BIOGRAPHICAL SKETCH (EXTENDED VERSION)

NAME: Van Blitterswijk, Marka M.

eRA COMMONS USER NAME: MVANBLITTERSWIJK

EMAIL: VanBlitterswijk.Marka@mayo.edu

POSITION TITLE: Assistant Professor of Neuroscience

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University Medical Center Utrecht, the Netherlands	Propedeuse (1st year)	2002-2003	Medicine
University Medical Center Utrecht, the Netherlands	M.D.	2003-2008	Medicine
Harvard Medical School and UMASS, MA, USA	Fulbright/VSB Fellow	2008-2009	Neuroscience
University of Utrecht, the Netherlands	Ph.D.	2009-2012	Neuroscience
Mayo Clinic Jacksonville, FL, USA	Postdoctoral Research Fellow	2012-2013	Neuroscience
University of Washington, Seattle, WA, USA	C++ Certificate	2015	Computer Science
University of Washington, Seattle, WA, USA	R Certificate	2016	Computer Science
Rare Diseases Clinical Research Network (RDCRN), Washington, DC, USA	Rare Diseases Certificate	2016	Medicine

A. Personal Statement

My research focuses on the genetics of amyotrophic lateral sclerosis (ALS). ALS, also known as Lou Gehrig's disease, is a devastating neurodegenerative disease that impairs both the upper and the lower motor neurons. A hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*) is the most common genetic cause of ALS identified thus far. Importantly, repeat expansions in *C9ORF72* are not only associated with ALS, but they are also a frequent genetic cause of frontotemporal dementia (FTD), and a rare cause of other diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). As an Assistant Professor of Neuroscience, I supervise a team of scientists working on the genetics of ALS at Mayo Clinic (Jacksonville, FL, USA), concentrating on the identification of novel ALS genes, genetic modifiers, and biomarkers. I have already published more than 50 articles in the field of neuroscience, including studies providing evidence for an oligogenic basis of ALS, characterizing *C9ORF72* expansion sizes, identifying transmembrane protein 106 B (*TMEM106B*) as the first genetic modifier in *C9ORF72* expansion carriers, and finding novel associations with specific *C9ORF72* transcript variants and RNA foci burden.

1. **Van Blitterswijk M.**, *et al.* (2012). Evidence for an oligogenic basis of amyotrophic lateral sclerosis. Human Molecular Genetics, 21(17), 3776-3784. PMID:22645277. DOI:10.1093/hmg/dds199.
2. **Van Blitterswijk M.**, *et al.* (2013). Association between repeat sizes and clinical and pathological characteristics in carriers of *C9ORF72* repeat expansions (Xpansize-72): a cross-sectional cohort study. Lancet Neurology, 12(10), 978-988. PMID:24011653. PMCID:3879782. DOI:10.1016/S1474-4422(13)70210-2.
3. **Van Blitterswijk M.**, *et al.* (2014). *TMEM106B* protects *C9ORF72* expansion carriers against frontotemporal dementia. Acta Neuropathologica, 127(3), 397-406. PMID:24385136. PMCID:3944829. DOI:10.1007/s00401-013-1240-4.
4. **Van Blitterswijk M.**, *et al.* (2015). Novel clinical associations with specific *C9ORF72* transcripts in patients with repeat expansions in *C9ORF72*. Acta Neuropathologica, 130(6), 863-876. PMID:26437865. DOI:10.1007/s00401-015-1480-6.
5. DeJesus-Hernandez M., *et al.* (2017). In-depth clinico-pathological examination of RNA foci in a large cohort of *C9ORF72* expansion carriers. Acta Neuropathologica. PMID:28508101. DOI:10.1007/s00401-017-1725-7 (in press; **last author**).

