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Towards the prediction of cardiovascular effects in human

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fingolimod

- Fingolimod is effective in the treatment of multiple sclerosis
  - In 2010 fingolimod was approved at a dose of 0.5 mg

- A dose of 0.5 mg resulted in:
  - A small increase in blood pressure
    - 1-2 mm Hg after 2 months
  - A transient bradycardia
    - 8 bpm at 5 hours after the 1st dose (attenuation after 6 hours)

Freedoms trial: patients with MS

Event	fingolimod 0.5 mg (N=425)	placebo (N=418)
Hypertension	26 (6.1 %)	16 (3.8 %)
Bradycardia	9 (2.1 %)	3 (0.7 %)

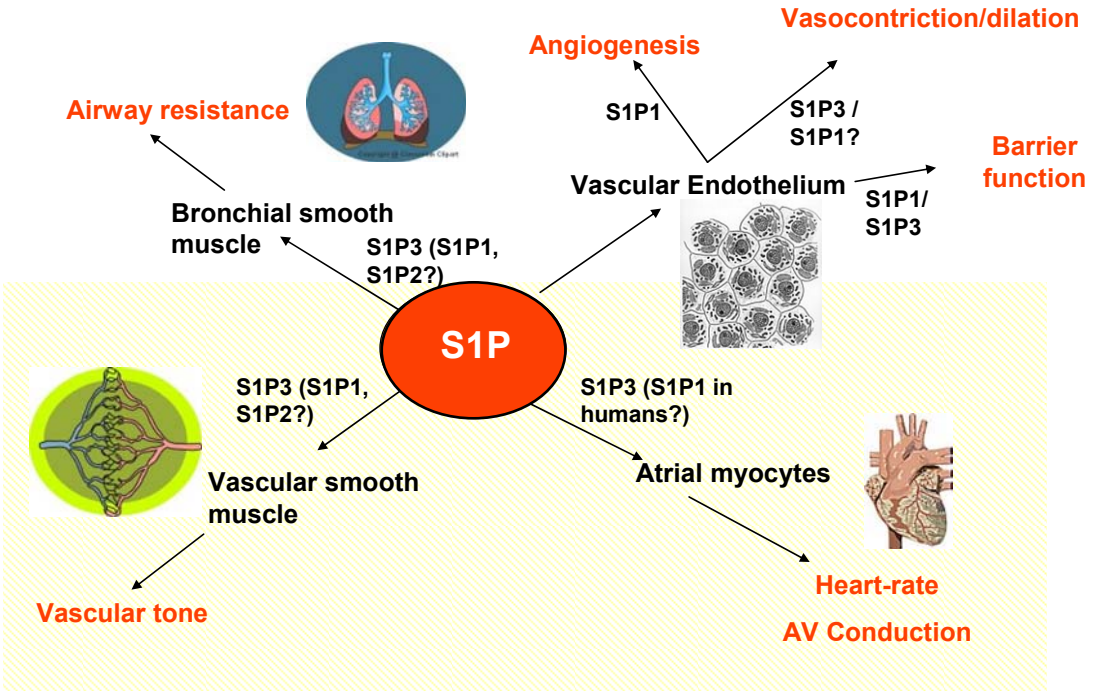
- Are cardiovascular effects of relevance for fingolimod?
  - Is the effect reversible?
  - What are the long term effects?

- Can early selection of follow-up compounds be improved?

Effect of fingolimod on the CVS

- Sphingosine-1-phosphate (S1P) is a major regulator of vascular and immune systems

- Fingolimod is a S1P agonist
  - Subtypes S1P1, S1P3, S1P4 and S1P5



- The mechanism of action needs further investigation

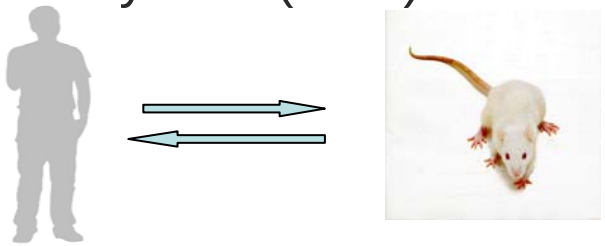
Hypothesis: a better understanding of the mechanism of action of compounds can result from a quantitative understanding of the system

- Physiological principles of BP regulation

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

  - Several feedback mechanism:
    - Baroreflex system
    - Renin-Angiotensin-Aldosterone System

- Preclinical research may contribute to a quantitative understanding of the cardiovascular system (CVS)



Objectives

1) Development of a systems pharmacology model characterizing the effects of drugs on the interrelationship between BP, TPR, CO, HR and SV

   ⇒ **Drug-independent CVS model**

2) Characterization of the effect of fingolimod on the CVS using the developed systems pharmacology model

   ⇒ **A better understanding of mechanisms leading to cardiovascular effects following administration of fingolimod**

CVS model

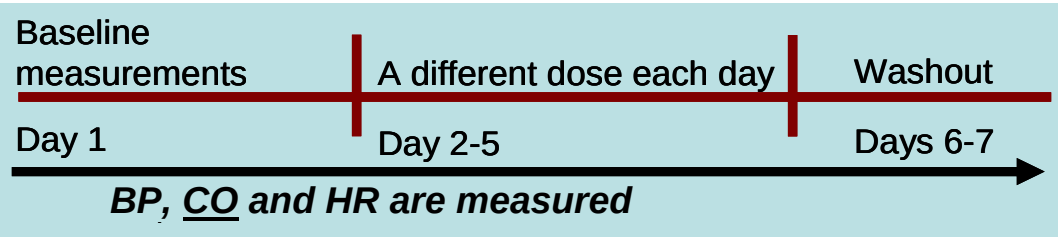
Collect preclinical data from different drugs acting on CVS to identify system specific parameters

