BIOGRAPHICAL SKETCH

NAME: POLETTI, ANGELO

eRA COMMONS USER NAME: apoletti

POSITION TITLE: Full Professor of Experimental Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	END	FIELD OF STUDY
Università degli Studi di Milano, Milano, MI	PHMD	11/1984	Chemistry and Pharmaceutical Technologies *Italian Laurea [5 years (FT)=Bachelor's Degr + BSc]*
Università degli Studi di Milano, Milano, MI	MOTH	11/1987	Experimental Endocrinology *Master [3 years (FT) = MSc/MRes]*
Università degli Studi di Milano, Milano, MI	PHD	12/1992	Endocrinological and Metabolic Sciences *PhD [4 years (FT)]*
Ist Endocrinologia, UNIMI, Milano, MI	Graduate Student	11/1984	Two years training for the experimental thesis in Pharmaceutical Technology (Mentor Prof. L. Martini)
Ist Endocrinologia, UNIMI, Milano, MI	Graduate Student	10/1987	Three years training for the experimental thesis for the Master School of Experimental Endocrinology (Mentor Prof. L. Martini)
Università degli Studi di Milano, Milano, MI	Other training	01/1990	Postgraduate student working on the role of androgens in the brain (Supervisor Prof. L. Martini)
Department of Cell Biology, Baylor College of Medicine, Houston, TX	Other training	07/1992	Two years and six months Fellow in Cell Biology of hormonal steroid receptors (supervisors, B.W. O'Malley, W.T. Schrader, N.L., Weigel)
Ist Endocrinologia, UNIMI, Milano, MI	Postdoctoral Fellow	11/1993	PostDoctoral fellow

A. Personal Statement

My laboratory is studying the molecular mechanisms at the basis of motor neuron (MNDs: spinal and bulbar muscular atrophy (SBMA) and amyotrophic lateral sclerosis (ALS)) and neuromuscular (NMDs, associated to mutation in BAG3 or HSPB8 genes) diseases. These MNDs and NMDs are linked to aberrant mutant protein conformations (misfolded proteins). The misfolded proteins exert neurotoxic activities in neurons and muscle cells and must be clear from cells by the intracellular protein quality control (PQC) system that prevent their accumulation and aggregation. Our major aims are to boost the PQC system to remove neurotoxic proteins from affected neuronal and muscle cells. We characterized a protective pathway which relies on the function of a small heat shock protein (HSPB8), that counteracts misfolded protein neurotoxicity via the facilitation of the autophagic process. HSPB8, and its partner BAG3, complex with HSP70 and CHIP delivering misfolded protein to autophagosomes via the Chaperon-Assisted Selective Autophagy (CASA). Drugs capable to enhance HSPB8 expression have been identified and are currently in phase II clinical trial with ALS patients. We are also studying forms of ALS associated to the C9ORF72 (G4C2)n expansion with particular focus on the unconventional RAN translation process that results in the production of five neurotoxic dipeptides present in ALS. We recently contributed to the identification of pathways that specifically inhibit RAN translation.

1. Tedesco B, Vendredy L, Timmerman V, Poletti A. The chaperone-assisted selective autophagy complex dynamics and dysfunctions. Autophagy. 2023 January 03; :1-23. Available from: https://www.tandfonline.com/doi/full/10.1080/15548627.2022.2160564 DOI: 10.1080/15548627.2022.2160564
2. Licata NV, Cristofani R, Salomonsson S, Wilson KM, Kempthorne L, Vaizoglu D, D'Agostino VG, Pollini D, Loffredo R, Pancher M, Adami V, Bellosta P, Ratti A, Viero G, Quattrone A, Isaacs AM, Poletti A, Provenzani A. C9orf72 ALS/FTD dipeptide repeat protein levels are reduced by small molecules that inhibit PKA or enhance protein degradation. EMBO J. 2022 Jan 4;41(1):e105026. PubMed Central PMCID: PMC8724771.