B. Positions and Honors

Positions and Employment

2013 – 2014 Instructor in Neuroscience, College of Medicine, Mayo Clinic, Jacksonville, FL
2014 – Assistant Professor of Neuroscience, College of Medicine, Mayo Clinic, Jacksonville, FL
2015 – Associate Consultant, Department of Neuroscience, Mayo Clinic, Jacksonville, FL

Other Experience and Professional Memberships

Professional Memberships & Services

2013 – Founding Member, International Society for Frontotemporal Dementias
2014 – Member, American Academy of Neurology
2015 – Member, American Statistical Association

Journal Review

2014 – *Ad Hoc* Reviewer, *Acta Neuropathologica*
2014 – *Ad Hoc* Reviewer, *Brain*
2015 – *Ad Hoc* Reviewer, *PLoS One*
2015 – *Ad Hoc* Reviewer, *Molecular Neurodegeneration*
2016 – *Ad Hoc* Reviewer, *Nature Communications*
2016 – *Ad Hoc* Reviewer, *Alzheimer's & Dementia*
2016 – *Ad Hoc* Reviewer, *Neurology Genetics*

Other Activities

2015 – External Referee, Motor Neurone Disease (MND) Association, which funds and promotes global research into MND and provides support to people in England, Wales, and Northern Ireland
2015 – External Referee, Health Research Board (HRB), which is the lead agency in Ireland supporting health research
2015 – Scientist Panel Reviewer, Congressionally Directed Medical Research Programs (CDMRP), which aims to transform healthcare through innovative and impactful research
2016 – Internal Referee, Mayo Clinic Alzheimer's disease Research Center (ADRC), which promotes research and education about Alzheimer's disease and related dementia disorders
2016 – International Scientific Committee Member, Italian Association for ALS (ariSLA), which supports scientific research with the ultimate goal to defeat ALS
2016 – Scientist Reviewer, Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Biomarker Project, which promotes the discovery and/or validation of biomarkers that are relevant to development of therapies for patients with ALS
2017 – Peer Reviewer, Medical Research Council (MRC), which works to improve the health of people in the United Kingdom - and around the world - by supporting excellent science, and training the very best scientists

Ongoing Education

2016 – The Johns Hopkins MS in Bioinformatics program, which immerses students in the topics and applied methods of computational modeling, molecular biology, systems biology, structural biology, proteomics, genomic sequencing and genomic analysis, microarrays and microarray analysis. Courses: Introduction to Programming using Java, Data Structures, Introduction to Bioinformatics, Epigenetics, Gene Organization and Expression, and Human Molecular Genetics

Recent Lectures

2013 24th International Symposium on ALS/MND, "Extensive Southern blot study of *C9ORF72* expansion carriers", Milan, Italy
2014 Milton Safenowitz Post-Doctoral Fellowship Workshop, "Genetic disease modifiers in carriers of *C9ORF72* repeat expansions", New York, NY, USA
2014 25th International Symposium on ALS/MND, "Genetic disease modifiers in individuals with *C9ORF72* repeat expansions", Brussels, Belgium
2015 67th Annual Meeting American Academy of Neurology, Advances in ALS and Other Motor Neuron Diseases Integrated Neuroscience Session, "Transthyretin as potential biomarker for *C9ORF72*-related diseases", Washington, DC, USA
2015 67th Annual Meeting American Academy of Neurology, Session S33: Aging, Dementia, Cognitive, and Behavioral Neurology: Biomarkers and Pathology Platform Blitz, "Transthyretin as potential biomarker for *C9ORF72*-related diseases", Washington, DC, USA

