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The road to Insurmountability: Novel avenues to better target CC Chemokine Receptors

Ortiz Zacarías, N.V.

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Author: Ortiz Zacarías, N.V.

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CURRICULUM VITAE

Natalia Veneranda Ortiz Zacarías was born in Monterrey, Nuevo León, Mexico on the 13th of February 1987. After graduating from high school at the *Research and Development Center for Bilingual Education (CIDEB)*, she studied Pharmaceutical Chemistry and Biology at the Faculty of Chemical Sciences of the *Autonomous University of Nuevo León (UANL)*. In 2009, she graduated with honors after pursuing a specialization in Pharmacy. She also received the first academic place award of her study generation 2005-2009.

Before continuing with a master degree, she worked for two years as Hospital Pharmacist in the San José Tec de Monterrey Hospital. In 2012, she obtained a scholarship from Mexican *National Council of Science and Technology (CONACYT)* and a Leiden University Excellence Scholarship (LExS) to study at Leiden University, in The Netherlands. Thus, she moved to Leiden to follow the master's program in Bio-Pharmaceutical Sciences, where she specialized in Medicinal Chemistry. During her master studies, she performed a 9-month research internship in the Division of Medicinal Chemistry, at the Leiden Academic Centre for Drug Research (LACDR), under the supervision of Dr. Arnault Massink, Dr. Laura Heitman and Prof. Dr. Ad IJzerman. The project focused on exploring the role of the sodium ion binding pocket in an adenosine receptor, and it resulted in a publication. After her first internship, she wrote a literature review under the supervision of Dr. Ron de Kloet, which was published later as a book chapter. In 2014, she performed a second 6-month research internship at the Centre for Human Drug Research (CHDR) under the supervision of Dr. Ingrid de Visser and Dr. Jasper Stevens. There, she worked on two projects focused on the revival of 'old' antibiotics for the treatment of multidrug-resistant bacteria. These projects led to the publication of two reviews and one research article. In 2014 she obtained her MSc. Degree *cum laude*, and was awarded the KNMP student prize 2014 for her academic achievements.

In November 2014, she started as PhD candidate at the Division of Drug Discovery and Safety, LACDR (former Division of Medicinal Chemistry), with Dr. Laura Heitman and Prof. Dr. Ad IJzerman as promotors. She also collaborated with Dr. Ilze Bot and Prof. Dr. Johan Kuiper, from the Division of BioTherapeutics at the LACDR, and with Dr. Irina Kufareva and Prof. Dr. Tracy Handel, from the University of California, San Diego. Throughout her PhD, she presented her research in posters and oral communications at several national and international conferences, including the FIGON Dutch Medicine Days (2015-2018), Keystone Symposia (2018) and the EFMC-ISMIC (2018). In 2017, she was awarded the 1st prize at the LACDR Spring Symposium and the 1st prize of the national PhD Student Competition at the FIGON Dutch Medicine Days 2017 for her oral presentation entitled "Killing one bird

with two stones: Insights from the CCR2 Crystal Structure”. In 2018, she obtained a FIGON travel award to present part of her research at the Keystone Symposia “GPCR Structure and Function: Taking GPCR Drug Development and Discovery to the Next Level” in Santa Fe, New Mexico, USA. Currently, she works at the same division as a postdoctoral research scientist under the umbrella of the Dutch Onco Institute.

LIST OF PUBLICATIONS

Ortiz Zacarías NV, Louvel J, Šimková T, Chahal K, Zheng Y, Theunissen E, Mallee L, van der Es D, Handel TM, Kufareva I, IJzerman AP, Heitman LH. *Design and characterization of an intracellular covalent ligand for CC Chemokine Receptor 2 (CCR2)*. Manuscript in preparation.

Ortiz Zacarías NV, van Veldhoven JPD, den Hollander L, Dogan B, Openy J, Hsiao Y, Lenselink EB, Heitman LH, IJzerman AP. *Synthesis and pharmacological evaluation of triazolo-pyrimidinone derivatives as noncompetitive, intracellular antagonists for CC chemokine receptors 2 and 5*. Manuscript submitted.

