ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Genetics
Project Title:	"The development of bio-informatics approaches to identify DNA damage response defects in aging".
Abstract:	Breakthroughs over the last decade from the field of accelerated aging syndromes and corresponding transgenic mouse models have identified DNA damage as an important instigator of aging. DNA is the only intracellular component that cannot be replaced upon damage and thus solely relies on repair. Moreover, DNA is at the top of the informational hierarchy. Hence damage to DNA may have many indirect and lasting effects. We discovered that persistent DNA damage signaling in aging determines a large part of all gene expression changes that occur with aging. Besides detrimental changes such as apoptosis and cellular senescence, we found that accumulation of persistent DNA damage also triggers a 'survival' response', which suppresses growth, arrests development and boosts defense and maintenance systems, resembling long-lived mouse mutants or dietary restriction, which extends lifespan in many species. The PhD student will develop novel bio-informatics approaches to identify DNA damage responses in aging using micro-array and RNA sequencing datasets. This will improve our understanding of aging and the etiology of age-related diseases. This is a prerequisite for identification of effective interventions which delay or prevent aging-associated diseases and promote healthy aging.
Requirements of candidate:	Background: The candidate should have a background in bio-informatics, programming skills and knowledge of molecular cell biology. Experience in analyzing next generation sequencing and micro-array datasets is an advantage, but not mandatory. Master degree: Yes IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*

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Supervisor information:	Prof. Dr. Jan H.J. Hoeijmakers / Dr. J. Pothof Email address: j.pothof@erasmusmc.nl Personal website: http://www.erasmusmc.nl/genetica/research/ Recent publication list, preferably last 3-5 years (1-2 pages) J.H. Hoeijmakers (2009) DNA Damage, aging, and cancer, **NEJM** 361, 1475-1485 G.A. Garinis, L.M. Uittenboogaard, H. Stachelscheid, M. Fousteri, W. van IJcken, T.M. Breit, H. van Steeg, L.H. Mullenders, G.T. van der Horst, J.c. Brüning, C.M. Niessen, J.H. Hoeijmakers, B. Schumacher (2009) Persistent transcription-blocking DNA lesions trigger somatic growth attenuation associated with longevity, **Nat Cell Biol**. 11, 604-615 Pothof, J., Verkaik, N.S., van IJcken, W., Wiemer, E.A.C., Ta, V.T.B., van der Horst, G.T.J., Jaspers, N.G.J., van Gent, D.C., Hoeijmakers, J.H.J. and Persengiev, S.P. (2009) MicroRNA-mediated Gene Silencing Modulates the UV-induced DNA Damage Response. **EMBO J.** *28*, 2090-2099. Pothof, J., Verkaik, N.S., Hoeijmakers, J.H.J. and van Gent, D.C. (2009) MicroRNA responses and stress granule formation modulate the DNA damage response. **Cell Cycle**, *8*, 3462-3468. Wouters, M.D., van Gent, D.C., Hoeijmakers, J.H.J., Pothof, J. (2011) MicroRNAs, the DNA damage response and cancer. **Mutat Res.** *717*, 54-66. B. Schumacher, I. van der Pluijm, M.J. Moorhouse, T. Kosteas, A.R. Robinson, Y. Suh, T.M. Breit, H. van Steeg, L.J. Niedernhofer, W. van IJcken, A. Bartke, S.R. Spindler, J.H. Hoeijmakers, G.T. van der Horst, G.A. Garinis. Delayed and accelerated aging share common longevity assurance mechanisms. **PLoS Genetics** 15, e1000161 (2008) I. van der Pluijm, G.A. Garinis, R.M.C. Brandt, T.G.M.F. Gorgels, S.W. Wijnhoven, K.E.M. Diderich, J. de Wit, J.R. Mitchell, C. van Oostrom, R. Beems, L.J. Niedernhofer, S. Velasco, E.C. Friedberg, K. Tanaka, H. van Steeg, J.H.J. Hoeijmakers, G.T.J. van der Horst. Impaired genome maintenance suppresses the GH/IGF1 axis in Cockayne syndrome mice. **PLoS Biol.** 5, 23-38 (2007) L.J. Niedernhofer, G.A. Garinis, A. Raams, S.A. Lalai, A.R. Robinson, E. Appeldoorn, H. Odijk, R. Oostendorp, A. Ahmad, W. van Leeuwen, A. Theil, W. Vermeulen, G.T. van der Horst, P. Meinecke, W. Kleijer, J. Vijg, N.G.J. Jaspers and J.H.J. Hoeijmakers. A new progeriod syndrome reveals that genotoxic stress suppresses the somatotroph

	axis. **Nature** 444, 1038-1043 (2006) (see also accompanying 'News and Views', Kirkwood) de Graaf EL, Vermeij WP, de Waard MC, Rijksen Y, van der Pluijm I, Hoogenraad CC, Hoeijmakers JH, Altelaar AF, Heck AJ. Spatio-temporal analysis of molecular determinants of neuronal degeneration in the aging mouse cerebellum. **Mol Cell Proteomics.** 2013 May;12(5):1350-62. doi: 10.1074/mcp.M112.024950. Epub 2013 Feb 11. Marteijn J.A., Lans H., Vermeulen W., Hoeijmakers J.H.J.(2014) Understanding Nucleotide Excision Repair and its roles in Cancer and Ageing. **Nature Rev Mol Cell Biol**; 15, 465-481.