Prot. n. 0054636 del 12/06/2024 - [AOO: USGEUNI] Decreti 3014/2024

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 G – "Development of biomarkers to identify patients in the early stage of neurodegenerative diseases and acute brain damage, to set individualized and preventive strategies, to improve patient prognosis and quality of life"** era pervenuta a mezzo PEC all'indirizzo air3@pec.unige.it la seguente proposta:

PROPONENTE: Istituto di Ricerche Farmacologiche Mario Negri
TITOLO PROPOSTA: BIOTRACT – Identification of common and distinct neurodegenerative blood biomarker trajectories in traumatic brain injury and mild cognitive impairment patients to improve patients' stratification and prognosis

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. 1127 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. 2290 del 10 maggio 2024 con cui è stata approvata la graduatoria di merito per la Tematica G – "Development of biomarkers to identify patients in the early stage of neurodegenerative diseases and acute brain damage, to set individualized and preventive strategies, to improve patient prognosis and quality of life", 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 15 maggio 2024 è stata inviata all'Istituto di Ricerche Farmacologiche Mario Negri la comunicazione con prot. 41935 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 17 maggio 2024 con prot. n. 43167 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 BIOTRACT – Identification of common and distinct neurodegenerative blood biomarker trajectories in traumatic brain injury and mild cognitive impairment patients to improve patients' stratification and prognosis per la **Tematica G – "Development of biomarkers to identify patients in the early stage of neurodegenerative diseases and acute brain damage, to set individualized and preventive strategies, to improve patient prognosis and quality of life"** con Soggetto proponente l'Istituto di Ricerche Farmacologiche Mario Negri - come rappresentato negli Allegati B e C alla proposta presentata con domanda di partecipazione prot. n. 74640 del 14 dicembre 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. 74640 del 14 dicembre 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)

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
MNESYS
Università di Genova

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

Topic g) Development of biomarkers to identify patients in the early stage of neurodegenerative diseases and acute brain damage, to set individualized and preventive strategies, to improve patient prognosis and quality of life

Biotract

Identification of common and distinct neurodegenerative blood biomarker trajectories in traumatic brain injury and mild cognitive impairment patients to improve patients' stratification and prognosis

- Name of the PIs' host institution for the project: Istituto di Ricerche Farmacologiche Mario Negri
- Name of the Principal Investigators (PIs): Elisa R. Zanier
- Proposal duration in months: 12

RESEARCH TEAM

ROLE IN THE PROJECT	*NAME*	*SURNAME*	*DEPARTMENT*	*QUALIFICATION*	*YOUNG (under 40 al 31.12.2023)*	*F/M*
Principal Investigator	Elisa R	Zanier	Acute Brain and Cardiovascular Injury	Head of Department		F
co-Principal Investigator (PI)	Gianluigi	Forloni	Neuroscience	Head of Department		M
Research collaborator	Valentina	Bonetto	Neuroscience	Head of Lab. of Translational Biomarkers		F
Research collaborator	Tiziana	Borsello	Neuroscience	Head of Unit of Neuronal Death and Neuroprotection		F
Research collaborator	Francesca	Pischiutta	Acute Brain and Cardiovascular Injury	Head of Unit of Cell Therapy	X	F
Research collaborator	Laura	Pasetto	Neuroscience	Head of Unit of Mechanisms of Proteinopathies	X	F
Research collaborator	Federico	Moro	Acute Brain and Cardiovascular Injury	Head of Unit of Pathobiology and Neuroimaging	X	M
Research collaborator	Giovanni	Nattino	Medical Epidemiology	Head of Unit of Causal Inference in Epidemiology	X	M

ABSTRACT

Presently, there are no definitive treatments for halting the progressive course of brain diseases following traumatic brain injury (TBI) or classical neurodegenerative diseases. Despite advancements in TBI and dementia diagnostics, early detection of mild cognitive impairment (MCI) remains challenging. Moreover, sensitive biomarkers to understand disease trajectories in terms of ongoing cognitive impairment and neurodegeneration are lacking. The intersection of TBI and dementia, a vast and expanding area, remains underexplored. Our project, **Biotract**, unites experts in TBI (Zanier team) and dementia (Forloni team) to address these gaps.
Leveraging existing cohorts of MCI and TBI patients with established brain injury blood biomarkers, we aim to conduct a detailed blood profiling, including innovative biomarkers of neuronal damage, synaptic dysfunction, and blood-brain barrier (BBB) damage. The goal is to identify a blood-based fingerprint associated with ongoing cognitive decline. Classical plasma biomarkers (NFL, total tau, p-tau 181, and GFAP) in MCI and TBI patient cohorts will be integrated with innovative blood analysis, including tauopathy (pTau217), BBB damage (MMP-9), and synaptic dysfunction (JNK3).
Biochemical profiles associated with cognitive decline at follow-up will be analyzed using advanced statistical methods. Comparative analysis between MCI and TBI cohorts' biomarker trajectories will reveal common and distinct disease mechanisms influencing disease progression. **Biotract** has the potential to identify a combinatorial peripheral biomarker signature informing on the risk of converting from initial cognitive impairment to progressive decline and dementia. Outcomes could significantly impact the development of novel strategies for diagnosing and assessing the risk of disease progression in TBI and MCI patients, substantially improving the quality of life for a significant portion of the population with clear impact on the healthcare system.

RESEARCH PROPOSAL

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

Neurodegenerative diseases together with acute brain damage, represent one of the major causes of morbidity and mortality, with high socioeconomic burden. The identification of biological markers to predict the pathophysiological trajectories is a fundamental challenge. The complexity arises from inter-individual variability in the occurrence, severity and progression rate phenotype within the same disorder, complicating the management of these conditions in terms of therapeutic strategies and timing of intervention. Over the past decade, traumatic brain injury (TBI) and dementia diagnosis have advanced rapidly. We now have FDA-approved and CE marked blood tests to aid in diagnosis of mild TBI. Blood tests to support diagnosis of Alzheimer's disease (AD) are approaching clinical use[1]. Dementia has entered the prevention and treatment era with FDA approval of immunotherapies that reduce cognitive decline in mild AD and mild cognitive decline (MCI). However, the large and expanding area where TBI, and dementia overlap has been left behind. Furthermore, minimally invasive approaches to identify ongoing cognitive impairment and its progression are lacking.

Increased risk of several neurodegenerative diseases, including AD, has long been recognized following exposure to TBI, with an estimated 5-10% of dementia in the community thought to be TBI associated[2]. As such, TBI represents a leading risk factor for neurodegenerative disease, with unique potential to inform on pathways to development of wider dementias. Neurodegeneration following TBI presents a singular opportunity to study the time course and drivers of dementia pathology from a single point in time forwards. Unlike other neurodegenerative diseases, in the case of TBI, the initiating event is known. This provides an exceptional opportunity to identify biomarker signatures that may shed light on distinct brain injury trajectories and help identify patients who are at risk of developing progressive cognitive decline and associated dementia.

