Modelling of Type 2 Diabetes

Useful for pharmaceutical industry?

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What do you know about diabetes?

- 1 of 16 people in the UK has diabetes
- 90% have type 2
- 2 time more cases in the last 20 years

Year	1996	2015
No. of cases	1.4 million	3.2 million

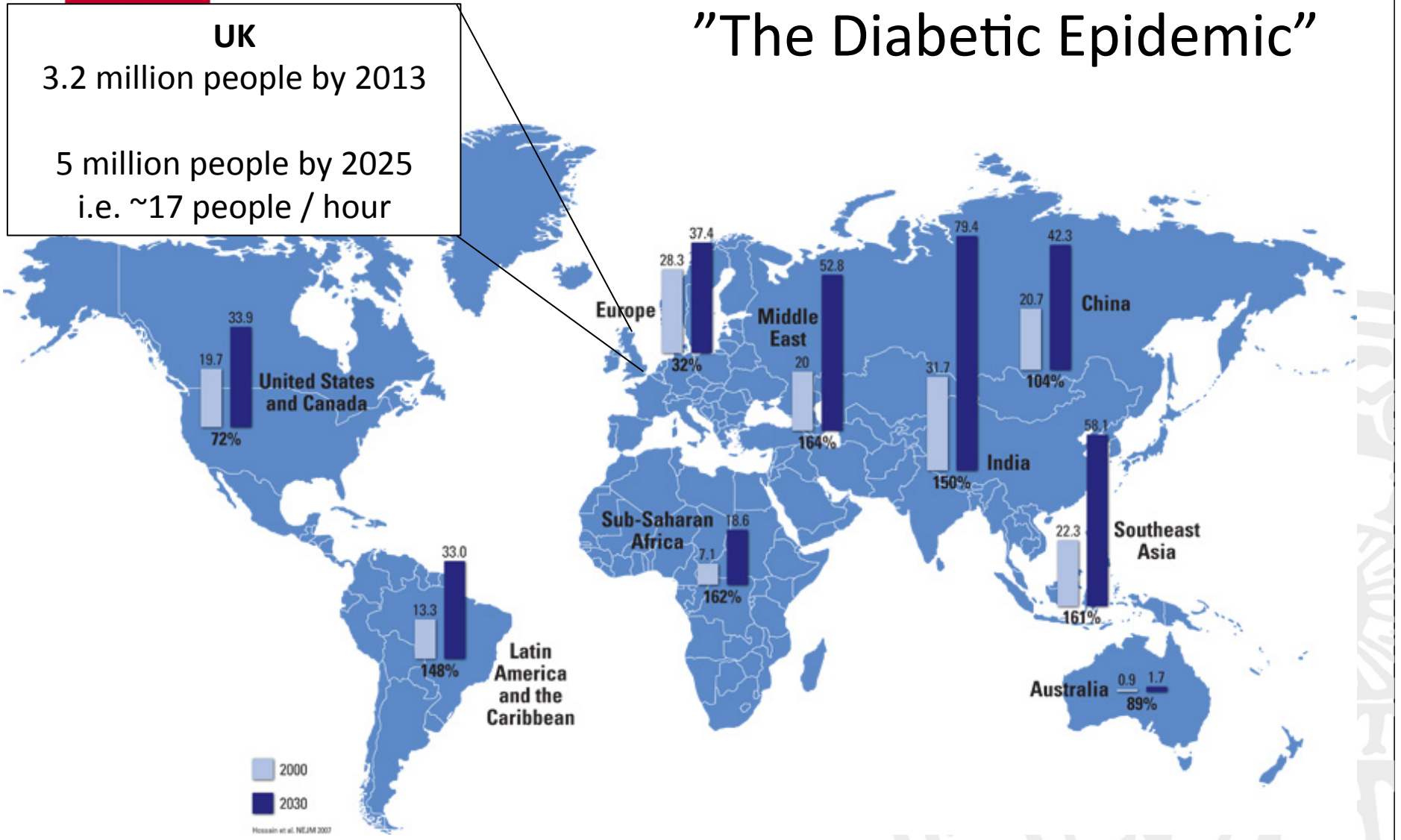
”The Diabetic Epidemic”

UK

3.2 million people by 2013

5 million people by 2025

i.e. ~17 people / hour



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Why is diabetes increasing?

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Glucose homeostasis

Glucose and insulin inhibits endogenous glucose production

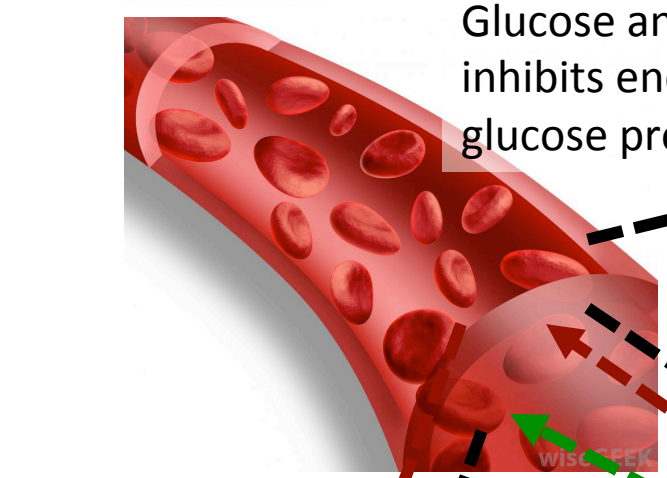
Glucose

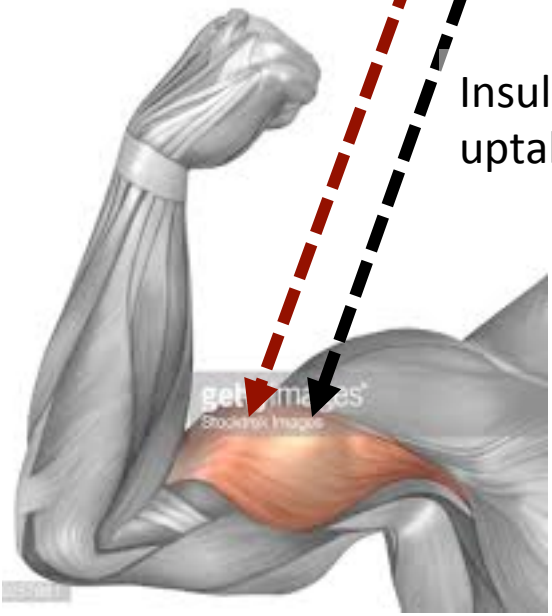
Glucose stimulates insulin secretion

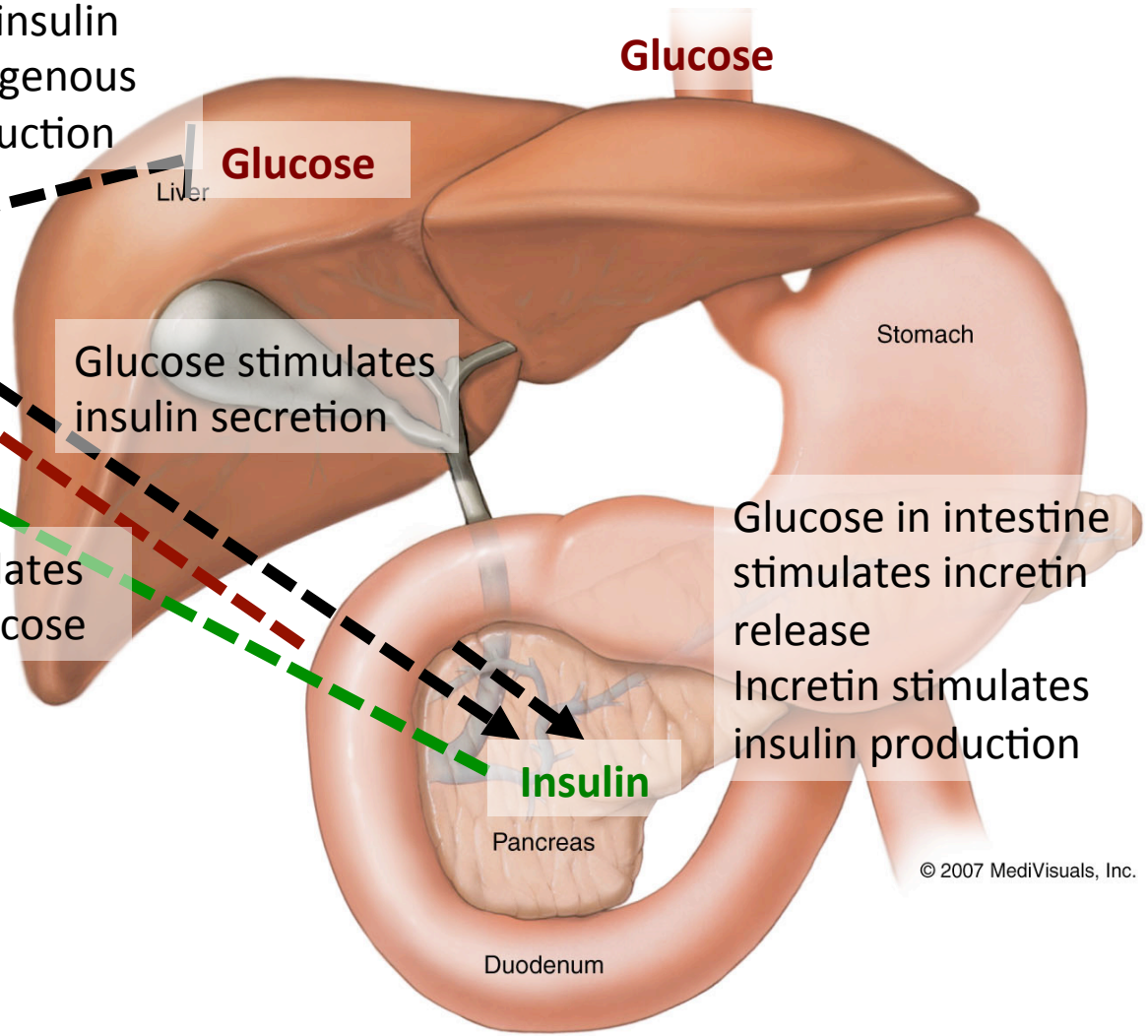
Insulin stimulates uptake of glucose

Glucose in intestine stimulates incretin release
Incretin stimulates insulin production

Insulin







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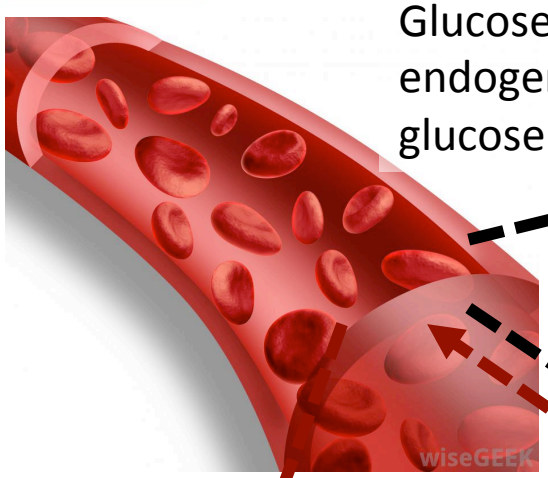
Type 1 Diabetes Mellitus

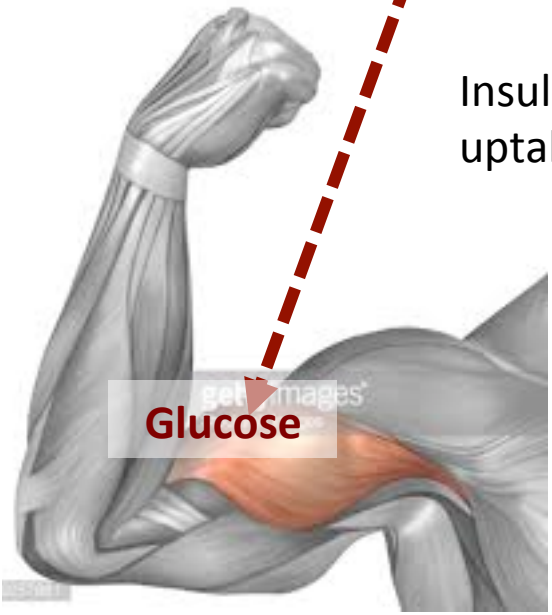
Glucose inhibits endogenous glucose production

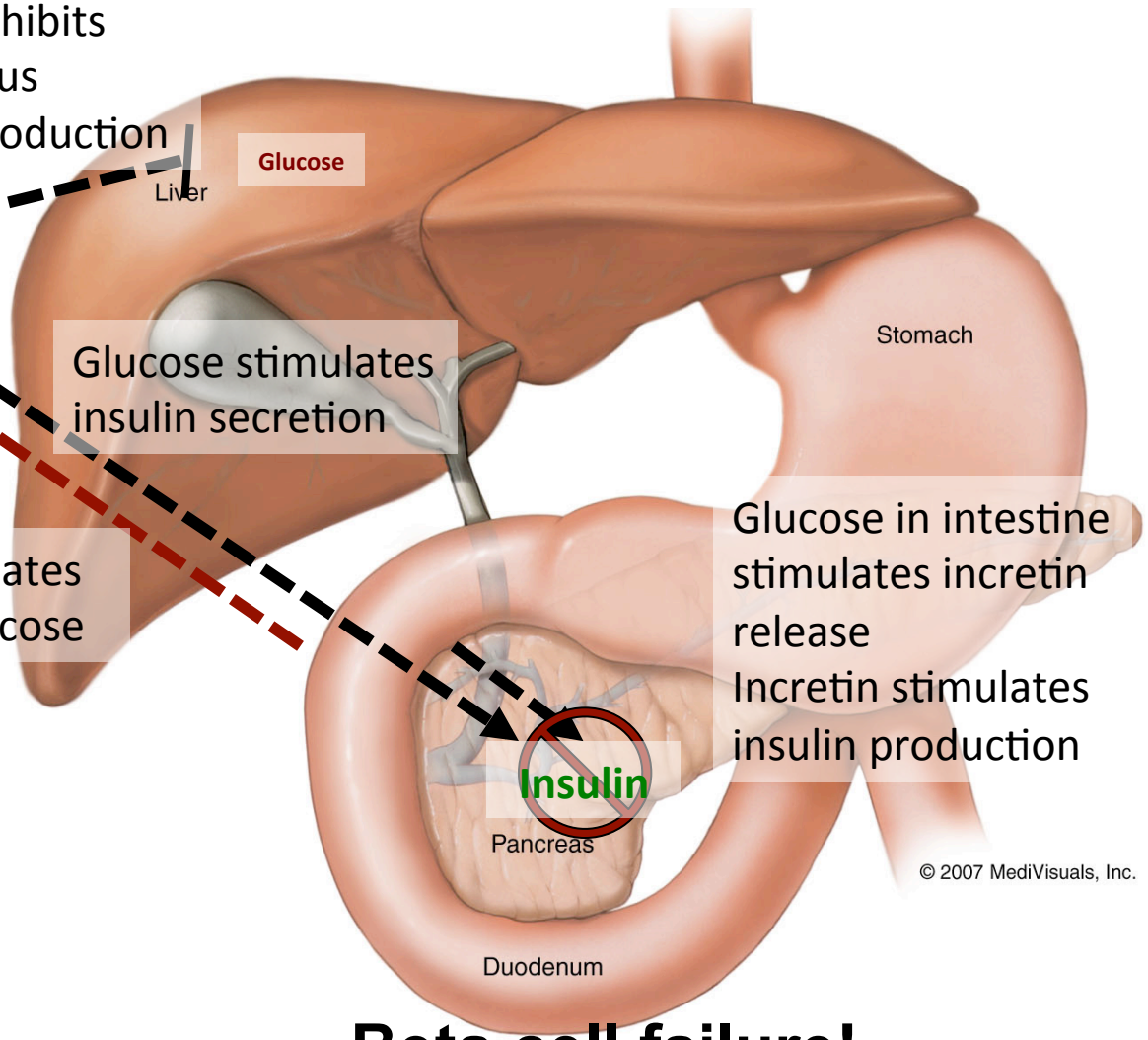
Glucose stimulates insulin secretion

Insulin stimulates uptake of glucose

Glucose in intestine stimulates incretin release
Incretin stimulates insulin production







Beta cell failure!

