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Dipartimento di Biologia
e Biotecnologie
Charles Darwin

Sapienza
Università di Roma

Scientific Report

First edition
2021

contents

ABOUT US

SERVICES&RESOURCES

RESEARCH

Editors
Monica **Ballarino**
Antonella **De Jaco**

Art Director
Paola **Valentini**

Research Centers

“MESSAGE FROM THE DEPARTMENT HEAD”

Prof. Marco **Oliverio**

Evolutionary Biology PhD

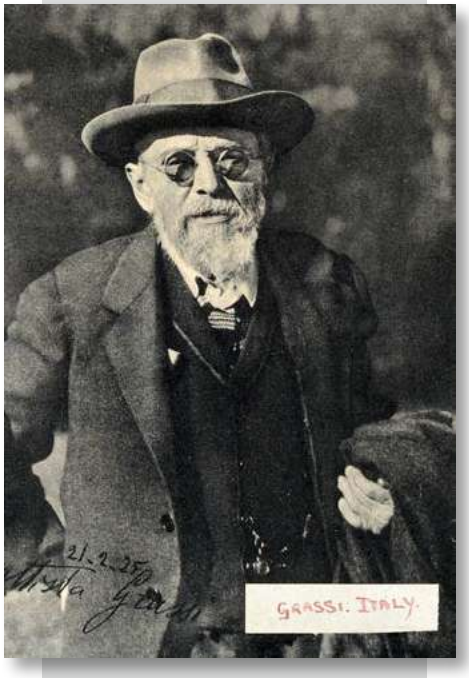
Head of Department

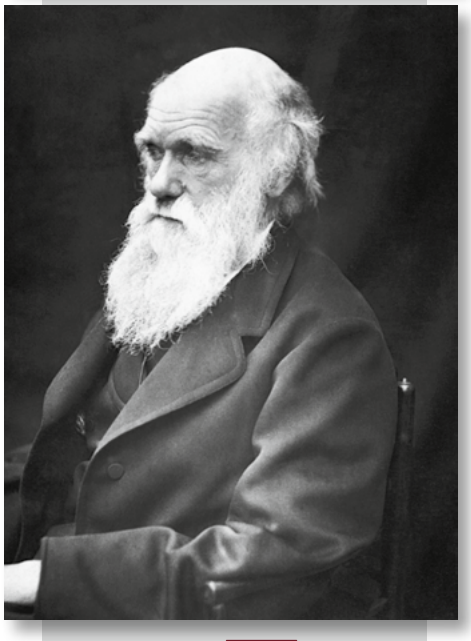
Our Department's aim can be summarized well by the word 'integration'. The Life Sciences are obviously paradigmatic of cultural diversity, spanning the whole diversity of life and a vast array of methodological approaches, which, together with scientists belonging to different areas of the department offer great opportunities as well as exciting challenges. From the very foundation of the Department, our primary aim has thus been to progressively implement such an integration, regarded – rather than a goal to reach – as an ongoing process to cultivate and continuously keep alive.

The process is hampered by our logistic heritage, with the staff and the facilities operating in several different premises, however the awareness has grown through the years: the higher the level of integration, the closer we get to the yields of excellence that are in our potential.

Our students belonging to the Bachelor's degrees in Biology and in Biotechnologies as well as the Master's degrees, are a continuous stimulus for all of us to keep our whole work well-rooted into the history of Life Science and our arms projected forwards. Our Department being named after Charles Darwin proves our extensive awareness of the deep and pervasive role of Evolution for Life, and we do our best in order to transmit this message to all our students.

Finally, as the Director of this Department, I want to warmly thank all of its components, from the Administration to the librarians, from the technicians to the scientists/teachers, including all students, for easing a significant part of my work and for sharing with me the goal of making the Department of Biology and Biotechnologies "Charles Darwin" a wonderful place to make and teach Science.





HISTORY | Department BBCD

The study of Biology in Rome has ancient roots. It is worthwhile to mention here ***Giovanni Battista Grassi****, with his research spanning from Zoology to Developmental Biology, from Epidemiology to Ecology. It was in this furrow that in July 2010, the Department of Biology and Biotechnologies was funded, upon the reorganisation of the old biological departments of Sapienza University of Rome ("Animal and Human Biology", "Cellular and Developmental Biology", "Genetics and Molecular Biology" and "Plant Biology"). The new Department took their teaching and research aims forward, perfectly positioning itself within the cultural framework of the Faculty of Science.*

The Department takes the name of ***Charles Darwin****, to affirm the* ***modern evolutionary matrix****, subtending and permeating almost every theoretical and experimental approaches in research and teaching.*

Within the Darwin Department many research lines are developed and integrated, which refer to the organisation and the functional analysis of ***biodiversity*** *at different levels:* ***molecular****,* ***cellular****,* ***systemic****,* ***organismic****,* ***populational*** *and* ***ecosystemic****. Research includes the fundamental aspects of the main biological disciplines, including the* ***biotechnological*** *and* ***applied*** *aspects. The experimental approaches are largely* ***interdisciplinary****, as this is increasingly demanded by the complexity of biological problems and by the fast-running methodological innovation. To this aim, the co-existence of a vast array of skills in the various fields within the Department proves crucial.*

The quality and variety of the existing disciplines in the Department allow a vast and highly qualified curriculum that is mostly focused on Biology and Biotechnologies, from Bachelor's to Master's degrees and PhD programmes, but also provide biology-related courses to other Departments' programmes (belonging to the Faculties of Science and Medicine).

COMPARATIVE ANATOMY
GENERAL PHYSIOLOGY
GENETICS
S. LORENZO
ZOOLOGY
PIAZZA VALERIO MASSIMO

THE DEPARTMENT

The Department is located into five major Research Centers (Comparative Anatomy, General Physiology, Genetics, S. Lorenzo and Zoology) that are distributed both inside and in the neighboring areas of the Sapienza University campus. In each Research Center are found research laboratories, offices, facilities, cabled classrooms for teaching, laboratories for didactical experimental practices, conference rooms.
Moreover two Museums belong to the Department, located outside the main campus: the Giovanni Battista Grassi is inside the Comparative Anatomy Center and the Museum of Zoology in the close proximity (Piazza Valerio Massimo).
The administrative staff and the librarians offices are located in the General Physiology and the Anthropology buildings, respectively.

Dipartimento di
BIOLOGIA E BIOTECNOLOGIE
CHARLES DARWIN

HEAD

Marco **Oliverio**

RAD

Paolo **Valenti**

STAFF MEMBERS

Raffaella **Angeli**
Elvira, Patrizia **Arceri**
Fabrizio **Blasi**
Alessandro **Cantarini**
Cristina **Corridore**
Elena **De Carolis**
Maria **De Rosa**
Sara **Di Pietro**
Francesca **Fantozzi**
Franca **Iarussi**
Maria **Ippolito**
Carlo **Lico**
Ines **Lonigro**
Silvia **Lopizzo**
Claudia **Marchionne**
Stefano **Marotta**
Simonetta **Mattei**
Roberta **Palleschi**
Daniele **Recchione**
Michela **Trovalusci**
Paola **Valentini**
Simone **Zambenedetti**
Gianni **Zega**

TECHNICIANS

Maria Antonietta **Bracci**
Silvana **Caristi**
Francesco **Castelli**
Mariangela **Coriandri**
Angela **Durante**
Maria Caterina **Galgano**
Bruno **Garulli**
Marcella **Marchetti**
Maurizio **Mei**
Daniela **Pontiggia**
Viviana **Orlando**
Andrea **Setini**

ADMINISTRATION AND ACADEMIC AFFAIRS

The head of the Department is the legal representative of the Institution, who guarantes autonomy and cultural unity to the department. The governance of the Department is represented by the Department Council, the Director and the Board. The Chief Administrative Officer (R.A.D.) assists the Director and is responsible for the administrative management and the coordination of the administrative-accounting activities.

Academic Management and Administration

The administrative management is fundamental for coordinating:

- *the accounting management of the funded projects;*
- *the recruitment of contract staff;*
- *the mainteinance departmental offices, laboratories and classrooms;*
- *supporting the activities of the governing bodies;*
- *the updating department's web page and the multimedia equipment.*

Students Affairs

The office supports and provides the student with all the information related to the didactic activities for the courses managed by the BBCD. It represents an interface between students, teachers and the general secretariat of the students; it supports the Coordinators and the Degree Course Councils. The office manages:

- *the first assistance desk;*
- *student counseling and guidance;*
- *the planning of the training and teaching offer;*
- *graduation sessions, in agreement with the student secretariat;*
- *the update of the official website contents.*

Academic Activities

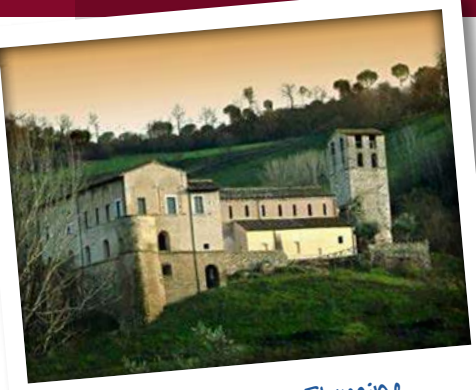
The BBCD Department hosts:

- *the undergraduate programs in "Biology" and "Food and Industrial Biotechnology"*
- *four master programs in "Genetics and Molecular Biology", "Neurobiology", "Cell Biology and Technology", "Biotechnology and Genomic for Industry and Environment".*
- *two PhD Programs:*

  PhD Program in Cell and Developmental Biology
  https://phd.uniroma1.it/web/CELL-AND-DEVELOPMENTAL-BIOLOGY_nD3489_EN.aspx

  PhD Program in Genetics and Molecular Biology
  https://phd.uniroma1.it/web/GENETICS-AND-MOLECULAR-BIOLOGY_nD3506_EN.aspx

- *three one year graduate master courses in "Scientific Journalism", "Stem Cells and genome editing", "Biology of Nutrition for Human Reproduction".*



Sant'Andrea in Flumine

Coffee break

Lunch and discussion

RETREAT | Department BBCD

*The annual Departmental retreat was started in **2006** from an idea of Prof. Sergio Pimpinelli, Director of the former Department of Genetics and Molecular Biology "Charles Darwin", with the aim of sharing and discussing the research results among faculty members and students.*

*The idea was to favor new scientific collaborations among scientists from different cultural backgrounds and stimulate a sense of belonging to the Department. Furthermore, this would have offered the opportunity to young researchers to present their results and to generate new ideas for their research projects. The **Abbey of Sant 'Andrea in Flumine in Ponzano Romano**, a medieval jewel located in the Roman countryside, was chosen as the institutional seat of the Conference. Since its inception and for all the first editions, the conference has hosted an opening Lecture such as the one on the "History of Science" held by Prof. Bernardino Fantini of the University of Geneva. After the establishment of the "Charles Darwin" Department of Biology and Biotechnologies, the retreat was conducted by its first Director, Prof. Stefano Biagioni.*

In 2016 and 2019 the retreat got an important institutional recognition by hosting the Rector Eugenio Gaudio for the opening days. Since 2015, Daikin Applied Europe S.p.A. collaborated with the department to support the Daikin Prize awarded to young researchers for their studies in the Conservation of Biodiversity. This collaboration and the Daikin award continue today under the direction of Prof. Marco Oliverio.
This retreat has become a regular appointment for the researchers of the department.

