1 - General information

Project code: PNRR-MAD-2022-12375761

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: sechi leonardo antonio

Istitution that perform as UO for UO1: Azienda Ospedaliera Universitaria di Sassari

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

Proposal title: Human Endogenous Retroviruses in neurological diseases (Multiple Sclerosis, Parkinson, Autism Spectrum Disease) and Type 1 Diabetes

Duration in months: 24

MDC primary: Neurologia

MDC secondary: Ematologia e Immunologia

Project Classification IRG: Immunology

Project Classification SS: Hypersensitivity, Autoimmune, and Immune

Project Keyword 1: Etiology of immune-mediated diseases: hormonal, developmental, environmental factors (infectious and non-infectious) and lifestyle factors, and genetic.

Project Request: **Animals:** ☐ **Humans:** ☒ **Clinical trial:** ☐

Project total financing request to the MOH: € 889.200

Free keywords: HERVs, Autism, Type 1 Diabetes, Multiple Sclerosis and Parkinson

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).	☒
2) The Principal Investigator declares that the information contained in this proposal is correct and complete.	☒
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).	☒
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.	☒

Personal data protection

Abstract

Different autoimmune diseases have been associated with components derived from human endogenous retroviruses (HERVs) integrated across the human genome as remnants of ancient viral infections. Among them, chronic neurological diseases such as Multiple Sclerosis (MS), Autism Spectrum Disorder (ASD) and recently, non neurological disease such as Type 1 Diabetes (T1D) have been linked to the expression of HERV-W (MS), HERV-K (ALS) and HERV-H (ASD).
Although HERVs are generally silenced, peculiar HERV copies can be activated by different environmental stimuli, leading to the expression of immunopathogenic proteins. Among environmental factors, HERVs may be transactivated by different microorganisms, including viruses, exogenous retroviruses and intestinal pathogens such as Epstein Barr Virus and Mycobacterium avium spp. paratuberculosis (MAP) in MS and T1D. In this regard, our recent data demonstrated that the HERV-W ENV is highly expressed in the T-lymphocytes of COVID- 19 patients and correlated with inflammatory markers and respiratory outcome and antibodies against HERV-W are statistically increased in MS and T1D patients.
The project will assess the expression of specific HERVs (HERV-H, HERV-K and HERV-W), the production of HERVs antibodies and the expression of markers associated with immunological alterations and molecules involved in the migration of inflammatory cells within the central nervous system in subjects with MS, T1D and ASD and relative age- and sex-matched healthy donors. The immunophenotype and the humoral and cellular responses against HERV-derived antigens and expression profiles of retroviral proteins will be compared with those found in healthy donors and correlated with biochemical and clinical parameters. The project will explore HERVs expression associated with immunological phenotype and markers of the immunological alterations in blood cells from individuals affected by SM, T1D and ASD, characterizing the humoral response to HERVs as well as the role of Epstein Barr and MAP in the reactivation of HERVs. Finally, the evaluation of the impact of SARS-CoV-2 vaccination on HERV-W and HERV-K ENV expression in MS patients and correlation with side-effects and/or immunization will be assessed.
The project is led by Scientists with a large experience on the field and has two units located at AOU of the University of Sassari (in charge of the management of the project activities), the AOU of the University of Tor Vergata and the AOU of the Turin University. Patients (with SM, T1D and ASD, along with matched Healthy controls) will be enrolled at both sites which will interact very strictly according to their expertise. The proposed project will produce valuable knowledge covering the pathological mechanisms involving EBV/MAP and HERVs, as well as identification of diagnostic trigger candidates in MS, T1D and ASD.

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-2022-12375761

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

Applicant Institution: Sardegna

Applicant/PI Coordinator: sechi leonardo antonio

Operative Units

Institution that perform as UO	CF Institution	Department / Division / Laboratory	Role in the project	Southern Italy	SSN
1 - Azienda Ospedaliera Universitaria di Sassari	80002870923	AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI, Italy	COORDINATION od the study. Recruitment and analysis of ASD, MS, Parkinson and T1D patients of Sardegna Region.	X	X
2 - Lazio	80143490581	Policlinico Tor Vergata, Child Neurology and Psychiatry Unit, System Medicine Department, Tor Vergata University Hospital of Rome, Rome, Italy	Enrollment and analysis of ASD patients, recruitment of ASD, MS, Parkinson and T1D patients from Lazio Region		X
3 - Piemonte	80087670016	AOU Città della Salute e della Scienza di Torino, corso Bramante 88, 10126 Torino	Enrollment and analysis of T1D and MS patients and recruitment of ASD patients from Piemonte Region.		X

Principal Research Collaborators

Key Personnel Name	Operative Unit	Role in the project
1 - MAZZONE LUIGI	Lazio	Responsible of UO2, Autism patients recruitment and anaysis
2 - SOLLA PAOLO	Azienda Ospedaliera Universitaria di Sassari	CoPI, responsible for MS patients recruitment and analysis, responsible of ethical committee documents
3 - MELONI GIANFRANCO	Azienda Ospedaliera Universitaria di Sassari	Responsible for T1D patients recruitments of Unit 1 and clinical analysis
4 - BERGALLO MASSIMILIANO	Piemonte	Responsible of T1D and MS patients recruitments and analysis of UO3
5 - GALLIANO ILARIA	Piemonte	Responsible of analyzing MS and T1D sample patients of UO 3
6 Under 40 - Siracusano Martina	Lazio	Responsible of Clinical data managenent of ASD patients
7 Under 40 - Carta Alessandra	Azienda Ospedaliera Universitaria di Sassari	Responsible for following and analysis of ASD patients of UO1

Key Personnel Name	Co-PI	Resp. CE	Resp. Animal	Birth Date	Gender
1 - MAZZONE LUIGI				17/01/1974	M
2 - SOLLA PAOLO	X			08/02/1971	M
3 - MELONI GIANFRANCO				13/05/1968	M
4 - BERGALLO MASSIMILIANO				24/01/1972	M
5 - GALLIANO ILARIA				21/06/1976	F
6 Under 40 - Siracusano Martina				05/06/1986	F
7 Under 40 - Carta Alessandra				08/10/1984	F

Person in charge for the animal experiment: sechi leonardo antonio

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 - Ruberto Stefano	Azienda Ospedaliera Universitaria di Sassari	12/05/1991	M	Analysis of expression of EBV and MAP	Master degree	University of Sassari. Fellowship till July 2022
1 - NOLI MARTA	Azienda Ospedaliera Universitaria di Sassari	19/04/1994	F	ELISA experiments to search autoantibodies against HERVs and Antibodies against human homologous epitopes of EBV and MAP	Master Degree	University of Sassari. fellowship till July 2022
2 - Cipriani Chiara	Lazio	06/03/1988	F	Recruitment of ASD patients, analysis of expression of HERVs	PhD	Project coordinator - Department of Urology, San Carlo di Nancy Hospital - GVM Care and Research, Rome-Italy ¿ Fondazione GVM per la ricerca scientifica

2.1 Administrative data of participating

Operative Unit Number 1:

Address: AOU SASSARI - Azienda Ospedaliera Universitaria di Sassari
Viale S. Pietro, 10, 07100, Sassari (SS)
PEC: protocollo@pec.aou.ss.it

Operative Unit Number 2:

Address: Policlinico Tor Vergata, Fondazione PTV Viale oxford 81, 00133 Roma
PEC: protocollo@ptvonline.postecert.it

Operative Unit Number 3:

Address: AOU Città della Salute e della Scienza di Torino, corso Bramante 88, 10126 Torino
PEC: protocollo@pec.cittadellasalute.to.it

Operative Unit Number 4:

Address: none
PEC: none

Operative Unit Number 5 (self financing):

Address: none
PEC: none

2.2 Principal Investigator (PI) Profile

Last Name: sechi
First Name: leonardo antonio
Last name at birth:
Gender: M

Title: Principal investigator
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 13/06/1965
Place of Birth: Ittiri

Official H index (Scopus or Web of Science): 45.0

Scopus Author Id:35480017300 **ORCID ID:**0000-0003-0566-2049 **RESEARCH ID:**Y-3109-2018

Contact address

Current organisation name: Azienda Ospedaliera Universitaria di Sassari
Current Department / Faculty / Institute / Laboratory name: AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI, Italy
Street: Struttura Complessa di Microbiologia e Virologia, AOU sassari
Postcode / Cedex: 07100
Town: Sassari
Phone:+393204299661
Phone 2: 3204299661

Education / training

Educational institution and location	Degree	Field of study	From year	To year
Università of Sassari	Specialization / Specializzazione	Microbiology and Virology	1989	1993

Personal Statement:
COORDINATOR of the project. Expert in different autoimmune diseases including Multiple Sclerosis, Type 1 Diabetes, Parkinson disease.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Sassari	Department of Biomedical Sciences	Sassari, Italy	Full Professor	2007	2022
University of Sassari	Department of Biomedical Sciences	Sassari, Italy	Associate Professor	2001	2007
University of Sassari	Science Faculty	Sassari, Italy	Researcher	1995	2001
Temple University	Microbiology and Immunology Department	Philadelphia, Pennsilvania, USA	Postdoctoral fellow	1990	1995

Other awards and honors
(2007) 1° classified ¿ Scientific Productivicty Award¿ Università di Sassari,
(2018-2021) Member of the National qualification Commission (ASN) for the evaluation of Microbiology

Professorship for the Italian Universities (A3/06, SSD MED/07)
(212-2015) Member "Gruppo Esperti Valutatori (GEV) 06 (Scienze Mediche) ANVUR"
2013-present. Director of the PhD School of life sciences (https://www.uniss.it/node/8692)
2018-present, regional delegate Italian Society for Microbiology

Other CV informations

My studies are focused on the host-pathogens interaction. In particular I investigate on the host immune response against persistent infection such as those sustained by Mycobacteria and Viruses. This lasting battle may drive to the reactivation of Human Endogenous Retroviruses which may trigger different autoimmune diseases such as Multiple Sclerosis (EBV and HERV-W), Type 1 Diabetes (M. paratuberculosis and HERV-W), Crohn¿s disease (M. paratuberculosis), Rheumatoid Arthritis (EBV, M. paratuberculosis and HERV-W), Amyotrophic Lateral Syndrome (HERV-K) and the role of HERVs in human cancer (HERV-K in Prostate Tumor).
Full profile at:
https://www.researchgate.net/profile/Leonardo-Sechi-3
https://scholar.google.it/citations?user=2CiA_SkAAAAJ&hl=it

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

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Are Mycobacterium avium subsp. paratuberculosis and Epstein-Barr virus triggers of multiple sclerosis in Sardinia?	Article	1181-1184	18	2012	10.1177/1352458511433430	22261119	31	L
Mycobacterium avium ss. paratuberculosis Zoonosis - The Hundred Year War - Beyond Crohn's Disease	Review	NOT_FOUND	6	2015	10.3389/fimmu.2015.00096	NOT_FOUND	88	L
Human interferon regulatory factor 5 homologous epitopes of Epstein-Barr virus and Mycobacterium avium subsp. paratuberculosis induce a specific humoral and cellular immune response in multiple sclerosis patients	Article	984-995	21	2015	10.1177/1352458514557304	25392335	35	L
Type 1 Diabetes at-risk children highly recognize Mycobacterium avium subspecies paratuberculosis epitopes homologous to human Znt8 and Proinsulin	Article	NOT_FOUND	6	2016	10.1038/srep22266	26923214	23	L
Epstein Barr Virus and Mycobacterium avium subsp. paratuberculosis peptides are recognized in sera and cerebrospinal fluid of MS patients	Article	NOT_FOUND	6	2016	10.1038/srep22401	26956729	29	L
Natalizumab therapy modulates miR-155, miR-26a and proinflammatory cytokine expression in MS patients	Article	NOT_FOUND	11	2016	10.1371/journal.pone.0157153	27310932	37	L
Serum BAFF levels, Methypredsinolone therapy, Epstein-Barr Virus and Mycobacterium avium subsp. paratuberculosis infection in Multiple Sclerosis patients	Article	NOT_FOUND	6	2016	10.1038/srep29268	27383531	14	L
Identification of a HERV-K env surface peptide highly recognized in Rheumatoid Arthritis (RA) patients: a cross-sectional case¿control study	Article	127-131	189	2017	10.1111/cei.12964	28324619	24	L