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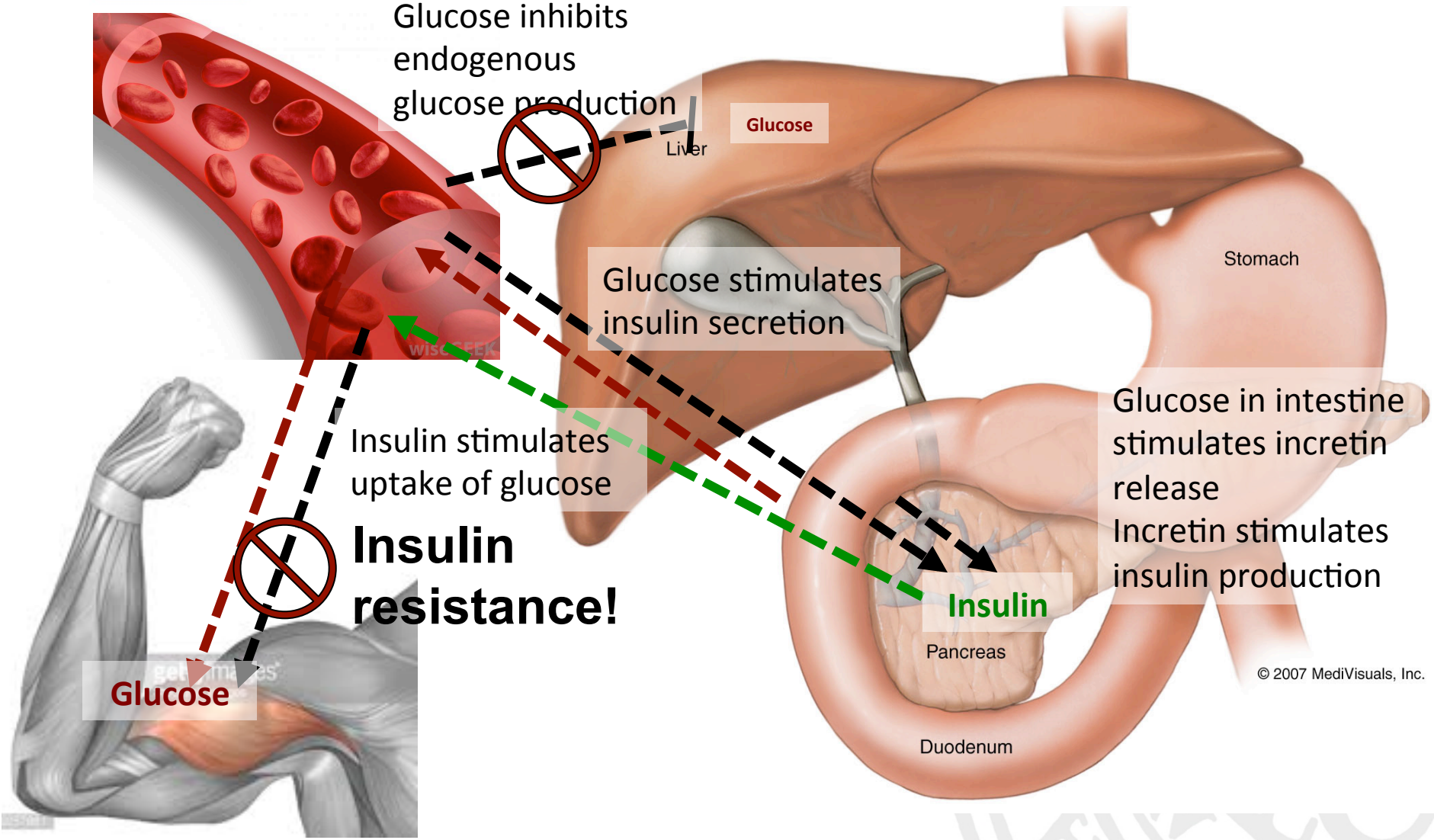
Type 2 Diabetes Mellitus



Why is modelling useful in studying diabetes?

- Dynamic disease – What we aim to describe/build
  - Short-term (hours, weeks): drug treatment, glucose homeostasis
  - Long-term: disease progression

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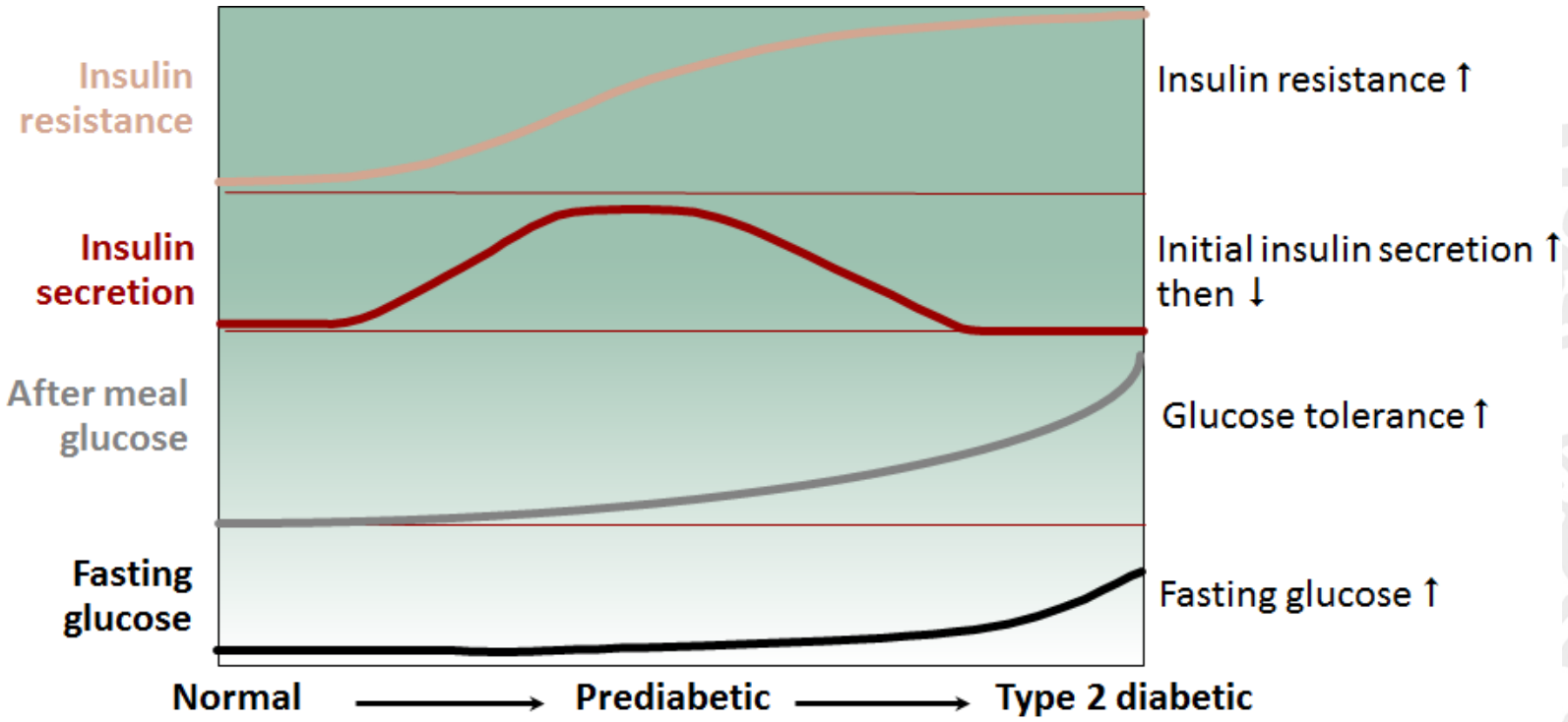
Progression to type 2 diabetes

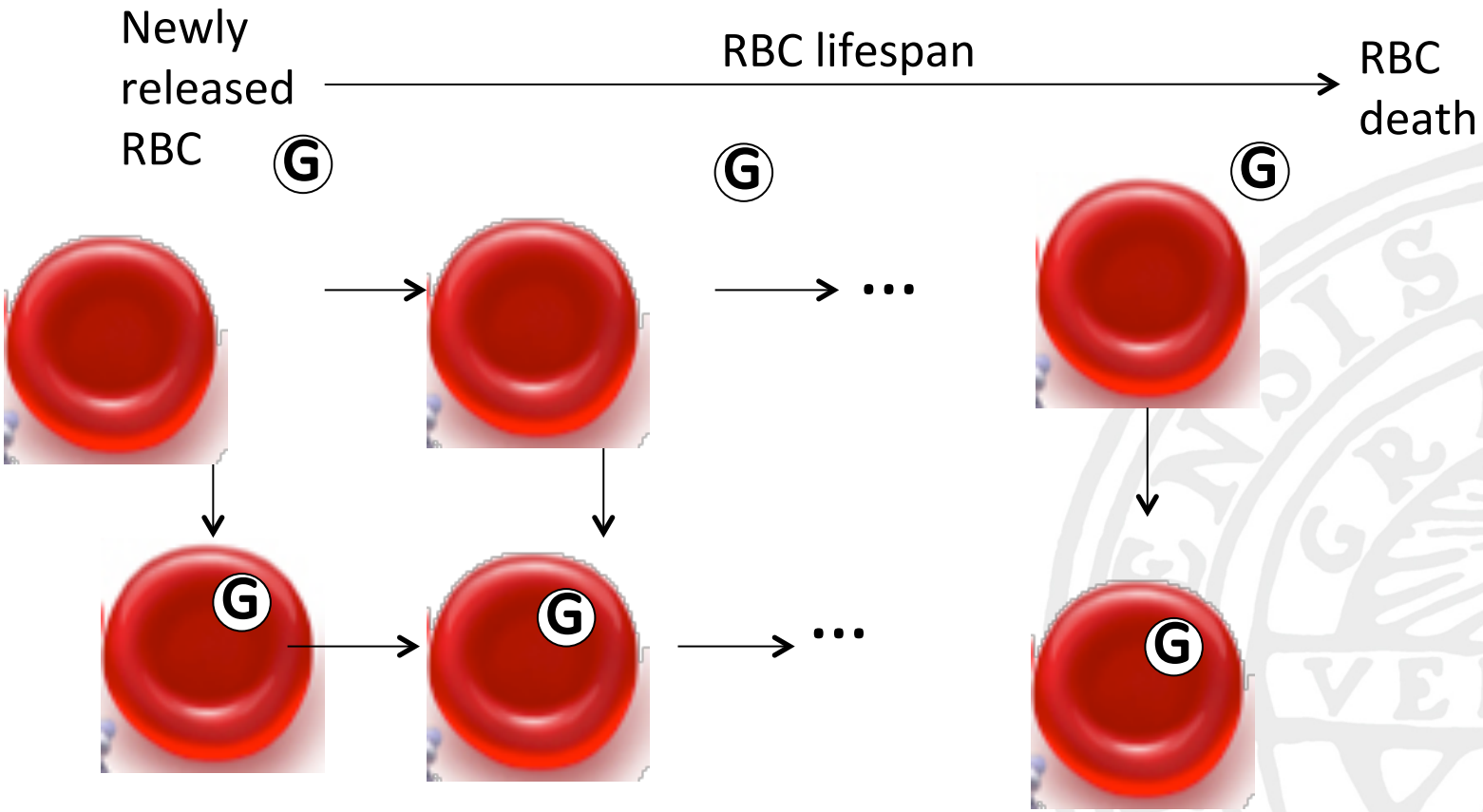


Insulin resistance and beta cell function are not directly measurable

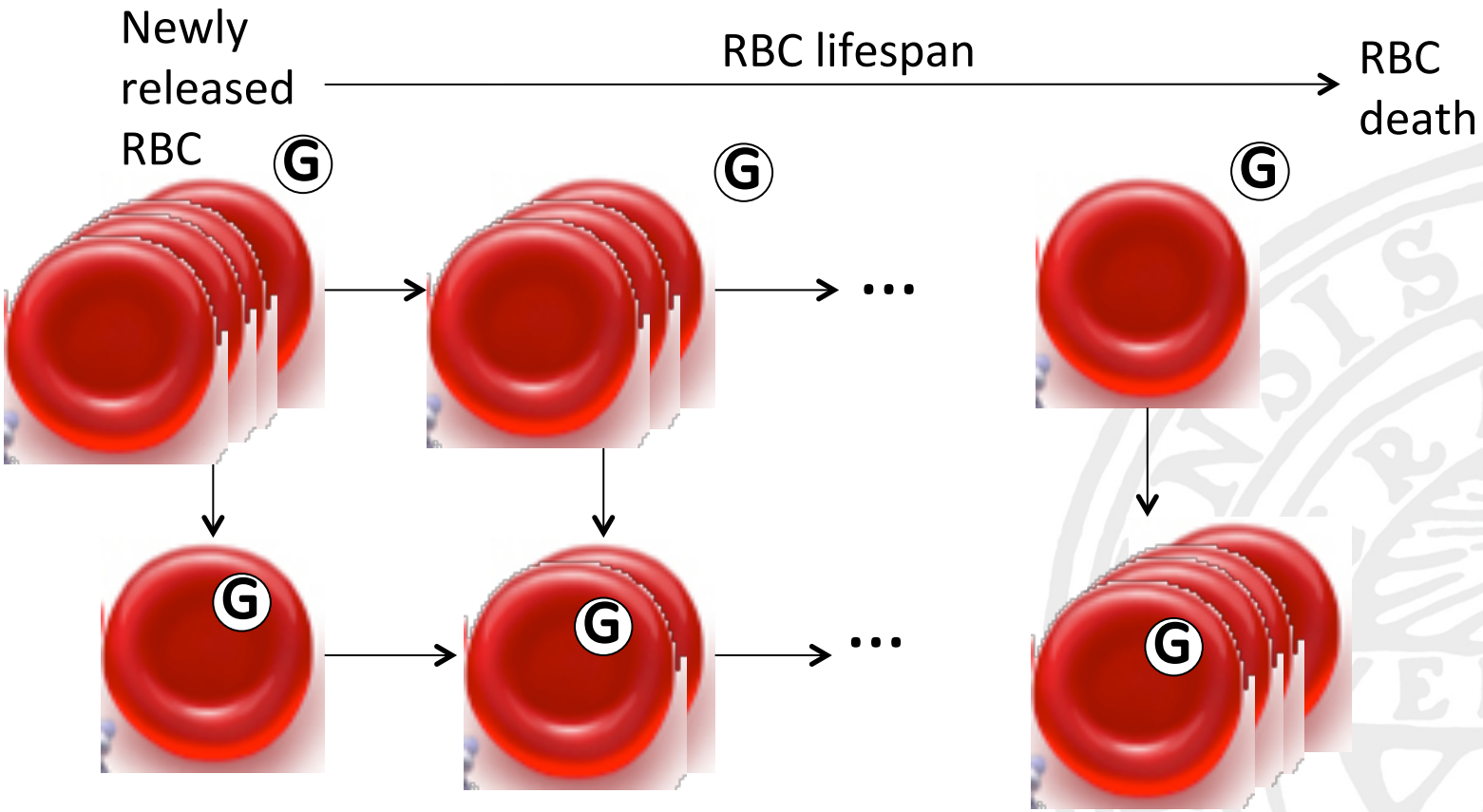
Why is modelling useful in studying diabetes?

