LAPP Leiden
Advanced PK-PD

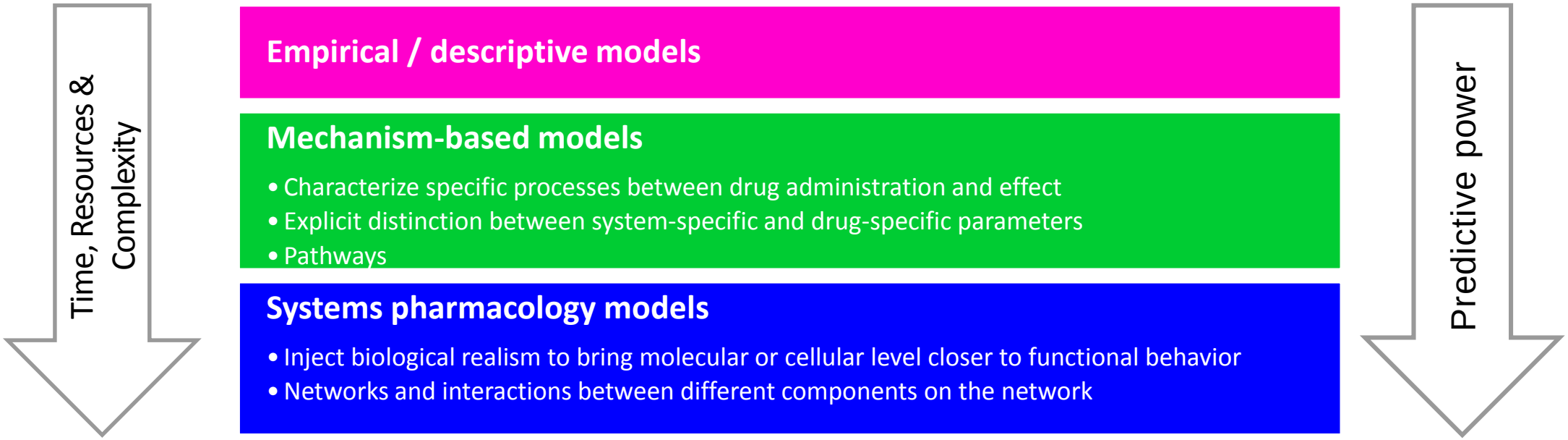
QSP modelling
at the heart of the action

Rosa webinar,
November 2017

Nelleke Snelder
Tamara van Steeg

Introduction

PKPD modelling has developed from an empirical approach into a scientific discipline based on the physiological mechanisms behind PKPD relationships



Exact definitions are under debate, but this is not essential for the modeller as the question remains the same:
"What level of detail is required and which modelling approach is preferred given the question at hand?"

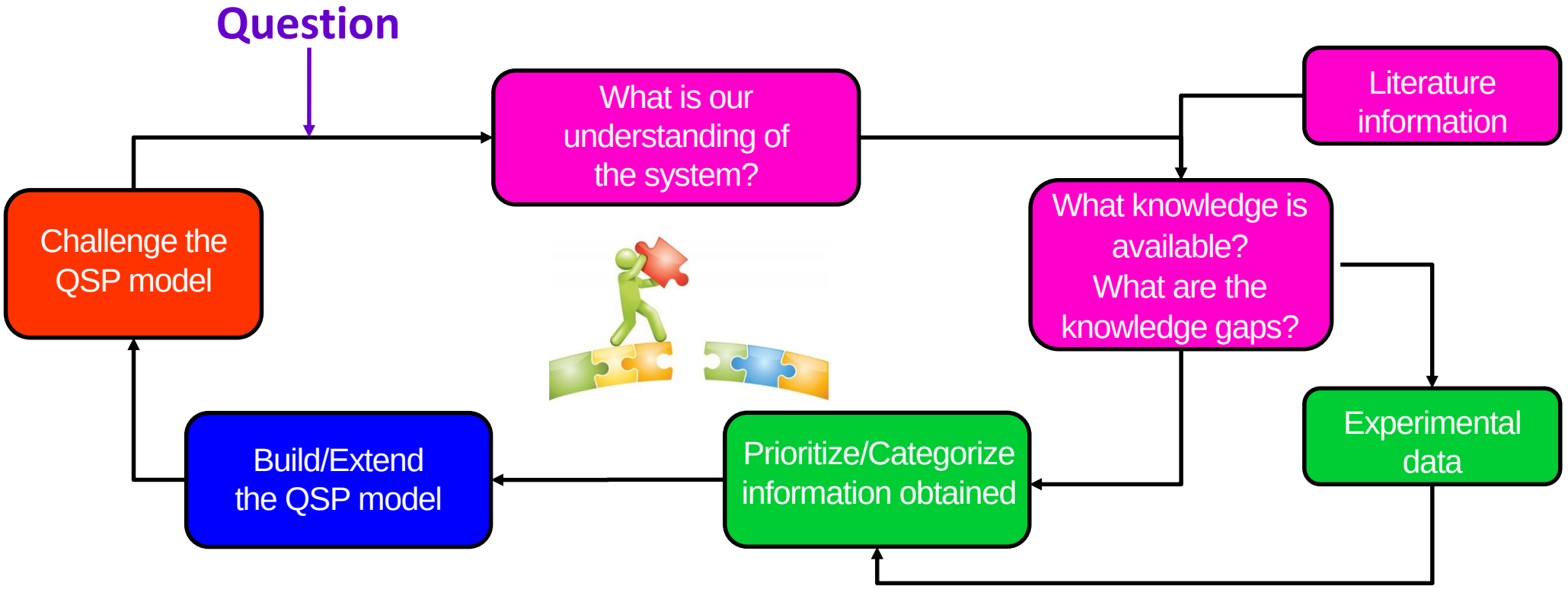
Focus of this presentation

Key questions for the modeller:

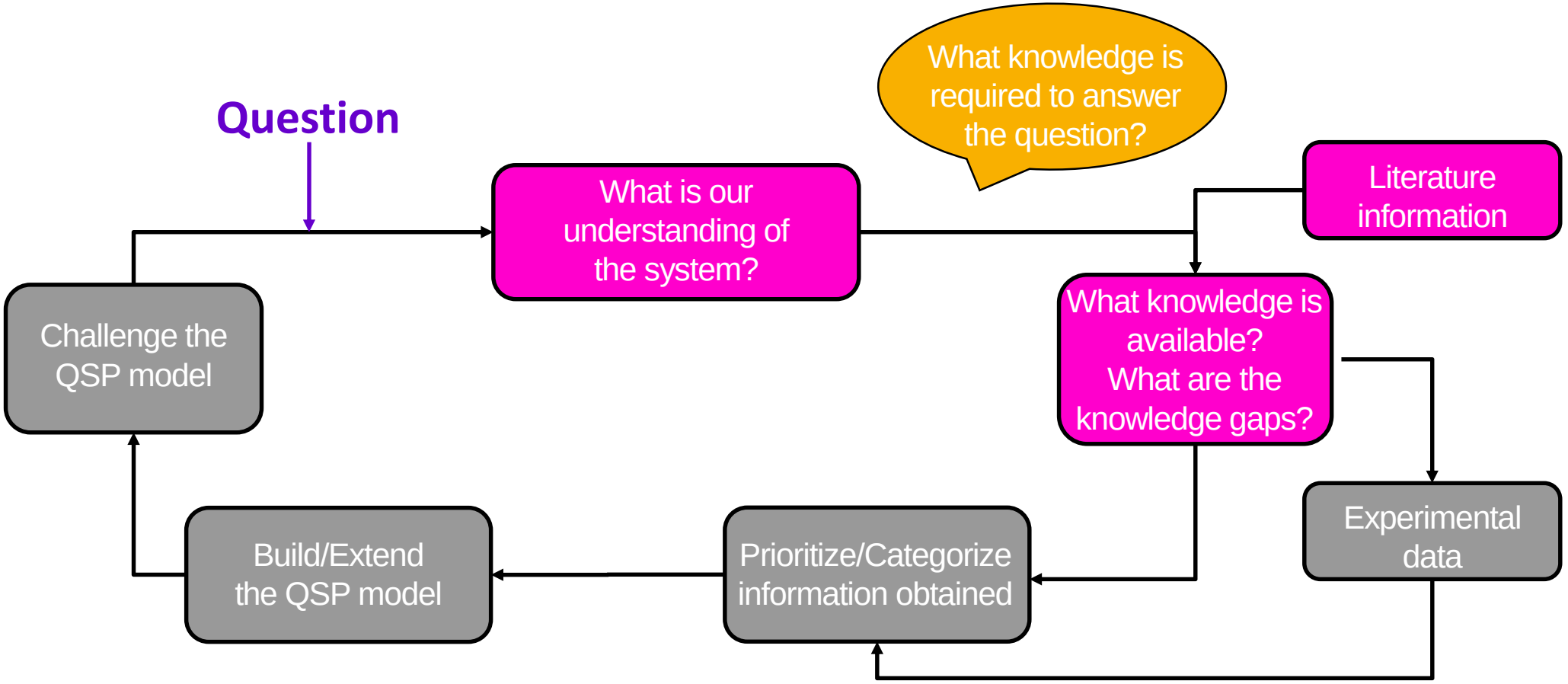
- What knowledge is required to answer the question?
- How to select and integrate informative data?
- How to balance between complexity and quantifiability?
- When am I happy to stop?

Questions will be addressed throughout this presentation on the basis of real-world examples

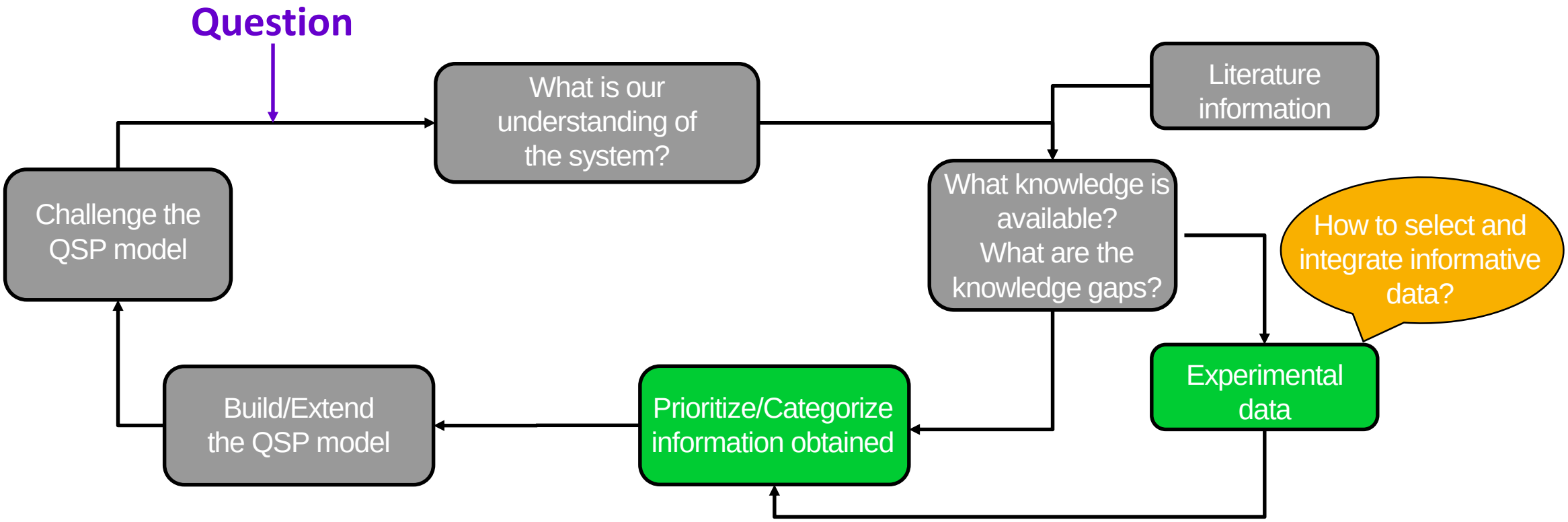
Building QSP models is an iterative process



