UNIVERSITÀ DEGLI STUDI DI GENOVA

AREA RICERCA, TRASFERIMENTO TECNOLOGICO E TERZA MISSIONE

SERVIZIO PER IL TRASFERIMENTO TECNOLOGICO E DELLE CONOSCENZE

SETTORE VALORIZZAZIONE DELLA RICERCA, TRASFERIMENTO TECNOLOGICO E RAPPORTI CON LE IMPRESE

IL RETTORE

Vista la Legge 9 maggio 1989, n. 168 - Istituzione del Ministero dell'Università e della ricerca scientifica e tecnologica e ss.mm.ii;

Visto lo Statuto dell'Università degli Studi di Genova;

Visto il Regolamento Generale di Ateneo;

Visto il Regolamento di Ateneo per l'Amministrazione, la Finanza e la Contabilità;

VISTA la legge 7 agosto 1990, n. 241 recante "Nuove norme in materia di procedimento amministrativo e di diritto di accesso ai documenti amministrativi" pubblicata sulla Gazzetta Ufficiale n. 192 del 18/08/1990 e s.m.i.;

VISTO il Decreto del Presidente della Repubblica 28 dicembre 2000, n. 445 (Disposizioni legislative in materia di documentazione amministrativa) e s.m.i.;

VISTO il Decreto Direttoriale MUR n. 341 del 15/03/2022 di emanazione di un Avviso pubblico per la presentazione di Proposte di intervento per la creazione di "Partenariati estesi alle università, ai centri di ricerca, alle aziende per il finanziamento di progetti di ricerca di base" nell'ambito del Piano Nazionale di Ripresa e Resilienza, Missione 4 "Istruzione e ricerca" – Componente 2 "Dalla ricerca all'impresa" – Investimento 1.3, finanziato dall'Unione europea – NextGenerationEU";

VISTO il Decreto Direttoriale MUR n. 1553 dell'11/10/2022 di concessione del finanziamento del progetto Codice identificativo PE00000006, Acronimo MNESYS, Titolo "*A multiscale integrated approach to the study of the nervous system in health and disease*", registrato alla Corte dei Conti il 23/11/2022 al n. 2948 e relativi allegati;

CONSIDERATO che l'Università degli Studi di Genova è leader dello Spoke 6, dal titolo "*Neurodegeneration, trauma and stroke*";

CONSIDERATO che gli Spoke possono emanare - nell'ambito dei limiti e con le modalità previste dall'Avviso - "bandi a cascata" finalizzati alla concessione di finanziamenti a soggetti esterni per attività coerenti con il progetto approvato;

VISTA la delibera della seduta del 27 settembre 2023 con cui il Consiglio di Amministrazione dell'Università degli Studi di Genova ha approvato l'emanazione del bando a cascata per organismi di ricerca nell'ambito del Progetto MNESYS - "*A multiscale integrated approach to the study of the nervous system in health and disease* - PNRR M4C2 per lo Spoke 6;

VISTO il Decreto del Direttore Generale n. 5418 del 14 novembre 2023 di nomina del Responsabile

del Procedimento;

VISTO il Decreto del Rettore n. 5439 del 14 novembre 2023 e il Decreto Rettorale n. 5474 del 15 novembre 2023 di emanazione del Bando a cascata per il finanziamento di proposte di intervento per le attività di ricerca svolte da Organismi di Ricerca nell'ambito del programma di ricerca PE MNESYS "*A multiscale integrated approach to the study of the nervous system in health and disease*", per lo Spoke 6 dal titolo "*Neurodegeneration, trauma and stroke*", nell'ambito del PNRR, Missione 4, Componente 2, Investimento 1.3 – finanziato dall'Unione europea – NextGenerationEU (CUP D33C22001340002);

CONSIDERATO che alla data di scadenza per la presentazione delle proposte progettuali, fissata entro e non oltre il giorno 14 dicembre 2023, per la **Tematica C – "Targeting non-neuronal proteostasis alterations in neurodegenerative diseases: focus on inter-organelle communication and identification of novel pharmacological targets"** era pervenuta a mezzo PEC all'indirizzo air3@pec.unige.it la seguente proposta:

PROPONENTE: Università degli Studi del Piemonte Orientale
TITOLO PROPOSTA: GENESIS – Dissecting Alzheimer's Disease-associated protein dyshomeostasis in non neuronal cells for identification of novel pharmacological targets

TENUTO CONTO che la Responsabile del procedimento, Ing. Patrizia Cepollina, ha ritenuto ricevibile, ammissibile e conforme la proposta sopra citata;

CONSIDERATO che nel Bando è previsto che la valutazione di merito tecnico-scientifico dei progetti pervenuti sia affidata ad una Commissione composta da almeno tre esperti esterni al Partenariato, indipendenti e competenti dell'Area tematica dello Spoke;

VISTO il Decreto Rettorale n. 6114 del 20 dicembre 2023 con cui è stato emanato l'Avviso di manifestazione di interesse per la costituzione di un albo di esperti indipendenti a supporto della valutazione di merito dei progetti PNRR presentati sui bandi a cascata del progetto MNESYS – A multiscale integrated approach to the study of the nervous system in health and disease;

VISTO l'Estratto del Verbale della Riunione del 12 febbraio 2024 del Comitato Scientifico del programma di ricerca MNESYS "*A multiscale integrated approach to the study of the nervous system in health and disease*" che ha approvato la "Rosa di Candidati" per le Commissioni di Valutazione dei Bandi a cascata sul Programma MNESYS;

VISTO il Decreto del Rettore n. 855 del 20 febbraio 2024 con cui è costituito l'Albo a supporto delle valutazioni dei progetti presentati in risposta al bando pubblico per la selezione di proposte progettuali da finanziare nell'ambito delle attività di ricerca dello Spoke n. 6 di cui al programma di "*A multiscale integrated approach to the study of the nervous system in health and disease*" – MNESYS, a valere sulle risorse del Piano Nazionale di Ripresa e Resilienza (PNRR), Missione 4 "Istruzione e Ricerca", Componente 2 "Dalla ricerca all'impresa", linea di Investimento 1.3 "Creazione di Partenariati Estesi alle università, centri di ricerca, alle aziende per il finanziamento di progetti di ricerca di base";

VISTO il Decreto del Rettore n. 1130 del 5 marzo 2024 con cui è stata nominata la Commissione di valutazione delle proposte pervenute in risposta al bando a cascata di cui al D.R. n. 5439 del 14 novembre 2023, indicato nelle premesse del presente decreto;

ACQUISITO il verbale della Commissione di Valutazione della seduta del 16 aprile 2024 (Prot. n. 37982 del 07/05/2024);

