Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

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BRIEF HISTORICAL NOTES

The Cavalieri Ottolenghi Foundation is a no-profit organisation recognized by the Piedmont Region committed to supporting research and development of structural and infrastructural Neuroscience. The Foundation comes from the legacy to the University of Turin of Annetta Cavalieri Ottolenghi in the 50s and aims, according to the Statute, that "to deepen the existing knowledge on the interdependence between physico-chemical state of the human body and the expression of the psyche: that is, on the causes and treatment of mental insanity."

After decades in which the Foundation has funded scientific research projects and purchase of scientific equipment, in the 90s an international scientific committee of eminent personalities in Neuroscience proposed to build a center for Neuroscience and chose Dr. Carlos Dotti, a foreign researcher, as scientific director. For some years, the research group of the Foundation was hosted at the San Luigi Hospital, Orbassano (Torino) while the construction of the building began in 2001 and was completed in 2009. Meanwhile, Dr. Dotti moved abroad with his group.

In 2009, the Board of Administrators identified in prof. Ferdinando Rossi, University of Turin, the figure of the scientific director of the Foundation, decided to issue an announcement of selection, limited to the Piedmont Region, to select the groups to be included in the new building. Eight groups (seven of the University of Turin, one of the San Luigi Hospital) were selected by a national committee (which included Professors Bentivoglio, Bogetto, Cattaneo and Saglio, assisted by Dr. Borio, Administrative Director at the University of Turin) and in May 2010 they moved into the new building. The institute was named Neuroscience Institute Cavalieri Ottolenghi (NICO).

Aims of NICO

1) The complexity of the studies on the brain requires a multidisciplinary approach. For this we combine complementary approaches and experiences, integrating basic research and clinical application. The birth of NICO takes full advantage of both the integration of the wealth of knowledge and the shared use of expensive equipment and laboratories formerly fragmented in university departments.

2) Our researchers are engaged in many activities of scientific dissemination, dedicated to the public (Open days at the NICO, Stem Cell Day and Night of Researchers, public conferences) and to high school students (Neuroscience Olympics and Scientific Summer Academy). These and other initiatives are designed both to bring young people to science, by sharing the commitment and passion that drives scientific research, both to communicate with competence and clarity a complex issue such as neuroscience.

The Institute of Neurosciences of the Cavalieri Ottolenghi Foundation (NICO) aims to perform high-level research in neuroscience geared toward the prevention, diagnosis and treatment of neurological disorders and in line with this principle, the research is focused on mechanisms that govern normal neural maturation and defects involved in mental retardation syndromes.

THE COLLABORATIVE VISION AT NICO

Since its foundation in 2011, the NICO adopted a new (relative to the Departments of origin) view of sharing all facilities, supplies and instruments by all groups. Excepted for the clinical-relevant activities, which have to be performed in dedicated and isolated rooms to maintain privacy related to human material, all instruments are located in common facilities which are shared by all the members of NICO. This has initially created an organizational burden, but it has also obliged people to meet, share decisions, collaborate and interact, also in the formation of new researchers.

Internal courses on the use of instruments and facilities have been organised to improve their correct usage. Starting from the practical needs of every day research life, this attitude has boosted collaboration and exchange of ideas among the individual researchers and ameliorated the scientific production of single researchers. To sum up, it has created a scientific environment which, respecting the peculiarities of single researchers, interacts and operates as a real community to apply for grants and develop multidisciplinary projects, and also acts as a whole institutional body in front of the scientific community and to the public. Finally, it represents a fundamental breakthrough to save money and to exploit the use of expensive instruments.

POSITIONING OF NICO IN THE UNIVERSITY OF TURIN

NICO is part of the University Interdepartmental center for Neuroscience (called Neuroscience Institute of Turin – NIT), which gathers most researchers active in the field in Turin (even outside the University). NICO researchers are part of doctorate schools (Neuroscience and Veterinary Medicine) of the University of Turin, and, as lecturers at the schools of Biology, Biotechnology, Pharmacy, Medicine, Psychology and Veterinary Medicine, are involved in the preparation of many theses for Graduate and Master degrees. NICO collaborates with several other research centers of the University of Turin, such as the Molecular Biotechnology center, the IRCCS Candiolo and the Brain Imaging Center.

The scientific director of NICO has participated to an Institutional visit of the University of Turin and the Polytechnic of Turin to the University of Haifa, as the University representative for Neuroscience.

Several groups of the NICO have projects and funding in collaboration with the Polytechnic of Turin.

Starting from 2016, microscopy facilities at the NICO will be part of the Open Access lab program of the University of Turin.

POSITIONING OF THE NICO IN ITALY AND IN THE WORLD

NICO researchers have several international collaborations in the world, as shown by their publication record. They have also a strong rate of exchange of visits and seminars, as it can be argued from their reports in attachment. Also they participate to exchange programs of bachelor, graduate and doctorate degrees, and NICO is often visited and attended by foreign students. They also participated in the international Young Investigators Training Program established in Italy in occasion of the 2011 World International Brain Research Organisation Meeting and of the 2014 European Neuroscience Meeting. Every second year, an international meeting (Steroids and Nervous System) is organized by Prof. Panzica's group (with the cooperation of prof. R.C. Melcangi, University of Milan): the meeting has an average 150 people attendance and more than 40 invited speakers from all over the world. The 2013 and 2015 editions were organized with the administrative help of the Ottolenghi Foundation at the Teaching center of the San Luigi Hospital. The Clinical Neurobiology group is organising local and national meetings on multiple sclerosis in the San Luigi Hospital.

NICO researchers are/have been members of committees for national and international meetings and societies, and acted as referees for international peer review journals and panels of funding agencies.

Researchers of NICO are involved in several collaborative grants at a local (Compagnia di San Paolo), national (PRIN) and international (7-FP and Horizon 2020) level, as detailed in the following reports.

NICO has recently (July 2015) applied to the MIUR (Italian Ministry of University and Research) in order to be included in the list of Research Institutes which are allowed to hire directly foreign researchers. Moreover, NICO has a pending application to the MIUR to receive public funds to support private research institutes: NICO has already been included in the list of admitted

institutions (http://attiministeriali.miur.it/anno-2015/febbraio/dcd-09022015.aspx) and the final decision on funding is awaiting the Ministry signature.
In 2014 NICO has signed an official agreement of collaboration with Italian Institute of Technology for the exchange of researchers and facilities, and in this frame researchers of the two institutions are already collaborating and preparing joint grant applications. Also, in the frame of NIT, an agreement has been signed with the Istituto Superiore Mario Boella (a research and innovation centre of the Compagnia di San Paolo operating in the Information and Communication Technologies (ICT) domain). As a result of this collaboration, a grant agreement within the Horizon 2020 program has just been signed in which the director of NICO is the coordinator.

THE NICO SPINOFF

In 2014 and 2015 some NICO researchers (prof. Eva, Geuna, Panzica, Buffo, Boido and Vercelli) collaborated in preparing the application for an academic spinoff (S&P Brain) of the University of Torino, to provide services to researchers, institution and companies related to behavioral neurosciences. This will allow to provide an income to the NICO, and also to apply for cooperative grants as a company. The spinoff has been approved by the adhoc committee of the University of Torino, and will be discussed in the Academic Senate and Council of Advisors of the University within end 2015.

Illustration of the organizational structure and research indicating the current staff, including contractors, and their qualifications, and of the goat educational, scientific and instrumental

Organization of the NICO (Neuroscience Institute Cavalieri Ottolenghi)

Scientific Director is prof. Alessandro Vercelli (appointed March 2014, up to February 2017). In addition to the scientific direction he performs also the function of Administrative Director.

Our activities are organized into **eight groups**:
Adult Neurogenesis (PIs Luca Bonfanti and Paolo Peretto)
Brain Development and Disease (PI Alessandro Vercelli)
Clinical Neurobiology (PI Antonio Bertolotto)
Nerve Regeneration (PI Stefano Geuna)
Neurobiology of Brain Plasticity (PI Annalisa Buffo)
Neuroendocrinology (PI Giancarlo Panzica)
Neurophysiology of Neurodegenerative Diseases (PI Filippo Tempia)
Neuropsychopharmacology (PI Carola Eva)

Staff

Employees directly depending from the Foundation consist of **two secretaries** (Maria Lo Grande and Susanna Monteleone) and **two technicians** (Sri Satuti Werdiningsih and Martyr).

We have a contract with a **Press Agent**, dr. Barbara Magnani, who is helping us in all dissemination activities.

According to the Convention with the University of Turin and with San Luigi Hospital of Orbassano, the NICO hosts:
- **University staff**: 4 full professors, 4 associate professors, 8 university research assistants, 1 technician, 12 post-docs and 14 doctoral students;
- **Hospital staff**: 1 Head physician, 1 manager biologist, 4 specialists in Clinical Biochemistry, 3 post-doc fellows, 3 laboratory technicians.

About 40 graduating students of Biology, Biotechnology, Medicine and Psychology perform experiments for their thesis at the NICO.

Labs and Equipment

Molecular and cellular neurobiology
Neuroanatomy
This laboratory is equipped with numerous, excellent quality research light microscopes. We have two confocal microscopes (Leica SP5 and Nikon). A two-photon microscope Nikon (A1MP) has just been acquired. There is also an electron microscope in the Department of Cell Biology, San Luigi Hospital, adjacent NICO.
There are also various imaging systems with computerized microscopes and photo / digital video cameras that allow morphometric investigations, studies densitometry quantitative autoradiography, image processing and statistical analysis. Two Neurolucida systems are in the facility.
For neurohistological studies, sliding or rotational microtomes, 3 vibratomes and 4 cryostats are available.
Animal facility

The structures dedicated to the experimental animals include rooms dedicated to farming and livestock buildings, spaces dedicated to behavioral tests and, finally, rooms equipped for surgery on rodents. The laboratory for behavioral tests is equipped with mazes and infrared camera for the behavioral analysis of locomotor activity, anxiety, depression and memory. There is also a computerized video analysis (Ethovision XT video track system) to analyze scanned images of behavioral tests.

There are spaces equipped with P2 for the use of viruses.

Cellular and molecular biology
NICO has excellent facilities for research in the field of molecular and cell biology, and a dedicated and experienced staff for tissue culture experiments and molecular biology.
Tools for cell biology experiments allow cell count, the freezing of cells, plating of cells for experiments of tissue culture and cell transfection. For in vitro and ex vivo cultures (primary cultures, tissue explants, organotypic cultures, neurospheres) inverted microscopes are available and a system that allows the acquisition of images in time-lapse of viable cells.
In addition, the NICO provides expertise and services related to molecular biology techniques, such as the preparation and analysis of DNA, RNA and microRNA. The instrumentation of molecular biology platform includes a semi-automatic system for the purification of nucleic acids, three machines for Real-Time PCR, a electroporator for bacteria or ES, as well as many other instruments as a standard laboratory for extraction and analysis of DNA, RNA and proteins.

Electrophysiology
The laboratory of neurophysiology provides tools for the preparation of micro-sections of nervous tissue, that can be maintained in vitro for several hours. There are two experimental stations for patch clamp recordings of membrane potential or ionic current of single neurons in sections. These positions are furnished with complete tools for the electrical stimulation of the axons and for application of pharmacological substances. They can also make extracellular recordings to study synaptic plasticity.

Clinical Neurobiology Laboratory (CNL)
The CNL offers diagnostic services and consulting for the interior (San Luigi Hospital) and external (10 departments of neurology in the region) diagnosis of multiple sclerosis.
The diagnostic tests offered include cytochemical examination of cerebrospinal fluid, immunoisoelectrofocusing to search for oligoclonal bands and several essays for the detection of viral nucleic acids. In addition, the laboratory provides a diagnostic service for neuronal paraneoplastic antibodies.
Currently the CNL is one of the few laboratories in Italy capable of providing a diagnostic service for the detection of antibodies NMO-IgG and anti-AQP4.
Finally, the CNL offers various services for monitoring patients with multiple sclerosis treated with different drugs; in this regard the lab performs a service in Italy and Europe for the serological titration of antibodies against interferon-beta (using three different methods) and natalizumab (Tysabri) potentially produced by patients treated with these drugs.
The laboratory is also equipped with a service for the evaluation of the biological activity of interferon-beta through the measurement of gene expression of specific proteins induced by interferon (such as MxA).

Common services
In addition to spaces dedicated to animal facility and laboratories, there are two rooms for the secretariat, a staff kitchen, a room for small meetings (up to 20 people), a seminar room and a room for deep freezers.

OUTREACH ACTIVITIES

From the perspective of educational and scientific dissemination the aims of NICO are:
• to promote scientific culture, and in particular knowledge of neuroscience, in high schools, through multimedia tools that reduce the economic impact of training initiatives
• provide basic skills on the normal functioning of the brain and neurodegenerative processes
• explain the importance of basic research and the impact on society of tomorrow
• create synergies and exchange of expertise / experience in the world of university research, the school and society, represented in this case from the large network of voluntary associations active in the field of disability and dementia

The NICO is engaged in scientific **activities dedicated to students** of high schools - Scientific Summer Academy, Olympic Neuroscience and Unistem Day, national and international - and to public (Researchers' Night, Open Day and Brain Awareness Week).
These activities - thanks to the network of partnerships that, starting by the University of Turin in the years has expanded throughout the country at other universities, associations (e.g. Non-profit Associations) and institutions like Centre Agora Science (which brings together the University of Turin and East Piedmont and Polytechnic of Turin) - have allowed to establish direct contacts with teachers and students of high schools.
NICO is organizing the regional competition of the World Olympics in Neuroscience: every year in the world, high school students participate in a competition to stimulate interest in the study of neuroscience. The competition begins with the sending of educational materials to schools, then a local selection in schools (in Piedmont hundreds of students), regional (at the NICO) and finally a national one in which the Italian "champion" is chosen for the world competition.
In order to further attract the interest of young people in the NICO's activities, a "Volley Brain" championship has been organised twice through the years.

The Institute has a strong link with the Piedmontese **Associations of patients** with disabilities (e.g. the Coordination Committee for Tetraplegic and Paraplegic patients of Piedmont) and neurodegenerative diseases and their families (CAAP - Coordination committee of Alzheimer Associations of Piedmont -12 local associations - the Ass. Of Parkinson friends of different provinces of the region, the Association Girotondo Onlus for SMA patients in Biella, etc.).

NICO is involved in the organization of a series of **dissemination lectures** for the public, some of which on the occasion of the "Brain Awareness Week " (which is held worldwide in March) at "Circolo dei Lettori" of Turin. The goal is to provide accurate information on scientific topics not easy to understand / disclose - such as the state of research and therapies available on neurodegenerative diseases - and often the subject of simplification and distortion (for example regarding the Stamina affair).

Recently, NICO, in **collaboration with the Museum of Human Anatomy of Turin**, has submitted an application to the Ministry of Universities for the installation of videos to be shown in the museum on "New techniques in the study of the nervous system at the microscopic level" and "macroscopic", as well as in writing a book on models of the nervous system, given the large number of visitors and of school students attending the museum.

SCIENTIFIC SEMINARS AT NICO

Over the last five years, an internal committee (Annalisa Buffo, Daniela Carulli and Silvia De Marchis) has been charged of the promotion and organisation of the seminar activities at NICO. The committee established a procedure according to which speakers to be invited are first proposed by NICO researchers and then selected based on a poll by all the NICO community. The committee also took the responsibility to organize the 'DISFEB meets NICO' series, agreed by the director of NICO and prof Melcangi of the Department of Pharmacological and Biomolecular Sciences-Center of Excellence on Neurodegenerative Diseases, Milan.

INVITED SPEAKERS

2011: Claudia Verderio, CNR, Milan; Roberto Furlan, Ospedale San Raffaele, Mlan; Alfredo Brusco, University of Turin; Elisa Vigna, IRCC Candiolo, University of Turin; Elsa Fabbretti, Sissa, Trieste; Helena Vieira (ITQB-UNL/IBET, Oeira, Lisboa); Claudio Giachino (Max planck Institute, Freiburg, Germany); Gaetano Donofrio (University of Parma).

2012: Julien Puyal, University of Lausanne; Anna Gualandris, University of Turin; Marco Sassoè-Pognetto, University of Turin; Silvia Nicolis, University of Milan Bicocca; Carla Taveggia, San Raffaele Hospital; Antonio Uccelli, University of Genoa; Patrizia Panzanelli, University of Turin; Ferdinando di Cunto, University of Turin; Glauco Tarozzo, IIT Genoa; Paolo Giacobini, Unv of Lion; Anna Gualandri, University of Turin; Silvia Nicolis, University of Milan; Antonio Uccelli, University of Genoa; Claudio Ciardelli, Politecnico, Turin; Giuseppina Tesco, University of Boston; Daniela Rossi, Salvatore Maugeri, Pavia; Adriano Chiò, University of Turin; Giorgio Merlo, University of Turin; Maurizio Giustetto, University of Turin; Cristina Becchio, University of Turin; Martina Amanzio, University of Turin; GianBattista Ferrero, University of Turin.

2013: Enzo Terreno, University of Turin; Luca Muzio, San Raffaele Hospital; Tommaso Fellin and Serena Bovetti, IIT Genoa; Laura Sacerdote, University of Turin; M. Miquel, University Jaume de Castelo; G Fisone, Karolinska Institute; L Chelazzi, University of Verona.

2014 – NICO seminars: Chiara Rolando, University of Basel; F. Cauda, Ospedale Koelliker - Università di Torino; Alessandro Sale, CNR di Pisa; Paolo Fabene, Università di Verona; Prof. Federico Bussolino, Istituto di Candiolo – IRCCS, Università di Torino; Alexander J. Graur, Ph.D - The New York Academy of Sciences; Maurizio Balistreri, Università di Torino; Carlo Ricciardi, Emiliano Descrovi, Fabrizio Pirri - Politecnico di Torino; Federico Cremisi, Scuola Normale Superiore di Pisa; Matteo Caleo, CNR, Pisa; Umberto Dianzani, Università del Piemonte Orientale "Amedeo Avogadro"; Cinthia Farina, - San Raffaele Scientific Institute, Milan.
DISFEB MEETS NICO: Roberto Melcangi, Barbara Viviani, Roberto Gardoni (University of Milan).

2015: F. Molinari, Politecnico di Torino; M. Tamietto, University of Turin; J. Kwok, University of Cambridge (UK); P. Palanza, University of Parma; M. Studer, University of Nice Sophia-Antipolis; D. F. Benfenati, IIT Genoa; De Pietri Tonelli, IIT Genoa; Toshitaka Oohashi (University of Okayama, Japan); F Laezza, University of Texas; A. Gozzi, University of Trento.
DISFEB MEETS NICO: N. Mitro; R. Molteni; A. Villa; M. Fumagalli; L. Musazzi; A. Poletti; Anna Cariboni; V. Magnaghi (University of Milan).

NICO lectures on Neuroscience:
Arturo Alvarez Buylla, University of California, San Francisco, May 2013
Ferdinando Rossi Lecture on Neuroscience:
Frank Bradke, German Center for Neurodegenerative Diseases, Bonn January 2015.

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name: Neurobiolologia Clinica, SCDO Neurologia 2 - CRESM

1. LABORATORY DESCRIPTION – PERSONNEL:

- **Principal Investigator**

Antonio Bertolotto — Birthdate (12/02/1952)
MD — Gender: M
Nationality: Italy — Phone: 00 39 011 670 66 00
Email: antonio.bertolotto@gmail.com

- **Personnel**

1. Arianna Sala — Birthdate (22/05/1972)
   MSc in Biology — Gender: F
   Role: Resident Biologist, Specialist in Clinical Pathology — Nationality: Italian
   Expertise: She is principally involved in the diagnostic process of inflammatory diseases of the nervous system and in the development of novel laboratory procedures for the advancement of diagnostic technologies.

2. Marzia Caldano — Birthdate (20/07/1975)
   MSc and Board Certification in Clinical and Analytical Biochemistry — Gender: F
   Role: Pharmacist — Nationality: Italian
   Expertise: relevant experience in drug immunogenicity, cell cultures, gene expression analysis and cerebrospinal fluid analysis. She is in charge of an Italian Service for the detection of anti-Interferon and anti-Natalizumab antibodies in multiple sclerosis patients. Currently her studies is focused on personalization of therapy and identification of new biomarkers to establish the efficacy of treatment.

3. Letizia Granieri — Birthdate (13/12/1980)
   MSc and Board Certification in Clinical Pathology — Gender: F
   Role: Biologist — Nationality: Italian
   Expertise: experience on cerebrospinal fluid examination, drug immunogenity evaluation and central nervous system autoimmunity. Her principal research fields are monitoring biological response to different treatments in multiple sclerosis patients and the study of anti-AQP4 antibodies in Neuromyelitis Optica (NMO) and related pathologies.

4. Fabiana Marnetto — Birthdate (14/12/1980)
   MSc and Board Certification in Clinical and Analytical Biochemistry — Gender: F
   Role: Medical Biologist — Nationality: Italian

Expertise: Detection of antibodies in autoimmune diseases (anti-KIR4.1 antibodies in MS and anti-Aquaporin 4 antibodies in NMO). Investigating the Epstein Barr virus (EBV) involvement in MS pathogenesis. Evaluation of clinical/biological response to different therapies in MS and NMO: biomarkers discovery and validation, assessing the clinical/biological response to different therapies in MS. Experience in performing cerebrospinal fluid evaluation and serological tests for anti- central nervous system antibodies, for diagnosis and management of patients with MS, NMO and other neurological disorders.

5. Serena Martire — Birthdate (01/08/1987)
   MSc and Master in *Medical and Genomic Statistics* — Gender: F
   Role: Medical Biotechnologist — Nationality: Italian
   Expertise: Molecular biology, data management, gene expression and genotype data analysis, biostatistics

6. Francesca Montarolo — Birthdate (14/05/1983)
   MSc and PhD in Neuroscience — Gender: F
   Role: Biologist — Nationality: Italian
   Expertise: Technical skills to work “in vivo” with experimental murine model, looking at cognitive behavior tests and at immunohistological and biomolecular aspects in the central nervous system.

7. Simona Perga — Birthdate (29/03/1977)
   MSc, PhD in Molecular and Experimental Pathology and Board Certification in Clinical and Analytical Biochemistry — Gender: F
   Role: Medical Biotechnologist — Nationality: Italian
   Expertise: Previous research activity concerned the investigation of the molecular mechanisms underlying the physiological pathological neuronal aging in “in vitro” primary neuronal and glial cultures and in vivo mice models and disease biomarkers research in biological fluids (cerebrospinal fluid and serum) through the application of proteomics and biochemical techniques. Her current research activity is relates to the molecular mechanisms involved in the pathogenesis of multiple sclerosis (MS). In particular this research is carried on performing gene and protein expression analysis in peripheral blood mononuclear cells or in sub-population isolated from whole blood obtained from patients and healthy controls; immunohistochemically and immunofluorescence analysis in post-mortem MS human brain tissues and in the EAE mouse models of MS.

8. Michela Spadaro Birthdate (10/03/1975)
   MSc and PhD in in Immunology and Cellular Biology Gender: F
   Role Biologist Nationality: Italian
   Expertise: Technical skills to work “in vivo” with experimental murine model and human samples to explore the immune mechanisms underlying multiple sclerosis pathology by flow cytometry and functional assays, molecular biology and data management.

9. Paola Valentino Birthdate (11/08/1981)
   MSc and Board Certification in Clinical and Analytical Biochemistry Gender: F
   Role: Medical Biotechnologist Nationality: Italian
   Expertise: gene expression analysis and evaluation of drug immunogenicity therapies in MS and NMO patients. Evaluation and validation of diagnostic and prognostic tests for the detection of biomarkers for MS and NMO. Cerebrospinal fluid evaluation and serological tests for diagnosis and management of patients with MS, NMO and other neurological disorders

10. Gabriele Bono Birthdate (30/03/1991)
    Bachelor's degree in Biomedical Laboratory Technicians Gender: M
    Role: Biomedical Laboratory Technicians Nationality: Italian
    Expertise: Analysis of whole blood , serum and plasma; dosage of serum proteins by capillary electrophoresis; seeding of organic samples on plates of agarose for microbiological analysis; processing of histological and cytological specimens; PCR, flow cytometry, mice manipulation, extracting of nucleic acids, immunohistochemistry and immunofluorescence.

11. Federica Brescia Birthdate (26/03/1984)
    Bachelor's degree in Biomedical Laboratory Technicians Gender: F
    Role Biomedical Laboratory Technicians Nationality: Italian
    Expertise: Cerebrospinal fluid analysis and serological tests, DNA and RNA extraction, databases management, Bio-Bank management, cells culture and CPE test.

12. Daniela De Nicolò Birthdate (03/05/1985)
    Bachelor's degree in Biomedical Laboratory Technicians Gender: F
    Role: Biomedical Laboratory Technicians Nationality: Italian
    Expertise: Cerebrospinal fluid analysis and serological tests, DNA and RNA extraction, databases management, Bio-Bank management, cells culture and CPE test.

13. Daniela Gramolelli Birthdate (31/01/1980)

Graduate Gender: F

Role Secretary Nationality: Italian

Expertise: compiling databases and acceptance samples.

2. PRINCIPAL INVESTIGATOR CURRICULUM VITAE (two pages)

Education and training:
1977 graduation cum laude, Medical Doctor, University of Turin, Italy
1981 specialization cum laude, Neurology, University of Turin, Ital

Employment and research experience:
1982 -1992 Neurological Clinic, University of Turin (Italy), vice-head
1992-2002 Neurological Clinic, University Hospital S. Luigi, Orbassano, vice-head
2002-2009 Multiple Sclerosis Regional Referral Centre (CRESM) & Clinical Neuro-Biology (CNB), AOU S. Luigi, Orbassano, Director
2009- today Neurological Unit 2 – CRESM, University Hospital S. Luigi, Orbassano, Director

Relevant discoveries: (Relevant contribution to basic and clinical topics)
Peri-neuronal nets and Extracellular Matrix components in CNS
Identification of subsets of resting microglia in normal CNS
Antibodies against bio-pharmaceutical
Procedure for lumbar puncture reducing pain
Anti-inflammatory molecules involved in Multiple Sclerosis
Auto-Antibodies specific for Multiple Sclerosis and NMOSD

Please list your grants according to the table below (last five yrs).

Starting-end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
	National vs International	PI vs. Component	MIUR, ERC, ecc…			€	€
2009-2010	national	Comp	FISM	*I meccanismi immuno-biologici della gravidanza: come possono indurre una spontanea remissione nella sclerosi multipla*		90.000	90.000#
2010-2011	National	Comp	FISM	*Analisi delle variazioni di singoli nucleotidi poliformi in TNFAIP3 associati alla sclerosi multipla*	FISM code 2010/R/28	40.000	40.000#
2010	National	PI	Alenia	*Nuove metodiche bio-molecolari per differenziare le malattie autoimmuni del Sistema Nervoso (SN)*		10.000	10.000
2010	National	PI	Alenia			40.000	40000
2010	National	PI	FISM	*Correlazione tra neurodegenerazione e infiammazione nella sclerosi multipla: NR4A2 come modulatore di infiammazione*	FISM code 2010/R/7	30.000	30.000#
2010-2013	National	Comp	Ministero Salute Italia	*"The ubiquintin-editing enzyme A20 (TNFAIP3) as a peacekeeper in inflammation and immunity: a link between TNFAIP3 deregulation and Multiple Sclerosis"*	Project Code: GR-2010-2315964	263.000	263.000*
2011	national	Comp	FISM	*Analisi dell'infezione con virus Epstein-Barr e della risposta immunitaria nel fluido cerebrospinale e nel sangue di pazienti con sclerosi multipla mediante tecniche altamente sensibili di PCR*		16.000	16.000
2011-2013	National	PI	Compagnia di SanPaolo	*Immunological mechanisms of pregnancy induces spontaneous remission in MS: microarray longitudinal analysis of gene expression in MS patients and healthy volunteers before and during pregnancy*		100.000	100.000
2012 - 2013	National	PI	Novartis Spa	*Clinical effect of a Nurr1 agonist on EAE*	-	€ 50.000	€ 50.000
2012-2014	National	PI	Merck	*Prediction of clinical IFNB response and differences among IFNB preparations*		200.000	200.000
2013	National	PI	FISM	*Diagnostic and prognostic biomarkers in multiple sclerosis: a possible role of Vitamin D Binding Protein isoforms*	FISM Code 2013/S/4	80.000	80.000#
2013	National	Comp	FISM	*Sviluppo e validazione preliminare della*		7000	

				versione abbreviata e computerizza dell'MSQOL-54			
2013-2014	National	PI	Novartis Spa	*Clinical effect of a Nurr1 agonist on Relapsing Remitting EAE*	-	€ 50.000	€ 50.000
2013-2015	National	PI	TEVA	*T regulatory cells (Treg) in pregnacy and Copaxone treated MS patients*	-	50.000€	50.000
2014	National	Comp	FISM	*Studio dell'espressione di geni dei virus di Epstein Barr e geni cellulari in pazienti con CIS, SM, recidivante remittente e SM primaria progressiva: ricerca di biomarcatori diagnostici e progonostici*		51.950	51.950#
2014	National	PI	Biogen	*SERVIZIO DOMPÈ per NAbs e anticorpi anti Tysabri*	-	199.379,72	199.379,72
2014	National	PI	FISM	*Una banca biologica ed un laboratorio dedicati alla raccolta ed alla distribuzione di campioni biologici di SMPP, la replicazione e la condivisione di dati e la validazione di metodi biologici*	-	74.800	74.800#
2014-2016	national	Comp	FISM	*"Ruolo della deubiquitinasi A20/TNFAIP3 nell'immuno-patologia della SM".*	FISM code 2014/R/14	100.000	100.000#
2015	National	PI	Biogen	*SERVIZIO DOMPÈ per NAbs e anticorpi anti Tysabri*	-	109.800	109.800
2015-2016	national	PI	Merck	*Regulatory cells: evaluation of the effect of IFN-beta treatment in MS patients"*	-	60.000	60.000
2015-2017	National	PI	Ministero Salute	*«Improving therapeutic appropiateness of Multiple Sclerosis treatments using biomolecular approaches to personalize therapy and save pharmaceutical spending»*		381.880	381.880*

*The financial management of the project was in charge to the administration of AOU San Luigi, but the research was performed mainly at NICO. Scientific instruments funded by the project are located at NICO and are available to all the researcher of NICO.
#The financial management of the project was in charge to the administration of FISM, but the research was performed mainly at NICO. The project overhead (5%) and scientific instruments funded by the project are located at NICO and are available to all the researcher of NICO.

Please list the name of PhDs you have supervised.
PhD: Dr Francesca Gilli

Board Certification in Clinical Pathology: Dr Arianna Sala, Dr Letizia Granieri

Board Certification in Clinical and Analytical Biochemistry: Dr. Fabiana Marnetto, Dr Marzia Caldano, Dr Paola Valentino, Dr Simona Perga, Dr Nicole D. Navone

Master in Medical and Genomic Statistics: Dr. Serena Martire

Please list honours, prizes or awards received, If applicable.

2003: member of "Therapeutics and Technology Assessment subcommittee of the American Academy of Neurology" for anti-IFNb antibodies
Since 2004 Coordinatore della Commissione Regionale SM dell'Assessorato alla Sanità
2009: member of Accademia di Medicina di Torino
2012: idoneità a Professore Universitario di Prima Fascia, Settore Neurologia

Please list your outreach activities

- Describe your international collaborative experiences.

University of Munchen (anti-KIR antibodies);
Muenster (European Bio-bank and LSelectin);
MAGE (European project for antibodies anti-biological drugs);
Tel Aviv (SNPS for prevention of PML in Natalizumab treated patients).

- Invited talks:

Since 1st May 2015:
19-20 XI Milano “Abbiamo risposto?” in tavola rotonda in “SM: una sola malattia?”
24 X Pero (MI) “SM e alimentazione: cibi e diete nell’era dei nuovi farmaci” in “Alla round MS”
10 X Barcellona “Hot Topics in MS: Best of ECTRIMS 2015”
11 IX Padova “Terapia: stato dell’arte” in “Due passi nel futuro della SM”
18 VI Orbassano “Interazioni fra ricercatori ed il comitato etico”
5 VI Brescia “L Selectina: un potenziale marker di richio con PML” in “Monitoraggio del trattamento long term con Natalizumab”
29 V Palermo “La cefalea post-rachicentesi: un dolore evitabile” in Seminari della Scuola di Specializzazione in Neurologia
28 V Baveno “Tavola rotonda: modelli organizzativi dei centri SM” in “Top Seminar”

Editorial duties Member of the Editorial Board of:
“Multiple Sclerosis International” since 2012
“Progress in Neuroscience” since 2012
“Dataset Papers in Neuroscience” dal 2012
“Journal of Multiple Sclerosis” since 2014
“Neurology and Therapy” since 2014

Member of the Scientific Committee of AISM 1997-1998; 2010-2013

Please list your organizational activities:
- Speakers invited:

Prof.ssa Farina C., Istituto Neurologico Besta, Milano, title: “Peripheral and central pathogenic processes in Multiple Sclerosis”, February 14th, 2014.

Prof Dianzani U., Dipartimento di Scienze della Salute, Università del Piemonte Orientale “Amedeo Avogadro” title: “Vaccinazione inversa nella terapia della Sclerosi Multipla”, March 21st, 2014

Workshops, Schools or Conferences organized:
XXI AINI Congress 22nd -25th September 2011, Pollenzo (Cuneo, Italy);
Since 2006: 18 Residential Courses “La gestione quotidiana del paziente con Sclerosi Multipla”
Every year a meeting focused on clinical management of MS.

Please list your technology transfer achievements (patents, etc.), if applicable

2012: Co-Titolare del brevetto n. 13168110.8 "BIOMARCATORI PER PATALOGIE DEL SISTEMA NERVOSO CENTRALE”

2013: Co-Titolare del brevetto europeo n EP2664923 European and USA patent extension with the title of “Biomarkers for central nervous system diseases”.

3. PI's PUBBLICATIONS:

(Please list below your publications in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science).
For each publication, please indicate:
* if you contributed equally to the fist-author, as stated in the published article

Please use the following format throughout:

Manca, A., Capsoni, S., Di Luzio, A., Vignone D, Malerba F, Paoletti F, Brandi R, Arisi I, Cattaneo A, Levi-Montalcini R. (2012). Nerve growth factor regulates axial rotation during early stages of chick embryo development. *Proc Natl Acad Sci U S A.*, 109(6):2009-14
IF= 9.67; R = 4/57; Times cited = 8

2015

1. Prosperini, L., Annovazzi, P., Capobianco, M., Capra, R., Buttari, F., Gasperini, C., Galgani, S., Solaro, C., Centonze, D., Bertolotto, A., Pozzilli, C., Ghezzi, A. (2015). Natalizumab discontinuation in patients with multiple sclerosis: Profiling risk and benefits at therapeutic crossroads. *Mult Scler*.; 21(13):1713-22.
   IF = 4.822; R = 19/144 (Neurology) 30/335 (Neurology clinical); Times cited = 0

2. Bertolotto, A. (2015). Evaluation of the impact of neutralizing antibodies on IFNβ response. *Clin Chim Acta*., 449:31-6.
   IF = 2.824; R = 11/57 (Biochemistry medical); Times cited = 1

3. Iaffaldano, P., Lucisano, G., Pozzilli, C., Brescia Morra, V., Ghezzi, A., Millefiorini, E., Patti, F., Lugaresi, A., Zimatore, G.B., Marrosu, M.G., Amato, M.P., Bertolotto, A., Bergamaschi, R., Granella, F., Coniglio, G., Tedeschi, G., Sola, P., Lus, G., Ferrò, M.T., Iuliano, G., Corea, F., Protti, A., Cavalla, P., Guareschi, A., Rodegher, M., Paolicelli, D., Tortorella, C., Lepore, V., Prosperini, L., Saccà, F., Baroncini, D., Comi, G., Trojano, M.; Italian iMed-Web database. (2015). Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. *Brain*; 138(Pt 11): 3275-86.
   IF = 9.196; R = 4/335 (Neurology Clinical); Times cited = 0

4. Schwab, N., Schneider-Hohendorf, T., Pignolet, B., Spadaro, M., Görlich, D., Meinl, I., Windhagen, S., Tackenberg, B., Breuer, J., Cantó, E., Kümpfel, T., Hohlfeld, R., Siffrin, V., Luessi, F., Posevitz-Fejfár, A., Montalban, X., Meuth, S.G., Zipp, F., Gold, R., Du Pasquier, R.A., Kleinschnitz, C., Jacobi, A., Comabella, M., Bertolotto, A., Brassat, D., Wiendl, H. (2015). PML risk stratification using anti-JCV antibody index and L-selectin. *Mult Scler.*, 15 Oct 2. pii: 1352458515607651. [Epub ahead of print]
   IF = 4.822; R = 19/144 (Neurology) 30/335 (Neurology clinical); Times cited = 0

5. Spadaro, M., Caldano, M., Marnetto, F., Lugaresi, A., Bertolotto, A. (2015). Natalizumab treatment reduces L-selectin (CD62L) in CD4+ T cells. *J Neuroinflammation*, 12:146.
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6. Veroni, C., Marnetto, F., Granieri, L., Bertolotto, A., Ballerini, C., Repice, A.M., Schirru, L., Coghe, G., Cocco, E., Anastasiadou, E., Puopolo, M., Aloisi, F. (2015). Immune and Epstein-Barr virus gene expression in cerebrospinal fluid and peripheral blood mononuclear cells from patients with relapsing-remitting multiple sclerosis. *J Neuroinflammation*, 12:132.
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7. Capobianco, M., di Sapio, A., Malentacchi, M., Malucchi, S., Matta, M., Sperli, F., Bertolotto, A. (2015). No impact of current therapeutic strategies on disease reactivation after natalizumab discontinuation: a comparative analysis of different approaches during the first year of natalizumab discontinuation. *Eur J Neurol*. 2015 Mar;22(3):585-7.
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8. Montarolo, F., Perga, S., Martire, S., Bertolotto, A. (2015). Nurr1 reduction influences the onset of chronic EAE in mice. *Inflamm Res.*, 64(11):841-4
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9. Perga, S., Giuliano Albo, A., Lis, K., Minari, N., Falvo, S., Marnetto, F., Caldano, M., Reviglione, R., Berchialla, P., Capobianco, M.A., Malentacchi, M., Corpillo, D., Bertolotto, A. (2015). Vitamin D Binding Protein Isoforms and Apolipoprotein E in Cerebrospinal Fluid as Prognostic Biomarkers of Multiple Sclerosis. *PLoS One*, 10(6):e0129291.
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16. Di Sapio, A., Bertolotto, A., Melillo, F., Sperli, F., Malucchi, S., Troni, W. (2014). A new neurophysiological approach to assess central motor conduction damage to proximal and distal muscles of lower limbs. *Clin Neurophysiol.*; 125(1): 133-41.
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IF = 7.271; R = 12/335 (Neurology Clinical); Times cited = 14

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IF = 2.474; R = 48/144 (Neurology) 81/335 (Neurology Clinical); Times cited = 5

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IF = 3.377; R = 34/144 (Neurology) 55/335 (Neurology Clinical); Times cited = 13

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IF = 9.977; R = 1/144 (Neurology) 3/335 (Neurology Clinical); Times cited = 21

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IF = 4.822; R = 19/144 (Neurology) 30/335 (Neurology Clinical); Times cited = 16

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IF = 2.474; R = 48/144 (Neurology) 81/335 (Neurology Clinical); Times cited = 3

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IF = 2.405; R = 77/335 (Neurology Clinical); Times cited = 37

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IF = 2.474; R = 48/144 (Neurology) 81/335 (Neurology Clinical); Times cited = 13

2010

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IF = 21.896; R = 1/335 (Neurology Clinical); Times cited = 89

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IF = 55.873; R = 2/1775 (Medicine miscellaneous); Times cited = 703

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IF = 3.028; R = 14/74 (Chemistry Analytical); Times cited = 10

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IF = 7.271; R = 12/335 (Neurology Clinical); Times cited = 20

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IF = 8.185; R = 9/335 (Neurology Clinical); Times cited = 61

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IF = 4.822; R = 19/144 (Neurology) 30/335 (Neurology clinical); Times cited = 32

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IF = 3.234; R = 38/207 (Biochemistry, Genetics and Molecular Biology); Times cited = 25

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IF = 4.822; R = 19/144 (Neurology) 30/335 (Neurology clinical); Times cited = 33

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IF = 1.859; R = 84/265 (Infectious diseases); Times cited = 0

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IF = 2.474; R = 48/144 (Neurology) 81/335 (Neurology Clinical); Times cited = 15

63. Chiò, A., Calvo, A., Ghiglione, P., Mazzini, L., Mutani, R., Mora, G.; PARALS. (2010). Tracheostomy in amyotrophic lateral sclerosis: a 10-year population-based study in Italy. *J Neurol Neurosurg Psychiatry*; 81(10):1141-3.
IF = 6.807; R = 17/335 (Neurology Clinical); Times cited = 25

4.GROUP's PUBBLICATIONS:

(Please list below up to ten most relevant publications of the other members of the group in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science)

Please use the following format throughout:

Manca, A., Capsoni, S., Di Luzio, A., Vignone D, Malerba F, Paoletti F, Brandi R, Arisi I, Cattaneo A, Levi-Montalcini R. (2012). Nerve growth factor regulates axial rotation during early stages of chick embryo development. *Proc Natl Acad Sci U S A.*, 109(6):2009-14
IF= 9.67; R = 4/57; Times cited = 8

2015

De Luca, A., Parmigiani, E., Tosatto, G., **Martire, S.**, Hoshino, M., Buffo, A., Leto, K., Rossi, F. (2015). Exogenous Sonic hedgehog modulates the pool of GABAergic interneurons during cerebellar development. *Cerebellum*; 14(2):72-85.
IF = 2.717; R = 63/335 (Neurology Clinical); Times cited = 1

2013

Montarolo, F., Parolisi, R., Hoxha, E., Boda, E., Tempia, F (2013). Early enriched environment exposure protects spatial memory and accelerates amyloid plaque formation in APP(Swe)/PS1(L166P) mice. *PLoS One*; 8(7): e69381.
IF 3.234; R = 38/207 (Biochemistry, Genetics and Molecular Biology); Times cited = 1

Di Gregorio, E., Bianchi, F.T., Schiavi, A., Chiotto, A.M., Rolando, M., Verdun di Cantogno, L., Grosso, E., Cavalieri, S., Calcia, A., Lacerenza, D., Zuffardi, O., Retta, S.F., Stevanin, G., Marelli, C., Durr, A., Forlani, S., Chelly, J., Montarolo, F., Tempia, F., Beggs, H.E., Reed, R., Squadrone, S., Abete, M.C., Brussino, A., Ventura, N., Di Cunto, F., Brusco, A. (2013). A de novo X;8 translocation creates a PTK2-THOC2 gene fusion with THOC2 expression knockdown in a patient with psychomotor retardation and congenital cerebellar hypoplasia. *J Med Genet*; 50(8): 543-51.
IF = 6.335; R = 9/94 (Genetical clinical); Times cited = 6

Hoxha, E., Tonini, R., Montarolo, F., Croci, L., Consalez, G.G., Tempia, F. (2013). Motor dysfunction and cerebellar Purkinje cell firing impairment in Ebf2 null mice. *Mol Cell Neurosci*; 52: 51-61.
IF = 3.840; R = 6/82 (Cellular and Molecular Neurosciences); Times cited = 1

2012

Boda, E., Hoxha, E., Pini, A., Montarolo, F., Tempia, F. (2012). Brain expression of Kv3 subunits during development, adulthood and aging and in a murine model of Alzheimer's disease. *J Mol Neurosci*; 46(3): 606-15.
IF = 2.343; R = 54/82 (Cellular and Molecular Neuroscience); Times cited = 7

Hoxha, E., Boda, E., Montarolo, F., Parolisi, R., Tempia, F (2012). Excitability and synaptic alterations in the cerebellum of APP/PS1 mice. *PLoS One*; 7(4):e34726.
IF 3.234; R = 38/207 (Biochemistry, Genetics and Molecular Biology); Times cited = 9

2011

Martin, M.G., Trovò, L., Perga, S., Sadowska, A., Rasola, A., Chiara, F., Dotti, C.G. (2011). Cyp46-mediated cholesterol loss promotes survival in stressed hippocampal neurons. *Neurobiol Aging*.; 32(5): 933-43.
IF = 5.013; R = 19/135 (Neuroscience miscellaneous) 5/32 (Aging); Times cited = 6

2010

Petzold, A., Altintas, A., Laura, C., Bartos, A., Achim, F., Blankenstein, M.A., Luc, H., Castellazzi, M., Cepok, S., Comabella, M., Constantinescu, C.S., Deisenhammer, F., Deniz, G., Gaye, M., Espino, M., Fainardi, E., Franciotta, D., Freedman, M.S., Giedraitis, V., Gilhus, N.E., Giovannoni, G., Glabinski, A., Grieb, P., Hartung, H.P., Hemmer, B., Herukka, S.K., Hintzen, R., Ingelsson, M., Jackson, S., Jacobsen, S., Jafari, N., Jalosinski, M., Jarius, S., Kapaki, E., Bernd, C.V., Koel-Simmelink, M.J.A., Kornhuber, J., Kuhle, J., Kurzepa, J., Lalive, P.H., Lannfelt, L., Lehmensiek, V., Lewczuk, P., Livrea, P., Marnetto, F., Martino, D., Menge, T., Norgren, N., Papuc, E., Paraskevas, G.P., Pirttila, T., Rajda, C., Rejdak, K., Ricny, J., Ripova, D., Rosengren, L., Ruggieri, M., Schraen, S., Shaw, G., Sindic, C., Siva, A., Stigbrand, T., Stonebridge, I., Topcular, B., Trojano, M., Tumani, H., Twaalfhoven, H.A.M., Vecsei, L., Van Pesch, V., Vanderstichele, H., Vedeler, C., Verbeek, M.M., Villar, L.M., Weissert, R., Wildemann, B., Yang, C., Yao, K., Teunissen, C.E. (2010). Neurofilament ELISA validation. Journal of Immunological Methods; 352: 23-31.
IF = 1.820; R = 97/200 (Immunology); Times cited = 20

5. GROUP's additional information:

Please list the grants of the other members of the group in the last 5 years -2010/2015- according to the table below:

Starting-end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
	National vs International	P. Rossi; PI vs. Component	MIUR, ERC, ecc…			€	€
2010-2011	National	S. Perga, PI	FISM	Analisi delle variazioni di singoli nucleotidi poliformi in TNFAIP3 associati alla sclerosi multipla	FISM code 2010/R/28	40.000	40.000#
2010-2013	National	S. Perga, PI	Ministero Salute Italia	*"The ubiquintin-editing enzyme A20 (TNFAIP3) as a peacekeeper in inflammation and immunity: a link between TNFAIP3 deregulation and Multiple Sclerosis"*	Project Code: GR-2010-2315964	263.000	263.000*
2013 - 2014	National	Dr. Martire, PI	FISM	Coordinated deregulation of microRNAs and their mRNAs targets causes defects of negative feedback loops that suppress inflammation in patients with multiple sclerosis	-	22000	22000
2014-2016	national	S. Perga, PI	FISM	*"Ruolo della deubiquitinasi A20/TNFAIP3 nell'immuno-patologia della SM".*	FISM code 2014/R/14	100.000	100.000#

*The financial management of the project was in charge to the administration of AOU San Luigi, but the research was performed mainly at NICO. Scientific instruments funded by the project are located at NICO and are available to all the researcher of NICO.

#The financial management of the project was in charge to the administration of FISM, but the research was performed mainly at NICO. The project overhead (5%) and scientific instruments funded by the project are located at NICO and are available to all the researcher of NICO.

Please list honours, prizes or awards received by other members of the group If applicable.

Dr Martire:

- Travel grant, XXIV National AINI Congress. Sorrento, Italy (2014)
- Travel grant, XXIII AINI Congress Satellite Conference of the 15th International Congress of Immunology – ICI. Milan, Italy (2013)
- Travel grant, XXI AINI Congress. Pollenzo, Italy (2011)
- Best poster award, XXI AINI Congress. Pollenzo, Italy (2011)

Dr Montarolo:

- Educational Grant to 2013 ESNI (Porto);
- Educational Grant to 2014 ACTRIMS-ECTRIMS Meeting (Boston, USA);
- Educational Grant to 2014 AINI Meeting (Sorrento, Italy)

Dr Perga:

- - Travel grant to participate at the ECTRIMS meeting (9-12 September), Dusseldorf, Germania (2009)
- - Travel grant to participate at the ECTRIMS meeting (13-16 October), Gothenburg, Sweden (2010)
- - Travel grant to participate at the XX AINI Congress (30 September-3 October:), Stresa, Italy (2010)
- - Travel grant to participate at ECTRIMS/ACTRIMS meeting (19-22 October 2011) Amsterdam, Holland (2011)

Please list outreach activities of other members of the group:

- Describe your international collaborative experiences

- Invited talks

Dr Caldano:

- Invited speaker at the meeting: “Exchanges meetings: aspetti clinici, terapeutici e gestionali della SM: esperienze a confronto”, 11/11/2011, Genova (Italy),
- Invited speaker at XX Congresso AINI (Associazione Italiana NeuroImmunologia), 30/09–03/10/2010, Stresa (Novara – Italy)
- Invited speaker at meeting “Real time PCR” 07/06/2011 and 20-21/09/2011 at Orbassano (Turin – Italy)
- Official speaker at “FIRST EUROPEAN INTER-COUNTRY WORKSHOP”, 24-25/11/2011 Orbassano (Turin – Italy)
- Invited speaker at workshop: “Evaluation of neutralizing antibodies against interferon beta in patients with multiple sclerosis”, 21-25/10/2013, Praha (Czech Republic).
- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (26-28/09/2011; 7-9/11/2011; 21-23/05/ 2012, 12-14/11/ 2012, 3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015).

Dr Granieri:

- Teacher in courses for italian neurologist “La gestione quotidiana del paziente con Sclerosi Multipla” organised by Biogen Idec (12-14/10/2009, 10-12/5/2010, 14-16/6/2010, 26-28/9/2011, 7-9/11/2011-, 21-23/5/2012, 12-14/11/2012, 3-5/6/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015), A.O.U San Luigi Gonzaga, Orbassano (TO)
- Teacher in the course for international neurologist “European Inter-Country Workshop” organised by Merck-Serono (24-25 November 2011), A.O.U San Luigi Gonzaga, Orbassano (TO)

Dr Marnetto:

- Teacher in the course for international neurologist “European Inter-Country Workshop” organized by Merck-Serono (24-25 November 2011), A.O.U San Luigi Gonzaga, Orbassano (Turin).
- Invited speaker at the meeting: “Aspetti clinici, terapeutici e gestionali della SM: esperienze a confronto”, Asti (Italy), 15/06/2012: “Risposta immunogenica alle terapie: l’impatto clinico ed economico dei servizi di titolazione degli anticorpi neutralizzanti.”
- Invited speaker at the meeting “Up Dates in Autoimmunity 2014: evidences and outcomes”, Modena (Italy, 23-24/05/2014): “Relevance of Acquaporin-4 antibodies: case report”.
- Invited speaker at the meeting “Autoimmunità in neurologia: stato dell’arte”, Padova (Italy, 28/11/2014): “Anticorpi anti-AQP4”.
- Invited speaker at the meeting “Qualcosa di nuovo a Nord Ovest: aggiornamenti in diagnosi e terapia nella SM”, Orbassano (Italy, 30/01/2015): “Gli anticorpi anti-KIR4.1: un test diagnostico e prognostico per la SM?”.
- Invited speaker at the meeting “Up Dates in Autoimmunity 2015: the need of harmonization”, Modena (Italy, 13-14/05/2015): “Expanding and debating Neuronal Diagnostics”.
- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (26-28/09/2011; 7-9/11/2011; 21-23/05/ 2012, 12-

14/11/ 2012, 3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015).

Dr Martire:

- FISM Fondazione Italiana Sclerosi Multipla Scientific Congress. Rome, Italy (2015) "Deeper insight into the mechanisms underlying the deregulation of the anti-inflammatory gene TNFAIP3 in patients with multiple sclerosis".
- XXIV AINI congress, "DBP isoforms and ApoE as early prognostic CSF biomarkers of MS aggressiveness"; 1-4 october 2014,Sorrento (NA).
- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015

Dr Montarolo:

- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015
- AINI Meeting, Sorrento Italy, 1-4 October 2014. Title: "Effects of isoxazolo-pyridinone 7e, a potent activator of the Nurr1 signaling pathway, on experimental autoimmune encephalomyelitis in mice"

Dr Perga:

- XX AINI Congress, “Transcriptional analysis of seven MS-associated genes after ex-vivo stimulation with LPS/PHA” 30 September-3 October 2010:Stresa, Italy.
- XXI AINI Congress, “Proteomic-based disease biomarkers identification in cerebrospinal fluid samples” 22-25 September 2011Pollenzo, Italy.
- Annaul scientific meeting AISM/FISM “Insieme siamo più forti della sclerosi multipla", “Analysis of single-nucleotide polimorphisms in TNFAIP3 associated with multiple sclerosis”; 28-29 Maggio 2014 Roma
- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (26-28/09/2011; 7-9/11/201; 21-23/05/2012, 12-14/11/2012, 3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015).

Dr Sala:

- Invited speaker at the meeting: “Appropriatezza nell’utilizzo diagnostico delle proteine nelle patologie ematologiche, oculistiche e neurologiche” 4 edizioni su territorio piemontese nell’anno 2011.
- Teacher in the course for international neurologist “European Inter-Country Workshop” organised by Merck-Serono (24-25 November 2011), A.O.U San Luigi Gonzaga, Orbassano (Turin).
- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (26-28/09/2011; 7-9/11/2011; 21-23/05/ 2012, 12-14/11/ 2012, 3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015).

Dr Spadaro

- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015).

Dr Valentino:

- Teacher in the course for international neurologist “European Inter-Country Workshop” organised by Merck-Serono (24-25 November 2011), A.O.U San Luigi Gonzaga, Orbassano (TO)
- Official speaker for MS patients' care courses at CRESM: "La gestione quotidiana del paziente con Sclerosi Multipla" organized by Biogen Idec (21-23/05/ 2012, 12-14/11/ 2012, 3-5/06/2013, 11-13/11/2013; 12-14/05/2014; 17-19/11/2014; 16-18/06/2015; 9-11/11/2015).

- Editorial duties

Please list your organizational activities:

- Speakers invited by members of the group

- Workshops, Schools or Conferences organized by members of the group

07/06/2011 and 20-21/09/2011: Real-Time PCR course: basic techniques and practical applications: “Genetic analysis (SNP, High Resolution melting, copy numbers)”, NICO, Orbassano. Sponsored by Applied Biosystem.

14/06/2013: “Using new technologies to study the genetics of disease”. Orbassano. Sponsored by Illumina

14/12/2015: “Verso l’infinito e oltre: nuove frontiere della biologia molecolare” Epigenetica, Next Generetion Sequencing, In vivo Applications. NICO, Orbassano.Sponsored by Euroclone.

Please list your technology transfer achievements (patents, etc.), if applicable

May 18th 2012: Italian patent filing entitled “Biomarcatori per patologie del sistema nervoso centrale”, protocol number MI2012A000865. Holders: Dr. Bertolotto Antonio e Fondazione Italiana per la Sclerosi Multipla (FISM). Inventors: Giuliano Albo A., **Perga S**., Corpillo D., Bertolotto A.

May 16th 2013: European and USA patent extension (EP2664923) with the title of “Biomarkers for central nervous system diseases”. Inventors: Giuliano Albo A., **Perga S.,** Corpillo D., Bertolotto A.

6 .Past Research activity

(Summarize the PI and group research activities in the last 10 years)

The Clinical Neurobiology Laboratory is housed at NICO and is part of SCDO Neurologia 2-Centro di Riferimento Regionale Sclerosi Multipla CRESM in the San Luigi Gonzaga Hospital; CRESM, directed by PI, is the reference Center for Multiple Sclerosis (MS) patients in Piedmont and is the core of a collaborative network with all the neurological divisions and clinics for MS pts in Italy. The whole staff of CRESM is fully dedicated to MS and has a long lasting experience in clinical and research aspects. CRESM manages more than 2000 MS pts and the clinical, therapeutic and instrumental information are registered in electronic database. The research activity of the Clinical neurobiology Lab covers several topics of MS, from differential diagnosis to immunopathogenesis. One typical feature of this Lab is the search and validation of biological markers that can be useful for the daily management of patients with MS and other demyelinating diseases. The main activities of the Clinical Neurobiology Lab in the last 10 years are summarized in the following chapters:

- *Diagnostic activity*
- *Biomarkers for MS (diagnostic/prognostic, treatment-response)*
- *Immunopathogenesis*
- *CRESM Bio-Bank*

Diagnostic activity

The Clinical Neurobiology Laboratory deals with routine CSF analysis from AOU San Luigi Gonzaga patients and from all over Piedmont centers. Even if CSF analysis is no more required for MS diagnosis, it is still important to offer diagnostic and prognostic information (to confirm a diagnosis of MS early in the disease course and be used to identify patients with a high probability of developing MS after a first clinical event) and to rule out differential diagnoses. Furthermore it's important to provide an important research tool. In particular, analysis performed in our laboratory are: cytological and biochemical CSF analysis, oligoclonal IgG bands detection, by Immunoisoelectrofocusing procedure, for evaluation of intrathecal IgG synthesis, and detection of Antibodies to AQP4 and to MOG proteins by immunofluorescence assay and FACS assay respectively.

Biomarkers for MS (diagnostic/prognostic, treatment-response)

a. Summary

Diagnostic biomarkers can be used to distinguish patients who have MS from patients with other neurological or autoimmune disorders, or from healthy individuals. Ideally, these biomarkers can be helpful in combination with clinical and radiological disease diagnostic criteria to improve the sensitivity and specificity of diagnosis.

b. Background and Rationale

Inflammatory demyelinating diseases (IDDs) of the CNS are a group of heterogeneous autoimmune inflammatory diseases that include multiple sclerosis (MS), neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and acute transverse myelitis (ATM). In 2005 Aquaporin 4 (AQP4) was shown to be the antigenic target of NMO-IgG, an antibody found specifically in patients with NMO and in formes frustes of NMO, such as longitudinally extensive transverse myelitis (LETM) or ON. This discovery facilitated the clinical, pathological, and radiological distinction of NMO and the spectrum of NMO-related disorders from classical multiple sclerosis. In addition to its use as a diagnostic tool, AQP4-IgG predicts a high risk of relapse in patients with a clinically isolated syndrome of either LETM or ON. As disability in NMO is attack-related, early diagnosis and treatment are predicted to have a major effect on long-term disability.

