LEVERAGING THE DIABETES QSP MODEL TO DRIVE DECISIONS IN TARGET ID AND VALIDATION IN THE PROINSULIN PROGRAM

Presented by

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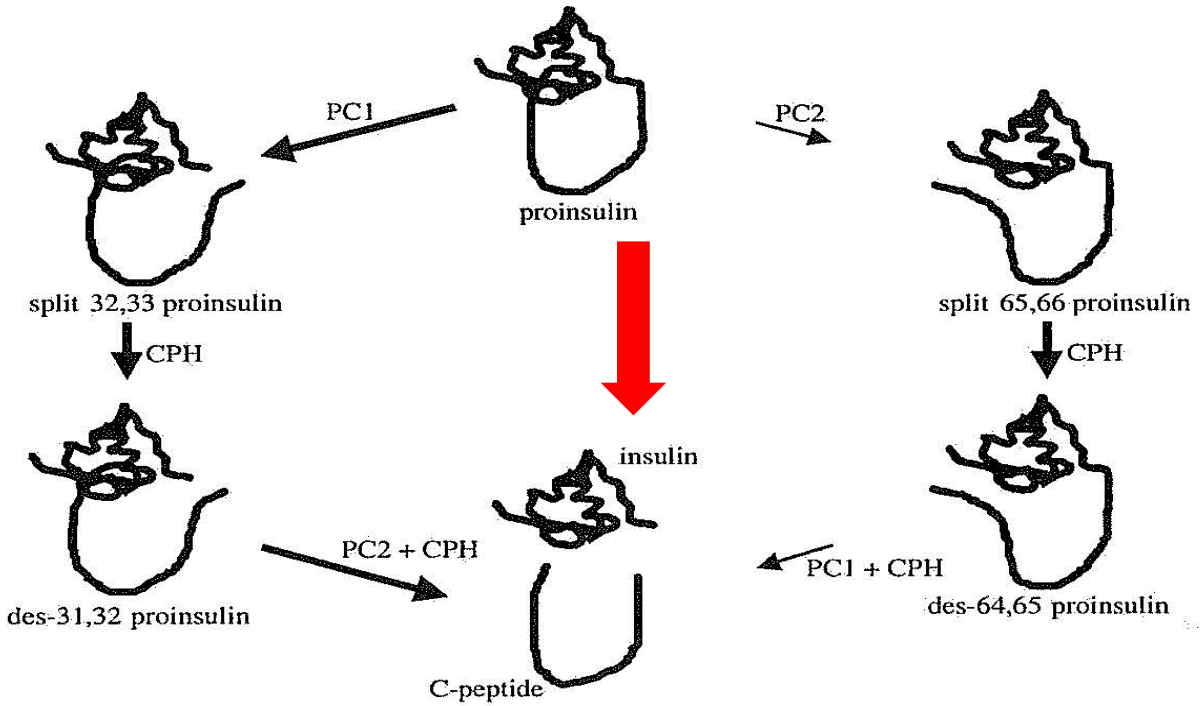
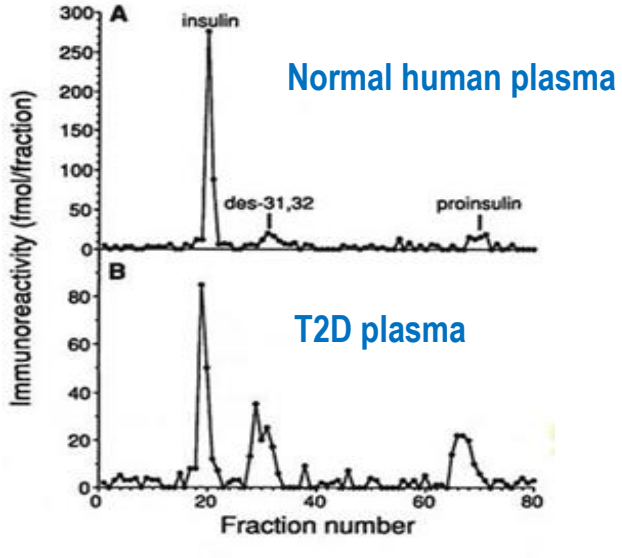
Proinsulin Biology

- Proinsulin binds the insulin receptor but is 10x less potent



Modified from Goodge KA and Hutton JC, 2000, Cell & Dev Biol, 11:235



Steven EK, Philippe AH, Diabetes 1997, Vol 46:1725

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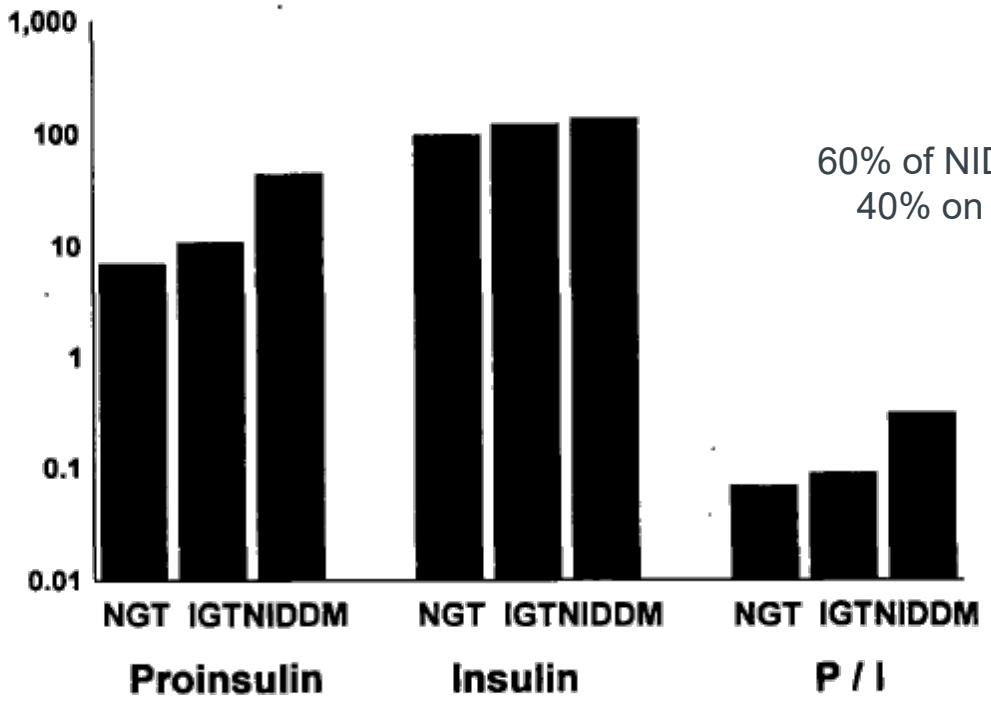
Circulating proinsulin is higher in individuals with T2DM vs. pre-diabetes vs. without diabetes

pmol/L (log scale)



60% of NIDDM on oral agents
40% on dietary treatment

FIG. 2. Fasting insulin (pmol/l) and fasting proinsulin (pmol/l) levels and the fasting proinsulin:insulin ratio in subjects with NGT, IGT, and NIDDM. *P* values are as follows: fasting insulin, $P = 0.032$ NIDDM vs. IGT, $P < 0.001$ NIDDM vs. NGT, and $P = 0.006$ IGT vs. NGT; fasting proinsulin, $P < 0.001$ NIDDM vs. IGT, NIDDM vs. NGT, and IGT vs. NGT; proinsulin:insulin ratio, $P < 0.001$ NIDDM vs. IGT and NIDDM vs. NGT, $P = 0.048$ IGT vs. NGT.

DIABETES, VOL. 43, DECEMBER 1994

NGT (n= 250) vs. IGT (n=79) vs. NIDDM (n=85)

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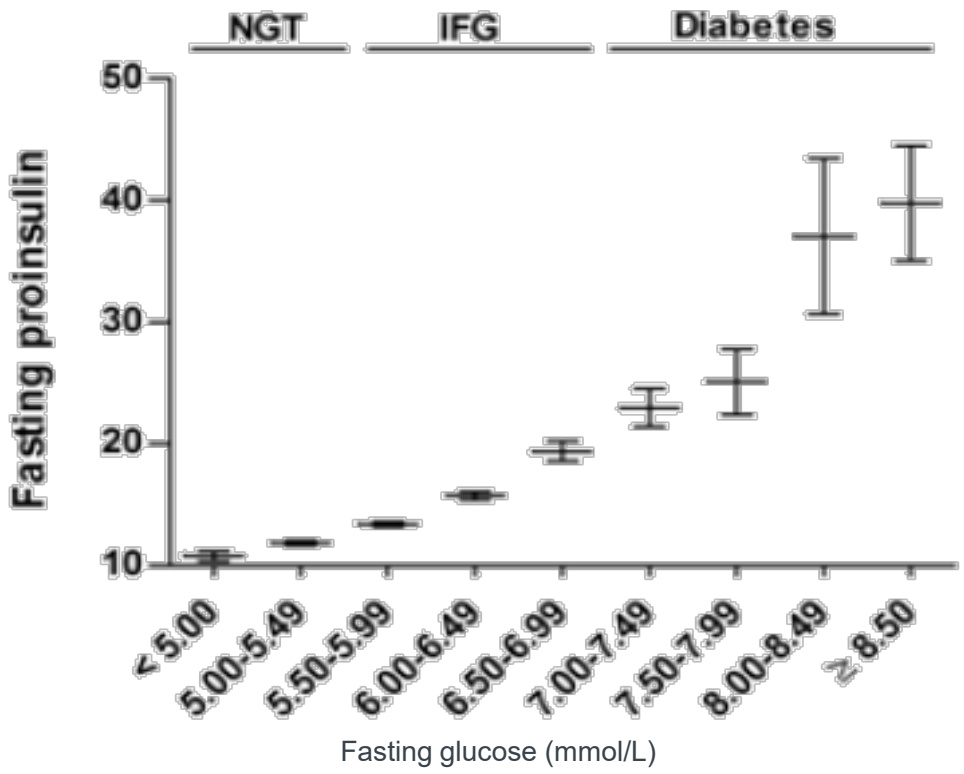
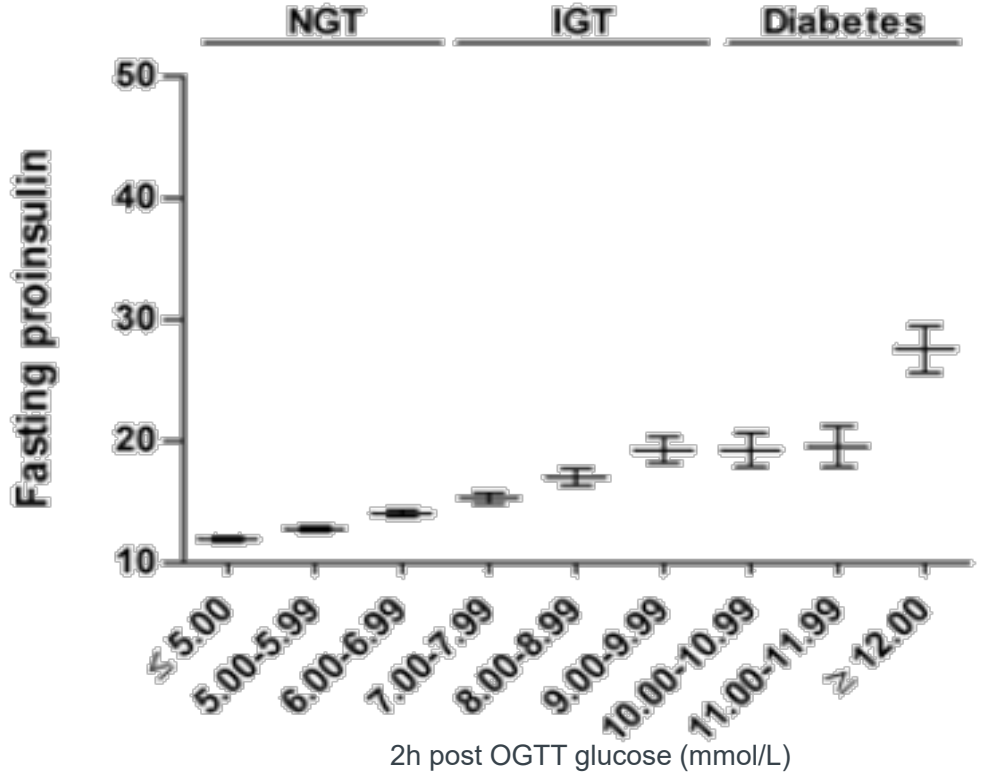
Circulating proinsulin correlates with fasting and 2-h glucose among treatment naïve individuals





Data from METSIM: 3,033 (32.3%) with NGT, 4,344 with isolated IFG (IIFG), 311 (3.3%) with isolated IGT (IIGT), 1,059 (11.3%) with IGT + IFG, and 649 (6.9%) with new T2DM. Proinsulin assay (pmol/L) includes both intact and des 31,32 split proinsulin.