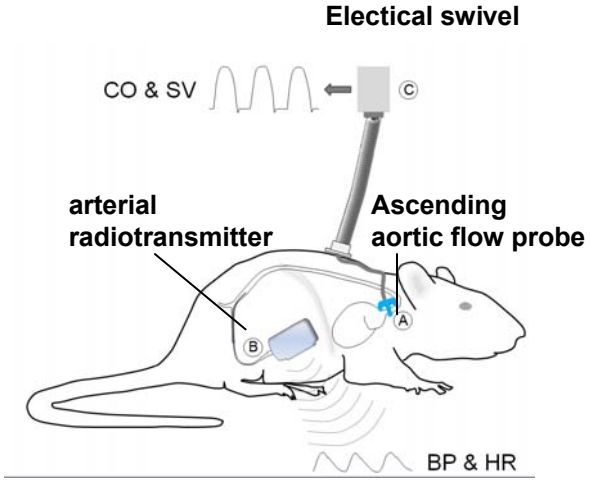
- **Compounds:**

Effect on HR	Effect on TPR	Effect on SV
atropine (M2 receptor antagonist)	amlodipine (calcium channel blocker)	amiloride (diuretic)
propanolol (non-selectiveβ blocker)	enalapril (ACE-inhibitor)	enalapril (ACE-inhibitor)
	fasudil (rho-kinase inhibitor)	HCTZ (diuretic)
	prazosin (selective α1 blocker)	

2-3 rats per compound

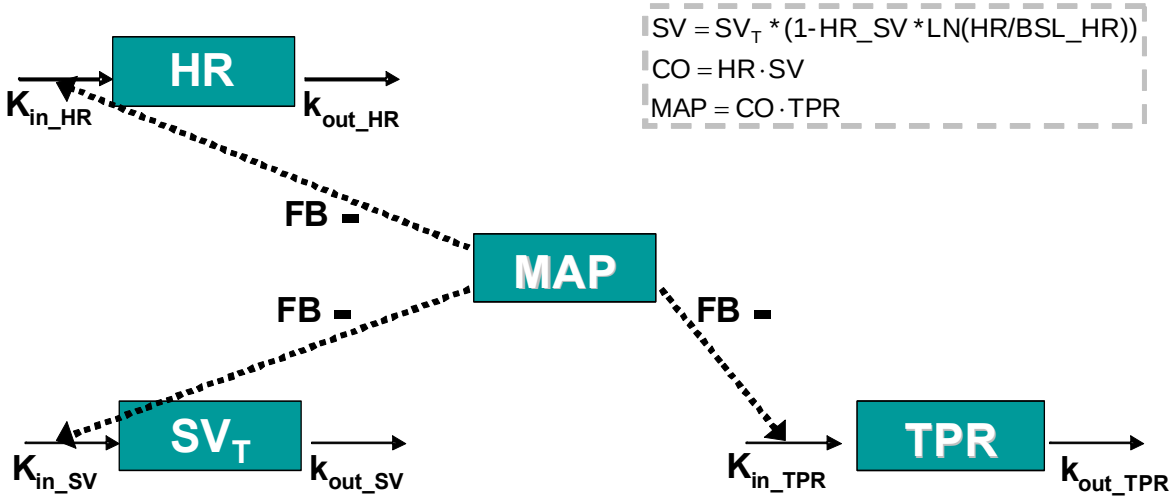
- **Study design:**





System-specific Model

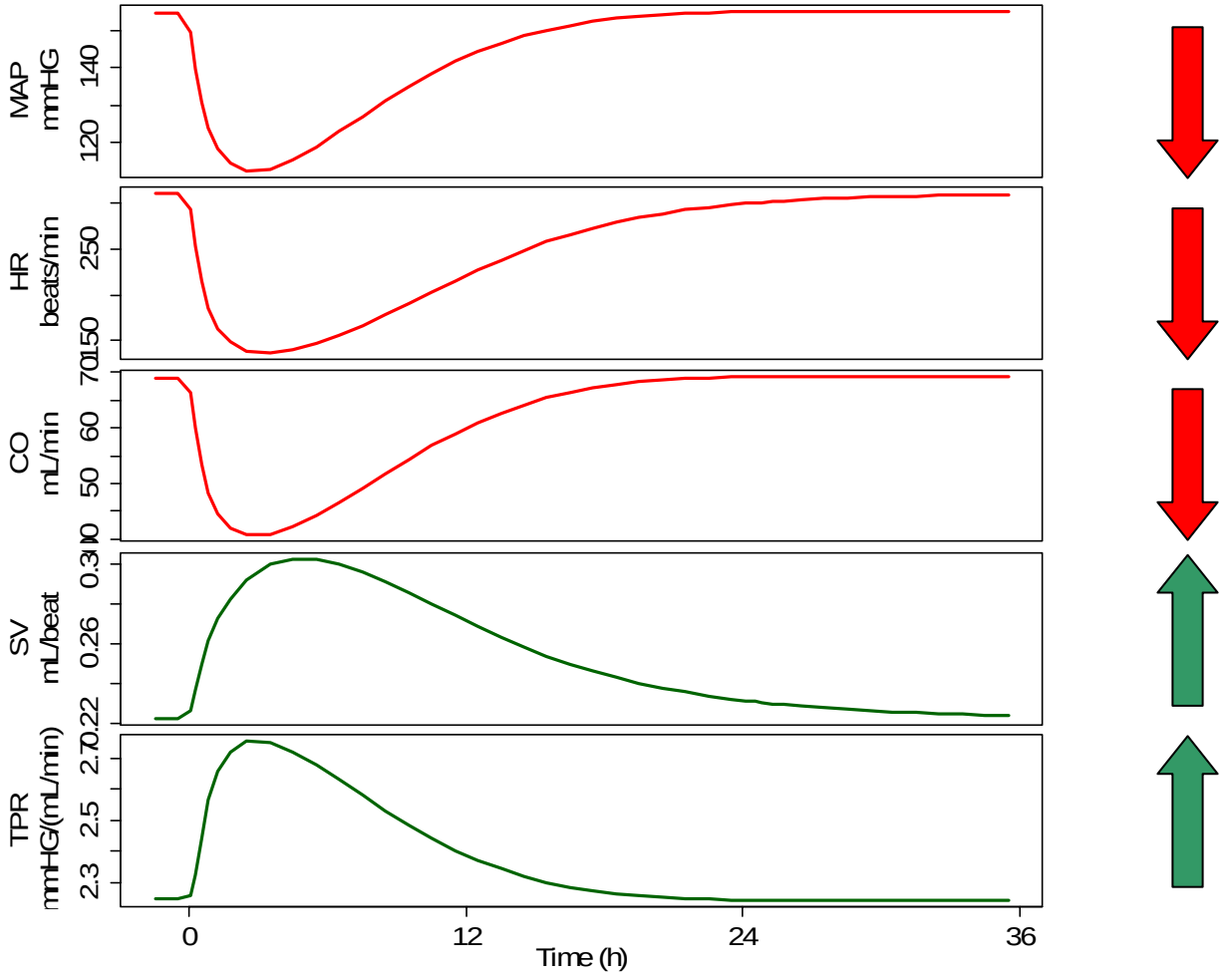
- Linked turnover model with differential equations for HR, SV and TPR linked by negative feedback through MAP
- Direct inverse relationship between HR and SV
- Circadian rhythm: two cosine functions, one influencing HR and one influencing TPR