2015 5th Annual Educational and Scientific Symposium, The ALS Association Greater Chicago Chapter, Scientific Session, "Genetic modifiers in patients with repeat expansions in *C9ORF72*", Chicago, IL, USA
2015 5th Annual Educational and Scientific Symposium, The ALS Association Greater Chicago Chapter, Patient Session, "What do we know about *C9ORF72*?", Chicago, IL, USA
2015 Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium, Online Webinar, "Characterization of transthyretin as biomarker for ALS and related disorders due to repeat expansions in *C9ORF72*", Jacksonville, FL, USA
2015 King's College London, "Novel clinical and pathological associations in *C9ORF72* expansion carriers", London, UK
2015 26th International Symposium on ALS/MND, "Characterization of *C9ORF72* expression in pathological cohort uncovers new clinical associations with specific *C9ORF72* transcripts", Orlando, FL, USA
2016 2nd Annual CReATe Meeting, "CReATe Fellow Presentation: characterization of transthyretin as biomarker for ALS and related disorders due to repeat expansions in *C9ORF72*", Miami, FL, USA
2016 Rare Diseases Clinical Research Network (RDCRN) Steering Committee Meeting, "Transthyretin as potential biomarker for diseases linked to a *C9ORF72* repeat expansion", North Bethesda, MD, USA
2016 Milton Safenowitz Post-Doctoral Fellowship Workshop, "Predicting the phenotype in *C9ORF72* expansion carriers using machine learning", New York, NY, USA (chair session)
2016 SURF Seminar, "Genetic modifiers and biomarkers for ALS and related disorders", Jacksonville, FL, USA
2016 Neuroscience Seminar Series, "Discovery and translational implications of novel ALS genes, disease modifiers, and biomarkers using innovative genetic approaches", Jacksonville, FL, USA
2016 Conference on Clinical Research for Rare Diseases (CCRRD), breakout session, "Career development and mentoring", Washington, DC, USA (discussion leader)
2016 27th International Symposium on ALS/MND, "Changes in expression levels of homeobox genes and transthyretin in patients with *C9ORF72* repeat expansions", Dublin, Ireland
2017 3rd Annual CReATe Meeting, "TTR & C9ORF72", Miami, FL, USA

Honors

2008 Erasmus Grant (European Union), which allows exchange of students between universities
2008 Fulbright Student Program (Fulbright Foundation, the Netherlands), which offers competitive, merit-based grants for foreign citizens to come to the USA
2008 VSB Grant (VSB Foundation, the Netherlands), which gives Dutch students the opportunity to study or perform research abroad after completion of their education
2008 Netherlands Brain Foundation Grant (Netherlands Brain Foundation, the Netherlands), which supports scientific research on causes of brain diseases and the possibilities to prevent these disorders, to assess and treat these disorders, and to ease their consequences
2014 Milton Safenowitz Post-Doctoral Fellowship Award (ALS Association, USA), which encourages and facilitates promising young scientists to enter the ALS field
2015 CReATe Clinical Research Fellowship Award (CReATe Consortium, USA), which is designed to provide talented and highly motivated clinicians and researchers with an opportunity to launch a career in clinical and translational research focused on ALS and related disorders
2016 Travel Award to attend the Conference on Clinical Research for Rare Diseases (CCRRD) in Washington, DC, USA

C. Contribution to Science

1. ***Insights into genetic causes of ALS.*** My early work at Harvard Medical School (Boston, MA, USA) and University of Massachusetts Medical School (Worcester, MA, USA) concentrated on the genetic causes of familial and sporadic ALS. I showed, for instance, that superoxide dismutase 1 (SOD1) antibodies are associated with survival in sporadic ALS patients. Additionally, to elucidate the role of fused in sarcoma (*FUS*) in ALS, I performed *in vitro* experiments, followed by RNA sequencing (RNAseq), to identify genes

that displayed differential expression or altered splicing patterns, which provided additional insights into the function of FUS and how mutations contribute to the development of ALS.

a. **Van Blitterswijk M.**, Gulati S., Smoot E., Jaffa M., Maher N., Hyman B.T., *et al.* (2011). Anti-superoxide dismutase antibodies are associated with survival in patients with sporadic amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis, 12(6), 430-438. PMID:22023190. PMCID:3446817. DOI:10.3109/17482968.2011.585163.

b. **Van Blitterswijk M.**, Wang E.T., Friedman B.A., Keagle P.J., Lowe P., Leclerc A.L., *et al.* (2013). Characterization of *FUS* mutations in amyotrophic lateral sclerosis using RNA-Seq. PLoS One, 8(4), e60788. PMID:23577159. PMCID:3620060. DOI:10.1371/journal.pone.0060788.

