UNIVERSITÀ DI FOGGIA

HR EXCELLENCE IN RESEARCH

CONVENZIONE ATTUATIVA TRA L'AZIENDA OSPEDALIERO UNIVERSITARIA DI CAGLIARI E L'UNIVERSITÀ DEGLI STUDI DI FOGGIA PER LO SVOLGIMENTO DEL PROGETTO PNRR-MAD-2022-12375802 – MALATTIE CRONICHE NON TRASMISSIBILI (MCnT) AD ALTO IMPATTO SUI SISTEMI SANITARI E SOCIO-ASSISTENZIALI – MODULATION OF NEUROINFLAMMATION AND ASTROCYTE ACTIVITY IN ALZHEIMER'S DISEASE: FUNCTIONAL CONSEQUENCES AND THERAPEUTIC PERSPECTIVES.

TRA

- la Dott.ssa Chiara Seazzu, la quale interviene al presente atto non in proprio ma esclusivamente in nome e per conto dell'**Azienda Ospedaliero Universitaria di Cagliari**, di seguito denominata anche Unità Operativa 1 o Soggetto attuatore/beneficiario o Soggetto Capofila, con sede legale in Cagliari, nella Via Ospedale n. 54, c.a.p. 09124, Cod. Fisc. 03108560925, che rappresenta nella sua qualità di Direttore Generale;

E

- Prof. Lorenzo Lo Muzio, il quale interviene al presente atto non in proprio ma esclusivamente in nome e per conto dell'**Università degli Studi di Foggia**, di seguito denominata anche Unità Operativa 4, con sede legale in Foggia, nella Via A. Gramsci n. 89/91, c.a.p. 71022, Cod. Fisc. 94045260711, che rappresenta nella sua qualità di Rettore pro tempore;

Visto

REGIONE AUTÒNOMA DE SARDIGNA
REGIONE AUTONOMA DELLA SARDEGNA

FSC Fondo per lo Sviluppo e la Coesione

- il Programma quadro per la ricerca e l'innovazione dell'Unione Europea 2021-27 Horizon Europe persegue, tra i suoi obiettivi, il sostegno ad attività di ricerca e innovazione che esercitino un impatto sul campo in settori strategici fondamentali quali la sanità;

- la Legge Regionale n. 7 del 7 agosto 2007 “Promozione della Ricerca scientifica e l’innovazione tecnologica in Sardegna”, con la quale la Regione Autonoma della Sardegna intende rafforzare il sistema della ricerca di base e quella scientifico-tecnologica della Sardegna e promuovere la Ricerca e l’Innovazione in settori strategici per l’economia regionale;

- il I° avviso pubblico per la presentazione e selezione di progetti di ricerca da finanziare nell’ambito del PNRR, pubblicato sul sito web del Ministero della Salute il 20 aprile 2022 e sulla Gazzetta Ufficiale della Repubblica Italiana, sulle seguenti tematiche: Proof of concept (PoC), Malattie Rare (MR) con esclusione dei tumori rari, Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e socio-assistenziali (Fattori di rischio e prevenzione; Eziopatogenesi e meccanismi di malattia);

- il progetto “Modulation of neuroinflammation and astrocyte activity in Alzheimer's disease: functional consequences and therapeutic perspectives” proposto dal Prof. Marco Pistis dell’Azienda Ospedaliero Universitaria di Cagliari per il bando PNRR 2022 del Ministero della Salute e acquisito sul sistema Workflow della ricerca 2.0 del Ministero della Salute con codice PNRR-MAD-2022-12375802;

Considerato

- che il progetto sopra citato non è stato oggetto di valutazione per il bando

PNRR del Ministero della Salute a causa di problemi tecnici riscontrati in fase di presentazione delle proposte e che, pertanto, a seguito di valutazione positiva di un referee scientifico esterno ai fini di un finanziamento con fondi regionali (prot. 9807 del 12 dicembre 2022), la Regione Autonoma della Sardegna – Centro Regionale di Programmazione ha stipulato una convenzione con il Soggetto attuatore/beneficiario Azienda Ospedaliero Universitaria di Cagliari per il progetto PNRR-MAD-2022-12375802 dal titolo Modulation of neuroinflammation and astrocyte activity in Alzheimer's disease: functional consequences and therapeutic perspectives, nell'ambito della realizzazione degli obiettivi previsti dalla L.R. n. 7 del 07.08.2007, facente parte integrante e sostanziale dell'anzidetta convenzione;

- che con la Legge Regionale 12 dicembre 2022, n. 22 è stato destinato l'importo di € 2.500.000,00 per la ricerca e l'innovazione;

Premesso che

- per l'Azienda Ospedaliero Universitaria di Cagliari, in qualità di Unità Operativa 1, partecipa al progetto la S.C. Farmacologia Clinica ed il Principal Investigator del progetto CUP G23C22002930002 è il Prof. Marco Pistis;

- il costo complessivo del progetto CUP G23C22002930002 ammonta ad euro 1.152.663,75 (unmilionecentocinquantaduemilaseicentosessantatre/75);

- la Regione Autonoma della Sardegna – Centro Regionale di Programmazione ha stabilito un finanziamento del progetto CUP

G23C22002930002 pari ad euro 926.200,00 (novecentoventiseimiladuecento/00);

- per la restante parte, pari ad euro 226.463,75 (duecentoventiseimilaquattrocentosessantatre/75), il progetto è cofinanziato dalle Unità Operative partecipanti;

- con Deliberazione n. ___ del __.06.2023 l'Azienda Ospedaliero Universitaria di Cagliari ha preso atto della convenzione attuativa tra la Regione Autonoma della Sardegna – Centro Regionale di Programmazione e l'Azienda Ospedaliero Universitaria di Cagliari in qualità di Soggetto attuatore/beneficiario;

- la Regione Autonoma della Sardegna – Centro Regionale di Programmazione ha erogato l'intero ammontare del finanziamento di euro 926.200,00 (novecentoventiseimiladuecento/00) in favore dell'Azienda Ospedaliero Universitaria di Cagliari, in qualità di Soggetto attuatore/beneficiario, incamerati da questa Azienda con ordinativo d'incasso n. 450 del 16.05.2023;

- ai fini della corretta attuazione della convenzione anzidetta è necessario ripartire il finanziamento alle Unità Operative 1, 2, 3 e 4, partecipanti al progetto PNRR-MAD-2022-12375802, secondo la ripartizione stabilita piano finanziario (Allegato 2), conferendo alle singole Unità Operative la porzione di competenza;

- il finanziamento è stato ripartito come segue: all'Azienda Ospedaliero Universitaria di Cagliari, in qualità di Unità Operativa 1, sono stati attribuiti euro 308.000,00 (trecentoottomila/00); all'Università degli Studi di Catania,

in qualità di Unità Operativa 2, sono stati attribuiti euro 203.100,00 (duecentotremilacento/00); alla Regione Marche, in qualità di Unità Operativa 3, sono stati attribuiti euro 212.000,00 (duecentododicimila/00); all'Università di Foggia, in qualità di Unità Operativa 4, sono stati attribuiti euro 203.100,00 (duecentotremilacento/00);

- in ossequio all'art. 7 della convenzione attuativa tra la Regione Autonoma della Sardegna e il Soggetto attuatore/beneficiario, ai fini della corretta definizione degli oneri ad essa conseguenti e per il conferimento della porzione di finanziamento così come definita in premessa, occorre stipulare singoli atti convenzionali tra l'Azienda Ospedaliero Universitaria di Cagliari e le singole Unità Operative partecipanti al progetto;

Tutto ciò premesso, le parti convengono e stipulano quanto segue:

Art. 1 – Premessa

Quanto precede forma parte integrante e sostanziale del presente atto.

Art. 2 – Oggetto

L'oggetto della convenzione è rappresentato dal finanziamento e la disciplina dei rapporti tra l'Unità Operativa 1 Azienda Ospedaliero Universitaria di Cagliari, in qualità di Soggetto Capofila, e l'Unità Operativa 4 Università degli Studi di Foggia, per la realizzazione del Progetto di Ricerca "Modulation of neuroinflammation and astrocyte activity in Alzheimer's disease: functional consequences and therapeutic perspectives".

Art. 3 – Descrizione delle attività

Le attività in capo ai partner della ricerca sono descritte nella scheda di Progetto (Allegato 1), allegata alla convenzione per farne parte integrante e

sostanziale, per un costo complessivo di euro 1.152.663,75 (unmilionecentocinquantaduemilaseicentosessantatre/75), di cui euro 926.200,00 (novecentoventiseimiladuecento/00) finanziati dalla Regione Autonoma della Sardegna e ed euro 226.463,75 (duecentoventiseimilaquattrocentosessantatre/75) cofinanziati dalle Unità Operative partecipanti, come indicato nel piano finanziario (Allegato 2).

Art. 4 – Modalità di esecuzione delle attività

I Partner si obbligano a realizzare il programma di ricerca secondo le modalità indicate nella scheda di Progetto (Allegato 1) e secondo il piano finanziario (Allegato 2).

Ogni variazione dell'intervento deve essere adeguatamente motivata e giustificata, anche quando scaturente da condizioni impreviste e imprevedibili.

I Partner si obbligano per tutta la durata di validità del presente atto a non condurre, né per conto proprio né per conto di terzi, altre attività e/o ricerche contenute nei programmi oggetto della medesima convenzione.

Art. 5 – Importo

Per la realizzazione dell'attività di ricerca oggetto del presente atto, l'Unità Operativa 1 Azienda Ospedaliero Universitaria di Cagliari corrisponderà all'Unità Operativa 4 Università degli Studi di Foggia euro 203.100,00 (duecentotremilacento/00).

Detto contributo, facente parte del finanziamento di euro 926.200,00 (novecentoventiseimiladuecento/00) corrisposto dalla Regione Autonoma della Sardegna – Centro Regionale di Programmazione al Soggetto

attuatore/beneficiario Azienda Ospedaliero Universitaria di Cagliari, trova copertura a valere sulla Legge Regionale 12 dicembre 2022, N. 22.

La porzione di contributo conferita dovrà essere utilizzata per spese inerenti strettamente ed esclusivamente alla realizzazione delle attività previste dal progetto e disciplinate dalla presente convezione.

Qualora le spese sostenute, che siano state correttamente rendicontate e riconosciute ammissibili dalla RAS-CRP a seguito della verifica amministrativa e contabile sul rendiconto finale, differiscano in eccesso dall'importo del contributo, l'importo di cui al comma 1 del presente articolo rimarrà invariato.

Art. 6 – Periodo di ammissibilità dei costi e durata delle attività

Il contributo è concesso a copertura dei costi sostenuti e regolarmente rendicontati dai Partner a decorrere dalla data dell'impegno di spesa ed entro i 24 mesi successivi, fatta salva la possibilità di proroga di ulteriori 12 mesi.

Art. 7 – Modalità di erogazione

Il contributo in favore dell'Unità Operativa 4 Università degli Studi di Foggia pari ad euro 203.100,00 (duecentotremilacento/00) sarà erogato dall'Unità Operativa 1 Azienda Ospedaliero Universitaria di Cagliari entro 30 giorni dalla data di stipula della presente convenzione, mediante accreditamento in un'unica soluzione su Girofondi Banca d'Italia n. 0159057, codice IBAN IT17Q0100003245432300159057.

Art. 8 – Disimpegni

In caso di disimpegno dei Programmi, la Regione Autonoma della Sardegna

– Centro Regionale di Programmazione ridurrà la dotazione finanziaria assegnata in misura corrispondente alla quota di spesa eventualmente non raggiunta.

Art. 9 – Durata e modifiche alla convenzione

L'efficacia della presente Convenzione è riferita all'annualità 2022 della L.R. n. 7/2007 e avrà il termine ultimo della completa realizzazione degli interventi trascorsi 24 mesi da tale data, salvo eventuale richiesta di proroga del progetto per un periodo non superiore a ulteriori 12 mesi.

L'eventuale richiesta di proroga potrà essere accolta da parte della Regione Autonoma della Sardegna – Centro Regionale di Programmazione solo se adeguatamente motivata.

È prevista la possibilità di una rimodulazione finanziaria iniziale delle voci di spesa nei primi sei mesi di attività.

La rimodulazione dovrà essere comunicata all'Unità Operativa 1 che dovrà avanzare la proposta alla Regione Autonoma della Sardegna – Centro Regionale di Programmazione e dovrà essere adeguatamente motivata.

Ulteriore rimodulazione, sempre motivata, potrà essere presentata in fase di chiusura del progetto.

Le rimodulazioni sono soggette all'approvazione del Regione Autonoma della Sardegna – Centro Regionale di Programmazione.

È prevista una valutazione intermedia dopo un periodo di 12 mesi dall'avvio del progetto. L'Unità Operativa 1 Azienda Ospedaliero Universitaria di Cagliari dovrà presentare una relazione scientifica delle attività svolte fino a quel momento e una rendicontazione parziale delle spese sostenute.

I Partner, al fine di ottemperare agli obblighi anzidetti, si impegnano a trasmettere all'Unità Operativa 1 Azienda Ospedaliero Universitaria di Cagliari entro i 30 giorni successivi allo scadere del periodo di valutazione le informazioni necessarie alla redazione della relazione scientifica sulle attività svolte nei 12 mesi considerati e la rendicontazione parziale delle spese sostenute di propria competenza.

La relazione scientifica e la rendicontazione saranno soggette alla valutazione in itinere da parte di un referee qualificato, secondo quanto previsto dall'art. 11, comma 1, della L.R. n. 7/2007.

La relazione scientifica finale e le attività di rendicontazione finale dovranno essere trasmesse alla RAS-CRP entro e non oltre i tre mesi successivi alla data di chiusura delle attività previste per il progetto.

I Partner, al fine di ottemperare agli obblighi anzidetti, si impegnano a trasmettere all'Unità Operativa 1 Azienda Ospedaliero Universitaria di Cagliari entro i 30 giorni successivi alla chiusura del progetto le informazioni necessarie alla redazione della relazione scientifica sulle attività svolte e la rendicontazione delle spese sostenute di propria competenza.

La documentazione finale trasmessa per i progetti finanziati sarà sottoposta alla valutazione ex post da parte di un referee qualificato, secondo quanto previsto dall'art. 11, comma 1, della L.R. n. 7/2007.

Eventuali modifiche e/o integrazioni alla presente Convenzione saranno apportate con apposito atto aggiuntivo.

Art. 10 – Obblighi di pubblicità

I Partner della ricerca dovranno dare adeguata pubblicità alla provenienza

del finanziamento.

Art. 11 – Aiuti di Stato

I Partner, nell'ambito del presente progetto, si impegnano a concordare preventivamente con la Regione Autonoma della Sardegna – Centro Regionale di Programmazione, tutte le previste attività eventualmente inerenti iniziative di trasferimento tecnologico ad imprese, nonché, in generale, tutte quelle che possano ricadere nell'ambito normativo degli aiuti di stato.

Art. 12 – Obblighi di custodia

Sarà cura dei Partner conservare tutta la documentazione originale relativa al progetto per l'intera durata e per almeno cinque anni dalla conclusione dello stesso, in modo da essere disponibile per eventuali controlli da parte dei funzionari della Regione Autonoma della Sardegna.

Art.13 – Proprietà intellettuale

I Partner convengono che nel rispetto delle norme e regolamenti di settore, i diritti di proprietà industriale e/o intellettuale relativi alla proposta oggetto della presente convenzione e i conseguenti diritti di utilizzazione economica sono attribuiti in parti eguali al Responsabile Scientifico e a RAS-CRP come anche ogni brevetto o qualsiasi altro diritto di proprietà industriale e/o intellettuale avente ad oggetto soluzioni innovative scaturenti dalla presente attività di ricerca.

Art. 14 – Adempimenti in tema di "Amministrazione Trasparente" ed Anticorruzione

I Partner si obbligano al rispetto della normativa sulla tracciabilità finanziaria

prevista dalla legge 13 agosto 2010, n. 136 e successive modifiche, nonché all'adempimento degli obblighi in materia di anticorruzione di cui alla legge n. 190 del 2012 e di pubblicità e trasparenza previsti dal D.lgs. 33/2013 con le modifiche di cui al D.lgs. 97/2016.

Al fine di dare attuazione agli obblighi in materia di trasparenza e anticorruzione, ogni Partner provvederà a nominare un Responsabile/Referente per la trasparenza e l'anticorruzione e a darne tempestiva comunicazione all'Unità Operativa 1 Azienda Ospedaliero Universitaria di Cagliari, che provvederà a darne comunicazione alla Regione Autonoma della Sardegna – Centro Regionale di Programmazione.

Il Partner si impegna alla adozione e all'utilizzo dei Patti di integrità da applicare nelle procedure per l'esecuzione di lavori e l'acquisizione di forniture e servizi avviate a valere sulle risorse trasferite in ossequio a quanto previsto dalla D.G.R n.30/16 del 16.06.2015 e a condividere i modelli dei patti di integrità adottati nell'ambito del protocollo d'Intesa sottoscritto in data 15 giugno 2015 dal Presidente della Regione e da Transparency International Italia.