Is hyperglycemia the only driver of increased proinsulin?

PLOS ONE | DOI:10.1371/journal.pone.0124028 April 8, 2015

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Proinsulin is generally elevated in the setting of increased beta-cell demand (*i.e.*, insulin resistance) among individuals with well-controlled T2DM

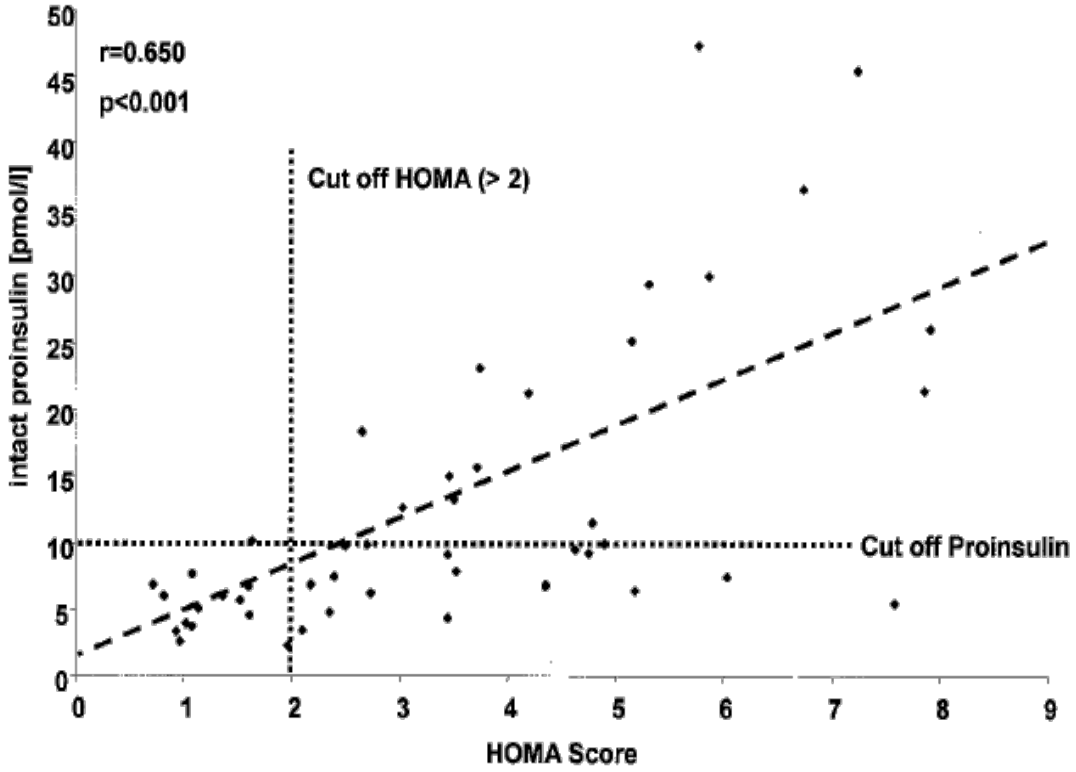

Figure 3—*Correlation between fasting intact proinsulin values and the S_I according to the HOMA analysis.*

Cross-sectional analysis of 48 subjects on oral therapy for T2DM with short disease duration (65 months for IS vs. 54 months for IR) and good glycemic control (HbA1c 6.2% for IS and 7.1% for IR)

DIABETES CARE, VOLUME 27, NUMBER 3, MARCH 2004

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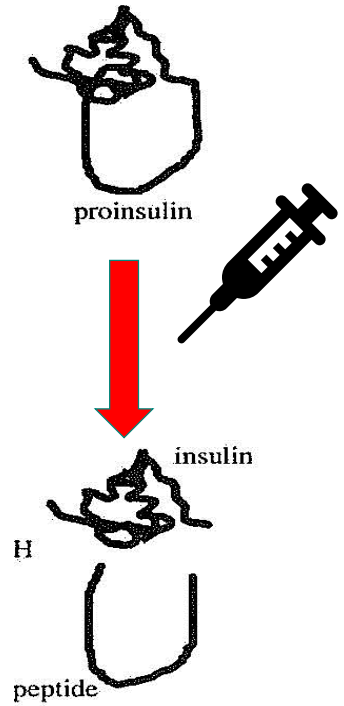
Leveraging the Diabetes QSP Model for the Proinsulin Program

- Key questions:
  - *Will the conversion of circulating pro-insulin to insulin reduce hyperglycemia in T2DM?*
    - *Impact of background therapies?*
    - *Is there a subpopulation of T2DMs where this would work best?*



Answers may provide sufficient evidence for TIDVAL…

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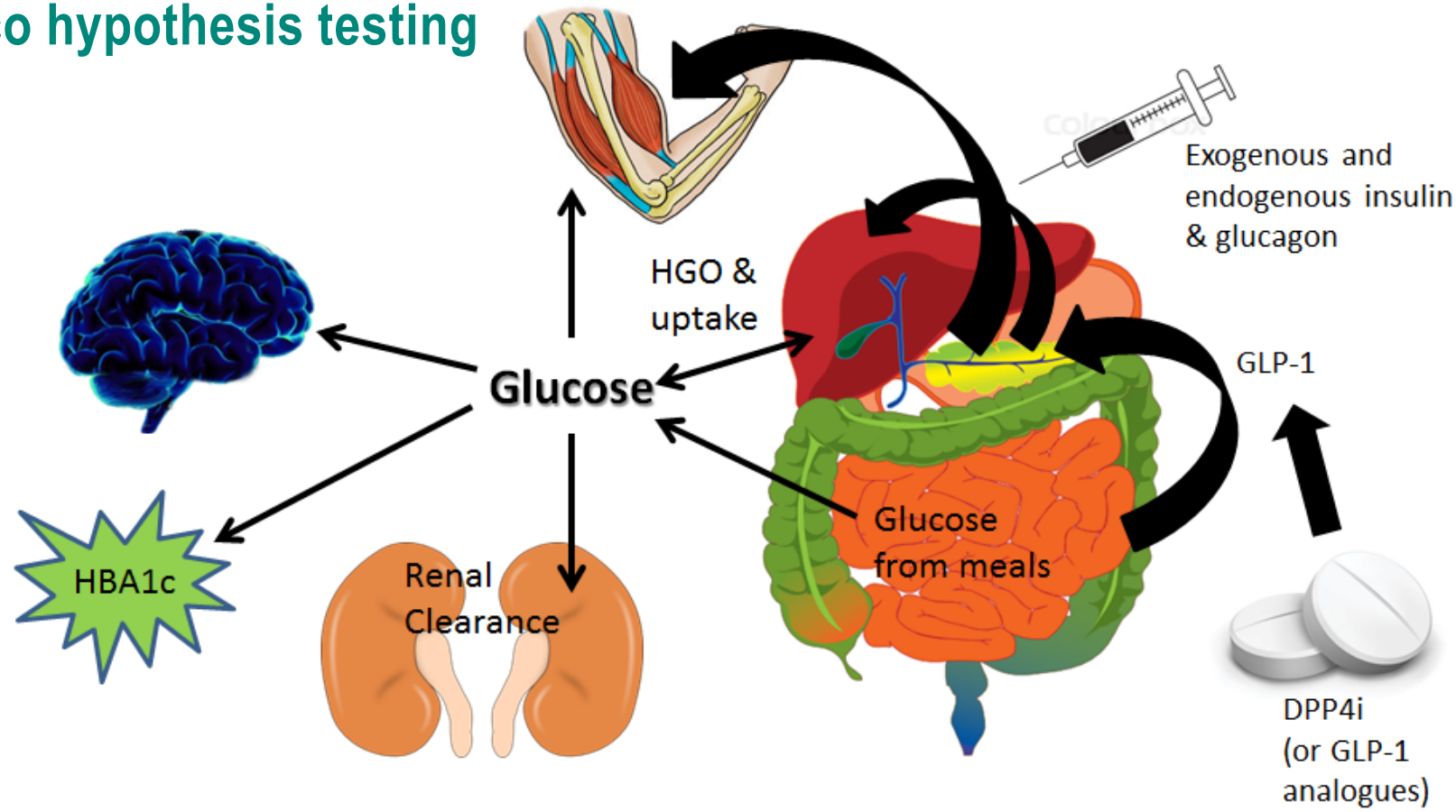
The Merck Diabetes Quantitative Systems Pharmacology Model

- Model of physiology and pharmacology
- Provides clinically relevant readouts
- Allows for **in silico hypothesis testing**



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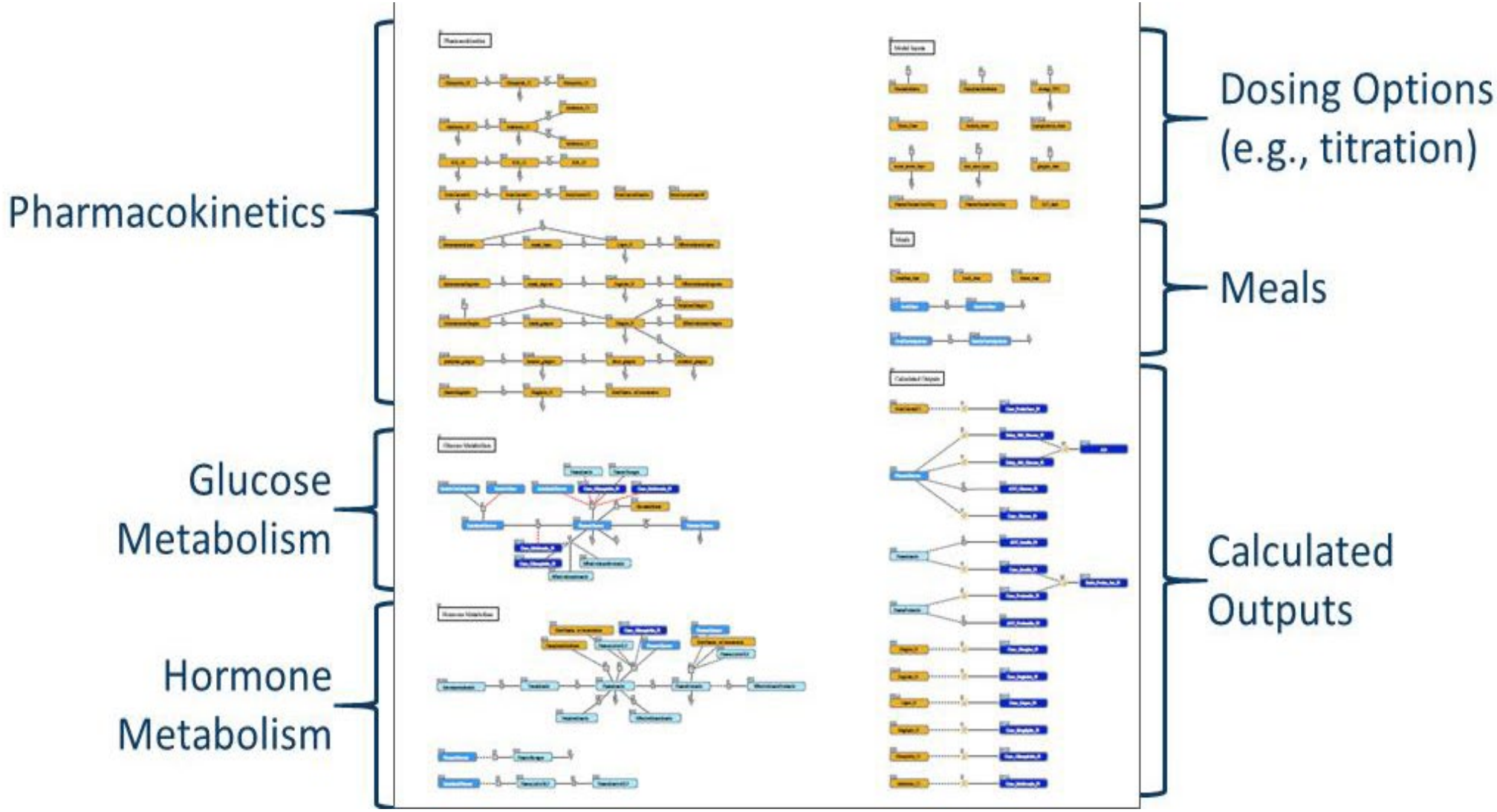
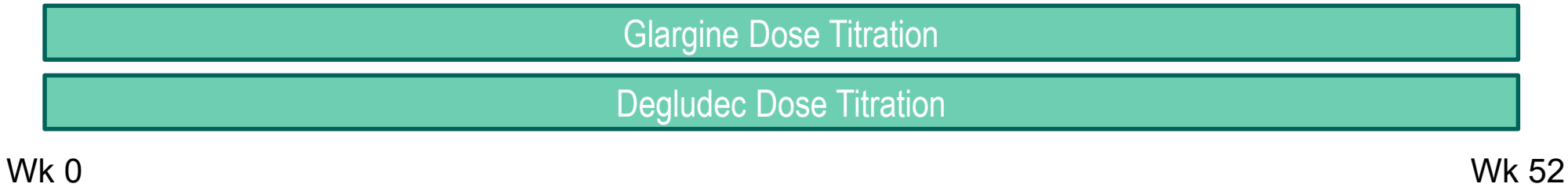
QSP Model as Represented in PhysioPD™ Platform in SimBiology® software