2. Evidence for oligogenicity in ALS and FTD. At the University Medical Center (Utrecht, the Netherlands), I examined the presence of mutations in more than ten genes in familial ALS patients of Dutch descent. The most frequent cause of familial ALS in the Netherlands was a repeat expansion in *C9ORF72*, followed by mutations in TAR DNA-binding protein (*TARDBP*) and *FUS*. Intriguingly, I discovered five families with multiple mutations in ALS-associated genes, which is in excess of what is to be expected by chance. Importantly, this study was the first to provide evidence for an oligogenic etiology of ALS. In 2012, I moved to the Mayo Clinic (Jacksonville, FL, USA), where I focused my research on *C9ORF72*. To determine whether oligogenicity is confined to ALS patients, I studied subjects with mutations in genes associated with a spectrum of neurodegenerative diseases and screened those subjects for repeat expansions in *C9ORF72*. Interestingly, I found four subjects who carried a *C9ORF72* repeat expansion in addition to mutations in FTD-associated genes progranulin (*GRN*) or microtubule-associated protein tau (*MAPT*). Oligogenicity, therefore, appears to contribute to FTD as well, and consequently, co-occurrence of two evidently pathogenic mutations may help to explain the clinical variability observed in expansion carriers.

a. Van Damme P.*, Veldink J.H.*, **van Blitterswijk M.***, Corveleyn A., van Vught P.W., Thijs V., *et al.* (2011). Expanded *ATXN2* CAG repeat size in ALS identifies genetic overlap between ALS and SCA2. Neurology, 76(24), 2066-2072. PMID:21562247. DOI:10.1212/WNL.0b013e31821f445b. (***equal contribution**).

b. **Van Blitterswijk M.**, van Vught P.W., van Es M.A., Schelhaas H.J., van der Kooi A.J., de Visser M., *et al.* (2012). Novel optineurin mutations in sporadic amyotrophic lateral sclerosis patients. Neurobiology of Aging, 33(5), 1016.e1-7. PMID:21802176. DOI:10.1016/j.neurobiolaging.2011.05.019.

c. **Van Blitterswijk M.**, van Es M.A., Hennekam E.A., Dooijes D., van Rheenen W., Medic J., *et al.* (2012). Evidence for an oligogenic basis of amyotrophic lateral sclerosis. Human Molecular Genetics, 21(17), 3776-3784. PMID:22645277. DOI:10.1093/hmg/dds199.

d. **Van Blitterswijk M.**, Baker M.C., DeJesus-Hernandez M., Ghidoni R., Benussi L., Finger E., *et al.* (2013). *C9ORF72* repeat expansions in cases with previously identified pathogenic mutations. Neurology, 81(15), 1332-1341. PMID:24027057. PMCID:3806926. DOI:10.1212/WNL.0b013e3182a8250c.

3. Characterization of C9ORF72 repeat expansions. In order to investigate whether *C9ORF72* expansion size could influence the disease phenotype or disease severity, I performed a large Southern blot characterization study. My examination uncovered that expansion size does not differ significantly between patients with ALS, FTD/ALS, or FTD. Moreover, it demonstrated that expansion sizes in the frontal cortex of FTD patients are associated with age at onset, whereas they are associated with survival after onset in the cerebellum of our overall cohort of expansion carriers. To further elucidate the substantial clinical heterogeneity observed in *C9ORF72* expansion carriers, I was also involved in a study that examined dipeptide-repeat proteins (DPRs) aberrantly translated from the expansion, which showed that cerebellar DPR (poly[GP]) levels are significantly lower in patients with ALS than in patients with FTD or FTD/ALS. Importantly, both cerebellar poly(GP) and poly(GA) also associated with the expression of *C9ORF72* transcript variant 3. Given this association with *C9ORF72* expression levels, I then evaluated the contribution of all known *C9ORF72* transcripts to disease pathogenesis. My study revealed that higher levels of *C9ORF72* transcript variant 1 are associated with prolonged survival after onset in expansion carriers, and provided support for the presence of truncated transcripts and pre-mRNAs that may serve as templates for repeat-associated non-ATG (RAN) translation. Additionally, I investigated the burden of RNA foci and showed that more antisense RNA foci are associated with a delayed age at onset in the frontal

cortex. Furthermore, I demonstrated that RNA foci are not the key determining factor of the clinico-pathological variability, and that the combined effect of multiple pathological lesions is probably a more suitable predictor. Aforementioned studies, thus, shed new light on disease pathogenesis and help to understand the phenotypic variability associated with repeat expansions in *C9ORF72*.