- Dynamic disease – What we aim to describe/build
  - Short-term (hours, weeks): drug treatment, glucose homeostasis
  - Long-term (years): disease progression
- Dynamic biomarkers – What we use to describe
  - Short-term (minutes, hours):
    - dynamic glucose (dG)
    - dynamic insulin (dI)
  - Long-term (weeks, months):
    - fasting glucose (FPG)
    - fasting insulin (FSI)
    - glycated haemoglobin (HbA1c)

HbA1c



HbA1c = glycated Hb/total Hb



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    - dyn…
    - dyn…
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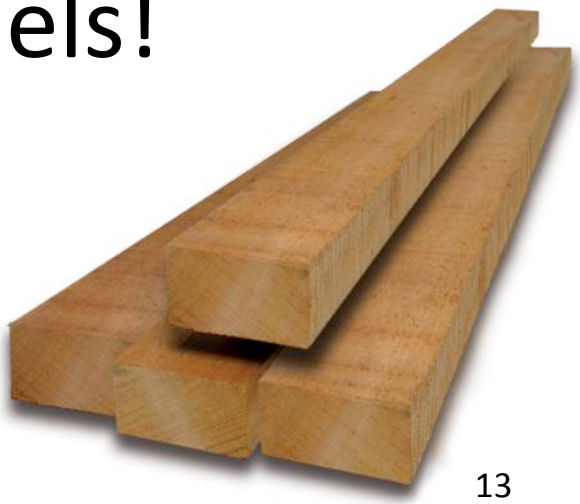
Models!



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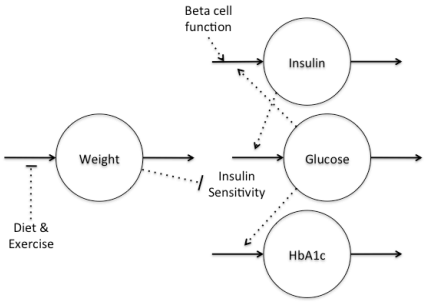
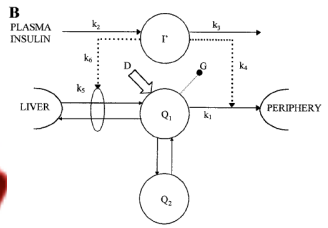
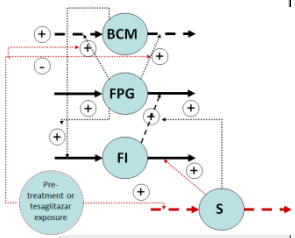
Toolbox of models



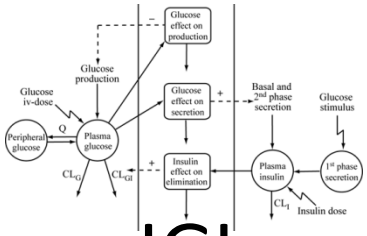
WHIG



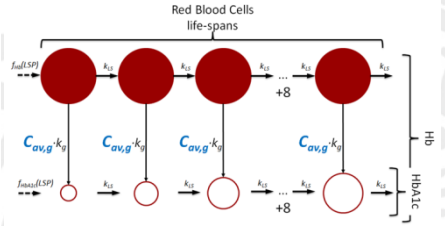
Minimal



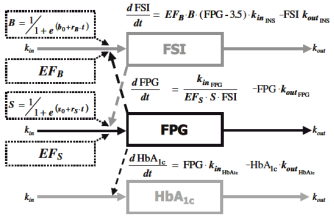
BIG



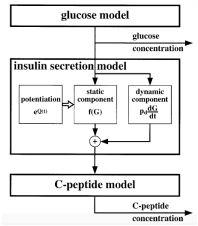
IGI



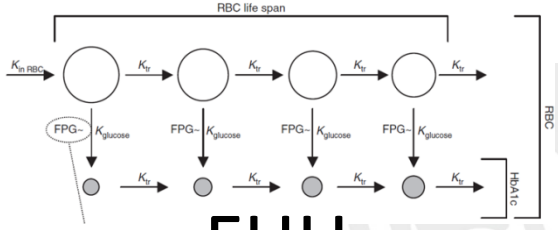
IGRH



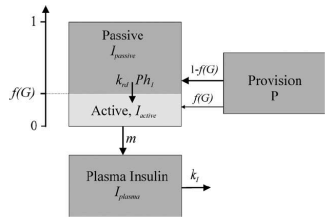
FFH



Beta cell



FHH



MBC

Model aided decisions

1. Disease progression
   - Placebo effect related to weight change
2. Identifying drug MoA
   a. Glucokinase activator with IGI model
   b. Tesaglitasar with BIG model
3. Impact of study design
   a. Optimising study design for phase 1 study
   b. Optimising method of analysis for phase 2a study
4. Translation between phases in drug development
   a. Translate between species
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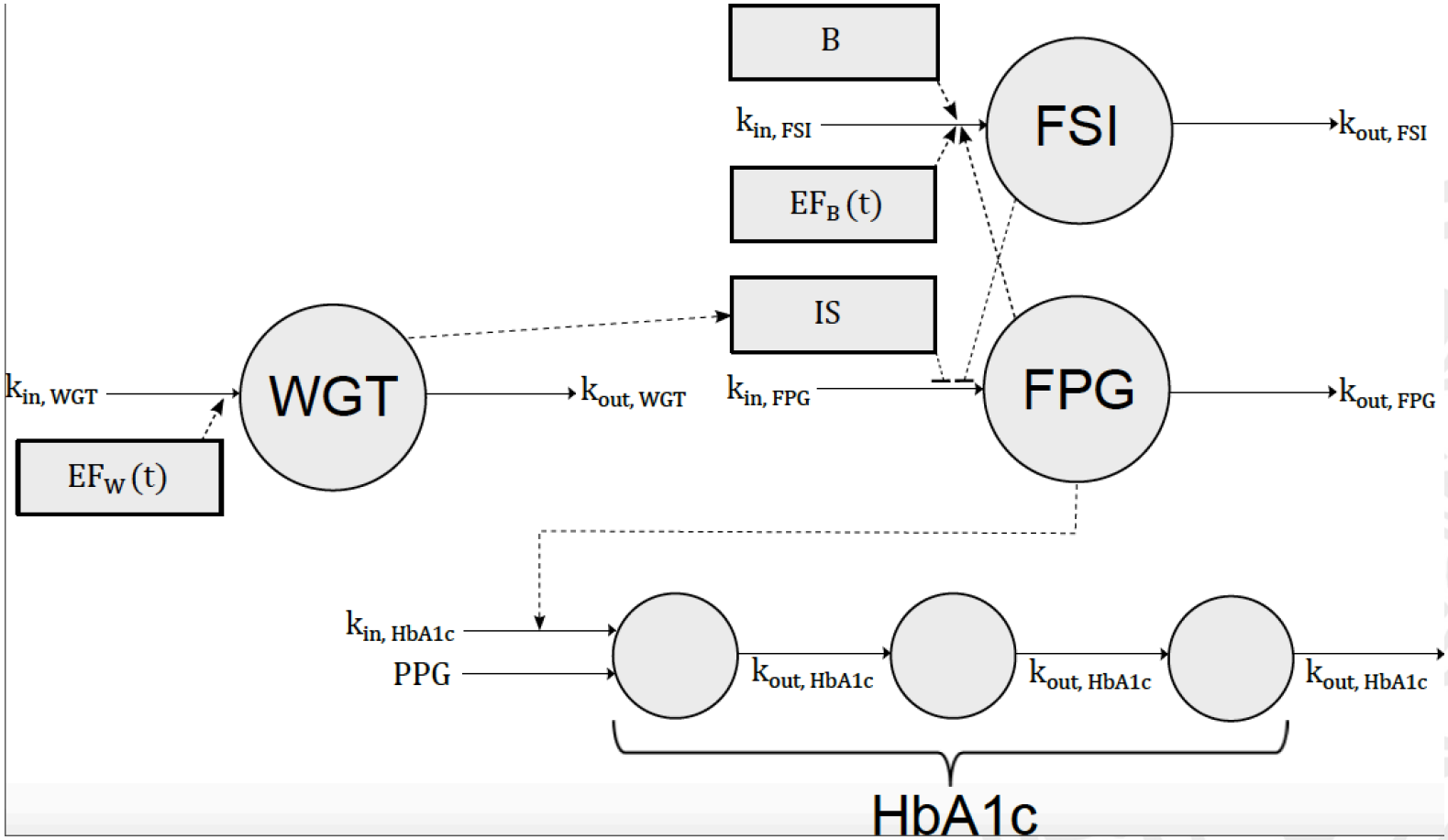
Application 1 – disease progression with the WHIG model

Placebo arm of study

- Biomarkers: FPG, FSI, HbA1c and weight
- 181 newly diagnosed T2DM patients
- Counselling on diet & exercise
- Screening, 7 weeks prior to start of study
- Study duration 60 weeks

Can we explain placebo by weight loss?

Weight HbA1c Insulin Glucose model*



*Choy, et al PAGANZ, 2013; Originally based on de Winter, et al J PKPD 2006

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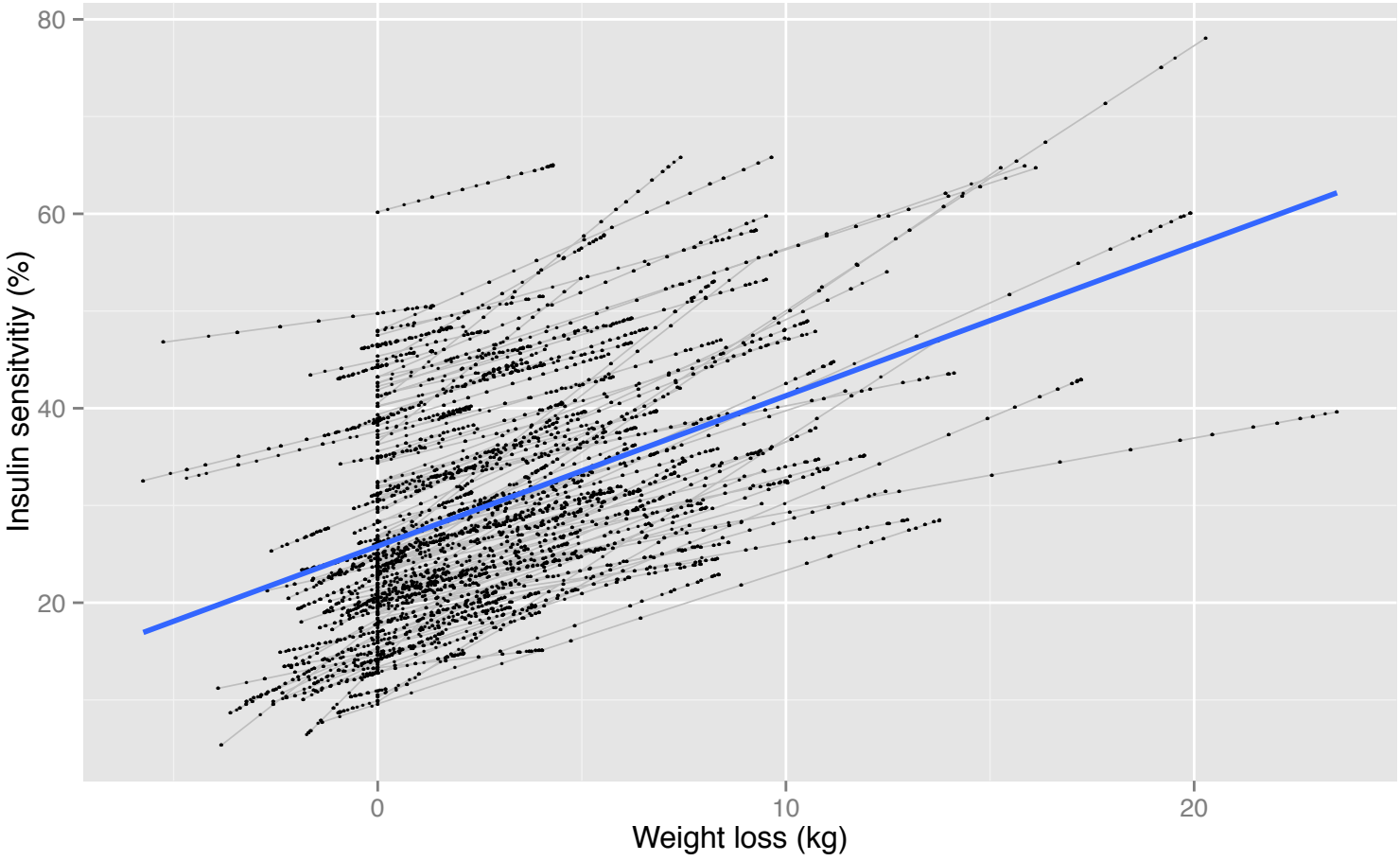
Relationship weight – insulin sensitivity



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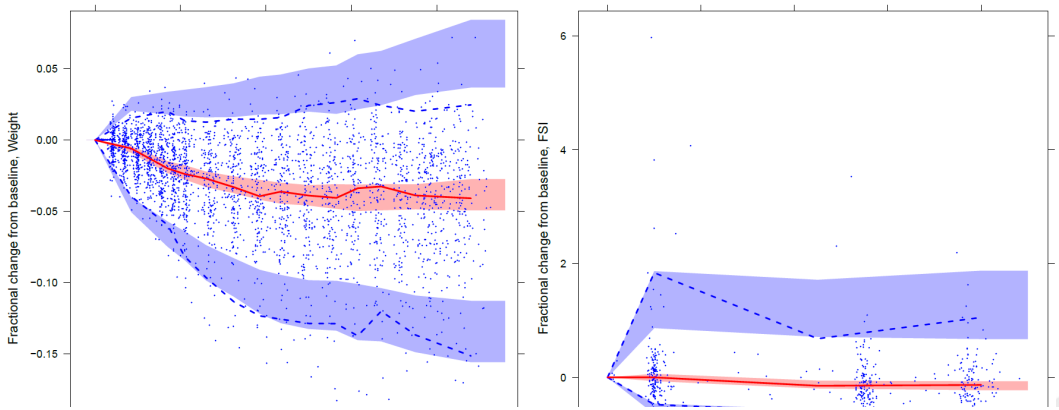
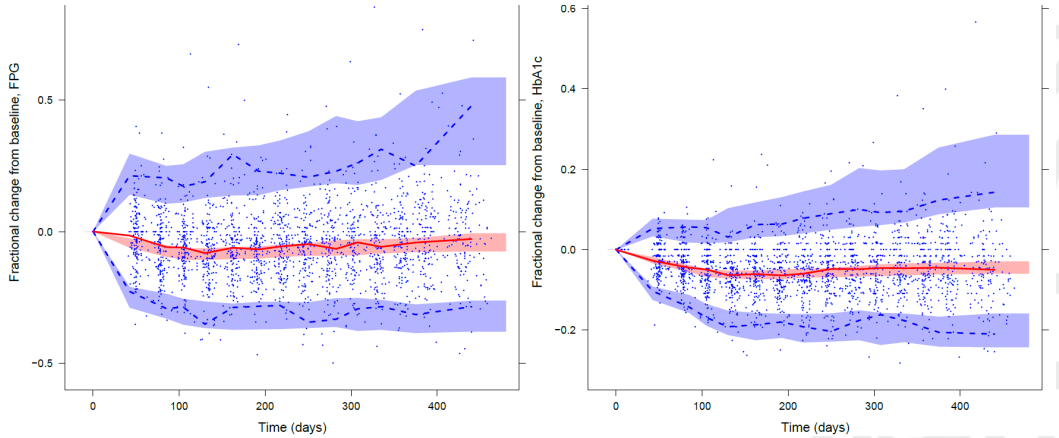
Results – application 1: VPC



Yes partly. FPG, through insulin sensitivity related to weight loss, but change in beta cell function.