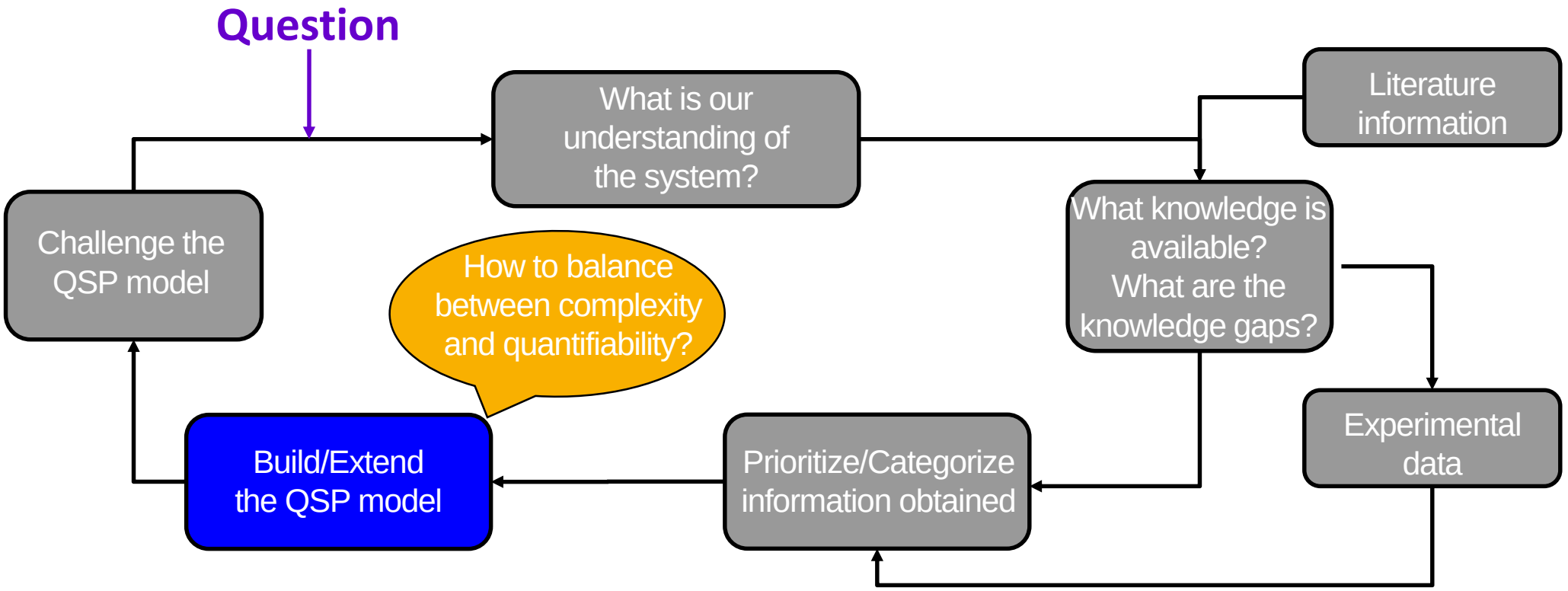
Building QSP models is an iterative process



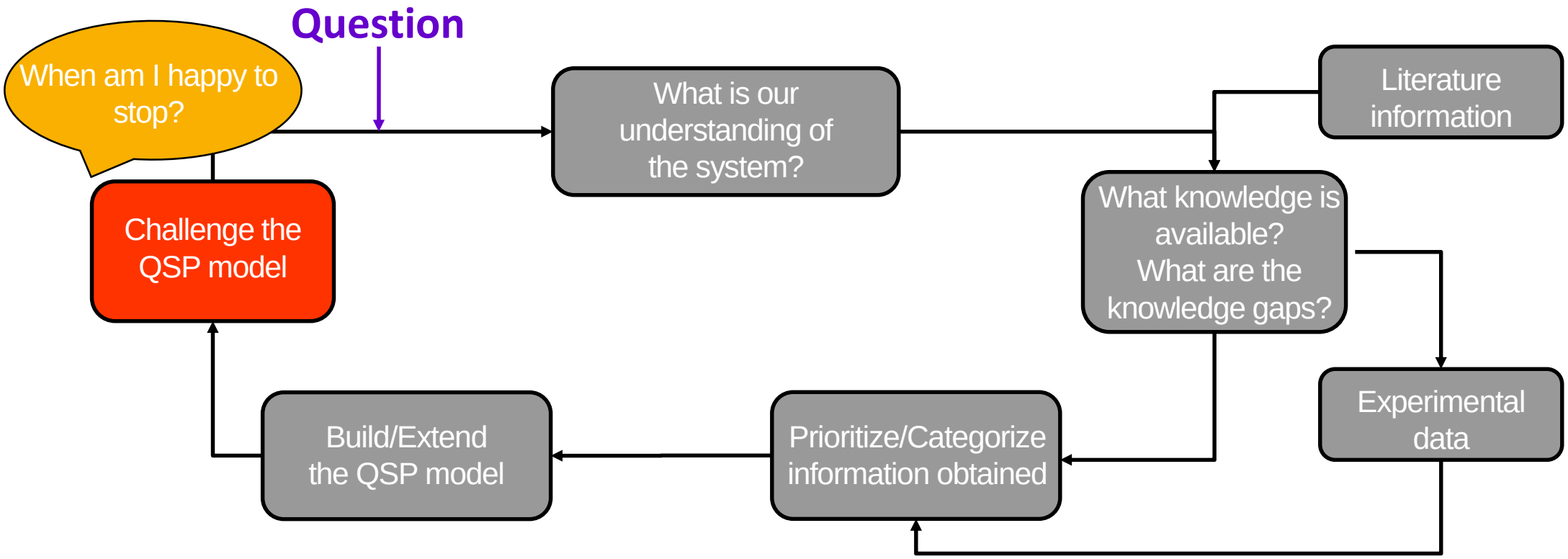
Building QSP models is an iterative process



Building QSP models is an iterative process



Building QSP models is an iterative process



Outline

Example 1: **Cardiovascular system (CVS) model**

- Using a QSP modelling approach to improve early compound selection
  - Conceptualizing + experimental design

Example 2: **Alzheimer's Disease model**

- QSP modelling to inform therapeutic strategies
  - Model-informed hypothesis testing

Example 3: **Osteoporosis model**

- From QSP modelling to late phase drug development support
  - Quantifiability

Example 1: CVS model

Using a QSP modelling approach to improve early compound selection

Conceptualizing + Experimental design

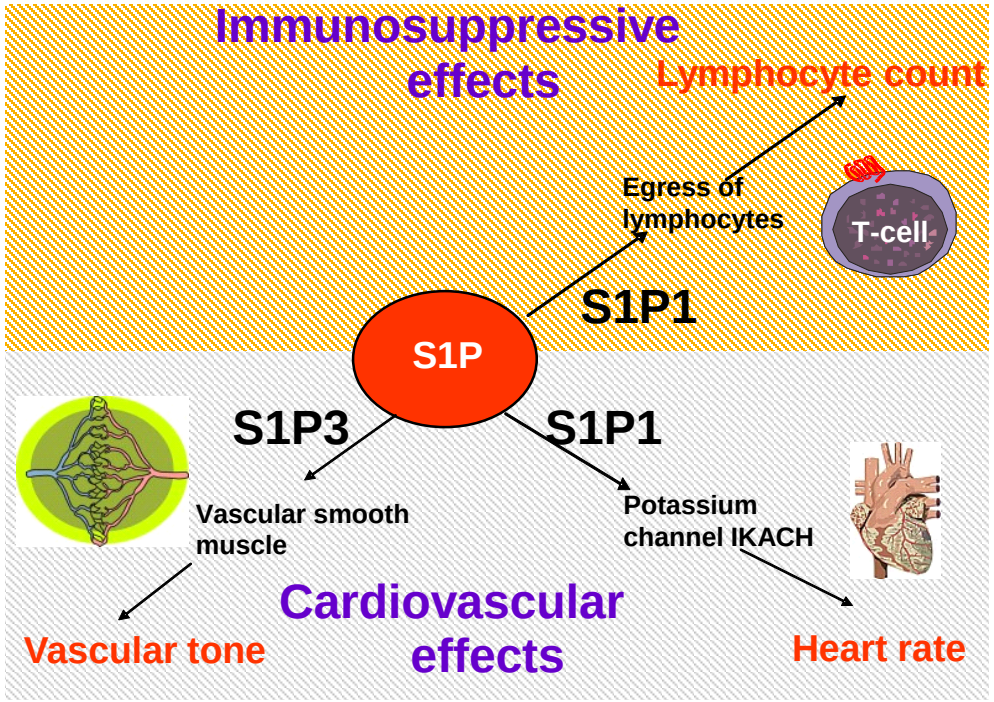
Modelling done by Nelleke Snelder in collaboration with LACDR and Novartis

Example 1
Sphingosine-1-phosphate (S1P) is a major regulator of the immune and cardiovascular system (CVS)

Lymphocyte effects and cardiovascular effects are mediated through the S1P receptor

Fingolimod-phosphate (fingolimod-P) and siponimod are S1P receptor agonists:

- Fingolimod: approved at a dose of 0.5 mg
- Siponimod: phase 3 study ongoing
- Treatment of multiple sclerosis
- Associated with cardiovascular effects



⇒A mechanistic and quantitative understanding of the cardiovascular effects of S1P agonists could improve early compound selection

Objectives & Strategy

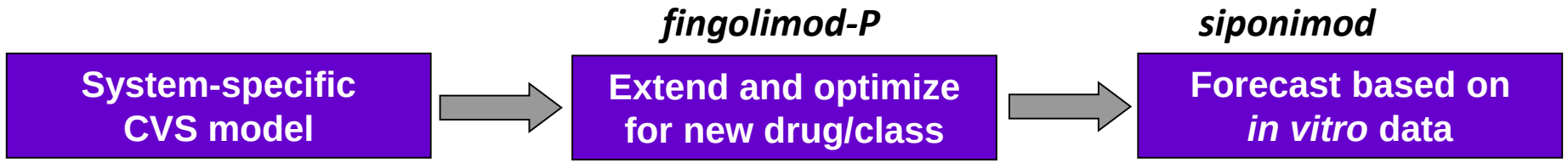
1) Development of a system-specific model to characterize drug effects on the CVS in rats

   ⇒ **Drug-independent CVS model**

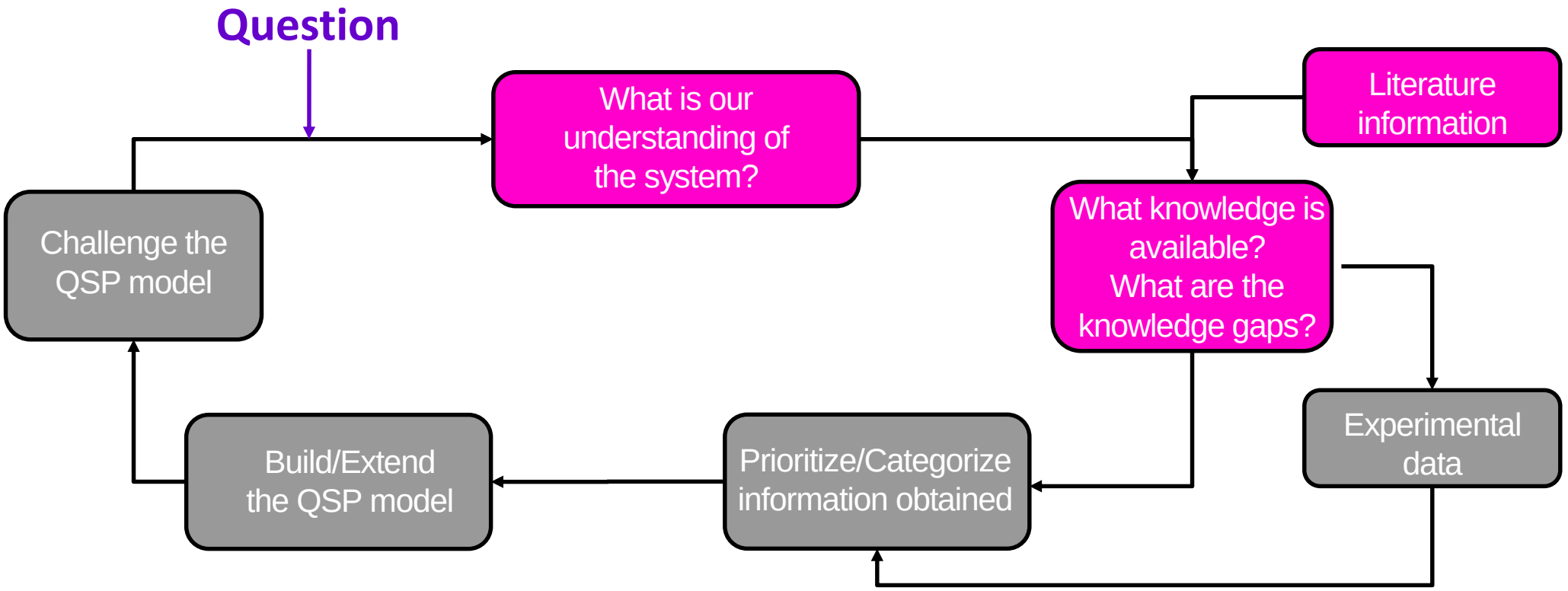
2) Characterization and prediction of the cardiovascular effects of S1P receptor agonists in rats

   ⇒ **A mechanistic and quantitative understanding of the cardiovascular effects of S1P agonists**

Modelling strategy:



Building QSP models is an iterative process
What knowledge is required to answer the question?



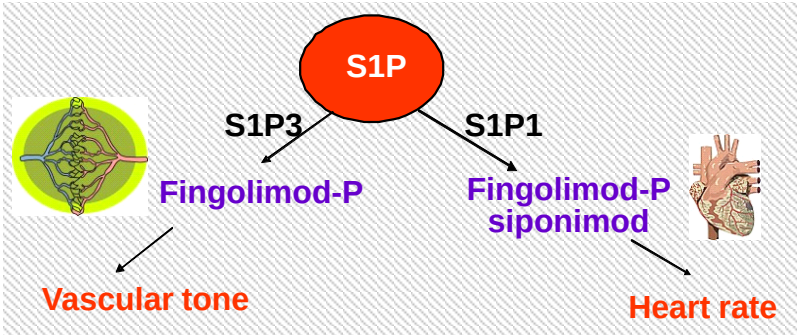
What knowledge is available and required and what are the gaps?

