EUROPEAN CURRICULUM VITAE FORMAT

PERSONAL INFORMATION

Name **LANZILLOTTA SIMONA**

RESEARCH EXPERIENCE

- **02/04/2024- in progress**
  - Employer: Laboratory of Redox Biochemistry in Neuroscience, Department of Biochemical Sciences, Faculty of Pharmacy and Medicine, Sapienza University of Rome
  - Position: PhD
  - Main Responsibilities: At the laboratory of Prof. Eugenio Barone, I am advancing research on brain insulin signaling and its alterations, which are critical risk factors for cognitive decline in Alzheimer's disease and Down syndrome. A core focus of my thesis project involves examining the role of insulin resistance in promoting Oxidative Stress (OS) within the brain. Specifically, I am investigating whether the absence of Biliverdin Reductase-A (BVR-A) and the resulting modifications in insulin signaling observed in mouse models correlate with elevated OS levels, with attention to any sex-specific differences. Additionally, I am assessing the impact of insulin deficiency on mitochondrial function, especially in memory-associated brain regions with high insulin receptor density. This deficiency has been shown to reduce mitochondrial ATP production and increase ROS emission. Using both female and male C57Bl/6j and BVR-A$^{-/-}$ mice, I am analyzing how BVR-A loss, along with insulin signaling alterations, may disrupt mitochondrial function in the prefrontal cortex–essential for maintaining respiratory chain efficiency.

- **01/11/2023-31/12/2023**
  - Employer: Laboratory of Redox Biochemistry in Neuroscience, Department of Biochemical Sciences, Faculty of Pharmacy and Medicine, Sapienza University of Rome
  - Position: Pasteur Institute Italy-Fondazione Cenci Bolognetti Fellow
  - Main Responsibilities:

- **01/11/2020-31/10/2023**
  - Employer: Laboratory of Redox Biochemistry in Neuroscience, Department of Biochemical Sciences, Faculty of Pharmacy and Medicine, Sapienza University of Rome
  - Position: PhD student
  - Research Project Main Responsibilities: I was admitted to the 36th Cycle of the PhD Program in Biochemistry at Sapienza University of Rome, conducting my thesis under the supervision of Prof. Eugenio Barone from the Department of Biochemical Sciences at Sapienza University of Rome.

PhD thesis focuses on the role of Biliverdin Reductase A (BVR-A) as a key mediator in insulin signaling (IS). Under physiological conditions, IS regulates synaptic plasticity, cellular stress response, and neuronal metabolism - central processes to cognitive and learning functions. For several years, our research group has focused on the study of IS alterations associated with metabolic (obesity and diabetes) and neurodegenerative diseases, identifying BVR-A as a novel molecular target involved in IS. We believe that BVR-A plays a key role in IS regulation and that loss of its activity leads to insulin resistance (IR) both in peripheral tissues and in the brain.

This study aims to evaluate BVR-A alterations as an early molecular event contributing to the development of brain insulin resistance, thus leading to cerebral dysmetabolism and potentially the development of neurodegenerative diseases such as Alzheimer's disease.

To achieve this, the study was conducted using two animal models:

- **C57Bl/6j**: a commonly used mouse model to study insulin resistance, obesity, and diabetes.
- **BVR-A Knock-out (BVR-A$^{-/-}$)**: to understand the role of BVR-A in insulin signalling.

The animals were fed to (i) standard (SD) and (ii) high-fat diet (HFD) regimens to promote metabolic changes favoring the onset of IR and cognitive decline. The diet lasted for 1 week and 8 weeks, respectively. These time points allowed us to identify the loss of BVR-A activity in the insulin signaling cascade. To further strengthen BVR-A's role in IS, the same experiments were performed on BVR-A$^{-/-}$ mice.

The research also focuses on the influence of sex differences (male/female), highlighting how gender can influence the onset of brain insulin resistance due to BVR-A deficiency. These alterations were further corroborated by cognitive function measurements through behavioral tests.

From a methodological perspective, I acquired solid experience in handling animal models, maintaining mouse colonies, performing behavioral tests, and administering drugs via intranasal and intraperitoneal routes. In molecular biology, I was experienced in genotyping BVR-A KO mice, including DNA extraction and Rt-PCR analysis. I also acquired all necessary skills for conducting the biochemical analyses required in the study: Western Blot, Bioplex Immunoassay, ELISA, immunoprecipitation, and immunofluorescence.