a. **Van Blitterswijk M.**, DeJesus-Hernandez M., Niemantsverdriet E., Murray M.E., Heckman M.G., Diehl N.N., *et al.* (2013). Association between repeat sizes and clinical and pathological characteristics in carriers of *C9ORF72* repeat expansions (Xpansize-72): a cross-sectional cohort study. Lancet Neurology, 12(10), 978-988. PMID:24011653. PMCID:3879782. DOI:10.1016/S1474-4422(13)70210-2.

b. Gendron T.F.*, **van Blitterswijk M.***, Bieniek K.F., Daughrity L.M., Jiang J., Rush B.K., *et al.* (2015). Cerebellar c9RAN proteins associate with clinical and neuropathological characteristics of *C9ORF72* repeat expansion carriers. Acta Neuropathologica, 130(4), 559-573. PMID:26350237. DOI:10.1007/s00401-015-1474-4. (***equal contribution**).

c. **Van Blitterswijk M.***, Gendron T.F.*, Baker M.C., DeJesus-Hernandez M., Finch N.A., Brown P.H. *et al.* (2015). Novel clinical associations with specific *C9ORF72* transcripts in patients with repeat expansions in *C9ORF72*. Acta Neuropathologica, 130(6), 863-876. PMID:26437865. DOI:10.1007/s00401-015-1480-6. (***equal contribution**).

d. DeJesus-Hernandez M., Finch N.A., Wang X., Gendron T.F., Bieniek K.F., Heckman M.G., *et al.* (2017). In-depth clinico-pathological examination of RNA foci in a large cohort of *C9ORF72* expansion carriers. Acta Neuropathologica. PMID:28508101. DOI:10.1007/s00401-017-1725-7 (in press; **last author**).

4. ***The role of TMEM106B, GRN, ataxin-2 (ATXN2), homeobox A5 (HOXA5) and transthyretin (TTR) in C9ORF72-linked diseases.*** In an ongoing effort to identify genetic disease modifiers and biomarkers, I performed extensive genetic studies, which showed that variants in *TMEM106B* appear to protect against developing FTD (but not against developing ALS), that variants in other genes (e.g., *GRN*) are associated with age at onset and/or survival after onset, and that intermediate repeats in *ATXN2* may render *C9ORF72* expansion carriers more susceptible to the development of ALS (but not to the development of FTD). Moreover, I recently discovered an up-regulation of multiple homeobox genes (top hit: *HOXA5*) that play a vital role in neuronal development as well as *TTR*, an extracellular protein that is thought to be involved in neuroprotection. The identification of genes functioning in developmental processes and neuroprotection points to compensatory mechanisms influencing the occurrence, presentation, and/or progression of *C9ORF72*-related diseases. As such, these studies help to uncover important targets for new treatment strategies and prognostic tests.

   a. **Van Blitterswijk M.**, Mullen B., Nicholson A.M., Bieniek K.F., Heckman M.G., Baker M.C., *et al.* (2014). *TMEM106B* protects *C9ORF72* expansion carriers against frontotemporal dementia. Acta Neuropathologica, 127(3), 397-406. PMID:24385136. PMCID:3944829. DOI:10.1007/s00401-013-1240-4.

   b. **Van Blitterswijk M.**, Mullen B., Wojtas A., Heckman M.G., Diehl N.N., Baker M.C., *et al.* (2014). Genetic modifiers in carriers of repeat expansions in the *C9ORF72* gene. Molecular Neurodegeneration, 9, 38. PMID:25239657. PMCID:4190282. DOI:10.1186/1750-1326-9-38.