Available knowledge

Physiological principles of the CVS

Mean Arterial Pressure (MAP)	=	Total Peripheral Resistance (TPR)	x	Cardiac Output (CO)
Cardiac Output (CO)	=	Heart Rate (HR)	x	Stroke Volume (SV)

Presumed mechanism of action



Fingolimod-P and siponimod S1P potency estimates from a GTPγS binding assay *in vitro*

Knowledge gaps

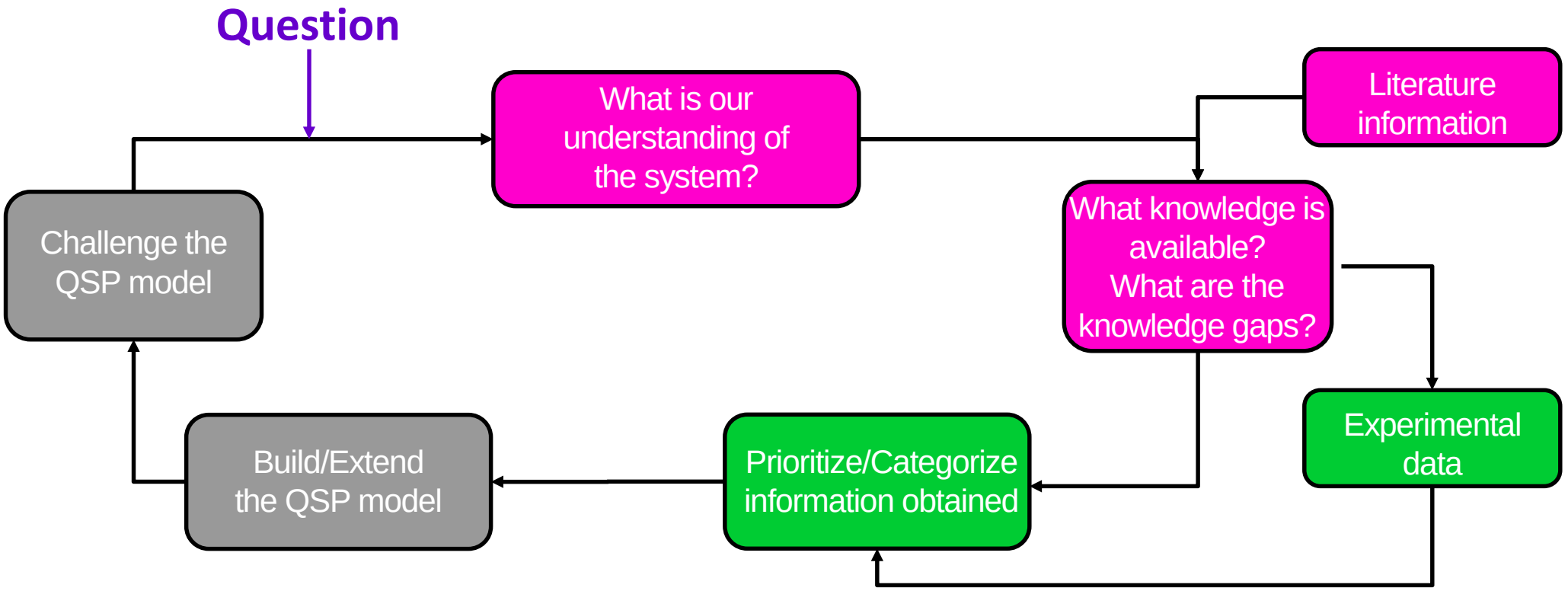
No quantitative understanding of the interrelationship between cardiovascular parameters

- No systems model available
- No sufficient published/open-access data available

Unknown dissociation binding constants of fingolimod-P and siponimod for the S1P receptor

Building QSP models is an iterative process

How to select and integrate informative data?



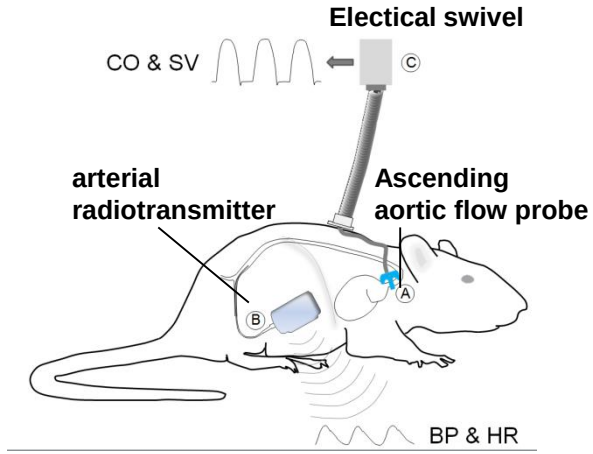
The experimental design is extremely important for development of the systems pharmacology model

Challenge the system with a variety of different compounds

Effect on heart rate	Effect on peripheral resistance	Effect on stroke volume
atropine	amlodipine	amiloride
propanolol	enalapril	enalapril
	fasudil	HCTZ
	prazosin	

Measure blood pressure, heart rate and cardiac output during onset and offset of the drug effects

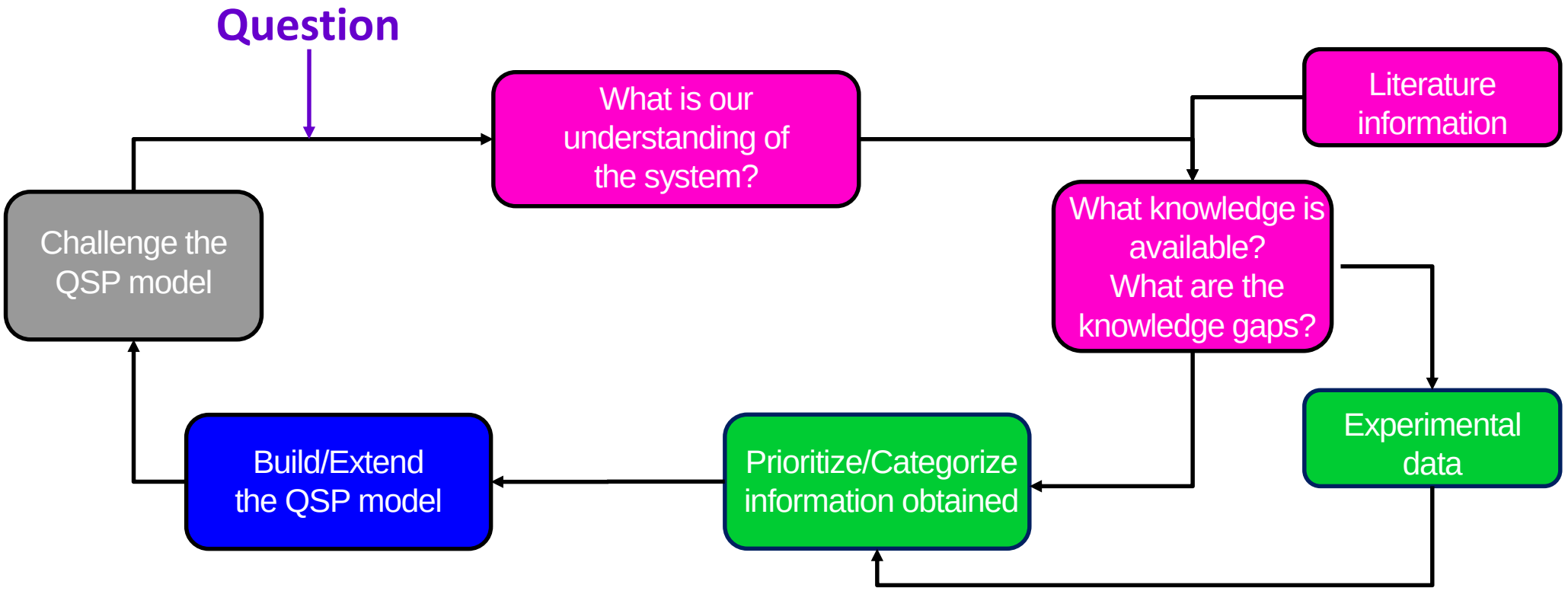
- Derive stroke volume and total peripheral resistance



Similar experiments were performed after administration of different doses of fingolimod

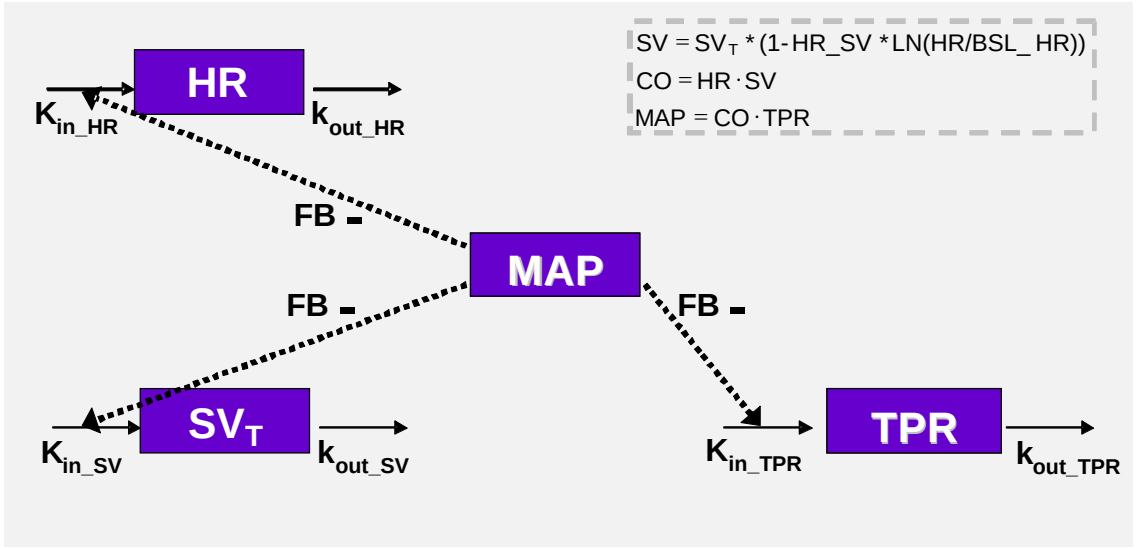
A multiple dosing telemetry study was performed to investigate the effect of fingolimod-P and siponimod on MAP and HR

Building QSP models is an iterative process
How to balance between complexity and quantifiability?



QSP model is an integration of a physiological and class-specific drug model

System-specific CVS model

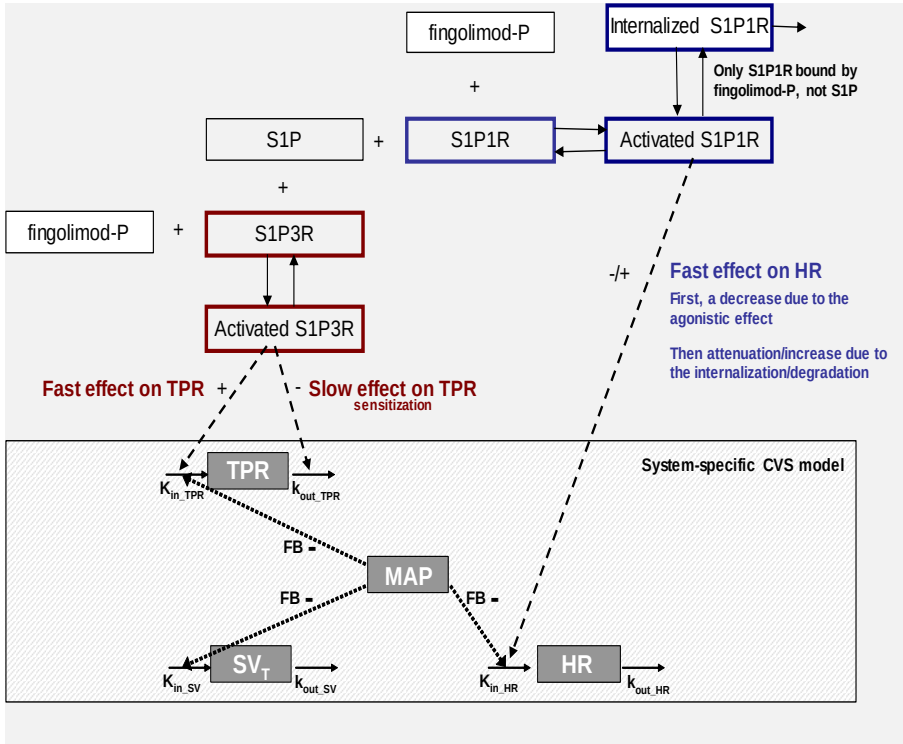


Modelling challenges:

- A sequential approach may not work with networks
- All markers at organ level were fitted simultaneously

Detailed Understanding the behavior of the proposed model is key for model development

S1P agonist model



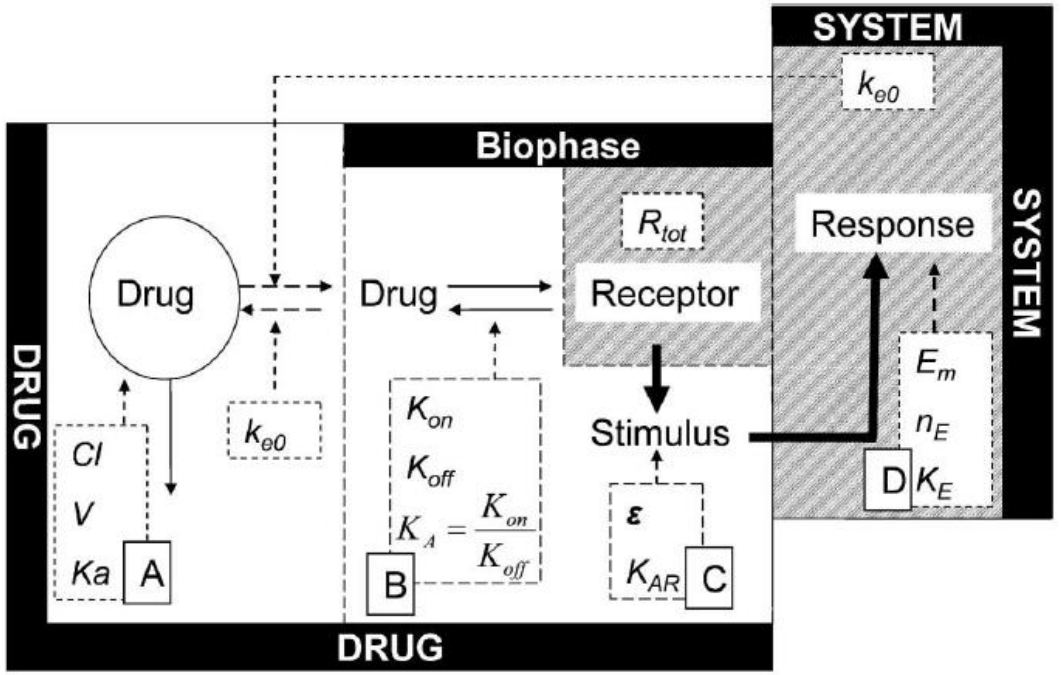
Modelling challenges:

- Site of action was first evaluated using a more empirical approach
- Knowledge on competitive binding to the S1P receptor with endogenous S1P used

Complexity and quantifiability were balanced by simplifying the operational model of agonism

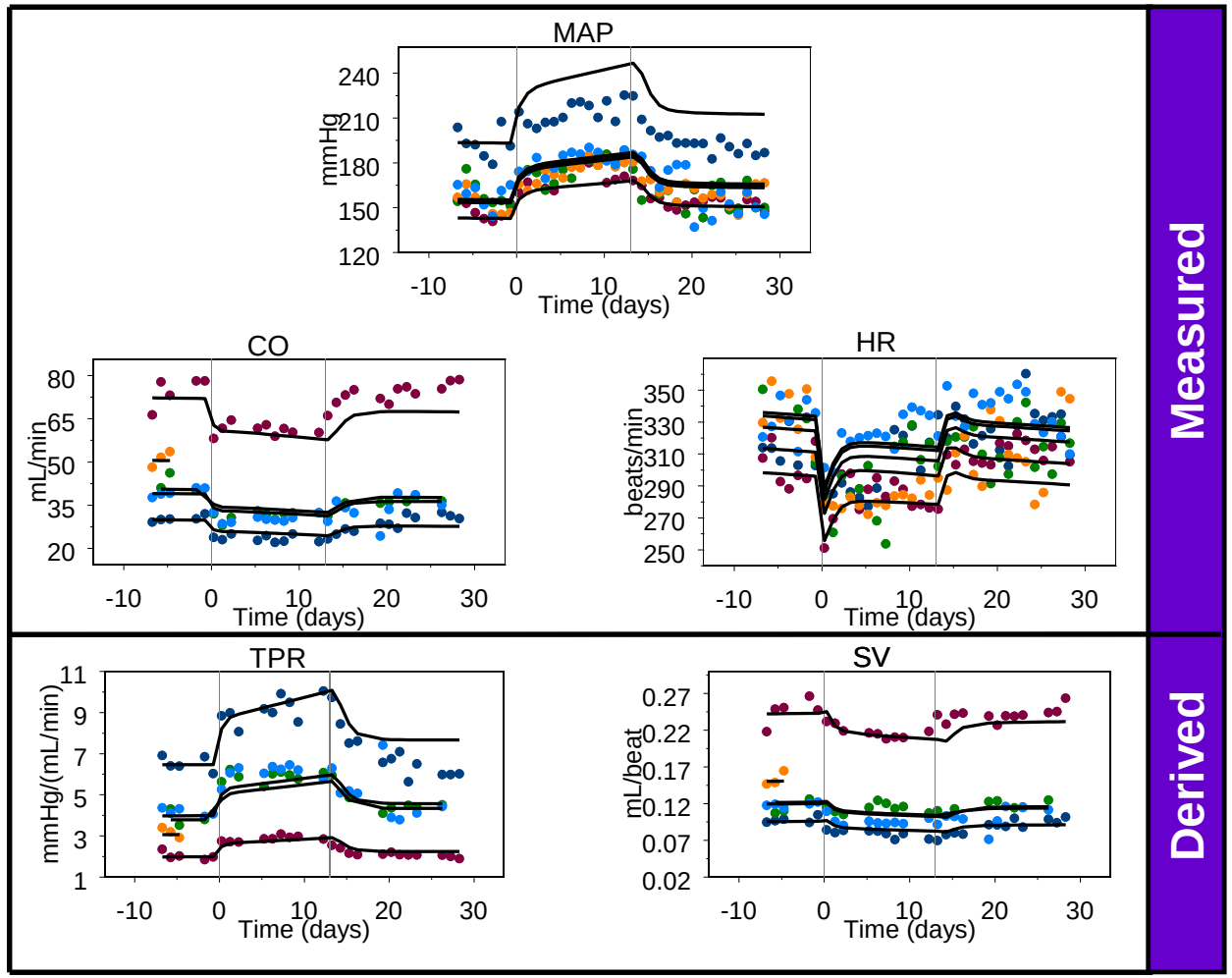
The operational model of agonism captures all steps from binding to signal transduction.

- Identification of the parameters of this model requires more detailed information



The estimated Kd for fingolimod-P is actually a composite of a Kd and EC_{50}. Therefore, we should call it an operational EC_{50}

Adequate description of the effect of fingolimod-P



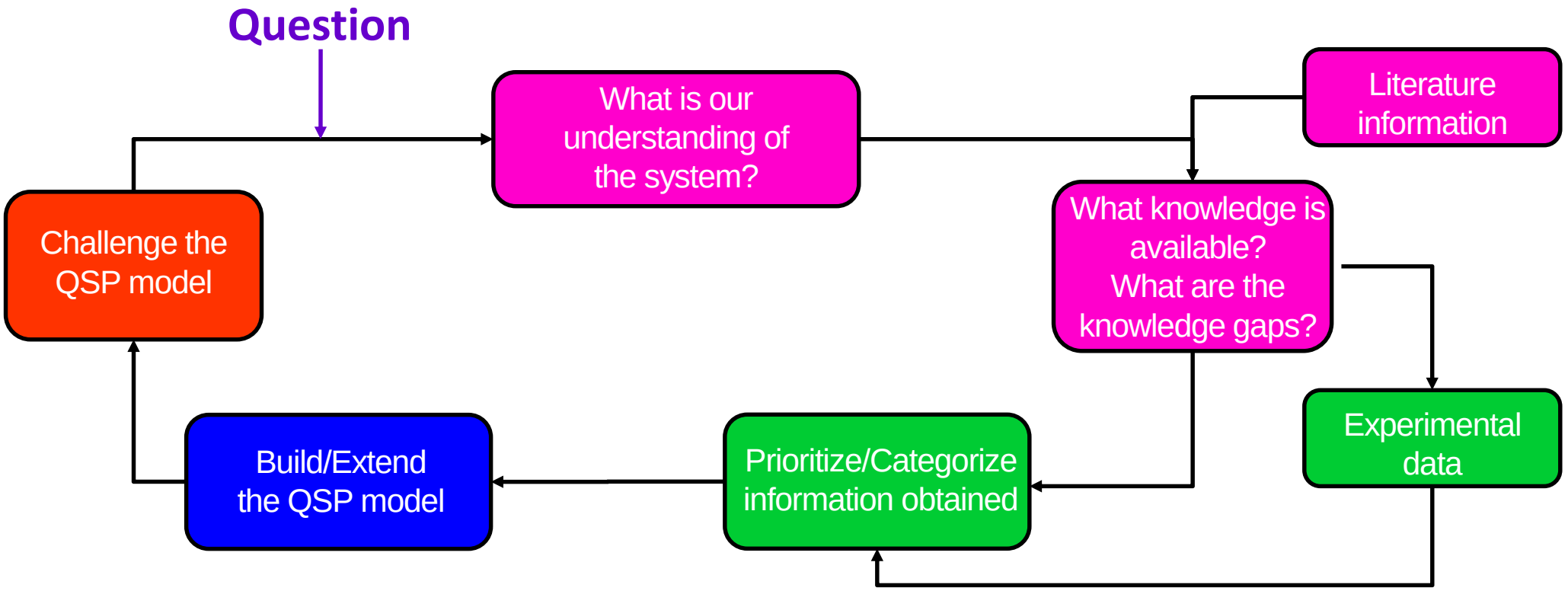
Effect on all five endpoints can be described by drug effects on HR and TPR

Oral administration of fingolimod at a dose of 10 mg/kg once daily for 14 days in hypertensive rats

— Individual prediction

● Observations (colored per rat)
(5 hypertensive rats per treatment group)

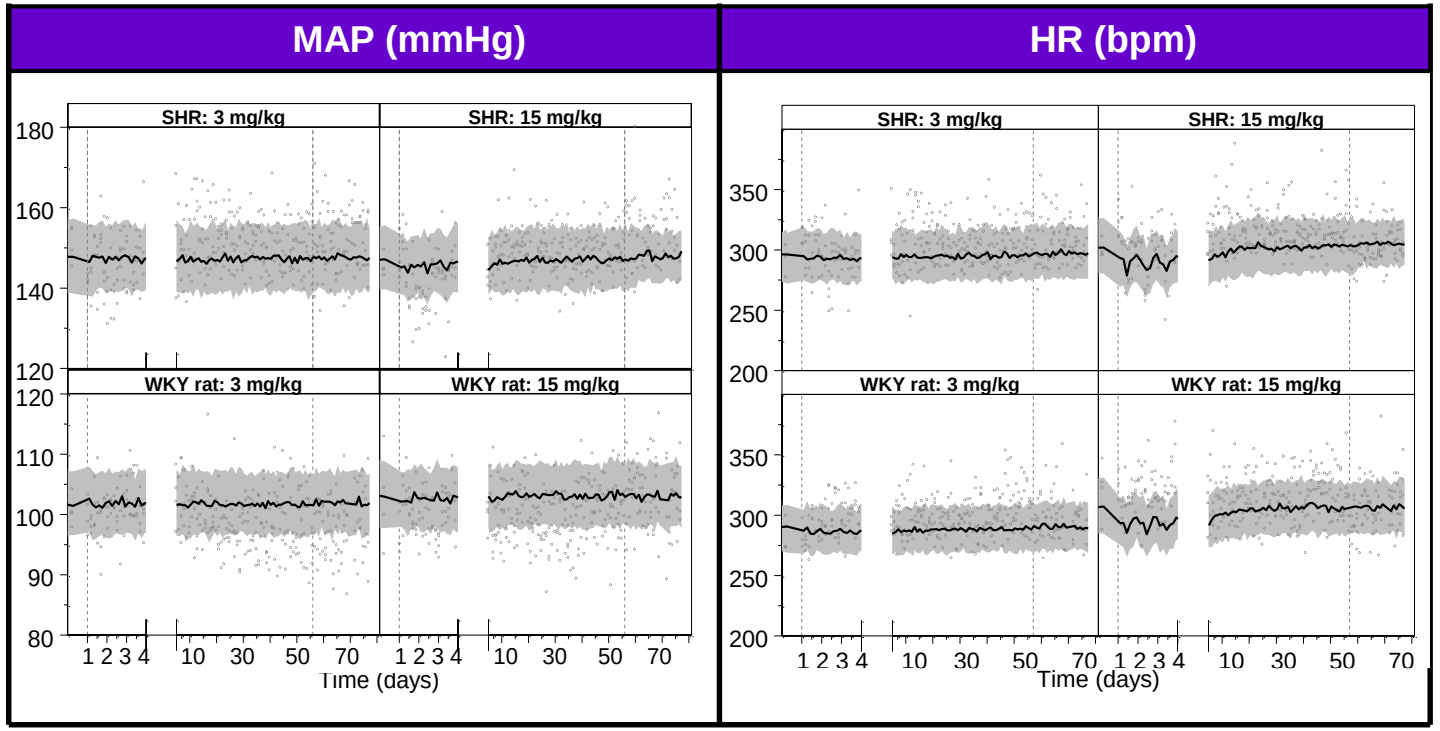
Building QSP models is an iterative process
When am I happy to stop?



