ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Erasmus MC, Internal Medicine, Calcium and Bone Metabolism
Project Title:	Is bone a central endocrine regulator of healthy aging?
Abstract:	Aging leads to progressive loss of function of organ systems, resulting in a wide array of aging-associated diseases, such as cardiovascular disease, osteoporosis, type 2 diabetes and arthritis. With the population getting older, the term 'healthy aging' has been coined and indicates the necessity to prevent or inhibit the processes that lead to aging and its associated financial impact on society. Defects in enzymes involved in DNA repair lead to accelerated aging in humans, such as trichothiodystrophy and Cockayne's syndrome. Mouse models resembling these disorders have revealed bone phenotypes indicative of accelerated bone loss. However, it is currently unknown whether the bone phenotype is a direct or indirect consequence of the deficiency. The first aim of the project is therefore to generate bone cell (osteoblast and osteoclast)-specific DNA repair enzyme deficient mice to determine its direct involvement in skeletal aging. Recent discoveries have identified bone as an endocrine organ, being the sole producer of fibroblast growth factor 23 and osteocalcin. These factors affect phosphate metabolism and insulin sensitivity, respectively, and both deteriorating with age. Given its central role and the fact that DNA-repair enzyme deficiency leads to accelerated bone aging, we will study these endocrine systems in the bone-specific DNA repair deficient mice during aging. Using these approaches, we aim to identify bone as a central player in these systemic processes during aging.
Requirements of candidate:	Master degree: Yes Background: The candidate preferably has gathered experienced in the field of bone biology. In addition, a certificate to perform animal experiments is desired, but not required. IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*

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Supervisor information:	Dr. B.C.J. van der Eerden/ Prof.dr. J.P.T.M. van Leeuwen Email address: b.vandereerden@erasmusmc.nl Personal website: http://www.erasmusmc.nl/inwendige_geneeskunde/endocrinologie/research/2341721/ Recent publication list, preferably last 3-5 years (1-2 pages):
Publication list (last 5 years):	- van der Eerden BC, ven der Heyden JC, van Hamburg JP, Schreuders-Koedam M, Asmawidjaja PS, de Muinck Keizer-Schrama SM, Boot AM, Lubberts E, Drop SL, van Leeuwen JP. A human vitamin D receptor mutation causes rickets and impaired Th1/Th17 responses. Bone, 2014; *In press.* - van der Eerden BC, Teti A, Zambuzzi WF. Bone, a dynamic and integrating tissue. Arch Biochem Biophys, 2014; doi: 10.1016/j.abb.2014.08.012. [Epub ahead of print] - Delhanty PJ, van der Velde M, van der Eerden BC, Sun Y, Geminn JM, der Lely AJ, Smith RG, van Leeuwen JP.Genetic manipulation of the ghrelin signaling system in male mice reveals bone compartment specificity of acylated and unacylated ghrelin in the regulation of bone remodeling. Endocrinology, 2014; 25:en20132055. [Epub ahead of print] - van der Eerden BC. MicroRNAs in the skeleton: Cell-restricted or potent intercellular communicators? Arch Biochem Biophys, 2014; doi: 10.1016/j.abb.2014.04.016. [Epub ahead of print] - van der Eerden BC, Oei L, Roschger P, Fratzl-Zelman N, Hoenderop JG, van Schoor NM, Pettersson-Kymmer U, Schreuders-Koedam M, Uitterlinden AG, Hofman A, Suzuki M, Klaushofer K, Ohlsson C, Lips P, Rivadeneira F, Bindels R, and van Leeuwen JP. TRPV4 deficiency causes sexual dimorphism in bone metabolism and osteoporotic fracture risk. Bone, 2013;57(2):443-54 - Delhanty P, van der Eerden BC, van Leeuwen JP. Ghrelin and Bone. Biofactors. 2014;40(1):41-8 - Woeckel VJ, van der Eerden BC, Schreuders-Koedam M, Eijken M, Van Leeuwen JP. 1α,25-dihydroxyvitamin D3 stimulates activin A production to fine-tune osteoblast-induced mineralization. J Cell Physiol. 2013;228(11):2167-74 - Woeckel VJ, Bruedigam C, Koedam M, Chiba H, van der Eerden BC, van Leeuwen JP. 1α,25-dihydroxyvitamin D3 and rosiglitazone synergistically enhance osteoblast-mediated mineralization. Gene. 2013;512(2):438-43. - Woudenberg-Vrenken TE, van der Eerden BC, van der Kemp AW, van Leeuwen JP, Bindels RJ, Hoenderop JG. Characterization of vitamin D-deficient klotho(-/-) mice: do increased levels of serum 1,25(OH)2D3 cause disturbed calcium and phosphate homeostasis in klotho(-/-) mice? Nephrol Dial Transplant. 2012;27(11):4061-8.