   c. **Van Blitterswijk M.**, Mullen B., Heckman M.G., Baker M.C., DeJesus-Hernandez M., Brown P.H., *et al.* (2014). Ataxin-2 as potential disease modifier in *C9ORF72* expansion carriers. Neurobiology of Aging, 35(10), 2421.e13-17. PMID:24866401. PMCID:4105839. DOI:10.1016/j.neurobiolaging.2014.04.016.

   d. Finch N.A., Wang X., Baker M.C., Heckman M.G., Gendron T.F., Bieniek K.F., *et al*. (2017). Abnormal expression of homeobox genes and transthyretin in *C9ORF72* expansion carriers. Neurology Genetics, 3(4), e161. DOI:10.1212/NXG.0000000000000161 (in press; **last author**).

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1J10Yp64ltyQu/bibliograpahy/48232107/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

NS092091 (Van Blitterswijk) NINDS 07/01/2015 – 06/30/2017

Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe)
Goal: This grant provides support to concentrate on the discovery of novel biomarkers for *C9ORF72*-related diseases using a unique cohort of patients with *C9ORF72* repeat expansions for whom brain tissue, plasma, and cerebrospinal fluid are available. Role: PI

R21 NS093118 (Van Blitterswijk) NINDS 04/01/2016 – 03/31/2018
TTR and C9ORF72 in ALS and related disorders
Goal: This project will determine whether transthyretin (TTR) is a suitable biomarker for *C9ORF72*-related diseases, by examination of TTR protein levels (plasma and cerebrospinal fluid), the histopathological context, and the presence of post-translational modifications. Role: PI

R35 NS097261 (Rademakers) NINDS 12/01/2016 – 11/30/2024
Genetic discovery and pathobiology of frontotemporal lobar degeneration and related TDP-43 proteinopathies
Goal: The goal of this project is to identify new genes and genetic modifiers of FTLD and related diseases and to study these in cellular and mouse models. Role: Co-Investigator

P01 NS084974 (Petrucelli) NINDS 09/30/2014 – 06/30/2019
Pathobiology of neurodegeneration in *C9ORF72* repeat expansion
Goal: The goal of this project is to study pathogenic mechanisms related to the *C9ORF72* repeat expansion, focusing on differences in repeat sizes between symptomatic and asymptomatic expansion carriers, changes over time, and associations with cross-sectional and longitudinal clinical measures. Role: Co-Investigator

Pending Research Support
NA (Van Blitterswijk) ALS Association 08/01/2017 – 07/31/2018
Discovery of genetic disease modifiers accounting for substantial variability in survival after ALS onset
Goal: The goal of this project is the identification of novel disease modifiers that help to elucidate the heterogeneity seen in survival after ALS onset through whole-genome sequencing. Role: PI

NA (Van Blitterswijk) ALS Association 08/01/2017 – 07/31/2020
Identification of novel biomarkers for *C9ORF72*-linked diseases, combining a targeted approach with an unbiased screen
Goal: This project aims to clarify the role transcript variants and protein isoforms of C9ORF72 play in the clinical heterogeneity associated with ALS, and to discover novel biomarker patterns through RNA sequencing of exosomal RNA. Role: PI

Completed Research Support
2302 (Van Blitterswijk) ALS Association 08/01/2013 – 07/31/2015
Milton Safenowitz Post Doctoral Fellowship for ALS Research
Goal: The goal of this project is to identify *C9ORF72* disease modifiers using whole-genome sequencing in a cohort of 30 *C9ORF72* expansion carriers from the Mayo Clinic Brain Bank. Role: PI

2013-F-024 (Rademakers) ALS Therapy Alliance 05/01/2014 – 04/30/2016
Understanding the ALS and FTD disease risk associated with chromosome 9p: renewal
Goal: This project focuses on the mRNA expression of *C9ORF72* in a well-characterized cohort of *C9ORF72* expansion carriers. Role: Co-Investigator

E. Copy of Passport

Mayo Clinic Jacksonville
Rosa Rademakers, PhD
Mildred A. and Henry Uihlein II Professor of Medical Research
Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224

June 27, 2017

Dear Members of the Judging Committee for the 9th PG Award:

I am delighted to support the application of Dr. Marka van Blitterswijk that focuses on elucidating the clinico-pathological variability observed in patients carrying a repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*) in amyotrophic lateral sclerosis (ALS) and related disorders. Dr. Van Blitterswijk is an Assistant Professor and Associate Consultant at the Department of Neuroscience here at Mayo Clinic Jacksonville.

