
BIOGRAPHICAL SKETCH

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NAME: Marco Lolicato

POSITION TITLE: Associate Professor of Molecular Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Catania, Italy	BS. <i>cum laude</i>	09/2005	Biology
University of Catania, Italy	M. Sci. <i>cum laude</i>	04/2008	Biomolecular Chemistry
Scuola Superiore di Catania, "Higher Education"	BS. + M. Sci. <i>cum laude</i>	10/2008	Biophysics
University of Milano, Italy	PhD	01/2012	Ion channel Biophysics
University of Milano, Italy	Postdoctoral Fellow	01/2013	Ion channel Biophysics
University of California San Francisco (UCSF) – Cardiovascular Research Institute, San Francisco, CA (USA)	Postdoctoral Fellow	02/2019	Membrane transport protein biophysics

A. Personal Statement

The research area of the proposed project is well within the expertise of the PI in membrane transport proteins structure, function and drug discovery (see most relevant publications, in particular #1-6, and the manuscript in preparation).

The full track record indicates the PI ability of conducting cutting-edge research in international laboratories and the experience acquired in the past 10+ years makes the PI skilled to perform *high-profile* projects such as the one here proposed.

During his career, which included 6 years postdoctoral training at UCSF, the PI investigated various aspects of protein functions using structural biology and biochemistry, including critical contributions to the molecular mechanisms of ion channel gating and the discovery of small molecule effectors.

The PI has hands-on technical experience in a variety of methods spanning from integrative structural biology (crystallography, cryo-electron microscopy, *in silico* docking) to biochemistry, electrophysiology and cell biology.

The experimental approaches described in this proposal are currently extensively used by the PI in his research lab to address different biological questions, thus the PI is in the most favourable state to turn this proposal into results.

The PI currently holds an Associate Professor position at the Department of Molecular Medicine within the University of Pavia where he is actively involved in research areas of translational medicine, trying to bring to life new therapeutic agents using a molecular and biophysical approaches.

The PI has started his independent position in 2019 thanks to the prestigious “*Bando per giovani ricercatori - Rita Levi Montalcini*” award and has been promoted to Associate Professor effective from February 2022.

Ongoing and recently completed projects

* 2025 – current	Fondazione Telethon, €240.000 – PI of the project. (Grnt # GMR24T2041)
* 2023 – current	Ministero dell'Università e della Ricerca - PRIN 2022, €131.500 - PI of the project
* 2023 – current	Ministero della Salute - POS: Piano Operativo Salute – ImmunoHUB, €45.000 – Responsible of Unit
* 2022 – current	Ministero dell'Università e della Ricerca - PNRR CN1 HPC - Big Data and Quantum Computing - Spoke 8: <i>In silico</i> Medicine and Omics Data, €75.000 Responsible of Unit
* 2020 – 2024	Fondazione Cariplo, €245.250 - Biomedical research conducted by young researchers - PI of the project
* 2019 – 2023	Ministero dell'Università e della Ricerca - <i>Bando per giovani ricercatori - Rita Levi Montalcini</i> , €249.973,66 - PI of the project

B. Positions, Scientific Appointments, and Honors

2022-	Associate Professor University of Pavia, Dipartimento di Medicina Molecolare, Pavia, Italy. Field of study: Translational Medicine, Biophysics and Structural Biology Activity: (i) Understanding the role of mechanosensation in tumor growth and metastasis (ii) Finding new therapeutic agents to slow down glycolysis in tumor cells. (iii) Orphan drugs repurposing/campaigns on ion channels and transporters
2019- 2022	Tenure-Track Assistant Professor University of Pavia, Dipartimento di Medicina Molecolare, Pavia, Italy. Field of study: Translational Medicine, Biophysics and Structural Biology
2013-2019	Postdoctoral Fellow University of California San Francisco, San Francisco, CA Field of study: Structural biology and electrophysiology of intact ion channels