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Homologous HSV1 and alpha-synuclein peptides stimulate a T cell response in Parkinson's disease	Article	26-31	310	2017	10.1016/j.jneuroim.2017.06.004	28778441	23	L
Humoral immunity response to human endogenous retroviruses K/W differentiates between amyotrophic lateral sclerosis and other neurological diseases	Article	1076-e84	25	2018	10.1111/ene.13648	29603839	19	L
Inflammation, infectious triggers, and Parkinson's disease	Review	NOT_FOUND	10	2019	10.3389/fneur.2019.00122	NOT_FOUND	84	L
Cows get crohn¿s disease and they¿re giving us diabetes	Review	NOT_FOUND	7	2019	10.3390/microorganisms7100466	NOT_FOUND	9	L
Identification of mycobacterium avium subsp. Paratuberculosis (map) in sheep milk, a zoonotic problem	Article	1-20	8	2020	10.3390/microorganisms8091264	NOT_FOUND	5	L
HCoV-NL63 and SARS-CoV-2 share recognized epitopes by the humoral response in sera of people collected pre-and during CoV-2 pandemic	Article	1-15	8	2020	10.3390/microorganisms8121993	NOT_FOUND	9	L
A comparative study on the efficiency of two mycobacterium avium subsp. Paratuberculosis (MAP)-derived lipopeptides of L3P and L5P as capture antigens in an in-house milk ELISA test	Article	NOT_FOUND	9	2021	10.3390/vaccines9090997	NOT_FOUND	3	L
Tdp?43 and herv?k envelope?specific immunogenic epitopes are recognized in als patients	Article	NOT_FOUND	13	2021	10.3390/v13112301	34835107	1	L
Increased seroreactivity to proinsulin and homologous mycobacterial peptides in latent autoimmune diabetes in adults	Article	NOT_FOUND	12	2017	10.1371/journal.pone.0176584	28472070	6	L
Anti-HERV-W <inf>Env</inf> antibodies are correlated with seroreactivity against Mycobacterium avium subsp. paratuberculosis in children and youths at T1D risk	Article	NOT_FOUND	9	2019	10.1038/s41598-019-42788-5	31000760	12	L
Herv-k modulates the immune response in als patients	Article	NOT_FOUND	9	2021	10.3390/microorganisms9081784	NOT_FOUND	2	C
Herv-w and mycobacterium avium subspecies paratuberculosis are at play in pediatric patients at onset of type 1 diabetes	Article	NOT_FOUND	10	2021	10.3390/pathogens10091135	NOT_FOUND	1	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.**
The consensus from the Mycobacterium avium ssp. paratuberculosis (MAP) conference 2017	Article	NOT_FOUND	5	2017	10.3389/fpubh.2017.00208	NOT_FOUND	56
Association of mycobacterium avium subsp. paratuberculosis with multiple sclerosis in sardinian patients	Article	NOT_FOUND	6	2011	10.1371/journal.pone.0018482	21533236	70

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Utility of quantitative T-cell responses versus unstimulated interferon-? for the diagnosis of pleural tuberculosis	Article	1118-1126	34	2009	10.1183/09031936.00005309	19386693	77
Inflammation, infectious triggers, and Parkinson's disease	Review	NOT_FOUND	10	2019	10.3389/fneur.2019.00122	NOT_FOUND	84
Mycobacterium avium subspecies paratuberculosis infection in cases of irritable bowel syndrome and comparison with Crohn's disease and Johne's disease: Common neural and immune pathogenicities	Article	3883-3890	45	2007	10.1128/JCM.01371-07	17913930	101
Clinical utility of a commercial LAM-ELISA assay for TB diagnosis in HIV-infected patients using urine and sputum samples	Article	NOT_FOUND	5	2010	10.1371/journal.pone.0009848	20352098	114
Incidence of virulence determinants in clinical Enterococcus faecium and Enterococcus faecalis isolates collected in Sardinia (Italy)	Article	491-498	52	2003	10.1099/jmm.0.05038-0	12748268	149
Within-subject variability and boosting of t-cell interferon-? responses after tuberculin skin testing	Article	49-58	180	2009	10.1164/rccm.200811-1704OC	19342414	158
Detection and isolation of Mycobacterium avium subspecies paratuberculosis from intestinal mucosal biopsies of patients with and without Crohn's disease in Sardinia	Article	1529-1536	100	2005	10.1111/j.1572-0241.2005.41415.x	15984976	160
Comparison of the incidence of virulence determinants and antibiotic resistance between Enterococcus faecium strains of dairy, animal and clinical origin	Article	291-304	88	2003	10.1016/S0168-1605(03)00191-0	14597001	202

** Autocertificated

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Sardegna Ricerche	University of Sassari	2021	Epitopes4cov: identificazione di epitopi specifici di Coronavirus leganti ACE2 in sieri di pazienti con diverse malattie autoimmuni ed oncologiche.	Coordinator	60.000,00	https://www.sardegnaricerche.it/documenti/13_493_20200612094049.pdf
Minister of University and Research	University of Sassari	2007	Interazioni batterio-cellula ospite: analisi genetica e molecolare di meccanismi di virulenza di patogeni enterici di rilevanza clinica con particolare riferimento alla loro capacità di alterare a proprio vantaggio la risposta immune innata dell¿ospite. PI unit 5	Collaborator	135.000,00	https://prin.mur.gov.it/Ricerca?Filtro.Anno=%25&Filtro.Ateneo=%25&Filtro.Argomento=&Filtro.Cognome=cappuccinelli

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ministero of University and Research	University of Sassari	2000	EFFETTORI DI VIRULENZA IN PATOGENI ENTERICI: CARATTERISTICHE E STUDIO DELLE LORO INTERAZIONI PI Unit 5	Collaborator	154.937,00	https://prin.mur.gov.it/Ricerca?Filtro.Anno=%25&Filtro.Ateneo=%25&Filtro.Argomento=&Filtro.Cognome=cappuccinelli
Minister of University and Research,	University of Sassari	2005	Caratterizzazione genetica e molecolare di ¿pathway¿ di virulenza comuni a patogeni enterici diversi: studio della capacità di indurre alterazioni citoscheletriche, apoptosi e l'innesco della risposta infiammatoria PI unit 3	Collaborator	116.000,00	https://prin.mur.gov.it/Ricerca?Filtro.Anno=%25&Filtro.Ateneo=%25&Filtro.Argomento=&Filtro.Cognome=cappuccinelli
Minister of University and Research , PRIN	University of Sassary	2009	STUDIO SULL¿ASSOCIAZIONE TRA MYCOBACTERIUM AVIUM SUBSPECIES PARATUBERCULOSIS E IL DIABETE MELLITO DI TIPO 1	Coordinator	68.208,00	https://prin.mur.gov.it/Ricerca?Filtro.Anno=%25&Filtro.Ateneo=%25&Filtro.Argomento=&Filtro.Cognome=sechi
Ministero della Salute,	University of Sassari	2011	Risk evaluation of human exposure to Mycobacterium avium subsp. paratuberculosis (Map) and comparative analysis of strains of human and animal origin. November 2011 - October 2014. Protocollo: RF-2009-1545765	Coordinator	320.000,00	https://www.izsler.it/bancadati_ricerca/risk-evaluation-of-human-exposure-to-mycobacterium-avium-subsp-paratuberculosis-map-and-comparative-analysis-of-strains-of-human-and-animal-origin/
Federazione Italiana Sclerosi Multipla (FISM)	Università di Sassari	2012	Geoepidemiologia della sclerosi multipla: i fattori ambientali, Eleonora Cocco P.I.	Collaborator	220.000,00	https://www.aism.it/sites/default/files/Compendio_della_ricerca_AISM_FISM_2014.pdf. page 145
Federazione Italiana Sclerosi Multipla	University of Sassari	2009	LINKING GENES AND ENVIRONMENT IN MULTIPLE SCLEROSIS	Coordinator	25.000,00	https://allegati.aism.it/manager/UploadFile/2/20120828_118_ricerca.pdf

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
EDCTP	University of Cape Town , University of Sassari	2015	P.I. of unit 2 within the project financed by ¿European & Developing Countries Clinical Trial Partnership¿ EDCTP, entitled: The utility of intensified case finding combined with a package of novel TB diagnostics performed at community-based clinics in Africa- a multi-centric prospective cohort study. Coordinator prof. K. Dheda, South Africa	Collaborator	45.000,00	https://www.edctp.org/publication/edctp-project-portfolio-a-compendium-of-clinical-trial-capacity-building-and-networking-projects-2003-2015/
ARISLA	Department of Biomedical Sciences , University of Sassari	2018-2019	IRKALS, role of HERV-K in Amyotrophic Lateral Disease.	Coordinator	57.000,00	https://www.arisla.org/wp-content/uploads/2018/01/4-scheda-progetto-2017-IRKALS.pdf

2.3 CO-PI Profile

Last Name: SOLLA
First Name: PAOLO

Last name at birth:
Gender: M

Title: CoPI, responsible for MS patients recruitment and analysis, responsible of ethical committee documents

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Cagliari

Nationality: Italiana
Date of birth: 08/02/1971

Official H index (Scopus or Web of Science): 22.0

Scopus Author Id:10539295100 **ORCID ID:**0000-0002-2982-0665 **RESEARCH ID:**R-5366-2016

Contact address

Current organisation name: Azienda Ospedaliera Universitaria di Sassari
Current Department / Faculty / Institute / Laboratory name: AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI, Italy
Street: Viale san Pietro, 10
Postcode / Cedex: 07100 **Town:** Sassari
Phone:+393273555636 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Cagliari	PhD	Cardiovascular and Neurological Sciences	2010	2013
University of Cagliary	Specialization / Specializzazione	Neurology	2002	2006
University of Cagliari	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine	1995	2001

Personal Statement:
Prof. Solla is the CoPI and it will be responsible for the recruitment of Multiple Sclerosis patients at the AOU of Sassari

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Sassari	Neurology, department of clinical medicine	Sassari	Associate professor	2021	2022
University of Cagliari	Neurology	Cagliari	Researcher	2013	2016
AOU Cagliari	Neurology	CAGLIARI	Consultant	2017	2021

Other awards and honors

Scientific director of the project "Study of cardiovascular reflexes in Sardinian patients suffering from Parkinson's disease and their correlation with motor and non-motor disorders", at University of Cagliari, from 2013 to 2015.
Scientific director of the project "Sardinian dance and Parkinson's disease: study of the efficacy of a non-pharmacological therapeutic approach on motor rehabilitation and non-motor symptoms of disease", at the University of Cagliari, from 2014 to 2016

Other CV informations

- PhD Academic Board Member in Life Sciences and Biotechnologies of the University of Sassari
2007-at present/ Member of Accademia LIMPE- DISMOV
2007-at present/ Member of Italian Society of Neurology (SIN).
2011-at present/ Member of The International Parkinson and Movement Disorder Society (MDS)