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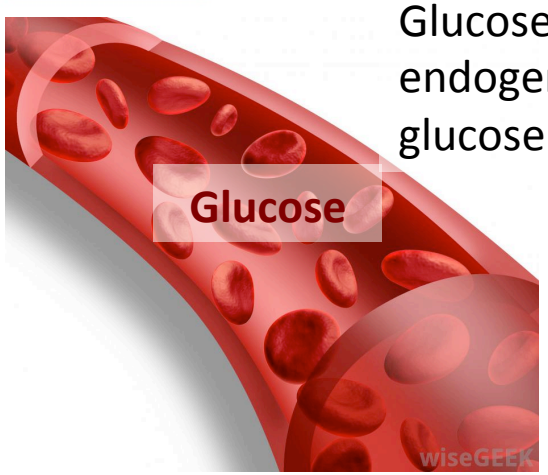
Application 2a – Identifying drug mechanism of action with the IGI model

Study of glucokinase activator

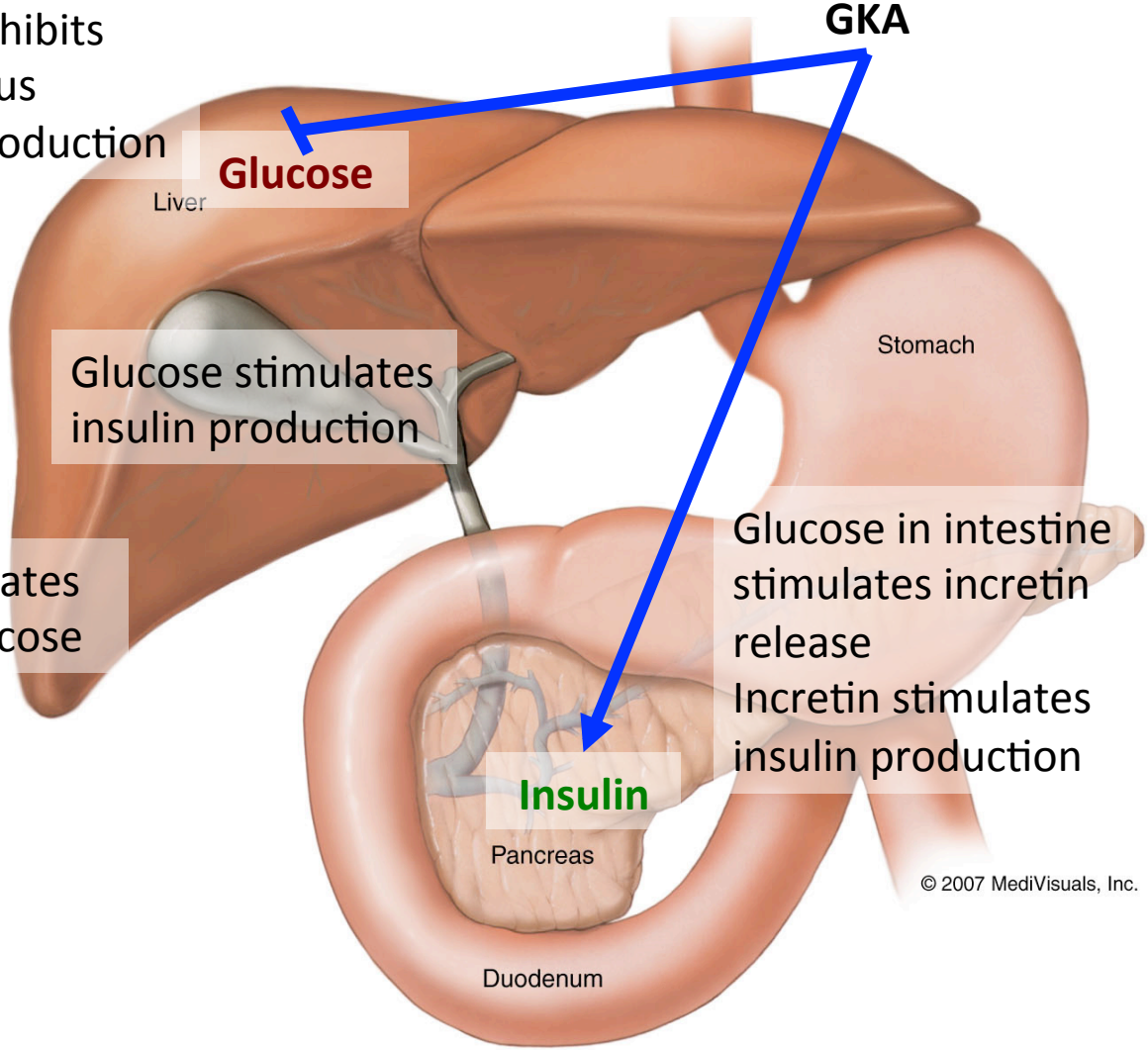
- Biomarkers: dG, dI
- 15 T2DM patients
- Full cross-over of OGTTs. WO 2 weeks
- Arms: placebo, 25 mg study drug and 100 mg study drug
- 5 hours test

Can we quantify and determine the mechanism of action of this GKA?

Drug effect of Glucokinase activator?

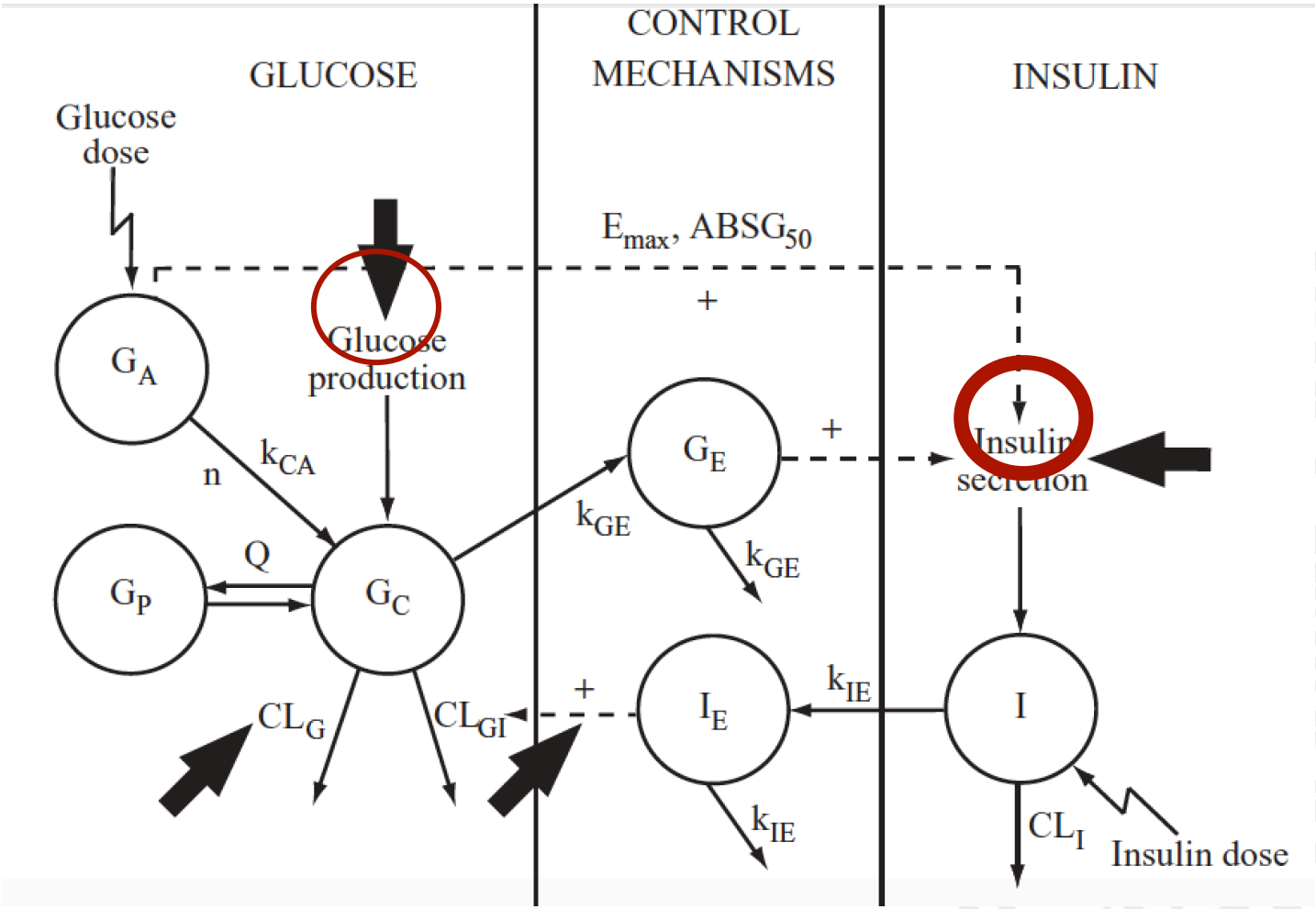


Glucose inhibits endogenous glucose production



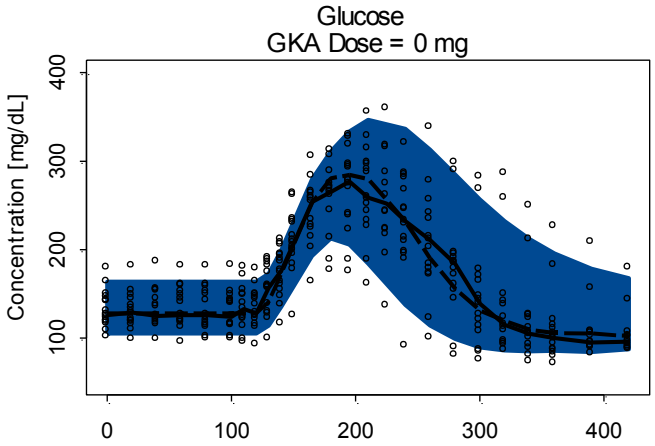
Insulin stimulates uptake of glucose

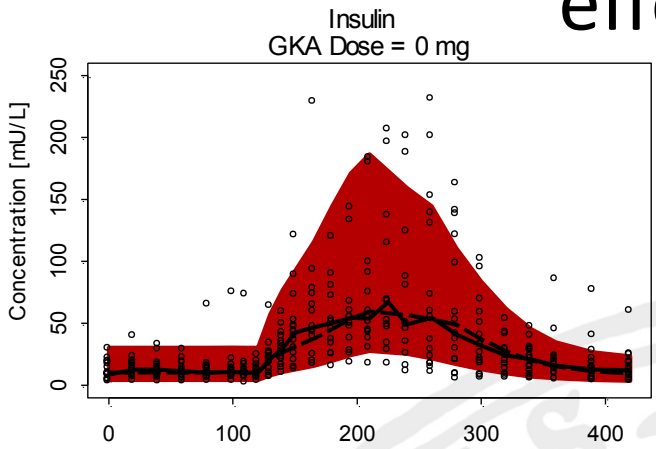
Integrated Glucose-Insulin Model - OGTT*



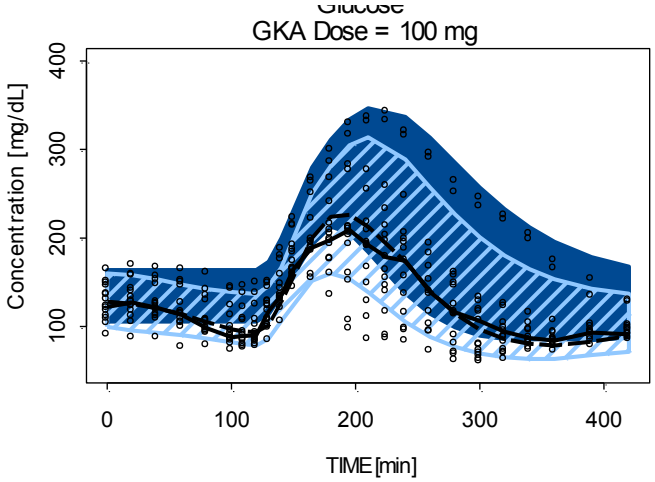
*Jauslin PM, *et al. J Clin Pharmacol* 2007; Jauslin PM, *et al. J Clin Pharmacol* 2011

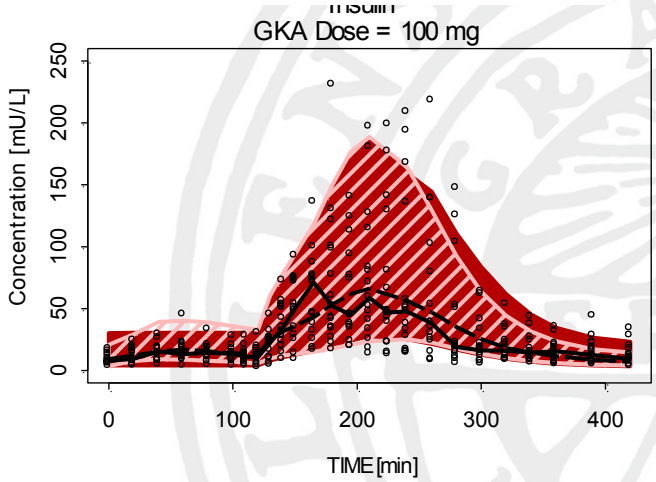
Results – application 2a: Impact of drug effect





Mechanism of action for drug was confirmed





Application 2b – Effect of long-term treatment with the BIG model*

3 phase 2/3 studies of tesaglitazar

- Biomarkers: FPG and FSI
- 1460 subjects: pretreated and naïve T2DM and non-diabetic obese
- Screening 50 days before start of study, Study duration 75 days, follow-up 25 days

What is the benefit of treatment of different groups long-term?