Art. 10 – Trattamento dei dati personali e obblighi di riservatezza

I Partner si impegnano al trattamento dei dati personali ai sensi della disciplina vigente di cui al Regolamento Generale sulla protezione dei dati del Parlamento Europeo e del Consiglio n. 2016/679 del 27 aprile 2016, mediante strumenti ed accorgimenti idonei a garantirne la sicurezza.

Il trattamento è lecito, senza previo consenso, solo se e nella misura in cui ricorrono le condizioni di cui all' art. 6 del Regolamento (UE) n. 2016/679 per

le seguenti finalità:

1. Esecuzione di un compito di interesse pubblico o esercizio di pubblici poteri;

2. Adempimento da parte del titolare di obblighi di legge.

3. Perseguimento di un interesse legittimo.

Al di fuori delle ipotesi di cui al comma precedente, il trattamento dei dati è consentito, solo previo specifico consenso dell'interessato, ai sensi dell'art. 7 del Regolamento (UE) n. 2016/679.

I Partner sono tenuti a fornire all'interessato l'informativa secondo quanto previsto dagli artt. 13 e 14 del Regolamento (UE) n. 2016/ 679 sui seguenti punti: sulle finalità e la base giuridica del trattamento, sulla natura obbligatoria o volontaria del conferimento dei dati e le conseguenze di un eventuale rifiuto a prestare il consenso, sui soggetti o le categorie di soggetti ai quali i dati personali possono essere comunicati o che possono venirne a conoscenza, in qualità di responsabili anche esterni del trattamento, gli estremi identificativi del titolare e del responsabile del trattamento, del Data Protection Officer nominato, i diritti di cui agli articoli 15, 16-21 del GDPR e il diritto di reclamo al Garante per la Privacy.

Art.16 – Pantouflage

I Partner si impegnano a informare e vigilare sull'osservanza del divieto di cui all'art. 53, co. 16 ter, del d.lgs. 30/03/2001, n. 165 (Norme generali sull'ordinamento del lavoro alle dipendenze delle amministrazione pubbliche) in forza del quale i soggetti che, negli ultimi tre anni di servizio, abbiano esercitato poteri autoritativi o negoziali per conto della pubblica

amministrazione o, in ogni caso, abbiano avuto il potere di incidere in maniera determinante sul contenuto dei provvedimenti di esercizio dei poteri autoritativi o negoziali da parte dell'amministrazione sono soggetti al divieto di intraprendere, nei tre anni successivi alla cessazione del rapporto, qualsiasi attività lavorativa o professionale presso i soggetti privati destinatari degli atti dell'amministrazione espressione dei poteri sopra indicati.

A tale fine, in fase di attuazione del presente atto, i Partner sono tenuti a:

- accompagnare i contratti di lavoro, subordinato o autonomo, e gli atti di conferimento di incarichi esterni da apposita clausola o dichiarazione informativa relativa al divieto di pantouflage;

- all'atto di cessazione del rapporto di lavoro, collaborazione o dell'incarico fornire idonea informativa relativa al divieto di pantouflage;

- prevedere nei bandi di gara o negli atti prodromici agli affidamenti di contratti pubblici, anche mediante procedura negoziata, oltre che negli atti di autorizzazione, concessione, sovvenzione, contributo, sussidio, vantaggio economico di qualunque genere che i partecipanti sottoscrivano apposita dichiarazione circa la condizione soggettiva di non aver concluso contratti di lavoro subordinato o autonomo e comunque di non aver attribuito incarichi a soggetti già dipendenti dell'amministrazione in violazione del divieto di pantouflage;

- inserire negli atti e bandi di cui ai punti che precedono un esplicito richiamo alle sanzioni conseguenti alla violazione del divieto di pantouflage consistenti nella nullità del contratto e nel divieto per i soggetti privati che

l'hanno concluso o conferito, di contrattare con le pubbliche amministrazioni per i successivi tre anni, con contestuale obbligo di restituzione dei compensi eventualmente percepiti ed accertati ad essi riferiti,

- effettuare le verifiche amministrative necessarie in ordine a eventuali situazioni di violazione del divieto di pantouflage.

Art. 17 – Controversie

Eventuali controversie che dovessero insorgere tra le parti in merito alla presente convenzione saranno demandate all'autorità giurisdizionale competente. Foro competente è quello di Cagliari.

Art. 18 – Spese contrattuali e registrazione

Sono a carico dell'Unità Operativa 4, senza diritto di rivalsa e per intero, tutte le spese della presente convenzione, tutti gli oneri connessi alla sua stipulazione, compresi quelli tributari, l'imposta di bollo da assolvere in modalità virtuale ed ogni altra inerente.

Le parti si riservano di procedere alla registrazione fiscale della presente convenzione solo in caso d'uso.

Art. 19 – Norma di chiusura e rinvio

Per tutto quanto non espressamente disciplinato dalla presente convenzione, si rinvia alle norme di legge e di regolamento vigenti in materia sanitaria, amministrativa, civile e penale.

Letto, approvato e sottoscritto.

Per l'Azienda Ospedaliero Universitaria di Cagliari	**Per l'Università di Foggia**
Il Direttore Generale	**Il Magnifico Rettore**

1 - General information

Project code: PNRR-MAD-2022-12375802

Project topic: C2) Malattie croniche non trasmissibili, ad alto impatto sui sistemi sanitari e socio-assistenziali: eziopatogenesi e meccanismi di malattia

Applicant Institution: Sardegna

PI / Coordinator: PISTIS MARCO

Istitution that perform as UO for UO1: Azienda Ospedaliero-Universitaria di Cagliari

Call section: Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e socio-assistenziali

Proposal title: Modulation of neuroinflammation and astrocyte activity in Alzheimer's disease: functional consequences and therapeutic perspectives

Duration in months: 24

MDC primary: Neurologia

MDC secondary: Diagnostica

Project Classification IRG: Brain Disorders and Clinical Neuroscience

Project Classification SS: Clinical Neuroscience and Neurodegeneration - CNN

Project Keyword 1: Alzheimer¿s disease and other dementias.

Project Request: **Animals:** [X] **Humans:** [X] **Clinical trial:** [X]

Project total financing request to the MOH: € 1.000.000

Free keywords: Nneuroinflammation, astrocytes, microglia, peripheral biomarkers

Declarations

In case of a Synergy grant application 'Principal Investigator'(PI) means 'corresponding Principal Investigator on behalf of all Principal Investigators', and 'Host Institution' means 'corresponding Host Institution'.

1) The Principal Investigator declares to have the written consent of all participants on their participation and on the content of this proposal, as well as of any researcher mentioned in the proposal as participating in the project (either as other PI, team member or collaborator).	[X]
2) The Principal Investigator declares that the information contained in this proposal is correct and complete.	[X]
3) The Principal Investigator declares that all parts of this proposal comply with ethical principles (including the highest standards of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity — and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct).	[X]
4) The Principal Investigator is only responsible for the correctness of the information relating to his/her own organisation. Each applicant remains responsible for the correctness of the information related to him and declared above.	[X]

Personal data protection

Project Code: PNRR-MAD-2022-12375802	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Sardegna	**Applicant/PI Coordinator:** PISTIS MARCO

The assessment of your grant application will involve the collection and processing of personal data (such as your name, address and CV), which will be performed pursuant to Regulation (EC) No 45/2001 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data. Unless indicated otherwise, your replies to the questions in this form and any personal data requested are required to assess your grant application in accordance with the specifications of the call for proposals and will be processed solely for that purpose. Details concerning the purposes and means of the processing of your personal data as well as information on how to exercise your rights are available in the privacy statement. Applicants may lodge a complaint about the processing of their personal data with the European Data Protection Supervisor at any time.

Abstract

Alzheimer's Disease (AD) is the most common form of dementia with chronic and progressive neurodegeneration resulting in severe cognitive, memory, and behavioral impairment. The neurodegeneration in AD involves early synaptotoxicity, neurotransmitter disturbances, mitochondrial structural and functional changes accumulation of extracellular ß-amyloid (Aß) deposits and intracellular neurofibrillary tangles, gliosis, overt neuronal cells loss and associated brain atrophy.
Microglia and astrocytes, the predominant innate immune cells in the CNS, are strongly implicated in AD neuropathology. Astrocytes are involved in Aß-mediated neurodegeneration, as they release Aß and can be activated into a neurotoxic form by activated microglia and pro-inflammatory cytokines. Among them, TNF-alpha plays a major role by both initiating and regulating the cytokine cascade during an inflammatory response and by triggering a positive feedback loop that sustains the pathology. Moreover, astrocytic Ca2+ oscillations release gliotransmitters (including glutamate) and modulate synaptic functions and might be involved in early behavioral deficits observed in AD. Abnormal Ca2+ signalling may trigger the production of reactive oxygen species (ROS), which have been also associated with AD. Indeed, astrocytes are actively involved in ROS clearance but might also act as one of the main sources of detrimental ROS in AD. Excessive ROS production can stimulate the activation of microglia or cause direct neural damage.Additionally, glutamate, whose availability is also controlled by astrocytes through the Na+-dependent excitatory amino acid transporters (EAATs), can be used by neurons as an alternative substrate to compensate for metabolic dysfunctions commonly observed in AD.
On these bases, the main hypothesis of this project is that astrocytes are major contributors to disease progression. Hence, besides inducing neuronal death when activated, they regulate synaptic functions and neuronal activity, neurotransmitter release, cell metabolism and/or intracellular Ca2+ homeostasis, redox balance. We expect that manipulation of astrocytic function, and ultimately neuroinflammation, might slow disease progression. We will also determine the contribution of astrocytes by activation or suppression of Ca2+ intracellular waves by chemogenetics and antisense oligonucleotides, respectively.
Blood-derived biomarkers for AD are urgently needed. The introduction of highly sensitive immunoassays led to a rapid increase in the number of potential blood-derived biomarkers for diagnosis and monitoring of neurological disorders, including AD.
To test our hypothesis, we will pursue a multidisciplinary approach in animal models and AD patients.
In a mouse model of AD (3xTg-AD) we will carry out experiments by employing astrocytic-neuronal and astrocytic-microglia co-cultures, in vivo techniques (behavioral analysis, neurophysiology, brain microdialysis and fast-scan voltammetry), ex vivo and in vitro techniques (redox balance analysis, biochemical-immunohistochemistry analysis, slice electrophysiology).
In patients and in animal models, we will monitor several oxidative stress-related, inflammatory, mitochondrial and astrocytic biomarkers. This monitoring will be paralleled by deep phenotyping and patient stratification and will give us information about the correlation between peripheral biomarkers and disease progression and severity.

In order to best review your application, do you agree that the above non-confidential proposal title and abstract can be used, without disclosing your identity, when contacting potential reviewers? Yes

2 - Participants & contacts

Project Code: PNRR-MAD-2022-12375802	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Sardegna	**Applicant/PI Coordinator:** PISTIS MARCO

Operative Units

Institution that perform as UO	CF Institution	Department / Division / Laboratory	Role in the project	Southern Italy	SSN
1 - Azienda Ospedaliero-Universitaria di Cagliari	03108560925	SC Farmacologia Clinica-Clinica Neurologica	Clinical studies and preclinical experiments in animal models	X	X
2 - Università di Catania	02772010878	Dipartimento di SCIENZE BIOMEDICHE E BIOTECNOLOGICHE	Preclinical experiments in animal models	X	
3 - Marche	01464630423	Struttura Organizzativa Dipartimentale Complessa di Igiene Ospedaliera	Clinical studies and preclinical experiments in animal models		X
4 - Università di Foggia	94045260711	Deipartimento di MEDICINA CLINICA E SPERIMENTALE	Preclinical experiments	X	

Principal Research Collaborators

Key Personnel Name	Operative Unit	Role in the project
1 - Floris Gianluca	Azienda Ospedaliero-Universitaria di Cagliari	Clinical studies
2 - Cantarella Giuseppina	Università di Catania	Preclinical studies
3 - Magi Simona	Marche	Preclinical studies
4 - TRABACE LUIGIA	Università di Foggia	Preclinical studies
5 - Morgese Maria Grazia	Università di Foggia	Preclinical studies
6 Under 40 - Lattanzi Simona	Marche	Clinical studies
7 Under 40 - MAUGERI GRAZIA	Università di Catania	Preclinical studies

Key Personnel Name	Co-PI	Resp. CE	Resp. Animal	Birth Date	Gender
1 - Floris Gianluca	X			01/01/1968	M
2 - Cantarella Giuseppina			X	22/07/1966	F
3 - Magi Simona				27/04/1977	F
4 - TRABACE LUIGIA				19/02/1966	F
5 - Morgese Maria Grazia				16/09/1978	F
6 Under 40 - Lattanzi Simona				14/03/1985	F
7 Under 40 - MAUGERI GRAZIA				31/01/1987	F

Responsible who requests CE authorization: PISTIS MARCO

Additional research collaborators under 40 to hire

Key Personnel Name	Operative Unit	Birth Date	Gender	Role in the project	Degree	Actual Pos. and Inst.
0 - Santoni Michele	Azienda Ospedaliero-Universitaria di Cagliari	13/02/1991	M	preclinical experiments	PhD	Bursary with the University of Cagliari
1 - Burgaletto Chiara	Azienda Ospedaliero-Universitaria di Cagliari	01/11/1991	F	preclinical experiments	PhD	Post-doctral researcher (Assegnista) with the University of Catania

2.1 Administrative data of participating

Operative Unit Number 1:

Address: Azienda Ospedaliero-Universitaria
via Ospedale, 54 - 09124 Cagliari
Italy

PEC: dir.generale@pec.aoucagliari.it

Operative Unit Number 2:

Address: University of Catania School of Medicine
Department of Biomedical and Biotechnological Sciences
via santa Sofia 97, I-95125 Catania
Italy

PEC: protocollo@pec.unict.it

Operative Unit Number 3:

Address: Ospedali Riuniti di Ancona
via Conca 71
Torrette di Ancona (AN) 60126
Italy

PEC: aou.ancona@emarche.it

Operative Unit Number 4:

Address: University of Foggia
Department of Experimental Medicine
Viale Luigi Pinto
71122 FOGGIA (Italy)

PEC: protocollo@cert.unifg.it

Operative Unit Number 5 (self financing):

Address: N/A

PEC: N/A

2.2 Principal Investigator (PI) Profile

Last Name: PISTIS
First Name: MARCO
Last name at birth:
Gender: M

Title: Principal investigator
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 24/04/1968
Place of Birth: Iglesias

Official H index (Scopus or Web of Science): 39.0
Scopus Author Id:6701636492 **ORCID ID:**0000-0002-4622-3205 **RESEARCH ID:**A-3773-2013

Contact address

Current organisation name: Azienda Ospedaliero-Universitaria di Cagliari
Current Department / Faculty / Institute / Laboratory name: SC Farmacologia Clinica-Clinica Neurologica
Street: Dipartimento di Scienze Biomediche, Cittadella Universitaria
Postcode / Cedex: 09042
Town: Monserrato
Phone:+393405697726
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Cagliari, Cagliari, Italòy	Specialization / Specializzazione	Pharmacology and Clinical Pharmacology	1993	1997
University of Cagliari, Cagliari, Italy	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1986	1992

Personal Statement:

Prof. Marco Pistis is the project's PI. He will coordinate both preclinical and clinical research activities within the project. His research lines are within the field of neuropsychopharmacology and neurobiology of neurological and psychiatric disorders, with a focus in understanding the functions of the endocannabinoid system and its involvement in brain disorders. Recently, his group has been investigating the role in neurodegenerative disorders of endocannabinoid-like lipid neurotransmitters that activate a nuclear receptor termed PPAR¿.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Dundee	Department of Pharmacology and Neuroscience	Dundee (United Kingdom	Post-Doctoral researcher	1995	1998
Società Consortile Ricerche Neuropsicofarmacologiche a r.l. (Neuroscienze s.c.ar.l.),	Neurophysiology lab	Cagliari (Italy)	Research assistant	1999	2000
University of Cagliari	Department of Neuroscience	Cagliari (Italy)	Assistant Professor of Biopsychology and Psychopharmacology	2000	2001
University of Cagliari	Department of Biomedical Sciences,	Cagliari (Italy	Associate Professor of Pharmacology	2001	2014
University of Cagliari	Department of Biomedical Sciences	Cagliari (Italy	Full Professor of Pharmacology	2014	2022

Other awards and honors

2019 Elected member of the Board of Directors of the Italian Pharmacological Society
2017 Elected member of the Board of Directors of the Italian Pharmacological Society
2006 Fellowship Award, ECNP (European College of Neuropsychopharmacology)
2003 Award for basic pharmacological research, SIF-Farmindustria (Italian Pharmacological Society-Association of Italian Pharmaceutical Industries)
1995 Fellowship of the Italian Pharmacological Society (SIF)

