Creating and Using a Physiological Model to Evaluate GPR119 Agonism as a Diabetes Therapy

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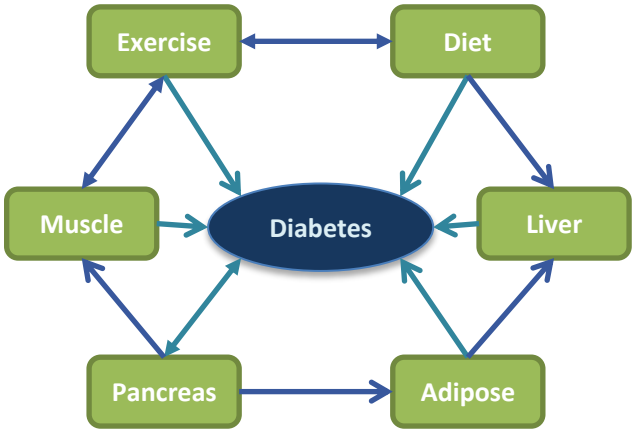
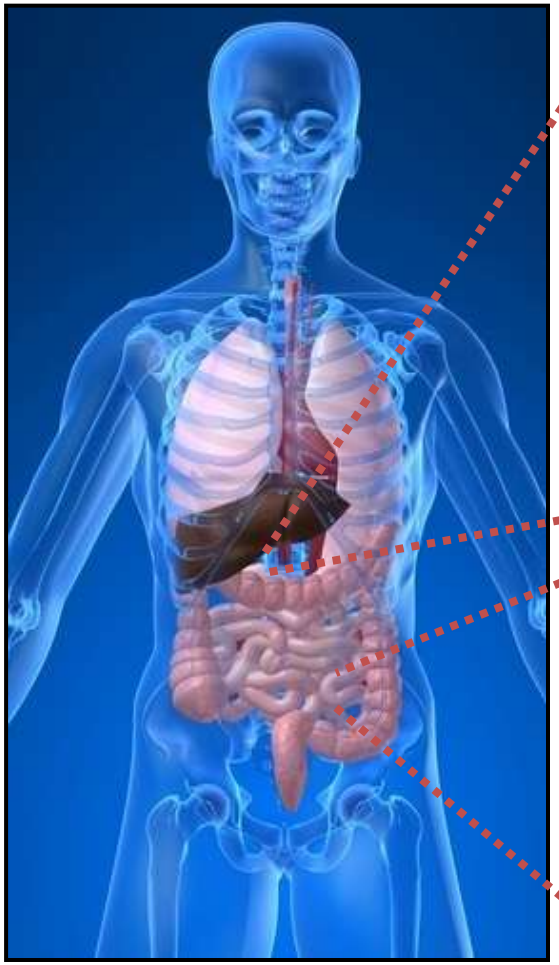
Diabetes

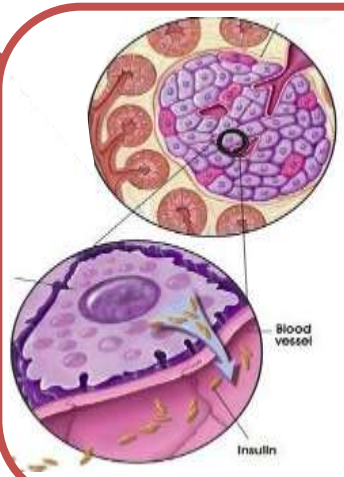
- Complex disease with multiple interacting systems
- Co-administered drugs
- Difficult to get drug approval
  - Other drugs on market
  - Cardiovascular impact
  - Efficacy can cause adverse events



GPR119: Class A GPCR

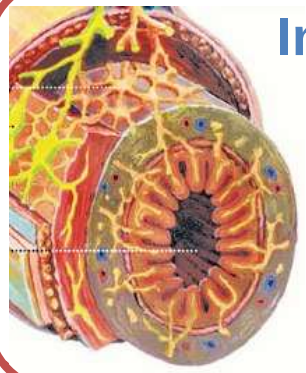
Two Sites of Action For Better Glycemic Control





Pancreas (islets):

- Increases intracellular cAMP
- Augments glucose-stimulated insulin secretion (direct effect)



Intestines (enteroendocrine cells):

- Increases secretion of gut peptides
  - GLP-1
  - GIP
  - PYY

} incretins — indirect effect

Why a Mechanistic, Physiological Model?

- Clarify mechanism of action
- Identify drivers of clinical response
- Evaluate drug class before clinical studies
- Address complexity in a quantitative manner
- Analyze mechanistic patient variability
- Comparative efficacy of competitor's drugs
- Optimize compound characteristics
- Identify limitations of animal models
- Set first-in-human dose

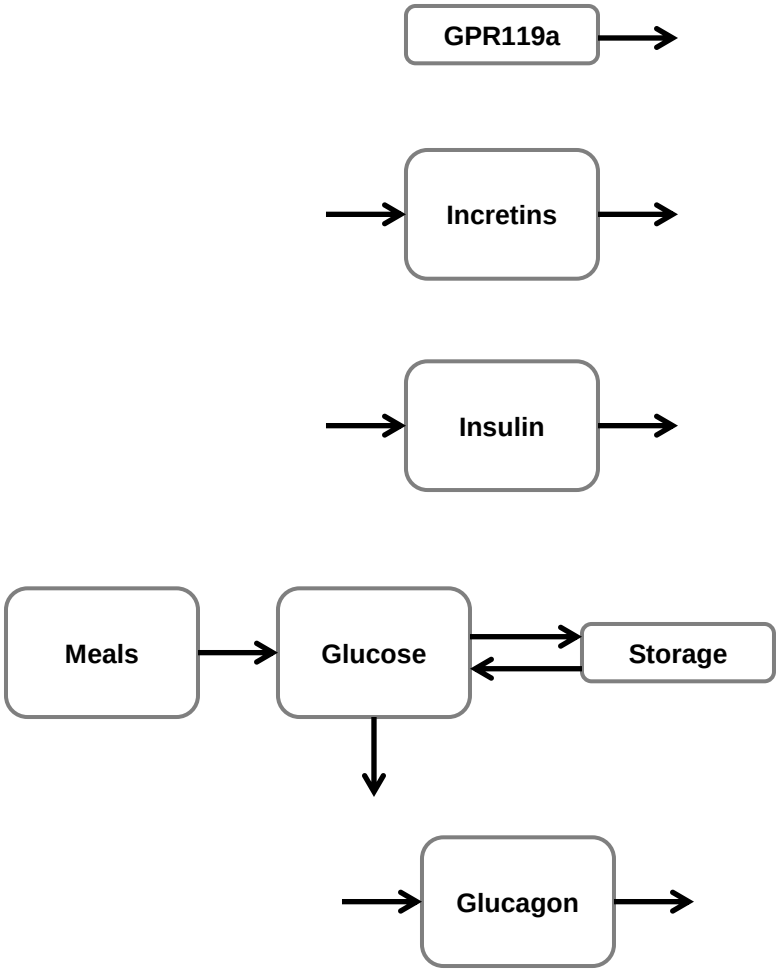
Physiological Model Goals

- Evaluate potential of GPR119 agonism as a diabetes therapy
  - Can GPR119 agonism provide comparable glucose control to current therapies (*e.g.* sitagliptin or exenatide)?
- Understand the relative contributions of direct and indirect action of GPR119a on glucose control
- Develop an internal knowledgebase of systems pharmacology model
- Serve as a platform for future target evaluations

