BIOGRAPHICAL SKETCH

NAME: POLETTI, ANGELO

eRA COMMONS USER NAME: apoletti

POSITION TITLE: Full Professor of Experimental Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	START	END	FIELD OF STUDY
Univ Studi Milano, Milano, MI	PHMD	11/1979	11/1984	Chemistry and Pharmaceutical Technologies *Italian Laurea [5 yrs (FT)=Bachelor's Degr/ BSc]*
Univ Studi Milano, Milano, MI	MOTH	11/1984	11/1987	Experimental Endocrinology *Master [3 yrs (FT) = MSc/MRes]*
Univ Studi Milano, Milano, MI	PHD	11/1988	12/1992	Endocrinological and Metabolic Sciences *PhD [4 yrs (FT)]*
Ist Endocrinol, UNIMI, Milano, MI	Graduate Student	11/1982	11/1984	Two years training: experimental thesis in Pharmaceutical Technology
Ist Endocrinol, UNIMI, Milano, MI	Graduate Student	11/1984	10/1987	Three years training: experimental thesis in Master School of Experimental Endocrinology
Univ Studi di Milano, Milano, MI	Other training	11/1987	01/1990	Postgraduate student: focus on the role of androgens in the brain
Dpt Cell Biology, Baylor College of Medicine, Houston, TX	Other training	02/1990	07/1992	Two years and six months Fellow in Cell Biology of hormonal steroid receptors
Ist Endocrinol, UNIMI, Milano, MI	Postdoc	07/1992	11/1993	PostDoctoral fellow

A. Personal Statement

My laboratory is studying altered molecular mechanisms involved in 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), which exert neurotoxic activities in neurons and muscle cells. Because of that, these misfolded species must be clear from cells by the protein quality control (PQC) system that prevent their accumulation and aggregation, e.g.: by boosting the PQC system to remove toxic species from cells. An alternative approach is to repair or prevent the production of the toxic protein. In the case of SBMA we are exploring this possibility, since SBMA is caused by an expanded CAG triplet repeat in the androgen receptor (AR) gene, which is translated into an elongated polyQ tract in AR (ARpolyQ) N-terminus. This polyQ tract induces ARpolyQ toxicity both in motoneurons and skeletal muscle cells. We recently demonstrated that another AR isoform (AR-A) is present in brainstem and in spinal cord, but not in skeletal muscle cells. The AR-A generates by alternative translation on an AUG of the same AR mRNA, but located few nucleotides downstream to the CAG repeat. Thus AR-A retains the entire AR sequence, except for the first 188 aa with the polyQ tract. Importantly, the AR-A counteracts ARpolyQ aggregation and toxicity, preserving its transcriptional competence in different SBMA models. For therapeutic purposes, we are focused to find approaches aimed to re-balance the ARpolyQ:AR-A ratio in motoneurons and skeletal muscle cells reducing ARpolyQ translation, while favoring AR-A production to prevent ARpolyQ toxicity.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 - President of the Steering Committee of Association of Professor of Experimental Biology, Italy

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: six different editions of the meeting "Molecular Mechanisms of Neurodegeneration"; and i) a Meeting entitled "RNA-based innovative therapies for neurological disorders", Naples, Italy, 5th-07th October 2025 ii) the Biennal Meeting of the "European Society for Neurochemistry" 2019; iii) the National Meeting of the "Italian association of Biologists and Genetists" 2019; iv) the International Meeting "Focus ALS: Motor neuron diseases" 2018; v) the II Meeting "The Small HSP world, 2016; vi) the Satellite Meeting FENS 2014 "Motor neuron diseases: molecular and cellular bases of selective vulnerability" 2014; vii) the First workshop "SBMA in Italy, 2010; viii) the National Congress of the Italian Society for Neuroscience in 2009; ix) 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: 5 Invited Presentations: Prof. Poletti has been invited to deliver: 5 Plenary Lectures to Neuroscience meetings; 54 Presentations to Symposia; 25 Oral Communications; 30 Seminars in Italian or Foreign Universities.

Editorial Activity: "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 past 10 years)*

- Fondazione TeleThon, Italy (n. GGP14039) "Motorneuron degeneration in Spinal and Bulbar Muscular Atrophy: from the molecular mechanisms to the potential therapeutical approaches "
- 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".
- Fondazione Cariplo, Italy (coordinator) "RAN-translation of normal and expanded nucleotide repeat containing transcripts to neurotoxic polypetides in neurodegenerative diseases"
- 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"