Merck QSP Model Qualification: Zinman et al 2012



52 week Phase III study

- Adults with type 2 diabetes with A1C of 7-10%
- Patients receive once daily degludec or glargine
- n = 257 Glargine, 766 Degludec

Outcomes

- A1c, FPG, SMBG, Hypoglycemia (<55 mg/dl)

Zinman B, et al. *Diabetes Care.* 2012;35(12):2464-2471.

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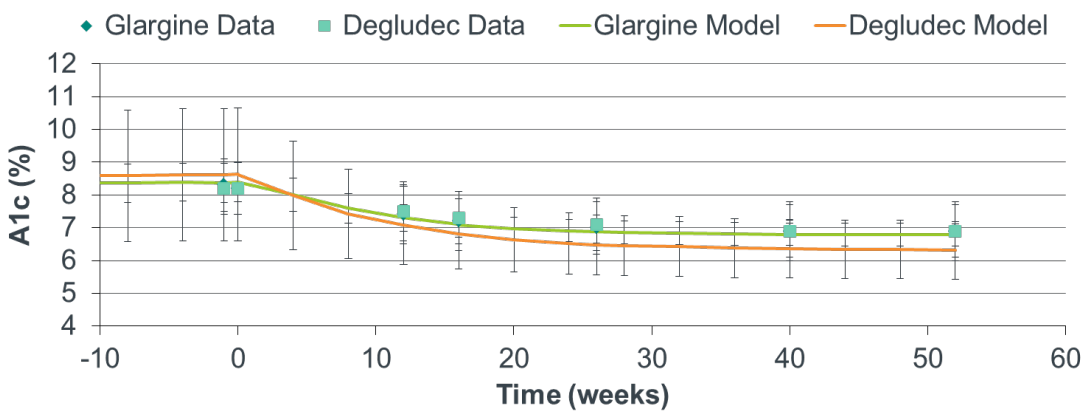
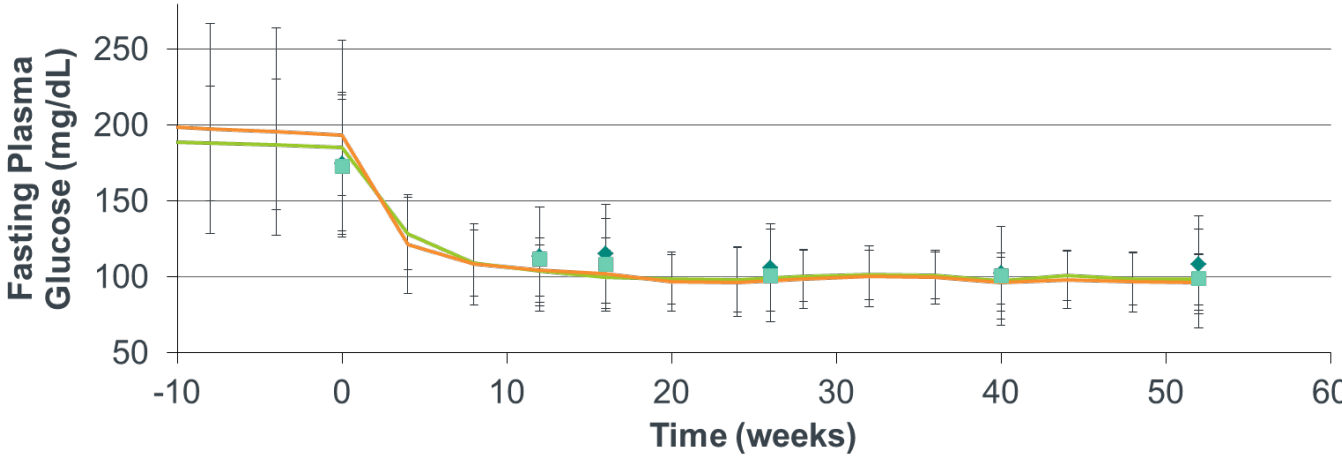
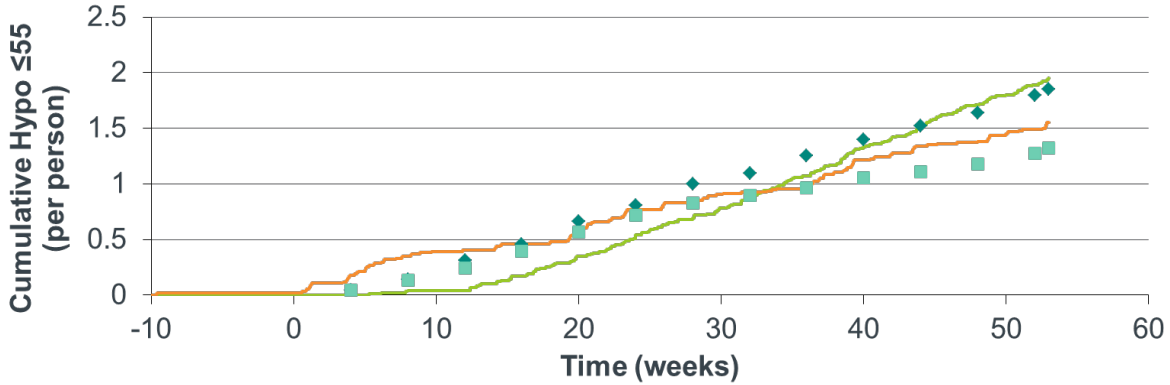
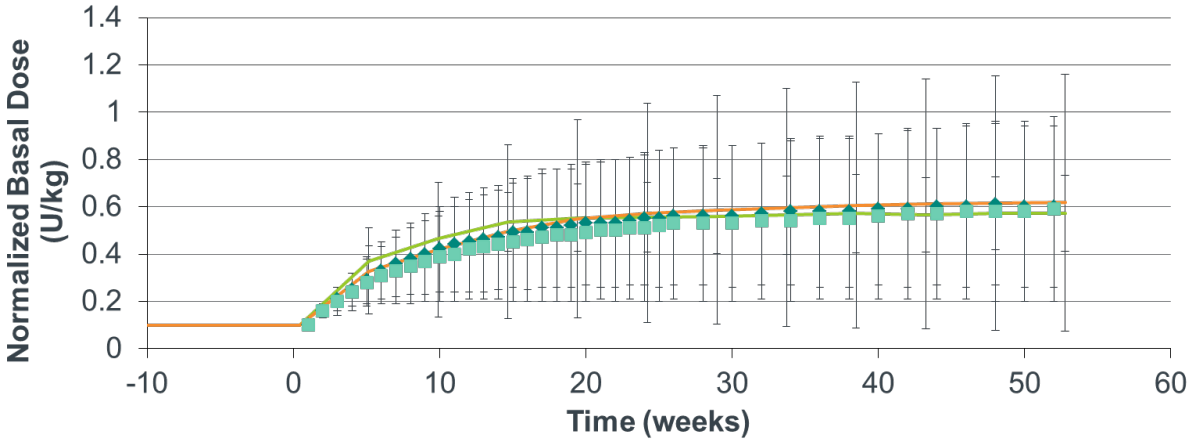
Calibration of QSP Model in T2DM Population to Clinical Outcomes Data from Zinnman et al









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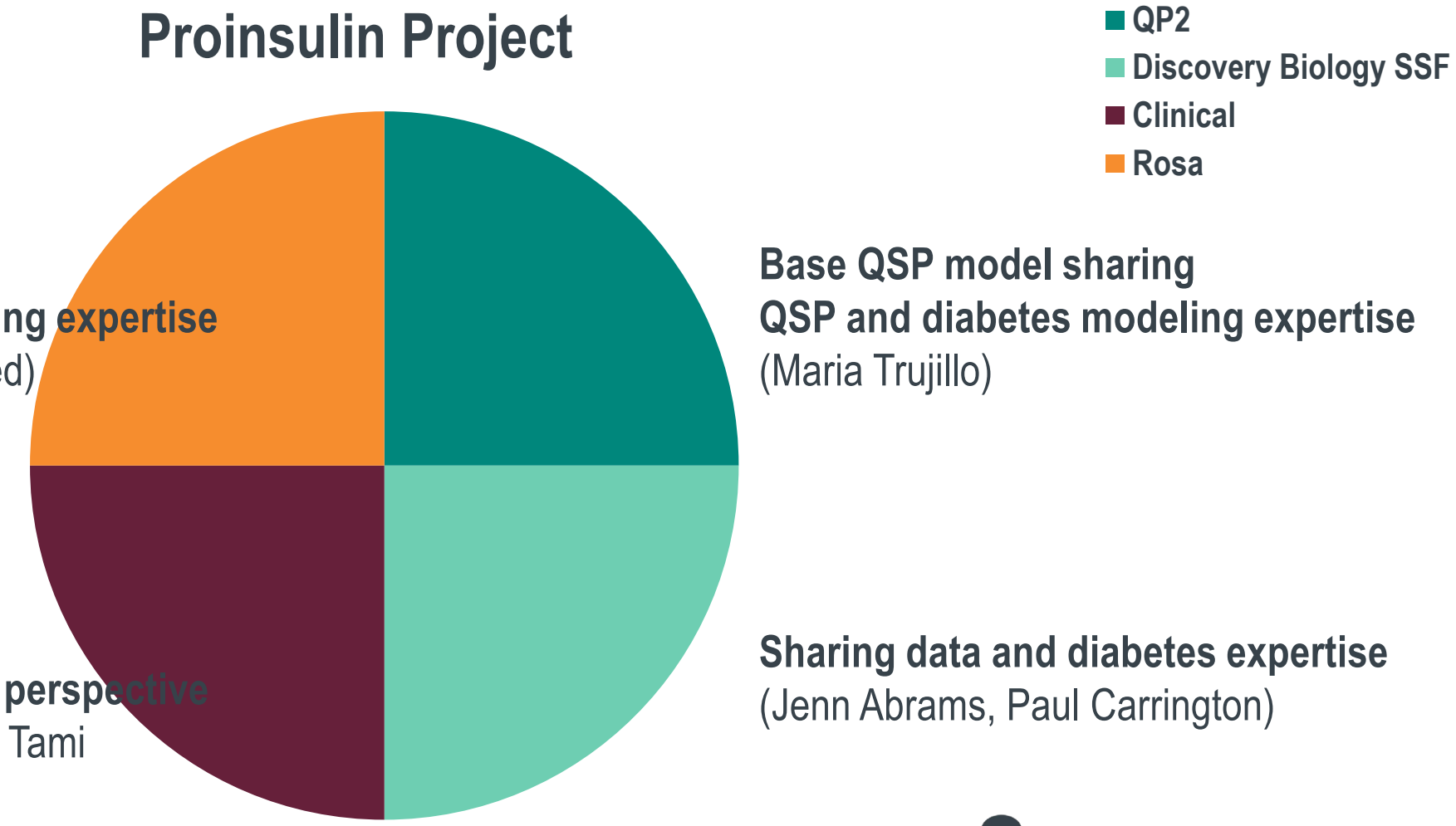
Leveraging the QSP/ Building a Team



