BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Maria Pennuto, Ph.D.	Associate Professor
eRA COMMONS USER NAME MARIAPENN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University "La Sapienza" Rome, Italy	M.S.	1990-1996	Biological Sciences
University of Milan, Italy	Ph.D.	1997-2000	Mol and Cell Biology

A. Personal statement:

My research focuses on the investigation of pathogenetic mechanisms underlying age-related diseases, such as cancer and neurodegenerative diseases. Focusing on prostate cancer and cancers with a sex-bias, as well as spinobulbar muscular atrophy and amyotrophic lateral sclerosis, my research contributed to show that: 1) Post-translational modifications (PTM): phosphorylation and arginine methylation modify the toxic gain of function of the disease proteins, and stimulation of specific cellular pathways modulating the function of the enzymes responsible for these PTMs has therapeutic potential; 2) Peripheral tissues: We contributed to show that skeletal muscle contributes to body weight loss, energy unbalance and neuronal degeneration, damage is often primary and not secondary to neuronal dysfunction and loss, and skeletal muscle is a valuable therapeutic target tissue; 3) Epigenetic dysregulation of gene expression: We showed that epigenetic writers are recruited by disease proteins working as transcription factors and contribute to pathogenesis in age-related diseases. Based on our work, two compounds, insulin-like growth factor 1 and beta-agonists (clenbuterol) were translated to *phase II clinical trials for SBMA*.

a. Prakasam R, Bonadiman A, Andreotti R, Zuccaro E, Dalfovo D, Marchioretti C, Tripathy D, Petris G, Anderson EN, Migazzi A, Tosatto L, Cereseto A, Battaglioli E, Sorarù G, Lim WF, Rinaldi C, Sambataro F, Pourshafie N, Grunseich C, Romanel A, Pandey UB, Contestabile A, Ronzitti G, Basso M, **Pennuto M*.** 2023. *LSD1/PRMT6-targeting gene therapy to attenuate androgen receptor toxic gain-of-function ameliorates spinobulbar muscular atrophy phenotypes in flies and mice.* Nature Comm 14:303.
b. Marchioretti C, Zanetti G, Pirazzini M, Gherardi G, Nogara L, Andreotti R, Martini P, Marcucci L, Canato M, Nath SR, Zuccaro E, Chivet M, Mammucari C, Pacifici M, Raffaello A, Rizzuto R, Mattarei A, Desbats MA, Salviati L, Megighian A, Sorarù G, Pegoraro E, Belluzzi E, Pozzuoli A, Biz C, Ruggieri P, Romualdi C, Lieberman AP, Babu GJ, Sandri M, Blaauw B, Basso M, **Pennuto M***. 2023. *Defective excitation-contraction coupling and mitochondrial respiration precede mitochondrial Ca2+ accumulation in spinobulbar muscular atrophy skeletal muscle*. Nature Comm 14:602.
c. Piol D, Tosatto L, Zuccaro E, Anderson EN, Falconieri A, Polanco MJ, Marchioretti C, Lia F, White J, Bregolin E, Minervini G, Parodi S, Salvatella X, Arrigoni G, Ballabio A, La Spada AR, Tosatto SCE, Sambataro F, Medina DL, Pandey UB, Basso M, **Pennuto M***. 2023. Antagonistic effect of cyclin-dependent kinases and a calcium-dependent phosphatase on polyglutamine-expanded androgen receptor toxic gain of function. Sci. Adv. 9(1):eade1694.
d. Polanco MJ, Parodi S, Piol D, Stack C, Chivet M, Contestabile A, Miranda HC, Lievens PMJ, Espinoza S, Jochum T, Rocchi A, Grunseich C, Gainetdinov RR, Cato ACB, Lieberman A, La Spada AR, Sambataro F, Fischbeck KH, Gozes I, **Pennuto M***. CDK2 inhibition by PACAP/AC/PKA signaling reduces polyglutamine-expanded androgen receptor phosphorylation and toxicity in SBMA. Sci Transl Med 2016, 8:370ra181.

