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

Annex 1 - Project proposal

Extended Partnership

Nr.	Legal names	Short names	Type of Institution
1	Università degli Studi di Genova – **Spoke 6**	UNIGE	University
2	Università degli Studi di Pavia	UNIPV	University
3	Università degli Studi di Verona – **Spoke 7**	UNIVR	University
4	Università degli Studi di Ferrara – **Spoke 5**	UNIFE	University
5	Alma Mater Studiorum - Università di Bologna – **Spoke 4**	UNIBO	University
6	Università degli Studi di Roma Torvergata	UNITOV	University
7	Università degli Studi di Napoli – Federico II – **Spoke 3**	UNINA	University
8	Università degli Studi della Campania "Luigi Vanvitelli" – **Spoke 2**	UNICAMPANIA	University
9	Università degli Studi "Magna Græcia" di Catanzaro	UNICZ	University
10	Università degli Studi di Bari - Aldo Moro	UNIBA	University
11	Università degli Studi di Parma – **Spoke 1**	UNIPR	University
12	Università degli Studi di Firenze	UNIFI	University
13	IRCCS Ospedale Policlinico San Martino	HSM	Hospital
14	IRCCS Istituto delle Scienze Neurologiche di Bologna	ISNB	Hospital
15	Scuola Superiore Sant'Anna di PISA	SSSA	Hospital
16	Ospedale Pediatrico Bambino Gesù	OPBG	Hospital
17	European Brain Research Institute Rita Levi-Montalcini	EBRI	Foundation
18	IRCCS SYNLAB SDN	SYNLAB	Hospital
19	Fondazione Telethon ETS	TIGEM	Foundation
20	Fondazione Don Carlo Gnocchi ONLUS-IRCCS	FDG	Hospital
21	IRCCS San Raffaele	SR	Hospital
22	Dompè Farmaceutici	DOMPE'	Company
23	Alfasigma	ALFASIGMA	Company
24	ASG superconductors	ASG	Company
25	TAKIS Srl	TAKIS	Company

Table A1: List of partners

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A. SCIENTIFIC QUALITY

A.1. Consistency and clearness of the objectives and activities planned in the program and relationship with the objectives and priorities of the NRP (National Research Plan)

The last decades have seen an explosion of neuroscience research and of the understanding of the nervous system functioning in health and disease. Despite the recent advances, however, we currently **lack a clear understanding of a number of key processes underlying nervous system functions** and **available clinical and instrumental measurements are able to capture only partially the underlying physio-pathological mechanisms**, thus leading to a significant difficulty in the care of subjects with nervous system disorders. As delineated in the Italian National Research Plan (NRP) **an unmet need in biomedical research in general, and in neuroscience in particular, is the lack of integration between research approaches with different experimental focuses such as molecular, clinical and computational neuroscience, also due to the different core competencies and professional figures involved in these areas of research**. Moreover, basic research in these areas tends to focus on disease categories based on the main driver of the pathologic process (e.g. neurodegenerative diseases, neuroinflammatory disorders etc.). However, **similar patho-physiological drivers are likely to occur in different complex and heterogeneous illnesses of the nervous system resulting in diverse clinical phenotypes due to the concurrence of other intrinsic (developmental, genetic/molecular) and extrinsic (environmental, social) factors and co-morbidities**.
In this program we decided to focus on a small number of key topics, highly relevant for the understating of the nervous system functions in health and disease, with the objective of identifying major pathological drivers of different conditions, allowing: 1) the **assessment of biomarkers to identify patients at preclinical or early stage of disease**, allowing to set-up **individualized and preventive strategies** for improving prognosis and patient's quality of life; 2) the identification of **new cellular and molecular targets for the development of innovative neuropharmacological tools**; 3) the set-up of **biology-inspired digital twins**, driven by multi-modal data and relying on intrinsically multi-scale computational techniques. A medium-long term goal may lead to genomically informed and individualized treatments, based on the patient's own genetics, biological profile, environment and habits.
For this purpose, we **will use a multi-disciplinary and multi-scale approach, starting from the molecular level and reaching the population level, taking advantage of cutting-edge technologies and complementary multidisciplinary expertise**. Overall, the project is structured around a simple matrix (see Fig. A1), in which each horizontal line represents a key theme of the project (i.e. a spoke), while each vertical line represents a different experimental approach (i.e. different scales to study the key themes of the spoke).

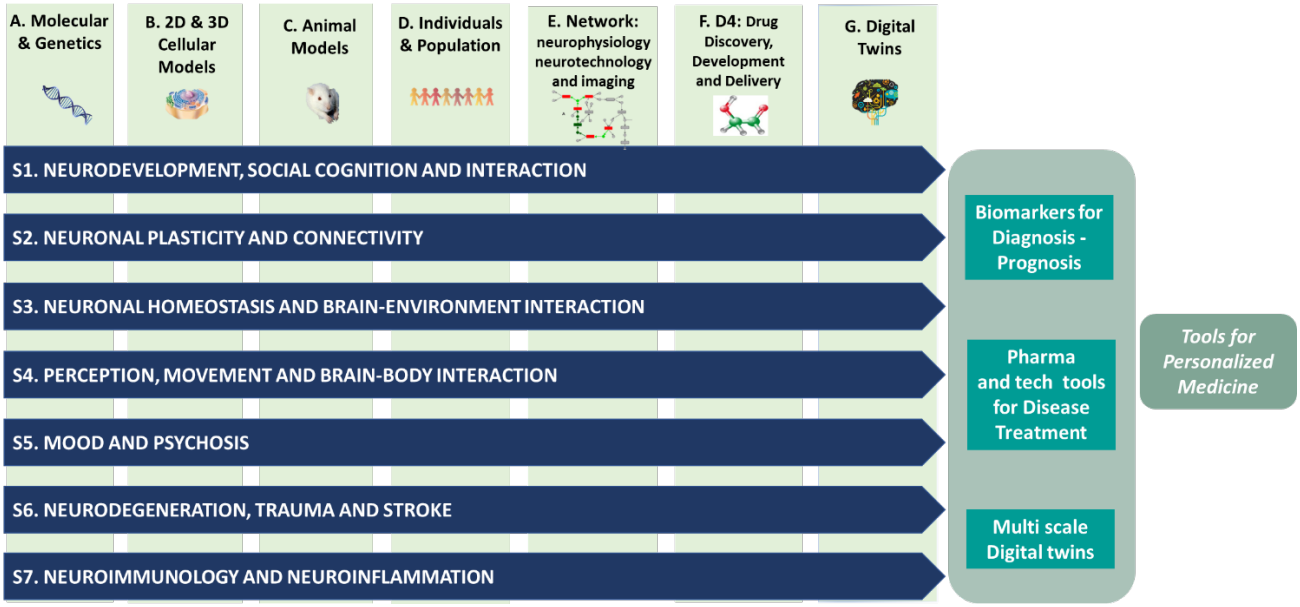

Fig. A1. The project matrix. Each horizontal line represents a Spoke and each vertical line represent a different experimental lens-scale. On the right are represented the main project outputs, that altogether will contribute to the application of personalized medicine in neuropsychiatric conditions.

The key topics representing the spokes and the different experimental scales have been selected according to the overall objectives and the desired effects of the NRP, such as: the characterization of the neurocognitive and physio-pathological mechanisms of neurological and psychiatric disorders and of the influences of biological and environmental risk factors on these conditions; the development of novel approaches and predictive biomarkers to help disease prevention and in the diagnosis, follow-up and care of patients with nervous system disorders; a better characterization of physio-pathological biological pathways (e.g. neurodevelopment, neurodegeneration, inflammation) and environmental cues (brain-body-environment interactions) driving disorders of the nervous system with diverse etiology to help in the stratification of patients for a better identification of therapeutic strategies; artificial intelligence and machine learning techniques to improve our understanding of neural diseases with the introduction of new technologies to boost the translational research. More in detail, the spokes and their overall aims are as follow:

S1. NEURODEVELOPMENT, SOCIAL COGNITION AND INTERACTION: S1 aims to tackle the major gaps of knowledge in neurodevelopment using a lifespan perspective, from preconception to childhood and adulthood, leveraging on cutting-edge technologies, animal models, and state-of-the-art modeling approaches. The activities of S1 will allow to respond to key **unmet needs** reported in the **NRP** such as the **clarification of the neural bases of cognitive development in health and disease including also the interaction between neural development and the environment; the development of novel biomarkers for disease monitoring and for deep phenotyping of complex pathologies** such as epilepsy and autism; the understanding **of key determinants of mental health** such as social cognition. These advancements will be instrumental to reach the "Destination 1" (Staying healthy in a rapidly changing society). and "Destination 3" (Tackling diseases and reducing disease burden) of the "cluster health" of the Horizon Europe 2021-2022 work plan (HE21-22).

S2. NEURONAL PLASTICITY AND CONNECTIVITY: S2 aims to understand the physiological bases of neural plasticity and connectivity at multiple scales, both to improve our understanding of the neural physiology and to develop novel biomarkers to track neural changes over time in pathological conditions. The activities of S2 are highly interdisciplinary and are full in line with the objectives reported in the **NRP of developing novel biomarkers for disease monitoring** (for example regarding the identification of markers associated with brain aging in health and disease), **understanding the impact of the environment on neural function** (and more in detail on neural connectivity) and **developing artificial intelligence and modelling approaches to better understand brain functions**. The results of S2 activities will be instrumental in reaching the "Destination 1" (Staying healthy in a rapidly changing society) and "Destination 5" (Unlocking the potentials of novel technologies), of the HE21-22 work plan.

S3. NEURONAL HOMEOSTASIS AND BRAIN-ENVIRONMENT INTERACTION: S3 aims to understand the regulatory mechanisms contributing to fundamental homeostatic responses in the brain, to identify **how maladaptive responses trigger or maintain brain disease states, and to develop innovative neuropharmacological tools to counteract disease-causing dis-homeostatic responses**. The activities of S3, based on cutting edge technological approaches, are highly interdisciplinary and will allow to reach the neuroscience objectives reported in the **NRP such as the understanding of the impact of the internal and external environment on nervous system function, the development of molecular biomarkers to improve our diagnostic, prognostic and therapeutic capabilities and the triggering factors** of neuro-psychiatric conditions. These advancements will be instrumental to reach the "Destination 1" (Staying healthy in a rapidly changing society). and "Destination 3" (Tackling diseases and reducing disease burden) of HE21-22 work plan.

S4. PERCEPTION AND BRAIN-BODY INTERACTION: S4 aims to develop an integrated approach to identify the biological and functional signatures of complex functions and brain-body reciprocal interactions, determinants, and biomarkers of physiology to pathology transition. The activities of S4 are highly holistic and based on cutting edge technological approaches and are in line with the objectives of the NRP related to the **development of computational and artificial intelligence approaches to understand nervous system disorders and the development of novel, integrated biomarkers to capture the heterogeneity of neurological and psychiatric conditions. These activities will promote personalized medicined approaches and identification of novel druggable targets**. The results of S4 activities will be instrumental in reaching the "Destination 3" (Tackling diseases and reducing disease burden) and "Destination 5" (Unlocking the potentials of novel technologies), HE21-22 work plan.

S5. MOOD AND PSYCHOSIS: S5 aims to collect research evidence from genetics, cellular models and advanced brain imaging which can contribute to the incremental effort to elucidate the etiopathogenetic

foundations of mood and psychotic disorders and their underling basic functions; to identify biological markers of subtypes of these disorders; to advance pharmacogenomic testing; and to foster the development or repurposing of innovative drugs. The interdisciplinary and holistic approach of this spoke will allow to reach **a key objective of the NRP, i.e. to reduce the burden of mental disorders combining approaches from molecular, cellular and clinical neuroscience working together with patients' associations**. Moreover, the research activities of this spoke will allow to develop novel biomarkers to capture the heterogeneity of mental disorders and to identify novel druggable target to reduce the burden on these highly prevalent conditions. These advancements will be instrumental to reach the "Destination 1" (Staying healthy in a rapidly changing society). and "Destination 3" (Tackling diseases and reducing disease burden) HE21-22 work plan.

S6. NEURODEGENERATION, TRAUMA AND STROKE: S6 aims to integrate multiple experimental methodologies to capture the neural bases of neurodegeneration and stroke as well as the interaction between trauma and brain function in order to shed light on the underlining processes and foster the development of novel biomarkers and therapeutic targets. The interaction between basic and clinical neuroscientists represents a key feature of this spoke and it will allow to reach **multiple objectives of the NRP including the understanding of the molecular pathways leading to neurodegeneration, the development of biomarkers of disease heterogeneity and of treatment response and novel druggable targets to reduce the disability burden** associated with these processes and conditions. These advancements will be instrumental to reach the "Destination 1" (Staying healthy in a rapidly changing society) and "Destination 3" (Tackling diseases and reducing disease burden) HE21-22 work plan.

S7. NEUROIMMUNOLOGY AND NEUROINFLAMMATION: S7 proposes a highly integrated cellular and molecular multiomics platform to tackle immune mechanisms and neuroinflammation in nervous system diseases and to understand the interactions between the nervous and the immunological system. The interaction between basic and clinical neuroscientists and a holistic approach represents the key feature of this spoke in line with the NRP. The activities of S7 will allow **to understand multiple molecular and cellular pathways at the interface between inflammation, immune response and neural function, to develop novel biomarkers to diagnose and follow over time patients with neurological conditions driven by inflammation and to identify novel targets to reduce the disability burden** associated with neuroinflammatory diseases. These advancements will be instrumental to reach the "Destination 1" (Staying healthy in a rapidly changing society). and "Destination 3" (Tackling diseases and reducing disease burden) of the HE21-22 work plan.

A.1.1 Interactions between spokes relevant to NRP Priorities

Beyond the spoke-specific goals, MNESYS proposes a multi-level integration of research themes and results to reach the objectives of the NRP. Indeed, all spokes individually, and through their interaction, contribute through a **concerted effort to develop novel biomarkers to allow early diagnosis, precise prognosis, and personalized therapies**. Moreover, the overall structure of **the project is intrinsically geared to a multi-disciplinary and inter-disciplinary approach thus allowing to integrate experimental approaches based on molecular and cellular neuroscience with those characteristics of computational neuroscience and of artificial intelligence**. Moreover, in line with the NRP, activities in multiple spokes are focused on the unravelling of the brain-environment interaction using molecular, imaging and modelling approaches. Lastly, a key interest of multiple spokes is represented by the characterization of mental, neurodegenerative and neuroinflammatory conditions with the overarching aim to recognize the intrinsic heterogeneity of nervous system pathologies, fostering cross-talk between basic and clinical neuroscientists, policy makers, industrial partners and patient associations.

A.2. Previous experiences, scientific and design skills concerning the specialization area of the extended partnership, in terms of innovation and technology transfer

Related to the creation of partnerships for research results exploitation, the partners are engaged with several **public initiatives**: two Universities included in the Extended Partnership (UNIGE and UNIPV) collaborate with Netval Research Universities Network, a consortium of Italian universities and institutions for Research Enhancement, cooperation and exchange of information on technology transfer and research policies; UNIGE also collaborates with ASTP-Proton, a European network of TT offices - public research bodies and universities; UNIPV is one of the founders of the technology transfer Foundation University 4 Innovation (U4I); UNIFE

houses the Technopole of Ferrara, participant of the High Technology Network laboratories and centres, where the access to innovation and to new technologies is favored and developed by the Emilia-Romagna public research system; UNIBO created the Industrial Research dedicated Interdepartmental Centers (CIRI) which manages and offers pre-competitive research, applied research, technology transfer and industrial development; UNINA is partner of RoboIT, the first national pole for technology transfer in the field of robotics; UNICAMPANIA participates to 7 international Networks and Joint Undertaking and to 7 Knowledge Innovation Communities; SSSA and FDG founded ARTES 4.0, one of the most important competence center in Italy, to provide partners and industry with dedicated technologies and services through innovation projects, industrial research and experimental development, with the aim to allow enabling technologies adoption in the framework of Health and Smart Hospitals innovation actions; SYNLAB is member of the European Institute for Innovation and Technology (EIT) - KIC Innostar as Italian node for "Healthy living and active aging" and collaborates with the Italian Institute of Technology (IIT) for the development of innovative contrast agents for multimodal imaging procedures; ALFASIGMA is engaged into a program of digital transformation that include Big Data and AI analytics for microbiome-related precision medicine approaches.

In addition, some partners have active **collaborations with private entities** to foster the translation of research into meaningful market applications: UNICAMPANIA and UNIGE have established a research cooperation initiative with General Electric Healthcare (USA) to facilitate technology transfer in the field of MRI applications to neuroscience; UNICZ is partner of the Biotecnomed consortium, managing body of the District for Health and Life Technologies in Calabria, with more than 70 companies operating in the field of biosciences and biotechnologies; HSM has several partnerships with private companies to facilitate research exploitation, including Bio4Dreams, Tib-Molbiol, Active Cells Srl and 3Brain; FDG developed a strong network of collaborations with national and international companies both in the life-science and pharma fields and in enabling technologies field.

All universities, and some of the IRCCS involved, have an **office dedicated to technology transfer** which offers assistance in patent applications, in setting up and developing spin-off companies, and setting up in TT projects. Moreover, they **support researchers in bringing their innovations to the market**: the Liaison Office of UNIVR periodically updates the data sheets of its patents within the Knowledge Share website, dedicated to the enhancement of the results of the research generated on the national territory; UNIFE has an incubator that provides logistic services to startup companies; HSM has legal resources expert in intellectual property rights.

All partners have **developed in total hundreds of patents on the results of their research** in areas highly pertinent to the PE12 Specialization Area and many of them **have founded spin-offs** focused on areas directly linked with the research themes proposed in MNESYS (e.g. neuroscience, next-generation sequencing, pre-clinical/clinical and pharmaceutical research and development). UNIGE promotes the creation of start-ups with two annual competitions and improves TRL through proof-of-concept programs. Moreover, it founded 3 spin-offs focused on neuroscience; UNIFE created 28 academic spin-off companies which operate in the fields of pre-clinical/clinical and pharmaceutical research, biotechnology, biology, genetics and chemistry; UNINA founded 81 operative spin-offs of which several revolve around next-generation sequencing and other omic technologies, and pharmaceutical development. Moreover, UNINA published several patents related to innovative diagnostic or therapeutic tools for neurological disorders; UNICZ founded the spin-off Medifarmagen and developed many patents on neuroscience and neuropharmacology; among UNIBA professors involved in the project there are founders of a SME (BioForDrug), focused on development of PET radiotracers for neurodegenerative diseases, and a spin-off (BROWSer srl), which provides bioinformatics analysis services applied to biological data in clinical neuroscience; in UNIPR several patents on endocannabinoid modulators have been licensed for drug development; UNIFI founded the spin-off FloNext, focused on the development of pharmacological strategies for therapeutic targets in glial cells, and established the Joint laboratory MIA-LAB "Microbiome-Immunity Axis research for a Circular Health"; HSM founded 3 spin-offs focused on neuroscience and neuropharmacology; the BioRobotics Institute of SSSA created the company IUVO, then acquired by Stellantis (via COMAU) and Ossur (leader in prosthetic development); FDG has 2 patent applications regarding technologies useful to innovate neurorehabilitation; SR established the spin-off Neuroconnect which operates in the area of brain connectivity and registered at worldwide level a patent in personalized training programs with the use of IA; ASG developed the MROpen MRI system which is being commercialized in the whole world. The CNR Spin-Off company Columbus Superconductors (now incorporated in ASG) is a successful example coming from the research collaboration with ASG Superconductors SPA for the production and commercialization of innovative MgB2 superconducting wires that are used in the system.

A.3. Previous experience of individual Spoke and affiliated entities in the management and implementation of projects with particular reference to the area of the partnership

All the participants in the MNESYS project have a great ability in the management and implementation of research projects in line with the topics of the call. Taken together, all the participants in the last ten years have obtained a considerable number of projects both as participants and as coordinators. All the spokes are represented by universities that have a primary role in the implementation of research projects in neuroscience and neuropharmacology, often as coordinators of national and international consortia. Projects managed directly by the spokes include research and development projects supported by National funding agencies (e.g. Ministry of University and Research, Ministry of Health, Regional bodies), the European Commission (including Collaborative project, Marie Skłodowska-Curie and ERCs grants), and other international governmental bodies (e.g. National Institutes of Health -USA). Several grants are also funded by international and national foundations (e.g. CARIPLO, Cariverona, Telethon, AIRC, ARISLA, Italian Multiple Sclerosis Association, Cure Alzheimer's Fund USA, Alzheimer's Disease Drug Foundation -ADDF, UK Alzheimer's Association, Armenise-Harvard Foundation, etc.) and international and national patients' advocacy groups. UNIBO is member of several European networks active in the domain, such as European Health Telematics Association (EHTEL), European Technology Platform for Nanomedicine (ETPN), Virtual Physiological Human Institute for Integrative Biomedical Research (VPH Institute) and EU-cognition. UNIGE, with its DINOGMI Department that includes neuroscience area of specialization has well-established partnerships with HSM and with IRCCS I. G. Gaslini, a national referral center for neuropsychiatric children' disorders.
The majority of the IRCCS participating as affiliated entities are members of the Italian Neuroscience and Rehabilitation Network (Rete IRCCS delle Neuroscienze e della Neuroriabilitazione - RIN), the largest Italian research network on neurologic conditions, founded in 2017 by Italian Ministry of Health to enhance the dissemination about clinical and research activities and promote international collaborations.
EBRI and UNIPV are part of the flagship Human Brain Project (HBP), which has the ambitious goal of achieving a multi-level integrated understanding of brain's structure and function at different biological scales and the development of brain-inspired computing systems. OPBG is currently involved 3 European Reference Networks (ERN) on Rare Diseases in the topic neuroscience: ERN EPICARE, European Reference Network for Rare and Complex Epilepsies, EURO-NMD, European Reference Network for Rare Neuromuscular Diseases and ERN-RND, European Reference Network for Rare Neurological Diseases. The aim of this virtual network is to involve healthcare providers across Europe, facilitate discussion on complex or rare diseases and conditions that require highly specialized treatment, and concentrated knowledge and resources.

A.4. Previous experience in conducting research programs with an interdisciplinary, holistic and problem-solving approach

In a prescient paper appeared in 1972 in the "Archives of Neurology" Howard Barrows and Kara Bennett pointed out that for a clinical neurologist, problem-solving approaches should not be any longer a matter of "random art" but should be framed into a "rigorous discipline". Thirty years later, Rita Levi Montalcini and Pietro Calissano (one of the PIs in this project) published a paper in BMC "Neuroscience" with the visionary title "The scientific challenge of the 21st century: from a reductionist to a holistic approach via systems biology". In that work the two Italian scientists argued that the reductionistic dogma at the basis of the 20th century biology was at its end, and that holistic approaches were the best possible strategy to integrate, in a comprehensible picture, the multi-modal data that the 21st century experimental practice would produce. Finally, in October 2019 "Cell" devoted one of its "Voices" to ask several neuroscientists about their views on the advantages of forging collaborations across disciplines. All those scientists enthusiastically agreed that interdisciplinary approaches to neuroscience are "the right thing to do" for many different reasons and especially so given the intrinsic "interdisciplinary" way in which our own neural circuits work while simultaneously processing heterogeneous and complex data. MNESYS Consortium had this intellectual legacy well in mind; even more than this, we all believe that holistic thinking and interdisciplinarity are keys for re-thinking any specific research problem in terms of impacts on modern society, in accordance with the spirit of the Next Generation EU program. MNESYS was therefore

designed as a multifaceted, overarching, and problem-solving-oriented project. Particularly, we wish to underline that computational and technological aspects (e.g., computational neuroscience, advanced data analysis, artificial intelligence and machine learning methods, micro- nanotechnologies) are not developed in separates work packages but integrated within each thematic spoke with specific reference to the scientific activities. MNESYS scientific vision embraces all aspects of the investigation of the nervous system. Chronologically, it ranges from neurodevelopment (S1) to neurodegeneration (S6). Clinically, our aim is to push forward the state-of-the-art concerning the comprehension and clinical treatment of both neurological diseases and neuropsychiatric disorders (S5). Environmentally, MNESYS starts from neuron-neuron connectivity (S2) to include neuronal homeostasis (S3), through the extensive, bi-directional communication between the nervous and the immune system (S7), up to the identification of the patterns in the central nervous system that coordinate the activity between the brain and the body (S4).
In order to accomplish this holistic mission, MNESYS needs to involve all the methodological weaponry available for the 21st century neurological and neuroscientific investigation. First, in terms of data we will collect, process, and integrate an impressively heterogeneous number of omics, biochemical, physiological, imaging, psychophysical, and drug-related experimental measurements. The data analysis phase will be delegated to state-of-the-art computational techniques that rely on the most modern methodological frameworks like machine learning (including its deepest releases), inverse problems theory, numerical discretization, pattern recognition. This AI-based approach to data analysis will allow the implementation of digital analogs (i.e., digital twins) of the many Ps (i.e., Predictive, Personalized, Preventive, Participatory) approaches to clinical treatment and will impressively increase the interdisciplinary flavor of MNESYS effort. Finally, the results of the whole data processing activity will be interpreted within the frameworks of advanced systems biology and systems medicine models, which will allow the design of systemic strategies for framing the whole MNESYS scientific outcome into an organismic view of the nervous system functions.
The operational structure of MNESYS is the natural representation of this scientific and methodological vision. Indeed, our program will not produce a coarse summary of strictly disciplinary activities but will rely on an activity matrix, designed based on problem-solving approaches. In the MNESYS Hub-Spokes network each topic will be investigated at many explanatory scales (i.e. biological, clinical, and technological work packages will be included in each Spoke) through the utilization of interdisciplinary tools to integrate the knowledge generated into an holistic cultural picture.

A.5. Previous national and international collaborations with other institutions and centres of high scientific quality

Members of MNESYS are involved in important national and international research networks, such as the RIN-Network, the Cochrane Center, the European Platform for Rehabilitation (ERP), the Network Rehabilitation in Multiple Sclerosis (RIMS), the International Society for Neurovascular Disease, Italian Society of Neurology, ENIGMA Consortium, European Academy of Neurology (EAN), ERN, Fresco Parkinson Network and others.
Moreover, the partners of the consortium have also established good collaborations with national and international Pharma and Biotech companies, and strategic collaborations with ISS, CNR, ENEA, INFN, Italian Ministry of Health, European Council, Medical Research Council and others public and private institutions and fundations, to develop innovative projects in neuroscience and neuropharmacology also through the identification of new disease biomarkers. Each member of MNESYS actively participate in research projects and in the applications of Calls at a national and international level such as ERC grant network, H2020 Programmes, IMI, PRIN, Ricerca Finalizzata etc..
Furthermore, the consortium is engaged in several scientific partnerships in close collaboration with University of Oxford, University of Cambridge, Harvard Medical School-Boston, University of California, King's College of London, Yale University, Ontario University and other prestigious Academic centers in the world working on neurosciences and neurotechnologies.
The IRCCS, the Foundations, the industrial partners and the Universities that are part of MNESYS consortium play an important role in a number of collaborative research projects on the development of novel biomarkers and have leading roles in specific initiatives such as: the Alzheimer's Disease Prevision Medicine Initiative (APMI) and the Neurodegeneration Precision Medicine Initiative (NPMI).

A.6. Description of the Extended partnership participants

DESCRIPTION OF UNIGE
Università di Genova UNIGE is a public institution, one of the oldest great European universities. **UNIGE** has campuses in Genoa, Imperia, Savona and La Spezia, representing the only Public University in Liguria. It hosts 22 departments within 5 schools, 13 interuniversity research centres, 1 Centre of Excellence. Its educational offer counts 132 Bachelor and Master courses, 28 PhD courses organized in 90 curricula, 44 specialization schools, 27 I and II level Masters and 5 Libraries. Its Teaching and Learning Centre organizes and manages all the teaching innovation and faculty development activities, and the Long-life learning. Office supports and manages all postgraduates and executive learning projects, in collaboration with enterprises. Within FP6 UNIGE was awarded 92 projects, 115 contracts within FP7, 94 contracts within Horizon 2020 and, up to now, 3 contracts within Horizon Europe. Since 2014, UNIGE has been awarded 26 projects within other research EU Programmes. Regarding international cooperation programs, since 2000, UNIGE has had 433 projects and is currently involved in 81 projects. The main ones are ERDF Interreg Programs (146 projects since 2000, 43 in 2007-2013 and 76 in 2014- 2020); Life Program (31 projects within the three last programme periods, of which 12 under LIFE+ and 9 under Life in 2014-2020) and US Research Programs (57 projects, 30 in 2014-2020). Since 2014, the Italian Ministry of Research funded 143 UNIGE projects (PRIN, FISR, SIR, etc.). At the same time private Foundations funded 50 projects. Neurosciences and neuropharmacology represent one of the key areas of interest for UNIGE, as shown by the track record of neuroscience research. Ten among the 22 Departments of UNIGE are currently involved in neuroscience and neuropharmacology research and are all included in the MNESYS project. Moreover, **both UNIGE Departments which were awarded the Italian Ministry of University and Research seal of Excellence for the 2018-2022 period (i.e. the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health and the Department of Physics) play a key role in this project**. The interest in neuroscience and neuropharmacology at the University of Genoa is widespread well beyond the classical boundaries of the Medical, Pharmacological and Biological Departments, and it is also a cornerstone of the Polytechnic Engineering School, which presents an established interest for neuro-engineering and is currently hosting a summer school in NeuroEngineering started in 2000, and of the Mathematics and Physics Departments, which present significant research lines on the analysis, modelling of molecular, imaging and neurophysiological data- The Neuroscience and Neuropharmacology community in Genoa is vibrant, as shown by the strong collaborations between UNIGE and the Ospedale Policlinico San Martino (which is recognized by the Ministry of Health as a IRCCS (Research Institute) for Neuroscience and is included in the project) and the Gaslini Institute (a world-renowned paediatric hospital and a reference center for a number of childhood neurological and psychiatric pathologies such as autism and epilepsy) as well as with the other research institutes present in the city and in the Ligurian Region, the policymakers and the patient advocacies associations, such as the Italian Multiple Sclerosis Society, which has its National Headquarters in Genoa. Thanks to the widespread interests for neuroscience and neuropharmacology in the UNIGE academic community, the aforementioned rich network of local connections and the epidemiological characteristics of the Liguria region (which is the Italian Region with the higher mean population age), UNIGE neuroscience research (as shown by the track record of its researchers) has been naturally driven to significantly impact different key facets of the Horizon Europe 2021-2022 work plan such as Destination 1" (Staying healthy in a rapidly changing society). and "Destination 3" (Tackling diseases and reducing disease burden) and Destination 5" (Unlocking the potentials of novel technologies)
A.2 SCIENTIFIC EXPERTISE
In the last five years, researchers working in the Departments with a significant interest in neuroscience (all included in the MNESYS project) published around 19.000 papers in impacted international journal and collectively collected more than 290000 citations. To date, UNIGE has 114 active patents, among those 16 are highly relevant for the neuroscience and neuropharmacology fields, including novel treatment approaches for Alzheimer 's Disease, novel neurophysiological and imaging markers for patients' stratification, novel experimental techniques relevant

to shed light on multiple cellular pathways relevant for neural cells function in health and disease, new tools for neural-interfaces and network electrophysiology.
From a technological point of view, UNIGE presents with a number of high-value, technological infrastructures able to support cutting-edge research in all fields of neuroscience, such as multiple facilities for patch clamp recording, in vivo live imaging, MEA recording, different microscopy facilities with access to confocal high resolution microscopy, two photon microscopy for in vivo imaging, TEM electro-microscopy for ultrastructural analysis, multiple clinical neurophysiology labs for high density EEG and polysomnographic studies as well as brain stimulation techniques, a lab for computerized assessment of cognitive functions and for quantitative assessment of motor performance including a virtual reality suite as well as access, together with Policlinico San Martino to a cyclotron for in house radiotracer production, two hybrid PET/CT scanners and a microPET facility for small animals preclinical imaging as well as to a 3T MRI Siemens Skyra scanner and a 7T MRI scanner for small animals. These facilities, together with a high-performance computing cluster, point to the inter-disciplinary and holistic approach of the neuroscience community of UNIGE. Lastly UNIGE has a dedicated in-house structure, the Research and Technology Transfer Valorization Office, which is tasked to provide operational support during establishment, information on funding opportunities and promotes spin-offs at events and fairs.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

The researchers included in the project have currently active 46 grants with a focus in neuroscience for a total higher than 4.500.000 euro directly managed by UNIGE. Among the projects directly managed by UNIGE, eight are supported by the Ministry of University and Research and two by the European Union, including a Marie Skłodowska-Curie Individual Fellowship (H2020-MSCA-IF-2019) and Virtual Brain Cloud (H2020-SC1-DTH-2019) (Personalized Recommendations for Neurodegenerative Disease) https://virtualbraincloud-2020.eu/tvb-cloud-main.html#. International and National patients' advocates societies (such as the US National Multiple Sclerosis Foundation and the Italian Multiple Sclerosis Foundation) significantly contributed to the active grants pointing to the good synergy between University of Genoa and the patients interest groups.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

UNIGE plays a key role in a number of national and international research networks and collaborations.
In the field of neurodegenerative conditions, UNIGE is a member of the European Alzheimer's Disease Consortium, the International Rapid eye movement (REM) sleep behavior disorder study group and the European Dementia with Lewy Bodies consortium, in all of those it currently plays a coordinator role in a number of collaborative research projects on the development of novel biomarkers. UNIGE center for Parkinson's disease and Movement Disorders is included in the Fresco Parkinson's Network that has been recognized in 2020 as a Parkinson's Network of Excellence by the Parkinson's Foundation (USA). Thanks to this achievement, UNIGE is participating to the "Parkinson's outcomes project", the largest-ever clinical study of Parkinson's disease with more than 13,000 participants in five countries.
UNIGE moreover is included in the Italian Multiple Sclerosis Registry in which coordinates a number of research projects on multiple sclerosis UNIGE has as strong collaboration with industrial partners and pharma industries with a focus on the development of novel biomarkers for diagnosis and for treatment selection for neurological and psychiatric disorders.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

UNIGE excels in science and technology with synergies with research organizations, SMEs and industries in Liguria and worldwide. To promote good practices in technology transfer, UNIGE collaborates with Netval, a network of Italian universities and institutions for Research Enhancement, and with ASTP-Proton, a European network of technology transfer offices - public research bodies and universities.
Research excellence gave rise to new technologies with 114 patents, often in co-ownership/collaboration with companies or research bodies. UNIGE promotes start-ups creation with two annual competitions and improving TRL through proof-of-concept programs. Thanks to this investment, 50 spin-offs were founded in the last few years. Among those, three spin-offs have a clear focus in neuroscience including novel pharmaceutical approaches to stroke and bioengineering.

DESCRIPTION OF UNIPV

UNIVERSITÀ DI PAVIA

The University of Pavia (UNIPV) is an Italian public university boasting a centuries-old tradition of excellence. At present, it is home to a vibrant and diverse academic community composed by more than 23'000 students (1800 international), >900 teaching staff and 273 technicians. UNIPV structure includes a central administration, 2 Faculties and 18 Departments organized according to homogeneous research sectors, aims, methodologies and teaching activities with the main goals of promoting and coordinating research activities, as well as organizing undergraduate, postgraduate and PhD courses. As a research-intensive university of high international profile, UNIPV benefits from the presence of important research infrastructures such as the Centre for Health Technologies (CHT), the National Centre for Oncologic Hadrontherapy (CNAO) and owns 6 laboratories hosting state-of-the-art equipment (Laboratory of Molecular, cellular and tissue Imaging; Laboratory of Magnetic Resonance Imaging and micro X ray tomography for small animals; Laboratory of Spectrometry NMR; Laboratory of Mass Spectrometry; Calculation Cluster; Laboratory 3DMetal@UniPV). There are three research hospitals associated with the University (I.R.C.C.S. Policlinico San Matteo, I.R.C.C.S. Mondino, IR.C.C.S. Fondazione Maugeri) that extend the biomedical applications of basic research. QS rankings: #3 in the CENSIS-Italian Universities ranking 2021/22, #11 Italy and #192 Europe ranking in the Times Higher Education-World Universities Ranking 2022.

A.2 SCIENTIFIC EXPERTISE

UNIPV hosts an active community operating in the Neuroscience and Neuropharmacology field centered on the Department of Brain and Behavioral Sciences (about 50 faculties and 10 technologists) and on the neurological institute IRCCS Mondino. Other departments (Biology and Biotechnology, Engineering) provide important contributions along with the interdepartmental Center for Health and Technology. Neuroscientific research spreads over several subfields, including cellular and integrative neurophysiology, neuropsychology and neuropathology and experimental therapeutics. The main themes currently addressed are: (1) the cellular and subcellular mechanisms of signal coding and synaptic transmission in neuronal circuits, (2) the anatomo-physiological architectures subtending sensorimotor and cognitive tasks, (3) the plastic processes subtending neurodevelopment, learning, memory and repair, (4) the neuropsychological correlates of behavior , (5) the pathophysiological mechanisms of several neurological and psychiatric disorders, including neurodegeneration and psychoses, (6) neurocomputation and brain modelling, (7) precision medicine stratification and experimental therapeutics of neurological and mental disorders, (8) deep phenotyping and digitomics, (9) artificial-intelligence based clinical prediction modelling and biomarker stratification with experimental therapeutics.. These activities are represented into 5 of the 7 spokes of the present project. The Department of Brain and Behavioral Sciences has produced a total of 2710 papers in the last 10 years. The average HI of the participants in this project is 46.4, with papers on top rank journals including Nature, Nature communications, Nature Neuroscience Review, Nature Communications Biology, Science, Neuron, Cell, TINS, TICS, World psychiatry, Lancet, Lancet Psychiatry, JAMA psychiatry, Journal of Neuroscience, Cortex, Neuroimage, Brain Structure and Function, Journal of Physiology, Psychological Sciences, Neurology, Molecular psychiatry, Schizophrenia bulletin.
The research related to this project leverages on state-of-the-art facilities for multiscale investigation of the nervous system: (A) molecular and cellular analysis (genomics, proteomics, metabolomics etc.); (B) Cellular neurophysiology (set-ups for patch-clamp, multi-photon calcium imaging, optogenetics, microendoscopic calcium imaging in vivo, high-density multielectrode arrays in vitro and in vivo); (C) System neurophysiology (EEG, EMG, polygraphy); (D) Neuroimaging (3T MRI, NIRS, high-density EEG for humans; 7T MRI and microtomography for small animals); (E) Neuromodulation (TMS, TDCI); (F) Neurocomputation (central computer cluster EOS in the Computing Center and peripheral clusters in the Neurophysiology Unit and IRCCS Mondino). The project will also benefit of a new Neuromorphic Cluster designed for multiscale brain modelling through a grant of Regione Lombardia. The facilities to develop spin-off and applications are hosted by a specific Technological Pole.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

UNIPV has >400 collaboration agreements to develop national, EU and international projects with public and private institutions, as well as partner universities throughout the world, and is member of several international networks (e.g. Coimbra, EUA and Netval). UNIPV is currently hosting several EU funded programs: 1 FLAGSHIP (Human Brain Project), 10 MSCA actions (3 ITN, 4 IF and 3 RISE), 11 ERC grants (8 Starting, 1 Consolidator and 2 Advanced), and is involved in 29 collaborative R&D projects for a total

of 26.5M€. During the last decade, UNIPV gained >120M€ total funding: 72% from public funds, 23% from private funding and 5% from public/private partnerships. Principal funding bodies are the European Commission (41%), the Italian Ministry of University and Research (17%), other Italian Ministries (MISE, MAE etc., 9%) and Regional Funding (9%). The Cariplo Foundation contributes for about 18% of the total secured funds. 723 research projects involving UNIPV have been approved in the decade 2011/2021, involving around 1.500 researchers; 45% of the approved proposals had UNIPV as lead coordinator. Highlights include the Human Brain Project (>4M€ for UNIPV), 2 ERC Advanced Grants (in the LS EU-Rhythmy), 3 Future and Emerging Technologies (FET: Silkfusion, NECTAR) projects and a Pathfinder Transition Grant (SikPlatet). With regards to "In silico Medicine", UNIPV researchers participate as Co-PIs or coordinators in several EU funded H2020 projects (i.e., PERISCOPE, PULSE, REALNET), and in actions of the Human Brain Project (EBRAINS, BRAVE). UNIPV researchers are also part of international consortia for large scale sequencing initiatives (iPsych, Lundbeck foundation). The overall scientific productivity is documented by approximately 30'000 scientific articles, 4'500 book chapters, 1'100 PhD theses, and the securing of 75 patents in the last 10 years.

The neuroscience sector is running the following main projects for an amount around 10 M€; EU Flagship Human Brain Project (D'Angelo - European deputy leader) for data-driven multiscale brain modelling; ITN project CEN (D'Angelo - European coordinator) for cerebellar network multiscale investigation and modelling; Regione Lombardia "Brain and Cancer" (Mattevi - D'Angelo) for neuroscience research infrastructures; JPND (Blandini - Europan coordinator) for studying the mechanisms of neurodegenerative diseases; COMOESTAS (Tassorelli - European coordinator) for telemedicine; ERANET (Tassorelli) to investigate the mechanisms of headache; PRIN (Borgatti, Gandini, Prestori, Vecchi) to investigate various aspects of neurophysiology, neuropsychology and neuropathology; PRONET (Fusar - Poli) to develop clinical prediction tools for emerging mental disorders, STEP (Fusar-Poli, global coordinator) to test new preventive interventions in psychosis; several donations (Politi) for the investigation of other mental conditions.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

Through its international projects, UNIPV Neuroscience takes part to an extend network of collaborations in Europe and worldwide. These include Erasmus Un. Rotterdam (NL), Un. College London (UK), Ecole Politechnique Federal de Lausanne (CH), Cajal Institute (ES), Ecole Normal Superieure (FR), Charite Berlin (DE), Un. of Julich (DE), Un. of Manchester (UK), CNRS and Un. Aix-Marseille (FR), Un. of Bonn DE), New York Un. (USA), Yale (USA), Allen Institute (USA), Un. of Jerusalem (IL), AMRITA Un. (India). Longstanding collaborations extend to industries and funders including European Commission, Wellcome Trust, National Institute of Health, Medical Research Council, European Council, ECNP.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

At the end of 2013, UNIPV has established the role of Third Mission Vice Rector, responsible for giving strategic direction and supervising all activities committed to the territory, society and industry in particular, such as technology transfer, intellectual property protection and exploitation of the research results, promotion of technological innovation produced in UNIPV, academic entrepreneurship and university spin-offs, life-long learning programs, and public engagement, such as the museum system and cultural events.

The Research and Third Mission Service supports operationally those activities. Since 2012, UNIPV has been a member of the Netval Research Universities Network, a consortium of more than 60 Italian HE institutions for cooperation and exchange of information on technology transfer and research policies.

Together with the Universities of Bergamo and Milano Bicocca, in 2018 UNIPV ha founded the technology transfer Foundation University 4 Innovation (U4I), to create critical mass and promote technology transfer for more than 2100 researchers with more than 122,000 scientific publications in the last 10 years, approximately 170 granted or published patents since 2000 and over 80 active academic spin-offs altogether.

Of special relevance for the project is the recent institution by UNIPV of the Brain Modelling Hub of EBRAINS, which allows the development of brain models, from the cellular/subcellular level up to virtual brains empowering the strategy of Digital Brain Twins. The hub is designed to offer a neurocomputational service to all interested users. This initiative wires the UNIPV into an extended European research system, bridging multiscale brain research with neurocomputation and fostering the development and application of digital neurotechnologies and biomedicine.

DESCRIPTION OF UNIVR

The University of Verona (UNIVR) is a State Higher Education institution with about 27,500 students and 1,500 teaching and administrative/technical staff. The institution was founded in the 1950s and in 1982 it was established as autonomous State University. The University of Verona is organized in 12 Departments and 3 Schools, offering a total of 69 Degree Programmes and 16 PhD Programmes (AY 2021-2022).
UNIVR hosts an Euraxess Contact Point and a Europe Direct contact point. UNIVR has recently adopted a Gender Budgeting and a Gender Equality Plan. All UNIVR gender policies and documents are available here: https://www.univr.it/it/politiche-di-genere. In the last ANVUR monitoring review of the Quality Assurance (AQ) on October 2018, UNIVR has received a B grade (fully satisfying) with final score of 7.05 points.

A.2 SCIENTIFIC EXPERTISE

The UNIVR staff has been involved in many research projects supported by the major programmes and funders (e.g. the Italian Ministry of Research and Universities and the Italian Ministry of Health, Regione Veneto, and the private funders AIRC, Intesa San Paolo and Fondazione Cariverona).
To date, the last ten years publications of UNIVR amounts to 44.178, thereof 26.893 articles, 8.518 book chapters, and 27 patents. From 2005 to today, 31 spin-offs have been established, of which 6 spin-offs in Life and Health Sciences. The research group is led by Prof. Constantin (h-index 38, 6.789 citations), who is an internationally recognized leader in neuroimmunology. Her studies are focused on the role of leukocyte trafficking in brain autoimmune and inflammatory diseases. She has contributed to the identification of key inflammation mechanisms in multiple sclerosis, epilepsy and Alzheimer's disease. Prof. Constantin's group is also active in systems biology approaches for the study of biological networks controlling T cell activation, inflammation and autoimmunity. Her projects are funded by national and international agencies including the European Research Council (ERC), the US National Multiple Sclerosis Society (NMSS), the US Alzheimer's Drug Discovery Foundation (ADDF) and, the Italian Fondazione Italiana Sclerosi Multipla (FISM). Prof. Chelazzi focuses his research on Neuroanatomy and neurophysiology, Sensory systems (e.g. visual system, auditory system) and Systems neuroscience. His main scientific interests revolve around a number of related topics, notably the neuro-cognitive mechanisms of visual perception, selective attention, learning and memory. Prof. Zanusso's research activity includes all neurodegenerative diseases due to protein misfolding. In particular, Alzheimer's disease, alpha-synucleinopathies and tauopathies. Prof. Decimo research is focused on o pharmacology and CNS regenerative medicine. Prof. Savazzi's research concerns the study of perception and awareness in healthy participants and brain-damaged patients with visual field defects or neglect. In her research, she uses several techniques: behavior, electrophysiology (EEG), neuroimaging (fNIRS) and direct brain stimulation (TMS and intraoperative electrocortical mapping). Prof. Ruggeri's current fields of interest include Early intervention (universal, selective and indicated primary prevention); staging trajectories of neurodevelopment during adolescence and young adulthood focusing on early and late onset diseases (Autism, ADHD, Mood Disorders, Psychosis) and emotional dysregulation including the impact of early trauma. Studies on the efficacy of innovative psychotherapeutic approaches. Promote actions that shed new light on the potential of primary preventive and promotion strategies for mental health of young people. She is the coordinator of the Research Unit "Clinical, Environmental and Biological Determinants of Outcome in Mental Health" at the Section of Psychiatry, Department of Department of Public Health and Community Medicine, University of Verona.
To support the researchers the University of Verona has a Research Office organized in four units:

- The Research Promotion and Development Unit, dedicated to pre-award grant phase, from idea conception to search for funding opportunities, until the proposal preparation.
- The Research Project Management Unit, dedicated to the post-award phase of funded projects, from the grant agreement until the final reporting.
- The PhD Unit, which oversees the doctoral programs of the University of Verona.
- The Liaison Office in charge of promoting IPRs and research results exploitation, guiding researchers during the creation of spin-offs as well as to enhance the cooperation with business sectors and non-academic sectors.

In addition, the Communication office oversees institutional communication and relations with the mass media by providing strategic consultancy, communication tools and services to the University structures.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

The UNIVR involvement in the EU Framework Programs has constantly improved, as shown in the table below (data are updated on December 4, 2021).

	FP7	**H2020**
Net EU Funding	20.71 million €	29.59 million €
No. of projects	59 (35.6% as coordinator)	55 (52.7% as coordinator)
ERC PIs	5	9
MSCA Actions	15	23

In the last ten years the leaders of the spokes and the affiliates of the spokes won 101 grants (almost all of them as coordinator center), of which about 40 are in progress.
In particular, Prof. Constantin won 3 ERC grants: one ERC AdG of 2,500,000€ ("IMMUNOALZHEIMER") and two ERC Proof of Concept ("IMPEDE" and "NeutrAD") for an amount of 300.000€. Prof. Zanusso won a Cariverona grant of 300.000€ for a project regarding the development and validation of a novel molecular assay for alpha-synuclein in patients with Parkinson disease and other alpha-synucleinopathies and a MJF Foundation grant of 367.000€ with a project entitled "Multicentre assessment of nasal swabbing approach: α-syn RT-QuIC assay diagnostic performance in olfactory mucosa and cerebrospinal fluid in patients with prodromal PD, PD or PD with neurocognitive impairment". Prof. Chelazzi has won several grants including a PRIN grant of 188.417€ as leader of a project titled "The Good and the Bad of Sensory Experience: Understanding the Impact of Emotionally charged Stimuli on Cognition and Behavior, and the Brain's Mechanisms to Cope with Them". He also won a Cariverona grant of 325.000 whit a project entitled "How the Brain deals with Emotional Stimuli" and a JPI - Eranet FLAG-ERA II of 141.700€ for the MAC-Brain project. His scientific profile pertains to integrative neurophysiology and cognitive neuroscience. Prof. Decimo won several grants including an EIC H2020 project (HERMES), led by Prof. Decimo, consisting of 12 partners for a total amount of 8.4 million euro (750.000 € for UNIVR). And others (FISM and Telethon) for projects regarding the "Targeting mitochondrial metabolism to promote full neural development in Allan Herndon Dudley syndrome" and "The role of meningeal neural progenitor cells in brain auto-reactive immune cell regulation". Furthermore, the Prof. Decimo team is partner of CureMILS-Project (EJPRD) which has a total budget of 2.360.688€. Prof. Savazzi won grants from MUR (DM737; Prin2015: 105.000€; Prin2017: 255.655€) and Cariverona Foundation (198.000€) for basic research on neural networks of visual awareness and other grants (NeuroTaxi: 149.615€, NeuroHelmet: 155.555€) for precompetitive research on neuro-navigation and 3D modelling of imaging data. Prof.Ruggeri conducted several research projects in the fields of Neurobiology, Clinical Psychopharmacology and Liaison Psychiatry. Her team is actually involved in H2020 projects (RESPOND and RE-DEFINE EUROPE) and in a project funded by AIFA (VESPA).

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

All UNIVR staff involved in this project has relevant connections with universities and research organizations in the world. In the last 10 years, UNIVR has invested more than 1.8 million € to finance over 250 incoming mobilities for Visiting Professors and Visiting Researchers and over 180 outgoing mobilities for UNIVR academic staff. UNIVR currently collaborates on neuroscience projects with several Universities, including University of Adelaide, Universidade de Brasília, University of Western Ontario, Ospedale Pediatrico Bambino Gesú, Centre Hospitalier Universitaire De Grenoble; Glasgow University, University of Haifa, (Israel), University Carl von Ossietzky Oldenburg, Velux Stiftung and University of Technology Sydney.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

From 2005 to today, n. 31 spin-offs have been established and there are 27 patent families owned by the UNIVR. As regards the enhancement of these patents, the Liaison Office periodically updates the data sheets of these technologies within the Knowledge Share website, a platform dedicated to the enhancement of the results of the research generated by universities, IRCCS and EPR on the national territory, with the aim of making the contents of patents easily usable, to convey in a clear and simple way the advantages that technologies can bring within the sectors of reference and put in contact the world of business, investors and innovators with researchers.

DESCRIPTION OF UNIFE

Università degli Studi di Ferrara

The University of Ferrara (UNIFE), founded in 1391, is one of the oldest in Italy. It consists of 13 Departments, including Neuroscience and Rehabilitation, Translational Medicine, Medical Sciences, and Life Sciences and Biotechnology ones. UNIFE enrolls more than 25.000 students, 695 Master students, 428 PhD students (including PhD Courses in Translational Neuroscience and Neurotechnology, Molecular Medicine and Advanced Therapies and Experimental Pharmacology) 701 permanent academic staff, 490 administrative and technology staff. UNIFE has been awarded with two UNESCO Chairs: "Urban and Regional Planning for Sustainable Local Development" and "Education, Growth and Equality". UNIFE's mission is to carry out research and educational programs, developing links with the surrounding area while respecting the environment, with the aim of creating, enriching and, at the same time, offering a scientific, cultural heritage to students, enterprises, institutions and in general to the whole community. UNIFE is a member of several International Networks, among which the ECSEL-ARTEMIS Industry Association and BBI Bio-Based Industries, UNIADRION, and EFSA – European Food Safety Authority.

A.2 SCIENTIFIC EXPERTISE

UNIFE enrolls 701 investigators as permanent academic staff involved in applied and/or basic research. In the last 10 years UNIFE's researchers published 23,349 scientific articles, 4,519 book chapters and obtained 126 patents. About 60 researchers with permanent position, 15 with non-permanent position and 29 PhD students focus on Neuroscience and Neuropharmacology research and will be directly or indirectly involved in the project. In the last 10 years, the researchers involved in the project published a total of about 1,550 scientific articles in the fields of Neuroscience and/or Neuropharmacology (total citations = 37,736; mean H index = 25; Scopus). The UNIFE research groups involved in the project are constituted by internationally recognized expert scientists mainly focused on the study of: 1) biopsychosocial and neurochemical factors contributing to psychiatric disorders together with the exploration of different psychopathological dimensions (e.g. cognitive, perception, ideation) and innovative treatment approaches based on non-invasive brain stimulation methods (e.g. rTMS); 2) cellular and/or molecular mechanisms underlying neuroinflammation, oxinflammation, neurodegeneration, epilepsy; 3) the effects of psychotropic drugs. This activity led to filing 2 patents in the last years. Concerning the high-value infrastructures, UNIFE is furnished with an Animal Facility (called Centralized Preclinical Research Laboratory; LARP) equipped with technologically advanced instruments for in vitro and in vivo studies/analyzes. LARP is a ~900 m^2 research infrastructure for preclinical and translational studies in high socio-economic impact fields, including neurological/degenerative diseases. Moreover, the Laboratory for Advanced Therapy Technologies (LTTA) - Tecnopolo has developed technical skills for the use of primary human cells to study the mechanisms of tissue differentiation and regeneration, genomic and post-genomic investigations in neurological and neurodevelopmental diseases, preclinical testing activities on in vitro (2D and 3D models including organoids) and in vivo systems (animal models), analysis of data derived from sequencing, ex vivo (biopsies and blood derivatives from patients). UNIFE shares with the University Hospital a rehabilitation facility equipped with robotics devices for brain stimulation and imaging for conducting clinical trials. The "Research Office" of UNIFE provides support to researchers in the elaboration and submission of Research Projects to national and international granting bodies and in the framework of European funding programs, also providing targeted information about available granting opportunities for research.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

In the last years, UNIFE successfully managed 42 international research projects funded by FP7, of which 4 Coordinated by UNIFE, 46 projects funded by Horizon 2020, 4 as Coordinator and 8 Individual Fellowship Marie Skłodowska-Curie, 1 project funded by Horizon Europe in Grant Preparation, several projects funded by other European research programs and around 1150 international cooperation agreements. Concerning the ongoing multi-Unit projects related to the Neuroscience and/or Neuropharmacology fields, UNIFE is coordinating projects funded by Cure Alzheimer's Fund USA (Prof. F. Di Virgilio), Alzheimer's Disease Drug Foundation (ADDF) USA (Prof. G. Koch) and Italian Ministry of Health (Prof. G. Koch), while is Leader/Partner in projects funded by Italian Ministry of Education (Prof. S. Gessi; Prof. M. Morari, Prof. Di Virgilio), Universities and Research, European Research Council (Prof. G. Koch), ADDF (Prof. G. Koch), Swedish Research Council (Prof. L. Ferraro), Silvio O. Conte Center for Translational Mental Health Research (Prof. L. Ferraro), Telethon Foundation (Prof. M. Morari), The International Rett Syndrome Foundation (Prof. G. Valacchi). UNIFE has also been granted with an ERC Starting Grant related to the role of inflammasomes in neurodegeneration. The total amount of funds related to the above grants is about 5,500,000.00 €. Some particularly relevant emerging results are: the implementation of genetic animal

models of Parkinson disease, the characterization of the purinergic signalling system in the CNS and identification of the key role of the P2X7 receptor, the role of biopsychosocial variables and comorbid chronic somatic conditions in mood disorders in the elderly and first episode psychosis in young people, the pharmacological characterization of novel molecules interacting with the endocannabinoid system as innovative neuroprotective agents, the development of novel non-invasive brain stimulation protocols to treat neurodegenerative disorders such as Alzheimer's disease and related dementias.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

UNIFE's research groups involved in the project established several national and international collaborations. Prof. L. Ferraro is member of the Board of "The Clust-ER Health", an association of large companies, SMEs, laboratories of the High Technology Network, research centers, health facilities and training institutions to support the innovation and competitiveness of the Health and Wellness Industries of Emilia-Romagna Region, Italy. This association will help result valorization and technology transfer. Prof. L. Ferraro also collaborates (as adjunct Professor) with the Psychiatric Department, School of Medicine, University of Maryland, Baltimore, which hosted the leading groups investigating the role of kynurenic pathway in schizophrenia. Dr. M. Ferrara collaborates (as adjunct Professor) with the Program for Specialized Treatment Early in Psychosis (STEP), Department of Psychiatry, Yale School of Medicine, New Haven, CT; Prof. L. Grassi coordinates the international network on cancer in patients with psychosis within the World Psychiatric Association Section on Psycho-Oncology and Psychiatry, Medicine and Primary Care. Dr. G. Valacchi collaborates with the North Carolina State University (Professor) and Kyung Hee University (Seoul South Korea) in understanding the modulation of oxinflammatory processes in diseases including neurodevelopment conditions.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

UNIFE established its Technology Transfer Office since 2004 with the aim to offer its researchers the following services: assistance in patent applications, assistance in setting up and further developing University Spin-off companies and setting up in technological transfer projects. In the last 10 years, UNIFE managed around seventy patent applications. Some of them were licensed or transferred to potential stakeholders for the exploitation. Onwards 28 academic spin-off companies have been created, which operate, among others, in the fields of pre-clinical/clinical and pharmaceutical research, Biotechnology, Biology, Genetics and Chemistry. UNIFE has also an incubator of ~300 m^2 that provides logistic services to the new startup companies. UNIFE houses the Technopole of Ferrara, accredited participant of the High Technology Network laboratories and centers, venues where know-how is transferred to the business sector and where the access to innovation and to new technologies is favored and developed by the entire Emilia-Romagna public research system. Researchers involved in the project are/have been consultant for several Companies such as Janssen Pharmaceuticals (Belgium), Astraea Therapeutics (Mountain View, CA, USA), Nikem Research (Baranzate, Milan), Trevena Inc. (King of Prussia, PA, USA), Zambon Pharma (Bresso, Italy), Eisai Europe (Hatfield, UK), Angelini (Rome, Italy), Allergan, Epitech (Padova, Italy), Axxam SpA (Milan, Italy), Biosceptre Ltd (Cambridge, UK), Affectis Gmbh (Munchen, Germany), Duska Inc (Philadelphia, PA, USA).

