Time is of the essence - investigating kinetic interactions between drug, endogenous neuropeptides and receptor

Nederpelt, I.

List of publications

From receptor binding kinetics to signal transduction; a missing link in predicting in vivo drug-action. I. Nederpelt, M. Kuzikov, P. Schnider, B. Tuijt, A.P. IJzerman, E.C.M. de Lange, L.H. Heitman. *Manuscript in preparation*

Kinetic Profile of Neuropeptide-Receptor Interactions. I. Nederpelt, J. Bunnik, A.P. IJzerman, L.H. Heitman. *Trends in Neurosciences* **2016** 39 (12): 830–839

Kinetic binding and activation profiles of endogenous tachykinins targeting the NK1 receptor. I. Nederpelt, D. Bleeker, B. Tuijt, A.P. IJzerman, L.H. Heitman. *Biochemical Pharmacology* **2016** 118: 88-95

Persistent GnRH receptor activation in pituitary αT3-1 cells analyzed with a label-free technology. I. Nederpelt, R.D. Vergroesen, A P. IJzerman and L.H. Heitman. *Biosensors and Bioelectronics* **2016** 79: 721-727

Characterization of 12 GnRH peptide agonists – a kinetic perspective. I. Nederpelt, V. Georgi, F. Schiele, K. Nowak-Reppel, A.E. Fernández-Montalván, A.P. IJzerman and L.H. Heitman. *British Journal of Pharmacology* **2016** 173 (1): 128-41

Kinetics for Drug Discovery – An industry driven effort to target drug residence time. D.A. Schuetz, W.E.A. de Witte, Y.C. Wong, B. Knasmueller, L. Richter, R. Bosma, D. Kokh, S. Kashif, I. Nederpelt, E. Segala, M. Amaral, D. Guo, D. Andres, L.A. Stoddart, S. Hill, R.M. Cooke, R. Leurs, M. Frech, R. Wade, E.C.M de Lange, A.P. IJzerman, A. Müller-Fahrnow, G.F. Ecker. *Drug Discovery Today* in press

Mechanistic models enable the rational use of in vitro drug-target binding kinetics for better drug effects in patients. W.E. de Witte, Y.C. Wong, I. Nederpelt, L.H. Heitman, M. Danhof, P.H. van der Graaf, R.A. Gilissen, E.C. de Lange. *Expert Opinion in Drug Discovery* **2016** 11 (1): 45-63

Multiple binding sites for small-molecule antagonists at the CC chemokine receptor 2. A.J. Zweemer, I. Nederpelt, H. Vrieling, S. Hafith, M.L. Doornbos, H. de Vries, J. Abt, R. Gross, D. Stamos, J. Saunders, M.J. Smit, A.P. IJzerman, L.H. Heitman. *Molecular Pharmacology* **2013** 84 (4): 551-61

Curriculum Vitae

Indira Nederpelt was born in Rotterdam, The Netherlands on October 4th, 1988. After graduating high school at the IJsselcollege in Capelle aan den IJssel, she studied Biopharmaceutical Sciences at Leiden University starting in 2006. During her studies she performed two research internships under supervision of Dr. Annelien Zweemer, Dr. Laura Heitman and Prof. Dr. Ad IJzerman. These internships were both focused on designing and validating kinetic binding assays for the GnRH receptor and CCR2 receptor. Her contribution to the CCR2 project resulted in a co-publication in Molecular Pharmacology. Subsequently she moved to San Diego, CA, USA to perform a third internship at Vertex Pharmaceuticals under supervision of Akiko Nakatani and Dr. Julie Selkirk. She studied ligand selectivity at the extracellular and intracellular binding site of a tyrosine receptor kinase in an industrial setting. Upon her return to The Netherlands she finished her MSc. degree *cum laude* in 2012.

In 2013, Indira started her PhD study at Leiden University at the Department of Medicinal Chemistry, under supervision of Dr. Laura Heitman and Prof. Dr. Ad IJzerman. Her PhD research was part of an Innovative Medicine Initiative (IMI) project named Kinetics for Drug Discovery (K4DD) (grant number 115366) in collaboration with 20 partners throughout Europe in academia, small and medium-sized enterprises (SMEs) and pharmaceutical companies. This project was founded to improve measurement techniques and the understanding of ligand-receptor binding kinetics. Indira's research was focused on two G protein-coupled receptors, the GnRH receptor (a continuation of the project from her research internship) and the NK1 receptor. Throughout her PhD studies she presented the work described in this thesis at numerous national and international conference. In 2014 she was awarded the Young Investigator Award at the 11th international symposium on GnRH for best oral presentation. Later that year she was awarded for the best oral presentation at the Dutch Medicine Days in the section medicinal chemistry.

Acknowledgements

Throughout my PhD I have found support, advice and inspiration in my students, colleagues, friends and family. I'm truly appreciative of all your contributions and I have become a better scientist because of it.

I would like to thank K4DD for enabling this research and introducing me to a large group of junior and senior scientists working in academia and pharmaceutical companies. Amaury, Felix, Victoria, Patrick, Maria, Wilbert and Liesbeth, thank you for the wonderful collaborations, you've taught me a lot about team-work. All other K4DD fellows have been equally important for all the fruitful scientific (and non-scientific) discussions during our bi-annual meetings. I am grateful to all my students who've taught me how to be a supervisor. More importantly, I'm happy to have been part of the start of your scientific endeavors and without your hard work and dedication this thesis wouldn't exist. Laura, your ambition and work ethic inspired me to dream big. Ad, the combination of your dry humor and leadership skills made you the group leader I aspire to be. It has been a pleasure to start my scientific career working in your group. All my colleagues at medicinal chemistry, thank you for making me laugh during all our coffee breaks. My office mates, Joey, Miriam, Julia, Andrea, Maarten, Xuesong and Anna, all our interesting, weird and funny (non-)work related discussions never failed to give me new perspectives and put a smile on my face. Maarten, Henk and Miriam, thank you for always listening when I needed to vent and for helping me destress.

Mijn lieve vriendinnen, Bo, Michelle, Lisette, Tamar, bedankt voor jullie begrip en vriendschap in de afgelopen 4 jaar. Al onze spelletjesavonden, wandelingen, bootcamp en squash avonturen hebben mij ontzettend geholpen te ontspannen en geluk te vinden in jullie aanwezigheid. Rochelle, super bedankt voor onze eindeloze gesprekken, puzzelmiddagen en het ontwerpen van de cover. Akiko and Neelu, although we are separated by an ocean, your words of encouragement and unconditional friendship mean the world to me. Pap, je bent een man van weinig woorden maar je bent er altijd als ik je nodig heb. Mirjam, mijn onofficiële zusje, onze vriendschap begon 25 jaar geleden en vanaf dag 1 is onze band heel bijzonder. Jouw rust, steun en liefde is onschatbaar.

Tot slot, mam, jij bent de moeder en beste vriendin die iedereen verdient. Dankzij jouw humor, advies, steun, begrip en onvoorwaardelijke liefde schijnt de zon altijd in mijn leven. Met jou in mijn leven durf ik de grootste uitdagingen aan te gaan omdat ik weet dat jij er altijd bent om me te vangen als ik val.