

BIOGRAPHICAL SKETCH

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NAME: Daniele Guardavaccaro

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POSITION TITLE: Professor of Molecular Biology

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 Rome La Sapienza	BS/MSc	07/1991	Biology
Consiglio Nazionale delle Ricerche	PhD equivalent	04/1998	Molecular Biology
University of Viterbo	PhD	08/2012	Genetics and Cellular Biology

A. Personal Statement

I am a professor of Molecular Biology in the Department of Biotechnology at the University of Verona. The main goal of my research program is to understand how fundamental cellular processes are controlled at the molecular and mechanistic levels. I have a long-standing interest in studying how eukaryotic cells receive, process, and transmit signals from the extracellular environment and how the integration of multiple signals results in a specific biological output. In the cell, such signaling networks are tightly controlled by post-translational modifications. We are particularly interested in the role of ubiquitylation, a multipurpose post-translational modification that controls all crucial biological processes either by targeting proteins for proteasomal degradation or by triggering a multitude of regulatory signaling events. We seek to expand our knowledge of how signaling networks control cellular processes and how their alterations result in human disease. To that end, we utilize a variety of biochemical, molecular and cell biological approaches, including proteomics, live imaging and organoid technology, along with genetic tools such as CRISPR genome editing and RNA interference.

Ongoing projects that I would like to highlight are:

- Italian Ministry of Foreign Affairs and International Cooperation (MAECI) and Swedish Research Council
Exploiting the Ubiquitin System to Target the "Undruggable" Cancer Proteome
1/1/2024 - 31/12/2026
- Italian Ministry of University and Research - PRIN-PNRR
Exploring the molecular mechanisms underlying the homeostasis of the intestinal epithelium
30/11/2023 - 30/11/2025
- Italian Ministry of University and Research - PRIN 2022
Decipher how ubiquitylation shapes membrane and membraneless organelles to promote neuronal homeostasis
28/9/2023 - 28/9/2025
- Fondazione Telethon ETS
Molecular mechanisms underlying Joubert syndrome
1/4/2023 - 1/4/2025

B. Positions, Scientific Appointments, and Honors

2018 – present	Professor of Molecular Biology, University of Verona, Italy
2008 – 2018	Group Leader, Hubrecht Institute, Utrecht, The Netherlands
2004 – 2008	Research Instructor, NYU School of Medicine, New York, USA
1999 – 2000	Visiting Scientist, Columbia University, New York, USA
1998 – 2004	Postdoctoral Fellow, NYU School of Medicine, New York, USA

Honors

2001	Susan G. Komen Breast Cancer Foundation
1999	AICF - American-Italian Cancer Foundation
1998	IARC - International Agency for Research on Cancer

