
BIOGRAPHICAL SKETCH

NAME: **Prof. Simona Polo**

eRA COMMONS USER NAME (credential, e.g., agency login): not applicable

POSITION TITLE: **Associate Professor of Pathology**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Milan	Associate Professor	present	Molecular machines in signaling pathways
IFOM ETS	Senior PI	present	Molecular machines in signaling pathways
IFOM ETS	Junior PI	2011	Regulatory roles of ubiquitin
University of Milan	Researcher	2019	Ubiquitin and signal transduction
European Institute of Oncology	Senior scientist	2005	Endocytosis
Dibit San Raffaele Hospital	Post- doctoral	1999	Virology
University of Milan	Specializati on	1995	Genetics
University of Milan	Degree in Biological Sciences	1991	Biology

A. PERSONAL STATEMENT

My primary research interest lies in exploring the intricacies of cell signaling, with a particular emphasis on the role of ubiquitin in orchestrating protein complex remodeling under both physiological and pathological conditions. My accomplishments include the discovery that ubiquitin acts as a signaling molecule, which was a groundbreaking revelation in the field. My lab characterized several Ub binding domains responsible for the recognition of specific Ub chains and demonstrated that ubiquitin targets the epidermal growth factor receptor for internalization and degradation via a clathrin-independent mechanism.

My research has also extended to the critical determinants of ubiquitin chain specificity, particularly HECT E3 enzymes responsible for ubiquitination and lysosomal targeting of GPCRs and transporters. We have shed light on the ubiquitination reaction catalyzed by NEDD4 family members and demonstrated that their enzymatic activity is tightly controlled through an auto-inhibitory interaction of the C2 with the HECT domain. My team also generated and patented NEDD4-specific inhibitors, with a manuscript related to their use in cancer currently submitted.

B. POSITIONS, SCIENTIFIC APPOINTMENTS, AND HONORS

Positions and Scientific Appointments

2021- present Associate Editor EMBO Reports

2021- present	Management Committee COST Action CA20113 ProteoCure (2021-2025)
2019- present	Associate Professor, Dipartimento di Oncologia ed Emato-Oncologia (DIPO)
2018- 2022	Member of the Departmental Council of DIPO
2017- 2022	Coordinator of the Molecular Oncology PhD program (SEMM)
2014	Panel member Advanced Grant ERC (LS1)
2013- 2020	Management Committee COST Action BM1307, PROTEOSTASIS
2013- 2019	Member of the SAC for evaluation of Worldwide Cancer Research (WCR) grants
2011- present	Senior Group Leader, IFOM, The FIRC Institute for Molecular Oncology
2006 - 2019	Researcher, Dipartimento di Oncologia ed Emato-Oncologia (DIPO)
2005- 2022	Member of the Educational Committee of SEMM (PhD program).
2005 - 2011	Tenure track Group Leader, IFOM, Milan, Italy
2002 - 2005	Staff scientist, European Institute of Oncology (IEO), Milan, Italy
1999 - 2002	Postdoctoral Fellow, European Institute of Oncology (IEO), Milan, Italy
1996 - 1999	Postdoctoral Fellow, Dilibit San Raffaele Hospital, Milan, Italy
1995 - 1996	Postdoctoral Fellow, LePetit Research center, Gerenzano, Italy
1991 - 1995	Post-graduate School in Genetics. University of Milan, Italy
1987 - 1991	M.Sc. in Biology. University of Milan, Italy

Honors

2018	Gold Medal (Ambrogino) for special contribution to the city of Milan
2016	Elected EMBO Member
2013	Elected Member of the AcademiaNet, portal for excellent female researchers
2009	EMBO Young Investigator Award
1995	LePetit Funds Research Award
1992	Best Graduate Thesis in Genetics (AGI) Award

Career breaks

02/2011-07/2011	Maternity leave
05/2009-10/2009	Maternity leave

C. CONTRIBUTIONS TO SCIENCE

My laboratory focuses on investigating the molecular mechanisms of ubiquitination and its impact on the pathogenesis of human diseases. My main contributions to the field include:

