



Universiteit
Leiden
The Netherlands

Quantitative systems pharmacology modeling of biotherapeutics in oncology

Betts, A.M.

Citation

Betts, A. M. (2021, June 3). *Quantitative systems pharmacology modeling of biotherapeutics in oncology*. Retrieved from <https://hdl.handle.net/1887/3176516>

Version: 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/1887/3176516>

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

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/3176516> holds various files of this Leiden University dissertation.

Author: Betts, A.M.

Title: Quantitative systems pharmacology modeling of biotherapeutics in oncology

Issue date: 2021-06-03

Quantitative systems pharmacology modeling of biotherapeutics in oncology

Alison M. Betts

Cover design: Edgar Stewart Design & Illustration, Concord MA 01742

Printing: Alpha Graphics, Concord MA, U.S.A

© Copyright, Alison Mary Betts, 2021.

ISBN: 978-0-578-89120-0

All rights reserved. No part of this thesis may be reproduced in any form or by any means without permission of the author

Quantitative systems pharmacology modeling of biotherapeutics in oncology

Proefschrift

Ter verkrijging van de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. dr. ir. H. Bijl,
volgens besluit van het College voor Promoties
te verdedigen op 3 juni 2021
klokke 15:00 uur

Door

Alison Mary Betts
Geboren te Edinburgh, Scotland
Op 4 juli 1972

Promotores:

Prof. dr. P.H. van der Graaf

Prof. dr. J. Burggraaf

Promotiecommissie:

Prof. dr. H. Irth, voorzitter

Prof. dr. J.A. Bouwstra, secretaris

Prof. dr. C. Kloft, University of Berlin

Prof. dr. J.P. Balthasar, University at Buffalo, The State University of New York

Prof. dr. A.D.R. Huitema, Netherlands Cancer Institute

Dr. J.G.C. van Hasselt

The research described in this thesis was performed at Pfizer Worldwide Research & Development, Groton CT, and Cambridge MA, USA.
Publication of this thesis was financially supported by Pfizer, Inc. and Applied BioMath, LLC, Concord MA 01742.

Table of contents

SECTION I	INTRODUCTION TO TRANSLATIONAL MODELING IN ONCOLOGY	
Chapter 1	Thesis introduction and scope	7
SECTION II	MODELING OF MONOCLONAL ANTIBODIES	
Chapter 2	Linear pharmacokinetic parameters for monoclonal antibodies are similar within a species and across different pharmacological targets: A comparison between human, cynomolgus monkey and hFcRn Tg32 transgenic mouse using a population-modeling approach	15
SECTION III	MODELING OF ANTIBODY DRUG CONJUGATES	
Chapter 3	Establishing in vitro–in vivo correlation for antibody drug conjugate efficacy: a PK/PD modeling approach	46
Chapter 4	Use of translational modeling and simulation for quantitative comparison of PF-06804103, a new generation HER2 ADC, with Trastuzumab-DM1	71
Chapter 5	Preclinical to Clinical Translation of Antibody-Drug Conjugates Using PK/PD Modeling: A Retrospective Analysis of Inotuzumab Ozogamicin	98
SECTION IV	MODELING OF BISPECIFIC ANTIBODIES	
Chapter 6	A Translational Quantitative Systems Pharmacology Model for CD3 Bispecific Molecules: Application to Quantify T Cell-Mediated Tumor Cell Killing by P-Cadherin LP DART®	125
Chapter 7	Mechanistic quantitative pharmacology strategies for the early clinical development of bispecific antibodies in oncology	158
SECTION V	SUMMARY, DISCUSSION, AND CONCLUSION	
Chapter 8	Summary, discussion, and conclusion	186
Chapter 9	Nederlandse samenvatting	197
SECTION VI	APPENDICES	
	Curriculum vitae and list of publications	211
	Affiliations of authors	216
	Acknowledgements	218