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Corpora non agunt nisi fixata : ligand receptor binding kinetics in G protein-coupled receptors

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List of Publications

1: **Xia L**, Kyrizaki A, Tosh DK, van Duijl TT, Roorda JC, Jacobson KA, IJzerman AP, Heitman LH. A binding kinetics study of human adenosine A_3 receptor agonists. *Biochem Pharmacol.* 2018 Jan 3. doi:10.1016/j.bcp.2017.12.026.

2: **Xia L**, de Vries H, Lenselink EB, Louvel J, Waring MJ, Cheng L, Pahlén S, Petersson MJ, Schell P, Olsson RI, Heitman LH, Sheppard RJ, IJzerman AP. Structure-Affinity Relationships and Structure-Kinetic Relationships of 1,2-Diarylimidazol-4-carboxamide Derivatives as Human Cannabinoid 1 Receptor Antagonists. *J Med Chem.* 2017; 60(23): 9545-9564. doi: 10.1021/acs.jmedchem.7b00861.

3: **Xia L**, de Vries H, Yang X, Lenselink EB, Kyrizaki A, Barth F, Louvel J, Dreyer MK, van der Es D, IJzerman AP, Heitman LH. Kinetics of human cannabinoid 1 (CB_1) receptor antagonists: Structure-kinetics relationships (SKR) and implications for insurmountable antagonism. *Biochem Pharmacol.* 2017 Nov 2. doi: 10.1016/j.bcp.2017.10.014.

4: **Xia L,** Burger WAC, van Veldhoven JPD, Kuiper BJ, van Duijl TT, Lenselink EB, Paasman E, Heitman LH, IJzerman AP. Structure-Affinity Relationships and Structure-Kinetics Relationships of Pyrido[2,1-f]purine-2,4-dione Derivatives as Human Adenosine A_3 Receptor Antagonists. *J Med Chem.* 2017; 60(17): 7555-7568. doi: 10.1021/acs.jmedchem.7b00950.

5: Soethoudt M, Grether U, Fingerle J, Grim TW, Fezza F, de Petrocellis L, Ullmer C, Rothenhäusler B, Perret C, van Gils N, Finlay D, MacDonald C, Chicca A, Gens MD, Stuart J, de Vries H, Mastrangelo N, **Xia L**, Alachouzos G, Baggelaar MP, Martella A, Mock ED, Deng H, Heitman LH, Connor M, Di Marzo V, Gertsch J, Lichtman AH, Maccarrone M, Pacher P, Glass M, van der Stelt M. Cannabinoid CB_2 receptor ligand profiling reveals biased signalling and off-target activity. *Nat Commun.* 2017 Jan 3;8:13958. doi: 10.1038/ncomms13958.

6: **Xia L,** de Vries H, IJzerman AP, Heitman LH. Scintillation proximity assay (SPA) as a new approach to determine a ligand's kinetic profile. A case in point for the adenosine A_1 receptor. *Purinergic Signal.* 2016; 12(1): 115-26. doi: 10.1007/s11302-015-9485-0.

7: Massink A, Gutiérrez-de-Terán H, Lenselink EB, Ortiz Zacarías NV, **Xia L**, Heitman LH, Katritch V, Stevens RC, IJzerman AP. Sodium ion binding pocket mutations and adenosine A_{2A} receptor function. *Mol Pharmacol.* 2015; 87(2): 305-13. doi: 10.1124/mol.114.095737.

8: Louvel J, Guo D, Agliardi M, Mocking TA, Kars R, Pham TP, **Xia L**, de Vries H, Brussee J, Heitman LH, IJzerman AP. Agonists for the adenosine A_1 receptor with tunable residence time. A Case for nonribose

4-amino-6-aryl-5-cyano-2-thiopyrimidines. *J Med Chem.* 2014; 57(8): 3213-22. doi: 10.1021/jm401643m.

9: Guo D, **Xia L**, van Veldhoven JP, Hazeu M, Mocking T, Brussee J, IJzerman AP, Heitman LH. Binding kinetics of ZM241385 derivatives at the human adenosine A_{2A} receptor. *ChemMedChem*. 2014; 9(4): 752-61. doi: 10.1002/cmdc.201300474.