MCI holds a critical position in the spectrum of cognitive decline, serving as a transitional phase between normal aging and AD. Individuals with MCI exhibit noticeable cognitive deficits beyond what is expected for

their age but do not meet the criteria for dementia. Recognizing MCI's proximity to AD is crucial, as not all MCI cases progress to AD. The population of MCI subjects is heterogeneous and the progression to AD involves about one third of the cases within the following three years. The capacity of peripheral biomarkers in the early phase of the disease to distinct subjects with higher risk to convert from initial cognitive decline to dementia might substantially change the quality of life of a large portion of elderly population and could have an extraordinary impact on health system. In AD, after two decades of failures, recent FDA approval of lecanemab and positive results with donanemab highlight the efficacy of immunotherapy with a disease modifying effect[3,4]. Expectations for authorization in Europe are reasonable, but treatments with anti-Aβ antibodies involve complex procedures and necessitate careful patient monitoring for associated cerebrovascular risks. The availability of reliable markers is crucial for selecting treatment candidates and optimizing therapeutic strategies. Within a recent network project, we have started exploring the possibility of developing a risk profile for early-phase neurodegenerative disorders in subjects with MCI, Parkinson's disease and amyotrophic lateral sclerosis (Ministry of Health, RCR-2022-23682291). This investigation combines classical and innovative plasma biomarkers. The project delves into the analysis of plasmatic levels of Aβ 1-40/42, the cytoskeletal microtubule associated protein (tau) and its phosphorylated form (p-tau)-181, the axonal neurofilament light (NFL), α-synuclein and glial fibrillary acid protein (GFAP) in cohorts with MCI. The results of these analyses are currently under statistical examination and will offer valuable insights to associate the biological profile with cognitive decline in different neurodegenerative conditions. The integration of these data with the results of the present study will offer the possibility to distinguish pathophysiological trajectories and stratify patients based on the clinical, neuroimaging and biomarker profiles.

Likewise, we have explored disease trajectories and the risk for neurodegeneration and progressive cognitive decline after TBI within network projects (including CREACTIVE, CENTER-TBI, ICON-TBI and BIOAX-TBI)[5–8]. After TBI, protein biomarkers are released into the blood including astroglial biomarkers s100 calcium binding protein B (s100B) and GFAP, NFL, Tau. The early concentration of GFAP and NFL scales with the extent of injury after TBI[9], and may help select patients who benefit most from MRI for detection of CT-occult lesion[10]. In addition, NFL and Tau concentrations in blood in the early chronic phase are predictive of ongoing white matter pathology and atrophy years after injury[7,11] - key pathological features of patients with MCI[12]. Such insights, while not currently used in clinical practice, show the potential for blood biomarkers to understand ongoing pathophysiology, to potentially guide future management strategies and stratify patients at risk of delayed cognitive decline. Notably, common and distinct blood biomarkers trajectories are evident between TBI and MCI patients. Indeed, both patients cohorts show progressive white matter damage and brain atrophy reflected by increase NFL levels[7,13] while different pattern of the Alzheimer-specific biomarker p-tau 181 has been observed. While in AD like pathologies a p-tau 181 increase in blood has been observed, no changes have been observed over a one-year period following moderate-to-severe TBI[7]. Thus, data suggest that other blood markers such as p-tau phosphorylation in threonine 217, could provide more informative insights into late neurodegeneration post-TBI[14].

In addition to Tau protein-mediated neurodegeneration, synaptic dysfunction and blood-brain barrier (BBB) breakdown are two shared pathological features of both TBI and MCI. Therefore, it is possible that specific mechanistic biomarkers of synaptic dysfunction and BBB damage could aid in patient stratification and development of late cognitive decline.

Synaptic dysfunction. The onset of synapse dysfunction marks the initial and pivotal toxic event shared among various neurodegenerative diseases. This dysfunction significantly impairs synaptic contacts, resulting in a profound impact on neuronal communication and the disruption of crucial neuronal networks. Extensive literature supports the observation that several neurological disorders, including AD and TBI, exhibit noteworthy changes in the morphology and quantity of dendritic spines—clear indicators of synaptic dysfunction[15]. In this context, we focus on MCI, a transitional state between normal aging and dementia characterized by a potentially reversible synaptopathy. Extensive research in neurodegenerative diseases has highlighted synaptic dysfunction as a crucial aspect, with c-Jun N-terminal kinase 3 (JNK3) emerging as a

novel and promising biomarker. Our recent patent on JNK3 as a predictive biomarker in AD underscores its significance (Borsello, granted two Italian patents in 2022, PCT in 2023). Furthermore, we have preliminary evidence for JNK3 increase in in the cerebrospinal fluid (CSF) of MCI patients (data unpublished). Additionally, we have preliminary observation of increased JNK3 levels in plasma in TBI and AD patients compared to controls (data unpublished). Thus, data suggest JNK3 as a potential predictive biomarker for brain neurodegeneration, with plasma levels allowing for multiple withdrawals to monitor disease progression.

BBB damage assessment. Astrocytic end-feet containing GFAP are an integral component of the BBB. High blood GFAP is a marker of structural damage in the acute phase of brain injury. Pericytes, crucial cells for vascular homeostasis and barrier function, are the main source of matrix metalloproteinase 9 (MMP-9). Inflammatory stimuli very rapidly activate MMP-9 at the pericyte somata, leading to degradation of the underlying tight junction complexes. Thus, MMP-9 becomes a detrimental factor in BBB disruption following acute brain injuries[16,17] and neurodegenerative diseases[18]. When combined with GFAP, circulating MMP-9 offers a valuable signature indicative of BBB damage.

Aims of the project

Under **Biotract** we propose to leverage the cohorts of MCI and TBI patients already characterized in terms of clinical outcome and neuroimaging by our groups and profiled towards the likelihood of developing progressive white matter pathology and brain atrophy by NFL and Tau longitudinal measures to i) conduct innovative targeted analysis in blood to better address the contribution of tauopathy (pTau217), BBB damage (MMP9) and synaptic dysfunction (JNK3) in disease progression, ii) address whether these new measures in isolation or combined to the already available blood profile will aid in the identification of ongoing cognitive decline and associated dementia in MCI and TBI patients, iii) to conduct comparative analysis between the two cohorts of patients to identify common and distinct biomarker trajectories driving neurodegeneration in the two disease context with important implication in terms of risk assessment, identification of druggable targets and therapeutic development. The last aim will leverage innovative machine learning techniques to provide a homogeneous description of the clinical evaluation of the single patient. This will be easily transferable to the clinic for the stratification of patients based on the different parameters analysed: i) parenchyma atrophy (white and grey matters), ii) BBB-damage and iii) extent of synaptic dysfunction / cognitive decline for an early and differential diagnosis based on the data recovery.

Significance of the project

Neurodegeneration following TBI presents a singular opportunity to study the time course and drivers of dementia pathology from a single point in time forwards. Leveraging unique and internationally recognized experience in the field of TBI (Zanier, Project PI) and dementia (Forloni, Project Co-PI) and resources, **Biotract** has the potential of identifying a combinatorial signature of peripheral biomarker informing on the risk to convert from initial cognitive impairment to progressive decline and dementia. Thus, outputs from **Biotract** have potential to inform the development of novel strategies for diagnosis and risk assessment of disease progression in patients with TBI and MCI. This will be an asset to substantially change the quality of life of a large portion of population and could have an extraordinary impact on health system.

Section b. Methodology

From the dataset and biorepository of the unique IRCCS network in Neuroscience and Neurorehabilitation (RIN) archive previously funded by the Italian Ministry of Health/AIFA, we will select and further characterize the large cohorts of already recruited and clinically characterized patients with MCI cohort (n=264 from the ADnet cohort, n=264 from the Interceptor cohort) with the consent from the scientific committee.

From the large cohort of TBI patients enrolled in the multicenter observational studies CREACTIVE and BIOAX-TBI previously funded by ERA-NET NEURON, European Commission, Seventh Framework Programme, we will select and further characterize the large cohort of mild to severe TBI patients (n=74, age 18-80y) with longitudinal blood sampling fully characterized in terms on clinical and neuroimaging studies[5,7,8].