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

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Influence of Parkinsonism on Hitler's Decision-Making	Note	4	86	2016	10.1016/j.wneu.2015.07.024	26856783	0	F
Pisa syndrome and scoliosis in Parkinson's disease	Article	143-144	151	2016	10.1016/j.clineuro.2016.10.006	27789062	1	F
Dopamine dysregulation syndrome and psychosis in 24-h intestinal levodopa infusion for Parkinson's disease	Article	144-145	31	2016	10.1016/j.parkreldis.2016.06.022	27423923	1	F
Prolonged B-cell depletion after rituximab in AQP4-IgG-positive neuromyelitis optica spectrum disorder	Article	NOT_FOUND	358	2021	10.1016/j.jneuroim.2021.577666	34298341	0	L
Chronic inflammatory demyelinating polyneuropathy after chadox1 ncov-19 vaccination	Article	NOT_FOUND	9	2021	10.3390/vaccines9121502	NOT_FOUND	0	L
Dopaminergic-induced paraphilias associated with impulse control and related disorders in patients with Parkinson disease	Letter with Data	2752-2754	259	2012	10.1007/s00415-012-6691-3	23096066	12	F
Dopamine dysregulation syndrome in Parkinson's disease patients with unsatisfactory switching from immediate to extended release pramipexole: A further clue to incentive sensitization mechanisms?	Article	563-566	27	2013	10.3233/BEN-129026	23242362	3	F
Association between fatigue and other motor and non-motor symptoms in Parkinson's disease patients	Article	382-391	261	2014	10.1007/s00415-013-7207-5	24375016	22	F
Fluctuating cotard syndrome in a patient with advanced Parkinson disease	Article	70-72	19	2015	10.1097/NRL.0000000000000010	25692512	8	F
Paraphilias and paraphilic disorders in Parkinson's disease: A systematic review of the literature	Article	604-613	30	2015	10.1002/mds.26157	25759330	24	F
Dopamine agonist withdrawal syndrome (DAWS) symptoms in Parkinson's disease patients treated with levodopa-carbidopa intestinal gel infusion	Article	968-971	21	2015	10.1016/j.parkreldis.2015.05.018	26071817	17	F

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Heart rate variability shows different cardiovascular modulation in Parkinson¿s disease patients with tremor dominant subtype compared to those with akinetic rigid dominant subtype	Article	1441-1446	122	2015	10.1007/s00702-015-1393-5	25797035	11	F
An unusual delusion of duplication in a patient affected by Dementia with Lewy bodies	Article	NOT_FOUND	17	2017	10.1186/s12883-017-0842-1	28424054	4	F
Dopamine agonist withdrawal syndrome in Parkinson's disease	Article	47-48	382	2017	10.1016/j.jns.2017.08.3263	29111017	3	F
Sardinian Folk Dance for Individuals with Parkinson's Disease: A Randomized Controlled Pilot Trial	Article	305-316	25	2019	10.1089/acm.2018.0413	30624952	21	F
Sex-related differences in olfactory function and evaluation of possible confounding factors among patients with Parkinson¿s disease	Article	57-63	267	2020	10.1007/s00415-019-09551-2	31555978	22	F
Frequency and determinants of olfactory hallucinations in parkinson¿s disease patients	Article	NOT_FOUND	11	2021	10.3390/brainsci11070841	NOT_FOUND	10	F
Chronic inflammatory demyelinating polyneuropathy after chadox1 ncov-19 vaccination	Article	NOT_FOUND	9	2021	10.3390/vaccines9121502	NOT_FOUND	2	L
Rasagiline Withdrawal Syndrome in Parkinson¿s Disease	Article	NOT_FOUND	12	2022	10.3390/brainsci12020219	NOT_FOUND	0	F
Gender differences in motor and non-motor symptoms among Sardinian patients with Parkinson's disease	Article	33-39	323	2012	10.1016/j.jns.2012.07.026	22935408	87	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 di Sardegna RAS	Dipartimento di Sanità Pubblica, Medicina Clinica e Molecolare (CA)	2014	Ballo sardo e Malattia di Parkinson: studio dell'efficacia di un approccio terapeutico non farmacologico sulla riabilitazione motoria e sui sintomi non motori di malattia	Coordinator	20.000,00	https://www.fondazionedisardegna.it/media/0/75531339243035/bilancio_consuntivo_2014.pdf
Fondazione di Sardegna	University of Cagliari	2013	Studio dei riflessi cardiovascolari in pazienti sardi affetti da Malattia di Parkinson e loro correlazione con disturbi motori e non motori	Coordinator	15.000,00	https://www.fondazionedisardegna.it/media/0/92900676841104/bilancio_consuntivo_2013.pdf

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
European Commission	University of Cagliari	2014	ECOST-STSM-BM1101-020514-043037 Grant, Dystonia Europe (Brussels, Belgium, BE) National and Regional Grants	Collaborator	30.000,00	https://e-services.cost.eu/user

2.3 Research Collaborators n. 1

Last Name: MAZZONE
First Name: LUIGI

Last name at birth:
Gender: M

Title: Responsible of UO2, Autism patients recruitment and anaysis

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Catania

Nationality: Italiana
Date of birth: 17/01/1974

Official H index (Scopus or Web of Science): 31.0

Scopus Author Id:55665558200 **ORCID ID:**0000-0002-5287-3386 **RESEARCH ID:**AAC-5210-2022

Contact address

Current organisation name: Lazio

Current Department / Faculty / Institute / Laboratory name: Policlinico Tor Vergata, Child Neurology and Psychiatry Unit, System Medicine Department, Tor Vergata University Hospital of Rome, Rome, Italy

Street: Viale Oxford 81

Postcode / Cedex: 00133
Town: Roma

Phone:00393395969516
Phone 2: 0668592734

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Catania	PhD	Stress, Emotion and Neural Substrate: An fMRI study.Using the Endocrinological Syndrome as a Natural Model	2003	2007
University of Catania	Specialization / Specializzazione	Children Neuropsichiatry	1998	2003
Medicine Degree at the Università di Catania, score 110 with honors	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine	1993	1998

Personal Statement:
Responsible of the recruitment of ASD patients at the Policlinico TorVergata supervisor of UO2.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Tor Vergata	Neuropsichiatria Infantile	Rome	Associate Professor	2019	2022
University of Tor Vergata	MED/39 Neuropsichiatria Infantile	Rome Tor Vergata	RTD-B	2016	2019
Ospedale Pediatrico Bambino Gesù di Roma	IRCCS Ospedale Pediatrico Bambino Gesù di Roma	Rome	Dirigente Medico di I Livell	2014	2016
Columbia University, New York	Division of Child and Adolescent Psychiatry del Department of Psychiatry	New York, USA	Post-doctoral visiting fellow	2006	2009
Intramural Program dell¿National Institute of Mental Health di Bethesda, Washington DC	Dr. Monique Ernst group	Bethesda, Washington DC, USA	Post-doctoral visiting fellow	2005	2006

Other awards and honors

2006-2007 Alexander Bodini Fellowship. Italian Academy for Advanced Studies in America at the Columbia University, New York (USA). The influence of risperidone on emotional stimuli processing in a sample of individuals with autism: a functional MRI study.

2008. Winner of the INational award -Arturo Reggio-, Fondazione Cesare Serono, rome with a project: Reward system in children and adolescents with ADHD and anxiety disorders.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Minister of Health	IRCCS Bonino Pulejo Neurolesi di Messina	2009	¿A longitudinal study of neural plasticity in children with Autism Spectrum Disorders¿	Coordinator	150.450,00	https://www.salute.gov.it/imgs/C_17_paginaAree_4517_listaFile_itemName_4_file.pdf

2.4 Research Collaborators n. 3

Last Name: MELONI
First Name: GIANFRANCO

Last name at birth:
Gender: M

Title: Responsible for T1D patients recruitments of Unit 1 and clinical analysis

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Sassari

Nationality: ITALIANA
Date of birth: 13/05/1968

Official H index (Scopus or Web of Science): 18.0

Scopus Author Id:7102933016 **ORCID ID:**0000-0002-0604-8924 **RESEARCH ID:**E-9426-2012

Contact address

Current organisation name: Azienda Ospedaliera Universitaria di Sassari
Current Department / Faculty / Institute / Laboratory name: AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI, Italy
Street: Viale S.Pietro 12 Sassari
Postcode / Cedex: 07100 **Town:** Sassari
Phone:+393396487303 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Sassari	PhD	Paediatrics	1992	1996
University of Sassari	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine	1986	1992

Personal Statement:
Prof Meloni is responsible of T1D patients recruitment and analysis of the UO1

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Sassari	Pediatrics	Sassari	Assistant Professor of Pediatrics,	1994	2022

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

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

2.5 Research Collaborators n. 4

Last Name: BERGALLO
First Name: MASSIMILIANO

Last name at birth:
Gender: M

Title: Responsible of T1D and MS patients recruitments and analysis of UO3
Nationality: Italiana
Date of birth: 24/01/1972

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Torino

Official H index (Scopus or Web of Science): 22.0

Scopus Author Id:6602512493 **ORCID ID:**0000-0002-9291-1332 **RESEARCH ID:**AHD-2214-2022

Contact address

Current organisation name: Piemonte
Current Department / Faculty / Institute / Laboratory name: AOU Città della Salute e della Scienza di Torino, corso Bramante 88, 10126 Torino

Street: p.za Polonia 94
Postcode / Cedex: 10126
Town: Torino
Phone:+393494714960
Phone 2: 0113131652

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Turin	Specialization / Specializzazione	Microbiology and virology	2000	2003
University of Turin	Single-cycle master's degree / Laurea magistrale a ciclo unico	Biology	1993	1997

Personal Statement:
Prof Bergamo is responsible of recruitment and analysis of patients of UO3

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Turin	Dipartimento di SCIENZE DELLA SANITÀ PUBBLICA E PEDIATRICHE	Turin	Associate professor	2015	2022
University of Turin	Dipartimento di SCIENZE DELLA SANITÀ PUBBLICA E PEDIATRICHE	Turin	assistant professor	2005	2015

Other awards and honors

Ricerca locale ex 60% regolarmente assegnata dal 2008 al 2019
Progetto di 18000 euro finanziato da Fondazione Ospedale Infantile Regina Margherita (FORMA) dal titolo¿ : La malattia linfoproliferativa post-trapianto (PTLD) : nell¿anno 2016
Progetto di 26000 euro con la Ditta Dicofarm (PI dott. Francesco Savino dirigente medico Pediatria AOU città della salute e della scienza di Torino) per lo studio ¿Lactobacillus rhamnosus GG (ATCC 53103) NEL TRATTAMENTO DELLE COLICHE INFANTILI¿ nell¿anno 2018

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Ditta Dicofarm	UNIVERSITY OF TURIN	2015	Nuove frontiere della immunologia clinica applicata alle malattie articolari e renali ed ai trapianti d¿organo in età pediatrica: i retrovirus endogeni e i microRNA, come biomarcatori innovativi	Coordinator	18.000,00	https://www.aopi.it/strutture/presidio-ospedale-infantile-regina-margherita/

2.6 Research Collaborators n. 5

Last Name: GALLIANO
First Name: ILARIA

Last name at birth:
Gender: F

Title: Responsible of analyzing MS and T1D sample patients of UO 3

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Venaria Reale

Nationality: Italiana
Date of birth: 21/06/1976

Official H index (Scopus or Web of Science): 10.0

Scopus Author Id:56436821300 **ORCID ID:**0000-0002-1273-3178 **RESEARCH ID:**AHD-2233-2022

