BIOGRAPHICAL SKETCH

NAME: Marc Vermulst

eRA COMMONS USER NAME: marc_vermulst

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Utrecht, the Netherlands	M.Sc.	2002	Biology
University of Washington	Ph.D.	2004-2008	Pathology
California Institute of Technology	Post-doctoral	2008-2009	Cell Biology
University of North Carolina Chapel Hill	Post-doctoral	2009-2013	Cell Biology

A. Personal Statement

The primary goal of my research is to understand the role of transcription errors in human aging and disease. To that end, we recently adapted a novel massively parallel sequencing assay termed the circle-sequencing assay (circ-seq), to identify transcription errors throughout the genome of eukaryotic cells with single base resolution. These experiments indicate that transcription errors can occur at any time, in any gene, and affect every aspect of protein structure and function. Moreover, we found that these errors contribute to protein aggregation in aging cells, and can modulate the impact of proteotoxic alleles on cellular health, including TDP-43, Aβ1-42, Huntingtin and prions. Thus, transcription errors represent a new mechanism by which the age of onset, progression and severity of diseases that are caused by protein misfolding can be altered. Interestingly, DNA damage is a powerful source of transcription errors, suggesting that DNA damage, DNA repair and environmental mutagens may all be linked to proteotoxic diseases through transcriptional mutagenesis. If so, transcription errors provide a new mechanism by which the environment and our lifestyle choices can change our predisposition to disease. Taken together, these results indicate that the impact of DNA damaging agents on human health has been greatly underestimated and that it will be important to re-evaluate the safety of these compounds from the perspective of transcriptional fidelity.

A second goal my research is to understand how mitochondrial mutations impact human aging and disease. A common thread throughout these experiments is the use of mice that carry an error prone copy of DNA polymerase γ, the enzyme that replicates the mitochondrial genome. As a result, these animals accumulate mtDNA mutations at an accelerated pace, which makes it easier to study the relationship between mutations and disease. By combining these mice with a novel mutation detection assay, termed the “random mutation capture assay”, which is capable of identifying 1 mutation among $1x10^7$ mutant bases, it was possible to provide the first reasonable estimate of the mitochondrial mutation rate in mammals and shed new light on the relationship between mutations and mammalian aging. In addition, I helped identify the first molecular mechanisms that control the impact of mtDNA mutations on organismal health. My laboratory is now expanding on these observations with so-called “mitochondrial mutator worms”, which allow us to rapidly screen genes that can be exploited to mitigate mtDNA disease and have identified at least 3 basic biological pathways that can do so. Currently, we are testing the therapeutic potential of these pathways out in mice.

B. Positions and Honors

B. Positions and Employment

2001-2002: Research assistant, Institute for Development, Aging and Cancer, Tohoku University, Sendai, Japan

2013-2018: Assistant Professor, Center for Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia at the University of Pennsylvania

2018-present Assistant Professor, School of Gerontology, University of Southern California, Los Angeles, California

C. Contributions to Science

1. As a graduate student I helped to design, adapt and perfect a novel assay to measure mutations in the mitochondrial genome. I subsequently used this assay provide the first reasonable estimate of the mitochondrial DNA mutation frequency in mammals. These experiments set a new benchmark for mutation research in mitochondria.

    a. **Vermulst M,** Bielas, JH, Loeb, LA. (2008) Quantification of mutation in the mitochondrial genome (2008) *Methods.* Dec;46(4):263-8. PMID: 18948200. PMCID:PMC2615251

2. For several decades, it has been suggested that mutations in the mitochondrial genome drive the human aging process. I used the technology we developed to test this >30-year old hypothesis by measuring the mitochondrial mutation rate of "mitochondrial mutator mice", and "mitochondrial anti-mutator mice".