DESCRIPTION OF UNIBO

Alma Mater Studiorum – Università di Bologna (UNIBO) is one of the largest and most active Italian universities in research and innovation. UNIBO is organized in a multi-campus structure (Bologna, Cesena, Forlì, Ravenna and Rimini), with 32 Departments and 5 Schools. UNIBO is very active in all research domains, with more than 10.000 publications per year and outstanding results in attracting research competitive funding at both European and national level: in Horizon2020, UNIBO was involved in 350 research projects, of which 98 with the role of coordinator, 26 PI ERC and more than 2300 partners involved, of which 1600 from the private sector. At national level, UNIBO is currently involved in about 200 PRIN projects, of which 62 as coordinator. First in Italy, 14 Departments have been awarded as Departments of Excellence. At regional level, UNIBO accounts for more than 214 funded projects. UNIBO is also very active in innovation and technology transfer, with 520 patented titles, 37 spinoffs and 12 start-ups, 7 Interdepartmental Centres for Industrial Research (CIRI), many agreements and collaborations with industries. The university is rooted in the local innovation ecosystem with a constant European and global perspective, taking part to the most important R&I networks at both national and EU level, both thematic and institutional ones (among which UNA Europa Alliance and of The Guild of European research-intensive universities). It is committed to SDGs as well as to promoting ethics at all levels, through the adoption of policies on diversity (among which the GEP) and research integrity. The UNIBO is in top positions at national level in all main relevant international rankings. For instance, in 2022 it is ranked 172nd in the Times Higher Education (THE) World University Rankings (20th in Impact Rankings and 126-150th in World Reputation Rankings). Research activities are carried out in Departments and Inter-departmental Centres, all staffed with research manager profiles. At central level, the Research Services Division (ARIC) oversees activities related to institutional research and competitive funding, including aspects such as open science, ethics, research integrity, providing management support for project implementation and monitoring. The Industrial Relations, Third Mission and Communication Division (ARTEC) has developed a full range of services related to a structured strategy of collaboration with industry, knowledge transfer (including patent portfolio management), exploitation of research results, also through spin-off and start-ups, and related collaborations with the local, national and international innovation ecosystem.

A.2 SCIENTIFIC EXPERTISE

Concerning the topic of PE12 Neuroscience and neuropharmacology within PNRR, about 3653 publications (Scopus) were published in the last 10 years on neuroscience from researchers of UNIBO, stating a strong involvement of Bologna scientific research in Neuroscience. A total of 160 researchers are involved in neuroscience and realized the papers indicated above. The scientific competences in the topic of PE12 are witnessed by the coordination of Spoke4, with a strong participation of highly productive researchers, half of them women, often awarded with highly prestigious grants. Relevant research infrastructures are present in 10 different Departments. The organization of this PE has seen a convergence of efforts from the bottom (critical mass of 160 researchers) but also from the top (the governance, starting from the Rector), strongly committed to this proposal success.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

In Horizon 2020, in the topic of Neuroscience, UNIBO is involved in 7 collaborative projects, of which 4 as coordinator and including 2 projects under the JTI-IMI. UNIBO focus is on several aspects of Neuroscience and Neuropharmacology, including rare mitochondrial and neuro-genetic diseases, movement and neuromuscular disorders, disorders of the autonomic nervous system, headaches, sleep medicine (narcolepsy), epilepsies, epidemiology of neurological diseases and innovative aspects of neurosurgical and neuroimaging procedures, as well as Parkinson's disease (PD), Alzheimer's disease (AD), Autism Spectrum Disorders and brain longevity. In addition, in one of these H2020 grants where UNIBO is the coordinator, efficient prosthetics systems are the focus of the research. In another UNIBO coordinated H2020 grant, the links between human-centric AI and neuroscience are studied in a FET-Proactive project that can benefit the resources drained with this PE. **In Horizon Europe**, UNIBO is involved in 4 collaborative proposals. In one of these grants, UNIBO focus is on the prediction of treatment resistance and outcomes for major psychiatric disorders. In another one, the cognition useful for human-robot interaction is investigated. The links between perception and arm actions and eye movements are investigated with a huge international consortium. **JPND Neurodegenerative Disease Research**: UNIBO is involved as partner. UNIBO is member of relevant **networks at European level**, such as European Health Telematics Association (EHTEL), European Technology Platform for Nanomedicine (ETPN), Virtual Physiological Human

Institute for Integrative Biomedical Research (VPH Institute) and EU- cognition. The pluri-potent view on Neuroscience is witnessed by the decennial interdepartmental research group of the UNIBO: "Neuromathematics and Visual Cognition" held by researchers involved in this PE. International, non-EU grants: Australian National Health and Medical Research Council (NHMRC- APP1082144 – and APP1020839); NATIONAL SCIENCE FOUNDATION grant (NSF 2019959) - "Visuospatial modulation of bimanual touch perception in real and virtual environments"; National Scientific Responsible of OPLON (Opportunities for Active and Healthy Longevity), smart cities, MIUR, 2014-2017. At national and regional level UNIBO has funding for research on PD, AD, interoperability and integrated data analysis, neurosurgery, neuroprosthesis, basic neurophysiology: 16 research projects under the theme funded since 2014, of which 14 coordinated by UNIBO; 1 project funded under the PON Imprese e competitività 2014-2020 Smart Factory Call, in the role of partner; "Alte competenze" call - Emilia-Romagna Region – (5 projects for the financing of research grants and doctoral scholarships); projects funded under the Program for Young Researchers "Rita Levi Montalcini"; 1 project funded by the Emilia-Romagna Region through European Structural Funds under the POR-FESR 2014-2020.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

UNIBO belongs to ART-ER: Attractiveness Research Territory is the Emilia-Romagna Consortium Company created to promote sustainable growth in the region through the development of innovation and knowledge, attractiveness and internationalization of the territorial system. ART-ER coordinates the Emilia-Romagna High Technology Network. Boasting both a national and international dimension but firmly rooted in the region and its economic system, the Emilia-Romagna High-Technology Network is already capable of effectively and professionally addressing business sector needs. The Network is composed of 82 Industrial research laboratories and 14 Innovation centres operating in life science, agri-food, construction, energy and environment, ICT and design, mechanics and materials. The laboratories are hosted within the Technopoles: 10 infrastructures located throughout the territory that stem from an initiative of the Region in collaboration with ART-ER, universities, research centers and local authorities. They organize activities and services for industrial research, technology transfer and for the development of high skills and careers on innovation. Technopoles have been recognized by the European Commission as best practice of European Funds use in the programming period 2007-2013. The Clust-ERs are associations of public and private bodies: companies, research centres and training institutions that share skills, ideas and resources to support the competitiveness of the industrial system in Emilia-Romagna. The Clust-ER Health is an association made up of large companies, SMEs, laboratories of the High Technology Network, research centers, health facilities and training institutions that share skills, ideas and resources to support the competitiveness of the Health Industries and Wellness of Emilia-Romagna.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Technology transfer: **(1)** UNIBO created Industrial Research dedicated Interdepartmental Centers. CIRI Life Sciences and Technologies for Health (CIRI-SDV) brings together biomedical and technological knowledge and skills for the diagnosis and treatment of diseases, for personal assistance and the improvement of the quality of life, which cover the entire research and development chain, from the laboratory bench to the patient's bed and home. It also manages and offers pre-competitive research, applied research, technology transfer and industrial development, from the design of studies to the realization of prototypes. It is characterized by high flexibility, which guarantees a prompt and effective response to even diversified requests. **(2)** The project OPLON is related to the Aging of Society, as OPLON aims to foster the development of innovative solutions to improve the quality of life and care of the elderly population through the development of new systems and services to assist mobility, active aging and reduce social isolation, including the creation of diagnostic and therapeutic approaches for critical diseases. **(3)** UNIBO National Scientific Responsible of IRMI (Italian Regenerative Medicine Infrastructure) for national technological clusters, MIUR, 2014-2017. *IRMI-creation of a multiregional infrastructure (Italian Regenerative Medicine Infrastructure) for the development of advanced therapies aimed at the regeneration of organs and tissues*. The general objective of the project is the creation of a multiregional research infrastructure able to enhance the development of regenerative therapies, to develop products and services with high added value and to create new business models in the area of health and well-being. Patents: Electrospun fibers for the local release of an anti-inflammatory and a promyelinating drug, Inventor, PCT/IT/2018/000084. Spin-off: https://site.unibo.it/idea/it/le-nostre-imprese-innovative-start-up-e-spin-off/vibre

DESCRIPTION OF UNITOV

The University of Rome Tor Vergata (UNITOV) is a young, medium-sized (40,000 students and over 2,000 staff members) research-oriented university in southeastern Rome, a 600-hectare campus. UNITOV comprises six schools, including Medicine and Surgery and its Hospital: Policlinico Tor Vergata (COVID-4 Hospital http://www.ptvonline.it/). In the 2011-2020 ten-year period, the University developed 4,785 international collaborations on all five continents, with 25,572 coauthored publications, demonstrating its full international character. UNITOV has been classified among the most successful young universities by Nature-based on its activity in attracting talent and levelling up through research results and high-quality international collaborations.
Over the years 2016-2021, UNITOV has activated 163 exchanges of structured personnel with foreign universities (funded project initiatives or international cooperation initiatives and/or visiting professors and/or staff exchange initiatives). Gender balance is reported at https://web.uniroma2.it/it/contenuto/bilanci_di_genere_di_ateneo. The University of Rome Tor Vergata has collectively published 65,205 scientific papers, of which 5874 are in the areas of neuroscience and pharmacology.

A.2 SCIENTIFIC EXPERTISE

The University of Rome Tor Vergata is involved in all the spokes of the project. The Institution provides vast and deep expertise in neuroscience and neuropharmacology across several medicines, biology, and engineering departments. The clinical neuroscience area in the University Hospital, which works synergically with the academic component, is dedicated to innovative research, including genetics, molecular biology, biochemistry, neurophysiology, computerized and digital evaluation of patients, and imaging. The psychiatric and motivational components resulting from specific activities of the brain have also been studied. For example, Nicola Mercuri has published important contributions dealing with the physiopathological and pharmacological aspects of the dopaminergic system in animal models and disease models. His work has appeared in Nature communication, Annals of Neurology, and Brain. Giuseppe Novelli is a world-renowned expert in molecular genetics and has published in the world's leading scientific journals, such as Nature Genetics and Science. Orazio Schillaci is a leading expert in molecular imaging, radiodiagnostics, and nuclear medicine, and his work has appeared in the world's most prestigious scientific arenas. Giovanni Carlesimo brings deep expertise in memory processes and memory formation. Diego Centonze was included in "Science" journal among "Six stellar neuroscientists based in North America and Europe" in 2005. He is a leading expert in multiple sclerosis and his research, conducted through a multidisciplinary approach has been published in the best-impacted journals of the field (Nat Rev Neurol, Annals of Neurology, Brain, J Neurosci, etc). Maria Rosa Ciriolo has deep expertise in the involvement of oxygen-free radicals and redox signaling in the pathophysiology of inflammatory/metabolic disorders and neurological defects. The research performed in the lab. of Nadia D'Ambrosi investigates the molecular and cellular mechanisms underlying the pathogenesis of ALS, the involvement of neuroinflammation in this disease, and pharmacological and non-pharmacological approaches applied to ALS mouse model and iPSCs-deriving cells. Massimo Federici is a leading expert on metabolic complications, multimorbidity, and aging. Francesco Lacquaniti, Germana Cappellini, and Francesca Sylos-Labini discovered the motor primitives of locomotion in neonates and how they develop over the first year of life. They established novel biomarkers of developmental motor disorders, and their work was published in Science, Science Advances, and PNAS. Claudia Bagni and Antonietta Gentile of the Department of Biomedicine and Prevention have an international reputation in the field of the neurodevelopment of social factors and cognitive effects in autism (ASD) and fragile X syndrome studied in animal models. Their work was published in Cell, Nature Neurosci, Neuron, and Nature Communications. Francesco Cecconi and Silvia Campello from the Department of Biology are world leaders in the field of molecular substrates of neural system development and its derangement due to pathology. Their work appeared in Nature, Nature Neuroscience, Nature Cell Biology, The EMBO Journal, Cell Reports. Myrka Zago of the Department of Civil Engineering and Computer Engineering and Director of the Center of Space BioMedicine of the University of Rome Tor Vergata discovered the internal model of gravity in the brain and worked extensively on the neuroscience of space flights. Her work was published in Science, Nature Neuroscience, Nature Partner Journal Microgravity, J Neuroscience. Virginia Tancredi has a well-consolidated research experience in motor and exercise

physiology, synaptic plasticity, muscle degeneration, and animal models of degenerative diseases. Her work appeared in major journals of motor physiology and has been funded by several national and international agencies. Nicola Toschi and Andrea Duggento contributed long and documented experience in the field of computational neuroscience and neuroimaging, while Alessandro Mauriello and Giuseppe Rizzo bring important research experience on cellular plasticity and neurodevelopment. Their work appeared in the Transactions of the Royal Society, various journals of the Nature Publishing Group, and Neuroimage. Emmanuele A. Jannini created the academic field of Medical Sexology and has been listed as one of the most-cited authors in physiology and pathophysiology of sexual behavior and the psychoneuroendocrinology and neurobiology of sexual pleasure studied with both central and peripheral imaging techniques and by psychometric tests generated and validated also to study the correlation with degenerative and chronic non-communicable diseases. His research is published in the best-impacted journals of the field (such as Sex Med Rev, J Sex Med, Andrology, etc), but also generalist journals (Nature Rev Urol, JCEM, etc). Alberto Siracusano is a leading expert in the field of psychopathology, specifically mood and affective disorders, schizophrenia, and the psychological and psychiatric impact of the COVID-19 pandemic. He authored several books with a wide general circulation, also among nonspecialists. He is also a leader in the field of sexual side effects of pharmacotherapies for major psychosis as well as sexual symptoms of psychopathology.

HIGH-VALUE RESEARCH EQUIPMENT AND CENTERS:

800 m2Animal research facility, 2D and 3D cellular models, animal models, microscopy setups of highest resolution for single-molecule analysis, human and animal tissue and live imaging and time-lapse, Video-EEG analysis laboratory, CISM center for mass-spectrometry, CISPIM (center with MRI, CT, PET and SPECT for small animals), CERM center for MRI, IFAC center for confocal microscopy, FT-LAB of forensic toxicology, DSBSC Molecular Medicine facility, NGS molecular and cellular core facility (Meyer Children Hospital), Technological Park for transcriptomic evaluation (Nanostring technology), High-performance computing clusters and GPU farms, setups for electrophysiological recording, electron microscopy facility equipped with both transmission and scanning electron microscopes, the center of histological studies

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

UNITOV has strong experience in managing and supervising research projects. UNITOV manages a portfolio of more than 245 projects financed by E.U. programs (FP7, H2020, and Horizon Europe) and other funding agencies. UNITOV currently coordinates 427 research programs of National Funds, including Program Agreements, Futuro in Ricerca, S.I.R., PRIN, MUR FISR, Diffusione Cultura (M.U.R.), and Reg. Lazio, INAIL, AIFA, INAPP, Ministero Salute, MIPAFF, Telethon, ARISLA, FISM. UNITOV launched and managed the following university research programs (2013-2019): Uncovering excellence; Consolidating the Foundations; Mission Sustainability; Beyond Borders.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

UNITOV is involved in 3 international networks (E.U.A., UNICA, YERUN VIU). 5 J.U. (F.C.H. Fitup, LOLIPEM, ECSEL, M2O, Harmony), and in 1 K.I.C. (HEInnovate). UNITOV has contributed to creating a project for the Young Universe of the Future YUFE (https://yufe.eu). The researchers of UNITOV have stood collaborations with a vast number (> 600) Universities and Academic Centers and with several National and International Research Centers and Networks. Members of MNESYS have leading roles in specific initiatives such as the Alzheimer's Disease Precision Medicine Initiative (APMI) and the Neurodegeneration Precision Medicine Initiative.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

The University of Rome Tor Vergata has been extremely active in terms of technology transfer, documented by 44 patents published in the last ten years. The institution has a dedicated technology transfer office that supports all researchers in bringing their innovations to the market. Additionally, academic spinoff companies have been generated by the University of Rome Tor Vergata in different scientific fields.

DESCRIPTION OF UNINA

The University of Naples Federico II (UNINA), founded in 1224 by Frederick Hohenstaufen, King of Sicily and Emperor of the Holy Roman Empire, is the oldest state-funded university and one of the largest research universities in the world. The primary mission of UNINA is a balanced combination of research and teaching, which the University pursues by promoting the organization, processing and transmission of knowledge, the cultural and professional training, and the growth of students' civic awareness and critical thinking. In addition, UNINA contributes to the progress of the cultural, social, and economic well-being of the country by cooperating with public and private corporations, both nationally and internationally.

A.2 SCIENTIFIC EXPERTISE

UNINA employs over 2800 faculty members (professors and researchers), affiliated to 26 Departments, 23 interdepartmental Research Centers and 17 inter-university Research Centers covering the full spectrum of disciplines. UNINA is also the recent founder of "Scuola Superiore Meridionale" (one of the international schools of higher education and research in Italy) and hosts 9 public-private "Academies" for specialized training, involving companies of international dimension (e.g. APPLE, CISCO). Since 2016, UNINA belongs to the Aurora European Network (https://aurora-network.global), including 9 top-class European universities which are excellent in research and dedicated to social responsibility and diversity. UNINA is strong advocate for gender equality and other nondiscrimination principles and has recently approved a gender equality plan. UNINA draws up the Gender Report as a most valuable instrument to pursue the objectives of equality. UNINA is uniquely positioned as a leading university in the south of Italy and is ranked in the top 2% of universities worldwide (QS ranking). **Five departments of UNINA (Pharmacy; Molecular Medicine and Medical Biotechnologies; Electrical Engineering and Information Technologies; Civil, Construction and Environmental Engineering; Economical and Statistical Sciences), three of which contributing to the current PE12 proposal, are recognized as "Departments of Excellence 2018-2022" by the Italian government** and have been awarded over 42 million euros of extra funding. With its over 5.000 active researchers, UNINA has an overall scientific output of around 7000 research papers per year in scientific journals, books, book chapters, patents and other research products. Following is a classification of total scientific production of the last 10 years by macro-area: Mathematical and Computer Sciences n. 4569; Physical Sciences n. 10725; Chemical Sciences n. 11946; Earth Sciences n. 4208; Biological Sciences n. 12039; Medical Sciences n. 30912; Agricultural and Veterinary Sciences n. 11689; Industrial and information engineering n. 21049. The PhD Program in Neuroscience of UNINA is coordinated by the investigator who also acts as Responsible for SPOKE 3 of the current PE12 Proposal (Prof. Maurizio Taglialatela), and is member of the network of Italian Research Doctorates of excellence NEIDOS, also actively contributing to the Network of European Neuroscience Schools (NENS). UNINA research members participating to the current PE12 proposal include 7 Executive Committee of the PhD Program in Neuroscience, as well as members of Committees of most of neuroscience-related Programs (i.e. Molecular medicine, Drug development, Chemistry etc.), and teach disciplines highly integrated to the research themes addressed by the proposal. Moreover, UNINA academics are or have recently been President or of Executive Committee Members of leading Scientific Societies related to Neuroscience (Italian Society for Neuroscience) and Neuropharmacology (Italian Society for Pharmacology) in Italy. Around 10000 scientific articles related to PE12 have been published in the last 10 years; *ca.* 38% of those have appeared in Q1-ranked journals and *ca.* 20% in the top 10% journals. These include top multidisciplinary Journals as well as discipline-related Journals, including Brain, Annals of Neurology, Neuropharmacology, Neurology, British Journal of Pharmacology, Journal of Neuroscience, Neurotherapeutics, and Molecular Therapy. UNINA can count on 93 top-level researchers covering different disciplines with an impact around the research themes PE12. Of the scientists involved in the PE12, 5 are listed in the top 2% of scientists in the world (ranking 2021, Stanford University). This important scientific production has been obtained thanks to the availability of state-of-the-art up laboratories equipped with the most up-to-date technologies for research implementation in each respective field. Specifically-related to PE12, UNINA hosts facilities for the development and characterization with omic technologies, advanced imaging (2-photon and confocal microscopes, several facilities for electron microscopy, etc.), electrophysiology (single channel and single-cell analysis, slice recordings, etc.), and flow cytometry and cell sorting of specific cellular models; moreover, animal models of neurological disorders (specific native species or genetically-, drug-, and surgically-induced rodent

models) are widely used in the different animal facilities of UNINA. Additional facilities available relevant for PE12 include the Augmented Reality for Health Monitoring Laboratory (ARHeMLab), a Current Good Manufacturing Practice (cGMP) production facility, Biosafety Level 3 (BSL-3) laboratories, and laboratories for the design and synthesis of various types of pharmaceutical products and methods to optimize their brain delivery process.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

UNINA is a strong attractor of national and international funds for advanced and complex research projects. UNINA has participated as partner in 114 projects financed by the European Commission within the H2020 framework, 23 of which coordinated by UNINA, with an average of 13 international partners and a total financial contribution of over 47 million euros from the EU. In the same time frame, UNINA has participated in 23 international projects other than H2020 ones, 6 of which coordinated by UNINA. UNINA ran 226 projects funded by the Italian Ministry for Research under the National Interest Research Projects program (PRIN), 48 as coordinator, and several tens of applied-research grants funded under the Operative National Program (PON) and Operative Regional Program (POR), with a total financial contribution of several tens of million euros. UNINA has been or currently is the host institution for 17 grants of the European Research Council (ERC) (not counting Proof of Concept grants) and UNINA faculty members have been principal investigators for 28 ERC grants (11 of which hosted by other research institutions with which UNINA has a permanent agreement). Several projects are related to neuroscience and neuropharmacology (in H2020-ERC, EYEGET, VECTOPUR, GENEVISION, UshTher, UPGRADE; cONCReTE, FFC#23/2017; FFC#25/2018, IG2016-2020, miRNA-STROKE; PathBio: Precision PathoBiology for Disease Models (http://www.pathbio.org/; "Regenerative medicine and tissue engineering: Novel approaches to damaged tissue repair"(EJP RD JTC 2020; "Targeted treatment for KCNQ related encephalopathies: retigabine analogues, repurposed drugs and allele specific knock down"). Relevant to the PE12 proposal, UNINA is a partner in the regional strategic projects PREMIO (Precision Medicine Infrastructure for Oncology), *Oncoterapie* (discovery of novel therapies for MDR cancers) and SATIN (biotechnology-based therapeutics). An overall of *ca.* 40 M€ granted in the last ten years (comprising AIRC, Telethon, Cystic fibrosis foundation grants), have been awarded to UNINA participants to PE12.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

UNINA has strong track record of collaborations that are well represented by authorships in the scientific papers. In the last 10 years, 60% and 45% of the publications have been produced with national and international collaborations, respectively. UNINA, in the last decade has signed over 260 international collaboration agreements with universities, research institutions, companies. UNINA is a member of 2 European networks in the frame of EU+ European Universities: European Foundation and AURORA and 4 international consortia (Bet for Jobs, Eu4EU, Seas 4.0, Sara-Lab). UNINA coordinates the Mediterranean Middle East Universities Agreements (30 Universities of the Mediterranean area). International cooperation agreements link UNINA with more than 340 research institutions in Europe, USA, UK, Africa, and Asia. Currently, 2000 Erasmus Agreements, 360 Research international agreements, 5 Joint Master Erasmus Mundus, 20 Degree courses in English and 8 International PhD programs are active. UNINA investigators participating to the PE12 proposal have a solid network of national and international collaborations (see CVs).

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

UNINA is also a strong driver of economic innovation; a third mission and technology transfer office are in place at UNINA, which manages hundreds of industrial patents (>600 in the last 20 years) and many spin-offs (81 currently operative). Several of these revolve around themes (such as digital twins, next-generation sequencing and other omic technologies, pharmaceutical development, etc.) highly pertinent to the current PE12 proposal. UNINA is partner of RoboIT, the first national pole for the technology transfer in the field of robotics. Investigators at UNINA have obtained several patents related to innovative diagnostic or therapeutic tools for neurological disorders, and several academia-industry collaborations are in place for the development drugs for neurological disorders, nanovectors and neurological rehabilitation devices.

DESCRIPTION OF UNICAMPANIA

Università degli Studi della Campania *Luigi Vanvitelli*

The University of Campania "Luigi Vanvitelli", founded in 1992, promotes a training offer integrated with the territory, supports quality research, and promotes the creation of business initiatives from research groups, in a constant perspective of internationalization and cultural exchange with other Universities. Currently there are nearly 1.300 professors and 16 Departments. The University is responsible for qualifying the human resources (Education) and for producing new knowledge (basic and applied Research). Moreover, the University is engaged with societal needs and market demands by linking the university's activity with its own socio-economic context (3rd mission). In particular, the School of Medicine aims to provide advanced healthcare services to the society. The University is subject to periodic accreditation by the AQ/ANVUR System that in the last periodic visit (2019) judged the Research and 3rd mission activities as excellent. In 2021, the University produced its first gender balance sheet / gender equality plan.

A.2 SCIENTIFIC EXPERTISE

The overall scientific production includes approximately 88,000 research items. In the last 10 years it includes 20,398 contributions in scientific journals, 26 patents, 958 books and 4,339 scientific conference proceedings. With reference to MNESYS, the research group led by Prof. G. Tedeschi is currently involved in the INTEROCEPTOR project coordinated by the Italian Drug Agency on the early diagnosis and treatment of the prodromal stage of Alzheimer disease. Prof. Tedeschi is PI in several multicenter clinical trials in collaboration with pharmaceutical companies (e.g., Janssen, Biogen, Novartis, Allergan, Teva, and Bioclinique). Prof. Tedeschi is also director of the Centre for Advanced Neuroimaging Studies in Neurology of the UNICAMPANIA, a hybrid research and clinical infrastructure dedicated to research activities in basic and clinical neuroscience. This facility includes a high magnetic field MRI scanner dedicated to the acquisition of advanced brain images for the study of neuronal connectivity and neuronal plasticity. The research groups of Prof. A. Tessitore and Prof. S. Bonavita are involved in neuroimaging projects on Parkinson's Disease (PD) and Multiple Sclerosis (MS), with special focus on the neuronal connectivity of large-scale brain networks. These researchers respectively lead the local PD and MS clinical units, with long experience patient assessment, recruitment and management. The Parkinson's Disease and Movement Disease Center led by Prof. Tessitore is fully committed to both clinical service and scientific research activity related to the diagnosis and treatment of parkinsonisms and other movement disorders. Patients admitted to neurological examinations also undergo highly accurate diagnostic investigations, including MRI, SPECT and DAT-SCAN. Thanks to the contribution of Prof. F. Esposito and Prof. M. Cirillo, the groups of neurologists investigate the functional and structural MRI correlates of the main neurological disorders, including MS, migraines, movement disorders and motor neuron diseases, with cutting-edge technologies. The research group led by Prof. Esposito is focused on to the study of physiological and pathological mechanisms affecting the in-vivo observation of neuronal networks in the living brain using neuroimaging methods. To facilitate technology transfer in the field of MRI applications to neuroscience, Prof. Esposito has been delegated by the Rector within an ongoing research cooperation initiative between UNICAMPANIA and General Electric Healthcare (USA) to facilitate the development and application of novel MRI sequence prototypes. Furthermore, he is co-supervising doctoral and post-doctoral industrial researchers in collaboration with biomedical companies in Italy (Kelyon S.r.l.) and abroad (Bran Innovation B.V., The Netherlands). The research groups of Prof. L. Trojano and Prof. G. Santangelo deal with the study of the relationship between mind and brain, thus integrating the approaches of traditional clinical neuropsychology with methods of the most modern cognitive neuroscience (i.e., behavioral, neuroimaging and other non-invasive brain stimulation techniques) to study human cognition in normal and pathological subjects. Besides supporting modern studies of the functional and structural brain correlates of the neurological disorders, degenerative diseases of the central nervous system are also studied in terms of pathogenetic (genetic-molecular) mechanisms. In addition to biomedical instruments for in-vivo data acquisition in humans, scanning transmission electron (STEM/TEM) and confocal, infrared and fluorescence microscopes and laser capture microdissectors are available to research groups involved in this project. An animal facility is equipped with microscopes and other devices for neurobehavioural tests on animals. The research groups of Prof. M. Papa and Prof. A. De Luca provide consolidated expertise in the analysis of cellular and animal models to address the determinants of neuronal plasticity. Young researcher Dr. Cirillo provides expertise in advanced microscopy imaging of central nervous system and non-invasive brain stimulation techniques to modulate neuroplasticity. Prof. A.

Usiello focuses his research on identifying altered levels of atypical molecules in serum and cerebro-spinal fluid of patients with developmental, neurodegenerative and psychiatric diseases. His expertise allows testing functional effects of molecular alterations on synaptic plasticity, behavior and brain structure in genetically/pharmacologically modified animal models. Prof. L. De Arcangelis deals with physical and computational aspects of the modeling and simulation of neuronal networks, with a focus on synaptic plasticity and neural signals. Her activities also pertain to algorithmic performances in complex learning and pattern recognition tasks.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

In the last 10 years, the University coordinated 241 national and international projects. UNICAMPANIA participated in: 33 projects of the 7th Framework Program (8 as Coordinator) and 21 projects of the Horizon 2020 program. Since 2017, the University has invested increasing resources in the VALERE Program, a tool for enhancing and promoting research activities. The research groups involved in this project have received grants from the Italian Ministries of University and Research and of Health, the Campania Region and the European Commission (EU), for more than 2M€. Prof. Trojano and Prof. Sant'Angelo are former and current Coordinator of the PhD Program in "Sciences of the Mind" and are involved in two EU projects (H2020 Marie Curie RISE 2017 and 2018 initiatives). Prof. Tessitore is local coordinator of a project founded by the Ministry of Health (2018) on "Tracking and predicting neurodegeneration along the PD continuum using clinical, cognitive and advanced MRI data". Prof. Esposito is member of Ph.D. program and has been previously benefited from a H2020 RISE initiative on the study of microstructural brain damages with MRI. Prof. Papa has previously coordinated a FIRB project on the development of MRI techniques for the study of patients with disorders of consciousness. Prof. De Luca is member of Ph.D. program and Ethical Committee and participates to the consortium of the EU project "Tique" (H2020 Research and innovation program) which aims at integrating cutting-edge AI-powered technologies for health monitoring. Prof. De Arcangelis is responsible for the "Modeling" Laboratory equipped with a Cluster Beowulf for parallel computing acquired via an EU grant to the UNICAMPANIA. Prof. Tedeschi has coordinated as PI a Research Program of National Interest (PRIN) on "Searching bio-morpho-functional markers of migraine brain" and a Finalized Research Program on "Network degeneration in motor neuron diseases (MND)".

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

The University promotes a global internationalization strategy. Initiatives implemented: "visiting professor", "visiting researcher", Mobility "Erasmus+" and "International Mobility" aimed at University Professors and Researchers, for a total of 150 grants. The University participates to 7 international Networks and Joint Undertaking and to 7 Knowledge Innovation Communities. For years, the University has placed the care of neurological patients among its main objectives, and currently more than 10,000 patients/year with neurological symptoms are examined, eventually diagnosed with neurological diseases, and treated in clinical neurological units, which are also constantly engaged in screening, research, diagnosis and treatment activities. Prof. Tedeschi is past President of the Italian Society of Neurology and a member of ITALSGEN (Italian Consortium for Amyotrophic Lateral Sclerosis Genetics), NiSALS (Neuroimaging Society in Amyotrophic Lateral Sclerosis) and TRICALS (international consortium devoted to finding effective treatments for ALS). The units are part of national and international networks for neurological diseases (e.g. the European Reference Network for motor neuron disease). Prof. Tessitore has ongoing collaborations with Harvard Medical School (USA), Hangzhou Normal University (China) and King's College London (UK) on movement disorders. Prof. Trojano is among the founders of the Italian Society of Neuropsychology. Prof. Esposito is "founder" of the Italian National Bioengineering Group (GNB) and has ongoing international collaborations with several institutions, including Maastricht University (The Netherlands), Max Planck Institute (Germany), Centre for Magnetic Resonance Research (CMRR, University of Minnesota, USA) and University of Zurich (Switzerland), on topics related to advanced neuroimaging, high-field (quantitative) MRI techniques, real-time functional MRI, neuro-cognitive modeling and brain computer interfaces. Prof. Papa has ongoing collaborations with the Weizmann Institute of Science (Rehovot, Israel) on the plasticity of dendritic spines in neuronal culture, University di Oslo (Norway) on the neural substrates of attentional deficit and hyperactivity disorders in children and animal models, University of California (USA) on the study of striatal neurons by double labelling techniques. Prof. Del Luca has ongoing collaborations with the College of Science and Technology (Temple University, USA). Prof. De Arcangelis has collaborations with NIH (USA), Imperial College (UK), ESPCI (France) and Ben Gurion University (Israel).

DESCRIPTION OF UNICZ

University of Magna Graecia of Catanzaro (UNICZ) is a small-medium university, made up of 2 schools and 4 departments. UNICZ is based at the "Salvatore Venuta" University Campus, on the outskirts of Catanzaro, in the locality of Germaneto, and counts on a teaching staff constituted by 293 units. The buildings of the Faculty of Medicine and the biomolecular area are strictly linked according to the from-bench-to-bed principle. The care activities find spaces and advanced technologies for diagnostics and for the treatment of major diseases, integrating with teaching and research provided at the faculties of Medicine and Surgery and Pharmacy of the "Magna Graecia" University. The Campus facilitates interactions between experts and researchers from multiple disciplines: doctors, bioengineers, biotechnologists, pharmacologists, contribute to a better quality of services in terms of diagnostics, therapy and prevention. The Campus also houses the "Mater Domini" University Hospital. In this way, assistance and research go hand in hand, guaranteeing technological innovation and better services. A total of sixteen University Research Centers (CR) are currently active, representing scientific and research institutions with the task of promoting, organizing and carrying out research activities, including in the context of interdisciplinary, inter-territorial and long-term projects. Within the Research Centers, two belong to the biomedical-pharmacological area with a high technological content and are Research Units which are established temporarily on the basis of a research project. Within the Germaneto Campus there are non-academic realities that operate in close synergy with the University, such as the National Research Council through the Organizational Support Unit (UOS) belonging to the Institute of Bioimaging and Molecular Physiology and the Mater Domini University Hospital.

A.2 SCIENTIFIC EXPERTISE

Over the last few years, the University has found the resources and made significant investments necessary to enhance its technological equipment and plan its subsequent development. For the biomedical area, the technological implementation carried out by UNICZ has made it possible to equip the University with interdepartmental core facilities able to provide the technology and know-how for cutting-edge research. Since 2015, is operative within the Germaneto University Campus the Research Infrastructure (RI) Biomedpark@UMG. This RI has made it possible to locate in a single structure, the most modern technologies for genomic, proteomic, and molecular diagnostics research of its laboratories, as well as the core facilities of advanced clinical imaging. The RI allows the carrying out of: **a)** research activities in the field of advanced biotechnologies and its applications in chronic and neurodegenerative diseases, with the aim of facilitating the transfer of research results both to the clinical sector and to the production sector of SMEs, as well as to favor spin-offs; **b)** high-tech service activities to support basic research; **c)** high-tech service activities to support clinical research and health care; **d)** high-level on-the-job training activities in the sectors of interest at various entry levels (including an international PhD). The functional genomics and molecular pathology platform carry out research and service activities in the field of human diseases through the development of cutting-edge techniques in the field of molecular pathology and cell imaging such as next-generation massive sequencing, biopsy liquid, digital pathology. The proteomics platform promotes research and service activities by identifying and validating new diagnostic/prognostic biomarkers by analyzing biological fluids, tissues and cell lines. The imaging platform carries out research and service activities in the field of human health, and promoting the transfer of results, supporting industrial development in the field of structural and functional genomics. The Neuroscience platform carries out research and service activities in the field of chronic neurodegenerative diseases (e.g. Parkinson's disease (PD), atypical parkinsonisms, dementias, demyelinating diseases), with the aim of providing healthcare professionals with a series of new quantitative diagnostic tools based on the use of high resolution images. The contribution of UNICZ will be provided by the research groups led by Prof. Quattrone, Prof. De Sarro and Prof. Cuda. Prof. Quattrone is currently Emeritus of Neurology at the UNICZ and his research activity is focused on PD, epilepsy, multiple sclerosis (MS), clinical, genetic, neuroimaging and radiological studies of diseases of the central and peripheral nervous system. The Neuroscience group is recognized as one of the most important centers for the study of movement disorders (PD, essential tremor) and epilepsies. In the latter area, it is part of the prestigious international consortium ENIGMA dedicated to understanding the structure, function in relation to epileptic syndromes. In the same area of epilepsies, the genetics group led by Prof. Gambardella is part of the international consortium of

the Epi25 Collaborative Group under the auspices of the NIH USA dedicated to the understanding of the genetic components of epilepsies. The research portfolio also includes the study of MS, headaches and neurodegenerative diseases such as Alzheimer's disease. The main lines of research are: **a)** identification of new biomarkers of PD and the characterization of sub-clinical phenotypes related to movement disorders; **b)** development of advanced technological methods related to different Neuroimaging protocols including structural/functional Magnetic Resonance Imaging and Near Infrared Spectroscopy; **c)** development of computerized diagnostic methods based on machine learning. The Neuroscience center is equipped with cutting-edge biomedical equipment in the field of neuroimaging: there is a hybrid PET/MRI 3 TESLA as well as tools to support the neuroimaging activity, such as a FMRI stimulation system which is necessary to carry out sophisticated studies of functional MRI on individuals with neurological diseases. The Center has also an MRI-compatible EEG and a software for processing MR images. Prof. De Sarro is the Rector of UNICZ and his research activity is focused on the study of new drugs and/or pharmacological targets for the treatment of epileptic disease. The research activity of Prof. Cuda, Vice Rector for Research and Technology Transfer of UNICZ, is focused on the development, characterization and study of in vitro models of neurodegenerative diseases through the reprogramming of terminally differentiated somatic cells in induced pluripotent stem cells (iPSCs). Through this approach, it is possible to obtain pluripotent cell lines that possess the genetic/epigenetic background of the patient with a specific pathology, which are subsequently differentiated towards the line of scientific interest for subsequent characterization and functional evaluation. The research team is also engaged in the development and production of 3D-brain organoids from iPSCs obtained from patients with neurodegenerative diseases.

A4. EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

As to funding, UNICZ researchers have gained considerable expertise in the management of complex, multi-partner projects. In the last 10 years the projects granted to UNICZ, through competitive calls issued by MIUR (n.201), Ministries such as MoH and MISE (n.19), EU (Framework Programs, n.11), Calabria Region (POR projects, n.90), AIRC (n.71) and Telethon (n.2), amount to about 50 million €. In most cases UNICZ has had a leadership role (national or international coordination, responsibility of local units). A summary of the most important projects coordinated by UNICZ with themes pertinent to Neuroscience and Neuropharmacology include: Horizon2020– PON 2014/2020 – MATE for the development of a multifunction smart bracelet for kids and elderly; Project ARS01_00566 Naditemm, that develops novel diagnostic and therapeutic approaches for neurological consequences of metabolic diseases; Project ARS01_00144 Molim OncobraiN lab, PRIN 2020 20209KY3Y7_003, that studies response and immune-related adverse reactions to cancer immunotherapy based on analysis of circulating biomarkers and advanced diagnostics in neurodegenerative diseases.

A5. NATIONAL AND INTERNATIONAL COLLABORATIONS

The UNICZ groups have consolidated active collaborations with prestigious Italian and/or international institutions, as can be seen from the numerous co-authorships in publications that have resulted from these collaborations. In this contest, the existing scientific collaborations have been supported by an intense program of staff exchange, especially outgoing. With a specific focus on the field of Neuroscience and Neuropharmacology, UNICZ collaborates with: German Center for Neurodegenerative Diseases (Bonn), Technische Universitat (Munich), Institute for Stem Cell Biology and Regenerative Medicine (Stanford), National Institutes of Health (Bethesda), University College Dublin.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Technology transfer and the creation of academic spin-offs and innovative startups are among the main objectives pursued by UNICZ as part of the so-called "third mission" of the Calabrian university. In the field of neuroscience and neuropharmacology, UNICZ researchers have produced several patents, including devices for the diagnosis of tremor and for the rehabilitation of individuals with cognitive impairment. Furthermore, an academic spin-off (Medifarmagen) was recently born for the study and development of diagnostic and response tests to therapy capable of reducing the improper prescription of drugs, increasing adherence to therapy and reducing development of adverse reactions and drug interactions. UNICZ is also partner of the Biotecnomed consortium, managing body of the District for Health and Life Technologies in Calabria, within which more than 70 local and national companies operate in the field of biosciences and biotechnologies. The interaction between UNICZ and these companies represents a strong added value for the enhancement of their innovative capacity and a potential job outlet for many graduates of the Calabrian university.

DESCRIPTION OF UNIBA

The University of Bari Aldo Moro (**UNIBA**) is one of the most renowned and prestigious Universities in the South of Italy, founded in 1924 (Edurank 517 / 14160 in the World, 17 / 88 in Italy). UNIBA, with currently over 43,000 students, is one of the largest generalist Universities in Italy with 22 Departments, covering all fields of research from basic to R&D, about 52 research and didactic centers and two schools: "Sciences and Technologies" and "Medicine". The University of Bari has important libraries of historical and scientific value, which include 1,689,442 books and 21,369 journals. The teaching staff includes about 1,500 professors and 1,400 administrative staff. UNIBA also includes several Interdepartmental Research Centers, Inter-University Research Centers and Excellence Centers that carry out research activities of national and/or international relevance, related to projects of multi-year duration involving competences of more than one department or more than one university. A significant metric of the UNIBA scientific track-record is provided by its all-time global scientific productivity which amounts to over 55,000 products (source: Scopus).

A.2 SCIENTIFIC EXPERTISE

The University of Bari Aldo Moro (UNIBA) includes many investigators and technicians. More specifically, the number of investigators involved in Neuroscience and Neuropharmacology is greater than 200. Seven Departments of UNIBA are involved in the operations and activities of the present project: 1) Biosciences, Biotechnology and Biopharmaceutics; 2) Basic Medical Science, Neuroscience and Sense Organs; 3) Pharmacy - Pharmaceutical Sciences; 4) Biomedical Sciences and Human Oncology; 5) Emergency and Organ Transplantation; 6) Psychology and Communication; 7) Physics. UNIBA will be affiliated to all spokes, with the involvement of 27 highly ranked and internationally renowned scientists. Scientific expertise in these subjects is vast at UNIBA, ranging from basic science, to pharmaceutical and pharmaceutical technology and clinical applications. For example, 1) Professor Palmieri (H index 42) has published important contributions detailing the role of mitochondria in Autism and other developmental disorders. Professors Frigeri (H index 44) and Nicchia (H index 36) have always been involved in astrocyte physiology as related to brain homeostasis in health and disease; 2) Professor De Tommaso (H index 36) has long been involved in assessing brain connectivity in health and disease with high density Electroencephalography (EEG) and, more recently, with MagnetoEncephalography (MEG); 3) Professor De Luca (H index 38) has reported extensively on neuronal homeostasis, genetic variations and the pathophysiology of neurological disorders; 4) Professor Gesualdo (H index 63) has recently started to investigate the brain-kidney crosstalk in chronic kidney disease and kidney transplant; 5) Professor Bertolino (H Index 59) has spearheaded the field of imaging genetics in the world of Psychiatry and provides availability of a MEG scanner on site and of a 3 Tesla Magnetic Resonance Imaging scanner; 6) Professor Colabufo (H index 34) brings to this consortium an extensive expertise in medicinal chemistry of Alzheimer's Disease with three patents (PCT/EP2011/058469, PCT/EP2011/058631 PCT IB2007/050029). Prof. Antonio Scilimati (H index 27) has a documented experience in basic sciences and technology transfer regarding development of PET radiotracers for neurodegenerative disorders (US 73/431,187: granted by 2021) and neuroinflammation (PCT/IB2017/052395). Moreover, Professor Pesole (H index 62) is part of the european ELIXIR network with his large center for genomics and epigenomics; 7) Professors Panaro (H index 34) and Castegna (H index 32) have produced important contributions in the pharmacology of neuroinflammation (patent GB 1711709.4). Each and every Department at UNIBA includes an administrative unit (on average 5 staff per Department) devoted to management of scientific projects, from design to communication and technology transfer. UNIBA has a specific Office to manage patents and support its Researchers for technology transfer.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

UNIBA is the recipient of large grant funding. For example, only the Basic Medical Science, Neuroscience and Sense Organs, one of 23 Departments, has received around 15M€ in research grants in the period of time between 2019 and 2021. UNIBA has received funding in the last few years from a series of different sources, including the EU (FP7, Horizon 2020 and Intellectual Property Booster Services), the Italian Ministry of University and Research (MUR), the Italian Ministry of Economic Development, the Apulian Regional Government and the National Institutes of Health USA, to name a few examples. One such example is represented by the project entitled "Technopole for Precision Medicine", a 5-year grant of the

Apulian Regional Government in collaboration with CNR providing funding for over 9M€ for 5 years, to study Neurodegeneration in the brain. Another example is the project "PON (MUR)" for the development of PET radiotracers, such as F-DOPA for the diagnosis of Parkinson' diseases and Neuroendocrine Tumors (project code: PON01_03054 R.A.I.SE.; financial support: 1.9 M€ of the total contribution received of 7,5 M€, 2013-2015). UNIBA is coordinating these projects and a large number of papers have been published and patents filed. Another such example is the project entitled "Early identification of risk for Psychosis", whose funding of over 3M€ is devoted to identifying early biomarkers of conversion of genetic risk into frank Psychosis. The latter project led by UNIBA and funded by the Apulian Regional Government has allowed the investigators at UNIBA to participate to a landmark paper just published in Nature about the genetics of Schizophrenia (Trubetskoy et al. Nature 2022 Apr;604(7906):502-508). Two more projects have been funded by the EU within the FP7 and Horizon 2020 schemes, PRONIA and REALMENT. Both these projects have included UNIBA as a spoke and have the common theme of precision medicine in Psychiatry. Another project has been funded by the MUR within the PON scheme. This project includes UNIBA as a spoke and it is entitled "4 Frailty- Intelligent Sensors, management models and infrastructure for frail people", especially in neurodegenerative disorders. UNIBA is also part of a large European grant (Horizon 2020) entitled "Sustainable ecosystem to improve the lives of rare disease patients", which includes patients with neurodegenerative disorders. Another EU funded project within the ITN Marie Curie Sklodowska scheme and entitled "ASTROTECH" is participated by UNIBA. Finally, three more projects funded by USA AFOSR regarding collective astrocyte dynamics are led by UNIBA.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

UNIBA is an active member of several different national and international collaborations. UNIBA is part of the Psychiatric Genomics Consortium, an international collaborative project on research of the genetics of psychiatric disorders. UNIBA is part of the ENIGMA consortium which brings together researchers in imaging genomics across the globe to understand brain structure, function, and disease, based on brain imaging and genetics data. UNIBA is centrally involved, and co-leader of the brain imaging spoke of a large national consortium, entitled the Italian Network for Research on Psychosis. UNIBA is also part of the European Research Network for Rare Diseases, which includes research in Huntington's Disease. UNIBA leads the Italian Registry of Multiple Sclerosis. UNIBA also has established a formal written collaboration of research with the Lieber Institute of Brain Development, at Johns Hopkins University in Baltimore (USA), for a collaborative effort on understanding the genetics of human brain development in health and in Schizophrenia.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

UNIBA is involved in this project with a selected group of qualified Scientists with a proven track record of identifying new bio-pharmacological targets which then become the object of active collaborations with Pharmaceutical Companies. In particular, Prof. Colabufo is president of an SME (BioForDrug, former spin-of UNIBA) focused on development of PET radiotracers for P-glycoprotein imaging at BBB level for neurodegenerative diseases (WO2016174496; Coffee blends for neuroprotection, ITUA20163931; Method of screening for therapeutic compounds useful in detoxifying central nervous system from beta amyloid peptide, WO2012159674; Novel tetrahydroisoquinoline compounds for use in the diagnosis and treatment of neurodegenerative diseases. US2014/0112868). Prof. Scilimati is a partner in the UNIBA spin-off Bioinformatics Resource for Omics Wide Services (BROWSer srl), which provides bioinformatics analysis services applied to biological data also in clinical neuroscience (patent "Stable F-DOPA formulations and their uses thereof", US 63/431,187. Granted in 2021; patent on neuroinflammation Multi-functions Selective COX inhibitors. PCT/IB2017/052395. Granted in 2021). Prof. Pesole filed "GeneUP algorithm to search optimal primers for RNA fingerprinting (Pat. 08/925,816), and "Method for the preparation and amplification of representative and strand- specific libraries of cDNA for high throughput sequencing, use thereof, kit and cartridges for automation kit (EP11738288) for use in clinical neuroscience. Prof. Denora filed a patent request for a PET radiotracer for diseases associated with translocator protein overexpression, translocator protein-targeting ligand for fluorescence imaging diagnosis and photodynamic therapy, and preparation method thereof, WO2019143016. Prof. Lacivita filed Combination serotonin specific reuptake inhibitor and serotonin 1A receptor partial agonist for reducing L-Dopa-induced dyskinesia, US2021393621. Prof. Leopoldo filed Novel tetrahydroisoquinoline compounds for use in diagnosis and treatment of neurodegenerative diseases, WO2012159666A1.

DESCRIPTION OF UNIPR

The University of Parma (UNIPR - www.unipr.it), founded in 962 AD, is one of the oldest universities in the world and one of the most well-known in Italy. Today, it deploys more than 1,700 staff personnel, of which more than 830 professors/researchers, and 30,000 students. It includes three campuses and offers 92 degree programs (7 of which delivered in English), 20 PhD programs, and 39 master programs, coordinated within 9 departments. The departments of the areas of social sciences and humanities, medicine and surgery and veterinary science are located in the city centre, whereas the other departments (areas of food and agriculture, pharmacy, engineering and architecture, mathematical, physical and natural sciences) are located in the Science and Technology Campus, a 77ha area in the southern side of the city, also hosting sports and recreational facilities for staff and students, a **Technology Transfer office**, which plays a valuable role in protecting and commercialising intellectual property developed by UNIPR researchers, and a leading **Industrial Technopole**, an infrastructure that hosts cutting-edge research centres and laboratories for industrial research and technological development. The technopole promotes the encounter between companies and researchers reducing the distance between innovation demand and supply.

Overall, UNIPR has centralized and unit-based support facilities, research infrastructures, and conference areas. Staff and students have access to computers, offices, reading and meeting rooms, software for various discipline/specific computing needs, face-to-face videoconferencing equipment, and a rich library collection. UNIPR has its own **High Performance Computing Cluster** used by researchers of different disciplines to strengthen and innovate their research.

To facilitate broad access to research results, UNIPR requests its researchers to deposit research data and metadata into the **Institutional Research Information System** (CINECA IRIS) to further disseminate them. The repository facilitates the collection and management of data related to all the research products and is **OPENAIRE-compliant**.

A.2 SCIENTIFIC EXPERTISE

UNIPR includes 833 professor/researchers, of which 45 members of this staff work on topics related to Neuroscience and Neuropharmacology. UNIPR is worldwide famous since 4 decades for the widely established contribution to the elucidation of the brain's motor function and anatomical organization, as well as for the demonstration of the so-called "motor-based perceptual and social functions". Among these latter, the discovery of "mirror neurons" in 1992 constitutes a foundational milestone in neuroscience, that gave rise to the now widely established field of "social and affective neurosciences". This discovery brought to the team members several international prizes (including the Brain Prize) and tens of thousands of citations; it impacted on neurodevelopmental and neuropsychiatric fields, as well as, more recently, in neurorehabilitation and newly developed technological approaches to boost plasticity of the brain's motor system.

UNIPR brings together different teams involved in Neurobiological/neuropharmacological and System neuroscience research. In the last 10 years, UNIPR researchers involved in the PE (n=14) published 430 papers in Neuroscientific and generalists peer-reviewed international journals, obtaining 21,125 citations, and exhibiting an average H-index of 39.

The discoveries achieved by UNIPR neuroscientific team members have been included in the most prestigious international Neuroscience handbooks (e.g. Principles of Neural Sciences by Erick Kandel), with several chapters contributed by UNIPR staff. Thanks to a consolidated tradition in the neurophysiological and neuroanatomical studies on animal models, particularly non-human primates, the Neuroscience group of UNIPR has obtained, among others, **6 ERC grants** (2 of which still ongoing, and 1 ERC CoG just started) and other important **European and International grants and awards**, which allowed to create state-of-the-art and unique facilities for housing monkeys and performing experiments with cutting-edge technologies, such as telemetric techniques for the unprecedented study of the cellular bases of unconstrained, spontaneous behaviors and social interaction. Several research lines on the interaction between environmental factors, such as psychosocial stress, and genetics in a life-span perspective involve highly multidisciplinary groups of researchers which combine skills ranging from neuroethology, to metabolomic, genetics, and clinical neuroscience. Research lines in the field of "social neuroscience" translated the mechanisms discovered in the animal model to the human brain using fMRI (3T scanner available at the Department of Medicine and Surgery), EEG, TMS and EMG: all these techniques are available in UNIPR laboratories and foster international collaboration with tens of national

and international institutions (see A5). The "action observation therapy" has been proposed and applied for motor neurorehabilitation in several types of patients, including children with cerebral palsy and neurodevelopmental disorders, and it has been recently recognized also by two grants from the Ministry of Health to UNIPR team members. Finally, UNIPR has a team involved in drug design with a long-standing expertise in modeling, synthesis, and developing new compounds (15 patents) such as those for modulating endocannabinoid signals.
Thus, UNIPR team combine expertise from neurobiology and neurophysiology to clinical neuroscience and development of new drugs; access to cutting-edge technologies and state-of-the-art facilities and laboratories supports research in the broad fields of neuroscience and neuropharmacology. UNIPR has a PhD program in Neuroscience with about 10 fellowships every year, one of which is for an Industrial PhD program.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

UNIPR is one of the best performing universities in Italy in the major EU funding schemes, with more than 100 grants in FP7 and H2020. The scientific production of the Institute's researchers in the last 10 years has been greater than 19,711 papers and 28 patents.
UNIPR has obtained numerous international and national projects focused on Neuroscience, for a total of more than € 17 million in the last 20 years. Thus, the experience of UNIPR in managing research project and of the quality of the research groups involved in the PE is proved by the following track record of grants awarded. In System Neuroscience, 2 ERC Advanced grants, 2 ERC Consolidator (one of which in collaboration with University of Turin), 1 ERC Proof of concept and 1 ERC Starting grant have been awarded to researchers hosted in UNIPR, for a total of about € 9 million. Furthermore, 5 European collaborative projects and 2 Marie Skłodowska-Curie Training Networks have been awarded to UNIPR neuroscientists. In the field of Neurobiology of development, one EU-LIFE project stands out. Other neuroscience projects, including those on neuropharmacology, have been awarded by funding agencies of the USA (ARO, NIH) and of the Italian Government (MIUR, Min. Salute), as well as by private foundations and companies. In the present moment, 8 international and 9 national projects on various neuroscience topics awarded to the researchers participating to the PE are ongoing, for a total of approximately € 8 million. In addition to these projects managed by PIs part of the PE, there are several national and international projects on neuroscience and neuropharmacology, in which UNIPR researchers are participating as collaborators.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

National collaborations: Italian Institute of Technology, Neuroscience and Behaviour, Rome; Fondazione Stella Maris and Imago7 (7Tesla MRI), Pisa; Istituto Neurologico Carlo Besta, Fondazione IRCCS, Milano; Fondazione Bietti IRCCS, Roma; IRCCS Mondino, Pavia; Istituto Superiore di Sanità.
Italian Universities: University of Turin and NICO-Neuroscience Institute Cavaliere Ottolenghi–University of Turin; University of Padua; University La Sapienza, Rome; University of Firenze; University Vanvitelli; University of Naples, Federico II.
International collaborations. **EU**: CNRS, Lyon, France; University of Freiburg, Germany; Leuven Brain Institute, KU Leuven, Belgium; School of Advanced Study, University of London, UK; University of Oxford, UK; University of Leeds, UK; University of Straithclide, UK; University of Sheffield, UK; Humboldt University, Berlin; Inserm Sorbonne, Paris; University of Cergy-Pontoise, CNR-ISC, Paris; University of Granada, ES; University of Eastern Finland; Bar Ilan University, Israel. **USA and Canada**: University of Minnesota Medical School; National Institute of Health; Columbia University, NYC; New York University Coll., NYC; Northeastern University, Boston; University of Missouri; University of California, Irvine; University of Maryland; University of Ottawa; McGill University, Montreal.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Development of probes and systems for recording neural activity: Atlas Neuro| Home Neuro Probe – Advanced Assay Instruments for the Bioscience Community, 15 patents granted in Italy, EU, USA, Canada, China and several other countries (M. Mor). Several patents on endocannabinoid modulators, assigned to the University of Parma, have been licensed for drug development.

DESCRIPTION OF UNIFI

UNIVERSITÀ DEGLI STUDI FIRENZE

The University of Florence (UNIFI) is one of the largest organizations for research and higher education in Italy, with 1,800 structured professors and researchers, a population of about 51,000 enrolled students, and over 1,600 doctoral and postdoctoral ones.

MISSION: It promotes the development of critical knowledge which is open to the exchange of information, cultural cooperation and interaction. It regards the furthering of knowledge as a qualifying characteristic of its activities and a foundation of cultural and professional education.

HUMAN RESOURCES STRATEGY FOR RESEARCHERS: The University of Florence has adhered to the principles of the European Charter and Code for Researchers and, since December 2018, is one of the 13 Italian universities that have been granted the HRS4R Human Resources Strategy for Researchers Award (https://www.unifi.it/vp-10899-hrs4r-excellence-in-research.html?newlang=eng).

A.2 SCIENTIFIC EXPERTISE

DIMENSION: The University of Florence is one of the largest organizations for research and higher education in Italy with 49,432 students, 388 Full Professors, 802 Associate Professors, 180 Researchers, 319 Temporary Researchers, 930 PhD students, 735 research fellows and 1,380 technical and administrative staff.