VISTO il Decreto del Rettore n. 2287 del 10 maggio 2024 con cui è stata approvata la graduatoria di merito per la Tematica C - "Targeting non-neuronal proteostasis alterations in neurodegenerative diseases: focus on inter-organelle communication and identification of novel pharmacological targets", di cui al bando a cascata di cui al Decreto del Rettore n. 5439 del 14 novembre 2023, indicato nelle premesse del presente decreto;

TENUTO CONTO che in data 14 maggio 2024 è stata inviata all'Università degli Studi del Piemonte Orientale la comunicazione con prot. n. 41376 in cui si rendevano noti gli esiti della procedura e si richiedeva la documentazione propedeutica all'adozione del provvedimento di ammissione del finanziamento;

VISTO che in data 16 maggio 2024 con prot. n. 42718 la documentazione richiesta è stata ricevuta dall'Università degli Studi di Genova che l'ha ritenuta conforme a quanto previsto nel bando a cascata di cui al Decreto del Rettore n. 5439 del 14 novembre 2023 e il Decreto Rettorale n. 5474 del 15 novembre 2023 , indicato nelle premesse del presente decreto,

DECRETA

ART. 1

L'ammissione a finanziamento del progetto GENESIS – Dissecting Alzheimer's Disease-associated protein dyshomeostasis in non neuronal cells for identification of novel pharmacological targets per la **Tematica C – "Targeting non-neuronal proteostasis alterations in neurodegenerative diseases: focus on inter-organelle communication and identification of novel pharmacological targets",** con Soggetto proponente l'Università degli Studi del Piemonte Orientale – come rappresentato negli Allegati B e C alla proposta presentata con domanda di partecipazione prot. n. 74549 del 14/12/2023.

ART. 2

L'entità dell'agevolazione concessa, a fondo perduto, ammonta a 150.000 euro complessivi come rappresentati nell'allegato C alla proposta presentata con domanda di partecipazione prot. n. 74549 del 14/12/2023. L'agevolazione è pari al 100% dei costi di progetto trattandosi di attività di ricerca fondamentale per Organismi di Ricerca. L'agevolazione è concessa a valere sui fondi PNRR - Programma "*A multiscale integrated approach to the study of the nervous system in health and disease*" – MNESYS Codice PE00000006 a valere sulla Missione 4, Componente 2, Investimento 1.3, ai sensi del Decreto di concessione n. 1553 dell'11 ottobre 2022, registrato alla Corte dei Conti il 23/11/2022 n. 2948, iscritto al Bilancio di Ateneo sul progetto UGOV 100009-2022-TF-PNRR-PE_MNESYS_BAC_DINOGMI.

ART. 3

Le attività, come indicate dettagliatamente nell'Allegato B alla domanda di finanziamento, dovranno essere avviate a partire dalla data di sottoscrizione del Contratto e concluse entro e non oltre 12 mesi, affinché siano rendicontate in tempo utile per consentire la chiusura del Programma PE MNESYS, il cui termine è attualmente previsto al 31 ottobre 2025.
Potrà essere valutata e concessa una sola proroga in presenza di ritardi dovuti a circostanze eccezionali e non dipendenti da scelte del Beneficiario esclusivamente nel caso in cui il MUR, a sua volta, proroghi il termine del Programma MNESYS.

ART. 4

Il presente atto sarà pubblicato sul sito UniGe https://unige.it/progetti-finanziati-dal-pnrr e laddove la normativa vigente lo richiede.
Il documento informatico originale sottoscritto con firma digitale sarà conservato presso l'Area Ricerca, Trasferimento Tecnologico e Terza Missione.

ALLEGATI:

Allegato B – Proposta progettuale
Allegato C – Piano economico-finanziario

IL RETTORE
Prof. Federico DELFINO
(documento firmato digitalmente)

ANNEX B

PE00000006
"A multiscale integrated approach to the study of the nervous system in health and disease"

MNESYS

SPOKE N. 6

Research proposal

Topic addressed by the project

C. Targeting non-neuronal proteostasis alterations in neurodegenerative diseases: focus on inter-organelle communication and identification of novel pharmacological targets

Acronym - **GENESIS**

Project Title

"Dissecting Alzheimer's Disease-associated protein dyshomeostasis in non neuronal cells for identification of novel pharmacological targets"

- Name of the PIs' host institution for the project
  Dipartimento di Scienze del Farmaco (DSF, Department of Pharmaceutical Sciences), University of Piemonte Orientale (UPO), Novara, Italy

- Name of the Principal Investigators (PIs):
  Mariagrazia Grilli, MD PhD
  Dmitry Lim, PhD

- Proposal duration in months: 12

- Name and qualification of the Principal Investigator (PI)
- Name and qualification of the co- Principal Investigator (PI)
- Name and qualification of the components the research team

ROLE IN THE PROJECT	*NAME*	*SURNAME*	*DEPARTMENT*	*QUALIFICATION*	*YOUNG (under 40 as of 31.12.2023)*	*F/ M*
Principal Investigator	*Mariagrazia*	*GRILLI*	*Dipartimento Scienze del Farmaco (DSF) Università del Piemonte Orientale (UPO)*	*Full Professor of Pharmacology*	*NO*	*F*
co- Principal Investigator (PI)	*Dmitry*	*LIM*	*DSF, UPO*	*Ass. Prof. of Physiology*	*NO*	*M*
Team member	*Laura*	*TAPELLA*	*DSF, UPO*	*RTD-B in Physiology*	*NO*	*F*
Team member	*Camilla*	*D'ANGELO*	*DSF, UPO*	*PhD student in Drug Innovation (1st year)*	*YES*	*F*
Team member	*Giulia*	*BONI*	*DSF, UPO*	*Research fellow*	*YES*	*F*

ABSTRACT

Neurodegenerative diseases (NDD), including Alzheimer's disease (AD), represent a tremendous scientific challenge which requires a focus on pathogenic mechanisms occurring at early disease stages and preceding neuronal loss/dysfunction. Non-neuronal cells, overlooked for decades, emerge as key determinants of NDD pathogenesis and promising targets for therapeutic intervention.

Neural Stem/Progenitor Cells (NSPC) represent a non-neuronal cell type giving origin to neurons, astrocytes, oligodendrocytes but also providing immunomodulatory functions in adult CNS. Deregulated neuro(glio)genesis is found in several NDD, including AD, earlier than neuronal dysfunction and onset of symptoms. However, the mechanisms of NSPC dysfunction in AD remain poorly understood.

