Table of contents

Chapter 1  General Introduction 8
  Vanishing White Matter 11
  Genetic background of VWM and the effect on protein translation 12
  Cells of the brain white matter are affected by VWM mutations 14
  Stem cell therapy 16
  Induced pluripotent stem cells 16
  Generation of patient-derived glial cells 17
  Stem cell-based therapy 18
  Outline 20

Chapter 2  Astrocytes are central in pathomechanisms of Vanishing White Matter 28

Chapter 3  New stem cell models reveal astrocyte subtype vulnerability in leukodystrophy 78

Chapter 4  Bergmann glia translocation: a new disease marker for Vanishing White Matter identifies therapeutic effects of Guanabenz treatment 106

Chapter 5  Cell replacement therapy improves pathological hallmarks in a mouse model of leukodystrophy Vanishing White Matter 136

Chapter 6  Modulation of hyaluronan levels in Vanishing White Matter mice 160

Chapter 7  Stem cell therapy for white matter disorders: don’t forget the microenvironment! 178

Chapter 8  Summary and Discussion 188
  Summary 190
  New models to study VWM 193
  In vivo models to study VWM disease pathomechanisms 193
  Studying human specific disease processes with iPSCs 194
  The future of disease modelling 195
  Treatment options for VWM 196
 Treating VWM with compounds 197
  The prospects of glial cell replacement therapy 198
  Finding the optimal combination to treat VWM patients 200
  Concluding remarks 201
Appendix

Nederlandse samenvatting 212
List of abbreviations 215
List of publications 218
Curriculum Vitae 219
Dankwoord 220