Other CV informations

2017-present Member of the Board of Directors of the Italian Pharmacological Society
2015-present. Director of the Residency program in Medical Pharmacology and Toxicology (University of Cagliari).
2015-2021. Vice Director of the Department of Biomedical Sciences (University of Cagliari).
2010-present. Affiliated with The Institute of Neuroscience of the National Research Council
2013-2021. Head of the Neuroscience and Clinical Pharmacology Division-Dept. of Biomedical Sciences.
2007-2012 Vice-Director of the Dept. of Neuroscience and Head of the Neurophysiology and Neurochemistry Section

Selected peer-reviewed publications of the PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Transgenerational Sex-dependent Disruption of Dopamine Function Induced by Maternal Immune Activation	Article	821498	13	2022	10.3389/fphar.2022.821498	35211019	0	L
Repurposing peroxisome proliferator-activated receptor agonists in neurological and psychiatric disorders	Review	1025	14	2022	10.3390/ph14101025	34681249	0	L
N-Acylethanolamine Acid Amidase Inhibition Potentiates Morphine Analgesia and Delays the Development of Tolerance	Article	2722-2736	18	2021	10.1007/s13311-021-01116-4	34553321	1	L
Neurophysiological and neurochemical effects of the putative cognitive enhancer (S)-CE-123 on mesocorticolimbic dopamine system	Article	779	10	2020	10.3390/biom10050779	32443397	4	L

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
¿9-Tetrahydrocannabinol During Adolescence Attenuates Disruption of Dopamine Function Induced in Rats by Maternal Immune Activation	Article	202	13	2019	10.3389/fnbeh.2019.00202	31551729	9	L
Interactions between the endocannabinoid and nicotinic cholinergic systems: preclinical evidence and therapeutic perspectives	Review	1765 - 1777	233	2016	10.1007/s00213-015-4196-3	26728894	32	L
The PPAR¿ agonist fenofibrate attenuates disruption of dopamine function in a maternal immune activation rat model of schizophrenia	Article	549-561	25	2019	10.1111/cns.13087	30461214	8	L
Inhibition of N-acylethanolamine acid amidase reduces nicotine-induced dopamine activation and reward	Article	327-336	144	2019	10.1016/j.neuropharm.2018.11.013	30439418	17	L
PPAR¿ modulation of mesolimbic dopamine transmission rescues depression-related behaviors	Article	251-259	110	2016	10.1016/j.neuropharm.2016.07.024	27457507	32	L
Maternal immune activation disrupts dopamine system in the offspring	Article	1-10	19	2016	10.1093/ijnp/pyw007	26819283	35	L
PPAR-Alpha Agonists as Novel Antiepileptic Drugs: Preclinical Findings	Article	e64541	8	2013	10.1371/journal.pone.0064541	23724059	35	L
Hub and switches: Endocannabinoid signalling in midbrain dopamine neurons	Review	3276	367	2012	10.1098/rstb.2011.0383	23108546	58	L
Anandamide and 2-arachidonoylglycerol: Pharmacological properties, functional features, and emerging specificities of the two major endocannabinoids	Review	374-392	46	2012	10.1007/s12035-012-8299-0	22801993	71	L
PPAR¿ modulation of mesolimbic dopamine transmission rescues depression-related behaviors	Article	251-259	110	2019	10.1016/j.neuropharm.2016.07.024	27457507	32	L
Maternal immune activation disrupts dopamine system in the offspring	Article	1-10	19	2016	10.1093/ijnp/pyw007	26819283	35	L
Enhanced serotonin and mesolimbic dopamine transmissions in a rat model of neuropathic pain	Article	383-393	97	2015	10.1016/j.neuropharm.2015.06.003	26113399	50	L
Enhanced endocannabinoid-mediated modulation of rostromedial tegmental nucleus drive onto dopamine neurons in sardinian alcohol-preferring rats	Article	12716-12724	34	2014	10.1523/JNEUROSCI.1844-14.2014	25232109	40	L
PPAR¿ regulates cholinergic-driven activity of midbrain dopamine neurons via a novel mechanism involving ¿7 nicotinic acetylcholine receptors	Article	6203-6211	33	2013	10.1523/JNEUROSCI.4647-12.2013	23554501	66	L

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Selected peer-reviewed publications of the PI for the evaluation CV

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Maternal immune activation disrupts dopamine system in the offspring	Article	1-10	19	2016	10.1093/ijnp/pyw007	26819283	35

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Sex-specific tonic 2-arachidonoylglycerol signaling at inhibitory inputs onto dopamine neurons of Lister hooded rats	Article	93	7	2013	10.3389/fnint.2013.00093	24416004	36
Enhanced endocannabinoid-mediated modulation of rostromedial tegmental nucleus drive onto dopamine neurons in sardinian alcohol-preferring rats	Article	12716-12724	34	2014	10.1523/JNEUROSCI.1844-14.2014	25232109	40
Enhanced serotonin and mesolimbic dopamine transmissions in a rat model of neuropathic pain	Article	383-393	97	2015	10.1016/j.neuropharm.2015.06.003	26113399	50
Novel use of a lipid-lowering fibrate medication to prevent nicotine reward and relapse: Preclinical findings	Article	1838-1847	37	2012	10.1038/npp.2012.31	22453137	56
Hub and switches: Endocannabinoid signalling in midbrain dopamine neurons	Review	3276-3285	367	2012	10.1098/rstb.2011.0383	23108546	58
Reducing cannabinoid abuse and preventing relapse by enhancing endogenous brain levels of kynurenic acid	Article	1652-1661	16	2013	10.1038/nn.3540	24121737	61
PPAR¿ regulates cholinergic-driven activity of midbrain dopamine neurons via a novel mechanism involving ¿7 nicotinic acetylcholine receptors	Article	6203-6211	37	2013	10.1523/JNEUROSCI.4647-12.2013	23554501	66
Anandamide and 2-arachidonoylglycerol: Pharmacological properties, functional features, and emerging specificities of the two major endocannabinoids	Review	374	46	2012	10.1007/s12035-012-8299-0	22801993	71
Cell-specific STORM super-resolution imaging reveals nanoscale organization of cannabinoid signaling	Article	75-86	18	2015	10.1038/nn.3892	25485758	157

** Autocertificated

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MIUR PRIN 2005	University of Cagliari	2005	¿Esposizione ai cannabinoidi e all¿alcol durante l¿adolescenza: studio comportamentale ed elettrofisiologico in un modello animale di consumo volontario di alcol¿	Coordinator	88.000,00	https://prin.mur.gov.it/Iniziative
MIUR PRIN 2009	University of Cagliari	2009	¿Modificazioni bio-molecolari, immunitarie e morfo-funzionali spinali e sovraspinali in un modello murino di dolore neuropatico: prospettive terapeutiche mediante cellule mesenchimali umane e manipolazione farmacologia del signalling purinergico.¿	Collaborator	42.148,00	https://prin.mur.gov.it/Iniziative

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
FIRE-AICE (Fondazione Italiana per la Ricerca sull¿Epilessia-Associazione Italiana Contro l'Epilessia) Bando 2011	University of Cagliari	2011	Interactions between PPAR¿ nuclear receptors and nicotinic acetylcholine receptors as a novel strategy in pharmacoresistant epilepsies: preclinical and translational studies.	Coordinator	20.000,00	http://www.aice-epilessia.it/
UNICA-Fondazione di Sardegna	University of Cagliari	2017	¿Targeting neuroinflammation in psychiatric diseases: a multidisciplinary approach¿	Collaborator	75.000,00	https://www.unica.it/unica/it/ricerca_s05_ss01_sss02_s02.page
Regione Sardegna	University of Cagliari	2019	`Terapie farmacologiche innovative e approccio nutraceutico per la neuroinfiammazione nelle patologie psichiatriche e neurodegenerative¿	Coordinator	110.000,00	https://www.unica.it/unica/it/ricerca_s05_ss04_sss01_ba_2017.page
MIUR-Proof of concept 2018	University of Cagliari	2018	¿Caratterizzazione delle proprietà specifiche dell¿acido linoleico coniugato (CLA) in forma fosfolipidica per il trattamento di patologie psichiatriche a base neuroinfiammatoria e individuazione di biomarcatori dell¿efficacia terapeutica¿	Collaborator	197.400,00	https://www.miur.gov.it/-/decreto-di-approvazione-delle-graduatorie-finali-avviso-proof-of-concept
UNICA-Fondazione di Sardegna	University of Cagliari	2021	¿Targeting neurosteroids for neuroprotection in Parkinson¿s disease¿	Collaborator	75.000,00	https://www.unica.it/unica/it/ricerca_s05_ss01_sss02.page
MIUR-PRIN2017	University of Cagliari	2018	¿Bioenergetics and inflammation: novel insights for new therapeutic approaches in Alzheimer's Disease¿.	Coordinator	637.053,00	https://prin.mur.gov.it/
Fondazione di Sardegna, Progetti "Salute Pubblica, Medicina Preventiva e Riabilitativa	University of Cagliari	2022	La riconciliazione farmacologica nella diagnosi e nella prevenzione di patologia iatrogena: formazione presso i medici del territorio e attivazione di un servizio di consulenza¿.	Coordinator	10.000,00	https://www.fondazionedisardegna.it/contributi/esiti-bandi

2.3 CO-PI Profile

Last Name: Floris
First Name: Gianluca
Last name at birth:
Gender: M

Title: Clinical studies
Country of residence: ITALY
Nationality: italiana
Country of Birth: ITALY
Date of birth: 01/01/1968
Place of Birth: Quartu Sant'Elena

Official H index (Scopus or Web of Science): 22.0
Scopus Author Id:35589179800 **ORCID ID:**0000-0002-4622-3205 **RESEARCH ID:**AAD-2113-2022

Contact address

Current organisation name: Azienda Ospedaliero-Universitaria di Cagliari
Current Department / Faculty / Institute / Laboratory name: SC Farmacologia Clinica-Clinica Neurologica
Street: Policlinico "Duilio Casula"- Neurologia
Postcode / Cedex: 09042
Town: Monserrato
Phone:+393494932435
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Cagliari	Specialization / Specializzazione	Neurology	1995	1999
University of Cagliari	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1986	1995

Personal Statement:

Dr. Gianluca Floris possess expertise in n the field of neurological diseases, in particular in the diagnosis and treatment of dementia and cognitive disorders of adult. He is also an expert in clinical neuropsychology, adult neuropsychological tests, diagnosis and therapy of Parkinson's disease and parkinsonisms and other neurodegenerative diseases.
In this project, he will study neuroinflammatory aspects in Alzheimer¿s disease patients.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Azienda Ospedaliero-Universitaria di Cagliari	Centro Sclerosi Multipla	Cagliari (CA)	Neurologist	2002	2004
Azienda-Ospedaliera-Universitaria di cagliari	Clinica Neurologica	Monserrato (CA)	Neurologist	2004	2022

Other awards and honors

N/A

Other CV informations

2008/2009 Contract Professor of adult clinical neuropsychology in the degree course of Speech Therapy at the University of Cagliari

2012/2013 -2015/2016 Contract Professor of psychometrics, specialist degree course in Neurophysiopathology at the Faculty of Medicine of the University of Cagliari aa.

2018/2019 Contract Professor of Neurology, Specialization in Neurology at the Faculty of Medicine of the University of Cagliari,

Speaker and Organizer of Courses and Congresses in the National and International context with invited talks on Dementias, Neuropsychology, Parkinson's disease, Parkinsonisms, ALS, Multiple Sclerosis

Selected peer-reviewed publications of the Co-PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Early juvenile reading epilepsy and later frontotemporal dementia (FTD): expanding the clinical phenotype of C9ORF72 mutation?	Article	139-142	23	2022	10.1080/21678421.2021.1903505	33818195	0	L
Progressive apraxia of speech in a patient with a C9orf72 mutation	Article	608-609	17	2016	10.1080/21678421.2016.1183680	27166164	1	L
Isolated bipallidal lesions caused by extrapontine myelinolysis	Article	1722-1723	81	2013	10.1212/01.wnl.0000435297.80023.9e	24189999	2	F
Multiple Spontaneous Cerebral Microbleeds and Leukoencephalopathy in PSEN1-Associated Familial Alzheimer's Disease: Mirror of Cerebral Amyloid Angiopathy?	Article	535-538	47	2015	10.3233/JAD-150165	26401689	3	F
Phenotypic variability related to C9orf72 mutation in a large Sardinian kindred	Article	245-248	17	2016	10.3109/21678421.2015.1111904	26575405	5	F
Constructional apraxia in frontotemporal dementia associated with the C9orf72 mutation: Broadening the clinical and neuropsychological phenotype	Article	8-15	16	2015	10.3109/21678421.2014.959450	25285776	7	F
C9ORF72 repeat expansion and bipolar disorder - is there a link? No mutation detected in a Sardinian cohort of patients with bipolar disorder	Article	667-668	16	2014	10.1111/bdi.12210	24798095	10	F
Clinical phenotypes and radiological findings in frontotemporal dementia related to TARDBP mutations	Review	375-384	262	2015	10.1007/s00415-014-7575-5	25408367	33	F
Bipolar affective disorder preceding frontotemporal dementia in a patient with C9ORF72 mutation: Is there a genetic link between these two disorders?	Article	1155-1157	260	2013	10.1007/s00415-013-6833-2	23314407	34	F

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Frontotemporal dementia with psychosis, parkinsonism, visuo-spatial dysfunction, upper motor neuron involvement associated to expansion of C9ORF72: A peculiar phenotype?	Article	1749-1751	259	2012	10.1007/s00415-012-6444-3	22323211	45	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Fondazione Banco di Sardegna	Azienda Ospedaliero-Universitaria di Cagliari	2013	¿Disturbo Bipolare e demenza: studio di associazione con il gene C9ORF72 in una popolazione Sarda.¿	Coordinator	20.000,00	https://www.fondazionedisardegna.it/contributi/esiti-bandi

2.3 Research Collaborators n. 2

Last Name: Cantarella
First Name: Giuseppina
Last name at birth:
Gender: F

Title: Preclinical studies
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 22/07/1966
Place of Birth: Catania

Official H index (Scopus or Web of Science): 20.0

Scopus Author Id:7004454574 **ORCID ID:**0000-0002-7670-9337 **RESEARCH ID:**AHD-9609-2022

Contact address

Current organisation name: Università di Catania
Current Department / Faculty / Institute / Laboratory name: Dipartimento di SCIENZE BIOMEDICHE E BIOTECNOLOGICHE

Street: via Santa Sofia, 97
Postcode / Cedex: 95123
Town: Catania
Phone:+393493242241
Phone 2: 3493242241

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Palermo and University of Catania	PhD	Immunopharmacology	2000	2003
University of Catania	Specialization / Specializzazione	Clinical Pathology	1993	1998
University of Catania (Catania, Italy)	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1985	1992

Personal Statement:

Prof. Cantarella group has long lasting experience in Immunopharmacology with special focus on the nervous system. The Unit has deep knowledge in in vitro model of AD as well as in murine model of AD, particularly on the role of central and peripheral inflammation in neurodegenerative diseases. The Unit is affiliated to the Dept. of Biomedical and Biotechnological Sciences where is located the Center for Advanced Preclinical in vivo Research (CAPIR) that promotes preclinical and translational research based on in vivo experimentation in the biomedical field. CAPIR is equipped with the main support services for preclinical and translational experimental research, including the facilities for preclinical imaging such as PET/CT multimodal system.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Weizmann Institute of Science	Dept. of Biological Chemistry	Rehovot, Israel	Visiting Fellow	1997	2002
Etna Biotech srl	N/A	Catania (Italy)	Researcher	2002	2006
University of Catania	Department of Biomedical and Biotechnological Sciences	Catania (Italy)	Assistant Professor of Pharmacology	2006	2014
University of Catania	Department of Biomedical and Biotechnological Sciences	Catania (Italy)	Associate Professor of Pharmacology	2015	2022

Other awards and honors

1992 Barbagallo-Sangiorgi Award for Medical Diplomates, University of Catania School of Medicine
1996 CNR Grant for Young Researchers,
1999 Grant for Young Researchers University of Catania
1997-2002 Fellowship, The Weizmann Institute of Science, Rehovot, Israel 1997- 2002.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MIUR-PRIN2017	University of Catania	2017	Bioenergetics and inflammation: novel insights for new therapeutic approaches in Alzheimer's Disease	Collaborator	200.000,00	https://prin.mur.gov.it/

2.4 Research Collaborators n. 3

Last Name: Magi
First Name: Simona

Last name at birth:
Gender: F

Title: Preclinical studies
Nationality: Italiana
Date of birth: 27/04/1977

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Senigallia

Official H index (Scopus or Web of Science): 16.0

Scopus Author Id:8918355100 **ORCID ID:**0000-0002-8115-8226 **RESEARCH ID:**O-4651-2019

