



Universiteit
Leiden
The Netherlands

Developing genetic therapies for polyglutamine disorders

Evers, M.M.

Citation

Evers, M. M. (2015, January 7). *Developing genetic therapies for polyglutamine disorders*. Retrieved from <https://hdl.handle.net/1887/30254>

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/1887/30254>

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

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/30254> holds various files of this Leiden University dissertation.

Author: Evers, Melvin Maurice

Title: Developing genetic therapies for polyglutamine disorders

Issue Date: 2015-01-07

DEVELOPING GENETIC THERAPIES FOR POLYGLUTAMINE DISORDERS

MELVIN EVERS

Cover design: M.J.J. Langewouters || Fruto internet, concepts & design

Layout: M.M. Evers

Printed by: Proefschriftmaken.nl || Uitgeverij BOXPress

Published by: Uitgeverij BOXPress, 's-Hertogenbosch

ISBN: 978-90-8891-992-3

© Copyright 2015 by Melvin Maurice Evers. All rights reserved. Copyright of the individual chapters rests with the authors, with the following exceptions:

Chapter 1: Frontiers Media SA

InTech

Springer US

Chapter 3: Public Library of Science

Chapter 4: Mary Ann Liebert, Inc.

Chapter 5: Elsevier

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without prior permission of the author.

Printing of this thesis was financially supported by:

Vereniging van Huntington

Prosensa Therapeutics B.V.

DEVELOPING GENETIC THERAPIES FOR POLYGLUTAMINE DISORDERS

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 7 januari 2015
klokke 16.15 uur

door

Melvin Maurice Evers

geboren te Rhenen
in 1982

Promotiecommissie

Promotor:

Prof. dr. G.J.B. van Ommen

Co-promotor:

Dr. W.M.C. van Roon-Mom

Overige leden:

Prof. dr. R.A.C. Roos

Prof. dr. Y. Temel (Maastricht UMC+)

Dr. J.C. Dorsman (VU Medisch Centrum, Amsterdam)

*Promovendi hebben lange en zware dagen omdat er meer mis dan goed gaat in het onderzoek,
maar aan het einde van de dag gaan ze naar huis om andere dingen te doen.
Patiënten met polyglutamine aandoeningen kunnen nooit een pauze nemen.*

Table of Contents

Chapter 1	General introduction: Genetic therapies for polyglutamine disorders	8
1.1.	Introduction	10
1.2.	Triplet repeat expansion disorders	11
1.3.	Huntington disease	15
1.4.	Spinocerebellar ataxia type 3	22
1.5.	Clinical and molecular genetics of other polyQ disorders	30
1.6.	Protein lowering approaches for polyQ disorders	34
1.7.	Antisense oligonucleotides in therapy for other neurodegenerative diseases	41
1.8.	Drug delivery to the brain, how to cross the blood brain barrier?	45
1.9.	Scope and outline of the thesis	49
<i>Frontiers in Molecular Neuroscience 2011, 4:10</i>		
<i>Huntington's Disease - Core Concepts and Current Advances 2012, InTech</i>		
<i>Molecular Neurobiology 2014, 49(3):1513-1531</i>		
Chapter 2	Making (anti-) sense out of huntingtin levels in Huntington disease	50
	<i>Under review</i>	
Chapter 3	Targeting several CAG expansion diseases by a single antisense oligonucleotide	72
	<i>PLoS One 2011, 6(9):e24308</i>	
Chapter 4	Preventing formation of toxic N-terminal huntingtin fragments through antisense oligonucleotide-mediated protein modification	94
	<i>Nucleic Acid Therapeutics 2014, 24(1):4-12</i>	
Chapter 5	Ataxin-3 protein modification as a treatment strategy for spinocerebellar ataxia type 3: Removal of the CAG containing exon	112
	<i>Neurobiology of Disease 2013, 58:49-56</i>	
Chapter 6	General discussion & future perspective	130
Chapter 7	References	142
Appendix		
	Summary	174
	Samenvatting	176
	List of abbreviations	178
	List of publications	181
	Curriculum Vitae	182
	Dankwoord	183