As part of my research, I developed and implemented an experimental protocol for the isolation of extracellular vesicles (EVs) of neuronal origin from human plasma samples. This protocol, now actively used in Prof. Barone's laboratory, is used as a diagnostic tool to evaluate brain insulin resistance. The goal is to establish a reliable, non-invasive method that can provide information on brain-related disease processes through a simple blood test, thus advancing early detection and intervention strategies.

EDUCATION AND TRAINING

- **11/2024**

• Institution	Sapienza University of Rome & Plaisant srl
• Qualification Obtained	**Certificate of training** 2nd edition of the Training course (D.M 5 agosto 2021) accredited by the Italian Ministry of Health 0024495-12/10/2022-DGSAF-MDS-P for obtaining the credits required to **perform functions a), b), c), d) e the roles of DV e RCW (d.lgs 26/2014) organized by the Research and Services Centre Preclinical Testing and Animal Welfare**.

- **01/11/2020-31/10/2023**

• Institution	Laboratory of Redox Biochemistry in Neuroscience, Department of Biochemical Sciences, Faculty of Pharmacy and Medicine, Sapienza University of Rome
• Qualification Obtained	PhD in Biochemistry with a grade of Excellent

- **03/2020**

• Institution	Master in Forensic Science and Criminal Investigation, Institute of Forensic Sciences (Corsico, MI) - ISO 9001:2015 Certification, 60 ECTS
• Qualification Obtained	Forensic Technician

• **09/2019**	
• Institution	Professional Qualification Exam for Biologists, University of Calabria
• Qualification Obtained	Qualified Biologist
• **2016/2018**	
• Institution	Master's Degree in Biology (LM-6), University of Calabria
• Qualification Obtained	Master's Degree in Biology with a grade of 110/110
• **2011/2015**	
• Institution	Bachelor's Degree in Biology (L-13), University of Calabria
• Qualification Obtained	Bachelor's Degree in Biological Sciences

PERSONAL SKILLS AND COMPETENCES

MOTHER TONGUE **ITALIAN**

OTHER LANGUAGES

ENGLISH

• Reading	GOOD
• Writing	GOOD
• Oral Expression	GOOD

TECHNICAL SKILLS AND COMPETENCES

In vivo:

- Manipulation of animal models;
- Maintenance of mouse colonies;
- Behavioral tests (Y-maze and Novel Object Recognition);
- Intranasal and intraperitoneal drug administration;
- Cardiac perfusion interventions.

Applied Biochemistry and Molecular Biology:

- Western Blot, Slot Blot, Bioplex Immunoassay, ELISA, Immunoprecipitation, and Immunofluorescence;
- Proteomic analysis;
- Nucleic acid extraction (DNA and RNA), genotyping, quantification, and analysis in PCR and Rt-PCR, electrophoresis;
- Cell cultures (SHSY-5Y, HEK293, U373-MG, Lymphocytes);
- Biological sample processing;
- Isolation and characterization of neuron-derived extracellular vesicles (EV) from human plasma samples.

OTHER SKILLS AND COMPETENCES

SOFTWARE:

- Microsoft Office Suite;
- Adobe Photoshop elements;

- Internet Browsers (Mozilla Firefox, Internet Explorer, Google Chrome);
- ImageLab (Acquisition and analysis of digital images from electrophoresis gels and blots);
- Prism-GraphPad (Data organizer, statistical analysis, graphics).

OPERATING SYSTEMS:

ADDITIONAL INFORMATION

PROFESSIONAL MEMBERSHIP:

- Member of the Italian Society of Biochemistry and Molecular Biology (SIB);
- Member of the Trisomy 21 Research Society (T21RS);
- Member of the Society for Free Radical Research Europe (SFRR Europe);
- Member of the European Society for Neurochemistry (ESN).

SEMINARS:

- **06/2024** ORAL PRESENTATION AND POSTER SESSION. At the 5th International Trisomy 21 Research Society Conference. Rome, Italy.
- **05/2023** ORAL PRESENTATION. At the 1st FEBS Redox Medicine Workshop: from cellular signalling to systems physiology and therapeutic targets. Luso, Portugal.
- **12/2022** Participation in the 3th International Conference "MORE THAN NEURONS - Changing the paradigm for novel therapeutich avenues".Turin, Italy.
- **09/2022** POSTER SESSION AND FLASH PRESENTATION at SFRR-Europe/IUBMB/FEBS advanced course "Redox alterations and cellular responses: From signalling to interventions". Spetses, Greece.
- **06/2022** POSTER SESSION. At the 4th edizione International Trisomy 21 Research Society Conference. Long Beach, California.