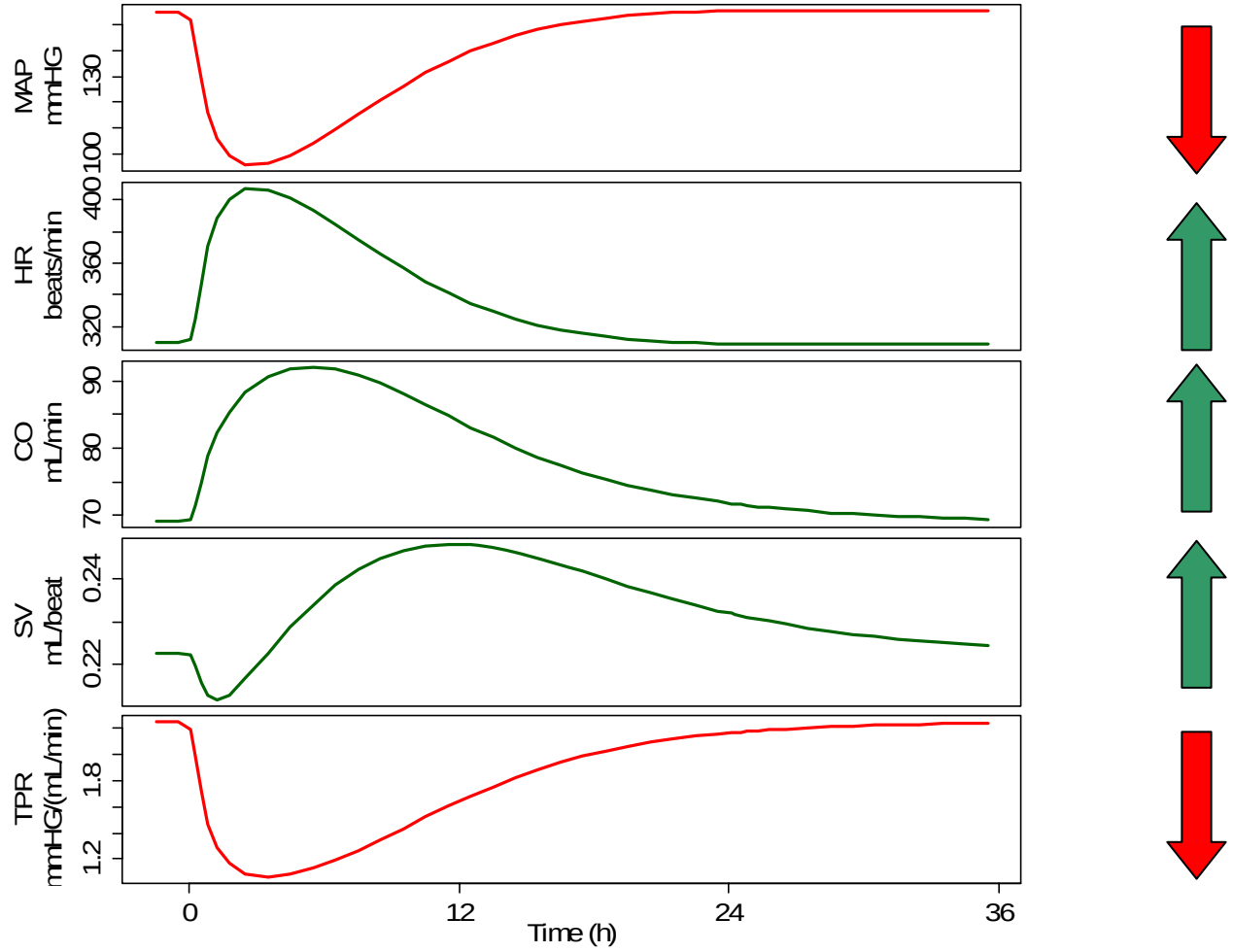
- Handling effect: exponentially decreasing functions influencing K_{in_HR} and K_{in_TPR}

- Differences between hypertensive and normotensive rats:
  - Different baseline
  - The feedback was found to be dependent on the baseline blood pressure

Negative effect on HR

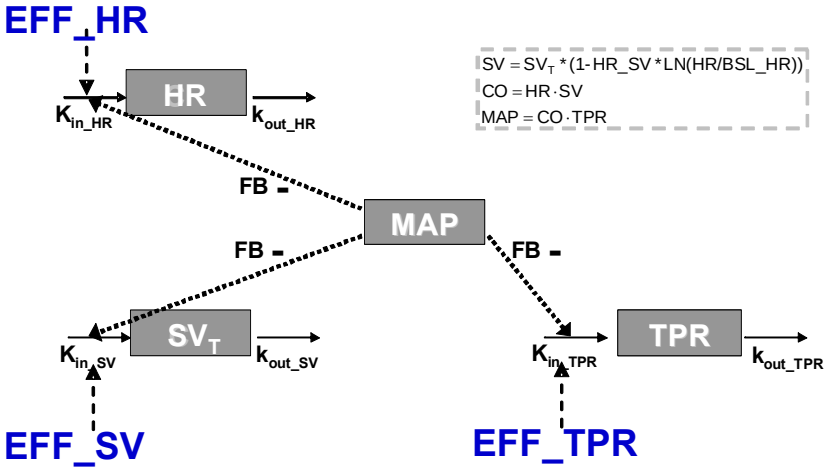


Negative effect on TPR



Drug-specific Model

- PKPD modelling approach (NONMEM): PK models from literature
- Drug effects on HR, SV or TPR