3. Cristofani R, Crippa V, Vezzoli G, Rusmini P, Galbiati M, Cicardi ME, Meroni M, Ferrari V, Tedesco B, Piccolella M, Messi E, Carra S, Poletti A. The small heat shock protein B8 (HSPB8) efficiently removes aggregating species of dipeptides produced in C9ORF72-related neurodegenerative diseases. Cell Stress Chaperones. 2018 Jan;23(1):1-12. PubMed Central PMCID: PMC5741577.
4. Ganassi M, Mateju D, Bigi I, Mediani L, Poser I, Lee HO, Seguin SJ, Morelli FF, Vinet J, Leo G, Pansarasa O, Cereda C, Poletti A, Alberti S, Carra S. A Surveillance Function of the HSPB8-BAG3-HSP70 Chaperone Complex Ensures Stress Granule Integrity and Dynamism. Mol Cell. 2016 Sep 1;63(5):796810. PubMed PMID: 27570075.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2022 -	Member of the Steering Committee, National Center for Gene Therapy and Drugs based on RNA Technology" Spoke 3 "Gene Therapy and therapy based on RNA Technology", Italy
2021 -	Council member, European Society for Neurochemistry
2020 -	Head Interdepartmental Study Programme, Università degli Studi di Milano, Interdepartmental Academic Board for the Bachelor's Degree Programme in Biotechnology, Milano
2018 - 2021	Member of the Scientific Board, Italian Association of Biologists and Genetists
2016 - 2019	Member of the Steering Committee, The Italian Society for Neuroscience
2014 - 2017	Coordinator, Università degli Studi di Milano, Section of Biomedicine and Endocrinology, Dpt Pharmacological and Biomolecular Sciences, Milano
2013 -	Member of the Steering Committee, Fondazione Carlo Erba
2013 - 2016	Director, Università degli Studi di Milano, PhD school in Endocrinological and Metabolic Sciences, Milano
2011 -	Full Professor of Experimental Biology, Università degli Studi di Milano, Milano
2005 - 2015	Member of the Steering Committee, InterUniversity Center on Neurodegenerative Diseases, Universities of Florence, Rome (Tor Vergata), Genoa and Milan, Milano
2003 -	Member of the Steering Committee and of the Scientific Board, Center of Excellence on Neurodegenerative Diseases, University of Milan, Milano
2002 - 2011	Associate Professor of Experimental Biology, Università degli Studi di Milano, Milano
1993 - 2002	Assistant Professor of Endocrinology, Università degli Studi di Milano, Milano
1992 - 1993	PostDoctoral Fellow, Inst of Endocrinology, Università degli Studi di Milano, Milano
1990 - 1992	Fellow, Department of Cell Biology, Baylor College of Medicine, Houston, TX
1985 - 1990	Fellow (as MSc/PhD student), Inst of Endocrinology, Università degli Studi di Milano, Milano
1985 - 1986	Mandatory Military service, Italian Army, Torino
1982 - 1984	Internship, Inst of Endocrinology, Università degli Studi di Milano, Milano

Honors

1996 - 1996	Chiodini's award for Neuroendocrinology, Italian Society for Endocrinology

Meeting organized:

- Organizer of: i) six different editions of the meeting "Molecular Mechanisms of Neurodegeneration"; ii) Biennal Meeting of the "European Society for Neurochemistry" 2019; iii) National Meeting of the "Italian association of Biologists and Genetists" 2019; iv) International Meeting "Focus ALS: Motor neuron diseases" 2018; II Meeting "The Small HSP world, 2016; v) Satellite Meeting FENS 2014 "Motor neuron diseases: molecular and cellular bases of selective vulnerability" 2014; vi) First workshop "SBMA in Italy, 2010; vii) the National Congress of the Italian Society for Neuroscience in 2009; viii) the "Triplet Repeat Diseases" Meeting 2000;

Symposia organized: Prof. Poletti organized more than 10 symposia to national and international meetings

Chairpersonships: Prof. Poletti served as chairman to more than 20 national and international meeting

Presentation to meetings: Invited Presentations: Prof. Poletti has been invited to deliver: 5 Plenary Lectures to Neuroscience meetings; 54 Presentations to Symposia; 25 Oral Communications; Several Seminars in Italian or Foreign Universities.