Plasma aliquots from TBI (early: 4-10 days post-injury and delayed: 12 months post-injury) and MCI (early and late) patients and age-matched healthy controls (n=165) are already banked at the Istituto di Ricerche Farmacologiche Mario Negri (IRFMN, SATURNE biobank) and readily available for the project. Consents are in place to perform research studies on these cohorts aimed at better understanding the pathogenetic mechanisms of disease.
Blood biomarkers. We will adopt a targeted approach to known pathogenetic mechanisms underpinning progressive cognitive decline in both TBI and MCI like axonal/neuronal damage, BBBD and synaptic impairment. We will measure in plasma: MMP-9 and GFAP, as biomarkers of BBB damage[19], p-tau 217[20] and JNK3[21], by next generation immunoassay platforms.

Multivariable analyses will be used to analyze the interrelationship of circulating biomarkers levels, age, and 6-month clinical outcomes (Glasgow Outcome Scale Extended). The area under the receiver operating characteristic curve (ROC AUC) will be used to evaluate the prognostic performance, in terms of discrimination, of plasma biomarkers alone, or in combination, on the outcome. ROC AUCs will be computed both in the whole cohort and stratifying by age group. A cluster analysis will be performed to stratify the cohort based on the profiles of new and established blood biomarkers both in the TBI and MCI cohort. The identified patterns by the two analyses will be compared and reconstructed on the other cohort, evaluating whether the identified patterns in the two pathologies are mutually prognostically relevant.

Power study. As the biomarkers are primarily evaluated in terms of predictive performance, this analysis is powered to provide a sufficient precision of the estimated ROC AUC. Assuming a very good discriminative performance of the biomarkers (AUC 0.9) and a proportion of unfavorable outcome of 25%, a sample size of 74 will be sufficient to attain a 95% confidence interval semiwidth of the ROC AUC smaller than 0.1, i.e., sufficient for proving a good discriminative performance (ROC AUC greater than 0.8) [22]. In the smallest of the two cohorts (n=74), in the simplest case where the blood profiles will be used to stratify the cohort in two equinumerous groups (i.e., low and high risk), the minimum detectable risk ratio will be of 1.85, assuming a 25% unfavorable outcome rate, a type-I error of 5% and a power of 80%[23]. Such a minimum detectable value is small compared to what found in previous analyses stratifying TBI patients based on established blood biomarkers of brain injury, where risk ratios of unfavorable outcomes as high as 4.1 were found[5]. Thus, our analysis is powered to assess the prognostic value of blood profiles on the outcome and to cross-evaluate the prognostic performance of the pathology-specific patterns.

With this complementary analysis we will identify a blood-biomarker based fingerprint associated with dementia (MCI). Chronic assessments in TBI patients will be interrogated to find out whether the specific biomarker fingerprint associated with dementia could also be found after TBI and can discriminate patients with good or bad recovery (Glasgow Outcome Score Extended – GOS-E, already available for TBI cohort).

We expect to generate a comprehensive dataset of clinical and blood biomarkers in MCI and TBI patients, which can be used to disclose novel and unexpected combinations of predictors of specific neurodegeneration trajectories at the individual level. Moreover, we expect to define machine learning-based unsupervised/supervised algorithms able to identify the most statistically significant and biologically relevant features of each of MCI and TBI with the purpose of shedding light on the common and specific pathogenic factors characterizing these pathologies.
Thus, in this phase the potential risks of failures are limited. In the statistical elaborations it is possible that predict correlations will not find confirmation, but this is part of our investigation.

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Section c. Available instrumentations and resources

The Mario Negri Institute for Pharmacological Research is a nonprofit biomedical research organization. Since the 1980's the Institute is promoting and coordinating national and international clinical trials by combining the mission and the identity of a nonprofit research institution with high quality standards. It has a large and state-of-the-art set of facilities for the analysis of biomarkers. Samples are stored in the institutional SATURNE biobank, certified ISO 9001:2015 that is part of the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI). Biobank's freezers are equipped with probes which sends continuously the temperature data to the remote-control system. The collected biological samples are de-identified by means of a 6-digit numerical code to prevent patient identification recorded in dedicated sample storage software.
Biomarker assessment will be performed by the following available instruments: the ultrasensitive Simoa Quanterix SR-X platform, the AlphaLISA® platform assisted by the Zephyr® liquid handler workstation and the EnSight Plate Reader (Revvity), ELISA multimode plate reader Infinite® M200 (Tecan).

Section d. GANTT diagram

Biotract	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
Approval from Scientific Board												
Blood biomarker analysis												
Definition of blood biomarker fingerprint associated with cognitive decline in MCI patients												
Definition of blood biomarker fingerprint associated with cognitive decline in TBI patients												
Identification of common and divergent biomarker signatures in MCI and TBI patients												
Report and dissemination												

Curriculum vitae of the PI: Elisa R Zanier

PERSONAL INFORMATION

Family name, First name: Zanier, Elisa R
Researcher unique identifier(s): ORCID: 0000-0002-3011-8718, Scopus ID: 6507932527
Date of birth: 02/11/1974
Nationality: Italian
URL for web site: https://www.marionegri.it/laboratories/traumatic-brain-injury-and-neuroprotection

- **EDUCATION**

2001-2002	Postdoc. Fellow at Neurotrauma Laboratory-Neurosurgery division, University of California Los Angeles (UCLA), USA
1998-2001	Residency - Anaesthesia and Critical Care Medicine, University of Milan, Italy
1998	School of Medicine - University of Milan, Italy

- **CURRENT POSITION(S)**

2023-present	Head of the Department of Acute Brain and Cardiovascular Injury Mario Negri Institute for Pharmacological Research (IRFMN), Milan, Italy
2023-present	Head of the Lab. of Traumatic Brain Injury and Neuroprotection, IRFMN, Milan, Italy
2007-present	Teaching assignment in Anaesthesia and Critical Care Medicine, University of Milan

- **PREVIOUS POSITIONS**

2016-2022	Head of the Lab. of Acute brain injury and therapeutic strategies, IRFMN, Milan, Italy
2012-2016	Head of the Unit of Cell therapy and acute brain injury, IRFMN, Milan, Italy
2008-2012	Associate researcher at the Lab. of Inflammation and Nervous System Diseases IRFMN, Milan, Italy
2003-2008	Assistant Physician, Neurosurgical Intensive Care Unit, Department of Anaesthesia and Critical Care Medicine, Fondazione IRCCS Ospedale Maggiore Policlinico, Milan, Italy
2000-2007	Consultant in Neurointensive Care, Critical Care Medicine and Anaesthesiology Department of Neuroscience, Fondazione IRCCS Ospedale Maggiore Policlinico, Milan

- **FELLOWSHIPS AND AWARDS**

2018	Interview by H. Wood published in Nat Rev Neurol 14, 570–571 (2018) as a research highlight commenting our paper (Zanier et al., Brain 2018) on traumatic brain injury and transmissible tau pathology
2018	Invited Speaker at the Nobel Forum attended by the Swedish Queen, Karolinska Institutet - Head trauma in sports and risk for dementia.
2014	Recipient of the Rita Levi-Montalcini Award, ESICM, Barcelona
2013	Academic qualification to function as Associate Professor in Anaesthesia and Critical Care Medicine, Italian Ministry of Instruction, University and Research (MIUR) - (06/D6), Italy
2013	Round Table conference on “Neuroprotection: clinical aspects”; Brussels
2010	Recipient of the Young Investigator Award, Italian Ministry of Health; Italy
2004	Recipient of the Young Investigator Award, International Neurotrauma Society; Australia
2001-2003	Postdoctoral Fellowship: Neurotrauma Laboratory - Division of Neurosurgery, University of California Los Angeles (UCLA), USA

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

2010-present	Co-supervisor of 8 Master Students (Faculties of Biotechnology, Biology, Pharmaceutical Chemistry and Technology, and Biomedical Engineering, Italy)
2009-present	Supervisor of 11 medical students (Faculty of Medicine, University of Milan, Italy)
2011-present	Supervisor of 5 PhD students (IRFMN IRCCS, Italy)
2014-present	Supervisor of 6 postdocs (IRFMN IRCCS, Italy)