Contact address

Current organisation name: Marche
Current Department / Faculty / Institute / Laboratory name: Struttura Organizzativa Dipartimentale Complessa di Igiene Ospedaliera

Street: Via Tronto 10/A
Postcode / Cedex: 60126
Town: Ancona
Phone:+393394967965
Phone 2: 0039 071 220 6040

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University "Politecnica delle Marche"	PhD	Food and Health	2003	2006
University "Politecnica delle Marche"	Single-cycle master's degree / Laurea magistrale a ciclo unico	Biological Sciences	2018	2022

Personal Statement:
Prof. Magi is a scientist with a broad background in pharmacology, biochemistry and cellular biology.Prof. Magi has studied ion channels and transporters. She has a strong background in pharmacology and cellular physiology.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Texas-Southwestern Medical Center,	Department of Physiology	Dallas (USA)	Postoctoral researcher	2007	2008
University ¿Politecnica delle Marche¿	Department of Biomedical Sciences and Public Health	Ancona (Italy)	Assistant Professor of Pharmacology	2006	2019
University ¿Politecnica delle Marche¿	Department of Biomedical Sciences and Public Health,	Ancona (Italy)	Associate Professor of Pharmacology	2019	2022

Other awards and honors

N/A

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MIUR-PRIN 2017	University ¿Politecnica delle Marche¿	2018	¿Bioenergetics and inflammation: novel insights for new therapeutic approaches in Alzheimer's Disease¿,	Collaborator	211.500,00	https://prin.mur.gov.it/

2.5 Research Collaborators n. 4

Last Name: TRABACE
First Name: LUIGIA
Last name at birth:
Gender: F

Title: Preclinical studies
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 19/02/1966
Place of Birth: Matera

Official H index (Scopus or Web of Science): 25.0
Scopus Author Id:6602105770 **ORCID ID:**0000-0003-3073-8404 **RESEARCH ID:**E-5239-2016

Contact address

Current organisation name: Università di Foggia
Current Department / Faculty / Institute / Laboratory name: Deipartimento di MEDICINA CLINICA E SPERIMENTALE
Street: Viale Pinto
Postcode / Cedex: 71100
Town: Foggia
Phone:+393207981454
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Bari "A. Moro", Bari, Italy	PhD	Pharmacology and Medical Therapy	1993	1996
University of Bari A Moro, Italy	Single-cycle master's degree / Laurea magistrale a ciclo unico	Pharmacy	1986	1991

Personal Statement:

Prof. Luigia Trabace has for years been engaged in the study of animal models of neurodegenerative diseases with particular attention to Alzheimer's disease. Prof. Trabace was involved in the functional and biomolecular study in the rat and mouse of the etiopathogenetic mechanisms underlying this neurological disorder and its comorbidities.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Foggia	Department of Clinical and Experimental Medicine,	Foggia Italy	Full Professor of Pharmacology	2006	2022
University of Foggia	Department of Biomedical Sciences	Foggia, Italy	Associate Professor of Pharmacology	2001	2006
University of Foggia	Department of Biomedical Sciences	Foggia, Italy	Assistant professor of Pharmacology	1996	2001

Other awards and honors

None

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MIUR PRIN 2015	University of Foggia	2015	Biological and pharmacological HDAC inhibitors in a genetic model of epilepsy and in experimental pain models: role of the microbiome and SCFAs	Collaborator	150.000,00	https://prin.mur.gov.it/Pages/Index/21
MIUR PRIN 2017	University of Foggia	2017	Control of Neuroinflammation by PPAR ligands in Epilepsy, Autism and their comorbidity	Collaborator	130.375,00	https://prin.mur.gov.it/Pages/Index/43
MIUR PRIN 2020	University of Foggia	2020	Glymphatic system: a new player in the gut-brain axis. Natural resources to maintain homeostasis	Collaborator	113.019,00	https://prin.mur.gov.it/Pages/Index/23

2.6 Research Collaborators n. 5

Last Name: Morgese
First Name: Maria Grazia

Last name at birth: Morgese
Gender: F

Title: Preclinical studies
Nationality: Italiana
Date of birth: 16/09/1978

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Bari

Official H index (Scopus or Web of Science): 21.0

Scopus Author Id:56416635000 **ORCID ID:**0000-0002-9887-5504 **RESEARCH ID:**AFP-4801-2022

Contact address

Current organisation name: Università di Foggia
Current Department / Faculty / Institute / Laboratory name: Deipartimento di MEDICINA CLINICA E SPERIMENTALE
Street: Via Napoli 20
Postcode / Cedex: 71122
Town: Foggia
Phone:+393491787955
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Bari, Bari (Italy)	Specialization / Specializzazione	Hospital Pharmacy	2010	2014
University of Bari, Bari (Iyaly)	PhD	Clinical Pharmacology and Medical Therapy	2004	2007
University of Bari, Bari(Italy)	Single-cycle master's degree / Laurea magistrale a ciclo unico	Chemistry and Pharmaceutical Technology	1997	2002

Personal Statement:

Dr. Morgese has been studying the etiopathogenetic role of beta amyloid protein in murine models of Alzheimer's for several years. Her study focused on the neurochemical impairment induced by this peptide at both central and peripheral levels. Furthermore, Dr. Morgese investigated the role of oxidative stress induced by this peptide and the effects of antioxidant molecules on behavioral and neurobiological outcomes secondary to the overproduction of beta amyloid.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Texas, Health Science Center,	Dept. of Pharmacology	San Antonio, Texas, USA.	Post-doctoral-research Fellow	2005	2008
university of Foggia	Department of Experimental and Clinical Medicine	Foggia (Italy)	Post-doctoral researcher (Assegnista di ricerca)	2014	2015
University of Foggia	Depatment of Experimental and Clinical Medicine	Foggia (Italy)	Assistant Professorof Pharmacology	2016	2022

Other awards and honors

2015- 2016 PI Award SIF- Merck Sharp & Dohme

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
University of Foggia	University of Foggia	2022	Effects of long term malnutrition and diet deficiencies on the development of chronic diseases associated with neuropsychiatric comorbidities: a gender perspective study	Coordinator	31.657,00	https://www.unifg.it/sites/default/files/2022-02/pra-he-unifg-approvazione-atti.pdf
Società Italiana di farmacologia	University of Foggia	2015	Effects of PUFA-enriched diet in the animal model of depression induced by beta¿amyloid: role of the endocannabinoid system	Coordinator	25.000,00	https://www.sifweb.org/

2.7 Research Collaborators n. 6 - Under 40

Last Name: Lattanzi
First Name: Simona
Last name at birth:
Gender: F

Title: Clinical studies
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 14/03/1985
Place of Birth: Genova

Official H index (Scopus or Web of Science): 26.0
Scopus Author Id:55356677100 **ORCID ID:**0000-0001-8748-0083 **RESEARCH ID:**H-2971-2019

Contact address

Current organisation name: Marche
Current Department / Faculty / Institute / Laboratory name: Struttura Organizzativa Dipartimentale Complessa di Igiene Ospedaliera

Street: Via Conca, 71
Postcode / Cedex: 60022
Town: Ancona
Phone:+393331786519
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University "Politecnica delle Marche", Ancona (Italy)	PhD	Life Sciences-Neuroscience	2016	2019
University "Politecnica delle Marche", Ancona (Italy)	Specialization / Specializzazione	Neurology	2011	2016
University "Politecnica delle Marche", Ancona (Italy)	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	2004	2010

Personal Statement:
Prof. Simona Lattanzi will be in charge of clinical studies in Alzheimer's disease patients and will analyze real-world data collected within this project

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University "Politecnica delle Marche"	Department of Experimental and Clinical Medicine	Ancona (Italy)	Assistant Professor of Neurology	2018	2021
University "Politecnica delle Marche"	Department of Experimental and Clinical Medicine	Ancona (Italy)	Associate Professor of Neurology	2021	2022

Other awards and honors
Investigator Award for innovative digital technologies (Italian Neurology Society, 2020); Investigator Awards for excellent

research in cerebrovascular diseases at the XXIV European Stroke Conference, Hipponion Stroke National Prize (VI, VII editions), Italian Stroke Organization (2017-2019), Pisa Stroke Challenges 2017, Italian Society for the Study of Stroke jointly with the Mediterranean Stroke Society (2017), annual regional meeting of the Italian Neurological Society (2018)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
None	N/A	N/A	N/A	Collaborator	0,00	N/A

2.8 Research Collaborators n. 7 - Under 40

Last Name: MAUGERI
First Name: GRAZIA
Last name at birth:
Gender: F

Title: Preclinical studies
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 31/01/1987
Place of Birth: Grosseto

Official H index (Scopus or Web of Science): 12.0

Scopus Author Id:56183945000 **ORCID ID:**0000-0003-0173-4885 **RESEARCH ID:**AAI-8709-2020

Contact address

Current organisation name: Università di Catania
Current Department / Faculty / Institute / Laboratory name: Dipartimento di SCIENZE BIOMEDICHE E BIOTECNOLOGICHE

Street: Via Santa Sofia n.87
Postcode / Cedex: 95100
Town: Catania
Phone:+393401295236
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Catania, Catania (Italy)	PhD	Neuroscience	2014	2018
University of Catania, Catania (Italy)	Single-cycle master's degree / Laurea magistrale a ciclo unico	Pharmacy	2008	2013

Personal Statement:
Dr. Maugeri will be in charge of preclinical experiments in mouse models of Alzheimer's disease

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Catania	Department of Biomedical and Biotechnological Sciences (BIOMETEC)	Catania (Italy)	Assistant Professor of Anatomy	2021	2022

Other awards and honors
2020 Award "Premio alla Ricerca per Giovani Ricercatori GISN", XXX Convegno Nazionale del Gruppo Italiano per lo Studio della Neuromorfologia (GISN).
2015 Award for best oral communication, 69° Congresso Nazionale della Società Italiana di Anatomia e Istologia (SIAI).

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MIUR-PRIN 2020	University of Catania	2020	New Therapeutic tools to prevent diabetic retinopathy	Collaborator	171.229,00	https://prin.mur.gov.it/
University of Catania	University of Catania	2021	Effetto sinergico dell'asse PACAP-ADNP sulla riparazione corneale	Coordinator	5.000,00	https://www.unict.it/it/ricerca/ricerca-su-fondi-di-ateneo

2.9 Additional Research Collaborators n. 2 - Under 40 to hire

Last Name: Santoni
First Name: Michele
Last name at birth:
Gender: M

Title: preclinical experiments
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 13/02/1991
Place of Birth: Cagliari

Official H index (Scopus or Web of Science): 1.0
Scopus Author Id:57219306778 **ORCID ID:**0000-0003-4603-2369 **RESEARCH ID:**AHD-9593-2022

Contact address

Current organisation name: Azienda Ospedaliero-Universitaria di Cagliari
Current Department / Faculty / Institute / Laboratory name: SC Farmacologia Clinica-Clinica Neurologica
Street: Dipartimento di Scienze Biomediche
Postcode / Cedex: 09042
Town: Monserrato
Phone:+393409463879
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Cagliari	PhD	Neuroscience	2018	2022
University of Cagliari	Single-cycle master's degree / Laurea magistrale a ciclo unico	Pharmacy	2011	2017

Personal Statement:
Dr Santoni will be hired to conduct neurophysiological and neurochemical experiments in animal models of Alzheimer's disease

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Paracelsus University of Salzburg	Vienna division	Vienna (Austria)	Graduate student	2021	2021
University of Cagliari	Department of Biomedical Sciences, Division of Neuroscience and Clinical Pharmacology	Cagliari, Italy	Research bursary	2022	2022
University of Cagliari	Department of Biomedical Sciences	Cagliari, Italy	PhD Student in neuroscience	2018	2021

Other awards and honors

Best oral communication: 40° Congresso Nazionale della Società Italiana di Farmacologia, 9-13 Marzo 2021, Congresso Online ¿Investigation on the endocannabinoid system in a neurodevelopmental model of schizophrenia induced by maternal immune activation¿

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
None	N/A	N/A	N/A	Collaborator	0,00	N/A

2.10 Additional Research Collaborators n. 3 - Under 40 to hire

Last Name: Burgaletto
First Name: Chiara
Last name at birth:
Gender: F

Title: preclinical experiments
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 01/11/1991
Place of Birth: Bronte

Official H index (Scopus or Web of Science): 4.0

Scopus Author Id:57205336915 **ORCID ID:**0000-0002-5517-8223 **RESEARCH ID:**AHD-9628-2022

Contact address

Current organisation name: Azienda Ospedaliero-Universitaria di Cagliari
Current Department / Faculty / Institute / Laboratory name: SC Farmacologia Clinica-Clinica Neurologica
Street: via Giudice Giovanni Falcone, 19
Postcode / Cedex: 95034
Town: Bronte
Phone:+393292249681
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Catania, Italy	PhD	Neuroscience	2018	2022
University of Catania, Italy	Master's Degree / Laurea Magistrale	Cellular and molecular biology	2015	2017
University of Catania, Italy	Bachelor Degree / Laurea Triennale	Biology	2010	2015

Personal Statement:

Dr. Chiara Burgaletto will hired to carry out neurochemical and immunochemical experiments in mouse models of Alzheimer's disease

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Catania	Department of Biomedical and Biotechnological Sciences (BIOMETEC),	Catania (Italy)	Ph.D. student in Neuroscience	2018	2022
Weizmann Institute of Sciences	Department of Neurobiology	Rehovot (Israel).	Visiting fellow	2021	2021
University of Catania	Department of Biomedical and Biotechnological Sciences (BIOMETEC),	Catania (Italy)	Visitor Scientist	2022	2022

Other awards and honors

Recipient of SINS travel grant for attendance to 18th National Congress of the Italian Society for Neuroscience. Perugia, 26th-29th September 2019

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
None	N/A	N/A	N/A	Collaborator	0,00	N/A

2.17 Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Santoni Michele	Dietary Phospholipid-Bound Conjugated Linoleic Acid and Docosahexaenoic Acid Incorporation Into Fetal Liver and Brain Modulates Fatty Acid and N-Acylethanolamine Profiles	Article	834066	9	2022	10.3389/fnut.2022.834066	35360687	0	O
MAUGERI GRAZIA	PACAP and VIP inhibit the invasiveness of glioblastoma cells exposed to hypoxia through the regulation of HIFs and EGFR expression	Article	NOT_FOUND	7	2016	10.3389/fphar.2016.00139	NOT_FOUND	31	F
MAUGERI GRAZIA	Curcumin prevents high glucose damage in retinal pigment epithelial cells through ERK1/2-mediated activation of the Nrf2/HO-1 pathway	Article	17295-17304	234	2019	10.1002/jcp.28347	30770549	41	O
MAUGERI GRAZIA	PACAP and VIP Inhibit HIF-1?-Mediated VEGF Expression in a Model of Diabetic Macular Edema	Article	1209-1215	232	2017	10.1002/jcp.25616	27661459	42	F
MAUGERI GRAZIA	PACAP Modulates Expression of Hypoxia-Inducible Factors in Streptozotocin-Induced Diabetic Rat Retina	Article	501-509	57	2015	10.1007/s12031-015-0621-7	26202258	49	O
MAUGERI GRAZIA	The impact of physical activity on psychological health during Covid-19 pandemic in Italy	Article	e04315	6	2020	10.1016/j.heliyon.2020.e04315	32613133	283	F
Burgaletto Chiara	Repositioning of Immunomodulators: A Ray of Hope for Alzheimer¿s Disease?	Review	614643	14	2020	10.3389/fnins.2020.614643	33343293	7	O
Cantarella Giuseppina	Involvement of caspase 8 and c-FLIP<inf>L</inf> in the proangiogenic effects of the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)	Article	1505-1513	281	2014	10.1111/febs.12720	24438025	12	F
Floris Gianluca	C9ORF72 hexanucleotide repeat expansions in the Italian sporadic ALS population	Article	e15-e20	33	2012	10.1016/j.neurobiolaging.2012.02.011	22418734	68	O
Floris Gianluca	Genetic counselling in ALS: Facts, uncertainties and clinical suggestions	Article	478-485	85	2014	10.1136/jnnp-2013-305546	23833266	79	O