Based on published and unpublished data we hypothesise that in AD inter-organellar and more specifically mitochondria-ER communication, may be disrupted early in NSPC. These alterations may cause ER-stress/UPR, impaired protein synthesis, degradation, secretion. NSPC dysproteostasis may compromise their neurogenic and non neurogenic functions, result in reduced homeostasis and increase neuronal vulnerability to aging and noxae. Coherently with MNESIS Spoke 6 themes, this proposal aims at investigating mechanisms linking protein dyshomeostasis with dysfunction of mitochondrial-ER contacts (MERCS) in NSPC from WT and 3xTG AD mice. In these cellular models we will exploit state-of-the-art technologies in order to: 1) perform multiomic analysis and cell type-specific RNA-sequencing of NPSC and their progeny; 2) comprehensively investigate pathophysiological mechanisms associated with MERCS alterations, including protein synthesis and degradation, ER-mitochondrial communication, Ca^{2+} signalling and mitochondrial bioenergetics; 3) to identify novel target molecules related to protein dyshomeostasis whose modulation, by pharmacological and genetic approaches, may rescue functional properties of NSPC and their progeny.

RESEARCH PROPOSAL

Section a. State-of-the-art and objectives

a1. State of the art. Neuronal loss in neurodegenerative diseases (NDD) represents the final occurrence in a series of decade-long events. Remarkably, non-neuronal cell dysfunction is present before detectable neuron dysfunction/loss and before overt clinical symptoms (Verkhratsky *et al.*, 2019; Zhou *et al.*, 2023). These key observations suggest implication of cells other than neurons in early events that could be considered causal/concausal in NDD. Dysregulated non-neuronal cells may indeed contribute to pathogenic mechanisms that ultimately lead to neuronal loss by establishing either harmful non-cell autonomous effects or as a consequence of loss of homeostatic control. Interestingly, such non-neuronal changes may represent a window of opportunity for novel therapeutic interventions.

Among non-neuronal cells, radial glia-like **adult neural stem/progenitor cells (NSPC)** are emerging as promising early therapeutic targets in various NDD, including Alzheimer's Disease (AD). In adult brain the generation of new cells from NSPC is referred to as Adult Neurogenesis (AN) and Adult (Astro-/oligodendro-)Gliogenesis (AG). AN is crucial for neural plasticity, cognition and emotional behaviour and its early dysfunction has been reported in several NDD (Terreros-Roncal *et al.*, 2021). In particular hippocampal AN (hAN) is impaired in AD patients and FAD mouse models. Recent work suggested that defective hNG contributes to memory failure in AD. Not only new adult-born immature neurons are actively recruited into the engram following a hippocampus-dependent task, but their recruitment is deficient in AD models where these cells exhibit compromised spine density and altered transcriptional profile. Targeted augmentation of neurogenesis in FAD mice restored number, structural integrity and transcriptional signature of both immature and mature neurons, ultimately leading to the rescue of cognitive impairment. Conversely, inactivation of immature neurons following enhanced neurogenesis reversed cognitive performance in AD models (Mishra *et al.*, 2022). In AD accumulation of toxic species like Aβ also disrupts AN and AG (Ribeiro *et al.*, 2019). However, AD-related mutations may also exert their detrimental effects well before amyloid pathology appearance: mutant PSEN1 is enriched in NSPC and induces premature defective neurogenesis (Arber *et al.*, 2021). In house preliminary data suggested that FAD linked mutations correlate with impaired proliferation and differentiation of NSPC; in particular these cells are specifically defective on their ability to generate new functional neurons (*unpublished data*). NSPC have been proposed to act as sort of "guardians of the brain" since they exert also "non neurogenic" functions (Bacigaluppi *et al.*, 2020; Bonetto *et al*., 2023). In aging and CNS disorders disrupted cross-talk among NSPC and other neural cell populations may affect their regenerative and immunomodulatory capacity resulting in a reduced resilience to noxae. In particular the relevance of NSPC secreted molecules with neuroprotective and/or antinflammatory activities has been demonstrated in several NDD (Mendes-Pinheiro *et al.*, 2018; Bacigaluppi *et al.*, 2020). Moreover, exosomes derived from hippocampal NSPC can abolish Aβ-induced suppression of LTP and memory deficits (Micci *et al.*, 2019).

Recent data suggest that AD-related cell dysfunction is associated with an increased interaction between mitochondria and ER (Paillusson *et al.*, 2016; Area-Gomez and Schon, 2017; Lim *et al.*, 2021). Mitochondria-ER contact sites (MERCS) are highly organised morpho-functional structures which host and control a number of important cellular processes such as phospholipid biogenesis, ER-mitochondrial Ca^{2+} transfer and mitochondrial energetics, apoptosis. MERCS are also implicated in the control of balance between ribosomal protein synthesis and protein degradation via autophagosome and proteasome. Many, if not all, of these processes are impaired in AD. Therefore, MERCS may provide a link between dysregulation of Ca^{2+} signalling, mitochondrial dysfunctions and protein dyshomeostasis in the disease. In this frame, we have demonstrated that hippocampal astrocytes from an established FAD model, the 3xTg-AD mice, have increased mitochondria-ER interaction which may be causal for a complex array of alterations including impaired ER functions and mitochondrial bioenergetics, dysregulated Ca^{2+} homeostasis and signalling, impaired protein synthesis and degradation and impaired secretion of pro-neurogenic/neurotrophic factors and extracellular matrix proteins (Rocchio *et al.*, 2019; Dematteis *et al.*, 2020; Tapella *et al.*, 2022; Gong *et al.*, 2023). As a result of these alterations, 3xTg astrocytic support to WT BBB and neurons is impaired (Kriaučiūnaitė *et al.*, 2020; Tapella *et al.*, 2022). Similarly, we recently observed that 3xTg astrocyte secretome does not promote neuronal differentiation of wt NSPC (*unpublished data*).

Herein we hypothesise that in AD dysfunction of NSPC and their cross-talk with other neural cells may impair both regenerative (neuro-glio-genic) and immunomodulatory capacity of the CNS thereby contributing to reduced ability to cope with aging and noxae, including accumulation of neurotoxic molecules. As such NSPC and their properties represent novel therapeutic targets. Specifically, we propose that **in adult NSPC**, **alterations of protein homeostasis** [including, but not limited to, ribosomal protein synthesis, endoplasmic reticulum (ER) protein dyshomeostasis, alterations of autophagosomal and proteasomal protein degradation, alterations in secretome composition and extracellular vesicles] **may result in compromised neuro-glio-genic properties, inter-cellular communication and reduced homeostatic capacity** thereby contributing to increased neuronal vulnerability and reduced regenerative capacity.