    Vermulst M, Bielas JH, Kujoth GC, Ladiges WG, Rabinovitch PS, Prolla TA and Loeb LA. (2007) Mitochondrial point mutations do not limit the natural lifespan of mice. *Nat Genet.* 39, 540-543, PMID: 17334366

    Associated Commentary: Mitochondrial DNA mutations and aging: a case closed? Konstantin Khrapko and Jan Vijg, Nat Genet. 2007 39: 445-446

    Vermulst M, Wanagat J, Kujoth GC, Bielas JH, Rabinovitch PS, Prolla TA and Loeb LA. (2008) DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice. *Nat Genet.* 40, 392-4. PMID: 18311139

3. Currently, there is no cure or treatment for mitochondrial disease. To identify these treatments, it will be important to first identify cellular pathways that either exacerbate or ameliorate mtDNA disease. As a post-doc in Dr. David Chan's lab, I helped identify the first of these pathways, and showed that mitochondrial fusion regulates the impact mtDNA mutations have on cellular health.

    a. **HC Chen*, Vermulst M*,** Wang YE, Prolla TA, McCaffery MJ, Chan DC. Mitochondrial fusion is required for mtDNA stability and tolerance of mtDNA mutations. *Cell,* 2010, April 16; 141(2): 280-9. PMID: 20403324. PMCID: PMC2858759 *** equal contributors**

4. Transcription errors occur continuously, in all of our cells, and in all of our genes; however, it is unknown how these errors affect cellular health. We recently used error prone versions of RNAPII to discover that these errors cause proteotoxic stress, and found that they determine the toxicity and rate of aggregation of proteins that are associated with protein-folding diseases, such as Alzheimer's disease, prion disease, Huntington's disease and amyotrophic lateral sclerosis. These findings provide new insight into the etiology and age of onset of age-related diseases.

    a. **M. Vermulst***, A. S. Denney, M.J. Lang, CW Hung, V. Madden, J. Gauer, K.J. Wolfe, D.W. Summers, J. Schleit, G.L. Sutphin, S. Haroon, A. Holczbauer, D. Cyr, M. Kaeberlein, J.N. Strathern,

M.C. Duncan, D. Erie* Transcription errors induce proteotoxic stress and shorten cellular lifespan (*Nature Communications*, 2015, Aug. 25;6;8065. Doi: 10.1038/ncomms9065. PMID: 26304740 ***corresponding authors**)

5. We recently published groundbreaking experiments that reveal the landscape of transcription errors in yeast and mice. With the help of a novel massively parallel sequencing tool, we were able to monitor the fidelity of transcription throughout the genome for the very first time and detail numerous genes and parameters that control the error rate of transcription in eukaryotic cells.

    a. J.-F. Gout, Weiyi Li, C. Fritsch, A. Li, S. Haroon, M. Lynch, **M. Vermulst**. The landscape of transcription errors in eukaryotic organisms. *Science Advances*, October 20, 2017.

Complete list of published work at:
http://www.ncbi.nlm.nih.gov/pubmed/?term=vermulst%2C+marc

D. Peer-Reviewed Publications and Manuscripts in Preparation

Vermulst M, Bielas JH, Kujoth GC, Ladiges WG, Rabinovitch PS, Prolla TA and Loeb LA. (2007) Mitochondrial point mutations do not limit the natural lifespan of mice. *Nature Genetics* 39, 540-543. PMID: 17334366

Associated Commentary: Mitochondrial DNA mutations and aging: a case closed? Konstantin Khrapko and Jan Vijg. (2007) Nature Genetics 39, 445-446.

