



Universiteit
Leiden
The Netherlands

Towards predictive cardiovascular safety : a systems pharmacology approach

Snelder, N.

Citation

Snelder, N. (2014, June 25). *Towards predictive cardiovascular safety : a systems pharmacology approach*. Retrieved from <https://hdl.handle.net/1887/26945>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/26945>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/26945> holds various files of this Leiden University dissertation

Author: Snelder, Nelleke

Title: Towards predictive cardiovascular safety : a systems pharmacology approach

Issue Date: 2014-06-25

Towards predictive cardiovascular safety - a systems pharmacology approach

Nelleke Snelder

The publication of this thesis was financially supported by LAP&P Consultants BV, Leiden,
The Netherlands

Lay-out and printing by Ridderprint BV, Ridderkerk

© 2014. Copyright by N. Snelder

**Towards predictive cardiovascular safety -
a systems pharmacology approach**

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 25 juni 2014
klokke 12.30 uur

door

Nelleke Snelder

geboren te Rotterdam
in 1980

Promotiecommissie

Promotoren:

Prof. Dr. M. Danhof

Prof. Dr. D.R. Stanski

Co-Promotor:

Dr. B.A. Ploeger

Overige leden:

Prof. Dr. A.H.J. Danser, Erasmus Universiteit Rotterdam

Prof. Dr. P.H. van der Graaf

Prof. Dr. J. Burggraaf

Prof. Dr. T. Hankemeier

Prof. Dr. B. van de Water

... The End is in the Beginning, and now we go on ...
A. van der Veen according to S. Becket

Table of contents

Section I General introduction

- | | | |
|----|--|----|
| 1. | A systems pharmacology approach for predicting drug-induced changes in hemodynamic variables | 11 |
| 2. | Scope and outline of the investigations | 31 |

Section II Development of a systems pharmacology model to characterize drug effects on the CVS

- | | | |
|----|---|----|
| 3. | PKPD modeling of the interrelationship between mean arterial blood pressure, cardiac output and total peripheral resistance in conscious rats | 39 |
| 4. | Drug effects on the cardiovascular system in conscious rats – separating cardiac output into heart rate and stroke volume using PKPD modeling | 69 |

Section III Application of the developed systems pharmacology model to S1P receptor agonists

- | | | |
|----|--|-----|
| 5. | Translational pharmacokinetic modeling of fingolimod as a paradigm compound subject to sphingosine kinase-mediated phosphorylation | 105 |
| 6. | Characterization and prediction of cardiovascular effects of fingolimod and siponimod using a systems pharmacology modeling approach | 131 |

Section IV Summary, conclusions & perspectives

- | | | |
|----|---|-----|
| 7. | A systems pharmacology approach to the prediction of cardiovascular side effects in man - Summary, conclusions & perspectives | 169 |
| | Samenvatting in het Nederlands | 193 |
| | Nawoord | 205 |
| | List of Publications | 207 |
| | Curriculum Vitae | 208 |

