

**Erasmus University Rotterdam, the Netherlands**  
**CSC PhD 2015 Project Description**

<b>School/Department:</b>	Molecular Medicine Postgraduate School, Department of Surgery
<b>Project Title:</b>	Micro-RNAs as mediators of the beneficial effect of short-term dietary manipulations on acute stress resistance
<b>Abstract:</b>	<p>One of the most robust interventions delaying aging and prolonging lifespan in a wide range of experimental animal species is life-long dietary manipulation (DM); a small reduction in nutrient intake or change in nutrient composition that does not cause malnutrition. Although the exact mechanisms by which DM delays aging are not known, it is thought that increased resistance to oxidative stress is a main component. Treatment of patients with cytotoxic chemotherapy can also result in substantial oxidative damage. Cancer patients are commonly treated with chemotherapy, which not only targets tumors, but also damages all other cells in the body and therefore has many side effects, of which some are caused by oxidative damage. Another example of clinical oxidative stress is ischemia reperfusion injury (IRI) during organ transplantation, which can lead to massive oxidative cell and organ damage. We showed that as short as two weeks of DM significantly prevented IRI in the kidney and liver, and prevented adverse side effects of chemotherapy, while it did not affect its anti-tumor activity in mice. We showed that DM is feasible in patients undergoing surgery but also noticed the practical limitations of short-term DM, even in well-motivated persons. Thus, it will be important to generate DM mimetics, agents that can be therapeutically applied and mimic the protective effect of DM. This requires knowledge about the underlying mechanisms of DM, which are largely unclear. MicroRNAs are endogenous small RNA molecules that are important regulators of gene expression. Since it is estimated that approximately 60% of the total genome can be regulated by microRNAs, it is likely that most cellular processes are at least partly under control of microRNAs. We have data to suggest that microRNAs are important mediators of oxidative stress, but also of the beneficial effect of DM. MicroRNAs have potential as DM mimetic, since they can be administered as therapeutic agent, and be knocked down effectively in mammals for prolonged periods of time without harmful side effects. In this proposal we will use RNA sequencing to profile the genomic microRNA responses to chemotherapy toxicity, renal IRI and dietary modulation mediated protection against both. Next, we will functionally characterize microRNAs found in our global expression analysis. By linking these micro RNA expression profiles to global gene expression profiles obtained by Affymetrix analysis we will identify microRNA-regulated pathways. This approach will yield</p>

**Erasmus University Rotterdam, the Netherlands**  
**CSC PhD 2015 Project Description**

	<p>multiple targets for microRNA therapy. Finally, we will design both microRNAs and antisense microRNAs and test these as therapeutic tools in our IRI and chemotherapy models. We expect that the experiments proposed in this application will improve our understanding of the mechanisms of DM on stress resistance and pave the way for development of miRNA-based DM mimetics that can be applied in humans.</p>
<p><b>Requirements of candidate:</b></p>	<p>Master degree: Yes</p> <p>Background: MSc in medical biology / molecular biology or similar, or MD with interest in research using animal models, molecular biological techniques and bioinformatics.</p> <p>IELTS Grade: 7.0 (<i>minimal 6.0 per component</i>)  or  TOEFL: 100 (<i>minimal 20 per component</i>)</p>
<p><b>Supervisor information:</b></p>	<p>Dr. R.W.F. de Bruin, associate professor. Department of Surgery, Laboratory for Experimental Transplantation and Intestinal Surgery, Room Ee100, email: <a href="mailto:r.w.f.debruin@erasmusmc.nl">r.w.f.debruin@erasmusmc.nl</a></p> <p>Selected publication list:</p> <p>Susa D, Mitchell JR, Verweij M, M van de Ven, Roest HP, van den Engel S, Bajema I, Mangundap K, IJzermans JNM, Hoeijmakers JHJ, de Bruin RWF. Congenital DNA repair deficiency results in protection against renal ischemia reperfusion injury. <i>Aging Cell</i>, 2009; 8: 192-200.</p> <p>Khan NA, Susa D, van den Berg JW, Huisman TM, Ameling MH, van den Engel S, Roest HP, IJzermans JNM, Dik WA, Benner R, de Bruin RWF. Inhibition of renal ischemia-reperfusion injury by synthetic oligopeptides related to human chorionic gonadotropin. <i>Nephrol Dial Transplant</i> 2009; 24: 2701-2708.</p> <p>TM van Ginhoven, JR Mitchell, M Verweij, JHJ Hoeijmakers, JNM IJzermans, RWF de Bruin. The use of preoperative nutritional interventions to protect against hepatic ischemia-reperfusion injury. <i>Liver Transplantation</i>, 2009; 15:1183-1191.</p> <p>JR Mitchell, M Verweij, Brand K, S van den Engel, F Forrer, C Muller, M de Jong, W van IJcken, JNM IJzermans, JHJ Hoeijmakers, RWF de Bruin. Short term dietary restriction and fasting precondition against</p>