Vermulst M, Wanagat J, Kujoth GC, Bielas JH, Rabinovitch PS, Prolla TA and Loeb LA. (2008) DNA deletions and clonal mutations drive premature aging in mitochondrial mutator mice. *Nature Genetics* 40, 392-394. PMID: 18311139

Vermulst M, Bielas, JH and Loeb, LA. (2008) Quantification of mutation in the mitochondrial genome. *Methods* 46, 263-268. PMID: 18948200. PMCID:PMC2615251

Dai D, Santana LF, **Vermulst M,** Tomazeva DM, Emond MJ, Macoss MJ, Gollahon K, Martin GM, Loeb LA, Ladiges WC and Rabinovitch PS (2009). Overexpression of catalase targeted to mitochondria attenuates murine cardiac aging. *Circulation* 119, 2789-2797. PMID: 19451351. PMCID: PMC2858759

Vermulst M, Wanagat J and Loeb LA. (2009) On mitochondria, mutations, and methodology. *Cell Metabolism* 10, 437. PMID: 19945399

Chen HC*, Vermulst M*, Wang YE, Prolla TA, McCaffery MJ and Chan DC. (2010) Mitochondrial fusion is required for mtDNA stability and tolerance of mtDNA mutations. *Cell* 141, 280-289. PMID: 20403324. PMCID: PMC2858759 *** equal contributors**

Ericson N, Kulawiec M, **Vermulst M,** Sheahan K, O'Sullivan J, Salk J and Bielas JH. (2012) Decreased mitochondrial DNA mutagenesis in human colorectal cancer. *PLoS Genetics* 8, e1002689. doi: 10.1371/journal.pgen.1002689. Epub 2012 Jun 7. PMID: 22685414. PMCID:PMC3369930.

Vermulst M, Khrapko K and Wanagat J. (2012) Mitochondrial mutagenesis in aging and disease. Book chapter for *Mutagenesis,* ISBN 978-953-51-0707-1

Vermulst M, Denney AS, Lang MJ, Hung CW, Madden V, Gauer J, Wolfe KJ, Summers DW, Schleit J, Sutphin GL, Haroon S, Holczbauer A, Cyr D, Kaeberlein M, Strathern JN, Duncan MC and Erie D. Transcription errors induce proteotoxic stress and shorten cellular lifespan. (*Nature Communications*, 6, article 8065, Aug. 25, 2015)

Haroon S, **Vermulst M**. Linking mitochondrial dynamics to mitochondrial protein quality control *Curr Opin Genet Dev*. 2016 Jun;38:68-74. doi: 10.1016/j.gde.2016.04.004. Epub 2016 May 25. Review.

Someya S, Kujoth GC, Kim MJ, Hacker TA, **Vermulst M**, Weindruch R, Prolla TA. Effects of calorie restriction on the lifespan and healthspan of POLG mitochondrial mutator mice. *PLoS One*. 2017 Feb 3;12(2):e0171159. doi: 10.1371/journal.pone.0171159. eCollection 2017.

J.-F. Gout, Weiyi Li, C. Fritsch, A. Li, S. Haroon, L. Singh, D. Hua, H. Fazelina, Z. Smith, S, . Seeholzer, K. Thomas, M. Lynch, **M. Vermulst**. The landscape of transcription errors in eukaryotic organisms. *Science Advances*, published online, October 20th 2017, Vol. 3. No. 10, e1701484. PMID: 29062891

S. Haroon, A. Li, C. Fritsch, N. Ericson, J. Alexander-Floyd, B.P. Braeckman, C. Haynes, J. Bielas, T. Gidalevitz, **M. Vermulst***. Multiple molecular mechanisms rescue mtDNA disease in C. elegans*. Cell Reports,* Mar 20;22(12):3115-3125. PMID: 29562168

Mitochondrial DNA Variation Dictates Expressivity and Progression of Nuclear DNA Mutations Causing Cardiomyopathy. Meagan J McManus, Hsiao-Wen Chen, Martin Picard, Hans J. De Haas, Prasanth Potluri, Jeremy Leipzig, Atif Towheed, Alessia Angelin, Partho Sengupta, Ryan M. Morrow, Brett A. Kauffman, **Marc Vermulst**, Jagat Narula Douglas C. Wallace, *Cell Metabolism*, 2019 Jan 8;29(1):78-90.e5. doi: 10.1016/j.cmet.2018.08.002. Epub 2018 Aug 30

C. Fritsch, JF Gout, **M. Vermulst.** Transcription errors: A new horizon for mutation research. *J Vis Exp*. 2018 Sep 13;(139). doi: 10.3791/57731

Somatic mutations in neurons during aging and neurodegeneration. Verheijen BM, **Vermulst M**, van Leeuwen FW. *Acta Neuropathol.* 2018 Jun;135(6):811-826. doi: 10.1007/s00401-018-1850-y. Epub 2018 Apr 28. Review.