10: Gutiérrez-de-Terán H, Massink A, Rodríguez D, Liu W, Han GW, Joseph JS, Katritch I, Heitman LH, **Xia L**, IJzerman AP, Cherezov V, Katritch V, Stevens RC. The role of a sodium ion binding site in the allosteric modulation of the A_{2A} adenosine G protein-coupled receptor. Structure. 2013; 21(12): 2175-85. doi: 10.1016/j.str.2013.09.020.

11: **Xia L**, Zhou M, Xiao Y, Li G, Chen X, Zhang G. Chemical constituents from Helwingia japonica. Chinese Journal of Natural Medicines 2010; 8(1): 16-20. doi: 10.3724/sp.j.1009.2010.00016

12: Wu H, Lin W, **Xia L**, Luo Y, Chen X, Li G, Zhang G, Pan X. 'N-Stereogenic Quaternary Ammonium Salts' from L-Amino Acids: Synthesis, Separation, and Absolute Configuration 2009; 92(4): 677-88. doi: 10.1002/hlca.200800326

Curriculum Vitae

Lizi Xia was born in Luzhou, China, on 4th December 1983. In 2002, after graduating from Shi Shi High School (Chengdu, China), he started his university education at Xiangya School of Medicine, Central South University (Changshang, China), majoring in biopharmaceutical sciences. In 2006 he received a bachelor degree, and then he continued a joint master training in University of Science and Technology of China (USTC) and Chengdu Institute of Biology, Chinese Academy of Sciences (CIB-CAS), majoring in medicinal (natural product) chemistry. After he had graduated as "excellent student", he worked as a medicinal chemist for Shanghai ChemPartner (Chengdu). In the beginning of 2011, he decided to follow a second Master program abroad and move to Leiden University, the Netherlands. During this study he performed two internships at the Division of Medicinal Chemistry, Leiden Academic Centre for Drug Research, under the supervision of Prof. dr. Ad IJzerman, Dr. Johannes Brussee and Dr. Laura Heitman. Both internships were focused on drug-target binding kinetics, from the perspectives of medicinal chemistry as well as molecular pharmacology.

In 2013, Lizi Xia started his PhD training at Leiden University in the same division, under supervision of Prof. dr. Ad IJzerman and Dr. Laura Heitman. His PhD research was part of an Innovative Medicine Initiative (IMI) project named Kinetics for Drug Discovery (K4DD) in collaboration with 20 partners throughout Europe in academia and industry. This consortum was founded to improve the understanding of drug-target binding kinetics. Lizi Xia's research was focused on several G protein-coupled receptors (GPCR). Lizi Xia together with his supervisors developed several valuable collaborations within and beyond K4DD partners, where he experienced the multiple working styles in academia and industry. The fruitful results of his research are described in this thesis and were presented at many international conferences and during webinars. Lizi Xia has an ambition to apply the concept of binding kinetics in a broader setting, and eventually to make his contribution to drug discovery.

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This thesis has not only been a work of the past four years, but also a fantastic travel log of the kinetic journey in my scientific career. In particular I would like to express my sincere appreciation to my promotors, Ad and Laura. Confucius said, “When I walk along with two others, they may serve me as my teachers.” I am extremely fortunate to have you both as my mentors and supervisors not just these four years, but ever since I came to Medicinal Chemistry many years ago. Ad, I admire you as an eminent scientist, brilliant group leader, as well as the most approachable mentor; your supervision is exactly the modern revelation of Confucius educational ideology, i.e. Education without Distinction. Laura, I got equal amount of inspiration from you and you were the catalyst for my transition from a chemist to a pharmacologist, in one way or another.

I would also like to thank my collaborators within and beyond K4DD for enabling this research and introducing me to many junior and senior passionate and talented scientists dedicating their life and energy to drug discovery. I have learned from you on how to collaborate with both pharmaceutical industry and academia.

Thirdly, I want to express my gratitude to my colleagues for all kinds of help and support. Particularly, I would like to thank Henk, who literally covered my pants when I was still a novice in binding assays. I want to thank Bart for all the beautiful computational work upon demanding request; to Julien, Jaco and Daan for all chemistry-related tasks. Especially, I must give great compliments to my master and bachelor students, Athina, Noortje, Tirsa, Wessel, Cornelia and Ellen, who were involved in parts of this thesis. I want to thank Andrea, Maarten, Xue and Zhiyi, for valuable suggestions regarding manuscript or rebuttal letter preparation.

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made my life colorful and enjoyable, and reminded me that the meaning of PhD goes beyond the pages of this thesis.