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Floris Gianluca	Genome-wide Analyses Identify KIF5A as a Novel ALS Gene	Article	1268-1283.e6	97	2018	10.1016/j.neuron.2018.02.027	29566793	253	O
Floris Gianluca	Frontotemporal dementia with psychosis, parkinsonism, visuo-spatial dysfunction, upper motor neuron involvement associated to expansion of C9ORF72: A peculiar phenotype?	Article	1749-1751	259	2012	10.1007/s00415-012-6444-3	22323211	42	F
Floris Gianluca	Mutations in the Matrin 3 gene cause familial amyotrophic lateral sclerosis	Article	664-666	17	2014	10.1038/nn.3688	24686783	296	O
Magi Simona	Physical and functional interaction of NCX1 and EAAC1 transporters leading to glutamate-enhanced ATP production in brain mitochondria	Article	e34015	7	2012	10.1371/journal.pone.0034015	22479505	30	F
TRABACE LUIGIA	Endogenous cannabinoid release within prefrontal-limbic pathways affects memory consolidation of emotional training	Article	18333-18338	111	2014	10.1073/pnas.1420285111	25489086	98	O
Morgese Maria Grazia	Memantine prevents memory consolidation failure induced by soluble beta amyloid in rats	Article	332	8	2014	10.3389/fnbeh.2014.00332	25285073	35	O
Morgese Maria Grazia	Extraction, characterization and in vivo neuromodulatory activity of phytosterols from microalga dunaliella tertiolecta	Article	3058-3067	19	2012	10.2174/092986712800672021	NOT_FOUND	42	O
Morgese Maria Grazia	Activation of PPAR gamma receptors reduces levodopa-induced dyskinesias in 6-OHDA-lesioned rats	Article	295-304	74	2015	10.1016/j.nbd.2014.11.024	25486547	46	O
Morgese Maria Grazia	Carvacrol: From ancient flavoring to neuromodulatory agent	Review	6161-6172	18	2013	10.3390/molecules18066161	23708230	66	O
Lattanzi Simona	Brivaracetam add-on for refractory focal epilepsy	Article	1344-1352	86	2016	10.1212/WNL.0000000000002545	26944275	82	F
Lattanzi Simona	Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage	Article	98-102	387	2018	10.1016/j.jns.2018.01.038	29571881	91	F
Lattanzi Simona	Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis	Review	1791-1804	78	2018	10.1007/s40265-018-0992-5	30390221	94	F
Lattanzi Simona	Neutrophil-to-Lymphocyte Ratio in Acute Cerebral Hemorrhage: a System Review	Review	137-145	10	2019	10.1007/s12975-018-0649-4	30090954	114	F

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Lattanzi Simona	Neutrophil-to-Lymphocyte Ratio Predicts the Outcome of Acute Intracerebral Hemorrhage	Article	1654 - 1657	47	2016	10.1161/STROKEAHA.116.013627	27165957	130	F
Morgese Maria Grazia	Emerging role of amyloid beta in stress response: Implication for depression and diabetes	Review	22 - 29	817	2017	10.1016/j.ejphar.2017.08.031	28844871	30	F
TRABACE LUIGIA	Neuroendocrine profile in a rat model of psychosocial stress: Relation to oxidative stress	Article	1385 - 1399	18	2013	10.1089/ars.2012.4569	23320850	68	L
TRABACE LUIGIA	Neurobiological links between depression and AD: The role of TGF-ß1 signaling as a new pharmacological target	Review	374 - 384	130	2018	10.1016/j.phrs.2018.02.007	29438781	80	O
TRABACE LUIGIA	Toll-like receptor 4-dependent glial cell activation mediates the impairment in memory establishment induced by ß-amyloid oligomers in an acute mouse model of Alzheimer's disease	Article	188 - 197	60	2017	10.1016/j.bbi.2016.10.012	27751869	86	L
TRABACE LUIGIA	Severe life stress and oxidative stress in the brain: From animal models to human pathology	Review	1475 - 1490	18	2013	10.1089/ars.2012.4720	22746161	173	O
Burgaletto Chiara	Tumor necrosis factor-related apoptosis-inducing ligand reduces the expression of the neuroprotective Na + /Ca 2+ exchanger isoform NCX3 in human neuroblastoma SH-SY5Y cells	Article	737-749	286	2019	10.1111/febs.14732	30552797	3	O
Burgaletto Chiara	Targeting the miRNA-155/TNFSF10 network restrains inflammatory response in the retina in a mouse model of Alzheimer¿s disease	Article	905	12	2021	10.1038/s41419-021-04165-x	34611142	3	F
Burgaletto Chiara	The immune system on the TRAIL of Alzheimer¿s disease	Review	298	17	2020	10.1186/s12974-020-01968-1	33050925	13	F
Cantarella Giuseppina	CHF5074 protects SH-SY5Y human neuronal-like cells from amyloid-beta 25-35 and tumor necrosis factor related apoptosis inducing ligand toxicity in vitro	Article	714-724	11	2014	10.2174/1567205011666140618104430	24938499	13	L
Cantarella Giuseppina	Beneficial effects of curtailing immune susceptibility in an Alzheimer's disease model	Article	166	16	2019	10.1186/s12974-019-1554-9	31409354	15	L
Cantarella Giuseppina	Ischemic tolerance modulates TRAIL expression and its receptors and generates a neuroprotected phenotype	Article	e1331	5	2014	10.1038/cddis.2014.286	25032854	24	F

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Cantarella Giuseppina	Neutralization of TNFSF10 ameliorates functional outcome in a murine model of Alzheimer's disease	Article	203-216	138	2015	10.1093/brain/awu318	25472798	42	F
Santoni Michele	N-Acylethanolamine Acid Amidase Inhibition Potentiates Morphine Analgesia and Delays the Development of Tolerance	Article	2722-2736	18	2021	10.1007/s13311-021-01116-4	34553321	1	O
Santoni Michele	Noradrenergic Source of Dopamine Assessed by Microdialysis in the Medial Prefrontal Cortex	Article	588160	11	2020	10.3389/fphar.2020.588160	33071798	7	O
Santoni Michele	Transgenerational Sex-dependent Disruption of Dopamine Function Induced by Maternal Immune Activation	Article	821498	13	2022	10.3389/fphar.2022.821498	35211019	0	F
Magi Simona	The dual face of glutamate: from a neurotoxin to a potential survival factor¿metabolic implications in health and disease	Review	1473 - 1488	8	2019	10.1007/s00018-018-3002-x	30599069	26	F
Magi Simona	Glutamate as a potential "survival factor" in an in vitro model of neuronal hypoxia/reoxygenation injury: Leading role of the Na+/Ca2+ exchanger	Article	731	9	2018	10.1038/s41419-018-0784-6	29955038	27	L
Magi Simona	Glutamate-induced ATP synthesis: Relationship between plasma membrane Na+/Ca2+ exchanger and excitatory amino acid transporters in brain and heart cell models	Article	603-614	84	2013	10.1124/mol.113.087775	23913256	38	F
Magi Simona	Intracellular Calcium Dysregulation: Implications for Alzheimer's Disease	Review	6701324	2016	2016	10.1155/2016/6701324	27340665	81	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

3 - Ethics

1. HUMAN EMBRYOS/FOETUSES	
Does your research involve Human Embryonic Stem Cells (hESCs)?	No
Does your research involve the use of human embryos?	No
Does your research involve the use of human foetal tissues / cells?	No

2. HUMANS	
Does your research involve human participants?	Yes
Does your research involve physical interventions on the study participants?	No
3. HUMAN CELLS / TISSUES	
Does your research involve human cells or tissues (other than from Human Embryos/ Foetuses?	No
4. PERSONAL DATA	
Does your research involve personal data collection and/or processing?	Yes
Does your research involve further processing of previously collected personal data (secondary use)?	Yes
5. ANIMALS	
Does your research involve animals?	Yes
6. ENVIRONMENT & HEALTH and SAFETY	
Does your research involve the use of elements that may cause harm to the environment, to animals or plants?	No
Does your research deal with endangered fauna and/or flora and/or protected areas?	No
Does your research involve the use of elements that may cause harm to humans, including research staff?	No
7. DUAL USE	
Does your research involve dual-use items in the sense of Regulation 428/2009, or other items for which an	No
8. EXCLUSIVE FOCUS ON CIVIL APPLICATIONS	
Could your research raise concerns regarding the exclusive focus on civil applications?	No
9. MISUSE	
Does your research have the potential for misuse of research results?	No
10. OTHER ETHICS ISSUES	
Are there any other ethics issues that should be taken into consideration? Please specify	No

I confirm that I have taken into account all ethics issues described above and that, if any ethics issues apply, I will complete the ethics self-assessment and attach the required documents. [X]

4 - Call-specific questions

Eligibility	
I acknowledge that I am aware of the eligibility requirements for applying as specified in the Call-PNRRXXXX_M6/C2, and certify that, to the best of my knowledge my application is in compliance with all these requirements. I understand that my proposal may be declared ineligible at any point during the evaluation or granting process if it is found not to be compliant with these eligibility criteria.	X
I confirm that the proposal that I am about to submit draws substantially don't repeat on an existing or recently finished GRANT funded.	X
Data-Related Questions and Data Protection (Consent to any question below is entirely voluntary. A positive or negative answer will not affect the evaluation of your project proposal in any form and will not be communicated to the evaluators of your project.)	
For communication purposes only, the MoH asks for your permission to publish,in whatever form and medium, your name, the proposal title, the proposal acronym, the panel, and host institution, should your proposal be retained for funding.	X
Some national and regional public research funding authorities run schemes to fund MoH applicants that score highly in the MoH's evaluation but which can not be funded by the MoH due to its limited budget. In case your proposal could not be selected for funding by the MoH do you consent to allow the MoH to disclose the results of your evaluation (score and ranking range) together with your name, non- confidential proposal title and abstract, proposal acronym, host institution and your contact details to such authorities?	X
The MoH is sometimes contacted for lists of MoH funded researchers by institutions that are awarding prizes to excellent researchers. Do you consent to allow the MoH to disclose your name, non-confidential proposal title and abstract, proposal acronym, host institution and your contact details to such institutions?	X
The Ministry of Health occasionally could contacts Principal Investigators of funded proposals for various purposes such as communication campaigns, pitching events, presentation of their project's evolution or outcomes to the public, invitations to represent the Ministry of Health in national and international forums, studies etc. Should your proposal be funded, do you consent to the Ministry of Health staff contacting you for such purposes?	X
For purposes related to monitoring, study and evaluating implementation of MoH actions, the MoH may need that submitted proposals and their respective evaluation data be processed by external parties. Any processing will be conducted in compliance with the requirements of Regulation 45/2001.	

5 – Description Project

Summary description

Astrocytes are major contributors to AD progression. They regulate synaptic functions and neuronal activity, neurotransmitter release, cell metabolism, Ca2+ homeostasis, redox balance and when activated they induce neuronal death. We expect that manipulation of astrocytic function, and ultimately of neuroinflammation, might slow disease progression. We will also determine the contribution of astrocytes by modulating Ca2+ intracellular waves by chemogenetics and antisense oligonucleotides, respectively.
To test our hypothesis, we will pursue a multidisciplinary approach in animal models and AD patients.

In a mouse model of AD we will employ astrocytic-neuronal and astrocytic-microglia co-cultures, in vivo, ex vivo and in vitro techniques. In patients, we will monitor a panel of peripheral redox, inflammatory, mitochondrial and astrocytic biomarkers. This monitoring will be paralleled by deep phenotyping and patient stratification to correlate with disease progression and severity.

Background / State of the art

Alzheimer's disease (AD) is a progressive neurodegenerative disorder responsible for most dementia cases in the elderly. The development of effective therapies is a priority in neuroscience research. However, the complexity of AD pathogenic framework has so far limited the identification of effective mechanism-based therapies.
Microglia and astrocytes, the predominant innate immune cells in the CNS, are strongly implicated in AD neuropathology. Microglial cells are major immunological effector of the innate immune system in the brain and mediate functions contributing to neuronal survival and synaptogenesis. Astrocytes contribute to maintain CNS homeostasis and sustain neuronal survival by releasing gliotransmitters and neurotrophic factors essential for normal brain functions and cognitive activity. Astrocytes participate in synaptic functions and might be involved in early behavioral deficits observed in AD.
Blood-derived biomarkers for AD are urgently needed. The introduction of highly sensitive immunoassays led to a rapid increase in the number of potential blood-derived biomarkers for diagnosis and monitoring of neurological disorders. In particular a wide range of metabolic, inflammatory and astrocytic peripheral biomarker are being investigated for their potential to predict or anticipate disease progression.

Description and distribution of activities of each operating unit

All UO are composed by researchers with a strong and internationally recognized background in Neuroscience and Neurology, with expertise required for the development of the present proposal. AOU-CA and Ospedali Riuniti di Ancona (ORA) involve experienced neurologists who will be in charge for clinical studies. Each Unit, except for UniFG, will be responsible for housing, genotyping, breeding and treatment of its own experimental animals. Animals will be bred in Animal Facilities in the 3 RU, all licensed by the Italian Department of Health and adhering strictly to the Italian regulations (D.L. 26/2014). UniFG will perform experiments on specimens delivered by the other UO. We have already the license for the use of experimental animals with full description of the protocols and procedures. The PI will monitor the progression of the experiments and will be responsible for sharing data and for the establishment of a constant information flow between each RU. Care will be taken to organize the treatments and experiments in accordance between structures. The PI will also encourage the publication of data in peer-reviewed open-access scientific journals.
Role of AOU-CA
UO1 will be in charge for enrolment deeply phenotyping of AD and dementia patients. Inflammatory markers will be measured in blood samples and, when available, in CSF. Preclinical eexperiments in in this UO will be carried out in AD mice. The progression of AD in mice will be monitored by measuring biomarkers of AD, central markers of neuroinflammation, and NFk-B signalling. In selected group of animals we will perform in vivo microdialysis for brain levels of Glu/DA and metabolites in the PFC, NAc, CPu; behavioral testing; in vivo and in vitro electrophysiology and chemogenetics in the PFC, NAc, CPu.
Role of UniCT.
This UO will study:
Glial activation and inflammatory/immune response in different in vitro experiments. Also the Unit will follow up of T cell tracking and glia activation in 3xTg-AD mice. The Unit will perform all the biochemical and immunohistochemical evaluation in the brain and in peripheral immune system organs to identify the glia phenotype status as well as the crosstalk between microglia and astrocytes and T cells trafficking.
Role of ORA(UO3)
In collaboration with UO1 ORA will be in charge for enrolment deeply phenotyping of AD and dementia patients. Astrocytic and mitochondrial markers will be measured in blood samples and, when available, in CSF. This Unit will investigate how astrocytic Ca2+ dysregulation, neuroinflammation and glutamate release could impact neuronal dynamics in an in vitro

model of AD.
Role of UniFG
UniFg unit will be in charge for the molecular analyses on the samples from the different experimental models developed by the other units. This UO will analyze mediators of redox balance and a panel of metabolic markers (i.e.e of the kynurenine pathway) in the biological samples derived from patients and AD mice.

5.4 Specific Aims and Experimental Design

Specific aim 1

Role of astrocytes and crosstalk between microglia and astrocytes in early deficits and neurodegenerative processes AD models: immunological, neurochemical, behavioral and neurophysiological correlates

In AD we observe a progressive neuronal damage associated with chronic activation of the brain resident innate immune cells and increased peripheral leukocyte access across the BBB. This supports the notion of a cross-talk system between peripheral and CNS immunocytes. In this regard, TRAIL, a cytokine belonging to the TNF superfamily and specifically expressed in the human AD brain, modulates both the innate and adaptive immune response in AD-related neuroinflammation, and is abundantly released by activated glia, CNS-infiltrating macrophages and damaged neurons, acting as a potential cell death signal. Since a fine-tuning of the immune response is crucial to ensure proper nervous system functioning, we focused on the role of the TRAIL in AD-related neuroinflammation. TRAIL contributes to neuroinflammation in AD mice by recruiting peripheral Treg cells into the brain, thus limiting the beneficial effects of the immune response against accumulating A¿. Consistently, anti-TRAIL antibodies blunt inflammatory processes either in the spleen and hippocampus. Considering that the brain-immune crosstalk is impaired in aging and in AD, and the orchestrating role of TRAIL in key events of the inflammatory/immune response, we will to comprehensively outline immune-responsiveness, monitoring it along with immunopharmacological modulation of TRAIL pathway and disease progression in blood, lymphoid tissues (i.e., spleen, liver), and in the brain in AD mice. This will allow us to dynamically characterize resident versus systemic immunocytes recruited into the CNS. In particular, we will study subtypes of T-cells (i.e., T-helper (Th), T cytotoxic or T regulatory (Treg)) or T-cell exhaustion, monocytes subsets using accurate gating strategy and complete flow cytometry panel. Moreover, with the aim to better understand whether AD progression is related to an impaired immune response depending upon alteration of a specific component of the immune system, we will study the immune profile in AD patients throughout the pathology progression. To achieve this goal, we will comprehensively investigate peripheral blood immunity using the whole blood quantitative flow cytometry. Since AD implies a systemic inflammatory response, in parallel we will test serum levels of immune/inflammatory mediators by multiplex ELISA test. Such comparative analysis will be supported by a bioinformatic approach.
To further assess the role of glial cells and their crosstalk with neurons, we will carry out the following analysis in animal models:
Chemogenetic experiments
In vivo chemogenetic stimulation of astrocytic Gq signaling can be achieved through adenovirus-mediated expression of the Designer Receptor Exclusively Activated Designer Drugs (DREADD)-hM3Dq receptor under the GFAP promoter, followed by systemic administration of the cognate synthetic ligand clozapine-N-oxide (CNO). CNO will selectively activate the Gq-coupled hM3Dq and trigger Ca2+ waves in astrocytes and release of gliotransmitters.
Vivo morpholinos.
vMO are modified antisense oligonucleotides designed to be delivered in vivo. We will chronically administer with ICV infusion, vMO designed to inhibit the expression of type 2 IP3R (IP3R2, the predominant form in astrocytes). This treatment will diminish o abolish IP2R2-mediated Ca2+ waves and gliotransmitter release..
In animals that undergo astrocytic manipulation, both by immunomodulation, chemogenetic or vMO, early markers of disease progression will be assessed at specific time points by measuring AD markers and markers of inflammation,

emotionality and anxiety-like behavior, synaptic connectivity and synaptic strength under different conditions of astrocyte activity induced by electrophysiological studies (in vivo and in vitro).

