ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Genetics
Project Title:	Extending healthy lifespan by anti-aging nutrition
Abstract:	Accumulation of DNA damage is a major contributor to the onset of cancer and age related diseases. Our DNA repair-deficient mouse mutants exhibit a wide spectrum of premature but bona fide aging features, including progressive loss of synaptic plasticity, motor, vision, auditory and cognitive functions, and extensive neurodegeneration. Depending on the type and severity of the DNA repair defect, the average lifespan of these progeroid mice ranges from 3 weeks to 1.5 year. We have recently discovered that 30% dietary restriction (DR), which is well-known to extend lifespan and reduce age-related pathology in many species including primates, resulted in an unprecedented ~3-fold increase in remaining lifespan of these repair deficient animals. More importantly, many health span parameters, such as age-related neuronal decline, vascularization and liver functioning, were all dramatically improved. Although it has been shown that DR may interfere with multiple pathways, the mechanisms by which it attenuates the effect of aging are not understood. Moreover, a voluntary DR lifestyle in humans will be hard to maintain due to a constant hunger feeling. It is therefore very important to understand the processes and pathways involved and to identify DR mimetics or other nutritional interventions strategies that promote healthy aging in humans. The extreme, highly reproducible response of our DNA repair mutant models to DR provides a unique competitive edge to explore the mechanism and nutritional elements in a 5-10-fold shorter timeframe with a much clearer outcome and dramatic reduction of animals, labor and costs. The PhD-student will analyze the effects of different nutritional interventions on various mouse tissues to elucidate the mechanism of life and health span extension by DR. Concomitantly, new ideas regarding timing, dietary interventions or compounds that alter specific parts of the DR response will be screened together with our research technicians.
Requirements of candidate:	Background: The candidate should have thorough knowledge of molecular and cellular biology. Experience in omics, histochemical techniques and animal handling is an advantage, but not mandatory. Master degree: Yes

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Supervisor information:	Prof. Dr. Jan H.J. Hoeijmakers / Dr. Ing. W.P. Vermeij Email address: w.vermeij@erasmusmc.nl Personal website: http://www.erasmusmc.nl/genetica/research/aging_cancer/ Recent publication list, preferably last 3-5 years (1-2 pages) J.A. Marteijn, H. Lans, W. Vermeulen, J.H.J Hoeijmakers. Understanding Nucleotide Excision Repair and its roles in Cancer and Ageing. **Nature Rev Mol Cell Biol** 15, 465-481 (2014). W.P. Vermeij, J.H.J. Hoeijmakers, J. Pothof. Aging: not all DNA damage is equal. **Curr Opin Genet Dev.** 26 (2014). E.L. de Graaf, W.P. Vermeij, M.C. de Waard, Y. Rijksen, I. van der Pluijm, C.C. Hoogenraad, J.H. Hoeijmakers, A.F. Altelaar, A.J. Heck. Spatio-temporal analysis of molecular determinants of neuronal degeneration in the aging mouse cerebellum. **Mol Cell Proteomics.** 12,1350-1362 (2013) 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. 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)