Several recent studies have shown the presence of myelin oligodendrocyte glycoprotein antibody (MOG-Ab) in the serum of adult patients with the NMOSD phenotype. However, the clinical relevance of MOG-Abs among adult patients with IDD is not yet clear.
The development and validation of sensitive and specific biologic assays for the detection of these auto-antibodies is very important from a diagnostic point of view, but also for a more adequate management of patients.
The hunt for biomarkers to predict MS disease evolution and identify patient subsets that may benefit from specific therapeutic regimens is a continuous effort in MS research. A test measuring biochemical biomarkers could be a useful tool in the diagnostic process, but, at present no validated biomarkers are available to diagnose disease, to monitor or predict disease progression, or to aid in assessment of early treatment effects.

c. Objectives

- To set up and validate biological assays for anti-AQP4, anti-MOG and anti-KIR4.1 antibodies detection, in order to improve the management of patients with inflammatory demyelinating diseases.
- To find new diagnostic and/or prognostic biomarkers in serum or cerebrospinal fluid (CSF) of patients: to date, there are no clinically-useful prognostic biomarkers in MS, even if they would be extremely useful for early patient intervention with personalized therapies.

d. Results

***DIAGNOSTIC BIOMARKERS*:**

- ***Oligoclonal IgG Bands in CSF:***
  The Clinical Neurobiology Lab performs routine CSF analysis for San Luigi Gonzaga Hospital and for several hospital in Piedmont: detection of oligoclonal IgG bands in CSF is the main CSF parameter that has a diagnostic value in MS (see DIAGNOSTICA).
- ***Anti-AQP4 Antibodies:***
  - Our first approach to set up of a test for anti-AQP4 antibodies detection was a western blot assay (WBA): eluted immunoprecipitated mouse AQP4 products are resolved in sodium-dodecyl-sulfate polyacrylamide (SDS-PAGE) gel, followed by transferring to membrane and incubating the blots with patients' sera. By using this assay we showed both good sensitivity (81%) and specificity (97%) for detecting AQP4 antibodies in NMO patients. Reliability of the procedure was also confirmed by comparing results with those of a commercial anti-AQP4 indirect immunofluorescence (IIF) assay. By using western blot, we were able, for the first time, to distinguish serum immunoreactivity against either of the two AQP4 isoforms (M1 and M23), showing that antibodies recognizing the linear AQP4-M1 isoform are specific for NMO (Marnetto et al, JNI 2009).
  - From January 2009 a multiparametric indirect immunofluorescence (IIF) assay was commercially available. In our lab we performed a “post-marketing” evaluation of this assay, in order to evaluate its diagnostic performance in distinguishing NMO from MS patients.
    This assay consists of an array of five different diagnostic substrates including HEK cells transfected with AQP4, non-transfected HEK cells, and three monkey tissue sections (cerebellum, cerebrum, and optic nerve). The assay was evaluated through the following steps: 1. Characterization of distinct immunofluorescence staining patterns. 2. Correlation between staining patterns and the patients’ clinical diagnoses. 3. Evaluation of the diagnostic sensitivity, specificity, and clinical utility (as assessed by calculation of likelihood ratios) of each pattern. 4. Analysis of the assay’s inter- and intra-laboratory reproducibility. We identified AQP4 specific and non-specific fluorescence staining patterns and established positivity criteria. Based on these criteria, this kit yielded a high sensitivity (95%) and specificity (100%) for NMO and had a significant positive and negative likelihood ratio (LR+ =∞, LR-= 0.05). Moreover, a 100% inter- and intra-laboratory reproducibility was found.

Our results show that this IIF assay has high sensitivity and specificity and represents a powerful tool for NMO serology, permitting the identification of different AQP4 specific and nonspecific patterns. Moreover this assay is fast to perform, highly reproducible and suitable for inter-laboratory standardization (Granieri et al, PlosOne 2012).

- Our Lab was involved in several national and international project for standardization of anti-AQP4 antibodies detection assays: San Raffaele Hospital (Fazio et al, 2009), Eden Project (Waters et al, 2014).

- ***Anti-MOG antibodies:***
  - A FACS assay for anti-MOG antibodies detection has been set up in our Lab: the test is now available in diagnostic routine for all Italian MS Centers.

***PROGNOSTIC BIOMARKERS*:**

- ***Proteomic approach***

  The analysis of inter-individual differences in CSF proteome may lead to the discovery of biological markers that are able to distinguish the various clinical forms of MS at diagnosis. A two dimensional electrophoresis study was carried out on individual CSF samples from 24 untreated women who underwent lumbar puncture for suspected MS. The patients were clinically monitored for 5 years and then classified according to the degree of disease aggressiveness and the disease-modifying therapies prescribed during follow up.
  The hierarchical cluster analysis of 2-DE dataset revealed three protein spots which were identified by means of mass spectrometry as Apolipoprotein E (ApoE) and two isoforms of vitamin D binding protein (DBP). These three protein spots enabled us to subdivide the patients into subgroups correlated with clinical classification (MS aggressive forms identification: 80%) (Perga et al, PlosOne 2015, in cooperation with the Bioindustry Park, Ivrea, Turin).

- ***Gene expression analysis approach***

  Using a Taqman-based pre-amplification real-time reverse-transcription polymerase chain reaction (RT-PCR) (PreAmp RT-PCR) to cDNA from CSF cells and PBMC of MS patients we analyzed multiple genes related to immune system function and genes expressed by Epstein-Barr virus (EBV), a herpesvirus showing strong association with MS. Using this enhanced RT-PCR method, we aimed at the following: (1) identifying gene signatures potentially useful for patient stratification, (2) understanding whether EBV infection is perturbed in CSF and/or blood, and (3) finding a link between immune and EBV infection status. The main results of this study are: 1) establishment of the methodology for quantification of 7 EBV and 41 cellular transcripts; 2) detection of EBV transcripts in 16% of RRMS patients, with 9.7% of CSF samples (3/31) and 6.9% (2/29) of PBMC samples showing EBV deregulation (disruption of EBV latency or productive infection); 3) identification of an immune signature associated with peripheral EBV reactivation in relapsing MS; 4) poor correlation between systemic and intrathecal transcriptional profiles; 5) identification of a set of genes associated with innate immunity (type-I IFN, pro-inflammatory macrophages) that are differentially expressed in CSF and discriminate with high accuracy between a group of remitting patients (n = 6; all females and EBV-, 5 of 6 MRI inactive) and a larger heterogeneous group (n = 24) comprising male/female, relapsing/remitting, MRI active/inactive, and EBV+/EBV- patients (Veroni, Marnetto et al, 2015, in cooperation with Istituto Superiore di Sanità, Rome).

e. Advancement in the field

- <u>Anti-AQP4 antibodies</u>:

  The current research in the field of anti-AQP4 antibodies is focused on the quantification or titration of antibodies (by using IIF and ELISA), in order to evaluate their possible

prognostic role in disease progression (in cooperation with Euroimmun and Policlinico di Bari).

- Anti-MOG antibodies:
  The current research in the field of anti-MOG antibodies is focused on 1. Investigating the presence of these antibodies in a cohort of NMOsd patients negative for AQP4 antibodies, in order to evaluate their prognostic role in disease progression; 2. Better characterize patients with anti-MOG antibodies (in collaboration with University of Hidelberg, Germany).
- Anti-KIR4.1 antibodies:
  In 2012 detection of anti-potassium channel KIR4.1 antibodies in sera has been suggested to be specific for MS, which could have a tremendous impact on disease management. In collaboration with Prof. Hemmer (Munich) we set up in our Lab the whole procedure for detection of anti-KIR4.1 antibodies in serum, showing positivity in 28% of MS patients and in 4% of Hcs (Marnetto et al, submitted) (See Future Projects).

TREATMENT-RESPONSE BIOMARKERS IN MS

a. Summary

Treatment-response biomarkers are evaluated in MS treated patients to monitor the biological response to therapy and identify risk factors.
Some MS treatment can induce anti-drug antibodies able to abrogate the biological and clinical action of the drug. Our research aimed at the evaluation of biological activity, and identification of specific markers to monitor clinical efficacy and response in the following treatment: Beta-Interferon, Natalizumab Glatiramer Acetate, and Rituximab.

b and c. Background and Rationale

MS is a heterogeneous disease and the therapy is rapidly evolving: several disease-modifying therapies (DMT) are approved, but each of them are only partially active and a variable percentage of patients are non-responders.
A subset of non-responder patients, develop Neutralizing antibodies that abolish the biological activity elicited by the drug. The biological activity of a drug is defined as the total effects determined by the interaction of the molecule with its receptor; it is a necessary, but not sufficient, condition for clinical efficacy of a drug. The measurement of biological activity in every patient, by the discovery of biomarkers, can allow the detection of non-responsive to the drug for lack of biological activity (Bertolotto, 2015).
We mainly focused on the following treatments:
Beta-Interferon (IFN-β) is the most commonly prescribed DMT in RRMS. The search for an IFN response biomarker is difficult, since the precise mechanism of action in MS remains unclear, probably attributable to numerous immunomodulatory activities.
Most patients are non-responders to treatment; IFN treatment can induce the production of binding and neutralizing antibodies (Babs, and Nabs). About 15-20% of IFN-β treated patients develop Nabs, which prevent the binding of IFN-β to its cell surface receptor IFNAR, abolishing the biological activity elicited by IFN-β. Biological activity can be studied by measuring a great number of Interferon Stimulated Genes (ISGs) (Bertolotto, 2015).
Natalizumab (NTZ) is a monoclonal antibody targeted to the α4 integrin. Blockade of α4β1 results in diminished T cell trafficking to the CNS and reduces relapse rate by 68%. A small proportion of NTZ treated patients (~ 6%) develop persistent anti-drug antibodies, which are associated with an increase in infusion-related adverse events, and in a reduced therapeutic efficacy. NTZ treatment is complicated by its association with progressive multifocal leukoencephalopathy (PML), a rare adverse event (3.7/1000 patients). It's caused by reactivation of a latent JC virus in immunocompromised individuals, leading to a debilitating encephalopathy fatal in up to 20–50% of cases. During therapy with NTZ, PML risk can be stratified depending on three risk factors: anti-JCV antibody status and level, treatment length and prior immunosuppressive therapy. However, while 50% of MS patients are JCV Ab seropositive, less than 1% will develop PML.

It is important to identify other factors allowing better identification of MS patients at high risk for PML. Recently, the expression of T lymphocytes surface markers in NTZ-treated patients was investigated, suggesting L-selectin on CD4+ T cells as a possible marker able to identify MS patients at high risk for PML.

Glatiramer acetate (GA) acts through the induction of specific T-cells characterized by protective anti-inflammatory T-helper 2 responses. Evaluation of responsiveness to GA has been tested mostly by clinical and neuroradiological parameters. An attempted biological approach was the analysis of interferon-gamma (IFNγ) and interleukin-4 (IL4) expression in PBMCs of MS treated patients.

Rituximab (RTX) is a monoclonal antibody directed against CD20, a B-cell surface antigen. RTX has been shown to limit relapses in RRMS and neuromyelitis optica spectrum disorders (NMOSDs). Relapses can be reduced only with repeated treatment with RTX.

Two different approaches are actually applied for re-treatment: a fixed re-treatment schedule approach (6- 9-month intervals), or a treatment-to-target approach, where treatment is based on monitoring the percentage of memory B cells in PBMCs, evaluating CD19 antigen by flow cytometry. This last approach seems to be a promising strategy to individualize RTX treatment.

The effects of anti-RTX antibodies are not completely investigated.

d. Objectives

The main aim was the evaluation of biological activity of treatment used in MS, and identification and validation of new specific markers to monitor clinical efficacy and response to each treatment to identify patients at risk for treatment failure or of serious adverse drug reactions and, therefore, are eligible for a treatment change, avoiding the cost associated with failed therapy.

IFN-β: our aim were 1) evaluation of MxA mRNA expression as marker of IFN-b biological activity in MS patients, and its biological and clinical validation ; 2) detection of Babs and Nabs by ELISA test and cytopathic assay (CPE), and CPE validation 3) correlation of Nabs and MxA levels, and clinical response; 4) set-up of Nabs titration service in collaboration with Biogen-Dompé for Italian Neurologies; 5) investigation of IFNAR regulation during IFN-β therapy and its correlation with the biologic responsiveness to IFN-β.

NTZ: our aims were 1) anti-NTZ antibodies detection (ELISA test, Biogen), and set-up of antibody detection service in collaboration with Biogen-Dompé for Italian Neurologies; 2) L-selectin evaluation on T CD4+ lymphocytes by flow cytometric analysis.

GA: our aim was to categorize GA-treated patients based on GA biological activity.

RTX: our aim was the evaluation of CD19 mRNA expression on B lymphocytes.

e. Results

IFN-β.

Among all IFN-b biological activity tested biomarkers, mRNA MxA expression in PBMC was chosen as the best one for its characteristics (Gilli, 2006). Low levels of mRNA MxA are expressed in untreated MS patient and in healthy controls. Injection of INF-b significantly increases mRNA MxA expression within 3 h, with peak levels at 12 h, with more than 10-fold increase [Gilli 2005].

MxA correlates with the clinical course of MS and have a prognostic value, as shown by the correlation with relapse-free survival and with the time till the first relapse in patient with or without MxA increase [Malucchi, 2008]

Our center is the once in Italy deputed to detect NABs in Italy since 2002. Methods used for Nabs titration are CPE, MxA Protein assay, MxA gene expression assay [Bertolotto 2007]. We collaborated with NABINMS project to the validation of CPE assay, approved by The World Health Organization**.**

Nabs positivity peaks after 6–12 months of treatment. BAbs development, precedes the appearance of Nabs. Nab-positive patients lack of IFN-b clinical efficacy [Bertolotto, 2015].

A strong correlation between the presence of Nabs and the absence of biological activity was demonstrated: MxA expression was higher in Nab-negative than in persistently Nab-positive

patients; in particular, patients with Nabs titres higher than 100 TRU are likely to experience loss of biological activity of IFN-b. Patients with titres between 5 and 100 are in a ‘‘grey area’’ [Malucchi 2011].
Since 2005, Biogen-Dompé offered a free service in Italy for NABs titration. The prevalence of NABs positive samples is 23%, slightly higher than reported in literature, probably due to sample selection applied by clinicians; Nabs positive samples >100 TRU were 12%.
In the last 10 years, Nabs-titration service should have led to a best economic allocation for SSN equal to 20 million euros, based on the number of non-responders patients with a titer >100 TRU for witch a treatment change was recommended.
Data obtained in our laboratory suggest that mechanisms other than Nabs could abolish biological activity, as regulation of IFNAR expression [Gilli 2007, 2008].

NTZ.

Our center is the once in Italy deputed to detect anti-NTZ antibodies in Italy since 2008: Biogen provided an ELISA test and validated with a rigorous procedure our lab to perform this assay; blinded samples were shipped every year to monitor our assay performance and accuracy.
Since 2008, Biogen-Dompé offered a free service in Italy for the evaluation of anti-NTZ antibodies. The prevalence of anti-NTZ antibodies persistent positive samples is 5%. In 7 years, NTZ-titration service should have led to a best economic allocation for SSN equal to 12 million euros, based on the number of persistent positive patients for witch a treatment change was recommended.
To validate the correlation between CD62LCD4+ T cells low expression and PML development in NTZ-treated patients, a flow cytometric analysis on PBMC was performed, confirming the reduction of the number of positive cells. The low level of CD62L found in a clinically asymptomatic PML patient strengthens its potential usefulness as a biomarker of high PML risk in NTZ-treated patients [Spadaro, 2015].

GA.

A pre-amplification Real Time PCR assay was used for measuring GA-induced IFNγ and IL4 mRNA responses in PBMCs from patients and healthy controls, showing that GA-treated patients with higher levels of cytokines have a better outcome [Gilli, 2012].

RTX.

A pre-amplification RT-PCR blood for CD19 mRNA quantification was set and compared with currently used flow cytometry (FC), to personalize RTX re-treatment in NMOSDs patients. Our approach showed major sensitivity: all samples positive at FC were confirmed also in RT-PCR, but CD19 mRNA was higher also in 8/39 samples resulted negative by FC, and CD19 RNA preceded the FC positivity in 7/8 samples by 1–3 months [Marnetto, 2014]**.**

f. Advancement in the field

Our research activity in treatment-response biomarker field is ongoing aiming at identification and validation of better and more sensitive and specific markers for each approved treatment for MS patients.
IFN-β. Nabs and MxA evaluation are now used in practical routine for IFN-β patients management.
RTX. A validation of our results obtained in RT-PCR is in progress in a great cohort of NMOSD samples to confirm the data and to evaluate a correlation between CD19mRNA increase and clinical relapse (see Future projects).
We are evaluating anti-RTX antibodies quantification and free circulating RTX dosage to personalize RTX re-treatment in NMOSDs patients. (see Future projects).

Immunopathogenesis

Summary

The rate of clinical signs in MS patients declines during pregnancy, and increases during the first three months post-partum. However, the biological mechanisms underlying the pregnancy-related decrease in disease activity are poorly understood. We seek to determine the factors

modulated during pregnancy in MS, which could form the basis for the development of new treatments for MS.

a. Background

MS is the most common autoimmune disease of central nervous system, characterized by chronic inflammation with immune cells infiltration, demyelination and axonal damage. Demyelination is the results of several mechanisms, including immune mediate effects by inflammation cytokines, macrophages or T-cells, as well as an antibody-mediated damage to the myelin and complement-mediated injury. The disease courses encompass a multitude of neurological defects and can be classified into 3 main sub-types: relapsing remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). The cause of the disease is not known, but epidemiological and familial studies support the consensus view that MS is a multifactorial disease with overlapping influences from genetics, the environment and epigenetic signatures, that together result in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS. Concerning genetic risk factors, intensive search reveals linkage mainly with the HLA locus, which accounts for less than 50% of the total genetic basis of the disease. New genetic approaches such as genome-wide association studies (GWASs) long with genome project data and larger datasets have recently identified new MS susceptibility loci within and outside the HLA region, and additional genes continue to be identified and validated.

b. Rationale

Pregnancy represents a physiological transitory state of immune tolerance to avoid the rejection of the fetus, and is frequently associated with reduced activity of autoimmune diseases, including MS.

To establish and maintain a successful pregnancy, selective immune tolerance and immunomodulation is required. No general immunosuppression takes place in the maternal immune system; on the contrary, there is an increased pro-inflammatory burden derived from the innate immune system, especially during the third trimester. The immunomodulatory mechanisms contributing to the control of harmful autoimmune activity are thus directed probably towards the adaptive immune system. Immunoregulatory factors specific for pregnancy include pregnancy-specific serum proteins and tolerance promoting signaling molecules. In addition, placenta-derived hormones, prolactin, estrogens and progesterone can directly affect the function of the immune cells, which express estrogen receptors. Other putative beneficial mechanisms in the control of autoimmune diseases during pregnancy include a shift from a prevailing Th1 response to a Th2-type response and an increase in the number of functional regulatory T cells. As a whole, however, little is still known about the molecular mechanisms behind the adaptive molecular processes of pregnancy in MS. Development of high-throughput technologies, such as microarrays, has made it possible to analyze physiological pathways and entire networks in biological processes to get better insights into the disease pathogenesis. Application of these technologies in MS during pregnancy will provide new information of the biological mechanisms of pregnancy related decrease of disease activity. This will ultimately lead to better understanding of the pathogenesis of MS and may provide basis for the development of novel therapeutic strategies.

c. Objectives

Owing to the presumed weak influence of single mechanisms on both disease susceptibility and maternal immunological adaptations, we proposed a large-scale analysis of transcriptional changes during pregnancy in MS, to identify genes potentially contributing to the reduced disease activity. In particular we planned to compare gene expression profiles in peripheral blood mononuclear cells (PBMCs) derived from MS patients and age-matched healthy controls (HC), before, during and after pregnancy, in order to identify genes whose expression altered in non-pregnant patients is reverted to normal during gestation. Subsequently we aimed at deepening our knowledge on the role of the most relevant genes identified and the causes of

their deregulation in MS before pregnancy. In this context our work focused on the following specific aims:
1. Study the influence of genetic mechanisms and hormonal factors on gene expression regulation;
2. Unveil specific cell type mainly involved in gene expression modulation;
3. Investigate the role of the putative genes in the appropriate murine model of MS;
4. Explore potential common pathogenic mechanisms shared by different autoimmune and neurodegenerative pathologies.

d. Results

In order to get better insight into the biological mechanisms underlying the pregnancy-related decrease in MS disease activity, we analyzed by microarray technology the gene expression profiles of PBMCs from MS patients and HC followed during their pregnancy cycle. Expression of 347 genes was found to be altered in PBMCs of non-pregnant MS patients with respect to HC, while complementary changes in expression occurring during pregnancy reverted this imbalance particularly for seven inflammation-related transcripts, namely SOCS2, TNFAIP3, STAG3L1, CXCR4, POLR2J, FAM49B, and NR4A2. Notably, these specific changes in gene expression were associated with a decrease in disease activity assessed by occurrence of relapses during the pregnancy. MS specific gene dysregulation was then consolidated in another study, analyzing larger and different cohorts of subjects, i.e. men and women, clinically active and stable patients, untreated and treated RRMS patients. The analysis confirmed the dysregulation of the seven target genes in MS patients respect to HC, also highlighting that this difference is not gender-specific. On these grounds, it is likely that this specific pattern of gene expression is associated to the pathogenesis of MS. Moreover, we observed that gene expression levels of TNFAIP3 and NR4A2, two potent NF-kB pathway inhibitors, correlate with a worse disease course. Therefore, we next explored the involvement of these most promising genes in the pathogenesis of MS.
To investigate the causes of TNFAIP3 and NR4A2 deregulation, we evaluated the influence of pregnancy-related hormones on whole blood gene expression levels, demonstrating that sex hormonal factors are able to regulate the expression of these target genes, although in different way between MS patients and HC.
In addition, since TNFAIP3 is genetically associated to MS, we evaluated possible genetic mechanisms testing whether its specific allelic variants may cause reduced transcript levels in MS patients, leading to decreased anti-inflammatory activity and influencing the development of the disease in individual bearing these variants. Genotype and gene expression data suggested that SNPs in TNFAIP3 genomic region and particularly in the promoter have a role in the TNFAIP3 gene expression regulation, even if others mechanism are probably involved.
Further researches performed in our laboratory, aimed at identifying particular cell subpopulations having a pivotal role in the unbalanced expression of TNFAIP3 and NR4A2, highlighted that the deregulated expression of both genes in MS patients is mainly due to the monocyte cell population. This is an important achievement, since to date the relative contribution of these genes in different human cell types to the pathophysiology of the disease is still unknown.
To better investigate the involvement of the target genes in MS pathogenesis we took advantage of the EAE (Experimental autoimmune encephalomyelitis), the best MS murine model.
Thanks to a collaboration with Prof. Conneely (Baylor College Medicine, Houston, USA) we obtained the NR4A2 knock-out (KO) mouse model that we immunized with MOG_{35-55} to induce chronic EAE. As results we observed an earlier disease onset and an increase of infiltrated cells in spinal cord of NR4A2-KO mice compared to their wild-type littermates.
In agreement, we demonstrated that the preventive administration of a potent activator of the NR4A2 signaling (isoxazolo-pyridinone7e; IP7e) delayed the EAE onset and reduced the incidence and the severity of the disease, down-regulating NF-kB downstream genes and improving neuroinflammatory pathological signs. Conversely, EAE course was not influenced by the therapeutic IP7e administration.

Finally, we evaluated the TNFAIP3 and NR4A2 gene expression levels in other autoimmune disorders commonly associated with MS and neurological diseases. We showed that both genes are down-regulated in Parkinson's disease, while experiments on Hashimoto's thyroiditis are underway.

e. Advancement in the field

On the basis of data obtained by our group we can hypothesize that the down-regulation of two important anti-inflammatory genes as TNFAIP3 and NR4A2 in MS might contribute to chronic invasive immune processes as well as participate to the development of autoimmunity, suggesting that MS arises from a defective negative feedback control of inflammation, rather than merely from an overactive pro-inflammatory reaction. This warrant further efforts to deepen the knowledge of the role of these genes in pathogenesis of MS, which could represent new therapeutic targets.

CRESM Bio-Bank

a. Summary

In chronic disease such as Multiple Sclerosis the available of biological materials is needed. The project intends collect and store different biological material from healthy controls and from selected MS patients treated with the available drugs proceeding their follow-up during time. In particular, people affected by PPMS will be included in the project.

b and c. Background and Rationale

Despite considerable investment in biological clinical research, very few laboratory results are transformed in drugs. Biological research suffers from poor reproducibility of published data, even in prestigious journals [Prinz et al., 2011], because of the lack of rigor in the collection of biological samples [Del Campo et al., 2012], the insufficient validation of the methods according to the instructions of FDA (FDA, 2001), the lack of availability of experimental protocol, and limited sharing of data [Huang and Gottardo, 2013].
In a chronic disease such as PPMS there are two further obstacles: the small number of patients makes it difficult to collect biological samples, and the patients need careful follow-ups through the collection of clinical, biological, MRI, neuro-cognitive and neurophysiological data.

d. Objectives

This project aims to address these problems by joining the activity of the Bio-bank, of the Clinical Neurobiology (CNB) Lab and of the Clinical Unit of CRESM that take care of 1800 patients with MS, of which 250 PPMS patients. In particular, to support of research projects funded by the International Progressive MS Alliance (IPMSA), the project will include:
1) Expansion of the biological bank which is already in operation at the CRESM, through the collection of biological samples (serum, plasma, CSF, urine, cells from blood and CSF for DNA and RNA,) of PPMS patients, others types of MS and various controls [Teunissen et al, 2013]. 2) The distribution of aliquots of the samples to projects funded by the IPMSA (or other institutions)
3) The researcher who receives samples from the bio-bank is committed to: i) providing the bio-bank with detailed protocols of the methods used in the research, ii) sharing raw data of his experiments with the bio-bank so that could be available for others studies.
4) Technical support from CRESM, which includes: i) co-validation of methods; ii) replication of data obtained by researchers who have used biological samples of the bio-bank, iii) implementation of educational courses for technicians/biologists on biological methods
5) Cooperation with other bio-banks: the bio-bank of CRESM will be included in the future network of bio-banks dedicated to MS research

e. Results

This project received the funds in April 2014 and, till now, in the CReSM biobank have been stored different biological materials (serum, plasma, DNA, total RNA, RNA from PBMCs and

PBMCs in DMSO) from more than 2000 blood draws of Multiple Sclerosis and Other Neurological Disease patients and from Healthy Controls.

f. Advancement in the field

The project is still ongoing: every day at least 4 blood draws are collected and stored following approved SOP of preservation of biological materials

7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do.

1) Improving therapeutic appropriateness of Multiple Sclerosis treatments using biological approaches to personalize therapy and save pharmaceutical spending.

a. Summary:

Non-responding patients may undergo irreversible disease progression and potentially severe outcomes during ineffective treatments; the overall cost of failed treatment puts tremendous pressure on public health budgets.
Approved and future therapies for MS are very expensive while the National Health Service (NHS) fund is getting slimmer every year. We propose a strategy to improve therapeutic appropriateness by using biological approaches, in particular:
1. early identification of biological non responders (NRs) to different approved treatments
2. better timing of drug administration, based on serum drug levels or specific drug biomarkers
3. study of the relationship, if any, between T-cells adhesion-molecule expression and the risk to develop serious adverse events during treatment.
Our strategy can improve the efficacy of treatment, selecting the best drug for each patient, and save, or better allocate, enormous amounts of NHS funds.

b. Background and Significance:

All drugs for MS treatment are very expensive, ranging from 7000 to 20000 €/year. As over 30000 pts are under treatment in Italy (50% of the MS population) the NHS total expense is about 400 million €/year. The development of specific Anti-Drug Antibodies (ADA) during ongoing therapy is a predictor of clinical efficacy and safety of treatment. The clinical worsening has been associated only with persistent ADA positivity. Among all different strategies to improve the therapeutic appropriateness proposed in this project, some of them are already supported by strong evidences, but still need to be refined (i.e. ADA for Interferon beta – IFNβ and Natalizumab - NAT and biological activity for IFNβ); others are emerging pharmacogenomics biomarkers (i.e. CD19 and CD27 for Rituximab – RTX; others have never been investigated: personalized dose and time of administration (NAT and RTX) and switch to other less immunogenic molecules as the new preparation of IFNβ 1a [Pegylated (PEG)-IFNβ 1a]. Moreover, the study of side effects influences the selection of treatment: L-selectin (CD62L) was recently introduced as a potential biomarker to assess individual risk to develop progressive multifocal leukoencephalopathy (PML) in MS pts under NAT treatment. The obtained results will be evaluated by a group of economists with a great expertise in pharmaco-economic studies.

c. General aim and integration with mission of the Institute

Early identification of Non-Responders to treatment is a milestone to improve appropriateness and save or better allocate a huge amount of money.
A well-known biological mechanism that causes lack of response is the development of specific and persistent Anti Drug Antibodies. Our MS Clinic is the Italian referral center for ADA against IFNβ and NAT. A new IFNβ formulation (IFNβ PEGylated) will be available this year and its immunogenicity, biological activity and cross-reactivity with old IFNβs must be investigated.
A strategy to improve appropriateness is to tailor time and dose of infusion for the single patient. This approach can be applied to NAT and Rituximab (and other anti-CD20 drugs)

that are infused at fixed schedule. Quantification of blood drug concentration and/or of specific biomarkers allows personalized treatment.
CD62L is a potential biomarker for the individual risk of progressive multifocal leukoencephalopathy (PML) in MS pts under NAT treatment. If this is confirmed CD62L will allow to reduce the risk of a very disabling and expensive adverse event.
Pharmaco-economic evaluation is an established tool to measure the real impact of the proposed biological strategies**.**

d. Specific objectives and strategies:

Aim 1:
Early detection of non-responders. Detection and titration of Binding/Neutralizing Antibodies (BAbs/NAbs) against NAT and RTX will be performed. Cross reactivity between NAbs against IFNβ and PEG-IFNβ and between different anti-CD20 monoclonal will be evaluated. The biological activity of PEG-IFNβ will be tested by analyzing mRNA expression of a specific biomarker. Biological data will be correlated with the responsiveness to the treatment measured by EDSS, MRI and clinical activity. An economic analysis will be performed to evaluate the therapeutic appropriateness.

Aim 2:
Optimization of dose and time of infusion of NAT and RTX. NAT and RTX responders are defined as patients without clinical activity and without new MRI lesions. NAT and RTX serum concentration in samples stored in our bio-bank will be correlated with responsiveness. The frequency of RTX infusion will be decided according to the number of circulating CD19+ and CD27+ B cells detected by FACS and by a new molecular (RT-PCR) approach set up in our center. This letter method could be used also for the new anti-CD20 drugs. The cost of traditional infusions will be compared with the optimized procedures.

Aim 3:
To analyze L-selectin expression in T-cells to detect the risk to develop Progressive Multifocal Leukoencephalopthy (PML). In fact, the major adverse event of NAT is PML that involves about 1 out of 1000 patients. The risk of PML limits the use of the highly effective NAT and PML early detection and management are very expensive. Recently, Schwab et al. (Neurology 2013) investigated the influence of NAT on adhesion molecules in T-cells and found a very low expression of L-selectin in patients who will develop PML.

e. Unique features of the project research:

The innovative aspect of the project is the implementation of biological parameters (ADA, Biological activity, Biological markers) in flow-chart of MS management that nowadays is mainly based on clinical and MRI evaluations. This new approach will allow better personalization of MS treatment and better use of economic resources.

2) EVALUATION OF BIOLOGICAL ACTIVITY BY RNA-SEQUENCING IN PEG-INTERFERON BETA 1a AND INTERFERON BETA 1a IM TREATED MULTIPLE SCLEROSIS PATIENTS AND COMPARISON OF GENETIC EXPRESSION BETWEEN DIFFERENT CELLULAR POPULATIONS

a. Summary:

The study intends to compare the Avonex and Plegridy biological activity in RRMS patients before the start of treatment and after at least 3 months of therapy. Blood draws will be collected at 7 different time points after the drug administration and a Next Generation Sequencing Analysis will be performed on PBMCs. For each patient, the time point showing the highest level of MxA gene expression will be selected for RNA-Seq in Tcells and

Monocytes. If the comparison will show differences in T-cells and monocytes gene expression, the level of expression of IFNAR1 on surface of the two cell types will be determined to identify or rule out this as a potential reason for differences. Moreover, the evaluation of serum neopterin concentration will be evaluated as pharmacological biomarker.

b. Background and Significance:

Several products containing Interferon Beta (IFNβ) were already approved for multiple sclerosis (MS) treatment: the currently available interferon beta therapies require either intramuscular or subcutaneous injections, administered once a week to as many as 3 to 4 times a week. In Plegridy, pegylation protects against enzymatic degradation and other clearance mechanisms and therefore prolongs the half-life compared to unmodified substances. Pegylation can be considered a well-established modification to reduce the frequency of dosing while maintaining safety and efficacy of an active substance.

Plegridy is interferon beta-1a conjugated to a single, linear 20 kDa methoxy poly(ethyleneglycol) molecule at the alpha-amino group of the N-terminal amino acid residue. Interferons are a family of naturally occurring proteins that are induced by cells in response to biological and chemical stimuli, and mediate numerous cellular responses that have been classified as antiviral, antiproliferative, and immunomodulatory in nature. The pharmacological properties of Plegridy are consistent with those of interferon beta-1a and are believed to be mediated by the protein portion of the molecule. Pharmacodynamic responses were evaluated by measuring the induction of interferon-responsive genes including those encoding 2′,5′-oligoadenylate synthetase (2′,5′-OAS), myxovirus resistance protein A (MxA), and several chemokines and cytokines, as well as neopterin (D-erythro-1, 2, 3,-trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP-cyclohydrolase I. Gene induction in healthy human subjects was greater in terms of peak level and exposure (area under the effect curve) for Plegridy compared to non-pegylated interferon beta-1a (IM) when both were given at the same dose by activity (6 MIU). The duration of this response was sustained and prolonged for Plegridy, with elevations detected up to 15 days compared to 4 days for non-pegylated interferon beta-1a. Increased concentrations of neopterin were observed in both healthy subjects and multiple sclerosis patients treated with Plegridy, with a sustained and prolonged elevation over 10 days compared to 5 days observed for non-pegylated interferon beta-1a. Neopterin concentrations return to baseline after the two week dosing interval

ADVANCE trial showed that, for patients with RRMS, Plegridy (125 µg), administered every 2 weeks, significantly reduced annualized relapse rate at 48 weeks, relapses and the risk of disability progression over 48 weeks, the number of T2 lesions at 48 weeks, and several tertiary MRI measures (including smaller and fewer gadolinium-enhancing lesions), compared with placebo.

The exact mechanism of action of interferon beta in MS is not completely known. To better understand the mechanism of action of a drug it is necessary to study its biological activity. Biological activity of a drug includes the total effects determined by the interaction of the molecule with its target receptor: a drug without biological activity is not clinical effective. The measurement of IFN β biological activity in every single patient can allow the identification of the subset of patients who are non-responsive to the drug. Till now, the biological activity of IFN β has been studied by measuring a number of Interferon Stimulated Genes (ISGs) including MxA at protein or mRNA level, β2-microglobulin, oligo-adenylate-synthetase, TNF related apoptosis inducing ligand (TRAIL), viperin, IFI27, CCL2 and CXCL10. The mechanism of action of Plegridy is considered to be the same than IFN β. Plegridy binds the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression; nevertheless, nor the ADVANCE trial nor other studies on Plegridy reported data about the biological activity in MS patients.

Gene expression profiling of peripheral blood samples, obtained from healthy human subjects in a phase 1 study [105HV101], showed the induction of interferon responsive genes both by IFNβ-1a and Plegridy, albeit with a temporal difference reflecting the slower

absorption time of the pegylated form. Plegridy showed a longer elimination half-life (t1/2), reduced clearance, and greater exposure than the unmodified protein. These observations suggest that the protracted IFNAR stimulation could influence both pharmacokinetics and pharmacodynamics of the drug, maybe inducing different degree of gene expression, but currently consistent data about the pharmacodynamics of Plegridy in MS patients are still lacking.

c. General aim and integration with mission of the Institute (up to 1000 characters)

This study is a pilot study that aims to evaluate biological activity in two groups of MS patients treated with Plegridy and Avonex respectively at different time points using the NGS technology. Data obtained from this pilot study can help to better understand IFNβ pharmacodynamic, which cellular subset is most influenced by treatment and the efficacy of treatment for every single patient

d. Specific objectives and strategies:

The main objective of the study is:
The comparison of biological activity between Plegridy and Avonex (Fig. 1)
Study population: 10 patients treated for at least 3 months with Plegridy and 10 patients treated for at least 3 months with Avonex
8 blood draws each patient will be done before and during Plegridy/Avonex treatment
Cellular population: PBMCs (Fig. 2)

The secondary objectives are:
The comparison of biological activity between Plegridy and Avonex (Fig. 2) in subsets of cellular populations (T cells and Monocytes): for each patient, the time point showing the highest level of MxA gene expression will be selected for RNA-Seq, total 40 samples (2/patient)
The evaluation of neopterin serum concentration of all collected samples as pharmacological biomarker
The identification of biomarker(s) for the evaluation of biological activity and the treatment adherence. The identified biomarker(s) will be used in every day clinical practice and will be selected by the NGS analysis

e. Unique features of the project research:

The unique feature of this study is the analysis of whole transcriptome of patients at 8 different time points before and during Avonex or Plegridy administration using Next Generation Sequencing technology

f. Methodology:

RNAseq data generation will be done using the TruSeq RNA Access Kit, which enables gene expression studies by focusing on the coding region of RNA. Furthermore, the TruSeq RNA Access Kit requires less input RNA and fewer reads, increasing the number of samples per run for more cost-effective transcriptome analysis. The kit includes > 425,000 probes, each constructed against the NCBI37/hg19 reference genome, covering 98.3% of the RefSeq exome. The probe set is designed to capture > 210,000 targets, spanning 21,415 genes of interest. Prof. Calogero lab has already experience in preparing libraries with a variety of different kits as well as the access kit. Libraries will be sent to external core lab for sequencing. Sequencing data, i.e. fastq files, will be then used for the bioinformatics analysis.

3) ANTI-POTASSIUM CHANNEL KIR4.1 ANTIBODIES IN MS: DIAGNOSTIC AND PROGNOSTIC ROLE.

a. Summary:

Biomarker research field is very active in MS. After decades of inconclusive search of pathogenic autoantigens, antibodies against the inward rectifying potassium channel KIR4.1 have been identified by Srivastava and colleagues in a substantial proportion (35-50%) of adult and pediatric MS patients by using a protein-based ELISA test. The specificity and presence of anti-KIR4.1 antibodies were not confirmed by other Authors. The conflicting results might be due to differences in the assay methodology. Since KIR4.1 expression is highly regulated in a cell dependent fashion, particular emphasis has to be paid to display the protein in the assay that reflects KIR4.1 expressed in oligodendrocytes (O-KIR4.1), the putative target of the immune response in MS. In collaboration with Prof. Hemmer we set up in our Lab the whole procedure for anti-KIR4.1 antibodies detection, and established rigorous acceptance criteria for each step. Our data showed anti-KIR4.1 antibodies positivity in 28% of MS patients and 4% of HCs. Supported by these encouraging data, and conscious that a serum autoantibody specific for MS would affect MS diagnosis, the monitoring of disease evolution, and treatment, we applied for funding to continue the research in this field.

b. Background and Significance:

In collaboration with prof. Hemmer and Dr. Srivastava, we have been working in setting up the whole procedure for KIR4.1 expression and purification, and finally ELISA test for detection of anti-KIR4.1 antibodies in our laboratory: 1. during our visit to their lab in August 2014, 20 serum samples from CRESM biobank were tested blinded for anti-KIR4.1 antibodies, showing positivity in 11/16 MS patients (all HC were negative). 2. The whole procedure from KIR4.1 expression to ELISA has been set up in our laboratory, showing for the first time that protein-ELISA for anti-O-KIR4.1 antibodies detection is reproducible, only if rigorous criteria for acceptability are applied to check the quality of each step [Marnetto et al, submitted].

Applying these acceptability criteria 7 out of 21 working sessions and 56 serum samples (24 HC and 32 MS patients) were accepted for analysis. ROC analysis set-up with specificity of 96% and 28% sensitivity showed that anti-O-KIR4.1 were detectable in 28% of MS patients and 4% of HC. Our work suggests that:

i) anti-O-KIR4.1 antibodies are detectable in a relevant percentage of MS patients, if stringent criteria of acceptability are applied.

ii) the present method is very complex and its reproducibility is hampered by variable expression of O-KIR4.1 and other not-yet identified factors

ii) Further studies are needed to develop an assay that allows easy and reliable quantification of the antibodies in serum samples.

c. General aim and integration with mission of the Institute

Improvement of daily management of MS patients, discovery and validation of MS biomarkers, opening of a new field of research in MS pathogenesis.

d. Specific objectives and strategies:

In the present project we aim to:

1. Optimize the whole procedure, leading to a more reproducible ELISA test;
2. Evaluate the diagnostic role of anti-KIR4.1 antibodies, testing a larger cohort of patients with MS, clinically isolated syndrome (CIS), and other neurological diseases (ONDs).
3. Evaluate the prognostic role of anti-KIR4.1 antibodies in patients with CIS followed for 3 years, and in patients with MS followed for 10 years (in terms of disease progression).
4. Evaluate the effect on anti-KIR4.1 antibodies of treatments that target B cells (Rituximab and Natalizumab) and of autologous hematopoietic stem cell transplantation.

e. Unique features of the project research:

The findings emerging from this project can lead to the first serological diagnostic test available for MS, and open a new research field in neuroimmunology for MS pathogenesis.

4) COMBINED ANALYSIS OF EBV AND CELLULAR GENE EXPRESSION IN CLINICALLY ISOLATED SYNDROME, RELAPSING-REMITTING AND PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS FOR THE IDENTIFICATION OF DIAGNOSTIC AND PROGNOSTIC BIOMARKERS.

a. Summary:

Because there is increasing evidence that EBV infection is strongly associated with MS and that the immune response to EBV differs qualitatively and quantitatively in MS patients compared to healthy controls, a reasonable hypothesis to test is that EBV deregulation might be implicated in the dysimmune process that damages the CNS. From this it follows that combining the study of EBV infection status with that of the host's immune system might help shed light into disease relevant virus-host interactions and identify biomarkers with predictive value.

b. Background and Significance:

Evidence that environmental factors play an important role in MS etiology has grown rapidly during the last few years. One of the leading infectious agents that has gained credibility and is being discussed as an etiological factor in MS is the ubiquitous B-lymphotropic herpesvirus EBV. Based on the available evidence linking EBV to MS, it has been proposed that MS might be considered as a rare neurological complication of a common viral infection. By using a recently established PCR methodology to investigate EBV and cellular gene expression in paired samples of CSF and peripheral blood from MS patients, this multicentre project aims at providing information that will be useful to shed light on disease relevant EBV-host interactions and, eventually, identify biomarkers useful to discriminate patient groups that show different disease characteristics or response to therapy and could benefit from early treatment with last generation antiviral drugs or B-cell depleting therapies.

c. General aim and integration with mission of the Institute

Investigating putative pathogenic mechanisms of MS, identification of prognostic biomarkers.

d. Specific objectives and strategies:

The specific tasks of this project will be:

1) To enlarge the panel of EBV and cellular transcripts analysed in the CSF and blood of the previous RRMS cohort.

2) To collect prospective data of the previous RRMS cohort that may help understand whether the CSF transcriptional profiles identified.

3) To collect CSF and PBMC samples from a larger cohort of recently diagnosed, therapy-free RRMS patients (n = 60) to confirm and expand the results on EBV and cellular gene expression obtained in the first cohort of 31 RRMS patients.

4) To analyse EBV and cellular gene expression in paired CSF and PBMC samples from therapy free, recently diagnosed PPMS (n = 20) and CIS (n = 30) patients in order to:

a) Understand whether the prevalence of EBV transcripts in CSF and/or peripheral blood differs among RRMS, PPMS and CIS patients and if different EBV infection programmes associate with similar or distinct immune signatures in the different categories.

b) Identify within the PPMS and CIS diagnostic categories transcriptional signatures that may help discriminate patient groups (i.e., more or less inflammatory PPMS clusters that may resemble distinct subgroups of RRMS patients);

c) as for RRMS patients (point 2), perform a follow-up study with serial radiological and clinical examination and PBMC collection for gene expression analysis from the recruited PPMS and CIS patients to understand how disease develops in patients who cluster together based on their transcriptional profiles.

5) Through the follow-up study understand whether EBV deregulation (viral latency disruption and/or reactivation) in PBMC is a transient or persistent feature in the minority of MS patients in which viral transcripts can be detected.

e. Unique features of the project research:

Our hypothesis is that the EBV-immune system interaction plays a key role in the development of MS and that the combined analysis of viral infection status and host's immune activation may help identify molecular biomarkers potentially useful to discriminate patient subsets with different disease course or response to therapy or to identify patients requiring specific therapies. To this end, we propose to perform a large scale gene expression analysis of paired CSF and blood samples from MS patients aiming to quantify both EBV and immune response-associated transcripts. This strategy is novel since no previous studies have assessed gene expression in paired CSF and PBMC samples from MS patients, analysed in parallel EBV transcripts to detect latent or lytic infection and cellular transcripts to capture activation of specific immune processes, and correlated the obtained transcriptional profiles with clinical and radiological evidence of disease activity and progression.

8. Letter of intent by the PI (1 page)

(In this letter the PI is invited to indicate: i) how she/he assesses him/herself in term of leadership and ability to manage his/her group ; ii) possible internal problems within his/her group and the strategies for the best solution; iii) his/her commitment in supporting the general activities of the Institute; iii) specific pitfall and difficulties to realize his/her projects; iv) ability in establishing internal and external collaborations.

i) how he assesses himself in term of leadership and ability to manage his group

The team I am leading has been created by me, step by step, during 23 years of work at AOU San Luigi; at the beginning the team was constituted by two medical students and now it includes 7 neurologists, 8 biologists, 3 lab technicians, 7 nurses, 1 neurophysiology technician, 5 secretaries, 2 psychologists. I spent a lot of time to co-ordinate, to stimulate, to support and to lead all the persons working in the Neurologia 2 – CRESM. The atmosphere of the team seems to be good as the co-operation among the components is intense. The biologists who left the team were excluded by me, with a clear explanation of the reason of the exclusion that was not a short of money, but a low level of scientific production. Other persons, in spite of an offer of higher salary for another position elsewhere, refused to leave the team.
The team is held together by a strong work ethics based on the consciousness that our work is directly dealing with the life of suffering persons; every action can have an important impact of the quality of life and choices of our more than 2000 patients.

ii)
Some scientist of the team have a permanent position and others, with the same age and experience, do not because the national health service has blocked new permanent positions in decades. I try to overcome this imbalance offering the same level of responsibility and chance to have a personal scientific project to all scientist; moreover I try to offer a competitive salary. This strategy allow all my colleagues to acquire scientific experience and independence, and to find personal fulfillment.

i) his/her commitment in supporting the general activities of the Institute;
   To support the general activity of NICO, I, and my collaborators constantly apply for national and international grants. I set up a fund raising activity, that allows NICO to receive a donation of 5 per thousand of the taxes.
   I also organized “services” such as biological tests for anti-biological antibodies that are supported by pharma-companies allowing NICO to receive overhead. All the scientific instruments I bought are available for all the scientists of NICO. I organize meetings, supported by pharma companies, at NICO, that allows NICO to have an extra-income for the utilization of the seminar room.

ii) specific pitfall and difficulties to realize his/her projects;
To be the only clinical and “not-university team” in NICO puts us in a peculiar administrative position that sometimes does not allow us to apply for University fundings. Nevertheless the very good cooperation with the other teams of NICO greatly reduces this negative impact.
The impossibility to offer a permanent position or, at least a three-year-long contract, does not allow to attract the very best.

iv) ability in establishing internal and external collaborations.
My team is an active part of the Italian network of MS centers and we are involved in several national and international clinical trials. The neurobiology lab is a world-wide recognized lab, with a specific competence in anti-biopharmaceutical antibodies, and in MS auto-antibodies (see published paper). Moreover the recent established bio-bank, partially supported by FISM (Fondazione Italiana Sclerosi Multipla), allows the team to be involved in international co-operations; for instance presently we are collaborating with the university of Munchen (prof Hemmer) and with University of yale (prof.) for the detection of MS specific auto-antibodies.

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name: **Adult neurogenesis**

1. LABORATORY DESCRIPTION – PERSONNEL:

NOTE: Since the birth of NICO (in 2010), the group **Adult Neurogenesis** was created from two independent research groups (already working and collaborating in Turin since 1994), which joined their expertise on structural plasticity and neurogenesis. Since then, the group at NICO has been organized with two PI coordinating four main, distinct but complementary, research lines.

- **Principal Investigator 1**

Paolo Peretto — Birthdate: (18 september 1963)
Associate professor — Gender: M
Nationality: Italian — Phone: 011 6706605
Email: paolo.peretto@unito.it

- **Principal Investigator 2**

Luca Bonfanti — Birthdate : (19 may 1962)
Associate professor — Gender: M
Nationality: Italian — Phone: 011 6706606
Email: luca.bonfanti@unito.it

- **Personnel**

1. First name: Silvia De Marchis — Birthdate (14/09/66)
   Degree: Associate professor — Gender: F
   Role: Senior researcher — Nationality: Italian
   Expertise: in vivo and in vitro molecular and cellular analyses

2. First name: Federico Luzzati — Birthdate (20/10/1974)
   Degree: assistant professor — Gender: M
   Role: Senior researcher — Nationality: Italian
   Expertise: in vivo morphological analyses and 3D reconstructions

3. First name: Roberta Parolisi — Birthdate (23/01/85)
   Degree: PhD student — Gender: F
   Role: researcher — Nationality: Italian
   Expertise: stem cell niche analyses and electron microscopy

4. First name: Giulia Nato — Birthdate (08/05/86)
   Degree: PhD student — Gender: F
   Role: researcher — Nationality: Italian
   Expertise: stereotaxic injections, stem/progenitor cell characterization

5. First name and surname : Sara Trova — Birthdate (25/04/89)
   Degree: PhD student — Gender: F
   Role: researcher — Nationality: Italian
   Expertise: behavioural aspects of AN in the olfactory system

6. First name: Sara Bonzano — Birthdate (22/03/87)
   Degree: PhD student — Gender: F
   Role: researcher — Nationality: Italian
   Expertise: cellular and molecular analyses of AN in the hippocampus

7. First name: Chiara La Rosa — Birthdate (01/07/88)
   Degree: PhD student — Gender: F
   Role: just starting PhD — Nationality: Italian
   Expertise: comparative analyses of AN in wild mammals

2a. PRINCIPAL INVESTIGATOR 1 (Paolo Peretto) CURRICULUM VITAE (two pages)

Education and training:
1993 - Degree in Biological Science, University of Turin, Italy.
1994 - Post degree training (Lab. of Neurobiology, Dept. of Animal and Human Biology, University of Turin, Italy and Dept. of Pharmacology, University of Basel, Switzerland).
1995 - Telethon Foundation's fellowship (Dept. of Neuroscience, University of Turin).
1998 - PhD in Neuroanatomy (Dept. of Veterinary Morphophysiology, University of Turin).
1998 - Cavalieri Ottolenghi Foundation's post-doc fellowship (Dept. of Animal and Human Biology, University of Turin).

Employment and research experience:
1999-2005: Assistant Professor (SSD, BIO06, SC, 05/B2 Anatomia Comparata e Citologia) at the Dept of Animal and Human Biology, University of Turin, Itlay.
2000 (Sept.-Dec.): Visiting Assistant Professor at the Dept. of Anatomy and Neurobiology, University of Maryland, Baltimore, USA.
2005-today: Associate Professor (SSD, BIO06, SC, 05/B2 Anatomia Comparata e Citologia) at the Dept. of Life Sciences and Systems Biology, University of Turin, Italy.

Relevant discoveries:
- Identification/characterization of the *"glial tubes"*, the structures that envelop and guide adult-born neuroblasts from the sub-ventricular zone to the olfactory bulb *(Peretto et al., 1997, Brain Res. Bull. 42, 9-21).*
- Identification/characterization of new physiologic neurogenic niches in the striatum of adult rabbit and postnatal guinea pig *(Luzzati et al., 2006, J. Neurosci. 26, 609-621; Luzzati et al., 2014, Development 141(21), 4065-75).*
- Identification/molecular characterization of local astroglial neurogenic progenitors in the injured mouse striatum *(Luzzati et al., 2011, PLOS ONE 6 (9) e25088, 1-16; Nato et al., 2015, Development 142(5):840-5)*.
- Identification/characterization of pheromonal-dependent mechanisms in the regulation of adult neurogenesis in the accessory olfactory bulb of female mice *(Oboti et al., 2009 Eur.J. Neurosci. 29(4), 679-692).*
- Identification/functional characterization of accessory olfactory bulb newborn neurons in the context of the neuroendocrine reflex known as the "bruce effect" *(Oboti et al., 2011, Front. Neurosci. 5, p. 1-14).*

Please list your grants according to the table below (last five yrs).

Starting-end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
2009-2012	National	PI	Compagnia San Paolo "Programma Neuroscienze"	"Experience-dependent modulation of adult neurogenesis in the accessory olfactory bulb of mice"	EDMAN 2008.2192	€ 70.000,00	€ 8000,00 "neurolucida system"
2013-2016	National	PI Local Unit	MIUR (PRIN)	"Analisi integrata dei processi molecolari e cellulari responabili dell'elaborazione di segnali sensoriali in condizioni normali e patologiche"	2010599KBR_010	€ 60.091,00	€ 25.000,00 (1 year stay payed at NICO)

Starting from 2014 participation to a COST Action: COST GNRH NETWORK: NEUROENDOCRINE CONTROL OF REPRODUCTION

Please list the name of PhDs you have supervised.
Claudio Giachino (XVI° cycle), Federico Luzzati (XVIII°cycle), Livio Oboti (XXII° cycle), Roberta Schellino (XXV°cycle), Giulia Nato (XXVII°cycle), Sara Trova (XXIX°cycle).

Please list your outreach activities
describe your international collaborative experiences.

- Dr. Paolo Giacobini, Jean-Pierre Aubert Research Center, School of Medicine, Lille (France) -*Interplay between adult neurogenesis and endocrine system*-
- Prof. Frank Zufall, Dept Of Physiology, University of Saarland School of Medicine, Homburg (Germany) -*Role of pheromones in the regulation of adult neurogenesis*-
- Dr. Parlato Rosanna, German Cancer Research Center (DKFZ), Heidelberg (Germany) –*Adult neurogenesis in neurodegenerative models*-
- Prof. Jeroen Pasterkamp, University Medical Center, Utrecht, The Netherlands – *Analysis of pheromone dependent reproductive behaviour in Sema 7A KO mice*
- Dr. Claudio Giachino, Dept. of Molecular Embryology, Max Planck Institute of Immunobiology, Freiburg (Germany) – *Molecular regulation of adult neurogenesis*-
- Dr. Livio Oboti, Children's National Health System, Center for Neuroscience Research, Washington, DC, (USA) – *Adult neurogenesis in the olfactory bulb*

- **Invited talks.**

2015-DiSFeBmeetsNICO, Milano- The interplay between reproductive-social stimuli and adult olfactory bulb neurogenesis;
2014- 75° Congresso UZI, Bari (Italy): the interplay between pheromones adult neurogenesis and reproduction;
2013- XV Congress SINS, Roma (Italy): Adult neurogenesis as a physiological mechanism to recognize mate pheromones in mice;
2009- XIX Congress ECRO, Cagliari (Italy): Integration and survival of newly-formed neurons in the AOB of adult mice;
2009- 9e Colloque Sociètè des Neurosciences, Bordeaux (France): Neurogenesis in the striatum of the adult mammalian brain;

- Editorial duties

In the Editorial Board of International journals:
Frontiers in Neurogenesis (Frontiers journal series, CH)
Guest Editor for Special Issues:
Adult neurogenesis twenty years later: physiological function versus brain repair (2014) Front. Neurosci. (with L. Bonfanti)

Please list your organizational activities:

- Speakers invited (a member of our group - S. De Marchis - is charged of this task; see below)

- Workshops, Schools or Conferences organized

h index: 28 Total citations: 2435 (source: ISI WOS)

2b. PRINCIPAL INVESTIGATOR 2 (Luca Bonfanti) CURRICULUM VITAE (two pages)

Education and training:

1987. Doctor in Veterinary Medicine cum laude, University of Turin.
1992. PhD in Veterinary Functional Neuroanatomy.
1993. Post-doctoral scholarship from the University of Turin (research in neuroscience at the Dipartimento di Morfofisiologia Veterinaria).

Employment and research experience:

1991. Two year stage at INSERM Unity 176 and "Laboratoire de Neuroendocrinologie Morphofonctionnelle" , University of Bordeaux II. STRUCTURAL PLASTICITY
1992. "Elba International Neuroscience Program" (Isola d'Elba)
1993. Stage at INSERM Unity 378 (Bordeaux), within a CNR/INSERM partnership. PSA-NCAM distribution in the mammalian CNS
1994. Assistant Professor (V30A group, then VET01) at the Dip. di Morfofisiologia Veterinaria, University of Turin. ADULT NEUROGENESIS AND STEM CELL NICHES
2000-today. Associate Professor (VET01) of Anatomy of the Domestic Animals.

Relevant discoveries:

- Distribution of PSA-NCAM in the mammalian brain and its role in AN
- Structural organization of the SVZ stem cell niche and rostral migratory stream; molecular and cellular aspects of SVZ niche
- Identification and characterization of novel neurogenic sites/processes in the brain parenchyma of different mammals (rabbit parenchymal chains; rabbit cerebellum)
- Identification and characterization of a novel, newly generated-nondividing glial cell subpopulation (mMap5 cells)
- Evidence that SVZ is not neurogenic in dolphins, and it contains differentiated neurons (ongoing project)

Please list your grants according to the table below (last five yrs).

Starting - end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
Jan 2015 - Sept 2016	National	Coordinator	Fondazione CRT	"Fonti endogene di cellule staminali neurali per la riparazione del sistema nervoso"	41436 (RF=2014 -1161)	€ 25.000	€ 2.238
2009-2011	International	Scientific supervisor (researcher: Giovanna Ponti)	IOF-Marie Curie actions	NEURALSTEMCELL IMAGING	FP7-PEOPLE-2007-4-1-IOF	€ 230.668 (to the researcher mobility)	(2 years stay payed at NICO)

Please list the name of PhDs you have supervised.

Giovanna Ponti (ending 2010); Maria Armentano (ending 2011); Paola Crociara (ending Dec 31, 2013); Roberta Parolisi (ending Dec 31, 2015); Chiara La Rosa (starting Oct 1, 2015)

Please list honours, prizes or awards received, if applicable.

- Invited professor at NorthEastern University, Dept of Biology; Boston, USA (two months stay for teaching Stem Cell Biology, 2011).

Please list your outreach activities

- ***describe your international collaborative experiences***.
  - *Arturo Alvarez-Buylla* (UCSF Neurological Surgery faculty, San Francisco, California, USA) STEM CELL NICHES
  - *Günther K.H. Zupanc* (Department of Biology, Northeastern University, Boston, USA) COMPARATIVE NEUROGENESIS.