Specific aim 2

Evaluating the role of oxidative stress in AD patients and in animal models of AD
Oxidative stress results from an imbalance between the production and accumulation of reactive oxygen species (ROS). These species are commonly produced during cell metabolism and hold both beneficial and detrimental properties thus representing a double-edged sword in biological systems. Indeed, it has been reported that under ROS can act as signaling molecules, but it is widely accepted that when produced in excessive amounts or in conditions of reduced antioxidant capacity, they can oxidize all major biomolecules. As regards to neurodegenerative pathologies, and as regard to Alzheimer's disease in particular, amyloid beta (Aß) represents a cellular insult prompting to neuroinflammatory and pro-oxidant conditions. Indeed, UNIFG unit has demonstrated that a single icv injection of this peptide leads to increased pro-oxidant species accompanied by pro-inflammatory and pro-oxidant molecules such as the tryptophan derivate Kynurenine (KYN). Accordingly, many authors have shown that AD progression can be monitored by using peripheral biomarkers and the use of oxidative stress biomarkers might represent an alternative that can be carried out and paralleled either in humans or in animal models. It is worth noting that oxidized biomolecule products produced by ROS can be used along with ROS levels and the activity of antioxidant enzymes. Therefore, in the present proposal, we aim to evaluate in peripheral plasma and erythrocytes from AD patients the levels of several oxidative stress biomarkers such as : MDA levels, 3-nitrotyrosine (3-NT) for protein oxidation; 8-OH-2¿-deoxyguanosine, 8-OH-guanosine, thiobarbituric acid-reactive substances (TBARS), iso- and neuroprostane formation, 2-propen-1-al (acrolein), and 4-hydroxy-2-trans-nonenal (HNE) for lipid peroxidation; considering that it has been shown that increased levels of 3-NT, and HNE have been reported as the earliest alterations in AD. Parallel evaluations will be carried out in central and peripheral samples derived from animal models.
In addition, the essential amino acid tryptophan (TRP), accounting for of serotonin synthesis for approximately 1% is largely (95%) converted into KYN and into its metabolites, ultimately resulting in oxidized form of nicotinamide adenine dinucleotide (NAD+). KYN metabolites, such as 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid have been involved in the development of oxidative damages in the central nervous system cells, also in AD, and they can be also produced in the blood. Therefore, we will quantify KYN and its metabolites, as well as producing enzymes, such as kynurenine 3-monooxygenase (KMO) and indoleamine 2,3-dioxygenase (IDO), in central and peripheral samples derived from animals and in peripheral samples of Ad patients.

Specific aim 3

Different interrelated factors may converge on AD progression, including mitochondrial alterations, oxidative stress, neuroinflammation, and dysregulation of intracellular Ca2+ homeostasis. Exaggerated Ca2+ signalling may trigger production of reactive oxygen species (ROS), which in turn may compromise mitochondrial activity and energy balance, fueling neurodegeneration. The activity/expression of proteins involved in controlling intracellular Ca2+ homeostasis (e.g. Na+/Ca2+ exchanger, NCX), can be significantly altered. Interestingly, a link between the dysregulation of Ca2+ homeostasis and the levels of pro-inflammatory cytokines has been described in AD, suggesting that Ca2+ dyshomeostasis is not restricted to neurons. Here, the active role of astrocytes in promoting or in arresting inflammation and neurodegeneration was recently highlighted also in AD. Aberrant Ca2+ signaling in astrocytes may significantly contribute to an inflammatory response in AD that, in turn, negatively impacts neuronal Ca2+ homeostasis. Furthermore, astrocytes, by releasing glutamate provide a fine control of neuronal metabolism and cell-to-cell comunication, which play a key role in AD. In this scenario, IP3-Receptor (R)-mediated Ca2+ signals represent a point of convergence as they control neuroinflammation and gliotrasmitter release. Astrocytic glutamate is crucial for neurons as they use glutamate as an alternative substrate in metabolic dysfunctions commonly observed in AD. Therefore, systems that modulate glutamate availability may be relevant to AD progression. Among them, the Na+-dependent excitatory amino acid transporters

(EAATs) such as EAAT2/GLT-1, expressed by astrocytes, may have a central role. Indeed, in cultured astrocytes, Aß treatment reduces GLT-1 expression, and human astrocytes derived from patients with AD display a decreased glutamate uptake, paralleled by a reduced expression of glutamate transportes, including GLT-1. This may actually reflect not only cell loss, but also deficits in metabolic pathways that utilize glutamate as metabolite for ATP synthesis.
In this framework, given the key role of mitochondria in energy production, the high energy expenditure of neurons and their close metabolic relationship with astrocytes, it is not surprising that mitochondrial impairment represents a key factor in neurodegeneration development and progression.
Interestingly, in AD mitochodrial dysfunctions seem to play a main role in the overall pathological setting, since also peripheral tissues of AD patients, such as platelets¿where no elevated A¿¿ levels have been found¿show mitochondrial dysfunction with enhanced ROS formation, increased oxidative stress and decreased ATP levels.
On these bases, we hypothesize that astrocytes, through the release of pro-inflammatory cytokines, the activation of IP3-R dependent mechanisms and GLT-1 can influence AD progression by affecting neuronal dynamics in terms of cell survival, mitochondrial activities (redox balance control, Ca2+ buffering, energy production) and cytoplsmic Ca2+ alteration. To verify our working hypothesis, we will manipulate astrocytic functions in astrocyte-neuron co-cultures that will reproduce AD features in in vitro preclinical studies. Clinical studies will be performed as well to investigate astrocytic contribution to AD progression, an aspect that has been so far largely overlooked. To this purpose, we will evaluate astrocyte biomarkers in blood and/or liquor from AD patients at different stages, in comparison with healthy age- and sex- matched controls.
Furthermore, to highlight the importance of mitochondria and energy balance in the overall AD setting, we will also perform a comprehensive evaluation of the mitochondrial profile in peripheral blood lymphocytes of AD patients, to assess whether peripheral mitochondrial biomarkers would be associated with AD diagnosis and heterogeneity in mitochondrial defects would exist according to disease stage.

Experimental design aim 1

Preclinical studies
To evaluate brain-immune crosstalk in AD, 3xTg-AD mouse model and WT mice will be characterized at different time-points (3, 9, and 15-months of age) [1].
To study immune response in peripheral blood, lymphoid tissues and brain of AD mice, the following protocol will be used:
WP1.1 Accurate gating strategies and complete flow cytometry panel will be used to study immunophenotype of T cells subtypes (Th, Tc, Tregs) or T¿cell exhaustion. CD4 and CD8 staining will be combined with specific extracellular markers, intracellular transcription factors and cytokine production profiles [2, 3]. Exhaustion of CD4 and CD8 T cells will be evaluated through the co-expression of inhibitory immune checkpoints .
WP1.2 Phenotype of monocyte/macrophage populations [4] will be studied using flow cytometry.
WP.1.3 Microglia activation markers (CD86, CD206 and CD68) within Iba1 positive cells and astrocytes activation markers (C3, S100A10) within GFAP positive cells [5] will be analyzed by IHC in specific brain areas. Protein analysis by WB and IHC will be used to investigate either the protective or detrimental effects of brain-resident and infiltrated immunocytes on neurons (i.e., cell death, toxic protein accumulation). Moreover, pro-inflammatory (i.e., TNF-a, IL-6 and IL-1¿) and anti-inflammatory (IL-10, IL-4, IL-13) cytokines production correlated to glial activation phenotypes will be evaluated in brain lysates by WB.
Next, to investigate the counter-perturbations induced by TRAIL-immunotherapy, 3xTg-AD mice and WT mice will be enrolled at 3-months of age and treated with TNFSF10-neutralizing antibody or vehicle twice a month for 12 months. Animals will be sacrificed at 15 months and the immune response will be delineated in the above-mentioned organs following the same experimental procedures.
To delineate the role of astrocytes and neuron-astrocytes crosstalk we will carry out the following experiments
WP1.4 Chemogenetic experiments will be carry out in neurophysiology set-ups. In vivo chemogenetic stimulation of astrocytic Gq signaling will be achieved through adenovirus-mediated expression of the DREADD-hM3Dq receptor under

the GFAP promoter, followed by systemic administration of the synthetic ligand clozapine-N-oxide (CNO). CNO will selectively activate the Gq-coupled hM3Dq and trigger Ca2+ waves in astrocytes and gliotransmitters release. The second approach will be with vMO, modified antisense oligonucleotides designed to inhibit the expression of type 2 IP3R (IP3R2, the predominant form in astrocytes). vMO will be ICV infused in vivo via Alzet minipumps [6, 7]. This treatment will diminish o abolish IP2R2-mediated Ca2+ waves and gliotransmitter release. During vMO infusion, mice will be monitored as described below. In these animals, synaptic connectivity and synaptic strength will be assessed by electrophysiological studies: in vivo extracellular single-unit recordings from neurons in the NAc /striatum and PFC [8-10]; ex vivo patch-clamp recordings [11-13] and multiarray electrodes (MEA) in acute brain slices.
WP 1.5 Behavioral experiments to assess cognitive performance, emotionality and anxiety-like behavior.
Clinical studies
WP 1.6 Study of the immune profile in AD patients throughout the pathology progression.
The Neurology Clinic of AOU-CA will enroll 200 AD patients and healthy controls, following the authorization of the Ethical Committee and informed consent. The diagnosis of AD will be based on the DSM-V, NINCDSADRDA criteria and MRI. The CDR (Clinical Dementia Rating) scale will be used to identify the stage of AD. Blood samples will be collected during routine examinations, shipped to the other OU and analyzed as described in AIM 1, 2 and 3
Phenotype of T cells and monocytes in the peripheral blood will be characterized using flow cytometry. In parallel, we will test serum levels of immune/inflammatory mediators by multiplex ELISA test.

Experimental design aim 2

Preclinical studies
Many authors have shown that AD progression can be monitored by using peripheral biomarkers and the use of oxidative stress biomarkers might represent an alternative that can be carried out and paralleled either in humans or in animal models [14]. On the other hand, the aberrant activation of the Kynurenine pathway, also called TRYCAT system because of the tryptophan catabolism, is an emerging field of research in AD and related comorbidities. Indeed, TRYCAT is over-activated after immune challenge, or in consequence to inflammatory and oxidative stressful conditions, all typical of AD.
WP 2.1 Therefore, according to the timepoints indicated in AIM 1 in 3XTgAD mice, UNIFG will evaluate several biomarkers related to the production of oxidative species and products of tissue oxidation. Thus, we aim to evaluate the levels of several oxidative stress biomarkers such as: 3-nitrotyrosine (3-NT) for protein oxidation; 8-OH-2¿-deoxyguanosine, MDA levels and thiobarbituric acid-reactive substances (TBARS), iso- and neuroprostane formation, 2-propen-1-al (acrolein), and 4-hydroxy-2-trans-nonenal (HNE) for lipid peroxidation. These quantifications will be carried out by ELISA and colorimetric/fluorometric assay kit.
WP 2.2 As regard to TRYCAT, KYN metabolites, such as 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid also involved in the development of oxidative damage either in the central nervous system, also in AD, and at the peripheral blood level. Therefore, we will quantify KYN and its metabolites, as well as producing enzymes, such as kynurenine 3-monooxygenase (KMO) and indoleamine 2,3-dioxygenase (IDO), the astrocytic located Kynurenine acetyl transferase II (KATII) by using western blotting techniques or by HPLC quantifications.

Clinical studies

WP 2.3
OU 1 and OU 3 will provide blood samples of AD patients and matched controls to carry out the analyses described in WP 2.2 and 2.3.

Experimental design aim 3

We hypothesize that astrocytes, through the release of pro-inflammatory cytokines (TNF¿, IL-1ß, IL-6), the activation of IP3R-dependent mechanisms and the activity of GLT-1 can significantly influence AD progression by affecting neuronal dynamics in terms of cell survival, mitochondrial activities (redox balance, Ca2+ buffering, energy production), cytoplasmic

Ca2+ levels and activity/expression of NCX isoforms. Our working hypothesis will be investigated through different steps that include both preclinical and clinical studies, which are represented by the following work packages (WP):
Preclinical studies
WP 3.1 Firstly, we will characterize the viability, pro-inflammatory, energetic, and redox status of primary astrocytes obtained from wild-type mice and subsequently challenged with the glycolysis inhibitor glyceraldehyde (GA). This treatment is aimed at creating a condition of hypometabolism accompanied by mitochondrial dysfunctions and redox imbalance, a condition often observed in the early stage of AD [14]. In neurons, GA induces AD-like alterations, including the increase of Aß and ptau levels [15; 16] and the activation of death paradigms such as AMPK/mTOR pathway. Astrocytes will be exposed to GA at different concentrations (0-0.3-1-1.5-3-5 mM) and times (0-3-9-16-24-48 hours). The status of control and GA-injured cells will be evaluated after time- and concentration-dependent treatments by LDH and MTT assays. The astrocytic reactivity will be assessed by measuring GFAP and S100B levels in the culture media. After identified the optimal concentration and time of exposure to GA, we will characterize the intracellular ATP content, the Reactive Oxygen Species (ROS) formation and the release of pro-inflammatory cytokines (TNF¿, IL-1ß, IL-6) in the culture medium. Ca2+ dynamics will be monitored as well. Expression of GLT-1 and NCX will be also evaluated.
WP 3.2 After GA challenge, the impact of functionally altered astrocytes on neuronal dynamics in terms of viability, inflammation, energetic and redox imbalance, intra-neuronal Ca2+ dyshomeostasis, will be evaluated in cortical astrocyte-neuron co-cultures from wt mice. The levels of Aß and ptau will be monitored, as well as the activation of AMPK/mTOR pathway. The role of IP3R signaling and GLT-1 will be monitored by treating astrocytes with xestospongin C (or by antisense oligonucleotide, i.e. morpholinos) or by specifically silencing GLT-1, respectively.
To examine the contribution of reactive astrocytes in AD progression, we will monitor the levels of the GFAP and S100B biomarkers in the peripheral blood of both wild type and 3xTg AD mice of different time points (3-9-15 months). Furthermore, to highlight the importance of mitochondria and energy balance in the overall AD setting, we will also perform an evaluation of the mitochondrial activity (mitochondrial membrane potential, reducing activity, ATP production) in splenocytes of both wild type and 3xTg AD mice of different time points (3-9-15 months). Together with in vitro studies, these studies will allow us to get preliminary insights on the possible association between peripheral biomarkers and AD progression.
Clinical studies
WP 3.3 Clinical studies will be performed to confirm astrocytic contribution to AD progression and to elucidate the importance of mitochondria and energy balance in the overall AD setting. Firstly, we will evaluate the astrocyte biomarkers GFAP and S100B in the blood and/or liquor from AD patients at different stages (mild, moderate, and severe AD), in comparison with age- and sex-matched healthy controls. Secondly, we will check the mitochondrial profile in peripheral blood lymphocytes of the same study population, to assess whether peripheral mitochondrial biomarkers would be associated with AD and whether heterogeneity in mitochondrial defects would exist according to disease stage.

Picture to support preliminary data

Hypothesis and significance

The overarching hypothesis of this project is that astrocytes are major contributors to AD progression. Hence, besides inducing neuronal death when activated, they regulate synaptic functions and neuronal activity, neurotransmitter release, cell metabolism and/or intracellular Ca2+ homeostasis, redox balance.
To test our hypothesis, we will carry out a multidisciplinary approach by employing astrocytic-neuronal and astrocytic-microglia co-cultures, in vivo techniques (behavioral analysis, neurophysiology, brain microdialysis), ex vivo and in vitro techniques (redox balance analysis, biochemical-immunohistochemistry analysis, slice electrophysiology).
The translational approach of this project is supported by the clinical study that will involve patients enrolled in the Neurology Clinics of UO1 and UO2, where extensive immunological profiling and the assessment of peripheral markers of neuroinflammation and astrocytic activation will be carried out and will be correlated with disease progression, phenotyping

and response to medications or non-pharmacological support.

