A Systems Approach to Accelerating the Pharmaceutical Industry Pipeline:

Competitive Preclinical and Clinical Modeling in Diabetes Drug Development

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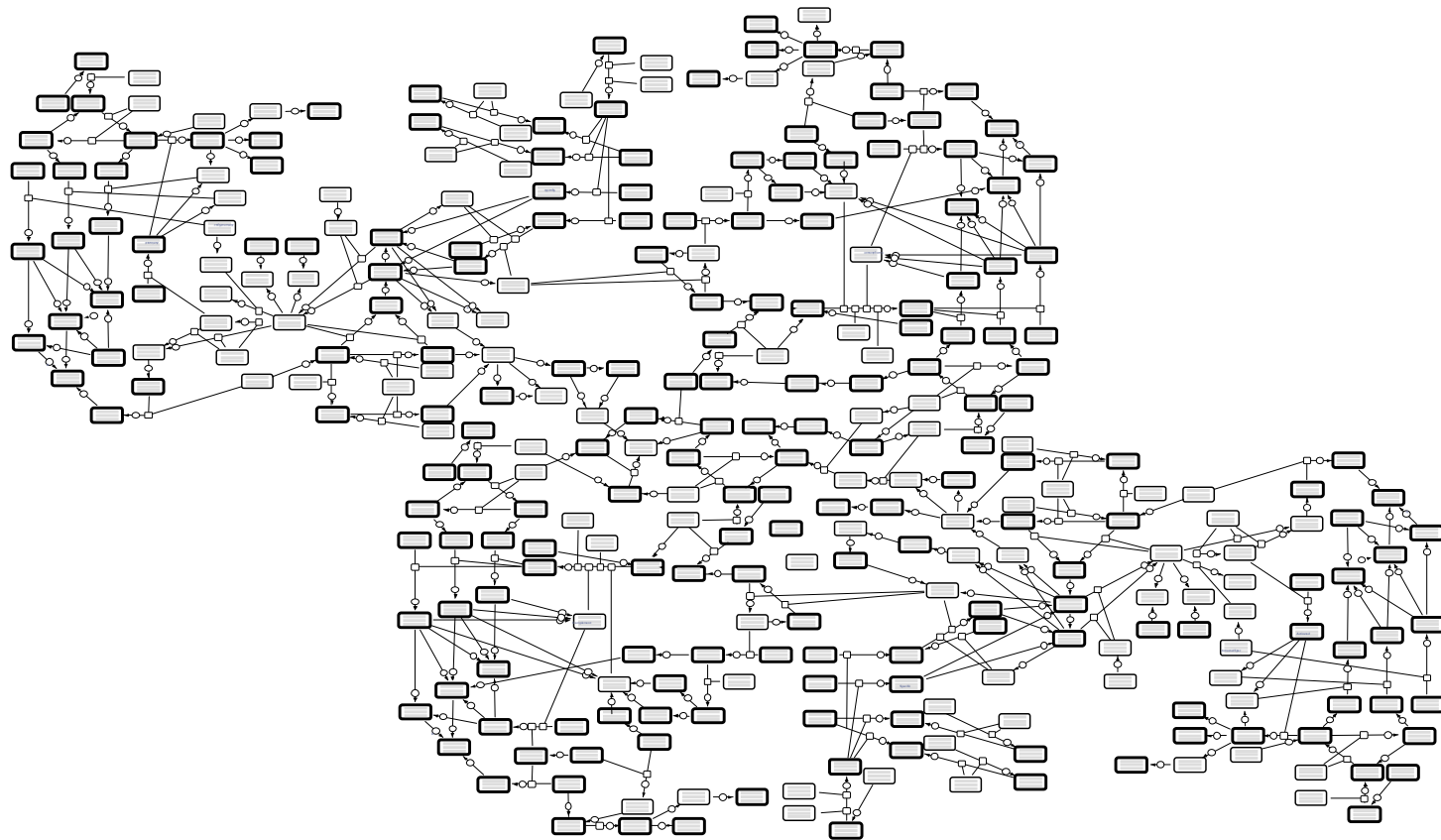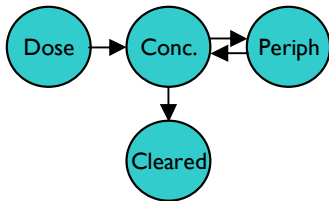[1] Pfizer Global Research & Development Groton, CT
[2] Entelos Inc., Foster City, Ca
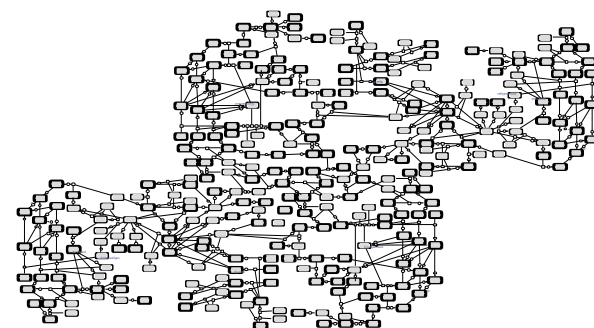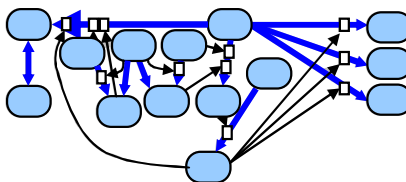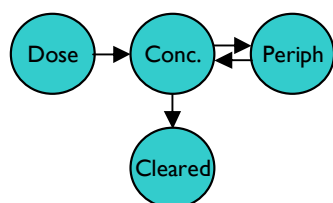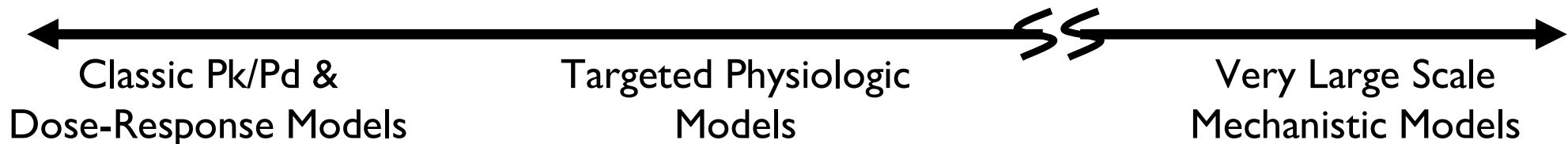[3] Rosa and Co., LLC, San Carlos, Ca

Models that help understand physiology, disease, drug action, and trial designs vary widely in scale and purpose.