- *Stefano Pluchino, Gianvito Martino* (Department of Clinical Neurosciences, University of Cambridge, UK) STEM CELLS AND BRAIN REGENERATION.
- *Juan Nacher* (Universitat de Valencia, Neurobiology, Cell Biology, Spain) PIRIFORM CORTEX IMMATURE NEURONS.
- *Irmgard Amrein, Hans P. Lipp* (University of Zurich, Switzerland) ADULT NEUROGENESIS IN WILD ANIMALS

- ***Invited talks***

- Postnatal and adult neurogenesis in aquatic mammals devoid of olfaction. *The Role of Adult Neurogenesis in Plasticity: Evolutionary Insights.* JB Johnston club, Karger workshop, Chicago, USA, 2015
- Adult neurogenesis in aquatic mammals devoid of olfaction. *Adult neurogenesis: evolution, regulation and function*, Dresda 6-8 may, 2015
- Ruolo potenziale delle cellule staminali cerebrali nelle malattie neurodegenerative. Convegno: *Invecchiamento di successo: un approccio multidisciplinare*. Alba, 2013
- La ricerca sulla riparazione del sistema nervoso: panorama attuale e prospettive. *XVI Giornata Nazionale Trauma Cranico*, Torino, 2013
- Il sistema nervoso e le sue potenzialità di rinnovare i costituenti cellulari. Meeting: *Età, Abilità e Apprendimento,* Torino, 2010.
- Evolutionary, anatomical and molecular constraints to therapeutically-aimed modulation of adult neurogenesis. VI SIF Symposium:*The pharmacological modulation of adult neural stem/progenitor cells.* Novara, 2010.
- Adult neurogenesis in mammals, with and without germinal layers. *International Neuroscience Winter Conference,* Solden, Austria (2009)
- Glia-independent chains of neuroblasts in the adult brain parenchyma*. F.E.N.S. Forum*, *Simposium: Understanding the different steps of adult neurogenesis*; Lisbon, 2004).
- Neurogenesis in Lagomorphs: from olfactory system to cerebellum. *Inserm U 862; Université VictorSegalen-Bordeaux II,* Bordeaux (2008)
- Structural plasticity in the rabbit brain and cerebellum: with and without germinal layers. *Department of Physiology, Anatomy and Genetics, University of Oxford*, UK (2008)

- **Editorial duties**

In the Editorial Board of international journals:
- *Frontiers in Neuroscience, Neurogenesis* (Frontiers journal series, CH), as Editor-in-Chief
- *Neurogenesis* (Taylor & Francis, USA), as Associate Editor

International Book Editing:
- Bonfanti L. (2013) *Neural stem cells: new perspectives*, INTECH PUBLISHER, Rijeka, pp. 420.

Guest Editor for Special Issues:
- Neural stem cell niches and parenchymal progenitors (2010) *Arch. It. Biol*. (with A. Mackay-Sim)
- Towards a comparative understanding of adult neurogenesis (2011) *Eur. J. Neurosci*. (with G.H. Zupanc)
- Adult neurogenesis twenty years later: physiological function versus brain repair (2014) *Front. Neurosci*. (with P. Peretto)

Please list your organizational activities:

- Speakers invited: in our group, S. De Marchis is charged of this task (see below)
- Workshops, Schools or Conferences organized (each year, since 2010: organization of *UNISTEM day* in Turin - National event on research, science and stem cells, involving university researchers and students of the secondary schools)

h index: 27 Total citations: 2921 (source: Scopus)

3a. PI's PUBBLICATIONS 1 (P. Peretto):

Nato, G., Caramello, A., Trova, S., Avataneo, V., Rolando, C., Taylor, V., Buffo, A., ***Peretto, P.**, Luzzati, F. (2015). Striatal astrocytes produce neuroblasts in an excitotoxic model of huntington's disease. *Development,* 142(5):840-5.
IF= 6.3; R= 4/41 (DEVELOPMENTAL BIOLOGY); Times cited= 2
*(Co-last Authorship and Correspondence)

Farinetti, A., Tomasi, S., Foglio, B., Ferraris, A., Ponti, G., Gotti, S., ***Peretto, P.**, Panzica, GC. (2015). Testosterone and estradiol differentially affect cell proliferation in the subventricular zone of young adult gonadectomized male and female rats. *Neuroscience,* 12:286:162-70.
IF= 3.3; R= 96/252 (NEUROSCIENCES) ; Times cited= 1
*(Co-last Authorship)

Peretto, P., Bonfanti, L. (2015). Adult neurogenesis 20 years later: physiological function vs. Brain repair. *Front Neurosci.*, 6.9-71.
IF= 3.7; R= 82/252 (NEUROSCIENCES) INSERITO VALORE DEL 2014, Time cited= 0

Luzzati, F., Nato, G., Oboti, L., Vigna, E., Rolando, C., Armentano M, Bonfanti L, Fasolo A, **Peretto P** (2014). Quiescent neuronal progenitors are activated in the juvenile guinea pig lateral striatum and give rise to transient neurons. *Development* 141: 4065-4075.
IF= 6,3; R= 4/41 (DEVELOPMENTAL BIOLOGY); Times cited= 3

Oboti, L., **Peretto, P** (2014). How neurogenesis finds its place in a hardwired sensory system. *Front. Neurosci.,* 8:102.
IF= 3.7; R= 82/252 (NEUROSCIENCES) Times cited =3

Bonzano, S., Bovetti, S., Fasolo, A., **Peretto, P.**, De Marchis, S. (2014). Odour enrichment increases adult-born dopaminergic neurons in the mouse olfactory bulb. *Eur J Neurosci.,* 40(10):3450-7.
IF= 3.2; R= 108/252 (NEUROSCIENCES); Times cited= 1

Peretto, P., Schellino, R., De Marchis, S., Fasolo, A. (2014). The interplay between reproductive social stimuli and adult olfactory bulb neurogenesis. *Neural Plasticity,* 497657.
IF= 3.6; R= 87/252 (NEUROSCIENCES) Times cited= 0

Peretto, P., Bonfanti, L. (2014). Major unsolved points in adult neurogenesis: doors open on a translational future? *Front. Neurosci.,* 8: 154.
IF= 3.6; R= 82/252 (NEUROSCIENCES); Times cited= 2

Bini, F., Frati, A., Garcia-Gil, M., Battistini, C., Granado, M., Martinesi, M., Mainardi, M., Vannini, E., Luzzati, F., Caleo, M., **Peretto, P.**, Gomez-Muñoz, A., Meacci, E. (2012). New signalling pathway involved in the anti-proliferative action of vitamin D(3) and its analogues in human neuroblastoma cells. A role for ceramide kinase. *Neuropharmacology,* 63(4):524-537.
IF= 4.1; R= 66/252 (NEUROSCIENCES); Times cited= 6

Bonfanti, L., **Peretto, P.** (2012). The missing chain. *Front. Neurosci.,* 6: 1.
IF= 3,2; R= 82/252 (NEUROSCIENCES); Times cited= 0

Luzzati, F., Fasolo, A., **Peretto, P.** (2011). Combining confocal laser scanning microscopy with serial section reconstruction in the study of adult neurogenesis. *Front. Neurosci.,* 5:1-14.
IF= 3.7; R= 82/252 (NEUROSCIENCES); Times cited= 8

Oboti, L., Schellino, R., Giachino, C., Chamero, P., Pyrski, M., Leinders-Zufall, T., Zufall, F., Fasolo, A., **Peretto, P.** (2011). Newborn interneurons in the accessory olfactory bulb promote mate recognition in female mice. *Front. Neurosci.,* 5:1-14.
IF= 3.7; R= 82/252 (NEUROSCIENCES); Times cited= 23

Luzzati, F., De Marchis, S., Parlato, R., Gribaudo, S., Gunther, S., Fasolo, A., **Peretto, P.** (2011). New striatal neurons in a mouse model of progressive striatal degeneration are generated in both the subventricular zone and the striatal parechyma. *PLOS ONE*, 6(9),e25088:1-16.
IF= 4.1; R= 8/55 (MULTIDISCILINARY SCIENCES); Times cited= 17

Oboti, L., **Peretto, P**., De Marchis, S., Fasolo, A. (2011). From chemical neuroanatomy to an understanding of the olfactory system. *Eur. J. Histochem*., 55:e35:194-199.
IF= 1.7, R= 145/181 (CELL BIOLOGY); Times cited= 3

Bonfanti, L., **Peretto, P.** (2011). Adult neurogenesis in mammals: A theme with many variations. *Eur. J. Neurosci*., 34:930-950.
IF= 3,2; R= 84/244 (NEUROSCIENCES); Times cited= 64

3b. PI's PUBBLICATIONS 2 (L. Bonfanti):

Parolisi, R., Peruffo, A., Messina, S., Panin, M., Montelli, S., Giurisato, M., Cozzi, B., **Bonfanti, L.** (2015). Forebrain neuroanatomy of the neonatal and juvenile dolphin (*T. truncatus and S. coeruloalba*). *Front. Neuroanat*. 9: 140.
IF= 3,5; R= 3/20 (ANATOMY & MORPHOLOGY); Times cited= 0

Feliciano, D.M., Bordey, A., **Bonfanti, L.** (2015). Noncanonical sites of adult neurogenesis in the mammalian brain. *Cold Spring Harb. Perspect. Biol.* 7(10) pii: a018846
IF= 8,6; R= 24/184 (CELL BIOLOGY); Times cited= 0

Lattanzi, W., Parolisi, R., Barba, M., **Bonfanti, L.** (2015). Osteogenic and neurogenic stem cells in their own place: unraveling differences and similarities between niches. *Front. Cell. Neurosci*. 9:455.
IF= 4,3; R= 55/252 (NEUROSCIENCES); Times cited= 0

Nacher, J., **Bonfanti, L.** (2015). New neurons from old beliefs in the adult piriform cortex? *Front. Neuroanat*. 9: 62.
IF= 3,5; R= 3/20 (ANATOMY & MORPHOLOGY); Times cited= 1

Luzzati, F., Nato, G., Oboti, L., Vigna, E., Rolando, C., Armentano, M., **Bonfanti, L.**, Fasolo, A., Peretto, P. (2014). Quiescent neuronal progenitors are activated in the juvenile guinea pig lateral striatum and give rise to transient neurons. *Development* 141: 4065-4075.
IF: 6,3; R=4/41 (DEVELOPMENTAL BIOLOGY); Times cited= 3

Peretto, P., **Bonfanti, L.** (2014). Major unsolved points in adult neurogenesis: doors open on a translational future? *Front. Neurosci*. 8: 154.
IF= 3,7; R= 81/252 (NEUROSCIENCES); Times cited= 2

Cattaneo, E., **Bonfanti, L.** (2014). Therapeutic potential of neural stem cells: greater in people's perception than in their brains? *Front. Neurosci.* 8:79.
IF= 3,7; R= 81/252 (NEUROSCIENCES); Times cited= 3

Kreiner, G., Bierhoff, H., Armentano, M., Rodriguez-Parkitna, J., Sowodniok, K., Naranjo, J.R., **Bonfanti, L.**, Liss, B., Schütz, G., Grummt, I., Parlato, R. (2013) A neuroprotective phase precedes striatal degeneration upon nucleolar stress. *Cell Death Differ*. 20: 1455-1464.
IF= 8,2; R= 25/291 (BIOCHEMISTRY AND MOLECULAR BIOLOGY); Times cited= 17

Crociara, P., Parolisi, R., Conte, D., Fumagalli, M., **Bonfanti, L.** (2013). Cellular and molecular characterization of multipolar Map5-expressing cells: a subset of newly generated, stage-specific parenchymal cells in the mammalian central nervous system. *Plos ONE* 8: 1-18.
IF= 3,5; R= 8/55 (MULTIDISCIPLINARY SCIENCES); Times cited= 2

Ponti, G., Obernier, K., Guinto, C., Jose, L., **Bonfanti, L.**, Alvarez-Buylla, A. (2013). Cell cycle and lineage progression of neural progenitors in the ventricular-subventricular zones of adult mice. *Proc Natl Acad Sci U S A.*, 110: E1045- E1054.
IF= 9,8; R= 4/55 (MULTIDISCIPLINARY SCIENCES); Times cited= 42

Bonfanti, L. (2013). The (real) neurogenic/gliogenic potential of the postnatal and adult brain parenchyma, *ISRN Neurosci*. Vol. 2013: 1-14.
(not yet indexed)

Santambrogio, S., Ricca, A., Maderna, C., Ieraci, A., Aureli, M., Sonnino, S., Kulik, W., Aimar P., **Bonfanti, L.**, Martino, S., Gritti, A. (2012). The galactocerebrosidase enzyme contributes to maintain a functional neurogenic niche during early post-natal CNS development. *Hum. Mol. Genet*. 21: 4732- 4750.
IF= 6,4; R= 32/291 (BIOCHEMISTRY AND MOLECULAR BIOLOGY); Times cited= 5

Bonfanti, L., Nacher, J. (2012). New scenarios for neuronal structural plasticity in non neurogenic brain parenchyma: the case of cortical layer II immature neurons. *Prog. Neurobiol*. 98: 1-15.
IF= 11,4; R= 10/252 (NEUROSCIENCES); Times cited= 16

Bonfanti, L., Peretto, P. (2012). The missing chain. *Front. Neurosci.* 6: 1.
IF= 3,7; R= 108/252 (NEUROSCIENCES); Times cited= 0

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Bonfanti, L., Rossi, F., Zupanc G. (2011). Towards a comparative understanding of adult neurogenesis. *Eur. J. Neurosci.* 34: 845-846.
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Bonfanti, L., (2011). From hydra regeneration to human brain structural plasticity: a long trip through narrowing roads. *TheScientificWorldJ.* 11; 1270-1299.
IF= 1,4 (2010); R= 13/59 (MULTIDISCIPLINARY SCIENCES); Times cited= 6

Martino, G.V., Pluchino, S., **Bonfanti, L.**, Schwartz, M. (2011). Brain regeneration in physiology and pathology: the immune signature driving therapeutic plasticity of neural stem cells. *Physiol. Rev*. 91: 1281-1304.
IF= 27,3; R= 1/83 (PHYSIOLOGY SCIENCES); Times cited= 65

Armentano, M., Canalia, N., Crociara, P., **Bonfanti, L.** (2011). Culturing conditions remarkably affect viability and organization of mouse subventricular zone in ex-vivo cultured forebrain slices. *J. Neurosci. Meth.* 197: 65-81.
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Ponti, G., Crociara, P., Armentano, M., **Bonfanti, L.** (2010). Adult neurogenesis without germinal layers: the 'atypical' cerebellum of rabbits. *Arch. Ital. Biol.* 148: 147-158.
IF= 1,5; R= 207/252 (NEUROSCIENCES); Times cited= 17

Ponti, G., Reitano, E., Aimar, P., Cattaneo, E., Conti, L., **Bonfanti, L.** (2010). Neural-specific inactivation of ShcA function results in anatomical disorganization of subventricular zone neural stem cell niche in the adult brain. *Neuroscience* 168: 314-322.
IF= 3,6; R= 96/252 (NEUROSCIENCES); Times cited= 6

4.GROUP's PUBBLICATIONS:

Parolisi, R., Peruffo, A., Messina, S., Panin, M., Montelli, S., Giurisato, M., Cozzi, B., **Bonfanti, L.** (2015). Forebrain neuroanatomy of the neonatal and juvenile dolphin (*T. truncatus and S. coeruloalba*). *Front. Neuroanat*. 9: 140.
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IF= 6.3; R= 4/41 (DEVELOPMENTAL BIOLOGY); Times cited= 2
*(Co-last Authorship and Correspondence)

Parkash, J., Messina, A., Langlet, F., Cimino, I., Loyens, A., Mazur, D., Gallet, S., Balland, E., Malone, S., Pralong, F., Cagnoni, G., Schellino, R., **De Marchis, S.,** Mazzone, M., Pasterkamp, J., Tamagnone, L., Prevot, V., Giacobini P. (2015). Semaphorin7A regulates neuroglial plasticity in the adult hypothalamic median eminence. *Nat. Commun.* 6: 6385.
IF= 11,5; R= 3/57 (MULTIDISCIPLINARY SCIENCES); Times cited= 2

Farinetti, A., Tomasi, S., Foglio, B., Ferraris, A., Ponti, G., Gotti, S., ***Peretto, P.**, Panzica, GC. (2015). Testosterone and estradiol differentially affect cell proliferation in the subventricular zone of young adult gonadectomized male and female rats. *Neuroscience*, 12:286:162-70. IF= 3.3; R= 96/252 (NEUROSCIENCES) ; Times cited= 1
*(Co-last Authorship)

Luzzati, F. (2015). A hypothesis for the evolution of the upper layers of the neocortex through co-option of the olfactory cortex developmental program. *Front. Neurosci*. 9:162.
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Luzzati, F., Nato, G., Oboti, L., Vigna, E., Rolando, C., Armentano, M., **Bonfanti, L.**, Fasolo, A., **Peretto, P.** (2014). Quiescent neuronal progenitors are activated in the juvenile guinea pig lateral striatum and give rise to transient neurons. *Development* 141: 4065-4075.
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Peretto, P., Bonfanti, L. (2014). Major unsolved points in adult neurogenesis: doors open on a translational future? *Front. Neurosci.* 8: 154.
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Oboti, L., **Peretto, P** (2014). How neurogenesis finds its place in a hardwired sensory system. *Front. Neurosci.*, 8:102.
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Kreiner, G., Bierhoff, H., Armentano, M., Rodriguez-Parkitna, J., Sowodniok, K., Naranjo, J.R., **Bonfanti, L.**, Liss, B., Schütz, G., Grummt, I., Parlato, R. (2013) A neuroprotective phase precedes striatal degeneration upon nucleolar stress. *Cell Death Differ.* 20: 1455-1464.
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Crociara, P., Parolisi, R., Conte, D., Fumagalli, M., **Bonfanti, L.** (2013). Cellular and molecular characterization of multipolar Map5-expressing cells: a subset of newly generated, stage-specific parenchymal cells in the mammalian central nervous system. *Plos ONE* 8: 1-18.
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Gribaudo, S., Bovetti, S., Friard, O., Denorme, M., Oboti, L., Fasolo, A., **De Marchis, S.** (2012). Transitory and activity-dependent expression of Neurogranin in olfactory bulb tufted cells during mouse postnatal development. *J. Comp. Neurol*., 520: 3055-3069.
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De Marchis, S., Puche, A.C. (2012). Cellular imaging and emerging technologies for adult

neurogenesis research. *Front. Neurosci*. 6: 1-2.
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Bonfanti, L., Rossi, F., Zupanc G. (2011). Towards a comparative understanding of adult neurogenesis. *Eur. J. Neurosci*. 34: 845-846.
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Bonfanti, L., (2011). From hydra regeneration to human brain structural plasticity: a long trip through narrowing roads. *TheScientificWorldJ.* 11; 1270-1299.
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IF= 27,3; R= 1/83 (PHYSIOLOGY SCIENCES); Times cited= 65

Armentano, M., Canalia, N., Crociara, P., **Bonfanti, L.** (2011). Culturing conditions remarkably affect viability and organization of mouse subventricular zone in ex-vivo cultured forebrain slices. *J. Neurosci. Meth.* 197: 65-81.
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Oboti, L., Schellino, R., Giachino, C., Chamero, P., Pyrski, M., Leinders-Zufall, T., Zufall, F., Fasolo, A., **Peretto, P.** (2011). Newborn interneurons in the accessory olfactory bulb promote mate recognition in female mice. *Front. Neurosci.,* 5:1-14.
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Luzzati, F., De Marchis, S., Parlato, R., Gribaudo, S., Gunther, S., Fasolo, A., **Peretto, P.** (2011). New striatal neurons in a mouse model of progressive striatal degeneration are generated in both the subventricular zone and the striatal parechyma. *PLOS ONE*, 6(9),e25088:1-16.
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Paina, S., Garzotto, D., **De Marchis, S.,** Marino, M., Moiana, A., Conti, L., Cattaneo, E., Perera, M., Corte, G., Calautti, G., Merlo, G. (2011). Wnt5a is a transcriptional target of Dlx homeogenes and promotes differentiation of interneuron progenitors in vitro and in vivo. *J. Neurosci*. 31(7), 2675-2687.
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Fregnan, F., Petrov, V., Garzotto, D., **De Marchis, S.,** Offenhäuser, N., Grosso, E., Chiorino, G., Perroteau, I., Gambarotta, G. (2011). Eps8 involvement in neuregulin1-ErbB4 mediated migration in the neuronal progenitor cell line ST14A. *Exp. Cell Res*. 317 (6) 757-769.
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Ponti, G., Reitano, E., Aimar, P., Cattaneo, E., Conti, L., **Bonfanti, L.** (2010). Neural-specific inactivation of ShcA function results in anatomical disorganization of subventricular zone neural stem cell niche in the adult brain. *Neuroscience* 168: 314-322.
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Rolando, C., Gribaudo, S., Yoshikawa, K., Leto, K., **De Marchis, S.,** Rossi, F. (2010). Extracerebellar progenitors grafted to the neurogenic milieu of the postnatal rat cerebellum adapt to the host environment but fail to acquire cerebellar identities. *Eur. J. Neurosci.* 31: 1340-1351.
IF= 3,7; R= 77/239 (NEUROSCIENCES); Times cited= 8

Edited Books:

Peretto P., Bonfanti L. Eds. (2014) *eBook - Adult neurogenesis twenty years later: physiological function versus brain repair*. FRONTIERS, pp. 120.

Bonfanti L. Ed. (2013) *Neural stem cells: new perspectives.* INTECH OPEN ACCESS PUBLISHER, Rijeka, pp. 420.

De Marchis S., Puche A.C. Eds. (2012) *eBook - Cellular imaging and emerging technologies for adult neurogenesis research*. FRONTIERS, pp. 120.

5. GROUP's additional information:

Please list the grants of the other members of the group in the last 5 years - 2010/2015- according to the table below:

Starting - end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
January 2014-June 2016	International	S. De Marchis	Università Italo-Francese	"Studio molecolare della neurogenesi adulta in un modello di topo transgenico" – mobility grant	G14-96	€ 4000,00	€

Please list honours, prizes or awards received by other members of the group If applicable.

Please list outreach activities of other members of the group:

De Marchis Silvia

- Describe your international collaborative experiences.
  - Dr. Michèle Studer, INSERM U636, Nice Sophia Antipolis, France. *Role of COUP-TFI in the adult neurogenic niches.*
  - Prof. Jeroen Pasterkamp, Utrecht University, The Netherlands. *Sema7A function in adult hippocampal neurogenesis.*
  - Dr. Paolo Giacobini, Inserm, Jean-Pierre Aubert Research Center, Unité 837; UDSL, School of Medicine, Lille, France. *Role of Sema7A in adult brain plasticity.*
  - Prof. Saadia Bamhamed, Cadi Ayyad University Marrakech, Morocco. *Effects of inhalants abuse on hippocampal neurogenesis and cognitive behaviour*

- Invited talks
  2015 – "COUPTFI functions in adult neurogenesis" - XVI Congress – SINS – Cagliari 8-11 October.
  2015 – "Expression and functions of the transcription factor COUP-TFI in Neurogenic regions of the adult mouse brain" 61° Convegno GEI 7-10 Giugno, Pisa.
  2014 - "The olfactory bulb as a model to study neural plasticity in the adult brain". La journeé Scientifique des Neurosciences - 2 May; Cadi Ayyad University, Marrakesh, Morocco.
  2011- "Developmental mechanisms regulating neural diversity: intrinsic and extrinsic factors in the generation of inhibitory interneuron subtypes" Scientific Conference for the ISIS Euro-Mediterranean Master in Neuroscience and Biotechnology; 16-19 October - Alexandria University, Egypt.

- Editorial duties
  In the Editorial Board of International journals:

- *Frontiers in Neuroscience, section Neurogenesis* (Frontiers journal series, CH)

Guest Editor for Special Issues:

- *Cellular Imaging and Emerging Technologies for Adult Neurogenesis Research". Front. Neurosci. 2011 (with A. Puche)* *http://frontiersin.org/neuroscience/neurogenesis/specialtopics/96/*

Reviewer in international grant projects:
Medical Research Council (UK) – Research Grants applications
Croatian Science Foundation - Research Grants applications

Federico Luzzati

- Speakers invited by members of the group
  - IV International Course on Morphological Interpretation in Neuroembryology, Murcia, Spain, 2007. "PSA-NCAM/Doublecortin (DCX) expression in extravertedneurons of the piriformcortex and neocortex: Facts and EvolutionaryHypothesis."
  - Stemcells, Development and Regenerative Medicine (SCDRM) meeting organized by ABCD, Turin, Italy, 2012. Title of the talk: "*Neuronalgenesis in the striatalparenchymaduring progressive degeneration*".
  - 59° Gruppo Embriologico Italiano (GEI) congress, Varese, Italy, 2013. *"Activation of local neuronal progenitors in the guinea pig striatum during post-natal development*".
  - Life Visions: Glimpses of Cell Biology, Turin, Italy, 2014. "*Brain regeneration: Dreams and harsh reality".*
  - Adult Neurogenesis: Evolution, Regulation and Function, Dresden, Germany, 6-8 May 2015. *"Quiescentneurogenicastrocytes can be activated in bothhealthy and lesionedstriatum".*
  - University of Mainz, host of Benedikt Berninger, Mainz, Germany, 30 May2015. "*Neurogenic Potential of Striatal astrocytes in Health and Disease"*

Please list your organizational activities:

- Speakers invited by members of the group

Over the last five years this member of the AN group has been an active promoter of the seminar activity at NICO. Together with Annalisa Buffo we have organized most part of the seminars and instituted a procedure according to which speakers to be invited are first proposed by NICO researchers and then selected based on a poll by all the NICO community. We also took the responsibility to organize the 'DISFEB meets NICO' series, that was agreed by the NICO director prof Vercelli and prof Melcangi (Department of Pharmacological and Biomolecular Sciences-Center of Excellence on Neurodegenerative Diseases, Milan).

- Workshops, Schools or Conferences organized by members of the group

- International PhD Course on "The Aging Brain: cellular mechanisms interfacing human pathology", PhD Program in Neuroscience, 28 September-2 October 2015

Dept of Neuroscience, University of Turin (Supported by The Company of Biologists).
- International PhD Course on Neural Development and Neurodevelopmental Disorders, PhD Program in Neuroscience, 22-26 September 2014, Dept of Life Sciences and Systems Biology, University of Turin. (NENS Sponsored).
- Symposium "Beyond cell replacement: functional plasticity and homeostatic activities of adult stem and progenitor cells" XV SINS Congress, Rome- 4 October 2013.
- 58° Convegno Gruppo Embriologico Italiano (GEI), Dip. di Scienze della Vita e Biologia dei Sistemi, Torino 13-15 Giugno 2012
- International PhD Neuroscience Program Workshop on "Molecular and Functional aspects of neural progenitor response to neurodegenerative events", Neuroscience Institute Cavalieri Ottolenghi (NICO), Orbassano, 13 Aprile 2012.

>> The Adult Neurogenesis group has been deeply involved in the **dissemination of science** and **public engagement** to promote the image of the NICO Institute within the society. Here are listed the more relevant activities:

Luca Bonfanti:
2010
- Settimana del cervello. Tavola rotonda: *Le cellule staminali, buone pratiche e cattive applicazioni*. Circolo dei lettori, Torino.
- Scuola estiva sulla comunicazione della scienza, Edizione speciale ESOF2010. Tavola rotonda: *Il ruolo della comunicazione nel mestiere del ricercatore.* Torino.
- *A qualcuno piace scienza*, Talk show per *La notte della ricerca* 2010, Piazza Castello, Torino.

2011
- *La passione per la ricerca*. Intervento al club Rotary Torino Dora.
- Partecipazione al panel di esperti del progetto Scienza Attiva (Agorà Scienza, Università di Torino).
- Organizzazione a Torino di: *Il lungo e affascinante viaggio della ricerca sulle cellule staminali*. In collegamento audio-video con gli Atenei di Milano, Firenze, Roma. Torino, Palazzo Nuovo.
- Organizzazione stand NICO (Neuroscience Institute Cavalieri Ottolenghi) alla Notte dei ricercatori 2011: "Salva i nostri cervelli per salvare il tuo".

2012
- "Aperitivo con la scienza". Caffè scientifico alla Notte dei ricercatori.
- Organizzazione a Torino di: UNISTEM DAY 2012 *Il lungo e affascinante viaggio della ricerca sulle cellule staminali*. In contemporanea con 20 Atenei italiani.
- Ideazione e realizzazione del cortometraggio "Il calcolo" sulla comunicazione della scienza in tema di staminali.
- Pizza col Prof (sezione Neuroscienze) alla Notte dei ricercatori.
- "Così lontano, così vicino: la ricerca in Neuroscienze per le malattie neurodegenerative" Conferenza per la giornata mondiale dell'Alzheimer, Asti.

2013
- *Le cellule staminali tra scienza e fantascienza*, dialogo con Piero Bianucci alla Fondazione Ferrero, Alba.
- "Perché è difficile riparare il sistema nervoso". Caffè scientifico alla Notte dei ricercatori.
- *La ricerca sulle cellule staminali: gli aspetti scientifici e le questioni etiche*, dialogo con Maurizio Balistreri, Circolo dei Lettori, Torino.
- *Esercizio fisico e neurogenesi*, conferenza nella Settimana del cervello, Circolo dei Lettori, Torino.
- Organizzazione a Torino di UNISTEM DAY 2013: *Il lungo e affascinante viaggio della ricerca sulle cellule staminali*, con 20 Atenei italiani.

2014
- *Staminali: cellule invisibili o troppo visibili?* Ordine dei Medici, Torino.
- Organizzazione di *UNISTEM DAY 2014* Torino, in contemporanea con 35 atenei italiani e stranieri.
- *Tutto e subito: è possibile? (traslazione e comunicazione della scienza)*; conferenza a UNISTEM DAY
- *Staminali e metodo scientifico*. Conferenza per la SCIENTIFIC SUMMER ACADEMY (Fondazione Agnelli) Rettorato, Torino.
- *Genesi di neuroni e di controversie nel cervello umano*. Conferenza alla Scuola di Comunicazione della Scienza per dottorandi, La Morra.
- *La necessità della Ricerca fondamentale*. Diretta radio ai CAFFE' SCIENTIFICI; Notte dei Ricercatori
- TRACKS: FACES IN THE RESEARCH. Video-intervista per la Notte dei ricercatori.
- Produzione ed esecuzione di una *graphic novel* e di un *video* nel contesto di HACKUNITO 2014: *La necessità della ricerca fondamentale* (con Alessandro Ciccarelli e Gabriele Ricchiardi).
- *Neuroni, staminali, malattie: viaggio nella complessità.* LE FRONTIERE DELLE NEUROSCIENZE. Incontro organizzato dal liceo scientifico Leonardo Cocito presso Fondazione Ferrero, Alba.
- *Cellule staminali e metodo scientifico*. Conferenza al Liceo Monti di Chieri.
- La porta chiusa sul futuro? Articolo su *Caratteri liberi*.

2015
- *Dai Tabù alla ragione. Tutto in un giorno*. Articolo su *La Stampa*.
- Organizzazione e coordinamento scientifico di UNISTEM DAY 2015 a Torino, Aula Magna del Rettorato - Cavallerizza reale; in contemporanea con 46 atenei italiani ed europei
- *Cellule staminali, tessuti, organi e medicina rigenerativa*; conferenza a UNISTEM DAY.
- *Dialoghi tra staminali, tessuti, scienziati e società*; intervento al liceo Cocito, Alba, marzo 2015
- *La scienza dal vivo per ventimila studenti*. Articolo per Caratteri Liberi
- *Cellule staminali e sistema nervoso: ricerca, prospettive terapeutiche e problemi da affrontare*; Circolo Leonardo (Torino), aprile 2015
- Speaker a: scuola di comunicazione della scienza per dottorandi, Pollenzo.
- *La scienza fa bene (se conosci le istruzioni)*. Dialogo con A. Massarenti a Torino Spiritualità
- *Il pensiero critico*. Conversazione con A. Massarenti, P. Legrenzi e Lucio Russo, Festival della Scienza di Genova.

Federico Luzzati:
- Giovedì Scienza - C'era una volta un Neurone: storia di un groviglio chiamato cervello
- Notte dei Ricercatori - Caccia al tesoro scientifica (Cajal)
- Notte dei Ricercatori - Le carte del cervello
- Notte dei Ricercatori - Responsabile Stand NICO
- Premio Giovedì Scienza: Rigenerazione nervosa tra sogni e dura realtà
- Scientific Summer Accademy: Rigenerazione nervosa tra sogni e dura realtà

Paolo Peretto:
2015- Brain Awareness week, Forrest Gump: Corsa e Cervello; Circolo dei Lettori, Torino;
2012- UNISTEM, l'Italia Unita dalla Scienza: Le cellule staminali e la plasticità del cervello; Aosta
2010- Settimana del Cervello- La neurogenesi nell'encefalo dei mammiferi adulti; Circolo dei Lettori, Torino;

The entire group Adult Neurogenesis has participated to all editions of: "*Porte Aperte al NICO"* (Cellule staminali: il sogno di rifarsi un cervello; Bufale scientifiche: beviamoci sopra - parlando di ricerca scientifica seria) and to some "Notti della ricerca".

6. Past Research activity

(Summarize the PI and group research activities in the last 10 years)

a. Summary (500 characters)

Adult neurogenesis (AN) is the lifelong production of new neurons and their functional integration into neural circuits. The main interest of the group has been the study of different aspects of AN in the brain of young and adult mammals. We have contributed to the definition of morphological, molecular, and functional features of postnatal/adult neurogenic zones, including neural stem cell niches and parenchymal progenitors, in brain homeostasis and in animal models of lesion/neurodegeneration.

b. Background (2000 characters)

The discovery of AN in the mammalian brain produced a fully renewed vision of brain plasticity, involving stem/progenitor cells capable of generating new neurons and glial cells throughout life. The fact that neural stem/progenitor cells (NSC) produce new elements that can functionally integrate within the mature brain, replacing lost neurons/glial cells or adding to pre-existent neural circuits, raised new hopes for regenerative therapeutic approaches, and unanswered questions regarding the role(s) of AN in brain plasticity. In this context, some relevant aspects were (and still are): the spatio-temporal organization of postnatal/adult neurogenic sites; whether AN was really restricted to the 'classic' stem cell niches (SVZ, subventricular zone; and SGZ, subgranular zone); which factors (intrinsic, extrinsic; physiological, pathological) modulate the different steps of the neurogenic process; the impact of AN on brain function and behaviour.

Although the basic elements of the morphological and molecular organization of adult neurogenic stem cell niches were already known, the transitional steps leading from an embryonic germinal layer to a constitutively active neurogenic site capable of producing new neurons within a mature brain tissue were still obscure. Meanwhile, some findings in different mammalian species started to suggest that additional examples of “parenchymal” neurogenesis and gliogenesis could also occur in various brain regions outside the two canonical niches (in both physiological and pathological conditions). Finally, relevant points which remained (and still remain) largely open involved the identification of factors regulating the activity of stem/progenitor cells, the specification, migration and integration of the newlyborn elements, along with their contribution to adult brain plasticity and behaviour.

c. Rationale (2000 characters)

The rationale of our research was focused on the study of AN basic mechanisms. We investigated the main steps in the neurogenic process, from anatomy to function, with the goal of understanding how a complex biological process can adapt differently to the brains of mammals, in order to clarify the role of AN in both physiology and pathology.

To address the spatio-temporal organization of postnatal/adult neurogenic sites, we planned a series of morpological and ultrastructural systematic studies aimed at defining the postnatal modifications occurring in germinal layers (SVZ/OB system and cerebellum) of mammals endowed with different lifespan and postnatal developmental phases. In parallel, by extending our developmental analysis to non rodent mammals we found new (noncanonical)

neurogenic sites in various parenchymal regions, not restricted to the 'classic' stem cell niches (SVZ and SGZ).
By means of both in vivo and in vitro approaches, the SVZ-OB neurogenic niche of mice has been exploited as a model system to investigate molecular factors involved in AN, focusing on molecules already known to play a role in neural plasticity or involved in the control of embryonic neurogenesis. In parallel, to evaluate the impact of the external environment on the process of AN we used experimental approaches involving either sensory deprivation (e.g., lesion of the olfactory mucosa or naris occlusion) or enrichment. In particular, more recently we investigated the role of pheromones in regulating AN in the context of rodents' social life.
Finally, the potential role of AN-related plasticity has been investigated in various models of genetically/pharmacologically induced brain lesions in order to explore the nature/behaviour of putative stem/progenitor cells residing in non-neurogenic areas.

d. Objectives (1500 characters)

Specific objectives of our research were:

i) definition of the structural organization during postnatal development of the SVZ neurogenic niche in laboratory rodents (mouse) and of germinal layers in other mammalian species (rabbit, dolphin);

ii) identification of molecular factors/pathways involved in adult SVZ neural stem/progenitor cell proliferation, migration and differentiation;

iii) characterization of the new parenchymal sites (striatum, cerebellum) of cell genesis in different mammals (rabbit, guinea pig); characterization of progenitor cells allowing parenchymal neurogenesis to occur in the absence of typical stem cell niches; characterization of the outcome of parenchymal neurogenesis;

iv) Environmental modulation of neurogenesis and function in the context of social/sexual behaviour (role of accessory olfactory bulb - AOB - newlyborn neurons in the perception of pheromonal stimuli);

v) identification of alternative forms of structural plasticity involving non newly generated cell populations expressing markers of immaturity (DCX+ neurons of the cerebral cortex layer II; mMap5 glial cells);

Whole objective of our research activity has been a comprehensive vision concerning how new neurons can be generated, integrate and play a role within pre-existing neural circuits of a mature brain, taking into account neuroanatomical and regional differences among mammalian species.

e. Results (4000 characters)

1. Structural organization and postnatal development of germinal layers

- Understanding that the rodent SVZ adapts to the mature brain environment during the first three postnatal weeks, by progressive organization of migrating neuroblasts into 'chains', in parallel with formation of astrocytic 'glial

tubes' and of a molecular barrier separating an inner and outer compartment (Peretto et al., 2005, *J Comp Neurol*).
- Identification of a process of 'protracted' neurogenesis on the cerebellar surface of peripuberal rabbits (subpial layer - SPL) (Ponti et al., 2006, *Dev Biol*).
- Evidence that no periventricular germinal layer is present in dolphins at birth (Parolisi et al., 2015, *Front Neuroanat*).

2. Molecular factors

- Identification of molecules involved in the control of SVZ neuroblast migration, including BDNF (Chiaramello et al., 2007, *Eur J Neurosci*), HGF (Garzotto et al., 2008, *J Neurosci*) and Eps8 (Fregnan et al., 2011, *Exp Cell Res*).
- Identification of: a role for CREB transcription factor in the differentiation and survival of OB newborn neurons (Giachino et al., 2005, *J. Neurosci*); evidence that lineage choice of adult NSCs is determined by intrinsic properties of the progenitors (De Marchis et al., 2007, *J Neurosci*); evidence that Wnt5a promotes differentiation of SVZ interneuron progenitors (Paina et al., 2011, *J Neurosci*); a role for COUP-TFI in the functional activation of adult OB generated cells (Bovetti et al., 2013, *Development*); expression of the post-synaptic protein Neurogranin in OB newborn granule cells (Gribaudo et al., *J Comp Neurol*, 2009; *2012*).

3. Parenchymal neurogenic sites in mammals

- Identification of a system of parenchymal chains of neuroblasts originating from the postnatal-young rabbit SVZ and directed to the frontal cortex (Luzzati et al., 2003, *PNAS*; 2006, *J Neurosci*; Ponti et al., 2006a, *J Comp Neurol*)
- Characterization of a spontaneous parenchymal neurogenic process in the striatum of adult rabbits (Luzzati et al., 2006, *J Neurosci*).
- Identification of a process of parenchymal neurogenesis within the cerebellar cortex of young/adult rabbits (Ponti et al., 2008, *Plos One*).
- Identification of a transient neurogenic process in the postnatal guinea pig striatum, sustained by quiescent parenchymal astroglial progenitors activated during weaning (Luzzati et al., 2014, *Development*).
- Evidence that local striatal progenitors do activate following genetic- (Luzzati et al., 2011, *Plos ONE*) and pharmacological-induced (Nato et al., 2015, *Development*) neurodegeneration, by producing transient neurons. Characterization of their astrocytic nature (Nato et al., 2015, *Development*).

4. Role of external cues and functional meaning of AN

- Demonstration that: i) sensory enrichment and/or deprivation influence adult neurogenesis modulating newborn cell maturation and survival (Bovetti et al., *PLos One,* 2009); ii) odour enrichment selectively increase adult-born dopaminergic neurons in the mouse OB (Bonzano et al., 2014, *Eur J Neurosci*).
- Evidence that male pheromones act as sensory stimuli enhancing selectively the integration/survival of newborn neurons in the AOB (Oboti et al., 2009; *Eur J Neurosci*).

- Definition of the functional involvement of AOB newborn neurons in the context of the Bruce Effect (Oboti et al., 2011, *Front Neurosci*).

5. Alternative forms of (non-neurogenic) structural plasticity

- Identification and characterization of a population of non-astrocytic glial cells (mMap5 cells; Crociara et al., 2013, *Plos One*) widely distributed in the CNS parenchyma, which express the cytoskeletal protein Map5 (or Map1B) usually abundant in neurons.
- Characterization and theories concerning the population of DCX+ layer II cortical neurons (immature neurons) (Luzzati et al., 2009, *Cereb Cortex*; Bonfanti and Nacher, 2012, *Prog Neurobiol*; Luzzati, 2015, *Front. Neurosci*).

f. Advancement in the field (1000 characters)

Major advancements specifically provided by our group in the AN field have been the identification and characterization of novel, parenchymal neurogenic sites (out of the canonical neurogenic sites) sustained by local progenitors whose nature in the striatum has been found to be astrocytic. These findings, obtained through comparative approach in mammals, have shown that AN strictly depends on the species and the brain regions considered, thus suggesting that different permissivity of the mature tissue is linked to neuroanatomy, lifespan, ecological niche.
Our studies also significantly contributed to the characterization of the molecular factors that control different steps in the adult neurogenic process: from progenitor cell specification to migration, differentiation and functional integration of newlyborn neurons. Moreover, they provided new insights into the responsiveness of AN to sensory inputs and to the functional relevance of AN in the context of sexual/social behaviors.

7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do

a. Summary (up to 2000 characters):

Future projects are committed to move forward on the characterization of the neurogenic processes taking place in the adult brain and determining their impact on brain function in physiologic and pathologic states. To achieve this goal we will combine multiple, complementary approaches that are well established in our laboratory, together with cutting-edge technologies including two photon microscopy and high-throughput technologies (i.e, genomics and transcriptomics).

The projects will be articulated into four main research lines:

I. ***Molecular mechanisms regulating AN*** : we will focus on molecular factors which we have recently shown to be involved in the control of OB neurogenesis to get deeper insights on their role in AN, extending the analysis to the dentate gyrus of the hippocampus;
II. ***AN and reproduction***: we will investigate the interplay occurring between AN and the endocrine system to address the role of AN in the reproductive function;
III. ***AN and neurodegeneration:*** the analysis of the potential reparative or "restorative" role played by the quiescent striatal astroglial progenitors in diverse models of striatal neurodegeneration;
IV. ***Comparative aspects of AN***: we will establish the definition of common and divergent traits in the process of AN in mammals through extensive comparative analyses.

Overall, our projects are aimed at enlightening the real impact AN plays in the normal and pathologic mammalian brain, through understanding the neurogenic potential of different brain regions/species, as well as the key extrinsic/intrinsic mechanisms/factors whose modulation can be used to foster adult brain plasticity/repair. Only by knowing the roles of AN in brain homeostasis and disregulation we could expect to use this biological process for translational purposes (novel therapeutic approaches for neurodegenerative diseases and preventive approaches for optimal brain function/plasticity; both goals ultimately in line with the NICO Mission).

b. Background and Significance (up to 4000 characters):

Molecular mechanisms regulating AN. The interplay of intrinsic and extrinsic factors regulates AN niches ensuring lifelong neuronal turnover, contributing to plasticity and homeostatic processes in the brain (Hsieh et al., 2012). In the last few years, the molecular control of AN has been intensively investigated, yet the picture is still largely incomplete. Here, we will focus on the trascription factor COUP-TFI, which has been shown to play a pleiotropic function in brain development (Alfano et al., 2014). In a previous study, we have demonstrated COUP-TFI role in the functional integration of adult generated OB neurons (Bovetti et al., 2013). We are now focusing on COUP-TFI role in the maintenance of the NSC population and in the progression from NSCs to lineage-committed progenitors and the generation of

mature functional neurons and glia in the SVZ and dentate gyrus of the hippocampus.

AN and reproduction. Several studies have shown that AN plays a key role in encoding social stimuli and in modulating reproduction (Peretto et al., 2014). Accordingly, continuous neurogenesis is required for sex-specific behaviors both in male and female mice (Firestein, 2011) and data from our lab have shown that the AOB newborn neurons are essential to avoid the exteroceptive block to pregnancy (Bruce Effect) elicited by male pheromones in mouse (Oboti et al., 2011). In addition, pheromonal perception in both sexes drives secretion of adenohypophyseal hormones and sex steroids, which in turn influence AN. Thus, evidences point to a role for AN in the control of reproduction mediated by the integration of pheromonal and sex hormonal cues, yet the mechanisms underlying such integration are still elusive. To address this issue, we plan to investigate AN in mice models characterized by hypogonadotropic-hypogonadism, such as the Sema7A ko mice (Messina et al., 2011).

Neurogenic astrocytes in the striatum. We recently demonstrated that besides constitutively-active neuronal progenitors of SVZ and dentate gyrus, other populations of neurogenic astrocytes can be activated only in specific conditions (Luzzati et al. 2014; Nato et al. 2011). These astrocytes reside into the striatal parenchyma, an environment classically considered non-permissive for neurogenesis. This unexpected finding urges the identification of the mechanisms that trigger and sustain this neurogenic activity. These factors are potentially linked to the role these progenitors and their progeny may play in the striatal circuits. Unfortunately, the great majority of newborn neurons appear to have a transient existence and their fate is still unclear. Yet, our analyses indicate that these cells attain complex morphologies and transiently associate with subsets of fiber bundles spanning the striatum. Given that transient neurons have been implicated in the formation of fiber tracts during development, we hypothesize that striatal neuroblasts are involved in some form of plasticity of long-range connections.

Comparative aspects of AN. Our knowledge of organization and function of AN regional sites in different mammals is still largely incomplete. Our studies revealed that both canonical and parenchymal AN sites can be heterogeneous among species, suggesting that AN has adapted differently to mammalian brain anatomy (Bonfanti-Peretto, 2011; Feliciano et al., 2015). In addition, it seems more and more clear that neurogenic processes (progressively decreasing in mammals with large brains and extended lifespan) coexist with immature populations of non-newly generated neurons which seem more represented in large-brained, long-living mammals (Bonfanti-Nacher, 2012; Luzzati et al., 2009). The quite incomplete picture of comparative AN to date available requires further investigations through a wide range of mammalian species, in order to understand the logic followed by neurogenesis (and plasticity) in relation with different neuroanatomies, ecological niches, lifespan.

c. General aim and integration with mission of the Institute (up to 1000 characters)

Our studies have two main goals: i) to define basic factors/mechanisms allowing the process of AN in adult mammals; ii) to use this knowledge in order to foster the brain function in both physiologic and pathologic condition. Although our studies largely involve basic research, our project is addressing fundamental

questions concerning the restorative potential of neural progenitors in brain injury/degeneration, and which way AN can be involved in implementing brain responses/behaviours elicited by the environment. We think these studies can positively contribute to both unravel basic mechanisms of neural plasticity (at present still largely obscure) and to identify profitable targets for brain therapeutic/preventive approaches, these latter representing the main purpose of the Institute.

d. Specific objectives and strategies (up to 4000 characters):

The specific objectives of our project are:

Molecular mechanisms regulating AN. Goal of this project is to get a comprehensive view on COUP-TFI role in the AN niches. We will address this issue by means of in vivo models in which the COUP-TFI gene is conditionally deleted in adult progenitors. Preliminary findings show COUP-TFI could act at different steps of the neurogenic process in the hippocampal DG: from the control of NSC switch form quiescence to the active state and fate choice. These findings support COUP-TFI relevance in the balance of AN, and suggest its dysfunction could be involved in aging and psychiatric disorders. We will characterize the effects of COUP-TFI deletion in AN in the two neurogenic niches. Moreover, we aim to identify the molecular target downstream of COUP-TFI and to validate their involvement in the observed phenotype through in vitro approaches. This project will benefit from the collaboration of M. Studer, University of Sophia Antipolis, Nice (F), which is an expert in the study of COUP-TFI, and of S. Oliviero, University of Turin, who has a long lasting experience in high-throughput technologies in embryonic stem cells.

AN and reproduction. To establish whether and how AN cooperates with the endocrine system to modulate the reproductive behaviour we will focus on models of impaired GnRH function. GnRH neurons orchestrate the activity of the HPG axis and therefore the production and secretion of sex-steroids. These hormones control reproduction and modulate AN in both niches. Behavioural and quantitative analyses of circulating hormones and AN in presence or absence of reproductive sensory stimuli (i.e., pheromones) will clarify the link between AN and the endocrine system.
It is worth noting that starting from 2014 P. Peretto is part of a COST Action dedicated to the Neuroendocrine control of Reproduction. This is important to promote new collaborations with relevant EU Laboratories involving PhD exchanges (e.g., Sara Trova has been 3 months in Lille) and reliable possibilities to apply to EU funding calls for research.

***Astrocytic neurogenic progenitors*.** We will explore the functioning of intrastriatal niches by correlating clonal analyses with single cell RNAseq analyses. In parallel we will study the potential role of striatal neurogenesis with: i) molecular/electrophysiological characterization of neuroblasts, and monosynaptic retrograde tracing of their inputs; ii) we will explore whether specific behavioral paradigms can modify number, distribution or morphology of striatal neuroblasts; iii) we will analyze anatomical (i.e. organization of fiber tracts, striatal volume, number of neurons) and behavioral consequences of their ablation. These analyses may reveal how neurogenic niches are set in the mature brain parenchyma, but it may also uncover unexpected roles for striatal neurogenesis. This study will benefit from the collaboration of Hongjung Song

(John Hopkins University, USA) and Benedikt Berninger (JGU medizin, Germany).

Comparative aspects of AN. Different sites of AN and DCX+ non-neurogenic cell populations will be studied in a variety of animal models, chosen between those listed below on the basis of tissue availability:
- cetaceans devoid of olfaction (*Tursiops truncatus, Stenella Coeruloalba*) and with residual olfactory structures (mink whale);
- sheep, in which preliminary data indicate the occurrence of DCX+ cell clusters in the external capsule;
- wild mammals: Primates (*Callithrix jacchus, Gorilla beringei beringei, Pan Paniscus*; and, if possible, humans), Carnivora (*Silver fox*), Chiroptera (*Straw-coloured fruitbat*), Macroscelidea (*Eastern rock sengi*).
Brains will be obtained through already existing collaborations: i) Mediterranean Marine Mammals Tissue Bank, Università di Padova; ii) CNRS, UMR6175, F-37380 University of Tours, Nouzilly, France; iii) Institute of Anatomy, University of Zurich, CH; Center for advanced study of human paleobiology, George Washington University, USA.

e. Unique features of the project research (up to 2500 characters):

First uniqueness of our group is that we are the most titled Italian group (in terms of publications) studying AN. We started working in this field 25 years ago, and our past and recent studies have been very well-recognized by the international scientific community (e.g., Bonfanti and Theodosis, 1994, *Neuroscience*; times cited=180; Peretto et al., *Brain Res Bull*, 1997, times cited=174; Bonfanti, *Prog Neurobiol,* 2006, times cited=213; De Marchis et al., *J Neurosci* 2007, times cited=100; Luzzati et al., *J. Neurosci*. 2006, times cited=75; Bonfanti and Peretto, *Eur J Neurosci*, 2011, times cited=64). Therefore, we can assure long-lasting expertise in studies concerning AN in mammals.
As regards the specific aims of this project they are original and relevant for the following reasons: i) the study of local parenchymal progenitors in the context of brain lesion/neurodegeneration can open interesting therapeutic opportunities for brain repair based on mobilization of endogenous progenitors; ii) the study concerning the interplay between AN and the endocrine system to modulate reproduction is expected to shed new light on the function of AN in the mammalian brain and to open new perspectives by identifying AN as a possible target to treat sexual disfunctions; iii) the identification of factors/molecular pathways underlying neural stem progenitor activity/specification is crucial to understand how to stimulate genesis and integration of new neurons in the mature brain circuits and to get insights on the possible mechanisms underlying AN disfunctions; iv) finally, the comparative approach offers unique opportunities to unravel basic rules controlling AN in mammals, such as the regional permissiveness of different brain regions, and whether this can be related to life extension and peculiar morpho-anatomical features. This knowledge is fundamental to figure out possible roles of AN in humans.

f. Methodology (up to 2000 characters): <u>please fill-out this section only in the case of innovative technologies</u>

During these years our group has progressively adapted a wide range of in vivo and in vitro techniques to specifically address the different aspects of adult

neurogenesis. These included ultrastuctural analysis, 3D tissue reconstructions, molecular and cellular quantitative analyses, stereotaxic injections of virus and cell tracers and behavioral tests. During the next three years we will introduce in our research recently developed technologies, such as the use of two-photon excitation microscopy (soon available in our Institute), which allows imaging of living tissue up to 1mm depth. In addition, thank to our collaborations, we will have also the opportunity to explore single cell RNAseq analyses, and monosynaptic retrograde tracing by using rabies-virus. It is expected that by using these innovative methods, we will get new important insights regarding the gene expression profile of newborn neurons, their lineage progression, as well as their functional recruitment within cerebral circuits.

8. Letter of intent by the PI (1 page)

i) *how she/he assesses him/herself in term of leadership and ability to manage his/her group:*

The group Adult Neurogenesis is composed by four researchers coming from two Departments of the University of Turin. The group is represented by two PIs, who started working and collaborating in this field since the early nineties. The other two researchers have been joined subsequently and progressively developed independent, but complementary, research lines in the study of AN. Hence, though the formal management of the group is deputed to the PIs, the choice and strict liability of scientific lines is left to each component, although through permanent and shared discussions. We believe this well-experienced "formula" represents the best way to manage our group.

ii) *possible internal problems within his/her group and the strategies for the best solution:*
The main problem in this group is related to the fund rising. This issue emerged in the last five years coinciding with our shift to NICO and with the general decrease in institutional funding for basic research in Italy (and in Europe). In contrast with such situation, the amount/level of publications in the group has not been affected, but maintained on good standards (see list of publications above). Among the strategies planned for the future we think important to increase our effort in trying new institutional applications and new, alternative sources for research funding. To do this, we have to re-think the potential of our research lines in a context of translational outcomes. Meanwhile, we will also increase our scientific, collaborative relationships, with the same goal of participating in international grant requests.

iii) his/her commitment in supporting the general activities of the Institute;
The group Adult Neurogenesis contributes to multiple activities for the Institute:
- organization and logistics of laboratory security;
- promotion of the image of the Institute and its research in the society (schools, people); participation in Science Festivals and social events;
- contribution to the organization of the Institute Website;
- promoter of the seminar activity at NICO;

iv) *specific pitfall and difficulties to realize his/her projects:*
This point is strictly related to point (ii). Although the level of publication has not been affected by the scarce availability of money, this aspect hampered the possibility to reach levels of excellence. We think mandatory for our group to increase our efforts in order to find more research funding.

v) *ability in establishing internal and external collaborations:*
During the last five years we shared competences, technologies, and publications with other research groups at NICO (see Luzzati et al., 2014; Nato et al., 2015; Farinetti et al., 2015; Rolando et al., *Eur J Neurosci* 2010, Rolando et al., *J Neurosci,* 2012). The group has presently many international collaborations (see institutions listed above). We think this is also due to the well-recognized value of our team in the field of AN.

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name:
Neurobiology of cerebral plasticity

1. LABORATORY DESCRIPTION – PERSONNEL:

- **Principal Investigator**

Annalisa Buffo — Birthdate (25/12/1967)
Degree PhD — Gender F
Nationality Italian — Phone: 00 39 011 6706614
Email: annalisa.buffo@unito.it

- **Personnel**

1. Daniela Carulli — Birthdate (17/04/1973)
   Degree PhD — Gender F
   Role Assistant Professor — Nationality Italian
   Expertise: Extracellular matrix, perineuronal nets
   Lead responsible of research on the role of ECM,PNN on neural plasticity
   Currently on sabbatical leave (from August 2015)

2. Ketty Leto — Birthdate (30/08/1980)
   Degree PhD — Gender F
   Role Senior researcher — Nationality Italian
   Expertise Cerebellar development
   Lead responsible of research on cerebellar morphogenesis

3. Enrica Boda — Birthdate (08/05/1981)
   Degree PhD — Gender F
   Role Senior researcher — Nationality Italian
   Expertise Oligodendroglial turnover and myelin
   Lead responsible of research on oligodendroglial physiopathology

4. Elena Parmigiani — Birthdate (26/03/1985)
   Degree PhD — Gender F
   Role PostDoc fellow — Nationality Italian
   Expertise Neurogenic properties of astrocytes and cerebellar interneurons

5. Elisa Fucà — Birthdate (10/07/1987)
   Degree MSc in Psychology — Gender F
   Role PhD Student — Nationality Italian

Expertise Rehabilitative training and cell replacement to foster functional repair in the lesioned CNS

6. Valentina Cerrato Birthdate (21/07/1988)
   Degree MSc in Biotechnology Gender F
   Role PhD Student Nationality Italian
   Expertise Generation of astroglial heterogeneity

7. Ishira Nanavaty Birthdate (06/08/1988)
   Degree MSc in Biology Gender F
   Role Technical assistant, part time Nationality Indian
   Expertise Histology, genotyping, behavioural tests

This research group has been leaded by Ferdinando Rossi until January 2014.