INTERNAL ORGANIZATION: Researchers at the University of Florence operate within 21 different departments and can benefit from approximately 40 research structures, including inter-departmental and inter-university centres, as well as specialized research, knowledge transfer and advanced training centres. Moreover, a significant part of the yearly budget is allocated to scientific research.

The University of Florence participates with about 250 researchers (mainly physicians, but also biologists, and physicists) in the Careggi University Hospital (Azienda Ospedaliero Univeritaria Careggi) following a partnership agreement with the Tuscan Region Government according to the Italian law 517/99. This General Hospital, accounting of 5000 employees, out of them 1000 physicians, and about 1000 inpatients places, is the largest of central Italy and is one of the main sites of biomedical research in Italy.

Number of publications (last 10 years):

Total UNIFI: 81,558

Neuroscience and Neuropharmacology: 593

Number of publications in the top 10% most cited publications worldwide: 15.90%

High value research equipment and centers:

Animal house, 2D and 3D cellular models, animal models, microscopy setups of highest resolution for single molecule analysis, human and animal tissue and live imaging and time-lapse, Video-EEG analysis laboratory, CISM center for mass-spectrometry, CISPIM (center with MRI, CT, PET and SPECT for small animals), CERM center for MRI, IFAC center for confocal microscopy, FT-LAB of forensic toxicology, DSBSC Molecular Medicine facility, NGS molecular and cellular core facility (Meyer Children Hospital), Technological Park for transcriptomic evaluation (Nanostring technology).

RESEARCH AREA: UNIFI Research Community can rely on dedicated staff with extensive experience in the field of support services for researchers. UNIFI Research Area can count on 40 staff units in charge of supporting research quality policies, technology transfer and participation in funding opportunities at regional, national, European and international level. The Area offers, among others, a dedicated information service, management and reporting activities for funded projects, support for patents, spin-offs, start-ups and joint labs.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

EUROPEAN FUNDING: Recently, the University of Florence has been ranked among top Italian Universities for the distribution of national research funds, and it is one of the most active Italian universities in terms of European projects and related grants. In the 7th Framework Programme UNIFI was funded 139 projects for a total of 38 million Euros. Within Horizon 2020 UNIFI is involved in 147 projects for a total funding of 54 million Euros.

Number of competitive active International and National Research Project Grants in Neuroscience and Neuropharmacology: 111

Total funding: € 13,691,931.58

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

The researchers of UNIFI have standing collaborations with 536 Universities and Academic Centers and with a number of National and International Research Centers and Netwoks, including: ERC grant networks, Horizon 2020, PRIN, Ricerca Finalizzata, IRCCS Health Ministry.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Patents

Italian priority #	Marketing name of the invention	Status
10201900001890	"A_atrofi" muscle mass regulators	Active
102019000025066	Early diagnosis of neurodegenerative disease and monitoring of anti-rejection transplant therapies	Granted
102016000070952	New compounds for the treatment of acute pain	Granted
102018000006166	Method and device for the analysis of oxidative stress	Granted
102021000025124	Medicamento per uso nel prevenire o trattare il dolore nocicettivo e/o viscerale	Active; secrecy ongoing
102020000012298	Metodo per valutare le accelerazioni subite dalla testa, e dispositivo di protezione per la testa	Active
102019000014748	Super-resolution spectroscopy	Granted
102016000132604	Real-time image-based autofocus	Granted
102018000008647	Non-invasive diagnostics of photonic circuits	Granted

Spin Off

FloNext Srl, spin-off UNIFI (Development of pharmacological strategies for therapeutic targets in glial cells).

Joint Laboratory MIA-LAB "Microbiome-Immunity Axis research for a Circular Health".

DESCRIPTION OF HSM

The Ospedale Policlinico San Martino (HSM) has always been a health landmark. With its five centuries of history, it is the main "health hub" attracting patients from the metropolitan area and from all over Liguria, but also from outside the Region. After the merging of the San Martino University Hospital and the Scientific Institute for Cancer Research, the "IRCCS San Martino Hospital – IST National Cancer Research Institute" was established in 2011, with a particular focus on hematology and oncology. At the end of 2017, the name of the Institute was changed to "IRCCS Policlinico San Martino Hospital". On May 3rd 2018 HSM was certified by the Italian Ministry of Health also for specialization in Neuroscience. The Institute provides healthcare services for the diagnosis and treatment of illnesses in in-patient and out-patient settings. In addition to being a general hospital, HSM is a leading institution in the field of research, diagnosis and treatment of neurological and psychiatric disorders of adulthood including immune-mediated diseases of the central and peripheral nervous system such as multiple sclerosis, neurodegenerative diseases such as Alzheimer and Parkinson disease, neuromuscular diseases, including genetically determined neuropathies, stroke, diseases linked to altered synaptic transmission, brain tumors and psychiatric diseases. Specific research lines are focused on psychiatry illnesses, stroke, immune-mediated diseases of the nervous system, neurodegenerative diseases, neuromuscular diseases, epilepsy and on neural plasticity under pathological conditions and upon neurorehabilitation treatments. In addition to the offer in all major surgical medical services, HSM is at the forefront in the diagnosis and treatment of major hemato-oncological diseases, with activities ranging from acute leukemia to marrow transplants, to solid tumors classified as "big-killers". The large cohort of patients allows clinical studies on chemotherapy drugs and also on new molecular targets.

A.2 SCIENTIFIC EXPERTISE

In 2021 HSM research staff was composed of 413 persons (130 researchers bench side; 201 researchers bed side; 57 administrative employers for research support activities; 55 technicians). The researchers are committed to a high level of scientific production with the publication of papers in the field of Oncology, Cardiology and Neuroscience (a total of 4,566 in the past ten years; Total Impact Factor: 22,644.17) and widespread participation at international conferences. Normalised Impact Factor for the year 2021 is 3,512.48 obtained from 767 publications (n. 669 publications with positive index of comparison with the IRCCS reference map). Among them 420 publications are related to neuroscience field. Furthermore, over the last year, two patent applications have been filed: one in drug delivery systems and one in pharmaceuticals. Clinical research is a core activity: in 2021 the number of patients recruited in multi-centre clinical trials which started in the last 5 years is 2,275, ongoing studies are 239. HSM promotes and coordinates about 70 no profit clinical studies per year (77 studies approved by Competent Authorities during 2021). Several of them are multicentre studies focused on neuroscience related fields aimed to improve standard therapies and diagnostic techniques, to find new prognostic criteria and techniques to personalize therapies and to improve clinical practice. HSM hosts the School of Medicine and Pharmaceutical Sciences which includes the Degree Course in Medicine and Surgery, Specialization Diplomas, PhD courses in several life sciences areas, first and second level Master Courses and Degree Courses in health professions. Thanks to an agreement with the University of Genoa, industrial PhDs courses are being implemented. HSM has specific research facilities such as a dedicated grant office, a clinical trial office and several core facilities including an animal facility, a Biological Resource Centre (CRB-HSM, repository of cancer and neural specimen), microscopy, genomic, proteomic, cytomic and imaging (for humans and small animals) facilities and the recently established Life Science Computational Lab for AI-based analysis of the data generated within the hospital campus.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

In 2021 the total value of funding on a competitive basis received in HSM during the year was 6,405,659,95; divided as follows: € 271,152.87 for research projects from EU public bodies; € 2,340,555.42 for research projects from non-EU public bodies and € 3,793,951.66 for research projects from private bodies. The total number of projects financed during the year by non-ministerial competitive funds from public bodies (other than the Ministry of Health) and Italian and foreign private bodies was 232. Selected ongoing projects in the field of Neuroscience_HSM as Coordinating Center: 2020/R-SINGLE/027, "Exploring pathogenic mechanisms associated with depression in multiple sclerosis: functional and structural dysconnectivity of neurotransmitter-related nuclei", Inglese Maria Matilde,

FISM; 2021/Special-Multi/001, "A prospective study for the evaluation of immunogenicity of anti-SARS-CoV2 vaccines in patients with Multiple Sclerosis. CovaxiMS: Covid-19 vaccine in Multiple Sclerosis", Sormani Maria Pia, FISM; "Solution Towards Occupational Rehabilitation for Multiple Sclerosis (STORMS)", Trompetto Carlo, Merck Sharp & Dhome; JPND2020-568-126, "Phage-based targeted neural stimulation in neurodegenerative diseases -NeuroPhage", Benfenati Fabio, EC; NET-2019-12371188, "All-Ages Malignant Glioma: Holistic Management in The Personalised Minimally-Invasive Medicine Era - From Lab To Rehab - GLI-HOPE", Zona Gianluigi, Ministero della Salute; "PRISMA: Prevenzione rischi, Reti collaborative, Inclusione lavorativa nella Sclerosi Multipla: dalla conoscenza della realtà lavorativa delle persone con SM in Italia alla messa a punto di modelli e programmi innovativi per l'inclusione lavorativa", Inglese Maria Matilde, INAIL, Roma; GR-2019-12370176, "Targeting the control of neuronal gene expression as a therapeutic approach to the EAE model of multiple sclerosis", Grasselli Giorgio, Ministero della Salute; 2019_R-SINGLE_038, "Comprendere il controllo neurale della linfopoiesi nell'Encefalite Autoimmune Sperimentale per designare nuove terapie e monitorare l'attivazione del sistema immunitario nella Sclerosi Multipla", Uccelli Antonio, FISM; E002117099, "Auto-anticorpi anti-NG2 come possibile biomaker prognostico di progressione di malattia in pazienti affetti da Sclerosi Multipla: possibili implicazioni nella rimielinizzazione", Ferrara Giovanni, Sanofi Genzyme; 2019.933, "Studio del controllo neurale della risposta immunitaria antitumorale per favorire la cura dei gliomi", Uccelli Antonio, Compagnia di San Paolo; 2019.935"La trascrizione di geni sinaptici come target per un approccio terapeutico al modello EAE della Sclerosi Multipla", Benfenati Fabio, Compagnia di San Paolo; EURONANOMED-2019-2366471, "Photosensitive nanotools for neural stimulation and rescue of degenerative blindness (NanoLight)", Benfenati Fabio, EC; NET-2018-12366666, "Artificial intelligence of imaging and clinical neurological data for predictive, preventive and personalized (P3) medicine (NeuroArt P3)", Uccelli Antonio, Ministero della Salute; RF-2018-12366238, "In vivo assessment of demyelination and remyelination in patients with Multiple Sclerosis: computational approach to brain and spinal cord amyloid PET", Morbelli S.D., Ministero della Salute; NET-2016-02361805, "Development and implementation of common strategy for the management of community-dwelling older subjects with multimorbidity and polypharmacy: integration with a multicomponent intervention platform by using domotic, robotic and telecare systems", Trompetto Carlo, Regione Liguria.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

HSM is included among the Institutes involved in the Thematic Networks promoted and financed by the Ministry of Health, i.e. the Alliance Against Cancer (ACC) and the Neuroscience and Neurorehabilitation Network (RIN). Because of its expertise in the study and treatment of cardiovascular diseases in adults, and in particular in the field of cardiological diseases, cardiac surgery and vascular surgery, HSM has also been admitted to the IRCCS Cardiological Network. HSM is member of OECI (Organization of European Cancer Institutes) and of two European Reference Networks for rare diseases (ERN) focusing on diseases of the nervous system (namely EURACAN, an ERN for all rare adult solid cancers, including two domains on neuroendocrine tumors and on rare neoplasm of the brain and spinal cord; EURO-NMD, Network for Rare Neuromuscular Disorders). In carrying out its experimental and clinical research programmes, HSM has developed scientific collaboration agreements with Universities, IRCCS, Institutions and public and private, national, and international entities in the fields related to its research activities. HSM is also a member of BMRI (Biobanking and Biomolecular Resources Research Infrastructure) and through its biobanking facility collects biospecimens from several neurological diseases and joined the European *BioMS – Consortium* for CSF biomarker research.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

HSM has a Technology Transfer Office with two people fully dedicated in supporting researchers for all the activities related to technology transfer and innovation. It also has legal resources working in all the different aspects of intellectual property rights. Patents: two patents have been developed by HSM in the last year. Spin off: HSM is involved in the creation of 4 new spin- offs, 3 of them focused on neuroscience and neuropharmacology. One spin-off is dedicated to the synthesis of nanoparticles as drug carriers able to overcome the blood brain barrier and to reach specific targets for the therapies of different diseases of the nervous system; two spin-offs focus on the design and development of wearables devices for post stroke rehabilitation. In addition, HSM has several partnerships with private companies and some of them are located within the campus including Bio4Dreams, Tib-Molbiol, Active Cells Srl and 3Brain.

DESCRIPTION OF ISNB

The Institute of Neurological Science is a Scientific Institute for Research and Healthcare (IRCCS) recognized by the Ministry of Health in 2011 in the discipline of Neurological Sciences. Like all IRCCSs, the Institute of Neurological Sciences (ISNB) is a research hospital of excellence that pursues clinical, translational and basic research. The ISNB organizes its research activities along lines approved by the Ministry of Health on a three-year basis. The Institute is currently pursuing four research lines: 1) neurological and neuropsychiatric diseases of adulthood and brain aging: genetic basis, pathogenetic mechanisms, deep phenotyping and personalized therapy; 2) acute and chronic neurological and neuropsychiatric diseases of the developmental age: genetic basis, pathogenetic mechanisms, deep phenotyping and personalized therapy; 3) emergency neurology; 4) neurosurgery, oncology of the nervous system, oncological neuropathology. The Institute promotes processes oriented towards the development of research, in particular spontaneous research and targeted research promoted by public and non-profit organisations, encourages and supports collaboration with private organisations and industry, also by developing partnership projects for long-term research programs, and pursues cooperation and the exchange of knowledge with other IRCCSs in the neurosciences and other Italian and international research centres, also through participation in the relevant networks and other forms of research organisation. The translational and basic neurosciences research is developed thanks to the following Laboratories: Neurogenetics (exome and genome NGS sequencing), Molecular and cell biology (iPSCs, gene editing, organoids), Neuropathology of neurodegenerative diseases (pathological and, Neuroimmunology and Neuromuscular disorders, Proteomics and Metabolomics (mass spectrometry), Brain Aging (geroscience: epigenetics, -omics) and Neuroimaging (pipelines of structural and functional MR imaging analysis, radiomics, connectomics).

A.2 SCIENTIFIC EXPERTISE

Currently there are more than 230 researchers and 32 clinical/research units, more than 1.000 square meters dedicated to neuroscience research laboratories, and a Neuroscience Biobank that collects biological samples (blood, CSF, DNA etc.), cell lines and brain and skeletal muscle biopsies/tissues. The overall scientific production in the last 10 years includes 1.630 contributions in neuroscience journals for a total normalised IF of 7.838. Since 2013 the institute has collected research grants for more than € 62 Ml from public (Land, Ministry of Health, Ministry of Economy, EU) and private institutions (research and bank foundations and research associations). The Institute is engaged in four Rare Diseases networks being recognized as European Reference Centers, within the European Reference Network (ERN) for Rare Diseases (Neurological, Neuromuscolar, Epilepsy and Adult solid Tumors), coordinates the Italian IRCCS Neuroscience and Rehabilitation Network (n. 30 IRCCS – Research Hospitals) and is part of the Italian IRCCS Paediatric Network (n. 11 IRCCS).

The Functional and Molecular Neuroimaging Unit, embedded within the Institute of Neurological Sciences, leads research, development, and translation of novel neuroimaging techniques. The lab benefits from a unique and vibrant milieu with clinicians, physicists, technologists, molecular biologists, and phycologists working side-by-side. Over the past 10 years, the lab generated 7883 citations through several papers in high-impact journals. The translational effort led to the development of acquisition and post-processing techniques to assess neuronal plasticity and connectivity in a clinical setting with the capability of deploying advanced imaging protocols in every patient referred to the Institute for advanced neuroimaging assessment. Currently, the lab is actively researching novel imaging techniques to refine the assessment of brain connectivity, plasticity, and metabolic activity. Spoke 4. In the context of the brain-body connection the Institute has focused its research activity on biomarkers of neurodegenerative diseases in easily accessible tissue such as the skin. As a result it has been developed a new biomarker for neurodegenerative disorders characterized by the abnormal aggregation of alpha-synuclein. The research group published in the last 9 years 22 papers in indexed journals focused on the differentiation of synucleinopathies from other neurodegenerative diseases as Alzheimer disease or atypical parkinsonisms related to tauopathies but also to differentiate the variants of synucleinopathy (e.g. PD from MSA or PD from DLB or DLB from MSA) usually presenting a different prognosis. Spoke 6. The Institute has an internationally recognized leadership in the study of biomarkers (liquoral, blood - liquid biopsy- and imaging), genetics and epigenetics of neurodegenerative diseases and their link to aging. Among biomarkers, it is most relevant the expertise in the study of eye (OCT, OCT-angiography,

neurophysiology, pupillometry) to get non-invasive biomarkers for AD and PD. An asset of Institute is the capability to correlate biomarkers of neurodegenerative disorders with in vivo functional connectivity MRI measures. Spoke 7. The research activity of the Institute is focused on the role of antibodies against neuronal and glial targets in CNS disorders. The Neuroimmunology Lab is one of the few national research laboratories for the diagnosis of autoimmune encephalitis and for the study of antibody-mediated disorders that are potentially responsive to immunotherapy. The Lab investigated the role of current clinical criteria and advanced techniques of antibody identification in the diagnosis of these rare conditions. Most recent achievements are: a) the pathogenic role of antibodies against CASPR2 in autoimmune encephalitis studied in animal models that could be used for investigating in vivo the effects of specific immunomodulatory treatments; b) the study of the frequency and role of antibodies to neuronal surface proteins in different neurological conditions of suspected autoimmune aetiology such as narcolepsy, movement disorders, chronic fatigue syndrome and nodding syndrome.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

The Institute supports, with almost 20 full time equivalents, the research activities through a Grant Office and a multidisciplinary and integrated Research Area that supports the researchers from the design of the study (methodological and statistical issues) to the submission to the Ethics Committee and to the executive phase (legal issues, project management, scientific and administrative reporting).
The Institute is currently participating to 19 pharmacological trials in neurological disorders (neurodegenerative, neuro-immunological) and to 3 industrial partnerships with an MRI vendor (Siemens Healthcare), in 2021 has started 65 non-profit studies, and is currently participating to 4 Horizon 2020 projects (MAIA, ORCHESTRA, ENIGHTME, TRIGGER) and has coordinated the PROPAG-AGEING project. The Institute is one of the partners of the AIFA-Ministry of Health INTERCEPTOR project.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

The Institute coordinates the Italian IRCCS Neuroscience and Rehabilitation Network which involves more than 500 researchers directly engaged in the scientific activities, mainly supported by the Ministry of Health, of five National Virtual Institutes (IVN) of pathology: Dementia, PD and Movement Disorders, SM and Neuro-immunological disorders, Rare Diseases and Cerebrovascular Disorders. The Institute is reference center of four the ERNs for Rare Diseases and is member of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium.
Spoke 2. Main international collaborations: Dr. D Zaca', Dr. G Buonincontri, Siemens Healthineers; Dr. F Riemer, Haukeland University Hospital; Dr. JT Grist, University of Oxford; Prof. FA Gallagher, University of Cambridge. Spoke 4. Main international collaborations: Prof. Martin Ingelsson (University of Toronto, Canada), Prof. Wenquan Zou (University of Cleveland, USA), Prof. Wolfgang Oertel, (University Marburg, Germany); Dr Kathrin Doppler (University Würzburg, Germany); Prof. Claudio Soto (University of Texas, Houston, USA); Prof. Chris Gibbons (Harvard Medical School, Boston, USA). Spoke 6. Main international collaborations. Aging and neurodegenerative disorders: Prof. Fabio Macciardi, University of California, Irvine; Prof. Kevin Mills, University College of London, UCL Great Ormond Street Institute of Child Health; Prof. Brit Mollenhauer, Professor for Translational Biomarkers in Neurodegenerative Disorders at University Medical Center Goettingen. Mitochondrial diseases: Prof. Alfredo A. Sadun, Doheny Eye Institute, Keck School of Medicine - University of Southern California, Los Angeles, California, USA; Prof. Jens Hannibal, Department of Clinical Biochemistry, Bispebjerg Fredriksberg Hospital, Copenaghen, Denmark Prof. Maya Koronyo-Hamaoui, Cedars-Sinai Medical Center, Los Angeles, USA; Prof. Patrick Yu-Wai-Man, Department of Clinical Neuroscience, Mitochondrial Biology Unit, MRC and Cambridge Centre for Brain Repair Dr. Jason Park, Department of Ophthalmology and Visual Sciences, University of Illinois, Chicago, USA. Degenerative diseases: Central Nervous System Unit at Istituto Superiore di Sanità, Rome, Italy (Dssa Ladogana, Dssa Poleggi); Eric Vallabh Minikel, Ph.D. Harvard Medical School, Boston, MA, US; Prof Simon Mead, UCL, London UK. Spoke 7. Main national and international collaborations: Associazione Italiana di Neuroimmunologia (AINI); European Academy of Neurology (EAN, panel of neuroimmunology); Dr Matteo Gastaldi, IRCCS Fondazione Mondino, Pavia; Prof. Alessandro Silvani, Università di Bologna; Prof. Angela Vincent, University of Oxford, UK; Dr Richard Idro, Makerere University, Kampala, Uganda.

DESCRIPTION OF SSSA

Scuola Superiore Sant'Anna (SSSA, http://www.santannapisa.it) is a public university whose mission is to address excellence in both education and research in engineering, medicine, agriculture, economics, management, law and political science. The scientists at SSSA have been involved in several activities on neuroscience, biorobotics, neuroengineering, photonics and optoelectronics, and translational medicine.

A.2 SCIENTIFIC EXPERTISE

Scuola Superiore Sant'Anna has been quite active in the past 10 years on the development of innovative devices for neuroscience and neuropharmacology with a particular attention to the development of wearable and implantable systems to understand sensory-motor control and to restore sensory, motor, and autonomic functions in people with different types of disabilities. Here few examples of the main achievements in the recent past:

1. **Development of neuroprostheses:** we developed and used different types of interfaces with the nervous system to develop advanced medical devices. Sant'Anna developed the first European bi-directionally controlled hand prosthesis by using PNS intraneural interfaces (Raspopovic et al., 2014, Oddo et al., 2016, Valle et al., 2018, D'Anna et al., 2019, Petrini et al., 2019) promoting neural plasticity (Rossini et al., 2010, Granata et al., 2019). We also recently showed that this approach for lower limbs (Petrini et al., 2019) and optic nerve stimulation (Gaillet et al., 2019). We also developed a system to restore grasping functions in tetraplegic subjects (Badi et al., 2021). Finally, in collaboration with Prof. Courtine (EPFL), we worked to restore locomotion after spinal cord injury using robotics and epidural electrical stimulation (Capogrosso et al., 2016, Formento et al., 2018). We are working on several aspects of deep brain stimulation therapies to render them a more effective treatment to tackle the symptoms of Parkinson's Disease and other movement disorders (Vissani et al., 2020) and to develop "electroceutical" solutions to address cardiac or metabolic issues (Cracchiolo et al. 2020).
2. **Development of robotic systems for neurorehabilitation:** we have a long tradition in design of advanced virtual reality devices, exoskeleton and robotic devices for stroke rehabilitation. Many robotic devices have been developed and validated in pilot and randomized control trials, and in particular upper limb exoskeleton (Frisoli et al., 2009, Frisoli 2022, Pierella et al., 2020), hand exoskeleton (Sarac 2019, Leonardis 2015), BCI for neuro-motor-control (Barsotti, 2015, Tortora et al., 2020), AI algorithms for prediction of motor recovery (Camardella 2022). We also worked in collaboration with Prof. Caleo (University of Padova and CNR, Italy) to understand the basic mechanism of robot-based neurorehabilitation in rodents (Spalletti et al., 2014, Micera et al., 2020, Pasquini et al., 2022)
3. **Development of animal models of brain-heart axis dysfunction:** we have a decades-long history of developing and characterizing clinically relevant animal models of heart failure using a multimodal approach (Recchia et al., 2013). Some alterations of brain-heart connection can induce anatomical and functional cardiac injury, and vice versa. A better understanding of bidirectional flow of information through the sympathetic and parasympathetic nervous system within the brain-heart axis is needed to improve management and prognosis of patients with heart failure (Baroni et al., 2021) or other severe multiorgan disease syndromes (Lionetti V et al. 2021).
4. **Development of in vitro models of neurodegeneration:** to study the contribution of cytoskeletal damage in neurodegenerative diseases, we have developed various murine and human cell models, to which chemical and physical stimulations can be applied depending on the context, including as an example hypergravity. We have also developed more complex models, that is 3D retinal organoids from mouse Embryonic Stem cells, for morphological, histological and electrophysiological analysis of pathological and wild type precursors of photoreceptors, in the context of studies on retinal neurodegeneration.

Scuola Sant'Anna has two large Institutes (BioRobotics and Mechanical Intelligence) with more than 20 faculties working on wearable and implantable devices and on organoids with more than 50 PhD students. In the past 10 years, the researchers of Scuola Sant'Anna have filled several patents on wearable and implantable devices related to PE12 and published papers in extremely prestigious high impact factor journals such as in Nature (1), Science (2), Science Translational Medicine (3), Nature Medicine (3), Science Robotics (2), etc.

Scuola Sant'Anna has advanced facilities to develop implantable devices (in particular a state-of-the-art clean room) and to perform animal experiments with small and medium size animals.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

Scuola Superiore Sant'Anna has a strong experience in managing and implementing very large research projects in different fields and in particular in biomedical engineering, robotics and neuroengineering. Just few examples are the European Projects Neurobotics (probably the first large EU project on neuroscience and robotics), Octopus (soft robotics with a large neuroscience partnership), NEBIAS (developing the first hand prosthesis with sensory feedback using neural implants).

More in general, as regards the resources needed to carry out its research, training and third mission, Scuola Sant'Anna is characterized by the ability to attract non-ministerial funding which, even in presence of critical exogenous factors determined by the pandemic crisis remained at relevant levels. For example, 2020 shows a strong resilience capacity, leading to an almost doubling of external funding acquired (around 38M€) compared to the average of the previous three years (around 22M€) with the largest average annual income per single faculty in Italy.

As part of the Horizon 2020 projects, it is worth noting that in 2020 we launched 28 projects, four of which in the role of coordinator. From the start of the Horizon 2020 Program, 2015, up to 2020, the Grant Agreements signed and therefore the projects started are in total 84, of which 18 as coordinators. More in general, Scuola Sant'Anna has currently more than 800 different projects active for a total funding of 168M€.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

Scuola Superiore Sant'Anna is currently involved in several collaborations with other prestigious universities working on neuroscience and neurotechnologies in Europe (Cambridge, Imperial College, EPFL, Clinatec Grenoble, Oxford etc.) and in Italy (Scuola Normale Superiore, IMT Lucca, SISSA etc.) and with clinical partners (IRCCS don Gnocchi, IRCCS, Stella Maris, IRCCS San Raffaele Pisana, University Hospitals of Pisa and Florence etc.). Scuola Sant'Anna is also involved in several European Training Networks in the field and in EBRAINS (the new network created as a follow-up of the Human Brain project).

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Scuola Sant'Anna has a large experience in creating innovative startup companies. For example, faculties of the BioRobotics Institute recently created IUVO, a company work on wearable devices, which was then acquired by Stellantis (via COMAU) and Ossur (leader in prosthetic development). Moreover, we created and are currently coordinating ARTES 4.0 (Advanced Robotics and enabling digital TEchnologies & Systems) with the aim of associating university partners, research institutions, highly qualified training institutes, foundations, third sector entities, companies and non-profit organizations, but also associations and companies innovative. The aim is to provide partners and industry (especially SMEs) with dedicated technologies and services that meet their needs through activities such as orientation, training, innovation projects, industrial research and experimental development. We are also coordinating the project FELIX (Integrated photonics and electronics for industry) funded by the Tuscany Region as part of the interventions of the European Regional Development Fund POR-CREO 2014-2020. The project made it possible to obtain a coordinated technological upgrade of the research infrastructures of the following public research organizations. The project makes it possible to offer interested companies, with particular attention to medium and small ones, a series of 17 technological services to support company research and development in the field of high technology.

DESCRIPTION OF OPBG

Ospedale Pediatrico Bambino Gesu' (OPBG) is a Scientific Institute for Research, Hospitalization and Health Care and an Academic Medical Center. It is Italy's main pediatric Hospital and provides third level health care for children while performing basic, clinical, and translational research activities. OPBG is part of the Italian National Healthcare System and is widely recognized as referral center for all pediatrics specialties at national and international level. The Hospital provides a complete range of healthcare services to children. OPBG has a total permanent staff of approx. 3,000, of which 550 physicians, involved both in clinical and in research activities. OPBG's researchers publish over 900 peer reviewed scientific publications, reaching approx. 3.500 points of Normalized Impact Factor by Italian Ministry of Health, for an overall crude Impact Factor approx. 4,000 points. Active projects – over 700 –, primarily in the areas of clinical/translational and biomedical research. More than half of the studies, above all interventional projects, were dedicated to rare diseases and cancers. The activities were undertaken in cooperation with approx. 2,000 organizations, of which over 80% foreign.

A.2 SCIENTIFIC EXPERTISE

OPBG's researchers publish over 900 peer reviewed scientific publications, reaching approx. 3.500 points of Normalized Impact Factor by Italian Ministry of Health, for an overall crude Impact Factor approx. 4,000 points. Active projects – over 700 –, primarily in the areas of clinical/translational and biomedical research. More than half of the studies, above all interventional projects, were dedicated to rare diseases and cancers. The activities were undertaken in cooperation with approx. 2,000 organizations, of which over 80% foreign.
Within the Department of Neuroscience activities are focused on different topics, the total Impact Factor for the 2021 reached almost 1.00 points for a total amount of 263 publications.

Research Area	N° Publications	Impact factor
Neurological Science and Rehabilitation medicine Research Area	152	536
Neuropsychiatry Research Unit	44	184
Neuromuscular Diseases Research Unit	67	262

The Department of Neurosciences is committed to the diagnosis and cure of nervous system diseases, from neurologic pathologies to psychiatric with a multidisciplinary approach. Due to the high level of clinical assistance and specialization and for their outstanding scientific performances and their engagement in national and international research projects, Several Operative Units of the Department of Neurosciences are currently involved in the activities of many European Reference Networks (ERNs) on Rare Diseases. Moreover, the Department is engaged is several academic activities in close collaboration with the High School of Child Neuropsychiatry of Università Cattolica del Sacro Cuore and Università di Roma Tor Vergata. OPBG's Research Laboratories are located in a 5,000 sqm meters research facility, fully equipped with high-tech systems, supporting genomics, metagenomics, metabolomics, proteomics, microarray technology, cytogenetic and FISH applications, cytofluorimetry and cell sorting, cell and molecular biology: fast real time qPCR systems, also with array technology to provide flexible solutions for high-throughput gene expression, miRNA, or genotyping analysis; new technologies for Sanger sequencing (up to 24 capillaries) with factory standardization and optional in-lane normalization and real-time data quality assessment; next generation sequencing systems (array-based pyrosequencing and sequencing by synthesis) for exome, transcriptome, and whole-genome analysis in genomics and metagenomics; high resolution microarray scanner system; cutting-edge array scanner for SNP genotyping, structural variation analysis, and genome-wide association studies (GWAS) with a productivity up to 96 multi-sample chips per day; high-performance liquid chromatography systems; QTRAP LC/MS/MS system, capable of functioning as either a dedicated triple quadrupole mass spectrometer for quantitative workflows or as a highly-sensitive linear ion trap mass spectrometer for qualitative workflows.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

OPBG is currently involved 20 European Reference Networks (ERN) on Rare Diseases: aim of this virtual network is to involve healthcare providers across Europe. They aim to facilitate discussion on complex or

rare diseases and conditions that require highly specialized treatment, and concentrated knowledge and resources. Among them the Department of Neurosciences is currently involved in the following ERN:

- ERN EPICARE, European Reference Network for Rare and Complex Epilepsies
- EURO-NMD, European Reference Network for Rare Neuromuscular Diseases
- ERN-RND, European Reference Network for Rare Neurological Diseases

The Department is also partner of RIN "*Rete IRCCS delle Neuroscienze e della Neuroriabilitazione*", the largest Italian research network on neurologic conditions funded in 2017 by Italian Ministry of Health to enhance the dissemination about clinical and research activities and promote international collaborations. In 2020 OPBG research activities involved 719 projects, 302 of which were in the biomedical area, 412 in the clinical/ translational area and five in the infrastructure area. Particular mention should be made of projects funded through dedicated calls for research proposals, promoted by national and international public and private organisations, which envisage a competitive selection mechanism based on the scientific curricula of the researchers, the quality of the project and the expected spin-offs in terms of improving care. There were 152 grants active in 2020, 43% of which were carried out exclusively by Hospital researchers and 57% in cooperation with other research institutes, universities or companies in the sector, including 28% coordinated by OPBG researchers. In the last 2 years, the Department of Neurosciences has been involved in 51 research projects for a total amount of more than 4 mln. €. Among them:

- *Gut Microbiota profiling of pediatric patients with migraine* (Supported by Italian Ministry of Health).
- *SCREEN 4 CARE - Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies* (supported by the European Commission – IMI2).
- *Telemedicine with mobile internet device for innovative care of patients with Epilepsy-TELE-EPIC* (Supported by Italian Ministry of Health).
- *Untreatable early-onset neurodegeneration: establishment of in vitro and in vivo disease models to dissect pathogenesis and develop targeted therapies* (Supported by Italian Ministry of Health).

Of particular interest is the participation of OPBG researchers to Horizon 2020 Funding Programme, recently concluded. In the seven-year period 2014-2020 period, the OPBG took part in 28 projects, obtaining total funding from the European Commission of €10.94 million.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

OPBG activities "*From Research to Market*" are included within the Technology Transfer area of the Scientific Directorate and have the dual purpose of exploiting the results obtained by its researchers and promoting the pathway for their translation into clinical practice. Five new patents applications were filed in 2020, and these are still in the confidentiality period (18 months from filing of the application). The OPBG's total portfolio now includes 15 active patent families. IPRs and Patent applications are the results of research projects conducted in close cooperation with industrial stakeholders. OPBG is increasingly participating in Industry-driven projects that may represent a point of contact with the present application. In particular, it is important to mention that OPBG is partner in 2 "*Accordi per l'Innovazione*" projects, supported by the Italian Ministry of Economic Development, and the lead of Lazio Innova Progetti Strategici 2019 "IMMUNO" a regional network of companies and research centres with the aim to develop a platform for the study and the production of CAR-T cells and their application in oncohematologic diseases. The project has been developed by OPBG together with 1 Pharma Company, one research Centre and 2 SMEs.

DESCRIPTION OF EBRI

Founded in 2005 by the Nobel Laureate Rita Levi-Montalcini in ROMA, EBRI is a non-profit International Research Institute whose aim is to conduct cutting-edge research in the field of Neurosciences, promoting translational clinical applications of the results obtained. The main objective of EBRI is to study higher brain functions such as learning, memory, emotions, at various levels, from molecules, synapses, nerve and glial cells, neuronal circuits and behaviour. Basic Research, will allow identifying the molecular and cellular mechanisms useful for the development of new therapeutic strategies for neuropsychiatric diseases, including Alzheimer's disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Epilepsy, chronic Pain, Neurodevelopmental Disorders and rare genetic diseases. According to the vision of its Founder, the Foundation aims at facilitating the return of young, qualified researchers who have completed their training abroad, giving them the opportunity to return to their home country to set up their independent research activities.

A.2 SCIENTIFIC EXPERTISE

Structured in 10 independent research groups and 3 centralized technological platforms (NGF, Genomics and Bioinformatics) EBRI includes around 50 people among researchers (40), technicians (2), administrators (8). The Foundation uses a multidisciplinary approach and state-of-the-art techniques in genomics, molecular biology, electrophysiology, high resolution imaging, opto/chemogenetics, behaviour, computational sciences and artificial intelligence, to study the brain. According to international standards, EBRI has a prestigious International Scientific Committee, whose objectives are those of assessing ongoing research activities, future projects and recruitment of new researchers. Seventeen years after its foundation, EBRI has become a national and international reference point in the field of Neurosciences, obtaining numerous and significant results. One of the leitmotifs of EBRI's scientific programs concerns Alzheimer's disease (AD), which affects over half a million people in Italy, with very high human and social burden and for which a cure does not exist yet. EBRI has developed an innovative pipeline of new molecules of therapeutic interest for Alzheimer's disease and other forms of Dementias, such as the painless NGF, the scFvA13 and mAb12A12 antibodies. This places EBRI in a very competitive position in the international R & D scenario in the field of AD. EBRI is also very active in the field of Chronic Pain, Neurodevelopmental disorders such as Autism Spectrum Disorders and Epilepsy. EBRI has recently developed a new experimental strategy (called Synactive), to specifically label synapses that have undergone Long Term Potentiation (as opposed to synapses that have simply been activated that could be identified with calcium reporters). The Synactive platform allows to tag potentiated excitatory synapse, by expressing any reporter of interest (including optogenetic or chemogenetic proteins, proteomic baits, intrabodies, imaging proteins etc.) selectively at potentiated post-synapses of a neuron activated during a learning task in vivo. A new line of research aims at identifying, using in vivo electrophysiological recordings from behaving animals during execution of behavioral tasks and optogenetic/chemogenetic tools, neuronal circuits involved in both spatial and social memory, in physiological and pathological conditions. Furthermore, mouse models of autism are currently used to study the mechanisms involved in the generation of brain rhythms, believed to be crucial for higher cognitive functions.

Prof. E. Cherubini (Scientific Director, spoke 1) is an International recognized authority in the field of synaptic transmission and activity-dependent synaptic plasticity processes during postnatal development; Prof. H. Monyer (Group Leader, spoke 2) made revolutionary discoveries in Neurosciences: she was a pioneer in studying inhibitory neurons and their function in neuronal networks, spatial learning and memory; Prof. P. Calissano (EBRI Co-founder, spoke 6) one of the first collaborators of Rita Levi-Momtalcini on NGF, discovered a novel therapeutic antibody targeting a tau toxic peptide, able to rescue memory impairment in AD.

In the last 10 years EBRI has produced 339 publications in the field of Neuroscience and Neuropharmacology (Average IF 6.07), in International Journals, including high impact ones (Cell, Nature Comm, Nature Methods, Neuron, Brain, Cell Death & Differ, PNAS, Biol. Psyc, Cell Report, etc).

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

Over the years, EBRI has been awarded with competitive grants from the EC (ERC, Cooperation, Marie Curie, FP7 and Horizon 2020), the American Alzheimer's Association, the UK Alzheimer's Association, the Armenise-Harvard Foundation, from MUR, Telethon, Italian Multiple Sclerosis Association, ARISLA, Regione Lazio, etc). Recently, the PAINCAGE project (FP7), involving 9 European partners from six countries focused on the identification of new therapeutic targets for chronic pain. The MADIA project

(Horizon 2020) involving ten partners from 5 countries, aimed at identifying biomarkers for the early diagnosis of neurodegenerative diseases. EBRI has also joined though a competitive grant the flagship Human Brain Project (HBP), which has the ambitious goal of achieving a multi-level integrated understanding of brain's structure and function at different biological scales and the development of brain-inspired computing systems. EBRI's task in HBP concerned the use the Intracellular Antibodies Capture Technology to develop intrabodies against proteins involved in trans-synaptic signaling to understand their function after selective silencing. EBRI has also established fruitful collaborations with nat. and internat. pharmaceutical companies.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

At the National level, EBRI has established a strategic collaboration with Scuola Normale Superiore (Pisa) to develop recombinant antibody libraries to select intrabodies directed against post-translational modification of proteins. EBRI collaborates with the Dept Physiol & Pharmacol La Sapienza Univ. (Roma) on glia-neurons interactions in both physiological and pathological conditions; has established with the Dept of Human Neuroscience a joint research and diagnostics lab for identifying new biomarkers for neurodegenerative diseases. EBRI is involved with Besta Institute (Milano) in a network aimed at studying pre-Alzheimer's progressive forms of dementia. EBRI is a partner of Technomed-Puglia five-year project (UNIBA), and CNR (Lecce). In this framework, an EBRI-CNR joint lab is projected at the Ecotekne Campus in Lecce, to measure diagnostic and prognostic biomarkers for neurodegenerative diseases. EBRI is collaborating with Policlinico Gemelli to test painless NGF for the treatment of paediatric optical glioma. EBRI collaborates with the Italian Institute of Health in various research projects in neuroscience, neurodegeneration, genomics, space medicine and artificial intelligence. EBRI has set up a joint laboratory with the Pediatric Hospital Bambino Gesù (Rome), to study in organotypic slices obtained from brain tissue taken during neurosurgery from young patients, drug-resistant forms of epilepsy.
At the International level, EBRI has established a scientific agreement with McGill Univ. (Montreal) and Hebrew Univ (Jerusalem) to address topics such as neurodevelopmental disorders and neurodegenerative diseases and to promote exchange of knowledge and expertise, also via student exchange programs.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Patents EBRI granted

Number	Marketing name	Inventors
1372046	hNGF muteins: therapeutic uses and pharmaceutical compositions	Cattaneo, Covaceuszach, Capsoni
2580595	Diagnostic and prognostic method for human tauopathies	Amadono, Calissano, Corsetti
16/928,735	Inhibitor astrocytic TNF α for treatment of neurological diseases (USA)	Cattaneo, Capsoni
17714288.2	Inhibitor astrocytic TNF α for treatment of neurological diseases (EPO)	Cattaneo, Capsoni
102016000022920	Inhibitor astrocytic TNF α for treatment of neurological diseases (Italy)	Cattaneo, Capsoni

Patents EBRI under examination

Number	Marketing name	Inventors
	Antibody directed against a tau-derived neurotoxic peptide	Amadono, Calissano, Corsetti
	Antibody directed against a tau-derived neurotoxic peptide (EPO)	Amadono, Calissano, Corsetti
	Method for early diagnosis of neurodegenerative diseases by quantification of Pro-NGF and its derivative forms (USA)	Cattaneo, Malerba

DESCRIPTION OF SYNLAB

The Institute for Hospitalization and Healthcare (IRCCS) SYNLAB SDN is an Italian approved multi-specialized healthcare laboratory and diagnostic provider that has been operating in the electrophysiology, imaging diagnostics and nuclear medicine sectors for more than 40 years. The main purpose of the IRCCS SYNLAB SDN is to satisfy the whole patient's diagnostic workout by means of an advanced high-tech environment (e.g., equipped with high-field MR, MR/PET, HD-EEG, HD-EEG/fMRI), steadily integrated and up-to-date.
Besides clinical care services, SYNLAB offers the opportunity to perform advanced scientific research (i.e. functional MR and tractography) aimed at high-precision pre-surgical planning and neurological functional sparing. In addition, SYNLAB supports research activities and scientific dissemination of in vivo and in vitro diagnostics, with methodological application and integration in the preclinical as well as clinical contexts, with particular interest in neurological, neurosurgical and psychiatric diseases.

A.2 SCIENTIFIC EXPERTISE

The Italian Ministry of Health recognized SYNLAB SDN as an IRCCS for "Integrated Diagnostics for Imaging and Laboratory" also in neurological disciplines on January 11, 2007 and following confirmed such qualification up to date.
In particular, the IRCCS SYNLAB SDN, together with its local collaborators, including hospital and academic units, is steadily involved in the research on Alzheimer's disease and other types of dementia, in which FDG-PET and cerebral PET with beta-amyloid tracers are used with simultaneous advanced MR acquisitions in an effort to reduce acquisition time and tracer injected dosage, improving patients' compliance. Furthermore, the institute is involved in the study of other neurodegenerative diseases such as Parkinson disease, multiple sclerosis, amyotrophic lateral sclerosis, in an attempt to clarify the pathological mechanisms and to identify early imaging bio-markers for prompt diagnosis and prognosis. Recently, the IRCCS SYNLAB SDN was granted a project on patients with disorders of consciousness aimed at improving clinical diagnosis and identify imaging parameters for prediction of functional recovery using MR/PET.
The SYNLAB Institute is constantly striving to enhance the quality of procedures and therefore voluntarily submits to external audits of its standards by national (quality management system "ISO 9001") and international organizations (Joint Commission International, European Union of Medical Specialists (UEMS) and European Board of Nuclear Medicine (EBNM)).
To support research activity, innovative core facilities are operating also partly open to external users:
• Imaging Processing Centre focused on connectomics, i.e. the study of how distinct brain regions interact among them; radiomics, i.e. the identification of complex quantitative parameters from digital medical images, and the definition of novel diagnostic, prognostic and treatment-response markers in neurodegenerative diseases.
• Laboratory of Statistics and Bioinformatics
• Radiopharmaceutical for novel PET molecular-targeting radio-tracer synthesis
• Nanotechnology laboratory for the development of new contrast agents at lower toxicity and higher pathology specificity
• Laboratory of Advanced Preclinical Imaging for the identification, validation and transfer of novel biomarkers as well as assessment of pharmacological treatments in terms of bio-distribution and efficacy
• Biobank involved in the preservation of biological samples, including tissues, serum, plasma, mononuclear cells, urine and feces for being analyzed and correlated with clinical history and imaging diagnostics in loco. The Biobank is part of the Biobanking and BioMolecular Resources Research Infrastructure (BBMRI) for the establishment of an Expert Center, ATMA-CE, a technological Hub focused on radiomics and validation of imaging biomarkers.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

For many years now, the IRCCS SYNLAB SDN had several formal and informal agreements with academies, private and public healthcare providers and organizations at both national and international levels for the implementation of experimental research and clinical programs. This was pursued for encouraging scientific cooperation through research personnel exchanging and sharing scientific knowledge in neurodegenerative disease and the other above-mentioned fields.
As research institute, the IRCCS SYNLAB SDN is involved in many local, national and international projects in the neuroscience field. Moreover, the IRCCS SYNLAB SDN is member of the Italian

Neuroscience and Rehabilitation Network (RIN), a research network founded in 2017 by the Italian Ministry of Health to: encourage collaboration between recognized Italian Research Hospitals (IRCCS), facilitate the spread of information on their clinical and scientific activities, and coordinate actions at international level in order to raise the profile and increase the competitiveness of the sector.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

The Institute actively participates in the following programs: ADNI – Alzheimer's Disease Neuroimaging Initiative; EIBIR – European Institute for Biomedical Imaging Research, EuroBioImaging – a large-scale infrastructure project of pan-European research of the ESFRI (European Strategy Forum on Research Infrastructure); EATRIS – European Advanced Translational Research Infrastructure in Medicine; BBMRI – Biobanking and BioMolecular Resources Research Infrastructure, research infrastructure involving biobanks and biological resource centers – European Expert Center (ATMA) and Network promoted by the Ministry of Health. Moreover, the IRCCS SYNLAB SDN actively cooperates with many national and international collaborators, including 'Federico II' University of Naples, University of Florence, Kings' College of London, and the University of Western Ontario, Canada.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Since 2016, the IRCCS SYNLAB SDN is member of the European Institute for Innovation and Technology (EIT) - KIC Innostar as Italian node for "Healthy living and active aging". Moreover, the Institute actively collaborates with the Italian Institute of Technology (IIT) for the development of new innovative contrast agents for multimodal imaging procedures.

DESCRIPTION OF TIGEM

Fondazione Telethon (FT) was founded in 1990 and is one of the biggest nonprofit biomedical charities in Italy, whose mission is to advance biomedical research towards the diagnosis, cure and prevention of human rare genetic diseases.
TIGEM is a multidisciplinary research institute devoted to the study of the mechanisms underlying rare genetic diseases and to the development of innovative therapies. The institute's main goal is to bring together significant critical mass and put together scientists, expertise and skills working towards: i) a unique, basic, pre-clinical and translational research that breaks new ground and defines scientific excellence; ii) new approaches to develop treatment for rare genetic diseases; iii) training of next generation biomedical researchers. TIGEM has contributed to the scientific development of several generations of scientists including graduate students and postdoctoral fellows, many now still actively pursuing a career in research both in academia and industry. We currently host 35 graduate students and 55 post-doctoral fellows in our programs from 12 different countries.

A.2 SCIENTIFIC EXPERTISE

The Telethon Institute of Genetics and Medicine mission is to elucidate the molecular mechanisms underlying rare genetic diseases and to develop novel therapeutic strategies for patients. Over the years, our efforts to reach this ambitious goal have evolved from disease gene identification to in-depth functional studies on disease mechanisms and to the development of novel therapeutic approaches. Our research portfolio is organized into three strategic programs: Genomic Medicine (GM), Cell Biology and Disease Mechanisms (CBDM), and Molecular Therapy (MT).
The **Genomic Medicine Program** deals with the generation, integration, and computational analysis of genomics and transcriptomics data with the goals of (i) identifying disease-causing mutations in patients affected by rare genetic disorders; (ii) discovering their functional consequences; and (iii) predicting potential therapeutic strategies. Recently, significant research efforts were undertaken to predict the functional role of microRNAs and other noncoding RNAs in the retina, in both physiological and pathological conditions, using high-throughput approaches, including transcriptome analysis and high content screening assays. A highly efficient transcriptomic pipeline and new tools and technologies adopted by the Bioinformatics Core Facility have been instrumental in carrying out this specific project.
The **Cell Biology and Disease Mechanisms** program is focused on the study of gene function and disease mechanisms, integrating modern cell biology approaches with state-of-the-art facilities [including Advanced Microscopy, High Content Screening (HCS) and Mass Spectrometry facilities] and -omics approaches. Understanding the pathogenic mechanisms of a genetic disease, using molecular and cellular biology and animal models, is a crucial step to reconstruct the overall sequence of events that lead from

the genetic defect to clinical manifestations. These studies are essential for the identification of molecular targets and the development of therapeutic approaches. Last years were marked by a significant number of important discoveries in the field functional studies and disease mechanisms, which was greatly facilitated by the substantial development of the institute's expertise in cell biology.

- The **Molecular Therapy** program aims at developing develop advanced strategies for the prevention and treatment of disease. A major effort of this program is devoted to the devise of new therapies, both gene-specific and mutation-independent, for Inherited Retinal Diseases, a group of neurodegenerative disorders with a significant clinical impact. Currently, microRNAs are strongly investigated in appropriate *in vivo* models, as attractive therapeutic targets and biomarkers for IRDs as well as other inherited neurodegenerative conditions.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

TIGEM Scientific Office (SO) ensures competitive funds to support research and other activities related to the institute. It gathers and organizes information on major sources of funds from national and international agencies, institutes and foundations to support research and fellowships. This allows researchers to identify the best funding opportunities for their projects. The SO acts as liaison between researchers and sponsoring agencies and assists the researchers in providing administrative and managerial skills to facilitate access to funding sources. The SO ensures the smooth running and effective operation of TIGEM's scientific projects by providing guidance and assistance for all stages and aspects of the project duration and follow-up and ensuring that researchers have consistent and tailored support throughout their research endeavours.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

The majority of TIGEM publications have international co-authors from foreign institutions, because of the numerous established collaborations with national and international scientists. Importantly, over the past 5 years, TIGEM research has been involved in 472 Material Transfer Agreements, with academic institutions worldwide, and 5 Consortium Agreements, for **H2020 Programmes**.

TIGEM has also a strong and interactive collaboration with local public **universities**. Most of our faculties (19 positions) hold joint appointments with the University of Naples "Federico II" and the University of Campania "Luigi Vanvitelli". This strong link with the universities has several advantages including access to motivated students, strong links with clinical structures, and scientific exchange.

DESCRIPTION OF FDG

Fondazione Don Carlo Gnocchi ONLUS (FDG) is a non-profit organization that includes a network of 26 Hospitals located in 9 Regions in Italy. With its centers (of whom 2 research institutes) and 5900 collaborators, FDG offers a huge national coverage and takes care of about 200000 outpatients and 13000 inpatients annually, being them in any phase of the lifespan. FDG expertise is focused on Medicine of Rehabilitation and Neuroscience with the aim to perform basic and translational research within a program of excellence of the Italian Ministry of Health. In this framework, the "Santa Maria Nascente Institute" in Milan and the "Don Carlo Gnocchi" hospital in Florence have been recognized by the Ministry as research hospitals (IRCCS).

The research mission of maintaining the centrality of each specific patient as an individual and looking for the tailored rehabilitative solutions, drives the research activities of FDG for the investigation of the brain mechanisms underpinning neuroplasticity and for developing the best effective, innovative and personalized rehabilitation treatments. Given its potential in capturing changes in the brain physical structure, the chemicals and the function, the study of plasticity via system medicine modalities will have a central role. To this aim the scientific production of FDG is rapidly increasing, as demonstrated by bibliometric indices (see section A.2).

A.2 SCIENTIFIC EXPERTISE

FDG has an important scientific expertise, with its 175 researchers working in strict collaboration with national and international partners (i.e. Universities, Scientific institutes), along these research topics: bioengineering of rehabilitation, molecular medicine and imaging in rehabilitation, rehabilitation in neurological conditions, musculoskeletal conditions, and cardiopulmonary conditions.

In the last 5 years, with an increasing publication rate, the FDG has produced around 1700 articles in WoS-indexed journals, of which 44% were published in Q1 journals. The impact of this activity is mirrored by

the increasing normalized Impact Factor of FDG, rapidly passing from 787 points in 2015 to 1343 points in 2021. Among the published articles, most of these studies are strictly belonging to the neuroscientific field, or broadly associated to neuroscience as being them in the Biochemistry, Genetics and Molecular Biology field and in Engineering, Psychology/Neuropsychology areas [source: *Scopus*].
The research in neuroscience performed in FDG covers multiple neurological conditions (e.g. multiple sclerosis, consciousness diseases, stroke, traumatic brain injury and neurodegenerative diseases), that are investigated from the molecular to the clinical levels, using different techniques hosted by dedicated laboratories. In FDG the presence of nanotechnology laboratory, biomolecular analyses and epigenetic techniques allow the study of the rehabilitation processes and clinical courses of diseases from a microscopic level. Moving to a larger scale, the correlates of neurological diseases on central and peripherical nervous systems and the effect of therapies are investigated using advanced technologies, such as EEG, stereo-photogrammetric systems, force platforms, surface EMG, markerless based systems (optoelectronic system, Inertial magnetic units), high-field magnetic resonance imaging and connectomics. Thanks to their study, FDG offers important advances in the development of new technological approaches widely studied at the worldwide level.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

FDG in the last decade developed research activities in the field of neuroscience and neurorehabilitation by means of a large number of projects won in competitive grants and also by means of profit trials and donations, both as coordinator and partner. The main topics that have been developed are inherent neurorehabilitation, also by using innovative and robotics technologies, cognitive rehabilitation, also in telerehabilitation framework and by means of innovative digital therapeutics approach, the study of newly biomarkers for diagnosis and rehabilitation outcomes of neurological disease. Following, a brief summary of the project where FDG acted as coordinator: EU programs participating in the last decade in 20 projects for a total of 2.7 M€, by the founding of the Italian Ministry of Health (RF, IRRCS-Network...) 20 projects for a total of 3.6 M€, by Italian regional grants (Regione Lombardia and Toscana, such as POR-FESR EU founding program) 22 projects for 5.2M€, others Private Foundations (e.g. Fondazione Cariplo, Fondazione Invernizzi, Fondazione Cassa di Risparmio Firenze) more than 21 M€ divided in more than 150 projects.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

In the last years, FDG have strengthened its **collaborations in national and international networks**, considered as being a pivotal aspect for the definition of the mid- and long-term scientific planning. In research projects and grant definition, FDG collaborates with many national and international universities and research institutes. In more detail, the FDG has established joined laboratories with the Sant'Anna School of Advanced Studies of Pisa (Movement Assistance and Rehabilitation Lab, MAReLab) and with the University of Milan and Florence. The research activity of these joined Labs mainly involves the robotics application for movement assistance after injury, the investigation of genetics and epigenetics characteristics that may influence the response to the rehabilitation treatment. Over the national involvement, FDG is also part of important **national research networks**, such as the National Network of Neuroscience and Neurorehabilitation (RIN-network), the Human Technopole, the Network of IRCCS for aging, and is also involved at the **international** level, as active part (among others) of the Cochrane Center, of the European Platform for Rehabilitation (EPR), of the Network Rehabilitation in Multiple Sclerosis (RIMS) and of the International Society for Neurovascular Disease (ISNVD).

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

In order to guarantee the intellectual property of projects and innovative products developed within FDG, the Technological Transfer Office (TTO) works in synergy with researchers to face with the needs of both patients and industries, allowing the best technologies to be used in rehabilitation. Significant knowledge transfer efforts have been recently translated into 2 patent applications regarding technologies useful to innovate neurorehabilitation (a device to improve the use of Functional Electrical Stimulation and a system to enhance control strategies on exo-robot for lower limb neurorehabilitation and assistance). Further, the FDG during last years developed a strong network of collaborations with national and international companies, both in the life-science and pharma fields and in enabling technologies field, such as robotics, brain-computer interfaces, wearable sensors and devices, digital therapeutics. In 2018 FDG has been one of the founding partners of one of the most important competence center in Italy, named ARTES 4.0 “Advanced Robotics and enabling digital Technologies & Systems 4.0”, with the aim to enhance and

support the industry development and to allow enabling technologies adoption, specifically in the framework of Health and Smart Hospitals innovation actions.

DESCRIPTION OF SR

SanRaffaele.it

The Scientific Institute for Research, Hospitalization and HealthCare (IRCCS) San Raffaele is devoted to continuing upgrade of healthcare and guarantee excellent patient care and the innovation in the health sector. It was first recognized by the Italian Ministry of Health in 2005 for its expertise in motor and sensory rehabilitation. As research is one of its founding principles, the institution performs an intense and qualified research activity thanks to the support of a modern Research Centre and an Interinstitutional Multidisciplinary Biobank (BioBIM), a biorepository with established experience within the National Health System and the international research community. The San Raffaele Institute has a cutting-edge facility for preclinical and translational research in the medical area, whose multidisciplinary organisation and approach allows pluripotency, flexibility and the involvement of several areas of expertise. Moreover, the Institute has a national and international network of collaborations with other Research Institutions and Universities strengthening the possibility of promoting cultural exchange at a national and international level, supporting projects, multicentric protocols and research agreements.
The Institute has performed significant research activity in the field of neuroscience and has 30 research laboratories operating at the institutional facilities with specific expertise in neuroplasticity and brain connectivity both experimental and clinical. The San Raffaele Institute is a landmark institution in the field of highly specialized neurorehabilitation. Strong related preclinical and clinical and health care build its core activities. Neurorehabilitation programs are developed for patients with both, motor and cognitive deficits. Health services are provided under an agreement with the National Health Service (SSN). The San Raffaele Institute covers a wide range of expertise and technological know-how in the preclinical fields of neurodegenerative disorders (eg. Parkinson's disease, Alzheimer's disease).