5.5 Methodologies and statistical analyses

Methods of data collection

AIM 1
Experimental models. Lymphoid tissues such as spleen, lymph node, thymus, peripheral blood as well as the brain will be collected from both wild type and 3xTg AD mice. Single-cell suspensions from each organ collected will be prepared and used for flow cytometry experiments. Protein lysates and tissue slices from each organ collected will be used respectively for western blot analysis and immunohistochemical analysis.
For electrophysiological experiments, firing activity, firing pattern, and synaptic properties (evoked and spontaneous excitatory and inhibitory currents) of selected neurons will be collected with standard procedures.
Human immunocytes will be isolated from the whole blood of AD patients and age- and sex- healthy matched controls.

AIM 2
Central quantifications will be performed in the prefrontal cortex, hippocampus, amygdala and in plasma of 3x-tg-AD mice at the different time points chosen and after treatment as above scheduled.
Kynurenine pathway/TRYCAT and Oxidative stress quantifications:
-neurochemical quantification: 5-HT, NA, tryptophan (TRP) and KYN concentrations will be determined by HPLC coupled with an electrochemical detector. The separation will be accomplished by a LC18 reverse phase column and detection will be performed through a thin-layer amperometric cell with a diameter glassy carbon electrode.
-ELISA for Quinolinic acid, Kynurenic acid (KYN pathway), 8OHdG, MDA, HNE, 3NT, acrolein will be evaluated by pan species or species-specific ELISA according to manufacturers¿ instructions.
-WB analyses for IDO, KMO, KATII (KYN pathway) quantifications.
-ROS and MDA-TBARS quantification: ROS measurement will be performed by using the fluorogenic dye 2¿-7¿dichlorofluorescein diacetate [17]. MDA and TBARs qualifications will be performed by using commercially available colorimetric/fluorometric (excitation length 475 nm, emission length 535 nm) assay kit.

AIM 3
Mouse primary cortical neurons and splenocytes will be prepared from both wild type and 3xTg AD mice as previously described [16, 18, 19]. Human lymphocytes will be isolated from the whole blood of AD patients and age- and sex- healthy matched controls [20].
Methods. Cell viability will be assessed by monitoring LDH activity retained in the culture media supernatant, while mitochondrial activity will be tested as the reduction of the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) by the mitochondrial metabolic activity of living cells. Mitochondrial membrane potential will be monitored in freshly isolated lymphocytes by means of JC-1 dye. Astrocytic biomarkers and pro-inflammatory cytokines levels in the culture media supernatant/blood/CSF will be assessed by enzyme-linked immunosorbent assay (ELISA). ATP content will be monitored by using a commercially available luciferase-luciferin system. The cell-permeative probe H2DCFDA and the MitoTracker CM-H2XRos dye will be used to monitor the overall cell redox status and the mitochondrial ROS formation, respectively. Protein expression will be assessed by western blot and/or immunocytochemistry techniques. Ca2+ monitoring experiments will be performed by loading cells with fluorescent Ca2+ indicators Fluo-4/AM or Rhod-2/AM, to monitor plasma membrane and mitochondrial NCX, respectively.

Statistic plan

Investigators that will carry out treatment and analyses will be blind to group labels. Group labels were unveiled after draft graph design and statistical analyses. The sample size will be chosen considering the calculation provided by power analysis and the possibility that mice would die or be excluded within 15 months-long experimental protocol. For animals

and relative samples, the exclusion criteria from experimental protocol were sudden death, loss of weight >20%, sign of distress (eyes squinted, contraction of the skin around the nose, ears pulled back, and lethargy or non-responsiveness). The number of animals used in this project will be determined for each experimental procedure by means of G-Power software. This project falls within the criteria of the 3Rs (replacement, reduction, refinement), ethical principles introduced by European legislation for the welfare of animals used in scientific experimentation. Indeed, the 3Rs not only provide a means to reduce animal suffering and numbers but have evolved in scientific society as a particularly significant tool for improving the translational value of animal models. Specifically, given the lowest expected difference between the means of two groups and homogeneous variance within the groups, the calculated sample size was n=4, for 1-ß set to 0.80 and alpha set to 0.05 (G*power software) [21].
As for in vitro studies, for controls and experimental treatments, each point will be tested in triplicates using mice primary cell cultures obtained from at least five independent cellular preparations. The parameters to be tested will include cell viability, mitochondrial activity, mitochondrial membrane potential, astrocytic biomarkers, pro-inflammatory cytokines, ATP content, ROS production, protein expression, cytoplasmic and mitochondrial Ca2+ levels.
As for clinical studies, comparison between healthy controls and AD patients will be evaluated using oneway analysis of variance (ANOVA) followed by Dunnett's post hoc test. Considering a drop-out of 20%, we estimate to include 50 subjects in each experimental group to detect a medium effect size, in the means of astrocytic biomarkers and mitochondrial indices, among the AD and control groups, with a power of 80% and an alpha error of 0.05. Subgroup analysis for ApolipoproteinE [22] will be performed according to clinical disease phenotype.

Statistical analysis

AIM 1: Data will be analyzed to test normality distribution. Data will be represented as mean±standard deviation (SD), from at least three independent samples, and three technical replicates. Data will be analyzed by the one-way analysis of variance (ANOVA) test, followed by the Tukey post-hoc test for multiple comparisons. Post-hoc tests will be carried out only if F had a p<¿0.05, and no significant variance in homogeneity will be found within the analyzed groups.
Graph design and statistical analyses will be done using the following software: SPSS (https://www.ibm.com/analytics/spss-statistics-software) and GraphPad Prism (https://www.graphpad.com/scientific-software/prism/).

AIM2 After evaluation of the normal distribution, data will be analyzed by means of one way, two-way or multi-way ANOVA, depending on the experimental setup. The biochemical and molecular data will be analyzed separately by area and always by means of ANOVA. Statistical significance, set at p=0.05, where appropriate will be confirmed by post-hoc testing (Tukey or Bonferroni¿s test, as required). Analyses will be carried out by using Graph Pad 9.02 version.

AIM 3 Data will be represented as the Mean ± Standard Error of the Mean (S.E.M.). Data distributions will be assessed for significant difference from a normal distribution using the Kolmogorov-Smirnov test. If data will be distributed normally, we will use parametric statistics; otherwise, we will log10-transform data to better approximate a normal distribution. Significant differences between data sets will be determined using either a 2-tailed Student's t-test when comparing two groups or ANOVA followed by Dunnett¿s test for multiple comparisons. The minimal level of significance chosen will be $p < 0.05$. Statistical comparisons will be carried out by using GraphPad Prism software. All data will be collected in a local database, specifically developed for the project, and complying the regulations for the protection of sensitive data.

Timing of analysis data

Preclinical studies
I year
The experimental procedures involving animal models will be performed in full compliance with the Ethics Committee for Animal Experiments of the University of Catania and with the guidelines of the Italian Ministry of Health (D.L. 26/2014).

OU1, 2, and 3 already possess the authorization for experiments on 3xTg-AD mice and house the colonies in their Animal Facilities. These mice (3, 9, 15-months old). will be sacrificed and lymphoid tissues such as the spleen, lymph node, thymus, peripheral blood as well as the brain will be collected. Each organ will be processed according to the different experimental procedures to be applied. In particular, organs will be processed to obtain single cell suspension to be used for flow cytometry experiments, protein lysates to be used for western blot analysis and tissue slices for immunohistochemical analysis.
Another set on animals will be used for drug administration study: 3xTg-AD and WT mice will be enrolled at 3 months of age and will be treated with TNFSF10-neutralizing antibody or vehicle twice a month and sacrificed at 15 months of age.
At the same endpoints chosen for AIM1, central and peripheral samples from 3xTg-AD mice will be sent to UNIFG and they will be processed for the quantification of Kynurenine derivative and oxidative stress parameter quantifications.
Preliminary experiments will be carried out in in vitro models and will be aimed at evaluating the influence of astrocytic damage on neuronal dynamics.
II year
After 12 months of treatment, animals will be sacrificed and lymphoid tissues such as spleen, lymph node, thymus, peripheral blood as well as the brain will be collected. Each organ will be processed according to the different experimental procedures to be applied. In particular, organ will be processed to obtain single cell suspension to be used for flow cytometry experiments, protein lysates to be used for western blot analysis and tissue slices for immunohistochemical analysis. During the second year, the immune profile in AD patients throughout the pathology progression.
During the second year of the project, the effect of the treatments performed by the other Units on 3X-tg AD mice on Kynurenine derivative and oxidative stress parameters at central and peripheral level will be also evaluated. In addition, the levels of these biomarkers will be measured on blood samples from AD patients and matched controls.
Both the astrocytic biomarkers and the mitochondrial indices will be evaluated in in vivo models represented by wild type and 3xTg AD mice.

Clinical studies
Concomitantly, the same studies on patients will be started. As for studies involving human patients, the project will be submitted to the local Ethics Committee. All the patients will be informed that their clinical data will be used for the study and their informed consent will be requested. The population in the study will be represented by clinically diagnosed AD patients at different stages of the disease (mild, moderate, and severe AD), that will get access to the Neurological Clinic of AOU-Cagliari and the Ospedali Riuniti Umberto I, Lancisi, Salesi¿ of Ancona.
The enrollment and the analyses of blood samples will be carried out for the first 12 months. Then, all patients will be followed-up and assessed for disease profigressionand changes in blood markers.

5.6 Expected outcomes

AIM 1: Results of this study could help to unveil the events that occur between the CNS and the peripheral immune system through the identification of subsets of T cell and monocyte/macrophage populations that regulate the neuroinflammatory processes and the regulatory mechanisms critical not only for dissecting the crosstalk between the periphery and CNS, but also for devising therapeutic strategies to modify such interactions.
Moreover, immunopharmacological modulation of TRAIL pathway will help us to understand how TRAIL could influence the crosstalk between the brain and peripheral immune system.
Moreover, we expect to elucidate if manipulation of astrocyte functions by pharmacological, chemogenetic or antisense oligonucleotides affects the progression of the disease as indexed by markers of neuroinflammation and neurodegeneration, by disruption of behaviour and deterioration of neuronal functions, synaptic connections and neuronal network connectivity.
The study of the immune profile of AD patients throughout the pathology progression could help us to identify key components of the immune system that might be useful diagnostically as well as in furthering understanding of the etiology

of the disease.

AIM 2: The expected results of this research project will contribute to clarify the role of peripheral biomarkers such as oxidative stress and kynurenine-related metabolites in AD patient peripheral samples and in various central areas and plasma of the 3Xtg transgenic AD mouse model at several endpoints and after specific treatments. This experimental design will also be useful to validate the role of these biomarkers for disease progression evaluation as well as for treatment monitoring. The deliverables will consist in at least one scientific publication per year in impacted peer-reviewed journals, and presentation of the results in national and international congresses.

AIM 3. We expect to elucidate the role of the astrocytic component in the pathogenesis and progression of AD. We expect that stressing stimuli (such as metabolic deregulation) could be able to alter astrocytic dynamics and induce significant damage in the neighboring neurons, thus fueling a neurodegenerative process that could represent the basis for AD development. In this line, in in vivo studies we expect to observe that astrocytic biomarker levels would be associated with AD diagnosis and with the disease worsening. Also, we expect that peripheral mitochondrial biomarkers would be associated as well with AD diagnosis and that heterogeneity in mitochondrial defects would exist according to disease stage. In this light, the project will allow getting further insights into the potential that astrocytic biomarkers and mitochondrial profiling may have in supporting AD diagnosis and prediction of disease worsening or progression.

5.7 Risk analysis, possible problems and solutions

AIM 1: We do not foresee major risks during the experimentation, since the scientific basis is very solid, and our unit are fully equipped to fulfill the proposed set of experiments. Although we are confident to be able to reasonably accomplish the scheduled time-plan, a possible problem could derive from the time needed to have the projects approved from the specific committees. To prevent the possible risk of delay, we will proceed to have the projects ready for submission as long as we will know whether the whole proposal will be financed.
AIM 2: A minimum number of animals will be used in order to have statistically significant and reproducible data, through a careful analysis of the experimental protocol. The animals will be divided into different experimental groups (based on the type of pharmacological treatment), each consisting of the minimum number for the planned experiments.
Furthermore, the experiments will be organized in such a way as to obtain the maximum possible amount of information from each sacrificed animal. In order to do so, samples from animals at different timepoints foreseen in the project will be shared between Units.
Indeed, based on the calculations carried out, we will reduce the animals to the minimum necessary to obtain, within 24 months, sufficient and statistically significant data.
AIM 3. We believe that the proposal bears limited risks, since the scientific basis is very solid, and our units are fully equipped to fulfill the proposed set of experiments. Although we are confident to be able to reasonably accomplish the scheduled time-plan, a possible problem could be the time needed to have the projects approved from the specific committees. The waiting time could delay the start of the studies. To prevent this risk , we will proceed in order to be ready for submission as soon as we will know whether the whole proposal will be financed.

5.8 Significance and Innovation

- Novel insights on brain-immune system crosstalk in AD mouse model and the immune profile of AD patients throughout the pathology progression. Our aim is to identify key components of the immune system that might be useful diagnostically

and to understand better the etiology of the disease.
- Monitoring the validity of oxidative stress-related and kynurenine pathway-related biomarkers at different stages of the pathology and following treatments. These evaluations will be paralleled to those in patients, that will be carried out with commercially available kits.
- Astrocytic contributions to AD progression were, until recently, largely overlooked [22]. This proposal will allow to get further insights on the potential that astrocytic biomarkers and mitochondrial profiling may have in supporting AD diagnosis and prediction of disease worsening or progression.

5.9 Bibliography

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5.10 Timeline / Deliverables / Payable Milestones

Milestones (please refer to the GANTT chart)
MX.0 Kick-off meeting
MX.1 : Mid-term workshop with research team
MX.2 Final workshop with research team

Milestones 12 month

AIM 1 12 months Milestones

M1.1a: Enrollment of 3-months old 3xTgAD and WT mice for drug administration study
M1.2a: Preliminari data on ex-vivo experiments performed on 3xTgAD and WT mice at different ages (3, 9, and 12 months old).
M1.3a Preliminary data on chemogenetic and electrophysiology experiments.
M1.4a vMO and behavioral experiments started
M1.5a Patient enrolled and sample collection started

AIM 2 12 month Milestones
M2.1a Preliminary evaluation of of oxidative stress biomarkers
M2.2a Preliminary quantification of KYN, metabolites and enzymes
M2.3a preliminary evaluation of ROS biomarkers in AD patient peripheral blood
M2.4a Preliminary evaluation of KYN pathway in in AD patient peripheral blood

AIM 3 Milestones
M3.1a : Preliminary data on in vitro studies on astrocytes.
M3.2a Preliminary analysis of both preclinical and clinical studies concluded
M3.3a Patient enrolled and sample collection started

Milestones 24 month

AIM 1 24-month milestones
M1.1f: Ex-vivo experiments performed on 3xTgAD and WT mice at different ages (3, 9, and 15 months old) concluded.
M1.2f: Analysis of preclinical data of 3xTgAD and WT mice receiving TNFSF10-neutralizing antibody or vehicle
M1.6f: Chemogenetic and electrophysiology experiments concluded
M1.7f: vMO and behavioral experiments concluded
M1.8f: Final data analysis
M1.8f: Dissemination of results

AIM 2 24-month milestones
M2.1f Evaluation of of several oxidative stress biomarkers completed
M2.2f Quantification of KYN, metabolites and enzymes completed
M2.3f Evaluation of ROS biomarkers in AD patient peripheral blood completed
M2.4f Evaluation of KYN pathway in in AD patient peripheral blood completed
M2.5f Final data analysis
M2.6f Dissemination of results

AIM 3 24-month Milestones
M3.1f : In vitro studies on astrocytes concluded
M3.2f Analysis of both preclinical and clinical studies concluded
M3.3f Final data analysis
M3.4f Dissemination of the results

Gantt chart

GANNT CHART.pdf

5.11 Equipment and resources available

Facilities Available

AOU-CA includes the Neurology Clinic and the Clinical Pharmacology Unit, that will be in charge of patient enrollment, clinical protocols and interactions with the Ethical Committee. Laboratories are equipped with neurophysiology and neurochemistry setups in vivo and ex vivo,
CeSAR Service Centre for Research is a multidisciplinary RI available to internal and external researchers hosts equipment of the highest technological level for advanced analysis in biomedicine (genomics, proteomics, metabolomics, flow cytometry, immunology, fluorescence/electron microscopy, cell culture).
An agreement with CeSASt (Center for Animal facilities) will be signed for preclinical experiments. CeSASt manages all UniCa¿s animal care facilities and ensure the welfare of the animals and optimal conditions for carrying out experimental activities in compliance with current regulations. It offers a wide range of equipment for preclinical neuropharmacology and behavior studies in experimental animals.
UNICT group is affiliated to the Dept. of Biomed. and Biotech. Sci. where is located CAPIR which promotes preclinical and translational research based on in vivo experimentation in the biomedical field. CAPIR is equipped with the main support services for preclinical and translational experimental research.
ORA laboratories are fully equipped with basic lab equipment and other instruments that will be used for the project, including: Zeiss confocal system, Olympus Flowview laser scanner microscope, LS 55 fluorescence spectrometer, NanoDrop 1000 spectrophotometer, StepOne real-time PCR system, Uvitec Cambridge chemiluminescence imaging system, Victor 1420 multilabel plate reader, animal facilities and surgery room. Prof. Lattanzi (Neurological Clinic) will take care of the patients¿ enrollment and will organize the sample collection.
UNIFG The Dept. of Clinical and Exp. Med. has been awarded Dept. of Excellence of Italian Universities and holds facilities that can be made available for this project. UNIFG has a large surface area for manipulation of human and mouse-type biological samples, with centrifuges, processors, instruments for chromatographic analysis (HPLC) and for protein quantification (ELISA readers, spectrophotometers). This group has a fully equipped workstation for WB measurements and qPCR analyses.