Adequate prediction of the effect of siponimod
Forecast using *in vitro* dissociation constants

The effect of siponimod on the CVS was predicted using its calculated dissociation constant:

$$Kd_{HR\_siponimod\_in\ vivo} = Kd_{HR\_fingolimod\text{-}P\_in\ vivo} \bullet \frac{EC_{50\_siponimod\_in\ vitro}}{EC_{50\_fingolimod\text{-}P\_in\ vitro}} \bullet \frac{fu_{fingolimod\text{-}P}}{fu_{siponimod}} \bullet \frac{MW_{siponimod}}{MW_{fingolimod\text{-}P}}$$

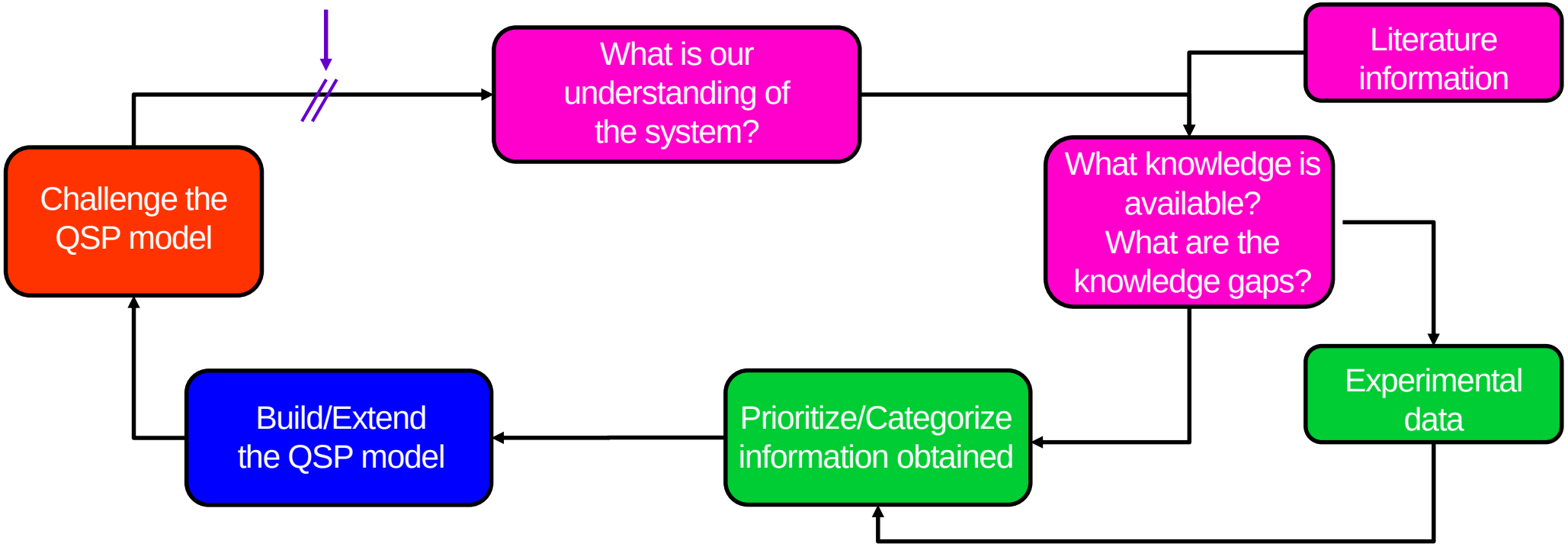


Oral administration of siponimod at doses of 3 or 15 mg/kg once daily for 8 weeks in rats

Predicted median
90% prediction interval
Start and stop of treatment
Observations (n=5 per treatment group)

Building QSP models is an iterative process
When am I happy to stop?

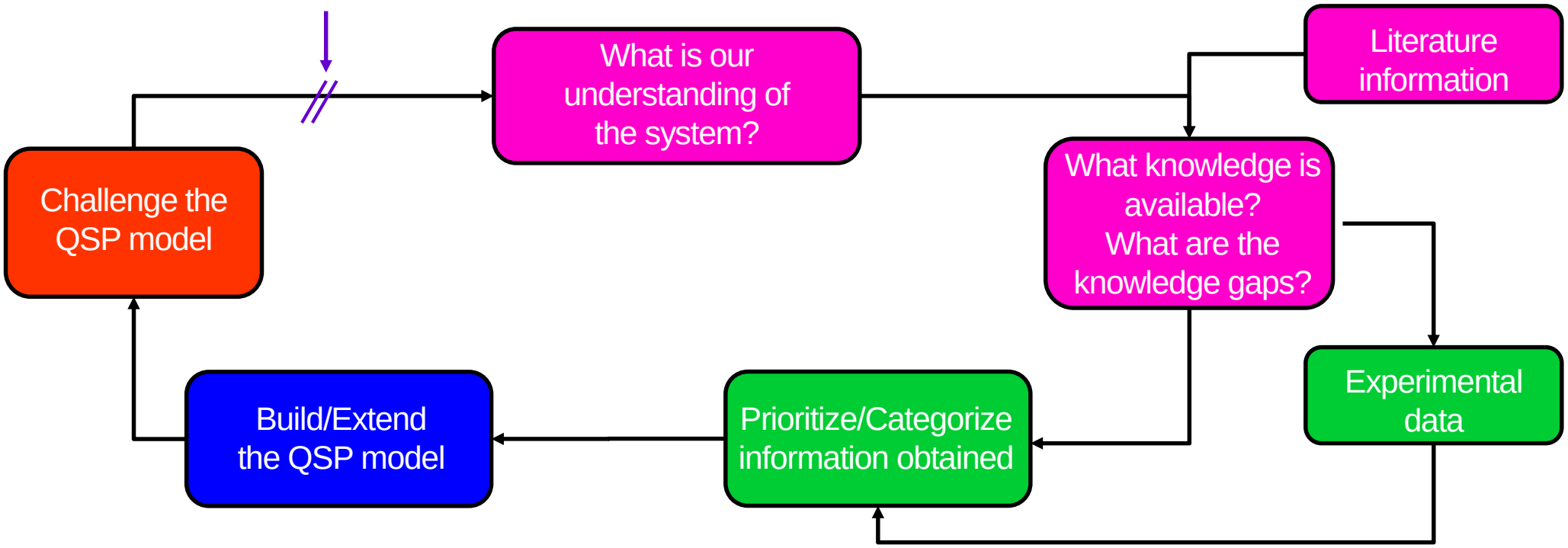
Answer to the Question provided → STOP



Reapply the QSP models for a follow-up question

New question: predict the clinical response of fingolimod-P and follow-up compounds on the CVS based on *in vitro* data

Extend the model to a more detailed level, e.g. receptor concentrations and tissue distribution should be taken into account



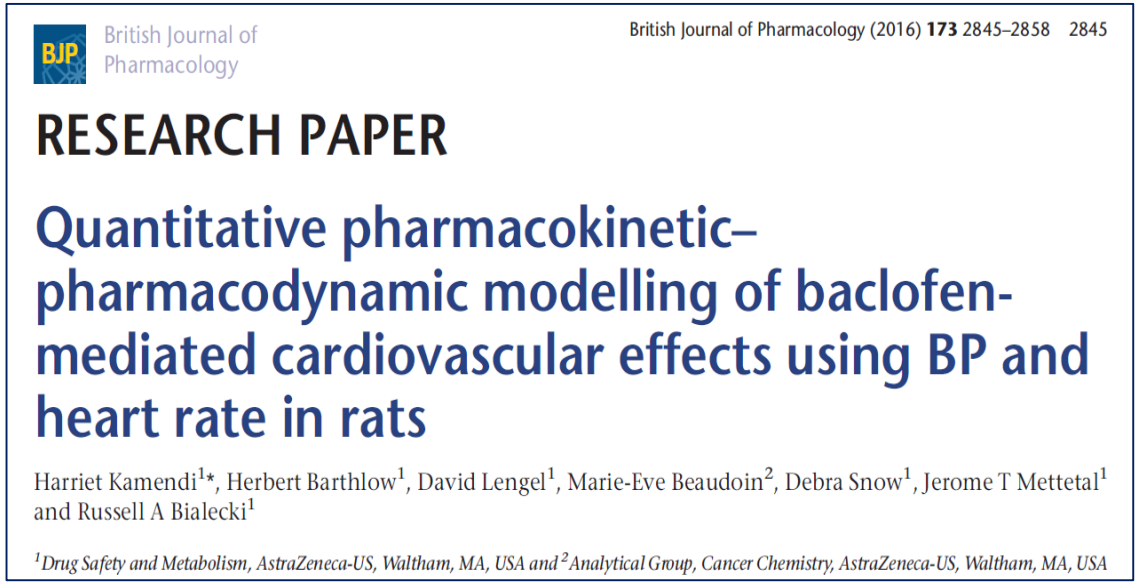
Reapply the QSP model for different compounds

Background: While the molecular pathways of baclofen toxicity are understood, the relationships between baclofen-mediated perturbation of individual target organs and systems involved in cardiovascular regulation are not clear.

Objective: Better elucidate the site(s) of baclofen activity.

Results/Conclusions: systems pharmacology model fits baclofen-mediated changes in MAP and HR well. Final model fits showed that the drug acts on multiple homeostatic processes. The findings correlate with known mechanisms of baclofen.

⇒This example shows that the established CVS model can be applied to other drugs (system specific processes have been established and quantified)



British Journal of Pharmacology

British Journal of Pharmacology (2016) **173** 2845–2858 2845

RESEARCH PAPER

Quantitative pharmacokinetic–pharmacodynamic modelling of baclofen-mediated cardiovascular effects using BP and heart rate in rats

Harriet Kamendi[1]*, Herbert Barthlow[1], David Lengel[1], Marie-Eve Beaudoin[2], Debra Snow[1], Jerome T Mettetal[1] and Russell A Bialecki[1]

[1]*Drug Safety and Metabolism, AstraZeneca-US, Waltham, MA, USA and* [2]*Analytical Group, Cancer Chemistry, AstraZeneca-US, Waltham, MA, USA*

Extend the QSP model for Cardiac Contractility in dogs

Development of a Mechanism Based Platform to Predict Cardiac Contractility and Hemodynamics in Conscious Dogs

UF College of Pharmacy UNIVERSITY of FLORIDA

Raja Venkatasubramanian[1], Teresa A. Collins[2], Lawrence J. Lesko[1], Jay T. Mettetal[3], Mirjam N. Trame[1]

AstraZeneca

[1]Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA
[2]Drug Safety and Metabolism, AstraZeneca, Cambridge, UK; [3]Drug Safety and Metabolism, AstraZeneca, Waltham, Massachusetts, USA
Corresponding author: mtrame@cop.ufl.edu

CVS model extended and sequentially fitted to data from 4 different compounds: albuterol, atenolol, milrinone and L-NAME

This example shows that:

- The established CVS model is likely to be applicable in other species
- Can be extended for other measures, i.e. cardiac contractility

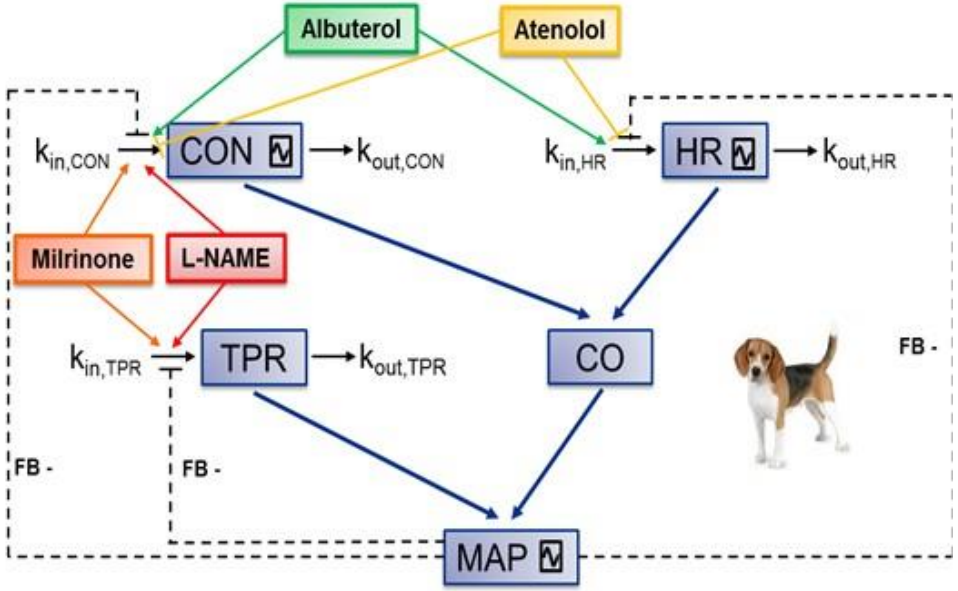


Figure 1: Mechanism Based Model Platform to Predict Cardiac Contractility.

IMI TransQST: Translational quantitative systems toxicology to improve the understanding of the safety of medicines

Task 7.3: Development of quantitative systems pharmacology models to translate drug-induced hemodynamic changes in preclinical species to humans

- **Aim:** Further develop the ‘Snelder’ model to include different species (rat, dog, pig, monkey, etc), up to human if possible, and to include different MoA, or to support the MoA already included.

Required data:

Longitudinal blood pressure, heart rate and cardiac output/contractility measurements and PK following the administration of different compounds at different doses during onset and offset of the drug effects in different conscious species (dog, pig, monkey and human)

Summary of example 1
Questions of the modeller

What knowledge is required to answer the question?

- Modelling at organ and protein level was sufficient as both compounds act at the S1P pathway

How to select and integrate informative data?

- Animal experiments were performed to develop the system-specific CVS model and the class-specific S1P agonist model

How to balance between complexity and quantifiability?

- The process of receptor binding and activation and signal transduction was simplified for quantifiability purposes

When am I happy to stop?