A.2 SCIENTIFIC EXPERTISE

Total number of people dedicated to research activities, including full-time preclinical researcher, clinical researchers and scientific-technical support is 122 with a total number of 54 dedicated to research in Neurosciences. Total number of institutional publications in the time period 2011-2021 is 2.634 with following bibliometric values in publication in Top 10% journals 35.0%, international collaboration 47.6% and citation 84.644. Number of publications in Neurosciences is 502, Top 10% journals 26.8%, international collaboration 48,8% and citation 15.387. Institutional infrastructures include a multidisciplinary biobank, clinical and molecular epidemiology, biostatistics, neuroimaging, advanced neurophysiology. Library and library services are part of a national Network, thus providing researchers with direct access to all available information and resources. The Institute has a Grant-Office to support researchers in the application of Calls at a national and international level. The Institute also has a Technology Transfer Office to promote translation of the research results into innovation, new pathways and patents. Dissemination of ongoing projects, publication and results of research projects is performed by the Communication Department. The Department of Neuroscience is located at the research institute in Rome and has appropriate preclinical, and clinical research spaces, facilities and infrastructures to support and conduct research activities described in the project. The Department is well connected to Universities and Research centers around Italy. Research laboratories include: Center for drug development and Clinical Trial Center, Center for Parkinson's Disease and Movement disorders, Laboratory of Brain Connectivity, Laboratory of Robotics Rehabilitation, Bioengineering Rehabilitation, Human Longevity Program, Functional Human genetics, Synaptic Immunopathology, Experimental Neurophysiology, Molecular and Cell Neurobiology, Advanced biotechnologies and biomarker discovery. Major facility avaible for electron microscopy (TEM, SEM), clinical and research setting EEG equipment, 1 digital 128 ch EEG system, TMS device, TMS-EEG device, TDCS device, software for cognitive training, software for standard attention and memory tests.
The research laboratories are fully equipped with PCR thermocycler (Applied Biosystems), gel imaging systems (Biorad), spectrophotometers (NanoDrop, A-EL-VIS), cryostat and ultramicrotome (Leica), micro dissector (Slee Medical). Stereomicroscope, Nikon Eclipse TI2 confocal laser-scanner microscope, and micro dissector laser capture (Nikon). Luminex technology (R&D), Fortessa X-20 cytofluorimeter (Becton Dickinson), cell culture rooms, rooms for molecular biology and biochemistry, freezers (-80 °C).

Professional figures include: MD (neurologists), Psychologists, Bio-Engineers, Biologists, pharmacologist,
Pharmacists, Informatic engineers, Statistician, Physics, Technicians for clinical neurophysiology.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

All researchers at the San Raffaele Institute have extensive experience in managing and implementing research projects, evidenced by the grants acquired at national and international level. In particular, Prof. PM. Rossini has participated as research leader in many large scale aging European research projects in neurosciences, e.g.:

Year	Abbreviation	Name	PI/Unit	Funding body	Amount
2021	ADOPTION	P.M. Rossini	Unit	CNR	€250.000
2021		F. Vecchio	PI	Fondazione Baroni	€50.000
2021	AI-MIND	P.M. Rossini	Unit	Horizon 2020	€543.437
2020	RCR-2020-23670067	F. Stocchi	Unit	Italian Ministry of Health	€51.973
2019		F. Miraglia	Unit	Italian Ministry of Health	€150.000
2019	RF-2018-12366144	G. Mandolesi	Unit	Italian Ministry of Health	€146.369
2018	INTERCEPTOR	P.M. Rossini	PI	AIFA/Mn. Salute	€4.300.000
2016*	RF-2013-02357386	B. Picconi	PI	Italian Ministry of Health	€380.200
2011*		B. Picconi	Unit	Cariplo	€80.000
2010*	GR-2008-1142336	B. Picconi	Unit	Italian Ministry of Health	€585.923
2008*	RFPS-2007-1-643500	B. Picconi	Unit	Italian Ministry of Health	€133.000

The projects and funding marked* were obtained and performed at another Institute.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

The San Raffaele Institute is founding member of the National Network of Excellence in Neuroscience and Neuro-rehabilitation of the Italian Ministry of Health. The Institutes are required to have excellence and expertise in neurosciences, neurology, psychiatry, and neurologic rehabilitation. The Institute is also part of the National Network of Virtual Institutes in Parkinson's Disease and Movement Disorders, Alzheimer's Disease and Cetebro vascular Disorders.
The Department of Neurosciences, the Brain Connectivity Lab, the Experimental Neurophysiology Lab and the Synaptic Immunopathology lab collaborate with numerous national and international Research Centers and Universities, e.g.: NIH Bethesda, UCL London, University Magdeburg Germany, University of Lausanne Switzerland, Un. Cattolica del Sacro Cuore Roma, CNR, Istituto Superiore di Sanità, Un. di Roma "Tor Vergata", AFaR, Emory University; Neurocentro della Svizzera Italiana (EOC); Fresco Parkinson Network, NY; Dept. of Pharmacological and Biomolecular Sciences, Un. Milan, Telethon Institute of Genetics and Medicine, Cellular Physiology & Molecular Neuroscience Un. Torino, CEINGE Biotecnologie Avanzate, Napoli, Dip. Medicina dei Sistemi, Un. di Roma Tor Vergata; AOU Sant'Andrea Roma, Un Genova, Dipartimento di Farmacia and Ospedale Policlinico IRCCS San Martino.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

The San Raffaele Institute has developed a specific patent in personalized training programs with the use of IA. The patent has been registered at worldwide level.
Prof. PM Rossini MD, Fabrizio Vecchio Phd and Francesca Miraglia PhD have established Neuroconnect, a spin-off in the area of brain connectivity. The activities of the spin-off include functional connectivity analyses and other EEG feature extraction via a machine learning approach already validated in a large population of healthy subjects and tested as a diagnostic tool for Alzheimer`s disease. The application of the novel developed procedure is foreseen in the European project AI-Mind, and recording and analysis will be standardized. Particular experience has been acquired in national and international projects in the field of innovation in e-health, tele-rehabilitation and tele-monitoring, electrophysiology, biomechanics,

motor control, applied rehabilitation robotics, artificial intelligence applied to biosignals, data mining applied to the study of the rehabilitation process, design of platforms for the multidomain evaluation of motor tasks, design and fine-tuning of medical devices and software. The main fields of interest can be applied in various degenerative diseases related to aging.

DESCRIPTION OF DOMPÈ

Dompé is one of the leading Italian biopharmaceutical companies focused on the development of innovative treatments for rare and orphan disease and high unmet medical need conditions. The company pursues this goal by promoting and actively participating in a network that brings together the main names in the pharmaceutical industry, from research to development, from production to marketing. The therapeutic areas with still unmet therapeutic needs of greatest commitment for Dompé are ophthalmology, oncology, diabetes, pain and organ transplantation, where Dompé promotes medical and scientific advancement, through its own research and open innovation ecosystem. Dompé conducts its research activities as part of a network of over 300 centers and universities across the world that has allowed the Company to conduct more than 30 clinical trials to treat over 2000 patients with Dompé experimental drugs. Dompé Research Centre is distinguished by the production of new chemical entities and recombinant proteins in accordance with the very highest standards of quality and its distinctive, high-skill analytical offer, and by the development of innovative formulations for new and old drugs. As for the biotech area, Dompé has developed distinctive competences in the field of therapeutic recombinant proteins manufacturing. Dompé is specialized in microorganism fermentation and can follow the overall process of protein manufacturing from lab to industrial scale according GMP, skilled in "difficult to express" proteins (inclusion bodies and refolding), early phase projects development and regulatory support.

A.2 SCIENTIFIC EXPERTISE

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A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

Dompé has a well-recognized experience in participating at national and international projects, both as coordinator and as partner of large consortia in the context of applied research and development activities.

Here below a short list of the most recent projects where Dompé has been and is involved either as coordinator or as a partner. Finally, several project proposals also in the field of neurosciences have been recently submitted for application to 2021/2022 Horizon Europe calls. Here below a short list of relevant research projects:

Grant nr.	Acronym	Grant	Duration	Topic
101003551	**EXSCALATE4CoV (E4C)**	H2020 –SC1-PHE CORONAVIRUS 2020	2020-2021	High Performance Computing HPC for new antivirals
101034145	**CoViRal**	DG SANTE – EU ESI: Call PPP-ESI-CTRM-2020 – SI2837140	2020–2021	COVID-19 clinical trial (validation and follow up of E4C project)
956137	**LIGATE**	Call H2020-JTI-EUROHPC-2019	2021-2023	HPC intelligent supercomputing
1666606	**MYEYE**	Call HUB Ricerca e Innovazione POR Lombardia 2014-2020 – I.1. B.1.3	2020-2022	Creation of a HUB for the development of innovative drugs and technologies in ophthalmology
F/05338/01/X32	**FARMIDIAB**	DM MISE "Horizon 2020 – PON 2014/2020"	2017-2018	R&D for new innovative targets and new treatments for metabolic and related pathologies
F/090033/01/X036	**PON_MiSE_ Industria Sostenibile**	DM 1 GIUGNO 2016 "Grandi Progetti R&S – PON 2014/2020"	2017–2020	Integrated technological platform for the identification and development of new drugs
ID 239047	**NeON**	POR FESR Lombardia 2014/2020 Accordi per la ricerca sviluppo e innovazione	2017-2021	Platform for the identification of drugs to treat CNS diseases

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

Research, supercomputing, and artificial intelligence to materials sciences, all aimed at developing the best therapeutic solutions of tomorrow. To this aim, Dompé operates in a context of Open Innovation and now embraces a network of more than 300 entities including research centers and universities around the world:

- 315 active collaborations around the world.
- 68 Material Transfer Agreements (MTA) signed.
- 27 collaborations started in 2021, including acquisitions, clinical trials, and licensing agreements.

Few recent examples:

1. VIMM - IT (Veneto Institute of Molecular Medicine) (neuro ophthalmology).
2. Tufts University – USA (neuro ophthalmology).
3. Institut de la Vision – FR (supervised by Sorbonne University, Inserm, CNRS) (neuro ophthalmology).
4. University of L'Aquila – IT (neuropathic pain).
5. University of Naples Federico II – IT (neuropathic pain).
6. Universidade de São Paulo (USP) – BR (neuropathic pain).

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

PCT application	***Title***	***Filing date***
WO2000022119	*Method For Obtaining Acitve Beta-Ngf*	*11/10/1999*
WO2013092776	*Novel Prongf Mutants And Uses Thereof In The Production Of Beta-Ngf*	*19/12/2012*
WO2015197640	*2-Aryl-4-Hydroxy-1,3-Thiazole Derivatives Useful As Trpm8-Inhibitors In Treatment Of Neuralgia, Pain, Copd And Asthma*	*23/06/2015*
WO2017121838	*Il-8 Inhibitors For Use In The Treatment Of Chemoterapy-Induced Peripheral Neuropathy*	*13/01/2017*
WO2019115493	*C5ar INHIBITORS FOR USE IN THE TREATMENT OF CHEMOTHERAPY-INDUCED IATROGENIC PAIN*	*11/12/2018*
WO2021214158	*Co-Crystal Of Gabapentin, Ketoprofen And Lysine, Pharmaceutical Compositions And Their Medical Use*	*21/04/2021*

WO2021214163	*Synergistic Admixtures Of Gabapentin And Ketoprofen, Pharmaceutical Compositions And Their Medical Use*	*21/04/2021*
WO2021224217	*Co-Crystal Of Ketoprofen, Lysine And Gabapentin, Pharmaceutical Compositions And Their Medical Use*	*04/05/2021*
Priority filed. Not yet published	*Nerve Growth Factor For The Treatment Of Rett Syndrome*	*23/12/2021*

DESCRIPTION OF ALFASIGMA

ALFASIGMA SPA is one of the 5 main players in the pharmaceutical industry in Italy, with a turnover that in 2020 was close to one billion euros. Over 75% of the company is owned by the Golinelli family. The history of ALFASIGMA begins in 1948 in Bologna (Italy) thanks to Marino Golinelli and is firmly anchored in a long tradition of innovation and success. The company strategy pursued is twofold, since its foundation: **i)** internally, a strong focus on research and development and production around some proprietary molecules, which today represent over 50% of turnover; **ii)** for external lines, a solid strategy of mergers and acquisitions with other Italian and international companies (Sigma Tau, Pamlabs).
ALFASIGMA currently has around 3,000 employees worldwide, 17 branches and a presence in more than 70 countries.

A.2 SCIENTIFIC EXPERTISE

ALFASIGMA and its affiliated companies has developed expertise in profiling the human gut microbiome and how gastrointestinal dysbiosis can influence a neurodegenerative disorder, the Overt Hepatic Encephalopathy (HE), by studying a GI-restricted clinically effective antibiotic, rifaximin. In particular, Rifaximin strongly affects the HE observed in cirrhosis patients, a result confirmed in a dozen of studies and indicated for use in USA and Europe. ALFASIGMA Corporate R&D is currently exploring other assets targeting key mechanisms of the Gut-Brain Axis. Moreover, has recently engaged into a program of digital transformation that include Big Data and AI analytics for microbiome-related precision medicine approaches. The aim of this project is to address the role of microbiome dysbiosis in contributing to neuronal dysfunction and/or degeneration in a well-defined set of neurological and psychiatric disorders. This goal will be achieved by: (1) Contributing to obtain GI microbiome genetic profiling and bioinformatic analysis of samples collected from patients, either those assessed by the clinical partners present in Spoke 5, 6 and 7 or from other collaborations; (2) Contributing to the identification and selections of microbiome-originated mediators of CNS or peripheral neuronal functions using Big Data in silico exploration and in vitro testing; (3) Implementing the new translational/precision medicine technology of the human inducible pluripotent stem cells (iPSC) donated by specific subgroup of patients that will be differentiated into GI and CNS organoids or 2D cultures of enteric nervous tissue for in vitro testing of the test microbiome-originated mediators or pharmacologic agents. These activities will be performed in collaboration with qualified consultants and with other members of the Spokes.
Publications: The Corporate R&D Head and current P.I. Emilio Merlo Pich has experience in neurobiological research and drug development, and is co-author of about 200 publications related to molecular and pharmacological mechanisms in Psychiatric and Neurological disorders, including translational models based on human iPSC-derived neuronal cultures. He also has an extensive experience in complex data analysis, modeling and simulations.
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DESCRIPTION OF ASG

ASG is an Italian company active for 60 years in the design and manufacturing of superconducting magnet systems.
Its main areas of technological expertise are:

- Guiding magnets for particles accelerators, such as LHC magnets at CERN Geneva.
- Magnets for proton therapy for cancer treatment.
- Coils for Plasma confinement for Nuclear fusion.
- Ultra High Field Magnets for MRI.
- MRI open systems.
- Superconducting wire development and manufacturing.

The company has about 200 employees, 52% of them are white collars. Most of the production is exported worldwide (EU, USA, Japan, Korea).
ASG has two manufacturing premises: one in Genova (headquarter), located in a covered area of 15.760 m2, and another workshop in the province of the Ligurian city of La Spezia (about 110 Km far from ASG headquarters), close to a commercial harbour. ASG's facility in La Spezia is composed by a 4 bays workshop with an Office building. Each of the four bays extends over a surface of 21 x 225 m, for a height of 14,2 m. The total surface area is around 25000 m^2.

A.2 SCIENTIFIC EXPERTISE

The main areas of expertise inside the company are superconducting technology applied to magnet and systems, and MRI medical imaging technology, both in terms of hardware and software.
Superconducting technologies and magnets are increasingly finding applications in the medical sector. ASG designs and builds magnets for MRI applications with magnetic field intensities ranging from fractions of one tesla up to Ultra High Field (UHF). Capitalizing on skills and experiences derived from research and industrial collaborations, ASG is constantly improving its competences and knows how to design and build new types of magnets for medical diagnostics and therapies. ASG will also develop other UHF MRI magnets to other leading medical and research sites addressing MRI research, and other magnet systems for medical diagnostics and therapy, like hadron therapy.
In the framework of R&D activities aimed at demonstrating the feasibility of a "cryogen-free" magnet using a MgB2 conductor, produced by Columbus Superconductors (now ASG Wire Business Unit), ASG has designed, manufactured and tested a 0.5 T cryogen free MRI scanner in open configuration (MROpen). For this project windings using magnesium diboride conductors (MgB2), operating at 20 K have been developed.
ASG owns 15 Patent families regarding production of Superconducting wires, superconducting joints and cryogen-free superconducting coils, Fault current limiters.

The company supports and funds the research activity of 3 PhDs (UNIGE, UNIFI, UNIBO) and 3 fellow researchers in (UNIGE, UNINA, UNIMI) regarding novel materials for superconducting wires and magnets.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

ASG has recently (beginning of 2022) completed a research project funded by Gachon University Gil Medical Center (South Korea) regarding the design and construction of a Ultra High Field magnet for MRI. The field is 11,74 T, the highest currently in the world for human MRI.
The MRI scanner developed by Gachon University, based on the UHF magnet developed by ASG Superconductors will be the world's first multi-channel/multi-nuclear simultaneous MRI system and will be used for Neuroscience research, for early diagnosis and treatment of incurable brain diseases such as Parkinson's disease, Alzheimer disease, stroke.
A similar project for neuroscience, with a slightly different patient bore, is currently on-going with the National Institute of Health (NIH) in Bethesda. The magnet has been delivered to the customer's site and is now waiting for the Site Acceptance Test, after a first successful test at ASG premises.
ASG has carried out in the recent past many complex projects in which the necessity to deal with a high number of parties, may them be suppliers or clients, was of the essence. The manufacturing of LHC's arc dipoles (nr. 445 magnet units delivered, thousands of components for each unit), the Barrel Toroid Coils for ATLAS detector (INFN/CERN), the non-planar coils for the W7-X Stellarator (nr. 30) for IPP, the solenoid for the CMS detector (INFN/CERN), the JT-60SA Toroidal Coils for ENEA/F4E (nr. 10) and the ITER Toroidal Field Coils project (71 double pancakes with tens of components each) are examples of productions where ASG had to interface with multiple clients (INFN and CERN, ENEA and F4E, F4E and ITER, etc.) and tens of suppliers of high priced, hardly replaceable components

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

ASG has contributed magnets to all the most illustrious high energy physics and thermonuclear fusion projects that have been endeavored in Europe and in the USA in the last 30 years, all of them under national or international governmental funding.
CERN, FERMILAB, GSI, F4E are only some of the partners with which ASG has collaborated most recently: these are all public institutions who have launched multimillion contracts characterized by the need of highly multidisciplinary and multiparty interactions.
Regarding national institutions, ASG has established a long-term relationship with ENEA, INFN, and various universities.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

Since its beginning in the early 60s, ASG has always been at the forefront of innovation. A notable recent example is the development of the MROpen MRI system, which is now being commercialized in the whole world. The CNR Spin-Off company Columbus Superconductors (now incorporated in ASG) is a successful example coming from the research collaboration with ASG Superconductors SPA for the production and the commercialization of innovative MgB2 superconducting wires that are used in the system. MROpen is a unique system in the MRI market panorama, providing exceptional patient comfort thanks to its peculiar open geometry, enabling the radiologist to perform MRI imaging of the patient both in supine and in the upright position.

DESCRIPTION OF TAKIS

Takis s.r.l. is a Biotech company founded in 2009 by a group of scientists from the multinational Merck & Co, Merck Research Laboratories (MRL) division. The group has over 20 years of experience in the discovery of new molecules, which have contributed to the development of new drugs for the treatment of cancer and viral diseases.

TAKIS laboratories are located in Technopole facilities, Castel Romano, Rome and in Campania at Biogem, Ariano Irpino (AV). All reagents and instrumentation (molecular biology, biochemistry, animal housing, qualified personnel, cell culture facilities) required for Oncology, Immunology and Virology projects are available. TAKIS' activities are currently 100% in Research and Development, both internally and externally. The company is gaining a position of absolute importance in the contract research sector, thanks to the competitive advantage in terms of previous experience in a Big Pharma and the ability to identify new leads and drug targets.

A.2 SCIENTIFIC EXPERTISE

As a Biotech, TAKIS pursues the discovery and development of innovative Vaccines based on viral vectors and DNA platform technology, leveraging on its strong track record in drug discovery. One of the main assets is the expertise in in vivo electro-gene-transfer (EGT), which can be used for a variety of clinically useful applications, from vaccine development to somatic gene therapy. TAKIS' scientists have recently shown immunogenicity and significant therapeutic efficacy of this technology in pet dogs affected by spontaneous B cell lymphoma with significant improvement of survival and permanent cure in a high proportion of vaccinated subjects. POC of the technology was also successfully achieved for Cancer Vaccines in Phase 1 trials in humans. COVID-eVax is a vaccine against COVID-19 currently in Phase I/II clinical trial planned to go on the market in the next years. TAKIS' Neomatrix is a personalized cancer vaccine approach wherein starting from tumor biopsy and Next Generation Sequencing, a DNA-EGT based, specific vaccine is synthesized and administered to the patient in few weeks. TAKIS has also a pipeline of projects based on DNA-EGT ranging from Cancer, Malaria, and monoclonal antibodies. In addition, TAKIS is actively involved in the generation of humanized monoclonal antibodies for use in Oncology and Infectious Diseases. TAKIS' anti-HER3 antibodies (Rever3mAb program) have shown significant therapeutic effects in a variety of preclinical models and were capable of reverting tumor resistance to chemotherapy. Currently, the antibodies are being used to develop CAR-T cells in collaboration with academic institutions. In the last couple of years, TAKIS has successfully executed tens of projects, all of them reaching the objectives. Such expertise has been applied for the treatment of tumors of the Central Nervous System origin (**gliomas**, **glioblastomas**) in vitro and in preclinical models.

A.4 EXPERIENCE IN MANAGING AND IMPLEMENTING RESEARCH PROJECTS

TAKIS has long-standing competitive research granting history. So far, 19 national and international projects (Lazio Innova, POR Campania, MiSE, IMI2, Horizon EU, Erasmus+, EIT Health, AIRC) have been financed either as coordinator or partner, for a total of **€ 6.170.131,53**. Most of them relate to the technologies relevant to the gene therapies, genetic vaccines and therapeutic antibodies topics.
Among them:

- MiSE. VECTOPUR: development of methods for the production of DNA Plasmids.
- MiSE. Fabbrica Intelligente: creation of a GMP facility for DNA plasmid production.
- MiSE. Q-RARE: development of genetic vaccines and antibodies to fight rare diseases.
- Lazio Innova. Rever3mab: an antibody to fight Cancer resistance to conventional therapies.
- Lazio Innova. HUMAD, TRAZIMAB, GEMMA, CARSA: generation of CAR-T cells for Cancer and infectious diseases.
- Lazio Innova. GENERAS: generation of tools to fight COVID-19.
- EIT Health. NEOMATRIX personalized cancer vaccines: second prize in European competition.
- IMI2. ARDAT: generation and characterization of Adeno-associated viral (AAV) vectors.

To address the urgent need to find solutions to the SARS-CoV-2 Pandemic, TAKIS has developed COVID-eVax. The project started in 2020 and in a first phase consisted of the molecular design of the vaccine, the development of the reagents and tests necessary to test its effectiveness and the experiments in animal models. Subsequently, a first batch of GMP-grade material was produced, all regulatory studies were conducted and finally a phase 1 study in humans, which ended in December 2021, achieving all the objectives set and providing the basis for evaluations in Phase 2 and 3 studies.
In addition to the great advantages of DNA, mRNA technology also has considerable flexibility. With a compressed timeframe from development to clinic and to approval, mRNA technology is attractive not only for responding to infectious disease outbreaks and pandemics, but also for developing novel therapeutic approaches to address diseases with need. For this reason, TAKIS is investing to develop new mRNA production methods as well.
Finally, as part of the COVID-emAbs program TAKIS has generated, through genetic immunization and hybridoma technology, a vast library of monoclonal antibodies that recognize the RBD portion of the SARS-CoV-2 Spike. From this library some monoclonal antibodies have been selected which are highly effective on some variants of SARS-CoV-2 and which can be further developed until their clinical application. Furthermore, the high diversity of the library will allow the isolation of monoclonal antibodies with a broad-spectrum activity to treat most, if not all, of the variants that may emerge in the future.

A.5 NATIONAL AND INTERNATIONAL COLLABORATIONS

TAKIS collaborates and develops projects with pharmaceutical companies such as Glaxo SmithKline, Novartis, Janssen, Crucell, Boehringer Ingelheim, Alfasigma, Dompè, Axxam, IGEA, Menarini, Rottapharm Biotech and various companies operating in the Biotech field. Some examples: the results obtained have allowed companies such as Janssen to select clinical candidates for a therapeutic vaccine against hepatitis B virus, Novartis to develop a kit for the release of clinical batches of the vaccine against meningococcus B based on antibodies generated by TAKIS and Alfasigma to develop a new technology for antibody delivery, as well as in vivo proof of concept for new oncology drugs. Furthermore, for internal research projects TAKIS makes use of a series of academic collaborations such as the Regina Elena National Cancer Institute in Rome, the Pascale National Cancer Institute of Naples, the Biogem Institute of Ariano Irpino, the Molecular Medicine department of La Sapienza University, the University of Catanzaro and various American Institutes. The Team is also internationally recognized for the design and implementation of a series of innovative technologies, including viral vectors based on Adenovirus (Ad) and DNA electroporation (EP) or Electro-Gene-Transfer (DNA- EGT), which has been refined and evaluated in preclinical models and phase I studies in humans in the United States. Studies have shown induction of immune response in the absence of significant adverse effects.

A.6 SKILLS AND RESULTS IN TERM OF INNOVATION AND TECHNOLOGY TRANSFER

During their experience at Merck & Co., TAKIS' team has developed a solid background in the fields of gene expression, gene therapies, cell signal transduction and immunology. Over the years it has provided important direct contributions to the development of new potential oncological therapies based on innovative technologies and concepts, including the use of biological drugs such as monoclonal antibodies and genetic therapeutic vaccines. In summary, TAKIS' skills are: 1) Development of new experimental drugs for the immunotherapy of tumors with the following objectives: a) generation of therapeutic anticancer vaccines aimed against various classes of "tumor antigens"; b) generation of monoclonal antibodies for therapeutic purposes; 2) Selection of new therapeutic targets and development of new drug prototypes and assays based on new biomarkers: an innovative concept that fits into the context of pharmaco-genomics.

B. CHARACTERISTICS, FEASIBILITY AND CONTROL

B.1. Composition of the critical mass

MNESYS HUB is constituted by **twelve public universities** and **nine research institutions,** selected based on their critical mass, as resulting through a careful critical evaluation of the documented scientific expertise in the field and proven skills in the management of complex proposals (described in paragraphs below) and **four companies** focused in medtech, biotech (i.e. ASG and ALFASIGMA) and pharma (i.e. DOMPE' and TAKIS) and very active in the field of nervous system disorders, that will foster industrial applications (Table A1 – list of partners).

MNESYS constitutes a network grouping specific scientific critical mass, provided by the involved institutions, around specific themes ("spokes") addressing patho-physiological processes occurring in multiples diseases of the nervous system. We adopted **seven scales** ranging from the molecular and cellular to the patient/population level (scale A-D, Fig. A1) and from advanced technologies to artificial intelligence and machine learning methods (scale E-G, Fig. A1) to address specific questions and generate new knowledge rapidly exploitable for technological and industrial development. Each spoke gathers an average of 50 scientists with multi and interdisciplinary skills to provide cutting-edge knowledge in the neuroscientific domain for translational research. Fig. B1 shows the **compositions of the 7 spokes**, the leader of each spoke and interactions among spokes.

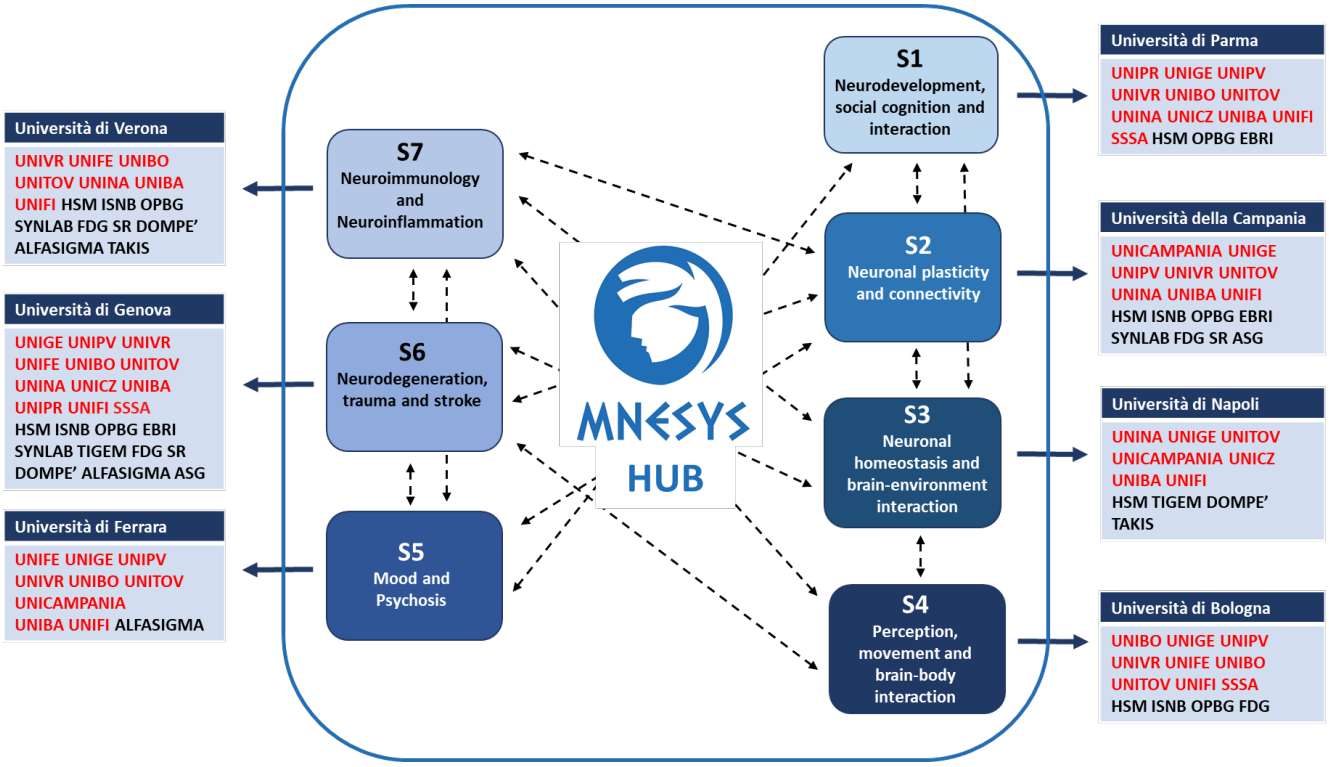

Fig. B1. Spokes composition and their interactions

There are many interactions between the research activities of the Spokes thanks to shared research methodologies (scales defined above), synergic scientific focus and synergic goals. S1, with its focus on neurodevelopment, S2 (neuronal plasticity) and S3 (neuronal homeostasis) are highly integrated spokes as they explore the theme of neural architecture development and maintenance from three complementary vantage points. S1, moreover, thanks to the WPs dedicated to social cognition development is also relevant for S5, given the role played by social cognition in mental health and in mood and psychotic disorders. S2 work, moreover, with its focus on neural connectivity, will help to better conceptualize and understand the findings of S5, S6 and S7 on psychiatric and neurodegenerative disorders, stroke and neuroinflammatory diseases, given the key role played by connectivity alterations in those conditions and the possible role of connectivity-based metrics to be used as clinically-relevant

biomarkers. Conversely, the results obtained in S5, S6 and S7 will be instrumental to better understand the findings of S2. Results generated in S3 will allow to better characterize one of the key factors leading to neuroinflammatory, neurodegenerative and neurovascular disorders, namely the loss of the neural cells homeostatic abilities, as well as, present a complementary point of view on the brain-environment interaction compared to S4. Conversely the results obtained in the latter spokes will provide a broader context to the findings of S3. S4 activities will provide useful insights on the relationship between cognition, movement and perception, all key aspects also for the more clinically-oriented activates among those included in S5, S6 and S7, which, in turn, could provide a testing ground for the approaches developed in S4. Lastly, S5, S6 and S7 also present with rich interactions between themselves give the role played by inflammation and neurodegeneration on mood and psychotic disorders and by the interaction between neuroinflammation and neurodegeneration.

Leading institutions for each spoke have been selected based on the profile of scientists bringing expertise to the spoke specific theme and the critical mass of each spoke was generated through the selection of researchers taking into consideration several parameters including:

- **the scientific track record related to the theme of the spoke;**
- **bibliographic metrics (H and M-index, number of citations);**
- **competitive grants, patents and spin-off;**
- **gender and age balance.**

Table B1 shows the average H-index (Scopus) for the researcher of each spoke, the total number of researchers involved, with indication for each spoke of the number of women and young scientist (less than 10 years from PhD). It is noteworthy that 40% of the researchers involved in the total critical mass of the spokes are women and 17% are young scientists with less than 10 years from their PhD completion. Table B1. shows the summary of the human resources involved for each spoke and for each partner.

Nr.	Legal names	Short names	S1	S2	S3	S4	S5	S6	S7	RESEARCHERS Total number	WOMEN	YOUNG SCIENTISTS
1	**Università degli Studi di Genova**	UNIGE	**6**	**4**	**7**	**6**	**3**	**13**	**0**	38	10	8
2	Università degli Studi di Pavia	UNIPV	**5**	**5**	**0**	**1**	**4**	**3**	**0**	18	6	5
3	**Università degli Studi di Verona**	UNIVR	**2**	**3**	**0**	**4**	**3**	**2**	**8**	22	10	4
4	**Università degli Studi di Ferrara**	UNIFE	**0**	**0**	**0**	**3**	**6**	**3**	**3**	15	6	3
5	**Alma Mater Studiorum - Università di Bologna**	UNIBO	**3**	**0**	**0**	**17**	**3**	**2**	**1**	26	14	4
6	Università degli Studi di Roma Torvergata	UNITOV	**5**	**3**	**5**	**3**	**4**	**5**	**4**	29	11	3
7	**Università degli Studi di Napoli - Federico II**	UNINA	**1**	**3**	**25**	**2**	**0**	**2**	**4**	37	17	5
8	**Università degli Studi della Campania "Luigi Vanvitelli"**	UNICAMPANIA	**0**	**12**	**1**	**0**	**10**	**0**	**0**	23	7	4
9	Università degli Studi "Magna Græcia" di Catanzaro	UNICZ	**3**	**4**	**4**	**0**	**0**	**2**	**0**	13	5	4
10	Università degli Studi di Bari - Aldo Moro	UNIBA	**2**	**3**	**5**	**0**	**5**	**3**	**6**	24	8	2
11	**Università degli Studi di Parma**	UNIPR	**11**	**0**	**0**	**0**	**0**	**3**	**0**	14	5	1
12	Università degli Studi di Firenze	UNIFI	**3**	**2**	**1**	**1**	**2**	**2**	**7**	18	9	3
13	IRCCS Ospedale Policlinico San Martino	HSM	**0**	**2**	**1**	**2**	**0**	**3**	**4**	13	5	3
14	IRCCS Istituto delle Scienze Neurologiche di Bologna	ISNB	**0**	**2**	**0**	**3**	**0**	**3**	**2**	10	7	4
15	Scuola Superiore Sant'Anna di PISA	SSSA	**3**	**0**	**0**	**2**	**0**	**2**	**0**	7	2	1
16	Ospedale Pediatrico Bambino Gesù	OPBG	**2**	**1**	**2**	**1**	**0**	**2**	**2**	10	4	2
17	European Brain Research Institute Rita Levi-Montalcini	EBRI	**2**	**1**	**0**	**0**	**0**	**2**	**0**	5	**3**	0
18	IRCCS SYNLAB SDN	SYNLAB	**0**	**3**	**0**	**0**	**0**	**1**	**2**	6	1	2
19	Fondazione Telethon ETS	TIGEM	**0**	**0**	**2**	**0**	**0**	**1**	**0**	3	0	0
20	Fondazione Don Carlo Gnocchi ONLUS-IRCCS	FDG	**0**	**2**	**0**	**4**	**0**	**1**	**3**	10	6	1
21	IRCCS San Raffaele	SR	**0**	**3**	**0**	**0**	**0**	**1**	**3**	7	4	2
22	Dompè Farmaceutici	DOMPE'	**0**	**0**	**0**	**0**	**0**	**0**	**1**	1	1	1
23	Alfasigma	ALFASIGMA	**0**	**0**	**0**	**0**	**0**	**1**	**0**	1	0	0
24	ASG superconductors	ASG	**0**	**0**	**0**	**0**	**0**	**0**	**0**	0	0	0
25	TAKIS Srl	TAKIS	**0**	**0**	**0**	**0**	**0**	**0**	**0**	0	0	0
			48	**53**	**53**	**49**	**40**	**57**	**50**	**350**	**141**	**62**
	% of young and female researchers										**40,3%**	**17,7%**
	Average H-index (scopus) per spoke		**37**	**39**	**37**	**35**	**42**	**43**	**38**			

Table B1. Human Resources. Personnel for each spoke and each partner of the consortium: the 12 University are indicated in light blue, other partners in light orange and Enterprises in green. The line in grey report the percentage of women and junior researchers. The last line provides the average H-index of the personnel for each spoke

B.2. Type of management and administrative structure

In MNESYS, the HUB plays a crucial role in terms of guidance, management and control. For this reason, the choice of the HUB founders has taken into account the need to implement **an efficient management and administration structure capable of guaranteeing, thanks to its own internal resources, all the functions necessary for a correct realisation of the programme both in terms of effective implementation of the activities and of correct execution in administrative terms**. The HUB will be constituted under the legal form of SCARL (Società consortile a responsabilità limitata), in which the majority of the members are Public Universities and Research Institutes supervised by the Ministry of University and Research and public "Istituti di Ricovero e Cura a carattere Scientifico" (IRCCS). Private companies and institutions represent only the minority of partners, as requested by the Call.

The organizational model for the management of the MNESYS HUB will guarantee:

a) to adopt a streamlined and non-rigid structure, with a view to a lean management;
b) to permit the most effective engagement of public and private actors in the management of the HUB;
c) to adopt timely measures and mitigation strategies to solve problems and correct potential hurdles, both at the scientific and administrative level, to achieve the proposed objectives;
d) to implement the integration of partners avoiding overlaps;
e) to foster the development of marketable products including biomarkers, technologies, patents and spin-off and attract investments based on the fundamental research program.

This structure is appointed to perform the functions of: 1) administrative and scientific project management 2) technology transfer 3) patent protection 4) communication and dissemination 5) management of product innovation processes 6) education and internationalization. Organs of the MNESYS HUB are:

- General Assembly (GA)
- President of the Board of Directors
- Board of Directors (BD)
- Scientific Director (SD)
- Scientific Committee (SC)
- Project Management Office (PMO)
- Technology Transfer Committee (TTC)
- Educational and Communication Committee (ECC)
- Patient Advocacy Committee (PAC)
- International Scientific Advisory Board (ISAB)

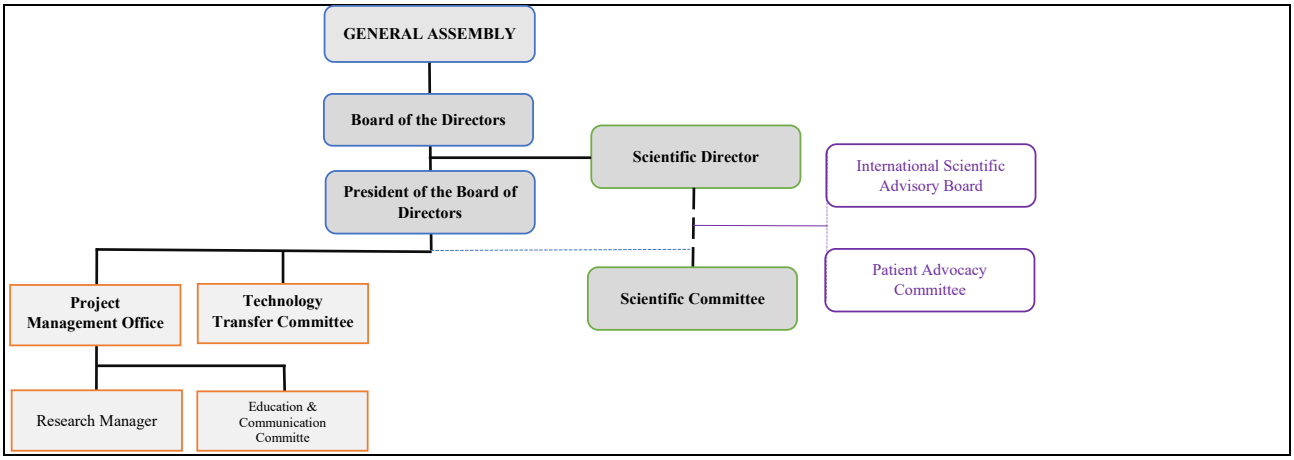

Fig. B2. MNESYS organization chart

The **General Assembly** of the consortium will be composed of the legal representatives, or their delegates, of the consortium members, and will be called by the President of the Board of Directors at least once a year. The GA of participants in the Network will have the following responsibilities:

- to elect the members of the Board of Directors;
- to approve the annual budget and the annual management report prepared by the Board of Directors;
- to deliberate on the exclusion of members of the Consortium as per the charter's rules;

- to deliberate the modifications of the contract and rules and the approval of disciplinary issues.

The **Board of Directors** will be responsible for the validation of the activities and costs incurred by the HUB and SPOKES, for the evaluations on possible proposals of variation with respect to the deliberated budgets, for the constant monitoring of the progress of the activities related to scientific and spending objectives. **The BD will consist of 9 people and composed of people with documented experience in the management of public-private partnerships, complex projects financed by public resources and proven planning and control skills**. The BD shall nominate the **President of the Board of Directors** chosen among its members.

Scientific Director (SD): The scientific director, Prof. Antonio Uccelli, will be in charge of supervising all the project scientific activities being the link among the Board of Directors and the Scientific Committee and all the other committees involved in the management of MNESYS. It will be also the point of contact with the ISAB.

Scientific Committee (SC). The scientific committee is the project highest scientific management body and has the task of supervising the proper development of the project and resolving any disputes among the participants. **The SC will be composed by 15 people including one coordinator, the spoke leader and a young PI, as defined by the criteria of the call, for each spoke**. It will be appointed with the role of leading, coordinating and monitoring research activities favouring interactions among the spokes and cross-collaborations of teams within and among different spokes (cf. Fig. B1). **At least 40% of members of SC will be women and young scientists**.

Spoke	Spoke Leader	Young PI*
Coordinator	UNIGE – S. Martinoia	
S1. Neurodevelopment, social cognition and interaction	UNIPR – L. Bonini	To be selected
S2. Neuronal plasticity and connectivity	UNICAMPANIA – G. Tedeschi	To be selected
S3. Neuronal homeostasis and brain-environment interaction	UNINA – M. Taglialatela	To be selected
S4. Perception, movement and brain-body interaction	UNIBO – P. Fattori	To be selected
S5. Mood and Psychosis	UNIFE – L. Grassi	To be selected
S6. Neurodegeneration, trauma and stroke	UNIGE – T. Florio	To be selected
S7. Neuroimmunology and Neuroinflammation	UNIVR- G. Constantin	To be selected

*Table B2. SC composition, including coordinator spoke leaders and young PIs. *Young PIs will be selected at the beginning of the project and presented at the project kick-off meeting.*

Project Management Office (PMO). It will be composed by **a representative of the administrative offices for each partner and will be chaired by an administrative coordinator**, Dr. F. Scorziello (http://www.rbiotransfer.it/index.htm). It will define, maintain and ensure project management standards across MNESYS HUB. The PMO will provide administrative support for the project management team and standardizes the project-related management processes and will manage the program governance process. As foreseen by the call, a **Research Manager (RM)** will be selected to support the PMO activities. The RM will also assist the Spokes activities in order to guarantee the proper management of the resources (timing, eligible costs, reporting modalities) and the correct application of the reference regulations (state aid regulation, procurement regulation). PMO will involve experienced administrative and managerial staff from the public institutions of the HUB with documented expertise in the management of projects, procurement procedures for the acquisition of goods and services. The RM will closely interact with the Board of Directors and the PMO and will ensure the appropriate level of synergies between research and the technology transfer activities.

Technology Transfer Committee (TTC). It will support the partnership related to the implementation of new entrepreneurship development program. The TTC will focus on strengthening the tie between MNESYS researchers and the industrial partners toward the identification, evaluation and protection of technologies and

deliverables, the management of intellectual property rights, the development of business plan and the negotiation of commercial deals, and will promote the interactions with incubators and accelerators based in science and technology parks and universities. The TCC will also revise prospects arising from the scientific results generated by the spoke's WPs with the aim of producing patents, giving priorities to the proposed opportunities and providing MNESYS enterprises with the priority for the acquisition of intellectual property from the Consortium for their pipeline. A primary task will be to review the results of MNESYS research projects to identify findings that could immediately lead to improvements in the products development process that will result in mitigation of risk. TCC will be composed of the spoke's leaders and managers in the community, inside but also outside the partnership, with expertise in technological readiness, legal and regulatory, social benefits and impact and economic and market factors.

Education and Communication Committee (ECC). ECC will organize dissemination of the scientific results, elements of innovation, potential transferability, and economic and social impact in order to endorse education and communication in brain health promotion and disease prevention and advocate improvements in the complexity of contemporary health education strategies. ECC will be responsible for the governance and implementation of the communication strategy of the partnership advising on the communication policy and its objectives and on the best strategies for implementation of the current programs for public outreach in order to increase public awareness about the benefits of brain research. ECC will promote public engagement providing mutual learning between the public and scientists. Different communication strategies will be implemented including the creation of a project website, a periodic newsletter, public lectures, workshops, graphic recording, podcasts, webinars, radio and TV broadcasting, virtual laboratories and social media events. Activities will be addressed to promote gender equal opportunities (cf. Sect. B5); to disseminate the curiosity towards neuroscience and the potential of their applications, encouraging in young generations the freedom to develop one's own inclinations, empowering talent development and scouting by the synergic collaborations of Education institution and companies. The Institutions responsible for the seven spokes will be part of the ECC and will be supported by a consultant media manager.

Patient Advocacy Committee (PAC): The Committee will be composed of patient advocates of national patient organisations representing patients with neurological and psychiatric diseases. PAC will ensure that advocates are effectively and consistently integrated with bodies conducting the project and involved in the evaluation of the outcomes through a beneficial interaction with the other committees and particularly with the scientific committee and ensuring that each step of the program include consideration for the patient community at large with a special focus on minority and underserved and underrepresented populations.

International Scientific Advisory Board (ISAB): The governance of the HUB will be completed by an external international advisory board composed of experts in the field of neuroscience with the aim of providing scientific monitoring of MNESYS activities, revising intermediate objectives and advising on actions to mitigate potential hurdles. ISAB will also recommend on the best strategies for positioning the expected outcomes of the proposal in the framework of the national and international horizon and will contribute to set up a medium-long term vision of MNESYS results with particular focus on their social and economic impact. Three internationally recognized scientists have already agreed in participating to the ISAB, namely **Prof. Claudio Bassetti**, president of European Academy of Neurology and director of the Clinical Research Program in Neuroscience at the University of Bern, Switzerland; **Prof. Pierluigi Nicotera**, Director of DZNE (German Center for Neurodegenerative Diseases), Bonn, Germany; **Prof. Stephen L. Hauser**, Director of the UCSF Weill Institute for Neurosciences at University of California, San Francisco, USA. The committee will also include at least one representative of an organization promoting spin-off and start-up companies. ISAB will be asked also to support the Board of Directors and the Scientific Committee to design a five-year plan (MNESYS Strategic Plan) combining the results of the research lines envisaged in the present proposal with future trajectories to favour their further strengthening.

B.3. Work Plan

As highlighted above and in section A, the MNESYS project is built upon a network of Universities, Research Institutions, and companies, with fully operational departments, administrative and legal offices and research laboratories. No activity envisaged in the various Spokes requires the establishment of new infrastructures thus allowing for an immediate start and full operation of all work packages. In addition, MNESYS will rely largely on internal human resources, who stand ready to detail and improve the planning and advancement of the work packages. Many of the players of the partnership have a long-standing history of cooperation – and are currently involved in many relevant ongoing research projects – which will further facilitate the rapid start of the activities. The working group involved in MNESYS was composed through a rigorous evaluation and selection process carried out by the Spokes' leaders who, within their organisations and on the basis of the affiliates' proposals, identified the best competences to carry out the activities, taking into account the criteria set out in Sect. B1. Particular attention was given to the correct gender balance as well as to the involvement of young researchers and strongly multidisciplinary skills within each Spoke.

In addition to ensuring the conditions to guarantee a quick start, **a dedicated Project Management methodology has been developed in order to efficiently run and timely complete the wide spectrum of activities foreseen throughout the planned 36 months of the programme, tailored to the complexity and scale of the project**. While the methodology is anchored and builds upon common international standards and best practices, it also presents distinctive and innovative features that have been tailored to address the specificities of the programme. Under the supervision of the **Scientific Director, Board of Directors and Scientific Committee**, following the negotiation phase with the competent agency, the programme workplan will be further defined, detailing tasks, refining milestones, and implementing a risk management plan. A continuous monitoring process will then be put in place to allow Spoke leaders to report on their activities, flagging potential delays and risks. The **Research Manager** – supported by the PMO – will therefore be in a position to regularly track the advancement of all streams of activity, to timely identify potential risks, and to implement mitigation or corrective actions. In line with risk management best practices, all delays and risks will be registered in a Risk Log, which will further ensure their continuous monitoring and also facilitate reporting to competent institutional bodies. The ISAB and SC will also perform periodic supervision meetings with WP and task leaders of each spoke to provide a continuous assessment of the risks, support the definition of mitigation actions and support in the response execution. In this way the project will implement the optimal contingency actions, based on peer-based scientific mentorship and collaborative remodulation of experimental activities. In addition to the constant monitoring of milestones and targets, a systematic review of scientific outputs will be conducted, under the responsibility of the **SC** and with the support of the **ISAB**, which will supervise the scientific efforts of each spoke, provide technical guidance and ensure the quality of the final results.

Each spoke will be responsible for publishing and managing "cascade" funding calls, on research topics that could successfully complement the spoke WPs and have the potential to contribute to the spoke objectives. The shared methodologies to select the applicants to the calls will be defined a priori and will be agreed among all spokes. The Extended Partnership will engage in all communication activities needed to ensure that the "cascade" funding calls reach a broad audience. In the selection process will be mainly considered scientific/technical excellence. The preferential involvement of actors that might facilitate the market development of research results might be considered in specific topics, that have exploitation potential.

The workplan is constituted by a section, under the responsibility of the HUB, composed of three work packages dedicated to the management and dissemination and by the seven spoke's projects with their corresponding work programmes. Below the description of the HUB and the Spoke's Work Packages (WP).

HUB

Work package number	HUB.WP1	Partner responsible	UNIGE
Work package title	***Project management and coordination* (M1-M36*)***		
Objectives: i) ensure that the project objectives are met within agreed budget and timeframe, carrying out quality control of the work performed and the deliverables ii) maintain communication among partners and execute deliverables, scientific and financial reports iii) assist partners in administrative issues and ensure compliance with EU rules iv) financial and legal management v) starting, development and management of the Partnership and support of the PMO and RM			
T1.1. Monitoring progress (Leader: UNIGE; others: all): monitoring the compliance with the work plan to guarantee that milestones are reached and deliverables duly achieved **T1.2. Administration and project reporting** (Leader: UNIGE; others: all): Coordination between partners and with the Ministry; financial and scientific reporting; bi-annual internal reporting; organization of kick-off and annual consortium meetings and of bi-monthly web-based meetings to ensure communications between partners and resolve particular issues. **T1.3. Ethical issues** (Leader: UNIGE; others: all): monitoring of ethical board approvals in all institution **T1.4. Data management monitoring** (Leader: UNIGE; others: all): monitoring of compliance with current regulations of data management and storage throughout the project **T1.5. Gender equality policy and support for young researchers:** (Leader: UNIGE; others: all): monitoring of gender equality and young researchers' policies implementations			
Deliverables: D1.1 Ethics board clearance for all partners. [M3] D1.2 Data management and publication policy plans publication in the project website [M3] D1.3 Periodic scientific and financial reports. [M12, 24, 36]			
Milestones: **M1.1**. Establishment of MNESYS governance and organs [M1] **M1.2** Application to institutional review boards. [M1] **M1.3** Kick-off consortium meetings [M2] **M1.4.** Periodic consortium meetings [M12, M24, M36]			

Work package number	HUB.WP2	Partner responsible	UNIGE
Work package title	***Project dissemination, comunication and exploitation* (M1-M36*)***		
Objectives: To ensure (i) dissemination, (ii) communication and (iii) exploitation of project results and promote them through appropriate communication means, respecting intellectual property rights, also in the context of the activities of the ECC and TCC. Interaction with institutional stakeholders and policymakers, with scientific societies and manufactures association and consortia.			
T2.1. Dissemination and training progress (Leader: UNIGE; others: all): execution and rolling review of the dissemination plan including of the role of young researchers. This task includes educational workshops and lecture for scientists/clinicians on project topics. **T2.2. Communication** (Leader: UNIGE; others: all): execution and rolling review of the communication plans including of the role of young researchers. Two workshops will be organized involving domain Patients Organizations. **T2.3. Exploitation** (Leader: UNIGE; others: all): execution and rolling review of the exploitation plan, for all the research results that have a market potential, including of the role of young researchers.			
Deliverables: D2.1 Project website. [M2]. D2.2 Review on all the key papers published and the patents obtained during the project. [M36] D2.3 Public workshops. [M20; M36] D2.4 Roadmap for future exploitation (including report on technology and market watches). [M36]			

Milestones: **M2.1**. Finalization of the dissemination, communication and exploitation plan. [M3] **M2.1** Internal review of the dissemination, communication and exploitation plan [M12, M24] **M2.3** Monitoring of the efficacy of the dissemination, communication and exploitation efforts [M12, 24, 36]

Work package number	HUB.WP3	Partner responsible	UNIGE
Work package title	***Scientific coordination of the project* (M1-M36*)***		
Objectives: i) supervision of the scientific activities of the Spokes together with the SC and ISAB ii) facilitate the interactions between the SD, the SC and the ISAB iii) support the activities of the PAC			
T1.1. Scientific coordination (Leader: UNIGE; others: all): support of the scientific activities of the spokes with a focus on fostering collaborations. Risk mitigation strategies. **T1.2. PAC** (Leader: UNIGE; others: all): support of PAC activities and interaction with patient advocacy groups and other not-for-profit stakeholders.			
Deliverables: D1.1. MNESYS Strategic Plan publication in the project website. [M3] D1.2. MNESYS Strategic Plan updates in the project website [M12, M24, M36] D1.2. Patient involvement strategy plan publication in the project website. [M3] D1.3. Periodic PAC reports. [M12, 24, 36]			
Milestones: **M1.1**. Kick-off ISAB, SC and spokes supervision meeting. [M2] **M1.2.** Periodic ISAB, SC and spokes supervision meetings [M6, M12, M24, M36]			

SPOKES

It is worth underlying that for each spoke we follow the concept presented in Fig. A1 in which different scales are addressed (and identified within each WP) and specific methods and technologies developed within the spoke itself. For the sake of clarity, the different scales presented in Fig. A1, are reported below.

A. Molecular Genetic	B. 2D & 3D cellular Models	C. Animal Models	D. Individuals and Population	E. Network: neurophysiology, neurotechnology and imaging	F. D4: Drug Discovery, Development, Delivery	G. Digital Twins

Table B3. Scales addresses in the spokes

SPOKE1. NEURODEVELOPMENT, SOCIAL COGNITION AND INTERACTION

S1.1 Description of the overall aim of the spoke

S1 will tackle the major gaps of knowledge in neurodevelopment using a lifespan perspective, from preconception to childhood and adulthood. Parallel, but strictly interrelated, research pathways will capitalize on cutting-edge technologies, animal models, and state-of-the-art modeling approaches to elucidate (WP1) the basic anatomo-functional mechanisms underlying sensorimotor and social development, from the genetic to the cellular and system level; (WP2) the identification of biomarkers of neurodevelopmental disorders (NDD) at multiple levels of complexity and resolution scales; (WP3) the biochemical, neurophysiological, genetic and epigenetic bases of novel intervention approaches and, finally (WP4), the identification of the environmental and social determinants of healthy and pathological neurodevelopment. This project will involve 14 leading national research institutions with a wide geographical representation, overall including more than 30 highly collaborative labs.

S1.2 Composition of the spoke

Institution	Type	Location	Role	Short name
UNIVERSITA' DEGLI STUDI DI PARMA	**University**	**Parma**	**Spoke responsible**	**UNIPR**
Università degli Studi di Genova	University	Genova	Affiliated	UNIGE
Università degli Studi di Roma Torvergata	University	Roma	Affiliated	UNITOV
Università degli Studi di Pavia	University	Pavia	Affiliated	UNIPV
Alma Mater Studiorum - Università di Bologna	University	Bologna	Affiliated	UNIBO
Scuola Superiore Sant'Anna di PISA	University	Pisa	Affiliated	SSSA
Università degli Studi di Verona	University	Verona	Affiliated	UNIVR
Università degli Studi di Firenze	University	Firenze	Affiliated	UNIFI
Università degli Studi di Bari Aldo Moro	University	Bari	Affiliated	UNIBA
Università degli Studi "Magna Græcia" di Catanzaro	University	Catanzaro	Affiliated	UNICZ
Università degli Studi di Napoli Federico II	University	Napoli	Affiliated	UNINA
European Brain Research Institute Rita Levi-Montalcini	Foundation	Roma	Affiliated	EBRI
Ospedale Pediatrico Bambino Gesù (Roma)	Hospital	Roma	Affiliated	OPBG
IRCCS Ospedale Policlinico San Martino	Hospital	Genova	Affiliated	HSM

S1.2.1 Description of the synergies

The University of Parma is a worldwide renown center for system neuroscience, which played a foundational role in the so-called "social and affective neuroscience" and in the investigation of neurodevelopment of motor and interactive competences in health and disease. In addition to an existing and long-lasting collaboration of UNIPR with SSSA and UNIBO, the creation or strengthening of collaborations among all Universities and Research Institutions belonging to the Spoke (see WPs), depending on individual expertise and competences, will contribute to a strongly interdisciplinary research effort, encompassing physiology, psychology, biochemistry, genetics, and computational modeling. Physician scientists (neurologists, neuropediatricians, etc), roboticists and AI experts will contribute to make basic research findings suitable for translational applications. The team includes a well-balanced mix of senior Professors with large expertise of leading major national and international research projects, as well as junior Researchers with demonstrated ability to secure extramural funding and lead a research lab.