*The last edition was in **2019** and it was held at **Sapienza** hosted by the classrooms of our department.*

Opening at Sapienza

Audience and Speakers

Poster presentation

MUSEUM OF COMPARATIVE ANATOMY

“ GIOVANNI BATTISTA GRASSI „

The Museum of Comparative Anatomy “Giovanni Battista Grassi” preserves the relics and the archive of the great Italian zoologist **Giovanni Battista Grassi** (1854 - 1925).
The collection includes objects belonging to the celebrated “Kircheriana” exhibition of the 17th century, ancient papier-mâché anatomical models by Jérôme Auzoux (1797-1880) and embryological wax models by Friedrich Ziegler (1860-1936).
Part of the museum is dedicated to the microscopic analysis with ancient instruments from the late 1700s up to the transmission and scanning electron microscopes of the 70s and includes the ancient istoteca with about 3000 slides.
The richest part of the exhibition is certainly the osteological collection which includes complete skeletons of large cetaceans and describes the balance between the evolutionary continuity of all vertebrates and adaptations to different environments.

The scientific collection has been implemented, in more recent years, with collections of small mammals and reptiles, especially from Italy, Africa, Central and South America, thanks to samples carried out by researchers belonging to the Comparative Anatomy headquarters.
The Museum carries out scientific dissemination activities for schools and it is open to the public two days a week.
The collections are used for research activities related to the study of evolutionary morphology and molecular phylogeny of vertebrates.

“ MUSEUM OF ZOOLOGY „

Awareness of the importance of global biodiversity as part of our natural heritage is growing in the society. Therefore, senior scientists and biology students must be given easy access to workable natural history collections for studies with traditional and innovative approaches, including both morphological and molecular methodologies. Metazoans represent a vast majority of the world's known living organisms, as well as of those still to be discovered. In this context, zoological museums represent cornerstones for the future of research in the field of natural history. The University Museum of Zoology (MZUR) is one of the oldest scientific museums in Rome. It hosts around one million specimens (both dry- and ethanol-preserved) belonging to all metazoan phyla, with a special focus on vertebrates and arthropods. MZUR preserves historical collections inherited from the Archiginnasio Pontificio as well as a large amount of material collected during the last decades by researchers during field campaigns. MZUR promotes and triggers high quality and collaborative research activities for scientific projects in nature conservation and biodiversity inventorying, currently with a main focus on insects. These activities include worldwide collecting fieldwork, and laboratory work for sorting, preparing, labelling, loan processing, management of supplies and equipment, as well as species identification (using both morphological and molecular approaches). Through these projects MZUR has seen its collections and international reputation significantly grown. Zoological collections at MZUR represent a big source of historical data which are critical to understand the impact of climate change on ecosystems.

Curatorial philosophy at MZUR

Researchers and technicians at MZUR give priority to networking with all major homologous institutions and taxonomists around the world and are involved with producing high-impact taxonomic revisions and monographs (at regional and global scale). Collections are essential for taxonomy and taxonomy is in turn inalienable from both pure and applied biology. A convincing communication of this concept at every education level is a contemporary challenge in order to highlight the role of natural history collections.

Our curatorial goals are:

- Enhancing the production of matrix-based interactive keys for taxa identification, supported by high quality specimen images and detailed distribution maps;
- Augmenting the arthropod collections through collaborative research programs, mainly focused on areas with high rate of biodiversity loss, e.g. South America, Africa and Australasia;
- Setting up different specimen preservation methods in order to further both morphological and molecular studies and widen the spectrum of possible collaborations.

In line with the objectives of the Sapienza Strategic Plan, BBCD aims to integrate the excellence of scientific research with THIRD MISSION ACTIVITIES. A complete list of BBCD third mission activities is available on the dedicated web page

http://bbcd.bio.uniroma1.it/bbcd/territorio-e-terza-missione

“THIRD MISSION”

The activity of BBCD towards society and the world of work is that of the Master “Life sciences in journalistic practice” (www.mastersgp.it) which, since 2006, has guaranteed excellent results in terms of job placement. With the Master, BBCD has obtained recognition from the National Order of Journalists as a continuing education institution, which more than 100 journalists/year to Sapienza. Many BBCD members are active in consultancy open to private citizens, media and the University Press Office, on scientific-applicative issues or involved in Citizen Science initiatives. BBCD members have registered numerous international patents as inventors in biology and biotechnology and have agreements with the private sectors for mutual research exchanges. BBCD has done activities with schools contributing to the National Science Degree Plan. This was born in 2004 from the collaboration among MIUR, Scienze and Confindustria to increase the number of students enrolled in degree courses through a process of professional growth of teachers in secondary school and the alignment of training courses from school to University and in the University for the world of work. BBCD also has numerous school-work alternation activities to its credit and has participated in the School Project in collaboration with the Pasteur Italia Institute. BBCD is engaged in museum activities with the Museums of Comparative Anatomy and Zoology which carry out guided tours with hundreds of students and teachers every year. In 2017 BBCD oversaw the preparation of the “DNA. The great book of life from Mendel to genomics at Palazzo delle Esposizioni in Rome, which had a great success with the public (about 90,000 visitors). BBCD participates in public engagement activities focused on science dissemination projects such as “Fragmenta entomologica”, a magazine indexed by SCOPUS, the Italian Fauna Committee and the “Fauna Europaea” project (https://fauna-eu.org). Since 2014 it is a partner of the International Union for the Conservation of Nature for the production of the database of species at risk of extinction and participates to the Intergovernmental science-policy Platform on Biodiversity and Ecosystem Services. Other engagement activities of the BBCD and the Master SGP group are the foundation of the magazine for science dissemination and Sapienza valorization, STAR and Erasmus agreements, double degrees and summer/winter schools, with Spain, France, UK, Denmark and Germany, as well as an exchange with Singapore. BBCD is committed to internationalization through Erasmus agreements, double degrees and summer/winter schools, with Spain, France, UK, Denmark and Germany, as well as an exchange with Singapore. In post-graduate training, doctorates and masters have activated a network of exchanges with the inclusion of foreign teachers and co-tutors. BBCD lecturers and researchers collaborate in research agreements with foreign universities in Australia, Germany, Netherlands, UK, Russia, France, Switzerland, China, Iran, Georgia, Mozambique, US and Singapore.

“LIBRARY”

Dipartimento di BIOLOGIA E BIOTECNOLOGIE CHARLES DARWIN
BIBLIOTECA

Charles Darwin Library’s staff works actively to support research, learning and teaching and play the role of bridge-building within the academic community.
We offer fertile and innovative ground mix ideas between science and everyday life and we want to be the space for multidisciplinary meetings and exchanges. All this beside offering the core library services:
acquisition, cataloguing, technical services, care of physical and virtual collections, scholarly communication, institutional repositories, open data management, open science policies, national and international interlibrary loan and document delivery services, user education and information literacy activities to increase the students’ skills to improve learning and to undertake research independently (es. PubMed-Labs). We are in a transition phase that is leading us to resemble a hub where our users can find opportunities to take part in conversations about books, or their scientific interests and much more besides: “the true collection of a library is not made up of documents or manuscripts, but in the innovation, experience, and brilliance of the community served”. (R. David Lankes, Libraries for learning <http://davidlankes.org/libraries-for-learning>).
Whether it is information literacy or support in the evaluation of research, we want to foster the birth of a community based on the sense of belonging, trust and good sharing practices. In the welcoming and friendly context we are building, the participation of our students, PhDs, teachers and researchers becomes the cornerstone of every activity.
We work with the purpose to facilitate the meeting and the inclusion and we pay particular attention to the international students. In our library you can find traditional services as loan, reading rooms, etc. but also spaces suitable for meeting, sharing an active and collaborative learning (e.g. group study rooms, Tandem Language Exchange, reading groups).

Library desk

To contact us: email website facebook instagram

Staff:

Elena De Carolis | *Director*
Raffaella Angeli | *Interlibrary Loan; Cataloguing Services*
Ines Lonigro | *Acquisitions; Institutional Repository*
Roberta Palleschi | *Reference Services; Institutional Repository; PubMed Labs*

"RESEARCH&FACILITIES"

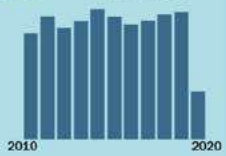
Researchers belonging to the Department cover a wide range of investigation at all levels of biological complexity, from molecular aspects to community of species. Specifically, the research fields include Molecular Biology, Biochemistry, Bioinformatics, Genetics, Microbiology, Cell Biology, Immunology, Neurobiology, Plant Physiology, Zoology, Comparative Anatomy, Nanobiotechnologies and Nanoscale Imaging. This offers an interdisciplinary environment that is an ideal milieu for new ideas and technological advancements. The different premises are equipped with shared instruments that characterize the experimental approaches carried out by the researchers of our Department.

INSTRUMENTS	LOCATION
Next generation sequencing for single small molecules Nanopore MinION (Oxford)	Phisiology
X-ray generator and 3D prefusion bioreactor	Genetics
Amersham Typhoon digital plate reader	Phisiology
Beckman Centrifuge Avanti J-25	Phisiology
Chemidoc Bio-rad	Phisiology
Ultramicrotome Reichert Jung Ultracut	Phisiology
Cryostat Leica Biosystem	Phisiology
Real time RT-PCR machine Quant Studio 3 Termofisher	Phisiology
Real time RT-PCR machine Biorad	Phisiology
Centrifuga Beckman Avanti J	Phisiology
X-ray machine	Genetics
High Performance Computing (HPC) Cluster	Zoology
Glo Max Multi+: Multidetection system	Phisiology
Micromanipulator Singer Instruments	Phisiology
Five termostat rooms range from +4 °C to 32 °C	Zoology
Animal house for roditors	Phisiology
Thermostat Rooms at 28°, 4° e 37°C	Phisiology
Rooms for growing plants	Phisiology
Cell culture room (BL2)	Phisiology

MICROSCOPY	LOCATION
ZEISS Apotome, upright fluorescence microscopy	Botany, Sapienza
ZEISS Apotome, inverted fluorescence microscopy Objectives 10X, 20X, 40X, 63X e 100X. Fluorescence (3 lasers)	Nanotechnologies, Sapienza
ZEISS Auriga EM (Field Emission Scanning Electron Microscopy, high resolution)	Nanotechnologies, Sapienza
Nikon Eclipse 90i, upright fluorescence microscopy	Via degli Apuli, CNR, IBPM
Nikon Eclipse Ti sCDD, inverted fluorescence microscopy and live imaging	Via degli Apuli, CNR, IBPM
Olympus, upright fluorescence microscopy	Via degli Apuli
Nikon, upright fluorescence microscopy	Genetics
Zeiss, Axio-Observer Z1 inverted fluorescence microscope, equipped with a High-resolution charged-coupled device (Axiocam 503 mono CD camera) and the ZEN2 software. Objective: 63x.	Genetics
Nikon Eclipse 600, upright fluorescence microscopy. Objectives 25, 40, 100x.	Genetics
Zeiss Axioplan, upright fluorescence microscopy. Objectives 25, 40, 100x. Fluorescence (3 lasers).	Genetics
DeltaVision Ultra High Risolution Widefield Deconvolution (GE Healthcare). Objectives 20, 60, 100x. Fluorescence (5 lasers).	Genetics
Spinning-disk confocal microscope with 70-µm pinhole disk. CARV LX Complete widefield+Full spectrum spinning disk widefield and confocal head	Via dei Sardi, 2nd floor
Zeiss LSM 780, inverted confocal Microscopy	Via dei Sardi, 2nd foor
Philips EM208S, electron microscopy	Phisiology
Zeiss Axioskop, brightfield/fluorescence microscopy	Phisiology
Zeiss, brightfield/fluorescence microscopy	Phisiology
Zeiss AxioObserver A1, inverted microscopy, Axiocam MRM R camera and Plan-Neofluar EC 10×/0.3 M27 and LD 20×/0.4. Acquisition software: AxioVision Rel.4.8. Objectives Korr (+40x 0.6 Korr;+63x1.25 oil).	Phisiology
Zeiss AxioObserver A1, inverted microscopy, equipped with Axiocam 305 color camera and Plan-Neofluar. Objectives 5, 10, 20, 40, 63x.	Phisiology