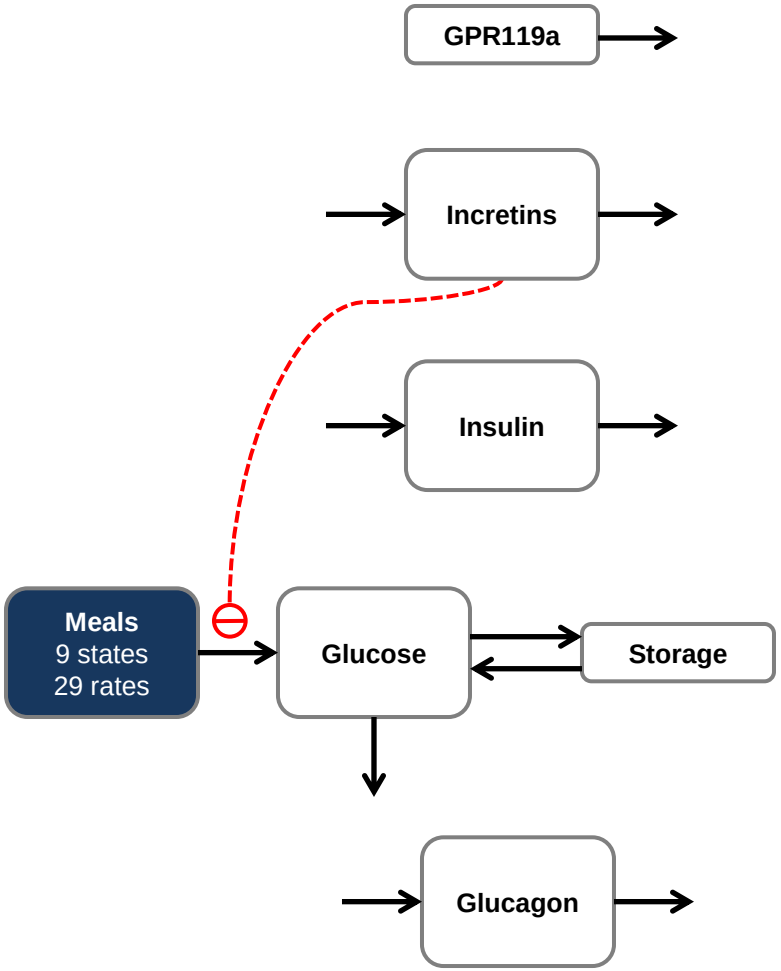
Physiological Model Constraints

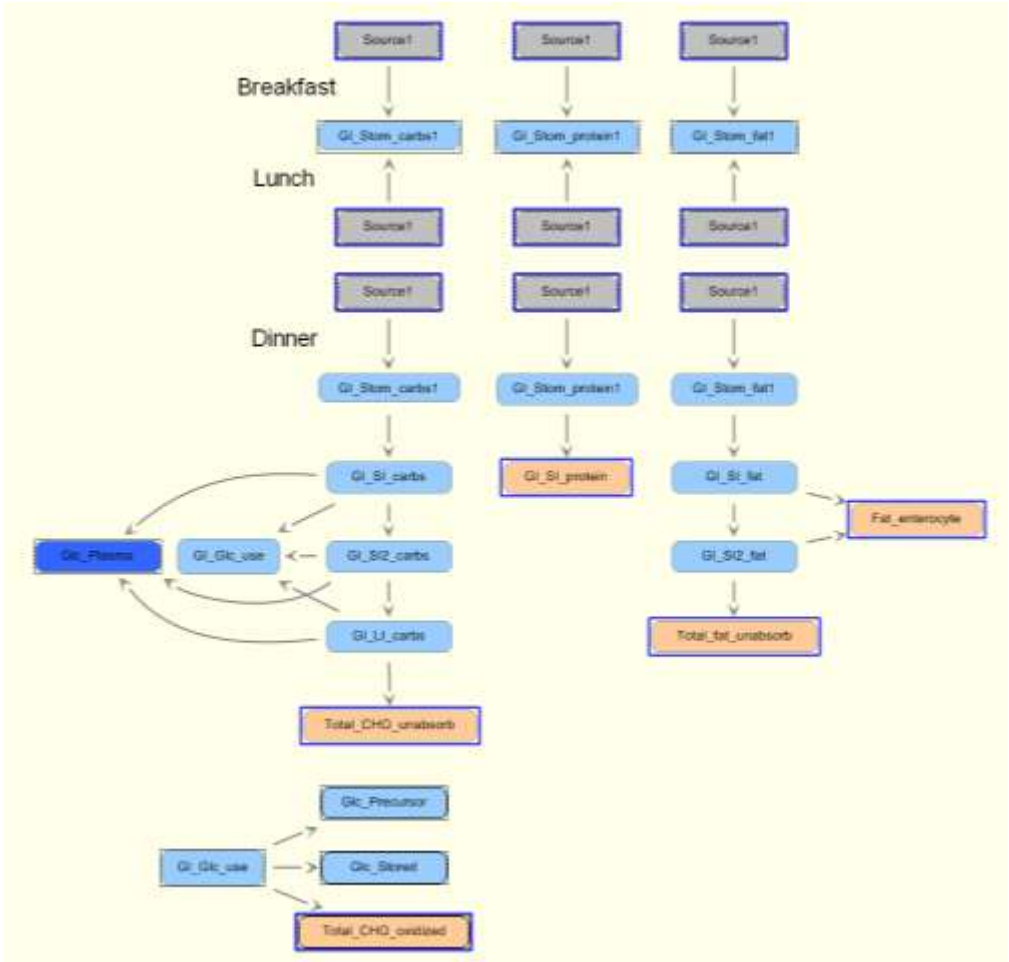
- A mass balance model of glucose metabolism
  - Sedentary lifestyle
  - Energy homeostasis (± 100 kcal/day)
  - No starvation; overnight fasting only
  - Proteins and fat utilization assumed
- Subchronic model (≤ 12 weeks)
  - No long-term disease progression or reversal by therapies