C. Contributions to Science

1. In my early studies, as a fellow at the Institute of Neurobiology, Consiglio Nazionale delle Ricerche, I investigated the molecular mechanisms linking cell cycle progression and neuronal differentiation. In these studies, I dissected the mechanisms by which, during the development of the nervous system, precursor cells divide a limited number of times before arresting and terminally differentiating into postmitotic cells. More recently, my laboratory has been focusing on the mechanisms regulating stem cell differentiation.
 - a. Guardavaccaro, D., Montagnoli, A., Ciotti, M.T., Lotti, L., Di Lazzaro, C., Torrisi, M.R., Gatti A., Tirone F. Nerve Growth Factor regulates the subcellular localization of the NGF inducible protein PC4 in PC12 cells. **J Neurosci Res** 37: 660-674, 1994.
 - b. Guardavaccaro, D., Corrente, G., Covone, F., Micheli, L., D'Agnano, I., Starace, G., Caruso M., Tirone F. Arrest of G(1)-S progression by the p53-inducible gene PC3 is Rb dependent and relies on the inhibition of cyclin D1 transcription. **Mol Cell Biol** 20: 1797-815, 2000.
 - c. Lasorella, A., Stegmüller, J. Guardavaccaro, D., Liu, G., Carro, M.S., Rothschild, G., de la Torre-Ubieta, L., Pagano, M., Bonni, A., Iavarone, A. Degradation of Id2 by the Anaphase Promoting Complex couples control of cell cycle exit and axonal growth. **Nature** 442(7101):471-4, 2006.
 - d. de Lau, W., Barker, N., Low, T.Y., Koo, B.K., Li, V.S., Teunissen, H., Kujala, P., Haegebarth, A., Peters, P.J., van de Wetering, M., Stange, D.E., van Es, J.E., Guardavaccaro, D., Schasfoort, R.B., Mohri, Y., Nishimori, K., Mohammed, S., Heck, A.J., Clevers, H. Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling. **Nature** 476(7360):293-7, 2011.
 - e. Lauriola, A., Enriqu  Steinberg, J.H., Sarubo, M., Maspero, E., Rossi, F.A., Mouri, Y., Pedretti, M., Hajisadeghian, M., Vettori, A., Vitulo, N., Assfalg, M., D'Onofrio, M., Rossi, M., Yasue, M., Astegno, A, Polo, S., Santi, S., Kudo, Y., and Guardavaccaro, D. The E3 ligase RNF32 controls NF- B signaling in intestinal stem cells. In revision, 2024.
2. In addition to the studies described above, with a team of collaborators, I described how various RING E3 ligases play crucial roles in the synchrony and unidirectionality of the cell cycle clock by tuning the activity of various cyclin-dependent kinases. These findings highlighted the complexity of this network and dissected the molecular mechanisms by which ubiquitylation controls the cell division cycle in unperturbed conditions as well as in response to DNA damage.
 - a. Guardavaccaro, D., Kudo, Y. Boulaire, J., Barchi, M., Busino, L., Donzelli, M., Yamasaki, L., Pagano, M. Control of meiotic and mitotic progression by the F-box protein  TrCP1 in vivo. **Dev Cell** 4: 799-812, 2003.
 - b. Busino, L., Donzelli, M., Chiesa, M., Guardavaccaro, D., Ganoth, D., Dorrello, N.V., Herskho, A., Pagano, M., Draetta, G. Degradation of Cdc25 by  TrCP during S phase and in response to DNA damage. **Nature** 426(6962):87-9, 2003.
 - c. Bashir, T., Dorrello, N.V., Amador, V., Guardavaccaro, D., Pagano, M. Control of the SCFSkp2-Cks1 ubiquitin ligase by the APC/CCdh1 ubiquitin ligase. **Nature** 428(6979):190-3, 2004.