B. Positions and Honors

Positions and Employment

2018-present Group Leader, Veneto Institute of Mol Medicine (VIMM), Padova, Italy
2017-present Associate Professor, Department of Biomedical Sciences, University of Padova, Italy
2018-2023 Deputy Director, Veneto Institute of Mol Medicine (VIMM), Padova, Italy
2013-2017 Assistant & Associate Professor, CIBIO, University of Trento, Trento, Italy
2009-2014 Group Leader, Italian Institute of Technology, Genoa, Italy
2008-2009 Staff Scientist, Dptm of Neurology, U. of Pennsylvania (Mentor: Dr J.P. Taylor, MD, PhD)

2005-2008 Visiting Post-Doc Fellow, NIH-NINDS (Mentor: Kenneth Fischbeck, MD)
2001-2004 Post-Doc Fellow, S. Raffaele Scientific Institute, Milan (Mentor: Lawrence Wrabetz, MD)
1997-2000 Ph.D. Program, University of Milan (Mentor: Flavia Valtorta, MD)
1996-1997 Intern, Biology, University of Rome "La Sapienza", Italy

Honors and awards

2024 The Chica & Heinz Schaller Foundation Award in Translational Neuroscience, FENS Vienna, Austria
2024 Alessandro Moretta Ambassador of Research Award, Genova, Italy
2023 Member of the Mentorship Program, ENMC
2022 National Science Career Award "Cenacolo delle Scienze", Milan, Italy
2019 Selected International Day of Women in Science, United Nations, Padova, Italy
2019 Marie Curie travel award, MCAA general assembly, Vienna, Austria
2013 Dulbecco Telethon Institute Career Award
2017 Arimura Foundation State-of-Art Lecture Award, 13th International PACAP meeting, Hong Kong
2011 IBRO Woman in Neuroscience Lecture, PACAP international symposium, Israel
2005 Telethon Post-Doctoral Competitive Fellowship Award
2003 Euresco Travel Award
1998 European Science Foundation Travel Award
1997 A. Marzullo National Award for the Undergraduate Thesis, University of Trieste (Italy)

Professional Activities and Memberships

International Conference committee and organizer:

2023 46th Annual meeting Japan Neuroscience Society, Sendai, Japan, August 3-5
2023 271th ENMC workshop on SBMA, Amsterdam, The Netherlands, October 20-22
2021 International virtual meeting on Kennedy Disease, September 20-22
2019 241th ENMC workshop on SBMA, Feb 15-17, Amsterdam, The Netherlands
2015 210th ENMC workshop on SBMA, March 27-29, Amsterdam, The Netherlands
2013 Summer school: "The core of neuronal communication: axonal biology, degeneration and regeneration", Cavalese, Trento, Italy, 30/09- 04/10

National Conference committee and organizer:

2023 Symposium "Gene therapy and MNDs: from preclinical validation to clinical application", 20th Italian Society of Neuroscience (SINS) meeting, Torino, Italy, 14-17 October
2023 6th SBMA Italian meeting, Florence, Italy, 30 November
2021 Meeting VIMM-fit-Trieste Science Park, Padova, Italy, 26 May
2020 V SBMA Italian meeting, Virtual meeting, Italy, 19 September
2019 Minisymposium "The RNA biology of motor neuron disease", XVIII Italian Society of Neuroscience (SINS) meeting, Perugia, Italy, 26-29 September
2018 IV SBMA Italian meeting, University of Padova, Italy, 5-6 October
2016 III SBMA Italian meeting, University of Milan, Italy, 11-12 November
2016 Fondazione Telethon Tri-Retreat, Rome, Italy, 26-28 May
2015 II SBMA Italian meeting, University of Trento, Italy, 18 April
2013 I SBMA Italian meeting, University of Padova, 29-30 October

Chair, Scientific Conferences:

2023 46th Annual meeting Japan Neuroscience Society, Sendai, Japan, 3-5 August
2019 VIMM retreat, Treviso, Italy, 12-13 September
2019 XVIII Italian Society of Neuroscience (SINS) meeting, University of Perugia, Italy, 26-29 September
2018 Round Table: "Metabolism, exercise & signaling pathways in muscle wasting", Interuniversity Institute of Myology XV meeting, Assisi (Italy), 11-13 October
2018 Session: "Update on molecular and therapeutic development for SBMA", IV Kennedy disease Italian meeting, University of Padova, Italy, 5-6 October
2015 Session: "Motor neuron diseases: from molecular targets to trial design", XVII Telethon Scientific Convention, Riva del Garda Trento (Italy), 9-11 March
2014 Satellite meeting: Motor Neuron Disease, FENS, Milan (Italy), 3-4 July
2011 Molecular Mechanisms of Neurodegeneration, Milan (Italy)

Membership:

2007-present SINS (Società Italiana di Neuroscienze)
2010-present Member of Marie Curie Alumni & Italy Chapter
2016-present IIM (Interuniversity Institute of Myology)
2018-present SIBBM (Società Italiana di Biofisica e Biologia Molecolare)

Editor

2016-present Editorial board member of "Scientific Reports"
2013-2017 Editorial board member of "Advances in Neuroscience"
2020-2022 Guest Editor, Special Issue on Cells Journal

Ad hoc reviewer

Research articles:

Neuron, Science Advances, Acta Neuropathologica, Acta Neuropathologica Comm, J. Clinical Investigations, J. Clinical Investigations Comm, Cell Report, The Lancet Neurology, Progress in Neurobiology, Human Molecular Genetics, Developmental Cell, European J. Neuroscience, J. Neuroscience Research, Experimental Neurology, Brain Research, Scientific Reports, J. Neurological Sciences, Archives of Biochemistry and Biophysics, Cellular & Molecular Life Sciences, International J Neuroscience, Plos One, Neurobiology of Disease, J. of Molecular Neuroscience, Molecular Therapy.

Grant applications:

European Research Council (ERC), Association Francaise for Myopathies (AFM), Neuromuscular Disease Association UK, MRC UK, Program for "Giovani Ricercatori Rita Levi Montalcini" Italy.

Patents

Italian Priority N. 102022000026595 "NEW INHIBITORS OF EPIGENETIC REGULATORS/NUOVI INIBITORI DI REGOLATORI EPIGENETICI"

C. Contributions to Science:

1. Post-translational modifications in age-related diseases. Spinal and bulbar muscular atrophy (SBMA) is a neuromuscular disease caused by polyglutamine expansion in the androgen receptor (AR). SBMA belongs to the family of polyglutamine diseases, which also includes Huntington's disease, DRPLA, and six types of spinocerebellar ataxia. We showed that polyglutamine-expanded androgen receptor (polyQ-AR) is phosphorylated by Akt/PKB as well as CDKs. Phosphorylation of polyQ-AR by Akt reduced androgen binding and toxicity, whereas phosphorylation by the CDKs has the opposite effect. Moreover, we showed that phosphorylation by Akt is mutually exclusive with arginine methylation by protein arginine methyltransferase 6 (PRMT6). We identified PRMT6 and LSD1 as novel co-activators of normal AR, whose function was enhanced by polyQ expansion. Inhibition of PRMT6 and LSD1 reduced the toxicity of polyQ-AR, indicating that these epigenetic writers are novel modifiers of SBMA pathogenesis. We identified signaling pathways that enhance AR PTMs and suppress toxicity in preclinical models, linking our findings to development of novel therapeutics. Thus, we validated our experimental approach to identify post-translational modifications that impact (enhance or suppress) toxicity and to use this information to screen for agents that modulate such modifications for therapeutic purposes.
   a) Piol, et al., **Pennuto M***. Antagonistic effect of cyclin-dependent kinases and a calcium-dependent phosphatase on polyglutamine-expanded AR toxic gain-of-function. Sci. Adv. (in press).
   b) Prakasam, et al, **Pennuto M***. Lysine demethylase 1 and protein arginine methyltransferase 6 synergistically escalate androgen receptor toxic gain of function causing neurodegeneration. Nature Comm 14:603.
   c) Polanco MJ, Parodi S, Piol D, Stack C, Chivet M, Contestabile A, Miranda HC, Lievens PMJ, Espinoza S, Jochum T, Rocchi A, Grunseich C, Gainetdinov RR, Cato ACB, Lieberman A, La Spada AR, Sambataro F, Fischbeck KH, Gozes I, **Pennuto M***. CDK2 inhibition by PACAP/AC/PKA signaling reduces polyglutamine-expanded androgen receptor phosphorylation and toxicity in SBMA. Sci Transl Med 2016, 8:370ra181.
   d) Scaramuzzino C, Casci I, Parodi S, Lievens P, Polanco M, Milioto C, Chivet M, Monaghan J, Mishra A, Badders N, Aggarwal T, Grunseich C, Sambataro F, Basso M, Fackelmayer F, Taylor J, Pandey U, **Pennuto M***. Protein Arginine Methyltransferase 6 Enhances Polyglutamine-Expanded Androgen Receptor Function and Toxicity in Spinal and Bulbar Muscular Atrophy. Neuron 2015, 85:88-100.

