

PhD Project Description

School/Department:	Department of Gastroenterology and Hepatology, Erasmus MC
Supervisor information:	<ul style="list-style-type: none"> Associate Professor dr Jaap Kwekkeboom Email: j.kwekkeboom@erasmusmc.nl Website: https://www.erasmusmc.nl/en/research/researchers/kwekkeboom-j Recent personal Grants: <ul style="list-style-type: none"> Merus NV research grant 2020: € 192,000 Pfizer research grant 2018: € 85,000 Health Holland Life Sciences & Health grant 2017: € 689,257 Erasmus MC PhD-grant 2016: € 150,000 Pfizer research grant 2015: € 499,591 Most important recent publications: <ol style="list-style-type: none"> Campos Carrascosa L, van Beek AA, de Ruiter V, Doukas M, Wei J, Fisher TS, Ching K, Yang W, van Loon K, Boor PPC, Rakké YS, Noordam L, Doornebosch P, Grünhagen D, Verhoef K, Polak WG, IJzermans JNM, Ni I, Yeung YA, Salek-Ardakani S, Sprengers D, Kwekkeboom J. FcγRIIB engagement drives agonistic activity of Fc-engineered αOX40 antibody to stimulate human tumor-infiltrating T cells. <i>J. Immunother Cancer</i> 2020; 8(2): e000816. Zhou G, Sprengers D, Mancham S, Erkens R, Boor PPC, van Beek AA, Doukas M, Noordam L, Campos Carrascosa L, de Ruiter V, van Leeuwen RWF, Polak WG, de Jonge J, Groot Koerkamp B, van Rosmalen B, van Gulik TM, Verheij J, IJzermans JNM, Bruno MJ, Kwekkeboom J. <i>J Hepatol</i>. 2019;71(4):753-762 Zhou G, Sprengers D, Boor PPC, Doukas M, Schutz H, Mancham S, Pedroza-Gonzalez A, Polak WG, de Jonge J, Gaspersz M, Dong H, Thielemans K, Pan Q, JNM IJ, Bruno MJ, Kwekkeboom J. Antibodies Against Immune Checkpoint Molecules Restore Functions of Tumor-Infiltrating T Cells in Hepatocellular Carcinomas. <i>Gastroenterology</i> 2017;153(4): 1107-1119 e1110. Sideras K, Biermann K, Verheij J, Takkenberg BR, Mancham S, Hansen BE, Schutz HM, de Man RA, Sprengers D, Buschow SI, Verseput MC, Boor PP, Pan Q, van Gulik TM, Terkivatan T, IJzermans JN, Beuers UH, Sleijfer S, Bruno MJ, Kwekkeboom J. PD-L1, Galectin-9 and CD8(+) tumor-infiltrating lymphocytes are associated with survival in hepatocellular carcinoma. <i>Oncoimmunology</i> 2017;6(2): e1273309.
Project Title:	Co-targeting of tumor-infiltrating T cells and NK cells to treat liver cancer and colorectal cancer
Abstract:	<p>The focus of our research group is to identify novel immunotherapeutic targets for hepatocellular carcinoma and mismatch-repair-deficient colorectal cancer. Current immune checkpoint inhibitors (anti-PD1, anti-PD-L1 and anti-CTLA-4 antibodies) have limited clinical efficacy in these cancer types. These antibodies target immune checkpoint molecules expressed on T cells only. We hypothesize that co-targeting of immune checkpoint expressed on both T cells and NK cells may show higher clinical efficacy. The aim of this PhD-project is to determine which inhibitory and/or stimulatory immune checkpoint molecules should be targeted to simultaneously enhance anti-tumor responses of T-cells and NK-cells in these types of cancer.</p> <p>You will isolate tumor-infiltrating lymphocytes from surgically resected human cancer tissues and, using flow cytometry, establish which inhibitory and stimulatory immune checkpoint molecules are over-expressed on both T cells and NK cells in these tumors. Subsequently, using different types of T-cell and NK-cell culture assays, you will determine whether antibodies against these over-expressed molecules, and combinations of these antibodies, can simultaneously enhance the functionality of tumor-derived T cells and NK cells. Human cancer cell lines and tumor-derived organoids will be used to study cytotoxicity of T cells and NK cells against cancer cells. The mechanisms-of-action by which antibodies targeting these immune checkpoints enhance functionality of tumor-infiltrating NK cells and T cells will be studied using RNA-sequencing. Together, this project will reveal potentially interesting molecular targets for immunotherapy in hepatocellular carcinoma and MMR-proficient colorectal cancer.</p>
Requirements of candidate:	<ul style="list-style-type: none"> We are looking for a highly motivated student to join our international team. Master degree or MD with at least basic expertise in cell culture and flow cytometry. Scholarship that will cover subsistence allowance and international air plane ticket (we will help in writing the scientific part of your scholarship proposal). English language requirement: <i>English speaking countries & Netherlands</i>: no requirement. <i>Other countries</i>: IELTS 7.0 (min 6.0 for all subs), TOEFL 100 (min 20 for all subs).

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Application requirements & Deadlines:

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

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** No.32 for Clinical Medicine US News 2020:*

<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>