S1.3 Work Packages

Work package number	**S1. WP1**	Partner responsible	UNIPR
Work package title	**Anatomo-functional mechanisms of neurodevelopment and social cognition (M1-M36)**		
Relevant scales	Animal Models, Individuals and Population, Network, Digital Twins		
Universities	UNIPR, UNITOV, UNIPV		
Other participants	SSSA		
Total number of partners	4		

Objectives. 1) Investigating the prenatal mechanisms of multisensory integration in high and low stress pregnancy; 2) identifying the neural mechanisms of muscular coordination in typically developing infants and pre-schoolers; 3) achieving a comprehensive anatomo-functional model of the primate social brain; 4) measuring the plastic potentials of the social brain network induced by observational learning and imitation.

T1.1. Prenatal development of multisensory integration (MI) (Leader: UNIPR; others: UNITOV, SSSA). Women with singleton pregnancy (28-32 weeks g.a.) exposed to high or low level of stress will undergo 2 and 4D sonographic assessment to record foetuses' movement kinematic profiles and facial expressions in response to uni- or multimodal (tactile and auditory) stimulation. We hypothesize that foetuses exposed to low level of stress show higher MI enhancement, assessed by capitalizing on newly developed machine learning algorithms. These experiments will allow to model the mechanisms of prenatal MI, and pave the way to foetal fMRI studies.
T1.2. Development of motor skills in infants (Leader: UNITOV; others: UNIPR, SSSA). Cutting-edge, non-invasive technologies will be applied to monitor kinematics, kinetics, and motoneurons activities (high-density

EMG of multiple muscles) in children during spontaneous movements, such as, kicking, reaching, stepping, crawling, independent walking and running. Longitudinal and cross-sectional studies will be carried out leveraging machine-learning algorithms to describe the neuromuscular modules at different time points of motor development, from birth to 4 years of age.

T1.3. **Architecture and dynamics of the social brain in the monkey** (**Leader: UNIPR**; others: SSSA). The connectional fingerprint of motor and emotional brain regions recruited during self- and other-related action and emotion processing will be studied in macaques, first with MRI-based connectional techniques at ultra-high field (7T), and next, at cellular resolution with neural tracer injections. Multi-area neuronal signals from freely-moving macaques will be chronically recorded with telemetric approaches, coupled with multicamera motion capturing, investigating the neural dynamics and longitudinal changes during face-to-face social interactions and the neural mechanisms for action planning based on action observation. Advanced signal processing and machine learning algorithms will allow us to achieve a comprehensive model of the social brain.

T1.4. Plastic potentials of the social brain (Leader: UNIPV; others: UNIPR). The role of cortical areas, basal ganglia, and cerebellum in mediating social cognition and their plastic changes during motor learning by observation and imitation will be investigated. We will adopt an integrated multilevel approach encompassing neuropsychological evaluation of social processes and multimodal neuroimaging in healthy human subjects and patients with different brain lesions occurred in developmental age (i.e. cerebral palsy) and adulthood (i.e. stroke).

Deliverables

D1.1. Piloting, preliminary version of algorithms and software, and preliminary data acquisition in human and animal subjects [Month 18]; **D1.2.** Completion of data acquisition and analysis [Month 33].

Milestones

M1.1. Construction and testing of the experimental setups and data analysis pipelines [12]. **M1.2**. Preliminary results [24]. **M1.3**. Final data set available for all tasks and quantitative results [36].

Work package number	**S1. WP2**	Partner responsible	UNITOV
Work package title	**Identification of new biomarkers for NDDs (M1-M36)**		
Relevant scales	All		
Universities	UNITOV, UNIPR, UNIVR, UNIGE, UNICZ		
Other participants	OPBG, SSSA		
Total number of partners	7		

Objectives. 1) To identify biomarkers of a range of NDD; 2) Discovering predictive factors of NDD; 3) Reaching early diagnosis of developmental and epileptic encephalopathies; 4) Studying the development of motor and social skills in autism and fragile X syndrome.

T2.1. Predictive factors of developmental motor disorders (**Leader: UNITOV**; others: UNIGE; UNIPR). Very preterm infants at risk of developmental motor disorders (DMD) and **c**hildren with clinical and anatomical (MRI) diagnosis of cerebral palsy (CP) will be followed-up with in-depth clinical, kinematic, kinetic, EMG, EEG measures during several tasks, in addition to genetic/molecular analysis, markers of perinatal inflammation, and MR imaging studies. Capitalizing on UNITOV's proprietary techniques, we will identify motoneuron properties and correlate them with general movement analysis and detailed kinetics, improving the early detection of DMD and measuring clinical and instrumental outcomes of innovative treatments. Innovative, active exercise interventions for CP performed at home during the first 2 years and rehabilitation based on observation and reproduction of daily-life actions will be compared with standard day-hospital rehabilitation.

T2.2. Early diagnosis of developmental and epileptic encephalopathies (**Leader: UNIVR**; others: UNICZ; OPBG). Subjects with NDDs will undergo clinical, neurophysiological, neuroradiological, and neuropsychological assessment, in addition to genetic analysis with CGH-array, epileptic encephalopathy, and exome panels. Follow-up evaluations will highlight the different trajectories of the various forms of developmental disorders, particularly the syndromes related to the mutations of SCN1A, PCDH19, CDKL5, SCN2A, SCN8A, KCNQ2, TSC1, TSC2, GLUT1 genes. We will clarify how early pharmacological treatment and rehabilitation modulate epilepsy associated NDDs.

T2.3. Neurodevelopment of motor and social skills in fragile X and ASD models (**Leader: UNITOV;** Others: UNIPR). Sensory-motor difficulties have been observed in children with Fragile X Syndrome (FXS), autism spectrum disorder (ASD) and other cognitive disabilities. UNITOV contributed evidence of social and motor impairment in adult mouse models of ASD (*Fmr1* KO, *Cyfip1* haploinsufficiency). Here, we propose that motor deficits during development can increase the skill learning gap, ultimately exacerbating ASD core symptoms,

such as in social interaction. We will 1) identify the critical period/s for the onset of motor dysfunctions in different mouse models of autism (*Fmr1* KO, *Cyfip1* haploinsufficiency, *Cyfip1* overexpression and *Shank3* haploinsufficiency and KO), 2) investigate neuronal activity of motor-related brain areas (motor cortex, striatum, cerebellum) and 3) the underlying molecular mechanisms. We will correlate motor and social deficits during different developmental stages.

T2.4. Sleep and circadian alterations in NDD: from genes and brain connectivity to emotional regulation and behaviour (Leader: UNIGE; OPBG). We will identify biomarkers distinguishing different phenotypes and developmental trajectories in NDDs. We will conduct a) genetic assessments (analysis of clock genes variants/polymorphisms and whole exome sequencing (WES)), including the contribution of identified microdeletions and microduplications (copy number variants) by CGH-array diagnostic test; b) long term Actigraphy-Derived Daily Rest–Activity Patterns analyses (interdaily stability, intradaily variability, relative amplitude, acrophase analyses); c) wake and sleep EEG recordings for the assessment of modules in connectomes of phase-synchronization and functional connectivity, to be correlated with measures of MRI-based connectivity in NDDs subjects; d) phenotypic typing of NDD subjects (internalizing, externalizing symptoms, emotional and behavioural features), using validated scales.

T2.5. Novel biomarkers based on EEG/MRI data. (Leader: UNICZ; Others: UNIVR; UNIGE). We will apply advanced imaging methods (MRI and EEG) to capture the complexity of neural dysfunction in subjects with developmental and epileptic encephalopathies and in individuals with psychogenic non epileptic seizures, in which cognitive functions are influenced by epileptiform activity and the underlying neurobiological processes. Identification of aberrant organization of neural networks function may allow the development, validation, and application of novel biomarkers based on hybrid EEG/MR data.

Deliverables

D2.1. Preliminary data acquisition in human and animal subjects [Month 18]; **D2.2.** Completion of data acquisition and analysis [Month 36].

Milestones

M2.1. Experimental design and setup validated, data analysis pipeline developed [12]. **M2.1**. Preliminary results reporting [24]. **M2.1**. Final data set for all tasks and quantitative analyses results [36].

Work package number	**S1.WP3**	Partner responsible	UNIGE
Work package title	**Neural and molecular mechanisms of NDD and targeted therapies (M1-M36)**		
Relevant scales	Molecular-genetics, 2D&3D cellular models, Animal Models, Individual and population, D4		
Universities	UNIGE, UNIFI, UNIPV, UNIBO, UNICZ, UNIBA, UNIVR. UNINA		
Other participants	OPBG, HSM, EBRI		
Total number of partners	11		

Objectives. 1) To identify genetic signatures of NDDs and their molecular and cellular phenotypes; 2) to discover the physio-pathological mechanisms of drug-resistant epilepsy; 3) to pave the way to new therapeutic strategies for NDDs.

T3.1. Genetic signatures in the developing brain (Leader: UNIGE; Others: UNIFI, UNIPV, UNICZ, UNIBO, OPBG). Genetic factors contribute to physiological and pathological neurodevelopment. We will explore the genetics underlying NDDs (e.g. epileptic encephalopathies, brain malformations, intellectual disability, ASD) to identify novel genes for rare Mendelian traits, non-coding variants affecting gene regulation and expression, and balanced and unbalanced structural variants in the non-coding genome affecting 3D genome architecture. Deep phenotyping of large cohort of patients will allow us to establish novel genotype-phenotype correlations; by using gene burden approaches and Network and Pathway analysis we will detect possible modifying factors influencing the expression and penetrance of major mutations. The impact and clinical significance of candidate pathogenic mutations and Variants of Unknown Significance (VUS) will be explored with cellular and in silico assays by combining next-generations sequencing approaches (short and long reads whole-exome/genome Sequencing, RNA-Seq), molecular modelling, *in vitro* functional assays and machine learning models.

T3.2. Pathogenetic pathways underlying altered neuronal development and excitability in genetic NDD models (Leader: UNIBA; Others: UNIGE, UNIFI, UNIVR, UNIBO, UNINA, OPBG, HSM). We will investigate the pathogenetic mechanisms underlying NDDs through multiple experimental models including 2D mouse primary and human IPSC-derived neuronal cultures, and 3D human brain organoids. We will cover a variety of NDD for which significant background, expertise and tools are already available within the consortium,

such as Channelopathies (KCNQ2,3, and 5-related disorders), Ciliopathies (Joubert Syndrome), Synaptopathies (STXBP1-, VAMP2-, STX1B-related NDDs), developmental brain disorders and brain malformations related to Tubulinopathies, ion channel dysfunction, APTase pump and V-ATPase disorders, Metabolic Disorders (AGC1-deficiency) and ASD. We will study the role of neural stem cells and neurogenesis in brain development and analyse the effect of specific genetic mutations on i) neural progenitor cells (NPCs) proliferation, migration and differentiation; ii) glial cells-neurons interactions (contacts, released molecules, exosomes) and iii) specific neuronal functions (e.g. intrinsic excitability, synaptic transmission). We will employ a variety of techniques including single-cell transcriptomics, biochemistry, electrophysiology, high-content and super-resolution imaging. Identification of markers of biochemical rewiring and bioenergetic dysregulation will define molecular and cellular NDD phenotypes prodromal to set assays for drug screening/repositioning and testing of innovative therapeutic molecules, as described in T3.4.

T3.3. Physio-pathological mechanisms of drug-resistant forms of cortical dysplasia-dependent epilepsy in children (Leader: EBRI; Others: OPBG**).** Organotypic slices from brain tissues removed during surgery for drug-resistant forms of epilepsy will be used to study whether this type of epilepsy is produced by ferroptosis, a recently discovered iron-dependent oxidative cell death. We will test potential therapeutic agents on inter-ictal and ictal activities maintained in vitro for periods of 6-8 weeks. Preliminary data in mice demonstrate that the ferroptosis inducer RSL3 triggers in cortical slices interictal discharges that can be prevented by antioxidants, such as vitamin E. Organotypic slices from children brain tissues will be also used to test whether GABA's shift from hyperpolarizing to depolarizing direction can contribute to network hyper-excitability by altering the excitatory/inhibitory balance. As in other forms of epilepsy, this can be caused by a reduced expression of the chloride [Cl-] exporter KCC2, with consequent changes in Cl^- homeostasis.

T3.4. Innovative therapeutic strategies for NDDs (Leader: UNIPV; Other: UNIVR, UNIGE, UNINA). With innovative precision-medicine approaches we will overcome the genetic defect underlying NDDs (focusing on those studied in T3.2). The mutated gene itself provides a potential druggable genomic target for therapeutic discovery design. NDDs associated to loss-of-function mechanisms will be approached by gene replacement (namely by introducing a healthy copy of the gene/mRNA into the cells) and SINEUPs (namely, synthetic antisense long non-coding RNAs that stimulate translation from a target messenger RNA). In case of gain-of-function or dominant-negative mechanisms, we will exploit gene silencing by antisense oligonucleotides (ASOs) or by siRNA-mediated RNA interference, as well as gene therapy approaches by CRISPR/Cas9-mediated genome editing. Modulation of specific molecular pathways will be pursued by delivering miRNAs. Finally, we will exploit novel pharmacological tools, based on drug screening/repositioning approaches or cell penetrating peptides by means of cell-based assays.

Deliverables

D3.1. Cell-based assays for druggable molecular targets [M18]; **D3.2.** Novel genes/mutations associated to NDDs [24]; **D3.3**. Candidate compounds/molecules for personalized medicine in NDDs [M36].

Milestones

M3.1. Genetic analysis and set-up of cell/tissue-based assays accomplished [M18]; **M3.2.** Screening of compound/molecules accomplished [M36].

Work package number	**S1. WP 4**	Partner responsible	UNIPR
Work package title	**Environmental and social determinants of neurodevelopment, health and disease (M1-M36)**		
Relevant scales	Molecular-genetics, 2D&3D cellular models, Animal Models, Individual and population, Network		
Universities	UNIPR, UNIGE, UNIPV, UNIVR, UNIBA		
Other participants	SSSA		
Total number of partners	6		

Objectives 1) To identify the epigenetic and genetic bases of neurodevelopmental vulnerability; 2) To clarify the mechanism of social and environmental factors on neurodevelopment, including potential interventions; 3) To identify the mechanisms of social stress and endocrine disruptors on neurological and cardio-metabolic diseases.

T4.1 Impact of the social and physical environment on early development and disease susceptibility (Leader: UNIPR; Others: UNIVR, UNIBA). We will study the effects of the physical and social environment on the neurodevelopment of parent-infant affective-emotional relation and of cognition in children with NDD, integrating contribution from psychobiology, disease susceptibility, environmental pollution, nutrition, music neuroscience, and psycholinguistics. We aim to unravel the relationship between endocrine disruptors and

subsequent NDDs in children and animal models, and to establish with a longitudinal study an early intervention 3-months-long program for infants/parents based on the musical interaction between an infant-parent dyad to build a healthy socio-affective bonding and a secure attachment style.

T4.2. Predictive models for environmental risk and protective factors related to Autism Spectrum Disorders (ASD) and other neurological disabilities (Leader: UNIPV; Others: UNIGE; UNIBA; UNIVR).
We will assess the psychobiological, epigenetic and biochemical pathways that are susceptible to regulation by environmental exposures increasing the risk for ASD and other neurological disabilities. Environmental exposures will include: pre/postnatal exposures to endocrine disruptors, parental/familial processes, toxic substances, social support, quality of early caregiving, psychopathological conditions of the caregivers. The molecular targets will include epigenetic processes (DNA methylation, microRNA, histones acetylation); telomere length; dysregulations of the HPA axis and pro/anti-inflammatory molecules, biomarkers of biochemical rewiring and mitochondrial dysregulation. Population of interest will include pregnant women, healthy (full-term) and at-risk (e.g., preterm; siblings) newborns.

T4.3. Epigenetic and biological mechanisms of individual vulnerability to social-stress related neuropsychiatric and cardiovascular disorders (Leader: UNIPR; Others: SSSA). Brain-heart dysfunctions often coexist, and social stress is a major risk factor. We will adopt a multimodal approach to investigate the role of social stress in rendering an individual vulnerable to cardiovascular and neuropsychiatric diseases. We will particularly focus on the impact of epigenetic mediators that increase disease risk in both sexes by leveraging animal models of social stress, healthy and clinical populations.

T4.4. **Development of preclinical models to investigate the mechanistic link between social stress mediators and brain dysfunctions causing neurological and metabolic diseases. (Leader: UNIPR;** Other: UNIBA).Chronic social stress conditions modelling social determinants of health in humans, are associated with a plethora of chronic neurological and metabolic diseases. We will capitalize on validated social stress models to investigate the link between stress mediators and the risk to develop Alzheimer`s disease and related dementia (ADRD), and the associated functional and molecular neural alterations. Because neurological diseases are often in comorbidity with metabolic diseases, such as obesity and diabetes, we will test in vivo the link between stress induced metabolic dysfunctions and gliosis with the risk to develop ADRD. Genetic models of ADRD, obesity, and diet induced obesity will be used, in addition to cell cultures (e.g. primary cultures of astrocytes and microglia) and metabolomic approaches.

Deliverables

D4.1. Validate screening questionnaires for the assessment of environmental risk factors [M18]. **D4.2.** Validate animal models of stress induced diseases [M24]. **D4.3**. Validate the effects of maternal ED exposure on behaviour and neurophysiological inter-brain biomarkers in children and mice [M30].

Milestones

M4.1. Identify candidate epigenetic, molecular and endocrine mechanisms for ED and social stress-induced exacerbation of brain-related diseases [M36]. **M4.2**. Complete psychobiological profiling and biomarker identification of the estimated sample size for clinical studies [M36].

S1.4 Cascade calls for funding

Tentative topics for the cascade calls that will be implemented to complement S1 activities are:

- The role of subcortical structures in neurodevelopment and plasticity of social information processing
- Early behavioral and neuroimaging markers of developmental disorders
- Behavioral and neural signatures of socio-cognitive mechanisms underlying deficits in social interaction skills.
- Role of impaired synaptic transmission and excitability in neurodevelopmental disorders
- Identification of new genes for undiagnosed neurodevelopmental disorders
- Indexing social processes from intracranial recordings and stimulation in children with drug-resistant epilepsy.

S2 NEURONAL PLASTICITY AND CONNECTIVITY

S2.1 Description of the overall aim of the spoke

The spoke aims at contributing to develop novel models and improved technological solutions for a deeper understanding of brain physiology and disease states. The spoke will coordinate basic and clinical research

addressing the mechanisms of neuronal plasticity and connectivity at multiple scales, to improve the knowledge of normal and altered pathways in the mammalian brain in different physiological and pathological conditions, paving the way to new therapeutic approaches.

S2.2 Composition of the spoke

Institution	Type	Location	Role	Short name
Università della Campania "Luigi Vanvitelli"	**University**	**Napoli**	**Spoke responsible**	**UNICAMPANIA**
Università "Magna Grecia" di Catanzaro	University	Catanzaro	Affiliated	UNICZ
Università degli Studi di Verona	University	Verona	Affiliated	UNIVR
Università degli Studi di Genova	University	Genova	Affiliated	UNIGE
Università di Napoli Federico II	University	Napoli	Affiliated	UNINA
Università degli Studi di Pavia	University	Pavia	Affiliated	UNIPV
Università di Roma Tor Vergata	University	Roma	Affiliated	UNITOV
Università degli Studi di Bari Aldo Moro	University	Bari	Affiliated	UNIBA
Università degli Studi di Firenze	University	Firenze	Affiliated	UNIFI
IRCCS Ospedale Policlinico San Martino	Hospital	Genova	Affiliated	HSM
IRCSS SynLab SDN	Res. Institute	Napoli	Affiliated	SYNLAB
Fondazione Don Gnocchi ONLUS	Foundation	Milano	Affiliated	FDG
IRCSS San Raffaele	Hospital	Roma	Affiliated	SR
European Brain Research Institute Rita Levi-Montalcini	Foundation	Roma	Affiliated	EBRI
IRCSS Istituto delle Scienze Neurologiche di Bologna	Hospital	Bologna	Affiliated	ISNB
Ospedale Bambin Gesù	Hospital	Roma	Affiliated	OPBG
ASG Superconductors	Enterprise	Genova	Affiliated	ASG

S2.2.1 Description of the synergies

Synergies will develop at two levels: Within the work package, most institutions will engage researchers with complementary expertise in multiple disciplines (e.g., physics, engineering and medicine) contributing to tasks via pre-existing collaborations. Across different work packages, researchers with similar expertise will find opportunities for new collaborations so that institutions will ultimately cover multiple scales of studies of neuronal plasticity and connectivity.

S2.3 Work packages

Work package number	**S2. WP1**	Partner responsible	UNIGE
Work package title	**Molecular and cellular mechanisms of neuronal communication & plasticity in vitro and in vivo (M1-M36)**		
Relevant scales	Molecular-genetics, 2D&3D cellular Models, Animal Models, Network		
Universities	UNIGE, UNIPV, UNICAMPANIA, UNIVR, UNIFI, UNITOV		
Other participants	EBRI, HSM, SR		
Total number of partners	9		

Objectives 1) Unravel the molecular and cellular determinants of physiological plasticity and model altered plasticity to study pathophysiological mechanisms of neurological disorders. 2) Provide constructive resources and the validation templates for the models generated in WP2.

T1.1. Synaptic, intrinsic structural and homeostatic plasticity in the healthy brain (Leader: UNIGE; others: UNIPV, UNIFI, SR). Investigation on the physiological mechanisms of neuronal plasticity in 2D and 3D neuronal circuits with single particle tracking, advanced single cell electrophysiological and imaging techniques and microtransducer arrays for electrical monitoring at network level.

T1.2. Role of aberrant neuronal plasticity in pathology (Leader: UNIGE; others: UNICAMPANIA, UNITOV, UNIVR). Employ transcriptomics, biochemical, electrophysiological and live imaging techniques in integrated cellular models of murine and human origin, to define the role of epigenetic factors, altered intracellular signalling, protein-protein interaction and homeostasis, neuro-vascular coupling and hormones in neuronal homeostasis and plasticity and their role in pathology.

T1.3. Altered brain plasticity in animal models of neurological disorders (Leader: UNIPV; others: UNIGE, EBRI; UNICAMPANIA; SR). Employ animal models of neurodevelopmental and neurodegenerative

disorders to study neuronal plasticity and connectivity with in vivo and ex vivo electrophysiology, live imaging and behavioural analysis.
Deliverables **D1.1.** Brain-on-a-chip models of engineered neuronal network [M24]; **D1.2.** Report on epigenetic mechanisms involved in aberrant plasticity [M24]; **D1.3.** Implementation of cellular models employing patient IPSC-derived neurons [M24]; **D1.4.** Generation of animal models with altered cerebral D-serine and D-aspartate levels [M24]; **D1.5.** Microscopic underpinning of cerebral network activity determined in normal and pathological mice including epilepsy, ataxia, autism, and paroxysmal dyskinesia [M36].
Milestones **M1.1.** Single molecule microscopy and force microscopy in single synapses in neuronal cell cultures [M24]; **M1.2.** Implementation of new intervention strategies in the treatment of neurological disorders associates to neural plasticity and connectivity dysregulation [M36].

Work package number	**S2. WP2**	Partner responsible	UNIPV
Work package title	**Multiscale brain modeling and digital brain twins (M1-M36)**		
Relevant scales	All except D4		
Universities	UNIPV, UNIGE, UNIFI, UNIVER, UNITOV		
Other participants	SYNLAB		
Total number of partners	6		
Objectives To model and simulate brain functions at multiple scales, from neurons and microcircuits up to virtual brains, promoting the development of Digital Brain Twins and of neuromorphic technology.			
T2.1. Molecular/cellular models. (Leader: UNIPV; others: UNIGE, UNIVR). To develop detailed (multi-compartment) and simplified (mono-compartment) models of neurons and microcircuits validated against WP1 data to enforce a multiscale modelling strategy toward T2-T3. **T2.2. Digital Brain Twins (Leader: UNIPV**; others: UNIGE). To develop Digital Brain Twins embedding available biological knowledge (other WPs) to simulate brain dynamics in normal and pathological subjects. **T2.3. Neuromorphic technologies (Leader: UNITOV**; others: UNIPV). To elaborate models for neurorobotics, neuromorphic computing and AI, based on biological principles of neural communication and plasticity. **T2.4. AI solutions and algorithms (Leader: UNIGE**; others: SYNLAB, UNIFI, UNIVR, UNIPV). To develop AI solutions and algorithms needed for network modelling and neurocomputational analysis in support to T1-T3.			
Deliverables: **D2.1.** Molecular/cellular models: Multiscale models of brain circuits and Digital Brain Twins of normal and pathological subjects developed and simulated [M36]; **D2.2.** Neuromorphic technologies developed for self-trainable spiking neural networks, large-scale extreme Edge Computing device with memristive technology, advanced brain computer interface (BCI), micro and mobile/wireless devices to improve motor function [M36]; **D2.3.** Inversion schemes to recover structural and functional information from ensemble signals and Machine Learning / Deep Learning -based models for electrophysiological and behavioural simulations [M36]; **D2.4.** New AI models to investigate brain network proprieties after cognitive and motor stimulation: system integration and segregation [M36].			
Milestones: **M2.1.** Molecular/cellular models: Multiscale models of brain circuits developed and applied to Digital Brain Twins [M18]; **M2.2.** Neuromorphic technologies for novel Spiking Neural Networks, memristive technology, BCI systems, micro and mobile/wireless devices to improve motor function designed [M18]; **M2.3.** Inversion schemes and Machine Learning / Deep Learning procedures set [M18]; **M2.4.** New AI models designed [M18].			

Work package number	**S2. WP3**	Partner responsible	SR
Work package title	**Neuronal plasticity in normal brain & neurological disorders (M1-M36)**		
Relevant scales	Anima Models, Network, D4		
Universities	UNITOV, UNIVR, UNIFI, UNICZ, UNIPV		
Other participants	SR, OPBG, EBRI, FDG, SYNLAB		
Total number of partners	10		

Objectives The distinction of biological vs. chronological brain age is of considerable interest. Healthy and aberrant neuroplasticity reflects brain adaptation to internal (genetics, aging) and external (learning, life experience, diseases) challenges. Aim of WP3 will be to collect a combination of candidates of neuroplasticity biomarkers (molecular, ionic channel physiology, metabolic/flow and neurophysiological imaging and peripheral biomarkers) from healthy subjects of different age to map trajectories of age-related brain plasticity in rest and learning conditions and to track them in different brain diseases and pharmacological/rehabilitative treatments (i.e. Parkinson, Alzheimer, stroke, epilepsy etc.). The WP foresees an advance from TRL2 (begin) to TRL4 (end).

T3.1. EEG markers of network architecture and brain plasticity at different ages combined to the study of neuroplasticity and neuromodulation of sensory-motor integration (visual, tactile and auditory) in health and disease (**Leader: SR**; others: UNIVR, FDG, UNIPV).
T3.2. Artificial Intelligence for early surgery in epilepsy (**Leader: OPBG**; others: SR).
T3.3. Hippocampal plasticity and changes of long-range GABAergic connections in murine Parkinson and Alzheimer models to identify new diagnostic/therapeutic targets; Neuronal networks of resting tremor by hybrid PET/MRI using a connectomics approach (**Leader: UNITOV**; others: UNICZ, EBRI).
T3.4. 3T-MRI and neurophysiological methods to explore standardized brain connectivity changes induced by learning and rehabilitation (**Leader: FDG**; others: UNIVR, SR).
T3.5. Estimation of peripheral SNAP-25 concentrations and neuronal and glial extracellular vesicles and the study of Ionic channel blockers designed, synthesised and tested in vitro and in vivo in animal models of pain and cough (**Leader: SYNLAB**; others: UNIFI).

Deliverables
D3.1. High density EEG database of young-adult healthy subjects to measure connectivity via graph-theory. Neuroplasticity measures (TMS-EEG, dual-TMS) in cognitively normal/abnormal aged subjects [M24]; **D3.2.** Platform for automated analysis of presurgical data in neurosurgery [M36]; **D3.3.** Electrophysiological/imaging of sensorimotor integration and brain tumors-related brain plasticity. Network parameters tracking adaptation/reorganization. Causality of neuronal interactions by fMRI and neurophysiology [M36]. **D3.4.** Report on gene expression and imaging findings [M24]; **D3.5.** Identification of cerebellar-isocortical loops regulating sensorimotor and cognitive processing [M36]; **D3.6.** Longitudinal characterization of the tremor-related multimodal connectome [M36]; **D3.7.** Long-range GABAergic projections and spatial memory deficits in AD [M36]; **D3.8.** Normative datasets for healthy and pathological conditions [M36]; **D3.9.** Development of potent and selective HCN nlockers with antihyperalgesic and antitussive activity [M36].

Milestones
M3.1. EEG analysis of brain connectivity via graph theory methods. Correlation between connectivity and neuroplasticity measures in cognitively normal aged subjects using a mixed-longitudinal design [M24]; **M3.2.** Retrospective analysis of paediatric operated patients. Prospective recruitment of pharmacoresistant epileptic patients to have a control group to verify the model defined in M1 [M18]; **M3.3.** Brain plasticity and reorganization in brain tumors [M24]; **M3.4.** Mouse model established. Ex-vivo gene expression pipeline established [M24]; **M3.5.** Cerebellar and isocortical neuromodulation to regulate neural plasticity in sensorimotor and cognitive tasks [M24]; **M3.6.** Acquisition of longitudinal PET/MRI data. Processing of hybrid scans and connectome construction [M24]; **M3.7.** Oscillatory and place cell activities in spatial memory deficits in AD animal models [M24]; **M3.8.** Collection of target sample size [M24]; **M3.9.** Roles of new HCN and Panx1 blockers in neuropathic pain and cough and their effect on neuronal plasticity [M24].

Work package number	**S2. WP4**	Partner responsible	UNICAMPANIA
Work package title	**Integrated technologies for brain connectomics (M1-M36)**		
Relevant scales	2D&3D cellular Models, Animal Models, Network		
Universities	UNIFI, UNINA, UNITOV, UNICAMPANIA, UNIVR, UNIBA		
Other participants	OPBG, FDG, SR, UNIPV, HSM, SYNLAB, ISNB, ASG		
Total number of partners	14		

Objectives Integrate multi-modal imaging technologies for brain connectomics into medically interpretable AI models and develop connectivity-based machine learning algorithms to address neuronal plasticity in health and disease for the design of personalized treatments. The WP foresees an advance from TRL1 (begin) to TRL3 (end).

T4.1. Cellular models of neuronal connectivity (**Leader: UNIFI**; others: UNICAMPANIA, UNIPV). Addressing the balance of excitatory and inhibitory neuronal connections using machine and deep learning technologies with biomimicry.
T4.2. Multi-modal brain connectivity (**Leader: UNICAMPANIA**; others: UNICZ, SYNLAB, HHSM, ASG). Role of structure, function, metabolism and connectome layers in explaining the neuronal plasticity in health and disease with multi-modal neuroimaging. Advancing diffusion tractography for ultra-high field MRI.
T4.3. Molecular substrates of neuronal connectivity (**Leader: UNINA**; others: ASG). Linking molecular substrates to brain connectomics and neuro-psychiatric symptoms with neurophysiology and multi-modal neuroimaging technologies.
T4.4. Causality in neuronal connectivity models (**Leader: UNITOV**; others: UNIPV, UNIFI). Addressing causality in neuronal connectivity with physically-constrained and physiologically-informed AI models.
T4.5. Neural dynamics and plasticity (**Leader: UNIVR**; others: FDG). Addressing neuronal dynamics and neuronal plasticity with neurostimulation and fast imaging technologies.
T4.6. Pediatric brain connectivity (**Leader: OPBG**; others: ASG).
T4.7. Advanced integration of neuroimaging techniques (Leader: UNIBA; others: SR, ISNB, HSM**).** Advancing E/MEG and fNIRS integration with f/MRI for brain connectomics in healthy and diseased brains.

Deliverables

D4.1. Framework for multi-layer connectome analysis and automated extraction of neuronal connectivity features [M36]; **D4.2.** Development and clinical translation of a standardised protocol for EEG-fMRI and DWI [M36]; **D4.3.** Publicly available implementations of the developed machine learning solutions [M36]; **D4.4.** Algorithms for physiological dynamics in ANN-enhanced causality toolbox and methods for directional (causal) influences of dynamical engagement of brain areas [M36]; **D4.5.** In-vivo multimodal evaluation of structural, functional, ad molecular networks underlying motor, cognitive and affective symptoms in neuropsychiatric disorders [M36].

Milestones

M4.1. Validation of the proposed algorithms and pipelines [M24]; **M4.2.**Connectivity networks under balanced conditions and excitation/inhibition balance in clinically relevant conditions [M24]; **M4.3.**Simulations and modelling of multimodal connectomes [M24]; **M4.4.** Ex-vivo dissection of cerebral hemispheres according to Klingler's method [M24]; **M4.5.**Cortico-cortical connectivity in health and disease [M24].

S2.4 Cascade calls for funding

Tentative topics for the cascade calls that will be implemented to complement S2 activities are:

- Development of tools for assisting and automating medical annotation of massive, unharmonized, incomplete and noisy neuroimaging data to stimulate interoperability and re-use of multi-modal data and metadata across centers.
- Innovative natural language processing tools for the analyses of behavioral and neuroimaging data.
- Innovative computational models to encode neural data accurately during text reading or listening, and to reduce bias in assessing language comprehension in healthy and diseased subjects.
- Regulation of ionic homeostasis: implications for excitability and brain physiopathology.

SPOKE 3. NEURONAL HOMEOSTASIS AND BRAIN-ENVIRONMENT INTERACTION

S3.1 Description of the overall aim of the spoke

The conception of homeostasis, embodied by Claude Bernard's aphorism "*The steadiness of the internal environment is the condition for a free and independent life*", is nowadays declined in cybernetic terms as an equilibrium state controlled by negative feedback regulatory mechanisms. In the brain, homeostasis is maintained at each level (from single molecules to complex behaviors) via interdependent networks of interoceptive (brain-body) and exteroceptive (brain-environment) interactions. S3 will investigate some regulatory mechanisms contributing to fundamental homeostatic responses, identify how maladaptive responses trigger or maintain brain disease states, and develop innovative neuropharmacological tools to counteract disease-causing dis-homeostatic responses. Four broad areas will be tackled to achieve such goals: adaptive and maladaptive responses in coordinated transport of ions and water (WP1), organelle homeostatic and dis-homeostatic mechanisms (WP2), genetic and epigenetic signatures of neural cell growth mechanisms (WP3), and sensory and autonomic interface for brain-environment interactions (WP4). The multidisciplinary and complementary research teams participating to S3 will contribute with state-of-the-art technologies in neural cell biology, structural and functional

investigation, cellular and animal models development and phenotypization, genomic, epigenomic and transcriptomic analyses, as well as digital technologies ranging from bioinformatics to neural network analysis and control. Experts in drug design, synthesis, and delivery methods participate to ensure that the project overall aims to provide novel neuropharmacological tools based on the investigated processes are met.

S3.2 Composition of the spoke

Institution	Type	Location	Role	Short name
Università degli Studi di Napoli Federico II	**University**	**Naples**	**Spoke responsible**	**UNINA**
Università degli Studi di Genova	University	Genova	Affiliated	UNIGE
Università degli Studi di Roma Torvergata	University	Roma	Affiliated	UNITOV
Università degli Studi di Bari Aldo Moro	University	Bari	Affiliated	UNIBA
Università degli Studi "Magna Græcia" di Catanzaro	University	Catanzaro	Affiliated	UNICZ
Università degli Studi della Campania "Luigi Vanvitelli"	University	Napoli	Affiliated	UNICAMPANIA
Università degli Studi di Firenze	University	Firenze	Affiliated	UNIFI
Ospedale Pediatrico Bambino Gesù (Roma)	Hospital	Roma	Affiliated	OPBG
IRCCS Ospedale Policlinico San Martino	Hospital	Genova	Affiliated	HSM
Fondazione Telethon ETS	Foundation	Napoli	Affiliated	TIGEM
Dompè Farmaceutici SpA	Enterprise	Napoli	Affiliated	DOMPÈ
Alfasigma SpA	Enterprise	Bologna	Affiliated	ALFASIGMA
Takis Srl	Enterprise	Napoli	Affiliated	TAKIS

S3.2.1 Description of the synergies

The University of Naples Federico II has well-documented expertise in molecular neuroscience, brain-environment investigation, and neuro-drug development applied to brain pathophysiology and treatment. Extensive collaborations are already in place among several research teams participating to S3, or will be implemented during the project course. The team assembled has a strong interdisciplinary nature and complementary expertise, ranging from the study of the fundamental processes at the single molecules level using genetic, biochemical, physiological, and computational modelling techniques, to neuropediatricians, neurologists, neuroendocrinologists, neuroradiologists, psychologists who will provide the required critical mass of biological samples, cases, and models needed for effective translation of basic findings into innovative neuropharmacological approaches. All participants have a demonstrated capacity to lead collaborative efforts at national and international levels, to secure and manage highly-competitive research projects, and to achieve the highest standards in national and international recognition in their respective field.

S3.3 Work packages

Work package number	**S3. WP1**	Partner responsible	UNINA
Work package title	**Adaptive and maladaptive responses in coordinated transport of ions and water as targets for neuropharmacological interventions for brain diseases (M1-M36)**		
Relevant scales	2D&3D cellular Models, Animal Models, Individual and Populations, D4		
Universities	UNINA, UNIBA, UNICZ, UNIGE		
Other participants	DOMPE’		
Total number of partners	5		
Objectives 1) Investigate the involvement of the coordinated transport of water and ions by specific classes of channels and transporters in astrocytic subcellular compartmentalisation, neurotransmitter release and neuronal excitability; 2) Identify the molecular, biochemical, and biophysical mechanisms by which ion channels and transporters dysfunction are responsible for both genetic and acquired brain and neuromuscular diseases (i.e. epilepsy, pain, ataxias, kinesigenic dyskinesia, migraine, myotonias, myasthenic syndromes); 3) Investigate how such dysfunctions affect cellular and tissue homeostasis in the brain; 4) Design, synthesize and evaluate pharmacological approaches and delivery methods targeting ion and water channels/transporters dysfunctions for the treatment of common and rare brain and neuromuscular diseases.			
T1.1 Novel 2D and 3D in vitro models of brain and neuromuscular ion/water channels diseases (Leader: UNIBA, others: UNINA, UNIGE**).** Implementation and characterization of novel 2D and 3D in vitro models			

of brain and neuromuscular ion channels diseases, including neurons differentiated from patients-derived IPSCs, exosomes from synaptic terminals, 2D and 3D models of BBB, NSCs, and mini brains.

T1.2. Novel animal models of brain and neuromuscular ion/water channels diseases (Leader: UNIBA, others: UNINA, UNIGE**).** Development and phenotypization of novel animal models to investigate specific biological functions of water and ion channels; these will include: 1. novel transgenic mice in which the astrocytic subcellular distribution of Aquaporin-4 (AQP4) is altered (AQ4 OAP-null mice; AQP4ex KO mice; and super-OAP mice); 2. constitutive or inducible KI mice carrying loss- or gain-of-function variants in KCNQ2 (R207, A317T), KCNQ3 (R230C), and KCNQ5 (G347S) genes encoding for voltage-gated potassium channels; 3. proline-rich transmembrane protein-2 (PRRT2) knockout mice. Differential proteomics and interactomic experiments will allow to identify novel druggable targets.

T1.3. Disease-related biomarkers and druggable cellular/molecular pathways in disease-relevant models (Leader: UNINA, others: UNICZ, UNIBA, UNIGE). Characterization of the expression and function of specific classes of ion channels, transporters, and their coupled neurotransmitter receptors (e.g. KCNQs, NCXs, ASICs, GIRK channels, TRPV1 channel and mGLU receptors) in pre-clinical rodent models of epilepsy and/or neurodegeneration (e.g. the WAG/Rij rat; the Kainate-induced model of temporal lobe epilepsy; additional models of non-dystrophic myotonias, stroke, or of epilepsy, also derived from Task 1.2), and identification of disease-related biomarkers and druggable cellular/molecular pathways.

T1.4. Micro- and nano-technology-based delivery system for BBB crossing (**Leader: UNINA,** others: UNIBA, UNICZ, DOMPE'). Development of micro- and nano-technology-based delivery system optimized for BBB crossing (tunable biomaterials, protein nanocages and stimulus-responsive lipid nanocarriers) to allow transport/release of the active principles targeting the ion/water transport process of interest, exploiting new molecular entities, repurposed drugs, nutraceuticals.

T1.5. Validation of the novel pharmaceutical product in disease-relevant models of stroke, epilepsy and/or neurodegeneration (**Leader: UNINA,** others: UNIBA, UNICZ, UNIGE).

Deliverables

D1.1. 2D and 3D models of brain and neuromuscular diseases [M12]; **D1.2.** New animal models of brain and neuromuscular diseases [M18]; **D1.3.** Pathophysiological roles defined (e.g. AQP4 in astrocytic function, NCXs, GIRKs, KCNQs in neuronal excitability, PRRT2 in neurotransmitter release) [M24]. **D1.4.** Formulation and proof-of-concept in vitro studies of novel pharmacological approaches [M30]. **D1.5.** Validation in relevant in vivo models [M36].

Milestones

M1.1 Number of 2D and 3D neural models validated [M18]; **M1.2** Number of water/ion channels variants causing brain and neuromuscular channelopathies characterized [M18]; **M1.3** Water/ion channels interacting partners identified [M24]; **M1.4** At least 2 novel therapeutic strategies developed and validated in vitro [M30]. **M1.5** At least 2 novel therapeutic strategies developed and validated in vivo [M36].

Work package number	**S3. WP2**	Partner responsible	UNINA
Work package title	**Organelle homeostasis in brain pathophysiology and innovative molecular interventions to correct organelle dysfunction (M1-M36)**		
Relevant scales	Moelcular-genetics, 2D&3D cellular Models, Individual and Population, D4		
Universities	UNINA, UNITOV, UNIBA		
Other participants	TIGEM		
Total number of partners	4		

Objectives To identify: 1) Regulatory mechanisms of organelle crosstalk and their role in neuronal pathophysiology; 2) Druggable targets in organelle crosstalk, lysosomal-autophagy, and proteostasis networks; 3) Correctors of organelle dis-homeostasis via drug repurposing and novel candidate compounds/molecules.

T2.1. Organelle cross-talk (**Leader: UNINA**, others: UNITOV, TIGEM). We propose to identify mechanisms regulating organelle homeostasis at the level of membrane contact sites (MCS) allowing inter-organelle exchange of lipids and ions via lipid transfer proteins and ion channels. To this aim cell models (neuron and glia cell lines, neurons, glia cells, and organoids derived from patient iPSC) expressing reporters of the different organelles (ER, mitochondria, Golgi, endo-lysosomes) suited to monitor the MCS by FRET and to study their role in neurodegenerative and neurodevelopmental disorders will be used. We will adopt an integrated approach including advanced microscopy, -omics (protein and mRNA) studies and identification of physical and functional interactomes of relevant candidates.

T2.2. The autophagy-lysosomal pathway (ALP) (**Leader: UNINA**, others: UNITOV, TIGEM). We will investigate: a. the distinctive features of the ALP in neurons and glia cells as compared to other cells; b. the molecular mechanisms responsible for ALP dysfunction induced by protein (synuclein or beta-amyloid) aggregates; c. the role of lysosomal calcium in neuronal homeostasis and in physiological conditions or neurodegenerative diseases.

T2.3. Cellular bioenergetics (**Leader: UNIBA**, others: UNINA, UNITOV, TIGEM). We will investigate the bioenergetics and mitochondrial metabolism of neurotransmitters (glutamine, glutamate, GABA, glycine, aspartate, and N-acetyl aspartate) and their role in neuron-glia interactions (including metabolic coupling) and in myelin synthesis during brain development in health and disease. We will perform a multiOmics (metabolomics, proteomic, transcriptomic) search for biomarkers underpinning neuronal homeostasis. To this end we will: 1. generate neuron and glia cell lines with altered levels (through overexpression and RNAi or CRISPR/Cas9) of mitochondrial proteins involved in the synthesis/recycling of neurotransmitters and myelin lipid precursors; 2. develop single cultures or co-cultures of iPSCs-derived neural cell types (neural progenitor cells, neurons, motor-neurons, astrocytes, oligodendrocytes, microglia) from patients with defects of mitochondrial transporters (SLC25 family) causing neurological diseases.

T2.4. Development of innovative therapeutic approaches for neurodegenerative disease (**Leader: UNINA**, others: UNITOV, UNIBA, TIGEM). We will exploit the resources generated in Tn1-3 to optimize the assays for high throughput and high content screening to test both FDA approved drug libraries for drug repurposing and focused libraries designed on those molecular targets identified in Tn1-3 that exhibit druggable properties. In addition, we will develop novel gene editing and RNA-based approach integrated with innovative delivery system. The hits of the primary screening will be validated in secondary assays, (using morphological, proteomic and transcriptomic approaches) including organoids derived from patient iPSCs and tested in suitable animal models.

Deliverables

D2.1 Cell-based assays for druggable molecular targets controlling organelle homeostasis [M18]; **D2.2**. Candidate compounds/molecules for neurodegenerative disease [M36].

Milestones

M2.1. Identification of regulatory mechanisms in organelle homeostasis and set-up of cell-based assays accomplished [M18]; **M2.2.** Screening of compound/molecules accomplished [M36].

Work package number	**S3. WP3**	Partner responsible	UNINA
Work package title	**Genetic and epigenetic signatures of neural cell growth mechanisms and novel treatment strategies for brain diseases (M1-M36)**		
Relevant scales	Molecular-genetics, Animal Models, D4		
Universities	UNINA, UNIGE, UNITOV		
Other participants	HSM, TAKIS		
Total number of partners	5		

Objectives 1) To trace epigenomic and genomic signatures accounting for the genesis, evolution and intratumor heterogeneity of neural cell derived tumors; 2) To establish cell and animal models recapitulating molecular features of patients' tumors and murine models allowing the dissection of molecular mechanisms of glioma progression and immunoevasion; 3) To develop and test strategies based on retargeted oncolytic herpes virus to revert glioma immunoevasion; 4) To target genetic and epigenetic alterations and revert the malignant phenotype by chemical drugs and theranostic approaches in patients derived tumor models.

T3.1 Epigenomic and genomic signatures of nervous system neoplasias (**Leader: UNINA**, others: UNIGE, UNITOV). Genomic, epigenomic and transcriptomic analyses of tumor samples, tumor microenvironment and multiple tumor-derived single cells to evaluate inter-tumors and intratumor diversity (tracing of molecular patterns). In parallel, theranostic approaches for pre-surgical diagnosis will be used in a subset of donor patients to then associate molecular and theranostic findings.

T3.2 Establishment of cell and animal models of gliomas, neuroblastomas and neuroendocrine neoplasias (**Leader: UNINA**, others: UNIGE). Tracing of molecular patterns (methylome, gene copy number variation, single cell transcriptomics) of patients-derived cultured tumor cells and isolated cancer stem cells to trace conservation of original molecular features. Heterotopic and orthotopic transplantation in nude mice, follow up of tumor growth by 3D fluorescence imaging and of molecular evolution by tracing molecular patterns.

T3.3 Establishment of high-grade glioma models in immunocompetent mice (**Leader: UNIGE**, others: UNINA, HSM, TAKIS). Somatic gene transfer mimicking molecular lesions found in human high-grade

glioma will be performed in mouse embryos in order to generate murine models of high-grade glioma. Serial transplantation assays will dissect the acquisition of malignant features (immunoevasive traits, methylome changes). In vivo cell lineage tracing of glioma initiating cells: genetic and epigenetic barcoding of neural progenitor cells following molecular lesions inducing glioma will be employed to establish the frequency of immunoevasive phenotypes. Single cells transcriptomic will be used to assess the involved pathways.

T3.4 Testing novel epigenetic drugs and immune-virotherapy of nervous system tumors (Leader: UNINA, others: UNIGE, UNITOV, HSM, TAKIS). HSV retargeted to glioma-relevant molecular markers and expressing different immunostimulatory molecules established on the bases of Task 3 results will be generated and tested in immune-competent murine models of high-grade glioma. Chemical libraries of drugs targeting epigenetic machinery and epigenetic drugs selected on the bases of findings in Task 1 will also be tested on Task 2 models. Theranostic approach will be also applied to modulate relevant genes discovered by tracing of molecular patterns as described in T3.1, T3.2 and T3.3.

Deliverables

D3.1 Epigenomic and genomic profiles of patients derived neural tumor cells [M10]. **D3.2** Neural tumors cells and animal models recapitulating patients' tumors molecular signatures [M18]. **D3.3** Glioma models induced by somatic gene transfer in immunocompetent mice [M18]. **D3.4** Glioma-specific HSVs able to disrupt immune-evasion [M36]. **D3.5** List of epigenetic drugs reverting the malignant phenotype in personalized models [M36].

Milestones

M3.1 Epigenomic and genomic profiling of patients' derived cells [M10]. **M3.2** Establishment of cell and animal models (task 2 and 3) [M18]. **M3.3** Characterization of the profiles of subclones at single cell level (tasks 1,2,3) [M18]. **M3.4** Generation of HSVs retargeted to molecules expressed by high grade gliomas armed with immunostimulatory molecules and assessment of efficacy (milestone of task 3 and 4) [M36]. **M3.5** Epigenetic drug identification and assessment efficacy (milestone of task4) [M36].

Work package number	**S3. WP4**	Partner responsible	UNINA
Work package title	**Sensory and autonomic interface for brain-environment interaction: tools, models, and neuropharmacological interventions (M1-M36)**		
Relevant scales	2D&3D cellular Models, Animal Models, Individual and Population, 4D		
Universities	UNINA, UNITOV, UNIFI, UNIGE, UNICAMPANIA		
Other participants	OPBG, ALFASIGMA		
Total number of partners	7		

Objectives 1) To analyse the role of the interaction between sympathetic neurons and target cells in the pathogenesis of neurological diseases, and the impact of cardiovascular diseases in neuronal dysfunction; 2) To evaluate the impact of sensory stimuli on the onset and progression of neurological disorders; 3) To investigate Microbiota-gut brain axis (MBGA) involvement in neuropsychiatric disorders.

T4.1. Novel 2D and 3D in vitro models (Leader: UNIFI, others: UNINA, UNICAMPANIA). Creation of 2D cultures and 3D organoids including multiple cell types, such as sympathetic neurons and their targets derived from patients with cardiomyopathies or neurological diseases, using nanopatterned surfaces (for 2D cultures) multicellular cardio-spheres or engineered heart tissues, also using 3D printing and bioprinting (for 3D cultures).

T4.2. Functional analysis (Leader: UNIFI, others: UNINA, UNICAMPANIA). Evaluation of the functioning and the possible alteration of the "synapses" between cardiomyocytes and sympathetic neurons in iPSC-derived organoids, and of the effect of selected drug treatments on the neuro-cardiac interface using a combined functional, molecular and structural approach (patch-clamp studies with multiple electrodes, fluorescence studies, intracellular Ca^{2+} measurements, FRET.

T4.3. Biomarker identification and drug screening (Leader: UNIFI, others: UNINA, UNICAMPANIA). Identification of therapeutic targets and biomarkers within the neuro-cardiovascular axis for the treatment of neurodegenerative diseases and autonomic dysfunction using 2D cultures, as well as animal models of cardiovascular diseases. The same models will serve as experimental platforms to screen the activity of known molecules (drug repurposing), and validate novel drugs and delivery strategies, including micro- and nano-technology-based delivery systems.

T4.4. Sensory influence in brain-environment interaction (Leader: OPBG, others: UNITOV, UNINA). Implementation of a combined functional and behavioral approach to evaluate neuronal responses to different environmental stimuli (ie auditory and nociceptive stimuli) in subjects with autism, schizophrenia, migraine

and dementia, and in drug addicts, at different neurodevelopmental stages. Genetic studies will correlate the changes of neuronal activity in the brain-environment interaction with polygenic risk, develop innovative therapeutic intervention strategies, and identify novel neural, physiological, and cognitive biomarkers.
T4.5. Gut microbiota in neuropsychiatric disorders (Leader: UNIGE, others: UNINA, OPBG, ALFASIGMA). Characterization of gut microbiota fingerprints, biomarkers and potential remodelling in neuropsychiatric disorders using a combined multi-omic (meta-genomic, proteomic and metabolomics) and a bioinformatic approach. Investigate how MGBA manipulation might affect the onset, progression, and therapy response in neurological disorders (migraine, epilepsy and neurodegenerative diseases like AD and PD). A correlation between microbiota profiles and inflammatory/oxidative stress markers in plasma intracellular vesicles (iEVs) will be established in both human and animal samples.

Deliverables
D4.1 New models [M18], mechanisms [M24] and biomarkers/drugs [M36] in the neuronal-cardiovascular systems crosstalk; **D4.2** Sensory and environmental influence in complex neuropsychiatric disorders [M24]; **D4.3** Identification of common microbiota "signatures" [M24] and new therapeutic approaches [M36] targeting gut microbiota in neurological disease.

Milestones
M4.1 Generation of iPSC lines and functional 2D and 3D culture [M12]; **M4.2** Data acquisition and drug screening from neurocardiac models [M36]; **M4.3** Behavioural, genetic and functional data acquisition in patients and specific groups of individuals [M24]; **M4.4** Gut microbiota analysis in patients, and markers identification [M24]; **M4.5** MBGA -based therapeutic strategies to target neurological disease [M36].

S3.4 Cascade calls for funding

Tentative topics for the cascade calls that will be implemented to complement S3 activities are:

- High-throughput technologies for screening drugs active on ion and water transport to correct brain disorders
- Set-up of genetically-encoded calcium and ROS indicators targeted to different organelles
- Development of research platforms for big data acquisition, handling, analysis and modeling to study brain-environment interactions
- Production of advanced bioinformatic tools for high power computational analyses of single cells and brain tumors "omics" big data and generation of international shared databases.

S4 PERCEPTION AND BRAIN-BODY INTERACTION

S4.1 Description of the overall aim of the spoke

This spoke will develop an integrated approach including all levels of the brain biological organization (genes and molecules, cell interactions, neural networks, individuals, social interactions) to identify the biological and functional signatures of complex functions and brain-body reciprocal interactions, determinants and biomarkers of physiology to pathology transition. A common methodological issue across the WPs will be the use of large-scale neurocomputational models and brain-inspired neural networks and artificial intelligence to simulate specific physio-pathological perceptual and motor circuits. Large-scale neurocomputational models will integrate biomolecular and functional data for multiscale/multidimensional biomarkers discovery and to optimize predictive disease models.

S4.2 Composition of the spoke: 13 institutions

Institution	Type	Location	Role	Short name
Alma Mater Studiorum - Università di Bologna	**University**	**Bologna**	**Spoke responsible**	**UNIBO**
Università degli Studi di Roma Torvergata	University	Roma	Affiliated	UNITOV
Università degli Studi di Napoli Federico II	University	Napoli	Affiliated	UNINA
Università degli Studi di Ferrara	University	Ferrara	Affiliated	UNIFE
Università degli Studi di Verona	University	Verona	Affiliated	UNIVR
Università degli Studi di Firenza	University	Firenze	Affiliated	UNIFI
Università degli Studi di Genova	University	Genova	Affiliated	UNIGE

Università degli Studi di Pavia	University	Pavia	Affiliated	UNIPV
Ospedale Pediatrico Bambino Gesù (Roma)	Hospital	Roma	Affiliated	OPBG
IRCCS Istituto delle Scienze Neurologiche di Bologna	Hospital	Bologna	Affiliated	ISNB
IRCCS Ospedale Policlinico San Martino	Hospital	Genova	Affiliated	HSM
Fondazione Don Carlo Gnocchi ONLUS-IRCCS	Hospital	Milano	Affiliated	FDG
Scuola Superiore Sant'Anna di PISA	University	Pisa	Affiliated	SSSA

S4.2.1 Description of the synergies

The members of S4 team share an innovative, up-to date, multidisciplinary knowledge based on a strong basic research science of preclinical studies on modern cellular and animal models of diseases (UNIBO, UNIFE, UNIVR, UNIPI, SSSA, UNITOV, ISNB) for CNS vulnerability and synaptic plasticity (SSSA, UNIFE, UNIVR), for novel neuropharmacology (UNIBO, UNIFE, UNIVR, UNIGE, HSM), for system biology of preclinical and clinical models towards new biomarkers (UNIBO, UNIFI, UNITOV, UNIGE, UNIVR, ISNB, HSM), for neural networks (UNIBO, UNIGE, UNIPV, UNIVR, SSSA, FDG, OPBG, HSM), for modelling and virtual reality (UNIBO, SSSA, UNIFE, UNIGE, UNIVR, UNITOV).

Many PIs have ongoing collaborations with other institutions participating to S4, as documented by joint PRIN founded projects and PON 2014-2020, but also international grants (FP7, Horizon-2020, Horizon-EU), confirming the synergic scientific research activity of this spoke and facilitating the interactions (e.g. UNIBO and UNIFE on PD, UNIBO and UNIVR on SUD, UNIBO and UNIFI on Pain; UNIBO, UNIFE and UNITOV on motor control).

S4.3 Work packages

Work package number	**S4.WP1**	Partner responsible	UNIBO
Work package title	**Preclinical models for the physio-pathological transition (M1-M36)**		
Relevant scales	2D&3D cellular model/Network/Animal models		
Universities	UNIBO, UNITOV, UNIGE, UNIFE, UNIVR		
Other participants	SSSA, HSM, ISNB		
Total number of partners	8		

Objectives 1) To model multicellular CNS systems from animal and human stem, precursor and iPCs cells; 2) To investigate brain-body interaction in view of CNS vulnerability and protection; 3) To discover novel druggable targets for the physiopathology transition.

T1.1. Dynamic, high throughput platforms for 3D and 4D neural spheroids derived from animal models and human iPCs (Leader: UNIVR; others: SSSA, UNIBO, ISNB): We will create biomaterial-assisted 3D cellular systems and brain organoids recapitulating cellular and extracellular matrix composition and stiffness of different CNS regions also for disease modelling and personalized therapy. Metabolic, mitochondrial and quality control pathways, molecular mechano-sensing and microelectrode arrays (MEAs) recording supported by phenotype modification by CRISPR/Cas9 library screening will provide new insight into key pathways for multipotency, differentiation and maturation.