2. Role of peripheral tissues in neurodegenerative diseases. We showed that skeletal muscle is a primary site of toxicity of polyQ-expanded AR. In detail, we demonstrated that SBMA muscles undergo an early glycolytic-to-oxidative fiber-type switch, metabolic alterations, dysregulation of ECC and contractile gene expression, and altered mitochondrial respiration, followed by accumulation of calcium into mitochondria, membrane depolarization, disruption of myofiber structure and ultimate degeneration of the NMJs. All these phenotypes were androgen-dependent, and reversible. These findings indicate that muscle is a viable therapeutic target for SBMA and provide proof-of-principle that intervention designed to target muscle has remarkable effects on spinal cord pathology.
   a) Marchioretti, et al., **Pennuto M***. Defective excitation-contraction coupling and mitochondrial respiration precede mitochondrial Ca2+ accumulation in spinobulbar muscular atrophy skeletal muscle. Nature Comm 14:602.
   b) Rocchi A, Milioto C, Parodi S, Armirotti A, Borgia D, Pellegrini M, Urciuolo A, Molon S, Morbidoni V, Marabita M, Romanello V, Gatto P, Blaauw B, Bonaldo P, Sambataro F, Robins DM, Lieberman AP, Sorarù G, Vergani L, Sandri M, **Pennuto M***. Glycolytic-to-oxidative fiber-type switch and mTOR signaling activation are early-onset features of SBMA muscle modified by high-fat diet. Acta Neuropathol 2016.132: 127-44.
   c) Palazzolo I, Stack C, Kong L, Musaro A, Adachi H, Katsuno M, Sobue G, Taylor J, Sumner C, Fischbeck K, **Pennuto M***. Overexpression of IGF-1 in Muscle Attenuates Disease in a Mouse Model of Spinal and Bulbar Muscular Atrophy. Neuron. 2009, 63:316-328.

3. Between 2001-2004, I expanded my interests from basic to translational neuroscience. During my first post-doctoral experience (2001-2004, Mentor Dr Lawrence Wrabetz) I studied the pathogenetic mechanisms that cause Charcot-Marie-Tooth type 1B (CMT1B) peripheral neuropathy. I showed that deletion of serine 63 in the myelin protein zero (MP0) causes protein unfolding, retention in the endoplasmic reticulum and induction of a stress response, i.e. the unfolded protein response (UPR). Deletion of one of the UPR effectors, CHOP transcription factor, rescued neurodegeneration and motor function. Our results indicate that mutant MP0 causes demyelination through a toxic gain of function mechanism in the endoplasmic reticulum (without arriving to the myelin sheet). Moreover, I showed that other MP0 mutants caused disease through similar mechanism if retained in the reticulum, extending the impact of these findings.
   a) Saporta MA, Shy BR, Patzko A, Bai Y, **Pennuto M**, Ferri C, Tinelli E, Saveri P, Kirschner D, Crowther M, Southwood C, Wu X, Gow A, Feltri ML, Wrabetz L, Shy ME. MpzR98C arrests Schwann cell development in a mouse model of early-onset Charcot-Marie-Tooth disease type 1B. Brain. 2012; 135:2032-47.
   b) **Pennuto M**, Tinelli E, Malaguti M, Del Carro U, D'Antonio M, Ron D, Quattrini A, Feltri ML, Wrabetz L. Ablation of the UPR-mediator CHOP restores motor function and reduces demyelination in Charcot-Marie-Tooth 1B mice. Neuron. 2008; 57:393-405.
   c) Wrabetz L, D'Antonio M, **Pennuto M**, Dati G, Tinelli E, Fratta P, Previtali S, Imperiale D, Zielasek J, Toyka K, Avila RL, Kirschner DA, Messing A, Feltri ML, Quattrini A. Different intracellular pathomechanisms produce diverse Myelin Protein Zero neuropathies in transgenic mice. J Neurosci. 2006; 26:2358-68.