- **ORGANISATION OF SCIENTIFIC MEETINGS**

2024 -to come International Conference on Post-Traumatic Epilepsy (IC-PTE) / NIH funded / participants: 200 / Milan, Italy
2016 7th Meeting of the Forum of Italian Researchers on Mesenchymal and Stromal Stem Cells / participants: 400 / Milan, Italy
2016 BIS16: Brain Ischemia and Stroke conference / participants: 350 / Rome, Italy

- **INSTITUTIONAL RESPONSIBILITIES**

2023-present Director of the SATURNE Biobank and member of the Scientific Technical Committee of the Biological Resources Centre (BRC), IRFMN IRCCS.
2022-present Member of the Executive board of the National Virtual Institute of Cerebrovascular Diseases, IRCCS Network, Ministry of Health.
2022-present Member of the High Council for the Evaluation of Research and Higher Education (France) – Neuroscience Panel Expert.
2021-present Coordinator of the PhD course organized in collaboration with the Open University UK

- **REVIEWING ACTIVITIES**

- Section editor of Intensive Care Medicine Experimental
- Editorial Board of the following Scientific Journals: Journal of Neurotrauma, Frontiers in Immunology,
- Reviewer for the following Scientific Journals: Brain, Lancet Neurology, Science Translational Medicine, JCI, JCI Insights, Intensive Care Medicine, Critical Care Medicine, Stroke, Neurology, Journal of Neurotrauma, Journal of Neuroinflammation, Experimental Neurology, Cell Transplantation, Clinical Science, Journal of Cerebral Blood Flow and Metabolism, Neuropharmacology, NeuroTherapeutics, PlosOne, Neuroscience, Frontiers in Immunology, Frontiers in Neuroscience, Stem Cell Research & Therapy, Stem Cells

- **MEMBERSHIPS OF SCIENTIFIC SOCIETIES**

2022-present Scientific Advisory Board: Member of the Executive Committee of the International TBI research network (InTBIR), Chair of the Fundamental and translational Working Group.
2022-present Member of European Neurotrauma Organization (ENO)
2018-present Member of the Translational Biology Group (TBG) section of the European Society of Intensive Care
2015-present Biomarker Committee, CREACTIVE (Collaborative REsearch on ACute Traumatic brain Injury in intensiVE care medicine; European FP7 project, and part of InTBIR)
2014-present Member of the NeuroIntensive Care (NIC) section of the European Society of Intensive Care Medicine

- **MAJOR COLLABORATIONS**

David K Menon, Therapeutic approaches in TBI, University of Cambridge, UK
William Stewart, TBI and human brain pathology, University of Glasgow, Scotland
Kevin K Wang, TBI biomarkers, University of Florida, Morehouse School of Medicine Atlanta (Georgia)
David Loane, TBI and Immunity, Trinity College, Ireland
Nino Stocchetti, Clinical studies in TBI, University of Milano
Giuseppe Citerio, Clinical studies in TBI, University of Milano Bicocca

- **CAREER BREAKS**

11-2006 – 11-2007 Maternity leave (12 months)
02-2011 – 09-2011 Maternity leave (7 months)

- **COMPLETE LIST OF PUBLISHED WORK**

https://www.ncbi.nlm.nih.gov/pubmed/?term=Zanier+ER (106 peer reviewed papers; h-index = 39, SCOPUS, total number of citations: 4468)

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

Current grants:

Project Title	*Funding source*	*Amount (Euros)*	*Period*	*Role of the PI*	*Relation to current proposal*
Mesenchymal stromal cells for Traumatic Brain Injury: the MATRIx study. A multicenter, double blind, randomized, placebo controlled, adaptive phase II dose finding study.	Italian Ministry of Health Project ID: RF-2021-12372642	Total: 450.000 € Site: 187.500 €	2023-2026	Project PI Major Goals: Clinical trial aimed at assessing safety and efficacy of allogeneic bone marrow-derived mesenchymal stromal cells, administered intravenously (IV) in severe TBI patients, within 48h from injury.	None
Mesenchymal stromal cells for traumatic brain injury	Fondazione Regionale per la Ricerca Biomedica (FRRB) - Unmet Medical Needs Project ID: 3440227	Site: 258.800 €	2023-2026	Site PI Major Goals: Multicenter, double-blind, randomized, placebo-controlled, adaptive phase II dose-finding study designed to assess safety and efficacy of the allogeneic bone marrow-derived MSCs, administered intravenously (IV) in severe TBI patients, within 48h from injury.	None
Prospective preclinical and clinical studies of gut microbiota, intestinal barrier, and related blood metabolites, following traumatic brain injury for developing prognostic biomarkers of chronic neurological sequelae, and for identifying targets to prevent the progressive evolution of brain injury and the chronic disabilities	Italian Ministry of Health – European Union Next Generation EU Project ID: PNRR-MAD-2022-12375695	Total: 1.000.000 € Site: 300.000 €	2023-2025	Project PI Major Goals: To study whether early gut dysbiosis associated with traumatic brain injury (TBI) is a prognostic index of progressive chronic neurological dysfunction.	None
Temporal Dynamics of Astrocytic Activation and Function in Posttraumatic Epilepsy	Department of Defense Epilepsy Research	Site: 400.000 €	2023-2028	Co-PI Major Goals: To establish the role of astrocytes in the onset	None

(PTE) Genesis and Progression	Program (ERP) Project ID: EP220047			and progression of post-traumatic epilepsy.	
TREM2 function and tau transmission in post-traumatic Alzheimer's disease	American Alzheimer Association Research Grant Program 2021 (AARG) Project ID: AARG-NTF-22-928660	Site: 250.000 €	2022-2026	Site PI Major Goals: We will test the hypothesis that TBI induces tau pathology that spreads in the brain in a prion-like manner, causing cognitive deficits, and that TREM2 signaling alters transmission rates, synaptic loss and cognitive function	None
The power o-f touch. Randomized, double-blind, sham-controlled crossover trial of interoceptive non-invasive tactile stimulation for the treatment of osteoarthritis chronic associated pain.	Pfizer Inc. - Advancing Chronic Pain Research (ADVANCE) Project ID: 70060325	Site: 45.000 €	2022-2024	Site PI Major Goals: to analyze circulating inflammatory cytokines and hormones related to stress.	None
Wearable interoceptive technologies. Non-invasive neuromodulation for stress reduction, artificial heart rate variability enhancement, and emotion recognition augmentation	Joy Ventures Neuro-Wellness research grant terms	Site: 29.000 €	2021-2023	Site PI Major Goals: to analyze circulating inflammatory cytokines and hormones related to stress.	None
Role of T-cells in injury evolution after aneurysmal subarachnoid hemorrhage. Clinical and experimental study	CARIPLO Foundation Project ID: 2019-1632	Site: 54.600 €	2020-2024	Site PI Major Goals: To establish a preclinical model of subarachnoid hemorrhage. To understand the role of T-cells in injury evolution after aneurysmal subarachnoid hemorrhage combining studies in patients and rodents.	None

Pending grants:

Project Title	*Funding source*	*Amount (Euros)*	*Role of the PI*	*Relation to current proposal*
Using a novel biomarker platform to measure PTE risk	US Department of Defense	Site: 75.000 €	Site PI Major Goals: To identify EEG biomarkers that can predict the risk of PTE following TBI	None
Transformative Target-specific magnetic Resonance Imaging of Tauopathy with novel blood-brain barrier-crossing Tau aptamer-DOTA[Gd3+] contrast ligands	US Department of Defense	Site: 700.000 €	Site PI Major Goals: To create and construct a novel aptamer ligand that is MRI-visible, BBB-crossing and targets Tau-aggregates	None
TBI-ADRD modelling with a team science approach	National Institutes of Health	975.000 €	Site PI Major Goals: To deliver a TBI-ADRD murine model that accurately recapitulates human TBI-ADRD phenotype and disease and enable other researchers to reproduce our model's core findings, and further its development to advance research in the TBI-ADRD field	None

