Towards predictive cardiovascular safety : a systems pharmacology approach

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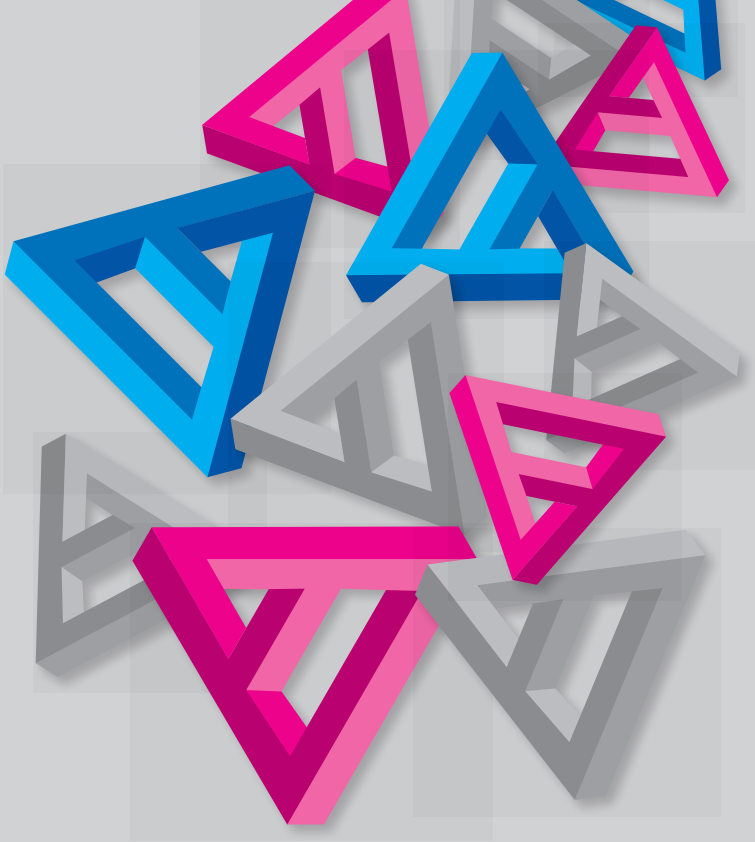

CHAPTER 2

Scope and outline of the investigations

Scope

In general, cardiovascular safety issues in drug development occur often (Sager *et al.*, 2013). In this context, an adequate understanding of the cadiovascular system (CVS) which regulates blood pressure in both preclinical species and human is pivotal to efficiently anticipate clinical effects of drugs on blood pressure in man. The development of such a translational PKPD model for the cardiovascular system requires a mechanistic understanding of blood pressure regulation (Ploeger *et al.,* 2009; Danhof *et al.*, 2007). The physiological principles of the CVS including BP regulation are well established and the homeostatic principles of the CVS are thoroughly understood. Briefly, mean arterial pressure (MAP) equals the product of cardiac output (CO) and total peripheral resistance (TPR) and CO equals the product of heart rate (HR) and stroke volume (SV) (Levick, 2003). However, drug effects on this interrelationship have not been analyzed in a mechanism-based and quantitative manner.

The objectives of the investigations described in this thesis were 1) to establish a systems pharmacology model to characterize the effects of drugs with different MoA's on the interrelationship between BP, TPR, CO, HR and SV in a quantitative manner and 2) to apply the model to the quantification of the cardiovascular effect of the sphingosine 1-phosphate (S1P) receptor modulator fingolimod on the CVS.

Outline

In **section I** an overview is presented of the analysis on drug effects on CVS (**Chapter 1**). First, the physiology of the CVS is described. Thereafter, it is discussed how the variables of the CVS can be monitored and, the assessment of drug-induced changes in BP during drug development is reviewed. Finally, the use of systems pharmacology modeling to provide a quantitative understanding of the pharmacological effects of (novel) drugs on the CVS early in preclinical development for the prediction of drug effects in humans is discussed. In **section II**, a systems pharmacology model is proposed to characterize the CVS in normotensive and hypertensive rats. As a first step a systems pharmacology model was developed that describes in a strictly quantitative manner the interrelationship between BP, CO and TPR (Snelder *et al.*, 2013). It is shown that this model can describe the pharmacological effects of cardiovascular drugs in hypertensive rats and can be can be applied to elucidate that MoA of novel compounds using MAP and CO measurements (**Chapter 3**). Subsequently, this model was extended by parsing CO into HR and SV (**Chapter 4**). This extension was deemed important as it facilitates the elucidation of the MoA of cardiovascular drug effects using MAP and HR measurements only. In other words no CO measurements are required, which is beneficial as measuring CO is invasive and technically demanding.