Editorial Activity: o "Triplet Repeat Diseases: From Basic to Clinical Aspects" Brain Res. Bull. 2001, 56:215-220.; "The Neurotoxicity of Mutant Proteins" Prog. Neurobiol. 2012, Vol 97, Issue 2 / Prog. Neurobiol. 2012, Vol 99,

Issue 3; “The Role of the Protein Quality Control in Neurodegenerative Diseases” Frontiers Media); Handling Editor of “The Journal of Neurochemistry”; Member of the Editorial Advisory Board of: Open Endocrinology Journal, Open Endocrinology Reviews, Behavioural Neurology, International Journal of Medical Sciences, Scientific Reports, Frontiers in Cellular Neurosciences, Frontiers in Molecular Neuroscience.

Research Support *(only those active in the past 5 years)*

- Fondazione TeleThon, Italy (coordinator) (n. GGP14039) "Motorneuron degeneration in Spinal and Bulbar Muscular Atrophy: from the molecular mechanisms to the potential therapeutical approaches " (2014-2019)
- Fondazione AriSLA “Fondazione Italiana di Ricerca per la SLA” multicentric project (Operative Unit): Granulopathy. “VCP and autophagolysosomal pathway: guardians of proteostasis and stress granule dynamics. Unraveling their implications in ALS”. (2014-2018)
- Fondazione Cariplo, Italy, multicentric project (coordinator) "RAN-translation of normal and expanded nucleotide repeat containing transcripts to neurotoxic polypetides in neurodegenerative diseases" (2015-2018)
- JPND: Joint Programme - Neurodegenerative Disease Research. Multicentric project (Operative Unit): ”European research projects on neurodegenerative diseases: risk and protective factors, longitudinal cohort approaches and advanced experimental models” "Stress granules and proteostasis in motor neurons: towards a mechanistic understanding of ALS" (2016 - 2019)
- Fondazione Regionale per la Ricerca Biomedica", Italy Multicentric project (Operative Unit): ”Translating molecular mechanisms into ALS risk and patient’s well-being (TRANS-ALS)” (2016 - 2020)
- Ministero dell'Istruzione, dell'Università e della Ricerca, Italy (coordinator) multicentric project "Progetti di ricerca di rilevante interesse nazionale (PRIN) – Bando 2015 " n. 2015LFPNMN entitled "From RNA to Protein toxicity in motorneuron diseases". (2016-2020)
- Agenzia Italiana del farmaco (AIFA) "Bando AIFA 2016 per la ricerca indipendente" Tematica: Brain Disorders and Clinical Neuroscience, Italy. ”Colchicine for Amyotrophic Lateral Sclerosis: a phase II, randomized, double blind, placebo controlled, multicenter clinical trial (AIFA-2016-02364678)” (coordinator: Dr. Jessica Mandrioli, dipartimento di Neuroscienze Nuovo Ospedale Civile S. Agostino Estense di Modena, Ausl Modena; 3 gennaio 2018 - 3 gennaio 2021 total 990.600,00 euro - our unit 115.000,00 euro). (2019-ongoing)
- Fondazione AriSLA", Italy Multicentric project (Operative Unit) “Target-RAN, Targeting RAN translation in ALS” (coordinatoe: Prof. Alessandro Provenzani; April 1st, 2019 – March 321st, 2022, total 240.000 euro - our unit 110.000 euro). (2019-ongoing)
- Fondazione AriSLA", Italy Multicentric project (Operative Unit) Italy “MLOpathy, Membrane-less organelle pathology in ALS: identification of causes and rescuing factors” (coordinator: Prof.ssa Serena Carra; April 1st, 2019 – March 321st, 2022, total 240.000 euro - our unit 66.000 euro) (2019-ongoing).
- Ministero dell’Istruzione, dell’Universita’ e della Ricerca Scientifica (MIUR) (coordinator) multicentric project "Progetti di ricerca di rilevante interesse nazionale (PRIN) – Bando 2017 " n. 2017F2A2C5 "The interplay between the “RNA/protein quality control system” and “exosomes” as a spreading mechanism in amyotrophic lateral sclerosis [ex_als] ". (665.139 Euro) (2019-ongoing).
- Fondazione TeleThon, Italy (coordinator) (n. GGP19128) multicentric project "Alternative translation initiation as a novel strategy to block toxicity of the mutant Androgen Receptor in SBMA" (330.000 euro) (2019-ongoing).
- AFM-Telethon, France (coordinator) (n. project 23236) multicentric project: "The involvement of the small heat shock protein HSPB8 in amyotrophic lateral sclerosis" (225.000 euro, our unit 88.000 euro) (2021-ongoing).
- Project PNRR CN3 “National Center for Gene Therapy and Drugs based on RNA Technology” “Gene Therapy and therapy based on RNA Technology”, Thematic Spoke 3 coordinator of the Units of UNIMI (our unit 1.586.000 euro) (2022-ongoing).