CITATION REPORT FOR 1.509 RESULTS (WEB OF SCIENCE CORE COLLECTION) | 2010-20

Total Publications
1.509 Analyze



2001 2020

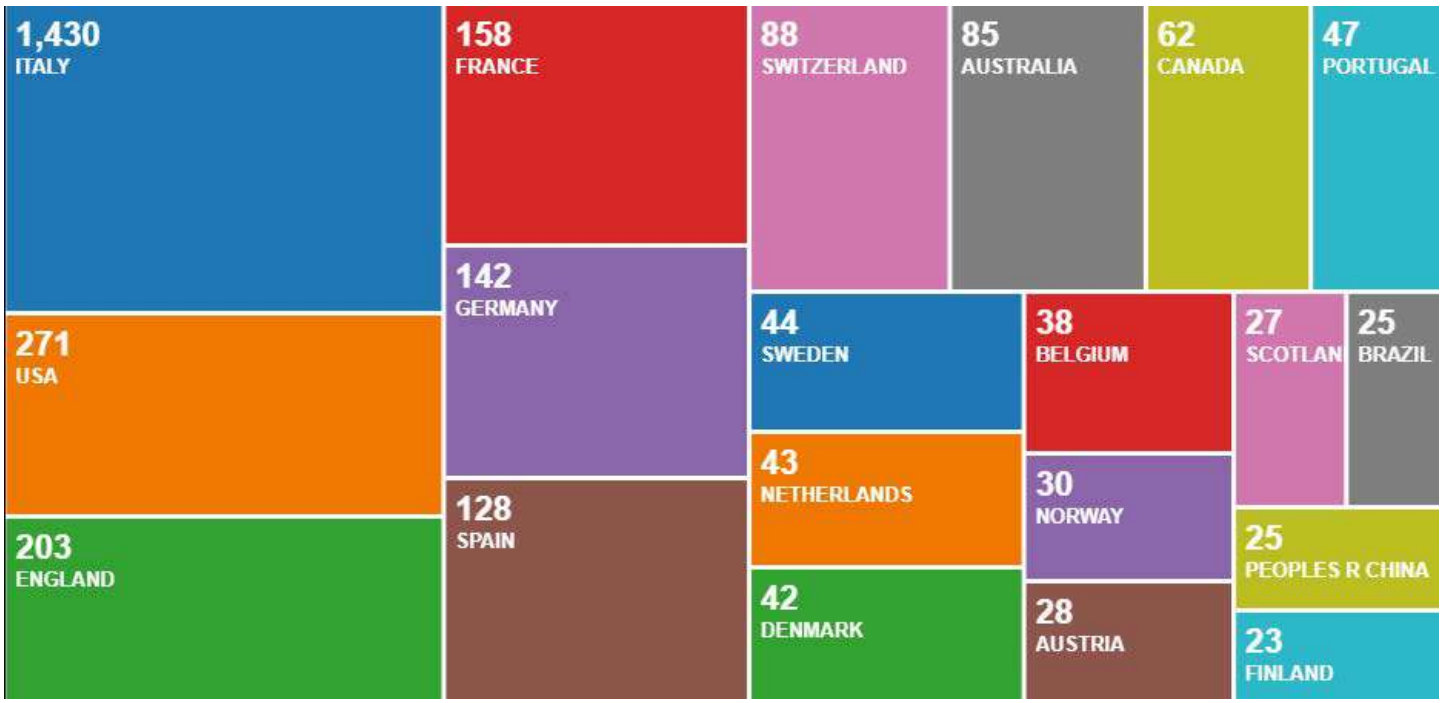
h-index
83
Average citations per item
26,27

Sum of the Times Cited
39.637
Without self citations
36.572

Citing Articles
31.775
Without self citations
30.800

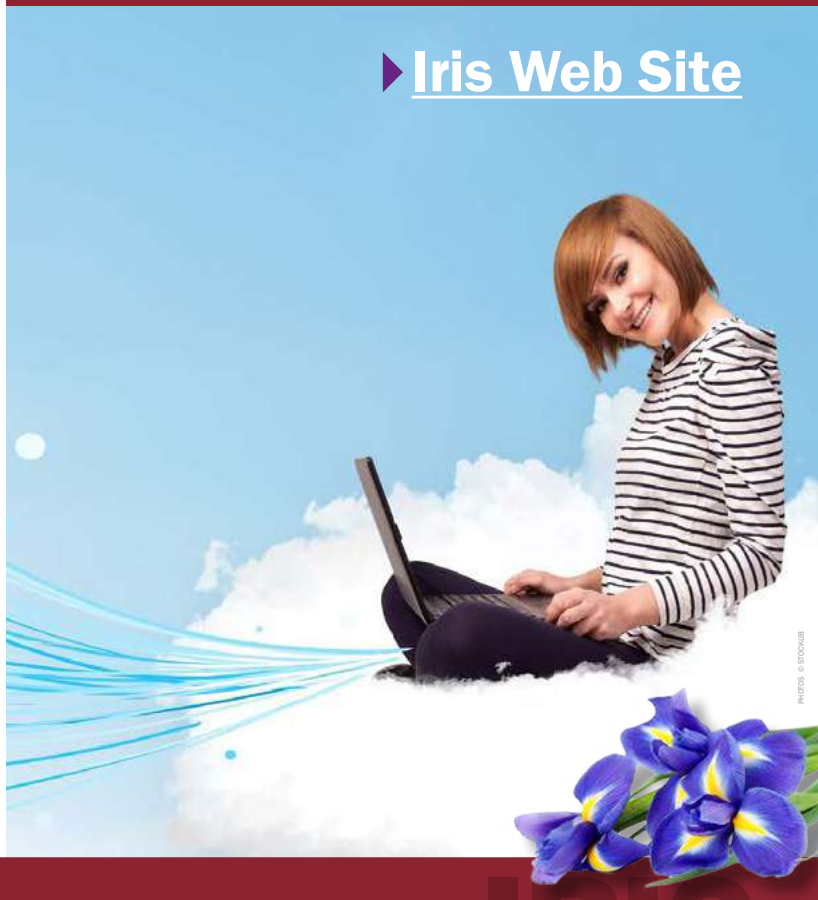
TOP TWENTY WEB OF SCIENCE CATEGORY VALUES | 2010-20

TOP TWENTY COOPERATING COUNTRIES | 2010-20



INSTITUTIONAL RESEARCH INFORMATION SYSTEM

Iris Web Site



"INSTITUTIONAL RESEARCH INFORMATION SYSTEM"

IRIS is an IT system which purpose is to valorize the research published in Italy and favor its wider dissemination into the scientific community. The research works included in the catalogue of the publications and the profiles of the researchers affiliated to the single institutions, provide high visibility and strong impact on increasing the number of citations, collaborations and shared projects. The system indeed is interoperable because of its interface with the data management.
Our department has embraced since the very beginning the use of the IRIS catalogue for its members. Research referents and librarians have trained and helped researchers for inserting the publications in the system and for curating and validating the publication catalogue. In line with Sapienza policy for Open Access (https://www.uniroma1.it/it/pagina/sapienza-lopen-access), our department supports the "open science" concept based on transparency, sharing and re-use of the data, and it encourages the open access publication of the scientific data obtained with public funding.

Prodotti per dipartimento	
DIPARTIMENTO "ISTITUTO ITALIANO DI STUDI ORIENTALI - ISO"	4435
DIPARTIMENTO DI ARCHITETTURA E PROGETTO	10893
DIPARTIMENTO DI BIOLOGIA AMBIENTALE	7550
DIPARTIMENTO DI BIOLOGIA E BIOTECNOLOGIE "CHARLES DARWIN"	7187
DIPARTIMENTO DI CHIMICA	10903
DIPARTIMENTO DI CHIMICA E TECNOLOGIE DEL FARMACO	5145
DIPARTIMENTO DI CHIRURGIA "PIETRO VALDONI"	4488
DIPARTIMENTO DI CHIRURGIA GENERALE E SPECIALISTICA "PARIDE STEFANINI"	4744
DIPARTIMENTO DI COMUNICAZIONE E RICERCA SOCIALE	7901
DIPARTIMENTO DI DIRITTO ED ECONOMIA DELLE ATTIVITA' PRODUTTIVE	3380

Prodotti per autore	
GIAGU, Stefano	1692
ORGANTINI, Giovanni	1449
DEL RE, Daniele	1398
RAHATLOU, SHAHRAM	1350
GENTILE, Simonetta	1283
BAGNAIA, Paolo	1229
PARAMATTI, Riccardo	1184
LUCI, Claudio	1176
LONGO, Egidio	1141
LENZI, Andrea	1117

successivo >

Prodotti per anno di pubblicazione	
2021	787
2020	13429
2019	16025
2018	16626
2017	16734
2016	16669
2015	15491
2014	18194
2013	18028
2012	18684

successivo >

SAPIENZA
UNIVERSITÀ DI ROMA

Dipartimento di
BIOLOGIA E BIOTECNOLOGIE
CHARLES DARWIN

RESEARCH CENTERS

COMPARATIVE ANATOMY
Via Borelli, 50

PHYSIOLOGY
University Campus
Piazzale Aldo Moro, 5

ZOOLOGY
Viale dell'Università, 32

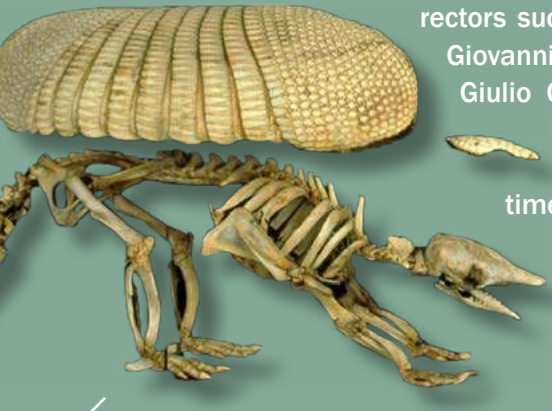
GENETICS
University Campus
Piazzale Aldo Moro, 5

S. LORENZO
Via dei Sardi, 70
Via degli Apuli, 4

“COMPARATIVE ANATOMY”

The headquarters of Comparative Anatomy has very ancient origins, dating back to the first half of the nineteenth century, when Comparative Anatomy and Zoology were associated in the same “Gabinetto di Zoologia e Anatomia Comparativa con annesso Museo” of the “Pontificio Archiginnasio della Sapienza”.

After the unification of Italy and the reorganization of the university in the “Regia Università di Roma”, in 1883, the “Istituto di Anatomia Comparata” was established in via De Pretis 97, in the university area of via Panisperna. Following the demolition of the building, in 1926, the Comparative Anatomy was housed, provisionally, in the new centre of Human Anatomy in via Borelli 50, where the headquarters of Comparative Anatomy is still located. Throughout its history, the institute has had prestigious directors such as Franz Böll, Giovanni Battista Grassi, Giulio Cotronei and Alberto Stefanelli.



In more recent times, since the 70s, two lines of research have emerged: the first on Comparative Neuroanatomy which then developed research concerning the effects of environmental stressors and the role of synucleins in the nervous system of non-mammalian vertebrates; the second on Comparative Cytogenetics of Vertebrates, which has been integrated with molecular phylogenetics/systematics and geometric morphometry approaches. At present the laboratories of the headquarters include an immunohistochemical laboratory, a Molecular Biology laboratory dedicated to systematics, and a cytogenetics laboratory.

Moreover, the facilities include cold rooms for the storage of biological samples, cell culture and a fluorescence microscope. There is also a meeting room equipped with a projector.