	<p>ischemia reperfusion injury in mice. Aging Cell 2010; 9: 40-53.</p> <p>van Ginhoven TM, Dik WA, Mitchell JR, Smits-Te Nijenhuis MA, van Holten-Neelen C, Hooijkaas H, Hoeijmakers JH, de Bruin RW, IJzermans JN. Dietary restriction modifies certain aspects of the postoperative acute phase response. J Surg Res 2011;171(2): 582-9.</p> <p>van Ginhoven TM, JW van den Berg, Dik WA, IJzermans JN, De Bruin RW. Preoperative fasting induces protection against renal ischemia-reperfusion injury by an corticosterone independent mechanism. Transplant Int 2010-07-28.</p> <p>Tessa M. van Ginhoven, Ron W.F. de Bruin, Marijke Timmermans, James R. Mitchell, Jan H.J. Hoeijmakers, Jan N.M. IJzermans. Preoperative dietary restriction is feasible in live kidney donors. Clin Transplant 2011; 25 (3): 486-94.</p> <p>van Ginhoven TM, van den Berg JW, Dik WA, IJzermans JN, de Bruin RW. Preoperative dietary restriction reduces hepatic tumor load by reduced E-selectin mediated adhesion in mice. J Surg Oncol 2010; 15;102(4):348-53.</p> <p>van Ginhoven TM, Huisman TM, van den Berg JW, IJzermans JN, Delhanty PJ, de Bruin RW. Preoperative fasting induced protection against renal ischemia/reperfusion injury is independent of ghrelin in mice. Nutr Res. 2010 Dec;30(12):865-9.</p> <p>JW van den Berg, WA Dik, M van der Zee, F. Bonthuis, C van Holten-Neelen, GM Dingjan, R Benner, JNM IJzermans, NA. Khan, RWF de Bruin. The <math>\beta</math>-hCG derived peptide LQGV reduces mortality and sepsis in a murine polymicrobial sepsis model. Crit Care Med 2011; 39: 126-134.</p> <p>JW van den Berg, M van der Zee, RWF de Bruin, C van Holten-Neelen, J Bastiaans, N Nagtzaam, JNM IJzermans, R Benner, WA Dik. Mild versus strong anti-inflammatory therapy during early sepsis in mice; a matter of life and death. Crit Care Med 2011; 39(6):1275-81.</p> <p>M Verweij, T M van Ginhoven, JR Mitchell, W Sluiter, S van den Engel, HP Roest, E Torabi, JNM IJzermans, JHJ Hoeijmakers, RWF de Bruin. Short-term fasting protects mice against hepatic ischemia reperfusion injury: mechanisms, and effect on liver regeneration. Liver Transplant 2011;17 (6): 695-704.</p>
--	---

	<p>WRR Farid, J de Jonge, JC Sliker, PE Zondervan, MGJ Thomeer, HJ Metselaar, RWF de Bruin, G Kazemier. The importance of portal venous blood flow in ischemic-type biliary lesions after liver transplantation. <i>Am J Transplant</i> 2011;11(4):857-62.</p> <p>Verweij M, van de Ven M, Mitchell JR, van den Engel S, Hoeijmakers JH, Ijzermans JN, de Bruin RW. Glucose supplementation does not interfere with fasting-induced protection against renal ischemia/reperfusion injury in mice. <i>Transplantation</i>. 2011; 15;92(7):752-8.</p> <p>van der Kaaij NP, Kluin J, Lachmann RA, den Bakker MA, Lambrecht BN, Lachmann B, de Bruin RW, Bogers AJ. Alveolar preservation with high inflation pressure and intermediate oxygen concentration reduces ischemia-reperfusion injury of the lung. <i>J Heart Lung Transplant</i>. 2012;31(5):531-7.</p> <p>Verweij M, Sluiter W, van den Engel S, Jansen E, Ijzermans JN, de Bruin RW. Altered mitochondrial functioning induced by preoperative fasting may underlie protection against renal ischemia/reperfusion injury. <i>J Cell Biochem</i>. 2013;114(1):230-7.</p> <p>van den Akker EK, Manintveld OC, Hesselink D, de Bruin RWF, IJzermans JNM, Dor FJMF. Protection against renal ischemia reperfusion injury by ischemic postconditioning. <i>Transplantation</i> 2013; 95:1299-305.</p> <p>TC Saat, D Susa, HP Roest, NFM Kok, S van den Engel, JNM IJzermans, RWF de Bruin. A comparison of inflammatory, cytoprotective and injury gene expression profiles in kidneys from brain death and cardiac death donors. <i>Transplantation</i> 2014; 98 (1): 15-21.</p> <p>Huisman SA, Oklejewicz M, Ahmadi AR, Tamanini F, Ijzermans JN, van der Horst GT, de Bruin RW. Colorectal liver metastases with a disrupted circadian rhythm phase shift the peripheral clock in liver and kidney. <i>Int J Cancer</i>. 2014 Jul 21</p>
--	--