Subcontract

The subcontract will be signed with Cesar (UNICA) to utilize the research facilities available in the core research center.

5.12 Desc. of the complementarity and sinergy of secondary collab. researchers

Applicant researchers for the projects will be selected on the basis of their potential for scientific excellence and their availability to work in a multidisciplinary environment. Recruitment will be transparent, open and equal, following the guidelines outlined in the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers. We aim to enroll at least one post-doctoral researcher (Assegnista) in all of the 4 UO. Each of these contracts will be for 24 months. These researchers will be involved in the experimental procedures in AD animals or will assist the neurologists of our research group in enrolling and studying AD patients. Among the skills required, we will consider:
a) expertise in neurophysiology
b) Expertise in neurochemistry and immunochemistry
c) Expertise in clinical neurosciences

5.13 Translational relevance and impact for the national health system (SSN)

What is already know about this topic?

Microglia and astrocytes are strongly implicated in AD neuropathology. Microglial cells are major immunological effectors of the innate immune system in the brain and mediate functions such as tissue surveillance, removal of pathogens and response to injury, contributing to neuronal survival and synaptogenesis. Astrocytes contribute to maintaining CNS homeostasis and sustain neuronal survival by releasing gliotransmitters and neurotrophic factors and they also safeguard

BBB structural integrity and permeability.
Astrocytes are involved in Aß-mediated neurodegeneration, as they release Aß and can be activated into a neurotoxic form by activated microglia and pro-inflammatory cytokines such as Il1ß, Il6 and TNF¿.

Arranz AM. & De Strooper B (2019). The role of astroglia in Alzheimer's disease: pathophysiology and clinical implications. The Lancet Neurology, 18, 406.
Liddelow SA et al, (2017). Neurotoxic reactive astrocytes are induced by activated microglia. Nature, 541, 481

Details on what is already know about this topic

Microglia and astrocytes, the predominant innate immune cells in the CNS, are strongly implicated in AD neuropathology. Astrocytes are involved in Aß-mediated neurodegeneration, as they release Aß and can be activated into a neurotoxic form by activated microglia and pro-inflammatory cytokines. Among them, TNF¿ plays a major role by both initiating and regulating the cytokine cascade during an inflammatory response and by triggering a positive feedback loop that sustains the pathology. Moreover, astrocytic Ca2+ oscillations release gliotransmitters (including glutamate) and modulate synaptic functions and might be involved in early behavioral deficits observed in AD. Abnormal Ca2+ signalling may trigger the production of reactive oxygen species (ROS), which have been also associated with AD. Indeed, astrocytes are actively involved in ROS clearance but might also act as one of the main sources of detrimental ROS in AD.

What this reasearch adds?

We aim to validate a panel of peripheral biomarker in AD that will help to phenotype patients and to allow an early diagnosis. Data will provide a rationale basis for target selection for novel or repurposed medications.

H.G. Lee, M.A. Wheeler, and F.J. Quintana, Function and therapeutic value of astrocytes in neurological diseases. Nat Rev Drug Discov 21 (2022) 339-358.

Details on what this reasearch adds

We will analyze the following peripheral biomarkers in peripherl blood of Ad patientsd:
1) Inflammatory biomarkers: Pro- and anti-inflammatory cytokines levels
2) Oxidative stress biomarkers
3) Kynureic pathway biomarkers
4) Astrocytic and mitochondrial biomarkers

What are the implications for public health, clinical practice, patient care?

The expected translational benefit could be substantial, as our effort to identify specific mechanisms underlying the role of astrocytes in AD could facilitate new targeted interventions. The knowledge that derives from our experiments will provide indications for drug repositioning but also for novel molecular targets for more effective pharmacological intervention. The project will also provide new knowledge for the promotion of resilience through the elicitation of mechanisms acting on the proper response (i.e. the potential antioxidant ability of astrocytes that may counteract the neuroinflammation that characterizes AD), thus limiting the development of the neurodegenerative disease. Notably, the identification of therapeutic or even preventive strategies in this field is a hot topic and a real unmet need that has to be achieved.
S.F. Carter, K. Herholz, P. Rosa-Neto, L. Pellerin, A. Nordberg, and E.R. Zimmer, Astrocyte Biomarkers in Alzheimer's Disease. Trends Mol Med 25 (2019) 7

Details on what are the implications for public health, clinical practice, patient care

Blood-derived biomarkers for AD are urgently needed. The introduction of highly sensitive immunoassays led to a rapid increase in the number of potential blood-derived biomarkers for diagnosis and monitoring of neurological disorders,

including AD.
In patients and in animal models, we will monitor several oxidative stress-related, inflammatory, mitochondrial and astrocytic biomarkers. This monitoring will be paralleled by deep phenotyping and patient stratification and will give us information about the correlation between peripheral biomarkers and disease progression and severity.
The project will also provide new knowledge for the promotion of resilience through the elicitation of mechanisms acting on the proper response (i.e. the potential antioxidant ability of astrocytes that may counteract the neuroinflammation that characterizes AD), thus limiting the development of the neurodegenerative disease. Notably, the identification of therapeutic or even preventive strategies in this f

6 - Budget

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	244.508,00	244.508,00	not permitted	0,00
2 Researchers' Contracts	264.000,00	0,00	264.000,00	26,40
3a.1 Equipment (Leasing -	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	513.600,00	0,00	513.600,00	51,36
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts *	24.000,00	0,00	24.000,00	2,40
5 Patient Costs	45.000,00	0,00	45.000,00	4,50
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	22.000,00	0,00	22.000,00	2,20
8 Publication Costs	27.000,00	0,00	27.000,00	2,70
9 Dissemination	24.000,00	0,00	24.000,00	2,40
10 Overheads *	65.400,00	0,00	65.400,00	6,54
11 Coordination Costs	15.000,00	0,00	15.000,00	1,50
Total	1.244.508,00	244.508,00	1.000.000,00	100,00

* percentage calculated as average value between all the Operating Units.

Report the Co-Funding Contributor:

Co-funding will be provided by the staff salary

Budget Justification

1 Staff Salary	Salary of staff participating in the project (3 or 2 months/person per year, depending on the UO)
2 Researchers' Contracts	This cost cover 2 contracts for 24 months for <40 researchers enrolled in the project. Three researchers will be enrolled with a 24-month contract, following selections according to Italian law.
3a.1 Equipment (Leasing - Rent)	Not requested
3a.2 Equipment (buying)	Not requested
3b Supplies	Laboratory consumable and animal purchasing and housing

3c Model Costs	Not requested
4 Subcontracts	This subcontract is for Cesar (Unica) for the use of central research facility
5 Patient Costs	This cost cover study insurance, costs for patient enrollment, blood sample collection at OU1 and OU 3
6 IT Services and Data Bases	Not requested
7 Travels	This cost will cover travel costs to international meetings and travel costs for 2 project meetings
8 Publication Costs	Publication of 10 open-acces articles
9 Dissemination	Participation in international and national congresses
10 Overheads	Overhead costs
11 Coordination Costs	Coordination costs, organization of project meetings,

Proposed total budget UO1 Institution: Azienda Ospedaliero-Universitaria di Cagliari (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	70.000,00	70.000,00	not permitted	0,00
2 Researchers' Contracts	120.000,00	0,00	120.000,00	35,05
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	120.000,00	0,00	120.000,00	35,05
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	24.000,00	0,00	24.000,00	7,01
5 Patient Costs	20.000,00	0,00	20.000,00	5,84
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	8.000,00	0,00	8.000,00	2,34
8 Publication Costs	5.000,00	0,00	5.000,00	1,46
9 Dissemination	8.000,00	0,00	8.000,00	2,34
10 Overheads	22.378,00	0,00	22.378,00	6,54
11 Coordination Costs	15.000,00	0,00	15.000,00	4,38
Total	412.378,00	70.000,00	342.378,00	100,00

Budget Justification	
1 Staff Salary	3 months/year for each partecipant
2 Researchers' Contracts	This cost cover 2 contracts for 24 months for <40 year old researchers enrolled in the project
3a.1 Equipment (Leasing - Rent)	Not requested
3a.2 Equipment (buying)	Not requested
3b Supplies	Laboratory consumable and animal purchasing and housing
3c Model Costs	Not requested
4 Subcontracts	This subcontract is for Cesar (Unica) for the use of central research facility
5 Patient Costs	This cost cover study insurance, costs for patient enrollement, blood sample collection
6 IT Services and Data Bases	Not requested
7 Travels	This cost will cover travel costs to 2 international meetings and travel costs for 2 project meetings
8 Publication Costs	Publication of 3 open-accces articles
9 Dissemination	Participation in international and national congresses
10 Overheads	Overhead costs
11 Coordination Costs	Coordination costs, organization of project meetings,

Proposed total budget UO2 Institution: Università di Catania (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	40.000,00	40.000,00	not permitted	0,00
2 Researchers' Contracts	48.000,00	0,00	48.000,00	22,89
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	130.000,00	0,00	130.000,00	61,99
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	6.000,00	0,00	6.000,00	2,86
8 Publication Costs	6.000,00	0,00	6.000,00	2,86
9 Dissemination	6.000,00	0,00	6.000,00	2,86
10 Overheads	13.720,00	0,00	13.720,00	6,54
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	249.720,00	40.000,00	209.720,00	100,00

Budget Justification	
1 Staff Salary	2 months/year for each partecipant
2 Researchers' Contracts	One contract for 24 months for a research collaborator
3a.1 Equipment (Leasing - Rent)	Not requested
3a.2 Equipment (buying)	Not requested
3b Supplies	Laboratory consumable and animal purchasing and housing
3c Model Costs	Not requested
4 Subcontracts	Not requested
5 Patient Costs	Not requested
6 IT Services and Data Bases	Not requested
7 Travels	This cost will cover travel costs to 2 international meeting and travel costs for 2 project meeting
8 Publication Costs	Publication of 3 open-accces articles
9 Dissemination	Participation in international and national congresses
10 Overheads	Overhead costs
11 Coordination Costs	Not requested

Proposed total budget UO3 Institution: Marche (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	68.000,00	68.000,00	not permitted	0,00
2 Researchers' Contracts	48.000,00	0,00	48.000,00	21,00
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	123.600,00	0,00	123.600,00	54,08
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	25.000,00	0,00	25.000,00	10,94
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	6.000,00	0,00	6.000,00	2,63
8 Publication Costs	6.000,00	0,00	6.000,00	2,63
9 Dissemination	5.000,00	0,00	5.000,00	2,19
10 Overheads	14.952,00	0,00	14.952,00	6,54
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	296.552,00	68.000,00	228.552,00	100,00

Budget Justification	
1 Staff Salary	3 months/year for each partecipant
2 Researchers' Contracts	One contract for 24 months for a research collaborator
3a.1 Equipment (Leasing - Rent)	Not requested
3a.2 Equipment (buying)	Not requested
3b Supplies	Consumables and animals management
3c Model Costs	Not requested
4 Subcontracts	Not requested
5 Patient Costs	Blood sample collection, patients insurance
6 IT Services and Data Bases	Not requested
7 Travels	This cost will cover travel costs to 2 international meetings and travel costs for 2 project meetings
8 Publication Costs	Publication of 3 open-accces articles
9 Dissemination	Participation in international and national congresses
10 Overheads	Overhead costs
11 Coordination Costs	Not requested

Proposed total budget UO4 Institution: Università di Foggia (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	66.508,00	66.508,00	not permitted	0,00
2 Researchers' Contracts	48.000,00	0,00	48.000,00	21,88
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	140.000,00	0,00	140.000,00	63,82
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	2.000,00	0,00	2.000,00	0,91
8 Publication Costs	10.000,00	0,00	10.000,00	4,56
9 Dissemination	5.000,00	0,00	5.000,00	2,28
10 Overheads	14.350,00	0,00	14.350,00	6,54
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	285.858,00	66.508,00	219.350,00	100,00

Budget Justification	
1 Staff Salary	2 months/year for Prof. Trabace and 3 months/year for Dr. Morgese
2 Researchers' Contracts	One contract for 24 months for a research collaborator
3a.1 Equipment (Leasing - Rent)	Not requested
3a.2 Equipment (buying)	Not requested
3b Supplies	ELISA kits, reagent and columns for chromatographic quantification, WB primary and secondary antibodies
3c Model Costs	Not requested
4 Subcontracts	Not requested
5 Patient Costs	Not requested
6 IT Services and Data Bases	Not requested
7 Travels	This cost will cover travel costs to 1international meeting and travel costs for 2 project meeting
8 Publication Costs	Publication of 4 open-accces articles
9 Dissemination	Participation in international and national congresses
10 Overheads	Overhead costs
11 Coordination Costs	Not requested

Principal Investigator Data

Cognome: PISTIS
Nome: MARCO
Genere: M
Codice fiscale: PSTMRC68D24E281L
Documento: Carta d'identità, Numero: AV4778673
Data di nascita: 24/04/1968
Luogo di nascita: Iglesias
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Struttura: Dipartimento di Scienze biomediche
Istituzione: Università di Cagliari
Datore/ente di lavoro? Yes
Datore/ente di lavoro SSN? No
Nome datore/ente di lavoro non SSN: Università degli Studi di Cagliari
Nome istituzione SSN: Azienda Ospedaliero-Universitaria di Cagliari
Tipo contratto: Professore Ordinario distaccato presso IRCCS/IZS/ISS/Ente SSN (convenzione di clinicizzazione e/o ricerca)

Con l'invio della presente proposta si dichiara che la stessa o parti significative di essa non sono oggetto di altri finanziamenti pubblici o privati e che di conseguenza vi è assenza del c.d. doppio finanziamento ai sensi dell'art. 9 del Regolamento (UE) 2021/241, ossia che non ci sia una duplicazione del finanziamento degli stessi costi da parte di altri programmi dell'Unione, nonché con risorse ordinarie da Bilancio statale.

By submitting this proposal, I declare that no significant part or parts of it are recipient of any other public or private funding and that consequently there isn't any so-called double financing pursuant to art. 9 of Regulation (EU) 2021/241, i.e. that there is no duplication in the financing of the same costs by other Euopean Union programs or any other ordinary resources from the State budget.

Project validation result

	AOU-Cagliari	UNICT (Catannia)	Policlinico Marche	UNIFG (Foggia)	
COFINANZIAMENTO	**75.308,61**	**49.659,67**	**51.835,80**	**49.659,67**	**226.463,75**
Contratti per personale da assumere	102.000,00	44.500,00	44.500,00	44.500,00	
Strumenti (leasing)	-	-	-	-	
Strumenti (acquisto)	-	-	-	-	
Materiale di consumo	111.000,00	120.400,00	114.800,00	130.000,00	
Costi per modelli	-	-	-	-	
Consulenze-contratti con esterni	22.300,00	-	-	-	
Costi per la gestione dei pazienti	18.500,00	-	23.200,00	-	
IT Services and Data Bases	-	-	-	-	
Missioni e partecipazionea congressi	10.900,00	10.000,00	5.500,00	1.900,00	
Costi per la pubblicazione	4.600,00	10.000,00	5.500,00	9.000,00	
Costi per organizzazione di eventi e convegni	5.000,00	5.500,00	4.500,00	4.400,00	
Spese generali	20.700,00	12.700,00	14.000,00	13.300,00	
Spese di coordinazione	13.000,00	-	-	-	
TOTALE	**308.000,00**	**203.100,00**	**212.000,00**	**203.100,00**	
926.200,00	0,33	0,22	0,23	0,22	

1.152.663,75

226.463,75

19,6470%