Contact address

Current organisation name: Piemonte
Current Department / Faculty / Institute / Laboratory name: AOU Città della Salute e della Scienza di Torino, corso Bramante 88, 10126 Torino

Street: p.za Polonia 94
Postcode / Cedex: 10126
Town: Torino
Phone:+393495512218
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Turin	Specialization / Specializzazione	Clinical Pathology	2005	2009
Biological Sciences	Master's Degree / Laurea Magistrale	Biology	2000	2005

Personal Statement:
Dr. Galliano will perform the molecular and immunological analysis on the patients samples of UO3

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Turin	Department of Sciences of Public Health and Pediatrics (Turin,, Prof. Bergalloo Group	University of Turin, Piemonte	Research Technician	2010	2022

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
University of Turin	University of Turin	2010	Thesis on clinical pathology	Coordinator	0,00	https://www.unito.it/persone/igallian

2.7 Research Collaborators n. 6 - Under 40

Last Name: Siracusano
First Name: Martina

Last name at birth:
Gender: F

Title: Responsible of Clinical data managenent of ASD patients
Nationality: Italiana
Date of birth: 05/06/1986

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Roma

Official H index (Scopus or Web of Science): 8.0

Scopus Author Id:55359644500 **ORCID ID:**0000-0002-3357-1788 **RESEARCH ID:**AAC-5207-2022

Contact address

Current organisation name: Lazio
Current Department / Faculty / Institute / Laboratory name: Policlinico Tor Vergata, Child Neurology and Psychiatry Unit, System Medicine Department, Tor Vergata University Hospital of Rome, Rome, Italy

Street: VIA MONTPELLIER 1
Postcode / Cedex: 00133
Town: ROMA
Phone:+393332135323
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Tor Vergata	Specialization / Specializzazione	Neuropsichiatria infantile	2013	2017
University of Tor Vergata	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine	2005	2011

Personal Statement:
Dr Siracusano will be responsible for recruitment and analysis of patients of UO2

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Tor Vergata	Dipartimento di Biomedicina e Prevenzione (SSD Med/39 - Neuropsichiatria Infantile),	Rome	RTD-A	2018	2022

Other awards and honors
Diploma di Specialista in Neuropsichiatria Infantile il 6 luglio 2017 presso l¿Università degli Studi di Roma Tor Vergata con votazione 50/50 e lode (Tesi Finale: ¿Analisi del Profilo Metabolomico Urinario in una popolazione di bambini affetti da Disturbo dello Spettro Autistico¿).

Grant

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

2.8 Research Collaborators n. 7 - Under 40

Last Name: Carta
First Name: Alessandra

Last name at birth: CARTA
Gender: F

Title: Responsible for following and analysis of ASD patients of UO1

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Sassari

Nationality: Italiana
Date of birth: 08/10/1984

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

Scopus Author Id:57195718037 **ORCID ID:**0000-0002-4066-2805 **RESEARCH ID:**AAH-9192-2019

Contact address

Current organisation name: Azienda Ospedaliera Universitaria di Sassari
Current Department / Faculty / Institute / Laboratory name: AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI, Italy
Street: Viale San Pietro, 42
Postcode / Cedex: 07100 **Town:** Sassari
Phone:+393405438579 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Sassari	PhD	¿Biological, phenotypical and immunogenetic heterogeneity of ADHD and ASD; clinical implications¿.	2016	2019
University of Cagliari	Specialization / Specializzazione	Neuropsichiatric	2010	2014
University of Sassari, Sassari	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine	2003	2009

Personal Statement:

Dr. Carta will be responsible for recruiting ASD patients and analysis of samples of UO1.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
AOU Sassari	and Consultant at the Complex Operating Unit	Sassari	Medical Doctor	2021	2022
Ospedale Pediatrico Bambino Gesù di Roma,	Unità di Neuropsichiatria Infantile	Rome	Medical doctor	2018	2020

Other awards and honors

Medicine Degree at University of Sassari: 110/110 cum summa laude.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
MIUR	University of Sassari	2018	Case manager with experience, also in foreign countries, in the field of clinical research, diagnosis and treatment of Autism Spectrum Disorder and associated neurodevelopmental disorders (Intellectual Disabilities, ADHD, Learning Disabilities).	Coordinator	30.000,00	http://bandi.miur.it/bandi.php/public/fellowship/id_fellow/140796

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

Last Name: Ruberto
First Name: Stefano

Last name at birth:
Gender: M

Title: Analysis of expression of EBV and MAP

Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 12/05/1991
Place of Birth: Catania

Official H index (Scopus or Web of Science): 3.0

Scopus Author Id:57203417957 **ORCID ID:**0000-0001-5478-999X **RESEARCH ID:**AAN-2924-2021

Contact address

Current organisation name: Azienda Ospedaliera Universitaria di Sassari
Current Department / Faculty / Institute / Laboratory name: AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI, Italy
Street: Department of Biomedical Science University of Sassari V.le San Pietro 43B 07100 Sassari, ITALY
Postcode / Cedex: 07100
Town: Sassari
Phone:+393478615277
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Padua	Master's Degree / Laurea Magistrale	Evolutionary Biology	2018	2020
University of Turin	Master's Degree / Laurea Magistrale	Natural Sciences	2015	2017
University of Catania	Bachelor Degree / Laurea Triennale	biology	2012	2015

Personal Statement:
Dr Roberto will study the HERVs expression in patients and controls

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Sassari	Biomedical Sciences	Sassari	fellow	2020	2022

Other awards and honors
INPS award fellowships: Human endogenous retroviruses (HERV) in ALS, new therapeutic targets and disease biomarkers

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Istituto Nazionale Previdenza Sociale (INPS)	University of Sassari	2020	Human endogenous retroviruses (HERV) in ALS, new therapeutic targets and disease biomarkers	Coordinator	25.000,00	https://www.uniss.it/sites/default/files/life_sciences_and_biotechnologies_15.pdf

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

Last Name: NOLI
First Name: MARTA

Last name at birth:
Gender: F

Title: ELISA experiments to search autoantibodies against HERVs and Antibodies against human homologous epitopes of EBV and MAP

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Ozieri

Nationality: Italiana

Date of birth: 19/04/1994

Official H index (Scopus or Web of Science): 1.0

Scopus Author Id:57254018400 **ORCID ID:**0000-0003-1087-4871 **RESEARCH ID:**AHD-2616-2022

Contact address

Current organisation name: Azienda Ospedaliera Universitaria di Sassari

Current Department / Faculty / Institute / Laboratory name: AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI, Italy

Street: Viale San Pietro 43b

Postcode / Cedex: 07100 **Town:** Sassari

Phone:+393401473647 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Sassari	Master's Degree / Laurea Magistrale	Biotechnology	2017	2019

Personal Statement:

Elisa and

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
University of Sassari	biomedical sciences	Sassari	fellow	2020	2022

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
none	none	none	none	Collaborator	0,00	none

2.11 Additional Research Collaborators n. 4 - Under 40 to hire

Last Name: Cipriani
First Name: Chiara

Last name at birth:
Gender: F

Title: Recruitment of ASD patients, analysis of expression of HERVs

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Sezze

Nationality: Italiana
Date of birth: 06/03/1988

Official H index (Scopus or Web of Science): 11.0

Scopus Author Id:56527986500 **ORCID ID:**0000-0001-7085-4966 **RESEARCH ID:**AAC-3669-2022

Contact address

Current organisation name: Lazio
Current Department / Faculty / Institute / Laboratory name: Policlinico Tor Vergata, Child Neurology and Psychiatry Unit, System Medicine Department, Tor Vergata University Hospital of Rome, Rome, Italy

Street: Via Montpellier, 1
Postcode / Cedex: 00133
Town: Roma
Phone:+393922689232
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Tor Vergata	PhD	PhD in Medical Microbiology, Immunology, Infectious Diseases, Organ Transplantation and Related Diseases,	2013	2017
University of Tor Vergata	Master's Degree / Laurea Magistrale	Medical Biotechnologies	2011	2013

Personal Statement:
Dr. Cipriani will recite patients and healthy controls at the UO2

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
GVM Care and Research, Rome-Italy	Fondazione GVM per la ricerca scientifica	Rome	Project coordinator	2019	2022

Other awards and honors
Grant for the oral presentation of ¿ENDOGENOUS RETROVIRUSES IN

NEURODEVELOPMENTAL DISORDERS: THE CASE OF AUTISM SPECTRUM DISORDERS¿ at ¿Young Researchers in Life Sciences¿, May18-20, 2016 Institut Pasteur-Paris.

Special Award 2014 for Immuno Tools with the proposal ¿Cytokines imbalance in autism spectrum disorders: interaction between genetic and environmental contributors¿. Supervisor: Prof. Paola Sinibaldi-Vallebona.

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
Institut Pasteur-Paris.	University of Tor Vergata	2016	¿ENDOGENOUS RETROVIRUSES IN NEURODEVELOPMENTAL DISORDERS: THE CASE OF AUTISM SPECTRUM DISORDERS¿	Coordinator	2.000,00	http://yrls.fr/wp-content/uploads/2014/12/YRLS_2016_Abstract_Book.pdf

2.17 Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
MAZZONE LUIGI	The role of anxiety symptoms in school performance in a community sample of children and adolescents	Article	NOT_FOUND	7	2007	10.1186/1471-2458-7-347	18053257	94	F
MAZZONE LUIGI	Genetic and functional analyses of SHANK2 mutations suggest a multiple hit model of autism spectrum disorders	Article	NOT_FOUND	8	2012	10.1371/journal.pgen.1002521	22346768	296	O
MELONI GIANFRANCO	High prevalence of lactose absorbers in Northern Sardinian patients with type 1 and type 2 diabetes mellitus	Article	582-585	73	2001	10.1093/ajcn/73.3.582	11237935	17	F
MELONI GIANFRANCO	Recommendations for self-monitoring in pediatric diabetes: A consensus statement by the ISPED	Article	173-184	51	2014	10.1007/s00592-013-0521-7	24162715	18	O
MELONI GIANFRANCO	Prevalence of silent celiac disease in patients with autoimmune thyroiditis from Northern Sardinia	Article	298-302	24	2001	10.1007/BF03343864	11407647	42	F
SOLLA PAOLO	Correlation among olfactory function, motors¿ symptoms, cognitive impairment, apathy, and fatigue in patients with Parkinson¿s disease	Article	1764-1771	265	2018	10.1007/s00415-018-8913-9	29804147	38	O
SOLLA PAOLO	Reversible Pisa syndrome in patients with Parkinson's disease on dopaminergic therapy	Article	390-395	256	2009	10.1007/s00415-009-0072-6	19319462	60	O
SOLLA PAOLO	Effects of a Nordic Walking program on motor and non-motor symptoms, functional performance and body composition in patients with Parkinson's disease	Article	245-254	37	2015	10.3233/NRE-151257	26484516	62	O
MELONI GIANFRANCO	The prevalence of coeliac disease in infertility	Article	2759-2761	14	1999	10.1093/humrep/14.11.2759	10548618	120	F
MELONI GIANFRANCO	A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes	Article	337-338	36	2004	10.1038/ng1323	15004560	1099	O