Continued:	- van der Eerden BC, Fratzl-Zelman N, Nijenhuis T, Roschger P, Zügel U, Steinmeyer A, Hoenderop JG, Bindels RJ, Klaushofer K, van Leeuwen JP. The vitamin D analog ZK191784 normalizes decreased bone matrix mineralization in mice lacking the calcium channel TRPV5. J Cell Physiol. 2013;228(2):402-7. - van der Velde M, van der Eerden BC, Sun Y, Almering JM, van der Lely AJ, Delhanty PJ, Smith RG, van Leeuwen JP. An age-dependent interaction with leptin unmasks ghrelin's bone-protective effects. Endocrinology. 2012;153(8):3593-602. - Nicolaije C, Diderich KE, Botter SM, Priemel M, Waarsing JH, Day JS, Brandt RM, Schilling AF, Weinans H, Van der Eerden BC, van der Horst GT, Hoeijmakers JH, van Leeuwen JP. Age-related skeletal dynamics and decrease in bone strength in DNA repair deficient male trichothiodystrophy mice. PLoS One. 2012;7(4):e35246. - Woeckel VJ, Koedam M, van de Peppel J, Chiba H, van der Eerden BC, van Leeuwen JP. Evidence of vitamin D and interferon-β cross-talk in human osteoblasts with 1α,25-dihydroxyvitamin D3 being dominant over interferon-β in stimulating mineralization. J Cell Physiol. 2012;227(9):3258-66. - Woeckel VJ, Eijken M, van de Peppel J, Chiba H, van der Eerden BC, van Leeuwen JP. IFNβ impairs extracellular matrix formation leading to inhibition of mineralization by effects in the early stage of human osteoblast differentiation. J Cell Physiol. 2012;227(6):2668-76. - Alves RD, Demmers JA, Bezstarosti K, van der Eerden BC, Verhaar JA, Eijken M, van Leeuwen JP. Unraveling the human bone microenvironment beyond the classical extracellular matrix proteins: a human bone protein library. J Proteome Res. 2011;10(10):4725-33. - van der Eerden BC, Weissgerber P, Fratzl-Zelman N, Olausson J, Hoenderop JG, Schreuders-Koedam M, Eijken M, Roschger P, de Vries TJ, Chiba H, Klaushofer K, Flockerzi V, Bindels RJ, Freichel M, van Leeuwen JP. The transient receptor potential channel TRPV6 is dynamically expressed in bone cells but is not crucial for bone mineralization in mice. J Cell Physiol. 2012;227(5):1951-9. - Bruedigam C, van Driel M, Koedam M, van de Peppel J, van der Eerden BC, Eijken M, van Leeuwen JP. Basic techniques in human mesenchymal stem cell cultures: differentiation into osteogenic and adipogenic lineages, genetic perturbations, and phenotypic analyses. Curr Protoc Stem Cell Biol. 2011;Chapter 1:Unit1H.3. - Woeckel VJ, Alves RD, Swagemakers SM, Eijken M, Chiba H, van der Eerden BC, van Leeuwen JP. 1Alpha,25-(OH)2D3 acts in the early phase of osteoblast differentiation to enhance mineralization via accelerated production of mature matrix vesicles. J Cell Physiol. 2010;225(2):593-600.