Model Modules

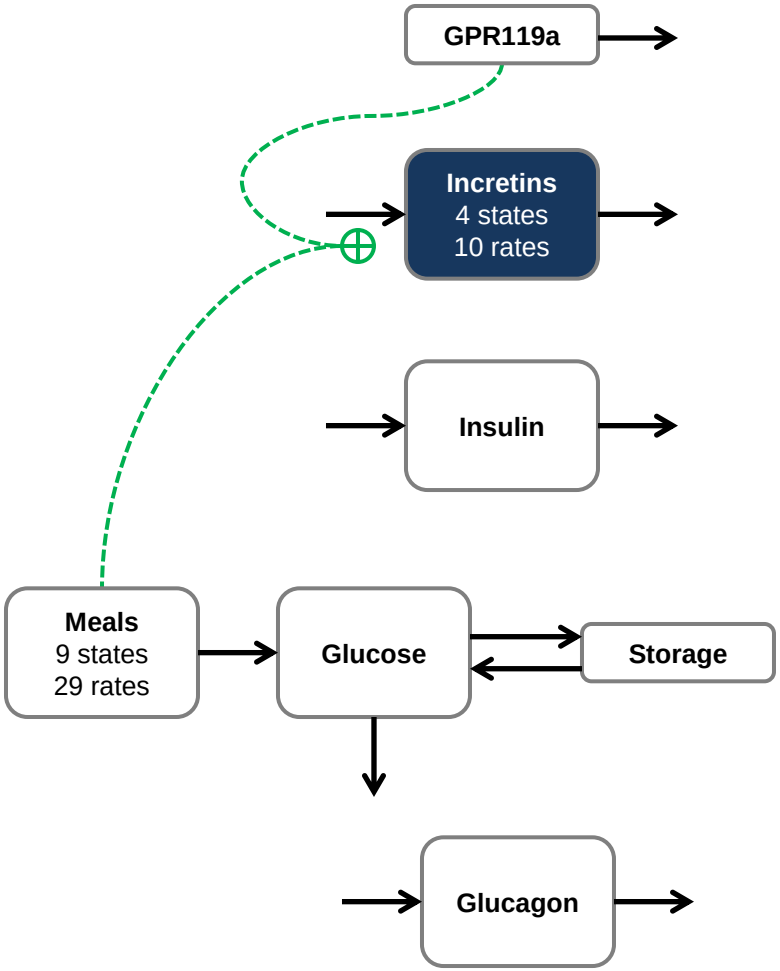


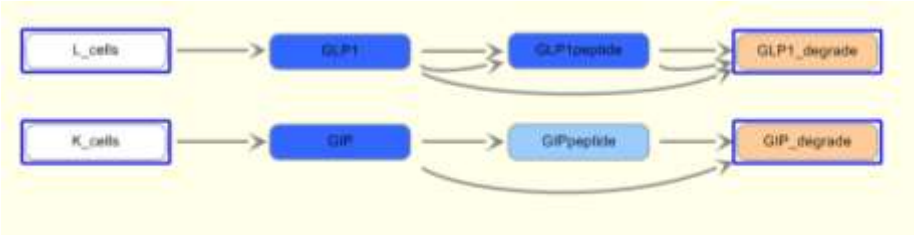
Glucose Absorption



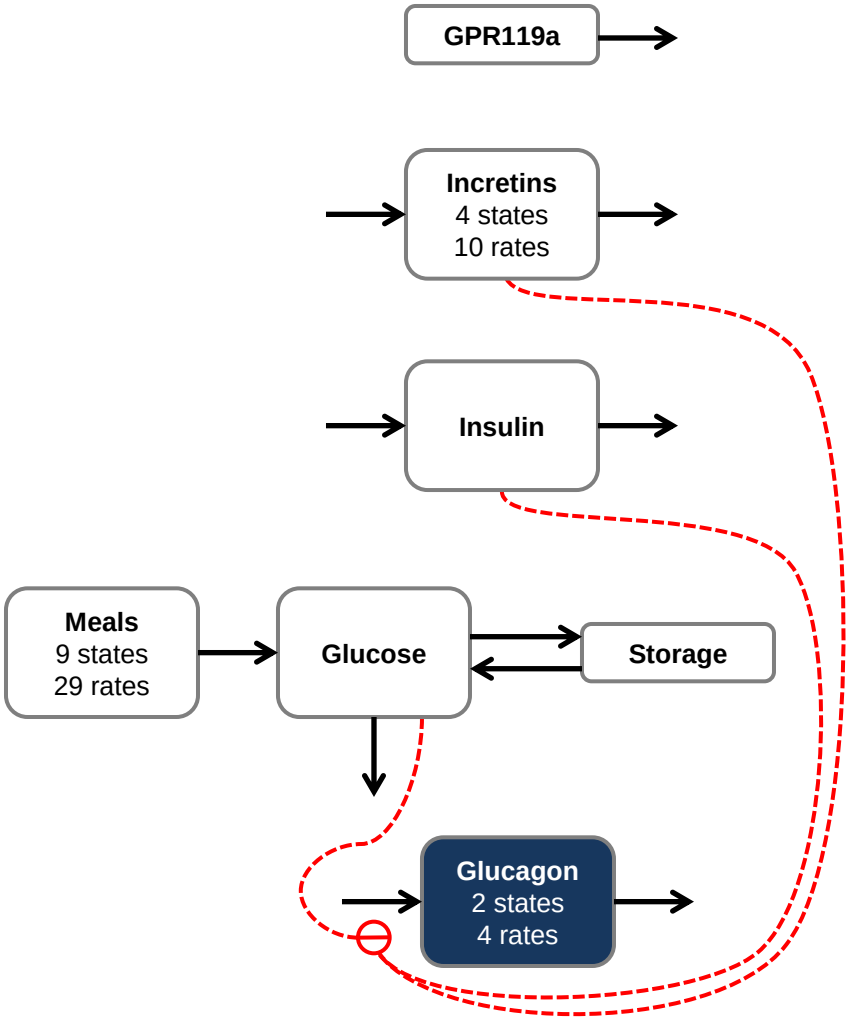


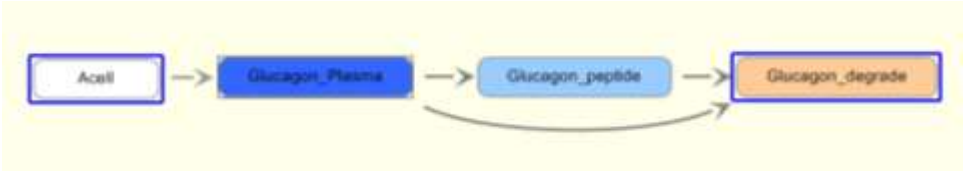
Incretins


GPR119a
Incretins
4 states
10 rates
Insulin
Meals
9 states
29 rates
Glucose
Storage
Glucagon

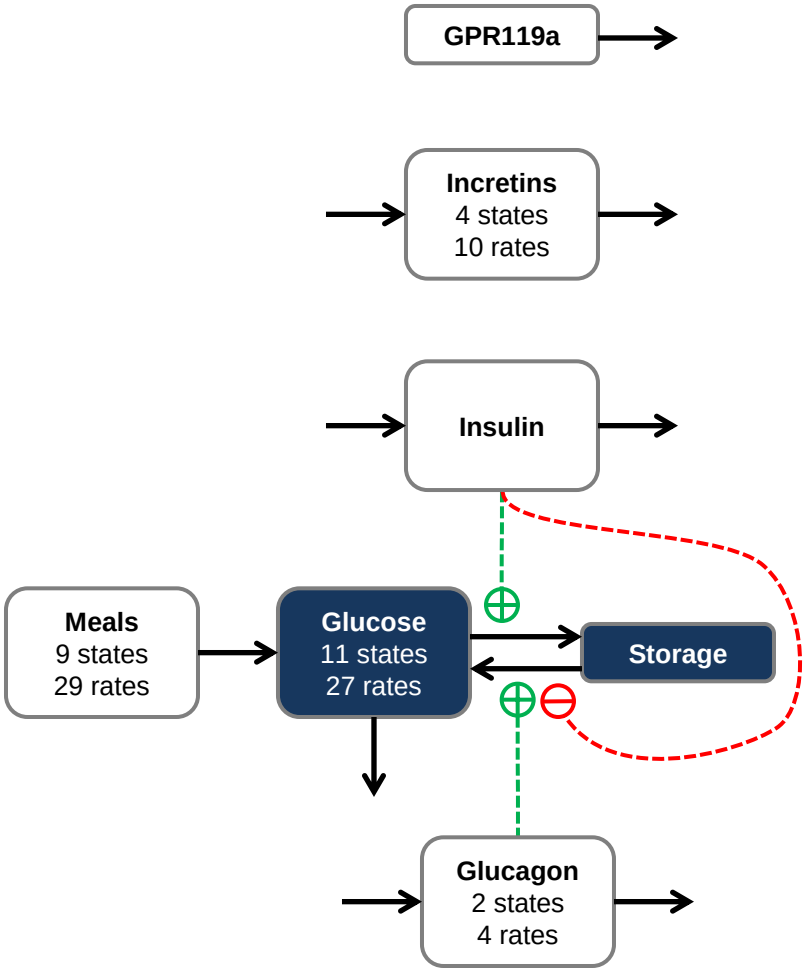

L_cells
GLP1
GLP1peptide
GLP1_degrade
K_cells
GIP
GIPpeptide
GIP_degrade

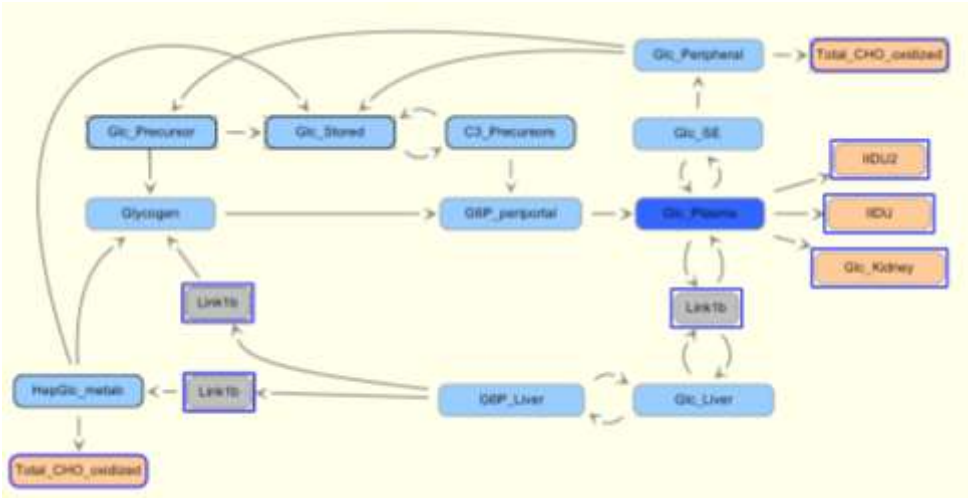
Glucagon


GPR119a
Incretins
4 states
10 rates
Insulin
Meals
9 states
29 rates
Glucose
Storage
Glucagon
2 states
4 rates