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
BERGALLO MASSIMILIANO	Transcriptional Activity of Human Endogenous Retroviruses in Response to Prenatal Exposure of Maternal Cigarette Smoking	Article	1060-1065	36	2019	10.1055/s-0038-1675768	30500959	8	F
BERGALLO MASSIMILIANO	Human Endogenous Retroviruses Are Preferentially Expressed in Mononuclear Cells From Cord Blood Than From Maternal Blood and in the Fetal Part of Placenta	Article	NOT_FOUND	8	2020	10.3389/fped.2020.00244	NOT_FOUND	9	F
BERGALLO MASSIMILIANO	Enhanced expression of human endogenous retroviruses in new-onset type 1 diabetes: Potential pathogenetic and therapeutic implications	Article	283-288	53	2020	10.1080/08916934.2020.1777281	32586158	11	L
BERGALLO MASSIMILIANO	Expression of the pol gene of human endogenous retroviruses HERV-K and -W in leukemia patients	Article	3639-3644	162	2017	10.1007/s00705-017-3526-7	28821995	19	F
BERGALLO MASSIMILIANO	CMV induces HERV-K and HERV-W expression in kidney transplant recipients	Article	28-31	68	2015	10.1016/j.jcv.2015.04.018	26071331	32	F
MAZZONE LUIGI	Risk and protective environmental factors associated with autism spectrum disorder: Evidence-based principles and recommendations	Article	NOT_FOUND	8	2019	10.3390/jcm8020217	NOT_FOUND	42	F
MAZZONE LUIGI	The role of anxiety symptoms in school performance in a community sample of children and adolescents	Article	NOT_FOUND	7	2007	10.1186/1471-2458-7-347	18053257	94	F
MAZZONE LUIGI	Impairment of quality of life in parents of children and adolescents with pervasive developmental disorder	Article	NOT_FOUND	5	2007	10.1186/1477-7525-5-22	17466072	245	L
SOLLA PAOLO	Behavioral, neuropsychiatric and cognitive disorders in Parkinson's disease patients with and without motor complications	Article	1009-1013	35	2011	10.1016/j.pnpbp.2011.02.002	21324349	41	F
SOLLA PAOLO	Gender differences in motor and non-motor symptoms among Sardinian patients with Parkinson's disease	Article	33-39	323	2012	10.1016/j.jns.2012.07.026	22935408	87	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?	Yes
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)?	No
5. ANIMALS	
Does your research involve animals?	No
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

Different autoimmune diseases have been associated with components derived from human endogenous retroviruses (HERVs) integrated across the human genome as remnants of ancient viral infections. Among them, Multiple Sclerosis (MS), Autism Spectrum Disorder (ASD) and Type 1 Diabetes (T1D) have been linked to the expression of HERV-W (MS),

T1D, and HERV-H/K (ASD).
Although HERVs are generally silenced, peculiar HERV copies can be activated by different environmental stimuli, leading to the expression of immunopathogenic proteins. Among environmental factors, HERVs may be transactivated by different microorganisms, such as Epstein Barr Virus and Mycobacterium avium spp. paratuberculosis (MAP) in MS and T1D. In this regard, we will investigate the activation of HERVs, the presence of autoantibodies against HERVs in different neurological diseases (MS, ASD and Parkinson as a control group) and T1D in order to understand their role in the etiology and development of the disease.

Background / State of the art

The increasing prevalence of chronic neurological diseases such as Multiple Sclerosis (MS), Autism Spectrum Disorder (ASD) and in Type 1 Diabetes (T1D) registered over recent decades have led to intensified efforts aimed at unravelling their aetiology. A close interplay between genetics and environmental factors underlies the alteration of cellular and molecular processes inducing imbalance in the immune system which becomes unable to correctly recognize own body's constituents, thereby directing immune responses against self-antigens. This occurs through the activation of T helper lymphocytes and the onset of antibodies and/or cytotoxic T cells leading to chronic inflammation and tissue damage. Genome-wide association studies reported that genetic determinants account for a minority of forms of autoimmunity, therefore environmental triggers appear to play a crucial role in the loss of self-tolerance and immune regulation. Among them, viral and bacterial infections emerged as events highly increasing the risk of autoimmune activation or persistent immune activation but still no direct evidence has been provided in favor of unique pathogen. A large body of literature links certain autoimmune diseases with components derived from human endogenous retroviruses (HERVs) integrated across the human genome as remnants of ancient viral infections. The HERV-W has been associated with MS and T1D, HERV-H/K with ASD.

Description and distribution of activities of each operating unit

Three operating units (UO) will carry out the project.
The UO1 is under the supervision of Prof L.A. Sechi, it is located at the Azienda Ospedaliera Universitaria of Sassari and will coordinate the other UOs. The group is studying the involvement of different triggers as potential activation of MS, in particular the immune response (both humoral and cellular) against HERV-W, Epstein Barr Virus and Mycobacterium avium subspecies paratuberculosis (MAP). In addition, the group is currently investigating the role of HERV-K in Parkinson disease. The other members of the group are Dott. Gian Franco Meloni, expert in Type 1 diabete and other autoimmune diseases and several PhD students and fellows dealing with HERVs and different autoimmune diseases. The laboratories have all the facilities and instruments to complete the proposed project. The collaboration with the Neurology Unit of UNISS, led by prof. Solla is ongoing, they¿ll oversee recruiting people living with MS and Parkinson. More than 600 patients diagnosed with Multiple Sclerosis are referred to the center and 400 Parkinson patients are followed within the North Sardinia territory. The Neuropschiatric clinic of the University of Sassari, led by prof. Stefano Sotgiu will enroll the ASD patients.In addition to in-house samples, the center will receive samples from UO2 and UO3 to perform all the characterization of the humoral response to HERVs, EBV and MAP.
UO2 is located at the policlinico of Tor Vergata, it has a consolidated experience on clinical studies involving autistic children and their parents to study the potential role of human ERVs and immune deregulation in ASD (Prof. L. Mazzone). In addition, the Multiple Sclerosis Center of the Tor Vergata hospital of Rome is a Regional Reference Center. Laboratories are equipped with all the instruments needed to perform the specific aims of the project (Bio-Rad CFX96 qPCR Instrument, CYTOFLEX Beckman Coulter, equipped with 3 lasers for 9 fluorescence detection, Elisa instruments).
UO3. The Laboratory of Pediatrics, University of Turin, is directed by Prof Bergallo. It is located at the Regina Margherita Children¿s Hospital, part of the AOU Città della Salute e della Scienza, Turin. The Lab is performing targeted studies on the expressions of HERVs, different types of interferons, and the innate and adaptive immune responses in children and adults with autoimmune diseases, and ASD. One inexplicable finding of MS is the spontaneous resolution of symptoms during pregnancy, which reappear a few months after delivery. Based on this, blood samples from pregnant MS-affected women will be collected before and at delivery. Following the original papers published from this equipe in patients with infection

diseases (Hepatitis C, COVID-19, and RSV), autoimmune disorders, (new-onset type 1 diabetes, celiac subjects), and ASD, blood samples from both children and adults affected by these diseases and other autoimmune disorders (in particular Chron disease and Ulcerative colitis) will be collected and tested with other participants of this proposal. A cooperation is underway with Dr. Hervé Perron (Geneuro, Lyon) for investigation on HERV expressions in various autoimmune diseases and Dr. Ottavia Delmonte (NIH, Bethesda, USA) for some immunological investigations in patients with infectious diseases and immune-mediated disturbances.

5.4 Specific Aims and Experimental Design

Specific aim 1

Exploring HERVs expression associated with immunological phenotype and markers of the immunological alterations in blood cells from individuals affected by SM, T1D, ASD compared with Healthy controls and Parkinson patients.
To characterize the humoral response to HERVs in individuals affected by SM, T1D, ASD against HERVs envelope proteins as a way to increase the range of biomarkers options to diagnose and follow. the progression of the different diseases investigated.

Specific aim 2

Investigating the role of microorganisms (e.g. Epstein Barr and Mycobacterium avium subspecies paratuberculosis,MAP) in the reactivation of HERV-W and Expression and Activation by Epstein Barr Virus of Human Endogenous Retroviruses-W in Blood Cells in individuals affected by SM, T1D, ASD and compared the results with those obtained from patients with Parkinson disease as a group control of other neurological disease in addiction to the Healthy control group.

Specific aim 3

Exploring the effect of treatment with antipsychotic drugs (Risperidone and Aripiprazole) on HERVs expression and markers associated with the immunological alterations to identify, within a subgroup of ASD children, the biological determinants of treatment response (UO2).
To evaluate the impact of SARS-CoV-2 vaccination on HERV-W and HERV-K ENV expression in MS patients and correlation with side-effects and/or immunization (UO1)

Experimental design aim 1

WP1 EXPLORING HERVS EXPRESSION ASSOCIATED WITH IMMUNOLOGICAL PHENOTYPE IN MS, T1D, ASD INDIVIDUALS
TASK1.1
MS Cohort (UO1, UO3)
80 MS subjects and 25 pregnant women affected by MS will be enrolled at the UO1 and UO3.
Inclusion Criteria
1. Written informed consent
2. 18 to 65 years
3. Recent diagnosis of MS according Revised Mc Donald criteria [1]
4. Relapsing-remitting course (RRMS)
Exclusion Criteria
1. Secondary or primary progressive disease course
2. Autoimmune comorbidities
3. Treatment with steroids in the 30 days prior to enrolment
Clinical Assessments at baseline and at 12-months follow-up
The clinical assessment (medical and MS history and brain MRI scan) will be recorded and Expanded Disability Status Scale (EDSS) and Symbol digit modality test (SDMT) will be administered.
Control individuals will be enrol at UO1 and include 80 sex and age-matched healthy controls and 80 idiopathic Parkinson disease patients (PD) [2].

TASK1.2 ASD cohort (UO1, UO2, UO3)
The study will enroll the following groups:
1. 80 ASD children, according DSM-5 criteria [3] and their parents (80 families) (UO1, UO2) [19,22-24]
2. 40 ASD children (UO3)
3. Age- and sex- matched healthy children and their parents without familiarity with ASD (UO2).
Inclusion criteria for ASD children
- 2 -18 years
Exclusion criteria
- age < 2 or > 18 years
- common variants are included
- chronic autoimmune and immune-mediated diseases; endocrine diseases; congenital deafness; ongoing infections.
ASD children will undergo a standardized evaluation measuring ASD symptoms [5].Quantification of clinical severity will be conducted with CGI-S (Clinical Global Impression-Severity Scale), Clinical Global Impression Scale-Improvement (CGI-I) and C-GAS - Developmental, Griffiths III Adaptive functioning will be studied with the Adaptive Behavior Assessment System, Second Edition [6] (ABAS-II). Control children will undergo a cognitive and behavioural evaluation according to age and language level. Parents' cognitive skills will be measured through the WAIS-IV [7].
TASK1.3 T1DM cohort (UO1 and UO3)
The study will enroll:
1) 40 subjects at diabetes onset (2-16 years), according to ISPAD criteria [8,18]
2) 60 T1DM patients of various ages by using the same criteria as in (1).
TASK 1.4 Characterization of humoral response to HERVs envelope proteins in individuals affected by MS, T1DM and ASD (UO1)
Self-reactive immune responses will be provided through screening of serum samples for the presence of autoantibodies against HERVs antigens by indirect ELISA. Either epitope presenting the highest antigenicity screened in our previous studies or newly identified protein fragments (from HERV-W and HERV-K) and autoantibodies [9, 25].
TASK 1.5 Analysis of HERV-K and HERV-W protein expression in leukocytes and immunophenotype analysis in MS, ASD and T1D individuals healthy controls by flow cytometry (UO2)
Flow cytometry will be used to evaluate:
- the expression of HERV-W and HERV-K ENV proteins [10]
- early viral infection status through CD169 expression on monocytes [11]
- the expression of intracellular related cytokines.
TASK 1.6 Analysis of plasmatic levels of molecules involved in the migration of inflammatory cells within the CNS in SM and ASD (UO2) Elisa assays will be applied to determine plasmatic levels of of ICAM-1,PECAM-1, and P- and L- selectins.
TASK 1.7 Transcriptional expression profile analysis in SM, T1D and ASD (UO1, UO2 and UO3)
RNA from blood samples will be retrotranscribed and amplified by Real-Time PCR by mean of specific primer pairs for HERVs (HERV-H, HERV-K, pHERV-W, HEMO, Syncitin 1 and 2), their receptors (ASCT1 and 2, MFSD, CD98), cytokines and chemokines (IL-beta, IL-6, IL-8, IL-10, IL-17, TNF-, INFs), toll-like receptors (TLR3, TLR4, TLR7 and TLR8), methylases (TRIM28 an SETDB1), and IFN-I stimulated genes (IFI44L, IFI27, ISG15, IFIT1, and SIGLEC), IFN-II, and IFN-III (IFN-l1, IFN-l2, IFN-l3, IFNl4)