- Fondazione Regionale per la Ricerca Biomedica", Italy Multicentric project (Operative Unit): "Translating molecular mechanisms into ALS risk and patient's well-being (TRANS-ALS)"
- Ministero dell'Istruzione, dell'Università e della Ricerca, Italy Coordinator of the multicentric project "Progetti di ricerca di rilevante interesse nazionale (PRIN) – Bando 2015 " n. 2015LFPNMN entitled "From RNA to Protein toxicity in motorneuron diseases".
- Agenzia Italiana del farmaco (AIFA) "Bando AIFA 2016 per la ricerca indipendente" Tematica: Brain Disorders and Clinical Neuroscience. "Colchicine for Amyotrophic Lateral Sclerosis: a phase II, randomized, double blind, placebo controlled, (Operative Unit) multicenter clinical trial (AIFA-2016-02364678)"
- Fondazione AriSLA", Italy Multicentric project (Operative Unit) "Target-RAN, Targeting RAN translation in ALS"
- Fondazione AriSLA", Italy Multicentric project (Operative Unit) Italy "MLOpathy, Membrane-less organelle pathology in ALS: identification of causes and rescuing factors"
- Ministero dell'Istruzione, dell'Universita' e della Ricerca Scientifica (MIUR) Coordinator of 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] ". Coordinator.
- Fondazione TeleThon, Italy (n. GGP19128) "Alternative translation initiation as a novel strategy to block toxicity of the mutant Androgen Receptor in SBMA". Coordinator.
- AFM-Telethon, France (n. project 23236): "The involvement of the small heat shock protein HSPB8 in amyotrophic lateral sclerosis". Coordinator.
- Project PNRR CN3 "National Center for Gene Therapy and Drugs based on RNA Technology" "Gene Therapy and therapy based on RNA Technology", (Operative Unit)
- Ministero dell'Università e della Ricerca Scientifica (MUR) Coordinator "Progetti di ricerca di rilevante interesse nazionale (PRIN) – Bando 2022 " n. 2022EFLFL8 " Developmental role of the mutant androgen receptor causative of spinal and bulbar muscular atrophy (SBMA)".
- NIH GRANT R21 PI Operative Unit "Mechanistic and Translational Investigations of HSPB8-associated dominant rimmed vacuolar myopathy" National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number R21AR080407 (Operative Unit)
- AFM-Telethon, France (n. 29514) "Pathogenic mechanisms of HSPB8 mutations in neuromuscular diseases: the role of the ribosomal and protein quality control system and the integrated stress response". Coordinator.

C. Contribution to Science

1. During my first two decades of research, I was involved in the study of the mechanisms of the steroid hormones and the activation of their receptors in the brain. I studied post-translational modifications of the progesterone receptor activated in response to the ligand progesterone that mediate its transcriptional activation. These observations 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 exert a potent antiproliferative, antimigratory and antimetastatic activity on prostate cancer cells. More recently we 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.
   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. 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. 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 (ARpolyQ) 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. Gianferrari G, Cuoghi Costantini R, Crippa V, Carra S, Bonetto V, Pansarasa O, Cereda C, Zucchi E, Martinelli I, Simonini C, Vicini R, Fini N, Trojsi F, Passaniti C, Ticozzi N, Doretti A, Diamanti L, Fiamingo G, Conte A, Dalla Bella E, D'Errico E, Scarian E, Pasetto L, Antoniani F, Galli V, Casarotto E; Co-ALS Investigators Group; D'Amico R, Poletti A, Mandrioli J. Colchicine treatment in amyotrophic lateral sclerosis: safety, biological and clinical effects in a randomized clinical trial. Brain Commun. 2024 Sep 5;6(5):fcae304. doi: 10.1093/braincomms/fcae304. eCollection 2024. PMID: 39291166
    b. 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 Mar;20(2):524-545. doi: 10.1007/s13311-023-01343-x. Epub 2023 Jan 30. PMID: 36717478
    c. 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.
    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 year 2000, 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. Cozzi M, Magri S, Tedesco B, Patelli G, Ferrari V, Casarotto E, Chierichetti M, Pramaggiore P, Cornaggia L, Piccolella M, Galbiati M, Rusmini P, Crippa V, Mandrioli J, Pareyson D, Pisciotta C, D'Arrigo S, Ratti A, Nanetti L, Mariotti C, Sarto E, Pensato V, Gellera C, Di Bella D, Cristofani RM, Taroni F, Poletti A. Altered molecular and cellular mechanisms in KIF5A-associated neurodegenerative or neurodevelopmental disorders. Cell Death Dis. 2024 Sep 27;15(9):692. doi: 10.1038/s41419-024-07096-5. PMID: 39333504
    b. 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
    c. 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
    d. 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

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. Tedesco B, Peric S, Kocak GS, Tan J, Duong H, Töpf A, Rakocevic-Stojanovic V, Milenkovic S, Parkhurst Y, Gibbs L, Martin-Rios A, Lambiase PD, Guttmann OP, Marini-Bettolo C, Harris E, Harms MB, Ivanovic V, Marchesi V, Milone M, Timmerman V, Straub V, Poletti A, Kimonis V. Novel HSPB8 mutations in severe early-onset myopathy with involvement of respiratory and cardiac muscles cause proteostasis defects in cell models.Eur J Hum Genet. 2025 Aug;33(8):1015-1024. doi: 10.1038/s41431-025-01868-z. Epub 2025 Jun 4. PMID: 40467930
b. 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. HSPB8 frameshift mutant aggregates weaken chaperone-assisted selective autophagy in neuromyopathies. Autophagy. 2023 19:2217-2239. doi: 10.1080/15548627.2023.2179780. PMID: 36854646
c. 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
d. Adriaenssens E, Tedesco B, Mediani L, Asselbergh B, Crippa V, Antoniani F, Carra S, Poletti A, Timmerman V. BAG3 Pro209 mutants associated with myopathy and neuropathy relocate chaperones of the CASA-complex to aggresomes. Sci Rep. 2020 May 29;10(1):8755. doi: 10.1038/s41598-020-65664-z.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/angelo.poletti.1/bibliography/public/