4. During my PhD (1997-2000, Mentor Prof Flavia Valtorta), I investigated the molecular mechanisms of synaptic vesicle (SV) neurotransmission in living neurons. Synaptophysin I (SypI) and Synaptobrevin 2 (VAMP2) are very abundant SV proteins. I tested the hypothesis that SypI regulates VAMP2 availability for exocytosis and sorting. SypI and VAMP2 form both homo- and hetero-oligomers. Using FRET, I showed that SypI oligomers disassemble upon complete fusion of SVs, whereas SypI-VAMP2 oligomers disassemble before massive exocytosis. Overexpression of VAMP2 in hippocampal neurons resulted in diffused distribution along the axon. Co-expression of SypI restored the correct sorting of VAMP2, but not VAMP1 and Synaptotagmin I, indicating that SypI specifically regulates the sorting of VAMP2 to synaptic boutons.
   a. Bonanomi D, **Pennuto M**, Rigoni M, Rossetto O, Montecucco C, Valtorta F. Taipoxin induces synaptic vesicle exocytosis and disrupts the interaction of synaptophysin I with VAMP2. Mol Pharmacol 2005, 67:1901-8.

b. Rigoni M, Schiavo G, Weston AE, Caccin P, Allegrini F, **Pennuto M**, Valtorta F, Montecucco C, Rossetto O. Snake presynaptic neurotoxins with phospholipase A2 activity induce punctate swellings of neurites and exocytosis of synaptic vesicles. J Cell Sci 2004,117:3561-70.

c. **Pennuto M**, Bonanomi D, Benfenati F, Valtorta F. Synaptophysin I controls the targeting of VAMP2/synaptobrevin II to synaptic vesicles. Mol Biol Cell 2003, 14:4909-19.

d. **Pennuto M**. Dunlap D, Contestabile A, Benfenati F, Valtorta F. Fluorescence Resonance Energy Transfer Detection of Synaptophysin I and Vesicle- associated Membrane Protein 2 Interactions during Exocytosis from Single Live Synapses. Mol Biol Cell 2002; 13:2706-2717.

D. Current Research Support

ASSOCIATION FRACAISE MYOPATHIES (AFM-24337) **2022-2025** **€180,000**
Pennuto (Coordinator, 4 research groups)
Development of a therapeutic strategy to suppress LSD1 and PRMT6-mediated toxic gain of function in SBMA
This project aims at identifying new co-regulators that modify SBMA.

Autifony Pharmaceutical company **2022-2023** **€30,000**
Pennuto (PI)
Efficacy of channel modifiers in ALS and SBMA

Arvinas USA clinical-stage biopharmaceutical company **2021-2023** **€110,000**
Efficacy of PROTAC in SBMA

FONDAZIONE JUST-ITALIA **2021-2024** **€300,000**
Pennuto (Coordinator, 4 Units)
Una nuova trasmissione su RAI (Retinoic-induced 1)
The Aim of this project is to elucidate the role of RAI1 in neurodevelopmental disorders, such as Smith-Magenis and Potocky-Lupsky syndromes.