a2. Objectives and expected results. Our experimental activities will be organized in workpackages aimed at addressing 5 distinct objectives. **AIM 1. Set up and phenotypic characterization of WT-NSPC, 3xTg-NSPC and WT-NSPC-10EML**. Two primary cellular models will be set up and initially characterized for their intrinsic properties: i) hippocampal NSPCs from adult 3xTg-AD mice (3xTg-NSPCs); ii) hippocampal NSPCs from WT littermates (WT-NSPCs). In addition, we will also generate a third model: hippocampal WT-NSPCs will be transduced with a construct expressing, in an inducible manner, mRFP-tagged 10 nm ER-mitochondrial linker (10EML), a kind gift from Dr. Gyorgy Hajnoczky (Jefferson University, PA, USA). The model will be referred to as WT-NSPC-10EML. *Expected outcomes*. We expect to confirm, based on preliminary unpublished observations, the presence of altered cell-autonomous properties of 3xTg-NSPC vs WT-NPSC. Moreover we expect to prove that WT-NSPC-10EML may display abnormalities associated with ER-mitochondrial increased interaction and disproteostasis, as previously observed in 3xTg-iAstro cells (Tapella *et al.*, 2022). **AIM 2. Multi-omics analysis of undifferentiated WT-NSPCs, 3Tg-NSPCs, WT-NSPC-10EML.** At least three replicates of each cellular model (total lysate, subcellular fractions, but also extracellular vesicles and soluble secretome) will be subjected to untargeted proteomic and metabolomic analysis. Whole cells RNA-sequencing will be performed on total RNA preparations. *Expected outcomes*: To identify distinctive signatures of gene transcription and protein dyshomeostasis associated with AD-like pathology in NSPC and their correlation with increased ER-Mitochondria interaction and/or MERCS-associated dysfunction. **AIM 3. Cell type-specific multi-omics analysis of Wt-NSPCs, 3xTg-NSPCs, Wt-NSPC-EML progeny.** We will perform proteomic and metabolomic analysis of NSPC-derived progeny. We hypothesize that AD-related alterations of 3xTg-NSPC, including increased ER-Mitochondria interaction and/or MERCS-associated dysfunction, may translate into specific morphofunctional alterations during differentiation into one or more NSPC-derived cell lineages (neurons, astrocytes, oligodendrocytes), and result in altered protein homeostasis and inter-cellular communication. *Expected outcomes*: To identify distinctive signatures of protein and metabolites associated with AD-like pathology in both neuronal and glial phenotypes, and in their cross-talk and correlate them with increased ER-Mitochondria interaction and/or MERCS-associated dysfunction. **AIM4. Targeted investigation of protein dyshomeostasis of undifferentiated Wt-NSPCs, 3xTg-NSPCs, Wt-NSPC-10EML.** In parallel with OMICS analyses, in the three cellular models we will carry on a careful assessment of validated dys-proteostasis-related targets, such as ER-stress/UPR, ribosomal protein synthesis, autophagic and proteasomal protein degradation, organellar Ca^{2+} handling and mitochondrial bioenergetics. *Expected outcomes:* To correlate protein dishomeostasis with increased ER-Mitochondria interaction and/or MERCS-associated dysfunctions in hippocampal neuronal and glial cells. **AIM5. Identification of targets/pathways whose pharmacological modulation results in normalization of AD-associated NSPCs dysproteostasis.** Our previous publications suggest that increased ER-mitochondrial interaction may be causative to protein dyshomeostasis and secretome alterations. Specifically, the chemical chaperone 4-PBA (Cuadrado-Tejedor *et al.*, 2013) applied to 3xTg-iAstro cells rescued both ER-mitochondrial interaction and proteostatic/secretome deficit, suggesting a mechanistic interaction between a low-grade chronic ER stress, ER-mitochondrial interaction and cell proteostasis (Dematteis *et al.*, 2020; Tapella *et al.*, 2022; Lim *et al.*, 2023). Based on these premises 4-PBA will be used as a pharmacological tool to rescue protein dyshomeostasis in 3xTg-NSPC cultures. In addition to 10EML, we have designed and

synthesised additional ER-mitochondrial linkers (15nm, 20nm and 30nm). Unpublished preliminary data suggest that each of these linkers differentially affect protein synthesis and degradation (*data not shown*). In particular, 20nm-EML rescued ER-mitochondrial Ca_{2+} transfer, mitochondrial ATP production and global protein synthesis, including phosphorylation state of eIF2α. The consequences of expression of different linkers will be tested in WT-NPSC. In a separate Task we will validate most promising hits, in terms of genes, proteins or pathways, emerging from omics and functional analysis. *Expected outcomes*: We expect to prove that both approaches, pharmacological (4-PBA) and genetic (20nm-EML) can rescue proteostasis abnormalities in NSPC and their secretome and correlate such correction with molecular signatures identified by omics and functional analysis in cell lysates and conditioned media. We also expect to identify novel molecular and functional targets for the development of pharmacological intervention to rescue proteostasis abnormalities in NSPC in order to normalize adult neurogenesis.

Section b. Methodology

AIM1. ***Set up and phenotypic characterization of WT-NSPC, 3xTg-NSPC and WT-NSPC-10EML. Task1.1***. NSPCs will be isolated from 8-12 week-old WT and 3xTg-AD mice and maintained as free floating neurospheres composed of undifferentiated, self-renewing and multipotent cells as previously described (Cvijetic *et al.*, 2017). Proliferation rate, expression of stemness and multipotentiality markers will be assessed by immunocytochemical and FACS analysis of NSPC. The relevance of NSPC model to AD will be assessed by WB for human APP and components of amyloidogenic pathway using 6E10 and BAWT antibody for oligomeric Aβ and sAPPβ (N-terminal soluble product of beta-cleavage). In addition, intracellular and secreted Aβ(40) and Aβ(42) will be quantified using a commercially available ELISA kit. WT-NSPC-10EML will be generated by lentiviral transduction of WT-NSPC with a construct expressing mRFP-tagged 10nm-EML in an inducible manner. At least three independent NSPC cultures will be established from synchronized pairs of WT and 3xTg-AD mice and used in our studies. ***Task1.2***. Assessment of neuro-glio-genic properties of 3xTg-NSPC vs WT-NSPCs vs WT-NSPC-10EML. 2D and 3D models of three NSPC cultures will be exposed to differentiating conditions. Cell fate determination and morphofunctional analysis (for neuronal, astroglial and oligodendrocyte lineages) will be assessed using immunocytochemistry, FACS, and high content analysis (Cytation 5).

AIM2 Multi-omics analysis of undifferentiated WT-NSPCs, 3xTg-NSPCs, WT-NSPC-10EML.

Task2.1 Proteomic and metabolomic analysis of undifferentiated WT-NSPCs, 3xTg-NSPCs, WT-NSPC-10EML, including i) whole cell lysates and/or subcellular fractions, ii) soluble secretome and iii) extracellular vesicles, will be carried out at UPO OMICS facility located in Novara at the Interdipartimental Center for Immune and Allergic Diseases (CAAD) (https://caad.uniupo.it/servizi/proteomics-and-metabolomics). Untargeted proteomics will be performed using nanoLC-MS/MS (Cvijetic *et al.*, 2017; Tapella *et al.*, 2021). Untargeted metabolomics will be carried out using GCxGC-MS (Barberis *et al.*, 2020, 2021). ***Task2.2***. Whole-transcriptome RNA-sequencing will be commissioned to Lexogen (https://www.lexogen.com/) or other competitive provider of RNA-sequencing service. Total RNA from non-differentiated WT-NSPCs, 3xTg-NSPCs and WT-NSPC-10EML will be extracted by Lexogen-SPLIT (or other suitable) RNA extraction kit following manufacturer's instructions. 50 ng of RNA will be subjected to library preparation and sequencing analysis. ***Task2.3*** Bioinformatic analysis will be performed using both free (DAVID, STRING, Metaboanalyst) as well as commercial (Ingenuity Pathway Analysis, Qiagen) platforms already available at UPO OMICS facility.