Moreover, differences in BP regulation between normotensive and hypertensive rats were quantified, which is important since it is anticipated that effects observed in normotensive rats may be more representative for hemodynamic side effects in normotensive persons. To develop these system pharmacology models, rigorous preclinical experiments were designed measuring, MAP, HR and CO during the on- and offset phases of the drug effects when challenging the hemodynamic system with a training set of cardiovascular drugs with well described, but different mechanisms of action.

In **Section III**, the system-specific model to characterize drug effects on the interrelationship between MAP, CO, HR, SV and TPR (**Chapter 4**) was applied to characterize the cardiovascular effects of S1P receptor agonists (Kappos *et al.*, 2006; Kappos *et al.*, 2010; Selmaj *et al.*, 2013; Gergely *et al.,* 2012) using fingolimod as a paradigm compound, as a basis for the prediction of its effects in humans. Fingolimod exerts its pharmacological effect through its active metabolite fingolimod-phosphate (fingolimod-P), which is formed by the enzyme sphingosine kinase (S1PHK) (Billich *et al.*, 2003; Kihara and Igarashi, 2008; Kharel *et al.*, 2005). First, a semi-mechanistic population PK model for the inter-conversion of S1PHK substrates and their respective phosphates in rats and humans was presented. Specific aim of this study was to investigate whether the rate of phosphorylation in blood platelets constitutes a basis for interspecies scaling using fingolimod as a paradigm compound (**Chapter 5**). In this model, differences in the rate of phosphorylation in blood, estimated from *ex vivo* inter-conversion measurements in platelets, partly explain the differences in exposure between rats and humans. It is demonstrated that in addition, differences in pre-systemic phosphorylation should also be taken into account. Subsequently, the in **Chapter 4** developed systems pharmacology model and the in **Chapter 5** developed PK model for fingolimod and fingolimod-P in rat was applied to obtain a quantitative understanding of the mechanisms leading to cardiovascular effects following the administration of fingolimod in normotensive and hypertensive rats (**Chapter 6**). To this end, the systems pharmacology model (**Chapter 4**) was integrated with expressions to describe S1P receptor binding kinetics, internalization and sensitization. This enabled the application of the model to the prediction of the effect of siponimod, a S1P receptor agonist with different receptor subtype selectivity, on MAP and HR in rat.

In **Section IV**, the next steps towards characterization and prediction of cardiovascular drug effects in human are discussed (**Chapter 7**). In this chapter, the results of the presented

research are summarized. In addition, the future perspectives are presented. An ultimate application of the developed systems pharmacology model would be the anticipation of the clinical response based on preclinical data for newly developed compounds and, more specifically, for S1P receptor agonists, i.e. follow-up compounds of fingolimod. First, the translation of the systems pharmacology model is discussed. Thereafter, the translation of the effect of S1P receptor agonists is addressed.

References

Billich A, Bornancin F, Devay P, Mechtcheriakova D, Urtz N, Baumruker T (2003). Phosphorylation of the immunomodulatory drug FTY720 by sphingosine kinases. J Biol Chem., 278, 47408-47415.

Danhof M, de Jongh J, De Lange EC, Della Pasqua O, Ploeger BA, Voskuyl RA (2007). Mechanism-based pharmacokinetic-pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. Annu Rev Pharmacol Toxicol., 47, 357-400.

Gergely P, Nuesslein-Hildesheim B, Guerini D, Brinkmann V, Traebert M, Bruns C, et al. (2012). The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. Br J Pharmacol., 167, 1035-1047.

Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, *et al*. (2006). Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med., 355, 1124-1140.

Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, *et al*. (2010). A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med., 362, 387-401.

Kharel Y, Lee S, Snyder AH, Sheasley-O'neill S L, Morris MA, Setiady Y, *et al*. (2005). Sphingosine kinase 2 is required for modulation of lymphocyte traffic by FTY720. J Biol Chem., 280, 36865-36872.

Kihara A, Igarashi Y (2008). Production and release of sphingosine 1-phosphate and the phosphorylated form of the immunomodulator FTY720. Biochim Biophys Acta., 1781, 496-502.

Levick JR (2003). An introduction to cardiovascular physiology.

Ploeger BA, van der Graaf PH, Danhof M (2009). Incorporating receptor theory in mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling. Drug Metab Pharmacokinet., 24, 3-15.

Sager P, Heilbraun J, Turner JR, Gintant G, Geiger MJ, Kowey PR, *et al*. (2013). Assessment of drug-induced increases in blood pressure during drug development: report from the Cardiac Safety Research Consortium. Am Heart J., 165, 477-488.

Selmaj K, Li DK, Hartung HP, Hemmer B, Kappos L, Freedman MS, *et al*. (2013). Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. Lancet Neurol., 12, 756-767.

Snelder N, Ploeger BA, Luttringer O, Rigel DF, Webb RL, Feldman D, *et al*. (2013). PKPD modeling of the interrelationship between mean arterial blood pressure, cardiac output and total peripheral resistance in conscious rats. Br J Pharmacol, 169, 1510-1524.