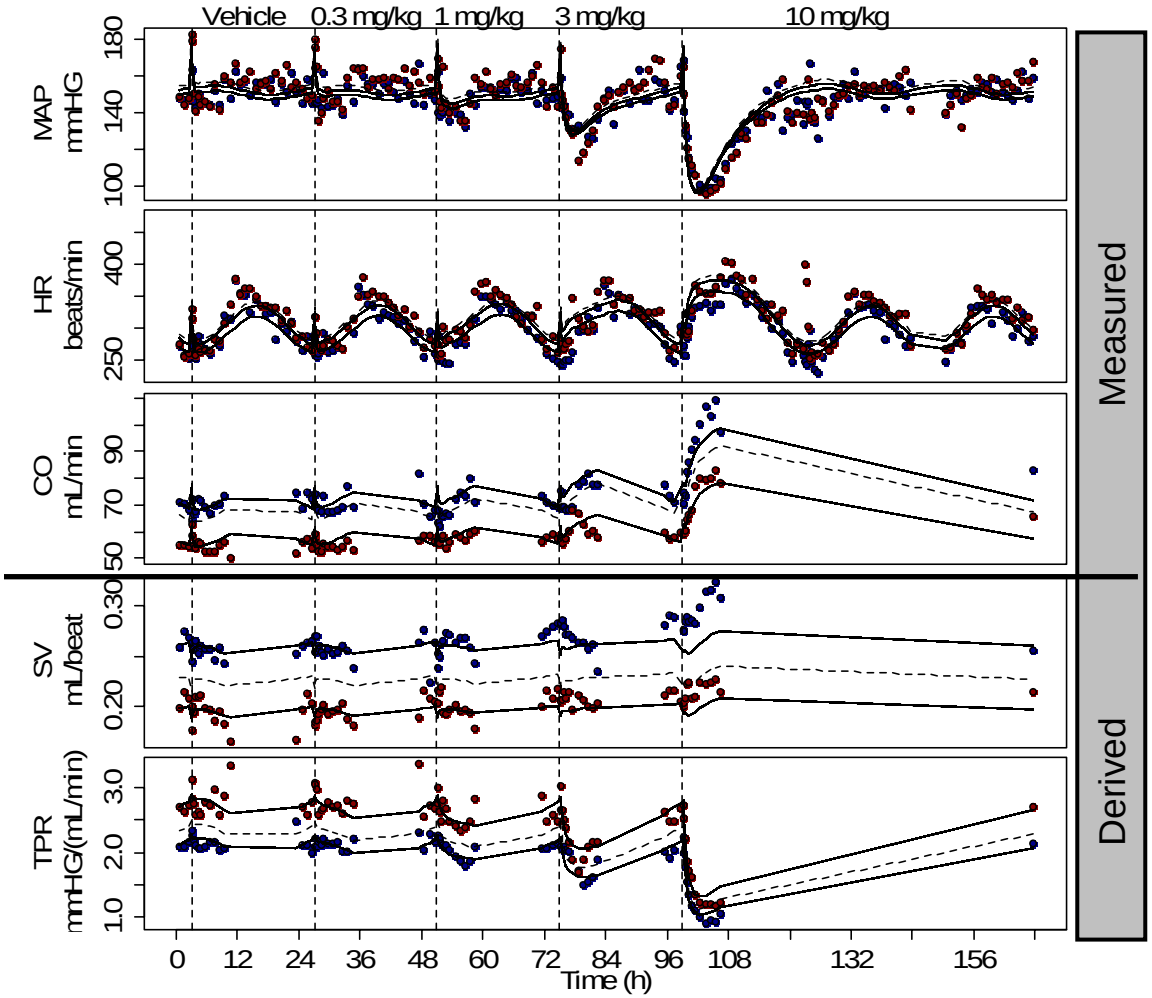
- Best drug effect models:

Compound	Effect site	Drug effect model
amiloride	SV	E_{max} with E_{max} fixed to 1
amlodipine	TPR	E_{max} with E_{max} fixed to 1
atropine	HR	Linear
enalapril	TPR and SV	E_{max} with E_{max} fixed to 1
fasudil	TPR	E_{max} with E_{max} fixed to 1
HCTZ	SV	E_{max} with E_{max} fixed to 1
prazosin	TPR	Power
propranolol	HR	No effect

- The effect of ACE inhibitors is delayed. This was described by an effect compartment model