- Understanding the role of ubiquitin in the endocytic pathway, with particular attention to the critical interface between endocytosis, trafficking, and intracellular signaling of receptor tyrosine kinases such as EGFR.
- Molecular dissection of the catalytic mechanism and function of Nedd4 family E3 ubiquitin ligases, and their pathophysiological impact, particularly in cancer and neurodegenerative diseases.
- Identification and characterization of alternative myosin VI isoforms affecting its ability to bind ubiquitin, dissection of the splicing mechanism, and study of the oncogenic isoform in ovarian and colon cancers.

Summary of Contributions:

We identified and characterized ubiquitin as a molecular determinant in the endocytosis process, capable of modulating both the EGFR receptor (Sigismund et al., PNAS 2005, Dev. Cell 2008, EMBO J. 2013) and endocytic adaptors such as Eps15, Epsins, and Hrs (Woelk et al., Nat. Cell Biol. 2006). We identified the E3 ligase responsible for Eps15 ubiquitination (NEDD4) and elucidated the events through which EGF stimulation induces Eps15 ubiquitination and its USP9X-mediated deubiquitination (Savio et al., Curr. Biol. 2016), both essential for proper receptor deactivation after stimulation.

We also focused on E3 ligases as critical determinants of ubiquitination specificity at both the substrate level and in the type of chains produced. We demonstrated that Nedd4 family enzymes generate K63-linked polyubiquitin chains and use a sequential model to attach them to substrates (Maspero et al.,

EMBO Rep. 2011). Through structural studies, we unveiled the ubiquitination reaction, capturing NEDD4 in its active state for the first time (Maspero et al., Nat. Struct. Mol. Biol. 2013). We showed that the enzymatic activity of these E3 ligases is tightly regulated by an autoinhibitory interaction (Mari et al., Structure 2014), released upon activation of EGFR or FGFR, which phosphorylate Src, subsequently phosphorylating Nedd4 at key sites (Persaud et al., Sci. Signal. 2014). More recently, we characterized Hecw, a NEDD4 family ligase selectively expressed in the nervous system (Fajner et al., Nat. Commun. 2021). Hecw is a key modulator of ribonucleoprotein complexes that regulate protein translation. Loss of its ubiquitin ligase activity leads to premature aging and motor defects associated with neuronal loss in the Drosophila model, mirroring human neurodegenerative processes.

A third research line in the lab arose from the characterization of myosin VI, a molecular motor that moves along actin filaments and was shown to function as a ubiquitin receptor. Notable findings include the identification of a novel structural domain in myosin VI that i) specifically binds K63-linked ubiquitin chains (He et al., Cell Rep. 2016), ii) is regulated by alternative splicing (Wollscheid et al., Nat. Struct. Mol. Biol. 2016), and iii) is positively selected in tumor cells highly dependent on myosin VI for migration (Wollscheid et al., Nat. Struct. Mol. Biol. 2016). Subsequently, we characterized the long isoform, selectively expressed in all epithelial tissues, and its interactor clathrin light chain (Biancospino et al., Nat. Commun. 2019). Together, they maintain the integrity of normal cellular and tissue architecture by regulating endocytic events on the apical surface of polarized cells. We elucidated the critical role of myosin VI in coordinating distal appendage formation and primary cilia assembly, with significant implications for genetic diseases known as ciliopathies (Magistrati et al., EMBO Rep. 2022). Finally, we identified and characterized the molecular mechanism of the short oncogenic isoform, which selectively affects the collective motility of tumor cell clusters. We discovered of MYO6-DOCK7-RAC1 axis that is essential to support the collective motion of jammed epithelia. This mode of motility drives carcinoma dissemination when cell cohorts invade stromal tissues (Menin et al. CELL Report 2023).