- The effect of novel S1P agonists, such as siponimod, on the CVS can be predicted *using in vitro* dissociation constants

Example 2: Alzheimer's Disease model

QSP modelling to inform therapeutic strategies

Model-informed hypothesis testing

Modelling done by Eline van Maanen in collaboration with LAP&P, LACDR and Merck & Co

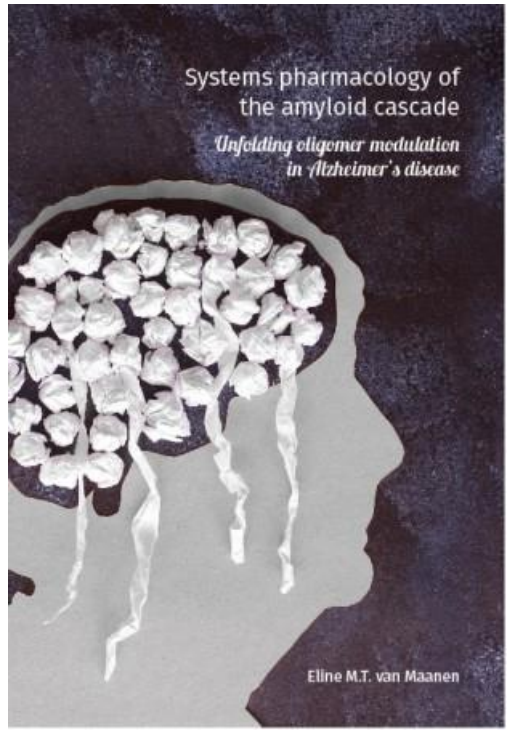
Example 2
Systems pharmacology of the amyloid cascade

Alzheimer's disease (AD) is the leading cause of dementia. Current therapies do not prevent progression of the disease. [1]

There is optimism that β-secretase inhibitors will eventually be successful [2], but, to be clinically effective, an inhibitor will need to be highly selective, very potent, and administered in the early stages of the disease.[3]

A biomarker is needed to measure the effect of drugs and detect the disease before symptoms as mental decline and brain damage occur

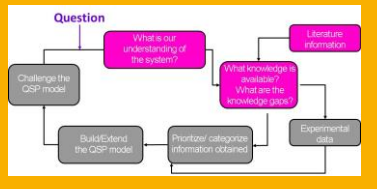
- Focus was on the combination of CSF biomarkers
- $A\beta_O$ is a potential biomarker for early disease progression of AD



⇒A mechanistic and quantitative understanding of the effects of Aβ production inhibitors on $A\beta_O$ concentrations could improve therapeutic strategies which may aid the reduction of Aβ burden

[1] Sen et al. (2017). Iran J Neurol.;16(3):146-155.
[2] Ghosh (2012) J Neurochem120(Suppl 1):71–83
[3] McGeer *et al.* (2013) Acta Neuropathol 126:479–497

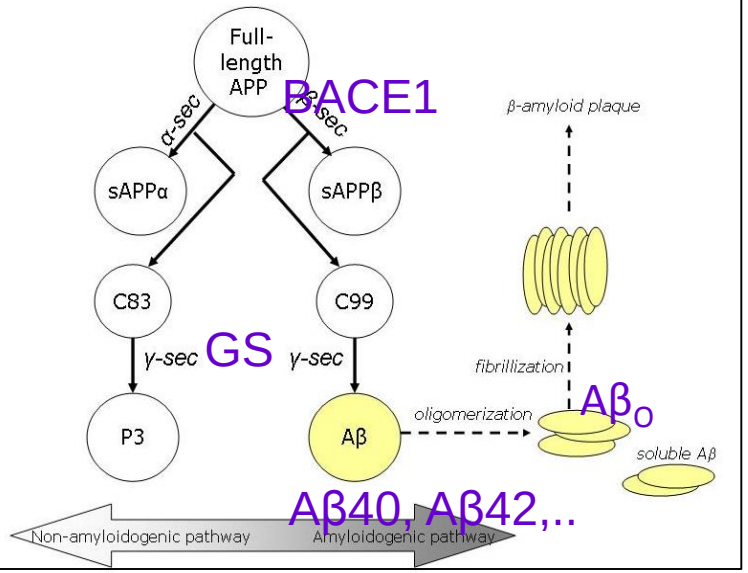
Example 2
What knowledge is required to answer the question



Available knowledge

Pathophysiology of Alzheimer's Disease (AD):
The Amyloid Hypothesis

- Build-up of amyloid-β-peptide ⇒ development of AD
- Aβ is a product of sequential cleavage from Amyloid precursor protein (APP) by β-sec (BACE1) and γ-sec (GS)
- Imbalance in production and clearance of Aβ
  ⇒ Aβ accumulation
  ⇒ plaques (Aβ42)
- Toxic soluble Aβ oligomers ($Aβ_O$) are primary drivers of neurodegeneration



Knowledge gaps

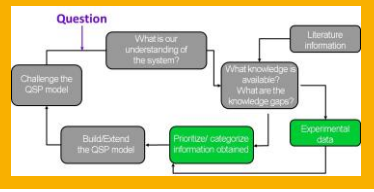
No quantitative understanding of the interrelationship between APP metabolites

- No systems model available

The effect on $Aβ_O$ after targeting Aβ monomers unknown

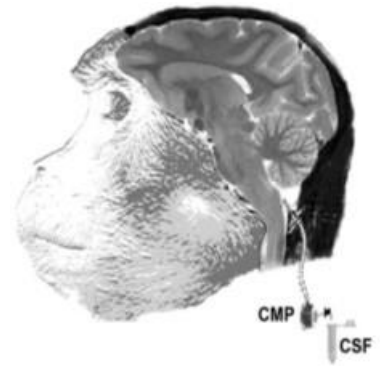
Dynamics between monomeric and oligomeric Aβ species unknown

Example 2
How to select and integrate informative data?



Data from 3 different studies were available in which the effect of BACE1 and GS inhibitors on APP metabolites was investigated in CMP rhesus monkeys

- The effect on $A\beta_O$ was not measured



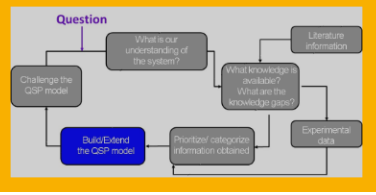
A 4th study was designed to investigate of BACE1 and GS inhibitors on $A\beta_O$ (and the other APP metabolites) using initial modelling results

Study	Inhibitor	Biomarker in CSF					
		sAPPβ	sAPPα	Aβ40	Aβ42	Aβ38	$A\beta_o$
1	BACE1	X	X	X	X	–	–
2, 3 *	GS	–	–	X	X	–	–
4	GS BACE1	X	X	X	X	X	X

Challenges

- APP metabolites (sAPPβ, sAPPα, Aβ40, Aβ42) levels and ratios in study 4 were different than in previous studies
  - ⇒ A within study comparison was done
- APP metabolites expressed in pM. Oligomers were expressed in pg/mL.
  - ⇒ A "conversion" factor on oligomers was estimated

Example 2
How to balance between complexity and quantifiability?

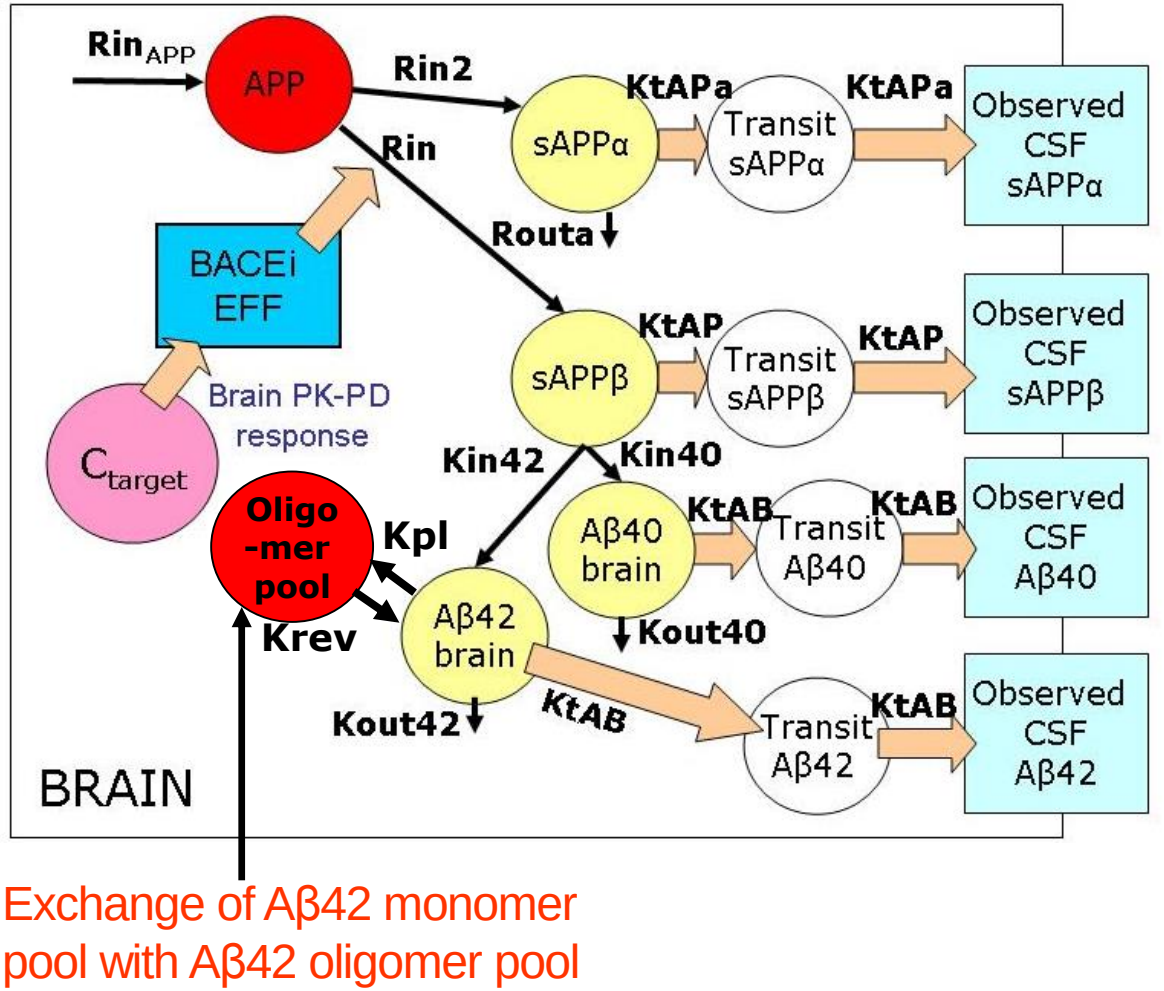


Integrating different biomarkers to model a biological cascade of responses results in technical challenges in NONMEM, such as model stability and parameter identifiability issues.

A step-wise modelling approach ensured quantifiability for a complex model:

1. Each biomarker-inhibitor combination was evaluated by separate models
2. BACE1 inhibitor on sAPPβ, Aβ40, Aβ42 and sAPPα

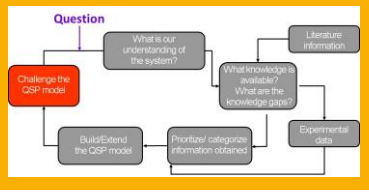
The modelling suggested an oligomer pool



Exchange of Aβ42 monomer pool with Aβ42 oligomer pool

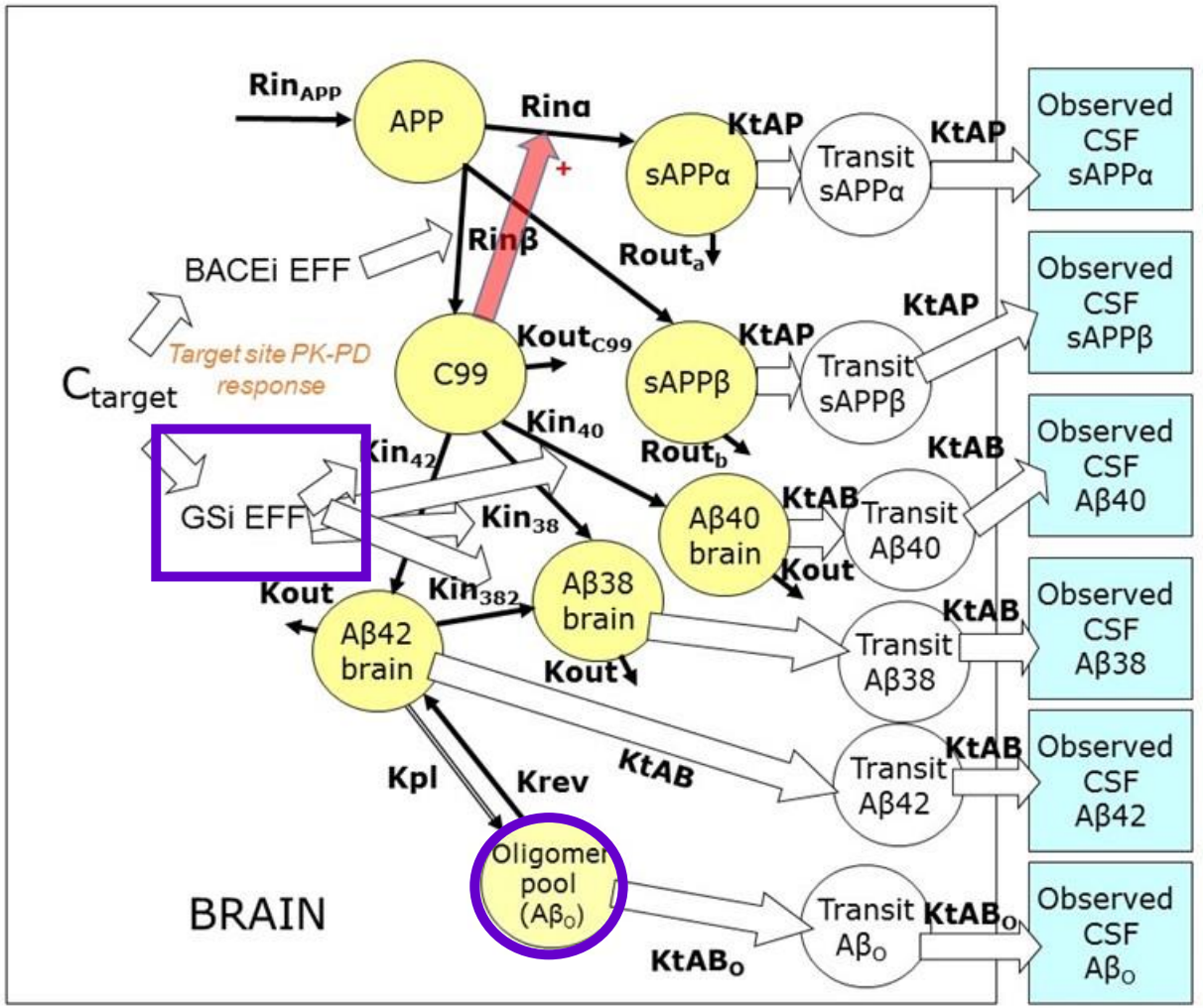
Van Maanen et al. (2016) J Pharmacol Exp Ther. ;357(1):205-16.