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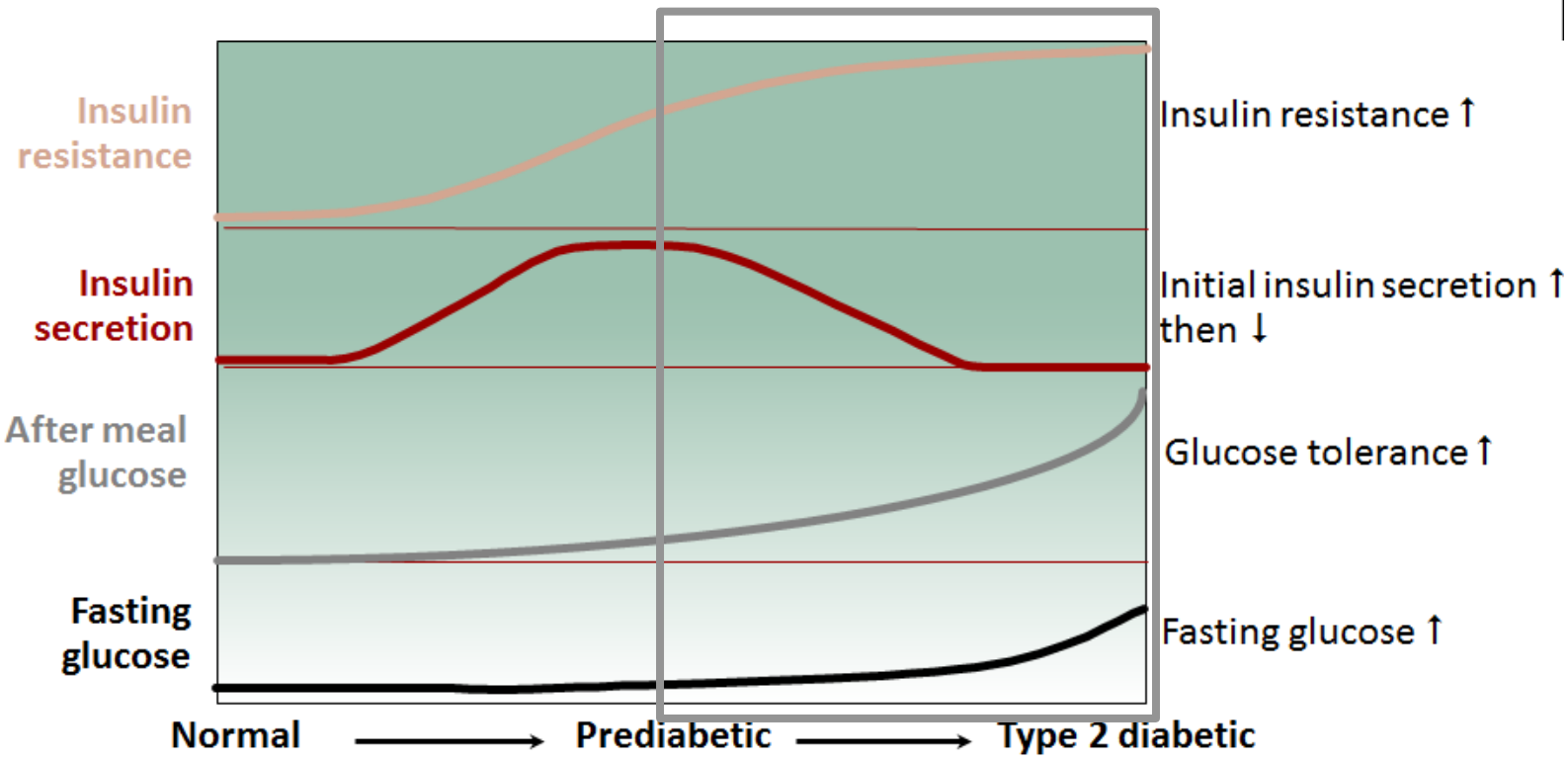
BIG Model

Focus on the possible regain of beta cells



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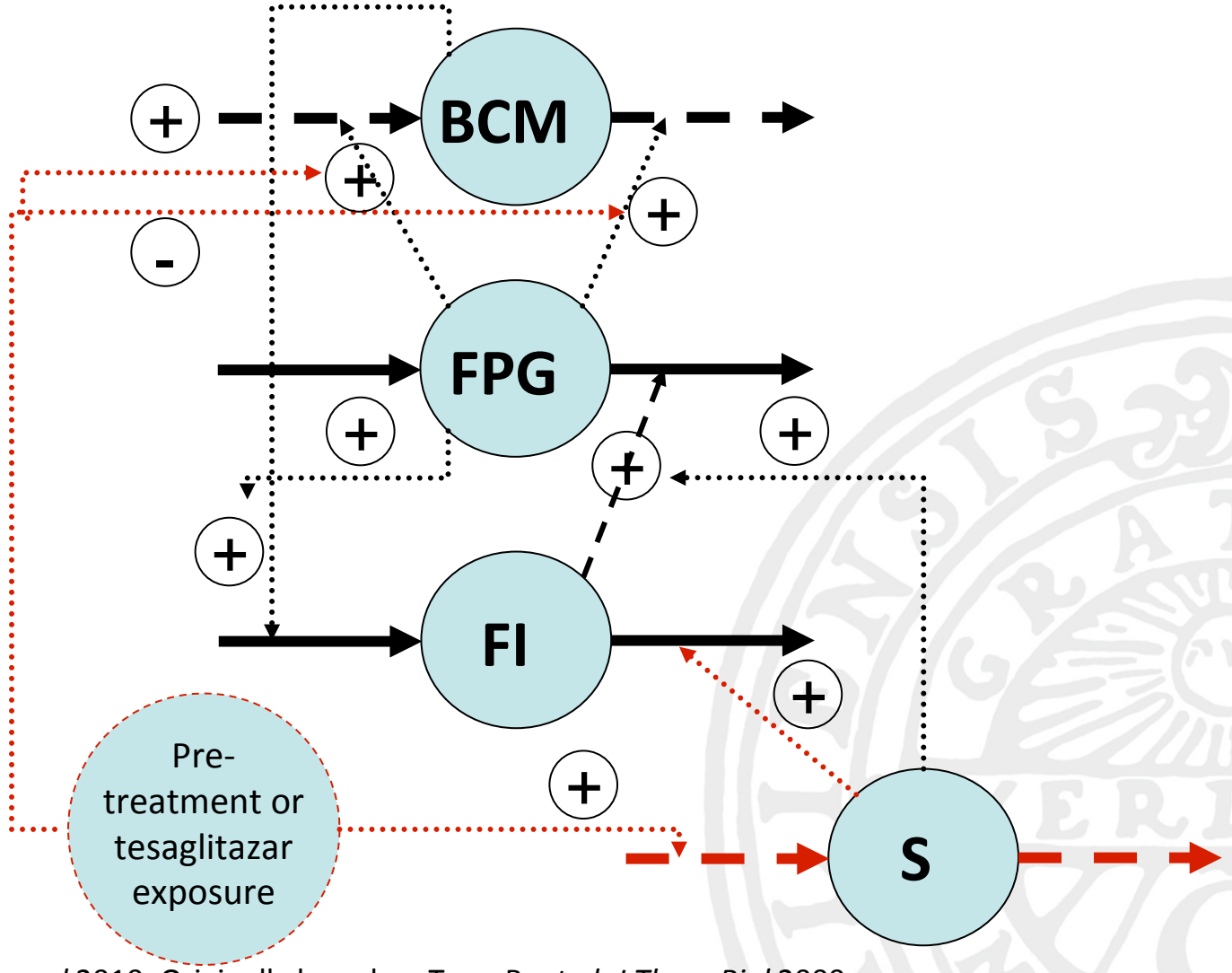
Betacell Insulin Glucose Model*



*Ribbing J, *et al. J Clin Pharmacol* 2010; Originally based on Topp B, *et al. J Theor Biol* 2000

Based on literature and observed data

Physiological Parameters

- Glucose-dependent growth rate of BCM
- Glucose dependent death rate of BCM
- BCM death rate at zero glucose (extrapol)
- Maximum insulin secretion per unit BCM
- EC_{50}, glucose stimulated insulin secretion
- Hill factor, glucose stimulated insulin secretion
- First order elimination rate of insulin
- Glucose production at zero glucose (extrapol)
- Total glucose effectiveness at zero insulin

Pharmacology parameters

- E_{max}, insulin sensitivity
- EC_{50}, insulin sensitivity
- EC_{50}, OFFSET
- Hill coefficient, OFFSET
- Pre-treatment effect, insulin sensitivity
- Pre-treatment effect, OFFSET

Pathophysiological parameters

- **OFFSET in BCM adaptation**
- **Insulin sensitivity**

Fixed and random effects estimated in NONMEM

Mixed origin parameters

- **K_{out}, insulin sensitivity**
- **Relation btw insulin elimination & insulin sensitivity**

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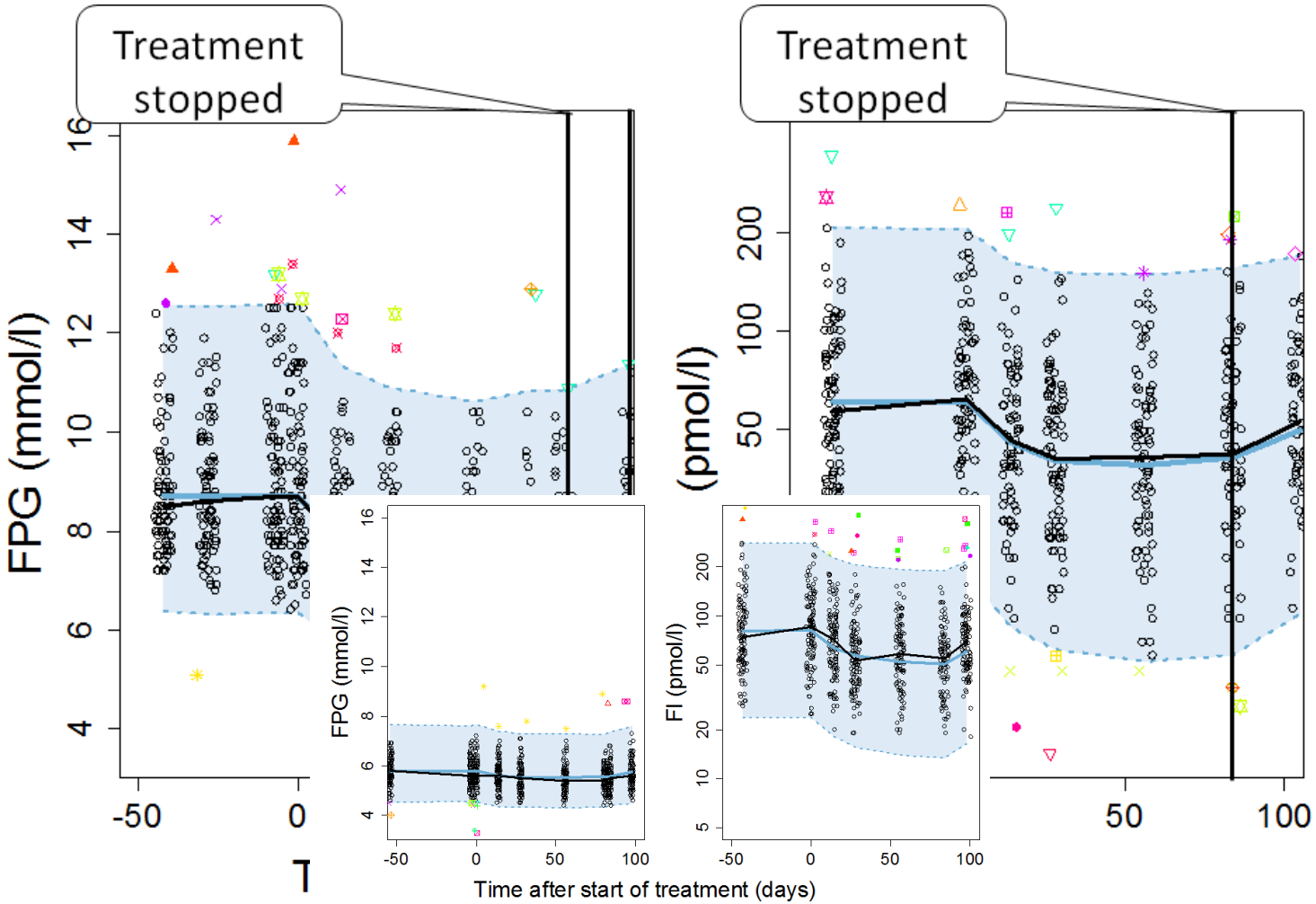
Results – application 2b: VPC



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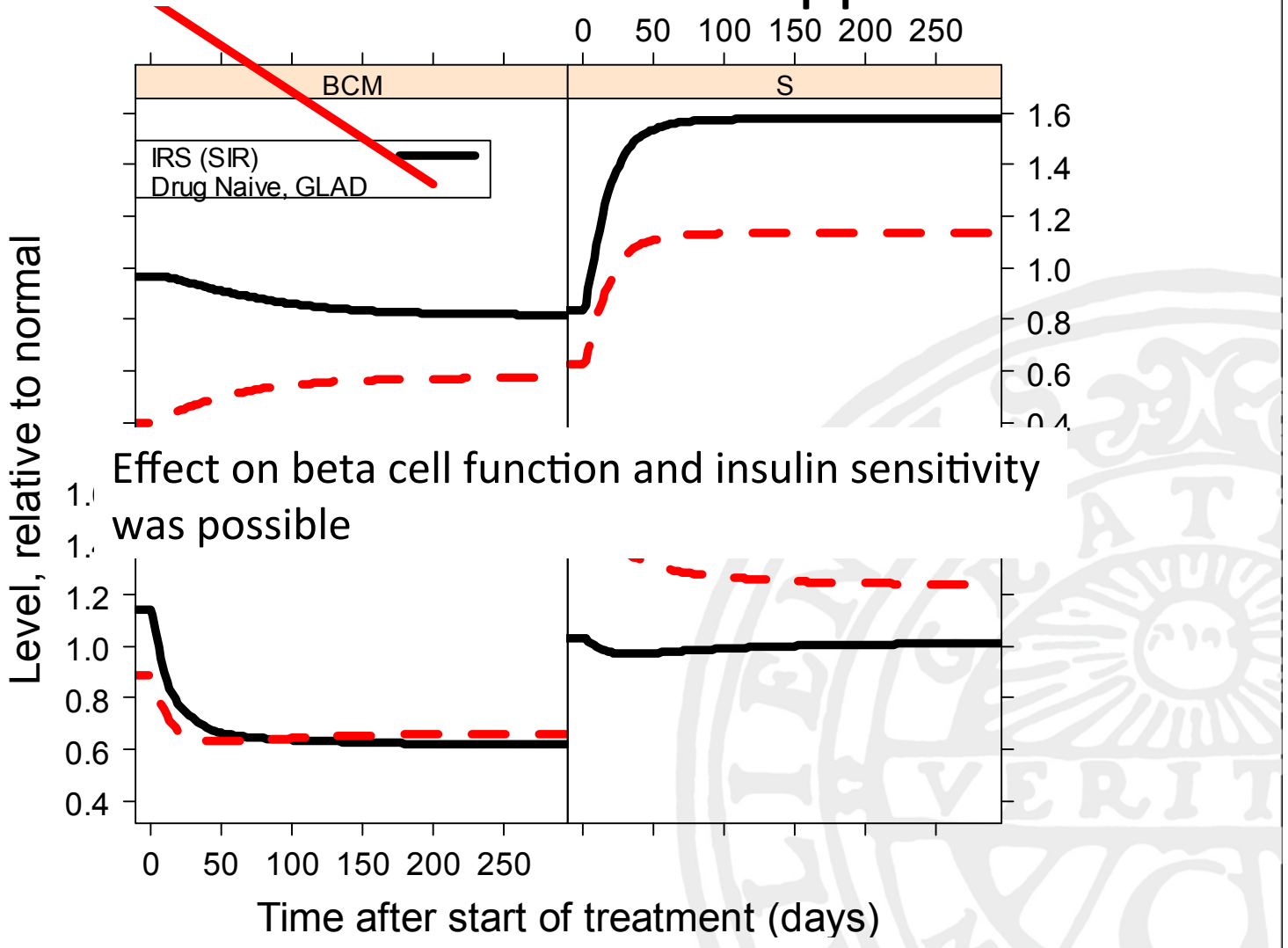
Results – application 2b