AIM3 Cell type-specific multi-omics analysis of WT-NSPCs, 3xTg-NSPCs, WT-NSPC-EML progeny.

We will perform cell type-specific multiomic analysis of differentiated NSPCs. For this purpose, neuronal, astroglial and oligodendroglial cell types will be tagged by lentivirus-assisted transgenesis to express fluorescent reporter proteins under control of cell-specific promoters (MAP2 for neurons, GFAP for astrocytes and BMP for oligodendrocytes). In the ***Task3.1***, a tri-cistronic construct will be created via assembly, into a lentiviral backbone vector, of three independent sequences (MAP2-EGFP, GFAP-mRFP and BMP-EBFP), synthetized by GenScript (https://www.genscript.com/). In ***Task3.2*** NPSCs will be stably transduced with the

tri-cistronic vector and the cell-specific expression of fluorescent proteins will be validated. In the ***Task3.3*** NPSCs, and their progeny neurons, astrocytes or oligodendrocytes, expressing relative reporter protein, will be FACS-separated and processed for whole transcriptome sequencing and proteomic/metabolomic analyses followed by bioinformatic analysis, as previously described in AIM2.

AIM4. Targeted investigation of protein dyshomeostasis of undifferentiated WT-NSPCs, 3xTg-NSPCs, WT-NSPC-10EML. ***Task4.1***. ER-stress/UPR will be assessed using relative qPCR quantification of UPR-inducible transcripts such as ATF4, HERP, Xbp1-spliced isoform and ATF6. Western blot analysis of abundancy and phosphorylated forms of canonical UPR transducers PERK and IRE1 will be performed as well as quantification of phospho-eIF2α and assessment of global ribosomal protein synthesis rate (using puromycin incorporation assay) as described (Dematteis *et al.*, 2020; Tapella *et al.*, 2022). ***Task4.2***. Autophagic and proteasomal protein degradation will be assessed as in (Gong *et al.*, 2023). Specifically, for assessment of autophagy, enzymes Cathepsins B and L expression as well as specific autophagic markers such as Beclin-1, LC3, p62, NRF2, HDAC6 and LAMP1 will be measured by Western blot. Number and dimensions of autophagic vacuoles will be assessed by staining with dansylcadaverine. Proteasomal composition will be assessed by WB for ubiquitin coniugates, components of constitutive (β1, β2, β5) as well as immunoproteasome (iβ1, iβ2, iβ5). ***Task4.3***. Ca^{2+} homeostasis and mitochondrial bioenergetics assessement in cellular models. Cytosolic, ER and mitochondrial Ca^{2+} handling will be assessed in WT-NSPCs, 3xTg-NSPCs, WT-NSPC-10EML by means of time-lapse epifluorescent microscopy using Ca^{2+} probes targeted to specific sub-cellular compartments: Fura-2 for cytosol, mito-Fura2 for mitochondria, and CEPIA1er (Suzuki *et al.*, 2014) or GAP (Navas-Navarro *et al.*, 2016) for ER lumen. Mitochondrial respiration and ATP production will be assessed using Oroboros oxygraphy (available at UPO facility); TMRE or JC-1 will be used to assess mitochondrial membrane potential, while ROS will be measured using MitoSOCS or DCF as described in (Dematteis *et al.*, 2020). Mitochondrial morphology will be assessed using Image J plugin and high content analysis.

AIM5. Identification of targets/pathways whose pharmacological modulation results in normalization of AD-associated NSPCs dysproteostasis. ***Task5.1***. Normalization of ER-stress by treatment with 4-PBA. 3Tg-NSPCs will be exposed to 4-PBA (3 μM, 48 h), followed by analysis of key parameters of proteostasis and secretome. ***Task5.2***. Normalization of ER-mitochondrial interaction by synthetic linkers. In addition to 10 nm-EM, we have designed and synthetized additional ER-mitochondrial linkers (15nm, 20nm and 30nm). We will express each of these linkers in both WT-NSPC and 3Tg-NSPC as previously described. ***Task5.3***, validation of the most promising hist, related key parameters of proteostasis and secretome, identified from omics and functional analyses, will be assessed as in AIM4.

Section c. Available instrumentations and resources

Research units involved in the present proposal occupy about 200 msq lab space fully equipped for routine cell culture, molecular biology and biochemistry equipment. Cell culture space includes approved BSL2 facility with Class II biological hoods, CO_2 incubators and an Eppendorf-Himac CR30NX high-speed centrifuge; molecular biology and biochemistry space includes RT-PCR, Real-Time and digital PCR systems (Bio-Rad SFX96), Perkin-Elmer VICTOR Nivo Multimode plate reader. Cyto-fluorimetric facility includes Becton Dickinson Accuri C6 cytofluorimeter and a Bio-Rad S3e cell sorter.

Interdepartmental Platforms include: ***Imaging platform*** equipped with: 1) Leica epifluorescent setup for time-lapse ratiometric imaging; 2) Leica SP8 confocal laser scanning microscope; 3) Leica Thunder imaging system for high-resolution multicolor imaging of 3D preparations; 4) Leica Stellaris 8 DIVE platform equipped with White Light Laser confocal scanning microscope, Two-photon laser scanning microscope equipped with 4Tune detector and FALCON FLIM module for fluorescence life-time analysis. ***Next-gen flow cytometry platform*** equipped with: 1) FACSymphony A5, an ultimate high-parameter flow cytometry system that allows the simultaneous measurement of up to 30 parameters; 2) FACSCanto II cytofluorimeter; 3) FACSAria Fusion four-way sorter; 4) BD Rhapsody scanner. ***Electrophysiological facility*** is equipped with a patch-clamp setup

and a high-density multi-electrode array system. ***Metabolomic and proteomics facility*** is equipped with: biological safety hood for blood and tissue biopsy sample processing, NanoPhotometer (Implen) and QUBIT Photometer 4 (Invitrogen), Thermo Scientific Exploris 480 + Ultima 2000, Thermo Scientific Q Exactive Plus Mass Spectrometer + Vanquish UHPLC Systems, Sciex Triple TOF 5600 plus + micro LC 200 eksigent or easy nanoLC Thermo, LECO Pegasus BT 4D GCxGC-TOF (SPME and HS), Ultimate 3000 biocompatible + DAD, Gel-proteomics (SERVA HPE blue Horizon, IEF Biorad, Chemidoc), FastPrep 24, Ultraturrax, point sonicator, Positive pressure-96 for SPE, Liquid handling for ELISA. Bioinformatic analysis softwares: IPA Ingenuity Pathway Analysis.