Adequate description of the effect of amlodipine

hypertensive rats

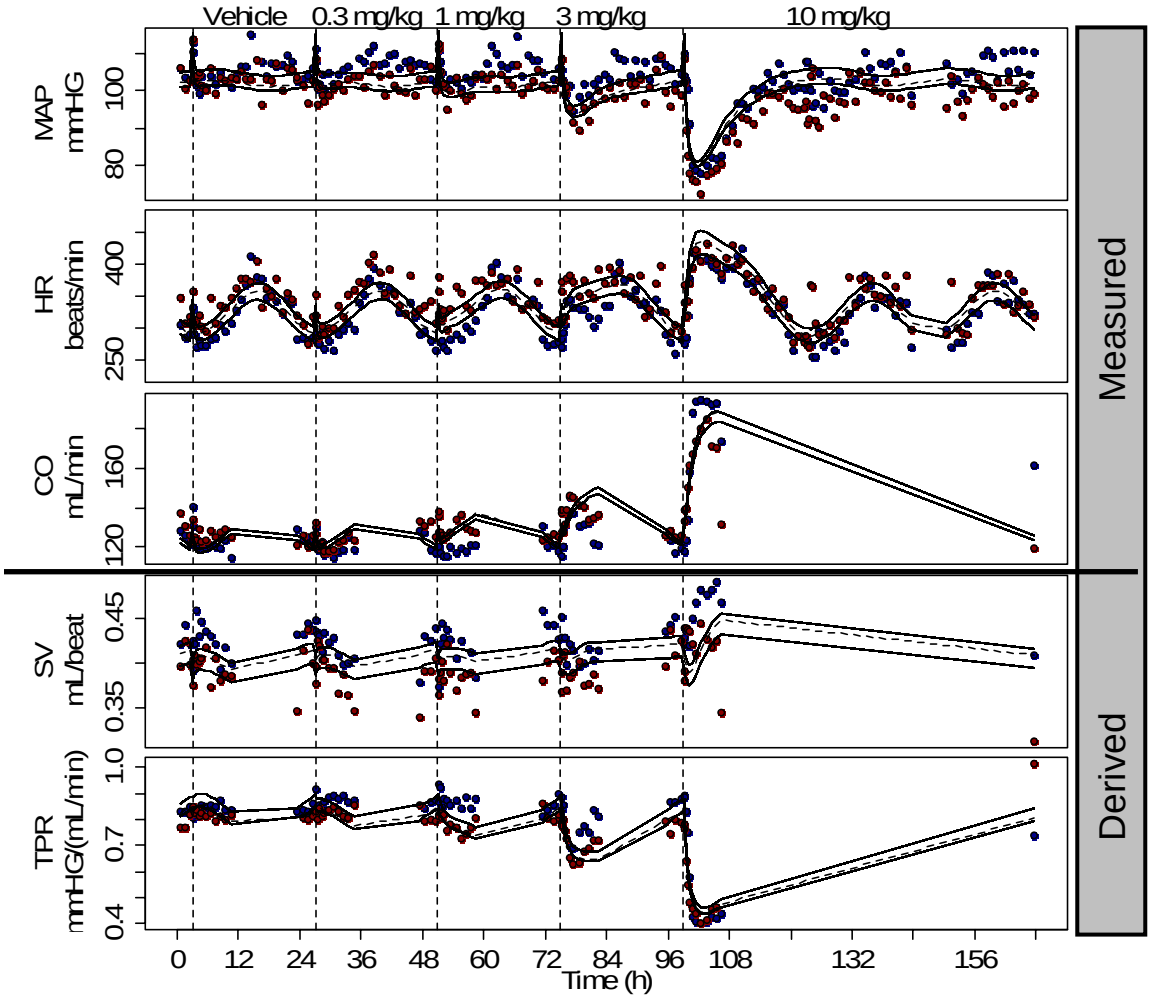


Effect on all five endpoints can be described by a single drug effect on TPR

- Individual prediction
- Population prediction (n=38)
- Observations (colored per rat)

Adequate description of the effect of amlodipine

normotensive rats



Effect of amlodipine described adequately in normotensive rats

- Individual prediction
- Population prediction (n=38)
- Observations (colored per rat)

Conclusions and Future perspective
CVS model

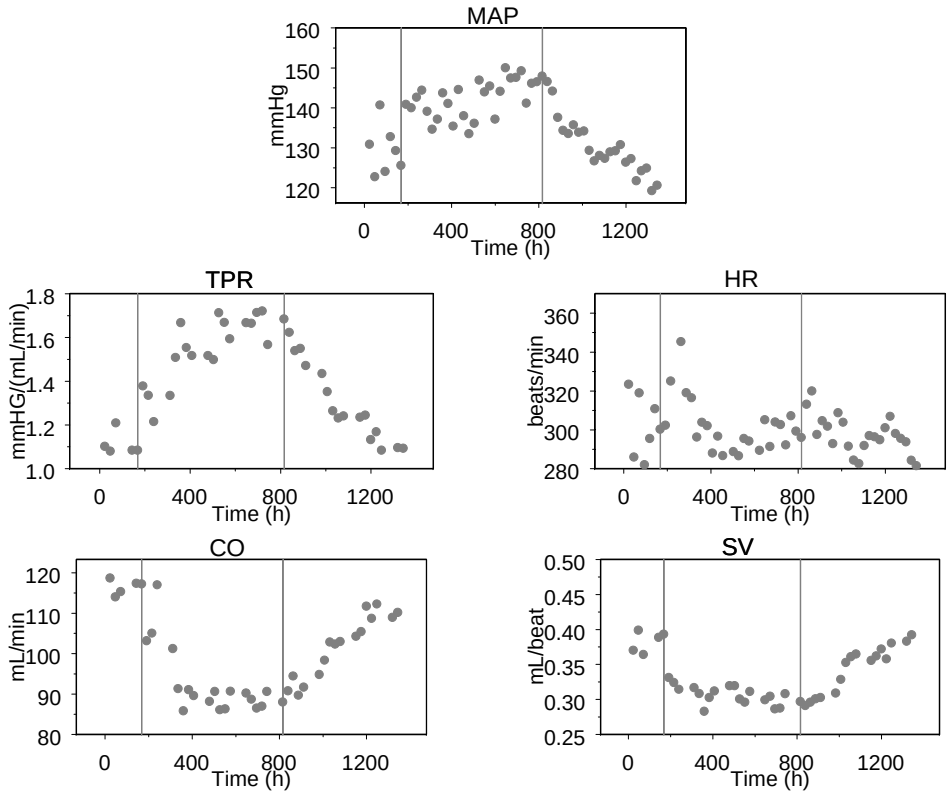
- A systems pharmacology model was developed to describe the interrelationship between MAP, CO, HR, SV and TPR
- The developed systems pharmacology model can be used to quantify cardiovascular drug effects of novel compounds
- Can the CVS model be used to elucidate the mechanism of action of novel compounds?

