



Universiteit
Leiden
The Netherlands

Systems pharmacology of the amyloid cascade : unfolding oligomer modulation in Alzheimer's disease

Maanen, E.M.T. van

Citation

Maanen, E. M. T. van. (2017, November 23). *Systems pharmacology of the amyloid cascade : unfolding oligomer modulation in Alzheimer's disease*. Retrieved from <https://hdl.handle.net/1887/55514>

Version: Not Applicable (or Unknown)

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

Downloaded from: <https://hdl.handle.net/1887/55514>

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

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/55514> holds various files of this Leiden University dissertation.

Author: Maanen, E.M.T. van

Title: Systems pharmacology of the amyloid cascade : unfolding oligomer modulation in Alzheimer's disease

Issue Date: 2017-11-23

Systems pharmacology of the amyloid cascade

Unfolding oligomer modulation in Alzheimer's disease

Eline M.T. van Maanen

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

Cover design by Esther Scheide, www.proefschriftomslag.nl
Layout by Eline M.T. van Maanen
Printed by Ridderprint BV, www.ridderprint.nl

ISBN 978-94-6299-766-0

©2017 E.M.T. van Maanen, Oegstgeest, The Netherlands.
No part of this thesis may be reproduced or transmitted in any form or by any means
without prior written permission of the author.

Systems pharmacology of the amyloid cascade

Unfolding oligomer modulation in Alzheimer's disease

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 donderdag 23 november 2017
klokke 15.00 uur

door

Eline M.T. van Maanen

geboren te Hoogezand-Sappemeer
in 1978

Promotor:

Prof.Dr. M. Danhof

Co-Promotores:

Dr. T.J. van Steeg

Dr. J.A. Stone, Merck&Co., Inc.

Promotiecommissie:

Prof.Dr. H. Irth, *voorzitter*

Prof.Dr. J.A. Bouwstra, *secretaris*

Prof.Dr. P. Scheltens, VUmc Amsterdam

Prof.Dr. T. Hankemeier

Prof.Dr. J.M.A. van Gerven

Prof.Dr. M.H.M. Noteborn

Dr. E.C.M. de Lange

*Doof uw inspiratie en verbeeldingskracht niet uit, wordt
geen slaaf van 't model.*

*Don't snuff out your inspiration and power of imagination, don't become a slave to the
model.*

Vincent van Gogh

Letter to Theo van Gogh, November 1882

Dutch post-impressionist painter

1853-1890

TABLE OF CONTENTS

Section I Systems pharmacology of the amyloid cascade - General introduction	5
1 Systems pharmacology of the amyloid cascade - Scope and outline of investigations	7
2 Systems pharmacology approach to the modulation of oligomers in protein misfolding neurodegenerative disorders	17
Section II Development of a systems pharmacology model to predict oligomer response following secretase inhibition	39
3 Systems pharmacology analysis of the amyloid cascade following β -secretase inhibition enables the identification of an A β 42 oligomer pool	41
<i>Supplemental material</i>	71
4 Integrating tracer kinetic data in a systems pharmacology model of the amyloid precursor pathway: effect of a β -secretase inhibitor	79
<i>Supplemental material</i>	111
5 Extending a systems model of the APP pathway: Separation of β - and γ -secretase sequential cleavage steps of APP	125
<i>Supplemental material</i>	155
Section III Application of a systems pharmacology model to characterize oligomer modulation following secretase inhibition	165
6 Systems pharmacology analysis of the A β oligomer response following β -secretase inhibition: Evidence for second-order A β 42 oligomerization	167
<i>Supplemental material</i>	195
7 A single systems pharmacology approach to unravel A β oligomer modulation upon administration of multiple APP cleavage inhibitors	201
<i>Supplemental material</i>	229
Section IV Systems pharmacology of the amyloid cascade Summary, Conclusions & Perspectives	235
8 Systems pharmacology of the amyloid precursor protein pathway in Alzheimer's disease – Conclusions & perspectives	237
<i>Supplemental material</i>	265
Synopsis in Dutch (Samenvatting in het Nederlands)	275
Nawoord	283
List of Publications	285
Curriculum Vitae	286
Abbreviations	289