Co-PI: Gianluigi Forloni

PERSONAL INFORMATION
Family name, First name: Forloni Gianluigi
Scopus Author Id:7005645883 ORCID ID:0000-0001-5374-3914 RESEARCH ID: AAB-2115-2020
Date of birth: 15/05/1956
Nationality: Italian

- **EDUCATION**

1985 Biological Science Doctor, University of Milano, Italy
1976 Diploma in Chemistry, Istituto Tecnico "Stanislao Cannizzaro", Rho, Italy

- **CURRENT POSITION(S)**

2002 Head of Neuroscience Department Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
1996 Head of Biology of Neurodegenerative Disorders Lab
Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy

- **PREVIOUS POSITIONS**

1988 – 1992 Research assistant, Laboratory of Geriatric Neuropsychiatry, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy
1986 – 1988 Postdoctoral fellow, Department of Psychiatry and Neuroscience, The Johns Hopkins University, School of Medicine, Baltimore, U.S.A.
1980 – 1985 Senior technician, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy
1977 – 1980 Technician fellow, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

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

- Satellite meeting of SFN "Brain Aging: identifying accelerators and brakes" San Diego (USA) 8-9 November, 2001
  Member of the Scientific Committee

- International Meeting: Prion 2004 - Paris - Pasteur Institute 24-28 May 2004
  Member of the Scientific Committee

- International Meeting: Prion 2006: Torino, Italy, 4-6 October 2006
  Organizers: Maria Caramelli; Gianluigi Forloni, Fabrizio Tagliavini

- International Meeting Prion 2008, Madrid, Spain, 8-10 Oct 2008
  Member of Scientific Committee

- XIII Congress of the Italian Society of Neuroscience, Milan, October 5-9, 2009
  Member of the Program Committee

- One-day Symposium: *Aging of the Mind: Immunity in the middle of mind/body relationship*, Rehovot, Israel, December 3rd, 2012
  Member of the Scientific Committee

- IX Congress Sindem: Italian Association for the study of Dementia linked to the Italian Neurological Society (SIN). Florence (I)March 13-15, 2014
  Member of the Scientific Committee

- Second International Meeting of The Milan Center of Neuroscience: *Prediction And Prevention Of Dementia: New Hope* Milan, July 6-8, 2016
  Member of the Scientific Board

- **INSTITUTIONAL RESPONSIBILITIES (if applicable)**

2021 – Executive board Italian Network (IRCCS) on Neuroscience
2021 – Executive board Italian Network (IRCCS) on Aging
2015 – 2016 Scientific Committee of the Trial Stamina appointed by Italian Ministry of Health
2014 – Scientific Committee of Dementia section (SINDEM) of Italian Society of Neurology

- **EDITORIAL BOARD**

2021 – Frontiers in Immunology
2020 – Journal of Neuroscience and Cognitive Studies
2020 – Frontiers in Aging Neuroscience (Associate Editor)
2019 – Neurological Disorders & Epilepsy Journal
2013 – International Journal of Epidemiology and Genetics
2011 – 2021 PlosOne (Academic Editor)
2003 – 2010 Brain Aging
2000 – 2007 Biochemical Journal

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

2020 – Member Dementia section (SINDEM) of Italian Society of Neurology
2008 – Member International Society to Advance Alzheimer Research and Treatment (ISTAART) 2008
2004 – Member European Academy of Science
1989 – Italian Association Research on Brain Aging, 1989– (1999– member of Directive Council, 2003– President)

Dr. Forloni has served as a member of several committees of the European Community for the examination of the projects in the Neuroscience field. He has been in charge of an elective course on genetic of neurodegenerative disorders at the Medical School of the University of Milan, he was invited for lectures and seminars in numerous Universities and Research Centers. Dr. Forloni is the author of about 390 peer-review scientific articles (H index Scopus = 73) and 35 reviews or book chapters.

Research collaborator: Valentina Bonetto

PERSONAL INFORMATION

Family name, First name: Bonetto, Valentina
Researcher unique identifier(s): ORCID: 0000-0003-0456-2054, Scopus ID: 6701810094
Date of birth: 13/04/1969
Nationality: Italian
URL for web site: https://www.marionegri.it/personale/valentina-bonetto

- **EDUCATION**

1999 PhD Karolinska Institutet, Department of Medical Biochemistry and Biophysics, Stockholm, Sweden.
1993 Master of Science (Laurea) in Pharmaceutical Chemistry and Technology, University of Padova, Padova, Italy.

- **CURRENT POSITION**

2023-on Coordinator of the Research Center for amyotrophic lateral sclerosis (ALS) at the "Istituto di Ricerche Farmacologiche Mario Negri IRCCS" (IRFMN)

- **PREVIOUS POSITIONS**

2009-on Head of the Laboratory of Translational Biomarkers. Department of Neuroscience, IRFMN, Milano, Italy. Field of research: Pathogenic mechanisms of ALS by *in vivo* and *in vitro* studies; development of therapeutic approaches for ALS; biomarkers of ALS.
2009-2014 Associate Telethon Scientist, Dulbecco Telethon Institute at IRFMN, Milano, Italy.
2007-2009 Head of the Unit of Medical Biochemistry. Department of Molecular Biochemistry and Pharmacology, IRFMN, Milano, Italy.
2002-2009 Assistant Telethon Scientist. Dulbecco Telethon Institute at IRFMN, Milano, Italy.
2000-2002 Postdoctoral Fellow. Department of Molecular Biochemistry and Pharmacology, IRFMN, Milano, Italy.
1994-1999 Graduate Student. Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden. Supervisor: Prof. Hans Jörnvall.
1994 Fellow. CRIBI Biotechnology Center, University of Padova, Italy.
1993 Undergraduate Student. Supervisor: Prof. Angelo Fontana. CRIBI Biotechnology Center, University of Padova, Italy.

- **OTHER INSTITUTIONAL ROLES**

Sep2023-on Member of the Board of Directors of the National Virtual Institute of the Motor Neuron Diseases (IVNMMN), Neuroscience and Neurorihabilitation IRCCS Network, Ministry of Health.
Sep2023-on Member of the Scientific Technical Committee of the Biological Resources Centre (BRC), IRFMN IRCCS.

- **FELLOWSHIPS AND AWARDS**

2009-2014 Associate Telethon Scientist (Carrier program), Telethon Foundation.
2002-2009 Assistant Telethon Scientist (Carrier program), Telethon Foundation.
2000-2002 Postdoctoral fellowship from Telethon Foundation.
1996-1998 Study award from the Foundation BLANCEFLOR Boncompagni-Ludovisi neè Bildt, Stockholm, Sweden.
1994-1995 Study abroad scholarship from the University of Padova.
Feb-Sep1994 Fellowship from the "Consorzio Padova-Ricerche".

