ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

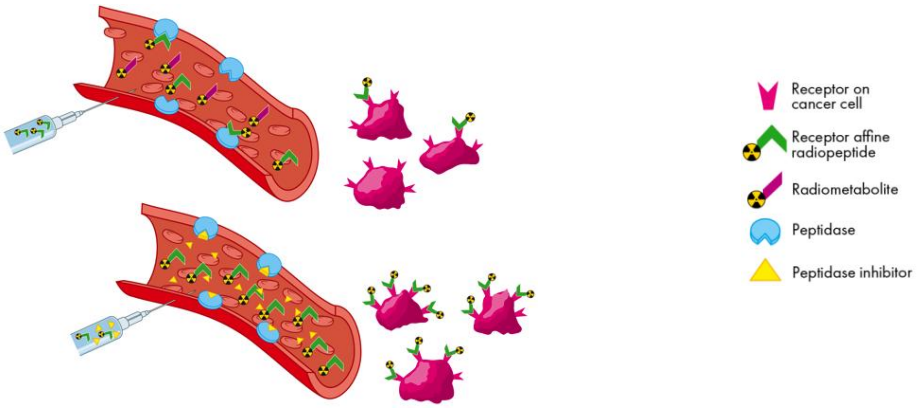
School/Department:	Departments of Nuclear Medicine and Radiology Erasmus MC Rotterdam, The Netherlands
Project Title:	Radiolabelled peptide tracers for tumor imaging and radionuclide therapy: a new approach.
Abstract:	Peptides have excellent properties as targeting radiolabelled tracers for diagnosis and treatment of tumors, because of their fast, specific and high-affinity binding to their receptor on tumors combined with very fast clearance; resulting in exceptionally high tumor to background ratios. Excellent results have been obtained worldwide with stabilized somatostatin-based tracers for tumor imaging and for radionuclide therapy. Yet, the extensive and successful use of radiopeptides in a broader spectrum of tumors has been restricted, mainly due to the fast degradation of peptides, a known and major hurdle to their use as medicinal drugs. We have recently proposed a highly efficient approach to improve the stability of peptide-tracers in the blood stream translating in a huge enhancement of tumor uptake in mice without influencing background clearance. We found a single enzyme, neutral endopeptidase (NEP), to be the major player in the in vivo degradation of a wide array of radiopeptides from the somatostatin, gastrin, and the bombesin families. By single co-administration of a **suitable enzyme-inhibitor** we could induce stabilization of circulating radiotracers; significantly increasing **supply to tumor-associated receptors** and **tumor-to-background ratios**. 

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	Figure: Representation of a radiopeptide on its way to the target receptor on cancer cells. Upper part: Peptidases degrade a big portion of radiopeptide molecules; leading to poor tumor uptake. Lower part: Coinjection with an enzyme inhibitor leads to radiopeptide stabilization and improved delivery at the tumor. This concept is expected to revolutionize the application of biodegradable peptide-based ligands for imaging and therapy. Aim of the project: • To establish new inhibitor/peptide pairs for in vivo nuclear and optical imaging Plan of investigation: • Generation (peptide synthesis, phage display) and preclinical validation a small array of new peptides for prostate and breast cancer imaging. • Radiolabeling and testing in preclinical nuclear imaging studies (PET, SPECT) in the absence and presence of enzyme inhibitors. In vivo studies will be performed in tumor-bearing nude mice. • Translate the best findings obtained with radioabelled peptides into fluorescent peptides for optical imaging.
Requirements of candidate:	Background: The candidate is expected to: - Have a background in (bio)chemistry, biology, medical physics (e.g. bio-engineering), or equivalent; - Have good people interaction skills for working in a team with people from different academic backgrounds. The candidate preferably has - Affinity with preclinical imaging studies - Affinity with animal studies - Affinity with state of the art imaging techniques Master degree: Yes IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*

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Supervisor information:	Prof. dr. Marion de Jong, Prof of Nuclear Biology Email address: m.hendriks-dejong@erasmusmc.nl Prof. Marion de Jong is co-author of >250 peer-reviewed papers (H-Index: 44) and PI in national and international research projects. Her scientific interests include tracer development and evaluation, multimodality molecular imaging in small animals as well as translational studies on tumour-targeted imaging and radionuclide therapy: See her YouTube movie "Radiopeptides destroy tumour cells" http://www.youtube.com/watch?v=0YvG_MCXZsw). She is chair of the expert committee of the applied molecular imaging facility (AMIE-facility); see http://www.erasmusmc.nl/amie Publication list: shortlist from >250 publications: • De Jong M., Essers J., van Weerden W.M. Imaging preclinical tumour models: improving translational power. Nature Rev. Cancer 14, 481–493 (2014). • Nock, B. A., Maina, T., Krenning, E. P., de Jong M. 'To serve and protect': enzyme inhibitors as radiopeptide escorts promote tumor targeting. J. Nucl. Med. 55, 121–127 (2014). • Pool SE, Kam BL, Koning GA, Konijnenberg M, Ten Hagen TL, Breeman WA, Krenning EP, de Jong M, van Eijck CH. [(111)In-DTPA]octreotide tumor uptake in GEPNET liver metastases after intra-arterial administration: an overview of preclinical and clinical observations and implications for tumor radiation dose after peptide radionuclide therapy. Cancer Biother Radiopharm. 2014 May;29(4):179-87 • Bernsen MR, Vaissier PE, Van Holen R, Booij J, Beekman FJ, de Jong M. The role of preclinical SPECT in oncological and neurological research in combination with either CT or MRI. Eur J Nucl Med Mol Imaging. 2014 May;41 Suppl 1:S36-49. • Tatsi A, Maina T, Cescato R, Waser B, Krenning EP, de Jong M, Cordopatis P, Reubi JC, Nock BA. [DOTA]Somatostatin-14 analogs and their (111)In-radioligands: effects of decreasing ring-size on sst1-5 profile, stability and tumor targeting. Eur J Med Chem. 2014 Feb 12;73:30-7. • Bison SM, Konijnenberg MW, Melis M, Pool SE, Bernsen MR, Teunissen JJ, Kwekkeboom DJ, de Jong M. Peptide receptor radionuclide therapy using radiolabeled somatostatin analogs: focus on future developments. Clin Transl Imaging. 2014;2:55-66. • Bison SM, Pool SE, Koelewijn SJ, van der Graaf LM, Groen HC, Melis M, de Jong M. Peptide receptor radionuclide therapy (PRRT) with [(177)Lu-DOTA(0),Tyr(3)]octreotate in combination with RAD001 treatment: further investigations on tumor

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