Example 2
When am I happy to stop?



- The model was challenged using another compound (GS inhibitor) with a different mechanisms of action

- $A\beta_O$ data provided an excellent opportunity to test the hypothesis previously obtained on the existence of an oligomer pool and further investigate the dynamics between monomeric and oligomeric response



Van Maanen *et al.* (2017) poster AAIC

Example 2
Adequate description of the effect BACEI and GSI by the integrated model

- The relationship between monomeric Aβ species and $Aβ_O$ was adequately characterized
- Of the measured Aβ species Aβ42 was the only major contributor to the oligomer pool

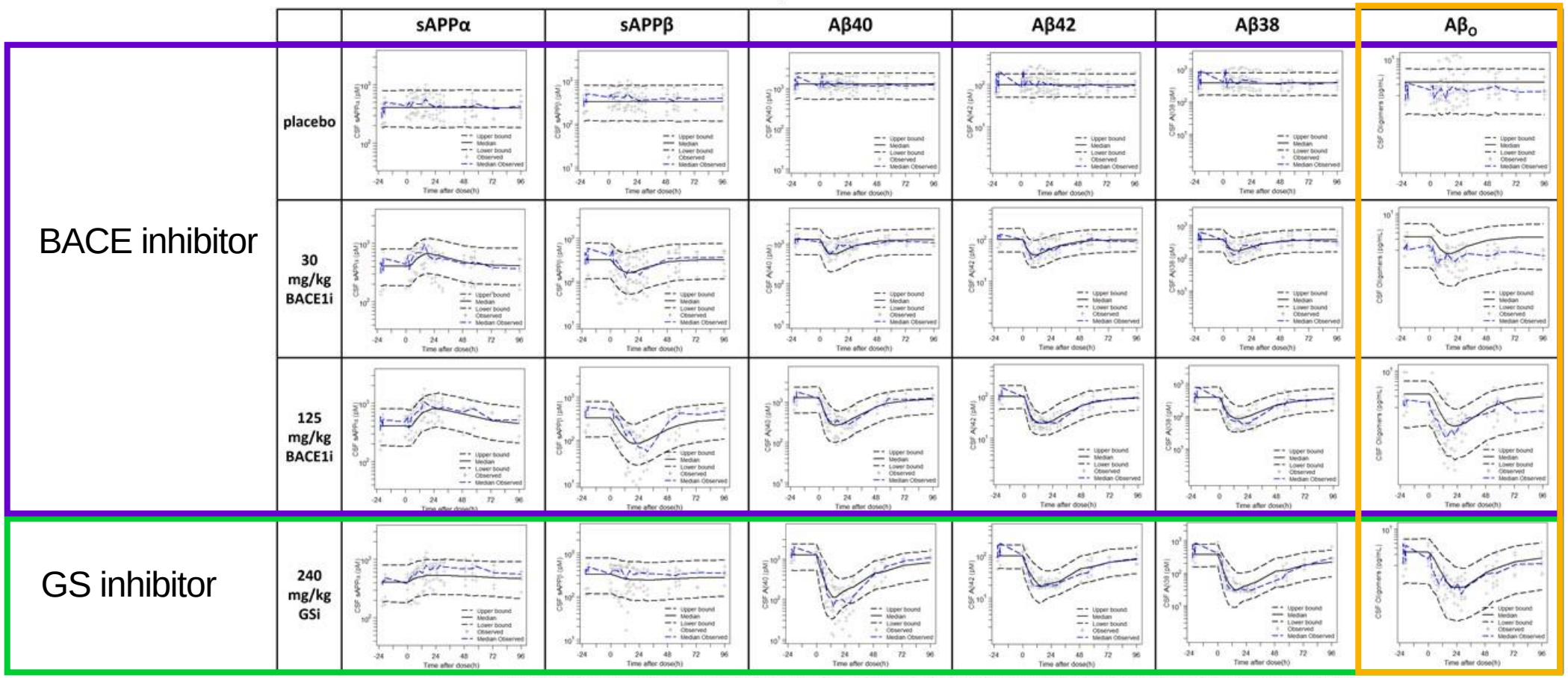


Figure 2. Description of sAPPα, sAPPβ, Aβ40, Aβ42, Aβ38 and $Aβ_O$ response to BACE1 and GS inhibitor by the APP systems model

Summary of example 2
Questions of the modeller

What knowledge is required to answer the question?

- The knowledge gap on a quantitative understanding of the dynamics between monomeric and oligomeric Aβ species was filled by the combination of informative $Aβ_O$ data and a quantitative modelling approach

How to select and integrate informative data?

- A new study was designed to investigate the effect of Aβ production inhibitors on APP species and $Aβ_O$

How to balance between complexity and quantifiability?

- A stepwise modelling approach ensured quantifiability for the different parts of the model

When am I happy to stop?

- Model-informed hypothesis testing suggested that Aβ42 was a major contributor to $Aβ_O$
- The APP systems model brings us closer to optimising the therapeutic interventions needed to reduce $Aβ_O$ burden.

Example 3: Osteoporosis model
From QSP modelling to late phase drug development support

Quantifiability

Modelling done by Teun Post and Jan Berkhout in collaboration with the LACDR and Merck & CO

Example 3
Disease system analysis in osteoporosis

Osteoporosis is a progressive bone disease characterized by a decrease in bone mass resulting in an increased risk of fracture

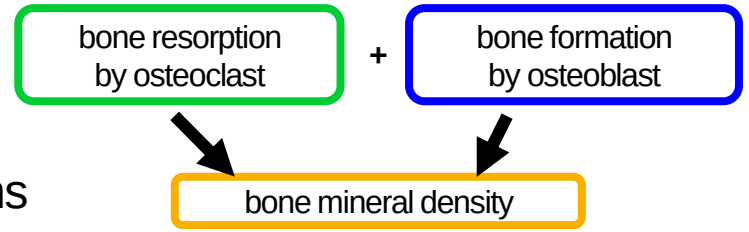
High prevalence of osteoporosis

In older adults in the USA:

- Most common metabolic bone disease
- Most common cause of fractures
- Hip fractures are associated with the highest morbidity and mortality
- 44 mln people are affected by osteoporosis and low BMD

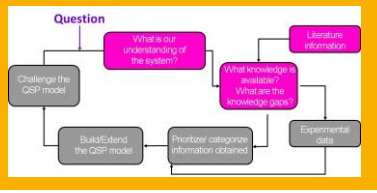
⇒Setting-up a framework model with a physiological basis to optimize drug development

- Specifications:
  - Should capture disease progression
  - Should capture balance between bone formation and bone resorption
  - Should be applicable for compounds with different mechanisms of actions
  - Should capture inter-individual variability



N Eng J Med (2010) 363:2027-35

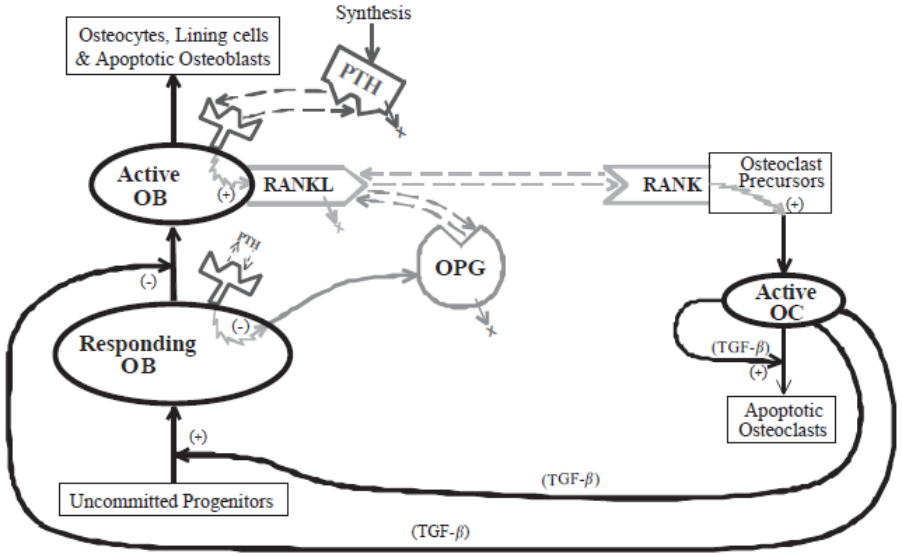
Example 3
What knowledge is required to answer the question



Available knowledge

Pathophysiology of osteoporosis

Conceptual model, which incorporates the interaction between osteoblasts and osteoclasts [1]



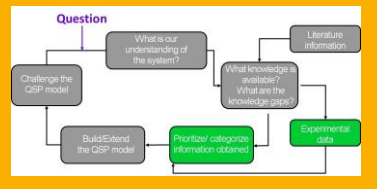
Biomarkers available for disease status/progression

Knowledge gaps

Not directly applicable for population approach

Activity of active osteoblasts and osteoclasts difficult to measure in a clinical setting

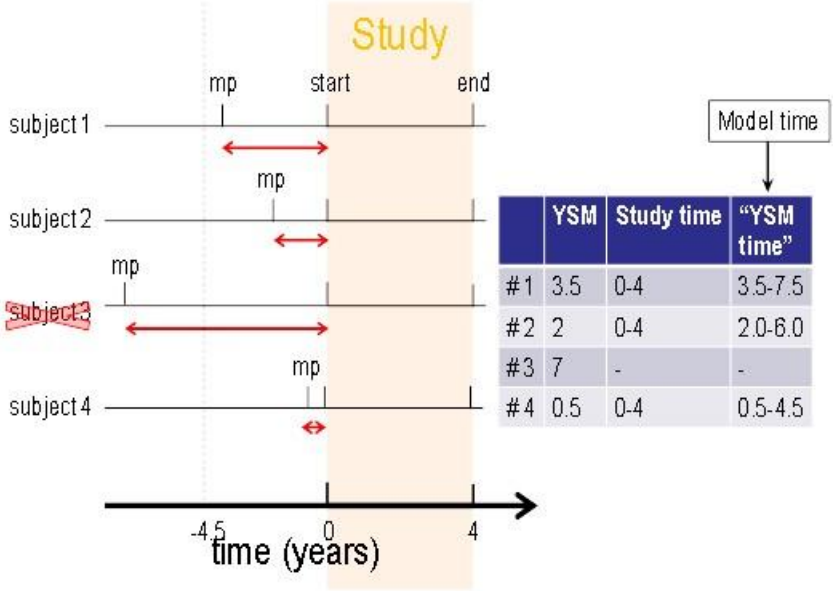
Example 3
How to select and integrate **informative** data?



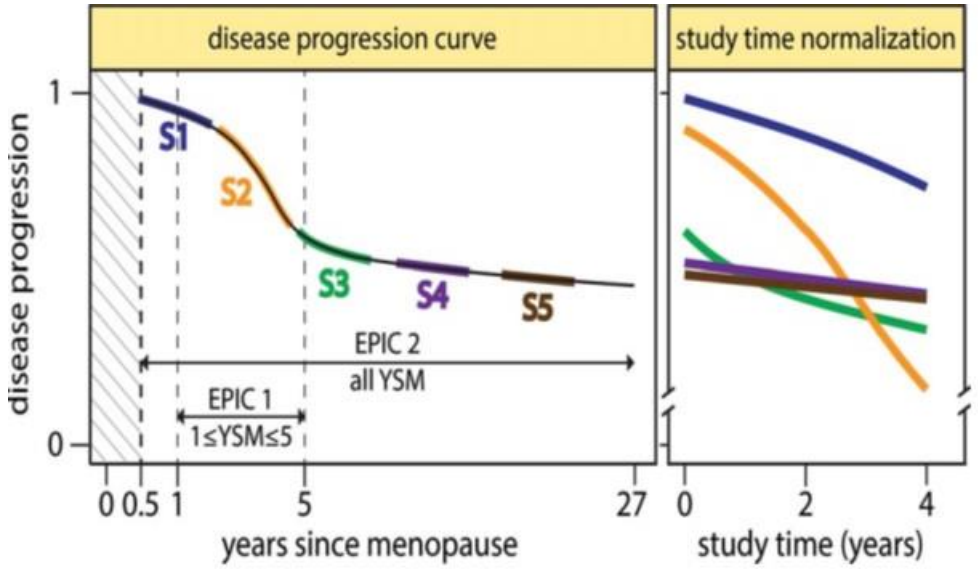
Select data: Sufficient clinical biomarker data was available after administration of tibolone and alendronate

- Challenges:
  - Measurement frequency low
  - Different timescales

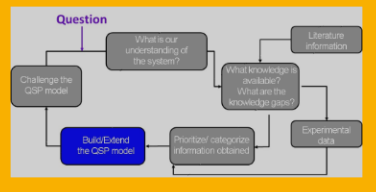
Informative data: Disease progression was incorporated using years since menopause instead of time since start of study and was related to the decrease in estrogen, which ensured that the data was informative



	YSM	Study time	"YSM time"
#1	3.5	0-4	3.5-7.5
#2	2	0-4	2.0-6.0
#3	7	-	-
#4	0.5	0-4	0.5-4.5



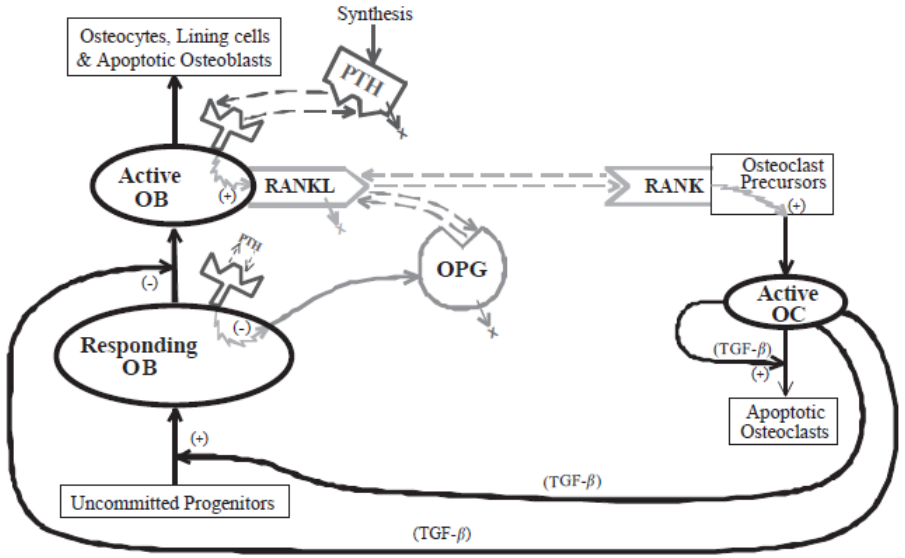
Example 3
How to balance between complexity and quantifiability?



