

Results: Monotherapy

Table 2. Monotherapy treatment of a DVP with GPR119 receptor agonists

	No Treatment (NT)	Drug X (5 mg q.d.)	GSK263 (600 mg q.d.)	DS-8500 (75 mg q.d.)	PSN821 (42.5%)
Fasting GLP-1 (pM)	5.7	8.7	9.5	8.0	9.9
Ave. 24 hr. GLP-1 (pM)	10.7	15.6	15.8	15.2	14.8
Breakfast GLP-1 total AUC	59.4	88.3	84.7	87.1	78.0
Breakfast GLP-1 total AUC, % Change from NT	0.0	48.5	42.5	46.5	31.3
Fasting plasma glucose (mg/dL)	154.7	136.2	131.3	140.9	129.9
Ave. 24 hr. glucose (mg/dL)	156.7	132.2	130.8	134.6	134.9
Breakfast glucose total AUC	706.6	594.3	607.1	602.4	627.7
Breakfast glucose total AUC Change from NT %	0.0	-15.9	-14.1	-14.7	-11.2

Monotherapy simulation results suggest that the Drug X may have slightly better plasma glucose lowering at select doses compared to the other compounds in the same class

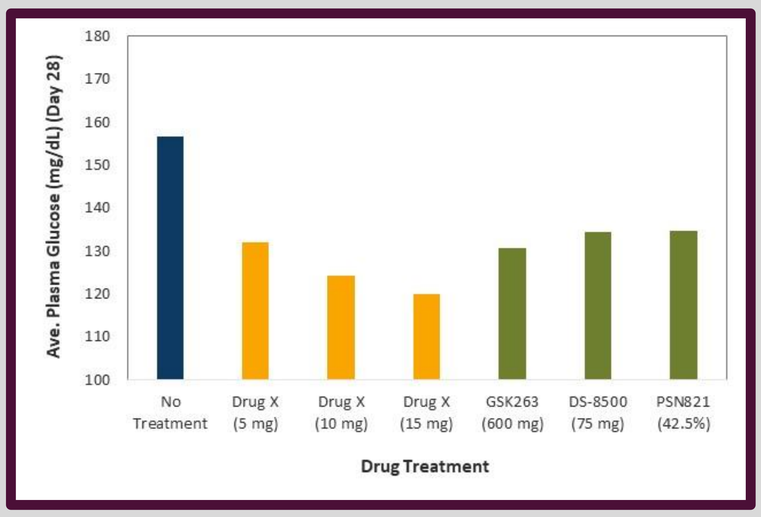
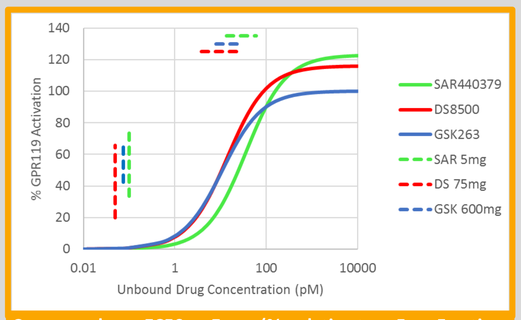


Figure 3. Comparison of glucose lowering by different GPR119 receptor agonists in the Platform



Compound	EC50 (nM)	Emax (%, relative to endogenous)	Free Fraction %
Drug X	36	123	14.5
GSK263	11	100	1.4
DS-8500	14	116	1.2
PSN821	26	109	-

Figure 4. Plasma concentrations of GPR119 receptor agonists are predicted to be near the center of dose response curves from Sanofi in vitro studies. Solid lines indicate dose-response curves derived from Sanofi in vitro data. Dotted lines indicate ranges of unbound drug concentration and GPR119 activation at steady state drug levels with the indicated doses. PD parameters were estimated from Sanofi in vitro experiments.

