

PhD Project Description

Department:	Department of Medical Oncology. Erasmus MC
Supervisor information:	<p>Supervisors: Dr. Antoinette Hollestelle (a.hollestelle@erasmusmc.nl) Prof dr. John Martens (j.martens@erasmusmc.nl)</p> <p>Website: https://www.erasmusmc.nl/en/cancer-institute/research/departments/medical-oncology</p> <p>Grants: Over 45 grants from national, European and international research funders, including 7 industry grants.</p> <p>Most important recent publications:</p> <ol style="list-style-type: none"> 1. Lindsay Angus, ..., John W.M. Martens. 2019. Genomic landscape of metastatic breast cancer and its clinical implications. Nature Genetics 51(10):1450-8. 2. Kyriaki Michailidou, ..., Antoinette Hollestelle, ..., Douglas F. Easton. 2017. Association analysis identifies 65 new breast cancer risk loci. Nature 551(7678):92-4. 3. Serena Nik-Zainal, ..., John W. M. Martens, ..., Michael R. Stratton. 2016. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. Nature 534(7605):47–54. 4. Marcel Smid, ..., John W. M. Martens. 2016. Breast cancer genome and transcriptome integration implicates specific mutational signatures with immune cell infiltration. Nature Communications 7:12910. 5. Alison M. Dunning, ..., Antoinette Hollestelle, ..., Stacey L. Edwards. 2016. Breast cancer risk variants at 6q25 display different phenotype associations and regulate ESR1, RMND1 and CCDC170. 2016. Nature Genetics 48(4):374-86. 6. Marjanka K. Schmidt, ..., Antoinette Hollestelle, ..., Douglas F. Easton. 2016. Age- and tumor subtype-specific breast cancer risk estimates for CHEK2*1100delC carriers. J Clin Oncol 34(23):2750-60 7. Hanne Meijers-Heijboer, ..., Antoinette Hollestelle, ..., Mieke Schutte. 2003. The CHEK2*1100delC mutation identifies families with a hereditary breast and colorectal cancer phenotype. Am J Human Genet 72(5):1308-14. 8. Hanne Meijers-Heijboer, ..., Antoinette Hollestelle, ..., Michael R. Stratton. 2002. Low-penetrance susceptibility to breast cancer due to CHEK2*1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nature Genetics 31(1):55-9.
Project Title:	<i>Unraveling the mechanisms underlying CHEK2 c.1100delC-driven breast tumorigenesis</i>
Abstract:	<p>In 2002, we discovered the <i>CHEK2</i> c.1100delC mutation as the first moderate-risk breast cancer (BC) susceptibility allele, conferring a 2.3-fold increased BC risk⁸. Although we gained much knowledge since then regarding the clinical features of women and BC patients carrying this allele, we still do not know how <i>CHEK2</i> c.1100delC drives the development of BC biologically.</p> <p>Therefore, we recently sequenced the BC genomes of patients carrying this particular <i>CHEK2</i> mutation and identified a structural variant signature specific to <i>CHEK2</i> mutation carriers. This signature provides clues to unraveling the biological mechanism of CHEK2-driven tumorigenesis. Furthermore, although CHEK2 is a key player in homologous recombination repair, like BRCA1 and BRCA2, the biological mechanism by which it promotes BC seems quite different.</p> <p>In this project the PhD student will develop a normal human ER-positive breast model system to study CHEK2-driven tumorigenesis by generation of induced pluripotent stem cells and gene editing techniques such as CRISPR/Cas9 or prime editing and stem cell differentiation protocols. Once this model system is developed the mechanism will be further studied using techniques such as whole genome and transcriptome sequencing as well as functional and DNA repair assays.</p> <p>Ultimately, we will apply this gained knowledge to improve treatment for breast cancer patients carrying the <i>CHEK2</i> c.1100delC mutation.</p> <p>The PhD student will be working in a project team with molecular biologists, clinicians/epidemiologists and computational biologists supervised by Dr. Hollestelle and prof. Martens. The student will take part in the excellent educational PhD and career guidance program of the Molecular Medicine postgraduate school at Erasmus MC.</p>

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Requirements of candidate:	<p>We are looking for a candidate with strong analytical and problem solving skills, being highly motivated and having excellent communication and writing skills and able to work independently.</p> <p>A background in cancer biology is of significant added value.</p> <p>Master degree in molecular/cellular biology or a related field.</p> <p>The candidate should have demonstrated excellent scientific writing and experimental laboratory skills.</p> <p>A scholarship that will, at least, cover subsistence allowance and international air plane ticket (we could help with the scientific part of your scholarship proposal)</p> <p>The student should be fluent in English (English speaking countries & Netherlands): no</p> <p>Requirement: IELTS 7.0 (min 6.0 for all subs), TOEFL 100 (min 20 for all subs).</p>
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Application requirements & Deadlines:

<https://www.eur.nl/en/about-eur/erasmus-university-china-centre/csc-scholarship>

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<https://www.usnews.com/education/best-global-universities/clinical-medicine?page=3>

** No. 30 Nature Index for Biomedical Sciences 2019:*

<https://www.natureindex.com/supplements/nature-index-2019-biomedical-sciences/tables/healthcare>