

BIOGRAPHICAL SKETCH

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NAME: Andrea Saponaro

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Tenure-track assistant professor in Physiology (RTD-B)

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Milan, Milan, Italy	MS	10/2010	Molecular Biology
University of Milan, Milan, Italy	PHD	01/2014	Molecular Biology
New University of Lisbon, Lisbon, Portugal	Postdoctoral	12/2012	Structural Biology (NMR)
Columbia University, NYC, USA	Postdoctoral	10/2019	Structural Biology (cryo-EM)

A. Personal Statement

I am a young PI of the University of Milan, from November 2023 tenure-track assistant professor (RTD-B) in Physiology, Dept. Pharmacological and Biomolecular sciences.

My research is focused on the study of the **molecular mechanisms of ion channel gating**. I have a broad **background in ion channel biophysics**, with specific **training and expertise in structural biology of membrane proteins and macromolecular interactions**. As PI or co-Investigator on several national and international-funded grants, I laid the groundwork for the proposed research by **establishing a successful research line on membrane protein biophysics, recently including high-resolution cryogenic electron microscopy (cryo-EM)**. Notably, this has provided new expertise to the national research community of ion channels biophysics.

In addition, I successfully administered the projects (e.g. staffing, research protections, budget), collaborated with other national and international researchers, and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget.

In summary, I have the expertise, leadership, training, expertise, and motivation necessary to successfully carry out the proposed research project.

Ongoing and recently completed projects:

- 2022 – 2024 Biomedical research (PI of the project), 250.000,00 €, co-granted by TELETION and CARIPLO foundations (rif. GJC21084). Title of the project: “At the origin of congenital muscular dystrophy: shedding light on the Tdark proteins DPM2 and DPM3”. Collaborator: Prof Yvan Torrente, University of Milan.
- 2019 – 2023 Biomedical research conducted by young researchers (PI of the project), 250.000,00 €, granted by CARIPLO foundation (rif. 2018-0231). Title of the project: “The crucial role of HCN2 channels

in inflammatory and neuropathic pain". Collaborators: Prof Rajesh Khanna, NYU, YNC, USA; Dr Emmanuel Bourinet, CNRS, Montpellier, France.

- SEED 2019 grant for interdepartmental projects (responsible of the departmental unit of cellular electrophysiology), 10.000,00 €, granted by University of Milan. Title of the project: "Photo-activable Ivabradine: a spatiotemporal control of HCN channels function with added therapeutic potential".
- Fulbright Visiting Research Program 2018-2019. Nine-month visiting research fellowship, Columbia University, NY, Dept. Physiology & Cellular Biophysics, laboratory of Prof Filippo Mancia. Structural study of membrane proteins by cryo-EM.
- 2015 - 2017, 40.000,00 € Postdoctoral fellowship granted by Accademia Nazionale dei Lincei. Title of the project: "A molecular prospective of memory: the interaction between HCN channels and their neural regulator TRIP8b"

Relevant publications for the proposed research:

1. Saponaro A. et al., "Structural determinants of ivabradine block of the open pore of HCN4". Proc Natl Acad Sci U S A. 2024 Jul 2;121(27):e2402259121. doi: 10.1073/pnas.2402259121.
2. Porro A., & Saponaro A.* et al., "A high affinity switch for cAMP in the HCN pacemaker channels". Nat Commun. 2024 Jan 29;15(1):843. doi: 10.1038/s41467-024-45136-y. * co-first author.
3. Saponaro A.* et al. "Validation of the binding stoichiometry between HCN channels and their neuronal regulator TRIP8b by single molecule measurements". Front Physiol. 2022 Sep 26;13:998176. doi: 10.3389/fphys.2022.998176. eCollection 2022. * Also, corresponding author.
4. Saponaro A. et al., "Gating movements and ion permeation in HCN4 pacemaker channels". Mol Cell. 2021 81(14):2929-2943.e6. doi: 10.1016/j.molcel.2021.05.033.
5. Porro A, Binda A, Pisoni M, Donadoni C, Rivolta I, Saponaro A*. "Rational design of a mutation to investigate the role of the brain protein TRIP8b in limiting the cAMP response of HCN channels in neurons". J Gen Physiol. 2020 152(9):e202012596. doi: 10.1085/jgp.202012596 *Corresponding author.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023– Present	Tenure-track assistant professor in Physiology (RTD-B), University of Milan, Milan, Italy
2022 – 2023	Postdoctoral fellowship granted by the CARIPLO grant 2018-0231. Title of the project: "The crucial role of HCN2 channels in inflammatory and neuropathic pain" (PI of the project). Dept Biosciences, University of Milan, Italy
2019	Fulbright Visiting Research fellowship, Columbia University, NY, Dept. Physiology & Cellular Biophysics, laboratory of Prof Filippo Mancia. Structural study of membrane proteins by cryo-EM.
2017 – 2022	Researcher (RTDA), Dept Biosciences, University of Milan, Italy. The extension of the RTDA contract beyond the three canonical years has been financed by the CARIPLO grant 2018-0231. Title of the project: "The crucial role of HCN2 channels in inflammatory and neuropathic pain" (PI of the project).