AWARDS AND RECOGNITIONS:

- **05/2023** FEBS WS23-016 YTF Award
- **09/2022** SFRR Travel Award
- **06/2022** T21RS Travel Award

RESEARCH GRANT:

- **2024** Grant awarded by Sapienza University of Rome. "**Projects for Initiating Research - Type 1**. Project title: Sex-associated differences in brain insulin signaling and energy metabolism uncover early pathological alterations driving Alzheimer's disease neuropathology

SCIENTIFIC PRODUCTION:

- **2025** Metabolic Breakdown: Linking Insulin Resistance and Mitochondrial Dysfunction to Neurodegenerative Disorders. Review NNR 2024 (under review). **Lanzillotta S**., Rolfi L.R., Zulli B., Eugenio Barone.
  IF 5.9
- **2025** Enhancing O-GlcNac Cycling Mitigates Cognitive Decline in Down Syndrome Mice byImproving Mitochondrial Function and reducing Alzheimer's Like Signatures (submitted). Lanzillotta C., Prestia F., Greco V., Iavarone F., Cordella F., Forte E., Tramutola A., **Lanzillotta S**., Sette C., Cassano T., Di Angelantonio S., Urbani A., Barone E., Perluigi M., Di Domenico F.
- **2025** The Evaluation of Markers of Aging in Neuron-Derived Extracellular Vesicles as a Tool for Identifying Individuals at Risk of Alzheimer's Disease: A Pilot Study (submitted). **Lanzillotta S**., Boccardi V., Angelini R., Cecchetti R., Butterfield D A., Mecocci P., Barone E.
- **2025** Sex-associated differences in brain insulin signaling and energy metabolism uncover early pathological alterations driving Alzheimer's disease neuropathology (submitted). **Lanzillotta S**., Lanzillotta C., Tramutola A., Forte E., Di Domenico F., Perluigi M., Barone E.
- **2024** Altered Mitochondrial Unfolded Protein Response and Protein Quality Control Promote Oxidative Distress in Down Syndrome Brain. **Lanzillotta S**., Esteve D., Lanzillotta C., Tramutola A., Lloret A., Forte E., Di Domenico F., Perluigi M., Barone E. freeradbiomed.

IF 7.1

- **2024** Biliverdin Reductase-A integrates insulin signaling with mitochondrial metabolism through phosphorylation of GSK3β (2024). Lanzillotta C, Tramutola A., **Lanzillotta S**., Greco V., Pagnotta S., Sanchini C., Di Angelantonio S., Forte E., Rinaldo S., Paone A., Cutruzzolà F., Cimini F.A., Barchetta I., Cavallo M.G., Urbani A., Butterfield D.A., Di Domenico F., D Paul B., Perluigi M., Duarte J.M.N., Barone E. Redox Biol (2024) 73:103221

  IF 11.4

  Spotlighted *by Chen W, Johansen VBI, and Legido-Quigley C. in Trends in Biochemical Sciences link here*

- **2024** Dynamic changes of BVRA protein levels occur in response to insulin: a pilot study in humans (2023). Cimini F.A, Tramutola A, Barchetta I, Ceccarelli V, Gangitano E, **Lanzillotta S**, Lanzillotta C, Cavallo M.G and Barone E. Int J Mol Sci (2023), 24(8):7282

  IF 5.6

- **2023** Intranasal administration of KYCCSRK peptide rescues brain insulin signaling activation and reduces Alzheimer's Disease-like neuropathology in a mouse model for Down syndrome (2023). Tramutola A, **Lanzillotta S**, Aceto G, Pagnotta S, Ruffolo G, Cifelli P, Marini F, Ripoli C, Palma E, Grassi C, Di Domenico F, Perluigi M, and Barone E. Antioxidants (2023), 12(1):111.

  IF 7.0

FUNDING INFORMATION [GRANTS AS PI-PRINCIPAL INVESTIGATOR OR I-INVESTIGATOR]

- **2024** **5th T21RS International Conference**
  I, Grant from Banca d'Italia, n. 2203141/23 del 21.12.2023
  € 51.332,00

- **2022** **Alterations of the DPP4/ DYRK1A/GSK-3β axis are associated with intellectual disability and Alzheimer's disease development in Down syndrome: search for novel therapeutic strategies**
  I, Jerome Lejeune Foundation, Project #2175 - GRT-2022B (France's number one funder for research in genetic disorders, develops and funds programs in France and abroad)
  € 80.000,00

Rome, 31/01/2025