T1.2. Body-derived risk and protective factors for CNS vulnerability and self-healing capability (Leader: UNIBO; others: UNITOV, UNIVR, UNIFE). We will explore body-derived factors in accelerating or delaying age-related cognitive decline in physiological conditions and in the presence of risk factors for neurodegenerative diseases, generating rodent models of life-style-related factors and co-morbidities also in transgenic mice. Neurodegeneration molecular pathways, adult neurogenesis, myelin turnover and repair, neuroglial and neurovascular unit interaction will be explored.

T1.3. Animal models and tools for synaptic plasticity and cognitive improvement (Leader: SSSA; others: UNIFE, UNIBO): We will explore mechanisms and strategies to improve neural performances, focusing on synaptic plasticity and glia-neuron interactions in model systems (e.g. mice visual cortex, striato-pallidal- and pallidal-subthalamic circuits, etc.) considering new tools (e.g. robotic neurorehabilitation, Torpor/hibernation).

T1.4. From preclinical models to druggable targets and novel neuropharmacology (Leader: UNIBO; others: UNIFE, UNIVR, UNIGE, HSM). By identifying endogenous systems underlying physiological and pathological functions, we will be able to determine druggable targets for new drug mechanisms, including HIF, metabolic, and growth/neurotrophic factor pathways. We will use preclinical models of diseases as PK, AD, neuropathic pain, autism, SUD, SM, SLA and peripheral pathologies, like muscular dystrophies, and vascular and traumatic injuries.

Deliverables **D1.1.** Reproducible 3D models [M12]; **D1.2.** WP2 data base population [M36]; **D1.3.** Report on animal modelling and druggable targets [M36].
Milestones **M1.1**. Animal studies authorization [M6]; **M1.2**. Human organoid establishment [M24]

Work package number	**S4. WP2**	Partner responsible	UNIBO
Work package title	**Systems Biology of pre-clinical and clinical models of neuro-functional phenotypes (NFP), towards new multidimensional biomarkers (M1-M36).**		
Relevant scales	Molecular/genetics, 2D and 3D Cellular models, D4		
Universities Other participants	UNIBO, UNIFI, UNITOV, UNIGE, UNIVR, UNIFE ISNB, HSM		
Total number of partners	8		

Objectives 1) To build repositories for i) *in vitro* and animal models data and ii) human sample and data from NFP, available within the spoke and federated institutions; 2) To generate and analyze new omic data to feed Systems biology reactors; 3) To analyze preclinical and clinical data with systems biology and network medicine approaches.

T2.1. Set up of sample and data repositories (**Leader: UNIBO**; others: UNIGE, HSM, UNIFE, UNIVR, ISNB). Generation and organization of sample and data repositories. Major neurological disorders impairing perception, movement and brain-body interactions will be considered e.g. synucleinopathies, amyotrophic lateral sclerosis and dementia, as well as adverse neurological effects of traditional and advanced therapies such as CAR-T gene therapy. Informative human specimens (CSF brain skin biopsies, intestinal and olfactory mucosa) will be collected, for the detection of protein aggregates (e.g. misfolded alpha-synuclein, TDP-43, Tau). IT facilities for data management, analysis and protection designed to ensure compliance to privacy, ethics, and IP guidelines and to facilitate data sharing according to open science principles.

T2.2. Data generation (**Leader: UNIBO**; others: UNIVR, ISNB). To complement the wealth of existing clinical and molecular data collected in task 1, omics characterizations will be carried out. Beside well-established protocols (e.g. genomics, transcriptomics, epigenomics) effort will be devoted to exploit high-sensitivity technologies to characterize proteins such as real-time quaking-induced conversion (RT-QuIC), single molecule array (SiMoA), and super resolution extracellular vesicles analysis (ONI nanoimager).

T2.3. Data analysis (**Leader: HSM**; other UNIGE, UNIBO). Systems biology and network medicine approaches will be applied to pre-clinical and human models, including already available open data (e.g from pharmacovigilance, pharmacodynamics and kinetics). Multi-omic data analysis will be performed by means of Statistical (e.g. generalized regression models, ridge/lasso penalization), Machine Learning (*e.g.* Random Forests, PLS), and Artificial Intelligence (e.g. Neural Network) methods. Data augmentation with prior biological knowledge will be obtained using Natural Language Processing and network-based methods (e.g. message-passing), exploiting publicly available databases (e.g. NCBI, KEGG, Reactome). Multi-layer network models (*e.g.* Gaussian Graphical models, network diffusion) will be used for multi-omic data integration, as well as to integrate human and pre-clinical results. The obtained results will be linked with state-of-the-art NFP markers to explore the potential translation in new network medicine biomarkers, and for drugs repurposing in neurological.

Deliverables **D2.1.** Report on data and samples repositories generation [M12]; **D2.2.** Report on new data generation [M24]; **D2.3.** Report on systems biology and network medicine analyses [M36].
Milestones **M2.1**. Obtainment of consensus and permissions for the data and samples aggregation in the envisaged repositories [M10]. **M2.2.** Standard Operative Procedures SOPs for sample collection and sharing [M12]. **M2.3.** Set up of system biology and network medicine methods based on the available and newly generated data and NFP models [M16].

Work package number	**S4.WP3**	Partner responsible	UNIVR
Work package title	**Neural networks: neurophysiology, neurotech and brain imaging of perception, movement and brain-body interactions and individual variability (M1-M36)**		
Relevant scales	Networks, Individuals and populations		

Universities	UNIBO, UNIGE, UNITOV, UNIVR, UNIPV, UNIFI, UNIFE
Other participants	HSM, SSSA, OPBG, FDG, ISNB
Total number of partners	12

Objectives 1) To characterize the neurophysiology of brain networks underlying sensorimotor functions and decode motor parameters from brain networks by deep learning techniques; 2) To characterize the multi-scale brain networks underlying brain-body regulation processes; 3) To exploit knowledge derived from intra- and inter-individual variability towards tailored understanding of brain- body interactions in healthy and subclinical cohorts for tailored therapeutical protocols.

T3.1. Multi-scale brain networks for sensorimotor functions: from physiology to models (Leader: UNIBO; others: UNIGE, UNIPV, UNIVR, SSSA, FDG, OPBG, UNIFE, HSM). Characterization of the functional organization of brain networks underlying motor control and sensorimotor integration, to understand the coding of information from perception to action. A variety of techniques will be used including psychophysics and kinematic analysis, mathematical modelling, advanced imaging, neurostimulation brain lesion mapping, and electrophysiology in humans and monkeys

T3.2. Characterizing brain networks underlying brain-body regulation processes (Leader: UNIVR; others: UNIGE, UNIPV, UNIBO, FDG, HSM, SSSA). Study of the functional organization of brain networks underlying processing and regulation of body-related signals (e.g., heart rate, breathing, pupil size, skin conductance) in physiological and pathological conditions, during interoceptive, emotional and cognitive tasks, with a multi-layered approach (neural, psychophysiological, behavioral and computational).

T3.3. Identifying the neural bases of intra- and inter-individual differences in perception, movement and brain-body interaction (Leader: UNITOV; UNIBO, UNIGE, UNIPV, UNIVR, UNIFI, FDG, HSM).
Multi-scale approach and computational models, to characterize neuroanatomical and neurofunctional differences contributing to individual variability in sensorimotor functions, brain-body interactions and their sensitivity to plastic changes, depending on age, gender, expertise and genotype. The research will allow interpreting residual functions in clinical cohorts, to test network breakdown and rehabilitation intervention.

Deliverables

D3.1. Report on quantitative models and tools for signal processing [M12]; **D3.2.** Functional organization of brain networks: experiments and related protocols [M24]; **D3.3.** Neural bases of individual differences: experiments and related protocols [M36].

Milestones

M3.1. Conclusion of the data collection necessary to feed modeling [M18].

Work package number	**S4.WP4**	Partner responsible	UNIBO
Work package title	**Neural network models and technologies to better understand perception, movement and brain-body interaction and to impact on society (M3-M36)**		
Relevant scales	Digital twins, Networks, D4		
Universities	UNIBO, UNITOV, UNIGE, UNIVR, UNIFE, UNINA, UNIPV		
Other participants	SSSA, FDG		
Total number of partners	9		

Objectives 1) To develop neural network models able to simulate perceptual and motor processes in the brain under physiological and pathological conditions: a tool to better understand disease mechanism as well as brain functions; 2) To develop virtual reality techniques for investigating brain functions and developing diagnostic and rehabilitative tools; 3) To develop technologies in systems (e.g. brain-machine instruments and neuromorphic prostheses) to link the brain with the external world.

T4.1. Modelling sensory and motor systems (Leader UNIFE; others: SSSA, UNIVR; UNIBO)
We will implement brain-inspired neural network techniques to model the functioning of sensory and motor systems and characterize the role of dopamine agonists in Parkinson's disease; convolutional and artificial neural networks with dendrites, and Hopfield models of associative memory inspired by peripheral codes. We will also simulate neurostimulation and develop specific signal processing algorithms.

T4.2. Modeling brain oscillations, connectivity, and network alterations (Leader: UNIBO; others: UNIPV, SSSA). We will implement connectivity estimation techniques and brain-inspired neural networks to understand the role of brain rhythms in perceptual and motor systems, in physiological and pathological conditions and the effect of virtual lesions. Neuropharmacological, imaging and connectivity data will be integrated for the comprehension of decisional processes and their alterations induced by substances, diseases or environment.

T4.3. Virtual reality for examining perception, motor control and brain-body interaction (Leader: UNITOV others: UNIGE, SSSA, FDG, UNIBO, UNIVR, UNINA). We will develop virtual reality techniques and protocols to investigate the functional and neural mechanisms underlying avatar embodiment, perception and action control and brain-body interactions, and integrated tools for diagnostic and rehabilitative purposes in clinical populations (e.g., brain damage patients, autism).
T4.4. Brain-machine interfaces and neuro-morphic robots for linking the brain to the external world (Leader: SSSA; others: UNIBO, UNIGE, UNINA, UNITOV, UNIVR). We will develop innovative instruments to improve BCI performance via EEG-based deep learning approaches, new hybrid FEM-neuron models, decoding algorithms, methods for encoding and administering sensorimotor stimuli, methods to detect emotion and improve human-robot collaboration, and implantable neural interfaces. We will also use explainable techniques of the solutions to understand brain dynamics.

Deliverables
D4.1. Preliminary prototype version of software programs, tools and reports [Month 18]
D4.2. Final version of software programs, tools and reports [Month 33]

Milestones
M4.1. Specification of the quantitative models and tools [M12]; **M4.2.** Preparation of a first prototype for each task [M18]; **M4.3.** Preparation of the final prototype for each task [M30]

S4.4 Cascade calls for funding

Tentative topics for the cascade calls that will be implemented to complement S4 activities are:

- Experimental approach to study the link between emotions and perception, movement and brain-body interactions
- From rodents to primates: comparative studies of the perception and movement dynamics in physiological conditions.
- System biology and network medicine for clinical studies: multiomics and multi-layer network models for patient profiling for brain-body interaction
- Large-scale recording of large populations of neurons and computational analysis of brain functions in sensorimotor coordination.

S5 MOOD AND PSYCHOSIS

S5.1 Description of the overall aim of the spoke

This spoke aims to collect research evidence from cellular models, genetics and advanced brain imaging which can contribute to the incremental effort to elucidate the etiopathogenetic foundations of mood and psychotic disorders; to identify biological markers of subtypes of these disorders; to advance pharmacogenomic testing; and to foster the development or repurposing of innovative drugs.

S5.2 Composition of the spoke

Institution	Type	Location	Role	Short name
Università degli Studi id Ferrara	**University**	**Ferrara**	**Spoke Responsible**	**UNIFE**
Università degli Studi di Genova	University	Genova	Affiliated	UNIGE
Università degli Studi di Pavia	University	Pavia	Affiliated	UNIPV
Università degli Studi di Verona	University	Verona	Affiliated	UNIVR
Alma Mater Studiorum - Università di Bologna	University	Bologna	Affiliated	UNIBO
Università degli Studi di Roma Torvergata	University	Roma	Affiliated	UNITOV
Università degli Studi della Campania "Luigi Vanvitelli"	University	Napoli	Affiliated	UNICAMPANIA
Università degli Studi di Bari Aldo Moro	University	Bari	Affiliated	UNIBA
Università degli Studi di Firenze	University	Firenze	Affiliated	UNIFI
Alfasigma SpA	Enterprise	Bologna	Affiliated	ALFASIGMA

S5.2.1 Description of the synergies

The researchers involved in this spoke have a long history of scientific collaboration, including partnership in the Italian Network for Research on Psychoses and joint participation in a range of studies funded by international

(e.g., European Commission, Wellcome Trust) and national (e.g., Italian Ministries of Education and of Health) bodies. The spoke includes participants from as many as thirteen disciplinary sectors, from molecular biology to genetics, biochemistry, physiology, pharmacology, psychobiology, neuroradiology, and clinical psychology, in addition to psychiatry.

S5.3 Work packages

Work package number	**S5. WP1**	Partner responsible	UNIPV
Work package title	**Drug discovery, development and delivery for mood and psychotic disorders (M1-M36)**		
Relevant scales	Individuals and population, D4, Digital twins		
Universities	UNIPV, UNIFE, UNIVR, UNICAMPANIA, UNIBA		
Other participants	-		
Total number of partners	5		
Objectives 1) To build up a national digital Clinical Service Platform for experimental therapeutics; 2) To implement P^5 (Predictive, Preventive, Personalized, Participatory and Polysystemic) drug development; 3) To ensure continuous evidence-based enablement of experimental therapeutics.			
T1.1. Harmonizing biomarker metrics and clinical endpoints (Leader: UNIPV, others: UNIFE, UNIVR, UNICAMPANIA, UNIBA). We will harmonize biomarker metrics and clinically relevant endpoints across the spoke. The harmonized measures will deeply phenotype a critical mass of individuals with stage I (at clinical high-risk), II (first episode) or III (early relapsing) mood or psychotic disorders. **T1.2. Implementing a national digital Clinical Service Platform for experimental therapeutics (Leader: UNIPV**, others: UNIFE, UNIVR, UNICAMPANIA, UNIBA). We will implement a digital Clinical Service Platform (CSP), including modules for electronic data capture of harmonized biomarkers and clinical outcomes, and processing and documentation of clinical processes. **T1.3. P^5 (Predictive, Preventive, Personalized, Participatory and Polysystemic) drug development (Leader: UNIPV**, others: UNIFE, UNIVR, UNICAMPANIA, UNIBA). We will embed individualized risk calculators developed for stages I-III mood and psychotic disorders in the CSP implemented across the spoke. This will allow stratifying of deeply-phenotyped patients with common biomarkers and clinical endpoints, enabling the appropriate pharmacological intervention to be identified, an old treatment to be repurposed, or a new treatment to be tested involving the most relevant patients.			
Deliverables **D1.1.** Standard procedures for common biomarkers and clinical outcomes across the spoke [M6]. **D1.2.** National digital Clinical Service Platform for experimental therapeutics [M12]. **D1.3.** First P^5 experimental therapeutic trial completed [M30]			
Milestones **M1.1**. Digital Clinical Service Platform deployed and operating across the spoke [M12]. **M1.2**. Completion of recruitment of trial participants [M30]. **M1.3**. Standard operating procedures updated with the new scientific evidence [M36]			

Work package number	**S5. WP2**	Partner responsible	UNICAMPANIA
Work package title	**Innovative cellular models for mood and psychotic disorders (M1-M36)**		
Relevant scales	Molecular-genetics, 2D&3D cellular Models, D4		
Universities	UNICAMPANIA, UNIFE, UNIBO, UNITOV, UNIFI		
Other participants	ALFASIGMA		
Total number of partners	6		
Objectives 1) Set up of neuro-glial differentiation of Multilineage-differentiating stress-enduring (Muse) stem cells; 2) *In vitro* neuro-glial differentiation of Muse cells obtained from patients with mood and psychotic disorders; 3) Analysis of molecular pathways in neuro-glial cells differentiated from Muse stem cells of patients.			
T2.1. Set up of neuro-glial differentiation of Muse cells (Leader: UNICAMPANIA, others: UNIFE, UNIBO, UNITOV, UNIFI). Multilineage-differentiating stress-enduring (Muse) cells, naturally present in stromal components of our body, are pluripotent stem cells with self-renewal ability and expression of pluripotency markers. Several neuro-glial induction protocols for Muse cells will be tested. Neural cell morphology, gene expression and epigenetic regulation will be investigated.			

T2.2. ***In vitro*** **neuro-glial differentiation of Muse cells obtained from patients with mood and psychotic disorders** (**Leader: UNICAMPANIA**, others: UNIFE, UNIBO, UNITOV, UNIFI). We will develop an *in vitro* neuro-glial differentiation model to assess pathophysiological mechanisms linked to mood and psychotic disorders.
T2.3. Analysis of molecular pathways in neuro-glial cells differentiated from Muse stem cells of patients (**Leader: UNICAMPANIA**, others: UNIFE, UNIBO, UNITOV, UNIFI; ALFASIGMA). In muse cells obtained from patients, we will analyze key molecular pathways relevant to mood and psychotic disorders.

Deliverables
D2.1. *In vitro* cellular models of mood and psychotic disorders [M10]. **D2.2.** Identification of molecular pathway alterations in neuro-glial cells from patients [M36]

Milestones
M2.1. Set up of Muse cells *in vitro* neuro-glial differentiation [M10]. **M2.2.** *In vitro* neuro-glial differentiation of Muse stem cells obtained from patients [M20]. **M2.3.** Analysis of key molecular pathways in cells differentiated from Muse cells of patients [M36]

Work package number	**S5.WP3**	Partner responsible	UNICAMPANIA
Work package title	**Looking for genetic variants as risk factors for mood and psychotic disorders (M1-M36)**		
Relevant scales	Molecular-genetics, Individuals and Population, D4		
Universities	UNICAMPANIA, UNIFE, UNIBO, UNIBA, UNIFI		
Other participants	-		
Total number of partners	5		

Objectives 1) To apply the specific background in the field of rare diseases to mood and psychotic disorders; 2) To evaluate how different classes of genomic variants, from single nucleotide variants (SNVs) to copy number variants (CNVs), can contribute to the risk for mood and psychotic disorders; 3) To correlate genetic data with specific phenotypes.

T3.1. Applying expertise in rare diseases to mood and psychotic disorders (**Leader: UNICAMPANIA**, others: UNIFE, UNIBO, UNIBA, UNIFI). A wide cohort of patients and their parents will be analyzed by whole exome sequencing (WES). We already have access to WES data from a cohort of patients with schizophrenia and to WES data from about 6,000 Italian controls. Additional cases will be recruited by the centers participating in the spoke, and further data will be obtained from the Network for Italian Genomes (NIG).
T3.2. Evaluating the contribution of different classes of genomic variants as risk factors (**Leader: UNICAMPANIA**, others: UNIFE, UNIBO, UNIBA, UNIFI). We will use WES data to identify single nucleotide variants (SNVs), copy number variants (CNVs) and more complex structural variants (SVs). We will then evaluate the contribution and distribution of rare variants and CNVs/SVs with respect to susceptibility loci identified until now.
T3.3. **Correlating genotypes and phenotypes** (**Leader: UNICAMPANIA**, others: UNIFE, UNIBO, UNIBA, UNIFI). We will integrate genetic data with clinical features and endophenotypes observed in patients with mood or psychotic disorders (including findings from the other Work Packages).

Deliverables
D3.1. Establishing a wide cohort of patients to be analyzed by WES [M6]. **D3.2.** WES analysis and data interpretation to identify rare variants in genes functionally related to mood and psychotic disorders [M12]. **D3.3.** Integrated bioinformatic analysis of next-generation sequencing data to identify CNVs/SVs [M24]. **D3.4.** Integration of genetic variation and symptom-based phenotypic variation [M36]

Milestones
M3.1. Defining a database of genetic data shared across the spoke [M12]. **M3.2**. Integrating genetic data with CNV/SV identification [M30]. **M3.3**. Integration of genetic variation and symptom-based phenotypic variation [M36]

Work package number	**S5.WP4**	Partner responsible	UNIBA
Work package title	**Advanced brain imaging for mood and psychotic disorders (M1-M36)**		
Relevant scales	Molecular-genetics, Individual and Population, Network		
Universities	UNIBA, UNIGE, UNIPV, UNIBO, UNICAMPANIA		

Other participants	-
Total number of partners	5

Objectives 1) Generating machine learning risk calculators based on functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) data to predict further course in people at clinical high-risk for psychotic or mood disorders; 2) Identifying common and distinct pathophysiological features in schizophrenia and bipolar disorder; 3) Predicting the differential diagnosis between mood and psychotic disorders through multimodal imaging

T4.1. Prediction of further course in people at clinical high-risk for psychotic or mood disorders (Leader: UNIBA, others: UNIGE, UNIPV, UNIBO, UNICAMPANIA). Resting-state fMRI, task-related fMRI and MEG data will enter a machine learning framework to predict – in individuals at-risk for psychotic or mood disorders – the level of symptom severity and cognitive functioning at one-year follow-up.
T4.2. Identification of common and distinct pathophysiological features in schizophrenia and bipolar disorder (Leader: UNIBA, others: UNIGE, UNIPV, UNIBO, UNICAMPANIA). We will derive neuroimaging genetic results allowing the identification of shared and distinct neurobiological signatures in patients with a diagnosis of schizophrenia or bipolar disorder, along with their clinical correlates.
T4.3. Prediction of differential diagnosis between mood and psychotic disorders through multimodal neuroimaging (Leader: UNIBA, others: UNIGE, UNIPV, UNIBO, UNICAMPANIA). Unsupervised machine learning methods will be used to derive latent components from multiple fMRI and MEG data sources. These components will be used to feed support vector machine algorithms in order to explore whether they are more useful than single neuroimaging modalities for the differential diagnosis between mood and psychotic disorders.

Deliverables
D4.1. fMRI- and MEG-based algorithms predicting symptom severity and cognitive functioning in people at clinical high-risk for psychotic or mood disorders [M24]. **D4.2.** A set of neurobiological similarities and differences between patients with a diagnosis of schizophrenia or bipolar disorder based on neuroimaging genetics [M36]. **D4.3.** Unsupervised multimodal machine learning solutions for the differential diagnosis between mood and psychotic disorders in internal and external samples [M36]

Milestones
M4.1. Generation of machine learning risk calculators to predict outcome in people at-risk for psychotic or mood disorders [M24]. **M4.2**. Neuroimaging genetic assessment of patients with a diagnosis of schizophrenia or bipolar disorder [M24]. **M4.4.** Availability of neuroimaging-based latent components to feed support vector machine algorithms [M30]. **M4.5.** Evaluation of clinical utility of multimodal machine learning solutions for differential diagnosis between mood and psychotic disorders [M36]

Work package number	**S5.WP5**	Partner responsible	UNIBO
Work package title	**Pharmacogenetics for precision medicine in mood and psychotic disorders (M1-M36)**		
Relevant scales	Molecular-genetics, Individual and Population, D4		
Universities	UNIBO, UNIGE, UNIFE, UNICAMPANIA, UNIBA		
Other participants	-		
Total number of partners	5		

Objectives 1) To identify the genetic component of treatment resistance (TR) across mood and psychotic disorders; 2) To combine genetic markers with information obtained through digital phenotyping to develop models predicting TR; 3) To validate the predictive models and demonstrate early identification of individuals at risk for TR.

T5.1. Identification of the specific and shared genetic component of TR (Leader: UNIBO, others: UNIGE, UNIFE, UNICAMPANIA, UNIBA). We will derive genetic variants associated with TR transdiagnostically in patients with mood or psychotic disorders. Innovative approaches will be implemented to improve the variance explained in TR, including methods for polygenic risk scores (PRS) estimation that will be enriched with information on the functional role of variants for prioritization/weighting.
T5.2. Combination of genetic markers with clinical, lifestyle and tracking information to predict TR (Leader: UNIBO, others: UNIGE, UNIFE, UNICAMPANIA, UNIBA). We will combine genetic results with clinical deep phenotyping to predict TR vs. non-TR using machine learning. Different algorithms will be tested.

T5.3. Validation of the developed predictive models (**Leader: UNIBO**, others: UNIGE, UNIFE, UNICAMPANIA, UNIBA). We will conduct a randomized controlled trial to validate the predictors of TR identified in the previous task.
Deliverables **D5.1.** Identification of genetic biomarkers of TR within and across disorders [M24]. **D5.2.** Creation of models combining genetic and non-genetic predictors of TR [M30]. **D5.3.** Results of an RCT testing the predictors of TR [M36]
Milestones **M5.1**. Harmonization of clinical and genetic data across cohorts [M6]. **M5.2**. Completion of genetic analysis [M18]. **M5.3.** Completion of machine learning predictive models [M24]. **M5.4.** Completion of the validation RCT [M36]

S5.4 Cascade calls for funding

Tentative topics for the cascade calls that will be implemented to complement S5 activities are:

- Biomarkers of trauma-related risk for mood and psychotic disorders
- Neurophysiological correlates of avolition/apathy
- Role of circadian rhythms on mood and behavior
- Inflammatory drivers of mood and psychosis.

S6 NEURODEGENERATION, TRAUMA AND STROKE

S6.1 Description of the overall aim of the spoke

The molecular and cellular mechanisms of neuronal damage in different pathological conditions, such as chronic neurodegenerative diseases, trauma and stroke are still rather elusive despite the enormous research effort in the last decades. As a consequence, therapeutic and rehabilitative treatment are still largely unsatisfactory. Research activities within Spoke 6 of this consortium aim to shed light on these issues with the ambition to accelerate biomedical research towards developing of novel options to treat patients affected with these invalidating disorders. In particular, the coordinated activities of research groups from 23 Universities, Hospitals and Research Institutions, and Enterprises will address these topics covering all the aspects related to neurodegeneration. By meansof complex experimental models (yeast, 2D and 3D cultures using patient-derived iPSCs, and animal models), the genetic, biophysical, molecular, and cellular bases of neuronal death will be studied to identify relevant druggable intracellular pathways on which novel molecular entities or repurposed drugs will be tested as anti-neurodegenerative agents. In addition, exploration of the role of Gut Microbioma-Brain Axis in the worsening of neurodegeneration will be performed by profiling microbiome-derived products in the mentioned models. The integration of different experimental methodologies will allow us to capture the heterogeneity of the pathological processes leading to clinical deficits in neurodegenerative disorder patients, thus allowing us to identify disease subtypes, and improving our ability to build a personalized medicine approach for these conditions Moreover, the identification of novel routes of administration to deliver nanoparticles and pharmaceuticals to diseased areas will also be pursued. Prognostic and diagnostic biomarkers will be analyzed using ultrasensitive and innovative technologies in biofluids and tissues, and using advanced imaging and EEG approaches, organized through AI and machine learning approaches, to define a precise relationship with the clinical symptomatology. The identification of actionable biomarkers to improve diagnosis and management, will predict clinical outcomes, and accelerate the development of new treatments. These approaches will also allow a precise evaluation of disease development (in prodromal disease stage) and progression, also directed to the optimization of a patient-oriented pharmacological and rehabilitative methodologies. Finally, innovative rehabilitation approaches using virtual reality, cognitive stimulation, HD-EEG and advanced neurotechnologies, combining neuroprostheses and robotics, will be developed for Alzheimer's and Parkinson's patients, and stroke survivors.

S6.2 Composition of the spoke

Institution	Type	Location	Role	Short name
Università degli Studi di Genova	**University**	**Genova**	**Spoke responsible**	**UNIGE**
Università degli Studi di Pavia	University	Bari	Affiliated	UNIPV
Università degli Studi di Verona	University	Bologna	Affiliated	UNIVR
Università degli Studi di Ferrara	University	Catanzaro	Affiliated	UNIFE
Alma Mater Studiorum - Università di Bologna	University	Ferrara	Affiliated	UNIBO
Università degli Studi di Roma Torvergata	University	Firenze	Affiliated	UNITOV
Università degli Studi di Napoli Federico II	University	Napoli	Affiliated	UNINA
Università degli Studi "Magna Græcia" di Catanzaro	University	Parma	Affiliated	UNICZ
Università degli Studi di Bari Aldo Moro	University	Pavia	Affiliated	UNIBA
Università degli Studi di Parma	University	Roma	Affiliated	UNIPR
Università degli Studi Firenze	University	Verona	Affiliated	UNIFI
European Brain Research Institute Rita Levi-Montalcini	Foundation	Roma	Affiliated	EBRI
Fondazione Don Carlo Gnocchi ONLUS-IRCCS	Hospital	Milano	Affiliated	FDG
IRCCS Ospedale Policlinico San Martino	Hospital	Genova	Affiliated	HSM
IRCCS San Raffaele	Hospital	Roma	Affiliated	IRCCS-SR
IRCCS Istituto delle Scienze Neurologiche di Bologna	Hospital	Bologna	Affiliated	ISNB
IRCCS SYNLAB SDN	Hospital	Napoli	Affiliated	SYNLAB
Fondazione Telethon ETS	Foundation	Pozzuoli	Affiliated	TIGEM
Ospedale Pediatrico Bambino Gesù (Roma)	Hospital	Roma	Affiliated	OPBG
Scuola Superiore Sant'Anna di PISA	University	Pisa	Affiliated	SSSA
Alfasigma SpA	Enterprise	Bologna	Affiliated	ALFASIGMA
ASG Superconductors SpA	Enterprise	Genova	Affiliated	ASG
Dompè Farmaceutici SpA	Enterprise	L'Aquila	Affiliated	DOMPE'

S6.2.1 Description of the synergies

S6, led by UNIGE, involves the participation of internationally acknowledged research Teams sharing non-overlapping and non-interchangeable scientific expertise in the study of brain disorders. This complementarity will be instrumental to create synergies in the activities of the different WPs to maximize the outcome of the project. By means of multidisciplinary approaches, such as animal models, patient-derived human organoids generated via iPSCs, neuronal phenotypic expression, clinical research and experimental therapeutics, the project is warranted to gain a detailed overview of the bases of the neurodegeneration and the possible pharmacological and rehabilitative approaches to counteract its consequences. This is an ambitious project, developed in an atmosphere of trust and respect, and based on solid preliminary data combined with original approach "off the beaten track".

Feasibility of this integrated research plan is documented by several already ongoing collaborative projects among different partners. For example, UNITOV, OPBG, TIGEM, have already in place several pre-clinical and clinical collaborations, also supported by other academic grants in the field of neurogenetics, molecular biology, biomarkers identification and characterisation in neurological disorders. SSSA and FDG a long-standing collaboration about the predictive role of prodromic EEG alterations in neurodegeneration (in the frame of Regione Toscana health project). Similarly, UNIBO and ALFASIGMA have been collaborating on neurodegenerative aspects of the Gut Microbiome-Brain Axis.The synergy between groups belonging to the spoke will consolidate the critical mass of skills and make our country a competitive partner for international projects and for the development of privileged collaborative partnerships. In addition, S6 is structured to develop win-win collaborations with pharmaceutical/life science biocompanies. The companies affiliated to the spoke not only will substantially contribute to the research activities, but also will facilitate the transferability of research results to industry, increasing the value of the intellectual properties (IPs) owned by Italian research centers, through the out-licensing of more mature technologies. These perspectives, together with the training capacity of a new generation of medical scientists, expert in emerging techniques, granted by the Academic counterpart, will advance our country to a high biotechnological level in the field, able to attract investors and developers from other countries.

S6.3 Work packages

Work package number	**S6.WP1**	Partner responsible	**UNIBO**
Work package title	**Mechanisms of neuronal cell degeneration and drug dependent reversal (M1-M36)**		
Relevant scales	Molecular-genetics, 2D&3D cellular Models, Animal Models, D4		
Universities	UNIBA, UNIBO, UNICZ, UNIFE, UNIFI, UNIGE, UNINA, UNIPR, UNIPV, UNITOV, UNIVR		
Other participants	ALFASIGMA, DOMPE', FDG, EBRI, ISNB, OPBG, SR, SYNLAB, TIGEM		
Total number of partners	20		

Objectives 1) To obtain *in vivo* and *in vitro* models, representative of neurodegenerative disorders; 2) To identify druggable neurotoxicity mediators, determinant of misfolded proteins, their diffusion and mechanisms of action; 3) To define neural circuitry alterations and the role of transcriptome in neurodegeneration; 4) To design and test new multitarget pharmacological approaches and new drug delivery systems against neurodegenerative diseases. 5 – To explore the role of Gut Microbiome-Brain Axis in the pathogenetic mechanisms of neurodegeneration and possible pharmacological reversal.

T1.1. To establish complex models of neurodegenerative diseases (**Leader: UNIBO**; others: UNIBA, UNICZ, UNIFE, UNIFI, UNIGE, UNINA, UNIPR, UNIPV, UNITOV, UNIVR, ALFASIGMA, FDG, ISNB, OPBG, SR, EBRI, TIGEM). We will develop i*n vitro* and *in vivo* models of rare and more prevalent neurodegenerative diseases and myotonic dystrophies using yeast, 2D and 3D neuronal cultures from patient-derived iPSCs and animal models.

T1.2. To identify altered mechanisms mediating neurodegeneration (**Leader: UNIVR**; others: UNIBO, UNIFI, UNIGE, UNINA, UNITOV, ALFASIGMA, ISNB, EBRI). We will define the intracellular mechanisms responsible of the neurodegenerative processes in the established models and define the pathways by which neurotoxic misfolded proteins spread within the brain.

T1.3. To characterize the structural features of Ab and a-synuclein and their interactome (**Leader: UNIGE**; others: UNIBA, UNIFI, UNIPV, UNIVR, EBRI, SR). We will define the structural determinants leading to the formation of neurotoxic entities (monomers, oligomers and fibrils) of misfolded proteins and their ability to interact with neuronal intracellular components.

T1.4. To define the functional role of epi-transcriptome and neural circuitry alterations in neurodegeneration (**Leader: UNIBA**; others: UNIFE, UNIFI, UNIGE, UNIPR, UNIPV, UNITOV, UNIVR, ALFASIGMA, ISNB, SR, SYNLAB, TIGEM). We will characterize the changes in transcriptome and epi-transcriptome (non-coding RNAs), and modification of local neuron activity and neural circuitry as determinants of neuronal survival or death, and the possibility to deliver genetic modifiers to treat hereditary amyloidosis with peripheral neuropathies.

T1.5. To develop novel pharmacological approaches to counteract neurodegeneration (**Leader: EBRI**; others: UNIBA, UNIBO, UNIFI, UNIGE, UNINA, UNIPR, UNITOV, DOMPE', TIGEM). We will test novel pharmacological entities of repurposed drugs able to modify the structure or to favor the clearing of neurotoxic molecules, or to revert the altered neuronal pathways mediated misfolded proteins.

T1.6. **To develop of brain-selective drug delivery approaches** (**Leader: SR**; others: UNIBA, UNIFI, UNIPR, UNIVR, DOMPE', EBRI). We will develop intranasal administrable biomimetic nano- and micro-platforms by which specifically deliver active molecules to diseased brain areas.

T1.7. To define the role of microbiome in neurodegeneration (**Leader: ALFASIGMA**, other: UNIBO, UNIGE). We will profile the microbioma in Parkinson's and Alzheimer's disease patients to identify postbiotic mediators of neurodegeneration and develop microbiome-targeted drugs.

Deliverables:
D1.1. Identification of druggable mechanisms of neurodegeneration [M36]. **D1.2.** Establishment of the efficacy of novel neuroprotective therapeutics and selective brain area drug delivery technologies [M36]. **D1.3.** Identification of a gut microbiome-dependent mechanism of enhancement of neurodegeneration [M36].

Milestones: M1.1. Development of different complexity models of neurodegenerative diseases and dystrophies [M18]. **M1.2.** Identification of the role of neural circuit alterations, transcriptome and ncRNA in neurodegeneration [M30]. **M1.3.** Development of neuroprotective neurotrophic molecules [M 30]. **M1.4.** Engineering of biomimetic drug delivery platforms [M30]. **M1.5.** Identification of a Gut Microbiome-based drug for reducing neurodegeneration [M30].

Work package number	**S6.WP2**	Partner responsible	**UNIPR**
Work package title	**Multi-modal approaches to monitoring progression of neurodegenerative diseases and definition of novel rehabilitation methodologies (M1-M36)**		
Relevant scales	Molecular-genetics, Individual and Population, Network, Digital Twins.		
Universities	UNIBA, UNIBO, UNIFE, UNIFI, UNIGE, UNIPR, UNIPV, UNITOV, UNIVR		
Other participants	ALFASIGMA, EBRI, FDG, ISNB, SYNLAB, SSSA, TIGEM		
Total number of partners	16		

Objectives 1) To establish a relationship between circulating and imaging biomarkers in the healthy population and in neurodegenerative disease patients; 2) To develop novel approaches to monitor neurodegeneration progression; 3) To identify the role of multiple genetic and epigenetic patterns in inducing the phenotypical heterogeneity of neurodegenerative diseases; 4) To assess the effectiveness of cognitive and virtual reality approaches to rehabilitation in Alzheimer's and Parkinson's diseases, and other neurodegenerative diseases

T2.1. Fluid biomarkers of neurodegeneration (**Leader: SYNLAB**; others: UNIBO, UNIFE, UNIFI, UNIGE, UNIPR, UNIPV, UNITOV, UNIVR, EBRI, FDG, ISNB, TIGEM). We will assess established and novel fluid biomarkers of neurodegeneration in healthy subjects and in patients with neurodegenerative diseases (in clinical and preclinical stages) to assess their ability to differentiate between healthy controls and patients and to evaluate their correlations with imaging metrics and cognitive performance.

T2.2. Genetic contributions to neurodegeneration (**Leader: ISNB**; others: UNIBO, UNIFI, UNITOV, UNIPV, ALFASIGMA, FDG). We will proceed to characterize the genetic and epigenetic profile of iPSC-derived cells, plasma and CSF cfDNA in MCI-AD and in GBA-related Parkinson's patients, and healthy controls to evaluate the contribution of genetic and epigenetic factors to neurodegeneration.

T2.3. EEG markers of neurodegeneration (**Leader: SSSA;** others: UNIGE, UNIPV, UNITOV, FDG).
We will evaluate multiple quantitative EEG and polysomnographic metrics to determine the presence and clinical usefulness of EEGraphic and sleep alterations in prodromal stages of neurodegenerative diseases.

T2.4. AI and conversion to dementia (**Leader: FDG**; others: UNIBA, UNIFI, UNITOV, EBRI, SSSA).
We will use AI-based and machine learning-based modelling approaches to predict the risk of conversion from subjective cognitive decline (SCD) to objective decline and clinical dementia.

T2.5. Pre-clinical and clinical correlates of impulse control disorders in Parkinson's Disease (**Leader: SSSA**; others: UniTOV, FDG). We will focus on the identification biomarkers, including neurophysiological metrics, of Parkinson's disease motor symptoms and of deep brain stimulation-dependent impulse control disorder both in patients and in and animal models.

T2.6. Neural and clinical correlates of rehabilitation in neurodegenerative conditions (Leader: UNIPV; others: UNIPR, UniTOV, FDG, ISNB). We will focus on the neural, neurophysiological (HD-EEG) and clinical correlates of cognitive training including motor and cognitive rehabilitation and virtual reality approaches in subjects with prodromal Alzheimer's disease and other neurodegenerative conditions.

Deliverables

D2.1. Identification of biomarkers related to neurodegeneration progression [M36]. **D2.2** Classification algorithms to detect the prodromal stages of Alzheimer's disease [M36]. **D2.3** Validation of cognitive training and virtual reality interventions in prodromal Alzheimer's and Parkinson's diseases [M36]. **D2.4.** HD-EEG predictive modelling report [M36].

Milestones

M2.1. Characterization of population and identification of circulating biomarkers [M18]; **M2.2** Correlation between circulating and imaging biomarkers [M30]; **M2.3** Virtual Brain model of the prodromal stage of AD [M24]; **M2.4** Development of cognitive training and virtual reality intervention packages [M24]; **M2.5** Evaluation of training efficacy by analysis of functional connectivity by fMRI data [M30].

Work package number	**S6.WP3**	Partner responsible	**UNIFI**
Work package title	**Neurodegeneration in stroke (M1-M36)**		
Relevant scales	All		
Universities	UNIBA, UNIFI, UNIGE, UNINA, UNITOV, UNIVR		
Other participants	ALFASIGMA, FDG, HSM, SR, SSSA		
Total number of partners	11		

Objectives 1) To identify molecular pathways and cellular interactions responsible for neuronal damage and neuroprotection in stroke and their pharmacological targeting; 2) To identify and validate prognostic serum markers of neurodegeneration and neuroinflammation in acute ischemic stroke; 3) To develop selective brain

targeting nanocarriers to deliver drugs overcoming BBB; 4) To develop novel technological approaches to quantify and restore grasping sensory-motor functions in stroke survivors
T3.1. To Identify mechanisms of neuroprotection in stroke (Leader: UNIFI; others: UNINA, UNITOV). We will develop preclinical models of stroke and hypoxic-ischemic encephalopathy (HIE) to be used to characterize altered intracellular pathways leading neurodegeneration and the assessment of the neuroprotective efficacy and the neuroradiological correlates of selective pharmacological approaches. **T3.2. To assess the role of peripheral inflammatory markers in stroke (Leader: HSM**; others: UNIGE, UNIFI, UniTOV, SR). We will identify specific peripheral inflammatory markers altered in stroke, will provide a relationship with patients' functional/clinical outcome, and will validate the relevance of the therapeutic monitoring of their modifications as prognostic index in the acute phase of ischemic stroke. **T3.3. To develop novel of therapeutic strategies in stroke (Leader: SR**; others: UNIBA UNIFI, UNIVR, ALFASIGMA). We will develop a novel brain targeting nano-drug delivery systems (NDDSs) to the brain as platform to obtain effective pharmaceutical level in lesion brain areas in stroke patients. **T3.4. To develop of innovative rehabilitation approaches for stroke survivors (Leader: SSSA**; others: UNIGE, FDG). We will develop an innovative neurotechnology to quantify and restore grasping sensory-motor functions in stroke survivors. Upper limb functions will be restored by using soft wearable exoskeletons used together with imaging information in a digital-twin approach.
Deliverables **D3.1.** Identification of peripheral prognostic markers and pharmacological targets in stroke and HIE [M36]; **D3.2.** Clinical test of implanted stroke neuroprostheses [M36].
Milestones **M3.1.** Validation of experimental models of cerebral ischemia and HIE and identification of druggable targets [M24]; **M3.2.** Identification of serological inflammation markers in stroke and their correlation with clinical and neuroimaging features [M24]; **M3.3.** Development of innovative strategies for NDDS [M24]; **M3.4**. Digital twin of upper limb musculoskeletal system [M30].

Work package number	**S6.WP4**	Partner responsible	**UNIGE**
Work package title	**Multi-parametric imaging and neurophysiological approaches to monitor neurodegeneration in the central and peripheral nervous system (M1-M36)**		
Relevant scales	Molecular-genetics, Individual and Population, Network, Digital Twin.		
Universities	UNIBA, UNIFI, UNIGE, UNIPR, UNIPV, UNITOV		
Other participants	ALFASIGMA, ASG, FDG, HSM, ISNB, SYNLAB		
Total number of partners	12		

Objectives 1) To verify the contribution of grey and white matter damage and alterations of diffuse projection systems to clinical symptomatology in neurodegenerative diseases; 2) To shed light on the impact of neurodegeneration on brain functional architecture in neurodegenerative diseases; 3) To discover the neural signature of peripheral biomarkers and polygenic risk in neurodegeneration; 4) To develop novel approaches to monitor neurodegeneration in CNS and PNS
T4.1. Integrated quantification of grey and white matter damage (Leader: UNIGE; others: UNIFI, UNIPV, FDG, ISNB, SYNLAB). We will acquire multi-parametric MRI metrics and molecular imaging data in a large cohort of subjects with Alzheimer's and Parkinson's Disease, other neurodegenerative pathologies and traumatic brain injury to explore the relative relevance and the underling nature of grey and white matter damage across neurodegenerative conditions. To better understand the impact of neurodegeneration on white matter organization, we will also use neurophysiological approaches to probe white matter alterations in central and peripheral neurodegenerative conditions. **T4.2. Quantification of diffuse projection systems damage in neurodegenerative conditions (Leader: UniTOV**; others: UNIGE, FDG, SYNLAB). We will combine MRI tractography, quantitative MRI metrics of structural damage, molecular imaging and neurophysiological approaches to explore diffuse projection system across different neurodegenerative conditions, with a focus on the dopaminergic and serotoninergic systems. **T4.3. Polygenic determinants of regional susceptibility to neurodegeneration (Leader: UNIPR**; others: UNIPV, FDG, ISNB). We will combine assessment of polygenic risk scores and measures of functional connectivity based on functional neuroimaging approaches to evaluate the role of inter-subject genetic differences on regional resilience to neurodegeneration. **T4.4. Development of novel markers of neurodegeneration (Leader: UNIBA**; others: UNIFI, UNIGE, UniTOV, ASG, FDG, HSM, ISNB, SYNLAB). We will develop and validate novel MRI approaches and

molecular imaging tracers (including novel PET/SPECT tracers) to study neurodegeneration using a trans-diagnostic approach, with a focus on reproducibility and on their possible uses in clinical trials.
Deliverables **D4.1.** Report on structural, EEG, and functional brain alteration in neurodegenerative diseases [M36]; **D4.2.** Definition of the regional association between damage, network disconnection, polygenic risk metrics and peripheral markers in neurodegenerative diseases [M24]; **D4.3** Identification of novel imaging markers and tracers of neurodegeneration [M36].
Milestones **M4.1.** Recruitment of experimental population and data acquisition [M24]. **M4.2.** Completion of processing of images [M30]; **M4.3.** Characterization of population [M24]; **M4.4.** Correlations between genetic scores and imaging data [M30]. **M4.5.** Development of relevant markers and tracers [M24]. **M4.6.** Validation against gold standard [M24].

S6.4 Cascade calls for funding

Tentative topics for the cascade calls that will be implemented to complement S6 activities are:

- Assessment of the signaling and interneural transmission mediated by apolipoprotein E and its receptor in neurodegeneration
- Definition of novel cognitive correlates to assess neurodegeneration progression and therapeutic interventions
- Development of behavioral models of stroke and neuroimaging analysis to assess long term evolution of the disease and the efficacy of rehabilitative treatments.

S7 NEUROIMMUNOLOGY AND NEUROINFLAMMATION

S7.1 Description of the overall aim of the spoke

This spoke proposes a highly integrated cellular and molecular multiomics platform to tackle immune mechanisms and neuroinflammation in nervous system diseases. We will profile immune cells, serum and cerebrospinal fluid from patients and advanced experimental models and identify novel disease-specific signatures and biomarkers promoting neuroinflammation and neurotoxicity. We will model nervous system diseases and develop digital twins allowing disease stratification and improvement of precision treatment. New drug targets will be identified by analyzing multiomics data using network-based tools and computational biology approaches. Finally, we will develop new therapeutic molecules and obtain proof of concepts for novel pharmacological approaches targeting neuroinflammation and immune dysfunction in nervous system disorders.

S7.2 Composition of the spoke

Institution	Type	Location	Role	Short name
Università degli Studi di Verona	University	Verona	Responsible	UNIVR
Università degli Studi di Roma Torvergata	University	Roma	Affiliated	UNITOV
Università degli Studi di Napoli Federico II	University	Naples	Affiliated	UNINA
Università degli Studi di Bari Aldo Moro	University	Bari	Affiliated	UNIBA
Alma Mater Studiorum - Università di Bologna	University	Bologna	Affiliated	UNIBO
Università degli Studi di Firenze	University	Florence	Affiliated	UNIFI
IRCCS Ospedale Policlinico San Martino	Hospital	Genova	Affiliated	HSM
IRCCS San Raffaele	Hospital	Rome	Affiliated	SR
Ospedale Pediatrico Bambino Gesù (Roma)	Hospital	Rome	Affiliated	OPBG
IRCCS Istituto delle Scienze Neurologiche di Bologna	Hospital	Bologna	Affiliated	ISNB
IRCCS SYNLAB SDN	Hospital	Napoli	Affiliated	SYNLAB
Fondazione Don Carlo Gnocchi ONLUS-IRCCS	Hospital	Milan	Affiliated	FDG
DOMPE' Farmaceutici SpA	Enterprise	Napoli	Affiliated	DOMPE'
Takis Srl	Enterprise	Naples	Affilated	TAKIS

S7.2.1 Description of the synergies

Spoke 7 has gathered an intergenerational team with Italian excellences in neuroimmunology and neuroinflammation, as demonstrated by the **7 European Research Council (ERC) grants won by its participants in this field:** 4 UNIVR (ERC-Stg Neurotrafficking #261079, ERC-PoC IMPEDE #693606, ERC-

Adv IMMUNOALZHEIMER #695714, ERC-PoC NeutrAD #101069397), 2 UNINA (ERC-Stg LEPTINMS #202579, ERC-Cons menTORingTregs #310496,) and 1 UNITOV (ERC-Stg FIRM #819600). The members of Spoke 7 team share a cutting-edge, transdisciplinary, complementary expertise spanning from strong basic science expertise on advanced cellular and animal models of disease (UNIVR, UNINA, UNIFI, UNITOV, SYNLAB, SR) to clinical research (UNITOV, UNIFI, UNIVR and several IRCCS), computational and synthetic medicinal chemistry (UNIBA, UNIVR, UNIBO) and therapeutics and business development (DOMPE'). For instance, UNIVR and UNIBO are already collaborating for the ERC Proof of Concept grant acronym NeutrAD (#101069397) to produce and test new drugs, including PROTAC-based drugs, targeting T cell specific enzymatic activity leading to neurotoxicity, highlighting the potentiality of synergic research lines of this spoke.

S7.3 Work packages

Work package number	**S7.WP1**	Partner responsible	UNINA
Work package title	**Identification of New Immune and Inflammatory Mechanisms in Cellular Models of Nervous System Disorders (M1-M16)**		
Relevant scales	Molecular-genetics, 2D&3D cellular Models, Network		
Universities	UNINA, UNIBA, UNIVR, UNITOV, UNIFI, UNIFE		
Other participants	OPBG, SR, SYNLAB		
Total number of partners	9		

Objectives 1) Dissecting novel in vitro molecular mechanisms leading to leukocyte-mediated neurotoxicity; 2) Defining the role of metabolism in the regulation of immune system in in vitro models with relevance to nervous system diseases; 3) Characterizing molecular and cellular interplays in in vitro systems mimicking neuroinflammation and nervous system dysfunction

T.1.1. Identification of molecular mechanisms leading to leukocyte-induced neurotoxicity in vitro and assessment of synaptotoxic inflammatory molecules (Leader: UNIVR; others: UNITOV, SR, UNINA, UNIFI). We will identify cytotoxic mechanisms exerted by neutrophils and lymphocyte subpopulations on neurons and astrocytes in vitro using multiomics, live-imaging and high resolution wide-field microscopy in models with relevance to Alzheimer's disease (AD) and multiple sclerosis (MS). Synaptotoxic effects of inflammatory molecules and vesicles will be assessed using translational chimeric ex-vivo models, including human samples and murine brain slices.

T.1.2. Immunometabolic control of immune tolerance and identification of neuroinflammatory metabolic targets (Leader: UNINA; others: UNIBA, UNIFE, UNIFI). We will determine the metabolic mechanisms affecting T cell differentiation and function in vitro, employing cellular, molecular and omics approaches (RNA-Seq, proteomics, metabolomics, epigenetics) using rodent and human cells under in vitro conditions with relevance to CNS diseases. Moreover, the role of glutamine metabolism in brain inflammation will be characterized, by means of MS metabolomics and ^{13}C isotope tracing.

T.1.3. Characterization of the interplay between oxidative stress, mitochondrial alterations and neuroinflammation (Leader: UNITOV; others: UNIFE, OPBG). We will investigate how ferroptosis underlies the epileptic activity by dissecting the main pathways of oxidative stress and neuro-inflammation in *in vitro* mouse brain slices and organotypic cultures. We will also investigate the interplay between mitochondria and inflammasome and tethering mechanism between mitochondria and nucleus in iPSC neuron/glia derived from patients with neuroinflammatory diseases.

T.1.4. Characterization of the interplay between the cells of the neurovascular unit in advanced cell culture models (2D and 3D cellular models) (Leader: UNITOV; others: UNIFI, UNIVR, UNIBA, SYNLAB, SR). We will perform next generation small RNA sequencing to determine tRNA fragments expression and RNA dysregulation in microglial cells in the presence of pro-inflammatory stimuli. We will characterize the cross talk between microglia, astrocytes and neurons and between leukocytes and CNS endothelial cells to define novel molecular pathways leading to neuroinflammation, oxidative stress and synaptic damage. Finally, by using ultra high field MRI spectroscopy, we will characterize the multiomic profiles of CNS cells generated from expanded CNS stem cells.

Deliverables

D1.1. Report on novel leukocyte neurotoxic mechanisms *in vitro* [M12]; **D1.2**. Report on metabolic control of T cell function [M16]; **D1.3.** Demonstrate molecular and cellular crosstalks [M12].

Milestones
M1.1. Identification of novel molecular mechanisms of immune and CNS cell dysfunction [M12]; **M1.2**. Characterization of leukocyte-mediated neurotoxicity in vitro [M12].

Work package number	**S7.WP2**	Partner responsible	UNIVR
Work package title	**Identification of Pathogenic Signatures and New Drug Targets in Animal Models of Nervous System Inflammation (M1-M18)**		
Relevant scales	Molecular and genetics, Animal models, Network, D4		
Universities	UNIVR, UNINA, UNIBA, UNITOV, UNIFE, UNIFI		
Other participants	SR, SYNLAB		
Total number of partners	8		

Objectives 1) Characterize new immune mechanisms leading to neuroinflammation and neurotoxicity in animal models of nervous system diseases; 2) Understand the role of metabolic dysregulation and identify new metabolism-based interventions in in vivo experimental models of CNS diseases; 3) Identify and validate new drug targets to tackle neuroinflammation.

T2.1. Identification of molecular pathways driving neuroinflammation and neurotoxicity induced by peripheral immune cells in animal models of CNS diseases (**Leader: UNIVR**; others: UNITOV; UNIFI, SR). To uncover novel neuroinflammatory, neurotoxic and synaptotoxic mechanisms, we will perform single-cell transcriptomics, proteomics and functional proteomics on neutrophils and lymphocyte subpopulations isolated from the blood and CNS using animal models of experimental autoimmune encephalomyelitis (EAE), AD and epilepsy. As recent data has shown a key role for meningeal immunity in CNS disorders, we will also determine the immune profile of leukocytes isolated from the meninges. These studies will be integrated with advanced immune cell profiling using single-cell spatial multiomics on tissue samples from animals with CNS diseases.
T2.2. Characterization of microglia dysfunction in models of nervous system diseases (**Leader: SYNLAB**; others: UNIVR). As described for WP1, we will perform multiomics studies to characterize microglia subpopulations and activation states in EAE, animal models of AD, stroke, spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). We will also study the cross-talk of microglial cells with astrocytes and neurons in vivo during neuroinflammatory responses.
T2.3. Role of metabolism in the control of neuroinflammation and immune tolerance during CNS diseases (**Leader: UNINA**; others: UNIBA, UNITOV, UNIFE, SR). We will deeply characterize at transcriptional, proteomic and metabolomic levels the impact of "metabolic pressure" of different dietary regimens to regulate immune cell function in mice with EAE, AD and Parkinson models. We will identify metabolic signatures associated to pro-inflammatory functional states in immune cells and reprogram neuroinflammatory responses using natural bioactive compounds. Finally, we will study microglia mitochondrial dysfunction and its relationship with inflammasome activation.
T2.4. Network analysis and identification of new drug targets for nervous system diseases (**Leader: UNIVR**; others: UNIBO, UNINA, UNIFI). We will identify new disease-specific signatures and drug targets by analyzing the data obtained at WPs1-3 using topological network analysis, indexes of node centrality, algorithms combining network topology and quantitative experimental data and network intersection. Integration of single-cell RNA-seq data on genome scale metabolic models will characterize the metabolic state of immune cells through flux balance analysis. New drug targets will be validated by multiple approaches, including proteomics, advanced imaging and flow cytometry.

Deliverables
D2.1. Report on multiomics data [M12]; **D2.2**. Demonstrate the immunomodulatory effect of new metabolic regimens and bioactive molecules [M18]; **D2.3**. Validate new drug targets [M14].

Milestones
M2.1. Identification of novel immune cell pathways leading to neuroinflammation and neurotoxicity [M12]; **M2.2**. Characterization of new metabolic approaches for CNS diseases [M18]; **M2.3**. Obtain indication on new drug targets with bioinformatics approaches [M12].

Work package number	**S7.WP3**	Partner responsible	UNIFI
Work package title	**Immuno-Inflammatory Profiling of Patients with Nervous System Diseases and Identification of New Biomarkers (M1-M36)**		
Relevant scales	Molecular, Genetics; Individual and Populations; Network; Digital twins		

Universities	UNIFI, UNITOV, UNINA, UNIVR, UNIBO, UNIFE
Other participants	SR, OPBG, DOMPE'
Total number of partners	9

Objectives 1) Integrated approach to identify disease-specific immune signatures promoting nervous system inflammation; 2) Identification of new biomarkers for central and peripheral nervous system diseases; 3) Identification of novel drug targets to tackle neuroinflammation; 4) Development and validation of digital twins of nervous system diseases and statistical methods for disease subtype stratification and modelling for improvement of precision treatment.

T3.1. Multiomics profiling of immune cells in patients with central and peripheral nervous system inflammatory diseases and identification of new drug targets (**Leader UNITOV**; others: UNIFI, UNIVR, UNIFI). To identify *disease-specific immune cell signatures*, we will integrate transcriptomics (mRNA or nsRNA, single-cell transcriptomics), proteomics, functional proteomics, metabolomics and MRi spectroscopy profiling of isolated CSF and blood leukocytes in patients with CNS and peripheral nervous system (PNS) autoimmune and neurodegenerative diseases. The results will be analyzed using bioinformatic tools and will be correlated with clinical, advanced neuroimaging, neurophysiological, neuropsychological parameters. Integrated multiple approaches will be also used to unravel chronic compartmentalized inflammation in intrathecal niches. As for pre-clinical studies, we will use single-cell spatial multiomics on CNS and PNS tissues as well as on meningeal. Finally, as for WP2, network analysis tools will be used to *identify new drug targets*.