2015 – 2017	Postdoctoral fellowship granted by “Giuseppe Levi Foundation” for Neurobiology Research, Lincean Academy (Italian Science Academy). Title of the project: “A molecular prospective of memory: the interaction between HCN channels and their neural regulator TRIP8b”.
2021 – 2022	Council member of the Italian Society for Pure and Applied Biophysics.
2021 – Present	Guest associate editor of “Frontiers in Physiology - Membrane Physiology and Membrane Biophysics”
2021 – Present	Review editor of “Frontiers in Physiology - - Cardiac Electrophysiology”
2020 – Present	Reviewer for Soft Matter and other Royal Society of Chemistry journals which fall within my area of expertise: Biophysics, Biochemistry, Molecular Biology
Honors	
2013	Award for Best Poster Presentation (European Biophysical Society)
2014	Award for Best PhD thesis in Biophysics (Italian society of Pure and Applied Biophysics)
2021 – 2033	National Scientific Qualifications: Biochemistry (05/E1); Molecular Biology (05/E2); Physiology (05/D1)

C. Contributions to Science

I have a robust experience in **biophysics of ion channels**, recently including **high-resolution cryogenic electron microscopy (cryo-EM)** of this protein family (for details, see Publications). The latter expertise has been developed thanks to a Fulbright visiting research fellowship at Columbia University, NY, in the laboratory of Prof Filippo Mancia, Dept. Physiology & Cellular Biophysics. In regards, my recent works on structure/function (cryo-EM and cellular electrophysiology) of pacemaker HCN4 channel (**Saponaro et al., Mol Cell 2021; Saponaro et al., PNAS 2024**) have provided new expertise to the national research community of ion channels biophysics.

Moreover, I am interested in unravelling the **connection between HCN channel regulation and chronic pain**, and in the use of **synthetic biology approaches to study this connection and control it**. My postdoctoral fellowship granted by “Giuseppe Levi Foundation” for Neurobiology Research, Lincean Academy (Italian Science Academy), and my Fulbright Visiting Research fellowship, together with my CARIPLO and TELETHON grants (for details, see Publications and CV) have significantly supported me in establishing this research line in my lab. Indeed, the synergistic combination of structural/functional studies (cryo-EM and cellular electrophysiology) and protein engineering (synthetic biology/optogenetics) approaches has, very recently, allowed me to demonstrate, for the first time, the direct connection between cAMP binding/potential of HCN2 channel and chronic pain (manuscript in preparation), till now only indirectly proven.

I have co-authored 26 articles (16 in the last 5 years – 2019 -2024) published in high-impact factor, peer-reviewed international scientific journals, with over **496 citations, h-index = 12 (Web of Science)**.

These publications are the result of **collaborations with scientists from prestigious international research centers**:

Prof Steven A Siegelbaum, Columbia University, New York, USA;

Prof Filippo Mancia, Columbia University, New York,

USA; Dr Bina Santoro, Columbia University, New York, USA;

Prof Gerhard Thiel, Technische Universität Darmstadt, Darmstadt, Germany;

Prof Kay Hamacher, Technische Universität Darmstadt, Darmstadt, Germany;

Prof Dario DiFrancesco, University of Milan, Milan, Italy;

Prof Lucia Banci, Magnetic Resonance Center, University of Florence, Florence, Italy;

Prof Anna Moroni, Department of Biosciences, University of Milan, Milan, Italy.

Complete List of Published Work: <https://orcid.org/0000-0001-5035-5174>