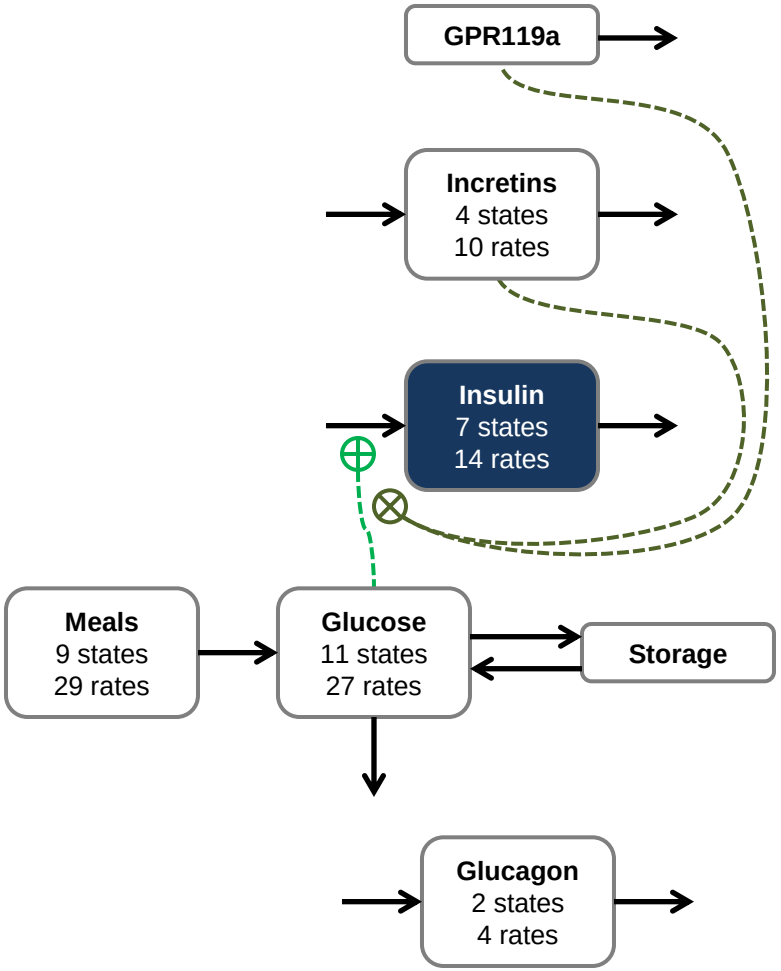

Acsll
Glucagon_Plasma
Glucagon_peptide
Glucagon_degrade

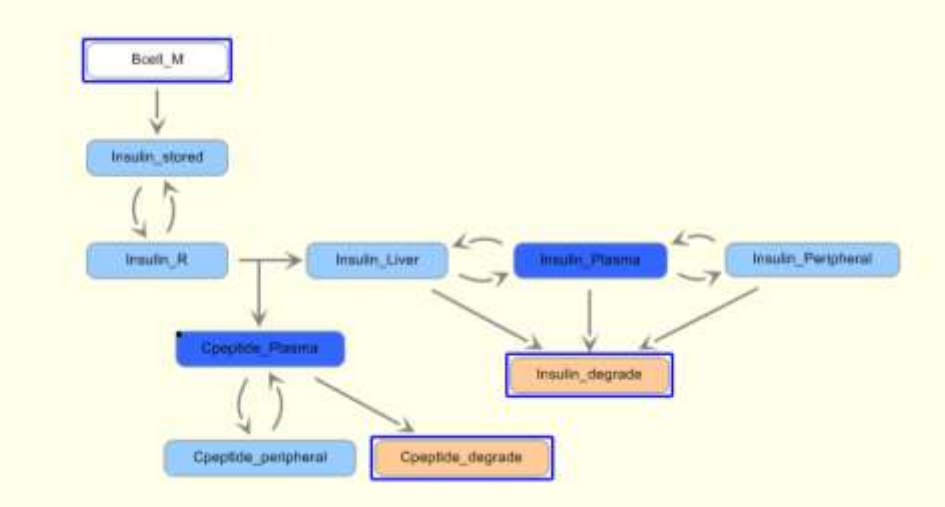
Glucose


GPR119a
Incretins
4 states
10 rates
Insulin
Meals
9 states
29 rates
Glucose
11 states
27 rates
Storage
Glucagon
2 states
4 rates



Insulin & C-peptide





Model Calibration

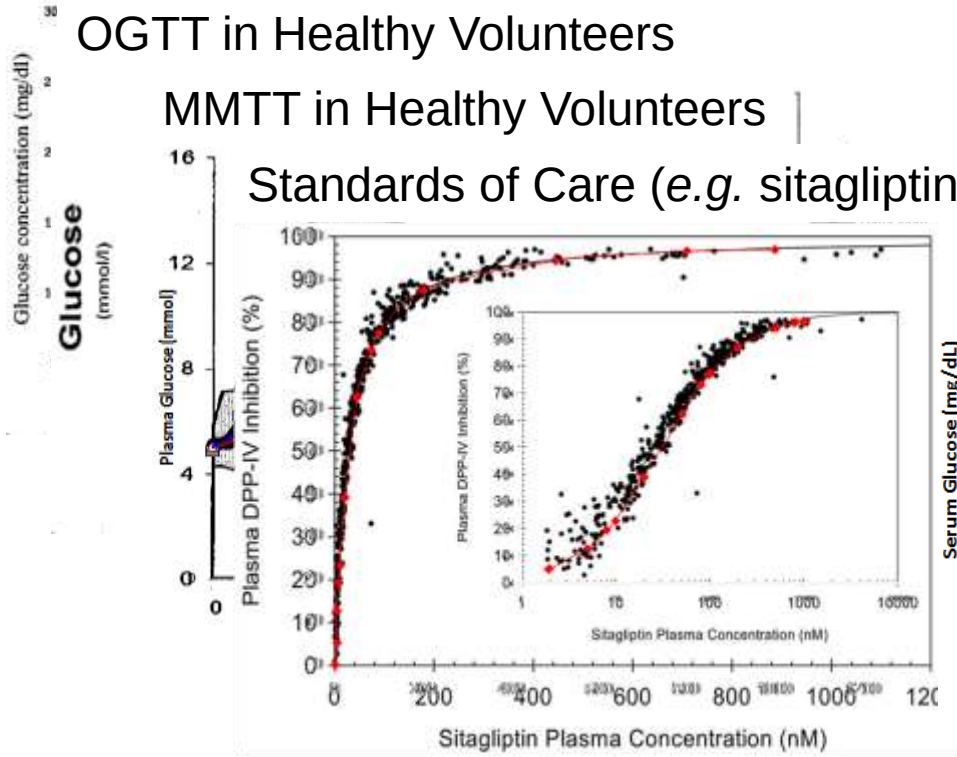
- The model was calibrated with hundreds of literature citations
- Approximately 10% withheld for final validation

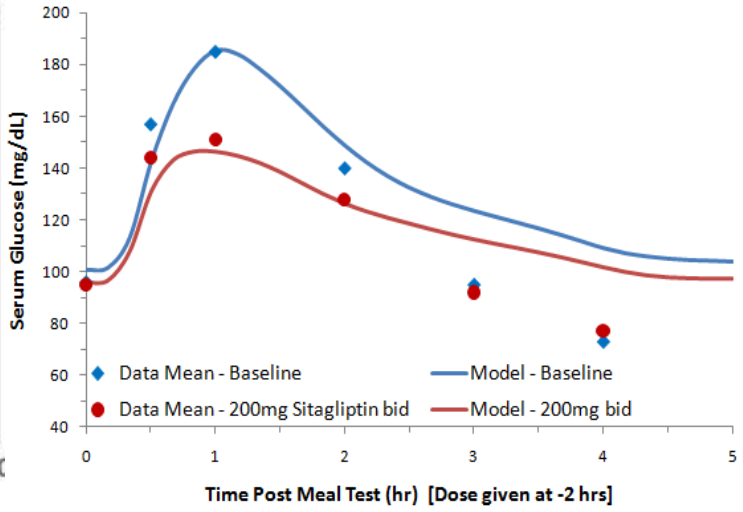
IVGTT in Healthy Volunteers

OGTT in Healthy Volunteers

MMTT in Healthy Volunteers

Standards of Care (*e.g.* sitagliptin)





GPR119a Parameterization

- Data reported for GPR119 agonism are sparse
- Metabolex described clinical results at ADA conferences[1,2]

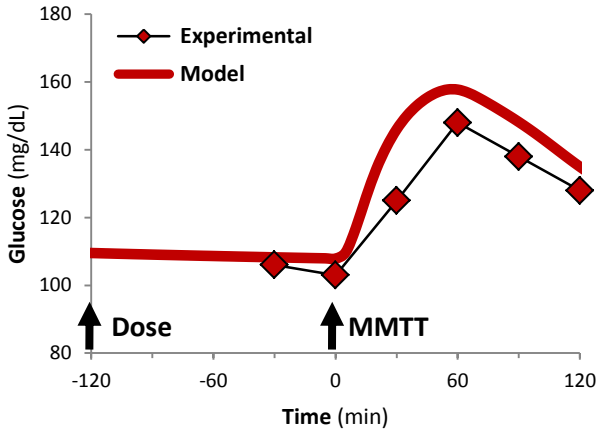
  MBX-2982 results are the only available GPR119a clinical data
  - Single and multi-dose PK
  - Mixed meal tolerance (MMTT)
    - Glucose lowering
    - Total GLP-1
- These data were used in our model to evaluate GPR119a

[1] Roberts, B., et al. (2009). "American Diabetes Association 69th Annual Scientific Sessions," New Orleans, LA, USA, 5–9 June, Abstract 164-OR.
[2] Roberts, B., et al. (2010). "American Diabetes Association 70th Annual Scientific Sessions," Orlando, FL, USA, 25–29 June, Abstract 603-P.