Effect on beta cell function and insulin sensitivity was possible

Model aided decisions

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Application 3a – impact of study design

Hypothetical drug

- MoA: insulin secretion, CLG, CLGI, EGP, glucose abs.
- 10% reduction in glucoseAUC
- Short-term provocations: IVGTT, GGI, OGTT, sMTT, MTT-24, fasting
- Biomarkers: dG, dI (FPG, FSI)
- Cross-over study with 2 arms: placebo, study drug

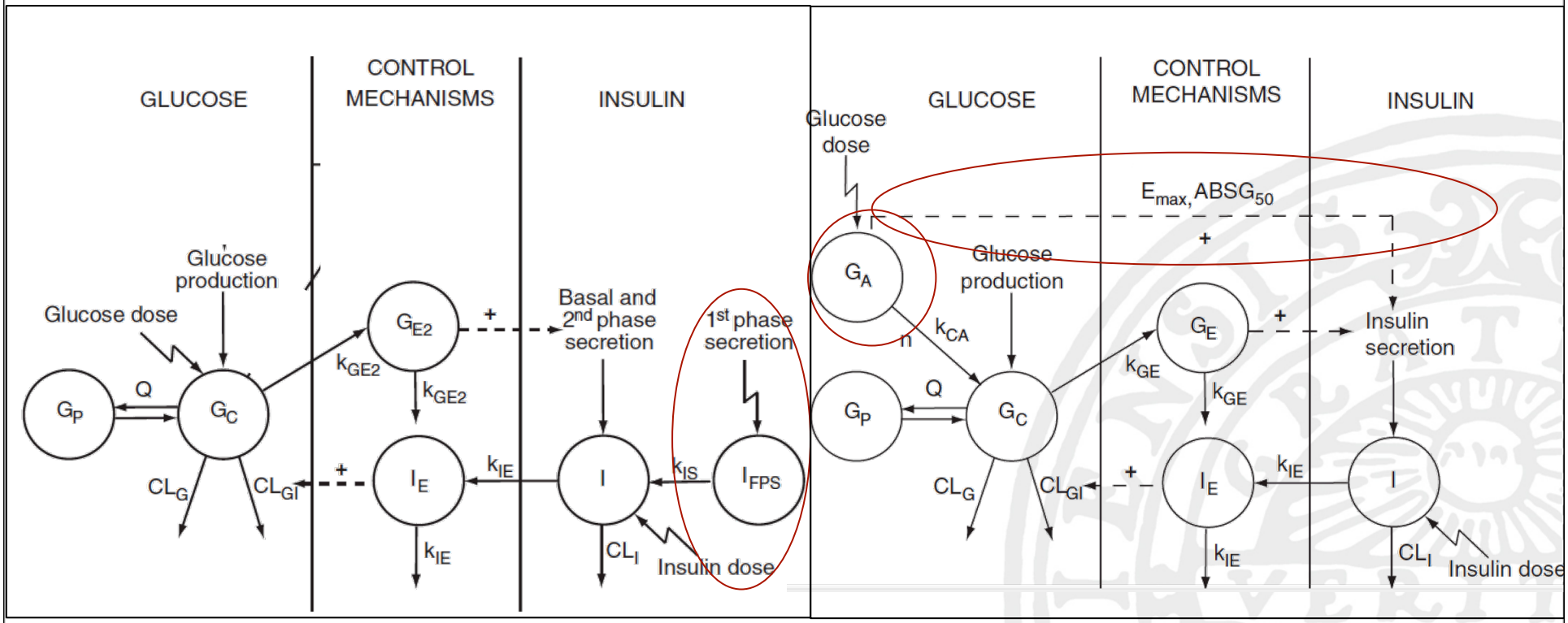
Which is the best provocation for the hypothetical MoAs?

*Hamrén *et al., CPT* 2008; Karlsson KE et al, CPT-PSP, 2013

IGI Model – IV vs oral

IVGTT

OGTT



GGI = IVGTT w/o first phase secretion

MTT = OGTT w different ka and incretin

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Results - Application 3a

IVGTT is high for all MoA, however highly invasive
MTT-24 is less invasive but not high for all

	OGTT	fasting	MTT-24	sMTT	IVGTT	GGI
Insulin secretion	1.5	2.0	8.7	1	5.8	5.4
CLG	0.3	0.8	0.6	1	2.8	3.9
CLGI	2.8	2.7	17.4	1	17.9	7.9
EGP	0.6	1.7	2.0	1	4.2	4.8
Glucose absorption	0.4	-	3.9	1	-	-

*Ibrahim *et al., PAGE 2015*

Application 3b – impact of study design

Tesaglitazar data

- 412 T2DM patients
- Biomarkers: FPG, HbA1c and Hb
- Parallel study with 5 arms: placebo, 0.1 mg, 0.5 mg, 1 mg, 2 mg and 3 mg tesaglitazar

Is power to detect drug effect increase with model based analysis?

*Hamrén *et al., CPT* 2008; Karlsson KE et al, CPT-PSP, 2013

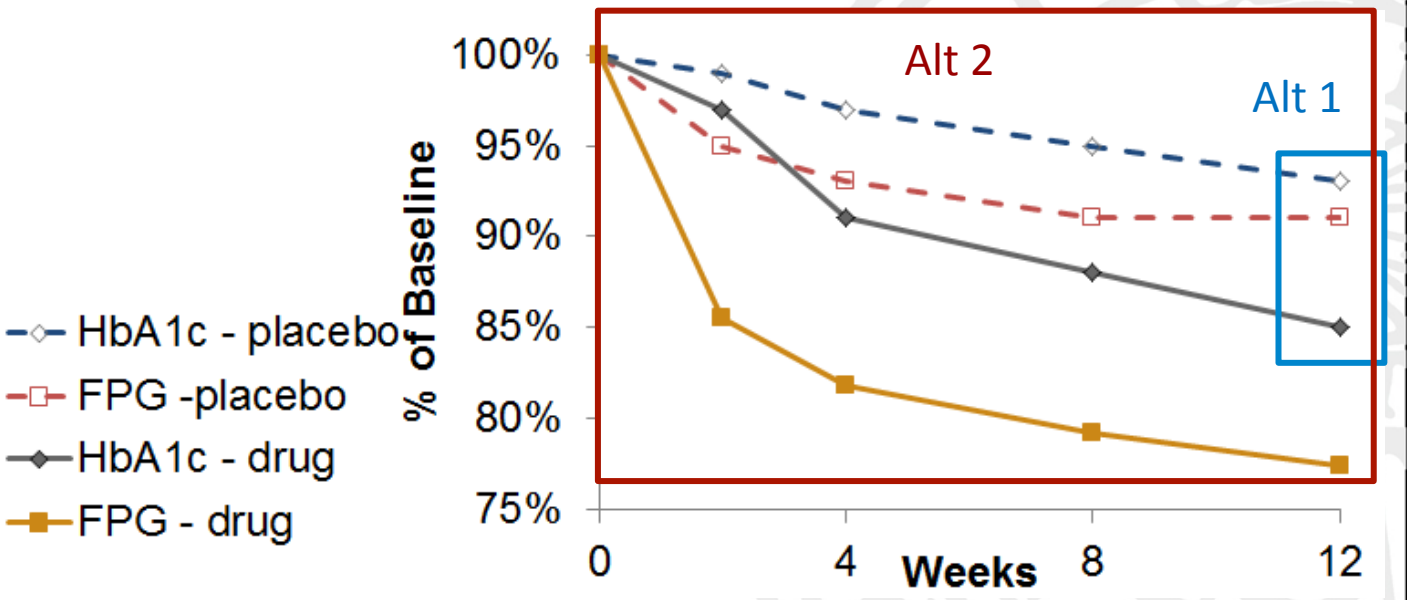
Alternative of analysis

Alternative 1 (two sample test):

- Test for difference between treatment groups in Δ HbA1c

Alternative 2 (model based):

- Test for significant drug effect on FPG using all data at all times



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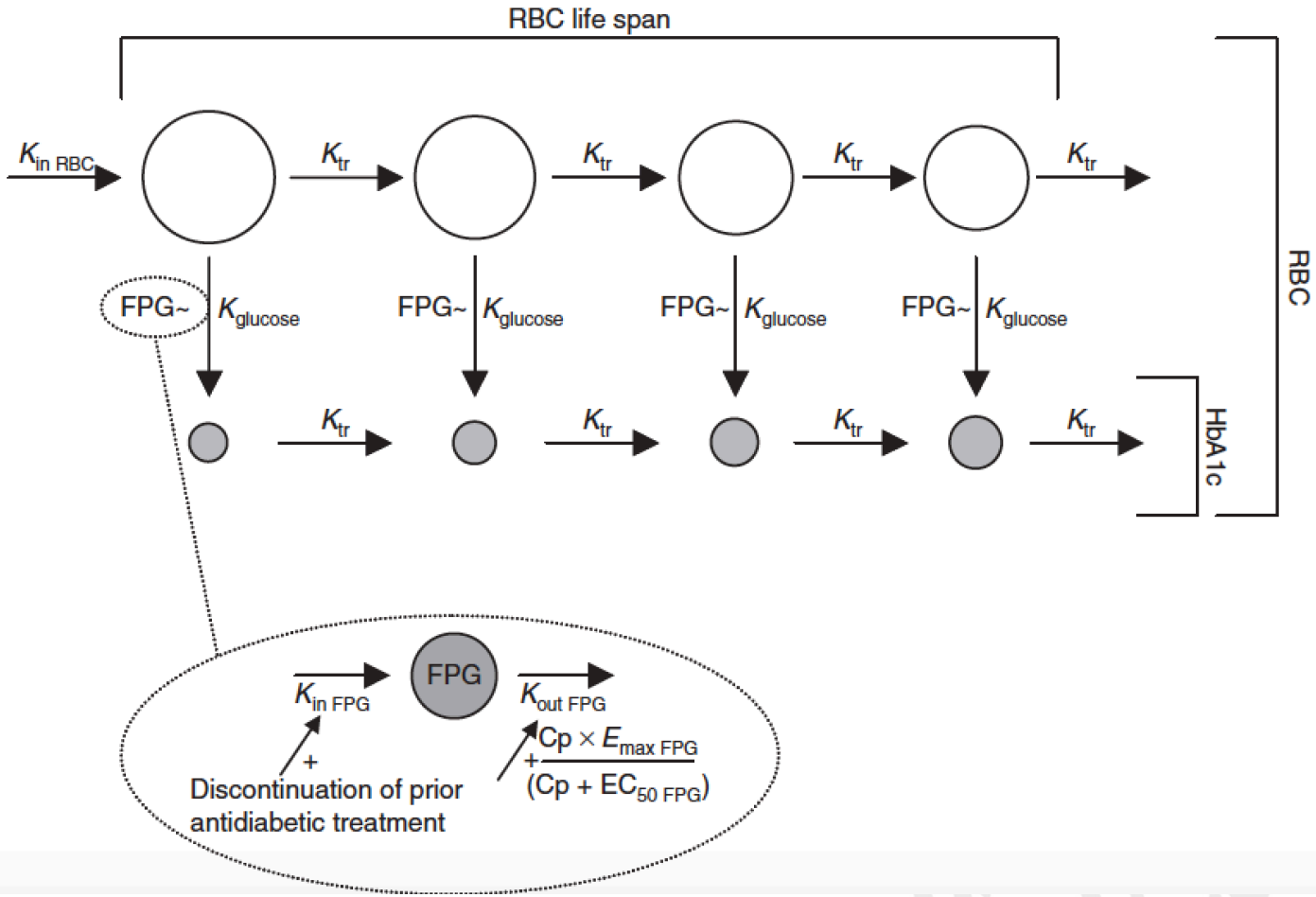
FPG-HbA1c-Hb Model



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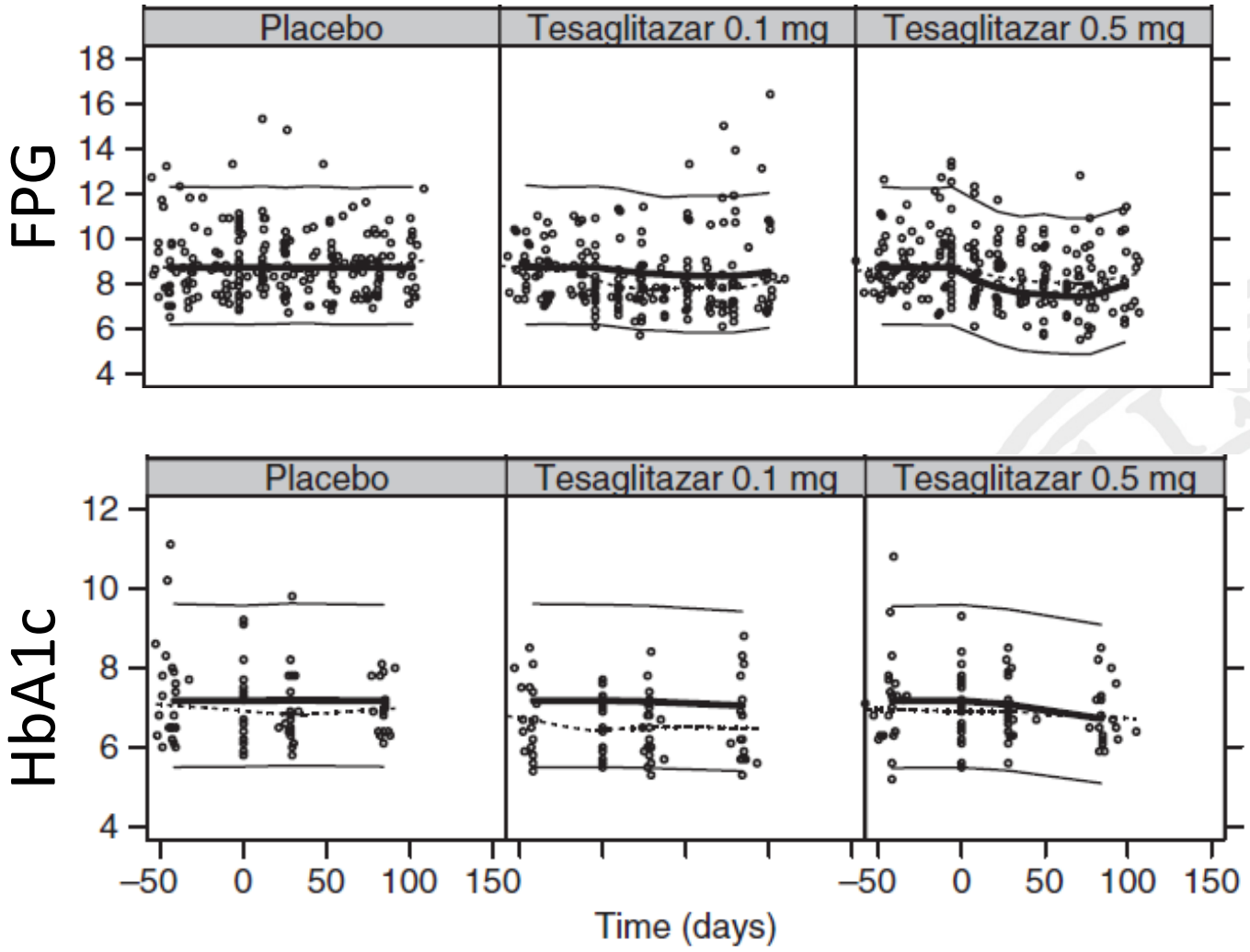
Results – application 3b: VPC