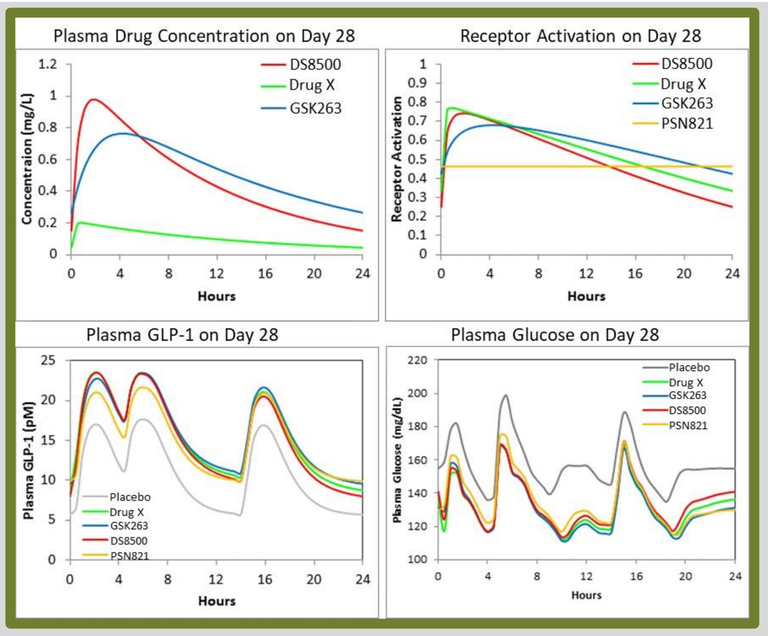


Figure 5. Simulations comparing GPR119 receptor agonist therapies after 28 days of treatment. Graphs show drug concentration, receptor activation, GLP-1, and glucose. Drugs were dosed as Drug X 5 mg, GSK263 600 mg, DS-8500 75 mg, PSN821 42.5% of maximum. PSN821 PK was unavailable, so was simulated at a steady state plasma level.

Results: Combination Therapy

- Simulation results suggest that combining a GPR119 agonist with sitagliptin causes higher GLP-1 concentrations and may have superior glucose lowering compared to either monotherapy

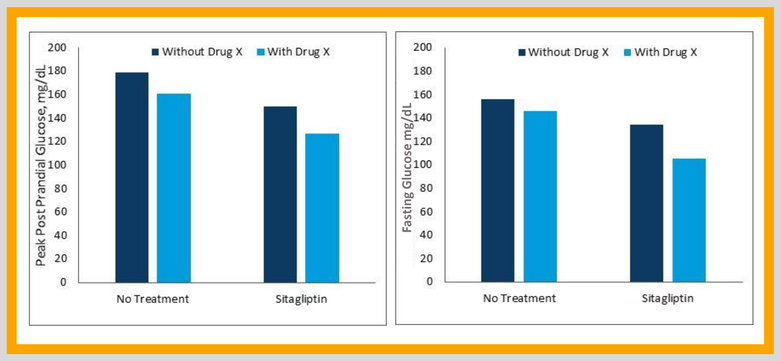


Figure 6. Administration of sitagliptin (100 mg q.d.) with Drug X (2.5 mg q.d.) results in decreased fasting and peak post prandial glucose concentration after 28 days of treatment as compared to administration of sitagliptin without Drug X

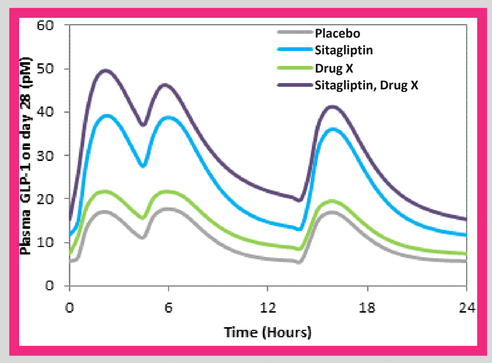


Figure 7. Co-administration of a GPR119 agonist with sitagliptin. Sitagliptin (100 mg q.d.) and Drug X (2.5 mg q.d.) co-administration results in a greater than additive increase in plasma GLP-1 concentrations

Table 3. Ave. plasma glucose in DVP treated with sitagliptin with/without Drug X

Ave. Plasma Glucose	No Treatment	Sitagliptin (100 mg q.d.)
Without Drug X	156.7	126.1
With Drug X (2.5 mg q.d.)	144.6	109.7

Conclusions

- Modification of an existing Diabetes Platform was a rapid and efficient method for comparing a GPR119 receptor agonist and other existing drugs from the same class
- Platform analysis indicated that the direct effects of Drug X contributed approximately 50% of the drugs efficacy
- The new GPR119 receptor agonist (Drug X) showed slight superiority in glucose lowering to existing GPR119 compounds at a lower dose
- GPR119 agonists in combination therapy with sitagliptin may be an effective method for treating Type 2 Diabetes

For more information about this work, please contact:
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