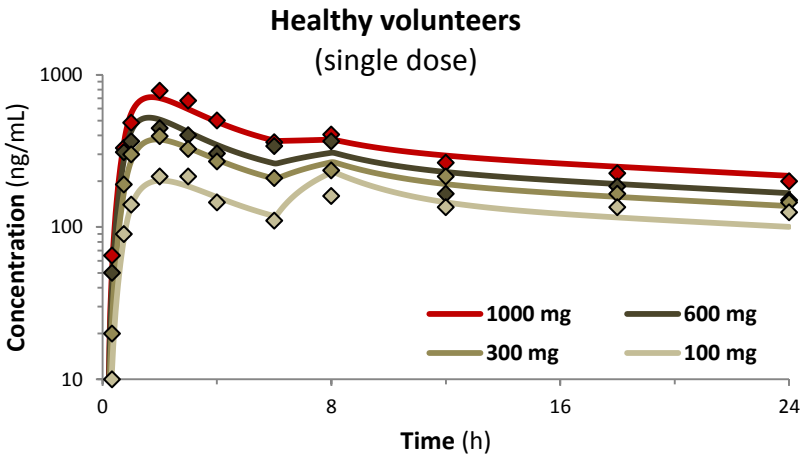
MBX-2982 Data Limitations

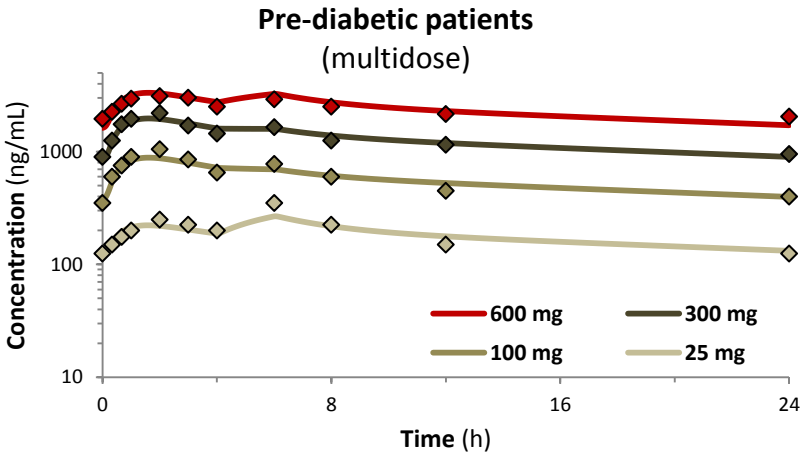
- Unknown demographics of study volunteers and patients
  - Model virtual patients selected to approximate reported fasting plasma glucose

- Unknown composition of the MMTT
  - Assumed an 8 oz Ensure Plus® challenge
  - Glucose absorption parameters modified to better fit reported glucose excursion



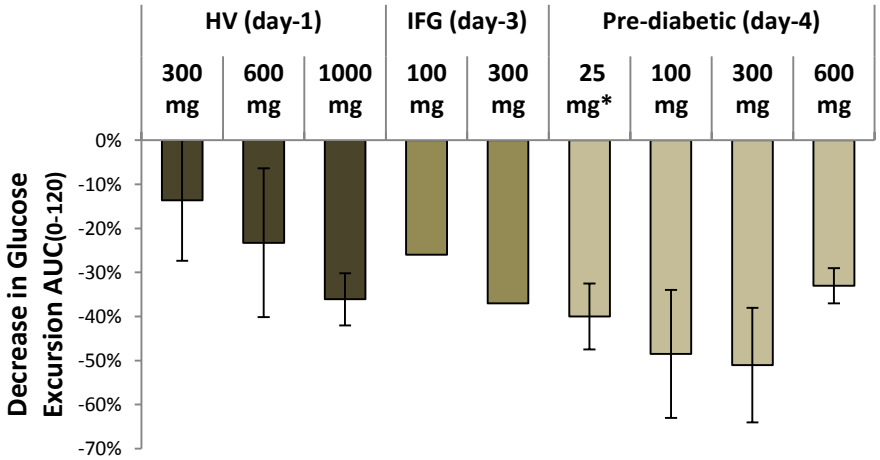
MBX-2982 Pharmacokinetics

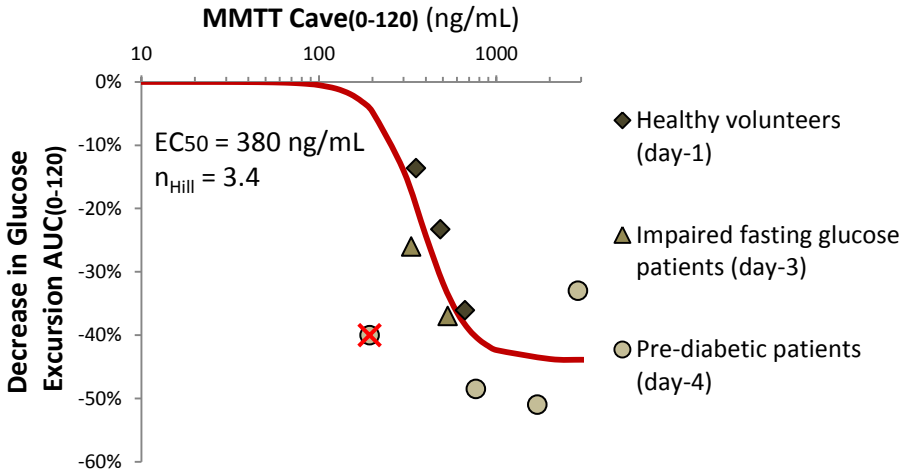




- 2-compartment oral kinetics
- Dose independent clearance, volume, and intercompartmental rates
- Dose dependent absorption rate and extent

MBX-2982 Pharmacodynamics

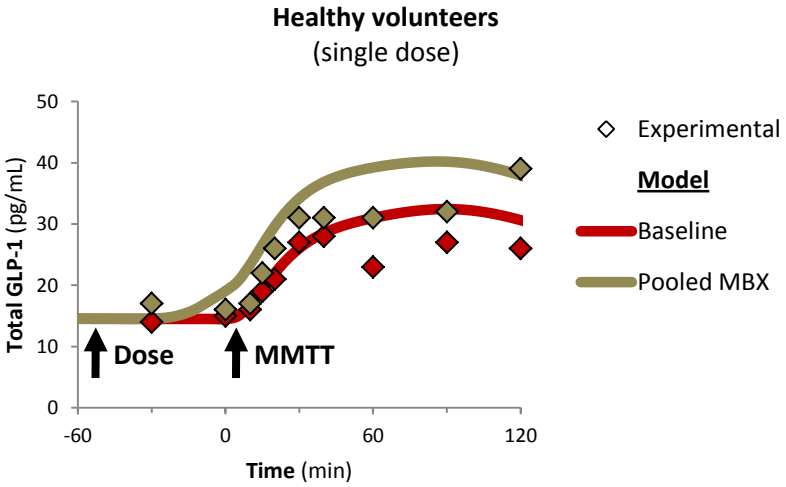




- MBX-2982 mixed meal tolerance test (MMTT) glucose excursion lowering provided a concentration-effect relationship to establish an effective EC_{50}
  - multiple studies of various populations and study lengths
- Both sites of GPR119 agonism (ß and L cells) were assumed to have equivalent potencies (EC_{50}) and Hill coefficients (n_{Hill})

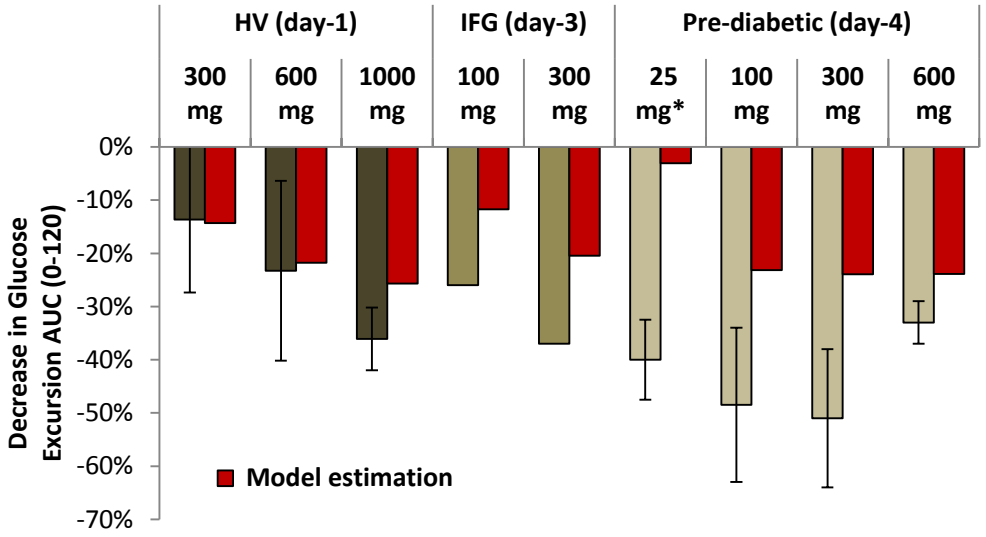
GPR119a Mediated GLP-1 Secretion

$$k_{in} = k_{basal} + k_{nutrients} \bullet [nutrients] + \frac{E_{max} \bullet [GPR119a]^n}{EC_{50}{}^n + [GPR119a]^n}$$



