

BIOGRAPHICAL SKETCH

NAME: Cristina Di Primio

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Research Scientist, Institute of Neuroscience (IN-CNR), Pisa, Italy

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Pisa, Pisa, Italy	M.S.	2001-10-15	Master of Science in Biology
Università di Pisa, Dipartimento di Biologia, Pisa, Italy	PhD	2006-07-01	PhD in Normal and pathological morphology and function in cells and tissues

A. Personal Statement

My research program sits at the intersection of molecular neuroscience, neurodegeneration and virus-inspired tool development. I lead an independent research group at the Institute of Neuroscience (CNR, Pisa), with a primary focus on Alzheimer's disease (AD) and Tauopathies, and on the design of nanobiology platforms to probe neuronal function with high spatial and temporal resolution.

My dual background – in neurodegeneration (Tau, AD, synaptic dysfunction) and in molecular virology / HIV-1 Gag engineering – is directly aligned with this HT NF proposal. During my postdoctoral training, I developed extensive expertise in engineering lentiviral and Gag-based vectors, HIV-1 biology and live-cell imaging (FRET/FRAP, advanced fluorescence microscopy). This unique technical foundation enabled my group to invent and deploy innovative nanosensors such as the CST FRET-based Tau biosensor, which has provided new insights into pathological Tau conformations and early synaptic alterations in AD models.

Building on this expertise, my team recently developed SNaP, a synthetic virus-like particle (VLP) platform derived from HIV-1 Gag and engineered with modular domains (e.g. TRBP, dendritic localisation sequences) to capture endogenous miRNAs from specific neural cell types and subcellular compartments. Our SNaP work, now accepted in *Journal of Nanobiotechnology*, demonstrates robust, modular miRNA loading and compartment targeting in neuronal systems and constitutes the direct experimental foundation for the present HT NF project on compartment-resolved miRNA profiling in A β -challenged human iPSC-derived neurons.

As PI of the proposed HT NF access project, I will oversee all experimental design, generation and quality control of neuronal and SNaP samples, and the biological interpretation and integration of the miRNA datasets produced by the NF for Genomics and the NF for Data Handling and Analysis. My group has stable access to mature iPSC-derived neuronal cultures, Seahorse and advanced confocal imaging, and we routinely manage and analyze omics datasets in R/Python within a robust institutional IT environment. My leadership and autonomy are supported by a sustained track record of competitive national funding (e.g. PRIN2022, Ministry of Health; RiPreL, Ministry of Health) and by my role within the PNRR THE-SPOKE 8 "Biotechnologies and Imaging in Neuroscience", which provides an ideal framework for data sharing, follow-up validation and dissemination of the first dendritic miRNA atlas in an early AD-like human neuronal model.

B. Positions, Scientific Appointments, and Honors**Academic and Research Positions**

- 2020–present – Research Scientist, Institute of Neuroscience (IN-CNR), Pisa, Italy

- 2018–2020 – Temporary Research Associate, Scuola Normale Superiore, Pisa, Italy
- 2013–2018 – Fixed-term Researcher, Scuola Normale Superiore, Pisa, Italy
- 2010–2013 – Postdoctoral Fellow (Antonino Cattaneo), Scuola Normale Superiore, Pisa, Italy
- 2007–2010 – Postdoctoral Fellow (Arturo Falaschi), Scuola Normale Superiore, Pisa, Italy
- 2006–2007 – Fondazione Adriano Buzzati-Traverso Fellowship
- 2005–2006 – Scuola Normale Superiore Fellowship
- 2002–2005 – PhD student, University of Pisa, School of Medicine
- 2001 – Degree in Biology, University of Pisa

Memberships and Honors

- 2019 – Associate Editor, Journal of Cellular and Molecular Medicine
- 2018 – Review Editor, Frontiers in Molecular Biosciences
- 2017 – Review Editor, Vascular Physiology
- 2014 – Member, Italian Society of Biophysics and Molecular Biology (SIBBM)
- 2012 – ICAR-CROI Award for Young Investigators in the HIV-1 field
- 2010 – Keystone Symposia Award “HIV-1 Biology and Pathogenesis” (Bill & Melinda Gates Foundation)

C. Contributions to Science

• C.1 Development of the SNaP Platform for Spatiotemporal miRNA Omics (Preliminary Data for the HT NF project)

To overcome the lack of tools for subcellular, cell-type-specific miRNA profiling, I conceptualized and led the engineering of the SNaP platform (Synthetic Nano-Particles). SNaP uses genetically encodable HIV-1 Gag-based VLPs as “molecular sensors” to capture endogenous small RNAs from selected neural cell types and compartments. My team has demonstrated that: (i) a Gag–TRBP fusion markedly enhances specific loading of miRNA cargo; (ii) neuron- and microglia-specific promoters enable cell-type-restricted capture; and (iii) a dendritic localization signal (DLS) can enrich for postsynaptic miRNAs while excluding presynaptic contaminants. This work, now accepted in Journal of Nanobiotechnology, establishes the technical feasibility and robustness of SNaP and provides the direct experimental foundation for the present HT NF proposal on compartment-resolved miRNA profiling in A β -challenged human neurons. The proposed HT NF access project will leverage this platform in human iPSC-derived excitatory neurons challenged with amyloid-beta, with the goal of generating the first compartment-resolved atlas of dendritic miRNA changes in an early Alzheimer-like synaptopathic context.