Manuscripts tentatively accepted, but under revision

C. Fritsch, J.F. Gout, S. Haroon, A. Towheed, X. Zhang, Y. Song, S. Simpson, P. Danthi, B. Benayoun, D. Wallace, K. Thomas, M. Lynch, **M. Vermulst**. Genome-wide profiling of transcription errors in response to genotoxic stress, *Nature Communications*, in revision.

D. Research support

R01AG054641 NIA Vermulst (PI) **04/01/2017-03/31/2022**
Transcription errors in aging and disease
The primary goal of this research project is to understand the impact of transcription errors on eukaryotic aging and disease, using yeast and mice that display an increased error rate of transcription (No overlap with this proposal)
Role: PI

R01GM124532 NIH Vermulst (PI) **07/01/2017-04/31/2022**
Exploiting the insulin signaling pathway to treat mtDNA disease
The primary goal of this research project is to exploit the insulin signaling pathway to treat diseases caused by mtDNA mutations, using worms and mice that display increased levels of mtDNA mutations as models.
Role: PI

Hanson Thorell Reseach Foundation Vermulst (PI) **07/01/2019-06/31/2020**
Using brainbow technology to monitor mitochondrial protein heterogeneity
The primary goal of this research project is to generate mice that express conditional fluorophores targeted to mitochondria.
Role: PI

Completed support

K99/R00 R00AG041809-01-03 Vermulst (PI) **08/01/2012-7/31/2016**
Non-genetic Mutations in Aging and Disease

The primary goal of this research project is to understand the impact of transcription errors on the health of aging yeast cells.

Institute on Aging Pilot Award Vermulst (PI) **07/01/2015-6/31/2016**
Identifying targets that can be exploited to ameliorate mtDA disease
The primary goal of this research project is to identify genes that modulate mtDNA disease

Mitochondrial Research Affinity Group Award **08/01/2014-9/31/2014**
Generation of Mitochondrial Brainbow Mice
The goal of this project was to generate mice that express conditional fluorophores targeted to mitochondria.

AFAR New Investigator in Alzheimer's Research Award Vermulst (PI) **07/01/2015-12/31/2017**
Transcriptional mutagenesis in Alzheimer's disease
The primary goal of this research project is to determine how transcription errors affect the pathology of Alzheimer's disease

E. Invited seminars

"Mitochondrial Point Mutations Increase With Age, But Do Not Limit the Lifespan of Mice" - Department of Pathology, Annual Retreat, Leavenworth, Washington, USA, 2011

"Mitochondrial mutagenesis in Aging and Disease" - Environmental Mutagen Society, Ventura Beach, CA, 2010

"Understanding the relationship between mitochondrial dynamics and mitochondrial DNA" - UMDF meeting, Chicago, IL 2011

Transcription errors: Linking Aging to Age-related diseases, NCI, 2015

Transcription Errors: Linking aging to Age-related diseases, Molecular Chaperones Meeting, Chicago 2016

Genome wide profiling of transcription errors in yeast, NCI, Frederick, MD, 2016

Multiple mechanisms rescue mtDNA disease in *C. elegans*, MitoCanada, Toronto, 2017

Biological errors in aging and disease, Grand Rounds, University of Florida, 2017

Genome wide profiling of transcription errors in yeast, PGIG, UPenn, 2017

Transcription errors in aging and disease, Northwestern University, 2018