Riccardo
Castiglia
Associate Professor

ORCID

RESEARCH LINES

- Evolutionary biology of the chromosomal races of the house mouse
- Phylogeography of small mammals and reptiles in the Mediterranean region
- Cytotaxonomy and chromosomal evolution of small mammals and reptiles in areas of high biodiversity
- Scientific Museology

STAFF | COLLABORATORS

Emanuela Solano,
Post-doc (Sapienza)
Paolo Colangelo,
Researcher (CNR, Monterotondo)
Oscar Alberto Flores-Villela,
Full Professor (UNAM, México)
Alexandra M.R. Bezerra,
Researcher (Museu Paraense E. Goeldi, Belém)
Gabriele Senczuk,
Researcher (Universiy of Molise, Campobasso)

RESEARCH ACTIVITY

Evolutionary biology of the chromosomal races of the house mouse
The house mouse, *Mus domesticus*, has numerous chromosomal races distributed in various European and non-European regions, characterized by a diploid number between 38 and 22 chromosomes. The research focuses on the mechanisms that determined the origin of these races and on the effect of chromosomal differences on gene flow. In particular, the chromosomal evolution of the races settled in central Italy, Sicily and the Aeolian archipelago is the object of the research line, through i) the identification of chromosome markers (metacentric Robertsonian), ii) phylogeny with molecular markers iii) analysis of gene flow in areas of natural hybridization (maternal and bi-parental molecular markers), and iv) analysis of fertility in natural hybrids for the study of the effect of structural heterozygosity at the individual level.

Cytotaxonomy and chromosomal evolution of small mammals and reptiles in areas of high biodiversity
The research line addresses the taxonomy of small mammals (Rodentia and Soricomorpha) and reptiles (Squamata) in the tropical regions of East Africa and the tropical forest along the Pacific coast of Mexico, mainly using the information obtained from the karyotype study (cytotaxonomy). Furthermore, the patterns of chromosomal evolution have been de scribed in some genera, and the chromosomal transformations of euchromatic and heterochromatic regions have been characterized. The methods used include various cytogenetic analyses: standard stains, differential stains and FISH (Fluorescent in situ hybridization) with repeated sequences.

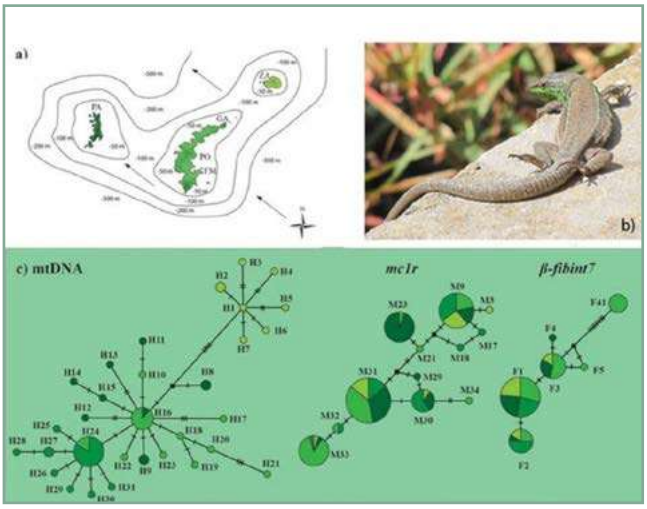


Figure. Genetic diversity of the lizard Podarcis latastei *from western Pontine Islands. Upper panel: map and bathymetry of the archipelago and a Podarcis latastei female from Zannone. Lower panel: statistical parsimony networks of the mtDNA and nuDNA genes.*

Phylogeography of small mammals and reptiles in the Mediterranean region
The objective of this line of research is to investigate the role of paleogeographic and paleoclimatic events of the Pleistocene on the distribution of genetic variability and speciation in some species of small mammals and reptiles in the Mediterranean area. The approach used is the phylogeography, through nuclear and mitochondrial genetic markers.

Third mission activity
Several scientific dissemination activities as Director of the Museum of Comparative Anatomy "Giovanni Battista Grassi".

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Carla
Cioni
Associate Professor

ORCID

RESEARCH LINES

- Line 1. Comparative Neurochemistry of the Central Nervous System in fish.
- Line 2. Expression of synucleins in neurons of nonmammalian vertebrates.
- Line 3. Effects of environmental stressors on neurochemical and behavioral parameters of teleost fish.

STAFF | COLLABORATORS

Mattia Toni,
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Maria Carmela Bonaccorsi di Patti,
Researcher (Sapienza)
Arianna Casini,
Researcher (Sapienza)
Rosa Vaccaro,
Researcher (Sapienza)

RESEARCH ACTIVITY

Line 1. Studies are concerned with the neurochemical characterization of neuronal populations in the central nervous system of teleost fish with the aim of comparing fish to the mammalian brain from which it differs by several aspects. Understanding the fish brain is important not only to appreciate the evolutionary changes occurring in this vertebrate lineage but also to develop new models for neuroscience research. Studies were performed on the characterization and/or distribution of urotensin I and II UI/UII, corticotropin-releasing factor (CFR), nitric oxide synthase (NOS) and choline acetyltransferase (ChAT). NOS expression in fish was also compared to that of a marine gastropod as representative invertebrate.

Line 2. Synucleins include proteins expressed in the central and peripheral nervous systems of mammals (α- β- and γ-syn). In particular, α-syn is responsible for amyloidogenic inclusions occurring in neurons and glial cells during human neurodegenerative disorders known as "synucleinopathies", that include Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, and a number of less well-characterized neuroaxonal dystrophies. Syn proteins have been sequenced in species representative of all vertebrates and the comparative analysis of amino acid sequences suggests that syns are evolutionarily conserved and fulfill important physiological functions. The aim of the research is to investigate syn expression in non-mammalian vertebrates to understand the evolution and the role of these proteins. The research also aims at identifying new species models for studies on syn-based neurodegenerative disorders.

Line 3. The aim of this research line is to analyze the effects of environmental temperature on the brain proteome and the behavioral responses of teleost fish exposed to temperature. The variation of the environmental temperature can indeed alter the habitat of aquatic species and impact on their lives at all the biological levels from population to molecules, thus affecting the survival and longevity of the organisms. Fish are particularly sensitive to thermal variations, since their body temperature varies with the environmental temperature, and water temperature is considered as one of the major ecophysiological variables influencing fish behaviour and distribution.

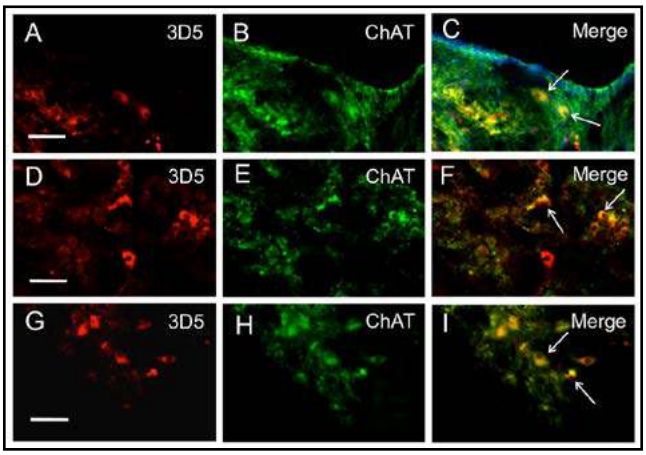

Figure. Transverse sections of carp medulla oblongata (A-D) and spinal cord (E,F) double immunostained for 3D5/ChAT (dark-blue/brown) (Ref. 1)

THIRD MISSION ACTIVITY

Coordinator, "Piano Lauree Scientifiche (PLS)" in Biology and Biotechnology for teachers and students of the secondary school, funded by the Italian Ministry of Education and Research (MIUR), Sapienza University.

References

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2. Angiulli E, Pagliara V, Cioni C, Frabetti F, Pizzetti F, Alleva E, Toni M (2020) Increase in environmental temperature affects exploratory behaviour, anxiety and social preference in Danio rerio. Sci Rep. 25;10(1):5385.
3. De Nonnis E. Angiulli, E. Maffioli, F. Frabetti, A. Negri, C. Cioni, E. Alleva, V. Romeo, G. Tedeschi & M. Toni (2021) Acute environmental temperature variation affects brain protein expression, anxiety and explorative behaviour in adult zebrafish, Scientific reports 11: 2521.

Anna Rita
Rossi
Associate Professor

ORCID

RESEARCH LINES

- Molecular phylogenetics and phylogeography
- Evolutionary biology
- Cytogenetics

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Lorenzo Tancioni,
Researcher (Tor Vergata)
Mauro Nirchio,
Assoc. Professor
(UT Machala, Ecuador)

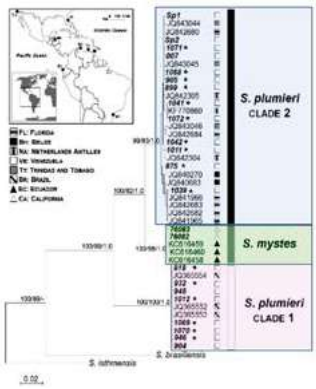
RESEARCH ACTIVITY

Research activity is focused on the analysis of genetic variability of marine, lagoon and freshwater Teleost fish. In detail:

Molecular phylogenetics and phylogeography of Italian freshwater endemic fish, through genotyping of microsatellite loci and mitochondrial sequence analysis (control region). This research line aims at the identification of local populations and management units to be preserved, as most of these species are threatened by habitat degradation and competition with allochthonous species. From an evolutionary biology perspective, these investigations allow us to infer the time of divergence and the colonization paths of different lineages, the historical demography of these lineages, and the geological and paleoclimatic events linked to them.

Molecular taxonomy and comparative cytogenetics of species of the Caribbean and South American area. This research line includes cytogenetic analysis and chromosomal mapping of repeated sequences (rDNA, telomeric sequences, U1 snRNA gene clusters) by Fluorescence in situ hybridization, and parallel analysis of mitochondrial DNA sequences (Cytochome Oxidase subunit I, 16S rDNA, Cytochrome b) of the same individuals. The combination of the two sets of data is necessary for molecular identification of karyotyped specimens, for all those taxa that show poor diagnostic morphological characters, to link cytogenetic data to certain taxonomic units, and for the identification of cryptic species. Phylogenetic relationships depicted by molecular data allow the reconstruction of evolutionary paths associated to karyotype diversification within genera and among closely related groups of fish.

Population genetics of Mediterranean marine species that represent a resource in fishery and aquaculture, through the analysis of microsatellite loci genotypes and mitochondrial markers analysis (RFLP and sequences). These researches aim at analysing patterns of genetic variability, and population structure. Data can help in the reconstruction of population connectivity patterns, in the identification of fish stocks, or for the identification of breeders within a broodstock, and attribution of unknown progeny to certain parents in farmed species.



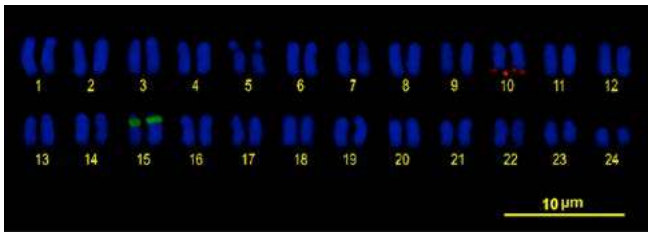


Figure. Left panel Neighbour-joining tree based on Scorpaena spp. cytochrome oxidase I gene sequences from Nirchio et al. J Fish Biol 2016; 89:1947–1957. Right panel. FISH karyotype of Mugil hospes after in situ hybridization 5S rDNA (green) and U1 snDNA (red) probes from Nirchio et al Frontiers in Genetics 2018; 9:17

THIRD MISSION ACTIVITY

Coordinator of the “Animal Biology” Lab2Go project, for students of the secondary school.

