



Universiteit
Leiden
The Netherlands

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

Gorostiola González, M.

Citation

Gorostiola González, M. (2025, January 24). *Getting personal: advancing personalized oncology through computational analysis of membrane proteins*. Retrieved from <https://hdl.handle.net/1887/4093962>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/4093962>

Note: To cite this publication please use the final published version (if applicable).

Cover design and thesis layout by Marina Gorostiola González, Fernando da Silva Domingo, and Miriam González López.

This thesis was printed by Ipskamp Printing

© Marina Gorostiola González 2024

ISBN: 978-94-6473-615-1

All rights reserved. No part of this thesis may be reproduced in any form or by any means without permission of the author.

GETTING PERSONAL

Advancing personalized oncology through computational analysis of
membrane proteins

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op vrijdag 24 januari 2025
klokke 11.30 uur

door

Marina Gorostiola González
geboren te Medina de Pomar, Spanje
in 1994

Promotores: Prof. dr. G.J.P. van Westen
Prof. dr. L.H. Heitman
Prof. dr. A.P. IJzerman

Promotiecommissie: Prof. dr. H. Irth
Prof. dr. E.C.M. de Lange
Prof. dr. E.H.J. Danen
Prof. dr. A. Plaat
Prof. dr. A. Volkamer, Saarland University
Dr. E.L. Willighagen, Maastricht University

The research described in this thesis was performed at the Division of Drug Discovery and Safety of the Leiden Academic Centre for Drug Research (LACDR), Leiden University, The Netherlands.

To mom, dad, and anyone else who has received
the terrifying diagnosis of an undruggable tumor

About this thesis title and cover:

The primary challenge in treating cancer stems from its extensive heterogeneity, resulting in a scenario where each patient presents with a distinct disease defined by their unique genetic profile. While this complexity may seem overwhelming, computational tools offer a valuable solution for compiling individual data from a large number of patients, ultimately identifying biomarkers and targets to enable personalized diagnosis and treatment for specific subpopulations. Essentially, the tools developed in this thesis facilitate the customization of oncological treatment for each patient. In short, we are Getting Personal.

TABLE OF CONTENTS

Chapter 1	General introduction	11
Chapter 2	Oncological drug discovery: AI meets structure-based computational research	23
Chapter 3	Computational characterization of membrane proteins as anticancer targets: Current challenges and opportunities	43
Chapter 4	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 modeling	65
Chapter 5	Pan-cancer functional analysis of somatic mutations in G protein-coupled receptors	123
Chapter 6	Molecular insights into disease-associated glutamate transporter (EAAT1 / SLC1A3) variants using <i>in silico</i> and <i>in vitro</i> approaches	157
Chapter 7	3DDPDs: Describing protein dynamics for proteochemometric bioactivity prediction. A case for (mutant) G protein-coupled receptors	201
Chapter 8	Connecting the dots: A patient-centric knowledge graph approach to prioritize mutants for selective anticancer targeting	241
Chapter 9	General conclusions and future perspectives	281
Appendix A	GDC SQL implementation v22.0. Quick start guide	293
Appendix B	Data and software availability	305
	Summary, List of publications, Curriculum vitae, Acknowledgements	309