Application of the developed drug-independent CVS model to fingolimod

Prediction of the effect of fingolimod on the CVS

Experimental design:

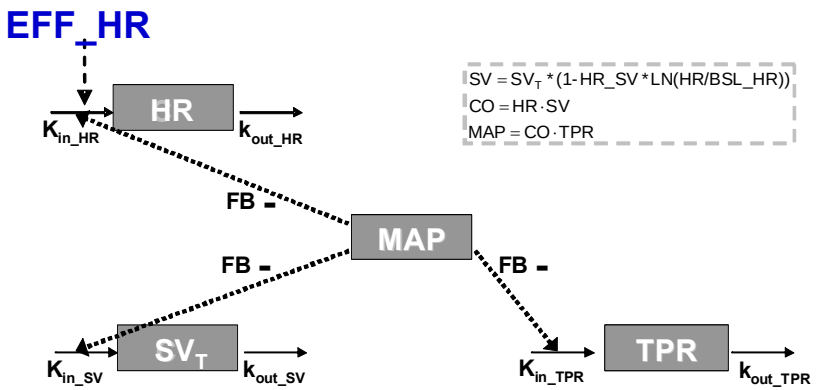
- Dose: 0, 0.1, 0.3, 1, 3 and 10 mg/kg
- MD administration (4 weeks)
- Hypertensive and normotensive rats
- 32 rats
- Measured: **MAP, HR and CO**



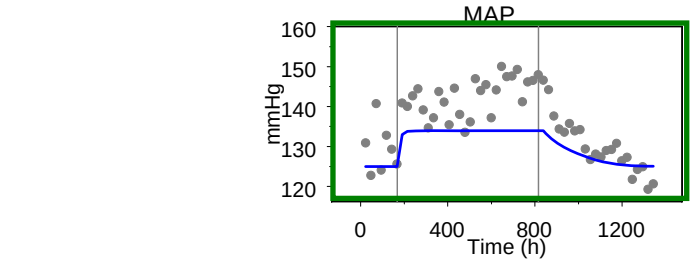
Example of a typical hyeprtensive rat (10 mg/kg)

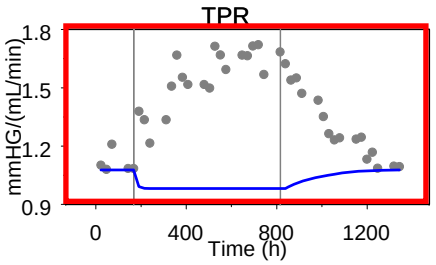
Prediction of the effect of fingolimod on the CVS

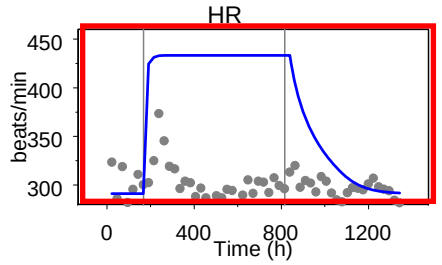
- The CVS model was used to predict the effect of fingolimod
  - System-specific parameters were fixed

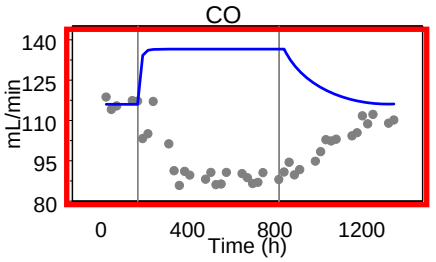


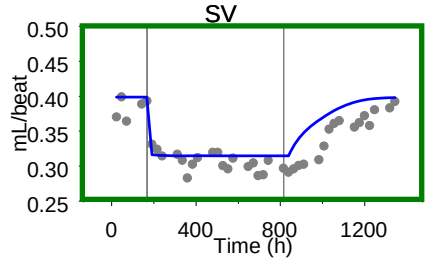
Hypothesis 1: effect is on HR







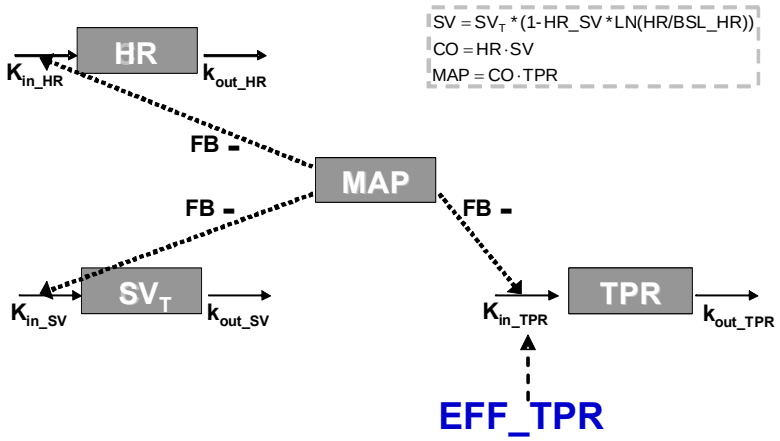




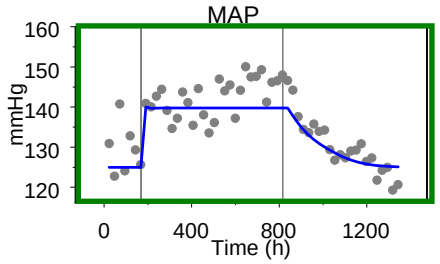
The CVS model indicates that it is not likely that the primary effect of fingolimod is on HR

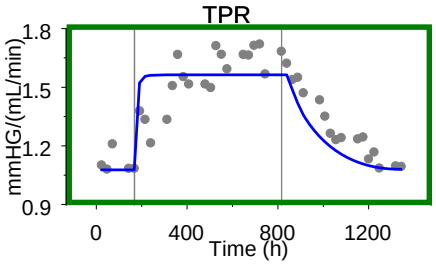
Prediction of the effect of fingolimod on the CVS

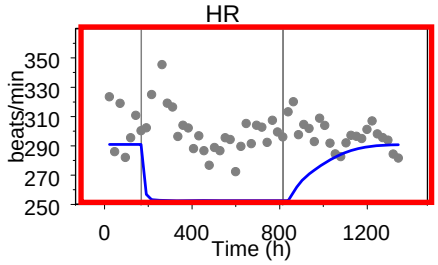
- The CVS model was used to predict the effect of fingolimod
  - System-specific parameters were fixed