References

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Mattia
Toni
Associate Professor

ORCID

RESEARCH LINES

- Line 1. Study of prion and prion-like proteins (PrPc and synuclein) in mammalian and non-mammalian vertebrates.
- Line 2. Study of the effect of environmental stress on neurochemical and behavioral parameters and learning of teleost fish.
- Line 3. Study of the evolution and physiological function of nitric oxide synthase isoforms in invertebrate and vertebrate organisms.

STAFF | COLLABORATORS

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Researcher (Sapienza)
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Researcher (Sapienza)

RESEARCH ACTIVITY

Line 1. Alpha synuclein (syn) belongs to the syn family together with β- and γ-syns. These proteins are particularly expressed at the level of the central (α- and β-syn) and peripheral (γ-syn) nervous system. The term "synucleinopathies" defines a group of human neurodegenerative disorders characterized by the presence of amyloidogenic α-syn inclusions that can occur in neurons and glial cells of the central and peripheral nervous system. These high social impact diseases include Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, and a number of less well-characterized neuroaxonal dystrophies. The syn family members were sequenced in species representative of all vertebrates and the comparative analysis of amino acid sequences suggests that syns are evolutionarily conserved and fulfill important physiological functions. The aim of the research is to investigate the syn expression in non-mammalian vertebrates, to understand the evolution and the role of these proteins and to identify new animal models for the study of Parkinson's disease.

Line 2. All organisms have to cope with changes in environmental parameters during their life. Among these, and particularly relevant, is the variation of the environmental temperature that can deeply alter the habitat of the species and have an impact at all the biological levels, from population to molecules, affecting the survival and longevity of the organisms. The poikiloterm animals such as fish, whose body temperature varies with the environmental temperature, are particularly sensitive to thermal variations and water temperature is considered the major ecophysiological variable for aquatic ectotherms, influencing the physiology, behaviour and distribution of animals. The aim of this research line is to determine the effects of environmental temperature on the brain proteome and the behavioural responses in teleost fish.

Line 3. Nitric oxide (NO) is a gaseous messenger that is endogenously produced in cells and tissues of all major groups of organisms and acts in a variety of biological processes. In animals, NO is enzymatically generated by complex and highly regulated enzymes, known as NO synthases (NOSs), that appear to be highly conserved during evolution as NOS homologues have been identified in various organisms including bacteria. The research line aims to investigate the role of NO and NOSs in the nervous system of invertebrates and teleost fish.

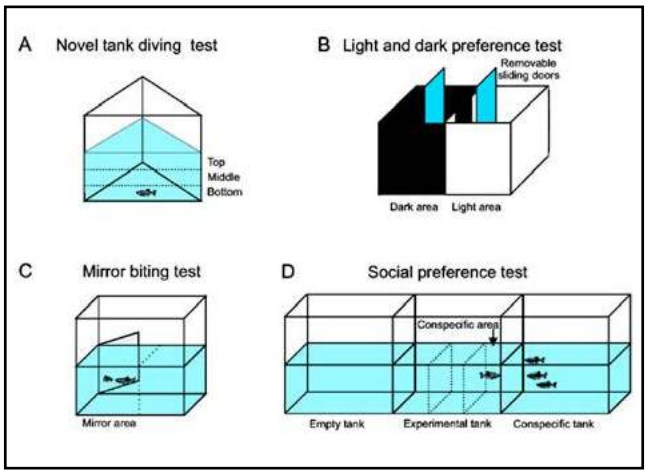

Figure. Schematic representation outlining the experimental design. The adult Zebrafish were maintained for 21 days at 26 °C (controls) and 34 °C (treated). After thermal treatment fish were subjected to a behavioural test battery consisting of NTT (A), LDT (B), MBT (C) and SPT (D). Behaviour was video-recorded for 10 min in each test 1.

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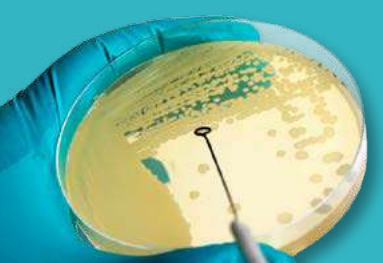
3. Cioni C, Angiulli E, Toni M. Nitric Oxide and the Neuroendocrine Control of the Osmotic Stress Response in Teleosts. Int J Mol Sci. 2019 23;20(3). pii: E489.

“PHYSIOLOGY”

The CU026 building, also called the Institute of General Physiology, was built in the 1930s by arch. Giovanni Michelucci under the supervision of chief architect Marcello Piacentini. The building was part of the construction of the University city inaugurated on March 31, 1935. The functionalism certainly inspired arch. Michelucci and the rationalist architects who designed the building. It consists of two independent buildings connected to the mezzanine floor. The building comprises several classrooms for the didactic activity of the bachelor degree courses in Biological Sciences, for the Master Programs in Genetics and Molecular Biology, Neurobiology, Cellular Biology and Biotechnology, and Environmental and Industrial Biotechnology. One of these classrooms is dedicated to Giorgio Tecce who in 1970 established the first CNR study center for nucleic acids in this building. He was also the “Rettore” of Sapienza from 1988 to 1997. A large amphitheater classroom is centrally located so that it is connected to both buildings. The classroom is dedicated to Daniel Bovet who won the Nobel Prize in Medicine in 1957, is one of the fathers of Psychobiology and held the first chair of Psychobiology in 1969.

His main discoveries and his contributions to medical science are remembered in the entrance hall belonging to the main entrance. Emphasizing the continued importance of basic research in inspiring translational research, the building houses a combination of important quality research groups that study fundamental biological processes of developmental biology, RNA metabolism, neurobiology, plant biology and microbial biotechnology. Researchers are also involved in first-rate national and international research programs.

This highly collaborative approach by departmental investigators led to the development of clinical and industrial applications. In addition to the research laboratories there are the student secretariat, the administrative staff and the library. The department’s research facilities are widely equipped with all the laboratory infrastructure necessary for molecular biology, biochemistry, cell culture, cell and tissue imaging experiments. An animal facility is also available to researchers for breeding animals and experimental procedures.



Monica
Ballarino
Associate Professor

ORCID

RESEARCH LINES

- Myogenesis and muscle diseases
- Long noncoding RNA (ncRNA)
- Epigenetics
- Human iPSCs for cardiac disease modeling

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Antonio Musarò,
Full Professor (Sapienza)
Emerald Perlas,
Researcher (EMBL/Monterotondo)
Radislav Sedlacek,
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GRANTS

INFRAFRONTIER "Disease model development and systemic phenotyping" International consortium CCP-IMG of the ASCR, Czech Republic (call 2017).
PI: Monica Ballarino

My Editor Roles

RESEARCH ACTIVITY

A unifying research theme in my lab is how non-coding (nc)RNAs, referred to as genomic "dark matter", influence cell differentiation and disease. Since my PhD at Sapienza, my interests have focused on the biogenesis and the function of small ncRNAs, such as snoRNAs and microRNAs. I have further deepened the study of microRNAs during my postdoctoral activity at IGBMC (Strasbourg, France), where I become interested in the implication of these species in tumorigenesis.
Current research lines converge on the identification and the functional analysis of long ncRNAs (lncRNAs), which represent the most prevalent and functionally diverse class of ncRNAs in the cell. My lab has pioneered the genome-wide discovery of novel muscle-specific lncRNAs and combined in-situ Hybridization (ISH), high-throughput biochemical assays and CRISPR-Cas9 approaches to characterize them.
A paradigmatic example is represented by *Charme*, an epigenetic lncRNA controlling myogenesis by influencing the three-dimensional organization of the genome. Importantly, *Charme* knockout mice develop a severe cardiomyopathy and reduced lifespan, due to cardiac conduction defects, as diagnosed with echocardiographic studies. The existence of a human orthologous, sharing with the mouse counterpart the same subset of target genes, suggests an evolutionarily conserved function for *Charme*. Then, to unveil the possible implication of *Charme* in human cardiomyopathies, we have raised iPSC lines carrying *Charme* mutations and standardized protocols for their differentiation into beating cardiomyocytes. Transcriptome and physiological studies are ongoing.

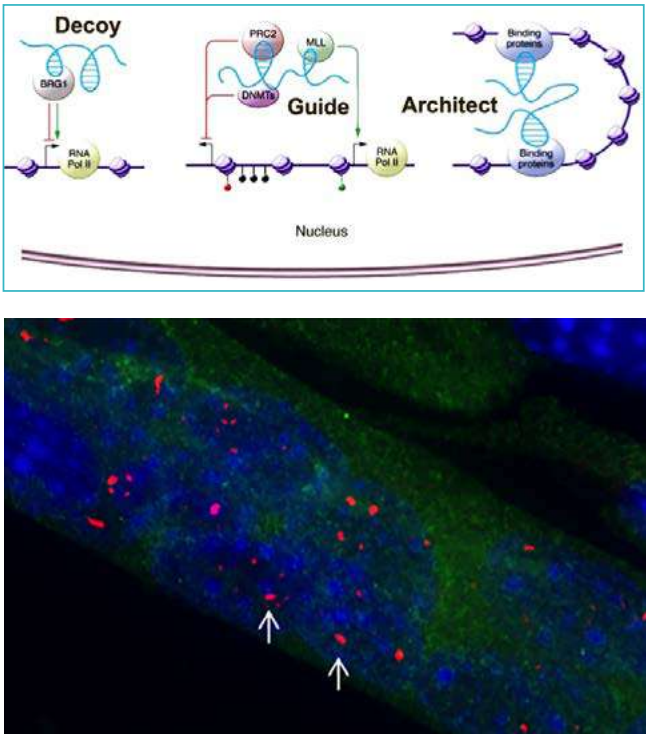

Figure. Upper panel: models of nuclear lncRNA function in myogenesis (modified from Ballarino et al., J Clin Invest. 2016; 126(6): 2021–2030. Lower panel: confocal images showing a co-staining between the myosin heavy chain (MHC) protein (green) and Charme RNA (red), in fully differentiated myotubes (modified from Ballarino et al., EMBO J. 2018 37:18).

The long-term goal of the laboratory is to decipher the aberrant regulatory information which impacts on the function of muscle, either directly, as in skeletal and cardiac diseases, or indirectly, as in neuromuscular disorders and neurodegeneration.

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Stefano
Biagioni
Full Professor

ORCID

RESEARCH LINES

- Role of FUS in neural stem cell properties.
- Transcription factor regulating proliferation and differentiation of neural stem progenitor cells.
- Functional role of cyclic nucleotide pathway in a DYT1 dystonia mouse model.
- In vitro evaluation of the anticancer activity of novel compounds.

STAFF | COLLABORATORS

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Viviana Orlando,
Technician (Sapienza)
Giancarlo Poiana,
Researcher (Sapienza)

RESEARCH ACTIVITY

The role of FUS in neural stem cell properties. Mutations of the Fused in sarcoma protein (FUS) have been found to be associated with amyotrophic lateral sclerosis (ALS). Notably, besides mutations in the coding sequence, also mutations in the 3′ untranslated region have been associated with the ALS pathology, which leads to increased levels of the wild-type protein. We study the effect of wild-type FUS overexpression on the responsiveness of mouse and human neural progenitor-derived astrocytes to a pro-inflammatory stimulus (IL1β). We found that astrocytes with increased FUS levels were more sensitive to IL1β, as shown by their enhanced expression of inflammatory genes. Astrocytes overexpressing FUS promote neuronal cell death and pro-inflammatory microglia activation, suggesting that overexpression of FUS affects astrocyte reactivity and drives them towards having pro-inflammatory and neurotoxic functions that cause neurodegeneration in FUS-mutated animals and patients.