C. Contributions to Science

PhD contributions

The main research outputs of my PhD program focused on the molecular determinants of the 'funny' current (I_f) of the pacemaker cells. This current is due to the biophysical properties of the HCN channels and it is activated by hyperpolarization of membrane voltage and regulated by intracellular cyclic AMP. These channels play a pivotal role in the autonomic regulation of heart rate. During the PhD I have made substantial contributions in understanding the structural and biochemical differences between the different HCN isoforms (Lolicato et al. *J Biol Chem*, 2011) and I have identified a previously unknown cyclic-di-nucleotide binding domain in the HCN4 channel, which enabled the discovery of a new chemical entity, the compound C11, able to affect HCN4 functions and able to slow down heart rate in isolated pacemaker cells (Lolicato et al. *Nat Chem Biol.*, 2013). During the three years of the program, I also collaborated on and enriched multiple ancillary projects helmed by fellow researchers. One of them aiming at understanding the structural organization of the DNA in plant viruses (Wulfmeyer et al. *Plos ONE*, 2012) and the other one in the role of c-di-GMP in bacteria signaling (Antoniani et al. *Appl. Microbiol. Biotechnol*, 2013).

Post-doctoral contributions

During my postdoctoral appointment, I made significant contributions to the ion channel field, in particular on the subfield of mechanosensitive channels. I have, indeed, shed light on how the mechanosensitive channels TREK-1 and TRAAK, belonging to the family of Two-pore domain potassium channels (K2P) are regulated by physical forces (Lolicato et al. *Neuron*, 2014) and small molecules (Lolicato et al. *Nature*, 2017 and Pope et al. *Cell Chem Biol*, 2020). The small molecule binding pocket discovered in 2017, has been instrumental for deciphering the activation mechanism and functioning of these type of channels (Lolicato et al. *Sci Adv.*, 2020) and led us to the development of covalent K2P activators for the potential treatment of chronic pain (Parker et al. *Nat Chem Biol*, submitted).

My main findings have profound implications for the broader scientific community. By uncovering the molecular intricacies of the K2P2.1(TREK-1) channel, I have paved the way for a deeper understanding of ion channel function, which is fundamental to numerous physiological processes. Moreover, the insights gained from this research have the potential to influence therapeutic strategies, especially in conditions where ion channel dysregulation plays a role.

I contributed as well at solving the structure of the saxiphilin bound to its drug saxitoxin (STX) to unravel the mechanism of binding of such important toxin involved in the paralytic shellfish poisoning (PSP) and to understand how proteins can mitigate the effect of the toxin (Yen et al. *Sci Adv*, 2019). This finding enabled a more consistent funding from the USA Department of Defense to develop novel strategies to fight PSP.

I have also collaborated with industries to solve the structure of a therapeutic antibody in complex with its target (Ely and Lolicato et al. *Structure*, 2018) and with other academic fellows to unravel the mechanism of chloride transport (Tien et al. *Nature*, 2017) and to design novel amyloid-mimicking peptides (Zhang et al. *Nat Chem Biol*, 2018).

Principal Investigator contributions

In 2019, I was honored to join the Department of Molecular Medicine as an Assistant Professor of Molecular Biology, a position made possible by the prestigious "*Bando per giovani ricercatori - Rita Levi Montalcini*" award. This recognition not only facilitated the introduction of innovative research avenues within the Department but also bolstered my autonomy as a Principal Investigator.

As a Faculty member, I have played an instrumental role in various projects at the University of Pavia, as evidenced by publications like Pallavio et al. (*Cells*, 2020) and Iannucci et al. (*Nat Comm.*, 2023). My collaborative efforts extend beyond the university, with notable contributions to works such as Longhitano et al. (*Cancer Immunol Immunother*, 2022) and Barbato et al. (*Cell Prolif.*, 2023) on cancer biochemistry. Additionally, I co-authored an editorial on ion channels with Dr. Saponaro from the University of Milano (Saponaro and Lolicato, *Front Physiol.*, 2022).