PK/PD and Dose-Response Models

Very Large-Scale Mechanistic Models

# Each scale of model has different strengths and weaknesses.

| Classic Pk/Pd & Dose-Response Models	Targeted Physiologic Models	Very Large Scale Mechanistic Models
▸ Narrowly targeted	▸ Decision-focused	▸ Broadly applicable
▸ Few physiologic insights	▸ Mechanistically insightful	▸ Physiologically sound
▸ Require human data	▸ Exploits nonclinical data	▸ Can use nonhuman data
▸ Lower cost	▸ Detail & cost focused on decision	▸ Significant investment
▸ Statistically rigorous	▸ Useful for trial simulation	▸ Not statistically tractable
▸ Phenomenologic	▸ Not general purpose	▸ Difficult to modify

Pfizer & Rosa created the Pfizer Diabetes Model with physiology targeted at addressing program decisions.
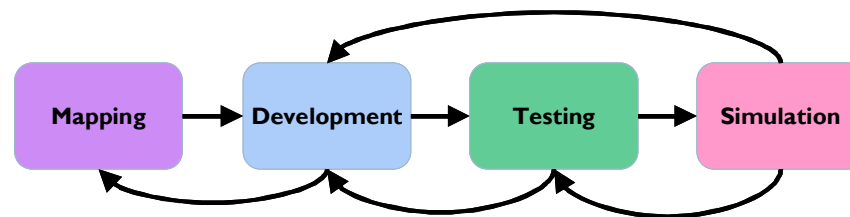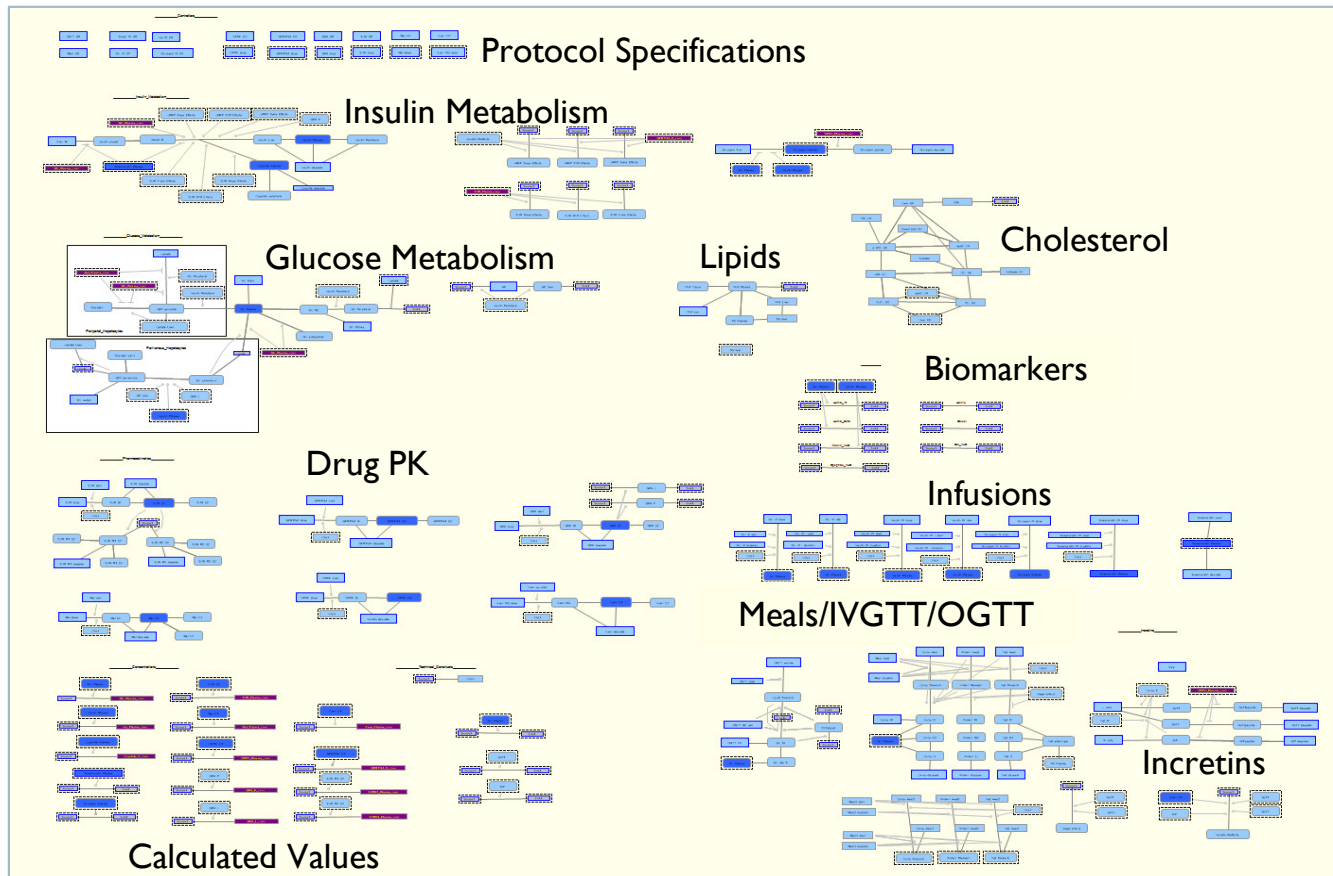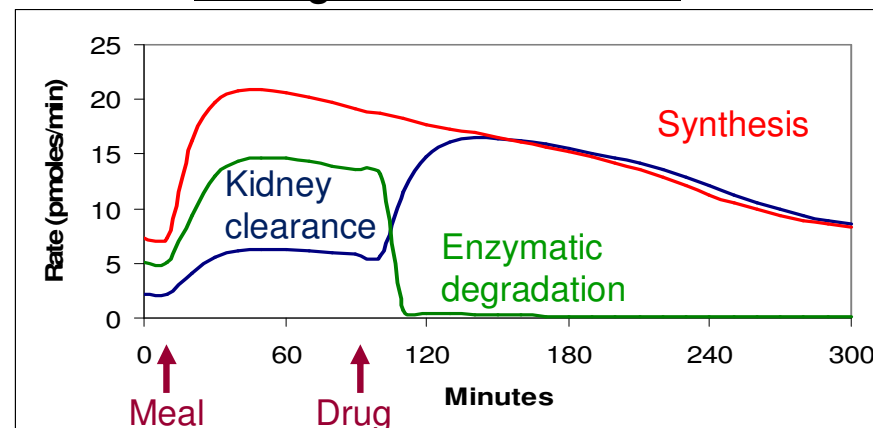