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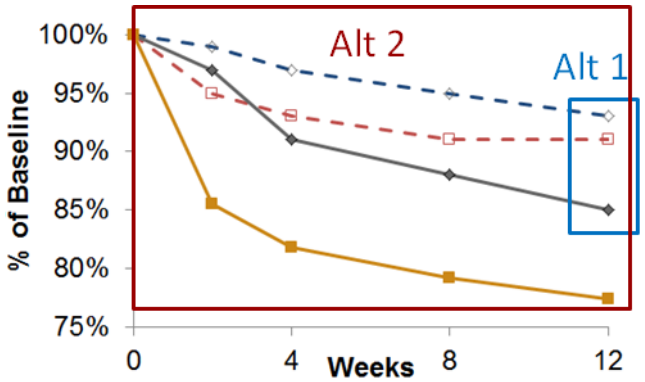
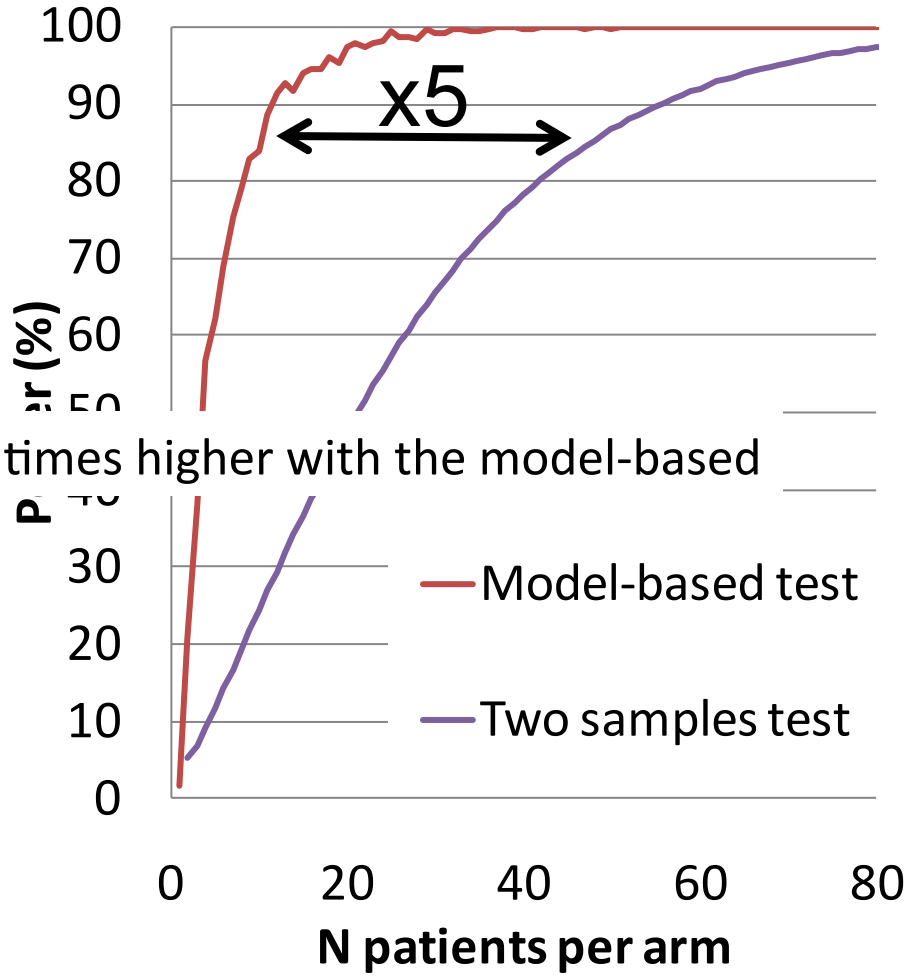
Results – application 3b





Yes, the analysis is 5 times higher with the model-based

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Model aided decisions

1. Disease progression
   - Placebo effect related to weight change
2. Identifying drug MoA
   a. Glucokinase activator with IGI model
   b. Tesaglitasar with BIG model
3. Impact of study design
   a. Optimising study design for phase 1 study
   b. Optimising method of analysis for phase 2a study
4. Translation between phases in drug development
   a. Translate between species
   b. Translate between drug development phases

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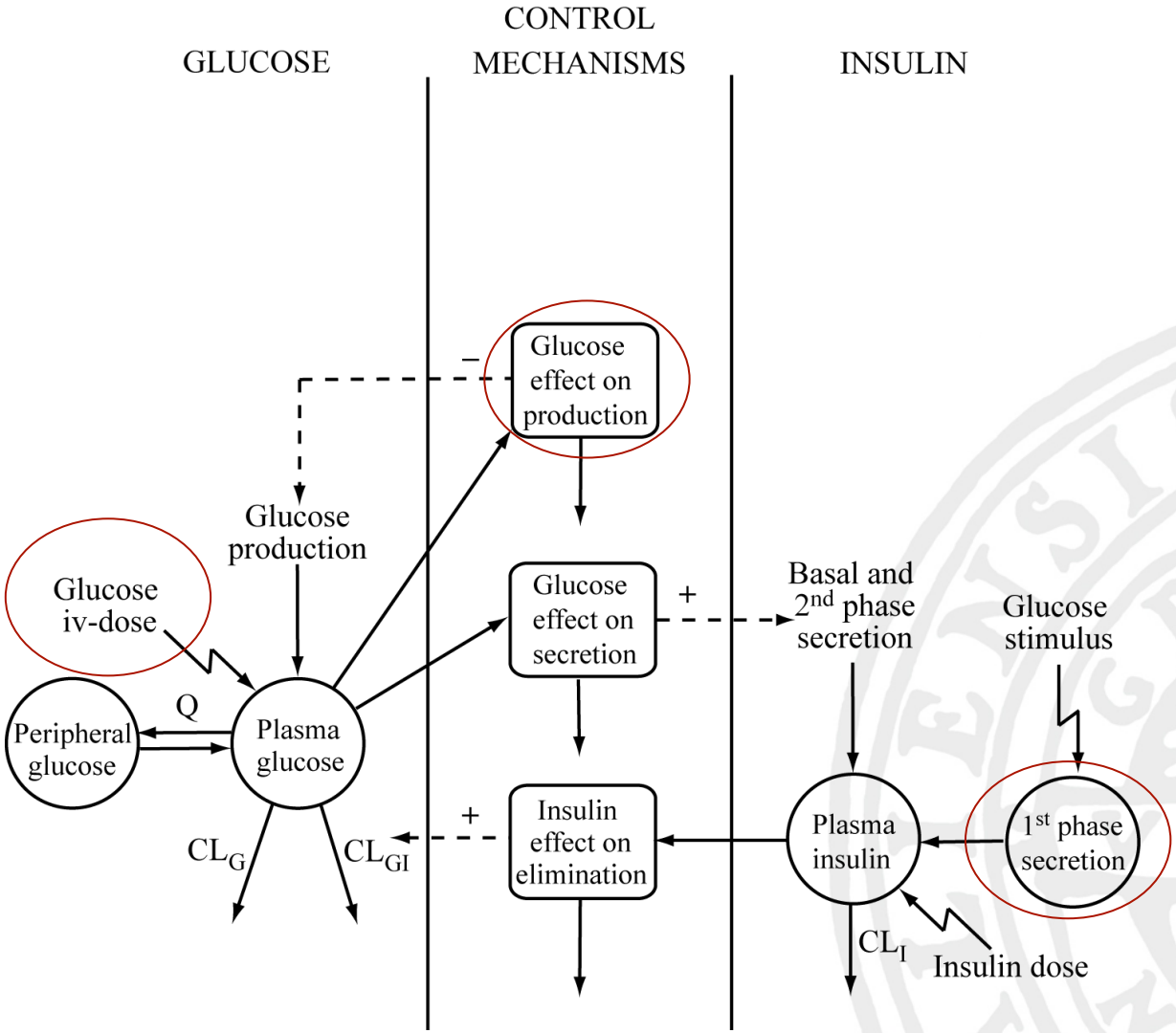
Application 4a – translation between species using the IGI model

Scale between human and animals

- Data of IVGTT in healthy mouse, rat, dog and pig
- Biomarkers: dG, dI
- Model for healthy humans of IVGTT exists

Can we scale dynamic glucose and insulin between species?

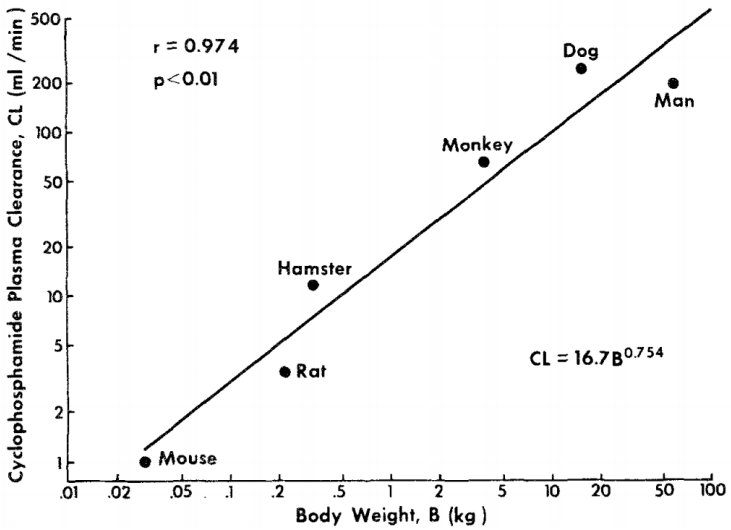
IGI Model – IVGTT, healthy

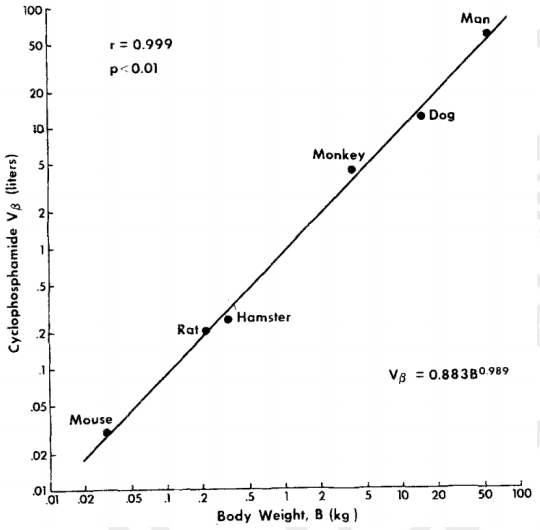


Application 4a – Approaches

Approach:

1. allometric scaling (weight)
2. species specific organ information
3. re-estimation