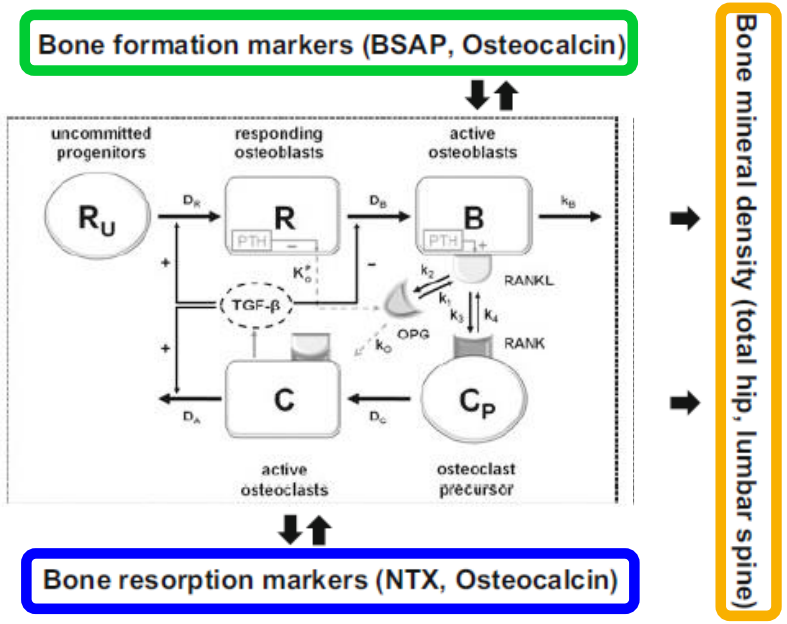
Model reduction needed to apply the Lemaire model to populations [1, 3]

- By introducing dimensionless variables the model could be reduced
- By removing non-influential parameters while capturing the key rate limiting steps the model could be further reduced

Lemaire model [2]:
3 variables

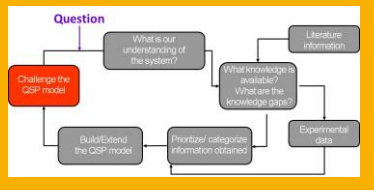


Post model (population model) [3]:
2 variables

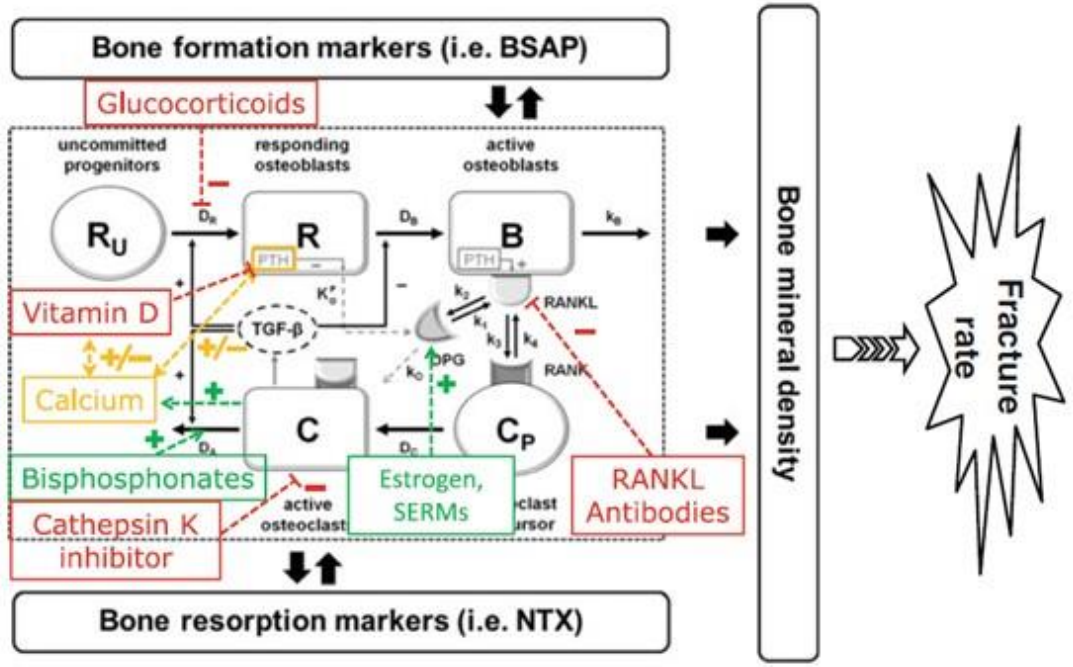


[1] Schmidt *et al.* (2011) J PK&PD
[2] Lemaire et al.(2004) J Theor Biol229:293–309
[3] Post (2009) thesis

Example 3
When am I happy to stop?



The proposed reduction was deemed sufficient, because it explicitly incorporates the dynamics of the two main bone cell types, and therefore, the model can still be used for other drug treatment effects [3]



Disease progression was captured:

- By separating the timescales of the markers through an underlying biological system, it was possible to identify a ‘symptomatic’ treatment effect in one set of markers and a ‘disease modifying’ effect in another

[3] Post (2009) thesis

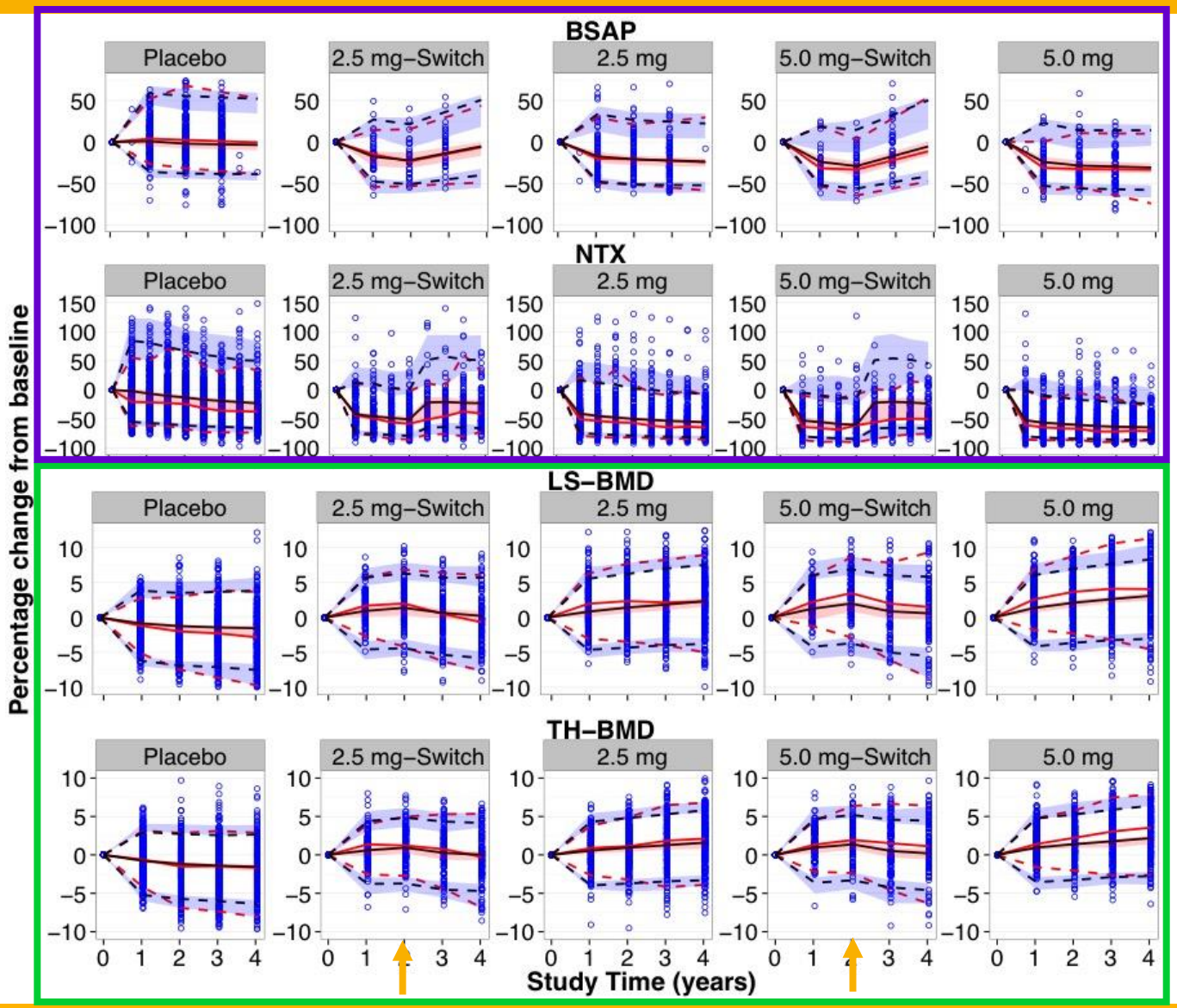
Example 3
Apply the model for alendronate

Alendronate is a bisphosphonate, which prevents bone breakdown and increases bone density

- Effect of alendronate was adequately described on a population level and on an individual level
- Alendronate seems to have a symptomatic effect on the bone turnover markers and a disease modifying effect on BMD

Model describing the interactions between osteoclast (bone removing) and osteoblast (bone forming) cells in bone remodelling on an individual level allows:

- Differentiation of treatment effects
- Quantitative insights in balance between bone formation and bone reduction for new compounds
- Quantitative insights in added value of combination therapy



Berkhout *et al.* (2016) CPT Pharmacometrics Syst. Pharmacol. 5(12):656-664

Summary of example 3
Questions of the modeller

What knowledge is required to answer the question?

- There was sufficient knowledge on the pathophysiology of osteoporosis on the cell and organ level available. Capturing this in a model, while ensuring quantifiability, was the challenge.

How to select and integrate informative data?

- By changing the time scale to years since menopause the informativeness of the data was greatly enlarged

How to balance between complexity and quantifiability?

- A literature model was reduced and fitted to clinical data to ensure quantifiability

When am I happy to stop?

- The framework model can be applied to support drug development on a population and individual level while capturing disease progression as was demonstrated for alendronate

  ⇒The specifications of the framework were met

Conclusions - Where does QSP fit into the modelling toolbox to support drug development?

Building QSP models is an iterative process with several challenges for the modeller as summarized by four key questions:

- What knowledge is required to answer the question?
- How to select and integrate informative data?
- How to balance between complexity and quantifiability?
- When am I happy to stop?

Our examples illustrate that building QSP models can be facilitated by systematically asking and addressing the right questions

Acknowledgements & Further reading

Acknowledgements

LACDR

NOVARTIS

Novartis-Leiden collaboration team

MERCK

LAP Leiden Advanced PK-PD

All colleagues at LAP&P with a special thanks to:

- Jan Berkhout
- Teun Post
- Eline van Maanen
- Tamara van Steeg

www.lapp.nl

n.snelder@lapp.nl

Further reading

CVS model:

- Snelder *et al.* (2013) Br J Pharmacol. 169(7):1510-24
- Snelder *et al.* (2014) Br J Pharmacol.171(22):5076-92
- Snelder *et al.* (2017) J Pharmacol Exp Ther. 360(2):356-367

Alzheimer disease model:

- Van Maanen (2017) thesis, “Systems pharmacology of the amyloid cascade
- Van Maanen et al. (2016) J Pharmacol Exp Ther. ;357(1):205-16.

Osteoporosis model:

- Post (2009) thesis, “Disease system analysis”
- Post *et al.* (2010) Clin Pharmacokinet. 49(2):89-118.
- Berkhout *et al.* (2016) CPT Pharmacometrics Syst. Pharmacol. 5(12):656-664