Incorporation of Renal SGLT Function into a Quantitative Systems Pharmacology (QSP) Model

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Introduction

- Sodium-glucose cotransporters (**SGLT1** & **SGLT2**) absorb glucose from the renal filtrate into the plasma and SGLT1 absorbs glucose in the GI tract.
- Inhibition of SGLTs reduces plasma glucose and is a successful therapeutic approach for **type 2 diabetes** (T2D).
- SGLT inhibitors (SGLTi) targeting both SGLT1 and SGLT2 may **overcome the adaptation** found with SLGT2 inhibition (Figure 4).

Objective

- Investigate the relative contributions of SGLT1 and SGLT2 to **kidney** glucose reabsorption.

Methods

Mechanistic, quantitative systems pharmacology models elucidate the connection between mechanisms and outcomes.

- A PhysioPD™ Research Platform is a graphical, mathematical QSP model of biology developed in SimBiology®[2] combining **engineering approaches** and **scientific data analysis** to clarify complex physiology and drug interactions.
- Rosa developed the SGLT QSP model integrating plasma glucose, glomerular filtration rate (GFR), and SGLT1 and SGLT2 function in the first three segments of the proximal tubule to explore the impact of alternative SGLTi's on urinary glucose excretion (UGE).
- The SGLT Platform was qualified in accordance with Rosa's Model Qualification Method[1] (MQM) (Figure 1).
- Healthy (HVP) and diabetic (DVP) virtual patients were developed to examine the effects of SGLT1and SGLT2 co-inhibition.

Figure 1. The Platform was qualified according to Rosa's Model Qualification Method[1] (MQM)

Results

Renal SGLT function was incorporated with glucose metabolism.

- The Platform included representation of the first three segments of the proximal convoluted tubule (PCT) (Figure 2).
  - GFR regulates the flow of plasma to the PCT
  - Outputs in the Platform include plasma glucose and urine glucose
  - SGLT2i and SGLT1,2i regulated the flow of glucose from PCT to plasma
  - Plasma glucose metabolism was incorporated as a separate Platform module

Platform Results

The Platform includes a simplified representation of renal glucose transport

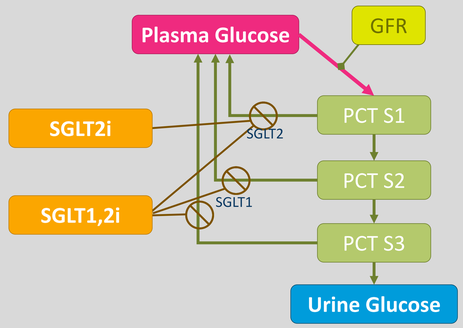

Figure 2. Graphical representation of the SGLT Platform

UGE is dependent on the activity of SGLT1, SGLT2, GFR and fasting and mean plasma glucose.

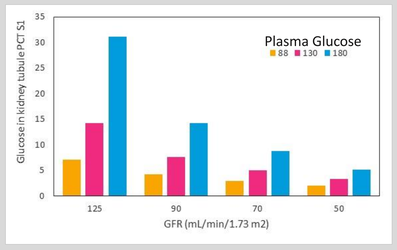

Figure 3. Simulated results show the relationship between plasma glucose and kidney function (GFR) in renal glucose resorption. A VP was simulated varying GFR and plasma glucose concentrations.

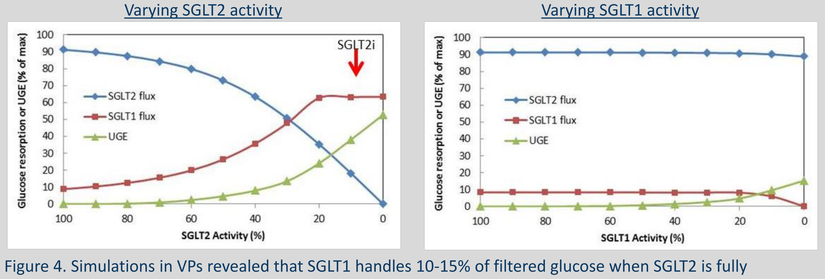

Figure 4. Simulations in VPs revealed that SGLT1 handles 10-15% of filtered glucose when SGLT2 is fully functional, and 60% of filtered glucose when SGLT2 is not functional demonstrating the adaptation of the kidney to SGLT2 inhibition.