- **NATIONAL SCIENTIFIC QUALIFICATIONS**

2017-2028 National Scientific Qualification of Professor in Applied Biology (05/F1)
2017-2028 National Scientific Qualification of Professor in General Biochemistry (05/E1)
2017-2028 National Scientific Qualification of Associate Professor in Applied Biology (05/F1)
2017-2028 National Scientific Qualification of Associate Professor in General Biochemistry (05/E1)

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

Supervisor of 4 students at the International Graduate Program in Life and Biomolecular Sciences of the Open University (Milton Keynes, UK) at IRFMN (Manuela Basso, Tania Massignan, Silvia Pozzi, Eliana Lauranzano). Supervisor of 2 students at the Advanced School in Applied Pharmacology program, IRFMN (Laura Pasetto, Saioa Elezgarai). Supervisor of 3 students at the II Grade Master in Drug Design and Development, University of Pavia, Italy (Valeria Giannone, Lorena Cucci, Serena Pantalone). Supervisor of 1 student at the PhD program in Pharmacological Sciences, IRFMN (Laura Pasetto). Co-supervisor of 1 student at the PhD program in Biochemistry and Molecular Biology, University of Parma, Italy (Giovanni Nardo). Co-supervisor of 1 student at the PhD program in Medical Bioengineering and Informatics, University of Pavia, Italy (Filippo Casoni). Currently supervising 3 students at the International Graduate Program in Life and Biomolecular Sciences of the Open University (Milton Keynes, UK) at IRFMN (Ilaria Lisi, Laura Camporeale, Stefano Fabrizio Columbro)

- **TEACHING ACTIVITIES**

2016 Docent at the Master in Biosciences, "Systems Neuroscience: from Molecule to Cognition", all'École Normale Supérieure, Lyon, France.
2015 Docent at the Master in Veterinary Biotechnological Sciences, University of Milano, Italy.
2014-2018 Docent at the II Grade Master in Drug Design and Development, University of Pavia, Italy.
2007 Docent at the PhD program in Research in Bioscience, University of Padova, Italy.

- **ORGANISATION OF SCIENTIFIC MEETINGS**

2019 Organizer and Scientifc Committee Member of the “International Workshop on the Heterogeneity of Amyotrophic Lateral Sclerosis”, IRFMN IRCCS, Milano Italy.

- **REVIEWING ACTIVITIES**

Grant reviewer for: the MND Scotland Foundation, UK; “L'Agence nationale de la recherché” (ANR), France; “Association pour la recherche sur la SLA” (ArSLA), France; the Estonian Research Council; the Weston Foundation, Toronto, Canada; the Motor Neuron Disease Association, UK; the Czech Science Foundation. Reviewer for the journals: Annals of Neurology, Brain, Cellular and Molecular Life Sciences, Frontiers in Molecular Neuroscience/Neuroscience/Ageing Neuroscience, Journal of Neurochemistry, Journal of Neurology, Journal of Neuroscience, Nature Reviews Neurology, Neurobiology of disease, Neurochemical International, Neuroscience, Scientific Reports, Science and Translational Medicine, Translational Neurodegeneration.
Associate Editor for Frontiers in Neuroscience

- **CAREER BREAK**

07-2010 – 12-2010 Maternity leave (5 months)

- **COMPLETE LIST OF PUBLISHED WORK**

72 peer-reviewed papers
(complete list at: https://www.scopus.com/authid/detail.uri?authorId=6701810094; H-index in November 2023: 32 according to Scopus, 3,539 citations).

Research collaborator: Tiziana Borsello

PERSONAL INFORMATION
Family Name, First Name: Borsello Tiziana
Researcher unique identifier(s): ORCID: 0000-0002-9729-7642, Researcher ID J-8232-2016, Scopus Author ID 6602373987, SciProfiles 1203353
Date of birth: 20/01/1965
Nationality: Italian

URL for website: https://www.marionegri.it/laboratories/traumatic-brain-injury-and-neuroprotection

- **EDUCATION**

1991-1994 PhD degree in Neurological Sciences, Department of Human Anatomy and Physiology, University of Turin, Italy under the supervision Prof. Ferdinando Rossi
1985-1990 B.A. Degree, Faculty of Biological Sciences, University of Turin, Italy

- **CURRENT POSITIONS**

2020-present Full Professor of Human Anatomy, Department of Pharmacological and Biomolecular Sciences (DiSFeB), University of Milan, Italy
2008-present Group Leader of Neuronal Death and Neuroprotection Unit, Mario Negri Institute for Pharmacological Research-IRCCS, Italy

- **PREVIOUS POSITIONS**

2015-2020 Associate Professor of Human Anatomy, DiSFeB, University of Milan, Italy
2003-2007 Maitre Assistant, Group Leader, Neuronal death and neuroprotection Laboratory, DBCM School of Medicine, UNIL-Lausanne-Switzerland. 1999-2003 Premier Assistant, DBCM School of Medicine, UNIL-Lausanne-Switzerland
1995-1998 Post-doc, Laboratory of Rita Levi Montalcini, CNR-Rome, Italy
1990-1994 PhD Student, University of Turin

- **FELLOWSHIPS AND AWARDS**

2005 Prize of the Pfizer Foundation: Neuroscience and Diseases Nervous System
2004 Prize of SGAHE Morphology: Swiss Society for Anatomy, Histology and Embryology, awarded alternating for either the best scientific paper in the field of morphological research Switzerland

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

2021-2023 Supervisor of Dr. C. Musi and Dr. E. Priori, University of Milan, Italy
2022-present Tutor of Giani, University of Milan, Italy
2021-2022 Supervisor of Dr. Tomaselli, University of Milan, Italy
2018-2022 Tutor of Dr. Musi, University of Milan, Italy
2019-2020 Co-tutor of dr. Iervasi, University of Genova, Italy
2017-2019 Supervisor of Dr. L. Buccarallo, University of Milan, Italy
2014-2015 Co-Tutor of Castaldo, University of Milan, Italy
2010-2013 Tutor of Sclip, Open University, UK

- **TEACHING ACTIVITIES**

2015-present Human Anatomy, Chemistry and Pharmaceutical Technologies and Pharmacy courses, University of Milan
2008-2012 Tutor of the Open University School (UK) for PhD students
2007-present Professor of the "Scuola della regione Lombardia" scholarship holder training

1999-2007 Gross anatomy of the entire human body for Medical students at the University of Lausanne under the supervision of Profs Hornung and Welker

- **ORGANISATION OF SCIENTIFIC MEETINGS**

2021 XXXII National Congress of G. Italiano per lo Studio Della Neuromorfologia (GISN), Milan, Italy
2017 Organization doctoral schools, evaluation of research "Biological Adaptation and Aging", Pierre et Marie Curie University

- **EDITORIAL ACTIVITIES**

Methods in Molecular Biology, Volume 399, 2007 Neuroprotection Methods and Protocols Editors: T. Borsello published by Humana Press, USA ISBN: 978-1-58829-666-5 (Print) 978-1- 59745-504-6 (Online)
Editor of the Special Issue "Role of c-Jun N-terminal Kinase (JNK) Signaling in Biological Diseases" of the Board of MAPK kinase new open access journal and for Himana Press, Quantum for the book "Neuroprotection methods and protocols"
Board Editor of "Molecular Neurobiology" of the International Journal of Molecular Sciences/ (IJMS, Associate Editor of the Journal of Alzheimer Diseases

- **REVIEWING ACTIVITIES**

2017-2020 Reviewer/Evaluator for the Fondation Recherche Medicale (Francia)
2007-2008 Reviewer/Evaluator for the European Commission: FP7

- **MEMBERSHIPS OF SCIENTIFIC SOCIETIES**

2020-present ORCHID, FENS and GISN
2007-present CEND
2005-present SIF and SINS

- **MAJOR COLLABORATIONS**

Prof. Garattini, Italian pharmacologist and researcher, President and founder of the Mario Negri Institute of Pharmacological Research and the actual director Giuseppe Remuzzi
Prof. Abbracchio, UniMi Pro-Rector, biochemical effect of drugs at the cellular level
Prof. Maggi, UniMi past pro-Rector of the innovation
Prof. Di Luca director of the DiSFeB Unimi
Prof. Mariani, Director of the Institut de la Longévité Charles Foix
Dr. Mayer, Extensive industry experience from biotech and medical technology to electronics and IT
Dr. Ravagnan, Physic CEO and co-founder at WISE Srl
Prof. Zetterberg, Sweden
Prof. Stitt, Belfast, North Ireland
Dr. Bonny, ENTEROME Paris, France
Prof. R.J. Davis, Massachusetts, USA
Prof. Rainero, Head of the Memory Molinette Turin, Italy
Prof. Vercelli, Vice Rector of Unito, Italy
Prof. Courtney, Turku, Finland
Prof. Stitt, Belfast, North Ireland
Prof R.J. Davis, Massachusetts, USA