2. PRINCIPAL INVESTIGATOR CURRICULUM VITAE (two pages)

Education and training:

1991	"Laurea" degree "summa cum laude" in Biological Sciences, University of Turin
1992-1993	Post-lauream apprenticeship at the II Neurological Clinic, Faculty of Medicine, University of Turin
1994	"Professional certificate for Biologists", University of Turin
1998	Research Doctorate in Neurological Sciences, Ministry of Education and Science, University of Turin
1994-1999	Research stays at the Rudolf Magnus Institute, University of Utrecht, Netherlands Institute for Brain Research, Amsterdam and University of Tuebingen

Employment and research experience:

1992-1998	Research fellow, University of Turin
1998-2000	Postdoctoral fellow, Department of Physiology, University of Turin
2001-present	Tenured Assistant Professor of Physiology, University of Turin
2004, 2005	Visiting Researcher at the Helmholtz Zentrum (GSF, now Deutsches Forschungszentrum für Gesundheit und Umwelt, GmbH) and Ludwig Maximilans University, Munich, Germany

2014 National Scientific Habilitation as Associate Professor in Physiology (05/D1 – FISIOLOGIA- Bando 2012, DD n. 222/2012)

Relevant discoveries:
i) The first demonstration of a physiological role for the myelin component Nogo-A in the restriction of both growth-associated gene expression (Zagrebelsky et al., J Neurosci 1998, cites=76,WoS) and aberrant growth in the intact CNS (Buffo et al., J Neurosci 2000, cites=144, WoS);

ii) The first demonstration that adult glial cells reacting to injury broaden their differentiation potential and can engage in neurogenesis in vivo by overexpression of neurogenic transcription factors (Buffo et al., PNAS 2005, cites=178, WoS);

iii) The first demonstration that quiescent astroglia produces scarring astrocytes and that, when reacting to a traumatic injury, astrocytes undergo dedifferention and behave as neurogenic stem cells ex vivo (Buffo et al., PNAS 2008, cites=283, WoS). Along this line, we contributed to one of the first evidence showing that reactive astrocytes become neurogenic in the striatum (Nato et al., 2015, cites=1, WoS);

iv) The first demonstration that the G-protein GPR17 receptor plays a key role in the lineage progression of oligodendrocyte progenitors (Lecca et al., PlosOne 2008, cite=49,WoS; Boda et al., Glia 2011, cites=20, WoS);

v) The first demonstration that the neural plasticity restrictors Nogo-A/NgR1 are active in the brain germinal niches where they act as potent negative regulators of adult neurogenesis (Rolando et al., J Neurosci, 2012, cites=21,WoS, *);

vi) The first demonstration that asymmetric divisions –typical of neural stem cells- occur in vivo in oligodendrocyte progenitors (Boda et al., Glia 2015, cites=1, WoS).

Please list your grants according to the table below (last five yrs).

Starting - end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
2016-2018	International	PI	Merck Serono/Grant for Multiple Sclerosis Innovation 2015	*Driving microglia metabolism toward remyelination and restoration of brain damage in MS*	-	€60000	€60000
2014	National	Co-PI with L Bonfanti, P Peretto	Fondazione Cassa di Risparmio di Torino	*Fonti 'endogene' di cellule staminali/progenitori neurali per la riparazione del sistema nervoso*	-	€25000	€25000
2013-2016	National	PI	MIUR (PRIN2010/2011)	*Effect of substances of abuse, psychoactive drugs, stress and maternal care on brain development and vulnerability to psychopathology*	20107MSMA4_006	€83000	€83000
2012-2014	International	PI	European Leukodystrophy Foundation	*Lamin B1 dysregulation in Autosomal Dominant Leukodystrophy (ADLD): cellular and animal models to understand pathogenesis and move towards* therapy	2011-006C2 - 2013	€32000	€32000
2009-2011	National	PI	Compagnia di San	*Glial plasticity in*	GLIAREP	€80000	€80000

			Paolo – Programma Neuroscienze	*reactive gliosis: novel approaches to promote brain repair*			
2014-2018	International	Team Component PI: F Rossi/A Vercelli	FP7 European Union	*Neurostem cellrepair*		€400000	€400000
2015-2018	National	Team component **PI: Enrica Boda** (see below)	Fondazione Cariplo	*Characterization of a novel microRNA involved in myelination: a new potential pathogenetic mechanisms in multiple sclerosis*	ID: 2014-1207)	€80000	€80000
2012-2015	National	PI	University of Turin (60% MURST/MIUR-annual grants)	*Meccanismi molecolari per il potenziamento della plasticità dell'astroglia reattiva: nuovi approcci per la riparazione del tessuto nervoso*	-	€3659,91 (2012) €3049,06 (2013) €2601,54 (2014)	€3659,91 (2012) €3049,06 (2013) €2601,54 (2014)
2008-2012	International	Team component PI: F Rossi	FP7 Marie Curie Action	*Axregen on Axonal regeneration, plasticity and stem cells*	GA 21 4003-2	€230000	€230000

Supervised PhDs:
Elena Parmigiani, currently PostDoc at the University of Turin, NICO
Chiara Rolando, currently PostDoc at the University of Basel
Enrica Boda, co-supervision with Filippo Tempia; currently PostDoc at the University of Turin, NICO
Annarita De Luca, Technical Assistant of the University of Turin, currently on leave
Dilek Colak, co-supervision with Magdalena Goetz; Assistant Professor of Neuroscience, Weill Cornell Medical College, NY, USA

Please list honours, prizes or awards received, If applicable:

- Von Humboldt Fellowship 2004, 2005 to develop strategies to foster glia plasticity and promote neurogenesis in collaboration with Prof. Goetz, Muenchen.
- DAAD Short Term Fellowship, 2004.to develop strategies to foster glia plasticity and promote neurogenesis in collaboration with Prof. Goetz, Muenchen
- COST Cooperation, Short Term Scientific Mission Fellowship, January 1999, to characterise a subtractive library from control and denervated adult rat Purkinje cells in the lab of Prof. Bähr, University of Tuebingen (now Goettingen), Germany.
- University of Turin, October 1999, awarded a competitive 2 year Post-Doc Fellowship in the field of Neurobiology.
- CNR Short Term Mobility Fellowship, September 1998, to generate a subtractive library from control and denervated adult rat Purkinje cells in the lab of Dr. Bähr, University of Tuebingen, Germany.
- Fondazione Cavalieri Ottolenghi, Turin, January 1998, awarded a one year Post-Doc Fellowship in Neurobiology
- European Science Foundation, Short Term Fellowship, 1994, to study B-50/GAP-43 expression in collateral sprouting in the CNS, under the supervision of Prof. W.H. Gispen of the Rudolf Magnus Institute, University of Utrecht, The Netherlands.

Please list your outreach activities

International collaborators:
• Dr. Andreas Bosio, Director of the Research Division in Neuroscience, Miltenyi Biotec (Köln, Germany): antigenic phenotyping of glial populations;
• Prof. Magdalena Götz Ludwig Maximilians University, Munchen, Germany: specification and properties of stem astroglial phenotypes and glial reactivity;
• Prof. Akiko Nishiyama (Storrs, University of Connecticut, USA): neuronal-mediated regulation of asymmetric division of oligodendrocyte progenitor cells and oligodendroglial neuromodulatory activity;
• Prof. Verdon Taylor (University of Basel, Basel, Switzerland): role of Notch signalling in oligodendroglial specification and oligodendrocyte progenitor heterogeneity;
• Prof. Laura Lopez-Masquaraque (Cajal Institute, Madrid, Spain): clonal approaches for astrogliogenesis;
• Prof. Martin Schwab (Brain Research Institute, University of Zurich: Nogo/NgR1 signalling in axon growth and astroglial functions).

Selection of invited talks:
• “Intrinsinc and extrinsic mechanisms balancing proliferation and self-renewal of oligodendrocyte progenitors in the mature brain” September 2015, Meeting of the Polish Society of Neuroscience, 6-8 September 2015, Danzica, Poland
• “Intrinsinc and extrinsic mechanisms balancing proliferation and self-renewal of oligodendrocyte progenitors in the mature brain” Meeting of the Spanish Society for Neuroscience Meeting, 23-25 September 2015, Granada, Spain
• “Ruoli omeostatici e riparativi della neurogenesi adulta” LIV CONGRESSO NAZIONALE SNO Genova, 21-23 maggio 2014
• “Proprietà neuronali intrinseche, molecole regolatrici estrinseche ed interazione con l’ambiente esterno nei processi di riparazione dei circuiti nervosi centrali danneggiati” CONGRESSO CONGIUNTO AINPeNC – AIRIC 5-7 Giugno 2014
• “Plasticity of the germinal niche: roles of Nogo-A and Nogo Receptor 1 in the homeostatic regulation of adult neurogenesis” Symposium Beyond cell replacement: functional plasticity and homeostatic activities of adult stem and progenitor cells Congresso della Società Italiana di Neuroscienze, Rome, 2013, Speaker and organizer

- “Basi biologiche della neuroriparazione: il ruolo degli astrociti” Congresso della Società Italiana di Neurologia, Workshop su “Basi Biologiche della Neuroriparazione”, 2012. (organizers: Prof. Antonio Uccelli, Università di Genova, Dott. Dario Centonze, Università di Roma Tor Vergata)
- “Isolation of astrocytes and neural progenitors to understand adult CNS germinal niche functioning” Satellite Symposium on “Rapid isolation of neural cell populations”, 41st annual meeting of the Society for Neuroscience, Washington, 2011
- “Cellule gliali: attori importanti nella neurogenesi adulta e nella riparazione cerebrale”, AINO and AIRC joint Congress, Squillace, 2010
- “Intrinsic growth potential, regulatory molecules and experience: the complex interplay regulating neuronal plasticity”, Meeting of the German Society of Neuroscience, Goettingen, 2009
- “Astrogliosis: origin, progeny and reparative potential”, Symposium on Reactive gliosis: molecular and cellular mechanisms to limit neural degeneration and promote repair, Congresso della Società Italiana di Neuroscienze, Milan, 2009, Speaker and organizer.
- “Lineage analysis of reactive gliosis – glial diversity and neuronal regeneration”, Conference on Brain Disease & Molecular Machines, Paris, 2008
- "Instructing neurogenesis in glia cells: reparative potential in neurodegenerative lesions" Meeting of the German Society for Cell Biology, Braunschweig 2006
- "Olig2 induction in cerebral amyloidosis: a novel oligodendrocyte reactivity." Glia cells in health and disease, Cold Spring Harbour, 2006, Selected Speaker.
- "Olig2 induction upon brain lesion - implications for neuronal repair", Annual Meeting of the Federazione Italiana Scienze della Vita, Riva del Garda 2006
- "Glial cells generate neurons: new approaches for neuronal reconstitution in the mammalian brain" Euresco Conference on Cellular and Molecular Basis for Regeneration, San Feliu 2004

Invited seminars at Research institutions and lectures:
- Specification mechanisms and lineage relationships of interneurons and astroglia in the rodent cerebellum, “Couse on Gene regulation and human disease’ University of Milan-Bicocca, november 27 2015
- “Roles of glial cells in physiology and pathology: implications for brain repair and re generation” Meeting of the Bioscience PhD Students Dresden, 23-24 JUNE 2014 – LEIPZIG
- “Nogo-A/Nogo receptor functions in the homeostasis of the adult SVZ”, Brain Research Institute, University of Zurich, Zurich, Switzerland, 2012 (host: Prof. Martin E. Schwab, Director)
- “Nicchie staminali nel sistema nervoso centrale adulto: fisiopatologia della neurogenesi ippocampale e potenzialità riparative della glia reattiva” 7° Corso di Aggiornamento in Neuroscienze Città di Catania su "Invecchiamento cerebrale e demenza", 2010, 2011, 2012
- “Meccanismi di regolazione della crescita assonale nei neuroni di Purkinje”, Dipartimento di Psicologia, Sezione di Neuroscienze, Università La Sapienza, Roma, Italy, 2009 (Ospite: Prof. Maria Teresa Fiorenza)
- “Glial diversity – lineage and reparative responses”, Center for Neurogenomics and Cognitive Research, VU University Medical Center, Amsterdam, 2009 (hosts: Prof. Marjo van der Knaap and Dr. Elly Hol, team leaders)
- “Origin, progeny and reparative potential of glial progenitor cells”, PhD Course in Neuroregeneration, International PhD Program in Molecular Medicine, Sections of Neuroscience, Neuroscience Technology and Experimental Neurology all’Istituto Scientifico San Raffaele, Milano, Italia, 2009

• “Progeny and reparative potential of reactive glia” McMaster University, Dept of Medicine, Hamilton, Canada, 2008 (host: M Rathbone),
• "Olig2 induction in reactive gliosis - glial lineage analysis and neuronal regeneration", Spring School for Regenerative Medicine "Isolation and induction of neuronal progenitor cells" Rostock 2006

- Editorial duties

Guest reviewer for the following journals:
Brain, Science Signalling, Progress in Neurobiology, The Journal of Neuroscience, Nature Communication, Nature reports, Glia, Journal of Neurochemistry, The Journal of Neurophysiology, Journal of Cerebral Blood Flow and Metabolism, Molecular and Cellular Neuroscience, European Journal Neuroscience, PlosOne, Neuroscience, Neurochemical Research, Neuroimmunology, Cell death and disease, Brain Research, Journal of Visualized Experiments, Archives Italiennes de Biologie.
Agencies: Telethon, French National Research Agency (ANR), ARSEP, DAAD, (Federazione Italiana Sclerosi Multipla), Estonian Science Foundation, Swiss National Science Foundation, FISM (Federazione Italiana Sclerosi Multipla), MIUR.

Please list your organizational activities:

- Speakers invited

Over the last five years I have been an active promoter of the seminar activity at NICO. Together with Silvia De Marchis and Daniela Carulli we have organized most part of the seminars and instituted a procedure according to which speakers to be invited are first proposed by NICO researchers and then selected based on a poll by all the NICO community. We also took the responsibility to organize the ‘DISFEB meets NICO’ series, that was agreed by the NICO director prof Vercelli and prof Melcangi (Department of Pharmacological and Biomolecular Sciences-Center of Excellence on Neurodegenerative Diseases, Milan).

2011: Claudia Verderio, CNR, Milan; Roberto Furlan, Ospedale San Raffaele, Mlan; Alfredo Brusco, University of Turin; Elisa Vigna, IRCC Candiolo, University of Turin; Elsa fabbretti, Sissa, Trieste; Helena Vieira (ITQB-UNL/IBET, Oeira, Lisboa); Claudio Giachino (Max planck Institute, Freiburg, Germany); Gaetano Donofrio (UNIveristy of Parma).

2012: Julien Puyal, University of Lausanne; Anna Gualandris, University of Turin; Marco Sassoè-Pognetto, University of Turin; Silvia Nicolis, University of Milan Bicocca; Carla Taveggia, San Raffaele Hospital; Antonio Uccelli, University of Genoa; Patrizia Panzanelli, University of Turin; Ferdinando di Cunto, University of Turin; Glauco Tarozzo, IIT Genoa; Paolo Giacobini, Unv of Lion; Anna Gualandri, University of Turin; Silvia Nicolis, University of Milan; Antonio Uccelli, University of Genoa; Claudio Ciardelli, Politecnico, Turin; Giuseppina Tesco, University of Boston; Daniela Rossi, Salvatore Maugeri, Pavia; Adriano Chiò, University of Turin; Giorgio Merlo, University of Turin; Maurizio Giustetto, University of Turin; Cristina Becchio, University of Turin; Martina Amanzio, University of Turin; GianBattista Ferrero, University of Turin.

2013: Enzo Terreno, University of Turin; Luca Muzio, San Raffaele Hospital; Tommaso Fellin and Serena Bovetti, IIT Genoa; Laura Sacerdote, University of Turin; M. Miquel, University Jaume de Castelo; G Fisone, Karolinska Institute; L Chelazzi, University of Verona.

2014 – NICO seminars: Chiara Rolando, University of Basel; F. Cauda, Ospedale Koelliker - Università di Torino; Alessandro Sale, CNR di Pisa; Paolo Fabene, Università di Verona; Prof. Federico Bussolino, Istituto di Candiolo – IRCCS, Università di Torino; Alexander J. Graur, Ph.D - The New York Academy of Sciences; Maurizio Balistreri, Università di Torino; Carlo Ricciardi, Emiliano Descrovi, Fabrizio Pirri - Politecnico di Torino; Federico Cremisi, Scuola Normale Superiore di Pisa; Matteo Caleo, CNR, Pisa; Umberto Dianzani, Università del Piemonte Orientale "Amedeo Avogadro"; Cinthia Farina, - San Raffaele Scientific Institute, Milan; DISFEB MEETS NICO: Roberto Melcangi, Barbara Viviani, Roberto Gardoni (University of Milan).

2015: F. Molinari, Politecnico di Torino; M. Tamietto, University of Turin; J. Kwok, University of Cambridge (UK); P. Palanza, University of Parma; M. Studer, University of Nice Sophia-Antipolis; D. De Pietri Tonelli, IIT Genoa; DISFEB MEETS NICO: N. Mitro, University of Milan R. Molteni, Università di Milano; A. Villa, University of Milan; M. Fumagalli, University of Milan; L. Musazzi, University of Milan; A. Poletti, University of Milan; Anna Cariboni, University of Milan V. Magnaghi, Università di Milan; Toshitaka Oohashi (University of Okayama, Japan); F Laezza, University of Texas.

NICO lectures on Neuroscience:
Arturo Alvarez Buylla, University of California, San Francisco, May 2013
Ferdinando Rossi Lecture on Neuroscience:
Frank Bradke, German Center for Neurodegenerative Diseases, Bonn January 2015

Over the last 5 years

- Workshops, Schools or Conferences organized

Workshops:

-Biology and pathology of synaptic and neuronal plasticity, March 2012, NICO and Doctoral School of Neuroscience, Turin;
- Molecular and functional aspects of neural progenitor response to neurodegenerative events, April 2012, NICO and Doctoral School of Neuroscience, Turin;
-Workshop of the Axregen Consortium (co-organizer: Daniela Carulli), 'Axon remodelling and myelin repair' 2 June 2-1 July, 2010, NICO.

Doctoral Courses:

- International PhD School 'The Aging Brain: Cellular Mechanisms Interfacing Human Pathology' International Doctoral School of Neuroscience, University of Turin, 26 September-2October 2015, sponsored by the Company of the Biologists (Co-organizers: Silvia De Marchis, NICO, University of Turin, Maurizio Giustetto, University of Turin) (http://dott-neuroscienze.campusnet.unito.it/do/home.pl);
- NENS School on 'Neural development and neurodevelopmental disorders' International PhD School, Doctoral School of Neuroscience, Università di Torino, 22-26 September 2014 (Co-organizers: Silvia De Marchis, NICO, University of Turin, Maurizio Giustetto, University of Turin) (http://dott-neuroscienze.campusnet.unito.it/do/home.pl/View?doc=2014.html).

Symposia at conferences:

- Symposium in honour of Ferdinando Rossi: a passionate journey through the cerebellar mysteries, FENS Forum, Milan, 2014 (co-organizers: Daniela Carulli, Ketty Leto, University of Turin and NICO);

- Symposium: Beyond cell replacement: functional plasticity and homeostatic activities of adult stem and progenitor cells Congresso della Società Italiana di Neuroscienze, Rome, 2013 (Co-organizer: Silvia De Marchis, University of Turin and NICO)
• Symposium: Reactive gliosis: molecular and cellular mechanisms to limit neural degeneration and promote repair, Symposio al Congresso della Società Italiana di Neuroscienze, Milan, 2009 (Co-organizer: Stefania Ceruti, University of Milan)

Please list your technology transfer achievements (patents, etc.), if applicable
No patents

3. PI's PUBLICATIONS:

(Please list below your publications in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science).
For each publication, please indicate:

1. Leto K, Arancillo M, Becker EBE, **Buffo A**, Chiang C, Ding B, Dobyns WB, Dusart I, Haldipur P, Hatten ME, Hoshino M, Joyner AL, Kano M, Kilpatrick DL, Koibuchi N, Marino S, Martinez S, Millen KJ, Millner TO, Miyata T, Parmigiani E, Schilling K, Sekerková G, Sillitoe RV, Sotelo S, Uesaka N, Wefers A, Wingate RJT, Hawkes R (2015) Consensus Paper: Cerebellar Development. *Cerebellum*. PMID: 26439486
IF=2.86 ; R=135/252; Times cited = 0
2. De Luca A, Cerrato V, Fucà E, Parmigiani E, **Buffo A**, Leto K (2015) Sonic hedgehog patterning during cerebellar development *Cellular and Molecular Life Sciences* DOI: 10.1007/s00018-015-2065-1
IF=5.8; R=37/290; Times cited = 0
3. Parmigiani E, Leto K, Rolando C, Figueres-Oñate M, López-Mascaraque L, **Buffo A***, Rossi F. (2015) Heterogeneity and Bipotency of Astroglial-Like Cerebellar Progenitors along the Interneuron and Glial Lineages. *J Neurosci*. 35 (19):7388-402. (*corresponding author)
IF=6.75; R=25/252; Times cited = 0
4. Boda E, Di Maria S, Rosa P, Taylor V, Abbracchio MP, **Buffo A**. (2015) Early phenotypic asymmetry of sister oligodendrocyte progenitor cells after mitosis and its modulation by aging and extrinsic factors. *Glia*. 63(2):271-86.
IF 6.031 (2015) R=26/252; Times cited = 1
5. De Luca A, Parmigiani E, Tosatto G, Martire S, Hoshino M, **Buffo A**, Leto K, Rossi F. (2015) Exogenous Sonic hedgehog modulates the pool of GABAergic interneurons during cerebellar development. *Cerebellum*. 14(2):72-85.
IF 2.86 (2015) R=135/252; Times cited = 1
4. Nato G, Caramello A, Trova S, Avataneo V, Rolando C, Taylor V, **Buffo A**, Peretto P, Luzzati F. (2015) Striatal astrocytes produce neuroblasts in an excitotoxic model of Huntington's disease. *Development*.142 (5):840-5.
IF 6.27 (2015) R=4/41; Times cited = 1
5. Boda E, **Buffo A**. Beyond cell replacement: unresolved roles of NG2-expressing progenitors. (2014) *Front Neurosci*. 23;8:122.
IF 3.70 (2014) R=82/252; Times cited = 5
6. Boccazzi M, Rolando C, Abbracchio MP, **Buffo A***, Ceruti S. (2014) Purines regulate adult brain subventricular zone cell functions: contribution of reactive astrocytes. *Glia*. 62(3):428-39. (*, co-last author)
IF 5.466 (2014) R=26/252; Times cited = 7
7. Leto K, Carulli D, **Buffo A**. (2014) Symposium in honor of Ferdinando Rossi: a passionate journey through the cerebellar mysteries. *Cerebellum*. 13(6):791-4.
IF 2.717 (2014) R=135/252; Times cited = 0
8. Buffo A, Rossi F. (2013) Origin, lineage and function of cerebellar glia. *Prog Neurobiol*. 109:42-63.
IF 10.301 (2013) R=11/252; Times cited = 14
9. Fratangeli A, Parmigiani E, Fumagalli M, Lecca D, Bonfante R, Passafaro M, **Buffo A**, Abbracchio MP, Rosa P. (2013) The regulated expression, intracellular trafficking, and membrane recycling of the P2Y-like receptor GPR17 in Oli-neu oligodendroglial cells. *J Biol Chem*. 288(7):5241-56.
IF 4.6 (2013) R=61/290; Times cited = 7
10. Behrendt G., Baer K., **Buffo A**., Curtis M.A., Faull R.L., Rees M.I., Götz M. and Dimou L. (2013) Dynamic changes in myelin aberrations and oligodendrocyte generation in chronic amyloidosis in mice and men. *Glia* 61(2):273-86.
IF 5.466 (2013) R=26/252; Times cited = 11
11. Rolando C., Parolisi R., Boda E., Schwab M.E., Rossi F. and **Buffo A**. (2012) Distinct roles of Nogo-A and Nogo receptor 1 in the homeostatic regulation of adult Neural Stem Cell function and neuroblast migration. *J Neurosci* 32(49):17788-99.
IF 6.908 (2012) R=25/252; Times cited = 22

12. Boda E., Viganò F., Rosa P., Fumagalli M., Labat-gest V., Tempia F., Abbracchio M.P, Dimou L., **Buffo A**. (2011) The GPR17 receptor in NG2 expressing cells: focus on in vivo cell maturation and participation in acute trauma and chronic damage *Glia*, 59(12):1958-73.
IF 4.82 (2011) R=26/252; Times cited = 20
13. Ceruti S., Viganò F., Boda E., Ferrario S., Magni G., Rosa P., **Buffo A**., Abbracchio M.P. (2011): The newly identified P2Y-like GPR17 receptor during oligodendrocyte cell maturation regulates sensitivity to ATP induced death. *Glia*, 59(3): 363-78.
IF 4.82 (2011) R=26/252; Times cited = 26
14. Kronenberg G., Gertz K., Cheung G., **Buffo A**., Kettemann H., Götz M., Endres M. (2010) Modulation of fate determinants Olig2 and Pax6 in resident glia evokes spiking neuroblasts in a model of mild brain ischemia. *Stroke*, 41(12):2944-9.
IF 5.756 (2010) R=14/192; Times cited = 14
15. Boda E., **Buffo A**. (2010) Glial cells in non-germinal territories: insights into their stem/progenitor properties in the intact and injured nervous tissue. *Arch Ital Biol*. 148(2), 119-36. IF 0.778 (2010) R=207/252; Times cited = 14
16. **Buffo A**., Rolando C., Ceruti S. (2010) Astrocytes in the damaged brain: molecular and cellular insights into their reactive response and healing potential. *Biochem Pharmacol* 79(2):77-89.
IF 4.889 (2010) R=23/255; Times cited = 110
R=2014

4.GROUP's PUBLICATIONS:

(Please list below up to ten most relevant publications of the other members of the group in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science)

Ferdinando Rossi, Enrica Boda, Daniela Carulli, Ketty Leto

1. Cupolillo, D., Hoxha, E., Faralli, A., De Luca, A., Rossi, F., Tempia, F., Carulli, D. (2015). Autistic-like traits and cerebellar dysfunction in Purkinje cell PTEN knock-out mice. *Neuropsychopharmacology*, doi: 10.1038/npp.2015.339.
IF=7.048(2015); R = 11/140; Times cited = 0

2. Faralli, A., Dagna, F., Albera, A., Bekku, Y., Oohashi, T., Albera, R., Rossi, F., Carulli, D. (2015). Modifications of perineuronal nets and remodelling of excitatory and inhibitory afferents during vestibular compensation in the adult mouse. *Brain Struct Funct*, doi: 10.1007/s00429-015-1095-7. IF=5.62; R = 30/252; Times cited = 0.

3. Tailor J, Kittappa R, Leto K, Gates M, Borel M, Paulsen O, Spitzer S, Karadottir RT, Rossi F, Falk A, Smith A. (2013) Stem cells expanded from the human embryonic hindbrain stably retain regional specification and high neurogenic potency. *J Neurosci.* 33(30):12407-22.
IF=6.747(2013); R=24/252; Times cited = 5

4. Magrassi L, Leto K, Rossi F. (2013) Lifespan of neurons is uncoupled from organismal lifespan. *Proc Natl Acad Sci U S A*. 110(11):4374-9.
IF=9.809(2013); R=4/57; Times cited = 4

5. Carulli, D., Foscarin, S., Faralli, A., Pajaj, E., Rossi, F. (2013). Modulation of semaphorin3A in perineuronal nets during structural plasticity in the adult cerebellum. *Mol Cell Neurosci*, 57:10-22. IF=3.734(2013); R =74/252; Times cited = 3.

6. Florio M, Leto K, Muzio L, Tinterri A, Badaloni A, Croci L, Zordan P, Barili V, Albieri I, Guillemot F, Rossi F, Consalez GG. (2012) Neurogenin 2 regulates progenitor cell-cycle progression and Purkinje cell dendritogenesis in cerebellar development. *Development* 139(13):2308-20.
IF=6.208(2012); R=4/41; Times cited = 16

7. Leto K, Bartolini A, Di Gregorio A, Imperiale D, De Luca A, Parmigiani E, Filipkowski RK, Kaczmarek L, Rossi F. (2011) Modulation of cell-cycle dynamics is required to regulate the number of cerebellar GABAergic interneurons and their rhythm of maturation. *Development.* 138(16):3463-72.
IF=6.596(2011); R=4/41; Times cited = 13

8. Foscarin, S., Ponchione, D., Pajaj, E., Leto, K., Gawlak, M., Wilczynski, G.M., Rossi, F., Carulli, D. (2011). Experience-Dependent Plasticity and Modulation of Growth Regulatory Molecules at Central Synapses. *PLoS ONE* 6(1): e16666. doi:10.1371/journal.pone.0016666.
IF= 4.092; R = 9/57; Times cited = 29.

9. Carulli, D., Pizzorusso, T., Kwok, J.C., Putignano, E., Poli, A., Forostyak, S., Andrews, M.R., Deepa, S.S., Glant, T., Fawcett, J.W. (2010). Animals lacking link protein have attenuated perineuronal nets and persistent plasticity. *Brain*, 133(pt8):2331-2347. IF= 9.19(2014); R =6/192 ; Times cited = 107.

10. Di Bella D, Lazzaro F, Brusco A, Plumari M, Battaglia G, Pastore A, Finardi A, Cagnoli C, Tempia F, Frontali M, Veneziano L, Sacco T, Boda E, Brussino A, Bonn F, Castelletti B, Baratta S, Mariotti C, Gellera C, Fracasso V, Magri S, Langer T, Pievani P, Di Donato S, Muzi-Falconi M, Taroni F (2010). Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28. Nat Genet 42:313-21.
IF 14.191(2010) R=5/252 Times cited = 105

5. GROUP's additional information:

Please list the grants of the other members of the group in the last 5 years - 2010/2015- according to the table below:

Ferdinando Rossi

Grants 2010-2015 (main grants are included in other group member's sections)

Starting- end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
2012 – 2015	National	PI ROSSI	Fondazione Piera, Pietro e Giovanni Ferrero	*La stimolazione ambientale come strumento per potenziare le capacità plastiche, riparative e compensatorie del sistema nervoso centrale.*	-	€5000	€5000
2010-2014	National	PI ROSSI	PRIN (MIUR)	*Neurogenesi e differenziamento neuronale: geni regolatori, segnali molecolari e meccanismi dipendenti dall'esperienza.*	2009TBCZJB	€88828	€88828
2012 – 2013	National	PI ROSSI	Università di Torino (ex60% MIUR, MURST)	*Target generation of cerebellar and striatal neurons as preventive strategy for CNS disorders.*	-	€4112 (2012) €3.840 (2013)	€4112 (2012) €3.840 (2013)

List of awards:
Annual Prize of the Fondation Simone et Cino del Duca, Paris, 1993.
Annual Prize of the Italian Physiological Society, 1994.

International collaborative experiences:
Dr. C. Sotelo, Université Pierre et Marie Curie, Parigi (F).
Dr. R. Hawkes, University of Calgary, Alberta (CDN).
Dr. M. E. Schwab, Brain Research Institute, University of Zurich (CH).
Dr. J. Verhaagen, Brain Research Institute, Amsterdam (NE).
Dr. J.W. Fawcett, Centre for Brain Repair University of Cambridge (UK).
Dr J. Oberdick, Ohio State University, Columbus (USA)
Dr Flavio Maina, Université de Provence (F)
Dr Marion Wassef, Ecole Normale Superieure, Paris (F)
Prof. Karl Schilling,University of Bonn (D)
Dr F De Castro, Cajal Institute, Madrid (E)

Invited talks (2010-2013):
F. Rossi, Phenotype specification and differentiation in cerebellar development; National Institute of Neuroscience (NCNP) a Kodaira, Tokyo, 22 Aprile 2013
F. Rossi, Research on Ageing at the University of Turin, Italian-Japanese Colloquium on Ageing Society, Istituto Italiano di Cultura, Tokyo, 23 Aprile 2013.
F. Rossi, Neural Stem Cell Therapies, Symposium “Brain Research: Broadening the Understanding”, Al-Quds University, East Jerusalem, 2 Giugno 2013.
F. Rossi, Science in Torino between two wars - the school of Giuseppe Levi. Symposium “Dare to Know, Startup! A Tribute to Rita Levi Montalcini”, The Peres Center for Peace, Jaffa, 3 June 2013
F. Rossi, Maturazione Normale e Patologica del Sistema Nervoso: Sviluppo e Plasticità. Fondazione Ferrero, Alba, 17 Giugno 2013.
F. Rossi, Neurogenesis and gliogenesis in the cerebellum, Gordon Conference on Cerebellum, Colby-Sawyer College, New London, NH, 15 Agosto 2013.
F. Rossi, Neural stem cells, Hydra IX 2013: European Summer School on Stem Cells & Regenerative Medicine, Hydra, 8 Settembre, 2013.
F. Rossi, Meccanismi evolutivi e adattamento neurale, Convegno, “Evoluzione e Cervello. Incontro dedicato ai 70 anni di Aldo Fasolo. Torino, 22 Novembre 2013.
Rossi F, Is neural plasticity Darwinian? BSB lab, Università di Torino, Febbraio 2012.
Rossi F, Structural plasticity and regulation of growth in the cerebellum. Sensory-motor plasticity and learning: from bench to bedside. Symposium in Honor of José Maria Delgado-Garcia, Venezia, Aprile 2012.
Rossi F, Regulation of intrinsic neuronal properties for neuritic growth, plasticity and regeneration, European Laboratory for non-Linear Spectroscopy, Università di Firenze, Aprile 2012.
Rossi F, Specification and development of cerebellar GABAergic neurons, The Netherlands Institute for Neuroscience, Amsterdam, Giugno 2012.
Rossi F, 8th Congress on Stem Cell Biology & Technology, Royan Institute, Teheran, Settembre 2012.
Rossi F, Age-dependent Neural Plasticity and Repair, 2012 International PhD Intensive School; Ageing
Society: Issues, Theories and Practices for an Active Ageing. Università di Torino, Settembre 2012.
F Rossi, public lecture, I Mercoledì dell’Accademia, Circolo dei Lettori, 26-01-2011, Turin
F Rossi, lecture, Convegno su La Medicina dal Passato al Futuro, Istituto Lombardo Accademia di Scienze e Lettere, 09-06-2011, Milano
F Rossi, Symposium on Building of cerebellar circuits: from neuronal specification to synapse formation. IBRO World Congress of Neuroscience, 17-07-2011, Florence
F Rossi, Symposium on Cerebellar Development, IVth International Congress of the Society for Research on the Cerebellum, 19-09-2011, Tokyo
F Rossi, keynote lecture, XXII Aini Congress, 22-09-2011, Pollenzo (CN)

9th Unistem Meeting, Milan, Italy, 11 June 2010
Cells, tissues, organs, and organisms: evolution of reparative processes in complex biological structures. ESOF 2010, Turin, 2-7 July 2010
Select Biosciences, Cellular Therapy Summit, Edinburgh, Scotland, 24-25 August 2010
8th Meeting of the School in Regenerative Medicine Karolinska Institute, Stockholm, Sweden, 3-5 september 2010

Editorial duties:
Rossi F. Handbook of The Cerebellum and Cerebellar Disorders, Springer, New York, Heidelberg. Editor in Chief per la sezione Cerebellar Development
F Rossi, Section editor (Cerebellar Development), The Springer HAndbook of Cerebellum and Cerebellar Disorders
F Rossi, Associate Editor of the European Journal of Neuroscience: Special Issue Towards a Comparative Understandings of Adult Neurogenesis

2008-today. Associate Editor, European Journal of Neuroscience
Member of the editorial board of:
The Cerebellum (2001-today)
Neuroscience (2002-today)
Neurobiology of Disease (2005-today)
Frontiers in Neurosciences (2008-today)
Guest Editor (with Filippo Tempia) of the special issue of The Cerebellum "Unraveling the Purkinje neuron" (June 2006)
Member of the Scientific Board of the International Insitute for Research in Paraplegia, Zurich (2004-today)
Member of the Scientific Board of the Fondazione Cavalieri-Ottolenghi di Torino (2006-today)
Member of the Program Committee FENS Forum, Geneva 2008
Guest Referee (journals and funding agencies):
Advances in Experimental Biology, BMC Developmental Biology, Brain, Brain Research Protocols, Brain Research Reviews, Development, Developmental Biology, Developmental Brain Research, Developmental Neurobiology, European Journal of Neuroscience, Experimental Brain Research, Experimental, Neurology, Functional Neurology, Glia, International Journal of Developmental Neuroscience, Journal of Biological Chemistry, Journal of Chemical Neuroanatomy, Journal of Comparative Neurology, Journal of Neurochemistry, Journal of Neurocytology, Journal of Neuroscience, Journal of Neuroscience Methods, Molecular and Cellular Neuroscience, PLoS ONE, Progress in Neurobiology, Science Signaling, Stem Cells, Synapse.
Alzheimer's Society, Biomedical Research Council Singapore, CNRS, European Commission, European Science Foundation, Federazione Italiana Sclerosi Multipla, Fondation pour la Recherche sur le Cerveau, Human Frontier Science Program, INSERM, Israel Science Foundation, Italian Ministry for University and Research, Italian Telethon, Ministry of Culture of the Republic of Serbia, National Science Foundation (USA), North Atlantic Treaty Organization, South African Medical Research Council, Università Italo-Francese, Wellcome Trust.

Examples of organised meetings and symposia:
Society for Research on the Cerebebellum, Annual Symposium on Mechanisms of Cerebellar Function, Chicago, July 2009 (with T. Ebner and M. Manto).
Cells, tissues, organs, and organisms: evolution of reparative processes in complex biological structures. ESOF 2010, Turin, July 2010 (with L. Bonfanti)

Daniela Carulli

Grants 2010/2015

Starting - end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
2015-2017	National	Component (PI: Carola Eva)	Progetto d'Ateneo Università di Torino	*Influence of maternal behaviour on the expression of brain plasticity brakes: a role in the susceptibility to anxiety?*	Torino_call2014_L2_185	€97918	€97918
2012-2015	National	PI CARULLI	University of Turin (MIUR/MURST ex 60%)	*Cellular and molecular mechanisms of vestibular compensation*	-	€3320,93 (2012) €2135,89 (2013) €2012,24 (2014)	€3320,93 (2012) €2135,89 (2013) €2012,24 (2014)
2014-2015	National	Co-PI with C. Eva	Fondazione Cassa di Risparmio di Torino	*Meccanismi complessi che sottendono gli effetti permanenti dell'ambiente perinatale sulla plasticità neurale la vulnerabilità a psicopatologie*	-	€26000	€26000
2008-2010	International	**Co-PI with F. Rossi**	International Foundation for Research in Paraplegia	*Interplay between experience and extracellular matrix in the control of physiological and compensatory plasticity in the adult CNS*	IRP-I-027/08	CHF 168'000 (€100000)	CHF 168'000 (€100000)

List of awards:
"Erasmus project" fellowship (1996)
"Fondazione Cavalieri Ottolenghi" fellowship (1999)
Short-Term fellowship of the COST B10 Cooperation (1999)
Short-Term fellowship of the COST B10 Cooperation (2000)
NWO (Nederlandse Organisatie voor Wetenschappelijk Onderzoek) mobility grant (2015)
University of Turin, World Wide Style mobility grant (2015)

International collaborative experiences
James W Fawcett and Jessica Kwok (Brain Repair Centre, University of Cambridge, UK)
Joost Verhaagen (Netherlands Institute for Neuroscience, Amsterdam)
Gregorz Wilczynski (Nencki Institute, Warsaw)
Toshitaka Oohashi (Okayama University, Japan)
Marta Miquel (University of Castellon, Spain)

Invited talks
XVI meeting of the Italian Society for Neuroscience, Cagliari, 2015
"DiSFeB meets NICO" seminar, University of Milan, 2015.
50° meeting of AINPeNC (Associazione Italiana di Neuropatologia e Neurobiologia Clinica) and 40° of AIRIC (Associazione Italiana di Ricerca sull'Invecchiamento Cerebrale), Verbania (Italy), 2014
2012 Invitation by Dr J. Verhaagen, Netherlands Institute for Neuroscience, Amsterdam, 2012.
2011 Workshop of the Doctorate school in Neuroscience, University of Turin, "From muscle to brain: role of dystroglycan in synaptic function and disease", 2011.
Invitation by Dr Sassoè-Pognetto, University of Turin, 2010.
Invitation by Dr Schilling, University of Bonn, Germany, 2007
Workshop of the EU-sponsored Network of Excellence NeuroNE, "Activity-dependent plasticity", Turin, 2007.

Editorial duties
Guest referee: Experimental Neurology, Brain Structure and Function, Journal of Cellular Science, Molecular and Cellular Neuroscience, European Journal of Neuroscience, Frontiers in Cellular Neuroscience, Cell Transplantation, The International Journal of Biochemistry and Cell Biology, Brain, Behavior and Immunity, Brain Research Bulletin, Journal of Neuroscience Research, Plos One.
Guest editor: leading guest editor for a Special Issue of Neural Plasticity, entitled "Perineuronal nets and CNS plasticity and repair".

Workshops organization
Organisation of the 5th Axregen workshop, held in Turin in 2010. AxRegen Consortium was a EU ITN PhD training program focused on the experimental and clinical problems associated with axonal damage and repair in the central nervous system.

Ketty Leto

Grants 2010/2015

Starting- end date	**Origin**	**Name and Role of Group Member**	**Funding Source**	**Project Title**	**Project ID**	**Overall Amount Funded**	**Directly Available to NICO**
2012 – 2015	National	PI LETO	FIRB (Miur)	*Target generation of cerebellar and striatal neurons as preventive strategy for CNS disorders*	RBFR10A01S_001	€246100	€246100

2012-2013	National	PI LETO	University of Turin (ex 60% MIUR/MURST)	*Terapie preventive di sostituzione cellulare per l'atassia spinocerebellare di tipo-2 (SCA-2)*	D15E12005700005	€ 3577,66 (2012) € 2847,86 (2013)	€ 3577,66 (2012) € 2.847,86

- International collaborative experiences:

Austin Smith (University of Cambridge); Alain Chedotal (INSERM, Paris); Mikio Hoshino (National Institute of Neuroscience, Tokyo).

- Invited talks:

Development and specification of cerebellar phenotypes. PhD School "Neural Development and Developmental Disorders", NENS Course, Turin, September 2014.
Lineage relationships and specification mechanisms in cerebellar neurogenic niches. Summer School "Neural Stem Cell in Development and Disease", Levico Terme, September 2012.Development of cerebellar GABAergic interneurons. XIII Sins Congress, Milan, October 2009.
Development of cerebellar GABAergic neurons. Institute of Anatomy, Anatomy and Cell Biology, University of Bonn, June 2009.
Development of cerebellar GABAergic interneurons. Regional multidisciplinary biomedical workshop-NEUROIMAGE. Opatija, December 2008.

- Editorial duties:

Guest referee for international scientific journals:
PLoS ONE; Neuroscience; Eur. J Neurosci.

Enrica Boda

Grants 2010/2015

Starting- end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
2015 – 2017	National	PI BODA	Cariplo Foundation	*Characterization of a novel microRNA involved in myelination: a new potential pathogenetic mechanisms in multiple sclerosis.*	ID: 2014-1207)	€80000	€80000

Awards:
-2015 Scientific Meeting Grant, to organize the Symposium “Intrinsic and extrinsic regulation of oligodendrocyte progenitor cell self-renewal and differentiation” in the frame of the XVI Congress of the Italian Society for Neuroscience (SINS), granted by The Company of Biologists, Cambridge, UK (6000£).
-2015 IBRO International Travel Grant, to attend the European Meeting on Glial Cells in Health and Disease 2015, Bilbao, Spain
-2015 Postdoctoral Fellowship granted by Fondazione Umberto Veronesi, Milan, Italy.Targeting oligodendrocyte progenitor cell division mode to improve myelin repair in the aging CNS
-2014 Poster prize at the Basel Stem Cell Network Meeting, 9-10 September 2014, Basel, Switzerland
-2014 One of the 30 Post-Doc and Young PIs selected for the Summer School for Young PIs, CSTF, University of Turin and Post-Doc Development Center, Imperial College (London, UK), Bardonecchia, Italy
-2014 One-year postdoctoral fellowship granted by Fondazione Umberto Veronesi, Milan, Italy. Rejuvenating the brain: targeting neural stem/progenitor cell division mode to improve cognitive functions and repair abilities of the aging CNS.
-2012 - 2013 Two-years postdoctoral fellowship granted by Giuseppe Levi Foundation, Accademia Nazionale dei Lincei, Rome, Italy. Oligodendrocyte progenitor self-renewal and differentiation: insights into symmetric and asymmetric divisions and possible implications in dysmyelination following peri-natal hypoxia.
-2012 One of the 42 students selected for the Advanced School on New Approaches in Glial Cell Research, International Society for Neurochemistry, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain
-2011 Travel grant to attend the 2011 IBRO congress (granted by the Italian Society of Neuroscience)
-2011 Short-term fellowship granted by the CRT Foundation, Alfieri Project. Host: Dept. of Neuroscience, University of Turin. PI: Dr. Annalisa Buffo
-2009 - 2010 Post-doc fellowship granted by the Italian Ministry of Health, Ricerca Finalizzata, RF-CNM-

-2005-2009 PhD fellowship granted by the CRT (Cassa di Risparmio di Torino) Foundation, Lagrange Project for the study of Complex Systems. Host: Dept. of Neuroscience, University of Turin. PI: Prof. Filippo Tempia
-2006 OPTIME Award 2005-2006 (The best graduate student at the Faculty of Biology, University of Turin) by Unione Industriale di Torino.
-2005 Antonio Marzullo Award (The best undergraduate students in Cellular Biology), granted by University of Trieste, Italy

- International collaborative experiences:

Verdon Taylor (University of Basel, SW); Akiko Nishyiama (UConn, USA)

Invited talks:
Heterogeneity and balance between proliferation and differentiation in the oligodendrocyte progenitor pool. 18 November 2015, "NICO meets DisFEB" Seminar Series, Department of Pharmacological and Biomedical Sciences, University of Milan, Italy
Balancing self-renewal and differentiation of the oligodendrocyte progenitor pool: insights into cell intrinsic regulatory mechanisms. 9 October 2015, SINS (Italian Society of Neuroscience) Meeting 2015, Cagliari, Italy
Dynamics of self-renewal and differentiation of the oligodendrocyte progenitor pool in the CNS parenchyma. 29 November 2013, CNR, Institute of Neuroscience, Milan, Italy
The GPR17 receptor in oligodendroglial cells: focus on cell heterogeneity, maturation and participation in CNS damage. July 2012, Advanced School on New Approaches in Glial Cell Research, International Society for Neurochemistry, Barcelona, Spain
The GPR17 receptor in oligodendroglial cells: cell maturation, heterogeneity and participation in CNS damage. November 2011, IV Convegno Monotematico della SIF, 'Immunità e infiammazione nelle malattie del cervello. Nuovi bersagli farmacologici per terapie innovative', Milan, Italy
Chairperson of the Data Blitz "Targeting specific neurotransmitter receptors in brain damage and repair" session of the IV Convegno Monotematico della SIF, 'Immunità e infiammazione nelle malattie del cervello. Nuovi bersagli farmacologici per terapie innovative', Milan, Italy, November 2011.

- Editorial duties:

Guest reviewer for: BMC Molecular Biology, Neurochemical Research, Purinergic Signalling. Ad-hoc reviewer for MS Research Australia

Please list your organizational activities:

- Workshops, Schools or Conferences organized by members of the group

Chairperson and organizer of the symposium: "Intrinsic and extrinsic regulation of oligodendrocyte progenitor cell self-renewal and differentiation" 9 October 2015, SINS (Italian Society of Neuroscience) Meeting 2015, Cagliari, Italy

Elena Parmigiani

- International collaborative experiences:

Andreas Bosio, Miltenyi Biotec, Koln; isolation of astroglial-like progenitors
Verdon Taylor, University of Basel, generation of lentiviral vectors for targeted Cre-expression

- Invited talks:

"Chasing cerebellar neurogenesis: lineage contiguities between interneurons and

astrocytes". "NICO meets DisFEB" Seminar Series, Department of Pharmacological and Biomedical Sciences, University of Milan, Italy. April 27, 2015.
"Heterogeneity of astroglial progenitors in the developing cerebellum". CNR, Institute of Neuroscienze, Milan, Italy June 19, 2015.
"Lineage relationship of neuronal and glial phenotypes derived from the prospective cerebellar white matter". Neurooscience 2012, New Orleans (LA, USA), October 13-17, 2012. Oral presentation in nanosymposia.
"Expression and trafficking of GPR17 in immortalized oligodendrocyte precursor cells". Oral presentation at the ABCD (Association of Cell Biology and Differentiation) congress "Stem cells, development and regenerative medicine", Parma (Italy), April 9-10, 2010

Elisa Fucà

- International collaborative experiences:

Brain Repair Group at Cardiff School of Biosciences (Cardiff University, UK). Director: prof. Stephen Dunnett.

Valentina Cerrato

Awards:
March 1st 2015. Training stay grant awarded by NENS Exchange Grant in the laboratory of Prof. Laura López-Mascaraque, Instituto Cajal, Madrid.
2015. Awarded IBRO stipend for the Introductory Course - Glia Meeting, Bilbao.

- International collaborative experiences:

Prof Laura López-Mascaraque, Instituto Cajal, Madrid, clonal analysis of astroglia
Prof Magdalena Gotz, LM, Munich, mechanism of Bergmann Glia proliferation

- Invited talks

- "Cerebellar astroglial heterogeneity and role of Bergmann Glia during cerebellar foliation", Instituto Cajal, Madrid (February 25th, 2015).

6. Past Research activity

(Summarize the PI and group research activities in the last 10 years) 2005-2015

a. Summary (500 characters)

We investigated CNS structural plasticity to exploit this knowledge for both understanding pathogenic mechanisms and implementing repair after damage. We identified key cellular and molecular players in the generation of cerebellar neurons, defined fundamental CNS changes triggered by environmental stimuli and promoting circuit remodelling, and unveiled unprecedented stem cells properties in reactive astroglia as well as mechanisms of oligodendrocyte progenitor maintenance and maturation.

b. Background (2000 characters)

The beginning of the 21st century has witnessed a substantial change in the way brain repair is conceived. A new vision has emerged from the discovery that the adult CNS retains a significant potential for cell replacement and circuit rewiring, as shown by the persistence of stem/progenitor cells and connections remodelling in response to external stimuli. Hence, intense efforts have been dedicated to understand these forms of structural plasticity in view of their exploitation to repair the damaged CNS. Developmental plasticity has been further targeted to unveil mechanisms that might be reinstalled in the adult brain.

Our research addressed:

i) Specification of multipotent progenitors and integration of new neurons into neural circuits Developmental studies can reveal how defined neural types are specified and circuits correctly formed. Mechanisms that regulate these steps are largely unknown but essential to develop therapies for neurological diseases where lost/dysfunctional cells have to be replaced by either endogenous sources or through transplantation.

ii) Interplay between experience, intrinsic growth-regulatory factors and extrinsic cues in the control of CNS axon plasticity Lesions to the CNS lead to neuronal death and circuit disconnection causing sensory, motor or cognitive impairment. Despite central neurons hardly regrow transected axons, the CNS can partly restore lost functions by circuit remodelling. Environmental stimuli promote remodelling and functional ameliorations but the underlying cellular and molecular mechanisms needed to be clarified.

iii) Stem/progenitor functions of glia Besides their neurosupportive and scarring activities, astrocytes were shown to include stem cells. Further, a new progenitor population was demonstrated at the source of myelinating oligodendrocytes and took the stage as the major pool of proliferative progenitors in the adult brain. Questions emerged on the regenerative potential of adult quiescent and reactive glia.

c. Rationale (2000 characters)

The capability of the adult mammalian CNS to regenerate or repair after damage is very limited as a consequence of the postnatal decline of neurogenesis and

gliogenesis, and of the upregulation of molecules inhibiting circuit remodelling. However, it retains significant levels of structural plasticity that, if fostered, might promote brain repair.
We therefore sought to understand the cellular and molecular mechanisms that underlie key components of CNS structural plasticity to exploit this knowledge for both understanding pathogenic mechanisms of neuro-developmental disorders, and defining strategies implementing functional and anatomic repair in developmental diseases and neurodegenerative pathologies.
To address these issues, we focussed on the rodent cerebellum as an experimental model to study developmental processes of fate specification, cell differentiation and circuit formation and the effects of enhanced environmental stimulation or sensory deprivation/deafferentation on neuronal connectivity and expression of perineuronal nets (PNNs) and their components. We further explored the functional contiguity between forebrain parenchymal astroglia and neural stem cells, and the regulatory mechanisms of adult neurogenesis. Finally we investigated mechanisms balancing proliferation and differentiation in oligodendrocyte progenitor cells (OPCs).

Overall, evidence gained with these studies provided the background knowledge to address the efficacy of preventive or therapeutic cell replacement approaches vs rehabilitative training (vs the combination of the two) in rodent models of Ataxia and Hungtington's disease (HD).

d. Objectives (1500 characters)

Main goal of our research is elucidating fundamental processes of CNS structural plasticity, including developmental and repair processes. This knowledge is crucial to understand pathogenic mechanisms of neuro-developmental disorders and to define efficient therapeutic approaches for a broad spectrum of CNS diseases, including neurodegeneration, developmental disorders and vascular or traumatic damage.

Specific aims:

a) disclosing how multipotent stem cells become specified to produce differentiated subtypes of neurons and glia and unveiling rules governing an efficient integration of new neurons in pre-existing circuits;
b) revealing how external stimuli interact with extrinsic and intrinsic growth-modulators in neurons to promote circuit remodelling;
c) understanding similarities and differences between parenchymal astroglia and stem cells and regulatory mechanisms of adult stem cells in order to implement the reparative properties of non-germinal glia upon brain damage;
d) understanding physiopathology of oligodendrocyte progenitor cells (OPCs);
e) exploiting the knowledge gained with these studies to define:

- effective strategies based on preventive/therapeutic cell replacement approaches in rodent models of Ataxia and HD;
- molecular manipulations and rehabilitative training protocols helpful to promote neuroprotection and recovery of lost functions through the broadening of glial and neuronal plasticity.

e. Results (4000 characters)

Major findings:
i) <u>Specification of multipotent progenitors and integration of new neurons into neural circuits</u> The transcription factor Neurogenin2 was shown to modulate the cell cycle of early progenitors and Purkinje cell (PC) dendritogenesis (Florio et al., Development

2012). We found that all GABAergic interneurons derive from a common pool of progenitors that proliferate in the prospective white matter (PWM) of the perinatal/early postnatal cerebellum and then delaminate to fully mature. The fate choices of postmitotic immature interneurons depend on environmental cues of the PWM (Leto et al., J Neurosci 2006; 2009) while their number is regulated by Shh and cyclin D2 (De Luca et al., Cerebellum 2015; Leto et al., Development 2011). Finally, we identified two astrocyte-like progenitor types in the PWM: bipotent progenitors generate both interneurons and WM astrocytes while gliogenic progenitors exclusively produce other astrocytes (Parmigiani et al. J Neurosci 2015). We are now investigating how the various cerebellar astroglial phenotypes are produced. As for cell integration, correct placement of grafted neurons depends on timing of their migration (Carletti et al., Dev Biol 2008; Williams et al Neurobiol Dis 2008) and neuronal lifespan is independent of the species-specific lifetime (Magrassi et al., PNAS 2013). These data were instrumental to study cell replacement and rehabilitative training in models of Ataxia or HD.

ii) Interplay between experience, intrinsic growth-regulatory factors and extrinsic cues in the control of CNS axon plasticity We found that increased environmental stimulation induces axonal plasticity and PNN reduction in the mouse cerebellar nuclei. These events are enhanced in mice overexpressing (*ov*) GAP-43 in PCs (Foscarin et al. PLoS ONE 2011). GAP-43 *ov* injured PCs also show a reduced sensitivity to myelin, due to altered subcellular distribution of receptors for myelin inhibitors (Foscarin et al., EJN, 2009). We also found axon terminal plasticity in concomitance with PNN reduction in the cerebellar nuclei or vestibular nuclei after deafferentation. Moreover, in the vestibular nuclei PNNs are restored when vestibular deficits are resolved (Carulli et al. MCN 2013; Faralli et al., Brain Struct Funct 2015). We discovered that the chemorepulsive molecule Sema3A is a PNN component that decreases in conditions of plasticity (Vo et al., MCN 2013; Carulli et al., MCN 2013), suggesting a key role of Sema3A in PNN inhibitory properties. Finally, lack of PTEN in PCs alters PC morphology and physiology, and induces autistic-like traits (Cupolillo et al. Neuropsych 2015).

iii) Stem/progenitor functions of glia We found that reactive glia can be engaged in neurogenesis by expression of neurogenic determinants (Buffo et al., PNAS 2005) and that a subset of reactive astroglia resume proliferation and behaves as neurogenic stem-cell ex vivo (Buffo et al. PNAS 2008). Notably, such a transition can occur spontaneously in striatal astrocytes after damage (Nato et al., Development 2015). We demonstrated that the plasticity restrictors Nogo-A/NgR1 are negative regulators of adult neurogenesis (Rolando et al. J Neurosci 2012) and that early damage signals (purines) affect adult stem cells both directly and through reactive astrocytes (Boccazzi et al., Glia 2014).
As regards OPCs, we identified the GPR17 receptor as a key marker of the pre-oligodendrocyte stage that modulates OPC differentiation (Lecca et al.,PLoS One 2008; Boda et al., Glia 2011; Ceruti et al. , Glia 2010; Fratangeli at al., J Bioch Chem 2013). We also discovered that, similar to stem cells, OPCs undergo asymmetric division and that their division mode is altered by aging and demyelination (Boda et al., Glia 2015). We also investigated molecular mechanisms implicated in OPC specification/differentiation (Jagged1, Beattle et al., in preparation), cell division (CitronK, Boda et al. in preparation) that might be exploitable to treat myelin alterations.

f. Advancement in the field (1000 characters)

Major findings:

i) -multipotent features of progenitors for cerebellar interneurons and role of extrinsic cues in their differentiation;
-demonstration that bipotent progenitors generate cerebellar interneurons and astrocytes.

ii) -role of PNN modulation in the regulation of plasticity both in physiological and injury conditions;
-key-role of the PTEN pathway in PCs in the induction of autistic-like traits.

iii) -unprecedented stem cells properties in reactive astroglia;
-inhibitory role of NogoA/NgR in the homeostasis of adult neurogenesis;
-the role of GPR17 in the regulation of oligodendrocyte maturation and characterization of OPC asymmetric divisions.

These findings contributed to the establishment of new paradigms in brain plasticity, as testified by the high citation index of several publications, citations on textbooks (eg Glial physiology and pathophysiology" by Verkhratsky and Butt, Wiley-Blackwell, 2013) and by the strong international visibility of the group (see sections 1-5).

7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do

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7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do

a. Summary (up to 2000 characters):

Our research will focus on the role of glia and progenitor cells in brain plasticity and repair, and on the implementation of cell replacement approaches and/or training protocols to promote functional recovery in CNS diseases.

We believe that specific issues regarding glia and neural progenitors are particularly promising to unveil new keys to the understanding of physiology, disease and repair. As for astrocytes, very little is known on how distinct astroglial subtypes are specified and how much it impacts the shaping of the circuits. Further, mechanisms underlying the acquisition of stem cell properties in parenchymal astroglia remain undefined. We will address these issues by studying the specification of astroglial subtypes in the cerebellum, and the latent stem cell properties of adult striatal astroglia, respectively. Oligodendrocyte progenitors self-maintain but have limited capability to repair myelin. Understanding their biology may help fostering myelin regeneration and reveal unsuspected functions of these progenitors in integration of information in the CNS, as provided by communication with neurons.