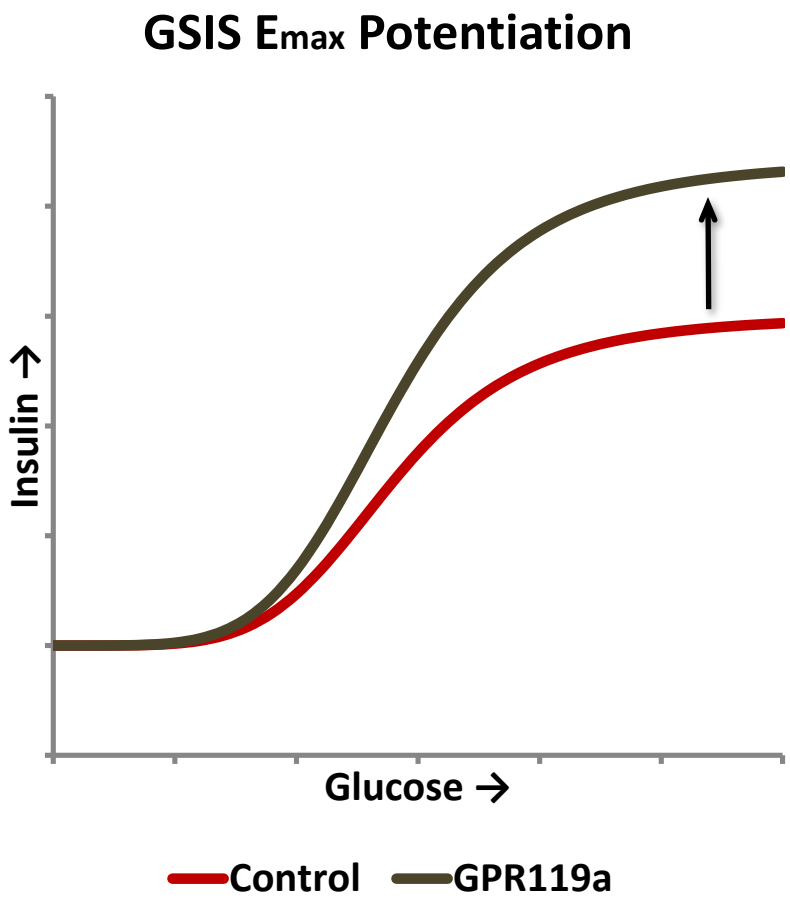
- In the model, GPR119a mediated GLP-1 secretion parameterized as additive to the basal- and nutrient-dependent secretion rates
  - [nutrients] represents the amount of carbohydrates and fat in the intestines
- GPR119 agonism is predicted to maximally stimulate basal incretin secretion by 1.8-fold based on the observed postprandial elevation in total GLP-1 during a MMTT following a single dose of MBX-2982 in healthy volunteers (pooled 300, 600, 1000 mg)

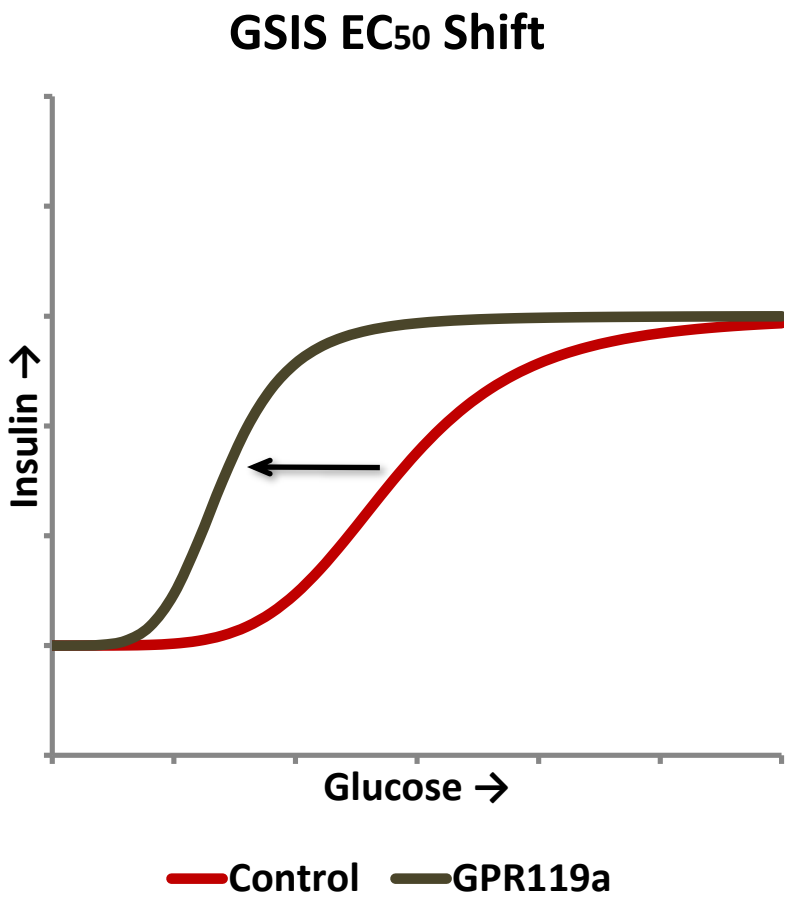
GPR119a Mediated GLP-1 Secretion



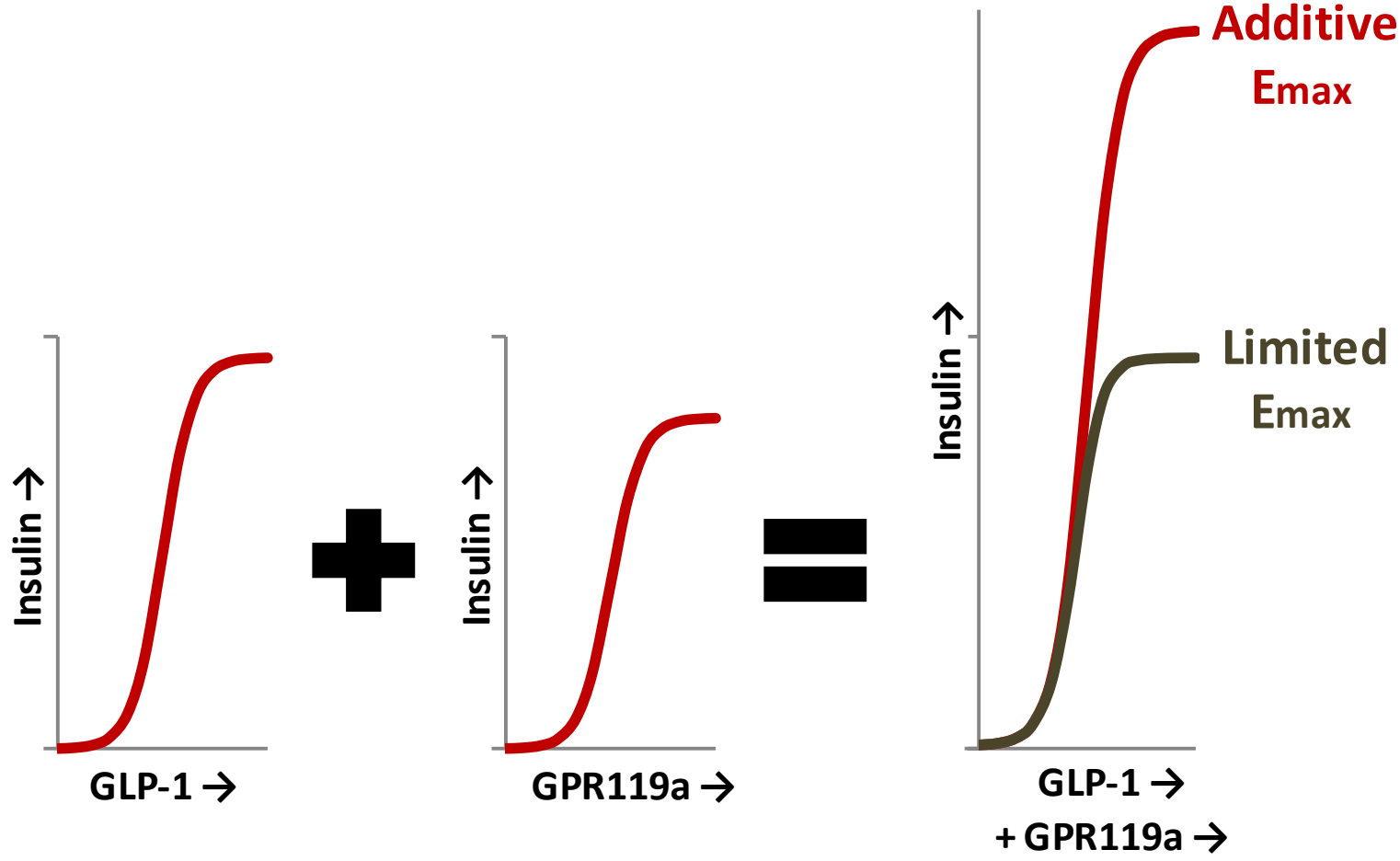
- While GPR119a mediated GLP-1 secretion contributes substantially to glucose lowering, it does not give explanation to all the glucose lowering
- The difference was parameterized through the direct influence of GPR119 agonism on GSIS