C. Contribution to Science

1. During my first two decades of research, I was initially involved in the study of the mechanisms of the steroid hormones and the activation of their receptors in the brain. Then, I studied post-translational modifications of the progesterone receptor activated in response to the ligand progesterone that mediate its transcriptional activation. These observations next contributed to clarify some events if ligand independent activation of steroid receptors in tumors. I identified a novel pathway by which androgen derivatives are converted into estrogenic compounds (3beta-diol) in prostate cancer cells and activate the estrogen receptor beta, which in

male exerts a potent antiproliferative, antimigratory and antimetastatic activity on prostate cancer cells. More recently, I focused also on breast cancer and melanoma. Selected publications related to this contribution.

a. Poletti A., Weigel N.L. Identification of a hormone-dependent phosphorylation site adjacent to the DNA-binding domain of the chicken progesterone receptor. Molecular Endocrinology. 1993; 7(2):241-246. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-0027509780&partnerID=MN8TOARS eid: 2-s2.0-0027509780
b. Dondi D, Piccolella M, Biserni A, Della Torre S, Ramachandran B, Locatelli A, Rusmini P, Sau D, Caruso D, Maggi A, Ciana P, Poletti A. Estrogen receptor beta and the progression of prostate cancer: role of 5alpha-androstane-3beta,17beta-diol. Endocr Relat Cancer. 2010 Sep;17(3):731-42. PubMed PMID: 20562232.
c. Guerini V, Sau D, Scaccianoce E, Rusmini P, Ciana P, Maggi A, Martini PG, Katzenellenbogen BS, Martini L, Motta M, Poletti A. The androgen derivative 5alpha-androstane-3beta,17beta-diol inhibits prostate cancer cell migration through activation of the estrogen receptor beta subtype. Cancer Res. 2005 Jun 15;65(12):5445-53. PubMed PMID: 15958594.
d. Cristofani R, Piccolella M, Montagnani Marelli M, Tedesco B, Poletti A, Moretti RM. HSPB8 counteracts tumor activity of BRAF- and NRAS-mutant melanoma cells by modulation of RAS-prenylation and autophagy. Cell Death Dis. 2022 Nov 18;13(11):973. doi: 10.1038/s41419-022-05365-9.