Hands on modeling
QSP and diabetes modeling expertise
(Rebecca Baillie, Mike Reed)

Base QSP model sharing
QSP and diabetes modeling expertise
(Maria Trujillo)

Clinical
Sharing data and clinical perspective
(Geoff Walford, Lori Mixon, Tami Crumley, Lenny Dragone)

Sharing data and diabetes expertise
(Jenn Abrams, Paul Carrington)

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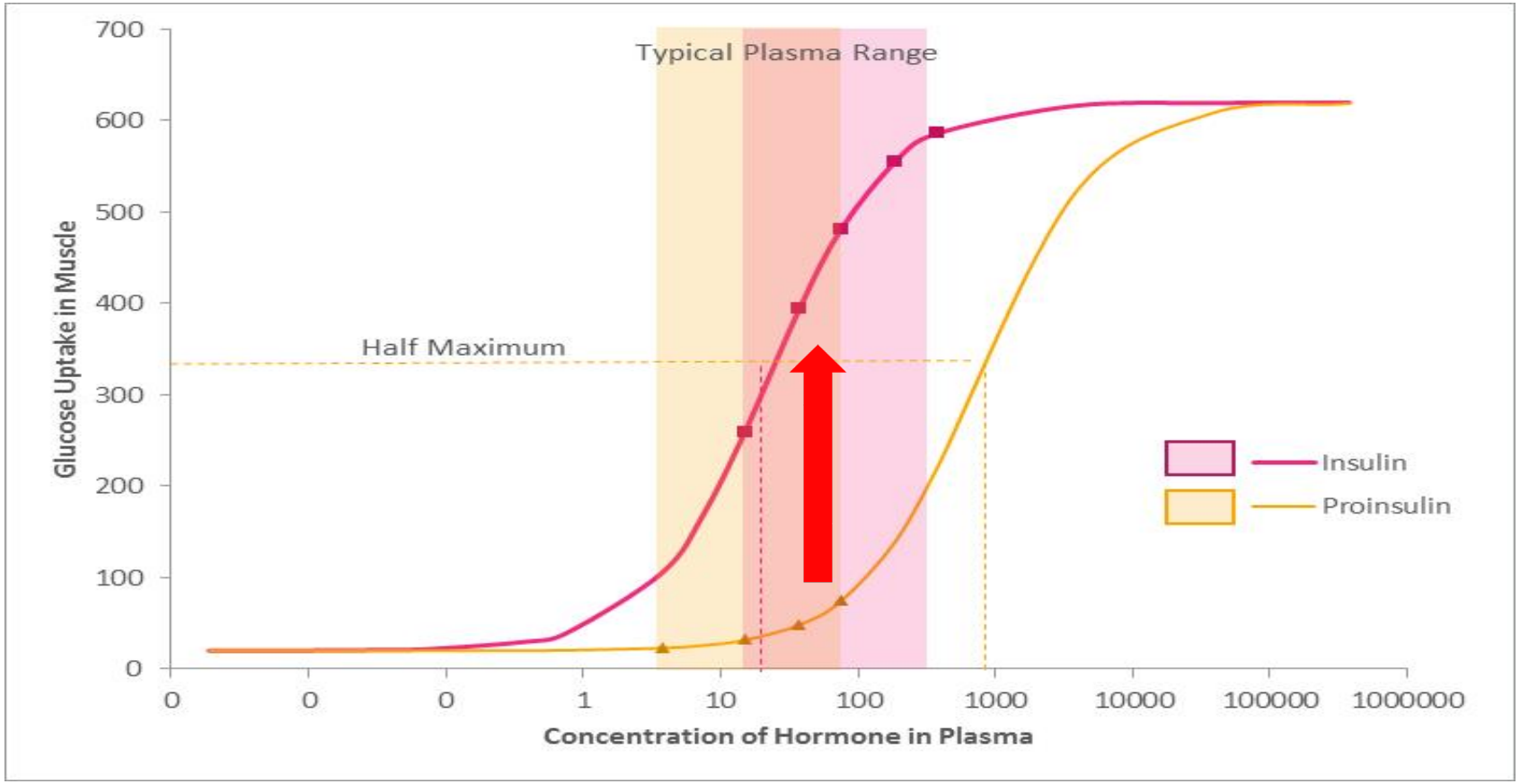
Literature provides insight:
Proinsulin will have minimal effects on glucose uptake into the muscle- unless its converted to insulin.

***Hypothesis*: Direct conversion of circulating proinsulin to insulin would lower glucose**



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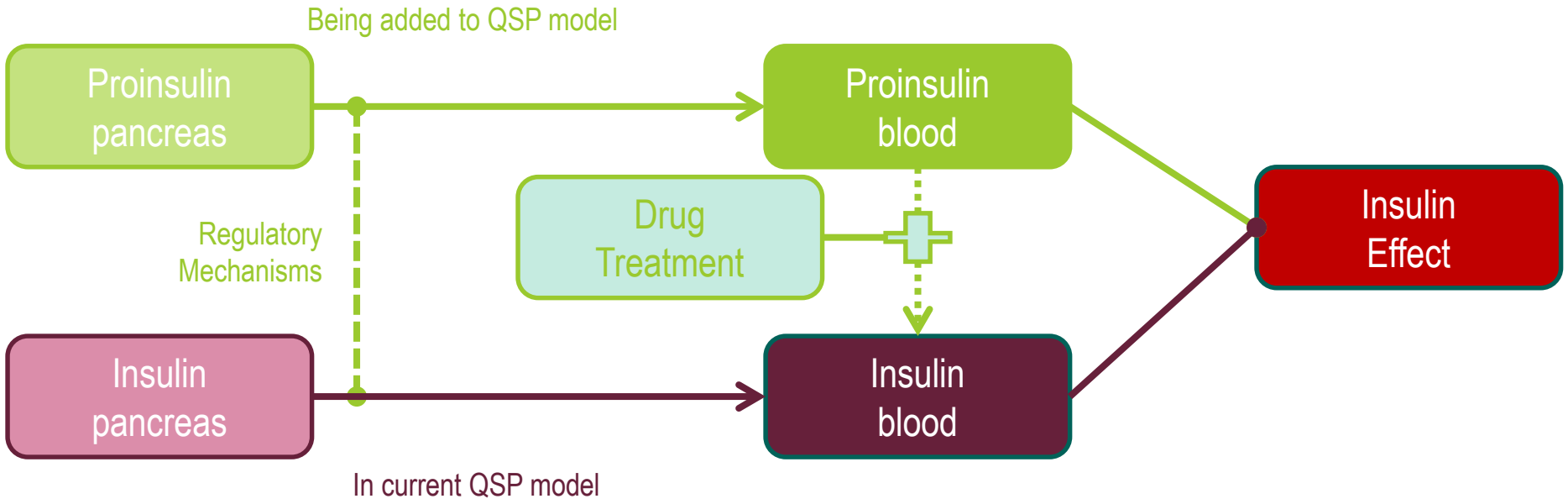
Proinsulin biology as implemented in the QSP model



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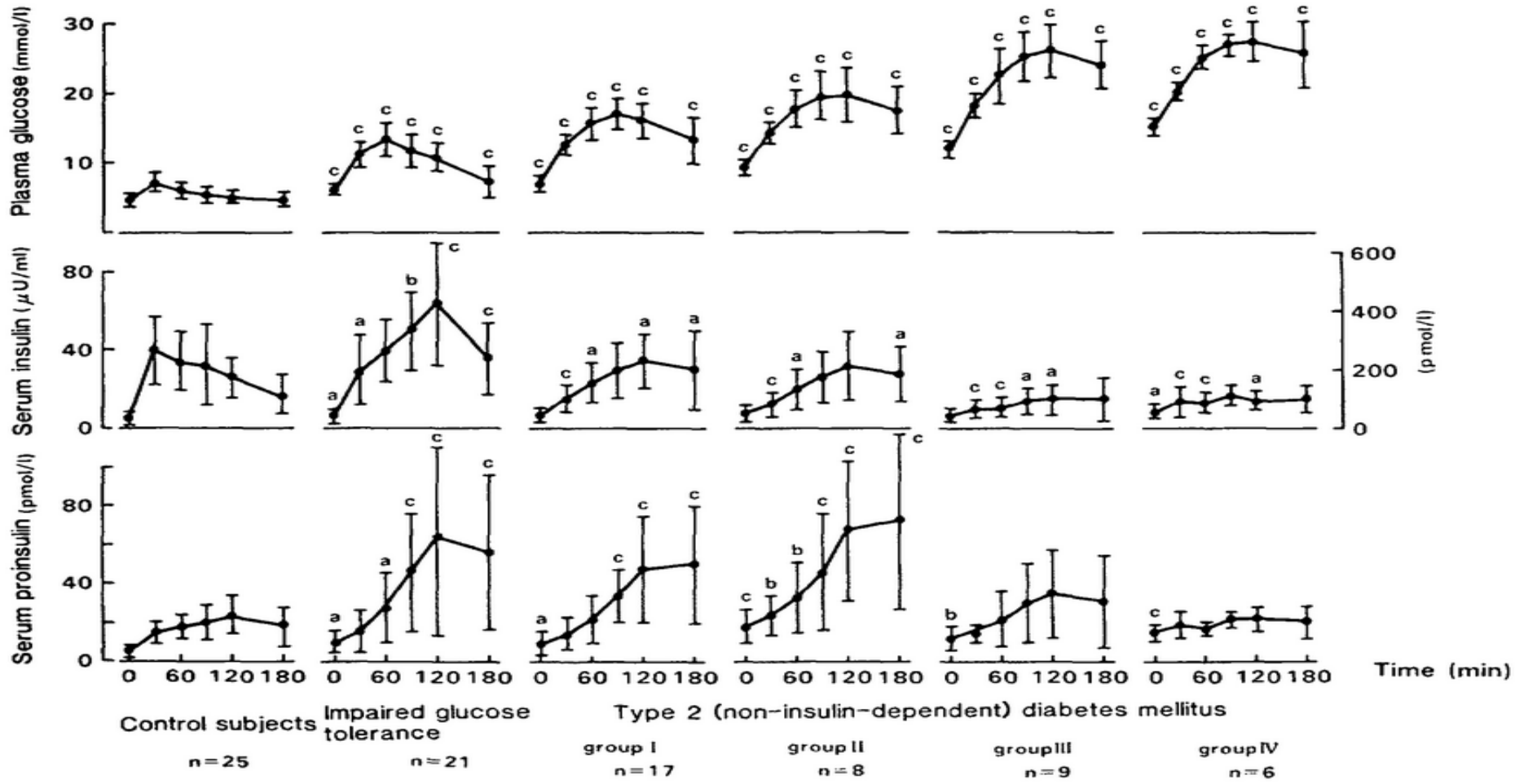
T2DM is heterogeneous! Design of Virtual Patients can help to explore different subpopulations.
Can we leverage internal data?