- **COMPLETE LIST OF PUBLISHED WORK**

84 peer reviewed papers (complete list at: https://www.scopus.com/authid/detail.uri?authorId=6602373987)
h-index = 30, SCOPUS, total number of citations: 4168

Research collaborator: Pischiutta Francesca

PERSONAL INFORMATION

Family name, First name: Pischiutta, Francesca
Researcher unique identifier(s): ORCID: 0000-0002-7151-0812, Scopus ID: 54934430300
Date of birth: 12/05/1984
Nationality: Italian
URL for web site: https://www.marionegri.it/laboratories/traumatic-brain-injury-and-neuroprotection

- **EDUCATION**

2011-2014 PhD in Translational and Molecular Medicine, University of Milan-Bicocca. Supervisor: Dr. Elisa R Zanier
2006-2010 Master's Degree in Medical Biotechnology, University of Milan-Bicocca
2003-2006 Bachelor Degree in Biotechnology, University of Milan-Bicocca

- **CURRENT POSITION(S)**

2023-present Head of the Unit of Cell Therapy, Lab. of Traumatic Brain Injury and Neuroprotection, Dept of Acute Brain and Cardiovascular Injury, Mario Negri Institute for Pharmacological Research (IRFMN), Milan, Italy

- **PREVIOUS POSITIONS**

01-06/2023 Researcher (permanent position) at Lab. of Traumatic Brain Injury and Neuroprotection, Dept of Acute Brain Injury, IRFMN, Milan, Italy
2019-2022 Junior researcher at Lab. of Acute Brain Injury and Therapeutic Strategies, Dept of Neuroscience IRFMN, Milan, Italy
2016-2019 Post Doc at Lab. of Acute Brain Injury and Therapeutic Strategies, Dept of Neuroscience IRFMN, Milan, Italy
2014-2016 Post Doc at Unit of Cell Therapy and Therapeutic Strategies, Dept of Neuroscience IRFMN, Milan, Italy
2011-2014 PhD student at Lab. of Inflammation and Nervous System Diseases, Dept of Neuroscience IRFMN, Milan, Italy

- **FELLOWSHIPS AND AWARDS**

2023 InTBIR Travel Scholarship recipient for the InTBIR General Assembly meeting (Bethesda, Maryland, USA, January 2024); NINDS-NIH funded
2017 Visiting Scientist at Department of Electronic and Electrical Engineering, University of Strathclyde, Glasgow, (UK)
2016 Fondazione Umberto Veronesi: Post-doctoral Fellowship
2015 Società Italiana di Farmacologia: Post-doctoral Fellowship
2015 Visiting Scientist at Department of Neuropathology, University of Glasgow (UK)
2014 International Brain Research Organization: InEurope Short Stay Program
2014 International Neurotrauma Society: Young Investigator award
2013 Forum of Italian Researchers on MSC: Young Investigator award
2012 Women in Neurotrauma Research Visiting International Scholar Award
2012 Visiting scientist at Brain Injury Research Center, University of California, Los Angeles (USA)
2012 Convegno Monotematico SIF: Best oral presentation

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

2023-206 Supervisor of 1 PhD student (Corso di Dottorato in Farmacologia Clinica e Sperimentale – MUR)

2022-2023 Co-supervisor of 1 Master Student (Master Degree in "Medical and Pharmaceutical Biotecnologies", University of Pavia)
2020-2023 Co-supervisor of 1 PhD student (PhD in "Translational and Molecular Medicine (DIMET)", University of Milan-Bicocca)

- **REVIEWING ACTIVITIES**

2019-2023 Reviewer for the following Scientific Journals: Biofactors, Intensive Care Medicine Experimental, Neurotherapeutics, Scientific Reports, Stem Cells and Development, Frontiers in Neurology, Multiple Sclerosis and Related Disorders, ACS Omega, Neurochemical Research

- **MEMBERSHIPS OF SCIENTIFIC SOCIETIES**

2022-present Member of European Neurotrauma Organization (ENO)
2014-2017 Member of the Società Italiana di Farmacologia (SIF)
2012-2015 Member of Neurotrauma Society

- **CAREER BREAKS**

10-2017 – 04-2018 Maternity leave (7 months)

- **COMPLETE LIST OF PUBLISHED WORK**

27 peer reviewed papers (complete list at: https://www.scopus.com/authid/detail.uri?authorId=54934430300)
h-index = 16, SCOPUS, total number of citations: 1166

Research collaborator: Laura Pasetto

PERSONAL INFORMATION

Family name, First name: Pasetto, Laura
Researcher unique identifier(s): ORCID: 0000-0003-0319-4448, Scopus ID: 55752441800, Research ID: I-6911-2018
Date of birth: 17/03/1985
Nationality: Italian
URL for web site: https://www.marionegri.it/laboratories/laboratory-of-translational-biomarkers

- **EDUCATION**

2015-2017 Diploma of the Advanced School in Applied Pharmacology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS (IRFMN)
Supervisor: Dr. Valentina Bonetto
2011-2014 PhD in Pharmacological Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS (IRFMN)
Supervisor: Dr. Valentina Bonetto
2008-2010 Master's Degree in Pharmacogenomics Biotechnologies, University of Milan-Bicocca
2005-2008 Bachelor Degree in Biotechnology, University of Milan-Bicocca

- **CURRENT POSITION**

2023-present Head of the Unit of Mechanisms of Proteinopathies, Lab. of Translational Biomarkers, Dept. of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS (IRFMN), Milan, Italy

- **PREVIOUS POSITIONS**

2022-2023 Researcher (permanent position) at Lab. of Translational Biomarkers, IRFMN, Milan, Italy
2018-2022 Post-Doc at Lab. of Translational Biomarkers, IRFMN, Milan, Italy
2015-2017 Student of the Advanced School in Applied Pharmacology at Lab. of Translational Biomarkers, IRFMN, Milan, Italy
2011-2014 Ph.D. student at Lab. of Translational Biomarkers, IRFMN, Milan, Italy
2008-2010 Under-graduate student at Lab. of Translational Biomarkers, IRFMN, Milan, Italy

- **FELLOWSHIPS AND AWARDS**

2022 Unione Nazionale Cavalieri d'Italia, Sezione Provinciale Varese: Premio Solidarità
2019 AriSLA annual congress: Award for the best poster
2015 PriSLA: Award for the best thesis on Amyotrophic Lateral Sclerosis

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

2023-2027 Co-supervisor of 1 student at the International Graduate Program in Life and Biomolecular Sciences of the Open University (Milton Keynes, UK) at IRFMN (Stefano Fabrizio Columbro)

- **OTHER INSTITUTIONAL ROLES**

2022-present Member of Mario Negri Animal Care Etichs Committee; IRFMN, Milan, Italy

- **REVIEWING ACTIVITIES**

2019-present Reviewer for the following Scientific Journals: Scientific Report, Journal of Neuroscience, Frontiers in Aging Neuroscience, Frontiers in Neurocognitive Aging and Behavior

2019-present Grant reviewer for: the MND Scotland Foundation, UK; "L'Agence nationale de la recherché" (ANR), France; "Association pour la recherche sur la SLA" (ArSLA), France