Functional role of cyclic nucleotide pathway in a DYT1 dystonia mouse model. DYT1 Dystonia is a movement disorder caused by a 3-bp deletion (Δgag) in the TorsinA gene. Our work using a DYT1 model overexpressing mutated torsinA, demonstrates the opposite changes in the levels of the catabolic cAMP enzyme, PDE10A, occurring in the direct and indirect pathways of the basal ganglia. This imbalance could be responsible for the improper focus on the movements in DYT1 dystonia, suggesting the involvement of striatopallidal and striatonigral neuronal subtypes in the pathophysiology of dystonia. We study the changes of the A2a receptor, as a mediator of cAMP synthesis, and of PDE10A levels using a DYT1 knock-in model reproducing the human mutation (Tor1a+/Δgag). The DYT1 knock-in mouse also displayed opposite PDE10A variations, moreover the expression of the A2a receptor showed opposite changes in striatopallidal and striatoentipeduncular/nigral circuits, similarly to the alterations in PDE10A. Our data suggest that an alteration of the cAMP pathway in the striatal direct and indirect circuitries can be a general mechanism in the pathophysiology of DYT1 dystonia and that the activation of adenylate cyclase via the up regulation of A2a receptor could be a compensatory mechanism.

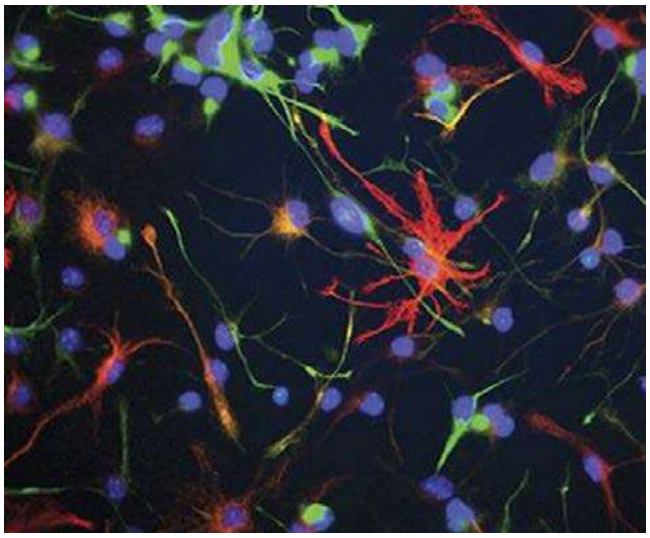

Figure. Culture of neural stem progenitor cells derived from adult mouse brain subventricular zone. bIII-tubulin-positive cells (green); glial fibrillary acidic protein-positive cells (GFAP, red); nuclei are counterstained with DAPI (blue).

In vitro evaluation of the anticancer activity of novel compounds. Cancer cells are characterized by a high rate of cell division. Microtubules (MTs) play a key role in regulating the eukaryotic cell machinery. Interfering with the MT dynamic equilibrium is an attractive option for the design of effective agents against a wide variety of cancers. Novel compounds are synthesized by the group of Romano Silvestri at the Department of Drug Chemistry and Technologies, Sapienza and their activity is assayed using cell cultures of several cancer lines by evaluating IC50.

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Michele Maria
Bianchi
Associate Professor

ORCID

RESEARCH LINES

- Hypoxic regulation of metabolism in yeast
- Fatty acid biosynthesis in yeast
- Environmental stress responses in yeast

STAFF | COLLABORATORS

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Teresa Rinaldi,
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Alessandro Giuliani,
Researcher (ISS, Rome)
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Researcher (Russian Academy of Sciences, Pushchino)

GRANTS

MAECI/Regolazione delle trascrizione nei lieviti: effetti degli stimoli ambientali in un gruppo di geni selezionati da Kluyveromyces lactis e Saccharomyces cerevisiae (PGR00208, PGR00209, PGR00746), 31.000€.
PI: Michele M. Bianchi

RESEARCH ACTIVITY

The research activity is focused on the effects of environmental factors on metabolism regulation and the identification of regulatory proteins involved in these responses. The evolution of aerobic organisms and respiratory metabolism depended on the appearance and accumulation of oxygen in the biosphere. However, oxygen becomes scarce or is completely absent or its concentration largely fluctuates in several environments: organism adaptation to these environments depends on the metabolic regulation between respiration and fermentation, governed by oxygen availability. Other environmental factors influence and regulate metabolism: among them, light has an extremely important role, either for energy supply to the biosynthetic metabolism, or for all metabolic activities related to the circadian cycle.
Photosynthetic organisms and organisms entrained to the day/night cycle are strongly dependent on light. Finally, another interesting environmental factor is carbon dioxide, massively produced and dispersed in the atmosphere by human activities.
The research is performed on yeasts, which are eukaryotic organisms extensively used in basic research as well as in biotechnological applications and in industrial scale productions. Yeasts are also used as model organisms for human disease studies. Yeast physiology and metabolism are tightly linked to growth conditions, in particular to oxygen concentration and the type and the amount of carbon sources. The research is based on the study of the connections between oxygen and glucose regulations in the Kluyveromyces lactis, in which they are reciprocally modulated. In particular, the research is focused on the hypoxic regulation of glycolysis and the fermentative metabolism and the hypoxic regulation of lipid biosynthesis. Proteins mediating the hypoxic response have been identified (Rag4, Sck1, KlMga2) and are currently studied.
Preliminary studies indicate that carbon dioxide interferes with the onset of fermentative metabolism: carbonic anhydrase and enzymes for carbon dioxide assimilation (Acetyl-CoA Carboxylase, Pyruvate Carboxylase) will be analyzed in detail. Light response is a well studied mechanism in filamentous fungi like Neurospora crassa. However, little is known about the light response in yeasts which are apparently lacking proteins with light sensitive domains. We have demonstrated that 24-hours light-dark cycles affect phenotypic suppression in K. lactis (Figure, reference 3). In Saccharomyces cerevisiae, light induces ROS formation and the nuclear displacement of the stress factors Crz1 and Msn2. The roles of these regulatory proteins are under current investigation in K. lactis, especially in relation to fatty acid desaturation that, in plants, is under the control of light - dependent genes.

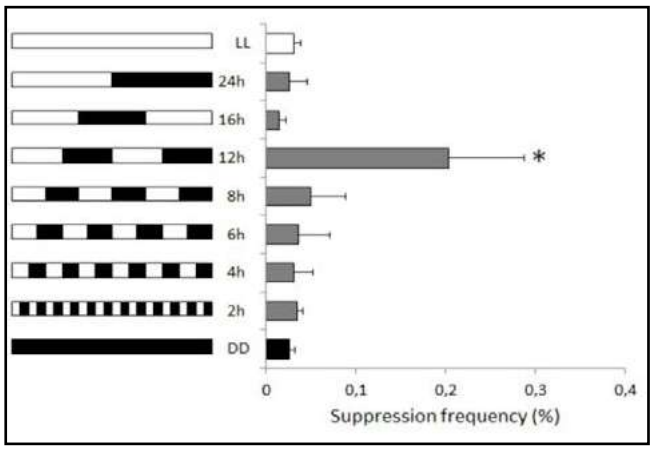

Figure. The average percentages of generation of suppressed cell colonies are reported in the histograms together with relative standard deviations. 12+12h cycles, Pmax<0.01. The left part of the figure reports the scheme of light-dark alternation. Length of light (dark) periods are indicated in hours (h). All light and all dark incubation experiments are indicated as LL and DD, respectively.

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Irene
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RESEARCH LINES

- Non coding RNAs in neurodegenerative processes
- CircRNAs in tumorigenesis
- RNA modifications in regulation of gene expression
- Assembly and phase Transitions of Ribonucleoprotein Aggregates

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GRANTS

PRIN 2017 n. 2017P352Z4 "Non coding RNAs [...] studying their role in neuronal differentiation and neurodegeneration" € 289.400
AIRC–IG-2019 Id.23053 "Circular RNAs: novel players and biomarkers in tumorigenesis" - € 815.000
H2020 - ERC-2019-SyG Project: 855923 ASTRA "Assembly and phase Transitions of Ribonucleoprotein Aggregates in neurons [...]" € 2,813,750.00

RESEARCH ACTIVITY

A large part of mammalian transcriptomes is composed of RNA molecules that do not encode for proteins (non coding RNAs) and whose role is to control gene expression at many different levels. These molecules, thanks to their intrinsic scaffolding ability, combine the dual function of tethering proteins as well as other nucleic acids. RNA-RNA and RNA-protein interactions allow the nucleation of different membrane-less compartments where the most essential cellular processes occur, such as transcription, processing, translation and intracellular transport. All these assemblies have a vast importance in physiological conditions; however, under specific conditions, as for instance upon stress, they can increase their viscosity leading to solid-like aggregates. Liquid-solid phase transitions can lead to the dysfunction of many cellular processes and their formation has been causatively linked to several neuro-degenerative diseases such as ALS, Alzheimer and many others. The main goal of our research is to study the activity of lncRNAs and circRNAs in normal and ALS pathological conditions in order to understand how they contribute to control RNP assembly, function and intracellular trafficking in motor neurons. We expect that these studies will strongly increase our understanding of basic molecular processes controlled by ncRNAs and should also constitute a largely unexplored territory for the development of novel therapeutics and diagnostics. Cellular model systems (mESCs and hiPSCs) will be employed together with ad hoc KO mouse models.

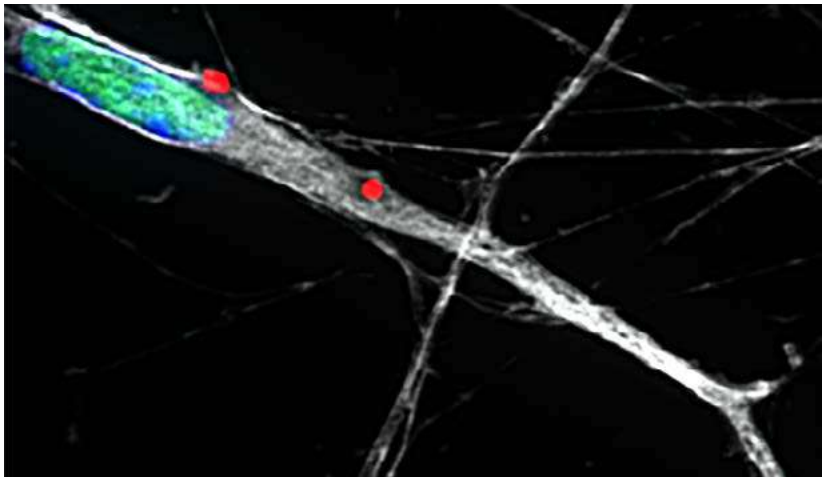

Figure. circRNAs have specific subcellular localization. *In situ detection of a MN-specific circRNA: circRNA (red), DNA (blue). The circRNA appears localized along the growing cellular processes.*

In an independent line of research we want to focus on the study of circular RNAs (circRNAs) as novel players in tumorigenesis. For these new molecules we want to define the molecular mechanisms through which they control cancer onset and progression. We also want to address the role of one of the most common RNA chemical modifications the N6-methyladenosine (m6A) in circRNA activity in normal and cancer states. Indeed, this modification has been shown to play critical functions in several types of human cancers and proteins associated to m6A homeostasis have been found deregulated in different tumours. We plan to test whether the m6A modification affects circRNA production and whether alteration of their expression occurs in different tumours. This analysis will be initially applied to a set of already characterized circRNAs to be subsequently extended at a genome wide level. Finally, since m6A has been also involved in translational regulation, we want to test whether specific m6A sites present in circ-RNAs are relevant for directing its translation along the cap-independent pathway. Both projects have a strong interdisciplinary nature, combining together molecular and cell biology techniques, advanced computational models and new physical methodologies for imaging.