Supervision of graduate students and postdoctoral fellows

20 PhD students (3 currently in progress)

15 Postdocs (3 currently in progress)

18 Master Students (1 currently in progress)

Invited Speaker

> 50 international meetings on ubiquitin and signalling, including:

Keystone symposia (2005, 2007, 2009, 2014, 2018, 2023),

FASEB meetings (2006, 2010, 2012, 2016, 2020, 2022, 2024),

CSHL meetings (2005, 2011, 2013, 2020),

EMBO meetings (2007, 2008, 2011, 2013, 2015, 2017, 2019, 2022, 2023, 2024),

FEBS meetings (2006, 2012, 2016, 2017).

Invited Organizer

2024 EMBO workshop 'Ubiquitin and Ubiquitin-like proteins in health and disease'. Cavtat, Croatia.
Co-organizer

2022 EMBO workshop 'Ubiquitin and Ubiquitin-like proteins in health and disease'. Cavtat, Croatia.
Organizer

2017 COST/IFOM Advanced lecture Course 'Ubiquitin-assisted autophagy from mechanisms to pathology'. Milan, Italy.

2017 ZOMES IX 'PCI Complexes and ubiquitin defining a hub for protein homeostasis'. Rome Italy.

2014 EMBO/CONICET Satellite Course 'Ubiquitin & ubiquitin-like proteins: At the crossroads from chromatin to protein'. Buenos Aires, Argentina.

2012-14 EMBO Practical Course on Ubiquitin and Sumo. Alghero, Italy

2008-10 EMBO Practical Course on Ubiquitin and Sumo. Split, Croatia

2009 Keystone Symposium 'The Many Faces of Ubiquitin'. Copper Mountain, Colorado

Patents

1. *HECT E3 ligase NEDD4 inhibitors and uses thereof*, International Patent Application No. PCT/EP2020/065372. Granted in Europe, pending in US.
2. *Rantes mutants and therapeutic applications thereof* (Fondazione Centro San Raffaele del Monte Tabor). UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT, August 2003

Publications

Research Unique identifier ORCID 0000-0001-5536-9399

Polo has authored more than 70 peer reviewed ISI-indexed publications, which include original articles (11 as first author and 32 as last or corresponding author) with an average IF over 10, 14 invited reviews and 7 book chapters.

Total Citations (Scopus): **6119**

H-index (Scopus): **46**

Relevant for this Application (last author):

- Fajner, V., et al. (2021). Hecw controls oogenesis and neuronal homeostasis by promoting the liquid state of ribonucleoprotein particles. *Nat Commun* 12, 5488.
- Weber, J., et al. (2019). HECT E3 Ligases: A Tale With Multiple Facets. *Front Physiol* 10, 370.
- Jackl, M., et al. (2018). beta-Sheet Augmentation Is a Conserved Mechanism of Priming HECT E3 Ligases for Ubiquitin Ligation. *J Mol Biol* 430, 3218-3233.
- Fajner, V., et al. (2017). Targeting HECT-type E3 ligases - insights from catalysis, regulation and inhibitors. *FEBS Lett* 591, 2636-2647.
- Savio, M.G., et al. (2016). USP9X Controls EGFR Fate by Deubiquitinating the Endocytic Adaptor Eps15. *Curr Biol* 26, 173-183.
- Persaud, A., et al. (2014). Tyrosine phosphorylation of NEDD4 activates its ubiquitin ligase activity. *Sci Signal* 7, ra95.
- Mari, S., et al. (2014). Structural and functional framework for the autoinhibition of Nedd4-family ubiquitin ligases. *Structure* 22, 1639-1649.
- Maspero, E., et al. (2013). Structure of a ubiquitin-loaded HECT ligase reveals the molecular basis for catalytic priming. *Nat Struct Mol Biol* 20, 696-701.
- Maspero, E., et al. (2011). Structure of the HECT:ubiquitin complex and its role in ubiquitin chain elongation. *EMBO Rep* 12, 342-349.