- **CAREER BREAKS**

08-2015 – 01-2016 Maternity leave (5 months)
07-2010 – 01-2011 Maternity leave (6 months)

- **COMPLETE LIST OF PUBLISHED WORK**

21 peer reviewed papers (complete list at: https://pubmed.ncbi.nlm.nih.gov/?term=Pasetto%20Laura)
h-index = 12, SCOPUS, total number of citations: 519

Research collaborator: Federico Moro

PERSONAL INFORMATION

Family name, First name: Federico Moro
Researcher unique identifier(s): ORCID: 0000-0002-2682-5583, Scopus: 57209041743
Date of birth: 11/01/1986
Nationality: Italy
URL for web site: https://www.marionegri.it/laboratories/traumatic-brain-injury-and-neuroprotection

- **EDUCATION**

2012-2017 PhD Course: Open University, Milton Keynes, UK, organized at the affiliate research center Mario Negri Institute for Pharmacological Research (IRFMN).
Supervisors: Dr Luigi Cervo, Prof Vincenzo Crunelli

2005-2011 Five years master's degree in Pharmaceutical chemistry and Technology. University of Milan, Italy. Supervisor: Prof Fabio Fumagalli

- **CURRENT POSITION(S)**

2023 – present Head of the Unit of Pathophysiology and Neuroimaging, Lab. of Acute Traumatic Brain Injury and Therapeutic Dept of Acute Brain and Cardiovascular Injury, IRFMN, Milan, Italy

- **PREVIOUS POSITIONS**

2020 – 2022 Junior researcher. Lab. of Acute Traumatic Brain Injury and Therapeutic Strategies, Dept. of Neuroscience, IRFMN, Milan, Italy.
2017 – 2019 Research assistant. Dept of Anesthesiology and Intensive Care, Fondazione Ca'Granda – Ospedale Maggiore Policlinico, Milan, Italy
2017 – 2019 Post-doctoral fellow. Lab. of Acute Traumatic Brain Injury and Therapeutic Strategies, Dept. of Neuroscience, IRFMN, Milan, Italy.

- **FELLOWSHIPS AND AWARDS**

2023 Junior investigator award, European Neurotrauma Organisation, Munich, Germany
2019 Best poster presentation, ERA-NET NEURON symposium, Bonn, Germany
2018 Travel grant for attending 11thFENS Forum of Neuroscience, Berlin, Germany
2017 Visiting Scientist at Lab. of Cognitive and Clinical Neuroimaging, Imperial College of London, UK
2016 Fellowship for attending FENS-SfN Summer School: Cellular mechanisms and networks in addiction, Bertinoro, Italy and for attending 10thFENS Forum of Neuroscience, Copenhagen, Denmark
2016 Travel grants for attending 10thFENS Forum of Neuroscience, Copenhagen, Denmark
2016 Best oral presentation at 3rd PhD student meeting, IRFMN, Milan Italy
2015 Travel grants for attending NEURONUS IBRO & IRUN Neuroscience Forum, Krakow, Poland.
2012 Fellowship for attending 2nd neurobiology summer school "The Invertebrate Brain: from Neurons to Behavior", Trieste, Italy

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

2023 – present Co-supervisor of 1 PhD Student (Open University, Milton Keynes, UK)

ORGANISATION OF SCIENTIFIC MEETINGS

2015 PhD student meeting, IRFMN, Milan, Italy

- **REVIEWING ACTIVITIES**

2021-2023 Reviewer for the following Scientific Journals: Intensive Care Medicine Experimental, Frontiers in Neurology.
2017 Addiction biology

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

2023-present Member of International Initiative for Traumatic Brain Injury Research (InTBIR)
2022-present Member of European Neurotrauma Organization (ENO)
2012-2016 Member of the Società Italiana di Farmacologia (SIF)

- **COMPLETE LIST OF PUBLISHED WORK**

27 peer reviewed papers (complete list at: https://www.ncbi.nlm.nih.gov/myncbi/1BUWvL-rMWfkfe/bibliography/public/)
h-index = 9, SCOPUS, total number of citations: 280

Research collaborator: Giovanni Nattino

PERSONAL INFORMATION

Family name, First name: Nattino, Giovanni
Researcher unique identifier(s): ORCID: 0000-0002-3034-6251, Scopus ID: 56020115800
Date of birth: 26/12/1987
Nationality: Italian
URL for web site: https://www.marionegri.it/personale/giovanni-nattino

- **EDUCATION**

2019 PhD in Biostatistics
Division of Biostatistics, College of Public Health, The Ohio State University, USA
Name of PhD Supervisors: Stanley Lemeshow and Bo Lu

2011 Master of Science in Applied Mathematics
Università degli Studi di Milano, Italy

- **CURRENT POSITION(S)**

2022 – Today Head, Unit of Causal Inference in Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy

- **PREVIOUS POSITIONS**

2019 – 2021 Researcher (permanent position), Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy

2016 – 2019 Graduate Research Associate, Ohio Colleges of Medicine Government Resource Center and College of Public Health, The Ohio State University, USA

2011 – 2015 Statistician, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy

- **FELLOWSHIPS AND AWARDS**

2023 InTBIR Travel Scholarship recipient for the InTBIR General Assembly meeting (Bethesda, Maryland, USA, January 2024); NINDS-NIH funded

2019 Student Travel Award, Biometrics Section, Joint Statistical Meetings, USA

2019 Distinguished Student Paper Award, International Biometric Society Eastern North American Region (ENAR), USA

2018 Student Travel Award, Survey Research Methods Section, Joint Statistical Meetings, USA

2018 Student Travel Award, International Conference on Health Policy Statistics, USA

2017 Lemeshow Travel Award, College of Public Health, The Ohio State University, USA

2015 – 2016 University Fellowship, Graduate School, The Ohio State University USA

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

2023 – today Supervisor of 1 PhD student in the International Graduate Program in Life and Biomolecular Sciences of the Open University (Milton Keynes, UK) at the Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy

2021 – 2022 Co-supervisor of 2 MD students at the Faculty of Medicine, Università degli Studi di Milano, Italy

- **ORGANISATION OF SCIENTIFIC MEETINGS**

2023 Organizer of the session: "Real World Evidence to drive clinical and regulatory decision-making: challenges and solutions" at the IBIG Forum, 9-11 October 2023, Milan, Italy.

- **REVIEWING ACTIVITIES**

Reviewer for the following scientific journals: BMC Medical Research Methodology, BMJ Open, Cancer Medicine, Clinical Sarcoma Research, Frontiers in Cardiovascular Medicine, Internal and Emergency Medicine, JAMA Network Open, Journal of the American Statistical Association, Journal of Biomedical and Health Informatics, Journal of the Royal Statistical Society, Journal of Critical Care, Statistics in Medicine

- **MEMBERSHIPS OF SCIENTIFIC SOCIETIES**

2023 – Today Italian Biostatistics Group, Italian Society of Pharmaceutical Medicine

- **COMPLETE LIST OF PUBLISHED WORK**

36 peer reviewed papers (complete list at: https://pubmed.ncbi.nlm.nih.gov/?term=Nattino+Giovanni)
h-index = 9, SCOPUS, total number of citations: 551

ALLEGATO C

TABELLA COSTI PERSONALE STANDARD

FASCIA DI COSTO /LIVELLO	NUMERO SOGGETTI	COSTO ORARIO vedi nota	MONTE ORE	COSTO DEL PERSONALE
Basso	**3**	27 €	1548	41,796 €
Medio	**1**	43 €	172	7,396 €
Alto	**0**	75 €	0	- €
TOTALI	**4**		**1720**	**49,192 €**

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
	49,192.00 €	7,378.80 €	0.00 €	0.00 €	70,929.20 €	22,500.00 €	150,000.00 €