Yoshioka 1988 PMID: 3046976

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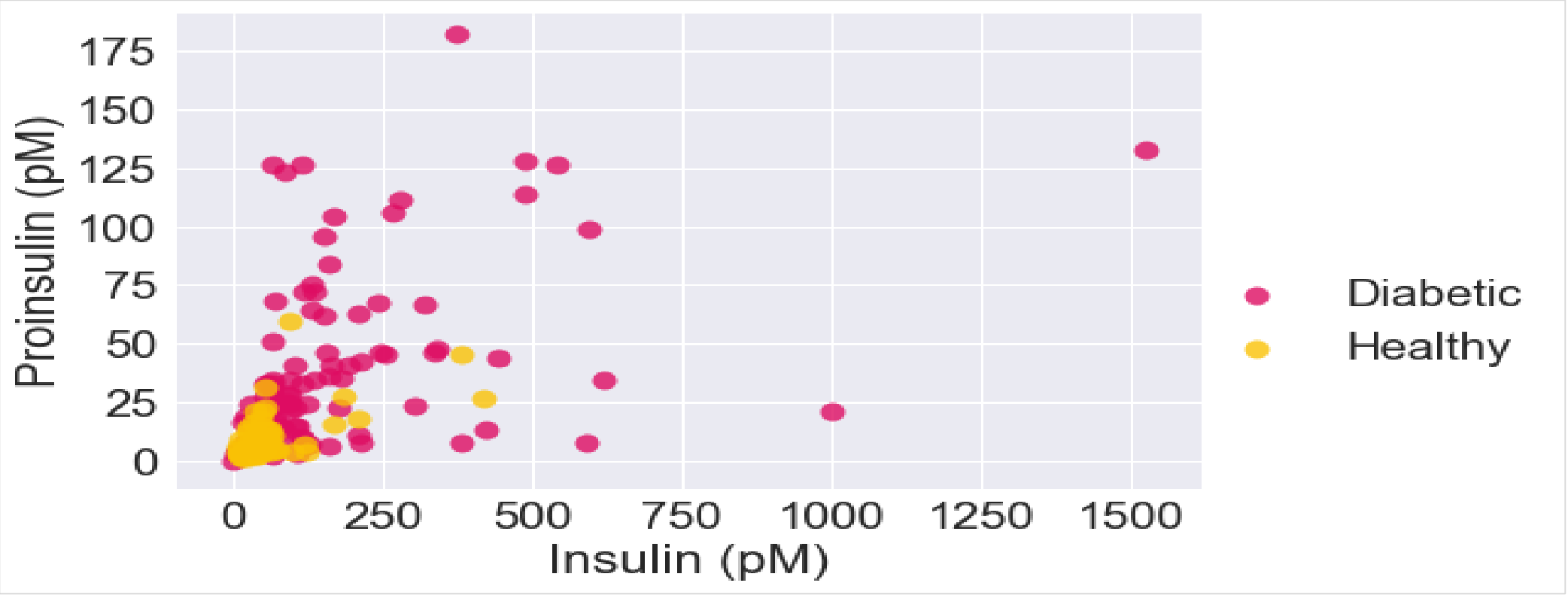
Insulin and proinsulin concentrations vary between healthy and diabetic subjects.



- Diabetic clinical subjects have a much higher concentration and higher variability in insulin and proinsulin

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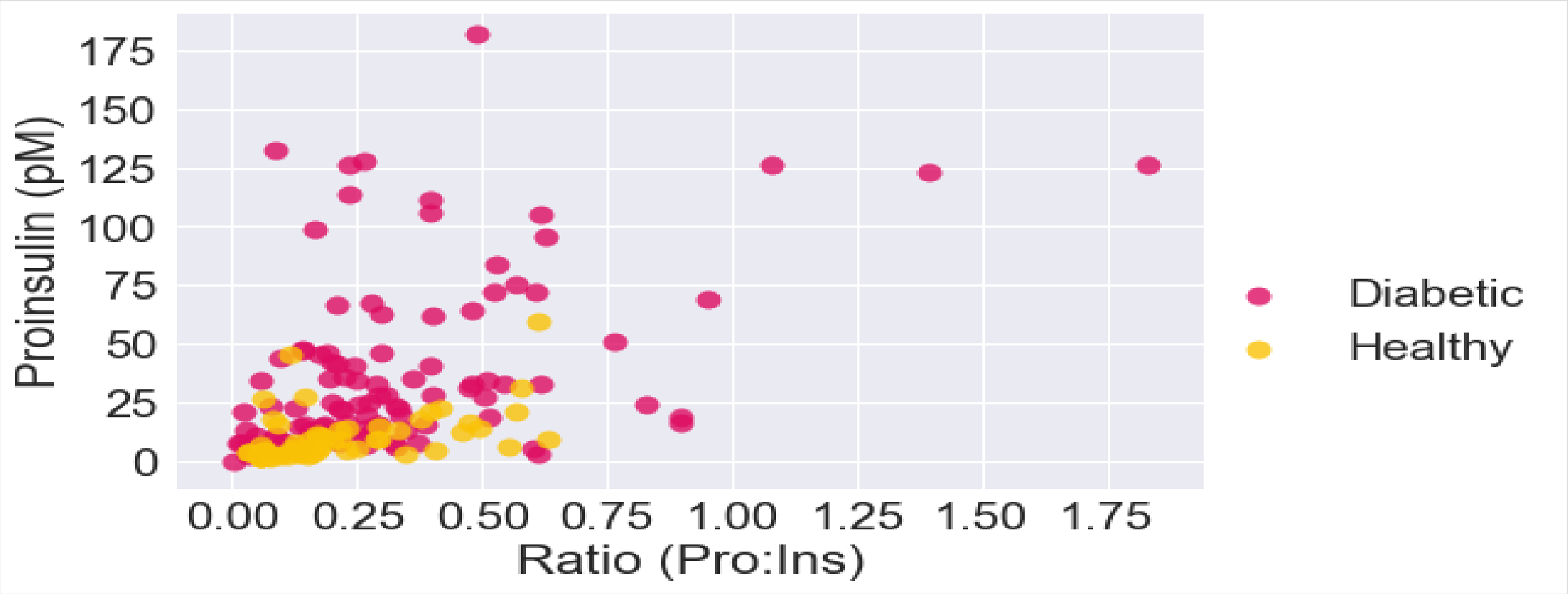
The variation in the ratio is due (largely) to variation in the proinsulin concentration



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Collaborative effort to design Virtual Patients and calibrate the model facilitated investigations

- TRIAD: Proinsulin data from Phase 3 trials (Omarigliptin FBR samples)
- Discovery SSF: Proinsulin data from healthy and diabetic volunteers
- Rosa: Model qualification through qualitative/quantitative testing
- In silico hypothesis testing with VPs!

	VPM005100	VPM005101	VPM005120	VPM005121
Disease Diagnosis	Healthy	Type 2 diabetes	Type 2 diabetes	Type 2 diabetes
Patient type representation	Moderately healthy VP with low insulin secretion and very high insulin sensitivity	Late stage type 2 diabetes with pancreatic failure	Early stage type 2 diabetes with high insulin resistance and pancreatic compensation	Early stage type 2 diabetes with high insulin resistance and pancreatic compensation
Fasting glucose, mg/dL	93	167	140	131
Fasting insulin, nM	0.028	0.01	0.02	0.034
Postprandial glucose, mg/dL	152	240	209	196
Postprandial insulin, nM	0.18	0.11	0.15	0.27
A1c, %	4.9	8.2	7.2	6.6

Fasting insulin/proinsulin concentrations are comparable to clinical data with appropriate deviations for sub-populations in T2DM.

	Insulin, pM (range)	Proinsulin, pM (range)	Proinsulin /insulin
Ave. T2D lit. data*	92 (41-370)	19 (6-51)	0.21
Ave. T2D lit. data*	56 (21-148)	7 (3-13)	0.12
MK clinical data T2DM	104 (13-295)	34 (8-173)	0.31 (0.14-0.68)
MK clinical data T2DM	133 (5-1120)	44 (2-263)	0.44 (0.03-4.81)
MK analysis dataset: T2D	166 (3-1521)	37 (0.014-182)	0.32 (0.004-1.8)
MK analysis dataset: Healthy	60 (9-418)	39 (19-81)	0.20 (0.03-0.63)
VPM005100- Healthy	28	5	0.18
VPM005101-Late T2DM	13	3	0.23
VPM005120-Early T2DM	17	7	0.41
VPM005121- Early T2DM	34	25	0.73

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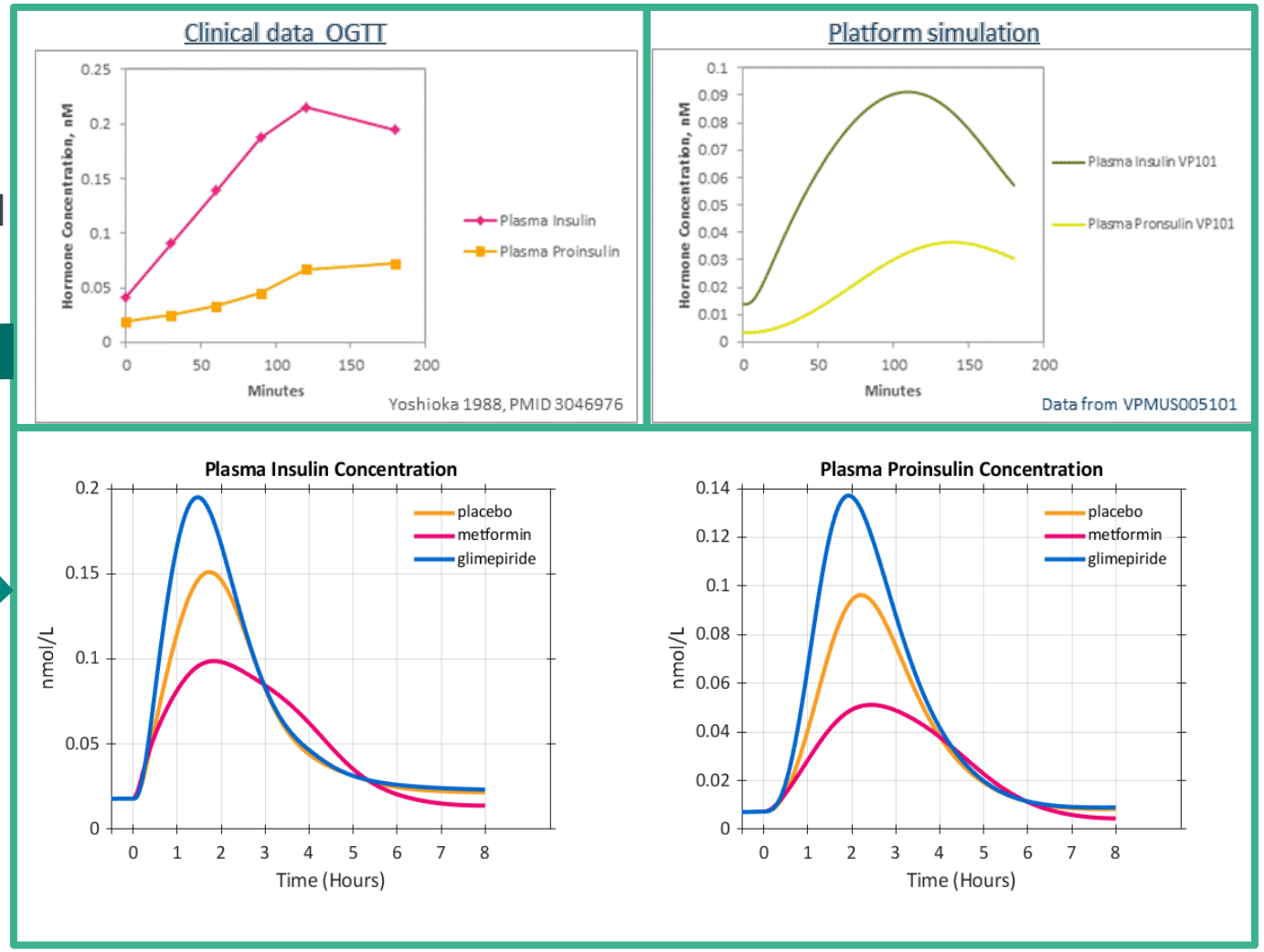
Model Qualification Through Qualitative/Quantitative Testing