GSIS Potentiation & Shift

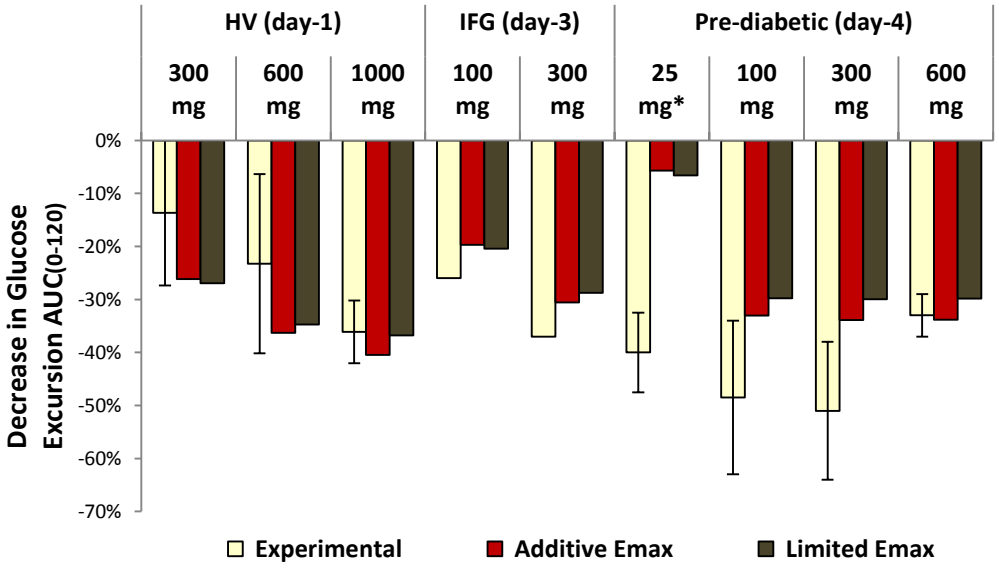




GPR119a & GLP-1 Additivity

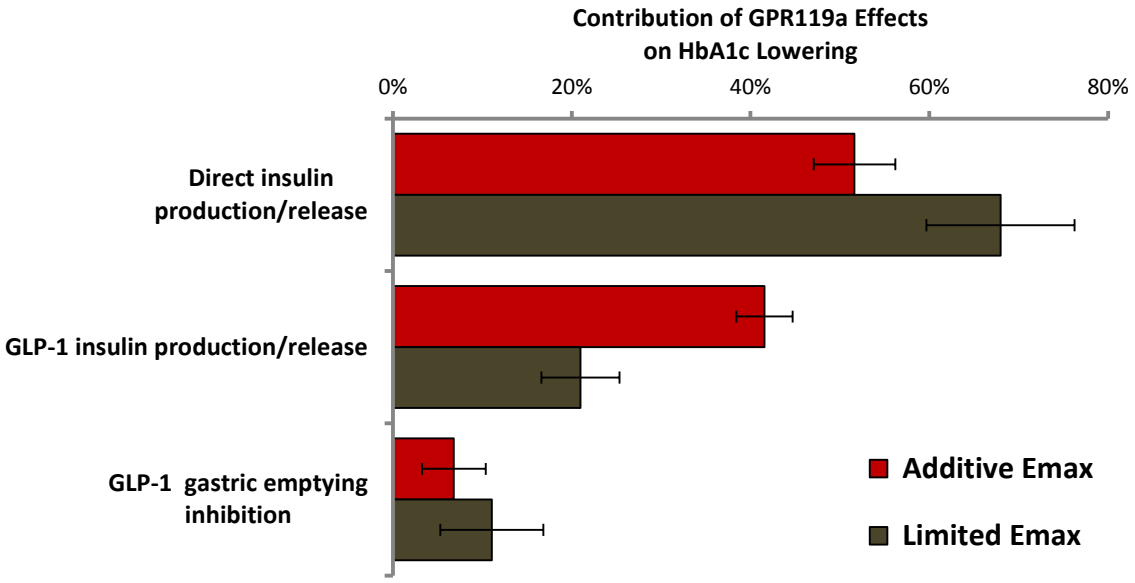


GPR119a Mediated GSIS



- Emax of potentiation and shift effects on GSIS were parameterized to best fit the MBX glucose lowering
- The additive and limited Emax hypotheses have different parameters

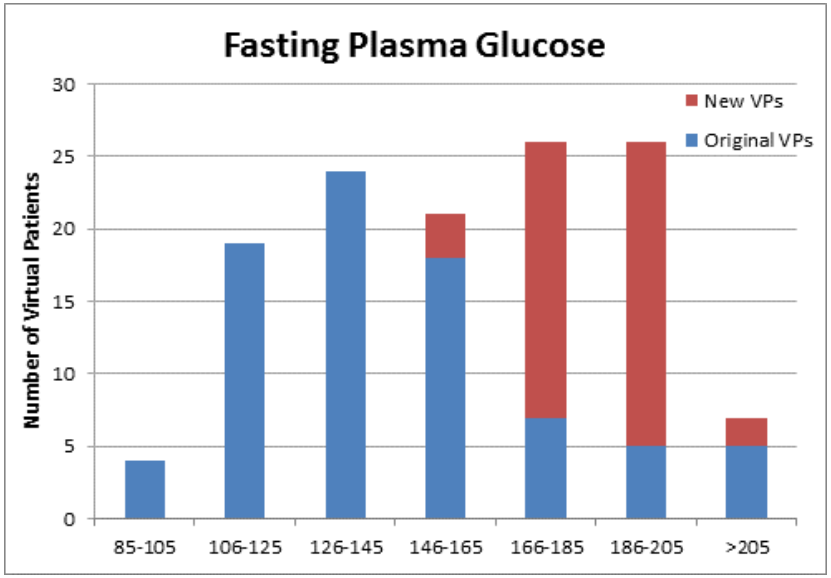
Contributions of GPR119a Effects on HbA1c Lowering



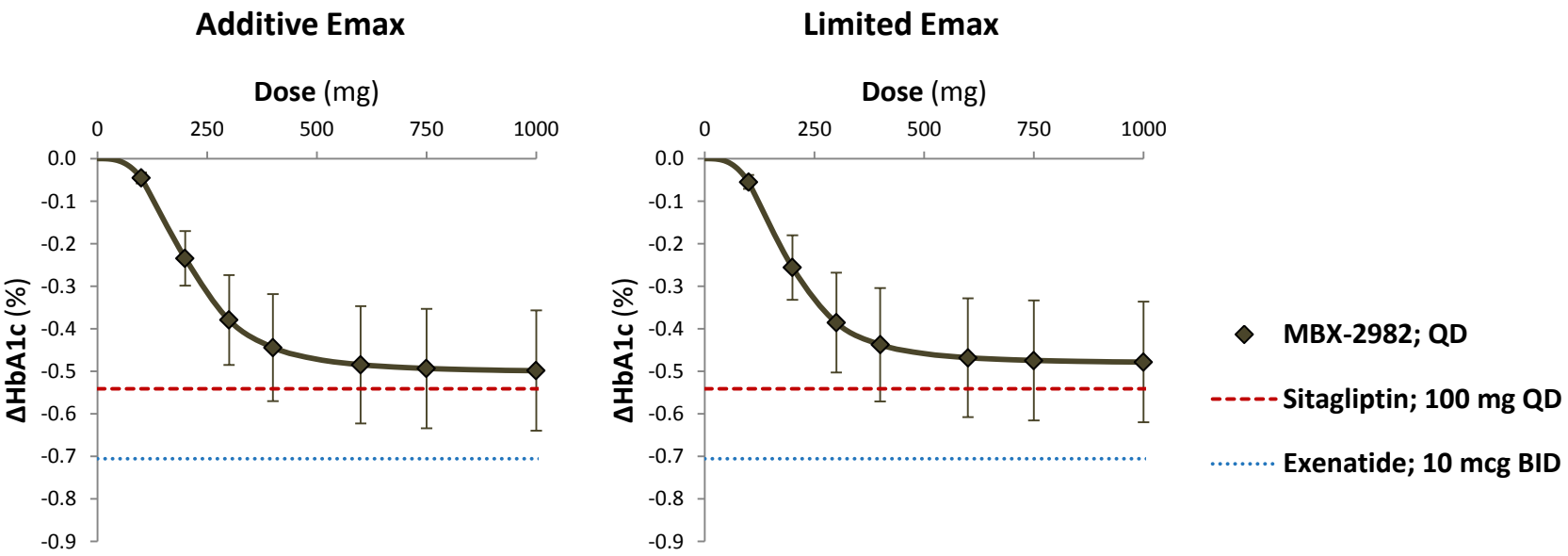
- Direct and indirect actions of GPR119 agonism equally contribute to glucose control

Virtual Patient Demographics

- 2003 NHANES database
- Age: 20-85 years
- Height: 142-187 cm
- Weight: 64-155 kg
- Body mass index: 20-60
- HbA1c: 5-11 %
- Fasting plasma glucose: 89-230 mg/dL
- Fasting plasma insulin: 17-448 pM