The model represents relevant pathways and drug actions at a level required to address the specific questions.
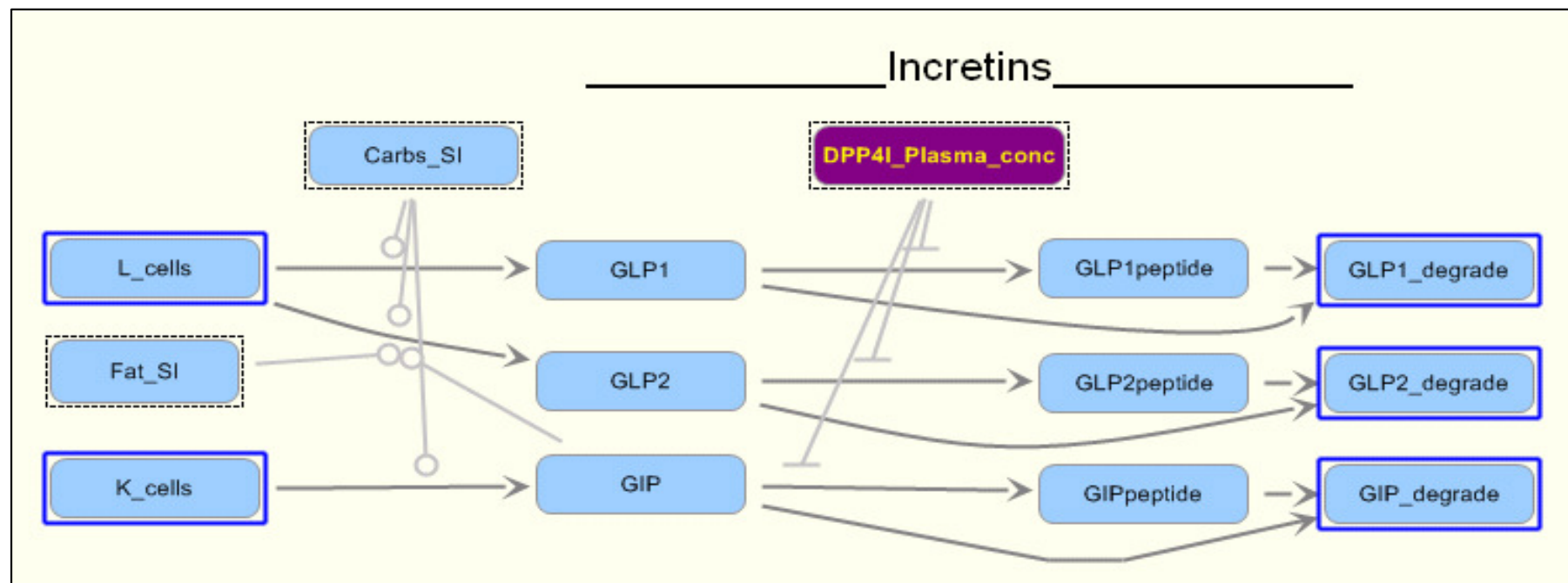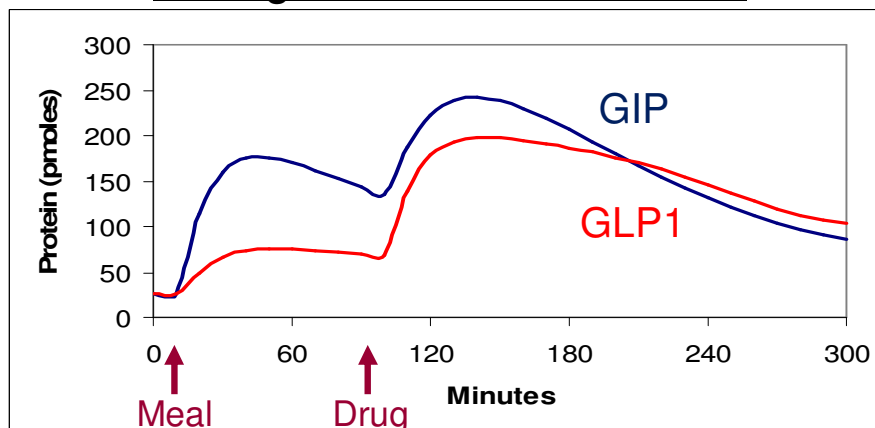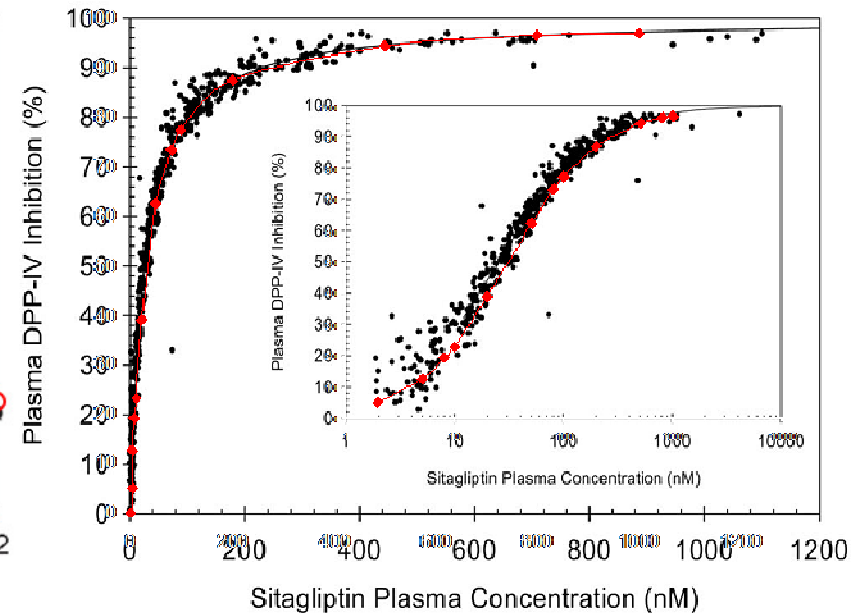
Including drug PK and drug action allowed both component and whole body testing of the model. This built trust in model.
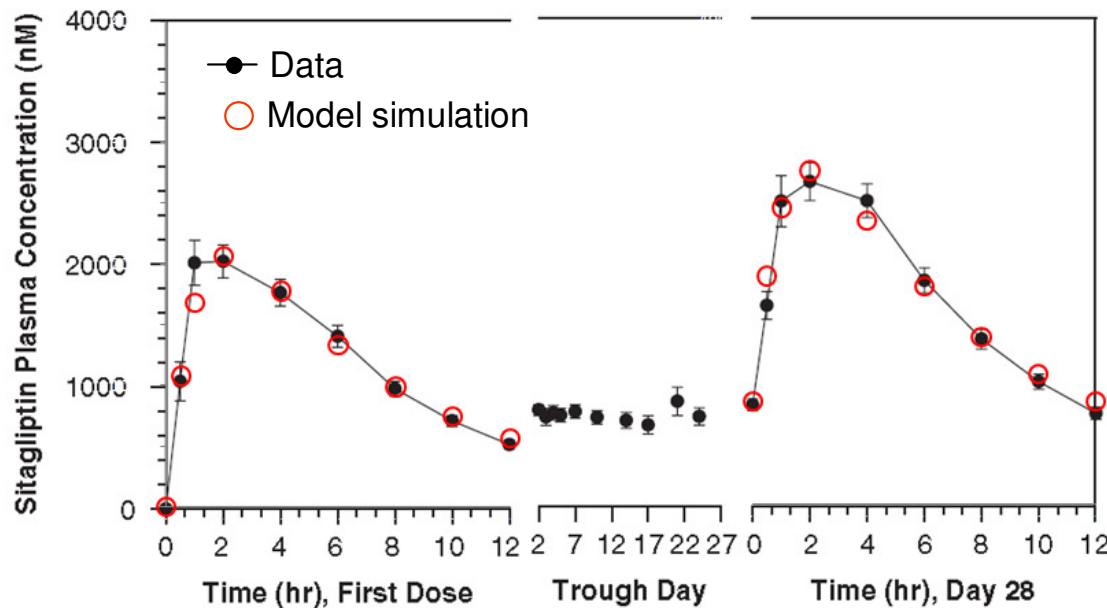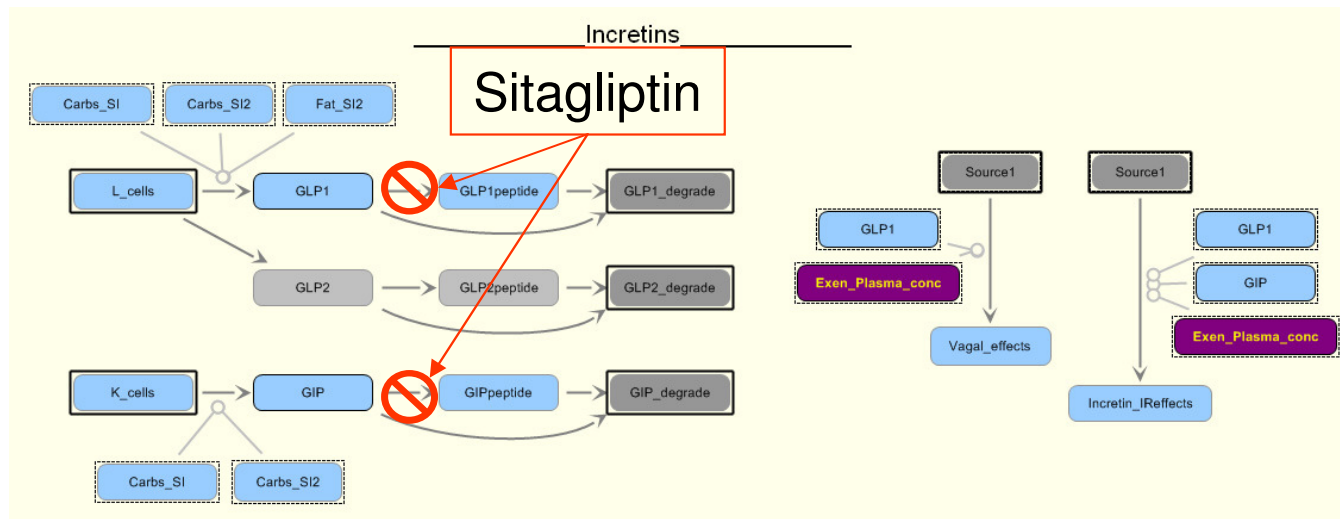
Herman et al. 2005