Experimental design aim 2

WP2 INVESTIGATING THE ROLE OF EPSTEIN BARR AND MYCOBACTERIUM AVIUM SUBSPECIES PARATUBERCULOSIS (MAP) IN THE REACTIVATION OF HERV-W/K AND EXPRESSION IN INDIVIDUALS AFFECTED BY MS, T1DM AND ASD (UO1)
The patients will be monitored for the presence of cross reactive antibodies against EBV, MAP and autoimmune targets such as GlialCAM, IRF5, Myelin Basic Protein (MBP)85-.98 in MS, T1DM and ASD.
TASK 2.1 Antibody responses to EBV, MAP and HERV [16]

Primary evidence of self-reactive immune responses will be provided through screening of serum samples for the presence of autoantibodies against HERVs, EBV and MAP antigens by indirect ELISA on serum samples. Either epitopes presenting the highest antigenicity screened in our previous studies or newly identified protein fragments (from HERV-W and HERV-K) and autoantibodies.
TASK 2.2 Expression of EBV, MAP and HERV genes
Retrotrascription of RNA extracted from collected blood will be followed by quantitative real-time PCR using specific primers and sequenced to confirm the identity of amplicons.
TASK 2.3 Cell culture experiments
Primary cultures of disease-specific cell types will be exposed to increasing loads of the infective agent (EBV or MAP) in order to observe effects on HERV expression rates, while non-infected cultures will be stimulated with different HERV proteins or their fragments to assess the impact on pathogenic changes within cells. Pro-inflammatory phenotypes will be determined through ELISA-based cytokine quantification and the presence of HERV will be performed through immunocytochemistry.
TASK 2.4 Detection of expanded T cell populations
Shifts in T lymphocyte subtypes will be determined through flow cytometric analysis in PBMC samples from patients and healthy volunteers.
/Users/leonardo/Desktop/Ministero Salute PNRR/Graph abs png.png

Experimental design aim 3

WP3 EXPLORING THE IMPACT OF SARS-CoV-2 VACCINATION ON HERV'S EXPRESSION IN MS PATIENTS (UO1).
Blood samples (80) have already been taken from people living with MS one week before the first COVID 19 (BNT162b2) vaccination with Pfizer biotech and 15 days after the second one (UNISS), processed and stored at -80°C, to study the humoral and cellular response against HERVs, EBV and MAP and the expression of the HERVs as described before. We will also evaluate:
1. the levels of neutralizing antibodies against Spike protein two weeks after the last dose of vaccine
2. the antigen-specific response to Spike protein on separated PBMCs from vaccinated individuals and T cell response to HERV-W and HERV-K ENV mRNA and protein expression
3. T cell-specific response in vaccinated after SARS-CoV2 specific S peptides stimulation in association with HERVs expression.
WP4 EXPLORING THE EFFECT OF TREATMENT WITH RISPERIDONE AND ARIPIPRAZOLE ON HERVs EXPRESSION AND IMMUNOLOGICAL MARKERS IN PBMCs OF ASD CHILDREN (UO2).
15-20 ASD children who will necessitate treatment with Risperidone and Aripiprazole for the treatment of irritability [4] will be enrolled (UO2).
We will evaluate HERVs expression associated with the immunophenotype and the plasmatic levels of molecules involved in the migration of inflammatory cells within the CNS in blood samples of ASD children, before and after 12 weeks of pharmacological treatment with antipsychotic drugs Risperidone and Aripiprazole.
WP 5 STUDYING THE EFFECT OF IN VITRO TREATMENT WITH ANTIRETROVIRAL DRUGS ON THE EXPRESSION OF HERVs AND IMMUNE MEDIATORS IN PBMCs FROM ASD CHILDREN AND THEIR MOTHERS (UO2).
Our recent data demonstrated that in vitro treatment with Efavirenz of peripheral blood mononuclear cells (PBMCs) from ASD children and their mothers reduces the expression of certain HERVs with concomitant modulation of cytokines [12]. Based on our observations, we will aim to test the effect of nucleoside or non-nucleoside reverse transcriptase inhibitors in PBMCs from ASD children, their mothers and controls in order to evaluate the modulation of HERVs and immune effectors applying custom microarrays to analyze the expression of HERVs and inflammatory mediators known to be modulated in ASD cohort.
WP6 STUDYING THE EFFECT OF IN VITRO STIMULATION WITH IMMUNOGENIC EPITOPES RELATED TO ENVELOPE SEQUENCES OF HERVs ON THE EXPRESSION OF IMMUNE MEDIATORS IN PBMCs FROM ASD CHILDREN AND THEIR MOTHERS (UO2).

Based on the knowledge concerning the close interplay between HERVs and immune system and ASD¿s immune-mediated pathophysiology, we will in vitro stimulate the lymphocytes from ASD children and their mothers, and healthy donors with immunogenic epitopes related to the envelope sequences of HERV-H, HERV-K and HERV-W in order to evaluate the response of immune effectors [20,24].
WP7. Communication and dissemination (UO1, UO2, UO3)
Results that cover the proof-of-concept pathological mechanisms involving HERVs will be published.
The researchers involved in the project will be encouraged to present the stage-to-stage research progress at local and international conferences and to integrate PhD candidates and Postdocs into the success of the project.
WP8. COORDINATION AND MANAGEMENT (UO1)
Patient-related data will be stored and transferred between partners in accordance with local data protection regulations. Biological samples will be coded, databases will be password protected and information will be stored in locked cabinets in a secure facility.
A data management plan will be formulated by UNISS in order to oversee all project and to:
(i) compile the final database to perform statistical analyses verifying the quality of data;
(ii) disseminate the information both locally and internationally.
At regular intervals (6 months) UO1 will carry out checks on the progression of the different WPs.
/Users/leonardo/Desktop/Ministero Salute PNRR/WPs.png

Picture to support preliminary data

HERVs in MS,ASD and T1D.pdf

Hypothesis and significance

The investigation of HERV-related factors will be our main objective in determining the connection between environmental stimuli and immune dysregulation in subjects who develop clinical symptoms in specific neurological diseases namely multiple sclerosis (MS) neurodevelopmental Autism Spectrum Disorder (ASD) and Typ1 Diabetes (T1D). The results will be compared with those obtained from Parkinson disease patients (an other neurodegenerative disease) and healthy Controls. To this aim, the project will assess the expression of specific HERVs (HERV-H, HERV-K and HERV-W), the production of HERVs antibodies and the expression of markers associated with immunological alterations and molecules involved in the migration of inflammatory cells within the central nervous system in subjects with MS, ASD, T1D and relative age- and sex-matched healthy donors along with Parkinson samples. The immunophenotype and the humoral and cellular responses against HERV-derived antigens and expression profiles of retroviral proteins will be compared with those found in healthy donors and correlated with biochemical and clinical parameters. Additionally, we will evaluate host¿s serological responses to environmentally diffused antigens putatively associated with the above-mentioned diseases indicative of past exposure and specific expression suggesting current viral/bacterial activity. Among such agents, EBV has been proved to transactivate HERV-K ENVprotein, and we have already demonstrated the presence of anti-EBV Abs at increased levels in individuals living with immune-mediated diseases, such as MS and Rheumatoid Arthritis. Another agent possibly involved in HERV transactivation might be Mycobacterium avium subsp. paratuberculosis (MAP) as suggested by an overlap between Abs patterns specific to MAP and HERV in a prospective study. MAP is associated to Crohn's disease in humans, probably by triggering autoimmunity through the mechanism of molecular mimicry (36). Our previous results showed a highly significant prevalence of Abs against envelope peptides of HERV-K and HERV-W (HERV-Wenv) family in autoimmune and neurological diseases when compared to healthy populations with decreased seroreactivity after immunomodulatory therapy.
Moreover, exposure to a variety of environmental insults in sensitive time windows during pregnancy could result in later altered neurodevelopment and has been associated with an increased risk to develop neurodevelopmental disorders. Recently, higher level of anti-EBV IgM antibody in the blood of ASD in comparison to neurotypical individuals was demonstrated, however, the IgG level against EBV in the serum of ASD patients showed no significant difference in comparison to healthy controls. Moreover, in animal models, prenatal exposure to Mycobacterium tuberculosis induces maternal immune activation and predisposes offspring to an increased risk of blood brain barrier damage, persistent

neuroinflammation, and development of autism-like phenotype in offspring of infected mice, suggesting a potential role of gestational Mycobacterium tuberculosis infections in the aetiology of ASD.
Via a detailed evaluation of the clinical relevance of biomarkers based on HERVs related antigens and antibody detection in MS, T1D and ASD patients at leukocytes level, the present study is pursuing the elucidation on the role of HERVs proteins in pathogenic mechanism associated to the above diseases, i.e. immune dysfunction, inflammation, and infections.

5.5 Methodologies and statistical analyses

Methods of data collection

Blood, and Serum samples, PBMCs will be collected and analyzed. The immunophenotype and expression of markers associated with immunological alterations, transcriptional and protein expression of HERVs, humoral and cellular response to EBV and MAP and reactivation of HERVs will be analyzed. The methods will include: flow cytometry, immunoassays (ELISA), Realtime PCR, custom microarrays. In the clinical field, biochemical analysis, magnetic resonance imaging (MRI) and specific tests for MS, ASD and T1D diagnosis will be conducted.

Statistic plan

We will use a general linear model for repeated measures (GLMRM) to determine whether HERVs-related markers change significantly within-subject (Time). Assuming a low effect size (0.25), ¿ (two-sided) = 0.05; power = 0.95, three timepoints, and minimal (0.1) correlation between repeated measurements, a total sample size of 78 individuals will be sufficient to detect even a small effect size (f>0.25) in a MANOVA- based f-test (see also Statistical analysis section).

Statistical analysis

Univariate analysis: For all continuous variables (immunological, biochemical, molecular, radiological, clinical), we will use a linear mixed model to examine significant changes in within- subject factors (i.e. time) while including within-subject factors (e.g. sex, age, lesion load, etc) as covariates of no interest. Whenever a significant effect will be observed, we will execute followed by pairwise comparisons amongst groups and Bonferroni correction for multiple comparisons whenever a significant f-test will be detected.
Multivariate analysis: Multivariate analyses will be performed to 1) evaluate redundancies and collinearities between all data, and 2) generate more parsimonious, compounded predictors, of disease progression and therapeutic outcome: all data will be entered into a factor analysis (principal component analysis followed by varimax rotation and kaiser normalization). A parallel analysis will be executed to retain only non-random factors. Remaining orthogonal factors will be examined for interpretability and third values entered into a multivariate linear mixed model as described above.