Recent advancements in human stem cell technology and reprogramming prompt the need of developing strategies to obtain proper differentiation into specific neuronal identities and functional integration in the recipient brain. Moreover, based on the efficacy of external stimuli and training to promote circuit plasticity, rehabilitation protocols appear as promising tools to promote adaptive remodelling of defective circuits and to enhance the integration of transplanted cells into the recipient tissue, therefore boosting functional recovery. We will perform preclinical studies to define therapies for neurological diseases based on adaptive cell replacement and/or manipulation of circuit plasticity.

b. Background and Significance (up to 4000 characters):

Building upon research developed over the last years, we will focus on the role of glia and progenitor cells in brain plasticity and repair, and on the implementation of cell replacement therapies and/or training protocols to promote functional recovery in neurodegenerative and developmental diseases.

Issues of glial biology considered to be most promising to unveil their role in pathology and brain repair include how the various astrocyte phenotypes are generated and how parenchymal astrocytes can be instructed to acquire stem cell properties in the injured CNS. Further, among the hot topics in the field of oligodendrocyte physiopathology are how to push the OPC balance between self-

renewal and differentiation towards the latter fate, and how OPC and neurons communicate. In our studies we will address all these aspects.

Astrocytes comprise extremely heterogeneous phenotypes, including stem cells (NSC) in the neurogenic niches and parenchymal subsets that spontaneously activate neurogenesis after damage. In the intact parenchyma, astrocytes participate in neuronal activity and are increasingly implicated in neurodevelopment and disease. However, how astroglial heterogeneity is achieved developmentally and how much it impacts on CNS functions is unknown. Understanding these aspects may reveal unknown features in the aetiology and progression of neurologic and psychiatric disorders. Further, the intrinsic and extrinsic mechanisms that trigger the transition of some astrocytes to a NSC status are largely unknown. Understanding how to implement these features in all astrocytes may lead to exploit their reparative plasticity not only to elicit neurogenic attempts, but, more broadly, to evoke in situ the 'bystander' neurosupportive/immunomodulary actions well-known for grafted and endogenous NSC reacting to damage (Martino and Pluchino 2006; Butti 2012).

OPCs are the major population of proliferative progenitors in the mature CNS, where they are the source of myelinating cells under basal and injury conditions. We have shown that during the adult life OPCs sustain both self-renewal and oligodendrogenesis by undergoing asymmetric divisions. They also display significant levels of phenotypic and functional heterogeneity. We are interested in unveiling: i) the molecular mechanisms underlying OPC self-maintenance through asymmetric divisions; ii) whether OPC phenotypic heterogeneity corresponds to progenies with distinct regenerative potential in disease; iii) factors promoting remyelination; iv) if and how OPC communicate to neurons. These studies aim at disclosing novel aspects of oligodendrocyte biology in view of fostering their capability to regenerate myelin. Further, they aim at revealing an unprecedented level of integration of information in the CNS as provided by OPC-to-neuron communication.

Knowledge gained from developmental studies and from investigations on mechanisms governing circuit remodelling provides crucial information to design effective therapeutic strategies based on **cell replacement** and/or **rehabilitative training** in case of neuronal loss or establishment of dysfunctional circuits. Here, advancements in human stem cell technology and reprogramming prompt the need of preclinical studies to develop strategies to obtain endurable donor cell engraftment in the host, including acquisition of specific neuronal identities and functional integration in the recipient brain. Moreover, based on the efficacy of external stimuli and training to promote circuit plasticity, generalized and/or specific rehabilitation protocols appear as promising tools to promote adaptive remodelling of defective circuits and to enhance the integration of transplanted cells into the recipient tissue, therefore boosting functional recovery. Our studies will address these issues to help the development of therapies for neurological diseases based on adaptive cell replacement and/or manipulation of circuit plasticity.

c. General aim and integration with mission of the Institute (up to 1000 characters)

Our work has two main aims:

- understanding glial/progenitor heterogeneity at the molecular, cellular and functional levels and clarify how such features impact on CNS pathophysiology in order to exploit adult glia and progenitors as therapeutic actors to treat disease;

- developing therapies for neurological diseases where loss/dysfunctional cells have to be replaced by either endogenous sources or through transplantation.

The contribution of our group will be to deliver innovative evidence and expand expertise on fundamental processes of brain plasticity implicated in developmental psychiatric disorders and neurodegenerative diseases, which may be fostered or manipulated to propose preclinical innovative therapeutic approaches for CNS diseases.

d. Specific objectives and strategies (up to 4000 characters):

To unravel mechanisms of astrocyte specification and plasticity we will:
-understand phenotypic specification of cerebellar astrocytes (A) and their role in neuronal functions We found that distinct embryonic progenitors produce the 4 types of cerebellar A (Cerrato,in preparation). Preliminary data suggest that Sox2 specifies Bergmann glia (Leto, in preparation), while Trnp1 regulates their amplification (Cerrato, unpublished). We will study the role of these targets, and their implications in cerebellar functions. *Coll: S Nicolis,Milan,M Goetz Munich, F Tempia,NICO*
- ***identify mechanisms underlying the acquisition of NSC properties in reactive A*** Upon damage striatal A acquire NSC properties and activate neurogenesis (Nato et al.,2015). We will examine implicated intrinsic (the stemness factor Sox2) and extrinsic factors (microglia). We will also unveil possible lineage contiguity between the responsive A and SVZ NSC. *Coll: F Luzzati,NICO, S. Nicolis,Milan*

To understand oligodendroglia physiopathology we will:
- assess whether OPC subsets exist with distinct potential for self-renewal and myelin repair Asymmetric divisions occur in OPCs and OPC subsets express Hes5 or Ascl1 (Boda, unpublished) that control NSC functions (ie maintenance/quiescence vs. activation and differentiation, respectively). We will assess if: i) Hes5+ OPCs maintain the pool while Ascl1+ OPCs are more prone to proliferate and differentiate; ii) the 2 subsets differently remyelinate. We will also assess the role of Notch ligands (Jagged1, Dll1,3)/effectors (Rbpj) in asymmetric divisions and choice of proliferation vs differentiation. *Coll: V Taylor,Basel*
- identify strategies to promote OPC remyelination
a) miR-125a is upregulated during OPC differentiation and affects their maturation in vitro (Lecca, unpublished). We will examine its expression pattern in models of toxic demyelination. Functional manipulations will be applied and, those promoting repair, extended to MS models. *Coll: D Lecca,MP Abbracchio,Milan*
b) Extracellular vesicles released by alternatively activated/mesenchymal stem cells exposed-microglia promote myelination in vitro (Verderio,unpublished). We will assess if they also prompt remyelination in vivo after toxic demyelination, and, if confirmed, in MS models. Underlying molecular mechanisms will be investigated. *Coll: C Verderio,Milan, A Uccelli,Genoa*
- ***define unconventional roles of OPCs*** Preliminary data (Boda, Marcantoni, unpublished) show that OPCs trigger the maturation of neuronal networks and enhance GABAergic transmission in mature circuits. Electrophysiology and analysis of candidate paracrine/contact factors will substantiate these data. In a mouse line where OPCs are inducibly deleted we will study electrophysiology in vivo and possible behavioural outcomes. *Coll: E Carbone,Turin, G Martino,Milan, A Nishyiama,UCONN*

Devising therapeutic approaches based on cell replacement and training

Purkinje cell (PC) grafts in the Ataxia model Tambaleante do not arrest neurodegeneration or ameliorate motor symptoms. Conversely, motor training improves motor deficits and slows PC degeneration (Fucà, in preparation). We will assess if the combination of training and grafts has synergistic/additive effects and how motor training reduces PC death.
Enriched environment and Constraint Induced Movement Therapy ameliorate motor symptoms in a HD rat model (Fucà,unpublished). We will examine if they enhance differentiation/integration of grafted human neural progenitors, and result in further functional repair. *Coll A Vercelli,NICO, E Cattaneo,Milan*

Expertise in myelin, PNN, rehabilitative training will be shared with C. Eva (NICO) to study the effects of early life experience (maternal behaviour) on plasticity brakes and susceptibility to anxiety in adults.

Approaches: in vitro assays, in vivo fate mapping, conditional deletion, GOF and LOF, clonal analysis, viral technology, microsurgery, electrophysiology, behavioural tests, high-resolution immunohistology.

e. Unique features of the project research (up to 2500 characters):

Several of the addressed questions (ie understanding and awakening latent reparative/regenerative potentials in glial cell, disclosure and understanding of neuromodulatory roles of OPCs) are highly innovative and essentially unanswered in the field. Moreover, we will combine several innovative approaches including the use of extracellular vesicles released by alternatively activated microglia as therapeutic agents, cutting edge technology for clonal analyses in vivo (see Parmigiani et al., 2015 to get insight on this technology), gene expression analyses on selected glial cell populations isolated from the CNS, strategies to deplete specific cellular populations (eg inducible NG2CreERT2iDTR), and specific rehabilitative training protocols. Thanks to our collaborative network, we will also employ induced human neuron precursors for transplantations in rodents, being therefore directly exposed to the fast evolving technology of reprogramming, and use rabies virus to trace connections. On top of this, we have generated and will develop inducible mouse lines that will constitute unique experimental models.

f. Methodology (up to 2000 characters): <u>please fill-out this section only in the case of innovative technologies</u>

g.

In collaboration with Filippo Molinari (Politecnico di Torino) and Federico Luzzati (NICO) we will develop a tool for the automathised analysis and interpretation of confocal images suitable to produce unbiased data and perform quantitative analyses for clonal studies or dispersion of cells in the nervous tissue. The system will: i) perform multiscale analysis, at low and high magnification, for the analysis of single cells or clusters or for the spatial analysis of the whole sample (ed mouse cerebellum, hemispheres etc); ii) couple automathised cellular detection and algorithms for numerical analysis and modelling, so to provide parameters related to cell dispersion in the tissue; iii) support morphofunctional modelling. We aim at developing a versatile tool to be applied for different mapping-related purposes and released as an open source tool.

8. Letter of intent by the PI (1 page)

Assessment on leadership and ability to manage his/her group

Back from a research stay in Munich, dr Buffo has established an independent research line and published high-quality papers, built new collaborative networks and obtained funds for research, attracted excellent graduate students and formed young scientists that now are continuing their research carrier at top research institutions. From January 2014 she has also taken the responsibility of Ferdinando Rossi's group, guided and supported all the research activity of the team during the transition toward the definition of a renewed group identity. Overall, the group has shown a stable production of high-quality original data, members have progressed in the acquisition of professional competence and skills, and several have undertaken key-steps for their carrier progression. Moreover, the group became the promoter of the organization of numerous science-related activities at NICO (from the organization of common services to the establishment of seminars and internal progress reports).

On the whole, and taking into account the limitations due to the dramatic shortening of funds for fundamental research at the local, national and even European levels, the aims defined for the group were achieved and innovative scientific concepts developed. Overall the PI's motivation to guide the group towards new excellence objectives is very high.

Possible internal problems within his/her group and the strategies for the best solution:

The main internal problem for the group is the upcoming reduction of group size while many projects are running. However, we are going to recruit one more Postdoc on the Merck-Serono grant and, together with Carola Eva, we have recruited dr Ishira Nanavaty to provide technical help. As a specific strategy to recruit new PhD students, we plan to submit an ESR Marie Curie application leaded by Fernando de Castro (Instituto Cajal-CSIC, ES) by January 2016.

Commitment in supporting the general activities of the Institute:

Contributions to general activities of the Institute: proposal to organise common facilities and their organization; establishment of two P2 labs for production, in vitro and in vivo use of viral vectors; proposal and organization of seminars and of internal progress reports; organization of outreach activities: open days, high school visits to the labs, researchers' night, promotion of NICO in public talks; proposal to acquire new instruments when funds were available (Q-RT PCRs, centrifuges, 2photon confocal microscopy); support to the SpinOff development; introduction of innovative research approaches (eg in vitro and in vivo assays for stem/progenitor cells, cre-lox based inducible technology, clonal analyses in vitro and in vivo, in utero electroporation, injections and transplantation, cell isolation by FAC/MACsorting).

Specific pitfall and difficulties to realize his/her projects:

In the last years we have submitted about 10 research proposal/year to private and public agencies. However, due to high competition, limited fund availability, and prevalent interest for translational issues, very few applications were successful. Funds limitation significantly slowed our work and partly frustrated the efforts we put in obtaining preliminary data to support grant applications and to establish collaborations. Despite these difficulties, we published original data, reviews and commentaries of broad relevance.

Established internal and external collaborations:

External collaborators include: MP Abbracchio, Milan, C Verderio, Milan, P Rosa, Milan, G Martino, Milan, A Uccelli, Genoa, Magrassi, Pavia, S Nicolis, Milan, E Cattaneo, Milan, B Taylor, Basel, M. Schwab, Zurich, L Lopez-Mascaraque, Madrid, M Goetz, A Bosio (Miltenyi) Koln (as testified by publications, exchanges of personnel and grant submissions). Local collaborators are: C Eva, F Luzzati, A Vercelli, F Tempia (NICO); E Carbone, F Di Cunto, A Brusco, A Roetto (UniTO).

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name: Neuropsychopharmacology

1. LABORATORY DESCRIPTION – PERSONNEL:

- **Principal Investigator**

Carola Eugenia Eva — Birthdate (21/07/1957)
PhD — Female
Italy — Phone:+390116706608
Email:carola.eva@unito.it

- **Personnel**

1. Alessandra Oberto — Birthdate (24/10/1967)
   PhD in pharmacology — Female
   Research Associate — Italy
   Biotechnology, behavioral analysis, immunohistochemistry

2. Ilaria Bertocchi — Birthdate (13/04/1982)
   PhD in pharmacology — Female
   Research contract — Italy
   Biotechnology, behavior analysis, immunohistochemistry

3. Angela Longo — Birthdate (19/03/1982)
   PhD in pharmacology — Female
   Postdoctoral fellow — Italy
   Behavioral analysis, immunohistochemistry

4. Paolo Mele — Birthdate (22/06/1973)
   PhD in pharmacology — Male
   Postdoctoral fellow — Italy
   Expertise Behavioral analysis, immunohistochemistry

5. Mattia Ghigo — Birthdate (12/08/1989)
   Master in Psychology — Male
   PhD Student — Italy
   Learning behavioral analysis and immunohistochemistry

2. PRINCIPAL INVESTIGATOR CURRICULUM VITAE (two pages)

Education and training:

1981 Doctoral, Summa cum Laude, University of Turin, Faculty of Science MFN
1988 Ph.D in Pharmacology and Toxicology.

Employment and research experience:

1982: National Institute of Mental Health, Washington D.C. , USA.
1983-85: Visiting Fellow, National Institute of Mental Health, Washington D.C. , USA.
1985-86: Research associate, School of Medicine, Georgetown University, Washington D.C., USA.
1987- 92: Postdoctoral Fellow, Medical School, University of Turin.
1989- 90: Centrum for Molecular Biology Heidelberg, Heidelberg University, Germany
1992-98: Research Associate, Medical School, University of Turin.
1998- 04: Associate Professor of Pharmacology, Medical School, University of Turin.
2004-present: Full professor of Pharmacology, Medical School, University of Turin.

Relevant discoveries:

Carola Eva is internationally recognized for her studies on NPY e Npy1r receptor that were performed by using biomolecular, histochemical, image analysis, behavioural and pharmacological techniques. In particular: cloning of orphan 7 TM receptors, Npy1r cDNA and gene; regulation of Npy1r gene transcription (NF-kappaB, estrogens); role of the Npy1r in the regulation of the feeding behavior; interaction between GABA, NPY and neuroactive steroids during pregnancy, stress response and ethanol consume.
The research group coordinated by Carola Eva has generated transgenic mice and conditional knockout mice for the murine Npy1r gene that represent innovative models to study the role of Y1R in anxiety, stress response and energy homeostasis.
The results of Dr. Eva's studies are published in 69 publications, 49 listed in PUB Med (1141 citations, H-index 18, mean IF 5,03).

Please list your grants according to the table below (last five yrs).

Starting - end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
2009-2012	National	PI	Compagnia di San Paolo Foundation	Conditional knockout NPY-YIR mice as an experimental model to study vulnerability to psychopathology		€150.000	€5.064,00
2010 - 2012	National	PI	MIUR	Conditional NPY-Y1R knockout mouse: stress physiology and biomedical implications.	2008 PLK P3E_ 003	94.000	
2013-2016	National	PI	MIUR	Effect of substances of	2010 7MS	121.000	

				abuse, psychoactive drugs, stress and maternal care on brain development and vulnerability to psychopathology	MA4_004		
2014-2017	National	PI	Cariplo Foundation	A novel hypothesis on the development of metabolic syndrome in women	2013-0786	100.000	7401,41
2014-2016	National	PI	CRT Foundation	Meccanismi complessi che sottendono gli effetti permanenti dell'ambiente perinatale sulla plasticità neurale e la vulnerabilità a psicopatologie: dalle molecole della matrice alle proprietà fisiche del tessuto nervoso al comportamento		26.000	2080
2015-2017	National	PI	Compagnia di San Paolo Foundation	Influence of maternal behaviour on the expression of brain plasticity brakes: a role in the susceptibility to anxiety?		97.918,38	7253.21

Please list the name of PhDs you have supervised.
Alessandra Oberto
Paolo Mele
Angela Longo
Ilaria Bertocchi
Rossella Brusa

Please list honours, prizes or awards received, If applicable.

Please list your outreach activities

- describe your international collaborative experiences.

1. With Dr. Rolf Sprengel (Max Plank Institute for Medical Research, Heidelberg, Germany) we collaborated in generation of Npy1r^{rfb} and Npy1r$^{Y5R-/-}$ conditional ko mice. A postdoctoral fellow from our lab (I. Bertocchi) has spent 5 years at Sprengel's laboratory and we have now started a collaboration to study the localization of fear memory engram.

2. We have sent our Npy1r floxed mice to Dr. Gavin Bewick (Division of Diabetes & Nutritional Sciences, School of Biomedical sciences, King's College London,London, UK). They will develop an adult Npy1r beta cell specific knockout mouse to understand the importance of signalling at this receptor on beta-cell function.
3. We have sent our Npy1r floxed mice to Dr. Roland Schuele (Department of Urology, Center for Clinical Research, University Freiburg Medical Center, Freiburg, Germany). They will induce cell-selective deletion of Npy1r in metabolic tissues such as liver and muscle to investigate whether histone demethylase LSD1 and Npyr1 might interplay to control LSD1-regulated gene activity.
4. Dr. Eric Grouzmann, (Centre Hospitalier Universitaire Vaudois, Département des Laboratoires, Laboratoire des Catécholamines et Peptides, Hôpital Beaumont, Lausanne, Switzerland) has kindly given us his policlonal and monoclonal NPY antibodies and he will measure cathecholamine plasma levels on our Npy1r^{rfb} mice.
5. We have started a collaboration with Dr. Janice Urban (Rosalind Franklin University of Medicine and Science, Physiology & Biophysics, North Chicago, Illinois, USA) to investigate the role of Npy1r in maternal behaviour in mice and rats.
6. Collaborations with Dr Jessica Kwok (Faculty of Biological Sciences, University of Leeds, UK), Dr. Ralf Ritcher (Parque tecnológico de San Sebastián, San Sebastian, Spain) and with Dr. Stefano Vicini (Department of Physiology and Biophysics, Georgetown University School of Medicine, Washington DC, USA) are widely described in Section 7,Future Projects (project 1)

- Invited talks

-Dep. of Life and Environmental Sciences, University of Cagliari
- Department of Pharmacological and Biomolecular Sciences, University of Milan
- Department of Molecular and Translational Medicine, Pharmacology Section, University of Brescia
- Molecular Biotechnology Center, University of Turin
- Simposium “Anxiety disorders: form animal models to clinical treatment” XVIII National Meeting of the Italian Society of Neuropsychopharmacology.
- Simposium “Estrogens and pathologies associated with ageing” 37° Meeting of the Italian Society of Pharmacology

Editorial duties

Reviewer of manuscripts for intrnational journals including Science, Translational Psychiatry, Life Science, PLOS, European J. Neuroscience, Peptides, Neuroendocrinology, Journal of Behavioral and Brain Science.

Please list your organizational activities:

- Speakers invited

Paola Palanza

- Workshops, Schools or Conferences organized

Please list your technology transfer achievements (patents, etc.), if applicable

PI's PUBBLICATIONS:

-Longo A., Oberto A., Mele P., Mattiello L., Pisu M.G., Palanza P., Serra M., Eva C. (2015). NPY-Y1 coexpressed with NPY-Y5 receptors modulate anxiety but not mild social stress response in mice. Genes Brain Behav., 14(7):534-42
IF= 3.661; R=7/51; Times cited= 0.

-Longo A., Mele P., Bertocchi I., Oberto A., Bachmann A., Bartolomucci A., Palanza P., Sprengel R., Eva C. (2014) Conditional inactivation of neuropeptide Y Y1 receptors unravels the role of Y1 and Y5 receptors coexpressing neurons in anxiety. Biol Psychiatry. 76(11):840-9
IF= 10.255; R=10/252; Times cited=4 .

-Fontana R., Della Torre S., Meda C., Longo A., Eva C., Maggi A.C. (2014) Estrogen replacement therapy regulation of energy metabolism in female mouse hypothalamus. Endocrinology. 155(6):2213-21.
IF= 4.503; R=28/128; Times cited=3 .

-Bertocchi I, Oberto A, Longo A, Mele P, Sabetta M, Bartolomucci A, Palanza P, Sprengel R, Eva C. (2011) Regulatory functions of limbic Y1 receptors in body weight and anxiety uncovered by conditional knockout and maternal care. Proc Natl Acad Sci U. S A. 108(48):19395-400
IF=9.681; R=3/56; Times cited=10 .

-Resaz R., Emionite L., Vanni C., Astigiano S., Puppo M., Lavieri R., Segalerba D., Pezzolo A., Bosco M.C., Oberto A., Eva C., Chou J.Y., Varesio L., Barbieri O., Eva A. (2011) Treatment of newborn G6pc(-/-) mice with bone marrow-derived myelomonocytes induces liver repair. J Hepatol. 55(6):1263-71
IF= 9.264; R=4/74; Times cited=3 .

-Martini M., Sica M., Gotti S., Eva C., Panzica G.C. (2011) Effects of estrous cycle and sex on the expression of neuropeptide Y Y1 receptor in discrete hypothalamic and limbic nuclei of transgenic mice. Peptides. 32(6):1330-4
IF= 2.434; R114/261=; Times cited=0 .

4.GROUP's PUBBLICATIONS:

Hasan M.T., Hernández-González S., Dogbevia G., Treviño M., Bertocchi I., Gruart A., Delgado-García J.M. (2013) Role of motor cortex NMDA receptors in learning-dependent synaptic plasticity of behaving mice. Nat Commun.;4:2258 doi: 10.1038/ncomms3258
IF= 10.742; R = 3/55; Times cited = 0

5. GROUP's additional information:

Please list the grants of the other members of the group in the last 5 years - 2010/2015- according to the table below:

Starting - end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
	National vs International	P. Rossi; PI vs. Component	MIUR, ERC, ecc…			€	€

Please list honours, prizes or awards received by other members of the group If applicable.
Paolo Mele received Emilio Marmo's prize in 2005.
Paolo Mele was one of the winners of Veronesi'fellowship in 2014

Please list outreach activities of other members of the group:

- Describe your international collaborative experiences.
- Invited talks
- Editorial duties

Please list your organizational activities:

- Speakers invited by members of the group
- Workshops, Schools or Conferences organized by members of the group

Please list your technology transfer achievements (patents, etc.), if applicable

6 .Past Research activity

(Summarize the PI and group research activities in the last 10 years)

a. Summary

The focus of our research activities was to study the neural circuitry underlying anxiety and stress response at molecular and cellular levels. A second emphasis of our research was to understand sex differences in brain control of energy balance. We are particularly interested in neuropeptide Y (NPY) and its cognate Npy1r and Npy5r receptors since they play a pivotal role in the regulation of these functions and many of the molecules controlling emotion and energy balance interact with NPYergic system in the limbic system and the hypothalamus.

b. Background

Variation in stress resilience influences both normal and pathological behaviour. Anxiety and emotionality are also strongly influenced by exposures to stress in a pattern consistent with gene–environment interaction. These observations point to the importance to identify stress-vulnerability associated genes. Preclinical and clinical studies suggest that NPY plays an important role in the response to stress and in psychiatric disorders. In humans, NPY haploinsufficiency is correlated with characteristic brain responses to emotional and stress challenges and with trait anxiety. In rodents, intracerebroventricular injection of NPY reduces both anxiety and stress-related behavior, an effect that is primarily mediated by Npy1r expressed in amygdala, hippocampus, and locus coeruleus (**Eva et al, 2006a; 2006b**). NPY exerts its anxiolytic-like effect in the brain via interactions with hypothalamus-pituitary-adrenal (HPA) axis and corticosteroids. NPY is coexpressed with GABA and it mimics antianxiety, anticonvulsant and sedative action of positive modulators of GABAA receptors. NPY is also involved with neurobiological responses to ethanol and it influences ethanol consumption by regulating anxiety.

In addition to its crucial role in emotional behavior, NPY is the prototype hormone to stimulate feeding, reduce energy expenditure and induce obesity via the activation of hypothalamic Npy1r. NPY-signaling in the hypothalamus is strongly influenced by the nutritional status, and estrogen receptors activate Npy1r gene transcription, strongly suggesting that brain Npy1r represents a key metabolic target gene through which estrogens modulate energy metabolism in relation to reproductive activity. Glucocorticoids stimulate the NPY system via inhibition of CRH, thereby promoting obesity. NPY may be a potentially important mediator of ‘emotional eating’.

c. Rationale

Role of limbic Npy1r

Although multiple studies demonstrated the effects of Npy1r on stress, anxiety, obesity and energy homeostasis, global knockout (ko) of the Npy1r gene has low or no impact on anxiety and body weight. This discrepancy might be due to compensatory mechanisms arising during development or to the loss of function of a gene in all tissues where it is expressed, producing a phenotype that is the sum of all lost functions. Indeed, NPY regulates feeding behavior via pathways in the hypothalamus and emotion integration via pathways in the amygdala. Moreover, it is likely that NPY, acting on different receptor subtypes, activates distinct neuronal circuits to regulate anxiety. To study the function of Npy1r expressed in the limbic system, and to exclude effects induced by the Npy1r gene inactivation in early development, in collaboration with R. Sprengel and P. Palanza we generated conditional ko mice in which the inactivation of the Npy1r

gene was restricted to specific neuronal populations of the forebrain, starting from juvenile stages. Additionally, given that early postnatal environment can modulate NPY levels, we investigated whether Npy1r signal may represent one of the targets of maternal care-induced programming of anxiety resilience.

Interaction with the GABAergic system

In collaboration with G. Biggio and M. Serra, we previously showed that Npy1r and GABAergic systems are strictly correlated and that neuroactive steroids modulate emotional behavior and neuronal excitability by acting on both GABAergic and NPYergic transmissions. In line with these data, we had investigated the functional interaction among neuroactive steroids, GABA and Npy1r in response to neurobiological effects of ethanol and mild chronic stress.

Sexual dimorphism of the NPY-Npy1r system

In collaboration with A. Maggi and GC. Panzica we had demonstrated that steroid environment may affect Npy1r-mediated signaling as well as the NPY and Npy1r expression. Our hypothesis was that this mechanism could mediate, at least in part, the effects of estrogen on energy balance and the link between fertility and energy homeostasis in female mammals. To verify this hypothesis, we developed a pilot study to investigate whether exposure to metabolic challenges might differentially affect Npy1r gene expression in the two sexes.

d. Objectives

The aims of our past research were:

a) "*Neuropeptide Y pathways in anxiety-related disorders*": to examine whether selective ablation of Npyr in specific neuronal populations (excitatory neurons or Npy5r-coexpressing neurons) of the forebrain may differentially regulate emotional behavior as well as vulnerability to psychopathology in adulthood.

b) "*Vulnerability to psychopathologies*": to uncover the extent of involvement of NPY and its cognate Npy1r in modulating inter-individual variation in emotion and stress resiliency, with specific attention to the role of NPY-Npy1r system in permanent effects of maternal care on behavioral and hypothalamic functions.

c) "*Neural circuits*": to uncover the neural circuits underlying anxiety, stress response and ethanol consumption by determining, the interaction between NPY and its receptors, GABA and CRH (through behavioral, immunohistochemical and biochemical analyses).

d) "*Gender difference in vulnerability to metabolic challenges*": to determine the effect of a moderate to high fat, high-energy diet on Npy1r gene expression in the hypothalamus of male and female mice.

e. Results

To study the function of limbic Npy1r, we generated conditional ko mice in which the Npy1r gene inactivation was restricted to forebrain excitatory neurons, starting from juvenile stages (Npy1r^{rfb} mice) (**Bertocchi et al., PNAS, 2011**). Y1R^{rfb} male mice display increased anxiety, reduced body weight, decreased amounts of adipose tissue, lowered serum leptin levels and higher corticosterone levels. Since hippocampus is an important component of neuronal circuitry controlling HPA axis activity via glutamatergic output, the selective inactivation of Npy1r in hippocampal excitatory neurons might increase HPA axis activity and, thereby, decrease body weight.

One of the most significant findings of this study was the observation that differences in phenotypes between Npy1r^{rfb} and Npy1r^{2lox} (control) mice became apparent when both genotypes were raised by dams with high levels of maternal care. When Npy1r^{rfb} and Npy1r^{2lox} were fostered to dams with lower levels of maternal care, Npy1r mRNA levels were similarly low and both mouse cohorts showed no significant phenotypic differences, suggesting that high levels of maternal care increase the expression of limbic Npy1r expression.

Using a similar approach but targeting a different neuronal circuitry, we demonstrated that the deletion of Npy1r in Npy5r–containing neurons (Npy1r$^{Y5R-/-}$) of the limbic system produced mice with some similarities but also major differences compared with the earlier model (**Longo et al., 2014**). Although increased anxiety was observed in both models, increased HPA axis activity and decreased body weight were not observed in Npy1r$^{Y5R-/-}$ mice under basal conditions or after acute or chronic mild stress (**Longo et al., 2015**). Npy1r$^{Y5R-/-}$ mice phenotype was independent of gender and maternal care in contrast to the Y1R^{rfb} mice. Npy1r and Npy5r share similar actions in the regulation of anxiety but they are differentially expressed in the nuclei of the stress/anxiety circuits. Npy1r is enriched in the central (CeA) and basalolateral amygdala (BLA) whereas Npy5r is only present in BLA. Since 50% of neurons co-expressing Npy1r and Npyr5 are GABAergic, whereas only 25% are glutamatergic, the ablation of Npy1r gene in Npy1r$^{Y5R-/-}$ mice might occur mainly in GABAergic neurons of the BLA. This suggests that the loss of Npy1r occurs in distinct cell populations in Npy1r$^{Y5R-/-}$ and Npy1r^{rfb} mice, and this may account for the different phenotypes displayed by Npy1r$^{Y5R-/-}$ and Npy1r^{rfb} mice .
We also demonstrated that Npy1r$^{Y5R-/-}$ mice display increased perseveration in spatial reference memory that might be related to lower behavioral flexibility. We recently investigated the specific contribution of Npy1r coexpressed with Npy5r to such behavioral inhibition system, whose functions are controlled by the hippocampal formation and the orbitofrontal cortex (OFC) (**Longo et al., in preparation**). Npy1r$^{Y5R-/-}$ mice exhibit an impairment in performing the reversal task of the MWM and the water T-maze, confirming the presence of perseverative behavior. Escitalopram reverts the inflexible phenotype of Npy1r$^{Y5R-/-}$ mice. In addition, c-Fos immunohistochemistry revealed a hyperactivation of OFC in Npy1r$^{Y5R-/-}$ mice, suggesting that a dysregulation of cortical projecting network may be implicated in the observed inflexible-perseverative phenotype of Npy1r$^{Y5R-/-}$ mice.

We also investigated the relationship between fluctuations of the brain content of neuroactive steroids induced by chronic voluntary ethanol consumption or ethanol discontinuation and both NPY and Npy1r gene expression in the amygdala of transgenic mice carrying a murine Npy1r gene promoter/ LacZ reporter gene (**Eva et al., 2008**). Ethanol discontinuation increases anxiety , reduces NPY and increases Npy1r gene expression in both the MeA and CeA. The ability of ethanol discontinuation to affect NPY–Npy1r signal in the amygdala depends on fluctuations in the brain concentration of 3a,5a-TH PROG, further suggesting the important role of GABA–NPY interaction in regulating emotional behavior.

We also demonstrated that long-term consumption of a moderate/high fat (MHF) diet differentially affects Npy1r gene expression in the hypothalamus of male and female mice. MHF diet increases consumption of metabolizable energy and body weight and decreases hypotalamic Npy1r gene expression in male but not in female mice. Leptin treatment failed to decrease body weight of both MHF diet- and chow-fed females (**Zammaretti et al., 2007**). These data, together with the observation that the phenotype of Npy1r^{rfb} mice is gender dependent, demonstrate a sexual dimorphism of the NPY-Npy1r-mediated control of energy intake.

f. Advancement in the field

Results of Bertocchi et al. provide the first experimental genetic evidence that limbic Npy1rs are required for regulation of body weight and that neuronal NPY/Npy1r pathways in the limbic system are key targets of maternal care-induced programming of anxiety and energy homeostasis.

The studies by Longo et al. and by Bertocchi et al. significantly add to the literature on the role of NPY and its receptors in anxiety-related behaviors (Dumont et al., Biol. Psych. 2014) since they suggest that NPY, acting on different receptor subtypes, activates distinct neuronal circuits to regulate anxiety-related behaviors.
Reversal learning impairment is a symptom of several psychiatric disorders, including Obsessive Compulsive Disorder. Since there are several mouse models with OCD-like behaviors, some of which also have defects in corticostriatal circuits, $Npy1r^{Y5R-/-}$ mice represent a further opportunity to determine the extent by which mouse models with similar behaviors share common circuit defects.
Results of Zammaretti et al. provide new insights into the mechanism by which diet composition affects the hypothalamic circuit that controls energy homeostasis.

7. Future Projects (Next 3 years)

a. Summary:

In continuation with our previous study, in the next three years we will investigate the role of limbic NPY-Npy1r signal in the resilience to psychopathologies and in the sex differences (and effect of chronic stress) in susceptibility to metabolic syndrome. We will therefore develop two main projects that are described below in details: 1) "**Influence of maternal behaviour on the expression of brain plasticity brakes: a role in the susceptibility to anxiety?"** (granted by Compagnia di San Paolo and CRT Foundations) and 2) "**A novel hypothesis on the development of metabolic syndrome in women**" (granted by Cariplo Foundation). In parallel, we will also continue to study the role of Npy1r in behavioural inflexibility of Npy1r$^{Y5R-/-}$ mice, by comparing the effect of different pharmacological treatments (SSRI, benzodiazepines, olanzapine) on the reversal task of the MWM and c-fos immunoreactivity in the OFC (see previous section). Finally, we will also focus on learning/memory and structural plasticity of Npy1rrfb mice. We recently found that Npy1rrfb mice show decreased spatial learning, which is associated with increased thickness of perineuronal nets (PNNs) around CA1 parvalbumin-positive neurons. PNNs are extracellular matrix aggregates that stabilize neuronal connections, therefore limiting neurite remodeling. Enzymatic digestion of PNNs significantly ameliorate the learning performance of Npy1rrfb mice (Mele et al., in preparation). Therefore our plan is to analyze synaptic remodeling of excitatory and inhibitory neurons in the hippocampus of those mice.

b. Background and Significance:

Project 1. Early life experience, such as maternal environment, has a central role in the susceptibility to psychopathology in adulthood. CNS of mammals possesses high levels of experience-dependent plasticity during restricted temporal windows of postnatal development, called "critical periods". Striking evidences support the idea that myelin and the extracellular matrix actively modulate neuronal activity and plasticity, challenging the view of their purely supporting role. In particular, the formation of a specialized form of extracellular matrix around neurons, named "perineuronal net" (PNN) contributes to the closure of the critical period. Lower expression levels of Npy1r in the limbic system of adult mice, induced by low levels of maternal care or by postnatal inactivation of Npy1r in excitatory neurons, increases anxiety, HPA axis activity (**Bertocchi et al, PNAS, 2011**) and PNN thickness in the PFC (**Mele et al, unpublished results**).

Given the role that PNN development and myelin maturation during juvenile development retain in regulating synaptic activity and structural stability and given that impaired PFC function and plasticity is thought to be a core pathological feature of several neuropsychiatric disorders, our main goal is to evaluate whether: i) a rearrangement of PNNs (in terms of thickness, molecular composition, sulfation pattern, physical properties) and myelin development in limbic areas is involved in maternal care programming of anxiety-like phenotype; ii) limbic Npy1r mediated transmission has an important function in maternal environment modulation of PNN. The present project is based on the integration of multiple disciplines (neurobiology, glycobiology, physics and electrophysiology), as well as on the synergic collaboration between groups working at NICO (A. Buffo and D. Carulli) as well as international groups characterized by diverse, but strongly complementary, scientific expertise. By connecting molecular interactions and matrix properties to behavior, we expect that this collaborative research will offer mechanistic insight into the role of plasticity modulators in inducing anxiety in early-life stressed mice.

Project 2. Metabolic syndrome (MetS) is characterized by visceral obesity, high fasting plasma glucose, hypertension, dyslipidemia and fatty liver. In women the

incidence of MetS increases significantly after menopause suggesting the potential involvement of ovarian steroids. Indeed, in females a very well conserved feature is the strict association between reproductive function and nutritional status, thus the cessation of reproductive functions might be the cause of deficiencies in energy homeostasis. During the fertile age, liver is a major target for estrogen action where stimulation of ERα regulates fertility in response to protein intake, and controls lipid and cholesterol synthesis, most likely in relation to the reproductive status. Being the liver a major organ for the control of energy homeostasis, it is conceivable that the activity of the hepatic ERα influences also synthesis and secretion of the signaling molecules necessary for a coordinated hormetic response among liver, fat, muscles and brain. In the brain, estrogen primarily acts at the arcuate nucleus where it increases activity of anorexigenic POMC neurons and represses synthesis of the orexigenic peptides AgRP and NPY. Preliminary results obtained in collaboration with the University of Parma demonstrate that Npy1rrfb male but not female mice show an increased vulnerability to metabolic challenges in adulthood, that is increased by the exposure to chronic psychosocial stress. When fed with HFD, Npy1rrfb male mice showed a rapid body weight increase, higher calories intake during the first HFD week, a longer time span to decrease fat food intake, higher perigonadic WAT, plasma basal glycaemia and lower tolerance to glucose as compared to controls, a phenotype in part recalling the MetS features. Thus, limbic Npy1r represents a key target gene through which estrogens in brain modulate energy metabolism in relation to reproductive functions. The goal of this collaborator study is to fulfill the gap of knowledge on MetS development by studying how different diets regulate liver ER transcriptional programs, prior and after ovariectomy (a condition mimicking menopause) and, most importantly, how this altered ER activity in liver may affect the whole body energy homeostasis.

c. **General aim and integration with mission of the Institute**

The mission of Cavalieri Ottolenghi Foundation is “to study in depth the current knowledges on the interconnections between chemical-physical condition of the human body and psychological symptoms namely, on causes and cure of mental disorders”.

Both of the projects well integrate with the mission since:

-project 1 will be focused on the understanding of neurobiological, biochemical, physical and neurophysiological mechanisms underlying structural neuronal plasticity and, in turn, a wide range of psychopathological disorders, characterized by unbalanced excitatory and inhibitory systems.

-project 2 will be focused on the understanding of brain molecular and neurochemical mechanisms underlying the gender related differences in vulnerability to the pathogenesis of obesity and MetS and their comorbidity with stress related disorders.

- both of the projects aim to reveal new targets for therapeutic interventions in stress and anxiety-related disorders.

d. Specific objectives and strategies:

Project 1) In the limbic system of mice exposed to high/low maternal care or maternal separation we will analyze:

-myelin/PNN appearance during juvenile development. We expect that the long term effect of maternal behavior on anxiety and stress susceptibility may be mediated by a precocious development of plasticity brakes;

- thickness and number of PNNs around specific populations of GABAergic neurons in adult mice.

- alterations of myelin structure and myelin plasticity inhibitors.

- remodeling of GABAergic, glutamatergic and NPYergic innervation and modifications of dendritic branching and dendritic spines.
To investigate the role of Npy1r in PNN formation, the same analysis will be run in wild type and Npy1r^{rfb} mice.
To prove that PNN in the limbic system is implicated in the maternal care-induced programming of anxiety, we will examine the effect of maternal environment on PNNs, neuritic modifications and behavior in: i) mice after PNN digestion by chondroitinase in specific limbic regions; and ii) mice exposed to environmental enrichment.
Moreover:
a) in collaboration with Dr. J. Kwok (Faculty of Biological Sciences, University of Leeds, UK), we will focus on:
- analysis of the molecular composition of myelin and of different nets in the limbic system
- detection of changes in myelin and PNN sulfation pattern in the limbic system
- proteomic analysis to detect binding partners of differently composed PNNs and of myelin. The rationale is to investigate whether PNNs bind different molecules upon low maternal care or conditional deletion of Npy1r gene, which may be important for the development of anxiety.
b) in collaboration with Dr R.Richter (University of San Sebastian, Spain), we will assess mechanical features of myelin and PNNs in the different experimental conditions, such as elastic compressibility (i.e. stiffness or Young's modulus), viscosity and threshold forces required for irreversible deformation.
3) in collaboration with Dr. S. Vicini (Georgetown University, Washington D.C., USA) we will address the central hypothesis that PNN regulates the reciprocal inhibition of interconnected neurons by locally controlling the [Cl-]i. Namely, we will determine changes in action potential firing and synaptic connectivity to identified neurons consequent to the behavioural manipulations used in the project.
Project 2)
Main goals are to analyze: a) the molecular consequences of ovx on energy metabolism and the role of liver ER and central Npy1r on metabolic functions; b) the effects of diets enriched in amino acids (AA) or lipids on an energy metabolism already deranged by ovx.
Female Npy1r^{2lox} and Npy1r^{rfb} mice, fostered to dams with high levels of maternal care, will be ovariectomized at 1 month of age and euthanized at 5 months of age. Groups subjected to AA-enriched and fat diets will be shift to dietary regimen at 2 months of age. Mice will be analyzed for:
-body weight, food consumption, glucose and insulin tolerance tests, locomotor activity, blood pressure.
- Npy1r, NPY and CRH mRNA expression in limbic system and hypothalamus
-histochemical analysis of αMSH and CART (anorexigenic peptides) and NPY and AgRP (orexigenic peptides) in the hypothalamus. This study will demonstrate the extent by which circulating estrogens protect females with low limbic Npy1r to develop MetS-like phenotype in response to nutritional challenges and which limbic and hypothalamic pathways regulated by estrogens underlie the resistance of females to metabolic challenges.
In addition:
- to investigate the physiological relevance of the liver-CNS axis for the control of energy metabolism, in collaboration with Dr. A. Maggi (University of Milano) we will analyze the effect of the different diets in combination with ovx on NPY signaling in limbic and hypothalamic areas of wild type and liver specific ERα ko mice.
-in collaboration with Dr. E. Nisoli (University of Milano) we will analyze: i) in liver, fatty acids, FGF21, Sirt1, lipid metabolism, mitochondrial biogenesis, activity and respiration; ii) in serum, IGF-1, GH, leptin, tryglicerides, FFA, LDL, HDL,

cholesterol, FGF21 Glucose, Insulin; iii) in WAT, BAT, muscle and brain, mitochondrial biogenesis, UCP1, mitochondrial analysis by electron and confocal microscopy, ATP and O2 consumption, glucose concentration, lipid metabolism, and insulin sensitivity, Sirt1; in WAT and BAT, white adipose fat and sympathetic parameters.
- in collaboration with Dr. P. Palanza we will investigate the effect of environment (exercise, enriched environment, chronic psychosocial/mild stress) on vulnerability to MetS-like phenotype of sham and ovx female Npy1r^{2lox} and Npy1r^{rfb} mice fed with fat diet.

e. Unique features of the project research:

Project 1. Epidemiologic evidence suggests a strong association between poor postnatal environments and the development of psychiatric disorders in adult life. The neuronal plasticity associated to brain development during early infancy might be considered a possible risk factor for psychopathology but also a potent mechanism for compensation. In this project we will combine several innovative approaches, including the study of the glyco-profile and mechanical features of PNNs/myelin, and optogenetic manipulation of neuronal activity , to address the role of plasticity-regulatory molecules in early-life stress-induced anxiety from entirely novel angles, spanning different levels of complexity, from molecules to the living organism. We expect to gain further insight into the complex and fine-tuned mechanisms underlying developmental programming. Moreover, we expect to elucidate whether pathological behaviours can be reverted to normal by enriched experience and/or pharmacological treatment in adulthood. The knowledge that will originate from this application has a tremendous potential in view of finding novel therapeutic approaches and early intervention strategies for the cure and possibly prevention of mental disorders, such as anxiety and stress-related disorders that have a strong relationship with early life adversities.

Project 2 . This is an innovative study focused on novel pathogenetic mechanisms that may lead to the age-related disorders in females. It is based on the integration of the knowledge of multiple disciplines (molecular biology, cell biology, behavioral science and metabolic phenotyping), as well as on the synergic collaboration between groups characterized by diverse, but strongly complementary, scientific expertise. It is expected that this collaborative research will allow: i.) to demonstrate the extent by which changes of ovarian estrogens and liver ERs are responsible for the increased incidence of MetS during menopause; ii.) to identify the potential mechanisms involved in this phenomenon, including chronic social stress; iii.) to evaluate the effects of specific dietary regimens in females with impaired ovarian functions. In case we were able to demonstrate a major involvement of liver ER in the dysmetabolisms consequent to the cessation of ovarian functions, our study will open the way to the generation of an entire class of novel Estrogen Receptor Modulators to be used for the therapy of MetS, thus allowing a major step forward in the development of therapies for a disorder that so far cannot be satisfactorily treated.

f. Methodology: <u>please fill-out this section only in the case of innovative technologies</u>

Project 1. One PhD student from my laboratory (M. Ghigo) will spend one year at the Vicini's lab where he will set up experiments to analyze maternal behavior and, meanwhile, he will learn the optogenetic innovative technology. In particular, he will study synaptic connectivity with optogenetic activation of defined populations of interneurons with simultaneous recording of putative postsynaptic target neurons in voltage or current clamp in mice with selective overexpression of channelrhodopsin2-EYFP.

8. Letter of intent by the PI

i) assesses in term of leadership and ability to manage my group. Members of my research group have been working together for several years, from when they were Phd students under my supervision. They are used to collaborate and to help each other and they recognize my leadership, even though I strongly encourage them to become independent developing their own ideas. To strengthen our collaborations, I organize regular meetings on specific subjects related to our research, I discuss with them about the ongoing experiments and I organize web meetings with our national and international partners.
ii) possible internal problems within my group. I do not think that there will be internal problems within my group. Two new members have just joint us: i) Dr. I. Bertocchi, who is now back after her long postdoctoral training at the Max Planck Institute of Heidelberg and will certainly will bring new ideas together with the innovative techniques that she had learned and ii) Dr. M. Ghigo, a new PhD student that will work together with I. Bertocchi e P. Mele on project 1 and has already demonstrated to get along well with the staff.
iii) commitment in supporting the general activities of the Institute I coordinated the project of a new academic spinoff, S&P BRAIN (www.spbrain.com), that will be set up in December by six NICO's PI and staff members (A. Buffo, M: Boido, S. Geuna, GC. Panzica, A. Vercelli and myself). P. Mele (from my laboratory) and S. Gnavi (from Geuna's laboratory) have actively worked on this project. Our mission is to provide a complete in vivo proof-of-concept research for pharmaceuticals, biotechnology and medical devices companies or research centers and to offer high quality experimental studies required for the preclinical phase. In 2015 the startup Chorion had commissioned us a proof of concept study. The overall income of this work was €14790 (NICO's overhead: €1479). The MBC of the University of Turin has commissioned us a behavioral research study on a genetically modified mouse that will start in January.
iv) specific difficulties to realize my projects. Project 1. Adult mice having experienced poor maternal care reveal increased anxiety, enhanced stress response and thicker PNNs in the limbic system. Thus, it is conceivable that early maternal environment might influence chemical and physical PNN features, thus affecting synaptic connections and, in turn, anxiety development. **Project 2.** Limbic Npy1r is a key target gene of maternal care-induced programming of energy homeostasis in male, but not in female mice Thus, it is conceivable that maternal care experienced might influence metabolic phenotype of ovx females. To prevent this problem, female Npy1r^{2lox} and Npy1r^{rfb} mice will be fostered to dams with high levels of maternal care. Having my laboratory a large experience in both of these fields, I can't see any significant problem from the technological point of view.
v) ability in establishing internal and external collaborations. Together with G. Biggio and M. Serra (Cagliari) we have been granted by MIUR (PRIN) since 1999 and we are coauthors in several international pubblications; Dr. P. Palanza is a Unit PI in the last PRIN granted and we are coauthors in several international pubblications; together with Dr. A. Maggi (we are coauthors in two international pubblications) and Dr. E. Nisoli we have been granted by Cariplo Foundation and we will apply for PRIN project expiring in December.
NICO: We collaborate with Dr. G.C. Panzica since 1998; Dr. A. Buffo is a Unit PI and Dr. Carulli a member of my Unit in the last PRIN granted; both of them are members of my Unit in the CRT's granted project and Dr. Carulli is a member of my Unit in the San Paolo Foundation's granted project.

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name: Peripheral Nerve Regeneration Unit

1. LABORATORY DESCRIPTION – PERSONNEL:

- **Principal Investigator**

Stefano Geuna
Birthdate: 25/09/1965
Degree: Graduated in Medicine and Surgery, University of Turin
Gender: Male
Nationality: Italian
Phone: +39 011/6705433
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- **Personnel**

1. Stefania Raimondo

Birthdate: 25/02/1977
Degree: Biological Sciences, University of Turin
Gender: Female
Role: Researcher
Nationality: Italian
Expertise:
- Light, confocal and electron microscopy
- Stereological and morpho-quantitative analysis
- Retro-transcriptase polymerase-chain-reaction (RT/PCR) and Western Blot
- Functional tests for motor recovery (grasping test)
- Cell and tissue transplantation
- Cell cultures

2. Giulia Ronchi

Birthdate 27/11/1982
Degree: Master degree in Neurobiology, University of Turin
Gender: Female
Role: Post-doctoral fellowship recipient
Nationality: Italian
Expertise:
- Light, laser confocal and electron microscopy.
- Immunohistochemistry and Western blot.
- RT-PCR and quantitative Real Time PCR
- Cell and tissue (DRG explants) culture.
- Surgical procedures to induce peripheral nerve damages.
- Stereological and morpho-quantitative analysis
- Functional tests for motor recovery (grasping test)

3. Federica Fregnan

Birthdate: 02/07/1976
Degree: biological sciences (five-year degree), University of Turin
Gender: Female
Role: Post-doctoral fellowship recipient
Nationality: Italian
Expertise:
- Optical microscopy and confocal analysis of histological and cytological specimens prepared by histological techniques, histochemical and immunofluorescence.
- Electron microscopy and ultrastructural analysis.

- Analysis of recovery of motor function in rats and mice using behavioral tests.
- Quantitative morphological analysis of the regeneration of nerve fibers by stereological methods.
- Extraction and culture of primary lines of ganglion sensory neurons.
- Analysis of protein expression (western blotting) and mrna (qualitative rt-pcr and real time quantitative rt-pcr).
- Cell culture, transient and stable transfection, proliferation assays, migration assays, time lapse.
- Recombinant techniques of molecular biology (cloning, production of fusion proteins with gfp or flag, preparation of constructs in plasmids, adenoviral and lentiviral vectors).
- Validation of microarray analysis.

4. Luisa Muratori

Birthdate 02/05/1984
Degree: Neurobiological Science, University of Turin
Gender: Female
Role: PhD Student
Nationality: Italian
Expertise:
- Light and laser confocal microscopy.
- Immunohistochemistry and Western blot.
- RT-PCR and quantitative Real Time PCR
- Cell and tissue (DRG explants) culture.

5. **Sara Gnavi**

Birthdate: 10/10/1985
Degree: Biomolecular Science, University of Turin
Gender: Female
Role: Post-doctoral fellowship recipient
Nationality: Italian
Expertise:
- Light and laser confocal microscopy.
- Immunohistochemistry and Western blot.
- RT-PCR and quantitative Real Time PCR
- Cell and tissue (DRG explants) culture.

6. Benedetta Elena Fornasari

Birthdate: 11/07/1989
Degree: Molecular and Cellular Biology, University of Turin
Gender: Female
Role: PhD Student
Nationality: Italian
Expertise:
- BIOMOLECULAR TECHNIQUES: DNA, RNA and protein extraction, quantitative Real-time PCR, primers study and design, Western blot.
- CELLULAR BIOLOGY: cell colture, primary colture of Schwann cells and dorsal root ganglia, cell transfection, cell migration assays, proliferation and viability assays, time lapse assays.
- MORPHOLOGICAL ANALYSIS: immunocitofluorescence, resin embedding procedures
- ANIMAL CARE

- BIOMATERIAL PRODUCTION: production of fibres through electrospinning technique

7. Michela Morano

Birthdate: 29/10/1988
Degree: Molecular and Cellular Biology, University of Turin
Gender: Female
Role: PhD Student
Nationality: Italian
Expertise:

- Manual ability with different type of cell cultures (cell lines and also primary cultures)
- Molecular and cellular biology techniques known and used: PCR, Real-Time PCR, cloning plasmids, western blot, cell transfection, transwell migration assay, immunofluorescence, ELISA, MTT survival assay.
- Informatics competences: well knowledge of programs with biological application (Annhyb, GraphPad, ImageJ, PlasmaDNA,) graphic software (Photoshop, Prezi, Inkscape), Microsoft Office (Excel, Word, PowerPoint) and editing software (Mendelev, Endnote).
-

8. Loredana Grasso

Birthdate: 13/08/1982
Degree:
Gender: Female
Role: Fellowship recipient
Nationality: Italian
Expertise:

- Cell (blood cell) cultures.
- DNA extraction from whole blood by Phenol / Chloroform
- Surgical procedures to induce muscle damages and muscle's extraction.
- Paraffin embedding
- Histological staining
- Western blotting
- Immunohistochemistry

9. Bompasso Simone

Birthdate 18/07/1986
Degree: laboratory technician, University of Turin
Gender: Male
Role: Fellowship recipient
Nationality: Italian
Expertise:

- Optical microscopy and confocal analysis of histological and cytological specimens prepared by histological techniques, histochemical and immunofluorescence.
- Light, confocal and electron microscopy
- Stereological and morpho-quantitative analysis
- Quantitative morphological analysis of the regeneration of nerve fibers by stereological methods.

2. PRINCIPAL INVESTIGATOR CURRICULUM VITAE (two pages)

Education and training:
Graduated in Medicine and Surgery at the University of Torino 1990.
Professional Licensure for Medical and Surgical Practice 1990
Member of the Professional Register of Physicians and Surgeons of the Province of Torino 1991
Specialization in Child Neurology and Psychiatry at the University of Torino 1991-1995.
Senior Researcher at the Department of Clinical and Biological Sciences of the University of Torino, 1998-2007

Employment and research experience:
Full-time employee of the University of Torino as Associate Professor of Anatomy at the Department of Clinical and Biological Sciences of the University of Torino and Research Leader of the Peripheral Nerve Regeneration Unit at the Cavalieri Ottolenghi Institute of Neuroscience.

Relevant discoveries:
The results of our recent research, in the context of the European Project funded (Biohybrid), allowed to put on the market Reaxon® Nerve Guide, a chitosan conduit design for the repair of peripheral nerves. Reaxon® Nerve Guide got the CE mark in January 2014.

Please list your grants according to the table below (last five yrs).

Starting-end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
2011-2014	National	PI	Regione Piemonte	Biconerve: Biomimetic constructs for nerve regeneration	POR-FESR Piemonte 2007-2013 - Attività I.1.2 Polo di innovazione	€ 170.742	
2012-2015	International	Component	EU	Biohybrid templates for peripheral nerve regeneration	EU FP7 research grant (HEALTH.2011.1.4-2)	€ 508,400	
2013- 2014	National	PI	Università degli Studi di Torino	Neurolink - Esercizio fisico e malattie del sistema nervoso: focus sulle cellule della glia	Fondo per la Ricerca Locale	€ 33.014	
2014-2015	National	PI	Università degli Studi di Torino	Neurolink 2 - Esercizio fisico e malattie del sistema nervoso: focus sulle cellule della glia	Fondo per la Ricerca Locale	€ 26.373	

Please list the name of PhDs you have supervised.

- Morano Michela
- Muratori Luisa
- Pascal Davide

Please list honours, prizes or awards received, If applicable.

July 2012, best paper award as author of the paper entitled: "Gene therapy for promoting nerve regeneration after tubulisation repair" at the European Congress of Microsurgery, Cluj Napoca, Romania.

Please list your outreach activities

- **International collaborative experiences.**
  2010-present: President of the Eurpean Microsurgical Research Association.
  2011- 2015: coordination board member of the project "Biohybrid templates for peripheral nerve regeneration" of EU-FP7-Health-2011.
  2014: Co-founder of the European Scoiety for Peripheral Nerve Repair and Regeneration, Bruxelles.

- **Invited talks**
  - "Tissue engineering of the peripheral nerve" 7th European Plastic Surgery Research Council, Hamburg, Germany (27–30 August 2015).
  - "Writing the draft of a scientific paper" 6th International Scientific Writing Workshop, Zanzibar Island, Tanzania (26-27 March 2015)
  - "Nanotechnology for nerve reconstruction" Frontier Research Academy for Young Researchers, Kyushu Institute of Technology; Fukuoka, Japan (9- 14 February 2015)
  - "Tissue engineering of the peripheral nerve" Termis EU 2014 Congress, Genova, Italy (10-13 June 2014)
  - "Biohybrid templates for peripheral nerve repair" 2013 TERMIS-AP Annual Conference, Shanghai, China (23-26 October 2013)
  - "Nerve repair and regeneration" FESSH Congress, Milan, Italy (14-16 January 2013)
  - "Stereology of peripheral nerve fibers" Asian and African Stereology Congress, Samsun, Turkey (6-8 November 2012)
  - "Advances in peripheral nerve tissue engineering" TERMIS World Congress 2012, Vienna, Austria (5-8 September 2012)
  - "Nerve tissue engineering" Pre 6th Congress of the World Society for Reconstructive Microsurgery Bucharest, Romania (25-27 June 2011)

- **Editorial duties**
  Member of Editorial Board of *Microsurgery*

Please list your organizational activities:

- **Speakers invited**
  - Carla Taveggia: San Raffaele Scientific Institute – Milan, Italy
  - Lars B. Dahlin: Department of Hand Surgery, Skane University Hospital – Malmo, Sweden

- **Workshops, Schools or Conferences organized**
  Member of the Organizing Committee:
  - 2nd International Symposium on Peripheral Nerve Regeneration, January 23rd - 25th, 2014 in Turin, Italy

- 3rd International Symposium on Peripheral Nerve Regeneration, September 24th and 25th , 2015 in Hannover, Germany
- 26th Annual Meeting of the Italian Society for Microsurgery (SIM), November 26th – 28th, 2015, Turin, Italy

Please list your technology transfer achievements (patents, etc.), if applicable
In 2015, a patent about the production of iron-conjugated neuregulin 1 for promoting peripheral nerve regeneration has been issued.