2. In the past twenty-five years, I also investigated the neurotoxicity in motoneurons of the androgen receptor containing an elongated polyglutamine tract (ARpoly) causing spinal and bulbar muscular atrophy. We demonstrated that the mutant ARpolyQ aggregates in motoneurons in response to the interaction with its natural ligand testosterone, as the consequence of conformational change during AR activation. This results in ARpolyQ accumulation causing dysfunction of the degradative systems proteasome and autophagy. We found that trehalose, which activate autophagy, also induces HSPB8 expression and reduces ARpolyQ accumulation. Using antiandrogens to prevent ARpolyQ concentration into the nucleus of motoneurons, in combination with trehalose, we found an enhanced ARpolyQ clearance. A combinatory treatment based on these two drugs is presently under testing in SBMA mice. Selected publications related to this contribution
   a. Galbiati M, Meroni M, Boido M, Cescon M, Rusmini P, Crippa V, Cristofani R, Piccolella M, Ferrari V, Tedesco B, Casarotto E, Chierichetti M, Cozzi M, Mina F, Cicardi ME, Pedretti S, Mitro N, Caretto A, Risè P, Sala A, Lieberman AP, Bonaldo P, Pennuto M, Vercelli A, Poletti A. Bicalutamide and trehalose ameliorate spinal and bulbar muscular atrophy pathology in mice. Neurotherapeutics. 2023. In press
   b. Cristofani R, Crippa V, Rusmini P, Cicardi ME, Meroni M, Licata NV, Sala G, Giorgetti E, Grunseich C, Galbiati M, Piccolella M, Messi E, Ferrarese C, Carra S, Poletti A. Inhibition of retrograde transport modulates misfolded protein accumulation and clearance in motoneuron diseases. Autophagy. 2017 Aug 3;13(8):1280-1303. PubMed Central PMCID: PMC5584856.
   c. Giorgetti E, Rusmini P, Crippa V, Cristofani R, Boncoraglio A, Cicardi M, Galbiati M, Poletti A. Synergic prodegradative activity of Bicalutamide and trehalose on the mutant androgen receptor responsible for spinal and bulbar muscular atrophy. Human Molecular Genetics. 2014 August 13; 24(1):64-75. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddu419 DOI: 10.1093/hmg/ddu419
   d. Rusmini P, Cortese K, Crippa V, Cristofani R, Cicardi ME, Ferrari V, Vezzoli G, Tedesco B, Meroni M, Messi E, Piccolella M, Galbiati M, Garrè M, Morelli E, Vaccari T, Poletti A. Trehalose induces autophagy via lysosomal-mediated TFEB activation in models of motoneuron degeneration. Autophagy. 2019 Apr;15(4):631-651. PubMed Central ID: PMC6526812.

3. In parallel, at the beginning of last millennium, I started project on amyotrophic lateral sclerosis (ALS), with the aim to counteract misfolded protein toxicity in familial and sporadic ALS forms (fALS and sALS); I focused my research on the alterations induced by the proteins SOD1, TDP-43, FUS, VCP, p62, as well as on the dipeptides (DPRs) coded by the C9ORF72 gene. With my research groups, we contributed to characterize the role of the proteasome and of autophagy in the clearance of aggregating misfolded proteins, as well as the role of chaperones in directing their preferential degradation to each of these degradative pathways. We recently focused on the RAN translation of the (G4C2)n in the C9ORF72, finding compounds capable to inhibits the aberrant production of the RAN translated neurotoxic DPRs in these fALS. Selected publications related to this contribution

   a. Licata NV, Cristofani R, Salomonsson S, Wilson KM, Kempthorne L, Vaizoglu D, D'Agostino VG, Pollini D, Loffredo R, Pancher M, Adami V, Bellosta P, Ratti A, Viero G, Quattrone A, Isaacs AM, Poletti A, Provenzani A. C9orf72 ALS/FTD dipeptide repeat protein levels are reduced by small molecules that

inhibit PKA or enhance protein degradation. EMBO J. 2022 Jan 4;41(1):e105026. doi: 10.15252/embj.2020105026. Epub 2021 Nov 18. PMID: 34791698

b. Ferrari V, Cristofani R, Cicardi ME, Tedesco B, Crippa V, Chierichetti M, Casarotto E, Cozzi M, Mina F, Galbiati M, Piccolella M, Carra S, Vaccari T, Nalbandian A, Kimonis V, Fortuna TR, Pandey UB, Gagliani MC, Cortese K, Rusmini P, Poletti A. Pathogenic variants of Valosin-containing protein induce lysosomal damage and transcriptional activation of autophagy regulators in neuronal cells. Neuropathol Appl Neurobiol. 2022 Aug;48(5):e12818. doi: 10.1111/nan.12818. Epub 2022 May 15. PMID: 35501124