Selected publications

- Synthetic nanoparticles for cell-type-specific, spatially resolved loading and export of miRNAs in neural cells. J Nanobiotechnology (in press).

• C.2 Invention of a FRET-based Tau Biosensor (CST) for Nanoscale Conformational Profiling

To investigate early conformational changes of Tau at the onset of pathology, I conceptualized and engineered CST, a FRET-based Tau biosensor. CST allows real-time visualization of Tau conformational states in living neurons and revealed distinct conformations in healthy versus damaged contexts. We established CST-expressing cell and zebrafish models, providing platforms for screening modulators of Tau aggregation and for dissecting the impact of FTDP-17 mutations. This work demonstrates my capacity to build and validate innovative nanobiosensors for neurodegeneration, a key element of my profile as a “tool-builder” for AD research.

Selected publications:

- Modulation of Tau Protein Neurotoxic Hallmarks by Novel σ 1R Agonists/HDAC Inhibitor Dual-Acting Compounds. ChemMedChem (in press)
- The Q336H MAPT Mutation Linked to Pick’s Disease Leads to Increased Binding of Tau to the Microtubule Network via Altered Conformational and Phosphorylation Effects. Front Mol Neurosci. 2020.

- Identification of an ERK Inhibitor as a Therapeutic Drug Against Tau Aggregation in a New Cell-Based Assay. *Front Cell Neurosci.* 2019.
- The Distance between N and C Termini of Tau and of FTDP-17 Mutants Is Modulated by Microtubule Interactions in Living Cells. *Front Mol Neurosci.* 2017.
- A new FRET-based biosensor to investigate the link between heart failure and Alzheimer disease. *Vascular Pharmacology.* 2016.

• **C.3 Uncovering the Role of Tau in the Nucleus**

My group has demonstrated that nuclear Tau can reshape the neuronal transcriptional landscape, particularly genes involved in glutamatergic transmission and synaptic function. We showed that Tau aggregation and mislocalization can impair the expression of disease-related genes, leading to toxic neuronal hyperexcitability – a hallmark of early AD stages – and recapitulating changes observed in human AD brains. These studies link Tau pathology to genome regulation and synaptic dysfunction, strengthening the biological context for the current proposal on early synaptopathic mechanisms.

Selected publications

- Tau mediates the reshaping of the transcriptional landscape toward intermediate Alzheimer's disease stages. *Front Cell Dev Biol.* 2025.
- Non-canonical roles of Tau and their contribution to synaptic dysfunction. *Int J Mol Sci.* 2021.
- Gene Expression of Disease-related Genes in Alzheimer's Disease is Impaired by Tau Aggregation. *J Mol Biol.* 2020.
- Tau Modulates VGluT1 Expression. *J Mol Biol.* 2019.

C.4 HIV-1 Vector Engineering and Cofactor Discovery (Foundational Expertise for SNaP) My foundational expertise in HIV-1 molecular engineering underpins the SNaP platform. During my postdoctoral work, I engineered HIV-1 genomes and Gag-based constructs to track the viral life cycle and integration at high resolution. I developed SCIP, a tool to visualize integrated HIV-1 proviruses in single cells, and identified several host cofactors (e.g. GCN5, KAP1, SUGT1) involved in integration and nuclear trafficking. This body of work, including a PNAS article and several mechanistic studies, demonstrates my ability to engineer complex viral backbones and to couple them with advanced imaging – skills that directly translate into the design and optimization of SNaP VLPs for miRNA capture.

Selected publications

- Single cell imaging of HIV provirus (SCIP). *Proc Natl Acad Sci U S A.* 2013.
- SUGT1 controls susceptibility to HIV-1 infection by stabilizing microtubule plus-ends. *Cell Death Differ.* 2020.
- Post-translational selective intracellular silencing of acetylated proteins with de novo selected intrabodies. *Nat Methods.* 2017.
- GCN5-dependent acetylation of HIV-1 integrase enhances viral integration. *Retrovirology.* 2010.
- Herpes Simplex 2 Virus Depletes Cells of DEAD-Box Helicase 3 Protein by Packaging It into Virions. *Viruses.* 2025

• **C.5 Long-Term Effect of SARS-CoV-2 (Application to Neuroinflammation)**

More recently, I have contributed to understanding how viral infections intersect with neurodegeneration. We showed that SARS-CoV-2 infection can trigger aberrant Tau phosphorylation at pathological epitopes in neurons, providing a plausible molecular link between COVID-19 and long-term neurological symptoms, including potential aggravation of AD-related processes. Additional work on SARS-CoV-2 entry, inflammasome activation and adipocyte remodelling further illustrates my expertise in combining

virology, imaging and cell biology, and reinforces my broader experience with virus–host interactions in the nervous system.

Selected publications

- Severe acute respiratory syndrome coronavirus 2 infection leads to Tau pathological signature in neurons. PNAS Nexus. 2023.
- SARS-CoV-2 Infection Alters the Phenotype and Gene Expression of Adipocytes. Int J Mol Sci. 2024
- The purinergic receptor P2X7 and the NLRP3 inflammasome are druggable host factors required for SARS-CoV-2 infection. Front Immunol. 2023.
- A spatial multi-scale fluorescence microscopy toolbox discloses entry checkpoints of SARS-CoV-2 variants in Vero E6 cells. Comput Struct Biotechnol J. 2021.