3. PI's PUBBLICATIONS:

Geuna S, Raimondo S, Fregnan F, Haastert-Talini K, Grothe C. (2015) In vitro models for peripheral nerve regeneration. *Eur J Neurosci.* Aug 26. doi: 10.1111/ejn.13054. [Epub ahead of print] Review. PubMed PMID: 26309051.
IF 3,181 R=108/252

Ribeiro J, Pereira T, Caseiro AR, Armada-da-Silva P, Pires I, Prada J, Amorim I, Amado S, França M, Gonçalves C, Lopes MA, Santos JD, Silva DM, Geuna S, Luís AL, Maurício AC. (2015) Evaluation of biodegradable electric conductive tube-guides and mesenchymal stem cells. *World J Stem Cells*. 26;7(6):956-75.
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Catalano F, Accomasso L, Alberto G, Gallina C, Raimondo S, Geuna S, Giachino C, Martra G. (2015) Uptake: Factors Ruling the Uptake of Silica Nanoparticles by Mesenchymal Stem Cells: Agglomeration Versus Dispersions, Absence Versus Presence of Serum Proteins.*Small*. 11(24):2919-28.
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Tos P, Crosio A, Pellegatta I, Valdatta L, Pascal D, Geuna S, Cherubino M. (2015) Efficacy of anti-adhesion gel of carboxymethylcellulose with polyethylene oxide on peripheral nerve: Experimental results on a mouse model. *Muscle Nerve*. doi: 10.1002/mus.24739. [Epub ahead of print] PubMed PMID: 26082205.
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Times cited =4

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IF= 13,262; R =3/123; Times cited =39
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IF 3,246; R 96/184; Times cited= 5

5. **GROUP's additional information:**

Please list the grants of the other members of the group in the last 5 years -2010/2015- according to the table below:

Starting-end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
	National vs International	P. Rossi; PI vs. Component	MIUR, ERC, ecc…			€	€
2015_2017	National	S. Raimondo PI	Compagnia di San Paolo	Moving Again: Integrated Therapies to Cure Post-Traumatic Paralysis	Progetti di Ricerca di Ateneo/ CSP 2014	€ 84.660	

Please list outreach activities of other members of the group:

- **Describe your international collaborative experiences**.

  - Dr. Stefania Raimondo: 2015: stage in IINS Bordeaux.

  - Dr. Stefania Raimondo: 2011- 2015: coordination board member of the project "Biohybrid templates for peripheral nerve regeneration" of EU-FP7-Health-2011.

  - Dr. Michela Morano: July- December 2014: Internship as PhD student Institute of Neuroanatomy, Hannover Medical School (MHH), Hannover, Germany.

  - Dr. Giulia Ronchi: 2013: Training at Medovent (Mainz, Germany) within the European project FP7-BIOHYBRID.

  - Dr. Federica Fregnan: 2013: Training at Medovent (Mainz, Germany) within the European project FP7-BIOHYBRID.

  - Dr. Sara Gnavi 2011-2012: stage at the Netherland Institute for Neuroscience, Amsterdam, The Netherland.

  - Dr. Giulia Ronchi 2009-2010: Exchanging scholar at the Washington State Univeristy (Pullman, WA).

- **Invited talks**

  - Dr. Stefania Raimondo: Fens 2010 – Amsterdam.

  - Dr. Sara Gnavi: Cellular and Molecular Neurobiology of Nervous system Degeneration and Regeneration Workshop, Centre for Neuroscience 2013 - Brno, Czech Republic.

- **Editorial duties**

  - Dr. Stefania Raimondo: Reviewer for Scientific International Journal (Acta Biomaterialia, International Review of Neurobiology, BioMed Research International).

- Dr. Giulia Ronchi Reviewer for Life Science and BioMed Research International.

Please list your organizational activities:

- Workshops, Schools or Conferences organized by members of the group

- 2nd International Symposium on Peripheral Nerve Regeneration, January 23rd - 25th, 2015 in Turin, Italy.
- 3rd International Symposium on Peripheral Nerve Regeneration, September 24th and 25th , 2015 in Hannover, Germany.

6 .Past Research activity

(Summarize the PI and group research activities in the last 10 years)

a. Summary (500 characters)

The research activities of Geuna's group have been focused on the study of peripheral nerve repair and regeneration. Different aspects have been studied: i) biological processes that occurs during peripheral nerve regeneration, ii) surgical techniques for nerve repair after different type of injuries, iii) biomaterials compatibility for nerve prosthesis constitution, iv) growth factors delivery strategies for the improvement of nerve regeneration or for the prevention of muscle atrophy.

b. Background (2000 characters)

Paralysis after peripheral nerve injury is a common condition and, although peripheral nerve fibres retain a considerable regeneration potential also in the adulthood, recovery is usually rather poor, especially in case of large nerve defects.
The increasing number of patients receiving nerve surgery will represent an enormous stimulus for more research in peripheral nerve regeneration and, most of all, for defining innovative strategies for improving functional recovery of repaired nerves.
Transected peripheral nerve fibers, unlike those of the central nervous system, are able to regenerate and lead to functional recovery provided that an appropriate milieu and guide is available. Thanks to this property, surgeons can obtain good functional recovery in patients who suffered a trauma that discontinued one or more nerve trunks by re-aligning and suturing the two stumps of the severed nerves. Unfortunately, severe traumas (especially at limb level) often cause substance loss in severed nerves so that direct repair is not possible, and a graft is required to bridge the proximal and distal stumps of the severed nerve(s). Transected fibers can thus regenerate inside the graft and reach their optimal milieu represented by the distal nerve trunk, which will eventually guide them towards their original peripheral target. Although autologous sensory nerve segments have proved to be an excellent graft material for bridging severed nerve trunks and have been widely used in the clinical practice, their employment implies the withdrawal of a healthy nerve, requires additional surgical incisions in adjacent areas and causes sensory residual deficits. Therefore alternative non-nervous graft materials, both biologic and synthetic, have been devised and successfully employed in the clinical practice.

c. Rationale (2000 characters)

Lesions of the nerve structure result in a decreased or a complete loss of sensitivity and/or motor activity in correspondence of the innervated territory. Since the clinical outcome after nerve lesions is far from being satisfactory and functional recovery is almost never complete, more research is needed in peripheral nerve trauma recovery field.

The poor outcome can be attributed to many factors, including (i) the lesion site, ii) the interval of time between the injury and the surgical repair, iii) the inability of denervated muscle to accept reinnervation and to recover from muscle atrophy, (iv) the reduced ability of injured axons to regenerate after a long axotomy and (v) the loss of the Schwann cell (SC) capability to support regeneration.
Such research bring together different disciplines which might contribute, not only to increase knowledge about the biological mechanisms that underlie the complex sequence of events which follows nerve damage, but also to define the best strategies for optimizing posttraumatic nerve regeneration and, eventually, the full recovery of the patient's motor and sensory function.
A complete rehabilitation after a peripheral nerve injury should follow three general phases: i) regeneration of the axons; ii) reinnervation of the targets; iii) recovery of function.

d. Objectives (1500 charcters)

The objectives of Geuna's group activities were to better understand biological process implicated in nerve regeneration and to study how improving functional recovery after peripheral nerve injuries, acting on peripheral nerve regeneration improvement and on prevention of denervated-muscle atrophy.
These goals have been reached: i) investigating new bioengineered and biomimetic graft materials for the repair of segmental nerve defects, as a powerful alternative to autographs, ii) developing new bio- and micro/nano-delivery systems of biomolecules stimulating nerve fiber regeneration with the effect to reduce the lag time before muscle reinnervation and inhibiting denervation-induced muscular atrophy until the nerve regeneration process has been completed and iii) analysing the changes in genes/proteins expression levels during the process of nerve injury-regeneration and muscle denervation–reinnervation.
Both in vitro and in vivo analysis have been conduct to describe the biological process implicated in peripheral nerve regeneration and to investigate new strategies for the repair of severe nerve lesions and to prevent muscle atrophy.
In vitro analysis have been useful to choose biomaterials that can be used for the constitution of the nerve prosthesis and to choose growth factors that act improving nerve regeneration and muscle tropism. The use of in vivo experimental models have been useful for the study of the basic biological processes and for the final pre-clinical testing of new strategies for improving peripheral nerve repair and regeneration.

e. Results (4000 characters)

Different activities have been carried out to reach the objectives. Both in vitro and in vivo analysis on animal models have been performed. All activities are summarized below.

<u>Peripheral nerve regeneration study</u>
In vitro and in vivo analysis have been performed in order to study the role on NRG/ErbB system during peripheral nerve injury and repair. The expression of NRG/ErbB genes and proteins have been analyzed in different type of nerve injury/repair (crush, end-to-end, tubulization) and at different time point after repair (early and late regeneration). Our results demonstrate that the components of the NRG1/ErbB system are differently regulated in the different phases a peripheral nerve undergoes after injury with the aim to regenerate. The precise regulation of this system indicates that each molecule is crucially involved in successful peripheral nerve regeneration and could be a target for pre-clinical evaluation of regeneration promoting factors. Moreover, also in vitro analysis allowed to evaluated the potential role of these molecules in the improvement of peripheral nerve regeneration and in the prevention of muscle atrophy.

<u>Peripheral nerve repair with conduits</u>

Main results about techniques of nerve repair have been obtained in the context of “Biohybrid” and “Biconerve” projects. Different type of chitosan conduits have been analyzed.
Basically, chitosan-based materials were used in in vitro and in vivo studies to evaluate the most efficient formulation in the context of nerve regeneration and to select the most promising types for the more complex approaches. We have demonstrated that fine-tuned chitosan conduits, with a degree of acetylation of ~5%, allow functional and structural regeneration across a 10-mm sciatic nerve gap in rats to a similar extent as autologous nerve grafts. These chitosan nerve conduits (Reaxon® Nerve Guide) got the CE mark in January 2014, market entry of Reaxon® Nerve Guide was performed in June 2014.
After that, the selected hollow chitosan tubes were modified with luminal fillers, biomatrices, and/or (genetically modified) cells and analysed in in vitro and in vivo studies, in order to then further support functional recovery especially in advanced animal models, across long gaps or even after delayed repair (45 days after nerve transection injury).

Study of muscle response to denervation/reinnervation
The regulation of NRG/ErbB system has also been investigated in skeletal muscles after different types of nerve injury/repair (crush injury, end-to-end repair, tubulization) at different time point (early and late regeneration). Results revealed a time-related modulation of both ErbB receptors and Nrg-1 suggesting that each molecule is crucially involved in processes related to muscle atrophy associated to denervation. Moreover, in vitro experiments with C2C12 cells stimulated with Nrg-1 were also performed to understand the involvement of this system during muscle atrophy. Our results, indeed, suggested that the system is deeply involved in this process and could be a target for new clinical therapies

f. Advancement in the field (1000 characters)

Results of our research, in the context of the European Project funded (Biohybrid), allowed to put on the market Reaxon® Nerve Guide, a chitosan conduit design for the repair of peripheral nerves.
Regarding the translational work Reaxon® Nerve Guide got the CE mark in January 2014. The product has already been implanted in patients with peripheral nerve defects at several German clinics. Moreover, FDA submission is under preparation. In addition, finalising of the translational work for clinical application of the hollow tube (ethic applications) and continuation of translational work for complex nerve conduits are ongoing activities. The preparation of a multicentre clinical trial on Reaxon® Nerve Guide in median and ulnar nerves is already completed.

7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do

a. Summary (up to 2000 characters):

In the last years Geuna's group worked mainly on peripheral nerve regeneration, studying, among the main aspects, the role of NRG/ErbB system in different type of nerve repair after lesion and evaluating if this system can be used to improve the regeneration.
In order to increase the integration of the group with the mission of the Institute the objectives of future activities will be twofold.
The first goal will be to realize an integrated therapy to improve the patients' outcome after peripheral nerve damage acting simultaneously at multiple levels over the entire neuromuscular system i) by potentiating axonal regeneration, ii) by preventing and recovering muscle atrophy, iii) by acting on central nervous system plasticity in order to facilitate functional recovery.
The second goal will be to study the role of NRG1/ErbB system in the central nervous system, indeed they are genes implicated in neuronal migration and deficits in neuronal migration during development that may contribute to psychiatric diseases. Experiments on this field started in the last year in collaboration with another group of NICO Institute.

b. Background and Significance (up to 4000 characters):

1.a Potentiation of axonal regeneration
Although the PNS has an intrinsic capability to regenerate after trauma, functional recovery is often incomplete and unsatisfactory. A need therefore exists for devising new strategies for promoting the outcome after nerve trauma, especially in cases of severe nerve lesions such as brachial plexus avulsions.

1.b Prevention of skeletal muscle atrophy
Trauma to the mixed peripheral nerves induces a denervation-related atrophy of the distal target skeletal muscles. Muscle atrophy is progressive and ends up with the disappearance of muscle fibers. In this case, even if the motor axons regenerated and reach again the target muscles, motor functional recovery cannot occur. A need therefore exists for devising new strategies for promoting complete skeletal muscle atrophy during posttraumatic peripheral nerve regeneration.

1.c Promote plasticity of central nervous system
External stimuli, which comprise sensory inflow, motor activity, cognitive elaboration, or social interaction, are crucial for functional recovery after peripheral nerve damage. These phenomena depend on the capability of neurons to modify their functional properties and/or their connections, generally defined as "plasticity". A need therefore exists for devising new strategies for manipulating CNS plasticity to improve functional recovery after nerve trauma.

2.a NRG/ErbB system role in neuron migration
Neuronal migration represents a critical step in the development of the central nervous system, where neuronal progenitors migrate from their birth site to their target and their final destination. The tyrosine kinase receptor ErbB4 and one of its ligands, the neuregulin1 (NRG1), are involved in the migration of neuronal progenitors from the medial ganglionic eminence (MGE) to the cortex during the development and from the subventricolar zone (SVZ) to the olfactory bulb (OB) during the development and in the adult life and it has been demonstrated that the conditional deletion of ErbB4 interferes with correct neuronal migration.
A need therefore exists for for better understand the role played by this system both in physiological and pathological (schizophrenia) conditions.

c. General aim and integration with mission of the Institute (up to 1000 characters)

The general aim of our group is to explore innovative solutions for improving functional recovery after nerve trauma. Nerve trauma represent one of the major cause of neuronal disability with significant influences on the patient quality of live, including the psychosocial and relational level. Significant advancements in the treatment of these patients requires an integrated approach which brings together bot CNS and PNS scientists in line with the mission of the NICO.
In addition, our research group aims to investigate the role of NRG1/ErbB system on neuronal migration in the perspective of better understanding some psychiatric diseases which might related to neuronal migration disorgers.

d. Specific objectives and strategies (up to 4000 characters):

The first specific objectives are:

i) Potentiating axonal regeneration after traumatic lesion. This objective will be pursued by investigating innovative strategies of tissue engineering of the peripheral nerve. These include the construction of nanostructured scaffolds, cell transplantation, gene therapy, and physical stimulation of tissue repair.

ii) Preventing denervation-related muscle atrophy. This objective will be pursued by investigating innovative strategies for the local release of myotrophic molecules such as ghrelin and neuregulin-1.

iii) Modulating central nervous system plasticity after nerve trauma. This objective will be pursued by investigating innovative strategies for improving functional recovery by means of rehabilitation protocols directed at facilitating the CNS adaptation to the new PNS conditions.

iv) Investigating the role of NRG1/ErbB system in the central nervous system. This objective will be pursued by investigating how the NRG1/ErbB system is implicated in neuronal migration and in the deficits in neuronal migration during development and how those deficits may contribute to psychiatric diseases.

e. Unique features of the project research (up to 2500 characters):

The unique features of our project research are the following:

1) the project research represents one of the most innovative approaches in Europe focused on the study of peripheral nerve repair and regeneration.

2) the research group brings together interdisciplinary competencies and skills.

3) the project research is carried out under good laboratory practice(GLP)-inspired procedures

4) the research group focus on the translational approach, i.e. on the applicability of the research results for developing new therapeutic strategies that could successfully been translated to the clinical practice.

5) the project research has also a potential for industrial spin off of the results, as demonstrated by the recent introduction on the marked of the Reaxon© nerve guides the patent on iron-conjugated neurogulin-1.

f. Methodology (up to 2000 characters): <u>please fill-out this section only in the case of innovative technologies</u>

One of the main technologies adopted by our group is the employment of modern unbiased stereological techniques for the morphoquantitative estimation of the nerve tissue (both in CNS and PNS). The PI has long term experience in this field and organizes stereological courses in different countries (Italy, Germany, Portugal, Turkey, Tanzania).

8. Letter of intent by the PI (1 page)

I believe that I have acquired, over the years in which I worked at the University of Torino, a good leadership attitude and ability to manage a research group. In addition, in the course of my specialization in child neuropsychiatry, I have acquired a number of relational and interpersonal skills that, today, help me very much in leading my lab.

During recent years, I did not experience major internal problems within my group. Anyway, the main source of problems inside the group may arise from conflicts between members, especially PhD students. To prevent this occurrence, a careful monitoring of the lab activities is carried out by regular lab meetings that are aimed not only to implement the research activities but also to solve immediately any relational troubles among lab members. In case this lab's conflicts occur, individual interviews are carried out with the aim of resolving the conflicts as soon as possible.

Since the beginning of NICO's activities, I had a strong commitment in supporting the its general activities. I am presently serving as responsible person for special waste disposal control and monitoring. Yet, I look actively for new collaborations with other colleagues inside the NICO. In many occasions, I have supported the colleagues of the NICO with our scientific expertise as well as with economically by participating to the maintenance of the institute equippments.

The main difficulties in the realization of our project is the recruitment of grants. Luckily, over the last 5 years, our group has managed to receive 3 large-scale grants which allowed to carry out a number of experiments that led to the publication of many good papers. The application of new grants is therefore considered as proprietary.

Over the last years I have been establishing a wide web of collaborations within other researchers at the NICO and our University, as well as with researchers in many other Universities in Italy and abroad. Well established and ongoing collaborations include academicians in the following cities: Milano, Genova, Trieste, Roma, Messina, Zurich, Hannover, Barcelona, Oporto, Manchester, London, Malmo, Istanbul, Tel Aviv, Reno, Chicago, Sao Paulo, Rio de Janeiro.

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name: NEUROENDOCRINOLOGY

1. LABORATORY DESCRIPTION – PERSONNEL:

- **Principal Investigator**

First name and surname	**GianCarlo Panzica**	Birthdate	(**17/08/1949**)
Degree	**PhD**	Gender	**male**
Nationality	**Italian**	Phone:	**011 670 6607**
Email:	**giancarlo.panzica@unito.it**		

- **Personnel**

1. First name and surname **Stefano Gotti** Birthdate (**17/06/1971**)
   Degree **PhD** Gender **male**
   Role **Researcher RTI** Nationality **Italian**
   Expertise Co-PI

2. First name and surname **Giovanna Ponti** Birthdate (**05/04/1975**)
   Degree **PhD** Gender **female**
   Role **Researcher RTD** Nationality **Italian**
   Expertise Neurogenesis, phytoestrogens

3. First name and surname **Alice Farinetti** Birthdate (**23/12/1981**)
   Degree **PhD** Gender **female**
   Role **Post-Doc** Nationality **Italian**
   Expertise Neurogenesis, Gonadal hormones

4. First name and surname **Marilena Marraudino** Birthdate (**08/06/1988**)
   Degree **Master Degree** Gender **female**
   Role **PhD Student** Nationality **Italian**
   Expertise Control of reproduction, endocrine disruptors

2. PRINCIPAL INVESTIGATOR CURRICULUM VITAE (two pages)

Education and training:
1973 Master degree in Biological Sciences (University of Torino, Italy).
1993 PhD in Neuroscience (University of Salamanca, Spain).
- After the degree in Biology, dr. Panzica had a fellowship (1974-1980) at the Institute of Histology and Embriology of the Faculty of Medicine, University of Torino, Italy. During this training period, I spent several months in Germany (University of Giessen and University of Ulm) to learn morphological techniques at light and electron microscopic level.
- After 1980, I spent several months at the University of Liege (dr. Balthazart lab) where I learnt behavioral techniques and started a cooperation that is still ongoing.
- In the period 1990-93 I spent several months at the University of Salamanca to develop my PhD thesis on the distribution of various peptidergic systems within the avian brain.
- In the period 1993-98 I spent several months at the University of Maryland, College Park, USA (Prof. Ottinger lab) to develop our joint studies on the Japanese quail.

Employment and research experience:
1980-1990 – Assistant Professor of Histology and Human Anatomy, University of Torino (Italy)
1990-2000 – Associate Professor of Human Anatomy, University of Torino (Italy)
2000-2006 – Full Professor of Comparative Anatomy, University of Torino (Italy)
2006-today - Full Professor of Human Anatomy, University of Torino (Italy)

During his career dr. Panzica was fellow at the University of Giessen, University of Ulm, University of Liege and University of Salamanca. He was visiting professor at the University of Madrid, University of Oviedo, University of Maryland (College Park, USA), charged of several PhD courses.

Management:
- 2003-2009 Coordinator of Master degree in Neurobiology, Faculty of Science, University of Torino (Italy)
- 2007-2012 Head of the Department of Anatomy, Pharmacology and Forensic Medicine
- 2010-2012 Member of the Board of the Directors of the University of Torino
- 2013-today Member of the Board of the Italian Anatomical Collegium
- 2013 - President of Master Degree in Evolution of animal and human behaviour, School of Science, University of Torino (Italy)
- 2013 – ViceDirector for Research, Department of Neuroscience
- 2014 – 15 and 2015-18 Director of the Department of Neuroscience

Relevant discoveries:
Dr. Panzica started his independent career as full time researcher (permanent position) in 1980, and his main interest was the study of hypothalamic circuits related to the control of different behaviors, in particular the reproductive behavior. During the period 1970-1980, many people started to investigate sex differences in brain structures, mainly in rodents (and in humans), but only a few studies were dedicated to this topic in other vertebrates. Dr. Panzica, in cooperation with dr. Balthazart (Liege) and dr. Viglietti (Torino), was the first to discover a sexually dimorphic nucleus within the preoptic area of the Japanese quail (Viglietti-Panzica et al., 1986). Several studies have been performed in our and other laboratories about the cellular populations, the presence of the enzyme aromatase, and the role played by this nucleus in the control of male copulatory behavior. The medial preoptic nucleus of the Japanese Quail is still considered the best model to link neural circuits, aromatase action and the control of a sexually dimorphic behavior. These discoveries were summarized in a review in the journal “Frontiers in Neuroendocrinology” (Panzica et al., 1996). This paper is still discussed in several classes of master courses in Behavioral Neuroendocrinology.
Following this research line, dr. Panzica and his coworkers tried to discover specific pathways particularly linked to the control of sexual behavior. They identified the parvocellular sexually dimorphic vasotocin system in the limbic system of the Japanese quail (Panzica et al., 1998). This paper was the first demonstration of a clear relationship among male sexual behavior and a

neurochemically defined circuit in birds (but also in all vertebrates) and gave a clean experimental model also in comparison with the several problems arising from the study of a similar system in mammals (De Vries and Panzica, 2006).
More recently, dr. Panzica and his team started to study the effects of endocrine disruptors over the neural circuits controlling food intake and energy metabolism. The current focus on the etiology of obesity remains on imbalance between food intake and energy expenditure, and the role of hypothalamic circuits in this process has been underestimated. Our team demonstrated for the first time a direct effect of one important obesogenic molecule (tributyltin, TBT) over hypothalamic circuits controlling feeding behavior and energy metabolism in mice, by using the c-fos technique (Bo et al., 2011). This study was the first morphological evidence that obesogenic compounds may act not only at the periphery stimulating the increase of fat tissue, but also at the level of the hypothalamic circuits. This study is opening a new field of studies for the action of the so-called "metabolic disruptors" (Heindel et al., 2015): the alteration of the brain circuits dedicated to the control of food intake and energy metabolism.

Please list your grants according to the table below (last five yrs).

Starting-end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
	National vs International	PI vs. Component	MIUR, ERC, ecc…			€	€
2009-2013	National	PI	San Paolo-Progetto Neuroscienze	Gender and affective disorders: role of vasopressin and neuroactive steroids		160.000	
2009-2014	National	PI (F.Rossi, previous PI)	PRIN	Neurogenesis and neural differeniation: regulatory genes, molecular signals and experience		60.000	
2010-2014	National	PI	Fondazione CRT-Progetto Lagrange (4 year PhD fellowship)	Environment and brain sexual differentiation: role of endocrine disrupters		60.000	
2013-2015	National	PI	UNITO-ex 60% 2012	Effetti cerebrali degli obesogeni		3.053	
2012-2014	National (Spain)	C	Ministerio de Ciencia e Innovación (Spain)	Participación del óxido nítrico en el control neurohormonal de la ingesta		60.000	
2014-2016	National	PI	UNITO-ex 60% 2013	Effetti cerebrali degli obesogeni: azione della TBT sul circuito a NPY		2.127	
2013-2016	International Foudation		Postfinasteride Foundation	Effects of finasteride on behavior and		14.656	1.465

				neurosteroids			
2015-2017	National	PI	UNITO-ex 60% 2014	Distruttori endocrini e circuiti che regolano l'assunzione di cibo ed il metabolismo energetico		2.343	187,43
2016-2019	National (Spain)	C	Ministerio de Ciencia e Innovación (Spain)	Involvement of estradiol on feeding neurohormonal circuit programming in the rat		70.000	

List of supervised PhDs.
Adriana Paraninfo (1996)
Nicoletta Aste (1996) joint PhD program with University of Liege (Liege, Belgium)
Claudia Castagna (1998)
Laura Plumari (2004)
Stefano Gotti (2004)
Monica Sica (2005) joint PhD program with University of Maastricht (Maastricht, Holland)
Mariangela Martini (2008) joint PhD program with UNED (Madrid, Spain)
Francesca Allieri (2008) joint PhD program with University of Paris VI (Paris, France)
Elena Mura (2009)
Daniela Grassi (2010) joint PhD program with UNED (Madrid, Spain)
Elisabetta Bo (2011)
Egidio Caricati (2011) joint PhD program with University of Marseille (Marseille, France)
Desiree Miceli (2012)
Alicia Rodriguez-Gomez (2013) joint PhD program with UNED (Madrid, Spain)
Alice Farinetti (2014)
Benedetta Foglio (2014)

Honours, prizes or awards received.
- Angelo Costa Prize (1986) for Anatomical, Embriological and Comparative anatomy studies, of the Faculty of Medicine.
- Prize "Extraordinario de Doctorado" (1994) of the University of Salamanca (Spagna), for the best PhD thesis of the year 1993
- Branemark Osseointegration Center Award for a paper presented at the 1st World Congress of Osseointegration (1994).

Please list your outreach activities

International collaborative experiences.
Dr. Panzica had several international cooperations, and many of them are still active. They are chronologically listed here:
1981-1990 Cooperation with dr. H. Korf (University of Giessen, Germany) on the hypothalamic magnocellular system in birds and its relations with osmoregulation.
1982-today Cooperation with dr. J. Balthazart (University of Liege, Belgium) on the definition of neural circuits controlling male copulatory behavior in the Japanese Quail.
1985-90 Cooperation with dr. R. Foster (University of Bristol, UK) on the photoperiodic control of the GnRH system in the Japanese Quail.
1990-today Cooperation with dr. M.A. Ottinger (University of Maryland, College Park, USA) on the effects of aging on vasotocin and GnRH systems in the Japanese Quail, and on the effects of endocrine disruptors on neural circuits and behaviors in birds.

1990-1995 Cooperation with dr. H. Vaudry (Rouen, France) on the distribution of the NPY system in birds.
1991-1996 Cooperation with dr. F. Sanchez and dr. J.R. Alonso (University of Salamanca) on the distribution of NADPH-diaphorase (nNOS) in the avian brain
1992-1999 Cooperation with dr. R. Grossman (Institute for Animal Science, Mariensee, Germany) on the sexually dimorphic vasotocin system in birds
2000-today Cooperation with dr. N. Harada (Kyoto University, Japan) on aromatase function in mammals, using a murine model knock-out for the aromatase gene.
2000-today Cooperation with dr. J. Bakker (University of Liege, Belgium) on sexually dimorphic vasopressin system in mice: effects of gonadal hormones in the differentiation and functioning of the system.
2001-today Cooperation with dr. P. Collado (UNED, Madrid, Spain) on the role of gonadal hormones in the regulation of nNOS expression, Vasopressin expression, and neural circuits controlling food intake and energy metabolism.
2005-2008 Cooperation with dr. K. Hallidin (Karoliska Institute, Stockholm, Sweden) on the effects of endocrine distruptors on sexual behavior and neural circuits in birds
2009-today Cooperation with L.M. Garcia Segura (Cajal Institute, Madrid, Spain) on the regulation of the expression of vasopressin in the paraventricular nucleus and in cell coltures in various experimental conditions
2009-today Cooperation with M.Keller (INRA, Tours, France) on the effects of endocrine disruptors on the kisspeptin system in mice

All these cooperations were supported by international grants from NATO, European training program, USDA, National Science Foundation, European Commission, France government, Spain Ministery of Science, CNR, FNRS.

NETWORKING
At present we are also involved in two European networks belonging to COST action.
COST ACTION: A systematic elucidation of differences of sex development (DSDnet)
http://www.cost.eu/COST_Actions/bmbs/BM1303
To study Differences or Disorders of Sex Development (DSD) that constitute a complex group of rare diseases caused by chromosomal, genetic and endocrine metabolic disturbances that affect the endocrine-reproductive system, thereby modulating the sexual phenotype of a given person.

COST ACTION: GnRH NETWORK
http://www.gnrhnetwork.eu/hhn_home/hhn-cost/hhn-costorganization/hhn-wg3basicsciences.htm
Devoted to developing an international network of clinicians and investigators in the fields of reproductive medicine and neuroscience. Specifically we aim to explore the causes of GnRH deficiency, including Kallmann syndrome.

Dr. Panzica is also member of EDCs EU-ES TASK FORCE
http://www.endocrine.org/membership/email-newsletters/endocrine-insider/2014/april-17-2014/society-expands-eu-advocacy-experts-talk-edcs-to-policymakers-in-brussels
It is a group of European and US scientists, working in the field of endocrine disruption, dedicated to to meet with EU policymakers on the issue of endocrine-disrupting chemicals. This group is part of a strategic initiative to ensure endocrine principles are incorporated into global EDC regulatory policies, the Endocrine Society established its EU EDC Task Force to inform and advocate with members of the European Parliament and officials within the EU Directorates General in charge of chemicals laws and regulations.

Invited talks (last ten years)

- Behavioral and neuroanatomical effects of xenoestrogens on avian models (Budapest, XXIX Ethological Conference, August, 2005)

- Gonadal hormones modulation of central nitrinergic systems (Int. Meeting Steroids and Nervous System, Torino, February, 2005)
- Xenoestrogens' action on brain and behavior differentiation: Avian models (International Conference on Food Contaminants and Neurodevelopmental Disorders, Valencia, March 2006)
- Xenoestrogens and Xenoandrogens action on Avian Vasotocin System (International Conference of Neuroendocrinology, Pittsburgh, August 2006)
- Sexual dimorphism and diergism of nitric oxide producing systems in the mammalian central nervous system (2nd World Congress on Gender-specific Medicine and Aging, Rome, March 2007)
- Effects of Xenoestrogens on the Differentiation of Behavioral Relevant Neural Circuits (24th Conference of European Comparative Endocrinologists, Genova, September 2008)
- Organizational Effects of Bisphenol-A on Kisspeptin Expression in the Hypothalamus of CD1 Mouse, 1st Kisspeptin World Conference, Cordoba, October 2008)
- Role of Androgens in the Differentiation of Rodent Arginine-Vasopressin System (XXXIII Congress of the Italian Society of Histochemistry, Rome, June 2009)
- Neuropeptidergic systems - Targets for the Action of Endocrine Disrupting Chemicals in the Vertebrate Brain (Int. Symposium on Disturbance of Cerebral Function Induced by Food and Water Contaminants, Valencia, March 2010**)**
- Neuropeptidergic systems - Targets for the Action of Xenoestrogens or Xenoandrogens in the Vertebrate Brain (Symposium on Neuroendocrine effects of Endocrine Disruptors - Rouen, July 2010)
- Avian vasotocin system: a model for the study of xenoestrogens' effects on brain circuits and behavior (International Conference of Neuroendocrinology, Rouen, July 2010)
- Environment and brain sexual differentiation: what role for endocrine disrupters? (Congresso Società Italiana di Anatomia, Padova, Settembre 2011)
- Hypothalamic NPY Expression in Adult Male Mice is Influenced by Adult Exposure to Environmental Endocrine Disruptors (The Obese Species, Erice, Italy, October 2011)
- Environment and brain sexual differentiation: what role for endocrine disrupters? (SiNAPSA Neuroscience Conference, Ljubljana, Slovenia, September 2011)
- Endocrine disruption of hypothalamic circuits controlling energy balance (Gordon Research Conference on Environmental Endocrine, Mount Snow, VT, USA, June 2012)
- Ambiente e Cervello: Come Nascono le Differenze tra i Sessi (Settimana del Cervello, Torino, Marzo 2012)
- Differenziamento Cerebrale e Ambiente - Quale ruolo per i distruttori endocrini? (10° Congresso Società Italiana Andrologia e Medicina Sessuale, Lecce, November 2012)
- Ambiente e Cervello: Come Nascono le Differenze tra i Sessi (Infinitamente, Festival di Scienza, Verona, Marzo 2013)
- Sistema a Kisspeptina e Interferenti Endocrini (1° Incontro Network Ipogonadismo Centrale, NICe, Milano , Novembre 2013)
- Sexually dimorphic effects of endocrine disruptors on brain and behavior (8th Int. Conf. on Hormones Brain and Behavior, Liege, Belgium, June 2014)
- Distruttori endocrini e circuiti ipotalamici che controllano il metabolismo energetico (4i, Incontri Italiani Ipotalamo Ipofisari, Milano, Febbraio 2014)
- Impact of endocrine disrupters on neuroendocrine circuits controlling food intake (8th Copenhagen Workshop on Endocrine Disrupters, Copenhagen, April 2015)
- The sexually dimorphic vasotocin system as target for neuroendocrine disruption in birds (North American Society for Comparative Endocrinology, NASCE, Ottawa, Canada, June 2015)

Editorial duties.

Member of the Editorial board of:

- Domestic Animal Endocrinology (2007-2010)
- European Journal of Anatomy (1995-2010)
- Cell and Tissue Research (1996-today)
- Hormones and Behavior (2000-2015)

- Journal of Chemical Neuroanatomy (2010-2015)
- Frontiers in Endocrinology (2015-today)

Guest editor of the following special issues:

- Neuropeptides and neuronal circuitries (a cura di G. Filogamo e G.C. **Panzica**), *Special Issue* di Basic and Applied Histochemistry, vol. 32/1, 1988, pp 1-192.
- Hormones, Brain, and Behavior (a cura di G.C.**Panzica** e J.Balthazart). *Special Issue* di Brain Research Bulletin, vol.44/4, 1997, pp.319-557.
- The Role of Nitric Oxide (a cura di G.C.**Panzica**). *Special Issue* di Eur. J. Anatomy, vol.2/1, 1998, pp.25-76.
- Neuroactive steroids in the third millenium (a cura di R.C.Melcangi e G.C. **Panzica**). *Special Issue* di Brain Research Reviews, vol. 37 (1-3), 2001, pp. 1-384.
- Steroids and The Nervous System. (a cura di R.C.Melcangi e G.C.**Panzica**), Annals of the New York Academy of Sciences, 2003, Vol. 1007, pp.1-406.
- Action of environmental estrogens on neural circuits and behavior (a cura di G.C. **Panzica** e M.A.Ottinger), *Special Issue*, Brain Research Bulletin, vol. 65, 2005, pp. 185-275.
- Neuroactive steroids: Old players in a new game (a cura di R.C. Melcangi e G.C. **Panzica**), *Special Issue,* Neuroscience, vol.138(3), 2006, pp.733-1048.
- The endocrine nervous system: source and target for neuroactive steroids. (a cura di R.C.Melcangi e G.C.**Panzica**)), *Special Issue,* Brain Res. Reviews, vol. 57, 2008, pp. 271-605.
- Neuroactive steroids: effects and mechanisms of action (a cura di R.C. Melcangi e G.C. Panzica), *Special Issue*, Psychoneuroendocrinology, vol. 34 (Suppl. 1) 2009, pp. 1-286 - ISSN.0306-4530.
- Neuroactive steroids: Focus on human brain (a cura di R.C. Melcangi, L.M. Garcia-Segura e G.C. Panzica), *Special Issue*, Neuroscience, vol. 191, 2011, pp. 1-158 – ISSN.0306-4522.
- Recent advances in peptides and neurotransmitters (a cura di G.C.Panzica e L. D'Este), *Special Issue*, J. Chem. Neuroanatomy, vol. 42, 2011, pp. 221-340 – ISSN.0891-0618.
- Steroids and the nervous system (a cura di G.C. Panzica e R.C. Melcangi), *Special Issue*, Journal of Neuroendocrinology, vol. 24, 2012, pp. 1-248 - ISSN 0953–8194.
- Steroids and the nervous system (a cura di R.C. Melcangi e G.C. Panzica), *Special Issue*, Journal of Neuroendocrinology, vol. 25, 2013, pp. 957-1238 - ISSN 0953–8194.
- Allopregnanolone: State of the art (a cura di Melcangi R.C., Panzica G.C.) *Special Issue*, Progr. Neurobiol, vol. 113, 2014, pp 1-136, ISSN: 0301-0082

Please list your organizational activities:

- **Speakers invited**

  In addition to the speakers invited for the conferences and symposia, in the last 5 years we invited the following speakers for seminars at the Department of Neuroscience and/or NICO: Jacques Balthazart (Liege, Belgium), Luis Miguel Garcia Segura (Madrid, Spain), Guy Mensah-Nyagam (Strasbourg, France), Manuel Tena Sempere (Cordoba, Spain)

- **Workshops, Schools or Conferences organized**

Conferences

- VI International Conference on Hormones, Brain and Behavior, Torino, August 1996
- VII International Conference on Hormones, Brain and Behavior, Torino, February 2009
- International Meeting Steroids and Nervous System, Torino. A series of conferences organized each two years in Torino, starting from 2001: 2001, 2003, 2005, 2007, 2009, 2011, 2013, and 2015 (8th edition).

Satellite Symposia-

- Satellite symposium: Behavior as a biomarker of the effects of estrogenic pollutants in higher vertebrates, Torino, September 2001
- Satellite symposium: Action of environmental estrogens on behaviorally relevant neural circuits, Torino, February, 2003
-- Satellite Symposium: Steroid hormone regulation of NPY system, Torino, February 2005.
- Satellite Symposium: Selective Estrogen Receptors Modulators and the Brain, Torino, February 2007
- Satellite Symposium: Neuroactive steroids: Focus on human brain, Torino, February 2011
- Satellite Symposium: Allopregnalonone: State of Art, Torino, February 2013
- Satellite Symposium: Gender Differences on Neurodegenerative and Psychiatric Disorders, Torino February 2015

Workshops
- Image analysis on neurohistology - Technical Workshop of ENA meeting, Torino, 1989
- Metodi e problematiche della neurobiologia comparata - Workshop for the Meeting of the UZI, Torino, Italy, 1993
- Il Ruolo del NO - Workshop for the Meeting of the Società Italiana di Anatomia, Torino, 1997
- Avian models for studying xenoestrogens action on brain and behavior - Workshop for the XXIX Ethological Conference, Budapest, August, 2005

3. PI's PUBBLICATIONS:

(Please list below your publications in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science).
IF and Ranking of the year of publication.

Farinetti, A., Tomasi, S., Foglio, B., Ferraris, A., Ponti, G., Gotti, S., Peretto, P., Panzica, G.C. (2015). Testosterone and estradiol differentially affect cell proliferation in the subventricular zone of young adult gonadectomized male and female rats. Neuroscience. 286, 162-170.
IF= 3.357; R = 96/252; Times cited = 0

Heindel, J.J., vom Saal, F.S., Blumberg, B., Bovolin, P., Calamandrei, G., Ceresini, G., Cohn, B.A., Fabbri, E., Gioiosa, L., Kassotis, C., Legler, J., La Merrill, M., Rizzir, L., Machtinger, R., Mantovani, A., Mendez, M.A., Montanini, L., Molteni, L., Nagel, S.C., Parmigiani, S., Panzica, G., Paterlini, S., Pomatto, V., Ruzzin, J., Sartor, G., Schug, T.T., Street, M.E., Suvorov, A., Volpi, R., Zoeller, R.T., Palanza, P. (2015). Parma consensus statement on metabolic disruptors. Environmental health : a global access science source. 14, 54.
IF= 3.37; R = 37/223 (Env Health) R=24/165 (Public Health); Times cited = 1

Bonomi, M. Cappa, M., Cariboni, A. Di Schiavi, E., Fabbri, A., Ferlin, A., Foresta, C., Ghizzoni, L., Jannini, E., Krausz, C., Loche, S., Lombardo, F., Maggi, M., Maggi, R., Maghnie, M., Mancini, A., Merlo, G., Panzica, G., Radetti, H., Russo, G., Simoni, M., Sinisi, A.A., Persani, L. (2014) Kallmann's syndrome and normosmic isolated hypogonadotropic hypogonadism: two largely overlapping manifestations of one rare disorder. J Endocrinol Invest. May;37(5):499-500.
IF= 1.448; R = 109/128; Times cited = 1

Grassi, D., Lagunas, N., Calmarza-Font, I., Diz-Chaves, Y., Garcia-Segura, L.M., Panzica, G.C. (2014). Chronic unpredictable stress and long-term ovariectomy affect arginine-vasopressin expression in the paraventricular nucleus of adult female mice. Brain research. 1588, 55-62.
IF= 2.843; R = 122/252; Times cited = 1

Melcangi, R.C., Panzica, G.C. (2014). Allopregnanolone: state of the art. Progress in neurobiology. 113, 1-5.
IF= 9.992; R = 11/252; Times cited = 11

Rodriguez-Gomez, A., Filice, F., Gotti, S., Panzica, G. (2014). Perinatal exposure to genistein affects the normal development of anxiety and aggressive behaviors and nitric oxide system in CD1 male mice. Physiology & behavior. 133, 107-114.
IF= 2.976; R = 19/51; Times cited = 2

Allieri, F., Spigolon, G., Melcangi, R.C., Collado, P., Guillamon, A., Gotti, S., Panzica, G.C. (2013). Androgen receptor deficiency alters the arginine-vasopressin sexually dimorphic system in Tfm rats. Neuroscience. 253, 67-77.
IF= 3.327; R = 104/252; Times cited = 2

Grassi, D., Bellini, M.J., Acaz-Fonseca, E., Panzica, G., Garcia-Segura, L.M. (2013). Estradiol and testosterone regulate arginine-vasopressin expression in SH-SY5Y human female neuroblastoma cells through estrogen receptors-alpha and -beta. Endocrinology. 154(6), 2092-2100.
IF= 4.644; R = 24/124; Times cited = 4

Grassi, D., Lagunas, N., Amorim, M., Pinos, H., Panzica, G., Garcia-Segura, L.M., Collado, P. (2013). Role of oestrogen receptors on the modulation of NADPH-diaphorase-positive cell number in supraoptic and paraventricular nuclei of ovariectomised female rats. Journal of neuroendocrinology. 25(3), 244-250.
IF= 3.507; R = 50/124; Times cited = 1

Grassi, D., Lagunas, N., Amorin, M., Pinos, H., Panzica, G.C., Garcia-Segura, L.M., Collado, P. (2013). Estrogenic regulation of NADPH-diaphorase in the supraoptic and paraventricular nuclei under acute osmotic stress. Neuroscience. 248, 127-135.
IF= 3.327; R = 104/252; Times cited = 0

Melcangi, R.C., Panzica, G.C. (2013). Neuroactive steroids and the nervous system: further observations on an incomplete tricky puzzle. Journal of neuroendocrinology. 25(11), 957-963.
IF= 3.507; R = 50/124; Times cited = 2

Frye, C.A., Bo, E., Calamandrei, G., Calza, L., Dessi-Fulgheri, F., Fernandez, M., Fusani, L., Kah, O., Kajta, M., Le Page, Y., Patisaul, H.B., Venerosi, A., Wojtowicz, A.K., Panzica, G.C. (2012). Endocrine disrupters: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. Journal of neuroendocrinology. 24(1), 144-159.
IF= 3.331; R = 47/122; Times cited = 79

Panzica, G.C., Balthazart, J., Frye, C.A., Garcia-Segura, L.M., Herbison, A.E., Mensah-Nyagan, A.G., McCarthy, M.M., Melcangi, R.C. (2012). Milestones on Steroids and the Nervous System: 10 years of basic and translational research. Journal of neuroendocrinology. 24(1), 1-15.
IF= 3.331; R = 47/122; Times cited = 14

Razzoli, M., Bo, E., Pascucci, T., Pavone, F., D'Amato, F.R., Cero, C., Sanghez, V., Dadomo, H., Palanza, P., Parmigiani, S., Ceresini, G., Puglisi-Allegra, S., Porta, M., Panzica, G.C., Moles, A., Possenti, R., Bartolomucci, A. (2012). Implication of the VGF-derived peptide TLQP-21 in mouse acute and chronic stress responses. Behavioural brain research. 229(2), 333-339.
IF= 3.327; R = 13/49; Times cited = 8

Bo, E., Viglietti-Panzica, C., Panzica, G.C. (2011). Acute exposure to tributyltin induces c-fos activation in the hypothalamic arcuate nucleus of adult male mice. Neurotoxicology. 32(2), 277-280.
IF= 3.096; R = 74/261 (Pharmacol); Times cited = 6

Genestine, M., Caricati, E., Fico, A., Richelme, S., Hassani, H., Sunyach, C., Lamballe, F., Panzica, G.C., Pettmann, B., Helmbacher, F., Raoul, C., Maina, F., Dono, R. (2011). Enhanced neuronal Met signalling levels in ALS mice delay disease onset. Cell death & disease. 2, e130.
IF= 5.333; R = 45/181; Times cited = 13

Gotti, S., Caricati, E., Panzica, G. (2011). Alterations of brain circuits in Down syndrome murine models. Journal of chemical neuroanatomy. 42(4), 317-326.
IF= 2.435; R = 141/244 (Neuroscience); Times cited = 9

Martini, M., Pradotto, M., Panzica, G. (2011). Synergic effects of estradiol and progesterone on regulation of the hypothalamic neuronal nitric oxide synthase expression in ovariectomized mice. Brain research. 1404, 1-9.
IF= 2.728; R = 126/244; Times cited = 4

Martini, M., Sica, M., Gotti, S., Eva, C., Panzica, G.C. (2011). Effects of estrous cycle and sex on the expression of neuropeptide Y Y1 receptor in discrete hypothalamic and limbic nuclei of transgenic mice. Peptides. 32(6), 1330-1334.
IF= 2.434; R = 114/261 (Pharmacology); Times cited = 0

Melcangi, R.C., Panzica, G., Garcia-Segura, L.M. (2011). Neuroactive steroids: focus on human brain. Neuroscience. 191, 1-5.
IF= 3.380; R = 94/244; Times cited = 47

Panzica, G.C., Bo, E., Martini, M.A., Miceli, D., Mura, E., Viglietti-Panzica, C., Gotti, S. (2011). Neuropeptides and enzymes are targets for the action of endocrine disrupting chemicals in the

vertebrate brain. Journal of toxicology and environmental health Part B, Critical reviews. 14(5-7), 449-472.
IF= 4.725; R = 7/83 (Toxicology); Times cited = 8

Aimetti, M., Romano, F., Cricenti, L., Perotto, S., Gotti, S., Panzica, G., Graziano, A. (2010). Merkel cells and permanent disesthesia in the oral mucosa after soft tissue grafts. Journal of cellular physiology. 224(1), 205-209.
IF= 3.986; R = 13/78 (Physiology); Times cited = 1

Grassi, D., Amorim, M.A., Garcia-Segura, L.M., Panzica, G. (2010). Estrogen receptor alpha is involved in the estrogenic regulation of arginine vasopressin immunoreactivity in the supraoptic and paraventricular nuclei of ovariectomized rats. Neuroscience letters. 474(3), 135-139.
IF= 2.055; R = 161/239; Times cited = 16

Gotti, S., Martini, M., Viglietti-Panzica, C., Miceli, D., Panzica, G. (2010). Effects of estrous cycle and xenoestrogens expositions on mice nitric oxide producing system. Italian journal of anatomy and embryology = Archivio italiano di anatomia ed embriologia. 115(1-2), 103-108.
IF= 0; Times cited = 6

Martini, M., Miceli, D., Gotti, S., Viglietti-Panzica, C., Fissore, E., Palanza, P., Panzica, G. (2010). Effects of perinatal administration of Bisphenol A on the neuronal nitric oxide synthase expressing system in the hypothalamus and limbic system of CD1 mice. Journal of neuroendocrinology. 22(9), 1004-1012.
IF= 4.650; R = 25/116 (endocrinology); Times cited = 12

4.GROUP's PUBBLICATIONS:

(Please list below up to ten most relevant publications of the other members of the group in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science)

Ponti, G., Obernier, K., Alvarez-Buylla, A. (2013) Lineage progression from stem cells to new neurons in the adult brain ventricular-subventricular zone. CELL CYCLE 12: 1649 – 1650.
IF= 4.565; R = 57/184; Times cited = 5

Ponti G, Obernier K, Guinto C, Jose L, Bonfanti L, Alvarez-Buylla A (2013) Cell cycle and lineage progression of neural progenitors in the ventricular-subventricular zones of adult mice**,** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA* (*PNAS* - ISSN:1091-6490), pp. E1045- E1054. Vol. 110.
IF= 9.674; R = 4/57; Times cited = 39

Ponti G, Reitano E, Aimar P, Cattaneo E, Conti L, Bonfanti L (2010) Neural-specific inactivation of ShcA function results in anatomical disorganization of subventricular zone neural stem cell niche in the adult brain, *NEUROSCIENCE* (ISSN:0306-4522), pp. 314-322. Vol. 168.
IF= 3.357; R = 96/252; Times cited = 6

Ponti G, Crociara P, Armentano M, Bonfanti L (2010) Adult neurogenesis without germinal layers: the "atypical" cerebellum of rabbits. Arch Ital Biol. 2010 Jun;148(2):147-58.
IF= 0.078; R = 213/239; Times cited =17

5. GROUP's additional information:

Please list the grants of the other members of the group in the last 5 years -2010/2015- according to the table below:

Starting-end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
	National vs International	P. Rossi; PI vs. Component	MIUR, ERC, ecc…			€	€
01/01/2013-31/12/2015	National	Gotti S; PI	UNITO-ex 60% 2012	**NEUROSTEROIDI E MODULAZIONE DELLA NEUROGENESI NELL'IPPOCAMPO DI RATTO**		2.787	
01/01/2014-31/12/2015	National	Gotti S; PI	UNITO-ex 60% 2013-progetti speciali di ateneo	**Effects of perinatal administration of estradiol in the development of the sexually dimorphic arginine-vasopressin system in mice**		10.300	
01/01/2015-31/12/2017	National	Gotti S; PI	UNITO-ex 60% 2014	**The Kisspeptin neuronal system: study of the distribution and of the pubertal development**		1.854	148,33
1/1/2015-31/1/2016	National	Ponti G; PI	UNITO-ex 60% 2013	Analisi dell'effetto dei fitoestrogeni sullo sviluppo del sistema nervoso centrale nei mammiferi		10.000	

Please list honours, prizes or awards received by other members of the group If applicable.

Ponti G.

- 2013 has achieved the National Academic Qualification as Associate Professor in Veterinary Anatomy
- 2009-2012 Marie Curie Outgoing International Fellowship: "*Imaging of the neural stem cell origin, proliferation, and fate within the stem cell niches of the mammalian brain*", University of California San Francisco, Department of Neurosurgery (Prof. Arturo Alvarez-Buylla lab.) in collaboration with the University of Turin, Italy, Department of Veterinary Morphophysiology (230669 €)

Please list outreach activities of other members of the group:

- Describe your international collaborative experiences.

Ponti G

2012-2014 National member of the COST ACTION: NANONET

Prof. Arturo Alvarez-Buylla, UCSF, San Francisco, California, USA Prof. Elly Hol (University of Utrecht) Prof. Roy Quinlan (University of Newcastle) Prof. J.C.V.M (Sjef) Copray (University of Groningen)

Gotti S
Prof. Guy Mensah-Nyagan, Equipe Stéroïdes, Neuromodulateurs et Neuropathologies, University of Strasbourg, France

- Invited talks

- Editorial duties

Ponti G

Since 2015 referee for FISM-AISM
Since 2014 Review panel member for Frontiers in Neuroscience
Since 2013 Euraxess expert
Since 2009 Associate Faculty Member of F1000

Gotti S
Since 2006 guest referee for these international scientific journals:
Brain Research, Journal of, Chemical Neuroanatomy, Cell and Tissue Research, Physiology and Behavior, Neurological Science, Histology and Histopathology

Please list your organizational activities:

- **Workshops, Schools or Conferences organized by members of the group**

Gotti S
Member of the Local Organizing Committee of the International Meeting Steroids and Nervous System (Turin, 2001, 2003, 2005, 2007, 2009, 2011, 2013, 2015) and co-editors of the scientific abstracts issue.

Ponti G
Member of the Local Organizing Committee of the International Meeting Steroids and Nervous System (Turin, 2013, 2015)

Please list your technology transfer achievements (patents, etc.), if applicable

6 .Past Research activity

a. Summary

The central focus of our researches has been the study of the interactions among steroids and nervous circuits. In particular, in the last ten years we studied the role played by early exposure to exogenous estrogens (XE) and androgens (XE) in the differentiation of sexually dimorphic circuits and behaviors in birds and mammals. Three main circuits and behaviors have been considered: arginine-vasopressin, NO-producing, and NPY systems, related to social, reproductive, and food intake behaviors.

b. Background

Among the hormonal signals with high impact on brain development, gonadal hormones, such as 17β-estradiol (E_2) and androgens, play key roles in the development of primary and secondary sex characteristics in higher vertebrates, including several steroid dependent behaviors. Our knowledge of how estrogens affect mammalian brain function and development has substantially broadened in recent years. After the demonstration that both nuclear estrogen receptors (ERα and ERβ) and the membrane receptor (GPER-1) are expressed in many brain areas during ontogeny, it was soon realized that estrogens may modulate neuronal differentiation, notably by influencing cell migration, survival and death, and synaptic plasticity of neurons. These effects were initially seen in the classical target area for E2, the hypothalamus and, later, also in other brain regions that revealed neuro-trophic effects of estrogen.
Appropriate levels of gonadal hormones are essential for normal development and sexual differentiation of the central nervous system (CNS), and of the reproductive behavior. Disturbing this developmental milieu, via exogenous estrogen treatment or gonadectomy, during critical periods of the pre- and/or postnatal development, may induce irreversible changes in the organization of the central nervous system and determine behavioral alterations in many species. Due to the fact that many endocrine distrupting chemicals (EDCs) are xenoestrogens (XEs) or xenoandrogens (XAs), they could, even in very low concentrations, deeply influence the development and the function of gonadal hormones-dependent neural circuits and related behaviors. Behavioral responses represent the culmination of several integrated systems, therefore, even small changes of neural or neuroendocrine components are likely to disrupt or modify behavior. Importantly, disturbances in normal behavior may influence the individual fitness and, therefore, assume a real biological significance in both animal and human ecosystems.

c. Rationale

When we started the study of neural and behavioral effects of EDCs, the current understanding of the activity and metabolism of XEs/XAs was based mainly on in vitro models, which do not provide detailed knowledge of XEs low dose effects. In addition, the traditional toxicological testing paradigms consider measures that are not tailored for impact on endocrine systems. In fact, EDCs' effects must consider end-points that are sensitive and reliable for assessing the effects of these compounds on the whole living organism, as well as on the integrated functions (behaviors) that could be affected.
An interesting example is bisphenol A (BPA), which is widely used in the food industry and in dentistry. BPA is known to have a weak estrogenic action due to its low affinity for the ERα. In spite of this weak binding activity, very low doses of BPA administered during the perinatal period have consequences on male mice, specifically increased prostate weight and decreased sperm production. In addition, mice fetuses exposed to BPA and then raised by untreated foster mothers still showed significant increase of body weight at weaning, earlier vaginal opening signaling accelerated puberty onset, as well as alterations of maternal behavior when adult.
EDCs acting at low levels can exert subtle effects by interfering with gene expression and other cellular activities, which can cause transient activational responses, or permanent impairment. Thus, the impact of EDCs will vary depending upon a variety of factors, including when exposure occurs in the life-cycle of an organism, as well as the duration and amount of the exposure. During the life-cycle of an organism, developmental stages are typically far more vulnerable to signal disruption than adult stages and the consequences of fetal exposure may be drastically different from those of adult exposure. This is thought to occur for several reasons, including the

absence of fully developed protective enzyme systems and higher metabolic rates. Most importantly, however, the events underway in development involve a series of organizational alternatives that are (largely) irreversible once the ‘‘choice’’ in development is determined.

d. Objectives

The combination of steroid sensitivity (or the presence of gender differences) of specific neural circuits controlling specific behaviors is not too easy to find. Therefore our priority objective was to select animal models that could be suitable for the investigation on the EDCs effects. In addition, we were also interested in obtaining a comparative approach to the problem.
Our main model is the sexual behavior and the neural circuits that are controlling this behavior. Many of these circuits are, in turn, sexually dimorphic and their differentiation is due to the exposure to the correct steroid hormone during a particular period of life called critical period. In birds and mammals, this effect is largely due to the intracerebral conversion of testosterone into estradiol via the enzyme aromatase. For this reason we have studied for a long time the cerebral distribution and activation of this enzyme, in particular in the avian brain.
However, contrary to other neural systems, the aromatase producing system does not show a strong dimorphism. Therefore, we have investigated, in turn, several neural systems, focusing mainly on the sexually dimorphic vasotocin (AVT)/vasopressin (AVP) system and the nitrinergic system.

e. Results

Sexually dimorphic AVT/AVP system. In the Japanese quail, embryonic exposure to estradiol benzoate (EB), prior to day 12 of incubation (critical period), irreversibly de-masculinizes both adult male copulatory behavior and the parvocellular AVT system of BST (**Panzica et al. 1998**). To test the estrogenic activity of different XE, eggs were injected at day 3 of incubation (simulating the accumulation of exogenous EDC by the mother within eggs). When 2-month old male quails were examined, XE affected both male copulatory behavior and AVT immunoreactivity. In particular, we observed a significant demasculinizing effect of diethylstilbestrol (DES), genistein, or ethylene, 1,1- dichloro-2,2-bis-*p*-chlorophenyl (DDE) on the sexually dimorphic parvocellular AVT system of the nucleus of the stria terminalis and on its projections to medial preoptic nucleus and lateral septum (**Viglietti-Panzica, et al. 2005; 2007; Mura et al. 2009**). For other EDCs the effects on this neural system were not significant or absent. Ethynylestradiol (EE_2) and methoxychlor (MCX), both affecting male sexual behavior, did not induce significant alterations of the AVT system (**Mattsson et al. 2008**).
A dissociation between demasculinization of behavior and demasculinization of the VT-ir system was found in these studies, suggesting that these effects are induced by estrogens via at least partly different pathways. Estrogen-induced effects on reproductive organ differentiation are mediated by ERα, whereas demasculinization of male copulatory behavior and AVT-immunoreactive (ir) system is not stimulated by activation of ERα alone. Therefore, it was postulated that ERβ might have a primary role for the development of these circuits and behavior. This is also supported by the observation that during development of hypothalamic and limbic regions of Japanese quail, ERα appears later than ERβ.
In mammals, we are investigating the AVP system and its regulation by gonadal hormones (**Grassi et al., 2010, 2013a**).
Nitric oxide synthase. Nitric oxide (NO) is a ubiquitous gaseous messenger molecule produced through the action of the enzyme nitric oxide synthase (NOS). NO is involved in various physiological activities, such as long-term potentiation, neuroprotection, or neural degeneration. NO plays a crucial role in reproduction at various level in the organism, from mounting behavior to lordosis and ovulation. We have published the first detailed description of the distribution of NO-producing neurons in mice (**Gotti et al. 2005**). NO-producing neurons were detected in several hypothalamic and limbic nuclei of rodents implicated in the control of reproduction (**Sica et al. 2009**). Our studies suggested complex relationships among nNOS system and gonadal hormones, suggesting the existence of significant neuroendocrine relationships (**Panzica et al. 2006; Carrillo et al. 2007; Gotti et al. 2009; Sica et al. 2009; Martini et al., 2009; Gotti et al. 2010; Grassi et al., 2013b, 2013c**). In addition, the analysis of mutant animals with knockout for ER-alpha or aromatase, and of Tfm rats with spontaneous mutation of the androgen receptor

demonstrated that both estrogens and androgens exert a relevant role for the sexual differentiation of the hypothalamic nNOS system (**Martini et al. 2008**).
We have, therefore, examined the longterm effects of early exposure of mice of both genders to BPA on the nitrinergic system. Mice of both genders were exposed for 10 prenatal and 8 postnatal days to BPA that was administered to the mothers. The maternally exposed mice were sacrificed at the age of 2 months. Significant effects of BPA exposure were detected on the number of nNOS immunoreactive cells in a gender-oriented and dose-dependent way (**Martini et al. 2010**).
In recent years, we started the study of the effects of adult exposure to a potent obesogen, (tributiltyn, TBT) over the system controlling food intake (**Bo et al., 2011; Panzica et al., 2011**). We are also exploring the effects of phytoestrogens on NO- (**Rodriguez et al., 2014**) and AVP-systems.

f. Advancement in the field (1000 characters)

The health problems related to endocrine disruptors (in particular those related to obesity) gained more attention then 10 years ago both for politicians and for the people. Our studies, as well as those performed in other laboratories, esthablished some new end-points to determine the EDCs activity, in particular the behavior and the brain circuits. In addition, these studies pointed to the importance of "windows of activity" to determine the effects of these molecules (Frye et al., 2012). Our activity generated also some interactions with the political authorities of the European Commission, to participate at the discussions about the new regulation of EDCs in Europe (task force of the Endocrine Society). A consensus paper about the new concept of "metabolic disruptors" was recently published (Heindel et al., 2015) and a commentary on the activity of the task force has been recently submitted to *Environmental Health Perspective*.