Additional targets and mechanism of action were added to the Pfizer Model as needed.

Small intestine
Intestines
SGLT1
Kidney
Glucose
Glomeruli
Blood vessel
SGLT2
SGLT1
Urine
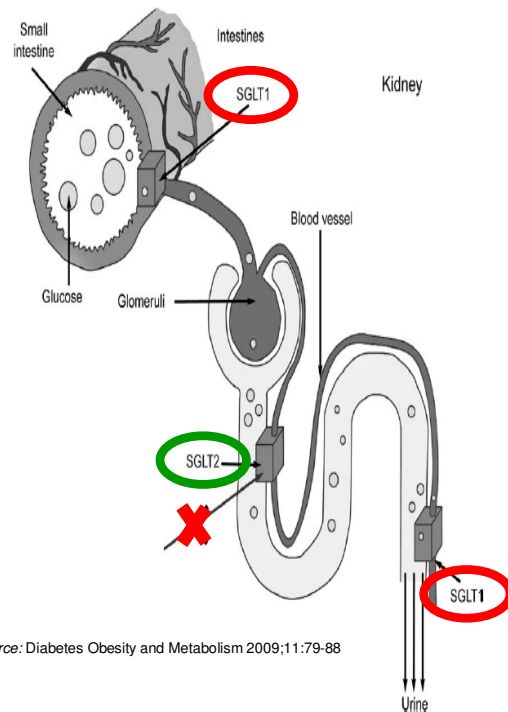
Source: Diabetes Obesity and Metabolism 2009;11:79-88

SGLT2 inhibitors promote Urinary Glucose Excretion Leading to:

- Plasma Glucose (PG) Lowering
- Weight Loss
- Favorable Blood Pressure Lowering

Urinary Glucose Excretion (UGE) provides a readily accessible mechanism based biomarker for clinical assessment

SGLT2 inhibitor PK and MOA were rapidly incorporated into and tested in the Pfizer Diabetes model.

SGLT2 inhibitor PK model accounts for fed/fasted state.
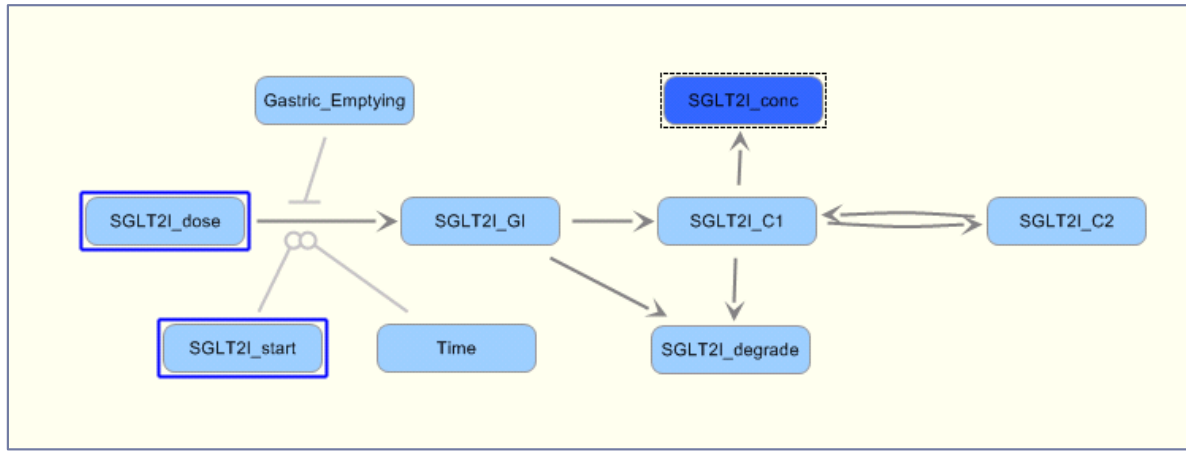
The Pfizer Diabetes Model was used to simulate chronic SGLT2i dosing in T2DM patients and healthy subjects.

The Model includes approximately 60 virtual patients, and more are currently being developed.

SGLT2 inhibitor PD action is based upon public data.
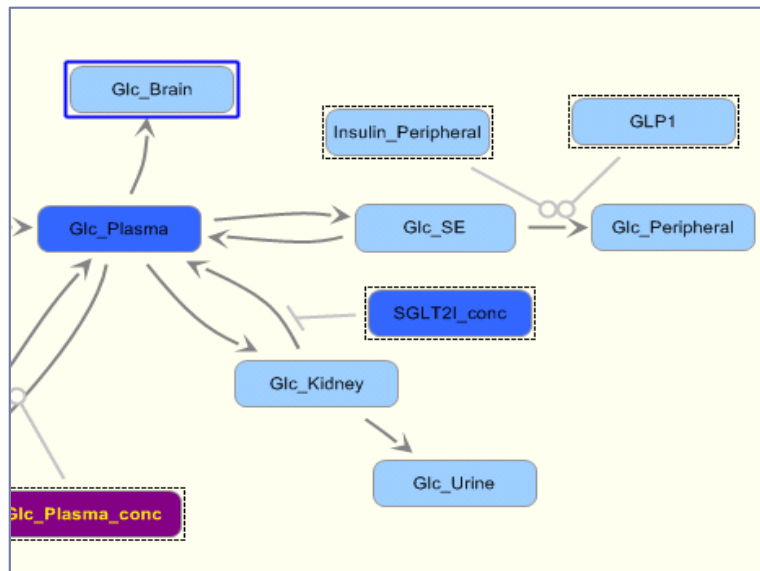
Simulations of chronic dosing in T2DM Subjects