T3.2. Identification of novel biomarkers for neuroinflammatory diseases (**Leader: UNIFI**; others: UNITOV, UNIVR, DOMPE'). We will perform multiomics profiling, including proteomics and lipidomics, in nervous system tissue, CSF and serum of patients with CNS and PNS diseases. We will also determine the antibody profiling of molecules against synaptic, glial and myelin proteins and antibody profiling of viral components in serum and CSF. We will also provide tRNA fragments (tRF) and MRi spectroscopy 'fingerprints' of drug effectiveness by means of next generation small RNA sequencing of blood/liquor of patients. We will integrate these data to identify novel disease-specific biomarkers for CNS and PNS diseases.

T3.3. Characterization of immune cell dysfunction and inflammation in paroxysmal nervous syndromes (**Leader: UNIFI**; others: HSM, UNITOV, UNIVR*)*. Our team has previously demonstrated a key role for inflammation mechanisms in epilepsy and pain. Here we will perform multiomics studies as described in Tasks 3.1 and 3.2 to identify new disease signatures and biomarkers in patients with these diseases.

T3.4. Identification of regulatory mechanisms and specific cellular and molecular interplays in nervous system diseases (**Leader: UNINA**; others: UNIFI, UNITOV, UNIBO, UNIFE, UNIVR, UNINA, SR). At this task we will perform phenotypical and functional profiling of MS regulatory T cells in the peripheral blood. Also, we will determine molecular components involved in the interplay between mitochondria and inflammasome system, the formation of mito-nuclear contact sites (NAM) and synaptotoxic signatures.

T3.5. Development and validation of digital twins and statistical methods for disease subtype stratification and modelling for precision treatment improvement (**Leader: UNIFI**; others: UNINA, HSM, UNIVR, UNITOV, IRCSS-OPBG, SR). This task will be pursued through: i) integration of big data, genetics, environmental and lifestyle-related risk factors, clinical, biological and molecular biomarkers as well as current and emerging imaging markers; ii) development and analysis of digital twins of CNS autoimmune diseases by machine learning algorithms and by specific statistical analysis. We will also deal with modelling diseases for individual stratification and precision treatment improvement.

Deliverables: D.3.1. Publicly accessible data and informational resources of new disease mechanisms and biomarkers (M28); **D.3.2** Report on new target molecules (M12); **D.3.3**. Documentation on implementation and usage of digital twins and network-based machine learning algorithms (M36).

Milestones: M.3.1. Identification of disease-specific signatures (M12); **M.3.2** Identification of new drug targets (M12); **M.3.3**. Identification of new disease biomarkers (M24); **M.3.4.** Disease modelling (M36).

Work package number	**S7.WP4**	Partner responsible	UNIBA
Work package title	**Drug Discovery, Development and Delivery for Targeting Neuroinflammation (M12-M28)**		
Relevant scales	2D & 3D cellular Models, D4		
Universities	UNIBA, UNIBO, UNIVR, UNIFI		
Other participants	SYNLAB, DOMPE'		
Total number of partners	6		

Objectives 1) To discover potential new drugs and repurposing of active pharmaceutical ingredients for the therapy and imaging of neuroinflammation diseases by in silico studies; 2) To develop novel anti-inflammatory and diagnostic agents capable of acting on markers known to be involved in neuroinflammatory pathologies or identified using computational techniques; 3) To develop advanced drug brain delivery systems targeting neuroinflammation.

T4.1. In silico drug discovery of potential new drugs and repurposing of active pharmaceutical ingredients (**Leader: UNIVR**; others: UNIBA). Using computational techniques, combined with structural experiments, we will characterize the target proteins involved in neuroinflammation processes, identified through proteomic analyses. We will then integrate protein bioinformatics, conventional physics-based simulations with data-science to perform drug repurposing and/or rational design.

T4.2. Design and synthesis of anti-inflammatory agents (**Leader: UNIBO**; others: UNIBA, UNIVR, SYNLAB, DOMPE'). Based on the T 4.1 outcomes, the range of identified drugs (repurposed or new structures) targeting neuroinflammation will be explored, followed by synthesis and characterization of the new derivatives. In particular, proteolysis-targeting chimeras (PROTACs) directed to the neuroinflammatory targets; drug-like pro-resolving and anti-inflammatory agents; new ligands for microglial druggable targets and imaging purposes.

T.4.3. Pre-formulation studies of new therapeutics (**Leader: UNIBA**; others: UNIBO, UNIVR, DOMPE'). Pre-formulation studies improving the physico-chemical properties of new therapeutics using both pharmaceutical and pharmaceutical technology-based approaches and testing non-specific pro-inflammatory effects of pharmaceutical excipients in specific cellular 2D and 3D models.

T.4.4. Design, development and characterization of advanced drug brain delivery systems targeting neuroinflammation (**Leader: UNIBA**; others: UNIBO, UNIVR, SYNLAB). Development of advanced lipid based nanodrug delivery systems produced by both bulk and microfluidics techniques loaded with anti-inflammatory agents and targeting immune cell function. Moreover, drug-encapsulation in exosomes will be explored as novel drug targeting strategy. We will also perform in vitro validation on specific cell lines in 2D and 3D models, also mimicking the BBB.

Deliverables

D4.1. Report with listed repositioned drugs along with emerged new structures for drug development [M16]; **D4.2.** Report of synthetic procedures and characterizations of the identified [M22]; **D4.3.** Report of preformulation studies of the identified neuroinflammation therapeutic and imaging compounds [M28]; **D4.4.** Report of the developed nanoformulations and drug delivery results [M28].

Milestones

M4.1. Characterization of new drug targets [M16]; **M4.2**. Identification and development of promising drug candidates [M22]; **M4.3.** Preformulation studies [M28]; **M4.4**. Development and assessment of nanoformulations effective disease targeting ability with no or negligible side effects [M28].

Work package number	**S7.WP5**	Partner responsible	UNITOV
Work package title	**In Vitro and in Vivo Drug Testing of New Immunomodulatory and Anti-inflammatory Drugs for Nervous System Diseases (M16-M36)**		
Relevant scales	2D&3D cellular Models, Animal Models, Network		
Universities	UNITOV, UNIVR, UNIFI, UNINA, UNIFE		
Other participants	OPBG, SR, TAKIS		
Total number of partners	8		

Objectives 1) To screen new molecules in advanced cellular models; 2) To validate lead compounds in experimental animal models by means of multidisciplinary approaches; 3) Obtainment of Proof of concept for lead compound delivery and new drugs to tackle neuroinflammation.

We expect to screen 15-20 compounds coming from WP4 in in vitro models and 2-3 lead compounds in in vivo models as well as NLRP3 inflammasome antagonists or antioxidant, anti-inflammatory and anti-epileptic combined treatments in specific in vitro and in vivo models.

T5.1. Screening of new compounds in advanced cellular models of leukocyte-mediated neurotoxicity (**Leader: UNIVR**; others: UNIFI, SR). New compounds will be tested for their ability to inhibit leuocyte-mediated toxicity in assays described at Task 1.1 (WP1).

T5.2. Screening of new compounds with anti-inflammatory, immunomodulatory and neuroprotective effects (**Leader: UNIVR**; others: UNITOV, UNIFI, UNIFE, SR; OPBG). New compounds will be tested by

comparing drug-treated and -untreated 2D and 3D cellular models of CNS and PNS diseases or iPSC-derived glia/ neurons derived from patients described at WP1.
T5.3. Validation of lead compounds in experimental animal models (**Leader: UNIVR**; others: UNITOV, SR; OPBG, TAKIS). We will test two best-ranked drugs in animal models mentioned at WP2 by assessing their in vivo therapeutic efficacy through: i) behavioral tests; (ii) electrophysiological recording; iii) neuropathological assessment, advanced imaging and molecular and biochemical assays.
T5.4. Evaluation of new immunosuppressive and anti-inflammatory biological drugs. (**Leader: UNITOV**; others: UNINA, UNIFI). Here we will: i) Test the effect of Treg cell-derived extracellular vesicles as novel immune suppressive biological drug in neuroinflammatory diseases; ii) Test libraries of compounds which pharmacologically regulate NAM (Nuclear Associated Mitochondria) as anti-inflammatory agents.
T5.5. Develop next-generation anti-inflammatory targeted nano-therapeutics. (**Leader: SR**; others: UNIVR). Biomimetic nanoparticles will be synthesized using purified leukocyte membrane proteins integrated into synthetic liposomes. The manufacturing protocols have been already established to guarantee scalability, GMP certification, translational value and approval for clinical use.

Deliverables
D5.1. Report on new compounds blocking immune- and inflammatory-mediated neurotoxicity [M28]; **D5.2**. Establish proof of concept on the effect of new compounds and therapeutic strategies [M36].

Milestones
M5.1. Screening of new compounds in advanced cellular models (M28); **M5.2.** Validation of lead compounds in experimental animal models and new therapeutic approaches (M36).

S7.4 Cascade calls for funding
Tentative topics for the cascade calls that will be implemented to complement S7 activities are:

- Role of the blood brain barrier and vascular inflammation in the regulation of neuronal plasticity and pathogenesis of diseases of the nervous system
- Role of nervous system meninges and choroid plexus during neuroinflammation.
- Metabolic and epigenetic drivers of the immune response in neurological disorders
- Neural control of hematopoiesis and immune responses in neurological psychiatric disorders.

B3.1 Main Milestones

The Main Milestones chart, as requested by the call, shows the main milestones extracted from the Work Plan to highlight the main check points of the WPs of all Spokes.

GANNT		1st year												2nd year												3rd year											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
SPOKE 1	**NEURODEVELOPMENT, SOCIAL COGNITION AND INTERACTION**																																				
WP1	M1.1 Construction and testing of the experimental setups and data analysis pipelines										M																										
	M1.2 Final data set available for all tasks and quantitative results																																			M	
WP2	M2.1 Experimental design and setup validated, data analysis pipeline developed										M																										
	M2.2 Final data set for all tasks and quantitative analyses results																																			M	
WP3	M3.1 Genetic analysis and set-up of cell/tissue-based assays accomplished																	M																			
	M3.2 Screening of compound/molecules accomplished																																			M	
WP4	M4.1 Complete psychobiological profiling and biomarker identification																																			M	
SPOKE 2	**NEURONAL PLASTICITY AND CONNECTIVITY**																																				
WP1	M1.1 Single molecule microscopy and force microscopy in single synapses																							M													
	M1.2 Implementation of new intervention strategies for neurological disorders																																			M	
WP2	M2.1 Multiscale models of brain circuits developed and applied to Digital Brain Twins																	M																			
	M2.2 Neuromorphic technologies for novel Spiking Neural Networks, ...																	M																			
	M2.4 New AI models designed																	M																			
WP3	M3.1 EEG analysis of brain connectivity via graph theory methods																							M													
	M3.4 Mouse model established . Ex-vivo gene expression pipeline established																							M													
WP4	M4.1 Validation of the proposed algorithms and pipelines																							M													
	M4.3 Simulations and modelling of multimodal connectomes																							M													
	M4.6 Acquisition of longitudinal PET/MRI data.																							M													
SPOKE 3	**NEURONAL HOMEOSTASIS AND BRAIN-ENVIRONMENT INTERACTION**																																				
WP1	M1.1 Number of 2D and 3D neural models validated																	M																			
	M1.4 At least 2 novel therapeutic strategies developed and validated in vitro																																			M	
	M1.5 At least 2 novel therapeutic strategies developed and validated in vivo																																			M	
WP2	M2.1 Identification of regulatory mechanisms in organelle homeostasis																	M																			
	M2.2 Screening of compound/molecules accomplished																																			M	
WP3	M3.1 Epigenomic and genomic profiling of patients' derived cells									M																											
	M3.2 Establishment of cell and animal models																	M																			
	M3.5 Epigenetic drug identification and assessment efficacy																																			M	
WP4	M4.1 Generation of iPSC lines and functional 2D and 3D culture										M																										
	M4.3 Behavioural, genetic and functional data acquisition																							M													
	M4.4 Gut microbiota analysis in patients, and markers identification																							M													
SPOKE 4	**PERCEPTION AND BRAIN-BODY INTERACTION**																																				
WP1	M1.2 Human organoid establishment																							M													
WP2	M2.2 Standard Operative Procedures SOPs for sample collection and sharing										M																										
	M2.3 Set up of system biology and network medicine methods														M																						
WP3	M3.1 Conclusion of the data collection necessary to feed modeling																	M																			
WP4	M4.2 Preparation of a first prototype for each task																	M																			
	M4.3 Preparation of the final prototype for each task																													M							
SPOKE 5	**MOOD AND PSYCHOSIS**																																				
WP1	M1.2 Digital Clinical Service Platform deployed and operating across the spoke										M																										
	M1.3 Standard operating procedures updated with the new scientific evidence																																			M	
WP2	M2.2 In vitro neuro-glial differentiation of Muse stem cells obtained from patients																			M																	
	M2.3 Analysis of key molecular pathways in cells differentiated from Muse cells of patients																																			M	
WP3	M3.1 Defining a database of genetic data shared across the spoke										M																										
	M3.2 Integrating genetic data with CNV/SV identification																													M							
WP4	M4.2 Neuroimaging genetic assessment of patients with a diagnosis of schizophrenia																							M													
	M4.5 Evaluation of clinical utility of multimodal machine learning solutions																																			M	
WP5	M5.2 Completion of genetic analysis																	M																			
	M5.4 Completion of the validation RCT																																			M	
SPOKE 6	**NEURODEGENERATION, TRAUMA AND STROKE**																																				
WP1	M1.1 Development of different complexity models																	M																			
	M1.3 Development of neuroprotective neurotrophic molecules																													M							
	M1.4. Engineering of biomimetic drug delivery platforms																													M							
WP2	M2.1 Characterization of population and identification of circulating biomarkers																	M																			
	M2.3 Virtual Brain model of the prodromal stage of AD																							M													
	M2.5 Evaluation of training efficacy by analysis of functional connectivity by fMRI data																													M							
WP3	M3.1 Validation of experimental models of cerebral ischemia																							M													
	M3.3 Development of innovative strategies for NDDS																							M													
WP4	M4.1 Recruitment of experimental population and data acquisition																							M													
	M4.4 Correlations between genetic scores and imaging data																													M							
SPOKE 7	**NEUROIMMUNOLOGY AND NEUROINFLAMMATION**																																				
WP1	M1.1 Identification of novel molecular mechanisms of immune and CNS cell dysfunction										M																										
	M1.2 Characterization of leukocyte-mediated neurotoxicity in vitro										M																										
WP2	M2.1 Identification of novel immune cell pathways to neuroinflammation										M																										
	M2.3 Obtain indication on new drug targets with bioinformatics approaches										M																										
WP3	M3.1 Identification of disease-specific signatures										M																										
	M3.3 Identification of disease-specific signatures																							M													
WP4	M4.2 Identification and development of promising drug candidates																					M															
	M4.4 Development and assessment of nanoformulations																										M										
WP5	M5.1 Screening of new compounds in advanced cellular models																											M									
	M5.2 Validtion of lead compounds in animal models and new therapeutic approaches																																				M

Table B4. MNESYS Gantt chart with milestones

B.4. Budget

The budget has been implemented by taking into account the activities that will be carried out overall and the respective costs with a breakdown by single Spoke and Partner participating to the consortium. **The cost breakdown identified by intervention fields as indicated in the call (i.e., 022, 023, 006) are all related to the field 006 (100%). The cost by territory has been respected and the total cost for the regions of the South is 40,5% of the total costs.**

B4.1 Budget summary per spokes

The total budget for the whole program is 149.129.400 euro; of those 11 million euro have been allocated to the activities of the HUB to the implementation, execution, monitoring, coordination and management of the extended partnership. The remaining 129.129.400 euro of the budget are divided among the spokes as reported in the Table below.

Spoke	Title	Lead	Personal-month per year critical mass	New reserachers RTDa	Budget "cascade funding call"	Total
S1	Neurodevelopment, social cognition and interaction	UNIPR	145	20	3.000.000	**15.652.800**
S2	Neuronal Plasticity and Connectivity	UNICAMPANIA	177	21	6.500.000	**21.156.400**
S3	Neuronal homeostasis and Brain-environment interaction	UNINA	231	26	7.500.000	**24.828.250**
S4	Perception, movement and brain-body interactions	UNIBO	152	23	3.000.000	**15.130.000**
S5	Mood and Psychosis	UNIFE	150	20	2.000.000	**14.262.750**
S6	Neurodegeneration, trauma and stroke	UNIGE	192	20	4.500.000	**20.856.400**
S7	Neuroimmunology and Neuroinflammation	UNIVR	169	20	3.000.000	**17.242.800**
Total			**1.216**	**150**	**29.500.000**	**129.129.400**

Table B5. Budget per spoke

B4.2 Budget summary per Partners

The budget subdivision for each Partner is reported in the Table below. As reported in the Table, the contribution for the Partners in the South (i.e. UNINA, UNICAMPANIA, UNICZ, UNIBA, SYNLAB, TIGEM, DOMPE' and TAKIS) is 56.751.250 euro.

Partner	Legal Name	Short Name	Number person-month per year	Number RTDa	Budget for "Cascade funding call"	Budget Partner
HUB		**MNESYS SCARL**				**11.000.000**
P1	UNIVERSITA' DEGLI STUDI DI GENOVA	UNIGE	111	15	4.500.000	12.848.850
P2	UNIVERSITA' DEDGLI STUDI DI PAVIA	UNIPV	51	9		4.718.300
P3	UNIVERSITA' DEGLI STUDI DI VERONA	UNIVR	61	11	3.000.000	7.991.950
P4	UNIVERSITA' DEGLI STUDI DI FERRARA	UNIFE	48	8	2.000.000	5.707.450
P5	ALMA MATER STUDIORUM - Università di Bologna	UNIBO	82	13	3.000.000	10.008.900
P6	UNIVERSITA' DEGLI STUDI DI ROMA TORVERGATA	UNITOV	88	12		6.532.300
P7	UNIVERSITA' DEGLI STUDI DI NAPOLI FEDERICO II	UNINA	175	20	7.500.000	18.810.600
P8	Università degli Studi della Campania "Luigi Vanvitelli"	UNICAMPANIA	103	13	6.500.000	15.005.400
P9	Università degli Studi "Magna Græcia" di Catanzaro	UNICZ	55	11		6.207.850
P10	UNIVERSITA' DEGLI STUDI DI BARI ALDO MORO	UNIBA	113	15		10.667.600
P11	UNIVERSITA' DEGLI STUDI DI PARMA	UNIPR	42	9	3.000.000	7.256.850
P12	UNIVERSITA' DEGLI STUDI DI FIRENZE	UNIFI	54	10		5.416.800
P13	IRCCS Ospedale Policlinico San Martino	HSM	42	0		1.715.900
P14	IRCCS Istituto delle Scienze Neurologiche di Bologna	ISNB	30	0		1.070.450
P15	Scuola Superiore Sant'Anna di PISA	SSSA	21	4		1.576.550
P16	Ospedale Pediatrico Bambino Gesù	OPBG	30	0		1.215.650
P17	European Brain Research Institute Rita Levi-Montalcini	EBRI	15	0		1.173.300
P18	IRCCS SYNLAB SDN	SYNLAB	23	0		1.350.500
P19	Fondazione Telethon ETS	TIGEM	15	0		1.819.050
P20	Fondazione Don Carlo Gnocchi ONLUS-IRCCS	FDG	27	0		1.036.550
P21	IRCCS San Raffaele	SR	24	0		1.116.150
P22	Dompè Farmaceutici Spa	DOMPE'	3	0		1.890.650
P23	Alfasigma SpA	ALFASIGMA	3	0		1.798.800
P24	ASG Superconductors spa	ASG	0	0		1.193.400
P25	Takis Srl	Takis	0	0		999.600
Total			**1.216**	**150**	**29.500.000**	**140.129.400**

Table B6. Budget per partner

B.5. Equal gender opportunities

In agreement with the United Nations Sustainable Development Goals, in particular with n. 3 (Good Health and well-being), n. 4 (Quality education), n. 5 (Gender Equality), n. 8 (Decent work and economic growth), n. 9 (Industry, innovation and infrastructure), n. 10 (Reduced inequalities), and n. 17 (Partnerships for Goals), and inspired by the postulates stated by the Women's Forum for Economy and Society (WFES), **MNESYS partnership envisages a world where women are equal actors and decision-makers across the spheres of politics, business and society**. It envisages a gender perspective and aims at inclusive solutions to its social and economic challenges. The path towards the **Zero Gender Gap** in economy and society follows a mix design between the top-down measures integrated in their governance by main public and private stakeholders. In fact, the WFES claims to address, for 10 years in G20 countries, 3% of the global corporate tax to balance gender in scientific and technological education, equal to 150 billion dollars, in the general benefit. In parallel, bottom-up voluntary adoption of good practices towards gender equity are proposed. **The MNESYS governance and all the researchers involved in MNESYS proactively acknowledge the principles on equal gender opportunities, as well as the European Commission Gender Equality Strategy for 2020-2025 and the strengthened provisions included in the Horizon Framework**. All the activities and actions described below will be periodically monitored by MNESYS governance, as reported in the hub work-packages, to ensure compliance and continuous improvement. The MNESYS project will address gender balance and woman empowerment at several levels, meeting the five dimensions of the Gender Equality Index (GEI): female leadership and talent pipeline, equal pay, inclusive culture, anti-sexual harassment policies and branding pro-women. MNESYS voluntary adhesion to GEI principles will be implemented through the three years' time span of the project and is meant to become a tool for an inclusive supply chain. In its starting stage, MNESYS Board of Directors and Scientific Committee are built according to the principle of gender equity. In the proposal we guarantee the involvement in the leadership of the project both women and young scientists. In the project, **two designated spoke leaders are women** and at least **3 out of seven of the young scientists** involved in the Scientific Committee **will be women**. Regarding the PIs, 141 researchers out of 350 are women. Moreover, at last 40% of the 150 fixed-term researcher (RTD a) and of the 150 PhD students we expect to hire in the project will be women. A gender equality plan (GEP) for the MNESYS project will be derived from UNIGE, adapted to the needs of the consortium and published, together with links to the GEPs of the partners of the consortium, in the project website. In addition, the **involvement of neurological and psychiatric advocacy organisations**, through PAC, at all decisional levels across the bodies of the partnership HUB will strengthen our efforts and give more leverage to this program ensuring that **the patient community will provide their own expertise and priorities creating shared objectives**.
MNESYS believes that raising social awareness on increasing science and technological education will provide better opportunities towards advanced, inclusive, and sustainable jobs. However, this rationale is hindered by a gender bias in education, conveyed by cultural roots and social expectations. With the support of the Education and Communication Committee (ECC), **young women's awareness and mentoring will be particularly attended to**. The orientation activities will be mainly addressed to teenagers through seminars, and activities dedicated to fill the gender bias. In this pervasive action, the synergic engagement of middle schools, University and companies will be the most effective tool. Finally, taking advantage from the contiguity of companies, public research entities and University, specific actions of targeted communication/formation on business creativity, case studies on resilient/intuitive solutions carried out by women will be designed.

B.6. Involvement of scholars who have obtained their PhDs from no more than 10 years and attraction from other EU and non-EU countries

One of the MNESYS objectives is to impact on the leading role of young scientists and on attracting young researchers from EU and non-EU countries to Italy. The HUB and all the Spokes will contribute synergistically to this objective. To involve and retain scholars who have obtained their PhD in the last 10 years (i.e. "young researchers"), MNESYS consortium will be guided by three basic principles, i.e. fairness in recruitment, acknowledgment of the role of young researchers in the project and their empowerment to ensure their satisfactory career development. Regarding recruitment, MNESYS consortium will adopt an approach and a development strategy that will ensure a fair and transparent selection and judge the merits of the candidates according to their potential, previous qualifications and experience. The recruitment process, open to all EU and non-EU nationals,

will follow the guidelines set out in the EC's Charter for Researchers and Code of Conduct for the Recruitment of Researchers, and it will be based on the European policy of non-discrimination and equality between women and men in the Treaty of the European Union (Articles 2 and 3). It will be widely publicized to attract top-level candidate irrespectively from their nationality; the candidate selection criteria will include research excellence, international research experience, research publications, growth potential and motivation. The MNESYS consortium plans to recruit at the start of the project **150 young researchers with fixed-term contracts as researchers (i.e. RTD-a contracts) and 150 new PhD students** to empower young scientists, enhance diversity and broaden the skill-set available in the critical mass of the consortiums and to foster their growth through their exposure to all phases of research.
Moreover, beside these actions, the consortium plan to further promote the attraction of high-quality young scientists through an independent call for international grants to be awarded to young researchers from EU and non-EU countries to participate in MNESYS activities. The grants will finance the salary and a budget for research and development activities focused on strategic topics for the development of each of the Spokes, which will highlight the multidisciplinary flavour of MNESYS topics and communicate their innovation potential. **At least one international grant for each spoke** is foreseen. To guarantee the effectiveness of this action, the grant will be integrated with specific initiatives to support the hosting of young researchers. An initiative of great importance for the achievement of the goal is the participation of the applicant, the University of Genova, in the European Ulysseus University (https://ulysseus.eu/). Ulysseus is a European university, one of 41 transnational alliances promoted by the European Commission with the aim of promoting European identity and values and revolutionizing the quality and competitiveness of higher education in Europe. All these actions, to ensure recruitment, will be supported by a **specific communication campaign to promote the identity and aims of the partnership** in the main universities and research centres operating in the MNESYS main field. The number of young researchers involved in the project will be measured through specific impact indicators.
To ensure the acknowledgment of the role of researchers who have obtained their PhD in the last 10 years through the project, the MNESYS consortium will employ a proactive stance, exemplified by the presence of activities, in the Hub work-packages, aimed to foster the role of young researchers and innovators in the project. Firstly, as reported in Sect. B1, **half of the representatives of the Spokes in the Scientific Committee will be represented by young researchers**. Moreover, the MNESYS governance will proactively promote an active role of young researchers in the project, through the organization of symposia and workshops led by young researchers, the monitoring of the fair representation of young scholars in the scientific products of the consortium including papers and conference communications and periodic evaluations from the recruited researchers on their satisfaction with their involvement in the activity of the consortium.
Regarding the empowerment of young researchers, the MNESYS consortium will also offer a personalized **Career Development Plan** which will cover: (i) short and long-term development goals, (ii) training (including task-oriented research skills, generic research skills, communication, IPR, ethics, grant writing, commercial exploitation of results, and research policy) and (iii) work-life balance assessment.
We believe that through the aforementioned proactive stance on recruitment, acknowledgment and empowerment, the MNESYS researchers will experience a wide range of interdisciplinary and intersectoral training and research experience in Neuroscience and Neuropharmacology ensuring their professional growth and their satisfaction with research in line with the observations of the European Directorate General for research and innovation (for example in the MORE3 study: Support data collection and analysis concerning mobility patterns and career paths of researchers studies, 2017).

B.7. Involvement of companies in the project

Industrial enterprises will contribute to the Consortium in 3 main ways: (a) **embedding into the WP activities experienced industrial scientists** that may contribute in designing the experiments so to generate original results amenable to the standardization and scaling up typical of industrial applications and, more important, with the potential to generate patents and thus create value across the wider production chain; (b) **providing the appropriate knowledge in area traditionally not attended by academic researchers**, i.e., Intellectual Property, Regulatory Strategies and requirements, capacity to identify the commercial values of the invention and help in preparing business plans and pitch presentations by working in interdisciplinary Teams with the academic members. In fact, the industrial enterprises, based on their available expertise & resources, will help the 'inventor' academic scientists to develop skills and awareness in these 'industrial' domains, with the aim to expand the capacity to collaborate also in the future; (3) **acquiring some patents and commit to engage in the development of this innovation, and/or contributing pre-competitively to the generation of innovative start-up** featuring

some of the academic scientists interested. In addition, we have designed in the framework of the bodies of the partnership the Technology Transfer Committee (TTC), coordinated by the SPOKE leaders, which will include senior industry/biotech strategy managers of the consortium enterprises and external specialists in innovation. The TCC will review the opportunities arising from the scientific results generated within the various WP, opportunities based on (1) originality and (2) possibility to produce patents out of these results. In fact, around the third year of activity it is expected from the WPs the generations of patents aimed to a specific intended use of biomedical relevance. The TCC will prioritize the proposed opportunities, identify a project leader for each opportunity that will coordinate external consultants the development of a high-level business plan and a presentation 'pitch', according with their specific domain of applications (e.g., a biomedical device, a diagnostic, a novel pharmacological agent for the treatment of a disease, a discovery platform, a service biomedical platform, etc.). The enterprises that are members of the consortium will have a priority in acquiring the intellectual property (IP) of interest from the Consortium for their pipeline, but also the duty to contribute pre-competitively to progress other non-selected opportunities into other business-relevant structures, i.e., working with the TTC to connect with Start Up Incubators, with other Biotech, Pharma or Medical Device companies of the Italian Ecosystem that could be interested in the IP generated by the Consortium. Evidence of a *bona fide* actual attempt to industrially develop the prioritized opportunities may be considered for the full reporting of the present PNRR Consortium investment, by providing a status report at three years from the end of the current project.

The collaboration of the industrial partners will allow to provide innovation, knowledge transfer and potential long-term services and health system improvement in key fields of neuroscience and neuropharmacology in the context of the priorities of the call.

In this context, the collaboration with **ASG** will be instrumental in the development of novel imaging approaches for the development of diagnostic and prognostic markers for early diagnosis for patients' stratification according to inter-individual pathological differences and for personalized treatment. Indeed, ASG is a leader in the field of MRI imaging with current projects in Ultra High Field (UHF) and portable MRI and thus well complements the clinical and research expertise in neuroimaging and biomarkers present across multiple spokes of MNESYS, with a focus on the development of neurodegeneration (within S6) and of connectivity markers (within S2) that could be easily applicable to clinical practice. The academic-industrial partnership with ASG will thus allow to leverage the fundamental and translational research competencies of the Universities and the Research Partners with the knowledge transfer and marketability vision of an established enterprise to ensure the exploitation of imaging biomarkers research conducted in MNESYS across the value chain and maximize their potential future impact on health systems.

The collaboration with **DOMPE'** will focus on a key area for Neuroscience and Neuropharmacology, namely the identification of treatment strategies for conditions with high social burden such as neuroinflammatory and neurodegenerative conditions. To this aim DOMPE' will play a key role in the activities of the Partnership, for example regarding drug repositioning in this context the co-crystal approach, pursued jointly by DOMPE' and by the academic partners in S7 or regarding the evaluation of the therapeutic relevance of physiological compounds such as the academic-industrial collaboration in S6 regarding the *in vitro* and *in vivo* studies addressing the therapeutic potential of exogenous neurotrophins in the brain.

The collaboration with **TAKIS** will be centered around the use of animal models and innovative drug delivery approaches to develop novel and personalized approaches to brain tumors, which include high-mortality conditions such as glioblastoma with a median survival time from diagnosis less than one year as well as to neuroinflammatory conditions of the central nervous system. The collaboration between TAKIS and the academic partners in S3 and S7 will thus allow to provide value to key areas of neuroscience and neuropharmacology identified in the Call.

The collaboration with **ALFASIGMA** will be focused on the evaluation of the potential of leveraging the gut-brain interactions to develop improve the understanding of the determinants of brain disorders for brain disorders as well as to develop innovative approaches to drug delivery. More in detail, the collaboration between ALFASIGMA and the academic partners in S2 will be focused on a multi-omic approach to gut microbiota fingerprints across brain disorders such as Alzheimer's Disease and epilepsy, the collaboration in S5 will be focused on celluar approaches to identify novel treatment targets for mood and psychotic disorders. while the collaboration in S6 will be focused on the development of novel drug delivery approaches to tackle stroke, i.e. a highly prevalent condition in the general population (2017, for example, there were 1.12 million incident strokes in the EU [Wafa et al., 2020]), which is estimated to increase by 27% between 2017 and 2047 in the European Union (Wafa et al., 2020).

B.8. Qualitative-quantitative indicators proposed for monitoring activities and for ex-post evaluation

In line with the principles reported in the Horizon Europe Regulations and the European Directorate-General for Research and Innovation, (A new horizon for Europe: impact assessment of the 9th EU framework program for research and innovation, Publications Office, 2018), **monitoring activities for the MNESYS project will be structured around three building blocks, namely (i) annual monitoring of the performance, (ii) fully-fledged (meta)-evaluations of performance at mid-term and ex-post (upon completion) and (iii) continuous collection of management and implementation data**. Moreover, indices will be collected using a time-sensitive approach to monitor key management and implementation data and the key impact indicators on the scientific, societal and economic pathways.
All the monitoring actions will be performed using a collaborative approach between the MNESYS governance and each partner, and it will be informed by insights from internal and external stakeholders involved in the project. The responsibility for monitoring will stay with the governance of MNESYS including the ISAB. All monitoring activities will rely on the principles of ensuring accountability, improving performance, and allowing proper documentation availability and mutual learning opportunities.
Regarding the monitoring of key management and implementation data during the project, we will focus on the **key performance indicators (KPI)** reported in the figure below (Fig. B3).

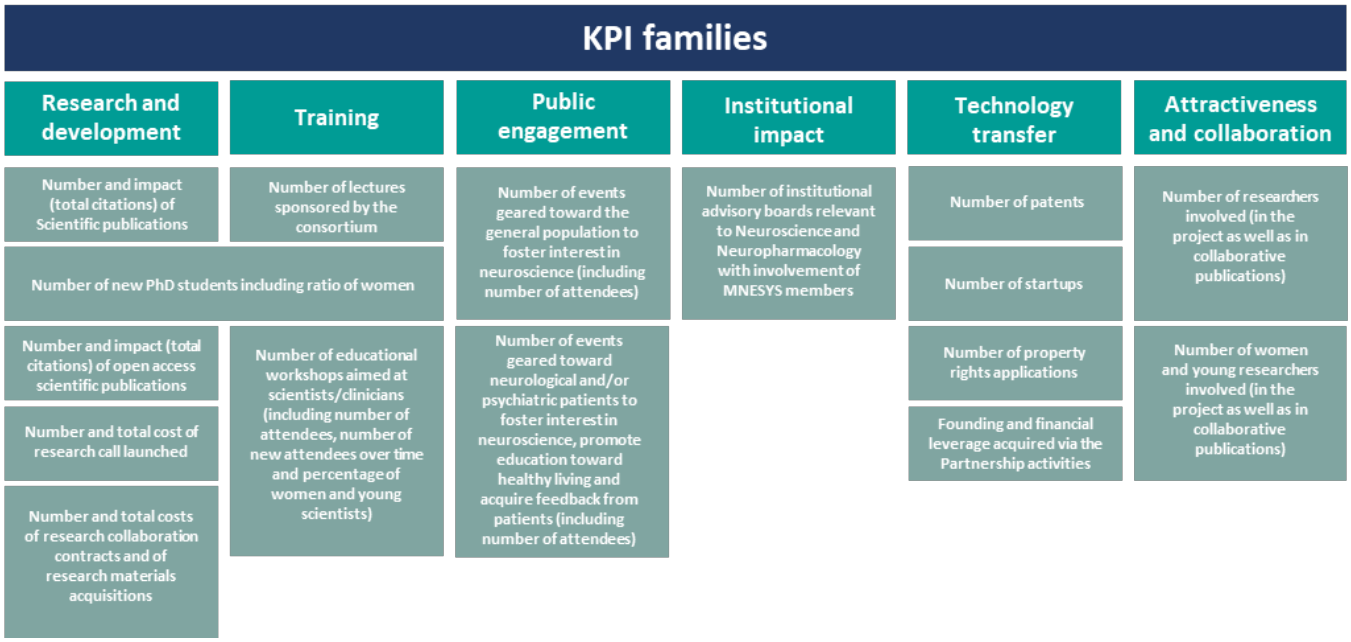

Fig. B3: KPI families and main KPI identified per each family.

All KPIs will be collected for each spoke individually and collectively for all the Partnership. Moreover the same KPIs will be monitored focusing on the key themes described in the Call for Neuroscience and Neuropharmacology: collaboration of fundamental and applied research (for example for the KPI scientific publications we will monitor the ratio of the publications based on the collaboration between fundamental and applied neuroscience over the total number of publications), neural networks, brain-body and brain-environment interaction, animal models, new technological approaches for the selective administrations of drugs, validation of novel biomarkers, validation of novel predictive models of disease, novel pathogenetic models, novel and reproposed pharmacological approaches and novel approaches to patients stratification, as well as the number of research products with academic and industrial co-authors. This granular, analytic approach to KPI assessment will assure the ability of the Partnership to have a significant impact of all the key themes of the Call. Each research products will be evaluated individually and assigned to any of the aforementioned categories by the SD and the SC, in collaboration with the ISAB.
The quantitative indices will be associated with four qualitative surveys:

- **A researchers' survey**: aimed to assess in the researchers, recruited through MNESYS initiatives, the professional satisfaction levels and their perceived growth as well as to assess the inclusiveness of the work environment.

- **A patients' survey**: aimed to assess in the patients involved in the MNESYS experimental activities and in their advocates, the perceived usefulness of MNESYS research on their health conditions as well as to help the PAC to provide suggestions regarding the perceived relevance for patients of MNESYS activities.
- **A peer researchers' survey**: aimed to assess in the relevant national and international scientific networks the perceived impact and relevance to the field of the MNESYS activities.
- **An industrial partners' survey**: aimed to assess in the industrial partners the progress of technology and knowledge transfer between the academic and industrial components of the Partnership.

All surveys will be used to complement and inform the KPI-based analyses and to gather data regarding the progress of the Partnership, with a focus on the assessment of the progressive strengthening of competencies; knowledge, and technology transfer; and the integration of technologies within social and health systems and services.
All data will be collected annually and examined critically by the scientific board and the ISAB in order to draft and disseminate annual reports to the founding agencies as well as to all stakeholders. The PAC, the industrial partners and the reference national patients' advocacy groups will be consistently involved in the process of internal evaluation of the project also to allow to point early on potential criticalities and execute corrective measures.

C. PROGRAM IMPACT

C.1. Analysis of the impact of the results on the scientific, economic and social system at the national and international level, focusing in filling the gaps defined by the NRRP

C.1.1 Introduction

The added value of MNESYS Partnership at the scientific, societal and technological level is multifaceted. Here we shall start focusing on the predicted scientific, social and technological values added by MNESYS thanks to its key characteristics. We will use a top-down approach, trying first to envision an overall quantification of the impact of MNESYS on society and then moving toward a more detailed, even if based on examples, description of its scientific, social, economic and technological impacts (section C1.3 for a description of impacts based on the Horizon Europe "*Key Impact Pathways*" approach and section C3.1 for a detailed description of the technological impacts, based on the planned Technological Readiness Levels). We will then describe the impact of MNESYS on relevant stakeholders' groups and on the the key areas identified in the NRRP and the positioning of the Italian System. After the analyses of impact, we will describe the dissemination, communication and exploitation plans for MNESYS, with the aim to describe the key measures aimed to maximise the impact including the policies for open access to publications and data.
From a methodological point of view, we will focus on both the effects on society and on MNESYS partners and their value chain. Regarding societal impacts we will describe the possible long-lasting effects obtained thanks to MNESYS outcomes and their possible long-term assessments using quantitative indices of official health and economics statistics (such as Eurostat).

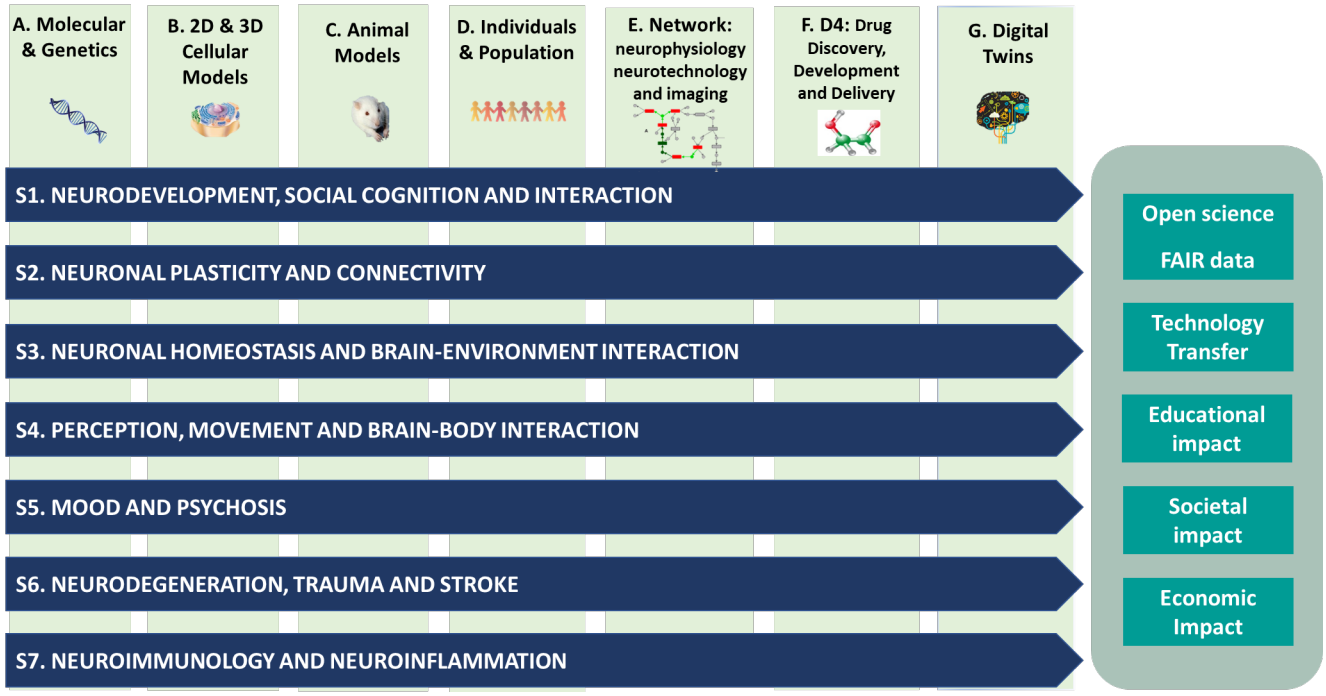

Fig C1: Overview of MNESYS main impacts

C.1.2 A case-study projection on MNESYS added value by 2050

To quantify the value for the national and international community and for the population at large derived from the founding of the MNESYS partnership, the first issue is the description of the impact of a multi-scale, inter-disciplinary approach to the scientific understanding and the clinical care of neurological and psychiatric diseases thanks to the scientific and industrial advancements provided by MNESYS. The key scientific underpinning of MNESYS architecture is represented by its focus on **acknowledging the complexity** (i.e. recognizing that brain health derives from the interaction in different scales of multiple physiological and pathological elements) intrinsic to brain physiology and pathology and thus **using an array of synergic experimental approaches to identify targets to improve diagnosis, prognosis, and treatment**. Using a top-down approach it is possible to

use an **analogy model** to try to quantify the possible overall long-term impact on clinical care due to the paradigm shift proposed in MNESYS and its multi-scale approach, focusing on the model of congestive heart failure (CHF), a condition which has seen in the last 50 years a significant delay in the onset of clinical symptomatology due not to a single pharmacological breakthrough, but to multiple changes in prevention, diagnosis and treatment. CHF has been proposed as a good epidemiological model to study the possible impact of multi-disciplinary interventions on complex diseases, including Alzheimer's Disease (Sloane et al., Annu Rev Public Health, 2002), one of the key targets of MNESYS.
The overall approach of MNESYS, **based on the integration of multiple experimental scales**, from the cellular level to the patient population and the development of digital twin models, with the aim to develop diagnostic and prognostic biomarkers, to understand the interaction between the environment and the brain and to identify and model new pathological pathways to improve therapy, is well suited to replicate the impact observed in CHF. According to Sloane and colleagues, the application of the CHF model to Alzheimer's Disease (here used as an example of the expected impact of MNESYS) would be associated with delay in symptoms onset of 6.5 years a reduction of AD prevalence by 2050 of around 35%; given the estimated cost for AD in the EU of 342 billion euros/year by 2050 (Petra et al., JAD 2016), this prevalence change will be associated with a cost reduction of 119,7 billion euros/year by 2050; even if only 1% of the aforementioned change was due to the multi-scale approach of MNESYS, the added value of the activities of the Partnership, for AD, would amount to 1,2 billion euros/year by 2050, with a 10x societal return for the initial investment.

C.1.3. Scientific, societal, and economic impact of MNESYS key components

Given the methodological, biological and clinical heterogeneity of the research projects included in MNESYS it is not feasible examine in detail the scientific, societal and economic impact of each WP, also taking into account their complex interactions. To tackle this, we will describe using both quantitative and qualitative indices, the impact on two key facets of MNESYS architecture, which are also described as desired impacts of the specific themes for the Neuroscience and Neuropharmacology extended partnership, i.e. the development of biomarkers for patients' stratification and of novel approaches to treatment including drug repositioning. Impacts will be evaluated using the *Key Impacts Pathways* approach, in line with the European Commission proposal for systematic reporting of Horizon Europe.

C.1.3.1. Methodological considerations

A first methodological consideration regards the assessment of MNESYS impact on health at the population level, which represents a significant fraction of the long-term societal value generated by the partnership. Indeed, the presence in MNESYS of multiple intervention areas that could impact on clinical care, such as improved understanding of brain physiology and pathology, novel biomarkers, new druggable targets and novel computational models including the digital twin approach, suggests that MNESYS, in the long-term, will impact on clinical practice at multiple levels. We thus decided to use a single synthetic indicator of the impact of MNESYS activities on health, i.e. changes in quality-adjusted life-year (QALY), a generic measure of disease burden, including both the quality and the quantity of life lived, widely used in economic evaluation to assess the value of interventions.
A second methodological consideration concerns the quantification of long-term impacts that could be associated with MNESYS activities. While the assessment of long-term impacts relies on the use of official societal, economic and health statistics, in the years following the end of the project released by funding agencies, institutional bodies and policymakers, it is possible to define in advance the project outcomes' indicators that could be measured at the end of the project to be used in correlation analyses with the measured long-term impacts in the following years.

Expected impact	Related spoke	Impact during the project	KPI (during the project)	Public	Impact after the project
KPI family: Research and Development					
Enhance scientific resources for the research and clinical communities addressing the priorities of NRP	S1/S2/S3/S4/S5/S6/S7	Better understanding of neurophysiology in health and disease	At least 10 publications in 1st quartile open-access journals regarding healthy brain function and disease for each related spoke	Y	Knowledge to steer future research
	S1/S2/S4	Analytical pipelines and models published in open source repositories	At least 3 pipelines shared with research community for each related spoke	Y	Periodic updates from the bioinformatics community
	S2/S6	Novel MRI acquisition protocols and PET tracers.	At least 2 methodological protocols published or presented for each related spoke	N	Commercial use
	S1/S2/S3/S4/S6/S7	Animal models	Ideation/refinement/validation in preclinical contexts, described in methodological papers, at least: 1 model of stress induced disease (S1), 1 model of brain plasticity (S2), 1 model of neuronal homeostasis and interactions with environment (S3), 2 models of cognitive and motor deficits (S4), 1 model for neurodegenerative disorders (S6) and 1 model for neuroimmunology (S7).	Y	Research use
	S1/S2/S6	Digital Twins	Models of brain circuits and Digital Brain Twins in health and disease (S2, at least 2). Digital twins of upper limb musculoskeletal systems (S6, at least 2) for the definition of neurorehabilitation	Y	Research use of the tools
	S1/S2/S3/S5/S6	Molecular/cellular models (2D and 3D)	At least 2 models developed for future commercial and research applications for each related spoke	Y	Define which model can be commercially exploited
	S3/S6	Characterization of gut microbiota and its modulation	At least 1 microbiota based prognostic marker for each related spoke	Y	Clinical validation
Societal impact Improve diagnosis and treatment of neurological diseases	S1/S2/S4/S5/S6/S7	Novel imaging & EEG biomarkers	At least 2 candidate biomarkers for each related spoke presented to international audience	Y	Validation of the biomarkers in larger cohorts and use in clinical trials
	S1/S5/S6/S7	Novel "omics" biomarkers	At least 3 biomarkers for each related spoke, presented to international audience	Y	Validation in independent cohorts and use in clinical trials
	S1/S2/S5/S6/S7	Potential therapeutic strategies targeting selected molecular pathways	At least additional candidate compound/therapeutic strategy for each related spoke	N	Development plan for each of the therapeutic strategy identified
	S1/S2/S4/S5/S6	Novel computational and AI models to	At least 1 computational/AI model for each related spoke	Y	Models validation

Expected impact	Related spoke	Impact during the project	KPI (during the project)	Public	Impact after the project
		support diagnosis and patient stratification			
KPI family: Public engagement					
Strengthen the uptake of the innovation from the society	HUB	Patient engagement	At least 2 meetings involving patient organizations	Y	Patients advocacy groups promoting the adoption of innovation
	HUB	General public engagement	At least 6 press releases for the general public	Y	
KPI family: Training					
Strengthen human capital	All Spokes	PhD students (including industrial doctorates) involved in MNESYS research activities	150 PhD students involved in the project	Y	Increased opportunities for young researchers
	All Spokes	Lectures and educational workshops for scientists and clinicians	Each spoke will organize at least one lecture and one educational event each year, promoting the involvement of young professionals	Y	Increased expertise
KPI family: Technology transfer					
Generate Innovation based growth	All Spokes	IP protection for future exploitation	At least 8 patents applications during project lifetime	N	Product development
	All Spokes	Start-up creation	Feasibility for the creation of at least 2 start-ups exploiting research results generated in MNESYS and at least 4 meetings with potential investors	N	Start-up founding
KPI family: Attractiveness and collaboration					
Create more and better jobs	All Spokes	Jobs creation	Recruitment of new 150 researchers (RTDa).	Y	Increased opportunities for young researchers
	All Spokes	Involvement of researchers, especially young and female researchers	Young research and women involved in 90% of project publications and congress presentations	Y	

Table C1: Summary of the main project impacts (divided in impacts achieved during and after the project), in which spokes will be achieved, and KPI that will be used to evaluate each impact. The impacts are linked to KPI families described in section B8.

C.1.3.2. Case studies of scientific, societal, and technological impact of MNESYS: biomarkers

In Table C2 below is represented the expected long-term scientific, societal and economic impact of research on novel biomarkers identified during MNESYS activities according to the Key Impact Pathways approach. Development of novel biomarkers will allow to address different unmet needs in neuroscience and neuropharmacology described in the Call, including early diagnosis, improved prognosis and stratification of patients to guide personalized therapeutic approaches. Development of robust biomarkers, moreover, will have a significant impact on clinical trials design thanks to their use as surrogate markers and thus accelerating drug approval, especially for rare conditions. Development of novel biomarkers, based on the combination of multiple experimental methodologies and competencies is a strong component of MNESYS activities and it is included in a significant number of WPs in multiple spokes.

BIOMARKERS		LONG-TERM IMPACT		ADDED VALUE ASSESSMENT
		Description	Assessment	
Towards scientific impact	Creating high-quality new knowledge	Clinical validation of biomarkers based on MNESYS research	Number of biomarkers identified in MNESYS approved by regulatory authorities for clinical use. Size of the patient population that can benefit from MNESYS' biomarkers.	Reduction in QALY lost due to tardive diagnosis
	Strengthening human capital	Impact on neuroscience by researchers previously involved in MNESYS biomarker research	Number of researchers previously involved in MNESYS biomarker research who obtained Principal Investigator positions after the end of the project. Amount of neuroscience grant obtained.	Improvement of international standing of national neuroscience research. Increased value due to MNESYS training investment
	Fostering diffusion of knowledge and Open Science	Impact of MNESYS biomarker research published using open access	Long term citation record of MNESYS open science publications in biomarker research	
Towards societal impact	Addressing call-relevant priorities	Clinical validation of biomarkers according to the priorities of the call	Number of biomarkers identified in MNESYS approved by regulatory authorities for clinical use divided according to the priorities of the call. Size of the patient population that can benefit from MNESYS' biomarkers.	Diagnostic markers: reduction in QALY lost due to delayed diagnosis; Prognostic markers: improved prognostic accuracy; Therapeutic markers: Reduction in QALY personalized therapeutic plan
	Delivering benefits and impact			
	Strengthening the uptake of research & innovation in society	Awareness about novel biomarkers in practicing physicians, patients and their advocates	Events involving patients' organizations and general press publications, related to the introduction of novel biomarkers generated in MNESYS in clinical practice	Patients empowerment. Societal cultural change
Towards economic/ innovation impact	Generating innovation-based growth	Private enterprises and new jobs generated via exploitation of MNESYS biomarker research and their derivatives	Number of new enterprises and new jobs, obtained for the exploitation of MNESYS biomarker research products and their derivatives. Total revenues. Number of intellectual properties applications. TRL advancement	Increased total value of the biomarker private market. Availability of innovative products
	Creating more and better jobs			
	Leveraging investments in R&I	Mobilization of public & private investment mobilized to scale-up MNESYS biomarkers results	Amount of public & private investment mobilized to exploit or scale-up MNESYS biomarkers results	Increased Research and development expenditures in the biomarker sector. Increased availability in the marker of MNESYS-related biomarkers products

Table C2: Expected long-term scientific, societal and economic impact of research activities conducted in MNESYS for the discovery of novel biomarkers, and specific added value to specific targets groups, according to the Key Impact Pathways approach.

C1.3.3. Case studies of scientific, societal, and technological impact of MNESYS: novel approaches to treatment

In **Table C3** below is represented the expected long-term scientific, societal and economic impact of research on new treatments in MNESYS according to the Key Impact Pathways approach. MNESYS activities are well positioned to significantly improve, in the long term, the therapeutic strategies available for brain disorders, thanks to its multi-disciplinary focus. Indeed, in MNESYS the problem of developing novel therapies for neurological and psychiatric disorders is tackled from multiple point of views, with an emphasis on the identification of novel druggable targets, novel drug delivery approaches, and development of personalized treatment, leveraging on the combination of computational models of brain function and on multiple animal and cellular models.

THERAPY		LONG-TERM IMPACT		ADDED VALUE ASSESSMENT
		Description	Assessment	
Towards scientific impact	Creating high-quality new knowledge	Clinical validation of novel therapeutic targets based on MNESYS research	Number of MNESYS-based therapies included in RCT; number of MNESYS-bases therapies approved by regulatory authorities for clinical use. Size of the clinical population impacted by MNESYS-based therapies	Reduction in QALY lost due to lack of therapies
	Strengthening human capital	Impact on neuroscience by researchers previously involved in MNESYS therapeutic research	Number of researchers previously involved in MNESIS therapeutic research who obtained Principal Investigator positions in the years following the end of MNESYS. Amount of neuroscience grant obtained	Improvement of international standing of national neuroscience research. Increased value due to MNESYS training investment
	Fostering diffusion of knowledge and Open Science	Impact of MNESYS therapeutic research published using open access	Long term citation record of MNESYS open science publications in therapeutic research	
Towards societal impact	Addressing call-relevant priorities	Clinical validation of novel therapeutic targets based on MNESYS research according to the priorities of the call	Number of MNESYS-based therapies included in RCT divided by call priorities; number of MNESYS-bases therapies approved by regulatory authorities for clinical use divided by call priorities. Size of the clinical population impacted by MNESYS-based therapies	Reduction in QALY lost due to lack of therapies divided according to call priorities
	Delivering benefits and impact			
	Strengthening the uptake of research & innovation in society	Awareness of MNESYS-developed therapies in practicing physicians, patients and their advocates	Number of MNESYS-based therapies approved by regulatory authorities for clinical use discussed in generalized press and in patients associations official publications	Patients empowerment. Societal cultural change

THERAPY		LONG-TERM IMPACT		ADDED VALUE ASSESSMENT
		Description	Assessment	
Towards economic / innovation impact	Generating innovation-based growth	Private enterprises and new jobs generated via exploitation of MNESYS therapeutic research and their derivatives	Number of new enterprises and new jobs via exploitation of MNESYS therapeutic research products and their derivatives. Total revenues. Number of intellectual properties applications. TRL advancement	Increased total value of the biomarker private market. Availability of innovative products Assessment
	Creating more and better jobs			
	Leveraging investments in R&I	Mobilization of public & private investment mobilised to scale-up MNESYS therapeutic results	Amount of public & private investment mobilised to exploit or scale-up MNESYS therapeutic results	Increased research and development expenditures in the neuroscience therapies sector. Increased availability in the market of MNESYS-related therapeutic products

Table C3: Expected long-term scientific, societal and economic impact of research activities conducted in MNESYS for the identification of new treatments, and specific added value to specific targets groups, according to the Key Impact Pathways approach.

C.1.4 Environmental impact

The impacts of the MNESYS HUB research do not cause significant damage to the environmental objectives, pursuant to Article 17 of Regulation (EU) 2020/852 and its realizations consistent with the specific principles and obligations of the PNRR relating to the principle of "Do Not Significant Harm" (DNSH), as well as with the relevant EU environmental legislation and national regulations.

C1.5 Benefits for stakeholders

MNESYS activities and outcomes are relevant for several stakeholders, both directly and indirectly involved in the project. In the table below it is reported the breakdown of the qualitative and quantitative descriptors of the expected impacts of MNESYS over the long-term, also declined according to the H2020 strategic plan.
The min group of stakeholders is represented by patients with neurological and psychiatric diseases and their caregivers, as well as the general population. Brain disorders, including neurological and mental health conditions, are a significant cause of morbidity and mortality in Europe, representing in 2017 the cause of around a quarter of deaths due to non-communicable conditions and a third of the total of years lived with disability due to non-communicable disease in the same period (Raggi and Leonardi, Burden of brain disorders in Europe in 2017 and comparison with other non-communicable disease groups, J Neurol Neurosurg Psychiatry 2020). Regarding caregiver burden, it is not only associated with emotional facets but also to the reduction of their productive abilities outside the household; on average across OECD (Organization for Economic Co-operation and Development) countries, around 13% of people aged 50 and over report providing informal care at least weekly, disproportionately affecting women, especially in Italy (OECD Health at a Glance 2019 report, (https://doi.org/10.1787/4dd50c09-en). It is worthwhile to notice that the impact on patients, caregivers and society, also via the effect of policymakers, is in line with the proposed multi-dimensional impact of MNESYS on health (population education, risk factors assessment, tools for early diagnosis and novel treatment), which is the basis of the analogy-based value assessment reported in C1.2. We also expect a significant benefit for academic and industrial stakeholders, mainly driven by the multi-disciplinary core of the MNESYS consortium and its focus on experimental approaches such as computational modelling and digital twins and multi-modal imaging, which have seen in the last years a significant increase both in the number of intellectual properties applications filed by academic partners and a raise in market value, as detailed in section C2.