Simulations mirror clinical data

T2DM

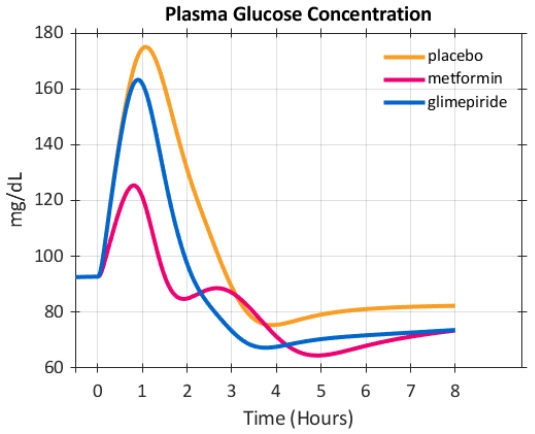


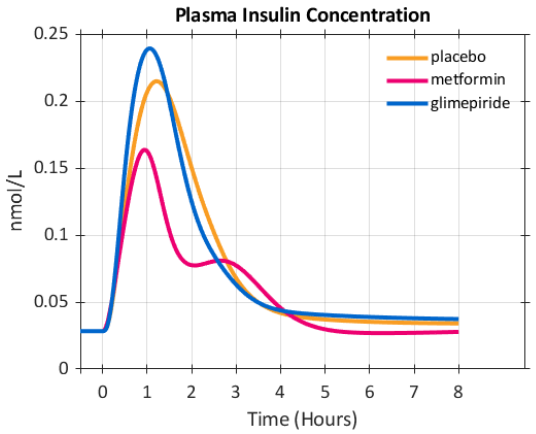
Healthy

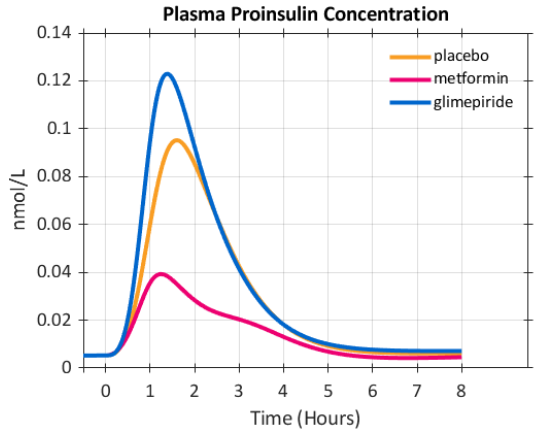
T2DM

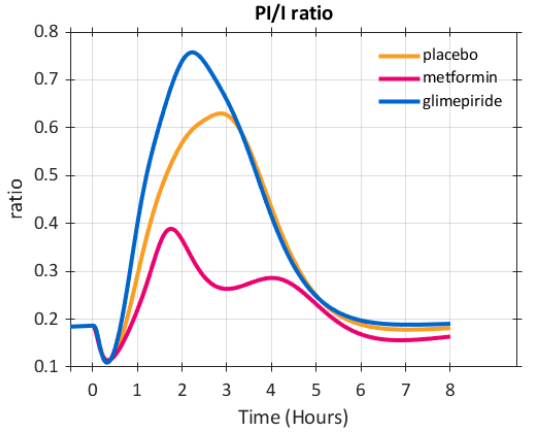
QSP Simulations Show Effects of Metformin and Sulfonylurea on Proinsulin Expected from Literature

Healthy

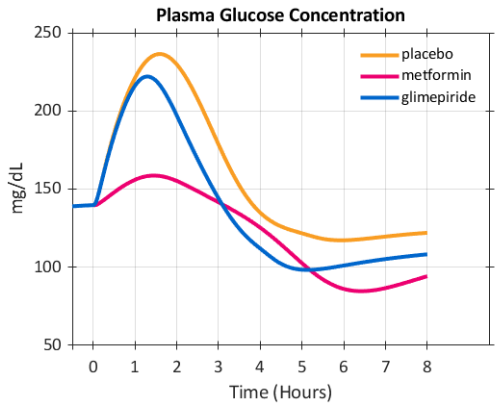


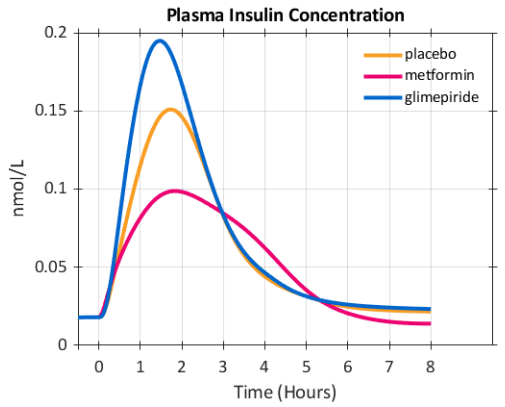


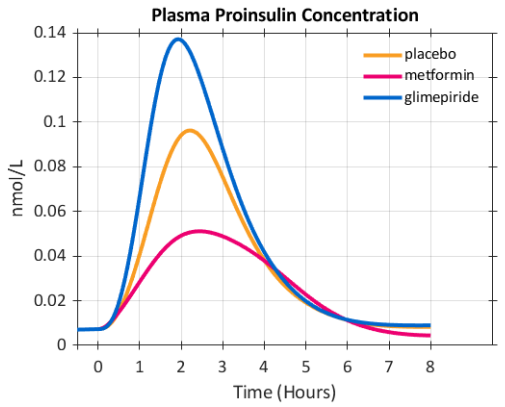


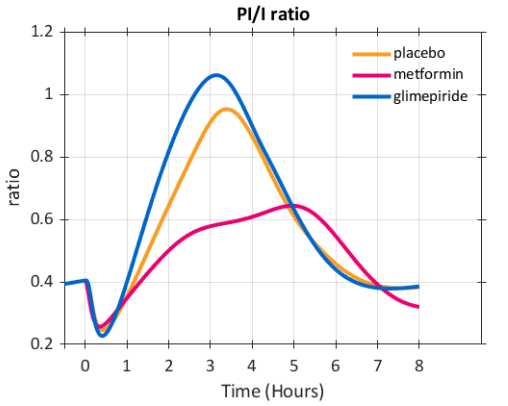


T2DM: Hyperinsulinemic









Glimepiride treatment	**↑ PI concentration and PI/I ratio**	**(Ohkura et al. 2013, (Forst et al. 2013)**
Metformin treatment	↓ PI concentration and PI/I ratio	(Nagi, Ali, and Yudkin 1996, Lachin et al. 2007)

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Clinically Relevant QSP Simulations for In Silico Hypothesis Testing

Hypothesis: Will conversion of circulating proinsulin to insulin ameliorate hyperglycemia in T2DM?

Objective: Evaluate the impact of increasing the conversion of proinsulin to insulin on glycemic outcomes in T2DM VPs

- VPs: 1 healthy, 3 diabetic VPs
- Treatment: Proinsulin converting drug
  - Increasing proinsulin conversion rate from 0 to 100% in 6 steps (0, 20, 40, 60, 80, 100)
- Measured outcomes: A1c, fasting plasma glucose, fasting plasma insulin, fasting plasma proinsulin, fasting proinsulin/insulin ratio, OGTT 2 hr glucose, OGTT 2 hr insulin, OGTT 2 hr proinsulin, OGTT glucose AUC, OGTTinsulin AUC, OGTT proinsulin AUC

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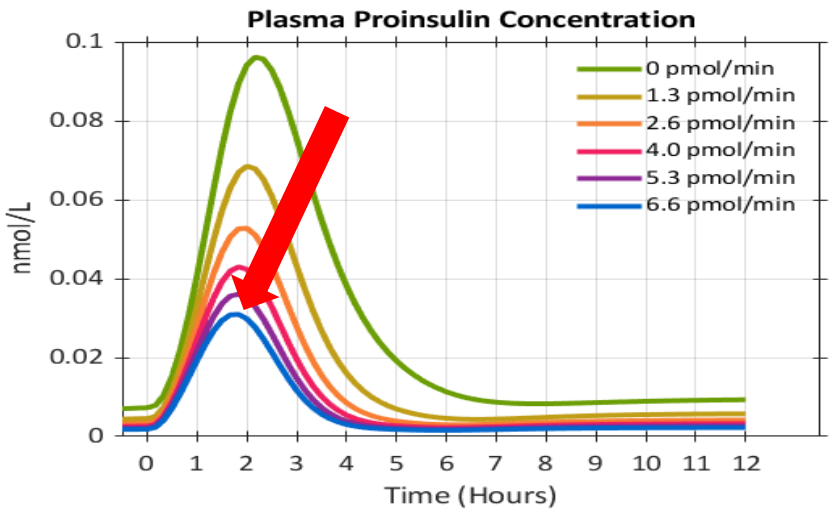
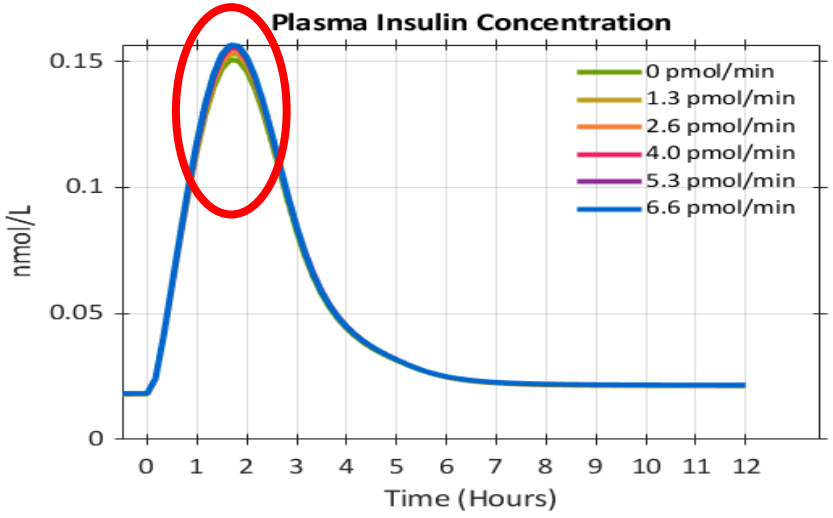
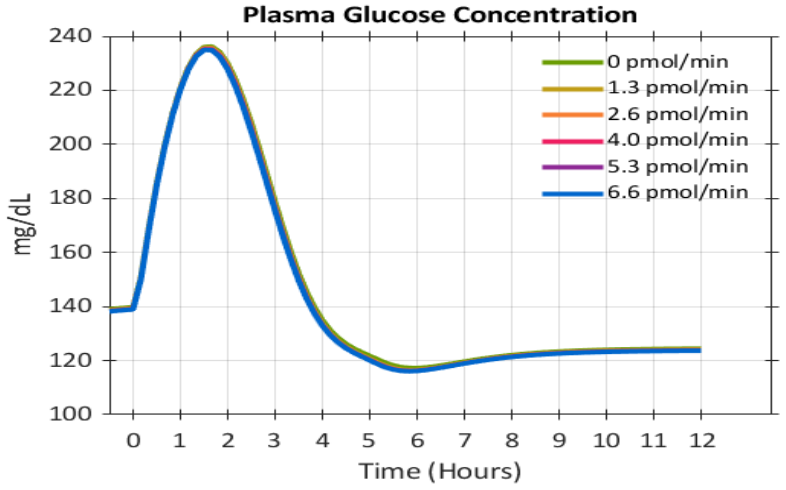
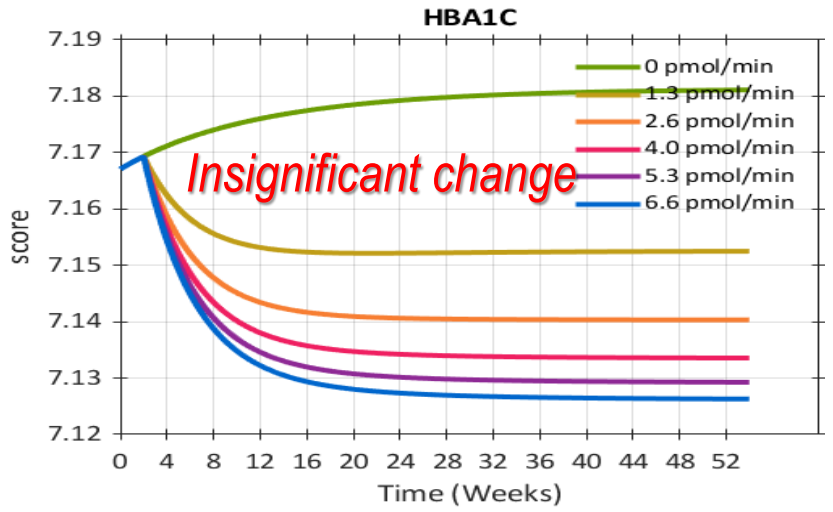
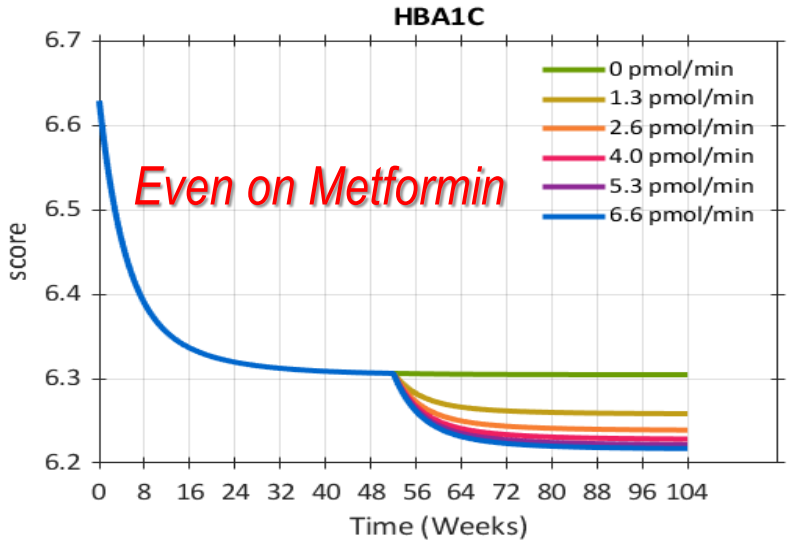
Initial simulations did not seem to show much effect of including the proinsulin conversion drug