- Clinical Data – Komoroski 2009
- DAPA Simulations - Pfizer/Rosa Model
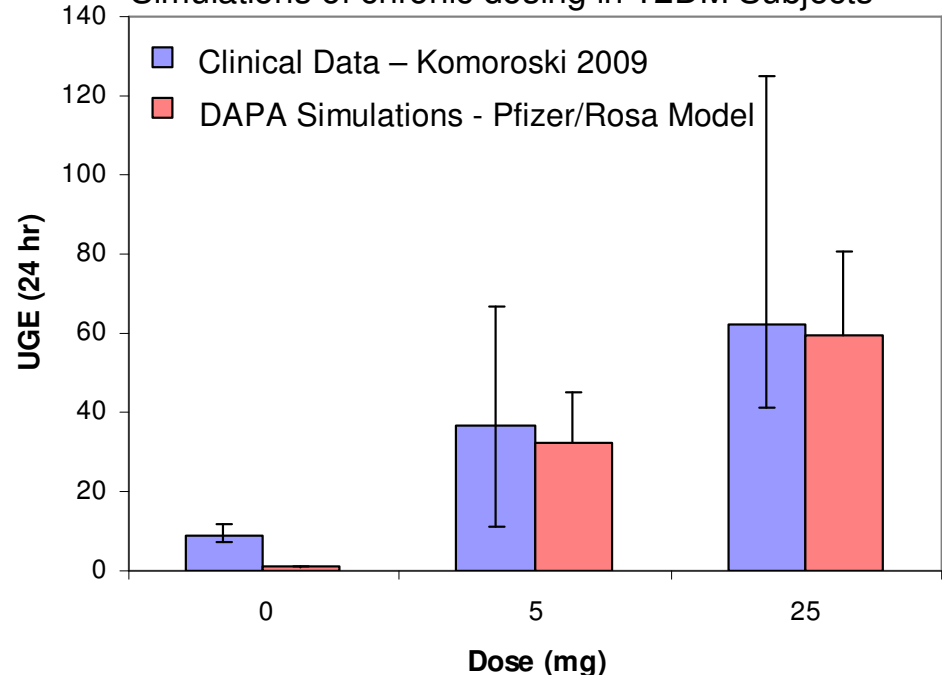
The Pfizer Diabetes Model is a <u>medium-scale</u>, targeted physiological model which yielded significant program impact.

- Collaborative development over a period of a few months

- Model accepted, adopted, and used by expert modelers and the clinical team

- Physiology is focused on and impacted program-relevant decisions

- More easily-understood model scale, for better regulatory discussions

- Rapid additions to the model allow use with new drug classes and targets

- Model represents selected targets well, but does not contain <u>all</u> targets

The same SGLT2I mechanism was modeled using a very large mechanistic model.

▸ Integrate:

  ▸ Available data on Pfizer Internal Candidate

  ▸ Physiological Understanding of the Mechanism of Action
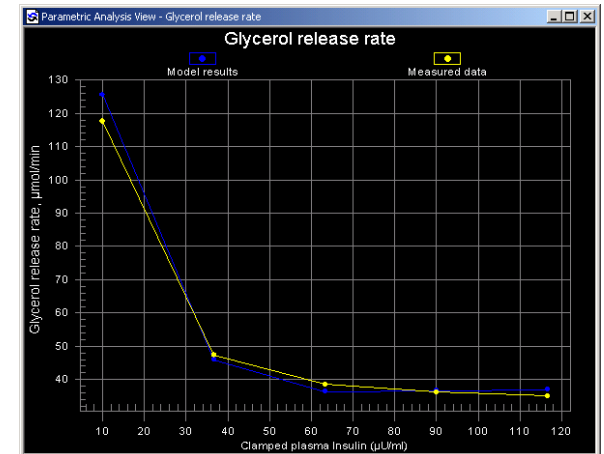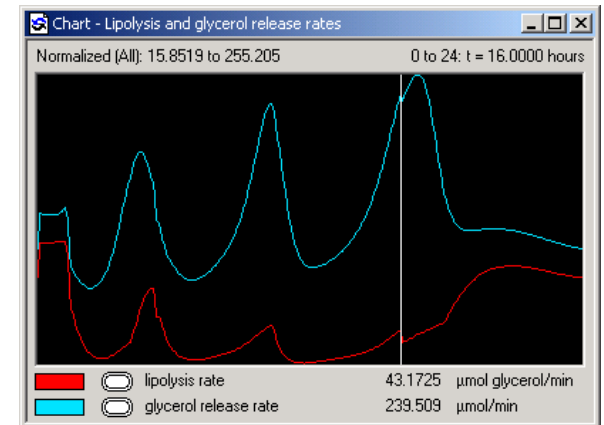
  ▸ Published Public Data on other SGLT2 compounds

▸ Within an Entelos Based Systems Model to improve :

  ▸ Clinical Trial Design

  ▸ Doses

  ▸ Dosing Regimens

Entelos Overview – SGLT2i

Systems Modeling used to predict human response and improve decision making throughout pipeline.

Target Selection → Lead Optimization → Clinical Development → Product Realization
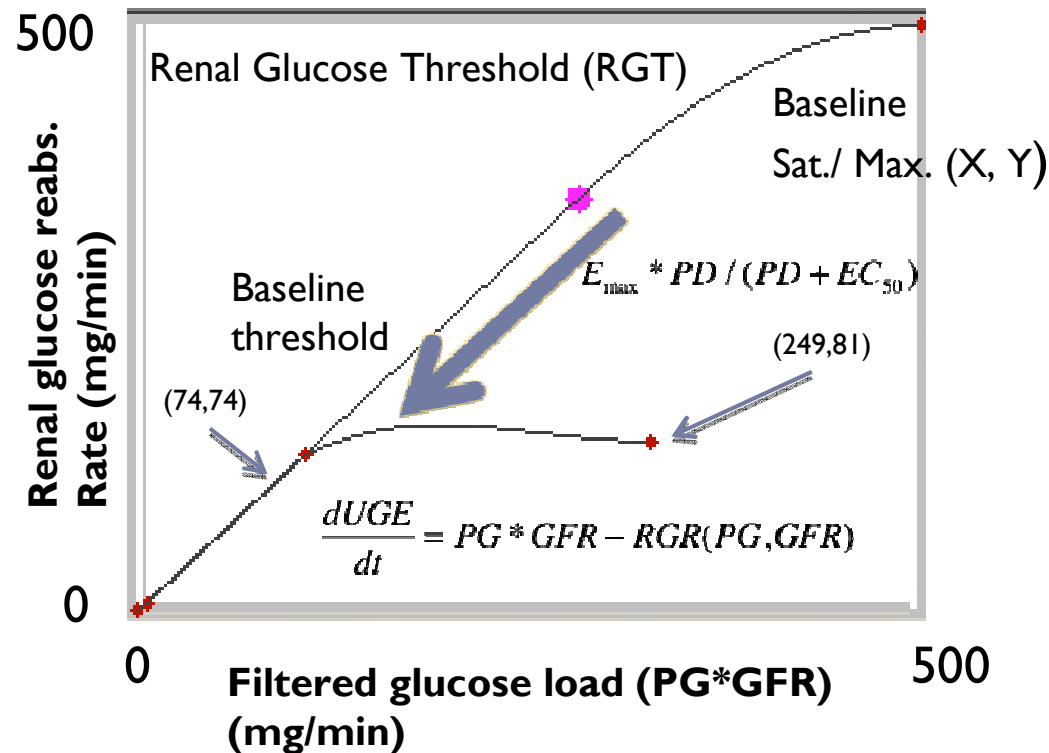
Qualitative relationship between plasma glucose and urinary glucose excretion