Benefits for stakeholders	Qualitative description of main benefits	Expected impact according to H2020 strategic plan 2021-2024	Quantitative indices (all focused on the impact due to MNESYS)
Patients	Improved understanding of brain disorders heterogeneity and risk factors	Cluster Health: Staying healthy in a rapidly changing society	QALY increase thanks to brain disorders burden reduction determined by increased awareness of risk factors
	Increased awareness in the general population regarding brain disorders reducing stigma	Cluster Health: Living and working in a health-promoting environment	QALY increase thanks to stigma-reduction
	Identification of novel druggable targets	Cluster Health: Tackling diseases and reducing disease burden	QALY increase thanks to brain disorders burden reduction determined by improved therapies
	Development of scalable candidate biomarkers for early diagnosis and prognostic assessment	Cluster Health: Ensuring access to innovative, sustainable and high-quality health care	QALY increase due to brain disorders burden reduction thanks to improved biomarkers
Caregivers	Improved understanding of brain disorders heterogeneity and risk factors	Cluster Health: Staying healthy in a rapidly changing society	QALY increase due to brain disorders burden reduction thanks to increased awareness of risk factors
	Increased awareness in the general population regarding brain disorders reducing stigma	Cluster Health: Living and working in a health-promoting environment	QALY increase due to stigma-associated combined effects thanks to increased understanding of brain diseases
	Improved characterization of the neural bases and treatment options for behavioral symptomatology across conditions	Cluster Health: Tackling diseases and reducing disease burden	QALY increase thanks to brain disorders burden reduction determined by improved therapies
	Advancements in the identification of the earliest symptomatology in progressive diseases	Cluster Health: Ensuring access to innovative, sustainable and high-quality health care	QALY increase due to brain disorders burden reduction thanks to improved recognition of disease progression
General population	Improved understanding of brain disorders heterogeneity and risk factors	Cluster Health: Staying healthy in a rapidly changing society	QALY increase due to brain disorders burden reduction thanks to increased awareness of risk factors
	Increased awareness in the general population regarding brain disorders reducing stigma	Cluster Health: Living and working in a health-promoting environment	QALY increase due to stigma-associated combined effects thanks to increased understanding of brain diseases
	Improved characterization of the modifiable risk factors for neurological and psychiatric disorders	Cluster Health: Tackling diseases and reducing disease burden	QALY increase due to brain disorders burden reduction thanks to increased awareness of risk factors
	Advancements in the identification of the earliest symptomatology in progressive diseases	Cluster Health: Ensuring access to innovative, sustainable and high-quality health care	QALY increase due to brain disorders burden reduction thanks to improved recognition of disease progression
Policymakers	Improved evidence of the risks factors and early symptoms of brain disorders to guide preventive medicine initiatives and policies	Cluster Health: Staying healthy in a rapidly changing society	QALY increase due to brain disorders burden reduction thanks to increased awareness of risk factors
	Novel biomarkers to quantify the impact of treatments on brain disorders to guide regulatory authority decision-making regarding	Cluster Health: Tackling diseases and reducing disease burden	QALY increase due to brain disorders burden reduction thanks to improved access to therapies

Benefits for stakeholders	Qualitative description of main benefits	Expected impact according to H2020 strategic plan 2021-2024	Quantitative indices (all focused on the impact due to MNESYS)
	reimbursement and prescribing of treatments		
	Improved evidence on the diagnostic and prognostic tools of brain disorders to inform health authorities policies on health system organization	Cluster Health: Ensuring access to innovative, sustainable and high-quality health care	QALY increase due to brain disorders burden reduction thanks to improved access to diagnostic process
University & Research Centers	Strengthening relationships between research groups in different geographical regions, including Southern Italy and Islands	Cluster Culture: Inclusive growth	Reduction of research productivity gaps between Italian regions
	Increased participation in research of young researches and women	Cluster Culture: Inclusive growth	Reduction of gender gap and of mean age of researchers
	Increased attractiveness of PhD programs, especially for young researches and women	Cluster Culture: Inclusive growth	Increase in completed PhD fellowships in neuroscience and neuropharmacology
	Enhancing the attractiveness and productivity of research programs in neuroscience and neuropharmacology	Cluster Health: Tackling diseases and reducing disease burden	Increase of total amount founding acquired in Neuroscience and Neuropharmacology
Enterprises	Support for the creation and development of research start-ups and spin-offs	Cluster Digital Industry and Space Industrial leadership and increased autonomy in key strategic value chains	Increase of neuroscience and neuropharmacology business sector volume and revenue
	Access of enterprises to research groups for knowledge exchange, training, and technology transfer in neuroscience and neuropharmacology	Cluster Digital Industry and Space Industrial leadership and increased autonomy in key strategic value chains	Increase in the number of collaborations between academia and industrial partners
	Identification of lead products for subsequent pharmacological development	Cluster Digital Industry and Space Industrial leadership and increased autonomy in key strategic value chains	Number of lead products reaching approval for clinical use
	Access to novel biomarkers concepts to guide clinical trials design	Cluster Digital Industry and Space Industrial leadership and increased autonomy in key strategic value chains	Number of biomarkers reaching approval for clinical use

Table C4: Benefits for the main stakeholders addressed by MNESYS proposal

C1.6 Dissemination, communication and exploitation

Dissemination and communication activities are considered as a key component in the successful implementation of the project. The work-package HUB.WP2, in strict collaboration with the ECC, is devoted to the implementation of the dissemination and communication activities aiming to: (i) **attract target audiences** (neurological patients and their caregivers, medical experts, scientific communities, policy makers, and companies, mainly in biotech and pharma domain), (ii) **carry the project outcome to the society and the market**, through the appropriate channels and at the appropriate timing depending on the result's maturity levels,

(iii) **inform end users** (healthcare professionals and patients) on the MNESYS results, (iv) create a durable impact on the society and the public audience.
All MNESYS partners have specific instruments and communication channels that will be used to maximize results dissemination and exploitation. Academic and research centers are national referral centers for their specific area of expertise, thus reaching a large audience target of the project. All members have long-term experience in the international neuroscience, neurological and psychiatric community (e.g. the European Academy of Neurology, the World Psychiatric Association, the Society for Neuroscience), also including, among researchers involved in the partnership, current and past national and international societies officials, as well as other scientific and patients communities including strong links with patient advocacy groups with involved researchers serving in advisory positions in different associations. In addition, dissemination of the project will also take place on the web with a dedicated website and social media connections. Dedicated meetings among the research groups will address strategies for dissemination and exploitation of results fostering their full comprehension with all the different partners (i.e., academics, health professionals, patients, caregivers, stakeholders). **Dissemination plans will follow the principles of Open Science** and we will follow the **FAIR (Findable, Accessible, Interoperable and Re-usable data) approach.** Final datasets will be deposited in repositories – generic, disciplinary, or national – that assign persistent identifiers for enabling discovery and allow to attach metadata according to widely adopted standards; whenever possible datasets will be made accessible and reusable by means of Creative Commons Attribution (CC-BY) license. The same principles will be applied to other research outputs (e.g., code, methods, experimental protocols, tools, etc.) that could be possibly shared and reused. The only boundaries to results dissemination will be i) **IP protection** and, ii) **guardianship of patients' personal and sensitive data**.
We have identified the following 3 main target audience groups:

A. Research and clinical community: Results will be discussed among peers in the main scientific congresses of the field (such as the European Academy of Neurology and the Society of Neuroscience), also organizing dedicated workshops within these congresses and independently. Themes arising from the project will be also included in the PhD courses held by the members of the HUB to foster the discussion and ensure the engagement of the novel generations of researchers. Further, the dissemination of the project will take place on a dedicated website. Dissemination topics will be related to project development and outcomes, describing activities, materials and methods and critically discussing the results. Manuscripts will prioritize ***high impact and open access journals*** with each partner allocating a budget to ensure open access to all peer-reviewed scientific publications relating to its results. ***Congresses and Symposia***: Most of the beneficiaries already participate to the major congresses in their specific area of research. We foresee participating with posters or presentations with the key findings of MNESYS at: 6 international congresses and 6 national congresses per spoke per year.

B. Patients and caregivers: The general public engagement will be strongly supported and fostered by press releases at the onset of the project and for every major step of the project. A lean communication that will give patients and caregivers the information they need to understand the projects development, with a minimum of time and effort, will be key. This will be achieved by dedicated language and spaces on the newspapers of patient's associations as well as through the use of social networks and a dedicated website, where publications and ad hoc videos will be made available to patients, caregivers and healthcare professionals. We strive for live communication with patients and their families, in respect to current restraint due to COVID-19-Pandemic and we foresee to organize at least two public workshops that will gather patient's associations and policy makers.

C. SME-investors-industrial stakeholders: Towards the end of the project, when exploitable results will have been identified, meetings with potential investors and interested companies will be promoted, leveraging the value chain of the industrial partners involved in the Partnership, as well as the rich network of start-ups and spin-offs described in section C3 below. Cooperation and investments will be prompted by an effective and targeted communication focused on stakeholders goals. Advancements in research and technology and their clinical application will be the main focus of dissemination to this audience group.

C.2. Synergy with programs financed under other investments envisaged by the NRRP and with other national and regional programmatic frameworks

The activities of the NRRP are organized around six missions (1. *Digitalization, innovation, competitiveness, and culture*; 2. *Green Revolution and ecological transition*; 3. *Infrastructures for Sustainable Mobility*; 4. *Education and Research*; 5. *Inclusion and Cohesion* and 6. *Health*) aiming to address three key problems of the Italian economy and social tissue namely gender inequality, social inclusion, and territorial gaps.
MNESYS activities shall provide significant impacts on *4. Education and Research* and *6. Health* missions but will also contribute in reaching the objectives of *5. Inclusion and Cohesion* and *1. Digitalization, innovation, competitiveness, and culture* missions, therefore **helping in the mitigation of gender inequality and territorial gaps and in the promotion of social inclusion**.
Regarding mission 4. *Education and Research*, MNESYS activities will be relevant for both its components, i.e. 4.1 *Enhancement of skills and right of education* and 4.2 *From Research to business*. Regarding the 4.1 objective, MNESYS training structure will provide **a case-study** for the implementation of an integrated, innovative and multi-disciplinary **research training** across fundamental, clinical and computational neuroscience, with strong links with industrial partners, for both PhD students and young researchers. Regarding 4.2 *From Research to business,* an immediate expected impact shall lead to an **increase in publications with an industrial-academic partnership** in order to close the gap between Italy and the other EU partners, with a target of at least 5% of MNESYS publications co-authored by industrial partners, based on the current levels of scientific publications with an industrial co-author (around 2% for Italian publications and an average of 4% for EU partners). Another impact of MNESYS in the 4.2 mission shall result in the **increase of patents** in the neuroscience and neuropharmacology field. Indeed, new patents in Italy are less than half those of other OECD countries after normalization for gross domestic product (GDP). To reach a significative impact on this regard, MNESYS has a strong technological component, with a significant number of activities linked with computational methods such as image analysis, development of new algorithms for biological models and pattern recognition techniques, which are all included in the fastest growing sectors in new AI-related patents reported in the 2019 OECD report on digital transformation (OECD 2019, *"A measurement roadmap for the future", in Measuring the Digital Transformation: A Roadmap for the Future,* OECD Publishing, Paris). Another striking impact of MNESYS in the 4.2 mission will be an increase of **profitability** from public investment in research via the close academic-industrial collaboration in neuroscience sectors with an expected significant growth in the market; as an example it is relevant to cite neuroimaging, one of the key technological approaches of the Partnership (thanks to the presence of expert researchers and to the inclusion of ASG), which is expected to present a market value increase from $31.2 billions in 2020 to $41.1 billions in 2025 (*Brain And Neuroimaging Devices Global Market Report 2021: COVID 19 Growth And Change to 2030, The business research company 2021*).
MNESYS contributions will also be of relevance to meet the Mission *6. Health,* especially regarding the *6.2 Innovation, Research and Digitisation of Healthcare* objective. Indeed, a key problem reported in the NRRP is the low GDP expenditure in Italy for healthcare compared to other OECD countries (6.5 percent, compared to 7.8 percent of the European average) associated nonetheless with a high life expectancy at birth (about 83 years according to the ISTAT survey for 2019) and a lower mortality rate (about 10.5 per thousand inhabitants) than in other OECD countries. A focus of MNESYS is the development of **biomarkers,** based on the integration of multiple biological, clinical and imaging approaches, including **digital biomarkers.** There is a growing consensus in the scientific community regarding the bi-directional relationship between the biomarkers and an efficient electronic health record (i.e. one of the key objectives of the NRRP 6.2 objective), with a relatively ease of integration of quantitative biomarkers in electronic health records on one hand and the usefulness of population-wide electronic health records as a key tool to validate clinical biomarkers and to verify the usefulness of the combination of multiple clinical and paraclinical data and biomarkers results into diagnostic algorithms and disease prevention (Wells et al, Accelerating Biomarker Discovery Through Electronic Health Records, Automated Biobanking, and Proteomics, JACC, 2019; van den Brink et al, Digital Resilience Biomarkers for Personalized Health Maintenance and Disease Prevention, Front Digit Health 2021). Moreover, the research activities of the Partnership on biomarkers for neurological and psychiatric diseases shall allow to identify not-only imaging and cerebrospinal fluid-based tests (i.e. approaches performed in the inpatient or outpatient setting)

but also new blood markers (that could thus be collected also in the home-care assistance setting) thus providing with significant impacts also on the future organization of home-care services for the elderly in line both with the 6.2 objective but also with the 6.1 *Territorial Assistance and Telemedicine* objective of the NRRP.
Based on the above considerations we can predict that many of the MNESYS activities will synergize with several actions that have been and will be released throughout other programs financed under the NRRP (Mission 4, Component 2 but also Mission 6 Component 2) and in coherence with the relevant national and regional programs. Keeping this in mind, we aim to optimize collaboration and pool investments (skills and infrastructure) that can strengthen the impact of the partnership at the regional, national and international level.
In details, most of the research organizations affiliated to MNESYS are involved, to different extent, in the main initiatives under the aforementioned Mission 4 (R&D National Centers, Research Infrastructures, Innovation Infrastructures and Extended Partnerships, Competence Centers and Digital Innovation Hubs): this may maximize potential synergies in terms of both science and planned actions.
Concerning the **National Centers (NC),** a special synergy can be envisaged with the National Center for "Gene Therapy and Drugs based on RNA Technology" (NC3). In particular, among the disease areas covered by **NC3**, neurodegenerative disorders are of major focus; one of the Spokes (Spoke3) is specifically dedicated to the development of RNA-based solutions for both common (Alzheimer's disease, Parkinson's disease, ischemic stroke) and rare neurodegenerative illnesses (genetically-determined neurodevelopmental disorders). MNESYS have done its best to exploit such synergy, capitalizing on common technological developments needed in both initiatives, but at the same time avoiding effort duplications; for that reason, RNA- or gene-based approaches have been given lower priority in the MNESYS proposal, rather reinforcing the exploration of therapeutic strategies based on small chemical molecules fitting critical regulatory domains of enzymes, structural proteins, transporters and channels, among others. Notably, several key institutions contributing to CN3 Spoke3 also participate in MNESYS proposal (such as UNINA, UNIBA, UNIBO, UNIFI, UNICZ, OPBG). It seems likely that, by combining knowledge and competences from two distinct but complementary areas such as nucleic acids- (RNA) and small-molecule-based therapeutics will speed the bench-to-bed process toward effective clinical translation of the solutions developed.
MNESYS activities are also synergic with those of **NC1** about "HPC, Big Data and Quantum Computing" including those in S1, Future HPC & Big Data, S2 Fundamental Research & space economy, S6 Multiscale modeling & engineering applications, SPOKE8 In-silico medicine & omics data and S10, Quantum Computing. MNESYS focus on computational aspects of neurosciences, as declined by the "digital twins" scale of Fig. 1A, could highly benefit from the HPC infrastructure and services set-up by this NC where UNIBO plays a key role. Some research institutes involved in the partnership (HSM, OPBG, ISNB, SR, SYNLAB, FDG) are part of the national project **"Health Big Data"** funded by the Italian Ministry of Economics and Finances (MEF) where data from different neurological diseases, provided by research institutes belonging to the Italian Neuroscience Network of IRCCS, will feed the AI algorithms. Another large national network project, named "Artificial intelligence of imaging and clinical neurological data for predictive, preventive and personalized (P3) medicine (- NeuroArt P^3-)" funded by the Italian Ministry of Health largely synergizes with MNESYS and involves, among the others, HSM, UNIGE and FDG.
NC5 Biodiversity: MNESYS will largely synergize with the National Biodiversity Future Center (NBFC) which involves UNIVR, UNIFI, UNIGE, UNIBO, UNINA. Particularly, NBFC, S6 - Activity 2: "Bioprospecting and bioactivity aims at finding new bioactive natural compounds blocking neuroinflammation and promoting neuronal survival", will synergize with the activities of MNESYS S7 focused on the characterization of new molecular mechanisms controlling neuroinflammation and identification of new drugs to tackle nervous system inflammatory diseases.
Another significant area of synergy arises from the **"Innovation Ecosystems"** call of the NRRP. Innovation ecosystems play a crucial role in the implementation of research and innovation activities, in technology transfer for the sustainability of a territory. Academic institutions of this partnership lead four "Ecosystems" which have been recently funded by the Italian Ministry of University and Research. RAISE (Robotics and AI for Socio-economic Empowerment), is led by UNIGE and includes also HSM and FDG and the activities of Spoke 2 "Smart devices and technologies for personal and remote healthcare" are synergic with several WPs of MNESYS related with robotics and AI domains connected with monitoring and care of frail individuals such as neurological

patients. In this respect, this ecosystem, and in particular the activities of SPOKE 1 and 2, will be instrumental for the activities of a new research hospital hosting a Centre of Computational Medicine and with a strong focus on biomedical technologies whose construction is planned in Genoa in the area of Erzelli starting 2023.
In addition, UNIBO has successfully submitted as project coordinator the proposal "Ecosystem for Sustainable Transition in Emilia-Romagna", which includes health as one of its targeted sectors. – Other two awarded Ecosystems, namely the Tuscany Health Ecosystem, coordinated by UNIFI and involving FDG and SSSA and "Tech4You - Technologies for climate change adaptation and quality of life improvement" involving UNICZ will focus on health issues synergizing with MNESYS.
At least four initiatives related to the calls of the **National Plan for Research Infrastructures (PNIR)** are relevant to this proposal, namely "Strengthening of the Biobanking and Biomolecular Resources Research Infrastructure of Italy" involving UNIVR, UNIBO, UNINA and HSM and connected to the European research infrastructure for biobanking BBMRI-ERIC; "ELIXIR IT" with UNIBO connected to the European ELIXIR Data Platform; "BioRobotics Research and Innovation Engineering Facilities" (BRIEF) with UNIPR and SSSA; the "Center for Technological Platforms" led by UNIVR.
Finally, many academic and research institutions of this partnership are also participating in other Extended Partnerships proposals focusing on other themes such as 1. Artificial intelligence, 6. Precision medicine, 8. Healthy ageing and 13. Infectious diseases, with limited but potentially relevant synergies with MNESYS.
MNESYS will also develop competences in areas relevant for other national frameworks, such as the platforms of the **Human Technopole (HT),** where the first level of consultation has identified three National Facilities to be implemented: the OMICS DOMAIN and the IMAGING DOMAIN and the DATA HANDLING AND ANALYSIS CORE. Despite the limited information yet available (the second level of consultation is still ongoing and is due to end on May 31, 2022), HT Strategic Plan 2020-2024 lists the "longitudinal phenotypization of brain organoids as models to convolute neurodevelopmental disorders in specific cohorts of patients" among the research themes, being complementary to activities carried out in MNESYS SPOKE1.
Some partners are also involved in some of the **"Highly Specialized Competence Centers"** funded by the Italian Ministry of Economics (MISE) including the BI-REX – Big Data Innovation & Research Excellence" involving UNIBO, UNIFE, UNIPR; ARTES "Advanced Robotics and enabling digital Technologies & Systems" involving SSSA, FDG, UNIFI; MEDITECH "Mediterranean Competence Centre 4 Innovation" involving UNINA, UNICAMPANIA and UNIBA; Competence Center Cyber 4.0 involving UNITOV and SYNLAB. Finally, several partners are involved in regional programs such as POR-FESR, on themes synergic with those addressed in the MNESYS partnership.

C.3. Technology Transfer, innovative start-ups/spin-offs, and Human Capital

MNESYS is a research project focused on a relatively small number of key topics deemed highly relevant for the understating of the nervous system functions in health and disease with the **objective of identifying major pathological drivers of different illnesses of the nervous system**. The proposal has also the mission to **boost the integration between different research viewpoints in neuroscience**: molecular-cellular, clinical and computational (also due to the different core competencies and professional figures involved in these areas of research). To this end, we will use a multi-disciplinary and multi-scale approach, starting from the molecular level and reaching the population level, taking advantage of ad-hoc developed and implemented cutting-edge technologies and of the combination of different professional figures. As reported in section A, the main general goals of the projects are:

- the assessment of **biomarkers** to determinate patients at preclinical or early stage of disease, **set-up individualized and preventive strategies** for improving prognosis and patient's quality of life;
- the **identification of new cellular and molecular targets** for the development of innovative **neuropharmacological tools**;
- setting up **biology-inspired digital twins**, driven by multi-modal data and relying on intrinsically multi-scale computational techniques.

The project is a research-oriented proposal with the ambition to lay the foundation for a new paradigm to neural diseases in which technology and computational aspects boost and accelerate the translational research toward the

actual **implementation of the 5 Ps in medicine (Predictive, Preventive, Personalized, Participatory and Purpose-driven)**.

C3.1 Technology Readiness Level

For the above reasons, as also foreseen by the call, the starting of the Technology Readiness Level for the research activities planned will be mostly 1, in some cases 2, and in very few cases 3. At the end of the project (after 3 years) we plan to achieve TRLs 3 or 4 and in few cases 5. In the following table the TRLs at start and at the end for each WP of the 7 Spokes is described.

Spoke	WP	TRL Start	TRL description - start	TRL End	TRL description - end
S1	*WP1. Anatomo-functional mechanisms of neurodevelopment and social cognition*	**1**	Identification of the neural mechanisms underlying specific forms of brain plasticity from prenatal age to adulthood, in humans and animal models, and their suitability to orient future clinical intervention.	**3**	Developing of new computational and data analysis approaches to the investigation of NDD and to the design of rehabilitation approaches based on brain plasticity and reorganization potential demonstrated at various developmental stages
	WP2. Identification of new biomarkers for NDDs	**2**	Investigating the predictive factors for a variety of NDD with a multidimensional approach, from the genetic to the physiological and system level.	**4**	Setting assays for drug screening/repositioning and testing of innovative therapeutic molecules.
	WP3. Neural and molecular mechanisms of NDD and targeted therapies	**1**	Identification of basic information related to physiological processes of neurodevelopment and disease mechanisms of NDD.	**3**	Characterization of novel druggable molecular targets, development of cellular assays for drug development, identification of candidate therapeutic compounds/molecules, definition of novel genotype-phenotype correlations
	WP4. Environmental and social determinants of neurodevelopment, health and disease	**1**	Identification of endogenous and exogenous environmental and social factors impacting on neurodevelopment	**3**	Identifying potential epigenetic, molecular and endocrine targets and their possible manipulation to reduce developmental risks
S1. Commentary on TRL changes: The Spoke provides robust guarantees to achieve the challenging objectives of its research agenda thanks to the significant and consolidated expertise of team members in highly complementary research activities and methodologies. The final TRL remains within the level of proof of applicability of the results, and the partners have exhibited consolidated capacity to develop computational, molecular, bioimaging and genetic/epigenetic markers of pathology as tools for personalized medicine, as well as to achieve breakthrough proof-of-concept and technological solutions for clinical conditions capitalizing on basic research results.					
S2	*WP1. Molecular and cellular mechanisms of neuronal communication & plasticity in vitro and in vivo*	**1**	Observation of neuronal plasticity within single cells with different existing technologies	**3**	New results on, and raised skills in implementing, cellular models for proof-of-concept experiments using brain-on-a-chip technologies and microscopy
	WP2. Multiscale brain modeling and digital brain twins	**1**	Observation of neuronal plasticity in neurons and microcircuits with different existing technologies	**3**	New results on, and raised skills in simulating, micro-circuits for proof-of-concept experiments using digital brain twins and similar technologies
	WP3. Neuronal plasticity in normal	**2**	Observation of neuronal connectivity using multiple	**4**	New results on, and raised skills in implementing platforms for,

Spoke	WP	TRL Start	TRL description - start	TRL End	TRL description - end
	brain & neurological disorders		network architectures for learning and explaining neuronal plasticity in health and disease		validation of automated analysis of clinical neuroimaging data
	WP4. Integrated technologies for brain connectomics	**1**	Observation of neuronal connectivity using advanced multi-modal neuroimaging for learning and explaining neuronal plasticity in health and disease	**3**	New results on, and raised skills in implementing platforms of, automated connectivity analysis with multi-modal neuroimaging and simulating treatment effects via digital connectomic twins
S2. Commentary on TRL changes: Each WP will be monitored with respect to the expected TRL change. Arising opportunities for new collaborations and initiatives or problems (e.g., delay in acquisition or recruitment, incomplete data sets) will prompt exchange and mitigation actions to prevent WPs from failing to deliver.					
S3	*WP1 Adaptive and maladaptive responses in coordinated transport of ions and water as targets for pharmacological interventions for brain diseases*	**2**	Characterization of the expression and function of specific classes of ion channels, transporters, and their coupled neurotransmitter receptors in pre-clinical models and identification of druggable cellular and molecular pathways	**4**	Validation of at least 2 novel pharmaceutical products in disease-relevant models of stroke, epilepsy and/or neurodegeneration.
	WP2. Organelle homeostasis in brain pathophysiology and innovative molecular interventions to correct organelle dysfunction	**1**	Identification of druggable targets in organelle crosstalk, lysosomal-autophagy, and proteostasis networks	**4**	Validation of a list of correctors of organelle dis-homeostasis via drug repurposing and novel candidate compounds/molecules.
	WP3. Genetic and epigenetic signatures of neural cell growth mechanisms and novel treatment strategies	**1**	Characterization of epigenomic and genomic signatures of nervous system tumors	**3**	Identification of a list of epigenetic drugs reverting the malignant phenotype in personalized models
	WP4. Sensory and autonomic interface for brain-environment interaction: tools, models, and pharmacological interventions	**1**	Identification of molecular mechanisms of sensory and environmental crosstalk involved in the pathogenesis of neuropsychiatric disorders.	**3**	Identification of new therapeutic approaches targeting gut microbiota to prevent and/or treat neurological diseases.
S3. Commentary on TRL changes: We acknowledge that some of the planned TRL changes are dependent on several hypotheses that need to be validated during the project. However, although the selection of specific molecular targets might pose a theoretical risk, the "druggability" of some of the molecular processes targeted by S3 has been already demonstrated and validated in humans (i.e. KCNQ-type channels). We will capitalize on this knowledge to generate novel molecular entities and delivery strategies, which will overcome some of the limitations associated to currently available drugs. Moreover, we feel that the high number of internationally-recognized investigators involved in the project, each with highly-specific but complementary expertise, together with the wide-range of technologies implemented, will allow us to identify solid disease biomarkers which will guide the selection of the most promising strategies and tools to effectively target brain diseases.					
S4	*WP1. Preclinical models for the physio-pathological transition*	**2**	Conventional in vitro and in vivo models for hypothesis testing	**4**	In vitro and in vivo validated prototypes for novel disease pathway identification drug discovery and safety

Spoke	WP	TRL Start	TRL description - start	TRL End	TRL description - end
	WP2. Systems Biology of pre-clinical and clinical models of neuro-functional phenotypes (NFP), towards new multidimensional biomarkers	**2**	Data and biological samples suitable for the development of Systems Biology and Network Medicine architectures.	**4**	Network Medicine and Systems Biology diseases pathways validated in pre-clinical and clinical models
	WP3 Neural networks: neurophysiology, neurotech and brain imaging of perception, movement and brain-body interactions and individual variability	**1**	Description and definition of the main principles in the models and technology.	**3**	Computer studies, laboratory and in vivo measurements to validate analytical predictions; initial interpretation in a clinical cohort.
	WP4. Neural network models and technologies to better understand perception, movement and brain-body interaction and to impact on society	**1**	Description and definition of the main principles in the models and technology.	**4**	Computer studies and laboratory measurements to validate analytical predictions of the models; validated prototypes of the main elements of the technology.
S4. Commentary on TRL changes: S4 is a high-risk-high-gain network of projects aiming at improving understanding of perception and movement through a multidisciplinary approach. All WPs start from basic principles to reach a level of enhanced knowledge, validated innovative methods and developed proof-of-concepts prototypes. Results can represent the starting point for future applications. We could expect potential difficulties in data acquisition and in the development of highly innovative methodologies in various fields, but these risks are limited by the application of well-documented techniques, by the recognized expertise of each PI in the team and by the existence of previous network collaborations between parties.					
S5	*WP1. Drug discovery, development and delivery for mood and psychotic disorders*	**2**	Some computational models available but limited clinical implementation.	**5**	Delivery of a Clinical Service Platform for experimental therapeutics that can engage industry.
	WP2. Innovative cellular models for mood and psychotic disorders	**2**	Very limited development of the research area.	**4**	The innovative use of Muse cells can lead to a burgeoning growth of this research area capturing the interest of industry.
	WP3. Looking for genetic variants as risk factors for mood and psychotic disorders	**2**	Advancing knowledge of common variants involved in the risk for mood and psychotic disorders, but limited clinical relevance.	**4**	Correlating genotypes and phenotypes has the potential to provide new scientific and clinical insights.
	WP4. Advanced brain imaging for mood and psychotic disorders	**3**	Increased potential of brain imaging in psychiatry, but limited applications in clinical practice.	**5**	Development of risk calculators and other measures usable in clinical practice.
	WP5. Pharmacogenetics for precision medicine in mood and psychotic disorders	**3**	Very limited role of biological indices in addressing treatment resistance.	**5**	Valid predictive models applicable in clinical settings.
S5. Commentary on TRL changes: The TRL changes of S5 reach also level 5 (pre-clinical validation) and will depend upon the harmonization of research methods across the participating centres, but the previous history of collaborative activities among the components of the spoke is reassuring in this respect.					

Spoke	WP	TRL Start	TRL description - start	TRL End	TRL description - end
S6	*WP1. Mechanisms of neuronal cell degeneration and drug dependent reversal*	**1**	Identification and characterization of the molecular determinants and pathways for several models of neurodegenerative conditions	**3**	Computer studies and laboratory measurements are performed to validate the analytical predictions of the models. Drug design, assessment of efficacy and definition of delivery systems to the brain
	WP2. Multi-modal approaches to monitoring progression of neurodegenerative diseases and definition of novel rehabilitation methodologies	**2**	Identification and characterization of omics-derived circulating, EEG and imaging biomarkers for neurodegenerative diseases	**4**	Validation of biomarkers to monitor disease development and progression. Validation of techniques for cognitive and virtual reality rehabilitation
	WP3. Neuro-degeneration in stroke	**1**	Characterization of experimental models to identify molecular mechanisms of post-ischemic injury and targets for therapeutic approaches.	**3**	Identification of delivery strategies for innovative drugs and markers for predictive prognostic models
	WP4. Multi-parametric imaging and neurophysiological approaches to monitor neurodegeneration in the nervous system	**2**	Availability of different imaging and neurophysiological biomarkers of neurodegeneration	**3**	Verification of the utility of the combination of multiple markers of neurodegeneration in a summary metric
S6. Commentary on TRL changes: We acknowledge that some of the planned TRL changes are dependent on several hypotheses that need to be tested during the project. For all WPs, a possible problem could be represented by the selection of specific molecular targets and of markers among those available. We feel that the high number of researchers involved in the project and the different fields of expertise available will allow us to analyze, at least in the first phase of the program, a high number of possible molecular targets and of imaging markers thus allowing us to select those more relevant to successful delivery of the project. Still, a theoretical risk that no biomarker will be found could be considered, although it is limited by the integrated technologies proposed in the WPs. In fact, "omics" is certainly the optimal approach to identify biomarkers on large and heterogeneous cases and it has already been successfully used in cancer and other complex and multifactorial diseases. The participation of industrial partners within the consortium will favour the development of prototypes of diagnostic kits and pharmaceutical. Thus, the close integration of interdisciplinary partners in S6 will progress innovative biomarkers and methods from the stage of academic research (TRL2), to efficient laboratory scale in WPs 1, 3 and 4 (TRL3), and to prototypes of diagnostic devices in the WP2 (TRL4).					
S7	*WP1. Identification of New Immune and Inflammatory Mechanisms in Cellular Models of Nervous System Disorders*	**1**	The main principles and molecular mechanism on the crosstalk between immune system and neural cells in different models and settings are defined and described	**3**	Experimental proof of concept will be demonstrated analytically and/or experimentally
	WP2. Identification of Pathogenic Signatures and New Drug Targets in Animal Models of Nervous System Inflammation	**1**	Basic principles and molecular mechanisms in in vivo animal models of disease are defined and described	**3**	Experimental proof of concept will be demonstrated by: analyzing clinical signs of disease, laboratory investigations, neuropathological studies, computational approaches, network analysis
	WP3. Immuno-Inflammatory	**1**	The expertise of clinicians and researchers as well as the	**3**	Laboratory measurements, bioinformatic analysis, network

Spoke	WP	TRL Start	TRL description - start	TRL End	TRL description - end
	Profiling of Patients with Nervous System Diseases and Identification of New Biomarkers		application of the technologies are defined and described		collaboration between parties raised technical and scientific skills leading to development of models that use 'omics information to predict disease phenotypes
	WP4. Drug Discovery, Development and Delivery for Targeting Neuroinflammation	**2**	Technology concept formulated for drug discovery and development	**4**	Technology validated in lab: obtainment of new immunomodulatory and anti-inflammatory molecules
	WP5. In Vitro and in Vivo Drug Testing of New Immunomodulatory and Anti-inflammatory Drugs for Nervous System Diseases	**1**	The main principles in the experimental models and technologies are defined and described.	**4**	Preclinical proof of concepts validating the effect of new compounds and therapeutic strategies
S7. Commentary on TRL changes: the Spoke is a high risk-high gain project aiming at finding new therapies to tackle immune system dysfunction and neuroinflammation in nervous system diseases. We could expect potential conflicting data, unreliability/unpredictability of the data acquired, large database management but these risks are limited by application of well documented advanced technique, long lasting expertise of each team and network collaboration between parties. To maximize feasibility: (1) we have implemented a robust workflow, carefully designed and tailored to the specific project's needs; (2) feasibility importantly relies on available expertise and preliminary findings supporting the idea that targeting immune cell functions can contrast neuroinflammation; (3) as evident from the PIs' track record, spoke 7 is best positioned to carry out this project and has the right "driving forces".					

Table C5. Technology Readiness Levels of project outcomes

C3.2 Innovative start-ups and spin-offs

Within the MNESYS consortium, many Universities and research institutions have established a network of consolidated collaborations among different research groups. Each Partner has its own Technology Transfer Office (TTO) supporting and promoting the creation of start-ups and spin-offs from research results. With the MNESYS project we seek at creating a milieu in which, starting from new discoveries and IP protection, scouting for new enterprises and initiatives for new entrepreneurship activities are implemented. To this end, we will take advantages of the network of public and private partners of the HUB with the support of specific incubators-accelerators which will be involved in the implementation phase. As an example, Bio4dreams (https://www.bio4dreams.com/) with its network of incubators is already actively collaborating with Partners of the consortium (e.g., UNIGE and UNINA).
To be more focused, pro-active and efficient in the implementation of such environment, the Spokes will be in charge to promote and monitor these activities supported by the TTC. The clear advantage is that we will not start from scratch as in each Spoke, institutions are already partners within networks involving spin-offs, stat-ups and industrial partners. In the following paragraphs, spin-offs, start-ups and industrial collaborations already in place are presented for each spoke.

S1. Neurodevelopment, social cognition and interaction
The network of institutions belonging to S1 will favor industrial engagement and technology transfer based on existing and newly created synergies with private companies and spin-off linked with, or derived from, ongoing and previously funded projects such as FET and ERC Proof of Concept (e.g. AtlasNeuroengineering, Cynexo). Furthermore, PIs of SSSA have a broad experience of technology transfer as they are co-funders of several start-up companies (e.g., IUVO, SMANIA, SensArs, Onward, FES-ability, Photrix) of great success, and their work led to dozens of international patents.

S2. Neuronal Plasticity and Connectivity
Most partners will benefit from consolidated collaborations of involved researchers with industrial partners (e.g., General Electric Healthcare, Brain Innovation, Chiesi Farmaceutici) and existing spin-offs (e.g., EBRAINS, Queen Square Analytics). Industrial engagement will stimulate the release of prototypes and new entrepreneurial initiatives (birth of innovative start-ups, growth of spin-offs).

S3. Neuronal homeostasis and Brain-environment interaction
The research network involved in S3 has been strategically assembled to favor industrial engagement and technology transfer. Pharmaceutical companies involved in the partnership (DOMPE' and ALFASIGMA) will actively contribute to research activities; most academic S3 researchers have already significant experience in collaborating with these industrial partners, in several cases leading to Academic spin-offs to exploit the technological knowledge generated. For example, >600 patents have been developed by UNINA investigators in the last 20 years, leading to 81 currently operative spin-offs (http://www.spinoff.unina.it/archivio-spin-off/). Several of these revolve around themes highly pertinent to the current PE12 proposal (such as digital twins, next-generation sequencing and other omics technologies, pharmaceutical development). UNINA investigators have already obtained patents related to innovative diagnostic or therapeutic tools for neurological disorders, and several academia-industry collaborations (i.e. UNINA) are in place for the development of drugs for neurological disorders, nanovectors and neurological rehabilitation devices.

S4. Perception, movement and brain-body interactions
The spoke leader team of UNIBO is engaged in spin-off activity (Vibre; https://www.cesenalab.it/portfolio-startup/vibre/). UNIBO, such as other members of the spoke (UNIFE, UNIPR), joints the Emilia-Romagna Regional Ecosystem for research & innovation dedicated to industrial engagement and technology transfer and to support the competitiveness of the industrial system. Numerous team members are inventors of published patents and are already involved in research projects with technological fallouts. We expect that several innovative methods developed during the project (in fields like neuropharmacology, neuro biomarkers, data analysis, and data repository, AI, computational modeling, signal processing) will be placed at the cutting-edge of industrial

research and can have a substantial impact in future technological challenges. Despite the focus on basic research, Spoke 4 aims at integrating technologies into systems and services.

S5. Mood and Psychosis

An obvious partner for the S5 in Italy will be Farmindustria, whose leadership has a long history of collaboration with some of the participants in the spoke. The Clinical Service Platform for experimental therapeutics (WP1) is likely to be of special interest for the industrial partners of the partnership. At the international level, some of the participants in the spoke have close relationships with leaders of several drug companies (including Lundbeck, Otsuka, Janssen, Boehringer Ingelheim, Angelini, Jazz Pharmaceuticals), which could also be interested in testing promising drug candidates.

S6. Neurodegeneration, trauma and stroke

The research network involved in the activities of the Spoke is organized to favor industrial engagement and technology transfer. On one hand, pharmaceutical and bioengineering companies (DOMPE', ALFASIGMA and ASG) will actively participate in the research activities, and, on the other hand, researchers involved in the spoke are already significantly engaged with industrial corporations, MUR-controlled Research Institutes and University spin-off. For example, SR collaborates with companies (e.g., Integra Srl, Integra R&D Srl), incubators (e.g., Bio4Dream, Como Next) and accelerators (Cube Labs, G-Factor) supporting academic research in the engagement of the pharmaceutical industry to license intellectual property and transfer technologies and processes from academia to the private sector. In the area of imaging markers in neurodegeneration, UNIGE has a long-standing collaboration with the Institute of Nuclear Physics and the Italian Association of Nuclear Medicine to develop and disseminate tools for image quantification in clinical practice. UNIBO has a long-standing collaboration with ALFASIGMA on microbiome-related research, new formulations and, more recently, on neurodegeneration. ALFASIGMA is also connected with the start-up incubator G-Factor and with expert of intellectual property to foster the creative Italian ecosystem. At UNIBA, researchers involved in the project developed BioForDrug Ltd, a company focused on the development of PET radiotracers for Imaging P-glycoprotein at the Blood Brain Barrier (BBB) level, used for early diagnosis of CNS pathologies, and are shareholders of the UNIBA spin-off BROWSer Srl (Bioinformatics Resource for Omics Wide Services), which provides bioinformatics analysis services applied to biological data. Another consolidated collaboration is with Itel Telecomunicazioni-Section Itel Pharma, Ruvo di Puglia (BA), to produce a newly patented (US 63/431,187) formulation of [18F]-F-DOPA for PD diagnosis. Moreover, EBRI developed and patented tools to be tested within Spoke activities, including candidate therapeutics for neurodegenerative diseases (anti-tau antibody [patent pending] and painless NGF [patents IT132046 and D389 for the purification process]). Painless NGF is currently in development with Chiesi Farmaceutici, for ophthalmic disorders (PCT/EP2020/075697), Alzheimer's disease in Down Syndrome (PCT/IB2017/0512469), and dermatological disorders (PCT/EP2019/074767). EBRI has also developed and patented (102021000025619) an immunoassay for measuring proNGF in human CSF, as biomarker for Alzheimer's and other neurodegenerative diseases and a diagnostic method for human tauopathies (EPO 2580595).

S7. Neuroimmunology and Neuroinflammation

UNIVR team is engaged in spin-off activity with Genartis Srl, Castel D'Azzano (VR) (co-founder M. Delledonne), itamPharma srl Padova (PD) (co-founder C. Nardon) and Leuvas Therapeutics, Mountain View, CA, USA (co-founder G. Constantin). Dompé enterprise is a spoke affiliate and will bring its business expertise to the team. Numerous members of spoke 7 team are inventors in published patents and we expect to generate new IP to be protected with the Legal Support Service of the participating Institutions.

C3.2 Human Capital and young investigators

One of the MNESYS objectives is to have an impact in terms of **enhancing the role of young scientists and attracting young researchers** from EU and non-EU countries to Italy. All the partners will contribute synergistically with the aim to involve and retain scholars who have obtained their PhD in the last 10 years. To this end, MNESYS consortium will be guided by three basic principles, i.e. **fairness in recruitment**,

acknowledgment of the role of young researchers in the project and their **empowerment** to ensure their satisfactory career development (cf. Sect B6). Specific initiative will be deployed at the start and during the development of the project with the support and advice of the Education and Communication Committee (ECC). At the beginning of the project 150 temporary positions of Researcher (RTDa) will be appointed for three years. These young researchers will have the opportunity to work in a multi-disciplinary milieu in all Spokes. They will be supported and guided from one side by senior researchers and well recognized scientists in their respective fields, and from the other side they will work as co-supervisors of 150 PhD students who will be hired at the beginning of the project. We are convinced that the young researchers and PhD students working at the various research activities of the projects will benefit and profit of the international and stimulating environment in which science, technology and also opportunities for entrepreneurial initiatives are supported by the Spokes and coordinated by the Scientific Committee and by the Technology Transfer Committee. We are confident that exploitation of the results obtained within the project might bring to a number of new patents and to the creation of new spin-off companies or industrial applications. In this respect, the support from the 4 companies included in the consortium and by industrial incubators involved during the project development will be fundamental.
From the educational and training point of view MNESYS is also committed to have an impact at national and international level. Starting from already developed initiatives by the academic partners and by the applicant (UNIGE) we plan to introduce and develop the following initiatives:

- **Master courses in the broad area of computational medicine**: at the University of Genova we started this year a Master dedicated to students of the Medical School with the goal of introducing not only technology awareness but to improve the skills of future medical doctors to the application and use of cutting-edge technologies in clinics (cf. Master in MedTech: Medical Technology and Digital Health; https://ianua.unige.it/medtech).
- **PhD programs** capable to integrate Neuroscience and Neurotechnology and open to a multidisciplinary audience.
- International Summer Schools for PhD and post-doc with the specific aim to promote multi-disciplinarity holistic approach in Neuroscience and Neuropharmacology integrated with neurotechnology. As an example, we have @UNIGE a long-lasting tradition with a multi-disciplinary school partially covering these themes https://www.neuroengineering.eu/)
- Organization of **advanced training programs** for medical and health professionals to meet the need of new specialists, such as the physician-scientist (physician-researcher with in-depth training in the Neuroscience-neuropharmacology field)
- Specific training programs for experts in computational medicine and big data analysis with focus on neuroscience and neuropharmacology.

Allegato 2

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

Allegato 2 – Sinergia con programma Horizon Europe (articolo 10 comma 3)

MNESYS

(Il presente allegato deve essere compilato e firmato digitalmente dal Rappresentante legale del Soggetto proponente)

Ministero dell'Università e della Ricerca

Allegato 2

SINERGIA CON IL PROGRAMMA HORIZON EUROPE

Descrivere le componenti della proposta progettuale sinergiche con le mission di Horizon Europe

Horizon Europe (HE), i.e the EU's flagship Research and Innovation Programme, aims to achieve three strategic objectives, is designed according to three vertical and one horizontal pillars, and takes charge of five thematic missions. MNESYS has kept track of all these aspects since the beginning of its drafting, up to recognize that synergies between HE and Next Generation EU should go beyond the combination of different funding streams, but should aim at maximizing the scientific, societal, economic impacts of public investments.

MNESYS and HE objectives. HE aims to "accelerate the green and digital twin transition", "strengthen resilience and crisis preparedness", and "support Europe's global competitiveness". Digital twins are at the core of MNESYS computational activities for essentially all its spokes and work packages, which will make our project an example of how AI-based digital analogs may allow many Ps approaches to clinical treatment and improve the interdisciplinary flavor of the applied methodologies. More than this, MNESYS digital twins will develop and implement AI solutions, which will be designed and optimized by exploiting all possible physical and biological information associated to the wealth of multi-modal data put at disposal by the many MNESYS labs. These biology-inspired machine learning algorithms will limit the use of energy-consuming brute force approaches to neural networks optimization and training, thus making the AI carbon footprint of MNESYS genuinely sustainable. Further, MNESYS ambitious scientific program has been conceived by an interdisciplinary crew of research groups that are used to test their competitiveness in the global scientific arena. Therefore, we believe that MNESYS multi-scale and multi-disciplinary perspective will lead to holistic outcomes with impacts not only on scientific research and clinical practice, but also on societal resilience to possible future crisis.

MNESYS and HE pillars. HE vertical pillars rely on 'Open Science', 'Global Challenges and Industrial Competitiveness', 'Open Innovation' and include horizontal actions with the aim of 'sharing excellence and reforming and enhancing the EU R&I system'. MNESYS commitment is to provide open access to its research outcomes, by adopting either 'gold' or 'green' models for publication, using part of the budget to cover open-access publication fees, by establishing a repository of anonymized data accessible by external users, and by sharing the AI algorithms at the core of our digital twins within an open project's GitHub repository. Our challenges are of course mainly concerned with health, although we believe that the results of our project will have impacts on the 'Inclusive and Secure Society' challenge, since the characterization of environmental risk factors on neurodegenerative and psychiatric disorders will foster the inclusion of fragile patients into modern societal mechanisms; and on the 'Digital Industry and Space' challenge, since the AI methods developed to generate MNESYS digital twins could be exploited in different domains according to a virtuous transfer of knowledge activity. Further, MNESYS gathers around a clear-cut scientific rationale a notable number of first-rate Italian labs with well-established international collaboration networks and include as well high-tech companies, which will certainly foster the sharing of up-to-date scientific results at a national, EU and international level. Therefore, the companies affiliated to this research project will facilitate the transfer of research results to industry, increase the value of intellectual property and enhance the overall Italian and EU R&I system.

MNESYS and HE missions. EC decided to assign HE five R&I missions covering areas in the 'Cancer', 'Adaptation to Climate Change Including Societal Transformation', 'Healthy Oceans, Seas, Coastal and Inland Waters', 'Climate-neutral and Smart Cities', and 'Soil Health and Food' areas. Although its connections with these missions are not direct, yet MNESYS may contribute to their accomplishment at two different levels. First, at a scientific level, some of the specific problems addressed by MNESYS are certainly of interest for cancer research. This is the case, by instance, for the study of tumor-related brain plasticity (WP3 in Spoke 2) or for the identification of genetic and epigenetic signatures of neural cell growth mechanisms (WP3 in Spoke

3). Second, at a methodological level, we believe that MNESYS might become a model of how complex R&I issues can be addressed according to a 21st approach to science. Indeed,

- the focus on a small number of key topics addressed via a holistic perspective that put together different disciplines and different data acquisition modalities;
- the systematic use of digital analogs of the system of interest based on advanced computational approaches that exploit all possible a priori information available on the system's dynamics, can inspire general strategies for the solution of open issues in all HE missions and become a methodological benchmark for the accomplishment of other impact-driven goals in HE.

Specificare la percentuale di budget allocata nelle specifiche mission e indicare le risorse allocate in termini di mesi/persona.

Il Partenariato Esteso prevede il 100% delle attività di Ricerca Fondamentale - Articolo 6 (Interventi finanziabili) riconducibili al Campo di intervento 006 - Investimenti in beni immateriali in centri di ricerca pubblici e nell'istruzione superiore pubblica direttamente connessi alle attività di ricerca e innovazione - Articolo 7 (Criteri di ammissibilità)

Il partenariato è composto da 25 soggetti giuridici rispettando i vincoli dell'Avviso - Articolo 4 (Soggetto proponente, soggetto attuatore e soggetto realizzatore).

PE	***12. Neuroscienze e neurofarmacologia***	022 - Processi di ricerca e di innovazione, trasferimento di tecnologie e cooperazione tra imprese incentrate sull'economia a basse emissioni di carbonio, sulla resilienza e sull'adattamento ai cambiamenti climatici	023 - Processi di ricerca e innovazione, trasferimento di tecnologie e cooperazione tra imprese incentrate sull'economia circolare	006 - Investimenti in beni immateriali in centri di ricerca pubblici e nell'istruzione superiore pubblica direttamente connessi alle attività di ricerca e innovazione
				Ricerca fondamentale
	MNESYS	-	-	**140.129.400**

Tabella 1 – Proposta di spesa - Art. 6 dell'avviso

Programma di spesa complessivo

Il costo complessivo del programma è pari a 140.129.400,00 Euro, prevedendo per l'HUB una spesa di 11 milioni, per l'avvio, l'attuazione, la gestione e le altre attività assegnate all'HUB Partenariato esteso, così come evidenziato nella Tab. 2 di seguito riportata.
Le spese di personale impegnato nel Programma di ricerca e innovazione del Partenariato esteso comprende la quota di spesa relativa ai nuovi ricercatori (*colonna A*) e la quota del personale strutturato considerato come 'massa critica' in sede di presentazione della proposta (*colonna B*) ivi comprese le borse dei dottorati e tecnologici di cui all'articolo 7 comma 3 dell'Avviso.

La *tabella 2* evidenzia il programma di spesa per voci di costo per ciascun soggetto del partenariato.

Partner	Short name	Number critical mass HR	Number New RTDa	Budget New RTDa	Personnel costs	Total Equipments, consumables	Cost contractual research, completences and licensed	General additional costs (15% B)	Sub Total	Budget "Cascade funding call"	TOTAL
				A	B	C	D	E	F=(B+C+D+E)	G	TC= F+G
P1	UNIGE	**38**	**15**	2.250.000	**6.399.000**	670.000	320.000	959.850	**8.348.850**	4.500.000	**12.848.850**
P2	UNIPV	**18**	**9**	1.350.000	**3.642.000**	360.000	170.000	546.300	**4.718.300**	-	**4.718.300**
P3	UNIVR	**22**	**11**	1.650.000	**3.693.000**	515.000	230.000	553.950	**4.991.950**	3.000.000	**7.991.950**
P4	UNIFE	**15**	**8**	1.200.000	**2.763.000**	360.000	170.000	414.450	**3.707.450**	2.000.000	**5.707.450**
P5	UNIBO	**26**	**13**	1.950.000	**5.286.000**	660.000	270.000	792.900	**7.008.900**	3.000.000	**10.008.900**
P6	UNITOV	**29**	**12**	1.800.000	**5.202.000**	400.000	150.000	780.300	**6.532.300**	-	**6.532.300**
P7	UNINA	**36**	**20**	3.000.000	**8.844.000**	730.000	410.000	1.326.600	**11.310.600**	7.500.000	**18.810.600**
P8	UNICAMPANIA	**23**	**13**	1.950.000	**6.396.000**	770.000	380.000	959.400	**8.505.400**	6.500.000	**15.005.400**
P9	UNICZ	**13**	**11**	1.650.000	**4.659.000**	550.000	300.000	698.850	**6.207.850**	-	**6.207.850**
P10	UNIBA	**24**	**15**	2.250.000	**8.124.000**	925.000	400.000	1.218.600	**10.667.600**	-	**10.667.600**
P11	UNIPR	**14**	**9**	1.350.000	**3.219.000**	350.000	205.000	482.850	**4.256.850**	3.000.000	**7.256.850**
P12	UNIFI	**19**	**10**	1.500.000	**4.032.000**	545.000	235.000	604.800	**5.416.800**		**5.416.800**
P13	HSM	**13**	**0**	-	**1.266.000**	190.000	70.000	189.900	**1.715.900**		**1.715.900**
P14	ISNB	**10**	**0**	-	**783.000**	120.000	50.000	117.450	**1.070.450**		**1.070.450**
P15	SSSA	**7**	**4**	600.000	**1.197.000**	140.000	60.000	179.550	**1.576.550**		**1.576.550**
P16	OPBG	**10**	**0**	-	**831.000**	165.000	95.000	124.650	**1.215.650**		**1.215.650**
P17	EBRI	**5**	**0**	-	**642.000**	315.000	120.000	96.300	**1.173.300**		**1.173.300**
P18	SYNLAB	**6**	**0**	-	**870.000**	-	350.000	130.500	**1.350.500**		**1.350.500**
P19	TIGEM	**3**	**0**	-	**1.347.000**	180.000	90.000	202.050	**1.819.050**		**1.819.050**
P20	FDG	**10**	**0**	-	**597.000**	230.000	120.000	89.550	**1.036.550**		**1.036.550**
P21	SR	**7**	**0**	-	**801.000**	115.000	80.000	120.150	**1.116.150**		**1.116.150**
P22	DOMPE'	**1**	**0**		**531.000**	230.000	1.050.000	79.650	**1.890.650**		**1.890.650**
P23	ALFASIGMA	**1**	**0**		**912.000**	300.000	450.000	136.800	**1.798.800**		**1.798.800**
P24	ASG	**0**	**0**		**516.000**	-	600.000	77.400	**1.193.400**		**1.193.400**
P25	Takis	**0**	**0**		**504.000**	260.000	160.000	75.600	**999.600**		**999.600**
HUB MNESYS											**11.000.000**
TOTAL		**350**	**150**	**22.500.000**	**73.056.000**	**9.080.000**	**6.535.000**	**10.958.400**	**99.629.400**	29.500.000	**140.129.400**

Tabella 2 – Programma di spesa complessivo per partner

Programma di spesa assegnato all'area del Mezzogiorno

Il programma di spesa assegnato nell'area del Mezzogiorno come da Avviso supera il 40% rispetto al costo complessivo della proposta MNESYS di Euro 140.129.400,00.

Partner	Short name	Total cost
P7	UNINA	18.810.600
P8	UNICAMPANIA	15.005.400
P9	UNICZ	6.207.850
P10	UNIBA	10.667.600
P18	SYNLAB	1.350.500
P19	TIGEM	1.819.050
P22	DOMPE'	1.890.650
P25	Takis	999.600
SUD ITALY - TOTAL COST		**56.751.250**

Tabella 3 – Programma di spesa per il Mezzogiorno

Programma di spesa per Spoke

Il programma di ricerca fondamentale si sviluppa in 7 Spoke, la cui spesa è pari a 129.129,400 Euro, la tabella 4 espone la ripartizione della spesa tra i singoli Spoke.

Spoke	Title	Lead	Personal-month per year critical mass	New reseracher s RTDa	Budget "cascade funding call"	Total Cost
S1	Neurodevelopment, social cognition and interaction	UNIPR	145	20	3.000.000	**15.652.800**
S2	Neuronal Plasticity and Connectivity	UNICAMPANIA	177	21	6.500.000	**21.156.400**
S3	Neuronal homeostasis and Brain-environment interaction	UNINA	231	26	7.500.000	**24.828.250**
S4	Perception, movement and brain-body interactions	UNIBO	152	23	3.000.000	**15.130.000**
S5	Mood and Psychosis	UNIFE	150	20	2.000.000	**14.262.750**
S6	Neurodegeneration, trauma and stroke	UNIGE	192	20	4.500.000	**20.856.400**
S7	Neuroimmunology and Neuroinflammation	UNIVR	169	20	3.000.000	**17.242.800**
		Total cost	**1.216**	**150**	**29.500.000**	**129.129.400**

Tabella 4 – Programma di spesa degli Spoke

Investimento in capitale umano

Il personale strutturato impiegato nel programma considerato come massa critica è pari a 350 unità. Il numero di nuovi ricercatori è invece previsto pari a 150, nel rispetto dell'Articolo 7 (Criteri di ammissibilità). Inoltre, si prevede l'attivazione di un numero di 150 borse di dottorato, pari a quello dei ricercatori. La tabella 5 fornisce i budget previsti.

MNESYS	Critical mass HR	Number New RTDa	Number new PhD	Budget New RTDa	Budget new PhD
	350	**150**	**150**	**22.500.000**	**9.000.000**

Tabella 5 – Nuovo capitale umano

Considerando in mesi uomo all'anno, saranno attivi: almeno 1216 mesi uomo della massa critica, 1.800 mesi uomo per ricercatori, 1.800 mesi uomo di studenti di dottorato e almeno 750 mesi uomo annuo strutturati e/o tecnologici.

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Data, 10-05-2022

Il Legale Rappresentante del soggetto proponente
(*Firma digitale*)

RICEVUTA DI INVIO RICHIESTA

N. 000000612052022150217 - generata il 12/05/2022 alle 15:02:17

Avviso pubblico per la presentazione di proposte progettuali per "Partenariati estesi alle università, ai centri di ricerca, alle azione per il finanziamento di progetti di ricerca di base" da finanziare nell'ambito del PNRR

Missione 4, "Istruzione e Ricerca" - Componente 2, "Dalla ricerca all'impresa" - Linea di investimento 1.3, "Partenariati estesi alle università, ai centri di ricerca, alle aziende per il finanziamento di progetti di ricerca di base", finanziato dall'Unione europea - NextGenerationEU

L'utente ANTONELLA PRATO (PRTNNL66P58A052H) ha inoltrato in data 12/05/2022 alle 15:02:17 l'istanza PE0000006 per conto di:

Denominazione: GENOVA - Università degli Studi

Codice fiscale: 00754150100

Protocollo dell'istanza: PE0000006 del 12/05/2022 alle 15:02:17

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