FONDAZIONE AIRC-Italy (24423) **2021-2026** **€620,000**
Pennuto (PI)
Targeting von Hippel Lindau protein/androgen receptor functional interaction to tackle renal cell carcinoma
The Aim of this project is to elucidate the role of AR in primary and metastatic renal cell carcinoma

UNISMART-PhD in the Industry (CARIPARO, Autiphony, UNIPD) **2020-2022** **€70,000**
Pennuto (academic partner)

TELETHON-Italy (GGP19128) **2019-2022** **€240,000**
Pennuto (co-PI)
Alternative translation initiation as a novel strategy to block toxicity of the mutant Androgen Receptor in SBMA
The aim of this project is to reduce expression of mutant androgen receptor without causing an AR loss of function.

PROGRAM RARE DISEASES CNCCS-Scarl-Pomezia **2019-2022** **€100,000**
Molecular mechanisms leading to neurodegeneration

E. Report of Training

Mentor of fellows that are now independent PIs:

2023 Diana Piol, my former PhD student, then post-doc fellow at VIB, Leuven, Belgium, now awarded an MDA and STARS UNIPD investigator to start as an independent group leader.

2023 Chiara Scaramuzzino, my former PhD student, promoted to group leader at the Grenoble Institute of Neuroscience, France.

2017 Emanuela Zuccaro, previous post-doc at Harvard University, USA, joined my lab as Staff Scientist, obtained Marie Curie & STARS fellow, University of Padova, now promoted to Assistant Professor.

2016 Maria Josè Polanco, trained in my lab as post-doc fellow at the University of Trento, promoted to Associate Professor at the University San Pablo CEU, Campus Montepríncipe, 28925 Alcorcón, Madrid, Spain.

2013 Manuela Basso, previous post-doc at the Burke-Cornell Medical Research Institute, NY, USA, joined my lab as Junior Group Leader, University of Trento, promoted to Associate Professor.

2012 Isabella Palazzolo, trained as a PhD student with me at the NIH, first hired by Biogen, now Director, Regulatory CMC, at Intellia Therapeutics, Cambridge, Massachusetts, Boston, US.

Tutoring of the following PhD students (name and position after PhD):

2023-present Simona Zito
2023-present Giacomo Bincoletto
2021-present Chiara Boschelle
2021-present Elisa Bregolin
2020-present Aishwarya Aravamudhan
2020-present Roberta Andreotti
2018-2022 Federica Lia (hired by a pharmaceutical company)
2017-2021 Caterina Marchioretti (Staff Scientist, Lab Pennuto)
2016-2019 Alice Migazzi (post-doc, University of Trento, Italy)
2015-2019 Diana Piol (post-doc at VIB, Leuven, Belgium)
2013-2016 Carmelo Milioto (post-doc, UCL, London, UK)
2010-2013 Tanya Aggarwal (post-doc, Karolinska Institute, Sweden)
2009-2012 Chiara Scaramuzzino (post-doc, University of Grenoble, France)
2005-2007 Isabella Palazzolo (post-doc, Harvard, Boston, USA)

Tutoring of the following MS students:

Daniela Michelatti (UNITN 2015-16), Davide Mastrovita (UNITN 2015-16), Eleonora Maino (UNITN 2016-17), Rajashekar Bodike (UNITN 2016-17), Alice della Marina (UNIPD 2019-20), Monica Piana (UNIPD 2019-20), Nicole Baratto (UNIFE, 2020-21), Shiva Ghasemi Firouzabadi (UNIPD 2021-22), Adham Kamaleldeen Omara Hegazy (UNIPD 2022-23), Anna Simona Daddario (UNIBA 2022-23), Simona Zito (UNIPD 2022-23), Sara Mennella (UNIPD 2022-23).

Tutoring of the following BS students:

Elisabetta Broseghini (UNITN 2015), Marco Destro (UNITN 2016), Michele Tebaldi (UNITN 2016), Piero Rigo (UNITN 2016), Riccardo Oliva (UNITN 2016), Ruggiero Cassatella (UNITN 2016), Stephanie Roilo (UNITN 2017).

Tutoring of the following Erasmus students:

Maria Roca Ceballos (from Spain 2018), Maria De La Sal (from Spain 2019), Gokce Gamze Arslan (from Turkey 2020), Gizen Tuktun (from Turkey 2019).