c. Casarotto E, Sproviero D, Corridori E, Gagliani MC, Cozzi M, Chierichetti M, Cristofani R, Ferrari V, Galbiati M, Mina F, Piccolella M, Rusmini P, Tedesco B, Gagliardi S, Cortese K, Cereda C, Poletti A, Crippa V. Neurodegenerative Disease-Associated TDP-43 Fragments Are Extracellularly Secreted with CASA Complex Proteins. Cells. 2022 Feb 2;11(3):516. doi: 10.3390/cells11030516. PMID: 35159325

d. Crippa V, D'Agostino VG, Cristofani R, Rusmini P, Cicardi ME, Messi E, Loffredo R, Pancher M, Piccolella M, Galbiati M, Meroni M, Cereda C, Carra S, Provenzani A, Poletti A. Transcriptional induction of the heat shock protein B8 mediates the clearance of misfolded proteins responsible for motor neuron diseases. Sci Rep. 2016 Mar 10;6:22827. PMCID: PMC4785366.

4. Since 2010, I was also involved in the characterization of the novel autophagic pathway known as carperone-assisted selective autophagy (CASA) wich is mainly based on the function of the hereromeric complex formed by HSPB8 with BAG 3. This complex associated to HSP70/CHIP to form the CASA complex active in the removal of toxic misfolded proteins by affected tissues in MNDs and NMDs. With my groups we contributed to clarify the mechanism of CASA. We showed that the drosophila hortolog of HSPB8 counteracts TDP-43 neurotoxicity in fly models of ALS. Thus, HSPB8 has a protective activity in ALS. We described how HSPB8 and BAG3 protect against accumulation of these misfolded proteins by enhancing autophagy and found FDA approved drugs that enhance HSPB8 expression and consequently misfolded protein clearance in ALS cell models. We also characterized mutated forms of BAG3 and of HSPB8 which are causative of different forms of MNDs, NMDs and cardiomyopathies. Selected publications related to this contribution.

a. HSPB8 frameshift mutant aggregates weaken chaperone-assisted selective autophagy in neuromyopathies.,Tedesco B, Vendredy L, Adriaenssens E, Cozzi M, Asselbergh B, Crippa V, Cristofani R, Rusmini P, Ferrari V, Casarotto E, Chierichetti M, Mina F, Pramaggiore P, Galbiati M, Piccolella M, Baets J, Baeke F, De Rycke R, Mouly V, Laurenzi T, Eberini I, Vihola A, Udd B, Weiss L, Kimonis V, Timmerman V, Poletti A. Autophagy. 2023 Feb 28:1-23. doi: 10.1080/15548627.2023.2179780.

b. Chierichetti M, Cerretani M, Ciammaichella A, Crippa V, Rusmini P, Ferrari V, Tedesco B, Casarotto E, Cozzi M, Mina F, Pramaggiore P, Galbiati M, Piccolella M, Bresciani A, Cristofani R, Poletti A. Identification of HSPB8 modulators counteracting misfolded protein accumulation in neurodegenerative diseases. Life Sci. 2022 Dec 24:121323. doi: 10.1016/j.lfs.2022.121323. PMID: 36574942

c. Cristofani R, Crippa V, Vezzoli G, Rusmini P, Galbiati M, Cicardi ME, Meroni M, Ferrari V, Tedesco B, Piccolella M, Messi E, Carra S, Poletti A. The small heat shock protein B8 (HSPB8) efficiently removes aggregating species of dipeptides produced in C9ORF72-related neurodegenerative diseases. Cell Stress Chaperones. 2018 Jan;23(1):1-12. PubMed Central PMCID: PMC5741577.

d. Crippa V, Cicardi ME, Ramesh N, Seguin SJ, Ganassi M, Bigi I, Diacci C, Zelotti E, Baratashvili M, Gregory JM, Dobson CM, Cereda C, Pandey UB, Poletti A, Carra S. The chaperone HSPB8 reduces the accumulation of truncated TDP-43 species in cells and protects against TDP-43-mediated toxicity. Hum Mol Genet. 2016 Sep 15;25(18):3908-3924. PubMed Central PMCID: PMC5291228.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/angelo.poletti.1/bibliography/public/