



Universiteit  
Leiden  
The Netherlands

## Pharmacogenetics of advanced colorectal cancer treatment

Pander, J.

### Citation

Pander, J. (2011, June 29). *Pharmacogenetics of advanced colorectal cancer treatment*. Retrieved from <https://hdl.handle.net/1887/17746>

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/1887/17746>

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

# **Pharmacogenetics of advanced colorectal cancer treatment**

Jan Pander

# Pharmacogenetics of advanced colorectal cancer treatment

## Proefschrift

ter verkrijging van

de graad van Doctor aan de Universiteit Leiden,  
op gezag van Rector Magnificus prof. mr. P.F. van der Heijden,  
volgens besluit van het College voor Promoties  
te verdedigen op woensdag 29 juni 2011  
klokke 15:00 uur

door

**Jan Pander**

geboren te Amsterdam  
in 1979

The research presented in this thesis was performed at the Department of Clinical Pharmacy & Toxicology of the Leiden University Medical Center, The Netherlands

The printing of this thesis was financially supported by AZL Onderzoeks- en Ontwikkelingskrediet (OOK) Apotheek

Cover design and lay-out by In Zicht Grafisch Ontwerp, Arnhem  
Printed by Ipskamp drukkers, Enschede

ISBN 978-90-90261126

© Jan Pander

All rights reserved. No parts of this thesis may be reproduced, stored in a retrieval system of any nature, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the publisher.

**Promotores**

Prof. Dr. H.-J. Guchelaar

Prof. Dr. A.J. Gelderblom

Prof. Dr. C.J.A. Punt, Radboud Universiteit Nijmegen

**Overige leden**

Prof. Dr. J.J. Houwing

Prof. Dr. G.J.B. van Ommen

Prof. Dr. J.H. Beijnen, Universiteit Utrecht

Prof. Dr. J.A. Gietema, Rijksuniversiteit Groningen

“For the first time I felt the truth that the sky begins a quarter of an inch from the ground. In the mornings the bush smelled like the best underarm deodorant you ever smelled, and I quickly got used to the mysterious movements of the trees, which heaved rhythmically like a man chloroformed. From time to time the night sky seemed uneven, closer in points, then smoothed out, like a tablecloth bunched up then suddenly pulled taut. I'd wake up to see low-lying clouds balanced precariously on the tops of trees. Sometimes the wind was so gentle it seemed to come from a child's nostril, while other times it was so strong all the trees seemed held tenuously to the earth by roots as weak as doubled-over sticky tape.”

*From: A fraction of the whole. Steve Toltz*

## Contents

<b>Chapter 1</b>	Outline of the thesis	9
	<b>Cetuximab</b>	
<b>Chapter 2</b>	Pharmacogenetics of EGFR and VEGF inhibition <i>Drug Discovery Today 2007 Dec;12(23-24):1054-60</i>	19
<b>Chapter 3</b>	Correlation between germline polymorphisms and the efficacy of cetuximab in metastatic colorectal cancer <i>Adapted from: European Journal of Cancer 2010 Jul;46(10):1829-34</i>	37
<b>Chapter 4</b>	Activation of tumor-promoting type 2 macrophages by the EGFR-targeting antibody cetuximab <i>submitted</i>	57
	<b>Capecitabine, oxaliplatin and bevacizumab</b>	
<b>Chapter 5</b>	Insights into the role of heritable genetic variation in the pharmacokinetics and pharmacodynamics of anticancer drugs <i>Expert Opinion on Pharmacotherapy 2007 Jun;8(9):1197-210</i>	73
<b>Chapter 6</b>	Regarding: 'Explorative study to identify novel candidate genes related to oxaliplatin efficacy and toxicity using a DNA repair array' <i>British Journal of Cancer 2010 Jun 8;102(12):1791-2</i>	99
<b>Chapter 7</b>	Pharmacogenetics of tomorrow: the 1 + 1 = 3 principle <i>Pharmacogenomics 2010 Jul;11(7):1011-7</i>	105
<b>Chapter 8</b>	Pharmacogenetic interaction analysis for the efficacy of systemic treatment in metastatic colorectal cancer <i>Annals of Oncology 2010 doi:10.1093/annonc/mdq572</i>	119
<b>Chapter 9</b>	Genome-wide association study of the efficacy of capecitabine, oxaliplatin and bevacizumab in metastatic colorectal cancer	135
	<b>General discussion and summary</b>	
<b>Chapter 10</b>	General discussion	149
	Summary	167
	Nederlandse samenvatting	173
	Dankwoord	179
	List of publications	181
	Curriculum vitae	183