Section d. GANTT diagram

		Months of the project											
AIMS	**Tasks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
AIM1	**T1.1**												
	T1.2												
AIM2	**T2.1**												
	T2.2												
	T2.3												
AIM3	**T3.1**												
	T3.2												
	T3.3												
AIM4	**T4.1**												
	T4.2												
	T4.3												
AIM5	**T5.1**												
	T5.2												
	T5.3												

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Barberis E, Timo S, Amede E, Vanella V V, Puricelli C, Cappellano G, Raineri D, Cittone M G, Rizzi E, Pedrinelli A R, Vassia V, Casciaro F G, Priora S, Nerici I, Galbiati A, Hayden E, Falasca M, Vaschetto R, Sainaghi P P, Dianzani U, Rolla R, Chiocchetti A, Baldanzi G, Marengo E and Manfredi M (2020) Large-Scale Plasma Analysis Revealed New Mechanisms and Molecules Associated with the Host Response to SARS-CoV-2, *International Journal of Molecular Sciences*, 21(22), p. 8623.

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Cvijetic S, Bortolotto V, Manfredi M, Ranzato E, Marengo E, Salem R, Canonico P L and Grilli M (2017) Cell autonomous and noncell-autonomous role of NF-κB p50 in astrocyte-mediated fate specification of adult neural progenitor cells, *Glia*, 65(1), pp. 169–181.

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Suzuki J, Kanemaru K, Ishii K, Ohkura M, Okubo Y and Iino M (2014) Imaging intraorganellar Ca2+ at subcellular resolution using CEPIA, *Nature Communications*, 5, p. 4153.

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Zhou Y, Wang X, Liu Y, Gu Y, Gu R, Zhang G and Lin Q (2023) Mechanisms of abnormal adult hippocampal neurogenesis in Alzheimer's disease, *Frontiers in Neuroscience*, 17, p. 1125376.

Curriculum vitae

PERSONAL INFORMATION

Family name: **GRILLI** First name: **Mariagrazia**

Researcher unique identifier(s): ORCID 0000-0001-9165-5827

Date of birth: August, 29 1962

Nationality: Italian

URL for web site: https://labgrilli.wixsite.com/home

- **EDUCATION**

1997 Residency School in Clinical Biochemistry, University of Brescia, Brescia, Italy (50/50 cum laude)

1993 PhD in Molecular Medicine, Dept. of Molecular Medicine, University of Brescia, Brescia, Italy (Supervisor: Prof. Maurizio Memo)

1987 Medical Degree, School of Medicine, Dept. of Molecular Medicine, University of Brescia, Brescia, Italy (Magna cum Laude)

- **CURRENT POSITION**

2020 – today Current Position: Full Professor of Pharmacology, Dept. Pharmaceutical Sciences (DSF), University of Piemonte Orientale (UPO), Novara, Italy

- **PREVIOUS POSITIONS**

2005 – 2019 Associate Professor of Pharmacology, DSF, UPO, Novara, Italy

2001 – 2005 Section Head Molecular and Cellular Biology, Schering-Plough Research Institute (SPRI), San Raffaele Science Park, Milano, Italy. Role: Project Leader & Biology Chairman for drug discovery programs in the area of chronic pain.

1997-2001 Principal Scientist, SPRI, San Raffaele Science Park, Milano, Italy. Role: Project Leader for drug discovery programs in neurodegenerative disorders (AD, PD, Stroke).

- **FELLOWSHIPS AND AWARDS**

1990-1992 Fogarty Fellowship, Laboratory of Immunology, NIAID, NIH, Bethesda, MD, USA. Supervisor: Dr. Michael J. Lenardo.

1987 – 1989 Fidia Scholarship, Visiting Scientist, NHLBI, Hypertension and Endocrine Branch, NIH, Bethesda, MD, USA; supervisor: Dr. Ingeborg Hanbauer.

2011 Francantonio Bertè Award of Pharmacology, University of Pavia, Pavia, Italy

2020 European Certified Pharmacologist

- **SUPERVISION OF GRADUATE STUDENTS & POSTDOCTORAL FELLOWS (2005-today)**

2005 – 2023 Number of Postdocs: 9 (DSF, UPO, Novara, Italy)
Number of PhD students: 12 (DSF, UPO, Novara, Italy)
Number of Master Students: 20 (DSF, UPO, Novara, Italy)

- **ORGANISATION OF SCIENTIFIC MEETINGS (selected, since 2010)**

2022 International Conference “More than neurons: changing the paradigm for novel therapeutic interventions” 3rd edition, Turin, Italy (Scientific Organizer).

2018 International Conference “More than neurons: towards a less neuronocentric view of brain disorders” 2nd edition, Turin, Italy (Scientific Organizer)

2016 International Conference “More than neurons: towards a less neuronocentric view of brain disorders”, Turin, Italy (Scientific Organizer)

2012 International Conference “Opportunity and challenges in the pharmacological modulation

of neural stem cells", Novara, Italy (Scientific Organizer)

2010 VI SIF Symposium "The pharmacological modulation of adult neural progenitor cells", Novara, Italy (Scientific Organizer)

- **INSTITUTIONAL RESPONSIBILITIES**

2005 - 2012 President of the Drug and Food Biotecnology Interdepartmental Center, UPO, Novara
2005 - 2013 Academic Board Member, PhD program in "Pharmaceutical and Food Biotechnologies", UPO,Novara Italy
2014 - 2019 Academic Board, PhD program in "Chemistry and Biology", UPO, Novara Italy
2020 - today Academic Board, PhD program in "Drug Innovation", UPO, Novara Italy
2009 - today Academic Board, Residency School for Hospital Pharmacists, UPO
2014 - 2019 Member of University Teaching Committee, UPO

- **REVIEWING ACTIVITIES**

2010 - today: Associate Editor, Neurodegeneration, for Frontiers in Neuroscience, Frontiers in Psychiatry, Frontiers in Neurology
2015 - 2017 Scientific Advisory Board, Angelini Pharma, Pomezia, Italy
2010 - 2017 Scientific Advisory Board, Grunenthal GmbH
2018 - today Prix Galien Italy Evaluator

- **MEMBERSHIPS OF SCIENTIFIC SOCIETIES**

1989- American Society of Neuroscience
1992- Italian Society of Pharmacology
1997- Italian Society of Neuroscience
1997- FENS
2002- International Association for the Study of Pain(IASP)
2014- Stem Cell Research Italy
2021- Mediterranean Neuroscience Society