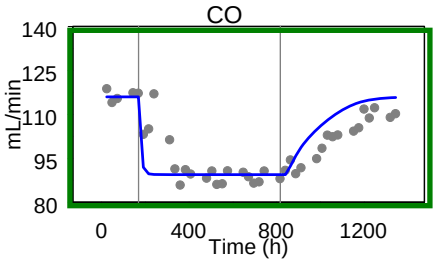


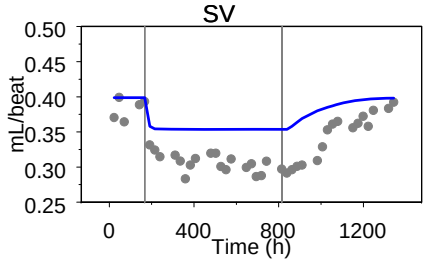
Hypothesis 2: effect is on TPR







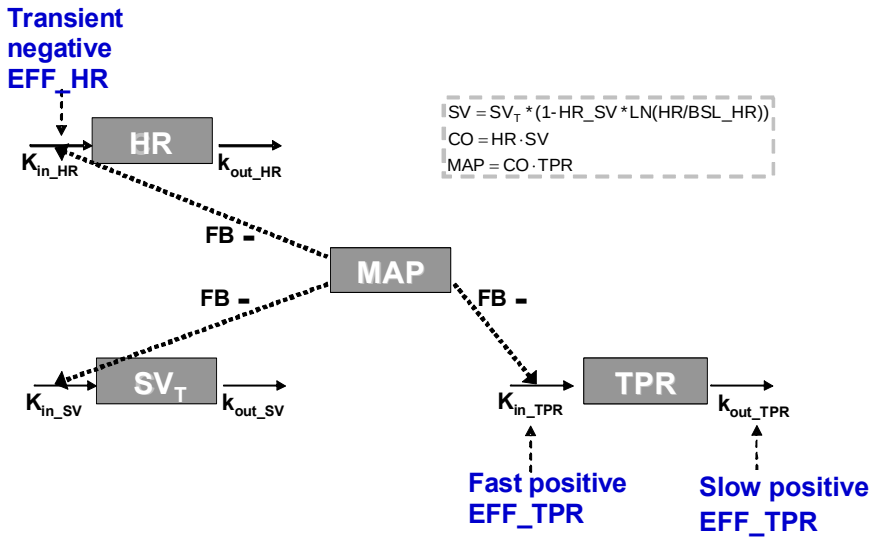




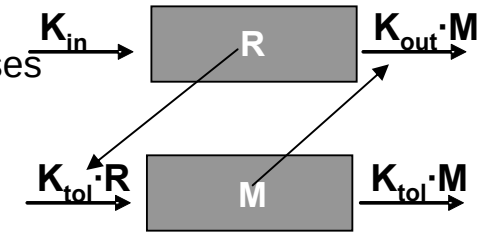
The CVS model indicates that the primary effect of fingolimod is on TPR
There may be a secondary effect on HR

Model to describe the effect of fingolimod

- PKPD modelling approach:
  - PK of the pro-drug fingolimod and its active metabolite were described simultaneously by a compartmental model



- The effect of fingolimod on the CVS was described by a combination of 3 effects:
  - Fast positive effect on TPR: log-linear model
  - Slow positive effect on TPR: linear model
    - Slow structural effect only in hypertensive rat at high doses
  - Transient negative effect on HR: power model
    - Tolerance was described by feedback model - type 1

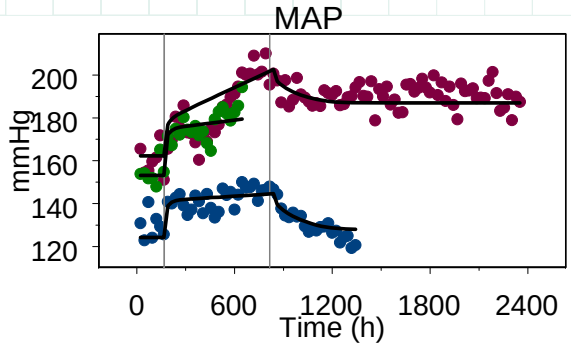


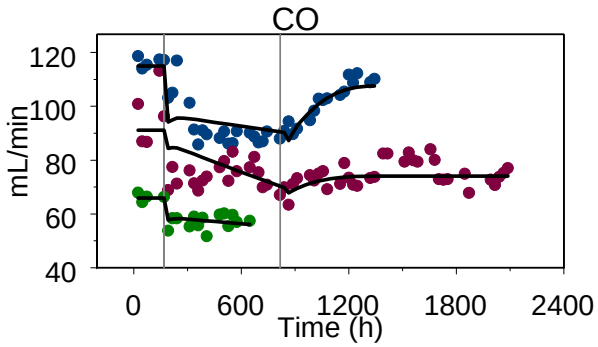
Adequate description of the effect of fingolimod on the CVS in hypertensive rat