- d. Guardavaccaro, D., Pagano M. Stabilizers and destabilizers controlling cell cycle oscillators. **Mol Cell** 22(1):1-4, 2006.
 - e. Bassermann, F., Frescas, D., Guardavaccaro, D., Busino, L., Peschiaroli, A., Pagano, M. The Cdc14B-Cdh1-Plk1 axis in the control of the G2 DNA damage response checkpoint. **Cell** 134(2):256-67, 2008.
 - f. D'Annibale, S., Kim, J., Magliozzi, R., Low, T.Y., Mohammed, S., Heck, A.J., Guardavaccaro, D. Proteasome-dependent degradation of Transcription Factor AP4 (TFAP4) controls mitotic division. **J Biol Chem** 289(11):7730-7, 2014.
 - g. Kim, J., D'Annibale, S., Magliozzi, R., Low, T.Y., Jansen, P., Shaltiel, I.A., Mohammed, S., Heck, A.J., Medema, R.H., Guardavaccaro, D. USP17- and SCF β TrCP-regulated degradation of DEC1 controls the DNA damage response. **Mol Cell Biol** 34(22):4177-85, 2014.
 - h. Magliozzi, R., Carrero, Z.I., Low, T.Y., Yuniati, L., Valdes-Quezada, C., Kruiswijk, F., van Wijk, K., Heck, A.J., Jackson, C.L., Guardavaccaro, D. Inheritance of Golgi apparatus and cytokinesis are controlled by degradation of GBF1. **Cell Reports** 23(11):3381-3391, 2018.
 - i. Yuan, R., Liu, Q., Segeren, H.A., Yuniati, L., Guardavaccaro, D., Lebbink, R.J., Westendorp, B., de Bruin, A. Cyclin F-dependent degradation of E2F7 is critical for DNA repair and G2-phase progression. **EMBO J** 2019 Sep 2:e101430
3. Moreover, my laboratory has investigated the role of the ubiquitin-dependent degradation of cancer-related substrates and analyzed how altered ubiquitylation by RING ubiquitin ligases contributes to tumor development. These studies demonstrated that the cellular abundance of proto-oncoproteins and tumor suppressors is controlled by the ubiquitin-proteasome system. Addressing how defective and overactive protein degradation contributes to tumor development has provided valuable knowledge for developing new therapeutic agents for cancer treatment.
- a. Guardavaccaro, D., Frescas, D., Dorrello, N.V., Peschiaroli, A., Multani, A.S., Cardozo, T., Lasorella, A., Iavarone, A., Chang, S., Hernando, E., Pagano, M. Control of chromosome stability by the β TrCP-REST-MAD2 axis. **Nature** 452(7185) 365-70, 2008.
 - b. Magliozzi, R., Low, T.W., Weijts, B.G.M.W., Cheng, T., Spanjaard, E., Mohammed, S., van Veen, A., Ova, H., de Rooij, J., Zwartkruis, F.J.T., Bos, J.L., de Bruin, A., Heck, A.J.R., Guardavaccaro, D. Control of epithelial cell migration and invasion by the IKK β - and CK1 α -mediated degradation of RAPGEF2. **Dev Cell** 27(5):574-85, 2013.
 - c. Infante, P., Faedda, R., Bernardi, F., Bufalieri, F., Severini, L.L., Alfonsi, R., Mazzà, D., Siler, M., Coni, S., Po, A., Petroni, M., Ferretti, E., Mori, M., De Smaele, E., Canettieri, G., Capalbo, C., Maroder, M., Screpanti, I., Kool, M., Pfister, S., Guardavaccaro, D., Gulino, A., Di Marcotullio, L. Itch/ β arrestin2-dependent non-proteolytic ubiquitylation of SuFu controls Hedgehog signaling and medulloblastoma tumorigenesis. **Nature Commun** 9(1):976, 2018.
 - d. Bufalieri, F., Infante, P., Bernardi, F., Caimano, M., Romania, P., Moretti, M., Lospinoso Severini, L., Talbot, J., Melaiu, O., Tanori, M., Di Magno, L., Bellavia, D., Puget, S., De Smaele, E., Canettieri, G., Guardavaccaro, D., Busino, L., Peschiaroli, A., Pazzaglia, S., Giannini, G., Melino, G., Locatelli, F., Gulino, A., Ayrault, O., Fruci, D., Capalbo, C., and Di Marcotullio, L. ERAP1 promotes Hedgehog-dependent tumorigenesis by controlling USP47-mediated degradation of β TrCP. **Nature Commun** 10(1):3304, 2019
 - e. Enriqu  Steinberg, J.E., Santucci, M., Rossi, F.A., Magliozzi, M., Yuniati, L., Rossi, M., Guardavaccaro, D. and Lauriola, A. SCF β TrCP-mediated degradation of SHARP1 in triple-negative breast cancer. **Cell Death Dis.** 2023 Nov 8;14(11):726.
4. We have been recently investigating the molecular mechanisms underlying spatially restricted substrate degradation. In fact, although the ubiquitin-proteasome system is known to control substrate degradation in all cellular compartments, substrate proteolysis at specific membrane compartments is not well understood. We have been studying how substrate ubiquitylation is spatially restricted at specific membrane compartments and characterizing the molecular mechanisms regulating the recruitment and activation of ubiquitin ligases locally at cellular membranes. Moreover, we have been analyzing the role of ubiquitylation in the dynamic remodeling of the ER. The importance of maintaining proper ER architecture is underscored by the evidence that mutations in proteins involved in ER formation and maintenance are

responsible for the primary pathological defects of the neurological disorder hereditary spastic paraplegia.

- a. Yuniati, L., Lauriola, A., Gerritsen, M., Abreu, S., Ni, E., Tesoriero, C., Onireti, J.O., Low, T.Y., Heck, A.J., Vettori, A., Cardozo, T., and Guardavaccaro, D. Ubiquitylation of the ER-shaping protein Lunapark via the CRL3^{KLHL12} ubiquitin ligase complex. **Cell Reports**. 2020 May 19;31(7):107664.
- b. Liang, D., Jiang, L., Bhat, S.A., Missiroli, S., Perrone, M., Lauriola, A., Adhikari, R., Gudur, A., Vasi, Z., Ahearn, I., Guardavaccaro, D., Giorgi, C., Philips, M., Kuchay, S. Palmitoylation and PDE6 δ regulate membrane-compartment-specific substrate ubiquitylation and degradation. **Cell Reports**. 2023 Jan 18;42(1):111999.

Complete List of Published Work in PubMed MyBibliography:

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