Timing of analysis data

Enrolment: 12 months
In regard to the subgroup of ASD participants who will be prescribed pharmacological therapy with Risperidone and Aripiprazole, a follow-up evaluation will be provided at a distance of 12 weeks from baseline.
An interim analysis will be done between the 8th and 15th months. All the molecular and immunological assays, detailed in the three experimental designs, will be performed in parallel with the enrolment. The statistical analysis will be concluded at 24 months, and will include clinical parameters and molecular and immunological results as well.

5.6 Expected outcomes

Building on the idea that HERVs might act as a bridge between environmental insults and the cascade of pathophysiological events underlying the onset and progression of various neurological and autoimmune diseases, our research project may provide new insights into early diagnosis and response to treatment, and suggest new therapeutic targets for personalized medicine that may reduce costs related to patients¿ management.

5.7 Risk analysis, possible problems and solutions

Recruitment of ASD children
Concerning the enrolment of ASD children, minor risks could be considered: difficulties related to blood sampling on a fragile population (children with behavioral problems) and enrollment of control individuals. However, the Clinical Unit of Child and Adolescence Psychiatry and the Regina Margherita¿s Hospital medical team (doctors, nurses and psychologists) has a deep experience in performing blood sampling on children with ASD for both clinical and research purposes. In particular, a desensitization process (adjustment phase to the environment, contact with medical supplies) is generally provided before the sampling.
Compliance
Contact with families will be ensured to monitor adherence to assigned treatment and the occurrence of intolerances and adverse events that will be taken care of by clinicians promptly.

5.8 Significance and Innovation

The need for a reliable biological set of markers that can predict the disease course and treatment response is overdue for the neurological diseases investigated. HERVs expression in immune cells and its correlation with clinical parameters by integrated bioinformatics analysis will be performed for the discovery of prognostic biomarkers, and new targets for therapeutics, and to assess a fast predictive test towards personalized therapy in MS, ASD and T1D. As such, antiretroviral drugs targeting HERVs have been proposed as a possible component in the treatment of MS [13,14] and recently, a phase 2 clinical study of Triumeq (a combination of antiretroviral drugs) demonstrated promising results in Amyotrophic lateral sclerosis (ALS) patients [15]. Moreover, the results of the research project will contribute to clarifying the mechanisms underlying the role of HERV in MS, ASD and T1D, exploring the interplay with microenvironmental factors/infectious agents and immune response [26].

5.9 Bibliography

[1] Thompson AJ et al (2018) et al. doi: 10.1016/S1474-4422(17)30470-2
[2] Berg D et al (2015) doi: 10.1002/mds.26431
[3] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders-5; American Psychiatric Association. APA 2013
[4] The Maudsley Prescribing Guidelines in Psychiatry 14th Edition. (2021) Taylor, Barnes, Young. Wiley-Blackwell 2021
[5] Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) and Social Responsiveness Scale tests (SRS)
[6] Oakland (2011) doi.org/10.1007/978-0-387-79948-3_1506
[7] Wechsler (2008) doi.org/10.1037/t15169-000
[8] Mayer-Davis EJ et al (2018) doi: 10.1111/pedi.12773
[9] Arru G et al (2018) doi: 10.1111/ene.13648
[10] Balestrieri et al (2021) doi: 10.1016/j.ebiom.2021.103341
[11] Minutolo et al (2021) doi: 10.3390/pathogens10121639
[12] Cipriani et al (2022), in press
[13] Morandi E et al (2019) doi: 10.3389/fimmu.2018.03092
[14] Gold J et al (2015) doi: 10.1136/jnnp-2014-307932
[15] Gold J et al (2019) doi: 10.1080/21678421.2019.1632899
[16] Mameli G et al (2015) doi: 10.1016/j.jneuroim.2015.03.003
[17] Levet S (2019) doi:10.1007/s11892-019-1256-9
[18] Noli M et al (2021) doi: 10.3390/pathogens10091135
[19] Balestrieri E et al (2019); doi:10.3390/ijms20236050
[20] Grandi N et al (2018) doi:10.3389/fimmu.2018.02039

[21] Derfuss T et al (2015) doi: 10.1177/1352458514554052
[22] Balestrieri E et al (2012) doi:10.1371/journal.pone.0048831
[23] Balestrieri E et al (2014) doi:10.3109/15622975.2013.862345
[24] Balestrieri E et al (2019) doi:10.3389/fimmu.2019.02244
[25] Carta A et al (2022) doi: 10.3390/biomedicines10061365
[26] Xue et al. (2020) doi: 10.3389/fmicb.2020.0169

5.10 Timeline / Deliverables / Payable Milestones

Mo 0-1: Kick-off meeting, Ethics Committee evaluation; DELIVERABLE 1: Statistical Analysis Plan definition will be completed
Mo 2-17: Recruitment, clinical and medical assessment
Mo 2-22: Analyses of biological samples
Mo 2-4: Molecular clinical immunological assessment before Risperidone and Aripiprazole administration
Mo 5-7: Molecular clinical immunological assessment post Risperidone and Aripiprazole treatment
Mo 8-15: Interim analysis; DELIVERABLE 2: Interim analysis report
Mo 2-22: Data collected through the project from all operative units and statical analysis
Mo 23-24: Preparation of the final report and dissemination process by all operative units
Mo 24: DELIVERABLE 3: Final report and dissemination of the results

Milestones 12 month

M1) Recruitment of 50% of patients
M2) Interim analysis

Milestones 24 month

M3) Recruitment completed
M4) Statistical analysis completed
M5) Final report

Gantt chart

GANTT.png

5.11 Equipment and resources available

Facilities Available

UO1: The laboratories of Microbiology of the Azienda Ospedaliera Universitaria of Sassari has all instruments necessary to perform the proposed research including automated ELISA washer and readers, biological woods, Real Time PCR machines, Miseq illumina, freezers at -°80C, Flow cytometry etc.
The UO1 collaborate with:
-Neurological Clinic of the AOU Sassari, diagnosis and clinical follow-up of different neurological diseases (more than 10000 visits per year).
- The Unit of Child Neuropsychiatry of AOUf Sassari (around 4000 outpatients per year). The Unit also includes a national center for diagnosis and treatment of ADHD. The Unit is provided with EEG, videoEEG, ENG, EMG, multimodal Evoked Potentials, and freezers at -20°C.
- The Center for Diabetes of the Pediatric Clinic of AOU Sassari is the main center for diagnosis and clinical follow-up of T1D for patients in Northern Sardinia.
UO2: The Child Neurology and Psychiatry Unit of the University of Rome Tor Vergata offers outpatient service (more than 5000 visits per year) for diagnosis and clinical follow-up. The Multiple Sclerosis Center of the Tor Vergata Hospital of Rome

is a Regional Reference Center. The Center performs outpatient examinations and independently manages the service of Neuropsychology and repetitive transcranial magnetic stimulation for the treatment of spasticity, neuropathic pain, and bladder disorders.
UO2 laboratories are equipped with all the instruments needed to perform the project (Bio-Rad CFX96 qPCR Instrument, CYTOFLEX Beckman Coulter, equipped with 3 lasers for 9 fluorescence detection, Elisa instruments, BLS2 cabinets, freezers at -80°C etc.).
UO3: The Laboratory of Specialist Pediatrics, SC Ematology, AOU Città della Salute e della Scienza di Torino. The group collaborates with:
- Child Neuropsychiatry Unit, for diagnosis and clinical follow-up of ASD children;
- Pediatric Diabetology, SSD Pediatric Endocrinology.
- Gynecology and Obstetrics Unit, for clinical follow-up of pregnant women affected by MS.
All instruments necessary to perform the proposed research are present including, biological hoods, automated extractors, spectrophotometer, PCR systems, Real Time PCR machines, freezers at -°80C.

Subcontract

Subcontracts will not be activated because to achieve the aims of the project, the operative units involved are equipped with all the instruments and the staff has the skills to cover all the objectives of the project.

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

The project will be conducted in the laboratories of AOU of Sassari under the supervision of Prof Sechi, who is also the coordinator of the project, the policlinico ofTor Vergata (UO2) under the guidance of prof Mazzone and at the Turin AOU under prof Bergallo supervision (UO3).
At UO1 the group is studying the involvement of different triggers as potential activation of MS, in particular the immune response (both humoral and cellular) against HERV-W, Epstein Barr Virus and Mycobacterium avium subspecies paratuberculosis (MAP). In addition, the group is currently investigating the role of HERV-K in other neurological diseases (Parkinson and ALS). An international collaboration on the topic is active with prof. Avindra Nath (NIH, Rockville, USA). The other members of the group are Dr. Alessandra Carta expert in ASD and Dott. Gian Franco Meloni, will coordinate the T1D enrollment and clinical aspects. The laboratories have all the facilities and instruments to complete the proposed project.
The collaboration with the Neurology Unit of AOU, led by prof. Solla is ongoing, he will oversee the recruitiment of people living with MS and Parkinson. More than 600 patients diagnosed with Multiple Sclerosis are referred to the center and 400 Parkinson patients are followed within the North Sardinia territory.
The Neuropschiatric clinic of the University of Sassari, led by Dr. Carta and prof Sotgiu will enroll the Autism patients. Healthy controls will be enrolled at the Blood Transfusion Center of the Azienda Ospedaliera Universitaria, Sassari and ASL of Sassari Hospital according to the pre-established criteria.
The other studies will be conducted at the Laboratories of Microbiology and Clinical Microbiology of the University of Rome, located at Policlinico of Tor Vergata (UO2) authorized and equipped for handling biohazard specimens, and supervised by Prof Luigi Mazzone and Dr. Chiara cipriani and Dr. Siracusano. The research group is currently employed with Dr. Hervé Perron (GeNeuro Biotech, Lyon, France) on several research fields on the investigation of the role of HERVs in etiopathogenesis of complex diseases such as cancer, neurodevelopmental disorder and infectious diseases. UO2 has a consolidated experience on clinical studies involving autistic children and their parents to study the potential role of human ERVs and immune deregulation in ASD. UO2 has also has an established collaboration with the Centre for Behavioral Sciences and Mental Health at Istituto Superiore Sanità (Dr Laura Ricceri) for conducting preclinical studies in ASD animal models.

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

What is already know about this topic?

The need for a reliable biological set of markers that can predict the disease course, treatment response, and disease activity is overdue for the neurological diseases investigated. Unfortunately, there are currently no validated biomarkers that can be easily accessible. HERVs expression in immune cells and its correlation with all the several clinical parameters analyzed could have an important impact in the diagnosis and prognosis of MS, T1D and ASD. Moreover, integrated bioinformatics analysis will be performed for the discovery of prognostic biomarkers, new targets for therapeutics, and to assess a fast predictive test and proceed towards personalized therapy in MS, T1D and ASD.
Impact: Via a detailed evaluation of the clinical relevance of biomarkers based on HERVs related antigens and antibody detection in MS, T1D and ASD patients at leukocytes level, the present study is pursuing the elucidation on the role of HERVs proteins in pathogenic mechanism

Details on what is already know about this topic

This scenario raises the possibility of HERV expression as a therapeutic target, as well as a potential biomarker for MS, ASD and T1D. Antiretroviral drugs have been proposed in the treatment of MS. The rationale is that patients with Human immunodeficiency virus (HIV) and treated with antiretroviral drugs have a lower risk of developing MS than non-infected, healthy population [13; 14]. Moreover, the chance of limiting neuroinflammation in MS finds expression in ongoing clinical trials of efficacy, potential adverse effects, and immunogenicity of the monoclonal, humanized IgG4 anti-HERV-W Env antibody, GNbAC1 (Temelimab) that providing encouraging results [21]. Moreover, Triumeq, an antiretroviral drugs for HIV patients, reduced HERV-K expression in ALS [15]. More recently, we demonstrated in a proof of concept study that a non-nucleoside reverse transcriptase inhibitor restored in vitro the expression of certain HERVs with a concomitant modulation of cytokines [12]

What this reasearch adds?