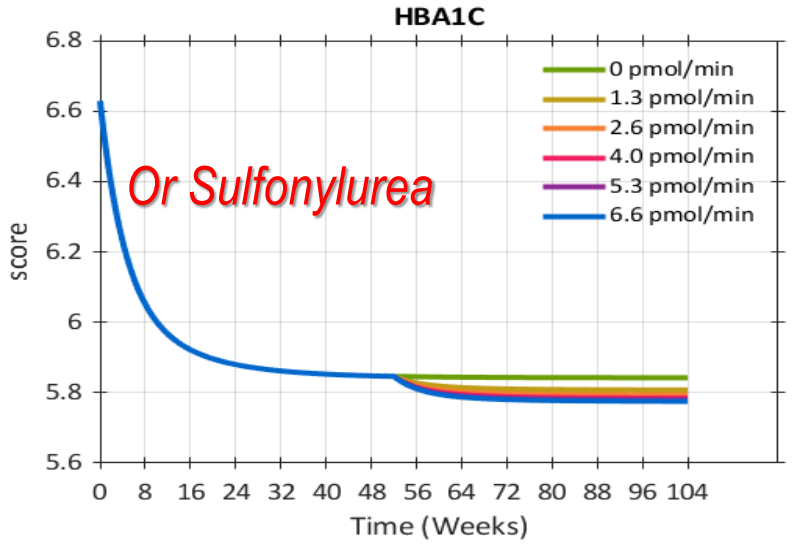








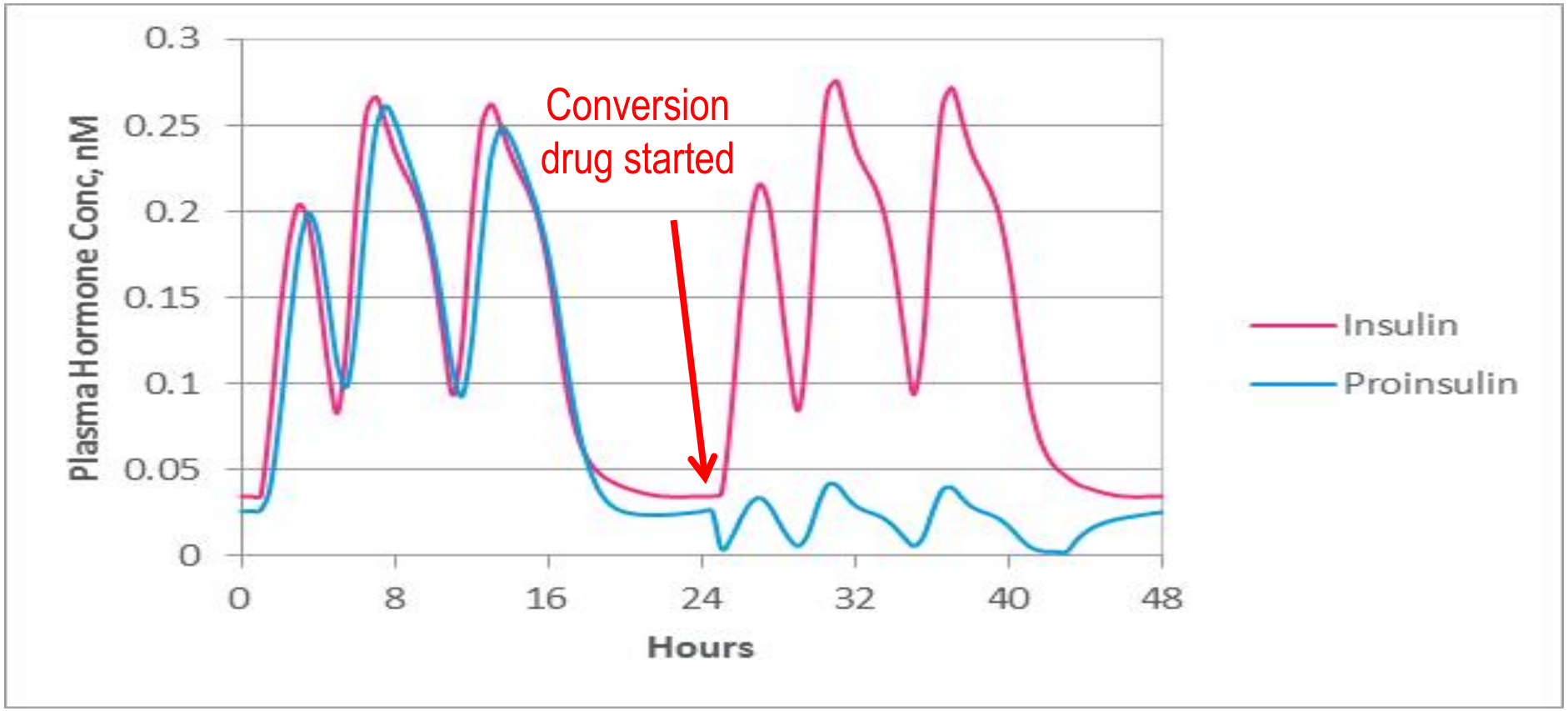




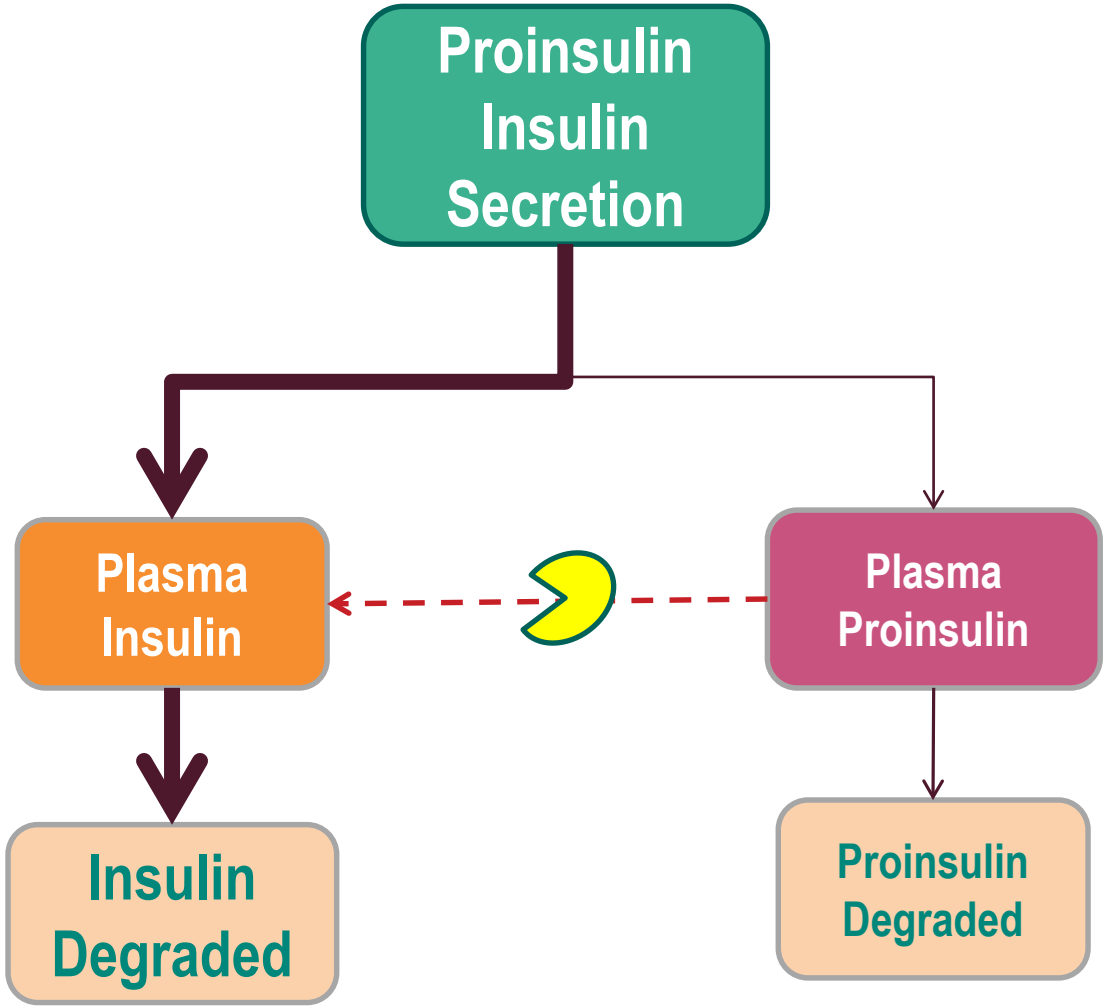
VPMUS005121 simulated for 52 weeks, then given an OGTT. Rates shown are the initial fasting rate of conversion when the drug is given.

Plasma proinsulin conversion to insulin does increase plasma insulin concentration.

Insulin peaks are ~10 pM higher for each meal



Proinsulin and insulin have vastly different secretion and degradation rates- the flux of insulin is much greater.