Dr. Van Blitterswijk came to Mayo Clinic in 2012 with impressive references and training. She completed her M.D. degree at Utrecht University in the Netherlands with very strong credentials. After successfully competing for a prestigious Fulbright fellowship which brought her to the United States to work with Dr. John Landers and Dr. Robert Brown at Harvard Medical School Boston and University of Massachusetts in 2008, she completed her Ph.D. in 2012 under the guidance of Dr. Leonard van den Berg, a highly respected Professor of Neurology at the University Medical Center Utrecht, the Netherlands.

Currently, Dr. Van Blitterswijk supervises a team of researchers working on *C9ORF72*, and her work has already resulted in important publications, including an extensive Southern blot characterization study to determine repeat sizes in *C9ORF72* expansion carriers (Van Blitterswijk *et al*., *Lancet Neurology*, 2013). In addition, Dr. Van Blitterswijk's findings demonstrate that variants in transmembrane protein 106 B (*TMEM106B*) affect the disease presentation (Van Blitterswijk *et al*., *Acta Neuropathologica*, 2014), that levels of *C9ORF72* transcript variant 1 are associated with survival after onset (Van Blitterswijk *et al*., *Acta Neuropathologica*, 2015), and that cerebellar abnormalities (e.g., dipeptide-repeat proteins [DPRs]) associate with neuropathological and clinical phenotypes in *C9ORF72* expansion carriers (Gendron & Van Blitterswijk *et al*., *Acta Neuropathologica*, 2015). Moreover, she recently showed that RNA foci are not the determining factor of the clinico-pathological variability, but that a combined effect of multiple pathological lesions is probably crucial (DeJesus-Hernandez *et al*., *Acta Neuropathologica*, 2017).

In total, she has published 53 articles, including 27 articles as first or last author. Dr. Van Blitterswijk has already obtained extramural funding; she is principal investigator, for instance, on an R21 (NS093118) grant to investigate whether transthyretin (TTR) may serve as a biomarker for ALS and related disorders, and co-investigator on several other grants, including P01 (NS084974) and R35 (NS097261) grants. She is regularly invited to give oral presentations at national and international conferences, she is an *ad hoc* reviewer for multiple scientific journals (e.g., *Brain*, *Nature Communications*, and *Acta Neuropathologica*), she serves as an external referee for many foundations (e.g., Motor Neurone Disease [MND] Association, Health Research Board [HRB], Congressionally Directed Medical Research Programs [CDMRP], Italian Association for ALS [ariSLA], Medical Research Council [MRC], and Clinical Research in ALS and Related Disorders for Therapeutic Development [CReATe]), and importantly, she is extremely professional and passionate about her work. There is no doubt that it is her ultimate goal to become a renowned investigator focusing on ALS genetics, and I am confident that this award would help her enormously to achieve this goal.

I have led an independent laboratory since 2007 and published more than 250 papers on the molecular genetics of frontotemporal dementia (FTD), ALS, and related disorders. Most relevant to Dr. Van Blitterswijk's application is the fact that I identified repeat expansions in *C9ORF72* as the long sought-after cause of FTD and ALS on chromosome 9p (DeJesus-Hernandez *et al*., *Neuron*, 2011). I am very proud to have received the PG Award in 2012, and I am convinced that Dr. Van Blitterswijk is a very talented scientist and an outstanding candidate for the 9th PG Award. Thus, I support with my highest enthusiasm Dr. Van Blitterswijk's application.

Please do not hesitate to contact me if you have additional questions.

Sincerely Yours,

Rosa Rademakers, PhD