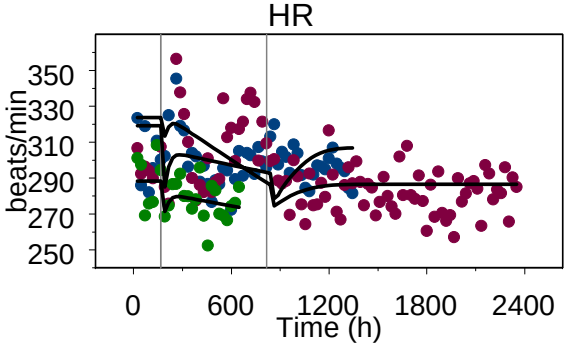
Example: Dose 10 mg/kg

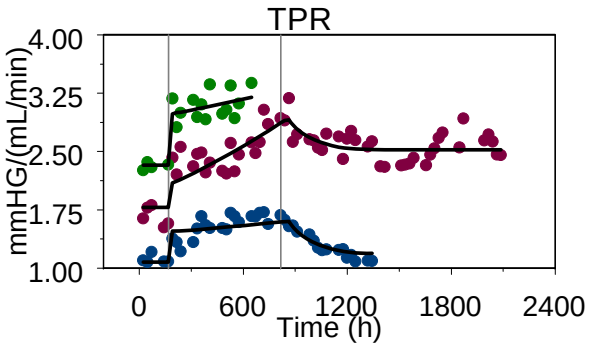
— Individual prediction

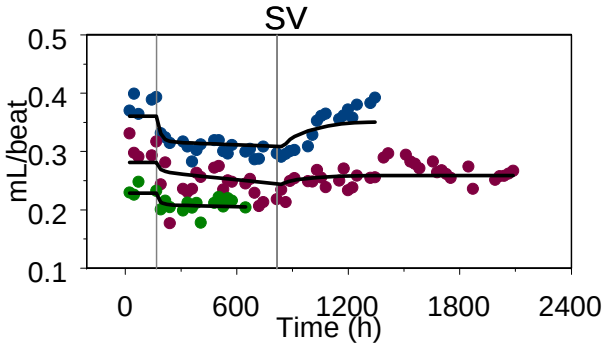
● Observations (colored per rat)









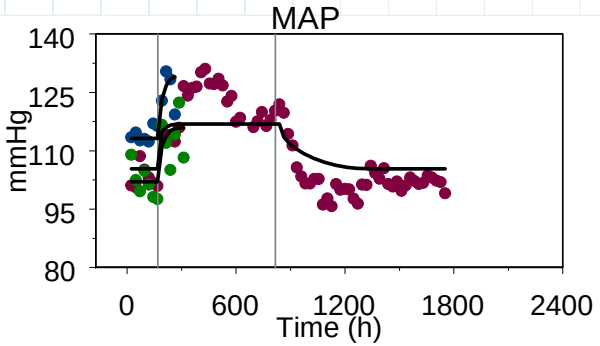


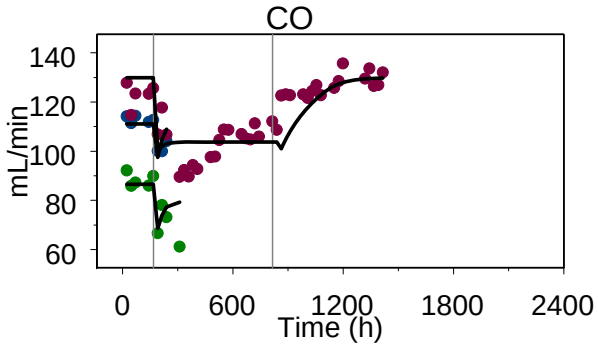
Adequate description of the effect of fingolimod on the CVS in normotensive rat

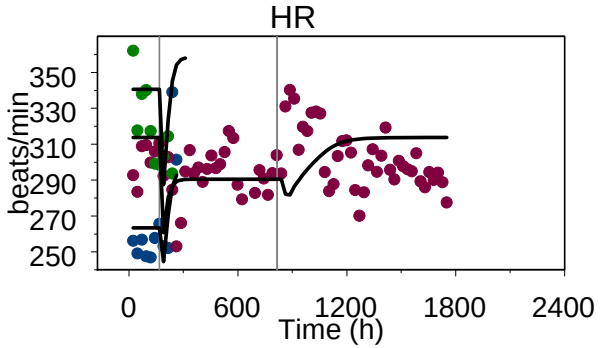
Example: Dose 10 mg/kg

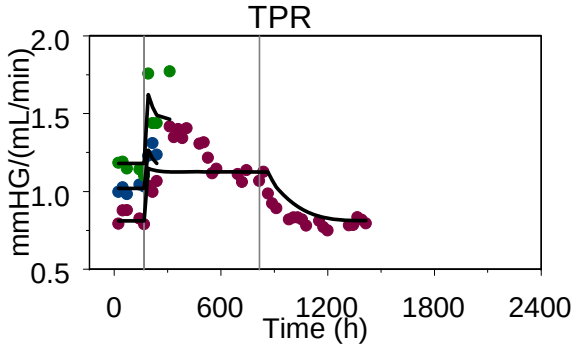
— Individual prediction

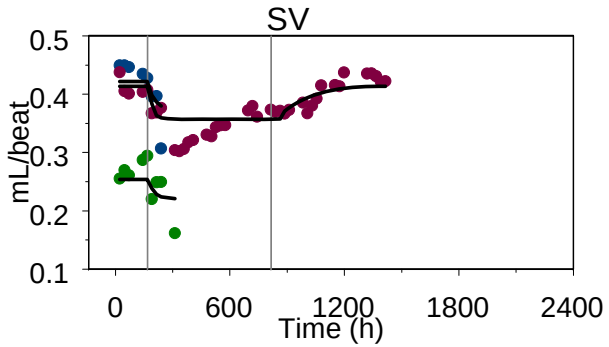
● Observations (colored per rat)











Conclusions
Effect of fingolimod on the CVS

- The effect of fingolimod on MAP, CO, HR, SV and TPR was characterized adequately using the developed CVS model

- The CVS model was used to elucidate the mechanism of action of the effect of fingolimod on the CVS
  - The long term effect of fingolimod on BP resulted from an effect on TPR
    - The primary effect was reversible
    - The secondary effect, which is relevant in hypertensive rat for extreme high doses, was structural
  - A transient effect on HR was quantified

General Conclusions and Future Perspectives

- A systems pharmacology model was developed to describe the interrelationship between MAP, CO, HR, SV and TPR in rat
- The CVS model can be used to elucidate the mechanism of action of novel compounds
- Future research: prediction of the clinical response based on preclinical data for fingolimod and other (follow-up) compounds

Acknowledgements

Novartis-Leiden collaboration

LAP&P Consultants BV

Further reading

BJP British Journal of Pharmacology

RESEARCH PAPER

PKPD modelling of the interrelationship between mean arterial BP, cardiac output and total peripheral resistance in conscious rats

N Snelder[1,2], BA Ploeger[1], O Luttringer[3], DF Rigel[4], RL Webb[5], D Feldman[4], F Fu[4], M Beil[4], L Jin[4], DR Stanski[3] and M Danhof[1,2]