7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do

a. Summary (up to 2000 characters):

The last published study of our group, is about the role played by testosterone and its metabolites in the regulation of adult neurogenesis in the subventricular zone of male and female rats (Farinetti et al., 2015). This study has left several unanswered questions, i.e., the receptors that are involved in this effect, and the action that some xenoestrogens or xenoandrogens could exert on this important physiological event. Finally, we don't know if gonadal hormones dependent neurogenesis is paralleled by an increase of migration and differentiation within the olfactory bulb, We are, therefore, planning to solve these questions.
A large effort of our team was directed to the study of the kisspeptin (Kiss) system (see our participation to a COST action) as a tool to understand the action of endocrine disrupters over the reproduction. One of the major targets of the Kiss system, is the paraventricular nucleus, where are located two major peptidergic systems controlling energy metabolism: CRF- and TRF-producing neurons. We want to investigate relationships among the Kiss- and these two other systems, that are located in the medial part of the PVN, where Kiss positive fibers show a higher density. One important point is to demonstrate the origin of these fibers and the involved receptor, in fact, in the PVN the classical Kiss1 receptor is missing.
Finally, our long-term cooperation with the laboratory of dr. Collado in Madrid, is dedicated to the study of the involvement of gonadal hormones (chiefly estradiol) on neuroendocrine circuits programming feeding in rodents. In particular, we will investigate if estradiol during first stage of development participates in the programming/organization of these circuits as well as in the expression of the feeding behavior and the receptor pathways that are involved.
All these three research lines will include groups of animals treated with EDCs (BPA, TBT, or genistein), in order to see how the exposure to these compounds will impact on these steroid hormone-dependent neuronal systems and behaviors.

b. Background and Significance (up to 4000 characters):

Steroid hormones, which are synthesised in adrenal glands, gonads or placenta, exert a large array of biological effects on the nervous system. These hormones play important roles in the development, growth, maturation, differentiation and protection of the central (CNS) and peripheral nervous system (PNS). In addition, the nervous system itself is capable of metabolize or de nove synthese active steroids (*neurosteroids*) which may control the activity and survival of nerve cells. In the living animal, there are mechanisms (i.e. the alpha-fetoprotein in rodents or the sex hormone binding globulin in primates) that protect the brain from the circulating gonadal hormones, in order to prevent “mistakes” in the differentiatiion of gonadal hormone-dependent circuits during specific windows of activity (critical perido) that occurs in the pre- or/and postnatal development.
Endocrine disrupting chemicals (EDCs) are compounds that are biologically active and often mimic endogenous hormones (largely estrogens or androgens), thereby altering hormone modulated responses. They are not blocked by protective mechanisms as the alpha-fetoprotein, therefore they have been shown to disrupt embryonic development, sexual differentiation, reproduction, immune function, behavior, and responses mediated by hormones. The issue of EDCs has gained increasing attention as it has become clear that these environmental contaminants have endocrine activity in humans, as well as in wildlife and domestic animal species. Some of these chemicals, most notably the plant phytoestrogens largely present in the food, may play an important role in the reproductive cycles of small rodents as well as have positive (or negative) effects in other animals including humans.
A range of EDC effects has now been documented in a number of animal species, both in laboratory studies and in wild populations, demonstrating that xenoestrogenic or xenoandrogenic compounds may exert deleterious effects, even long time after exposure. The data derived from women exposed prenatally to diethylstilbesterol provided powerful evidence for long-term effects and endocrine disruption associated with selected compounds. Experimental data in galliforms and rodents showed that EDCs exposure, though nonlethal,

left the individual impaired or even incapable of reproducing (Panzica et al., 2007). A recent acquisition is the concept of metabolic disruptors, i.e. substances that are able to induce profound alterations of the metabolism and inducing diseases like the diabetes (Heindel et al., 2015).
Many studies on EDCs have a toxicological approach and are performed in vitro. Among those done in vivo, only a few studies have considered the brain as a major target. In this field, our laboratory is very active and we will continue our researches covering 3 research lines dealing with different aspects of the interactions gonadal hormones-nervous system.
The first one is adult neurogenesis that, in rodents is chiefly limited to the subventricular zone (SVZ) and the hippocampus. Our recent study (Farinetti et al., 2015) demonstrated that, in male rats, the lack of T affects adult neurogenesis in the SVZ, by reducing the rate of cell proliferation. Neurogenesis in gonadectomized animals is restored by E_2 administration and not by DHT, indicating that local aromatization of T in E_2 should play a major role in this effect. The SVZ population shows a sexually dimorphic sensitivity to gonadal hormones. In fact, we found that both ovariectomy and acute administration of T or E_2 in OVX females did not modify the number of cycling cells in the SVZ neurogenic niche.
A second research line is strictly related to the control of reproduction and the interaction with the metabolic state of the animals. It appears from our preliminary studies that the hypothalamic paraventricular nucleus could be a privileged site for these interactions. In fact in addition to TRH and CRH system, we have observed a large supply of kisspeptin fibers ending in this region that could potentially interact with the other peptidergic systems. Kisspeptin system is particularly vulnerable to EDCs and part of the metabolic effects of these compound could be explained through the action over the kisspeptin system.
The third research line involves the study of the effects of estrogens over the orexigenic and anorexigenic neuroendocrine circuits (NPY, Orexin, and POMC/MSH). It is well known the anorexigenic effect of estradiol in the adult life. We want to investigate its effects during early development and those of EDCs administered both in adult and in early life.

c. General aim and integration with mission of the Institute (up to 1000 characters)

Our research lines are covering three important physiological activities, as the adult neurogenesis, the reproduction, and the control of energy metabolism. The general aim of our research is to understand how the steroid hormones (chiefly the gonadal hormones) may interact and regulate the neural circuits that are involved in these functions, with particular consideration of gender differences. This is particularly related to the topic of neuroendocrine basis of some neurodegenerative diseases in which it is present a significant sex dimorphism. The approach to cure these diseases should always consider that some basic mechanisms could be sexually differentiated. In addition, in some cases it appears that environmental factors may have a role in the development of these diseases, therefore EDCs, that may interact with gonadal hormones receptors, are good candidates for this environmental action. The elucidation of how these compounds interact with nervous circuits will open a new frontier in our knowledge.

d. Specific objectives and strategies (up to 4000 characters):

A variety of models have been used in our and other laboratories during these last years for the study of the interactions of steroid hormones and the nervous system, and we will focalize, during the next 3 years, to: adult neurogenesis, regulation of food intake and energy metabolism, and the interactions among reproduction control and energy metabolism in rodents.
Researches in the field of neuroendocrinology always face on the problem of receptors, trying to couple effects and exact localization of hormone receptors. Part of our research will be, therefore, devoted to the study of the distribution of classical estrogen (alpha and beta) and androgen receptors and of the recently discovered estrogen membrane receptor (GPR-30 or GPER-1) in specific regions of interest for our studies (the subventricular zone, the hyppocampus, the paraventricular nucleus, the arcuate nucleus). To test what receptors are involved in the observed effects, we will use agonist and antagonist of different receptors (these are now on the market ensuring a good reliability of results). This technique has been previously used in our studies on the regulation of the expression of vasopressin *in vivo*

(Grassi et al., 2010) and *in vitro* (Grassi et al., 2013a), as well as on the regulation of the NADPH-diaforase activity (Grassi et al., 2013b). In addition, we will investigate the effects of adult of precocious exposure to EDCs for two specific reasons: one is to investigate the perturbations of normal physiology when the experimental animals are exposed to these compound, and the second is the use of these compounds as an additional tool to investigate the mechanisms of actions of steroid hormones.
The EDCs' administration will be during late pregnancy and/or during the first week of life, during the prepuberal period, or during adult life. This strategy is to understand if different EDCs may have organizational and permanent effects (pregnancy or early life exposure), or they may alter the postnatal events, like the onset of puberty (prepuberal exposure), or, finally, if they may alter also correctly established circuits (adult exposure).
We plan to use 3 EDCs: bisphenol A (BPA), tributyltin (TBT), and genistein (GEN). BPA and GEN are xenoestrogens that should act mainly through ERalpha (BPA) or ERbeta (GEN), while TBT has an anti-androgenic activity. At the moment it is not known if one or more of these compound may act also to the GPR-30 (membrane estrogen receptor). BPA and TBT are largely diffused in the world, due to their presence in the plastic and the PVC and are under strong discussion by the regulatory authorities. GEN is a phytoestrogen, with little or no regulation at all, that is largely present in human and animal food. For example, it has been calculated that more than 4.5 millions of babies drink soy-milk each day only in USA. Our recent study (Rodriguez et al., 2014) demonstrated that prenatal administration of GEN to pregnant mice, induced behavior and neural alterations in the puppies when adults. We think therefore, that more efforts should be put in this research line to discover potential dangers linked to the exposure to GEN and other phytoestrogens.
Finally all these compounds are suspected of an obesogenic action (i.e. induce fat tissue accumulation), but very few studies tried to investigate if this effect is due to only a peripheral action or to some imbalance of neuroendocrine circuits controlling food intake and energy metabolism. Our previous data (Bo et al., 2011) indicate that TBT may act directly on the neurons of the arcuate nucleus, but nothing is known about GEN or BPA. EDCs may have orexigenic but also anorexigenic effects, and may act differentially in the two sexes, therefore this research line is important both to understand some of the additional causes of obesity or of anorexia.

e. Unique features of the project research (up to 2500 characters):

Our research unit is devoted to the study of the interactions among steroid hormones and the nervous tissue, using as main physiological end point the behavior. Due to the large distribution of steroid hormone receptors within the brain and the importance that steroid hormones have for neuronal and glial differentiation, survival and protection, a better understanding of the relationships steroids-nervous system seems to be of crucial importance.
In addition to this, the importance of gender medicine is increasing, and the interactions among gonadal hormones and the nervous system can partly explain gender differences in both physiological and pathological conditions.
This is the general context, but, in last two decades the problem of how the environment can interact with human and animal physiology to induce pathologies became an important topic for the biomedical sciences. It is not surprising that a large number of synthetic substances may interact with hormone receptors and therefore induce endocrine unbalance and diseases. However, for many years the neuroendocrine effects were underestimated and the nervous tissue was not the main target of studies as well as, more importantly, it was not considered as an important end-point to be included to develop toxicological tests for the regulations of the EDCs use. Our researches, coupled with the lobbing activity to the members of the European parliament, will induce, hopefully, major attention to the dangers that EDCs may have mainly at the level of the central nervous system.
In summary, we believe that our researches can improve our understanding of gender differences in the healthy brain, as well as in several neural pathologies, and the complex interactions among the neural circuits, behavior, and environmental contaminants.

8. Letter of intent by the PI (1 page)

(In this letter the PI is invited to indicate: i) how she/he assesses him/herself in term of leadership and ability to manage his/her group ; ii) possible internal problems within his/her group and the strategies for the best solution; iii) his/her commitment in supporting the general activities of the Institute; iii) specific pitfall and difficulties to realize his/her projects; iv) ability in establishing internal and external collaborations.

Dr. Panzica has a long experience as group leader. He started in 1980 to develop his own group, when he was fellow at the Institute of Histology and Embryology, Faculty of Medicine, University of Torino. From the beginning of his independent activity dr. Panzica developed a wide range of Italian and foreign cooperations. In particular, after the periods spent in Germany and in Belgium he developed long-term cooperations with drs Korf and Balthazart. Dr. Panzica had always numerous undergraduate students in his laboratory and his group was characterized by particular harmony of intent. Several of his students have reached permanent positions in Italy or in other countries. At present the group is small: the PI, one researcher with permanent position and one researcher with temporary position, plus one PhD student (up to the end of 2017) and a two-years postdoctoral fellow (up to the end of 2017), plus several undergraduate students. The leadership of dr. Panzica is reinforced by his position as head of the Department of Neuroscience (up to 2018).
Presently and for the next 3 years dr. Panzica is the head of the Department of Neuroscience. This represent at the same time a problem and an opportunity. The problem is that, due to the time that he has to dedicate to the Department, his presence at the NICO is not continuous. However, the position of Head of the Department is an opportunity for the group and for the NICO, in order to reinforce the linkage with other (mostly) clinician groups working in the Department and the possibility of having direct news from the management of the University for funding opportunities, training programs and other important informations.
To partly solve the problem, the group has a journal club each two weeks in order to have all the members of the lab attending and exchanging results, opinions and new ideas.
Dr. Panzica is strongly supporting the activities and the organization of the NICO. In fact, the majority of members of the NICO are belonging to the Department of Neuroscience and dr. Panzica, head of the Department, is constantly trying to reduce at minimum the administrative and burocratic problems among the two entities. He was also able to provide some technical support to the NICO from the Department.
The major problem of dr. Panzica's lab is the financial situation. In spite of several applications no large grant arrived for the 2015. We have already applied to some agencies for the 2016 and we are confident that some grant will arrive. At the moment we have a cooperation with Madrid and a common grant from the Spanish Ministry of Science. In addition, we started a cooperation with prof. Fassino (Dept. Neuroscience, psychiatry) for the study of the biological basis of anorexia, and through this cooperation we received a two year postdoctoral fellowship.
As explained before, dr. Panzica has a long record of external cooperation with several European and US laboratories that will continue in the next 3 years, in particular with Madrid and Tours. We started some discussion to develop an European project involving one group in Slovenia (dr. G. Madjic) and the psychiatry group of the Department. The internal cooperation is very strong with the group of dr. Peretto (neurogenesis) and the group of dr, Eva (neuropsicopharmacology), these cooperations will continue in the next years.

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name:
Neurophysiology of degenerative diseases

1. LABORATORY DESCRIPTION – PERSONNEL:

- **Principal Investigator**

First name and surname Filippo Tempia
Birthdate 20/08/1960
Degree MD, PhD
Gender male
Nationality Italian
Phone: +390116706609
Email: filippo.tempia@unito.it

- **Personnel**

1. First name and surname Eriola Hoxha
   Birthdate 26/01/1981
   Degree PhD
   Gender female
   Role Postdoc
   Nationality Albanian
   Expertise patch-clamp, immunohistochemistry, molecular biology, behavior

2. First name and surname Francesca Montarolo
   Birthdate (14/05/1983)
   Degree PhD
   Gender female
   Role Phd student, then postdoc
   Nationality Italian
   Expertise: immunohistochemistry, behavior, enriched environment

3. First name and surname Mohcene Sadallah
   Birthdate (06/12/1981)
   Degree PhD
   Gender male
   Role Phd student, then postdoc
   Nationality Algerian
   Expertise: immunohistochemistry, transplantation of embryonic tissue

2. PRINCIPAL INVESTIGATOR CURRICULUM VITAE (two pages)

Education and training:

1979-1986: Medical School at the University of Torino

1986: M.D. degree with 110/110 cum laude. Thesis on "Functional aspects of the olivocerebellar pathway". The thesis was recognized as "worth of publication".

1986-1989: Ph.D. student in "Neurological Sciences" at the Department of Human Anatomy and Physiology of the University of Torino.

1990: Ph.D. degree with a thesis on "Role of the olivo-cerebellar system in dynamic and adaptive control of gaze stabilization".

Employment and research experience:

1986: guest scientist at the Hirnforschung Institut of Zürich working on a project on the role of the inferior olive in the plasticity of the vestibulo-ocular reflex, in collaboration with Dr. B.J.M. Hess.

1989: Short-term fellowship of the European Science Foundation for an overall period of 4 months of stay in Munich to work in collaboration with prof. N. Dieringer at the Ludwig Maximilian Universität, on a project on the role of the inferior olive in the adaptation and short-term habituation of the vestibulo-ocular reflex.

1990-1998: Assistant Professor (“Ricercatore Universitario”) at the Department of Human Anatomy and Physiology (Department of Neuroscience since 1996), University of Torino.

1992-1993: on sabbatical leave at the Max Planck Institut für biophysikalische Chemie, Göttingen (Germany) and at the I. Physiologisches Institut der Universität des Saarlandes, Homburg/Saar (Germany) to work with prof. Arthur Konnerth on calcium permeability of glutamate receptor channels of Purkinje cells, medial septum neurons and hippocampal pyramidal cells.

1998-2004: Associate Professor of Human Physiology at the Section of Human Physiology of the Department of Internal Medicine, University of Perugia, Italy.

1998, 2000: short visits to the RIKEN Brain Science Institute in Wako-Shi (Japan) for a collaboration with Dr. Thomas Knöpfel.

2004-2005: Associate Professor of Physiology at the Faculty of Medicine of the University of Torino, Italy.

Since 2005: Full Professor of Physiology at the Faculty of Medicine of the University of Torino, Italy.

2006-2012: Member of the "Rita Levi-Montalcini Center for Brain Repair" of the University of Torino and of the “National Institute of Neuroscience “ (INN).

Since 2008: Tenured Full Professor of Physiology at the Faculty of Medicine of the University of Torino, Italy.

Since 2010: Group Leader at the Neuroscience Institute Cavalieri Ottolenghi (N.I.C.O.)

April 18–June 24, 2012: Visiting Scientist at the University of Texas Medical Branch, Galveston, Texas (USA).

August 2013-August 2014: in sabbatical leave, Visiting Scientist at the Department of Pharmacology and Toxicology of the University of Texas Medical Branch at Galveston, Texas (USA).

Relevant discoveries:

- synaptic integration and maturation of electrophysiological properties of synaptic currents of Purkinje cells from embryonic cerebellum grafts
- postsynaptic currents due to metabotropic glutamate receptors in Purkinje cells
- electrophysiological alterations of Purkinje cells in an animal model of the human genetic disease ataxia telangiectasia
- synaptic physiology of deep cerebellar nuclei
- cerebellar synaptic plasticity induced by fear conditioning
- expression and physiological roles of voltage-dependent potassium currents (I_A, Kv3, erg) and resurgent sodium current in Purkinje cells
- role of neuronal activity on the progression of the pathological lesions in murine models of Alzheimer's disease
- mechanisms of spreading of pathological lesions in Alzheimer's disease models, by means of transplantation
- structural and functional alterations in animal models of hereditary ataxia

Grants (last five yrs).

Starting-end date	Origin	Role	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
	National vs International	PI vs. Component	MIUR, ERC, ecc…			€	€
2012	International (USA)	PI	National Ataxia Foundation	Pilot study of the first knock-in animal model of SCA28, harboring the M666R mutation		€ 16,000 ($15,000)	€ 16,000 ($15,000)
2012/2015	National	co-PI	MIUR	Morphological and functional alterations in knock-in mice, model of spinocerebellar ataxia SCA28		€ 110,000	€ 110,000
2012/2015	National	co-PI	Telethon-Italy	Spinocerebellar ataxia type 28: cellular and animal models to unravel the pathogenesis and to identify potential therapeutic targets	GGP12217	€ 156,800	€ 156,800
2013/2014	National	PI	University of Turin – Local Grants	Integration of healthy embryonic nervous tissue in the adult brain of mice models of Alzheimer's disease		€ 3,000	€ 3,000
2014/2015	National	PI	University of Turin – Local Grants	Sintomi cerebellari e meccanismi cellulari in un modello murino di atassia spino-cerebellare tipo 38 (SCA38)		€ 2,400	€ 2,400
2014/2017	National	co-PI	Telethon-Italy	Translating molecular pathology into a therapeutic strategy in SCA38, a newly identified form of spinocerebellar ataxia	GGP14225	€ 86,400	€ 86,400

Please list the name of PhDs you have supervised.

1999-2003 **Tiziana Sacco**, Neuroscience PhD Program. **PhD thesis Mentor**, University of Torino.

2006-2010 **Enrica Boda**, Neuroscience PhD Program. **PhD thesis Mentor**, University of Torino.

2007-2011 **Eriola Hoxha**, Neuroscience PhD Program. **PhD thesis Mentor**, University of Torino.

2008-2012 **Francesca Montarolo**, Neuroscience PhD Program. **PhD thesis Mentor**, University of Torino.

2010-2013 **Mohcene Sadallah**, Neuroscience PhD Program. **PhD thesis Mentor**, University of Torino.

Please list honours, prizes or awards received, If applicable.

2006: Invited Member of the "Rita Levi-Montalcini Center for Brain Repair" of the University of Torino

2006: Invited Member of the "National Institute of Neuroscience" (Consortium of Neuroscience Research Universities)

2007: Member of the Interdepartmental Center "Neuroscience Institute of Turin" (NIT)

2008: Invited Member of the Gallarate Center of Philosophical Studies (Italian National)

2010: Appointed Group Leader at the Neuroscience Institute Cavalieri Ottolenghi (N.I.C.O.)

2010: Appointed Director of the Animal Facility of N.I.C.O.

2012 (April 18–June 24): Invited Visiting Scientist at the Department of Pharmacology & Toxicology of the University of Texas Medical Branch, Galveston, Texas (USA).

2014: Appointed member of the Scientific Board of the Center for Interdisciplinary Documentation of Science and Faith (DISF) of the Pontifical University of the Holy Cross (Rome, Italy).

Please list your outreach activities

- describe your international collaborative experiences.

  1986: guest scientist at the Hirnforschung Institut of Zürich working on a project on the role of the inferior olive in the plasticity of the vestibulo-ocular reflex, in collaboration with Dr. B.J.M. Hess.

  1989: Short-term fellowship of the European Science Foundation for an overall period of 4 months of stay in Munich to work in collaboration with prof. N. Dieringer at the Ludwig Maximilian Universität, on a project on the role of the inferior olive in the adaptation and short-term habituation of the vestibulo-ocular reflex.

  1992-1993: on sabbatical leave at the Max Planck Institut für biophysikalische Chemie, Göttingen (Germany) and at the I. Physiologisches Institut der Universität des Saarlandes, Homburg/Saar (Germany) to work with prof. Arthur Konnerth on calcium permeability of glutamate receptor channels of Purkinje cells, medial septum neurons and hippocampal pyramidal cells.

  1998, 2000: RIKEN Brain Science Institute in Wako-Shi (Japan) for a collaboration with Dr. Thomas Knöpfel.

April 18–June 24, 2012: Visiting Scientist at the University of Texas Medical Branch, Galveston, Texas (USA).

August 2013-August 2014: in sabbatical leave, Visiting Scientist at the Department of Pharmacology and Toxicology of the University of Texas Medical Branch at Galveston, Texas (USA).

- Invited talks

18/08/1993: II. Institute of Physiology, University of Saarland, Homburg/Saar (Germania).

09/10/1998: Brain Science Institute, RIKEN, Wako-shi (Japan)

28/02–01/03/2000 "The cerebellum: from development to higher brain functions" Paris (France).

25-27/09/2000: Round Table "Cerebellar modules: anatomical and functional aspects" 51[a] Riunione Autunnale della Società Italiana di Fisiologia, Catania (Italy).

22/02/2001: (invitation) Dept. of Biochemical Sciences, Iowa State University, Ames, Iowa (U.S.A.)

25-28 /09/2001: Round Table "Channelopathies: what link between genetic heterogeneity and clinical phenotype? 52nd Annual Meeting of the Italian Physiological Society, Ancona (Italy).

20-23/06/2003: Second Conference on Epileptogenesis, Ferrara (Italy).

10-15/07/2003: Symposium at the IBRO Meeting, Prague (Czech Republic).

VI Convegno Nazionale Istituto Nazionale di Biostrutture e Biosistemi (INBB), Napoli 4-6 novembre 2004.

VIII Congresso Nazionale SIAMOC, Cuneo 24-27 ottobre 2007.

- Editorial duties

(Editorial Boards)
Frontiers in Aging Neuroscience (Review Editor)
Frontiers in Dementia (Review Editor)
Frontiers in Synaptic Neuroscience (Review Editor)
International Journal of Brain Science
Journal of Neuroscience and Rehabilitation
TheScientificWorldJOURNAL
The American Journal of Alzheimer's disease
American Journal of Life Sciences

(Reviewer)
Behavioural Brain Research
British Journal of Pharmacology
European Journal of Neurology
European Journal of Neuroscience
Frontiers in Aging Neuroscience
Frontiers in Cellular Neuroscience
Frontiers in Dementia
Frontiers in Synaptic Neuroscience
Journal of Neurophysiology
Journal of Physiology (London)
Molecular Neurobiology
Nature Communications

Neurobiology of Disease
Neurochemistry International
Neuropharmacology
Neuroscience
Neuroscience Research
Pflügers Archiv - European Journal of Physiology
Physiological Research
Physiology & Behavior
PLoS ONE
Proceedings of the National Academy of Sciences of the United States of America (PNAS)
The Journal of Physiological Sciences

Please list your organizational activities:

- Speakers invited
- Workshops, Schools or Conferences organized

Please list your technology transfer achievements (patents, etc.), if applicable

3. PI's PUBBLICATIONS:

Di Bella D, Lazzaro F, Brusco A, Plumari M, Battaglia G, Pastore A, Finardi A, Cagnoli C, Tempia F, Frontali M, Veneziano L, Sacco T, Boda E, Brussino A, Bonn F, Castellotti B, Baratta S, Mariotti C, Gellera C, Fracasso V, Magri S, Langer T, Plevani P, Di Donato S, Muzi-Falconi M, Taroni F. (2010) Mutations in the mitochondrial protease gene *AFG3L2* cause dominant hereditary ataxia SCA28. *Nature Genetics* 42: 313-331 (doi:10.1038/ng.544).
IF: 36.377; R = 1/156 ; Times cited = 94

Sacco T*, Boda E*, Hoxha E, Pizzo R, Cagnoli C, Brusco A, Tempia F. (2010) Mouse brain expression patterns of *Spg7*, *Afg3l1*, and *Afg3l2* transcripts, encoding for the mitochondrial *m*-AAA protease. *BMC Neuroscience* 11: 55 (doi:10.1186/1471-2202-11-55).
IF: 3.091; R = 101/239 ; Times cited = 5

Bianchi FT, Camera P, Ala U, Imperiale D, Migheli A, Boda E, Tempia F, Berto G, Bosio Y, Oddo S, LaFerla FM, Taraglio S, Dotti CG, Di Cunto F (2011) The collagen chaperone HSP47 is a new interactor of APP that affects the levels of extracellular beta-amyloid peptides. *PLoS ONE* 6(7): e22370 (13 pages) (doi:10.1371/journal.pone.0022370).
IF: 4.411; R = 7/56; Times cited = 3

Boda E, Viganò F, Rosa P, Fumagalli M, Labat-gest V, Tempia F, Abbracchio MP, Dimou L, Buffo A. (2011) The GPR17 receptor in NG2 expressing cells: focus on *in vivo* cell maturation and participation in acute trauma and chronic damage. *Glia* 59:1958-1973 (doi: 10.1002/glia.21237).
IF: 5.186; R = 46/244; Times cited = 21

Boda E*, Hoxha E*, Pini A, Montarolo F, Tempia F (2012) Brain expression of Kv3 subunits during development, adulthood, aging and in a murine model of Alzheimer's disease. *J Mol Neurosci* 46: 606-615 (doi: 10.1007/s12031-011-9648-6).
IF: 2.922; R = 137/290; Times cited = 6

Hoxha E, Boda E, Montarolo F, Parolisi R, Tempia F (2012) Excitability and synaptic alterations in the cerebellum of APP/PS1 mice. *PLoS ONE* 7(4): e34726 (13 pages) (doi:10.1371/journal.pone.0034726).
IF: 4.411; R = 7/56; Times cited = 10

Hoxha E, Tonini R, Montarolo F, Croci L, Consalez GG, Tempia F (2013) Motor dysfunction and cerebellar Purkinje cell firing impairment in *Ebf2* null mice. *Mol Cell Neurosci* 52: 51-61. (doi: 10.1016/j.mcn.2012.09.002).
IF: 3.734; R = 82/252; Times cited = 1

Di Gregorio E, Bianchi FT, Schiavi A, Chiotto AM, Rolando M, Verdun di Cantogno L, Grosso E, Cavalieri S, Calcia A, Lacerenza D, Zuffardi O, Retta SF, Stevanin G, Marelli C, Durr A, Forlani S, Chelly J, Montarolo F, Tempia F, Beggs HE, Reed R, Squadrone S, Abete MC, Brussino A, Ventura N, Di Cunto F, Brusco A. (2013) A de novo X;8 translocation creates a PTK2-THOC2 gene fusion with THOC2 expression knockdown in a patient with psychomotor retardation and congenital cerebellar hypoplasia. *J Med Genet*. 50: 543-551. (doi:10.1136/jmedgenet-2013-101542).
IF: 5.636; R = 19/165; Times cited = 4

Montarolo F, Parolisi R, Hoxha E, Boda E, Tempia F (2013) Early enriched environment exposure protects spatial memory and accelerates amyloid plaque formation in $APP^{Swe}/PS1^{L166P}$ mice. *PLoS ONE* 8(7): e69381. (doi:10.1371/journal.pone.0069381).
IF: 3.730; R = 8/55 ; Times cited = 1

Di Gregorio E, Borroni B, Giorgio E, Lacerenza D, Ferrero M, Lo Buono N, Ragusa N, Mancini C, Gaussen M, Calcia A, Mitro N, Hoxha E, Mura I, Coviello DA, Moon YA, Tesson C, Vaula G, Couarch P, Orsi L, Duregon E, Papotti MG, Deleuze JF, Imbert J, Costanzi C, Padovani A,

Giunti P, Maillet-Vioud M, Durr A, Brice A, Tempia F, Funaro A, Boccone L, Caruso D, Stevanin G, Brusco A. (2014) ELOVL5 Mutations Cause Spinocerebellar Ataxia 38. *Am J Hum Genet* 95: 209-217. pii: S0002-9297(14)00310-3. doi: 10.1016/j.ajhg.2014.07.001.
IF: 10.931; R = 6/197; Times cited = 8

Lippiello P, Hoxha E, Volpicelli F, Lo Duca G, Tempia F*, Miniaci MC. (2015) Noradrenergic Modulation of the Parallel Fiber-Purkinje Cell Synapse in Mouse Cerebellum. *Neuropharmacol* 89: 33-42. DOI: 10.1016/j.neuropharm.2014.08.016. (* corresponding author).
IF: 5.106; R = 20/255; Times cited = 0

Nenov MN, Tempia F, Denner L, Dineley KT, Laezza F. (2015) Impaired firing properties of dentate granule neurons in an Alzheimer's disease animal model are rescued by PPARγ agonism. *J Neurophysiol* 113: 1712-1726.DOI: http://dx.doi.org/10.1152/jn.00419.2014.
IF: 2.887; R = 28/83; Times cited = 1

Sallam HS, Tumurbaatar B, Zhang WR, Tuvdendorj D, Chandalia M, Tempia F, Laezza F, Taglialatela G, Abate N. (2015) Peripheral adipose tissue insulin resistance alters lipid composition and function of hippocampal synapses. *J Neurochem* 133: 125-133. DOI: http://dx.doi.org/10.1111/jnc.13043
IF: 4.281; R = 56/252; Times cited = 0

Tempia F, Hoxha E, Negro G, Alshammari MA, Alshammari TK, Panova-Elektronova N and Laezza F (2015) Parallel fiber to Purkinje cell synaptic impairment in a mouse model of spinocerebellar ataxia type 27. *Front. Cell. Neurosci*. 9:205. doi: http://dx.doi.org/10.3389/fncel.2015.00205
IF: 4.289; R = 55/252; Times cited = 0

Sadallah M, Labat-Gest V, Tempia F. Propagation of neuronal damage to embryonic grafts transplanted in the hippocampus of murine models of Alzheimer's disease. *Rejuvination Res*. 2015 November 5 epub ahead of print. doi: http://dx.10.1089/rej.2015.1672.
IF: 3.311; R = 15/50; Times cited = 0

Lippiello P, Hoxha E, Speranza L, Volpicelli F, Ferraro A, Leopoldo M, Lacivita E, Perrone-Capano C, Tempia F and Miniaci MC. The 5-HT7 Receptor Triggers Cerebellar Long-Term Synaptic Depression via PKC-MAPK. *Neuropharmacol* 101:426-438 doi: http://dx.doi.org/10.1016/j.neuropharm.2015.10.019
IF: 5.106; R = 20/255; Times cited = 0

Cupolillo* D, Hoxha* E, Faralli A, De Luca A, Tempia F, Rossi F, Carulli D. Autistic-like traits and cerebellar dysfunction in Purkinje cell PTEN knock-out mice. *Neuropsychopharmacol* 2015, November 5: epub ahead of print. doi: 10.1038/npp.2015.339
IF: 7.048; R = 11/255; Times cited = 0

4.GROUP’s PUBBLICATIONS:

The publications of the group coincide with those of the PI.

5. GROUP’s additional information:

There is no additional information that wasn't mentioned in the PI's profile.

6 .Past Research activity

(Summarize the PI and group research activities in the last 10 years)

a. Summary (500 characters)

Neurodegenerative diseases currently lack a therapy aimed at stopping or reverting cell death mechanisms. We have studied several murine models of ataxia in order to identify the cell types affected and the molecular mechanisms. In animal models of Alzheimer's disease we have defined several novel mechanisms responsible for early functional deficits, neuronal lesions and propagation of the pathology inside the brain.

b. Background (2000 characters)

At present there is no effective therapy to stop cell death in neurodegenerative diseases. At the time of the transfer of our laboratories to the NICO we started to exploit the technology and knowledge of physiological brain functions to tackle the problem of the causes and pathogenesis of neurodegenerative diseases like spino-cerebellar ataxias (SCAs) and Alzheimer's disease.

SCAs are relatively rare autosomal dominant motor disorders with a prevalence of about 1/30,000. They mainly affect the cerebellum, but other brain regions are often involved. No therapy is currently available to slow or stop the progression of motor disability in SCA patients. The gene involved in SCA28 (*AFG3L2*) was discovered in 2010 (Nature Genetics 42: 313-331) by a large collaborative effort, with our contribution in defining the expression of *AFG3L2* in the cerebellum. Most of the current knowledge about SCA28 derives from studies of knock-out mice, which lack one or both *Afg3l2* alleles instead of having one mutated allele like patients. The laboratory of Genetics led by Dr. Alfredo Brusco at the University of Torino generated a knock-in mouse model of SCA28 introducing the mutation associated with the most severe phenotype. The discovery of a druggable mechanism is highly awaited, with the hope that it might have a generalizable beneficial effect in all types of SCA. Several other rare forms of ataxia have been discovered, and for some of them an animal model is available.

Alzheimer's disease (AD) is the most frequent neurodegenerative disorder. In year 2015 about 44 million people worldwide live with AD or a related dementia. In spite of the discovery in the 1970's of the specific proteins forming the pathological lesions (extracellular beta-amyloid and intracellular tau protein), so far all clinical trials aimed at stopping AD progression failed. Recent advances in the field showed that both synaptic transmission and intrinsic excitability are disrupted in animal models of AD. New discoveries of the mechanisms responsible for these alterations are needed to better understand why cognitive symptoms arise and to design a first therapeutic approach to stop or revert AD progression.

c. Rationale (2000 characters)

Utilizing previous experience of studies of physiological functions of the cerebellum, spanning from synaptic transmission to the bases of intrinsic excitability and to motor control, we started collaborations with laboratories of Genetics that were investigating novel forms of SCA. Since the mechanisms responsible for ataxic symptoms in SCA28 are not known, we studied a knock-in animal model. The functional consequences of the mutation are also unknown, although is has been hypothesized that loss of function or negative dominant effects could be involved. An answer to this question could come from a

comparison of the knock-in model with the knock-out (obtained from Dr. Giorgio Casari of San Raffaele Institute). An unanswered question for most neurodegererative diseases is the selective loss of a specific cell type. A first hint can derive from the pattern of expression of the protein involved. We pursued this initial approach for several proteins involved in ataxia, like SCA28, SCA27, SCA38, ataxias caused by mutation or loss of *PTK2/THOC2*, *Ebf2*. The overall plan is to find, whenever possible, animal models of these diseases, and to study them in order to understand the pathophysiological mechanism.

Regarding AD, we followed different lines in order fill some gaps in the current knowledge of the mechanisms involved. We used two animal models, a double and a triple transgenic mouse. HSP47 is a protein that recent research showed to be associated with AD; Kv3 potassium channels allow fast action potential firing in interneurons involved in dementia; changes in membrane excitability are an early dysfunction in AD models; the level of neuronal activity has been linked to the velocity of formation of neuronal lesions; insulin resistance is considered as a major mechanism triggering AD; it has been proposed that cell damage propagates from affected to healthy neurons. The aforementioned mechanisms are currently hot topics in the research aimed at underpinning the critical mechanisms of AD, which might be targeted by novel therapies.

d. Objectives (1500 characters)

The common objective of the last decade of research of my laboratory has been to discover pathophysiological mechanisms responsible for specific neurodegenerative diseases, ranging from ataxias (**Aim 1**) to AD (**Aim 2**).

Aim 1.1. Experiments on the knock-in model of SCA28 were aimed at finding structural, functional or molecular alterations, caused by the mutation in the cerebellum or in other regions of the nervous system related to neurologic diseases linked to the m-AAA protease. Similar goals were related to the projects on SCA27 (**Aim 1.2**), SCA38 (**Aim 1.3**), *PTK2/THOC2* (**Aim 1.3**), *Ebf2* (**Aim1.4**). A specific aim about SCA28 was to elucidate loss of function versus negative dominant effect of the mutation and the consequences of the mutation in homozygous animals.

Aim 2. Regarding the projects on AD, the final goal was to discover novel mechanisms of cell damage and propagation of neuronal lesions. The specific aims were to establish the role of HSP47 (**Aim 2.1**) and of Kv3 potassium channels (**Aim 2.2**) in AD; to investigate the changes in membrane excitability in a brain region relatively spared by AD pathology, like the cerebellum (**Aim 2.3**); to define the consequences of an increased versus decresed level of neuronal activity in the formation of amyloid plauqes (**Aim 2.4**); to demonstrate that insulin resistance can impair synaptic transmission in the hippocampus (**Aim 2.5**); to illustrate the propagation of AD lesions to healthy neurons (**Aim 2.6**).

e. Results (4000 characters)

AIM 1: MODELS OF ATAXIA

Aim 1.1. We showed that the gene mutated in SCA28 (*AFG3L2*) is highly expressed by cerebellar Purkinje cells (Di Bella et al., 2010, *Nature Genetics* 42: 313-331; Sacco et al., 2010, *BMC Neuroscience* 11: 55). The knock-in model of SCA28 was developed and studied in detail (Hoxha et al., 2015, 45th annual meeting of the Society for Neuroscience, Abstract), showing that the cerebellum is intact, while mitochondria of peripheral nerves are disrupted. Our results rule out a dominant negative effect of the mutation, and point to a partial loss of function.

Aim 1.2. Mice knock-out for *Fgf14*, mutated in SCA27, in addition to a decrease in excitability also show synaptic deficits in the cerebellar cortex (Tempia et al., 2015, *Front. Cell. Neurosci*. 9:205)
Aim 1.3. Initial evidence about a role of *ELOVL5*, mutated in SCA38, was provided by showing that the ELOVL5 protein is enriched in cerebellar Purkinje cells of mice and humans (Di Gregorio et al., 2014, *Am J Hum Genet* 95: 209-217). Mice knock-out for *Elovl5* have been obtained from the UT Southwestern Medical Center and are currently bred in our vivarium.
Aim 1.3. PTK2 and THOC2, associated with a case of cerebellar hypoplasia, were upregulated during development and were highly expressed by cerebellar Purkinje cells, supporting the hypothesis of their involvement in cerebellar impairment (Di Gregorio et al., 2013, *J Med Genet*. 50: 543-551).
Aim 1.4. Mice knock-out for *Ebf2*, associated with cerebellar hypotrophy, showed deficits in motor coordination and learning and their Purkinje cells were hyperexcitable because of alterations in passive and active membrane properties (Hoxha et al., 2012, *PLoS ONE* 7: e34726).

AIM 2: MODELS OF ALZHEIMER'S DISEASE
Aim 2.1. HSP47 is a collagen chaperone, which physically interacts with APP, accumulates in amyloid plaques and modulates the rate of Abeta secretion (Bianchi et al., 2011, *PLoS ONE* 6: e22370): it might be a novel therapeutic target in AD. Kv3 potassium channels allow generation of action potentials at high rates in cortical interneurons that degenerate in AD.
Aim 2.2. In a murine model of AD Kv3 channels were found to be strongly downregulated, indicating a role in cognitive impairment (Boda et al., 2012, *J Mol Neurosci* 46: 606-615).
Aim 2.3. In the cerebellum, which is relatively spared by AD pathology but is reached by soluble forms of Abeta, cerebellar Purkinje cells showed reduced excitability and impaired GABAergic signaling (Hoxha et al., 2012, *PLoS ONE* 7: e34726).
Aim 2.4. An increased neuronal signaling induced by exposure to an enriched environment accelerated the rate of amyloid formation, while a block of neuronal activity slowed down amyloid deposition (Montarolo et al., 2013, *PLoS ONE* 8: e69381).
Aim 2.5. Insulin resistance, induced by high fat diet in mice with the ENPP1 transgene targeted to the adipose tissue, caused a suppression of synaptic transmission selectively in the CA1 field of the hippocampus, establishing a link between metabolic syndrome, insulin resistance and memory impairment in AD (Sallam et al., 2015, *J Neurochem* 133: 125-133).
Aim 2.6. We showed that embryonic neurons transplanted into an adult brain with AD pathology integrate well in the host tissue. However, the growth of axons in the host is impaired, they present a deficit of dendritic spines, they accumulate amyloid deposits and they are targeted by a microglial reaction of the host (Sadallah et al., 2016, *Rejuvination Res*.).

Other projects. In addition to these two main research lines, we also conducted studies on the following topics:
3.1. role of the GPR17 receptor in the reaction to traumatic brain injury and to AD pathology (Boda et al., 2011, *Glia* 59:1958-1973),
3.2 role of noradrenaline (Lippiello et al., 2015, *Neuropharmacol* 89: 33-42) and of serotonin (Lippiello et al., 2016, *Neuropharmacol*) in the modulation of synaptic transmission and plasticity in the cerebellar cortex.
3.3 effect of a PPARgamma agonist to revert the excitability alteration in a model of AD (Nenov et al., 2015, *J Neurophysiol* 113: 1712-1726).

3.4 Purkinje cell-selective model of autism presents with alterations in cerebellar excitability and synaptic signaling (Cupolillo et al., *Neuropsychopharmacol*).

f. Advancement in the field (1000 characters)

In animal models of ataxia we have shown novel mechanisms of structural and functional alterations in specific cell types of the cerebellar cortex, including changes in membrane excitability, synaptic signaling, mitochondrial structure. In murine models of AD we discovered new molecules and mechanisms involved in the pathology, electrophysiological dysfunctions, the transmission of neuronal lesions to neural transplants. Some of these discoveries are currently the basis to design novel therapies, including drugs acting on mitochondrial function, membrane excitability, synaptic transmission, transplantation.

7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do

a. Summary (up to 2000 characters):

Hereditary ataxias currently lack a therapy able to stop or revert cell death. We plan to study 2 animal models: *Elovl5*$^{-/-}$ mice, a model of SCA38, and *Fgf14*$^{-/-}$ mice, a model of SCA27.
With *Elovl5*$^{-/-}$ mice we plan to investigate the consequences of the loss of this enzyme on cerebellar function. The aim is to find novel functions of Elovl5 and to discover the mechanism responsible for cell death in the cerebellum of SCA38 patients.
The loss of Fgf14 in SCA27 has been associated with impairments of action potential firing in cerebellar granule and Purkinje cells. Our recent report on the deficit in synaptic transmission between parallel fibers and PCs shifts the attention to the mechanisms of neurotransmitter release. This might be a novel breakthrough in understanding the physiological and pathological roles of Fgf14.
FGF14 has been linked, in very recent studies, to psychiatric diseases like schizophrenia and mood disorders. In the next three years we plan to develop a new line of research investigating the role Fgf14 in cognitive functions and in the regulation of mood and motivation. The most relevant brain areas related to these functions are hippocampus, prefrontal cortex and ventral striatum. This is the only research line about structures other than the cerebellum.

b. Background and Significance (up to 4000 characters):

Spinocerebellar ataxias (SCAs) are autosomal dominant neurological disorders characterized by gait ataxia, incoordination of eye movements, speech, and hand movements, and usually associated with cerebellar atrophy (1).
In a large collaborative study, we recently identified a novel form of spinocerebellar ataxia (SCA38) due to missense mutations in the elongase of very long chain fatty acids 5 gene, *ELOVL5* (2). To date, seven fatty acid (FA) elongases (ELOVL1-7) have been identified in mammals, and each shows substrate specificity towards acyl-CoA (3). It is interesting to note that also ELOVL4 is associated with a spinocerebellar ataxia (SCA34) (4). Molecular pathogenesis of SCA38 has not been studied yet. It is unclear if the disease is due to a loss of function of ELOVL5 leading to a decreased pool of long chain poly-unsaturated FA (PUFA) or a toxic gain of function of the misfolded protein. The omega-3 long chain PUFA, eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA), are two important final products of ELOVL5. The serum of SCA38 patients shows a reduction of EPA and DHA, in line with the loss of function mechanism (2). DHA is quantitatively the most important omega-3 FA in the brain (5). DHA preferentially accumulates in neuronal growth cones (6) and mature synaptic membranes, where it modulates membrane signaling dynamics and synaptogenesis. Furthermore, DHA is very important for synaptic transmission within corticostriatal synapses (7), and neuronal excitability in vitro (8; 9). Studies in non-cerebellar cell types have shown that DHA reduces neuronal excitability via partial inhibition of voltage dependent sodium channels (10; 11), and may potentiate gamma-aminobutyric acid (GABA) activity (12).
An *Elovl5* knockout (KO) mouse model was developed by Dr. Horton and Dr. Moon at UT Southwestern Medical Center (Dallas, USA) to study the role of Elovl5 in lipid metabolism (13). The neurological phenotype was not investigated. We recently acquired *Elovl5* KO mice from Dr. Horton and Dr. Moon laboratory and we are currently breeding the colony in our animal facility.

Another topic we are focused on is SCA27 ataxia, which is associated with mutations in the fibroblast growth factor 14 (*FGF14*) gene (14; 15). *FGF14* is widely expressed throughout the nervous system (16; 17; 18) and in neurons it is concentrated at the action initial segment (AIS) (19). Several studies have found that FGF14 interacts directly with the C-termini of Nav α subunits, including Nav1.1, Nav1.2, and Nav1.6, in HEK293 cells (19, 20; 21). The targeted deletion of FGF14 results in an ataxia-like phenotype (14) with markedly attenuated excitability in cerebellar Purkinje (22; 18) and granule (23) cells. In addition, FGF14 can regulate synaptic transmission in hippocampal neurons (18). More recently *in vitro* studies, in cultured cerebellar neurons, showed that FGF14 also regulates members of the presynaptic Cav2 Ca^{2+} channel family (24). Furthermore, in a recent study we showed that in *Fgf14* KO mice synaptic transmission is altered at the parallel fiber to Purkinje cell synapse (25).

Humans with an autosomal dominant missense mutation in *FGF14* present not only with a progressive spinocerebellar ataxia but also with impaired cognitive abilities (18). It is important to note that recently *FGF14* has been listed in the top 28 candidate genes associated with neurological or psychiatric disorders (26). *Fgf14*$^{-/-}$ mice display a range of neurologic symptoms including ataxia and severe deficits in cognitive functions (14). Hence, *FGF14* might be a genetic locus of multiple disorders linked to deficits in cognitive processing.

c. General aim and integration with mission of the Institute (up to 1000 characters)

The final aim of our SCA projects is to find the pathogenic mechanisms linking the loss of specific genes to cerebellar atrophy and ataxia and to identify targets for possible therapeutic interventions. The main effort of our laboratory in the last few years has been focused on neurodegenerative diseases, while future projects also include a study on Fgf14 related to psychiatric diseases such as schizophrenia and mood disorders. These themes are in line with the mission of the Institute to achieve research on the neural bases of brain disorders.

d. Specific objectives and strategies (up to 4000 characters):

Aim 1: SCA38

Aim 1.1. To verify whether *Elovl5* KO mice develop ataxic symptoms when fed with a diet lacking downstream products of Elovl5. In order to see the effect of knocking out *Elovl5* we chose a more natural diet, which does not contain the PUFA downstream products of Elovl5 (EPA and DHA) but only linoleic and alpha-linolenic acids, which are substrates of Elovl5. In these conditions only the mice with functional Elovl5 can proceed with FA elongation and produce EPA, DHA and other downstream molecules. In order to assess motor symptoms related to ataxia, with a series of motor tests we will investigate motor coordination, gait abnormalities, motor learning, skilled walking, intention tremor and other clinical signs of motor dysfunction (27).

Aim 1.2. To search for electrophysiological alterations of Purkinje cell (PC) signalling in *Elovl5* KO mice. PCs of *Elovl5* KO mice will be recorded by patch-clamp in acute cerebellar slices. Intrinsic excitability of PCs and the function of synapses impinging on them will be analyzed. We expect that functional PC deficits precede structural alterations.

Aim 1.3. To search for evidence of cellular lesion in the cerebellum of *Elovl5* KO mice. We will assess, in addition to the overall cerebellar gross morphology, the number of PCs and cortical GABAergic interneurons. The neurons of the deep cerebellar nuclei (DCN) will be counted in Nissl stained sections and classified according to somatic size. The presence of an astrocytic reaction will be evaluated. Signs of axonal damage will be assessed. In order to study the alterations of synaptic

contacts, the pre- and the postsynaptic elements will be labeled with specific antibodies.

Aim 2: SCA27

Aim2.1. To verify the role of Fgf14 in cerebellar GABAergic transmission. It has been recently reported that GABAergic inhibition is impaired in the brain of *Fgf14*$^{-/-}$ mice. The paroxysmal dyskinesia seen in these animals in combination with the abnormal locomotor activity in response to the dopamine receptor D2 agonist, quinpirole, has been attributed to a reduction of the GABAergic transmission to the thalamus with the consequence of an increased glutamatergic transmission in the cortex (14). Importantly, recent evidence indicates that cerebellar GABAergic Purkinje neurons in *Fgf14*$^{-/-}$ mice show reduced spontaneous firing (23). These data are consistent with a potential decrease of GABAergic transmission in the CNS of *Fgf14*$^{-/-}$ mice. We will explore GABAergic synapses converging on PCs by means of electrophysiological recordings. Miniature inhibitory postsynaptic currents (mIPSCs) will be recorded by means of the patch clamp technique.

Aim2.2. To shed light on the mechanisms underlying the altered synaptic transmission between parallel fibers and PCs. Recently we provided evidence of a critical role of Fgf14 in maintaining presynaptic function at PF-Purkinje neuron synapses (25). We will study synaptic transmission by means of patch clamp at this synapse applying different agonists and/or antagonists for cannabinoid receptor 1 and $GABA_B$ receptors to deeply understand how Fgf14 regulates presynaptic function.

Aim 3: role of Fgf14 in psychiatric disorders

Aim3.1. Full behavioral characterization of *Fgf14*$^{-/-}$ mice. We are planning to perform a wide range of behavioral tests in *Fgf14*$^{-/-}$ mice including those related to anxiety (open field, elevated plus maze, marble burying test), spontaneous behavior, motivational tests (food intake, sucrose preference test) and sociability tests.

Aim3.2. On the basis of the results obtained in Aim 3.1 we will proceed with patch clamp recordings on the prefrontal cortex (for anxiety related phenotype), and nucleus accumbens (for deficits in motivational phenotype).

Aim3.3. We plan to use real time RT-PCR in order to verify if there is an altered gene expression in the regions mentioned in aim 3.2 for dopamine receptors and endocannabinoid receptors, which are involved in the signaling between striatum and prefrontal cortex.

e. Unique features of the project research (up to 2500 characters):

- *Elovl5* knock-out mice have never been studied as a model of ataxia or other neurologic disorders. Ours is the first project to investigate, in this animal model, the mechanisms of SCA38, which was discovered very recently with our collaboration. This research has unique features, including the search for novel roles of enzymes like Elovl5 in the nervous system and the tight collaboration with geneticists and neurologists who discovered SCA38.
- SCA27 has been attributed so far to impairments of action potential firing in cerebellar granule and Purkinje cells. Our report on the deficit in synaptic transmission between parallel fibers and PCs shifts the attention to the mechanisms of neurotransmitter release. This might be a novel breakthrough in understanding the physiological and pathological roles of Fgf14.
- *FGF14* has been linked, in very recent studies, to psychiatric diseases like schizophrenia and mood disorders. At present no study has been published on this topic. Our project on the role of Fgf14 in psychiatric disorders has the potentiality to be a pioneering research opening a new pathway in the study of these diseases, for which only elusive results are available at present.

f. Methodology (up to 2000 characters): please fill-out this section only in the case of innovative technologies

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8. Letter of intent by the PI (1 page)

i) The research group of "Neurophysiology of neurodegenerative diseases" has a small number of members, and typically in the last 10 years it has been composed by one postdoc an one PhD student. In spite of this reduced size, this laboratory succeeded in producing significant results about several topics related to neurodegenerative disorders. The current composition of the group, of a stable postdoc (Dr. Eriola Hoxha) and several graduate students, is proving very efficient. The basic principle that I follow to lead my research group is to discuss daily with the postdoc about all new data and problems that arise in the lab. This has been possible recently, at least in the days in which the teaching duties allowed me to spend at least some hours in the lab. Regarding graduate students, I mainly provide general guidance and motivation, which are necessary and must be constantly refreshed to overcome the problems related to lab activities.

ii) Since our research group has a small size, internal problems are not an important issue and are easily solved by directly taking care of technical troubles and directly talking to the person who shows a drop in motivation and enthusiasm.

iii) NICO is a great Institute thanks to the sharing of all resources. Every PI is strongly committed to the care of the whole NICO Institute and in addition is appointed to supervise a specific facility. My duty is to act as Director of the Animal Facility and to take responsibility for the care and welfare of all animals used in experimental procedures in NICO's laboratories. I have a strong sense of belonging to this institution, so that I promptly point out any problem I notice and, whenever possible, I take care of it personally. I'm glad to take part in seminars and journal clubs when I have time.

iv) I hardly find problems related to the organization of NICO. In my experience this is a very successful experiment of sharing resources and I'm happy to be here. The main problem is the limited access to funding since the world crisis of 2008. Our plans when we moved to NICO was to expand our research activities, but now, 5 years later, I'm happy that I've been able to keep a fairly constant inflow of financial support, so that several research lines were pursued and continued. A big problem in my past research activities was the complete lack of funding of all my projects on AD, which caused the fragmentation in too many explorative research lines, as can be seen in the list of my publications on AD of the last 10 years. This problem is now solved by leaving from the unfunded field of AD, and concentrating on ataxia, with the only exception of the novel research line on the role of Fgf14 in psychiatric disorders.

v) In the past years and also currently we took advantage of collaborations with other, mostly external, research groups. This allowed us to obtain funding by Telethon Foundation and by the Italian Ministry of Research. My vision of research is that collaboration cannot be forced, but must stem from the need to put together complementary expertise and techniques. This worked out very well with groups of genetics focused on finding novel forms of ataxia by large screenings of patients. In the last two years our lab had a boost thanks to the collaboration with a group in the USA, that is currently supporting us in every way with the only exception of funding. We are planning conjunct projects of several types, from graduate student exchange to technical advancements to exchange of expertise.