These collaborative endeavors have expanded my horizons beyond ion channel biophysics, allowing me to delve deeper into oncology and the role of channels and transporters in cancer evolution. In collaboration with my academic peers, I have identified a series of molecules capable of displacing NADH from its mitochondrial entry point. These molecules have demonstrated a unique ability to

target and eliminate cancer cells in organoid environments, while sparing healthy cells. This discovery is particularly groundbreaking given the recent FDA endorsement of organoids as viable alternatives to animal testing, paving the way for these molecules to be directly incorporated into clinical trials. I am currently authoring a manuscript detailing these findings, which has been published on *iScience* (DOI: 10.1016/j.isci.2024.109853).

D. Relevant Publications

1. Conti Nibali S, Magrì A, Messina A, Armin Wagner, Ramona Duman, De Pinto V, Turato C, Arrigoni C, **Lolicato M**. Protocol for high-yield bacterial expression and purification of the voltage-dependent anion channel 1 for high-throughput biophysical assays. *STAR Protocols* 2024 <https://doi.org/10.1016/j.xpro.2024.103557>
2. Conti Nibali S, De Siervi S, Luchinat E, Magrì A, Messina A, Brocca L, Mantovani S, Oliviero B, Mondelli MU, De Pinto V, Turato C, Arrigoni C, **Lolicato M**. VDAC1-interacting molecules promote cell death in cancer organoids through mitochondrial-dependent metabolic interference. *iScience*. 2024 Apr 30;27(6):109853. doi: 10.1016/j.isci.2024.109853
3. Arrigoni C., **Lolicato M.**, Shaya D., Rohaim A., Findeisen F., Colleran C.M., Dominik P., Kim S.S., Schuermann J., Kossiakoff A.A., and Minor D.L. Quaternary structure independent folding of voltage-gated ion channel pore domain subunits. *Nat Struct Mol Biol.* (2022). page 2021.08.15.456357
4. **Lolicato M.***, Natale A. *, Aberemane-Ali F., Crottes D., Capponi S., Duman R., Wagner A., Rosenberg J.M., Grabe M., and Minor D.L. K2P channel c-type gating involves asymmetric selectivity filter order-disorder transitions. *Science Advances* (2020). doi: 10.1101/2020.03.20.000893.
* equal contribution
5. **Lolicato M.**, Arrigoni C., Mori T., Sekioka Y., Bryant C., Clark K.A., and Minor D.L. K2P2.1 (TREK-1)-activator complexes reveal a cryptic selectivity filter binding site. *Nature*, 547(7663):364–368 (2017).
6. **Lolicato M.**, Bucchi A., Arrigoni C., Zucca S., Nardini M., Schroeder I., Simmons K., Aquila M., DiFrancesco D., Bolognesi M., Schwede F., Kashin D., Fishwick C.W.G., Johnson A.P., Thiel G., and Moroni A. Cyclic dinucleotides bind the C-linker of HCN4 to control channel cAMP responsiveness. *Nat. Chem. Biol.*, 10(6):457–462 (2014).
7. **Lolicato M.***, Ely L.*, Tovo D., Lowe K., Kim Y.C., Samuel D., Bessette P., Garcia J.L., Mikita T., Minor D.L., and Coughlin S.R. Structural Basis for Activity and Specificity of an Anticoagulant Anti-FXIIa Monoclonal Antibody and a Reversal Agent. *Structure*, 26(2):187–198 (2018).
* equal contribution.
8. **Lolicato M.**, Riegelhaupt P.M., Arrigoni C., Clark K.A., and Minor D.L. Transmembrane Helix Straightening and Buckling Underlies Activation of Mechanosensitive and Thermosensitive K2P Channels. *Neuron*, 84(6):1198–1212 (2014).
9. **Lolicato M.**, Nardini M., Gazzarrini S., Möller S., Bertinetti D., Herberg F.W., Bolognesi M., Martin H., Fasolini M., Bertrand J.A., Arrigoni C., Thiel G., and Moroni A. Tetramerization Dynamics of C-terminal Domain Underlies Isoform-specific cAMP Gating in Hyperpolarization-activated Cyclic Nucleotide-gated Channels. *J. Biol. Chem.*, 286(52):44811–44820 (2011).

Full list of publication can be found on NCBI:

<https://www.ncbi.nlm.nih.gov/myncbi/marco.lolicato.1/bibliography/public/>