- Urinary glucose appearance is a function of:

  - GFR: Glomerular Filtration Rate

    60 – 135 ml/min

  - RGT: glucose reabsorption threshold

    Baseline Threshold 200 – 275
    Baseline Saturation 375 – 450
    Baseline Maximum 295 - 360

  - Plasma glucose

- In T2D virtual patients, the impact of variability in GFR and RGT on SGLT2 inhibitor efficacy was explored

  – An increase in RGT (i.e., increased SGLT2 expression) was generally required to eliminate UGE in untreated T2D virtual patients

Renal Glucose Reabsorption Rate

Renal Glucose Threshold (RGT)

Baseline Sat./ Max. (X, Y)

Baseline threshold

$E_{max} * PD / (PD + EC_{50})$

(249,81)

(74,74)

$$\frac{dUGE}{dt} = PG * GFR - RGR(PG, GFR)$$

Renal glucose reabs. Rate (mg/min)

Filtered glucose load (PG*GFR) (mg/min)

$$\frac{dUGE}{dt} = \begin{cases} PG(t) < RGT, & 0 \\ PG(t) > RGT, & GFR(PG - RGT) \end{cases}$$

Initial PD representation in model tuned to DAPA

Methods

- Clinical data from Komoroski, 2009a,b (SAD/MAD in healthy subjects and T2D patients)
- Clinical trial protocols, including meal timing and composition, were implemented
- For HNV, n=1 virtual patient
- For T2D, n=98 virtual patients prevalence weighted for GFR

This representation was validated using publicly disclosed information on the PK and UGE profile for a competitor SGLT2 inhibitor in both HV and T2D patients in studies spanning from single dose to multiple dose trials and with different meal protocols [5,6,7]
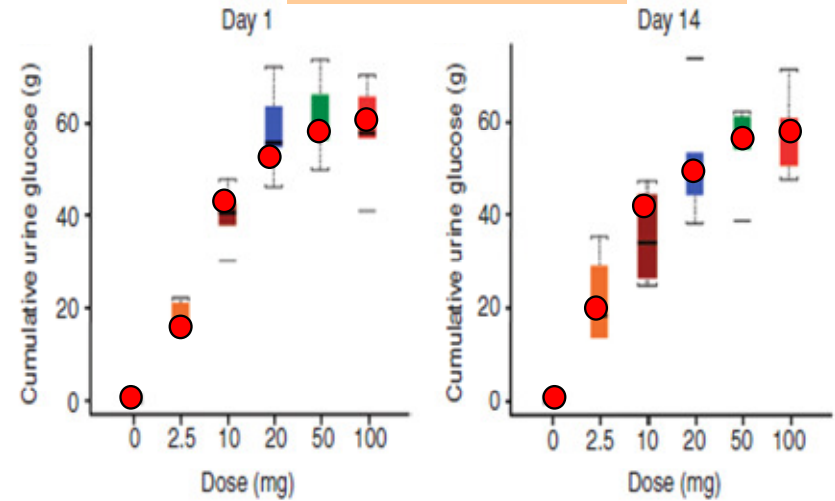

Healthy Volunteers
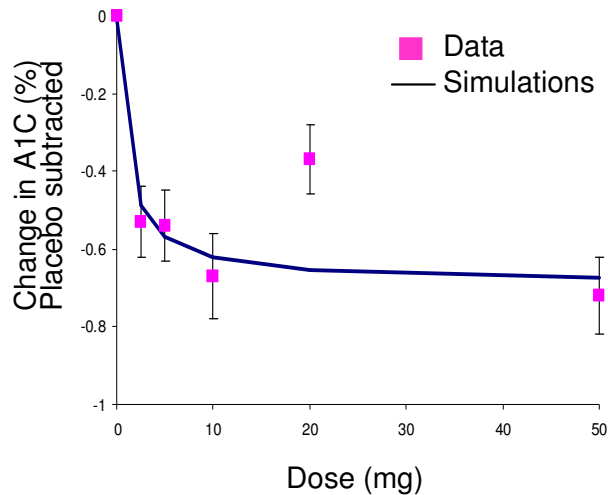
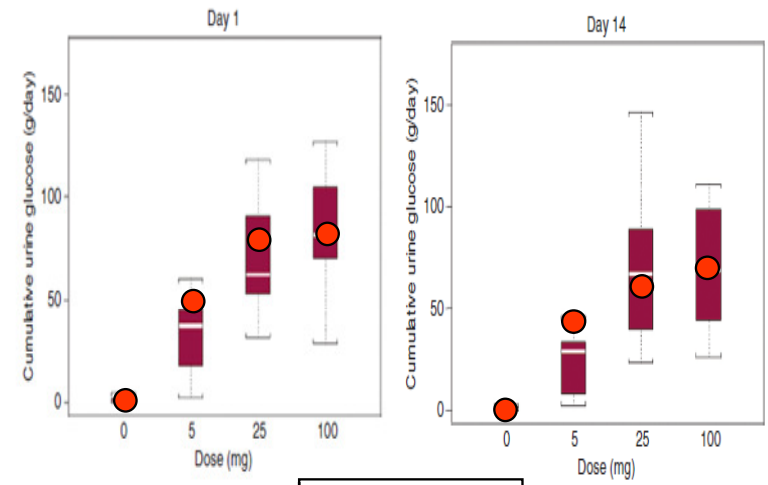