Ortiz Zacarías NV, van Veldhoven JPD, Portner L, van Spronsen E, Ullo S, Veenhuizen M, van der Velden WJC, Zweemer AJM, Kreekel RM, Oenema K, Lenselink EB, Heitman LH, IJzerman AP. *Pyrrrolone derivatives as intracellular allosteric modulators for chemokine receptors: selective and dual-targeting inhibitors of CC chemokine receptors 1 and 2*. *J Med Chem* **2018**, 61, 9146-9161.

Ortiz Zacarías NV, Lenselink EB, IJzerman AP, Handel TM, Heitman LH. *Intracellular receptor modulation: novel approach to target GPCRs*. *Trends Pharmacol Sci* **2018**, 39, 547-559.

Bot I,* Ortiz Zacarias NV,* de Witte WE, de Vries H, van Santbrink PJ, van der Velden D, Kroner MJ, van der Berg DJ, Stamos D, de Lange EC, Kuiper J, IJzerman AP, Heitman LH. *A novel CCR2 antagonist inhibits atherogenesis in apoE deficient mice by achieving high receptor occupancy*. *Sci Rep* **2017**, 7, 52.

*these authors contributed equally.

Zheng Y, Qin L, [Ortiz Zacarías NV](#), de Vries H, Han GW, Gustavsson M, Dabros M, Zhao C, Cherney RJ, Carter P, Stamos D, Abagyan R, Cherezov V, Stevens RC, IJzerman AP, Heitman LH, Tebben A, Kufareva I, Handel TM. *Structure of CC chemokine receptor 2 with orthosteric and allosteric antagonists*. Nature **2016**, 540, 458-461.

[Ortiz Zacarías NV](#), Dijkmans AC, Burggraaf J, Mouton JW, Wilms EB, van Nieuwkoop C, Touw DJ, Kamerling IMC, Stevens J. *Fosfomycin as a potential therapy for the treatment of systemic infections: a population pharmacokinetic model to simulate multiple dosing regimens*. Pharmacol Res Perspect **2018**, 6, e00378.

de Kloet ER, [Ortiz Zacarias NV](#), Meijer OC. *Chapter 37 - Manipulating the Brain Corticosteroid Receptor Balance: Focus on Ligands and Modulators*. In: Stress: Neuroendocrinology and Neurobiology. Fink, George (Ed), Academic Press: San Diego, **2017**; pp 367-383.

Dijkmans AC, [Ortiz Zacarías NV](#), Burggraaf J, Mouton JW, Wilms EB, van Nieuwkoop C, Touw DJ, Stevens J, Kamerling IMC. *Fosfomycin: Pharmacological, Clinical and Future Perspectives*. Antibiotics **2017**, 6, 24.

Thum S, Kokornaczyk AK, Seki T, De Maria M, [Ortiz Zacarias NV](#), de Vries H, Weiss C, Koch M, Schepmann D, Kitamura M, Tschammer N, Heitman LH, Junker A, Wunsch B. *Synthesis and biological evaluation of chemokine receptor ligands with 2-benzazepine scaffold*. Eur J Med Chem **2017**, 135, 401-413.

Dijkmans AC, Wilms EB, Kamerling IMC, Birkhoff W, [Ortiz Zacarias NV](#), van Nieuwkoop C, Verbrugh HA, Touw DJ. *Colistin: Revival of an Old Polymyxin Antibiotic*. Ther Drug Monit **2015**, 37, 419-427.

Massink A, Gutierrez-de-Teran H, Lenselink EB, [Ortiz Zacarias NV](#), Xia L, Heitman LH, Katritch V, Stevens RC, IJzerman AP. *Sodium ion binding pocket mutations and adenosine A2A receptor function*. Mol Pharmacol **2015**, 87, 305-313.

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