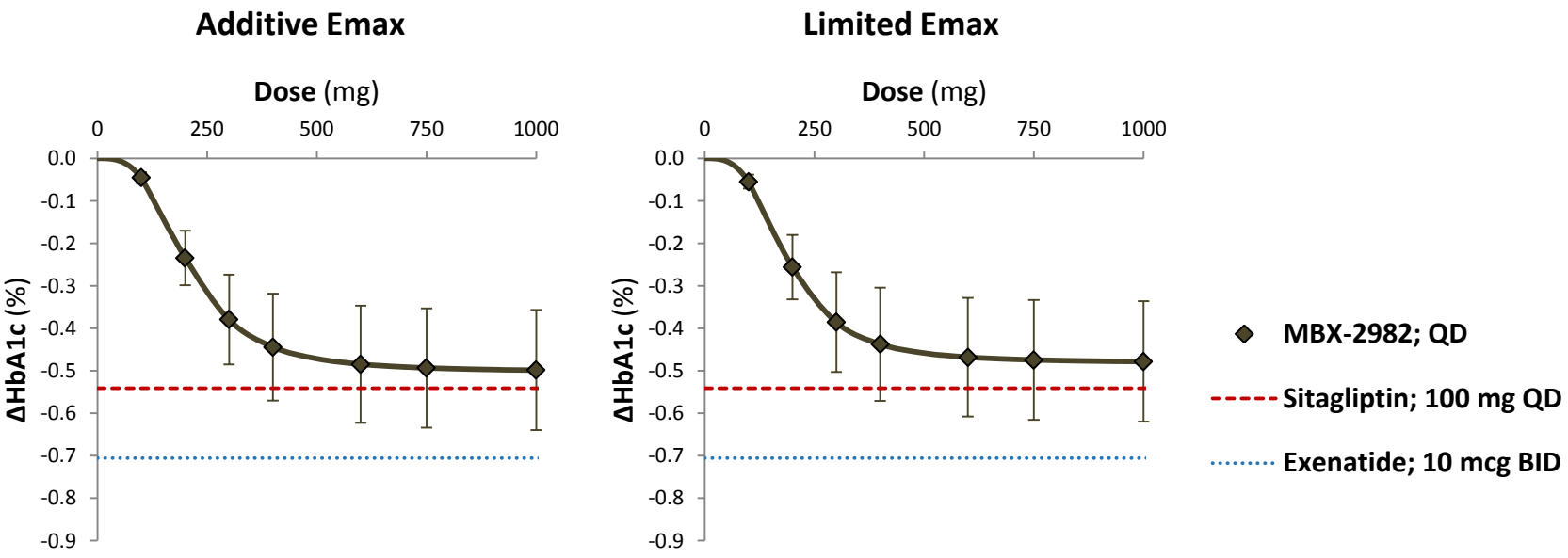


Target Population Outcome



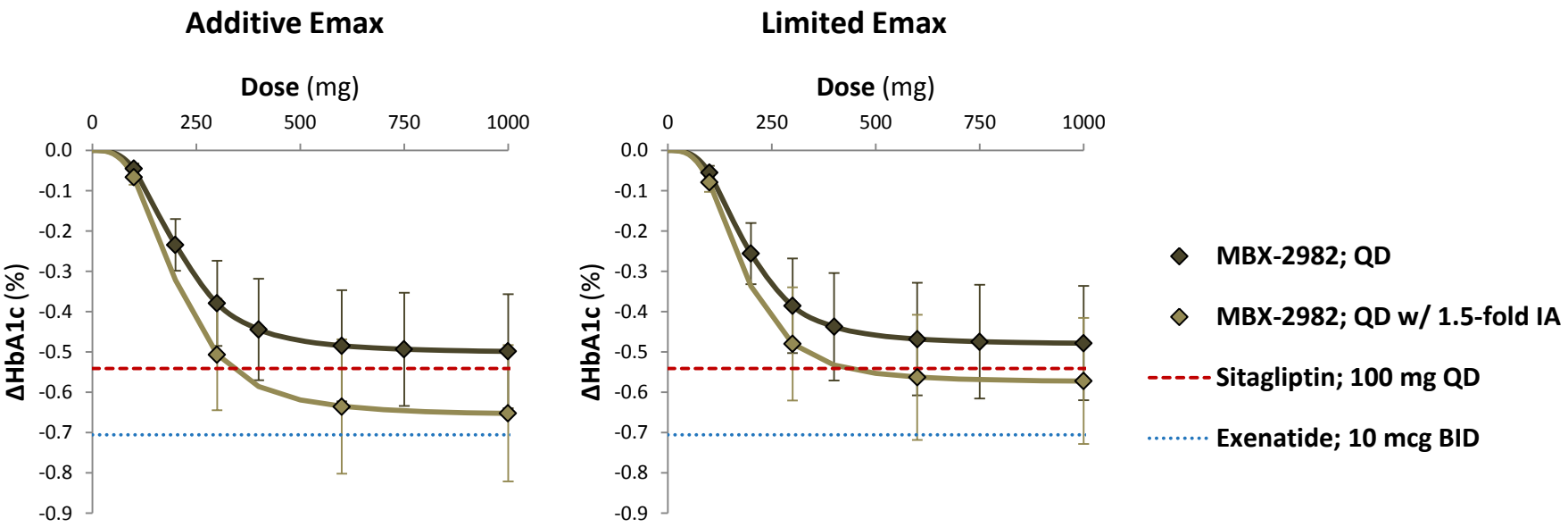
- MBX-2982 forecast to only achieve sitagliptin-like HbA1c lowering in type 2 diabetics

Target Population Outcome



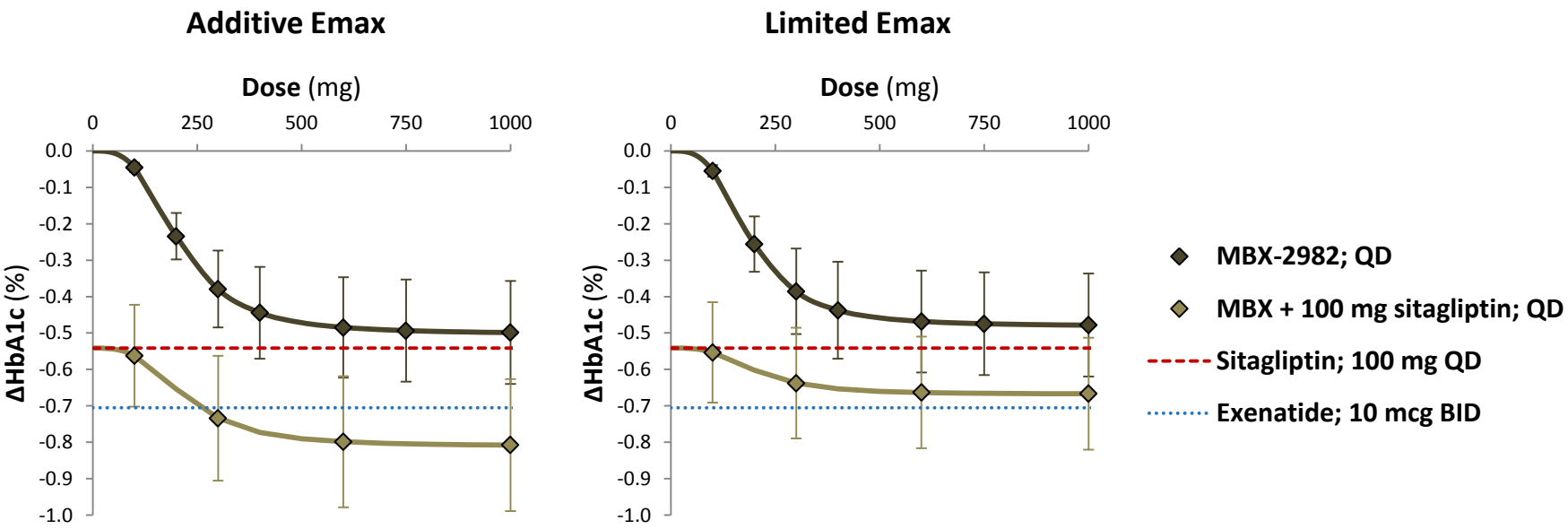
- What if higher intrinsic activity is achievable?

Target Population Outcome



- What if higher intrinsic activity is achievable?
- Exceed sitagliptin- and approach exenatide-like HbA1c lowering in Type 2 diabetics

Combination Therapies



- Allows exploration of combination therapies
- Model suggests that understanding the additivity of GPR119a and GLP-1 may be of critical importance to this mechanism's commercial viability

Conclusions

- Systems approach was used to create a predictive model of GPR119 agonism, without clinical data
- Even with sparse data, we could quantify the relationship between the GPR119 agonism Emax and likely human outcome
- Predicted results from chronic trials (HbA1c) using subchronic model results (average plasma glucose)
- Used modeling analysis to better assess potential for GPR119 agonism as a diabetes target

Observations

- Systems pharmacology models allow forecasting of late stage (phase II & III) outcome from early signs of efficacy (preclinical and phase I)
- Systems models have significant initial resource requirements, yet provide unique insights
- Their benefit-to-resource ratio improves with each addition utilization

Acknowledgments

- Pfizer
  - Tristan Maurer
  - Danny Chen
- Rosa & Co., LLC
  - Jim Bosley
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    Caltech