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Associate Professor

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RESEARCH LINES

- Structure and function of human telomeric chromatin
- Epigenetic status of human telomeres in normal and cancer cells
- Structural organization of drosophila telomeres
- Impact of the space environment on telomeres

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Grazia Raffa,
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Annamaria Biroccio,
Researcher (Regina Elena Institute)
Matteo Lulli,
Researcher (Firenze University)

GRANTS

European Space Agency/Coenzyme Q10 prevents proton beam radiation-induced damages in retinal pigment epithelial, Muller, photoreceptor and endothelial cells, € 32.000.
PI: Matteo Lulli, Stefano Cacchione

RESEARCH ACTIVITY

In humans, telomeres play a pivotal role in several regulatory pathways that determine the cell fate. At birth, human telomeres are 10–15 kb long, consisting of thousands of TTAGGG repeats organized in a unique and compact chromatin and bound by the six-protein complex, shelterin. The enzyme telomerase maintains telomere length in germinal and embryonic stem cells, but is inactive in somatic cells. Consequently, telomeres shorten at each replication cycle till they reach a critical length that triggers a DNA damage response (DDR) pathway leading to permanent cell cycle arrest (see figure). To proliferate indefinitely, cancer cells must acquire a telomere maintenance mechanism, in most cases by reactivating telomerase, in 10–15% tumors developing an alternative mechanism named ALT, based on homologous recombination. About 80% of telomeric DNA is organized in nucleosomes characterized by an unusually short spacing and enriched in the histone variant H3.3, deposited in a replication-independent way by the complex ATRX/DAXX. Double-stranded telomeric repeats are bound by TRF1 and TRF2, two shelterin subunits that anchor the complex to the telomere. It has been often overlooked that TRF1 and TRF2 bind to telomeric repeats in a tight chromatin context, implying that they have to bind on the nucleosome or on the short linker DNA between nucleosomes, competing and/or interacting with the histone octamer. We found that the binding of TRF1 and TRF2 to telomeric sequences is modulated by the histone octamer by interaction of the histone tails with their divergent N-terminal domains. We are now focused on the role of H3.3 at telomeres. Strikingly, dominant mutations in H3.3 are frequent in ALT pediatric cancers, often in combination with loss of ATRX. Telomere heterogeneous length (about 2-10 kbp in humans) coupled with the uniformly repeated sequence renders hard to establish whether the telomere has a regular structural organization along its overall length and how its structure changes when telomeres shorten and uncap. To go deeper in telomeric chromatin organization, we developed new tools and strategies, namely specific chemical cleavage and single molecule sequencing of long telomeric fragments by oxford nanopores, with the aim to obtain a more detailed map of nucleosome organization at human telomeres, particularly of H3.3 nucleosomes. Currently, we have projects in collaboration with Dr. Grazia Raffa on the structure and function of telomeres in Drosophila melanogaster, in which specialized retrotransposons assure telomere maintenance, and on the role of the protein TGS1 in regulating telomere elongation. Finally, in collaboration with Dr. Matteo Lulli we are studying the effect of space radiations and microgravity on chromosome instability and telomere function.

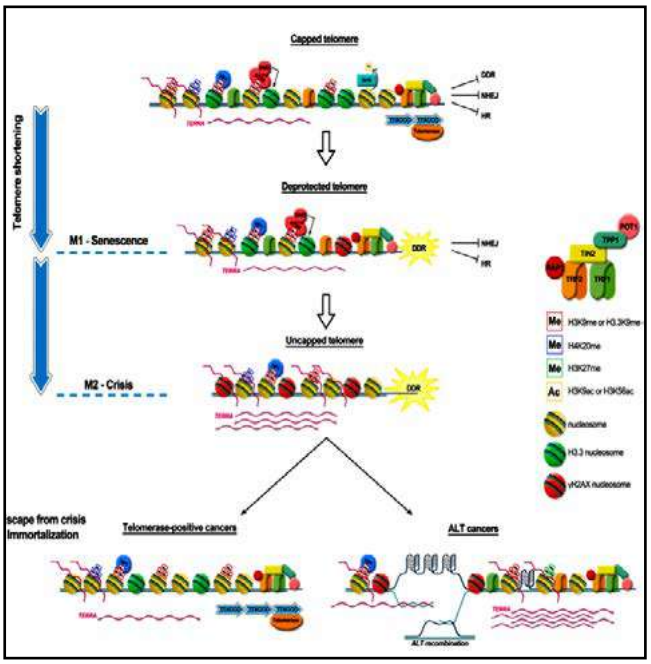

Figure. Schematic representation of different healthy and pathological telomeric states. The figure shows the changes of the telomere structure from a capped telomere to neoplastic transformations (from top to bottom)

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RESEARCH LINES

- Regulation of adult hippocampal neurogenesis in R451C NLG3 knock-in mice
- Effects of neuroinflammatory cells (i.e. microglia and astrocytes) on differentiation and survival of neural stem cells and neurons.

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RESEARCH ACTIVITY

Analysis of adult neurogenesis in a mouse model of autism spectrum disorder (ASD)
Neurogenesis continues throughout adulthood in the dentate gyrus (DG) and its alteration has been associated with a number of neuropsychiatric disorders. Decreased DG neurogenesis and impairment of neural stem cell (NSC) properties have been observed in animals carrying mutations in genes linked to ASDs, such as Cntnap2 and Shank3. We have been studying DG neurogenesis in R451C Neuroligin3 (NLG3) knock-in mice, a model of a monogenic form of ASDs carrying the R451C substitution found in autistic patients. Newly born neurons are detected by immunofluorescence on mice injected with Bromodeoxyuridine and sacrificed at different time points. R451C knock in (KI) mice show decreased hippocampal neurogenesis, as demonstrated by the reduction of immature (BrdU/DCX +cells) and mature neurons (BrdU/NeuN +cells; Fig 1) with respect to wild type (WT) mice.

We have been currently investigating whether decrease in neurogenesis depends on reduced neuronal survival and/or alterations in the NSC pool. Furthermore, as neurogenesis impairment can account for a subset of ASD features we have been assessing whether neurogenesis levels can be restored in KI mice by using a pharmacological stimulus (i.e. fluoxetine). Behavioural tests at the end of fluoxetine treatment will allow exploring whether deregulated neurogenesis underlies behavioural deficits in ASD mouse models. These in vivo studies will be also complemented by using cell culture approaches. Taking advantage of our previous experience in the field, we isolated hippocampal NSCs from WT and KI mouse brains, and established cell lines that can be used as a cellular model to gain insight into the molecular mechanisms underlying the reduced adult neurogenesis in the KI animals.

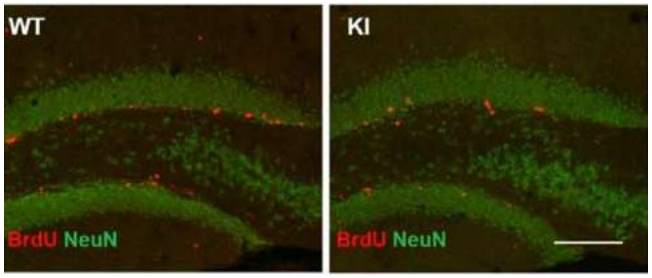

Figure. Detection of newly born neurons in the DG of adult mice. Mature neurons newly generated in the adult DG are immunolabeled with BrdU (red) and NeuN (green). A consistent reduction in the number of double-labelled neurons is observed in KI with respect to WT mice.

Effects of glial cells (i.e. microglia and astrocytes) on NSC properties
One major goal in the stem cell biology field is to understand the interplay between NSCs and the cell types residing in the specialized microenvironment called stem cell niche.
Microglia, the resident brain macrophages, are involved in the modulation of the niche both in physiological and pathological conditions. Our group has contributed to demonstrate that activated microglia (activation is a multifaceted phenomenon modulated by several factors) can be detrimental to neuron regeneration due to the release of noxious pro-inflammatory cytokines, but in certain circumstances can promote neurogenesis from NSCs.
Similarly to microglia, astrocytes have been described as stem cell niche players. NSCs from different species, including humans, can be differentiated into astrocyte-like cells very efficiently, and be used to study their function in vitro. We have recently started to investigate their properties in different contexts and demonstrated for example that both human and mouse astrocytes expressing a mutated form of the ALS-associated gene FUS show increased reactivity and acquire neurotoxic functions.
An aim of our studies is to explore how aging affects the properties of astrocytes. Specifically, astrocytes ovexpressing Dbx2 or other age-associated genes will be characterized for their properties (e.g. production of cytokines, chemokines, growth factors and responsiveness to pro- and anti-inflammatory stimuli). Furthermore, we will evaluate the capability of aged astrocytes to support proliferation/survival/differentiation of NSCs into their progenies. This study will deepen our knowledge about the contribution of the astrocytes in the age-related decline of adult neurogenesis.

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RESEARCH LINES

- DNA topoisomerase 1 and gene expression
- Epigenetic control of gene expression
- *S. cerevisiae* rDNA locus regulation
- *S. cerevisiae* aging

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RESEARCH ACTIVITY

How the gene expression is regulated is fundamental to most aspects of biology. Research in our laboratory focuses on understanding how gene expression is regulated at the transcription level, particularly studying the interactions between protein and DNA as they occur in vivo: in the chromatin. Our experiments are mostly performed in the yeast Saccharomyces cerevisiae, and our attention is focused on the ribosomal DNA (rDNA) locus and the biological function of DNA topoisomerase 1 in vivo.

Regulation of gene expression: transcriptional regulation and epigenetics. We are studying proteins that regulate transcriptional silencing and genome stability (Sir2p, yeast sirtuins, Top1p, histones) using classical and modern molecular biology techniques. Our present studies focus on yeast mutants with reduced histone proteins, altered epigenetic modifications and metabolic pathways (1). Dependence on genetic and epigenetic regulations during aging processes are also objects of our interests. The purpose of the studies of our lab is to discover more about the ways that cells regulate transcription. Our findings will increase our perception of how chromatin dynamics influence gene expression and maintain the genome integrity. Several factors we study have counterparts in higher eukaryotes signifying that our discoveries may provide insight into mechanisms that regulate gene expression also in human cells.

DNA topoisomerase I studies. For more than thirty years, the lab has engaged in the study of DNA topology and DNA topoisomerase I functions in eukaryotes. Our interest is the biological function of DNA topoisomerase 1 in vivo using yeast Saccharomyces cerevisiae as a model system. Recently, we discovered the new capability of DNA topoisomerase 1 to act as scaffold protein (2, 3) and studies on different genes where with topoisomerase 1 engagement are ongoing.

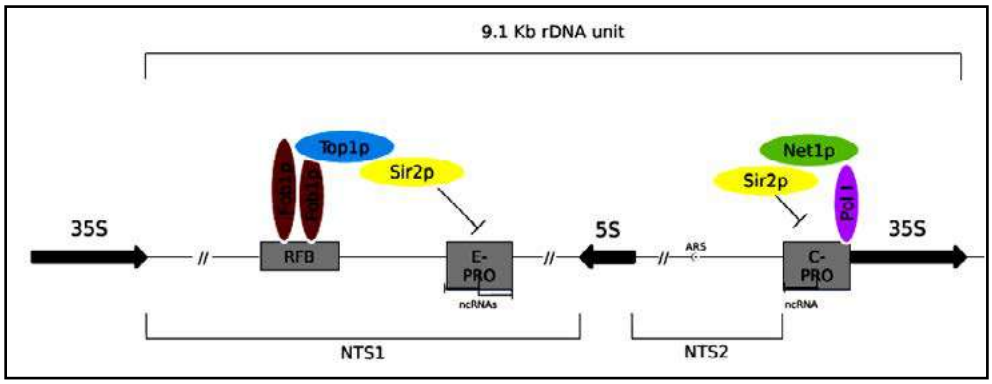

Figure. Top1 Scaffold activity at rDNA of Saccharomyces cerevisiae. Sir2p recruitment by Top1 allows silencing of RNA polymerase II transcription at cryptic promoters.