- Proinsulin and insulin have similar plasma concentration levels
- Secretion and degradation rates of proinsulin are much lower than insulin
- Half-life of insulin (4-8 min)is much shorter than proinsulin (20 min)
- When proinsulin is converted to insulin, it is much more rapidly cleared having minimal impact on insulin levels

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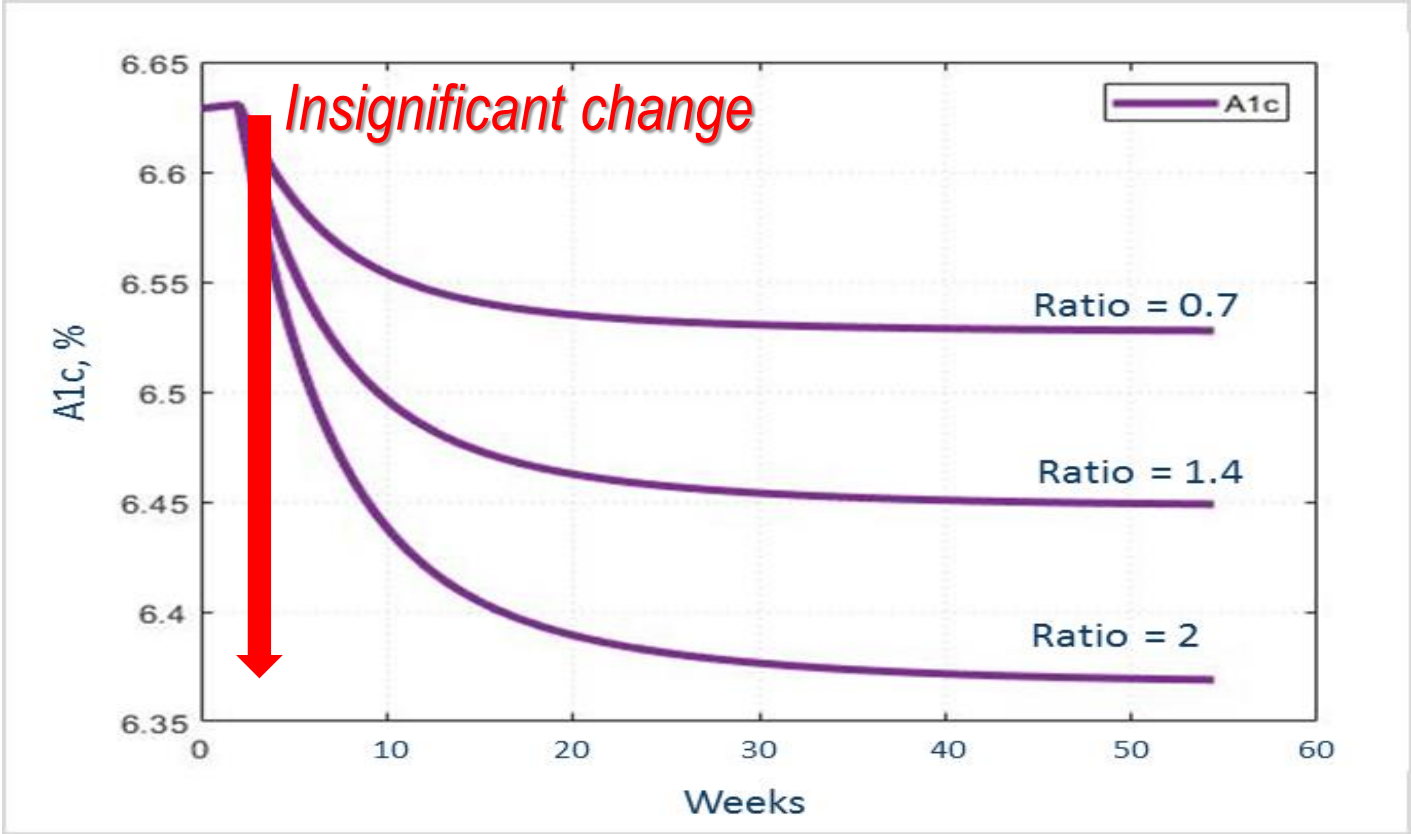
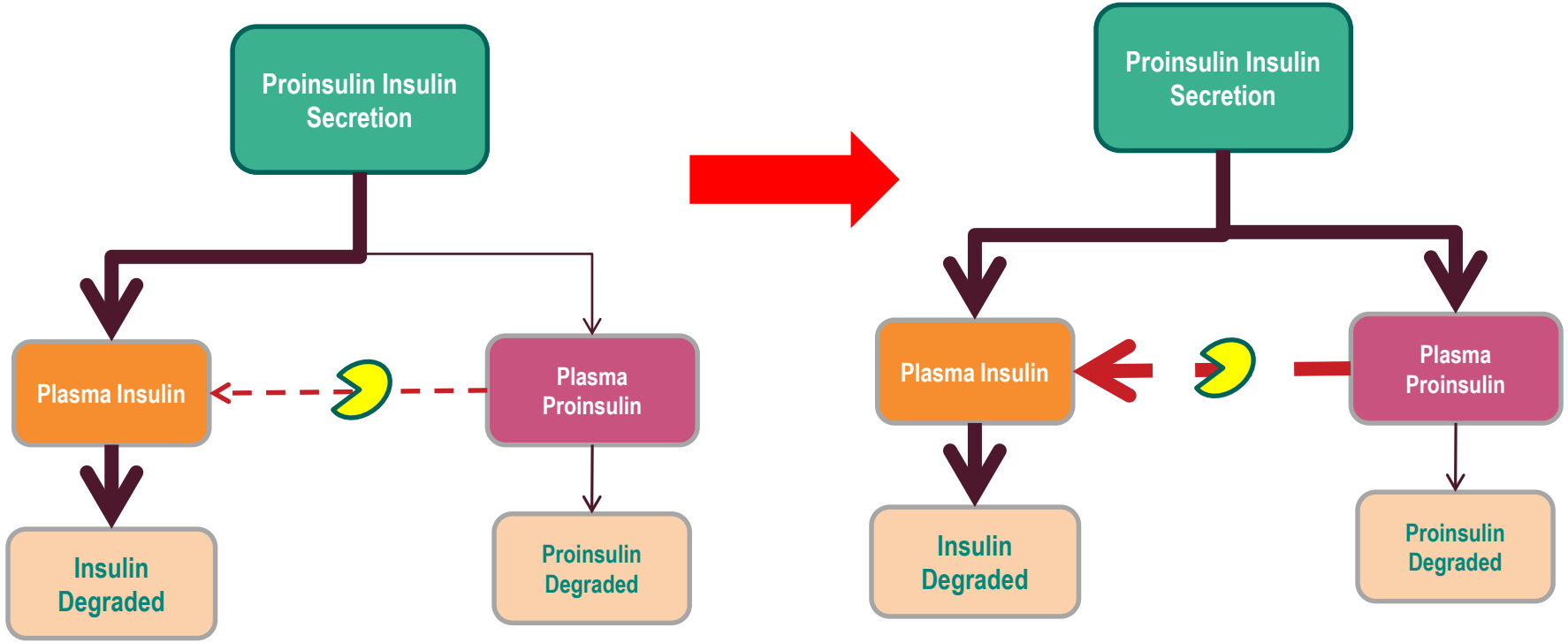
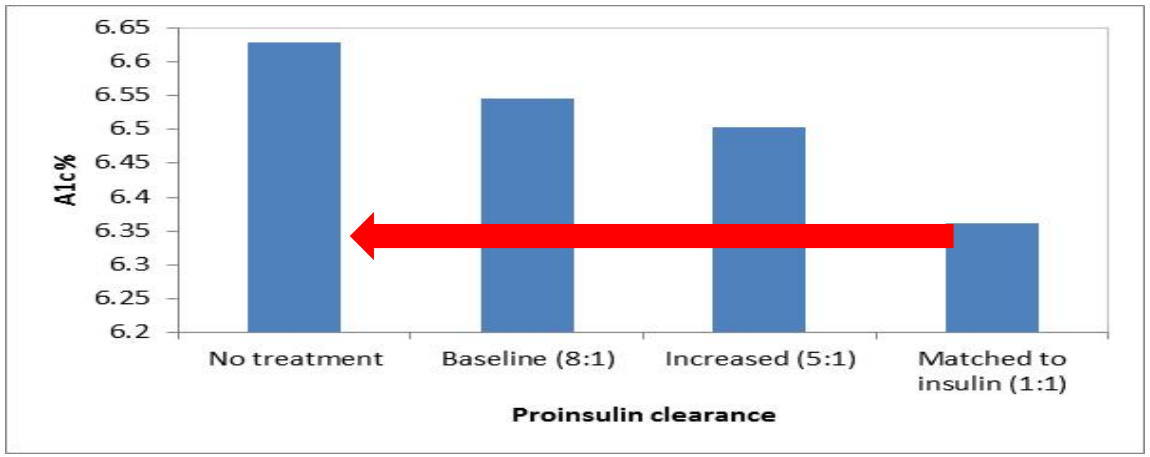
Would patients with higher proinsulin/insulin ratio show greater efficacy?



Yes, but no…proinsulin/insulin ratios observed ranged from: 0.05-4.8, majority of subjects had a ratio < 1.2 where no meaningful changes in HBA1c were observed

In silico hypothesis testing:
Could increasing the flux rate of proinsulin provide efficacy?

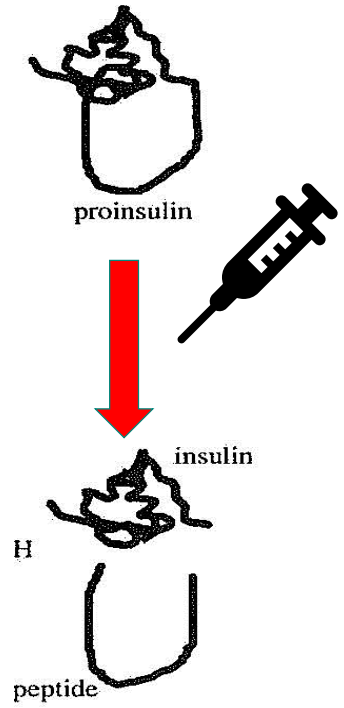




Increasing proinsulin flux rate provides a larger bolus of proinsulin to convert but delivers insufficient change in HBA1c even if flux is matched to insulin (which is not plausible)

Leveraging the Diabetes QSP Model for the Proinsulin Program

- Key questions:
  - *Will the conversion of circulating pro-insulin to insulin reduce hyperglycemia in T2DM?*
    - *Impact of background therapies?*
    - *Is there a subpopulation of T2DMs where this would work best?*



NO GO for TIDVAL based on in silico hypothesis testing with QSP!

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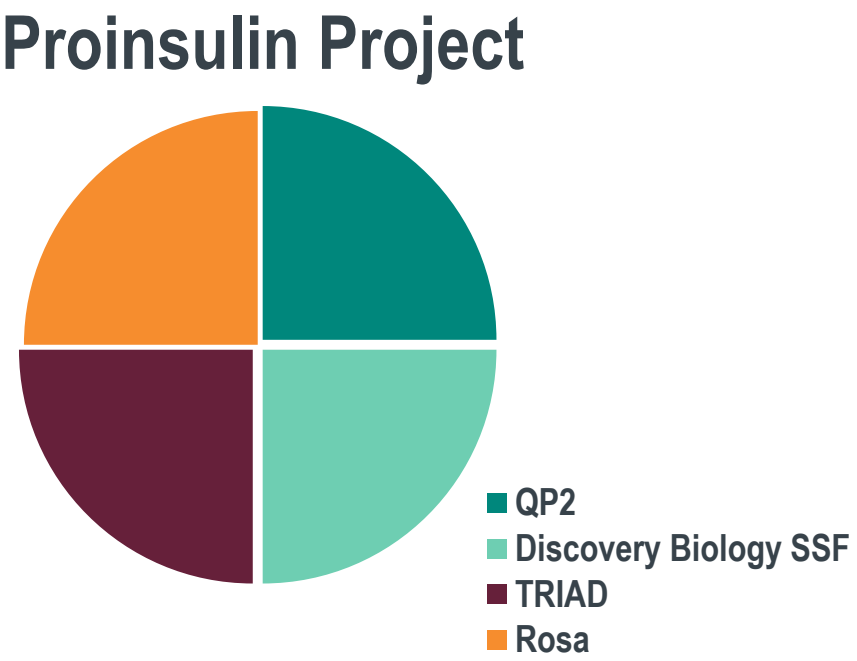
Leveraging the QSP to drive decisions in TIDVAL:

- ***NO GO for TIDVAL based on in silico hypothesis testing with QSP!***
- **Minimal lab work was required**
- **Project timeframe ~9 months**
- **A great example of collaboration & creativity!**



Discovery SSF
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Rosa
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