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Getting personal: advancing personalized oncology through computational analysis of membrane proteins

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List of publications

Part of this thesis

1. Gorostiola González, M., Janssen, A.P.A., IJzerman, A.P., Heitman, L.H. & van Westen, G.J.P. Oncological drug discovery: AI meets structure-based computational research. *Drug Discovery Today*, **27**, 1661–1670 (2022).
2. Gorostiola González, M., Rakers, P., Jespers, W., IJzerman, A.P., Heitman, L.H. & van Westen, G.J.P. Computational characterization of membrane proteins as anticancer targets: Current challenges and opportunities. *International Journal of Molecular Sciences*, **25**, 3698 (2024).
3. Gorostiola González, M.[†], Béquignon, O.J.M.[†], Manners, J.M., Zdrazil, B., Leach, A.R., IJzerman, A.P., Heitman, L.H. & van Westen, G.J.P. Excuse me, there is a mutant in my bioactivity soup! A comprehensive analysis of the genetic variability landscape of bioactivity databases and its effect on activity modelling. Preprint at *ChemRxiv* <https://doi.org/10.26434/chemrxiv-2024-kxlgm> (2024).
4. Bongers, B.J.[†], Gorostiola González, M.[†], Wang, X., van Vlijmen, H.W.T., Jespers, W., Gutiérrez-de-Terán, H., Ye, K., IJzerman, A.P., Heitman, L.H. & van Westen, G.J.P. Pan-cancer functional analysis of somatic mutations in G protein-coupled receptors. *Scientific Reports*, **12**, 21534 (2022).
5. Gorostiola González, M.[†], Sijben, H.[†], Dall'Acqua, L., Liu, R., IJzerman, A.P., Heitman, L.H. & van Westen, G.J.P. Molecular insights into disease-associated glutamate transporter (EAAT1 / *SLC1A3*) variants using *in silico* and *in vitro* approaches. *Frontiers in Molecular Biosciences*, **10**, 3389 (2023).
6. Gorostiola González, M., van den Broek, R.L., Braun, T.G.M., Chatzopoulou, M., Jespers, W., IJzerman, A.P., Heitman, L.H. & van Westen, G.J.P. 3DDPDs: describing protein dynamics for proteochemometric bioactivity prediction. A case for (mutant) G protein-coupled receptors. *Journal of Cheminformatics* **15**, 74 (2023).
7. Gorostiola González, M., IJzerman, A.P. & van Westen, G.J.P. A patient-centric knowledge graph approach to prioritize mutants for selective anti-cancer targeting. Preprint at *BioRxiv* <https://doi.org/10.1101/2024.09.29.615658> (2024).

[†] These authors contributed equally

Other publications

8. Dilweg, M.A., Gorostiola González, M., de Ruiter, M.D., Meijboom, N.J., van Veldhoven, J.P.D., Liu, R., Jespers, W., van Westen, G.J.P., Heitman, L.H., IJzerman, A.P. & van der Es, D. Exploring novel dilazep derivatives as hENT1 inhibitors and potentially covalent molecular tools. *Purinergic Signalling*, online ahead of printing (2024).
9. van den Maagdenberg, H.W., Sicho, M., Alencar Araripe, D., Luukkonen, S.,

- Scoenmaker, L., Jespers, M., Béquignon, O.J.M., Gorostiola González, M., van den Broek, R.L., Bernatavicius, A., van Hasselt, J.G.C., van der Graaf, P.H. & van Westen, G.J.P. QSPRpred: a Flexible Open-Source Quantitative Structure-Property Relationship Modelling Tool. Preprint at *ChemRxiv* <https://doi.org/10.26434/chemrxiv-2024-m9989> (2024).
10. van Veggel, L., Mocking, T.A.M., Sijben, H.J., Liu, R., Gorostiola González, M., *et al.* Still in Search for an EAAT Activator: GT949 Does Not Activate EAAT2, nor EAAT3 in Impedance and Radioligand Uptake Assays. *ACS Chemical Neuroscience*, **15**, 1424-1431 (2024).
 11. Mullooney, M.W., Duncan, K.R., Elsayed, S.S. *et al.* Artificial intelligence for natural product drug discovery. *Nature Reviews Drug Discovery*, **22**, 895-916 (2023).
 12. den Hollander, L.S., Béquignon, O.J.M., Wang, X., van Wezel, K., Broekhuis, J., Gorostiola González, M., de Visser, K.E., IJzerman, A.P., van Westen, G.J.P. & Heitman, L.H. Impact of cancer-associated mutations in CC chemokine receptor 2 on receptor function and antagonism. *Biochemical Pharmacology*, **208**, 115399 (2023).
 13. Feng, C., Wang, X., Jespers, W., Liu, R., Zamarbide Losada, S.D., Gorostiola González, M., van Westen, G.J.P., Danen, E.H.J. & Heitman, L.H. Cancer-Associated Mutations of the Adenosine A2A Receptor Have Diverse Influences on Ligand Binding and Receptor Functions. *Molecules*, **27**, 4676 (2022).
 14. Kovacikova, K., Gorostiola González, M., Jones, R., Reguera, J., Gigante, A., Pérez-Pérez, M.J., Pürstinger, G., Moesslacher, J., Langer, T., Jeong, L.S., Delang, L., Neyts, J., Snijder, E.J., van Westen, G.J.P. & van Hemert M.J. Structural insights into the mechanisms of action of functionally distinct classes of Chikungunya virus nonstructural protein 1 inhibitors. *Antimicrobial Agents and Chemotherapy*, **65**, e02566-20 (2021).
 15. Burggraaff, L., Lenselink, E.B., Jespers, W., van Engelen, J., Bongers, B.J., Gorostiola González, M., Liu, R., Hoos, H.H., van Vlijmen, H.W.T., IJzerman, A.P. & van Westen, G.J.P. Successive statistical and structure-based modeling to identify chemically novel kinase inhibitors. *Journal of Chemical Information and Modeling*, **60**, 4283-4295 (2020).