Fondazione Cavalieri Ottolenghi

Neuroscience Institute Cavalieri Ottolenghi

Internal Peer Review 2015

Auto-evaluation form

Laboratory name: Brain development and disease

1. LABORATORY DESCRIPTION – PERSONNEL:

- **Principal Investigator**

Alessandro Vercelli — 09/07/1961
MD PhD — Male
Italian — Phone: 011/6706617
Email: alessandro.vercelli@unito.it

- **Personnel**

1. Adriano Ceccarelli — Birthdate (28/10/1957)
   MD PhD — Male
   Role Associate Professor — Nationality Italian
   Expertise molecular biology

2. Elena Tamagno — 14/07/1967
   PhD — Female
   Role Assistant Professor — Nationality Italian
   Expertise Alzheimer's disease

3. Marina Maria Boido — Birthdate 06/09/1980
   PhD — Gender Female
   Role Assistant Professor RTD — Nationality Italian
   Expertise: Spinal cord injury, motoneuron diseases, stem cell transplantation

4. Michela Guglielmotto — Birthdate (28/02/1977)
   PhD — Female
   Role Post-doc — Italian
   Expertise Alzheimer's disease

5. Debora Monteleone — Birthdate (06/02/1986)
   PhD — Female
   Role Post-doc — Nationality Italian
   Expertise Alzheimer's disease

6. Roberta Schellino — Birthdate (11/02/1985)
   PhD — Female
   Role Post-doc — Nationality Italian

Expertise: Neurogenesis, motoneuron diseases. Behavior

7. Olena Butenko — Birthdate (12/05/1981)
   PhD — Female
   Role Post-doc — Nationality Ukrayne
   Expertise: Electrophysiology, behavior, motoneuron diseases

8. Giusi Manassero — Birthdate (01/11/1979)
   PhD — Female
   Role Post-doc — Nationality Italian
   Expertise Alzheimer's disease, neuropathic pain

9. Ivan Enrico Repetto — Birthdate (11/09/1986)
   MS Biotechology — Male
   Role doctorate student — Nationality Italian
   Expertise neuronal death, stroke models.

10. Matilde Ghibaudi — Birthdate (19/09/1988)
    MS Biotechology — Female
    Role doctorate student — Nationality Italian
    Expertise spinal cord injury, miRNA, molecular biology

11. Marta Tropiano — Birthdate (09/06/1985)
    MS Biotechology — Female
    Role doctorate student — Nationality Italian
    Expertise confocal microscopy, stem cell transplantation

12. Elena Signorino — Birthdate (06/10/1976)
    Biology degree — Female
    Role technician — Nationality Italian
    Expertise molecular biology

2. PRINCIPAL INVESTIGATOR CURRICULUM VITAE (two pages)

Education and training:
PhD Anatomy – Lausanne 1992; PhD Ophthalmology – Torino 1990
MD – Torino 1986 (110/110 cum laude)

Employment and research experience:
2/7/2015 **full professor** in Human Anatomy, University of Torino Medical School
1/6/2014 **Scientific director** of the Neuroscience Institute Cavalieri Ottolenghi.
26/3/2014 **President** of the Consorzio Interuniversitario "Istituto Nazionale di Neuroscienze"
From July 2013 **Director** of the interdepartmental center Neuroscience Institute of Turin (NIT).
In the past, **guest researcher** at the Dept. of Brain & Cognitive Sci., MIT, Cambridge, MA, USA (c/o proff. G.Schneider and S.Jhaveri), Department of Physiology, Oxford (c/o prof. Zoltan Molnàr), Harvard Medical School (c/o prof. Arlotta) and **assistant médecin** at the Institute of Anatomy of the University of Lausanne, CH (supervisor prof. G.M. Innocenti, Dir. prof. H. van der Loos).
PhD in Anatomy (Lausanne, supervisor G.M.Innocenti) and Ophthalmologic Sciences (Torino, supervisor Prof. G.Filogamo).

Relevant discoveries:
Characterization of pyramidal dendritic bundles, stem cell therapy for ALS, role of JNK in neuronal death

Please list your grants according to the table below (last five yrs).

Starting - end date	**Origin**	**Role**	**Funding Source**	**Project Title**	**Project ID**	**Overall Amount Funded**	**Directly Available to NICO**
	National vs International	PI vs. Component	MIUR, ERC, ecc…			€	€
2016-19	International	Coordinator	Horizon 2020	My-AHA		€ 4.3 M	480.000 (overhead 38400)
2015	National	Coordinator	Compagnia San Paolo	Grandi apparecchiature		€ 400000	No overhead on funding, but overhead on use
2015	International		Aargau Canton	fellowship		€ 27000	27000 (overhead 2700)
2015	International		Pharmafox	fellowship		€ 28000	28000 (overhead 2800)
2015	National		Girotondo Onlus			€ 30000	30000 (overhead 3000)
2014	National		Girotondo Onlus			€ 25000	25000 (overhead

							2500)
2013	National		Girotondo Onlus			€ 10000	10000 (overhead 1000)
2015	National		SMAratho n	fellowship		€ 15000	15000 (overhead 1500)
2014	National		SMAratho n	fellowship		€ 15000	15000 (overhead 1500)
2014-18	International	PI: succeeded to F Rossi/ with A. Buffo	FP7 European Union	*Neurostemc ellrepair*		€ 400000	€400000 (overhead 32000)
2012-15	National	PI	MIUR	Generazione di neuroni umani striatali autentici da cellule staminali pluripotenti per il trapianto nell'Huntingt on	2010J MMZL Y_002	€ 95882	95882 (overhead 7670)
2012-13	Local	PI	Cassa Risparmio Cuneo	Il dolore neuropatico postoperatori o: studio sperimentale e clinico		40000	40000 (overhead 4000)
2009-15	National	PI	Ministero Salute (Ric Fin)	Motor neuron death in Spinal Muscular Atrophy (SMA): new animal models and innovative therapeutic strategies		105000	105000 (overhead 10500)

Please list the name of PhDs you have supervised. 2004 Mariaelena Repici, 2005 Madalina Mereuta and Patrizia Muzzi, 2011 Marina Boido and Giada Spigolon, 2012 Simone Tomasi and Giusi Manassero, 2013 Antonio Piras and Valentina Grande

Please list your outreach activities

- describe your international collaborative experiences.
- Invited talks

A. Vercelli was an **expert for the Court of Brescia in the Stamina affair** in two different trials.

In Turin

9 giugno 2013, Staminali cosa sono e cosa servono? Torino, Politecnico
Maggio 2014 “La bellezza delle neuroscienze: la cellula piramidale” Torino, rassegna “Now new”
Maggio 2014 “Il metodo Stamina” rassegna “Le bufale in Medicina”
10 ottobre 2014, Torino, Hotel Santo Stefano, Corso di Urologia Funzionale: Il pavimento pelvico: come funzionano i muscoli.
14 March 2015 The Neuroscience Institute Cavalieri Ottolenghi Alzheimer Associations Chieri
24 March 2015 Come ti senti? La consapevolezza del proprio corpo. Rotary
30 September 2015 Alzheimer disease Infine Onlus, Biblioteca Civica Amoretti
5 October 2015 Alzheimer disease Infine Onlus UIL
19-20 November 2015 Stem cell therapy in neurodegenerative diseases "Engineered Biomaterials And Biomedical Devices In The Regenerative Medicine Of The Nervous System"

In Italy

2011 Stem cells in spinal cord injury repair, Brescia
March 2012 L’ambiente Interagisce con i geni e li modifica permanentemente nello sviluppo del cervello, InfinitaMente, Verona;
April 2012 Trapianti di cellule staminali in modelli murini di traumi del midollo spinale, riunione FAIP presso Ministero Salute, Roma;
17 April 2012 Il movimento e l’atrofia muscolare spinale, Soroptimist Biella
17 May 2012 Ruolo di JNK nella morte neuronale da eccitotossicità e sua inibizione: cittadini pacifici diventano killer, Università Cattolica, Roma;
22 June 2012 Of mice and man: MSC in ALS. Lost in translation? Università di Cagliari.
17 June 2013 Sviluppo normale e patologico della corteccia cerebrale, Fondazione Ferrero, Alba (CN)
23 April 2014, Verona; Staminali: cosa sono e cosa servono
10 October 2014 Milano, Dipartimento di Bioscienze, Morfometria nel sistema nervoso centrale
27 October 2014 Milano, Department of Pharmacological and Biomolecular Sciences, Center of Excellence on Neurodegenerative Diseases, Development of cortical pyramidal neurons in the control and pathological brain
30 October 2014 Ferrara, “Immunomodulation and neuroprotection by stem cell administration”
26 November 2015 Venice, Nanobiotech, Microvesicles/exosomes, biological nanosized systems for the pathogenesis and therapy of neurodegenerative diseases
26 February 2015 SOPSI, Milano, Development, neural plasticity and schizophrenia.
24 September 2015 Anatomical connectivity of cortical projection neurons, in The brain and gliomas, Brescia
23 October 2015 Mesenchymal Stem Cells progress in stem cells research for ALS/MND, Novara

Abroad

MGH Ctr for Regenerative Medicine (Massachusetts General Hospital), Boston 2010: Development, plasticity and organisation in modules of cortical pyramidal neurons.
Stem cell therapy in spinal cord disease, Buzios (Brazil), 2010.
EPFL, Lausanne 2011 Development, plasticity and organisation in modules of cortical pyramidal neurons
2 June 2013, Role of JNK in neuronal death in development and disease, Al Quds University (Jerusalem Arab University)

3 June 2013, Understanding cortical maldevelopment, Peres Center for Peace, Jaffa (Israele)
13 December 2013 “I am not my body, I am my mind” in “2013: year of the Italian Culture in the US”, Italian Embassy in Washington.
12 December 2014 Interoception and the insula. Anatomical and functional connectivity of the insula. 2nd Italy-Japan colloquium on the neurosciences and the aging society, Sendai, Organized by Tokyo Italian Embassy.
13 March 2015 Immunomodulation and neuroprotection by stem cell administration, Hasselt (Belgium)
22 April 2015 Role of JNK in neuronal death in development and disease, Karolinska Institute
18 October 2015, Chicago Neuroscience Meeting Exploring the role of MKK7 in excitotoxicity and cerebral ischemia: a novel pharmacological strategy against brain injury
9 December 2015: 3rd Italy-Japan colloquium on the neurosciences and the aging society, Tokyo, Organized by Tokyo Italian Embassy.

Please list your organizational activities:

- Speakers invited see general list of the Institute
- Workshops, Schools or Conferences organized
  Treasurer of IBRO 2011 World meeting (Florence); Member of the Host Committee FENS2014 meeting (Milano); Member of the Young Investigator’s Training Committee (2014); organizer of Neurosciences Olympic Games in Piedmont (2012-15); organizer of several Brain Awareness Weeks (2012-15)

Please list your technology transfer achievements (patents, etc.), if applicable
US Patent No: 6,030,949 Macrophage stimulating protein for the treatment of pathologies of the nervous system (con P. Comoglio et al.).
Participation to development and experimentation of D-JNKI-1, named XG-102, from Xigen SA, Lausanne

3. PI's PUBBLICATIONS:

(Please list below your publications in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science).
For each publication, please indicate:
* if you contributed equally to the fist-author, as stated in the published article

1) Valenza, M., Chen, J.Y., Di Paolo, E., Ruozi, B., Belletti, D., Ferrari, Bardile, C., Leoni, V., Caccia, C., Brilli, E., Di Donato, S., Boido. M.M., Vercelli, A., Vandelli, M.A., Forni, F., Cepeda, C., Levine, M.S., Tosi, G., Cattaneo, E. (2015). Cholesterol-loaded nanoparticles ameliorate synaptic and cognitive function in Huntington's disease mice. *EMBO Mol Med.*, [Epub ahead of print]
IF= 8.665; R = 9/123; Times cited = 0
2) Mazzini, L., Vescovi, A., Cantello, R., Gelati, M., Vercelli, A. (2015). Stem cells therapy for ALS. *Expert Opin Biol Ther.*, [Epub ahead of print]
IF= 3.74; R = 30/163; Times cited = 0
3) Vercelli, A., Biggi, S., Sclip, A., Repetto, I.E., Cimini, S., Falleroni, F., Tomasi, S., Monti, R., Tonna, N., Morelli, F., Grande, V., Stravalaci, M., Biasini, E., Marin, O., Bianco, F., di Marino, D., Borsello, T. (2015). Exploring the role of MKK7 in excitotoxicity and cerebral ischemia: a novel pharmacological strategy against brain injury. *Cell Death Dis.*,13;6:e1854
IF= 5.01; R = 50/184; Times cited = 0
4) Grande, V., Manassero, G., Vercelli, A. (2014). Neuroprotective and anti-inflammatory roles of the phosphatase and tensin homolog deleted on chromosome Ten (PTEN) Inhibition in a Mouse Model of Temporal Lobe Epilepsy. *PLoS One.*, 12;9(12):e114554
IF= 3.23; R = 9/57; Times cited = 1
5) Valsecchi, V., Boido, M.M., De Amicis, E., Piras, A., Vercelli, A. (2015). Expression of Muscle-Specific MiRNA 206 in the Progression of Disease in a Murine SMA Model. *PLoS One.*,1;10(6):e0128560
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6) Perino, A., Beretta, M., Kilić, A., Ghigo, A., Carnevale, D., Repetto, I.E., Braccini, L., Longo, D., Liebig-Gonglach, M., Zaglia, T., Iacobucci, R., Mongillo, M., Wetzker, R., Bauer, M., Aime, S., Vercelli, A., Lembo, G., Pfeifer, A., Hirsch, E. (2014). Combined inhibition of PI3Kβ and PI3Kγ reduces fat mass by enhancing α-MSH-dependent sympathetic drive. *Sci Signal.*, 18;7(352):ra110
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7) Guglielmotto, M., Monteleone, D., Piras, A., Valsecchi, V., Tropiano, M., Ariano, S., Fornaro, M., Vercelli, A., Puyal, J., Arancio, O., Tabaton, M., Tamagno, E. (2014). Aβ1-42 monomers or oligomers have different effects on autophagy and apoptosis. *Autophagy.*, 1;10(10):1827-43
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8) Boido, M., Piras, A., Valsecchi,V., Spigolon, G., Mareschi, K., Ferrero, I., Vizzini, A., Temi, S., Mazzini, L., Fagioli, F., Vercelli, A. (2014). Human mesenchymal stromal cell transplantation modulates neuroinflammatory milieu in a mouse model of amyotrophic lateral sclerosis. *Cytotherapy.*, 16(8):1059-72
IF = 3.29; R = 42/163; Times cited = 3
9) Queiroga, C.S., Vercelli, A., Vieira, H.L. (2015). Carbon monoxide and the CNS: challenges and achievements. *Br J Pharmacol.*, 172(6):1533-45
IF = 4.84; R = 24/255; Times cited = 3
10) Tomassy, G.S., Berger, D.R., Chen, H.H., Kasthuri, N., Hayworth, K.J., Vercelli, A., Seung, H.S., Lichtman, J.W., Arlotta, P. (2014). Distinct profiles of myelin distribution along single axons of pyramidal neurons in the neocortex. *Science.*, 18;344(6181):319-24
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11) Cauda, F., Geminiani, G.C., Vercelli, A. (2014). Evolutionary appearance of von Economo's neurons in the mammalian cerebral cortex. *Front Hum Neurosci.*, 14;8:104
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12) Innocenti, G.M., Vercelli, A., Caminiti, R. (2014). The diameter of cortical axons depends both on the area of origin and target. *Cereb Cortex.*, 24(8):2178-88.
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14) Verderio, C., Muzio, L., Turola, E., Bergami, A., Novellino, L., Ruffini, F., Riganti, L., Corradini, I., Francolini, M., Garzetti, L., Maiorino, C., Servida, F., Vercelli, A., Rocca, M., Dalla Libera, D., Martinelli, V., Comi, G., Martino, G., Matteoli, M., Furlan, R. (2012). Myeloid microvesicles are a marker and therapeutic target for neuroinflammation. *Ann Neurol.*, 72(4):610-24
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19) Manassero, G., Repetto, I.E., Cobianchi, S., Valsecchi, V., Bonny, C., Rossi, F., Vercelli, A. (2012). Role of JNK isoforms in the development of neuropathic pain following sciatic nerve transection in the mouse. *Mol Pain.*, 22;8:39
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31) Innocenti, G.M., Vercelli, A. (2010). Dendritic bundles, minicolumns, columns, and cortical output units. *Front Neuroanat.*, 12;4:11
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IF = 4.01; R = 24/123; Times cited = 8

4.GROUP's PUBBLICATIONS:

(Please list below up to ten most relevant publications of the other members of the group in the last 5 years -2010/2015-. Please indicate the journal IF, ranking, and the number of citations as reported in the ISI Web of Science)

Boido M., Garbossa D., Vercelli A. (2011). Early graft of neural precursors in spinal cord compression reduces glial cyst and improves function. *Journal of Neurosurgery – Spine*, 15(1):97-106, 2011.
IF = 2.38; R = 56/198; Times cited = 12

Boido M., Garbossa D., Fontanella M., Ducati A., Vercelli A. (2014; Epub. 2012). Mesenchymal stem cell transplantation reduces glial cyst and improves functional outcome following spinal cord compression. *World Neurosurgery*. 81(1):183-90.
IF = 2.878; R = 39/198; Times cited = 10

d'Errico P.*, Boido M.*, Piras A., Valsecchi V., De Amicis E., Locatelli D., Capra S., Vagni F., Vercelli A., Battaglia G. (2013). Selective vulnerability of spinal and cortical motor neuron subpopulations in delta7 SMA mice. *Plos One*, e82654. *co-authorship.
IF = 3.23; R = 9/57; Times cited = 3

Gamba, P., Leonarduzzi, G., Tamagno, E., Guglielmotto, M., Testa, G., Sottero, B., Gargiulo, S., Biasi, F., Mauro, A., Viña, J., Poli, G. (2011). Interaction between 24-hydroxycholesterol, oxidative stress, and amyloid-β in amplifying neuronal damage in Alzheimer's disease: three partners in crime. Aging Cell. 10(3):403-417.
IF = 6,34; R = 2/50; 36/184; Times cited = 28

Garbossa D.*, Boido M.*, Fontanella M., Fronda C., Ducati A., Vercelli A. (2012). Recent therapeutic strategies for spinal cord injury treatment: possible role of stem cells. *Neurosurgical Review*, 35(3):293-311. *co-authorship
IF = 2.18; R = 63/198; Times cited = 21

Guglielmotto, M., Giliberto, L., Tamagno, E., Tabaton M.(2010). Oxidative stress mediates the pathogenic effect of different Alzheimer's disease risk factors. Front Aging Neurosci., 9;2:3
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Guglielmotto, M., Monteleone, D., Giliberto, L., Fornaro, M., Borghi, R., Tamagno, E., Tabaton, M. (2011). Amyloid-β_{42} activates the expression of BACE1 through the JNK pathway. J Alzheimers Dis. 27(4):871-883.
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Gunetti M., Tomasi S., Giammò A., Boido M., Rustichelli D., Mareschi K., Errichiello E., Parola M., Ferrero I., Fagioli F., Vercelli A., Carone R. (2012). Myogenic potential of whole bone marrow mesenchymal stem cells in vitro and in vivo for usage in urinary incontinence. *Plos One*, 7(9):e45538.
IF = 3.23; R = 9/57; Times cited = 9

Mastrocola, R., Guglielmotto, M., Medana, C., Catalano, M.G., Cutrupi, S., Borghi, R., Tamagno, E., Boccuzzi, G., Aragno, M. (2011) Dysregulation of SREBP2 induces BACE1 expression. Neurobiol Dis. 44(1):116-124.
IF= 5,078; R= 39/252; Times cited= 3

Tamagno, E., Guglielmotto, M., Monteleone, D., Tabaton, M. (2012). Amyloid-β production: major link between oxidative stress and BACE1. Neurotox Res. 22(3):208-219.
IF = 3,538; R = 90/252; Times cited = 20

5. GROUP's additional information:

Please list the grants of the other members of the group in the last 5 years - 2010/2015- according to the table below:

Starting - end date	Origin	Name and Role of Group Member	Funding Source	Project Title	Project ID	Overall Amount Funded	Directly Available to NICO
01/01/14 – 31/12/15	National	M. Boido	UNITO	Unraveling the role of miRNA206 in the cross-talk between motor neurons and muscle		€ 6700	€ 6700 (overhead 536)
17/11/14 – 18/09/16	National	M. Boido	CRT	Utilizzo di scaffold biomimetici e di cellule staminali per sostenere la rigenerazione del midollo spinale lesionato	41491	€ 30000	€ 30000 (overhead 2400)

Please list honours, prizes or awards received by other members of the group If applicable.

Boido M. - June 2010: Travel fellowship for the FENS-IBRO European Neuroscience School "Neuroproteomics in animal model for neurodegenerative disorders" (Smolenice, Slovakia, 20-25/06/2010).

Boido M. - June 2011: Travel fellowship for the meeting "XXI Convegno Nazionale del Gruppo Italiano per lo Studio della Neuromorfologia (G.I.S.N.)" (San Benedetto del Tronto, Italy, 9-10/06/2011).

Schellino R. – October 2011: Award for the best oral presentation in "Plasticity" section; Italian Society of Neuroscience SINS; 6th Meeting on Molecular Mechanisms in Neuroscience, Rome Italy

Schellino R. – June 2012: Selected for the FENS-IBRO Summer School on "Chemical Senses: Neurobiology and Behavior". Bertinoro (FC), Italy.

Schellino R. – June 2013: Award for the best poster in Neuroscience topic; D-Day 2013, Doctoral School in Life and Health Sciences; University of Turin, Italy.

Ghibaudi M. – September 2014: Award "OPTIME" Industry Union of Turin, Certificate of merit for study.

Boido M. - November 2014: EFEM (European Federation for Experimental Morphology) travel grant, spent in the Lab. headed by Prof. Puyal (Department of Cellular Biology and Morphology (University of Lausanne, Switzerland).

Ghibaudi M. – November 2014: FENS-IBRO stipend awarded to attend the course "Stem cells in Neuroscience", Lausanne, Switzerland.

Please list outreach activities of other members of the group:

- Describe your international collaborative experiences.
- Invited talks

Boido M. Immunomodulation and neuroprotection by stem cell transplantation. DiSFeB meets NICO: Neuroscience builds a bridge from Milan to Turin, Milano, 18/11/2014.

Tamagno E. Abeta 1-42 monomers and oligomers have different effects on autophagy and apoptosis: role in the pathogenesis of Alzheimer Disease. DiSFeB meets NICO: Neuroscience builds a bridge from Milan to Turin, Milano, 11/12/2014.

Boido M. Nanotechnologies and neurosciences. 2015 E-MRS Spring Meeting, Simposio “Nanomedicine advancing from bench-to-bedside: the role of materials”, Lille, 11-15/05/2015.

Tamagno E. Study of the different effects of amyloid beta oligomers and monomers on aggregation of tau protein. Role on the pathogenesis of Alzheimer’s disease. “New perspectives on the role of Tau in neurodegeneration” Torino, Italy. 09/03/2015

Tamagno E. La proteina Beta amiloide: la “primula rossa” della malattia di Alzheimer. Emergenza Alzheimer - Tra realtà e futuro, Chieri (TO), Italy, 14/03/2015.

Tamagno E. Oxidative stress and Beta-Amyloid Production. X Convegno Nazionale Sindem, Genova, Italy, 27/03/2015

- Editorial duties

Please list your organizational activities:

- Speakers invited by members of the group see attached list
- Workshops, Schools or Conferences organized by members of the group

Please list your technology transfer achievements (patents, etc.), if applicable

6 .Past Research activity

(Summarize the PI and group research activities in the last 10 years)

a. Summary (500 characters)

We study the development of the CNS from the embryo to the aged, and the common neurobiological mechanisms and molecular pathways which lead to normal development and to neurodegeneration. We are interested in the molecular pathways leading to neuronal cell death, which we study in development and in experimental models of transient/permanent cerebral ischemia, acute/chronic glaucoma, epilepsy, SMA (spinal muscular atrophy) and AD (Alzheimer disease). Finally, we are studying cell therapy in ALS (amyotrophic lateral sclerosis), SCI (spinal cord injury) and HD (Huntington disease).

b. Background (2000 characters)

The study of the CNS represents a great challenge to the scientist of the 21st century, and neurodevelopmental and neurodegenerative disorders provide major insights in the understanding of its anatomy, physiology and pathology and the design of new therapies. Many cellular events and mechanisms occurring during development may have profound influences on the adult nervous system, and healthy aging may be considered as the last phase of neural development.

Recently, Europe with the Human Brain Project and USA with the Connectome project, together with similar projects launched by other countries such as Japan and China, targeted the micro-, meso- and macro-connectome from a normal and pathological point of view. In the meanwhile, collaborative projects such as the Joint Program for Neurodegenerative Diseases and ERA-NET Neuron in Europe aim to investigate the basic mechanism underlying neurodegenerative diseases, with a translational aim to design new diagnostic and therapeutic measures. Networks from genes to miRNAs and molecules, from neurons to brain areas represent the building blocks of neural function. On the one hand, they may represent pathways for spreading of neurodegenerative diseases and, on the other, some nodes in the network (such as the “hubs”) may be more liable to disease. Therefore, only an holistic approach, from molecules to brain areas, from development to disease and from a multidisciplinary point of view can provide new insights and concept on brain function, disease and repair.

c. Rationale (2000 characters)

Understanding the development of the CNS, and how neurons can form axonal connections participating in anatomical and functional networks is fundamental to the comprehension of brain function and disease, and to design new therapeutic strategies. To this aim we take advantage of the study of normal brains and of the brains of transgenic mice, in which specific molecules are knocked down to investigate their function. On the other hand, we have developed through the years several cellular and animal models of neurodegenerative diseases, in which to study the molecular mechanisms involved and to target them with stem cell therapy or specific inhibitors to prevent disease and promote brain repair at cellular, network and behavioral levels. Finally, we maintain a close connection with clinicians in order not only to favor a translation from bench to bedside but also to have a continuous feedback on the clinical needs.

The advancement of science does not only consist of new ideas, concepts and mechanisms to be understood but also of new tools which allow to investigate the nervous system from new points of view. To this aim, we are spending part of our time and economical efforts to technological improvement and to apply other disciplines to neuroscience, believing that only the contamination among different

forms of knowledge may provide breakthrough innovation in the field. The collection of increasing amount of data with IoT (Internet of things) and big data pose new challenges to Neuroscience and we would like to participate to this new era.

d. Objectives (1500 characters)

We aim to the structural and functional building blocks of the cerebral cortex and their circuitry, as substrate for brain activities and entities which may be disrupted in several congenital and degenerative diseases. In particular we study pyramidal neurons and the organization of their dendritic bundles and axonal projections. At a larger extent, we aim to study neural networks and connectivity, and how they are disrupted in disease.

We study the mechanisms of neuronal death during development and disease, such as excitotoxicity, apoptosis, autophagy and oxidative stress induced in different models of human disease, in order to prevent them. In particular, we have addressed the role of a MAP-kinase (JNK) in neuronal death and using specific inhibitors we have obtained substantial prevention of neuronal death in models of cerebral ischemia, AD and epilepsy.

In several neurodegenerative diseases, the pathology is not cell-autonomous, i.e. pathogenesis involves other cells in addition to neurons. Therefore, we study neuroinflammation in stroke, ALS and SMA and how to prevent it to delay the onset and the development of disease.

Stem cells are a growing field of research related to normal development, disease and cancer. We study the integration of neural stem cells and neural progenitors grafted into the striatum or spinal cord. Moreover, we use neural and/or mesenchymal stem cells to treat neurodegenerative diseases, to provide trophic and immunomodulatory substances to host neurons.

e. Results (4000 characters)

Development of cerebral cortex

We studied the development of pyramidal neurons and their assemblies in minicolumns and the composition of apical dendritic bundles (Innocenti and Vercelli, 2010). We have also investigated the morphology of their axons, the relationship between axonal size and the pattern of projection / the area of origin showing that they have both a strong correlation with size (Innocenti 2014). Studying the myelination of axons of pyramidal neurons with a new electron microscope which allows 3D reconstructions, we observed that myelination is layer-specific and that single axons have several interruptions in the myelin envelope (Tomassy 2014). These findings have a profound relevance in the study of the oligodendroglia/axonal relationship and of the factors which influence axonal myelination, size, geometrical and time computing properties.

Mechanisms of neuronal death in neurodegenerative diseases

We investigated the molecular mechanisms of cell death in models of excitotoxic death (stroke, glaucoma, epilepsy) and neurodegenerative diseases, focusing on apoptosis and autophagy. We identified the pathways of JNK (Vercelli 2015) and PTEN (Grande 2014) as key molecular pathways in eliciting cell death and therapeutic targets. We also put in evidence a role for CO in eliciting neuroprotective mechanisms (Queiroga 2012, 2015; Vieira 2011).

We studied the mechanisms of motoneuron death in SMA (d'Errico 2013), highlighting the role of autophagy (Piras, in preparation). We showed that miRNA-206 is activated as a survival endogenous mechanism in order to induce reinnervation,(Valsecchi 2015).

Part of our group studies the molecular mechanisms involved in Alzheimer disease. Oxidative stress (Tamagno 2002; 2005), together with important oxidative stress-related risk factors related to AD such as hypoxia (Guglielmotto 2009), hyperglycemia (Guglielmotto 2012) and hypercholesterolemia (Gamba 2011;

Mastrocola 2011), are potential causes of the increased BACE1 activity. We discovered that BACE1 activation is regulated by the γ-secretase activity, and that Aβ1-42 is the product of the γ-secretase cleavage that up-regulates BACE1 expression (Tamagno 2008; Giliberto et al., 2009). Aβ1-42 increases BACE1 gene transcription through the activation of JNK/c-jun signaling pathway (Guglielmotto et al., 2011). Thus, Aβ1-42-induced gene expression may have important implications in the neuronal dysfunction and degeneration that occurs in AD.

Stem cell therapy in SCI and neurodegenerative diseases

Our group has investigated the potential effects of cell therapy in experimental models of neurodegenerative diseases and in SCI. We showed that MSCs transplanted in a model of ALS into the spinal cord (Vercelli 2008) and in the lumbar cistern (Boido 2014) can prevent astrogliosis and microglial activation, delay cell death, and ameliorate motor performance. Moreover, they can modify the expression of immunomodulatory and inflammatory molecules by the host. Therefore MSCs are good candidates for ALS cell therapy (Mazzini 2009, 2010, 2012 and 2015).

We also showed that, in SCI, stem cell transplantation reduced significantly glial cyst volume, increased number of serotonergic fibers and promoted functional recovery (Boido 2009, 2011, 2012, 2014; Garbossa 2012). Recently, we labelled MSCs with the MRI agent Gadoteridol, to track the cells *in vivo* (Filippi submitted).

With E. Cattaneo and A. Buffo we are exploring the potential of human IPSCs in an experimental model of HD, with promising results in terms of cell replacement and establishment of new connections.

Functional anatomy of the human insula

With F. Cauda, we studied the connectivity of the human insula by resting state fMRI and metaanalysis (Cauda 2011, 2012, 2013a and 2013b), putting in evidence the partition of the human insula in different areas, involved in different networks, respectively related a) to the limbic system and the processing of emotional aspects and b) to sensorymotor integration. Areas involved in interoceptive and emotional processing such as the insula are characterized by the presence of von Economo's neurons, affected in several neuropsychiatric diseases and found in higher mammals (Cauda 2014). We are studying VENs in schizophrenia and frontotemporal dementia, in neuropathological samples, voxel-based morphometry and fMRI.

f. Advancement in the field (1000 characters)

Our group is actually working in several hot topics in Neuroscience, such as axonal development and growth in the normal brain and disease, neuronal cell death and stem cell therapy. It is also involved in the study of anatomical and functional connectivity of the human brain, and how it is altered in disease. Some of our contributions to the field were very relevant, and we are collaborating with other groups worldwide. Also, we are involved in the technical revolution about microscopy to investigate micro- and meso-connectome, with the use of confocal microscopy and, more recently, 2 photon microscopy. Moreover, we collaborated with Harvard University in a paper using the new Multisem Electron Microscope. On the other hand, we are collaborating with groups working on fMRI aiming to macroconnectome, and the PI is involved in the Brain Imaging center of the University of Torino.

7. Future Projects (Next 3 years)

Please describe the following information relevant to the research that you are planning to do

a. Summary (up to 2000 characters):

We intend to exploit our previous research on i) axonal growth in the CNS, ii) molecular and cellular mechanisms of neuronal death in neurodegenerative diseases, iii) network analysis at multiscale level, iiii) stem cell therapy. We want to identify some new therapeutic targets (such as autophagy for neurodegenerative diseases, JNK-related molecules for neuronal death, miRNA for neural development, neuronal cell death and axonal growth). We also intend, in collaboration with internal and external groups, to import in the institute new techniques, such as the organoids for in vitro analysis of brain development and disease modeling, 2 photon microscopy (we have just bought the Nikon A1R Multiphoton Confocal) and optogenetics for in vivo analysis, Multisem microscopy for ultrastructural 3D reconstructions. We will continue to collaborate with the Brain Imaging center to study human brain morphology (voxel-based morphometry and tractography) and functional networks (fMRI).

More recently, the PI has been involved as a coordinator in a 4 year Horizon 2020 grant, my-AHA (my Active and Healthy Aging), beginning on January 1, 2016. His task is mostly related to the overall organization of the activities, to be performed on human subjects and not involving directly the structures of NICO. Nevertheless, being the scientific coordination acted by A. Vercelli, this will allow the NICO to receive overheads. Other applications on the same line of research will be presented in 2016 to EEC.

b. Background and Significance (up to 4000 characters):

There is a growing interest in studying the development and disease of the CNS in terms of networks: genes, miRNAs and molecular networks at a ultramicroscopic level of magnitude, synaptic networks at the microscale, and anatomical and functional networks at the meso- and macroscale. Perturbances in the networks at the different scale levels may result in developmental or neurodegenerative disorders. To this extent, one may refer to “damage networks”: is it possible that some brain areas are more vulnerable than others to damage, or maybe more relevant than others for the onset of disease and of functional disorders?

Such perturbances may be responsible for developmental disorders, such as schizophrenia, autism, epilepsy where there is an altered connectivity in terms of synapses and axonal connections, and of excitability. Also, neural networks may underlie the spread of neurodegenerative diseases in the CNS, such as for the Braak hypothesis of the molecular and cellular damage.

Understanding the mechanisms of the onset and establishment of neural disorders at different scale levels is dramatically relevant to design neuroprotective and repair strategies to prevent and modify disease progression. These strategies therefore may be at a genetic, molecular, cellular and behavioral level, and must be considered in a holistic strategy. To this aim we will collaborate with F. Di Cunto (molecular biologist) and F. Cauda (fMRI) to investigate the existence of damage networks in some neurodegenerative and psychiatric diseases.

We are strongly connected to clinicians working within the field of neurodegenerative diseases, such as A. Chiò (Turin, ALS), G. Battaglia (Besta, SMA), I. Rainero (Turin, AD), Tabaton (Genoa, AD), P. Rocca (Turin, Schizophrenia): we intend to continue and implement this kind of collaborations in order to have a continuous exchange of

ideas, data and therapeutic strategies to favor a back and forth flow of information and bidirectional translation to find innovative therapeutic solutions.

c. General aim and integration with mission of the Institute (up to 1000 characters)

Our research aims to understand some basic mechanisms of neural development, whose alterations may be involved in the onset of neuropsychiatric diseases, and of neuronal cell death in neurodegenerative diseases. We are also interested in investigating the micro-, meso- and macro-scale of the CNS as the fundamental principles of brain function and disease.
Our findings are finally aimed to develop new therapeutic strategies to prevent neurodegenerative diseases and to brain repair. Therefore we believe that our research is perfectly fitted to study "the interdependence between physico-chemical state of the human body and the expression of the psyche", and is fully integrated with the mission of the Neuroscience Institute.

d. Specific objectives and strategies (up to 4000 characters):

Axonal growth. A fundamental issue in the building of neural connections and in their conduction properties consists in axon formation and maintenance during brain development, disease and repair. Therefore we will study, in collaboration with A. Buffo, the relationship between cortical axons and oligodendrocytes and their precursors, and some molecules which may affect this interaction in the normal brain and in experimental models of disease, such as schizophrenia. Moreover we will study the activity-dependence of this process in the normal brain and in disease, for example, in collaboration with G. Fisone in L-Dopa induced dyskinesia in PD.

miRNA networks. A novel class of regulatory molecules called microRNAs (miRNAs) seem to be implicated in several neurological diseases such as neurodegenerative/psychiatric disorders and traumatic CNS injury. Indeed every single miRNA binds to many transcripts, such that each mRNA is regulated by several miRNAs resulting in a complex network of inner gene expression control. It has been demonstrated that they control the activity of at least 20-30% of human protein-coding genes and a large number of these regulators has been found in mammalian nervous system, including brain and spinal cord, where they exert a key role in neurodevelopment and plasticity. The wide number of events miRNAs are able to control is due to their coordinated action and convergent roles. Based on preliminary results obtained in the last year, and in collaboration with the IIT, we will study miRNA networks in disease starting from SCI and SMA.

Stem cell therapy. We will continue previous work on stem cell transplantation in experimental models of neurodegenerative diseases and SCI. On one hand, we will dissect the neuroprotective and immunomodulatory properties of stem cells, in particular of mesenchymal stem cells, as reservoirs to deliver molecules to the diseased brain. We study their microvesicles as vehicles for the spread of disease or of therapeutic molecules. On the other hand, we will aim at cell replacement, using IPS and reprogrammed MSCs to replace lost neurons, using HD and ALS as paradigms. To this aim we are involved, together with A. Buffo, in Italian and European Consortia to obtain a translation to clinics within two years. As a secondary aspect, we aim to model disease in vitro by IPS technology after obtaining tissue samples from patients of neurological and psychiatric diseases, and growing it in cell culture or into organoids. This is an essential step to drug testing and personalized medicine.

Molecular mechanisms of cell death. We will continue to investigate the role of specific genes and molecules in neuronal cell death in neurodegenerative diseases. With A. Chiò, we want to study the interrelationship between genes involved in two motoneuron diseases, ALS and SMA. In fact, TDP-43 and FUS/TLS (genes involved in ALS) and SMN (involved in SMA) are involved in RNA metabolism, colocalize in nuclear Gems and play a role in maintaining the spliceosome. This alteration in the integrity of the spliceosome could be the basis for the selective vulnerability of motoneurons.
Having investigated the role of autophagy in neurodegenerative diseases, we intend to understand whether manipulating autophagy may alter the progression of disease. We will also study mitophagy, i.e. autophagy in mitochondria, to specifically target a key organelle in neuronal death.
Literature data indicate that ubiquitin C-terminal hydrolase L1 (Uch-L1) could play an important role in the pathogenesis of ischemic and vascular damage as well of AD. We found that Aβ1-42 down-regulates the activity of Uch-L1, through the activation of NF-κB pathway, and that this event is associated with BACE1 up- regulation due to a transcriptional effect and to an impairment of its lysosomal degradation (paper submitted). Now we aim to study Uch-L1 inhibition in different models of brain injury related to AD and HD pathogenesis.

e. Unique features of the project research (up to 2500 characters):
Some of our research topics, the methodologies employed and the external collaborations with top institutes and scientists, allow us to be involved in hot topics of research.
Our studies on axonal thickness and its plasticity depending on the neuronal pattern of origin/projection, and on activity represent a new field which may have very important significance not only for normal development but also for disease.
Our experience on some molecular pathways related to neuronal death, such as JNK and those related to autophagy is a specific competence which allowed us to design new therapeutic drugs.
The emergence of new concepts in brain function and disease in terms of networks and damage networks may be fundamental for investigating the onset of disease and eventually prevent its full development.
Also, our group is one of the major groups working with stem cell therapy at a preclinical level in Italy and Europe.

f. Methodology (up to 2000 characters): please fill-out this section only in the case of innovative technologies
We are collaborating with IIT (Italian Institute of Technology) in the study of miRNA networks, and with T. Dalmay (University of East Anglia) to develop new techniques to exploit miRNA analysis from small samples of cells.
In collaboration with groups of the Polytechnic of Turin, we are developing new biocompatible materials to promote and support axonal growth in the CNS.

8. Letter of intent by the PI (1 page)

i) how she/he assesses him/herself in term of leadership and ability to manage his/her group;

Notwithstanding my many duties related to the Direction of the Institute and to other academic duties (teaching, direction of an interdepartmental center), and to the administration of funds (such as the coordination of the my-AHA research group), I am strongly involved in the research activities and scientific coordination of the group. We organize frequent journal clubs, lab meetings to comment specific projects and individual meetings to supervise the activity of doctorate students and post-docs. Moreover, I take advantage of the support of two experienced, independent and collaborative research assistants (Dr. Boido and Tamagno) who help me to run the group. Also, my former students, some of which now are abroad, represent an international networks which supports and still collaborates with the group contributing to its scientific success.

ii) possible internal problems within his/her group and the strategies for the best solution;

The only flaw is represented by the very low level of collaboration with Prof. Ceccarelli, who entered the Institute from the beginning as member of our group to provide Molecular Biology expertise, with whom we had problems to collaborate, from both sides.

iii) his/her commitment in supporting the general activities of the Institute;

Our group is naturally devoted to supporting the general activities of the Institute, being involved in all kind of outreach activities at all levels, from the PI (who is also the Director of the Institute) to the students which participate to and organize conferences, Neuroscience Olympics, Researcher's night, School Academy etc… Also, members of the group participate in the spinoff which will be launched in 2016. Finally, we are strongly implicated in the organization of the labs and technical activities of the Institute.

iii) specific pitfalls and difficulties to realize his/her projects

The major difficulty is the lack of trained technicians in the Institute, to run the specific labs and to instruct new students and postdoc to the rules of good practice in the lab. To this aim, we agreed with other groups in the Institute to create new position(s) for technicians, sharing the cost.

We also need some competencies in the field of Molecular Biology, that at the moment we are obtaining from Prof. Di Cunto at the Molecular Biotechnology center of Torino.

iv) ability in establishing internal and external collaborations.

In the Institute we have strong collaborations with the group of Prof. Buffo, with whom we participate to the Neurostemcellrepair FP7 project. We are also collaborating with her group in the study of the relationship between cortical axons and oligodendrocytes, due to her specific expertise. We have also collaborations with the group of Geuna in the field of neuropathic pain.

We have a complex network of collaborations in Italy and around the world. In particular in Torino we are collaborating with the groups of Cauda and Di Cunto, to create a network aimed to study the relationship between genes, anatomy and functional connectivity in the human cerebral cortex. Also, we aim to collaborate with Di Cunto in Torino, P. Arlotta in Harvard and E. Cattaneo in Milano in the generation and analysis of organoids. We are collaborating with the Polytechnic of Torino in the production of new biocompatible materials which allow axonal growth and regeneration in the central nervous system. We are collaborating with the group of prof. Terreno at the Molecular Biotechnology Center in Torino to develop new MRI contrast agents to track stem cells in the nervous system. We have several collaborations with clinicians in Torino working in the field of ALS (A. Chiò), AD (I. Rainero and D. Imperiale) and schizophrenia (P.Rocca). We are collaborating with

prof. Tabaton (Genova) and O. Arancio (Univ. Columbia, New York) to study the molecular mechanism of AD. We are collaborating with G. Fisone at Karolinska in an experimental model of Parkinson disease to study the cellular and molecular mechanisms of L-DOPA-induced dyskinesia.
We have recently established a collaboration with the group of prof. Tonelli at IIT, to study miRNA networks in neurodegenerative diseases, in the frame of the Collaboration protocol between the IIT and the NICO. Also, to study miRNA networks, we are collaborating with the group of Prof. T.Dalmay (University of East Anglia). With them we are applying for grants to Telethon and foundations abroad.
Finally, the PI has recently opened a new series of projects in which he plays the role of coordinator. First of all the project my-AHA, recently signed by EEC, in which we are coordinating 16 groups to promote Active and Healthy Aging around Europe, Australia, Japan and South Corea. Also, we are preparing a new Europe-Japan collaborative application for the use of robotics in the aging population.

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20.10.2015
SINTETIZZATO UN FARMACO CHE PUÒ LIMITARE I DANNI NEURONALI IN SEGUITO A ISCHEMIA
Pubblicati su Cell Death and Disease i risultati di una ricerca condotta dall'IRCCS Istituto di Ricerche Farmacologiche Mario Negri in collaborazione con il NICO - Università di Torino

10.06.2015
INDIVIDUATE NEL CERVELLETTO CELLULE STAMINALI ATTIVE DOPO LA NASCITA
Sul Journal of Neuroscience lo studio delle ricercatrici del NICO - Università di Torino apre nuove prospettive per "riparare" il cervello che invecchia o si ammala

6.05.2015
Sabato 16 maggio 2015 - PorteAperte@NICO
INVITO A SCOPRIRE LA RICERCA DI BASE: IL PRIMO PASSO PER SCONFIGGERE SCLEROSI MULTIPLA,ALZHEIMER E LE ALTRE MALATTIE DEL CERVELLO
Una giornata alla scoperta delle Neuroscienze, anche per i bambini

20.04.2015
NICO Volley*Brain*2015 - 3° edizione
Giochi tu, Vince la ricerca su Sclerosi Multipla, Alzheimer e Parkinson
Un torneo aperto a tutti: a Torino dal 12 maggio all'11 giugno 2015. Iscrizioni entro il 2 maggio

20.04.2015
OLIMPIADI DELLE NEUROSCIENZE 2015 - Novara e il Piemonte ancora campioni nazionali
Luca Inguaggiato, III anno al Liceo Scientifico Antonelli di Novara, ha vinto la finale nazionale di Brescia. Dello stesso liceo la vincitrice 2014, Anna Pan

23.03.2015
I VINCITORI DELLE OLIMPIADI 2015: NOVARA IMBATTIBILE IN NEUROSCIENZE
Arrivano tutti dal Liceo Antonelli di Novara i tre finalisti per il Piemonte

10.03.2015
RIPARTE L'UNISTEM DAY: IL 13 MARZO LA GIORNATA EUROPEA DEDICATA ALLA RICERCA SULLE CELLULE STAMINALI
A Torino si parlerà di cosa frena il passaggio della ricerca di base alla terapia, dell'importanza di una corretta comunicazione scientifica e di "fuga dei cervelli"

12.1.2015
Olimpiadi delle Neuroscienze: una sfida che coinvolge ogni anno 30mila studenti in 30 paesi
SCUOLE MEDIE SUPERIORI: ISCRIZIONI ENTRO IL 31/1 - PIEMONTE CAMPIONE IN CARICA DEL 2014

2014

15.10.2014
Sabato 25 ottobre - PorteAperte@NICO
Una giornata dedicata alle Neuroscienze, aperta a tutti
RICERCA DI BASE: LA LOTTA CONTRO LE MALATTIE NEURODEGENERATIVE PARTE DA QUI
I ricercatori del NICO invitano a visitare i laboratori di Orbassano (To)

22.09.2014
Su GLIA la ricerca di NICO-Università di Torino, Università e CNR di Milano
GEMELLE, MA DIVERSE: COME NASCONO E SI RINNOVANO LE CELLULE CHE FORMANO LA MIELINA DEL CERVELLO
Individuato un nuovo meccanismo per potenziare il riparo della guaina mielinica nel cervello anziano e nelle patologie demielinizzanti come la Sclerosi Multipla

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18.09.2014
Notte dei ricercatori 26 settembre 2014
UNA NOTTE DI ESPERIMENTI, SPETTACOLI TEATRALI, CAFFÈ SCIENTIFICI ED EVENTI UN VIAGGIO NEL MONDO DELLA RICERCA
Il NICO tra i protagosti del Caffè Scientifico e con lo spettacolo "C'era una volta un neurone"

10.09.2014
La pubblicazione sulla prestigiosa rivista Autophagy
CHIARITO UN MECCANISMO CHE PUÒ RALLENTARE L'ALZHEIMER
I ricercatori del NICO – Università di Torino hanno studiato il meccanismo che, impedendo alle cellule di ripulirsi, favorisce lo sviluppo della malattia

11.08.2014
Washington - finale internazionale delle Olimpiadi delle Neuroscienze
STUDENTESSA DI NOVARA PRIMA IN EUROPA, SESTA AL MONDO

15.07.2014
DA TELETHON FINANZIAMENTI ALLA RICERCA SCIENTIFICA ALLA CITTA' DI TORINO
Selezionati i vincitori del bando di concorso Telethon 2014 per la ricerca scientifica sulle malattie genetiche rare: in Piemonte finanziati 5 gruppi di ricerca a Torino per un totale di 869.000 euro

6.05.2014
Settimane della Scienza 2014
Quest'anno il NICO partecipa con "Porte aperte sulle Neuroscienze" il 28/5

22.04.2014
La scoperta pubblicata su Science
UN NUOVO TASSELLO NEL MECCANISMO CHE REGOLA LA CONDUZIONE DEI SEGNALI NERVOSI
La ricerca svolta in collaborazione tra Harvard University, MIT e NICO-Università di Torino

14.4.2014
Olimpiadi delle Neuoroscienze – finale di Trento
STUDENTESSA DI NOVARA VINCE LA FINALE NAZIONALE
Anna Pan del Liceo Scientifico Antonelli di Novara rappresenterà l'Italia alla competizione internazionale che si disputerà a Washington ad agosto

27.03.2014
Grant della Fondazione Veronesi a due ricercatori del NICO - Università di Torino
La premiazione in Campidoglio a Roma

16.03.2014
Olimpiadi delle Neuroscienze: i finalisti per il Piemonte
Arrivano da Novara e da Alba i tre studenti che accendono alla finale nazionale di Trento

10.3.2014
14 marzo: UniStem Day 2014
Torna la giornata di divulgazione sulle cellule staminali dedicata agli studenti delle superiori. 45 gli atenei coinvolti tra italiani e stranieri, insieme a 20.000 studenti. A Torino in 600 al Campus Einaudi

22.1.2014
Il 24-25/1 gli esperti mondiali di rigenerazione dei nervi periferici riuniti a Torino
DAL GUSCIO DEI CROSTACEI UN BIOMATERIALE PER RIPARARE LE LESIONI NERVOSE
Il progetto Biohybrid finanziato dall'UE coinvolge imprese biotech e centri di ricerca in sei paesi, tra cui il NICO dell'Università di Torino.

4.01.2014
Iscrizioni entro il 15 gennaio per le scuole medie superiori
OLIMPIADI DELLE NEUROSCIENZE 2014
Nel 2013 il Piemonte ha vinto per numero di adesioni, con 12 scuole in gara.

2013

18.11.2013
GIOVEDÌSCIENZA 28a EDIZIONE. Un opificio di storie. Di scienza.
Dal 21 novembre al 20 febbraio 2014 al Teatro Colosseo di Torino.

Il NICO partecipa con "C'*era una volta un neurone*..." incontro dedicato agli studenti delle elementari.

20.09.2013
Notte dei Ricercatori: il 27/9 la neo senatrice a vita Elena Cattaneo ospite del NICO.

25.07.2013
Cellule staminali umane: dopo il trapianto generati nuovi neuroni che mantengono le caratteristiche originali.
Sul Journal of Neuroscience la ricerca dell'Università di Cambridge in collaborazione con il NICO. Un nuovo sistema per produrre cellule utili per la cura di patologie degenerative.

12.06.2013
SCIENTIFIC SUMMER ACADEMY - IV edizione, 17-21 giugno 2013
Una settimana da scienziati per i migliori studenti del Piemonte.

20.05.2013
Settimane della Scienza. Anche il NICO ospite della Tenda della Scienza
Dal 24 al 26 maggio in Piazza San Carlo a Torino.

15.04.2013
Maggio 2013 - MESE EUROPEO DEL CERVELLO
A TORINO LO SCIENZIATO DELLA NEUROGENESI
Arturo Alvarez-Buylla ospite del NICO. Lo scienziato americano vent'anni fa ha dimostrato la possibilità di formazione di nuovi neuroni nel cervello dei mammiferi.

25.03.2013
Da Biella, Novara e Alessandria i 3 vincitori tra 12 scuole in gara
OLIMPIADI DELLE NEUROSCIENZE - I FINALISTI DAL PIEMONTE

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PNAS, rivista della National Academy of Sciences USA
DALLE STAMINALI 10MILA NUOVI NEURONI AL GIORNO
La scoperta di un team dell'Università della California e del NICO risponde a domande aperte da decenni

8.03.2013
15 marzo - in tutta Italia e all'Università di Torino
LA GIORNATA UNISTEM SBARCA IN EUROPA

25.02.2013
Su PNAS, rivista della National Academy of Sciences USA
SE I NEURONI SOPRAVVIVONO ALL'ORGANISMO CHE LI GENERA
La scoperta di un team dell'Università di Pavia e del NICO apre una nuova strada nella ricerca sulle malattie neurodegenerative

13.02.2013
Dal 16 al 20 febbraio presso l'Ospedale San Luigi di Orbassano (Torino)
7° Convegno internazionale "Steroidi e sistema nervoso"
Malattie neurodegenerative, ansia e depressione: i progressi degli studi sugli ormoni steroidei

10.02.2013
LE CELLULE STAMINALI TRA SCIENZA E FANTASCIENZA
22/2 Fondazione Ferrero: Luca Bonfanti (NICO) in conversazione con Piero Bianucci

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14.12.2012
Scuole medie superiori: iscrizioni entro il 15 gennaio
OLIMPIADI DELLE NEUROSCIENZE 2013
Una sfida che coinvolge ogni anno 30mila studenti in 30 paesi

14.12.2012
LA RICERCA IN GARA AL RALLY DI MONTECARLO
Sclerosi multipla. Il neurologo e rallista Lorenzo Fabiani corre per il NICO, Istituto di Neuroscienze di Orbassano

5.12.2012
Se il cervello dice *NO GO*
Un nuovo meccanismo che controlla le cellule staminali. La scoperta dei ricercatori del NICO di Orbassano (TO) sul Journal of Neuroscience.

28.9.2012
LA NOTTE DEI RICERCATORI 2012
Per la 7a edizione "la notte dei ricercatori" è la più grande di sempre.

17.07.2012
TELETHON INVESTE NELLA RICERCA SCIENTIFICA PIEMONTESE
Cinque ricercatori dell'Università di Torino riceveranno per la loro ricerca 950mila euro.

13.06.2012
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Una settimana da scienziati in 13 laboratori dell'Università e del Politecnico di Torino per i migliori studenti del Piemonte.

09.03.2012
UNISTEM 2012: IL LUNGO E AFFASCINANTE VIAGGIO DELLA RICERCA SULLE CELLULE STAMINALI
Da Torino a Catania: 9000 studenti incontrano i ricercatori.

21.11.2011
LE MAMME SONO IMPORTANTI QUANTO I GENI. NUOVA SCOPERTA ALL'UNIVERSITÀ DI TORINO

23.09.2010
INAUGURAZIONE DELL'ISTITUTO DI NEUROSCIENZE FONDAZIONE CAVALIERI OTTOLENGHI (NICO)

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Ischemia cerebrale, nuovo farmaco riduce danni neuronali del 50%

La Stampa.it 21.10.2015
Scoperta italiana: farmaco che può ridurre del 50% i danni cerebrali post ictus

Huffingtonpost.it 21.10.2015
Ictus, scoperto farmaco che limita danni al 50% dopo 6 ore: lo studio del Mario Negri di Milano e del NICO di Torino

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Ictus, scoperto in italia un farmaco che riduce del 50% i danni al cervello

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Sintetizzato un farmaco che può limitare i danni neuronali in seguito a ischemia

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Nuovo farmaco limita danni neuronali da ischemia

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Un inibitore contro l'ischemia cerebrale

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Ischemia: sintetizzato farmaco che ne può limitare i danni neuronali

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Rallentare la quarta età: c'è una nuova strategia
La lezione di Franceschi: cambia la prospettiva di un processo ancora enigmatico. Una chiave sono le neurodegenerazioni, al centro del progetto europeo "Propag-Aging"

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C'era una volta un neurone

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Al Nico di Torino individuate nel cervelletto cellule staminali attive dopo la nascita

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Al Nico di Torino individuate nel cervelletto cellule staminali attive dopo la nascita

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Anche il cervelletto ha le sue staminali

Il Giornale del Piemonte 11.06.2015
Scoperto a Torino un metodo per "riparare" il cervello

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Le ricercatrici del Nico guidate da Annalisa Buffo hanno dato una nuova speranza alla ricerca. I loro studi sono stati pubblicati sul Journal of Neuroscience

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Italia - Staminali contro il cervello che invecchia

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Dal 4 partono le settimane della scienza per tutti

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Novara e il Piemonte vincono le Olimpiadi delle neuroscienze per la 2ª volta

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Olimpiadi studentesche, il liceo Antonelli sforna i geni di Neuroscienze

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Olimpiadi delle neuroscienze 2015: Novara vince ancora

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Olimpiadi, l'Antonelli ancora al top
Tre allievi del liceo di Novara davanti a tutti nella finale di Neuroscienze

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Porte aperte all'Università per 3 mila bambini torinesi
Da domani riparte il progetto che avvicina i piccoli allievi al mondo della ricerca

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In gara 400 studenti di 18 istituti del Piemonte

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Novara imbattibile alle Olimpiadi delle Neuroscienze
Sono tre studenti del liceo scientifico Antonelli i vincitori della finale regionale. In Piemonte 400 studenti di 18 scuole in gara

Primaradio Piemonte 16.03.2015
Intervista al direttore del NICO Alessandro Vercelli
Settimana del Cervello 2015 > dal 16 al 21 marzo

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La scienza dal vivo per ventimila studenti

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A Biella la prima edizione della Settimana del Cervello

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Dai tabù alla ragione. Tutto in un giorno
Conto alla rovescia per "Unistem": faccia a faccia tra studenti e ricercatori nelle scuole italiane
Luca Bonfanti, Università di Torino - NICO

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Al via le Olimpiadi ma gareggia il cervello
Anche in Italia gli studenti si sfidano sui saperi delle neuroscienze.

Dopo le regionali il vincitore nazionale affronterà il resto del mondo

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Studenti delle scuole superiori alle Olimpiadi delle Neuroscienze

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Intervista a Enrica Boda che, grazie al sostegno di Fondazione Veronesi, studia come si dividono i progenitori di neuroni e oligodendrociti e come sfruttare questa capacità per ringiovanire il cervello e combattere le malattie neurodegenerative

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Luca Bonfanti del NICO spiega **"La Necessità della ricerca fondamentale"**

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Cinquanta studenti eccellenti nelle discipline scientifiche ospiti della Fondazione Agnelli. Una full immersion tra lezioni ed esperimenti nei laboratori di Università e Politecnico

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Carote glaciali, domande impossibili, riflessi atletici, le ultime sui neuroni
I neuroni sono cellule che non si riproducono e quindi col tempo si deteriorano. Oppure no? C'è chi dice che si rinnovano, in continuazione. Alcune domande a Luca Bonfanti del NICO (dal minuto 30:30) - **ascolta la puntata**

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FONDAZIONE CAVALIERI OTTOLENGHI

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