Type 2 Diabetic

Summary

- Acute and chronic UGE predictions were generally consistent with observed data in HNV (upper figures) and T2D patients (lower figures)
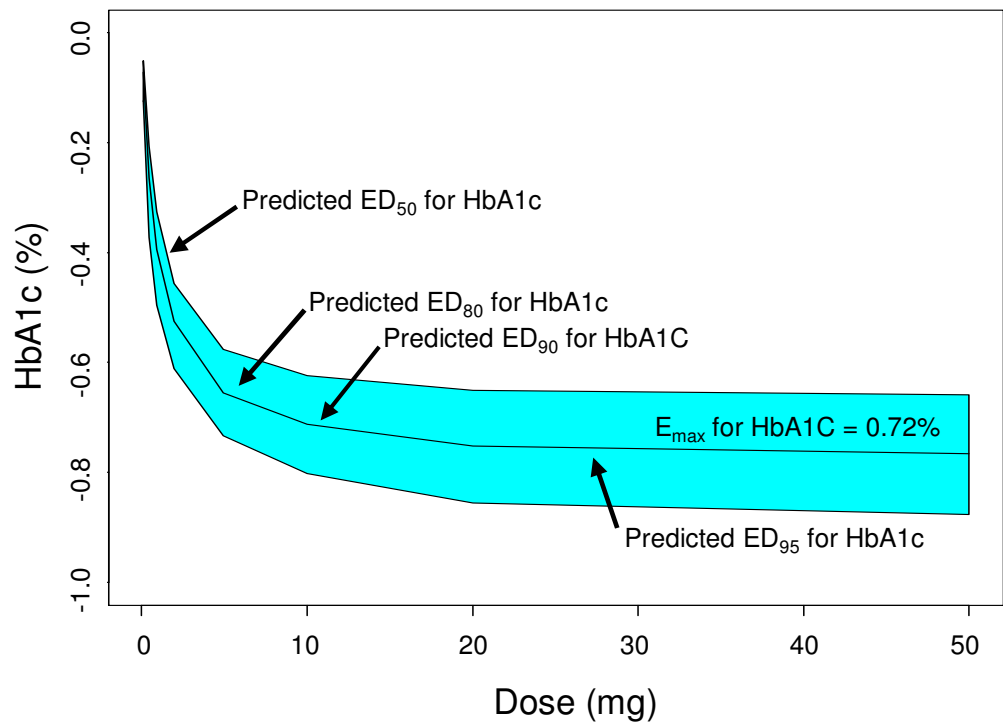
Published Clinical Data and Simulation Results

Internal Pfizer Candidate

▶ **Model Design (Based on FIH data):**

- ▶ Study Design: Dosing Protocol, Meals, HV Characteristics incorporated into Physiolab Platform.

- ▶ PK: As soon as internal candidate PK became available, popPK parameters included in platform representation.

- ▶ PD: Drug potency (EC50), and maximal effect (Emax) tuned in "real time" to match observed exposure-response characteristics (24 hr UGE, time course UGE).

▶ **Model Prediction:**

- ▶ FIH parameterized Model

- ▶ HV Derived Model used to simulate T2D 12 week studies

FIH UGE Response

Predicted Placebo Adjusted Change from Baseline

HbA1c (%) vs Dose (mg)

- Predicted ED$_{50}$ for HbA1c
- Predicted ED$_{80}$ for HbA1c
- Predicted ED$_{90}$ for HbA1C
- E$_{max}$ for HbA1C = 0.72%
- Predicted ED$_{95}$ for HbA1c

FIH Biomarker Dose Response

UGE (g) vs Treatment (A, B, C, D, E, F, G)
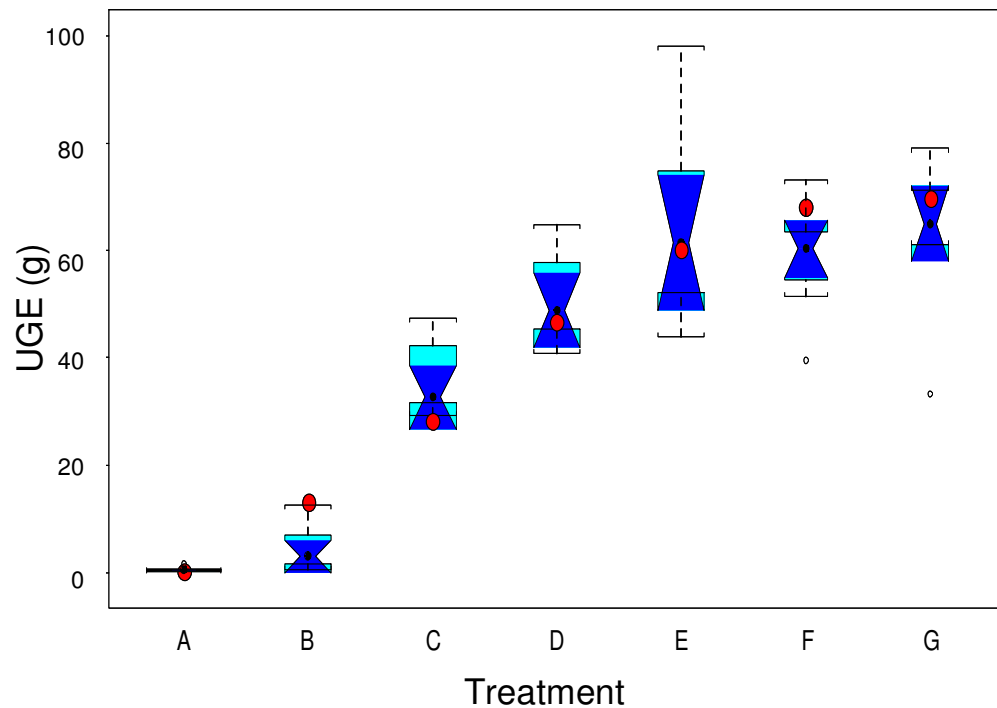
Example 2: Conclusions

▸ SGLT2i / Systems Pharmacology Modeling:

  ▸ Design Lean / Informative Phase I Program

  ▸ Update "real time" PK and PKPD during the course of the FIH trial

    ▸ Analysis provided Dose Rationale and Design for Dose Ranging Studies

    ▸ Combine Phase IIa and IIb

    ▸ Generate / test *in silico* quantitative hypotheses for differentiation from Competitor SGLT2i.

Acknowledgements

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