Scientific communications

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| 2024 | Excuse me, there is a mutant in my bioactivity soup! A comprehensive analysis of the genetic variability landscape of bioactivity databases and its effect on activity modelling (<i>poster</i>).
24th EuroQSAR. Barcelona, Spain. |
| 2023 | Analysis of cancer mutations directed towards rational design of selective inhibitors for RTKs (<i>poster</i>).
9th Joint Sheffield Conference on Cheminformatics. Sheffield, UK.

Assessment of cancer-related glutamate transporter (EAAT1 / <i>SLC1A3</i>) mutants using a combination of <i>in vitro</i> and <i>in silico</i> approaches (<i>poster</i>).
ONCODE Annual Scientific Meeting. Amersfoort, the Netherlands.

Accelerating personalized oncology: AI and structural methods in oncological drug discovery (<i>oral</i>).
LACDR Spring Symposium. Leiden, the Netherlands. |
| 2022 | Pan-cancer analysis of somatic mutations in G protein-coupled receptors (<i>poster</i>).
ULLA Summer School. Uppsala, Sweden.

Describing protein dynamics for proteochemometric bioactivity prediction: 3DDPDs (<i>oral, selected</i>).
12th International Conference on Chemical Structures (ICCS). Noordwijkerhout, the Netherlands.

Assessment of cancer-related glutamate transporter (EAAT1 / <i>SLC1A3</i>) mutants using a combination of <i>in vitro</i> and <i>in silico</i> approaches (<i>poster</i>).
FIGON Dutch Medicines Day & EUFEPS Annual meeting. Leiden, the Netherlands.

Assessment of cancer-related glutamate transporter (EAAT1 / <i>SLC1A3</i>) mutants using a combination of <i>in vitro</i> and <i>in silico</i> approaches (<i>poster</i>).
LACDR Spring Symposium. Leiden, the Netherlands. |
| 2021 | Pan-cancer analysis of somatic mutations in G protein-coupled receptors (<i>poster</i>).
ONCODE Annual Scientific Meeting. Online.

Pan-cancer analysis of somatic mutations in G protein-coupled receptors (<i>poster</i>).
LACDR Spring Symposium. Online. |
| 2020 | Analysis of cancer mutations directed towards rational design of selective inhibitors for RTKs (<i>poster</i>).
FIGON Dutch Medicines Day. Online.

Analysis of cancer mutations directed towards rational design of selective inhibitors for RTKs (<i>poster</i>).
LACDR Spring Symposium. Online.
<i>Awarded poster prize.</i> |

Curriculum Vitae

Marina Gorostiola González was born on November 20th, 1994 in Medina de Pomar, Spain. After graduating with honors in 2012 from the International Baccalaureate program at Cardenal López de Mendoza in Burgos, she started her university studies in the city of Salamanca, Spain. In 2017, she graduated with honors from the five-year BSc and MSc program in Pharmacy at the Faculty of Pharmacy of the University of Salamanca. In addition to her academic pursuits, Marina served as a class representative in the student union. During her studies, she explored different career options with curricular and extracurricular training in clinical pharmacy at the Valdecilla University Hospital in Santander, Spain, and at the Mount Carmel Hospital in Attard, Malta; community pharmacy at her mother's pharmacy in Burgos, Spain; and research at the Cancer Research Center, as well as the department of Pharmaceutical Sciences at the Faculty of Pharmacy in Salamanca, Spain. It was at this department that during her fifth year, Marina performed the first computational research project of her design supervised by Prof. dr. Maria José García Sánchez and Prof. dr. María Dolores Santos Buelga to investigate *in silico* drug absorption in celiac patients, which was later published in the journal *FarmaJournal*, edited by the University of Salamanca.