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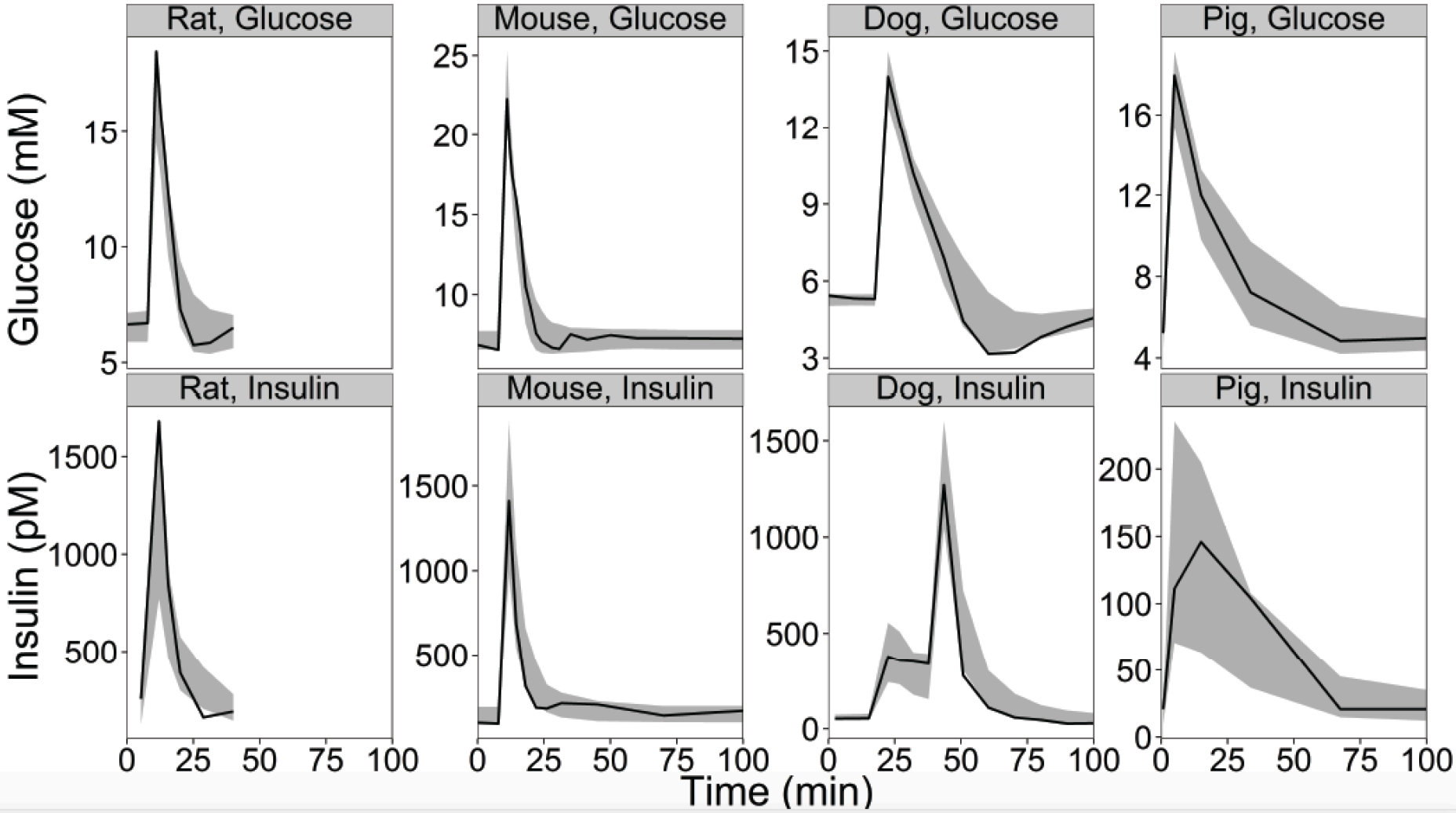
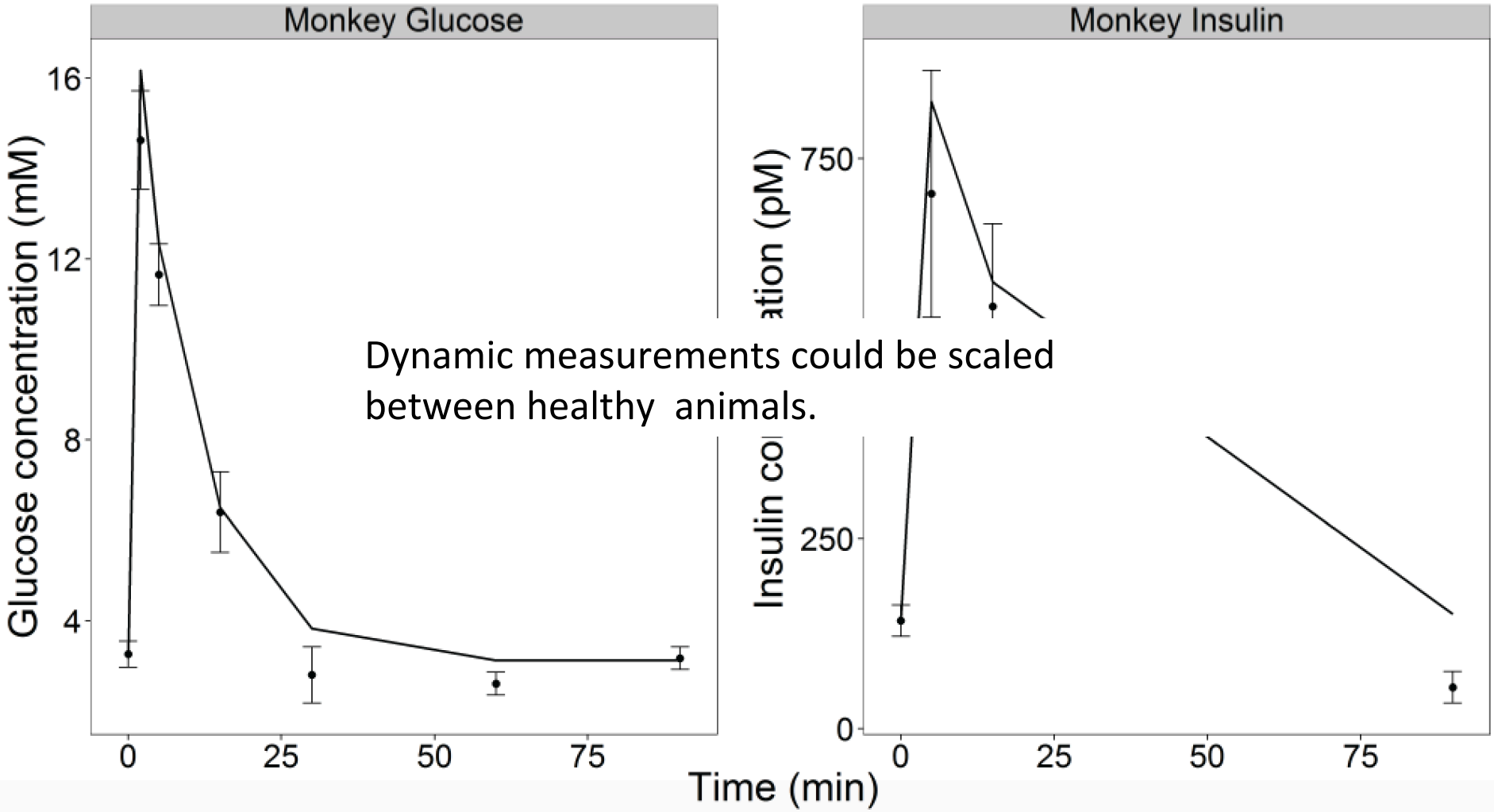
Results – application 4a: VPC*



*Alskär O et al. Diabetologia, 2015.

Results – application 4a: Prospective predictions



Dynamic measurements could be scaled between healthy animals.

Application 4b – translation between phase 1 and phase 2

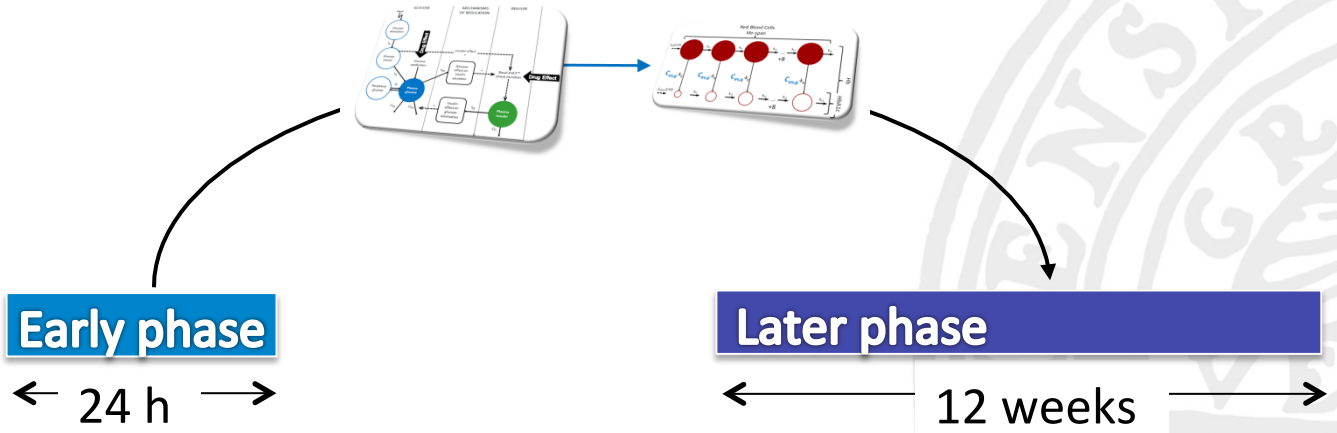
Bridge between phase 1 and phase 2

- Data of repeated MTT in T2DM
- Biomarkers: dG, dI
- Full cross-over: placebo and 5 dose levels

Can we predict drug effect on HbA1c using only data of dG and dI?

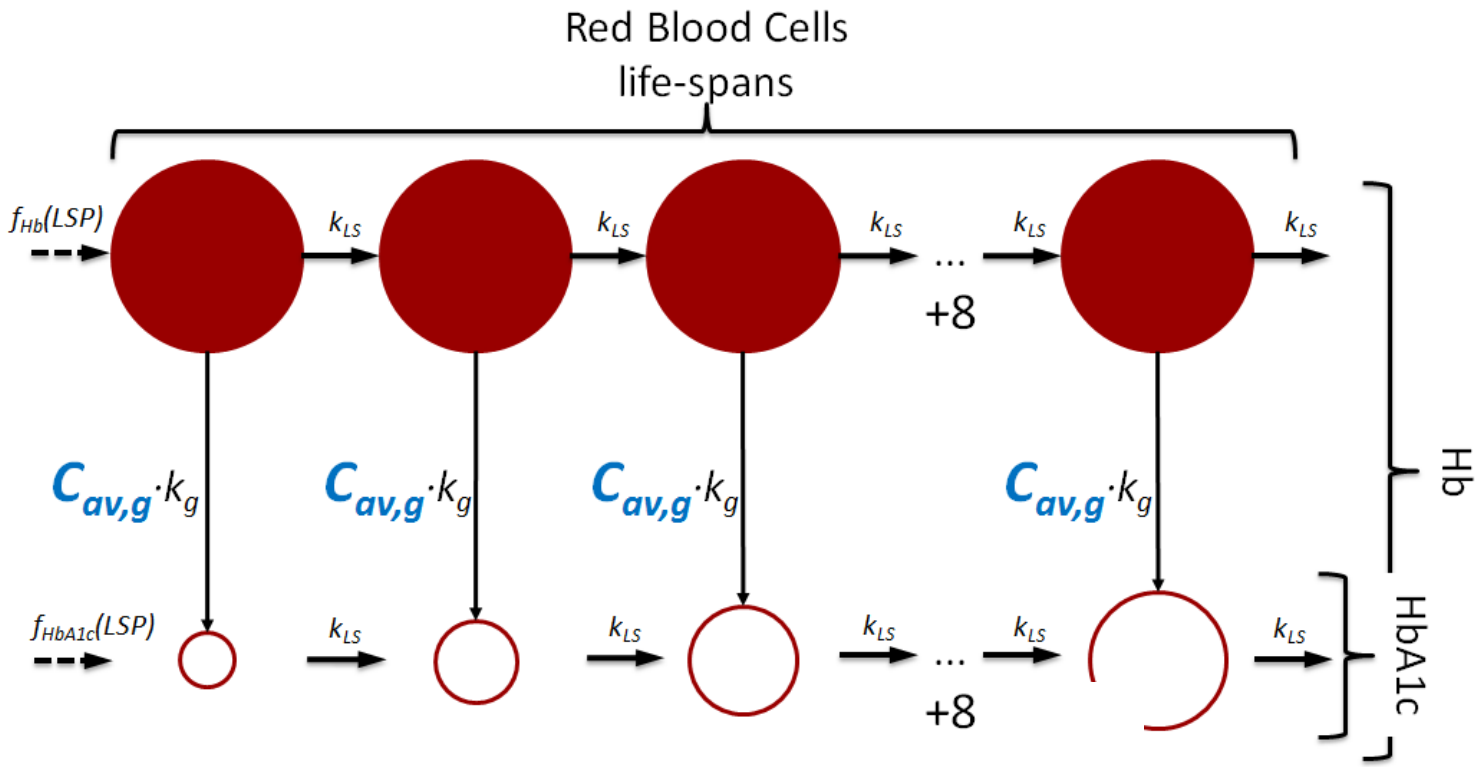
Application 4b - Approach*

- Prediction of HbA1c from glucose and insulin
  - Use IGI model to assess drug effects of a GKA
  - Simulate glucose using that model with a phase 2 design
  - Use IGRH model and simulated glucose to predict HbA1c



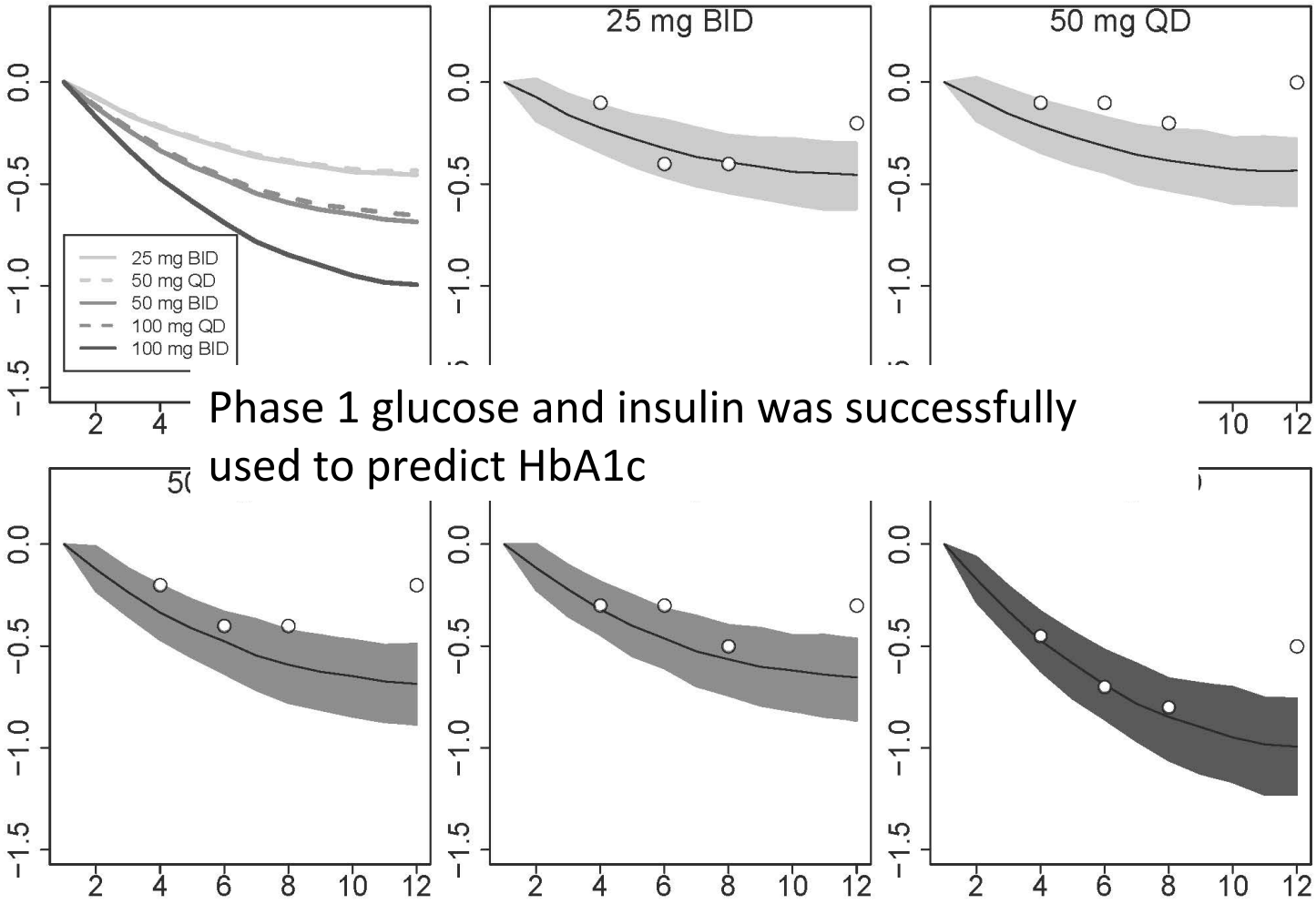
*Kjellsson MC *et al. J Clin Pharmacol, 2014.*

Integrated Glucose-RBC-HbA1c Model*



*Lledo-Garcia R, et al J PK PD 2014.

Results – application 4b: Prospective simulations



Phase 1 glucose and insulin was successfully used to predict HbA1c

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Modelling of T2DM: Useful for pharmaceutical industry?

- Dynamic, complex system of biomarkers
- Dynamic disease progression
- High need for new treatments quickly

Modelling increase understanding of

- Disease progression, patient behaviour and drug MoA
- Impact of study design
- Translation between phases in drug development

YES! Modelling is useful for pharmaceutical industry!

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Thank you for your attention!

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