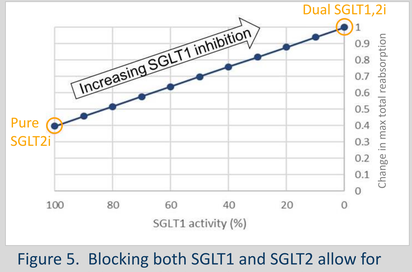

Figure 5. Blocking both SGLT1 and SGLT2 allow for greater inhibition of kidney glucose reabsorption. SGLT2 inhibition set at 100%.

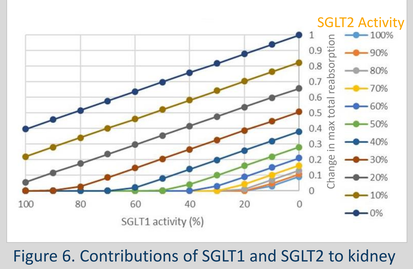

Figure 6. Contributions of SGLT1 and SGLT2 to kidney glucose reabsorption Sensitivity Analysis

The effect of SGLT1 inhibition alone on UGE is minor but may be significant with co-inhibition of SGLT2.

VPs & Clinical Tests

VPs were used to explore mechanistic uncertainties.

Alternative VPs were designed to explore the impact of variability in key pathways of interest:

- Explore interactions between kidney function and drug effects
- Explore interactions with fasting glucose
- Explore variability around drug function

Table 1. VP characteristics

Virtual Patient	FPG	FPI	HbA1c	HOMA-IR	GFR
	mg/dL	pM	%	%	mL/min/1.73 m2
DVP1	131	70	7.2	3.3	74
DVP2	134	82	7.2	3.9	110
DVP3	145	51	7.6	2.6	74
DVP4	145	68	7.5	3.5	96
DVP5	155	130	8.5	7.2	74
DVP6	178	42	9.3	2.7	25
DVP7	178	42	9.3	2.7	96
DVP8	187	67	9.2	4.5	74
DVP9	179	43	9.7	2.8	74
DVP10	179	43	9.7	2.8	50

SGLTis were tested to understand how the variability implemented in the VPs alters response to therapy. Empagliflozin was implemented as a pure SGLT2i with a hypothetical SGLT1,2i created by adding SGLT1i to empagliflozin (Figure 7). HbA1c was predicted from plasma glucose concentration.

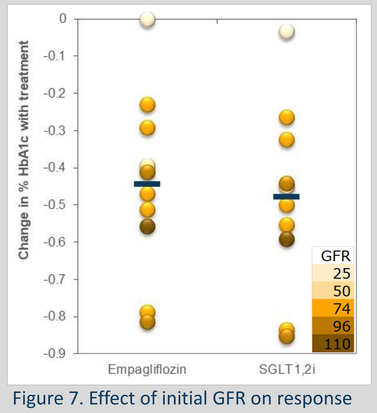

Figure 7. Effect of initial GFR on response to SGLTi. Bar marks median value.

Simulated co-inhibition of SGLT1 and SGLT2 demonstrated higher treatment effect among DVPs with high GFR and high baseline FPG. Reductions in HbA1c among DVPs were slightly greater with co-inhibition of SGLT1 and SGLT2 vs. inhibition of SGLT2 alone. Implementation of additional SLGT1 effects regulating glucose uptake in the intestine could increase the predicted efficacy.

Conclusions

- Co-inhibition of SGLT1 and SGLT2 may be an effective treatment for T2D with drug efficacy dependent the balance of SGLT1 vs. SGLT2 inhibition, kidney function and plasma glucose concentration.

References

1. Friedrich, CM. (2016) CPT: Pharmacometrics & Systems Pharmacology 5, 43-53 (MQM)
2. Schmidt H, Jirstrand M. (2006) Bioinformatics 22, 514-5 (SimBiology)
3. Frank TB, Ravishankar RV, Herbert MS. (2006) Current Proteomics 3, 181-97 (Jdesigner)

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