- **MAJOR COLLABORATIONS**

Monica Di Luca, University of Milan, Milan, Italy; Sleep and circadian rhythm abnormalities in AD animal models and patients; **Elena Marcello**, University of Milan, Italy; Topic: ADAM10 inhibitors as adult neurogenesis modulators; **Daniela Uberti**, University of Brescia, Brescia, Italy; Topic: NRF2 signalling pathway in neuroprotection and in aging associated cognitive impairment; **Ferdinando Nicoletti**, University Sapienza Rome, Italy; Topic: mGLUR3 as therapeutic target in Parkinson's Disease; **Agata Copani**, University of Catania, Catania, Italy; Topic: Drug Repurposing for Ataxia-telangectasia associated neurodegeneration; **Sandra Guidi**, University of Bologna, Italy; Topic: new pharmacological targets for intellectual disabilities in Down Syndrome; **Cesare Patrone**, Department of Clinical Science and Education, Södersjukhuset, Internal Medicine, Karolinska Institutet, Stockholm, Sweden; Effects of High fat diet on adult hippocampal neurogenesis.

Appendix: All current grants and on-going and submitted grant applications of the PI (Funding ID)

Mandatory information (does not count towards page limits)

Current grants Mariagrazia Grilli (Please indicate "No funding" when applicable):

Project Title	*Funding source*	*Amount (Euros)*	*Period*	*Role of the PI*	*Relation to current proposal*
"RE-Plast: targeting functional and structural plasticity in Alzheimer disease. From diagnosis to treatment" ID 20202THZAW_005	MUR-PRIN 2020	130,000	4/25/2022-4/24/2025	UNIT- PI	None
"Hub per il riposizionamento di farmaci nelle malattie rare del sistema nervoso in età pediatrica" ID T4-AN-04	Ministero della Salute - Traiettoria 4 "Biotecnologie, Bioinformatica e Sviluppo Farmaceutico", Linea di Azione 4.1 "Creazione di Hub delle Scienze della Vita" - Piano Sviluppo e Coesione Salute	1.687.500,00	2/14/2023-13/02/2027	UPO Scientific Coordinator	None

Curriculum vitae

PERSONAL INFORMATION

Family name, First name: **LIM, Dmitry**

Researcher unique identifier: ORCID 0000-0002-4316-2654.

Date of birth: 29/10/1968

Nationality: Italian

URL for web site: https://www.scopus.com/authid/detail.uri?authorId=14037788400

- **EDUCATION**

2003 PhD program of The Open University of London (London, UK), sponsoring establishment at the Stazione Zoologica di Napoli "Anton Dohrn", Naples, Italy. PhD in Physiology and Cell Biology. Supervisor, Dr. Luigia Santella, Co-Supervisor, Prof. Ernesto Carafoli.

1999 The Moscow State University, Moscow, Russia. Master degree in Physiology Cum Laude.

1988 Novokuybishevsk school of nursing, Novokuybishevsk, Russia. Diploma in Nursing Cum Laude.

- **CURRENT POSITION(S)**

2019 – present Associate Professor of Physiology, Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy.

- **PREVIOUS POSITIONS**

2016 – 2019 Assistant Professor of Physiology (RTDb), Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy.

2009 – 2016 Senior Postdoctoral Fellow. Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italia.

2004 – 2009 Postdoctoral Fellow. Department of Biochemistry, University of Padova; Venetian Instutute of Molecular Medicine (VIMM), Padova Italia.

1989 – 1993 Nurse at the Children Surgery Department. The Samara "Pirogov" Clinical Hospital, Samara, Russia.

- **FELLOWSHIPS AND AWARDS**

2021 National Qualification for Full Professorship (Abilitazione Nazionale di prima fascia), Call D.D. 2175/2018. S.C. 05/D1, S.S.D BIO/09 Physiology.

- **SUPERVISION OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS**

2016-present Scientific supervisor of n. 23 students during their experimental thesis;

2020-2023 Scientific supervisor of n. 1 PhD students for the PhD course in Drug Innovation, Department of Pharmaceutical Sciences, Università del Piemonte Orientale.

2015-present Supervisor of n. 5 postdoctoral fellows.

- **ORGANISATION OF SCIENTIFIC MEETINGS**

2021 Organizer and chair of a symposium "Causes and consequences of mitochondrial dysfunction in brain diseases." in frame of the PENS Regional Meeting 2021, Krakow, Poland.

2021 Organizer and chair of a symposium "Remodeling of glial cells in brain diseases: all roads lead to neuroinflammation?" in frame of the Congress of the Italian Society for Neuroscience 2021, Brescia, Italy.

2918 Organizer of the National congress on Intracellular Calcium Signalling "Calcium Day 2018", Novara, Italy

- **INSTITUTIONAL RESPONSIBILITIES**

2021-present Delegate for International Relations, Department of Pharmaceutical Sciences, Università del Piemonte Orientale.
2021-present Vice president of the Master Degree in Pharmaceutical Biotechnologies, Department of Pharmaceutical Sciences, Università del Piemonte Orientale.
2021-present Member of Technical-Scientific Committee, Interdipartimental Center for Allergic and Autoimmune Diseases (CAAD), Università del Piemonte Orientale.
2020-present Member of the Academic Board of the PhD in Drug Innovation, Università del Piemonte Orientale (37-39 cycles).
2019-present Member of the Council of the Department of Pharmaceutical Sciences, Università del Piemonte Orientale.

- **REVIEWING ACTIVITIES**

2021-2022 Organizer and Editor of Special Issue "Molecular Aspects of Cellular Dysfunction in Alzheimer's Disease" in Biomolecules journal, MDPI.
2019-present Topic Editor of Cells Journal, MDPI.
2018-present Associate Editor of Frontiers in Neurology, Neurodegeneration section (10 manuscripts edited).
2008-present Invited as an expert reviewer for the following peer-reviewed journals: Neurobiology of Disease, Acta Neuropathologica, Prion, Cell Calcium, Frontiers in Cellular Neuroscience, Cell Death and Disease, Redox Biology, Clinical and Translational Medicine, Neuropharmacology, Plugers Archive-European Journal of Physiology, Aging Cell. (In total, 58 manuscripts revised)

- **MEMBERSHIPS OF SCIENTIFIC SOCIETIES**

2016-present Member of the Italian Society of Physiology.
2016-present– Member of the Italian Society of Neuroscience.