In September 2017, Marina started her MSc in Bio-Pharmaceutical Sciences specializing in computational drug discovery research at the University of Leiden, the Netherlands. She first performed a nine-month internship at the Division of Drug Discovery and Safety (now Division of Medicinal Chemistry), under the supervision of Prof. dr. Gerard van Westen and Dr. Lindsey Burggraaff in the computational drug discovery (CDD) group. This work entailed the computational prioritization of cancer-related kinase mutants to target selectively and inspired this thesis. During her time in the CDD group, Marina also participated in the “Multi-Targeting Drug” DREAM challenge, culminating in her first contribution to a computational drug discovery publication. As part of her MSc program, Marina wrote a literature review under the supervision of Dr. Joost Beltman and took several courses on Pharmaceutical bioinformatics from Uppsala University. Finally, she performed a six-month internship at the Molecular Modelling & Design Department in Galapagos NV, Belgium, under the supervision of Dr. Nicolas Triballeau and Dr. Bart Lenselink. This project focused on the development of a 3D machine learning-based scoring function for kinase-ligand interactions. In September 2019, Marina graduated *cum laude* from her MSc at Leiden University.

In December 2019, Marina started her PhD in computational drug discovery at the Division of Drug Discovery and Safety at Leiden University under the supervision of Prof. dr. Gerard van Westen, Prof. dr. Laura Heitman, and Prof. dr. Ad IJzerman. This PhD position was supported by the Oncode Institute, an independent research institute dedicated to cancer research in the Netherlands. This project focused on developing methods to characterize membrane proteins as anticancer targets using a combination of AI and structure-based computational tools. During her PhD research project, Marina presented her work at several national and international conferences both as poster and oral presentations. These included Oncode meetings and FIGON Dutch Medicine Days in the Netherlands, the International Conference on Chemical Structures (ICCS) in the

Netherlands in 2022, and the Joint Sheffield Conference on Cheminformatics in the UK in 2023. She also participated in the Lorentz Workshop in AI for natural product drug discovery in the Netherlands in 2021 and the ULLA summer school in Sweden in 2023. As part of her PhD, Marina also supervised several bachelor and master students in their research projects and initiated several national and international collaborations.

Marina continues her career in computational drug discovery as a researcher at Chemotargets in Barcelona, Spain.

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Life is simply a series of random turns and events, and it is up to us to navigate our way through them effectively. I would not have reached this point without the support of the people who guided me to make the right decisions along the way, both scientifically and personally.

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I am extremely grateful for my promotion team. Challenging as it was to have three supervisors - Gerard, Laura, and Ad - you have significantly improved my scientific output and personal development. More importantly, you have taught me through your own experience the significance of collaborative work and the necessity to maintain a balanced personal-professional life. I cannot stress enough the exceptional job you are doing in promoting this and how crucial it is for young scientists to witness.

I would like to express my gratitude to all the colleagues and external collaborators who have played a significant role in both the development of this thesis and other related projects. Your contributions have been instrumental in enhancing my skills and fostering my scientific curiosity. A special thanks goes to Brandon, Olivier, Huub, and Willem for their invaluable input in this thesis.

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I would not have stayed sane during this PhD if it was not for the magnificent working environment fostered at the Medicinal Chemistry division. I have truly enjoyed scientific and social events alike. To all present and past colleagues: thank you for making it possible! Special mention to Brandon, Olivier, Majlen, Jara, Willem, Andrius, Sohvi, and David. I have no words to describe the magnificent people you are. Instrumental to my sanity were also all friends outside of University. Leiden became home thanks to you, and I will miss you deeply.

Mamá, papá, sois la razón y el propósito de esta tesis. Gracias por darme las alas para perseguir mis sueños y el apoyo incondicional para alcanzarlos. Todos mis éxitos son vuestros, siempre. [*Mom, Dad, you are the reason and purpose behind this thesis. Thank you for giving me the wings to pursue my dreams and for the unconditional support to achieve them. All of my successes are yours, always.*]

Finally, to my life partner, Konsta, a special thanks for enduring the ups and downs of my PhD journey. Your calm keeps me grounded and your confidence gives me the strength to step beyond my comfort zone. I could not have done this without you. Now, what's next?