The possibility that HERVs plays a crucial role in the pathophysiology of ASD,MS and T1D is attractive for several reasons. What triggers the expression of HERVs in adult neurons of patients and T1D patients remains unknown. HERVs RT expression was strongly correlated with severity of MS and ASD diseases. Recently, Garcia Montoyo M. et al. have reported that antiretroviral therapy in patients inhibited HERV-K, in ALS patients and a possible association between the change in HERV-K levels and clinical outcome was established. Therefore, the results obtained with this project will establish the HERVs involvement in neurological diseases and T1D with a range of possible applications: from the possible use of antiretrovirals in these patients, to the use of monoclonal antibodies against HERVs protein (GenEuro).

Details on what this reasearch adds

Evidence that could come from this research project could provide definitive proof on the role of HERV in complex diseases such as MS, ASD and T1D. Specifically, it could definitively clarify the interplay between HERVs and the immune system in onset and/or progression of these pathological conditions in terms of immunological phenotyping of patients, immunological alterations and humoral response. On the other side, the effect of the in vivo exposure to SARS-CoV-2 vaccination, antipsychotic drugs, and of the in vitro treatment using infective agents and antiretroviral drugs on lymphocytes obtained from patients could provide results useful in the view to target HERV activity in the setting of new therapeutic approaches.

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

Regarding ASD, the results obtained from the project could have an impact on the identification of patients eligible for specific treatment by identifying predictive HERV-related immunological markers. In addition, the knowledge gained will be translated into preclinical models. By means of the use of antiretroviral drugs, immune- and epigenetic-modulators, we will explore whether by acting on the crosstalk between the activity of ERVs and the immune response, the ASD-like phenotype could be restored.
Research infrastructure: The proposal will enhance the group's ability to identify antigenic proteins or their fragments with downstream evaluation through in-house developed protocols, in vitro proof- of-concept experimental approaches and testing on human samples in collaboration with local hospitals. The equipment and methodology employed will create sustainable research capacity at the relevant research institutions.

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

These findings could open new perspectives to propose clinical trials employing inhibitors of HERV activity (i.e. antiretroviral drugs, epigenetic drugs, monoclonal antibodies), immunomodulators or a combined approach to achieve results that are robust enough to offer a tailored approach in MS, ASD and T1D management. Having new potential targets for integration into common clinical practice that can also be used as biomarkers of treatment response is a major challenge in scientific research and one of the most important contributions to be made to public health.

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	221.389,18	221.389,18	not permitted	0,00
2 Researchers' Contracts	355.000,00	0,00	355.000,00	39,92
3a.1 Equipment (Leasing -	20.000,00	0,00	20.000,00	2,25
3a.2 Equipment (buying)	50.000,00	0,00	50.000,00	5,62
3b Supplies	284.000,00	0,00	284.000,00	31,94
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	22.000,00	0,00	22.000,00	2,47
8 Publication Costs	19.000,00	0,00	19.000,00	2,14
9 Dissemination	18.000,00	0,00	18.000,00	2,02
10 Overheads *	61.200,00	0,00	61.200,00	6,88
11 Coordination Costs	60.000,00	0,00	60.000,00	6,75
Total	1.110.589,18	221.389,18	889.200,00	100,00

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

Report the Co-Funding Contributor:

The contribution of the three UO include the staff salary of the professors and researchers involved in the study (full professors, assistant professor and researchers). In addition the major parts of instruments necessary to perform the experiments are already present as well as the instruments for analysis of data and for maintaining the clinical sample.

Budget Justification

1 Staff Salary	Staff salary is the sum of the months that structured personnel of each unit will dedicate to the project
2 Researchers' Contracts	New research contracts are foreseen for each UO: Sardegna (4 units), Lazio (3 units) and Piemonte (2 units)
3a.1 Equipment (Leasing - Rent)	a digital PCR leasing is foreseen by the Torino Unit.
3a.2 Equipment (buying)	Instruments for automatized ELISA and freezers at -80°C to store the samples are foreseen by Sassari and Tor Vergata units
3b Supplies	Purchase of specific antibodies (to be used in cytofluorimetry), ELISA Kit, PCR reagents and consumables

3c Model Costs	no
4 Subcontracts	no
5 Patient Costs	no
6 IT Services and Data Bases	no
7 Travels	Travels among different UOs. Presentation of the results to international scientific meetings.
8 Publication Costs	Open-access publications concerning activities of the project
9 Dissemination	The results of the project will be disseminated at the local, regional, National and International level through publications and social media
10 Overheads	Institutional overheads
11 Coordination Costs	Additional costs are due to the enrollment of thee personnel units (one for each unit) to coordinate the whole projects, analyze and integrate the data among the three UOs. A final reports will be prepared and disseminated.

Proposed total budget UO1 Institution: Azienda Ospedaliera Universitaria di Sassari (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	100.000,00	100.000,00	not permitted	0,00
2 Researchers' Contracts	150.000,00	0,00	150.000,00	36,75
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	40.000,00	0,00	40.000,00	9,80
3b Supplies	100.000,00	0,00	100.000,00	24,50
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	10.000,00	0,00	10.000,00	2,45
8 Publication Costs	10.000,00	0,00	10.000,00	2,45
9 Dissemination	10.000,00	0,00	10.000,00	2,45
10 Overheads	28.200,00	0,00	28.200,00	6,91
11 Coordination Costs	60.000,00	0,00	60.000,00	14,70
Total	508.200,00	100.000,00	408.200,00	100,00

Budget Justification

1 Staff Salary	The staff salary is the sum of the months that the PI (a full professor, 2 months), one associate professor (6 months), one assistant professor (RTI, 8 months) and one type B researcher (8 months) will dedicate to the project
2 Researchers' Contracts	The enrollment of an experienced Researcher and two young researchers (under 40) is foreseen
3a.1 Equipment (Leasing - Rent)	no
3a.2 Equipment (buying)	Instruments for automatized ELISA (Spectrometer, Washermachine, Workstation). Freezers at -80°C and -20°C to stock plasma cells and plasma
3b Supplies	All the materials necessary to carry out experiments described : reagents for qPCR, ELISA, Citofluorimetry (conjugated antibodies etc)
3c Model Costs	no
4 Subcontracts	no
5 Patient Costs	no
6 IT Services and Data Bases	no
7 Travels	Presentation of the results to international scientific meetings. travel to the other UO
8 Publication Costs	Publishing costs in open science qualified international scientific journals
9 Dissemination	The results of the project will be disseminated at the local, regional, National and International level through publications and social media
10 Overheads	Costs due to the Department for general costs (electricity etc.)
11 Coordination Costs	Additional costs are due to the enrollment of thee personnel units (one dedicated to each unit) to coordinate the whole projects, analyze and integrate the data among the three UOs. A final reports will be prepared and disseminated.

Proposed total budget UO2 Institution: Lazio (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	61.389,18	61.389,18	not permitted	0,00
2 Researchers' Contracts	125.000,00	0,00	125.000,00	41,12
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	10.000,00	0,00	10.000,00	3,29
3b Supplies	134.000,00	0,00	134.000,00	44,08
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	0,00	0,00	0,00	0,00
5 Patient Costs	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	1,97
8 Publication Costs	4.000,00	0,00	4.000,00	1,32
9 Dissemination	4.000,00	0,00	4.000,00	1,32
10 Overheads	21.000,00	0,00	21.000,00	6,91
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	365.389,18	61.389,18	304.000,00	100,00

Budget Justification	
1 Staff Salary	Staff salary derives from 2 month dedication to the project of a Full Professor and 3 months form a Researcher (Both child Psichiatrists)
2 Researchers' Contracts	1 Researcher contract for 1 year for recruitment and 2 researcher contracts for two years for laboratory research work
3a.1 Equipment (Leasing - Rent)	no
3a.2 Equipment (buying)	-80°C freezer
3b Supplies	Purchase of specific antibodies (CD3, CD4, CD8, CD43, CD19,CD56, CCR7, CD45RA, CD38, CD25, HLA-DR, CD64, CD169, IL-1beta, IL-5, IL-6, IL-10, IL-15, IL-17, TGF-beta, TNF-alpha, IFN-alpha, IFN-beta), ELISA Kit, PCR reagents and consumables
3c Model Costs	0
4 Subcontracts	no
5 Patient Costs	no
6 IT Services and Data Bases	no
7 Travels	Travel expenses for meetings between operative units and related congresses
8 Publication Costs	Open-access publications concerning activities of the project
9 Dissemination	Meetings for dissemination of findings of the project
10 Overheads	Institutional overhead
11 Coordination Costs	no

Proposed total budget UO3 Institution: Piemonte (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	60.000,00	60.000,00	not permitted	0,00
2 Researchers' Contracts	80.000,00	0,00	80.000,00	45,20
3a.1 Equipment (Leasing - Rent)	20.000,00	0,00	20.000,00	11,30
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	50.000,00	0,00	50.000,00	28,25
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	3,39
8 Publication Costs	5.000,00	0,00	5.000,00	2,82
9 Dissemination	4.000,00	0,00	4.000,00	2,26
10 Overheads	12.000,00	0,00	12.000,00	6,78
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	237.000,00	60.000,00	177.000,00	100,00

Budget Justification

1 Staff Salary	staff salary comes from the 6 months of an associate professor dedicated to the project and the contribution of a research technician (10 months)
2 Researchers' Contracts	two young people will be recruited for this project
3a.1 Equipment (Leasing - Rent)	a dPCR will be used for the project
3a.2 Equipment (buying)	no
3b Supplies	All the materials necessary to carry out experiments described: reagents for extraction, RT and PCR
3c Model Costs	no
4 Subcontracts	no
5 Patient Costs	no
6 IT Services and Data Bases	no
7 Travels	Travels to the other UO
8 Publication Costs	Publishing costs in open science qualified international scientific journals
9 Dissemination	Presentation of the results to international scientific meetings
10 Overheads	Costs due to the Department for general costs (electricity, etc.)
11 Coordination Costs	no

Principal Investigator Data

Cognome: sechi
Nome: leonardo antonio
Genere: M
Codice fiscale: SCHLRD65H13E377D
Documento: Patente, Numero: U18791646C
Data di nascita: 13/06/1965
Luogo di nascita: Ittiri
Provincia di nascita: SS
Indirizzo lavorativo: Struttura Complessa di Microbiologia e Virologia, AOU sassari
Città: Sassari
CAP: 07100
Provincia: SS
Email: SECHILA@GMAIL.COM
Altra email: sechila@uniss.it
Telefono: +393204299661
Altro telefono: 3204299661
Qualifica: Professore Ordinario, Dirigente Medico
Struttura: dipartimento di scienze biomediche
Istituzione: università di sassari
Datore/ente di lavoro? Yes
Datore/ente di lavoro SSN? No
Nome datore/ente di lavoro non SSN: Università degli studi di Sassari
Nome istituzione SSN: AZIENDA OSPEDALIERA UNIVERSITARIA DI SASSARI
Tipo contratto: Professore Ordinario convenzionato SSN con contratto art.6 comma 10 legge 240/2010 con obbligo di 16 ore

---

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 Code: PNRR-MAD-2022-12375761	**Call section:** Malattie Croniche non Trasmissibili (MCnT) ad alto impatto sui sistemi sanitari e
Applicant Institution: Sardegna	**Applicant/PI Coordinator:** sechi leonardo antonio

Project validation result