- **MAJOR COLLABORATIONS**

Francesco Moccia, University of Pavia, Pavia, Italy, topic: Calcium signalling toolkit in health and disease; **Egidio D'Angelo**, University of Pavia, Pavia, Italy, topic: Deletion of calcineurin from GFAP-expressing astrocytes impairs excitability of cerebellar and hippocampal neurons through astroglial Na+/K+ ATPase; **Chiara Verpelli**, CNR, Milan, Italy; topic: Pharmacological enhancement of mGlu5 receptors rescues behavioral deficits in SHANK3 knock-out mice; **Maria Rosa Antognazza**, IIT, Milan, Italy, topic: Conjugated polymers optically regulate the fate of endothelial colony-forming cells; **Alexej Verkhratsky**, University of Manchester, Mancester, UK, topic: Calcium signalling in neuroglia; **Cristina Meregalli**, University Milano Bicocca, Monza, Italy, topic: Interplay between NEuroactiVe stEroids and endoplasmic Reticulum-MitOchondRia intEraction: a novel therapeutic horizon in chemotherapy-induced peripheral neurotoxicity (NEVERMORE)

Appendix: All current grants and on-going and submitted grant applications of the PI (Funding ID)

Mandatory information (does not count towards page limits)

Current grants (Please indicate "No funding" when applicable):

Project Title	*Funding source*	*Amount (Euros)*	*Period*	*Role of the PI*	*Relation to current Proposal*
Interplay between NEuroactiVe stEroids and endoplasmic Reticulum-MitOchondRia intEraction: a novel therapeutic horizon in chemotherapy-induced peripheral neurotoxicity (NEVERMORE) – ID P2022R43RA	Ministero dell'Università e Ricerca - PRIN 2022 PNRR	58.100,00	30/11/2023 – 29/11/2025	Dmitry Lim (co-PI is PI of the PRIN 2022 PNRR project)	None

PERSONAL INFORMATION

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Date of birth: 17/01/1982 Magenta (MI), ITALY.

Nationality: Italian

URL for web site: https://upobook.uniupo.it/laura.tapella

- **EDUCATION**

2008-2011 **PhD,** Mario Negri Institute for Pharmacological Research, Department of Neuroscience, Milan, Italy. Biochemistry and neuroscience study on Prion and Alzheimer's disease. PhD Supervisor: Dott. Roberto Chiesa

2004-2007 **Master's Degree in Medical and Pharmaceutical Biotechnology,** University of Eastern Piedmont, Novara, Italy.

2001-2004 **Degree in Biotechnology,** University of Eastern Piedmont, Novara, Italy.

- **CURRENT POSITION(S)**

2022-present **RTdB (Assistant professor Physiology),** University of Eastern Piedmont, Department of Pharmaceutical Sciences, Novara, Italy

- **PREVIOUS POSITIONS**

2017-2022– **Postdoc**, University of Eastern Piedmont, Department of Pharmaceutical Sciences, Novara, Italy. Neurobiology, neuroscience, and biochemistry study on Astroglial dependent dysfunction in Alzheimer's disease.

2017-2014– **Postdoc**, University of Milan, Milan, Italy. Neurobiology and neuroendocrinology study on GH-secreting tumors.

2014-2011 **Postdoc**, Mario Negri Institute for Pharmacological Research, Department of Neuroscience, Milan, Italy. Neurobiology, neuroscience, and biochemistry study on Prion and Alzheimer's disease.

- **FELLOWSHIPS AND AWARDS**

2021 PRIN postdoc fellow

2018-2020 CRT postdoc fellow (Call 1393-2017) by CRT Foundation (40000 euro/24 months). Project title: "REGULATION OF NEURONAL PROTEIN EXPRESSION AND FUNCTION BY ASTROGLIAL CALCINEURIN". This was an open competition that awarded 14 fellowships funded by the Cassa di Risparmio di Torino

2018 Cariplo postdoc fellow

2017 PRIN postdoc fellow

2013 SAFA postdoc fellow

2017 PRIN postdoc fellow

2011 TELETHON postdoc fellow

2009 Prion 2009", Thessaloniki, Best Presented Poster,"Characterization of the molecular heterogeneity of mutant prion proteins" L. Tapella Poster.

- **ORGANISATION OF SCIENTIFIC MEETINGS (if applicable)**

2021 "10° National congress of Italian society for neuroscience-SINS2021" **organization of the symposium "Under 40"** in the session "Proteinopathies in neurodegenerative diseases". Titled: "The complexity of proteinopathies in neurodegenerative diseases: a highlight of new models, mechanisms and possible therapies" Chair: L. Tapella, Italy

2018 "Calcium Day", **supporting staff and organizing committee**, University of Eastern Piedmont Novara, Italy.

- **INSTITUTIONAL RESPONSIBILITIES (if applicable)**

2023-2017 **Co-relator,** together with relator Prof. Lim, of thesis project for degree in pharmacy, CTF and Biotechnology

2022 **Member of the Faculty Committee organizing seminars** for the Department of Pharmaceutical Sciences, University of Eastern Piedmont, recruiting speakers, setting the calendar, and moderating the event.

2020-2019 **Tutoring of Physiology** course (05/D1) for University of Eastern Piedmont, Department of Pharmaceutical Sciences, Novara, Italy.

- **REVIEWING ACTIVITIES (if applicable)**

2021 MDPI-Life **-Guest editor** "The Non-Cellular Autonomic Mechanism of Neuronal Degeneration: Protein Synthesis and Secretion".

2020 **Reviewer** for Biology, indexed by SCIE (Web of Science) and PubMed (NLM), Scopus (CiteScore 6.20). https://www.mdpi.com/journal/biology

2017 – **Review** Editor the Editorial Board of Neurodegeneration, a specialty of Frontiers in Neurology, Neuroscience and Psychiatry

- **MEMBERSHIPS OF SCIENTIFIC SOCIETIES (if applicable)**

2022– **Member,** Research Network "*SIF-Società italiana di fisiologia*", *Italy.*

2021– **Member**, Research Network "*SINS-società italiana di neuroscienze", Italy.*

2020– **Member**, Research Network "*SIF-Società italiana di farmacologia", Italy.*

- **CAREER BREAKS (if applicable)**

Maternity leave:
1) 3/1/2015-7/9/2015
2) 28/4/2016-5/2/2017

ALLEGATO C

TABELLA COSTI PERSONALE STANDARD

FASCIA DI COSTO	NUMERO SOGGET	COSTO	MONTE ORE	COSTO DEL PERSONALE
Basso	**1**	31 €	625	19375 €
Medio	**1**	48 €	500	24000 €
Alto	**1**	73 €	375	27375 €
TOTALI	**3**		**1500**	**70750 €**

COSTO ORARIO: si deve far riferimento al Decreto Interministeriale n. 116 del 24/1/2018

ALLEGATO C

BUDGET DI PROGETTO	COSTO DEL PERSONALE	OVERHEAD	Costi per servizi di Consulenza Specialistica	Costi per licenze direttamente imputabili al progetto	Costi per materiali e attrezzature direttamente imputabili al progetto	Costi per altre tipologie di spese direttamente imputabili al progetto	COSTO TOTALE
	70750.00 €	10612.50 €	25000.00 €	0.00 €	33637.50 €	10000.00 €	150000.00 €