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Antonella
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RESEARCH LINES

- Cellular mechanisms in monogenic forms of ASD caused by misfolding mutations in synaptic cell adhesion proteins
- Rescue strategies for impaired trafficking of synaptic proteins

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RESEARCH ACTIVITY

Our research interest focuses on mutations in genes encoding for cell adhesion synaptic proteins and linked to Autism Spectrum Disorders (ASD). ASD are neurodevelopmental syndromes characterized by behavioural deficits and a strong genetic background. Among the risk genes several encode for molecules that play a role in maturation and functioning of the synapses. Neuroligins (NLGNs) are cell adhesion molecules anchored at the post-synaptic membrane, where they act as synaptic organizers. The first mutation in NLGN genes associated with ASD has been found in Neuroligin3 (NLGN3) and it represents the reference mutation in the field, since 2003. It results in the amino acid substitution Arg451Cys in the extracellular domain of NLGN3 which causes a local misfolding along with the retention of the mutated protein in the endoplasmic reticulum (ER) and its reduced trafficking to the cell surface.The accumulation of misfolded proteins in the ER can lead to the activation of the Unfolded Protein Response (UPR), which is a hallmark of several neurological disorders, such as neurodegenerative diseases. Our work establishes the first evidence between the retention of the R451C NLGN3 in the ER and the activation of UPR both in vitro, in inducible PC12 cell lines, and in vivo, in the cerebellum of the Knock-In (KI) mouse model of ASD carrying the R451C mutation in the endogenous NLGN3 gene (1,2). In particular, we found higher expression of ER markers specifically in the cerebellar Purkinje cells of the KI mouse (fig.1) and synaptic transmission alterations that resulted to be UPR-dependent.Our data are part of a large body of evidence correlating the role of UPR and the regulation of synaptic functions. We aim to "correct" the autistic-like behaviors observed in the R451C NLGN3 KI mouse model by identifying a pharmacological strategy to rescue altered protein folding of mutant NLGN3, in order to favor its trafficking from the ER to the cell surface and thus reducing the activation of UPR.

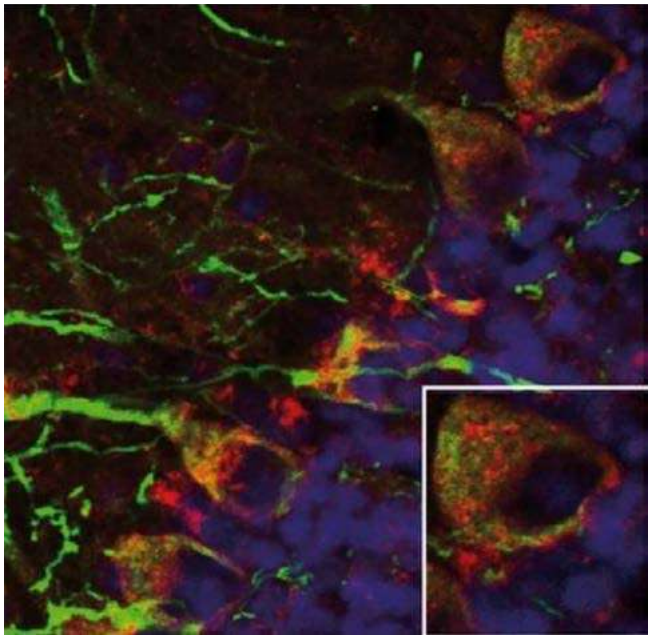

Figure. Immunofluorescence staining of cerebellar slices from R451C KI mice. Neuronal marker (green), ER marker (red), nuclei (blue). In the zoomed square, the cell body of a Purkinje cell is shown with high intensity red staining.

We have developed an in vitro cell-based model system consisting of HEK293 cell lines stably expressing a truncated form of NLGN3, either WT or R451C, fused to a fluorescent protein. These cell lines produce a fluorescent and truncated NLGN3, either WT or R451C that is secreted by the cell, allowing the assessment of protein trafficking via the measurement of fluorescence levels in the culture medium. Cell lines expressing mutant-fluorescent-NLGN3 present a drop of around 50% in the secretion of the protein in the medium compared to the WT-expressing cell lines (3).
Screening of a library of compounds is providing candidate compounds to be tested in vitro and in vivo.
These results highlight cellular mechanisms underlying a monogenic form of ASD characterized by the retention of a misfolded protein and offer an easy-to-use system to select pharmacological compounds to revert the cellular phenotype characterized by the ER-retention of R451C NLGN3 or other disease-associated misfolded proteins.

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Maria Egle **De Stefano**

Associate Professor

ORCID

RESEARCH LINES

- Neurodevelopmental alterations in the Duchenne Muscular Dystrophy
- Cytoskeletal dynamics of axonal growth and regeneration
- Neuroinflammation in aging and neurodegenerative diseases

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RESEARCH ACTIVITY

In the past two decades, the research activity of Prof. Maria Egle De Stefano has been mainly focused on the neurodevelopmental alterations associated with Duchenne Muscular Dystrophy. This is a severe X-linked myodegenerative disease caused by the defective expression of full-length dystrophin, a cortical cytoskeletal protein of 427 kDa (Dp427). The protein is highly expressed in muscles, but has also been revealed in a number of selected neuronal populations of both central and autonomic nervous systems.

Lack of Dp427 and of a variable number of its short isoforms (all encoded by the same gene) determines a high incidence of significant neurological disorders, the severity of which depends on the type, number and location of mutations within the DMD gene. Along these years, Prof. De Stefano's group has demonstrated that Dp427 is implicated, directly and/or indirectly, in a number of neurodevelopmental and neurophysiological activities, among which: clustering of specific subtypes of nicotinic acetylcholine receptors at post-synaptic specializations in sympathetic superior cervical ganglion neurons and their electrophysiological properties; sensitivity of these same neurons to the Nerve Growth Factor, probably by stabilizing its high affinity receptor TrkA; cytoskeletal dynamics during axonal growth and regeneration (Fig. 1); stabilization and/or physiological activity of glucocorticoid receptors in hippocampal neurons, possibly contributing to the hippocampal regulation of stress response. In the past three years, an involvement of this cytoskeletal protein in aspects of adult hippocampal neurogenesis and in the fate determination of retinal ganglion cells in late retinogenesis has been highlighted.

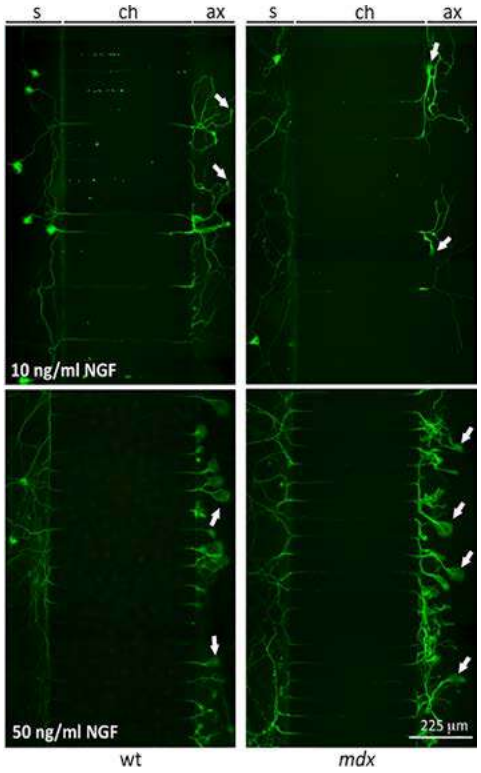

Figure. Wild type (wt) and dystrophic (lacking the Dp427) mdx mouse neurons cultured in the presence of either 10 or 50 ng/ml NGF, 22–24 h after axotomy. Neurons are immunolabeled for βIII-tubulin. In the presence of 10 ng/ml NGF, early axon regeneration in mdx mouse neuron cultures is dramatically reduced compared to wt. This difference is not observed when neurons are grown in the presence of 50 ng/ml NGF. White arrows indicate growth cones on which morphometric analysis was conducted. s: soma compartment; ch: micro-channels; ax: axon compartment.

This has brought to the latest venues of investigations related to the role of Dp427 in myelinogenesis of central (cerebellum) and peripheral (motoneuron) neurons during early post-natal dates and its impact in neuronal physiology. Another important aspect of Prof. De Stefano's research is related to the impact of acute and chronic neuroinflammation in neurodegenerative diseases (i.e. Parkinson's disease) and aging.

Recently, a new Italian-Spanish collaborative project has begun on a peculiar animal model, the *Octodon degus*, characterized by the spontaneous development of Alzheimer's Disease histopathological hallmarks (neurofibrillary tangles, amyloid plaques), cognitive impairment, memory damage, and altered social skills, typically associated to the pathology.

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RESEARCH LINES

- Nanobiomedicine and Nanotoxicology
- Micro and nanoplastics
- Cell death
- Exosomes and microvesicles

STAFF | COLLABORATORS

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GRANTS

2019-21. PON: Green chemistry nanotechnologies for the sustainable protection of plants: NEMESI.

RESEARCH ACTIVITY

Nanobiomedicine and Nanotoxicology. The research is approached by different perspectives: Characterization of nanomaterials. Nanoparticles and their interaction with biological systems. Safety of nanoparticles and nanomaterials in cells, tissues and organisms. Nanotoxicology issues regarding engineered nanoparticles. Biomedical application of engineered nanoparticles. Study design assessment of nanomaterials in agri/food/ products. Assessment of nanoproduct based food on animal and human health and environmental impact.

Micro and nanoplastics. Detection of microplastic in the environmental matrices. Qualitative and quantitative characterization of the nano and microplastics isolated from matrices and from organisms. Analysis of the presence and distribution inside vertebrate and invertebrate marine organisms and the dynamics of bioaccumulation. Evaluation of the physiological and pathophysiological response to the nano and microplastic exposure.

Cell death. Apoptosis, necrosis and autophagy are studied from the morphological and physiological points of view. In particular phagocytosis of apoptotic cells and bodies and the immunogenic cell death in particular conditions like the photodynamic therapy are studied.

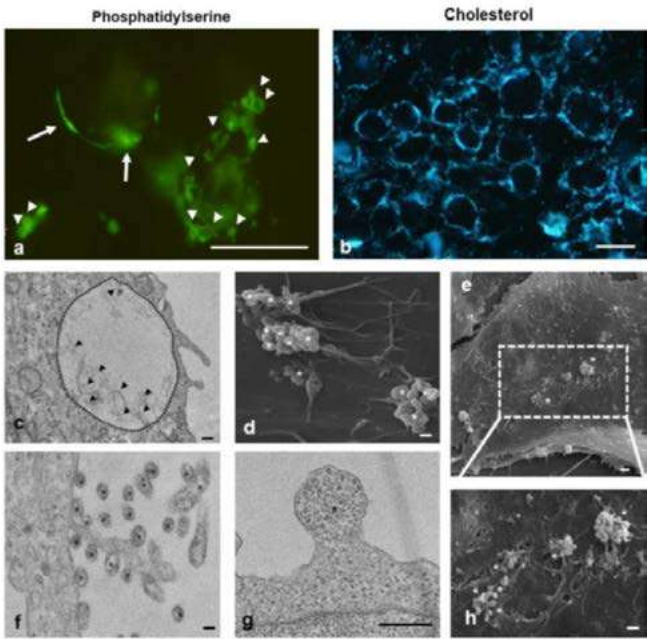

Figure. a,b: FITC-conjugated annexin-V and cholesterol (filipin) on plasma membrane of U-87 MG cells. Bar=10 µm. c,f,g TEM, d,e and h SEM images of EXOs and MVs from U-87 cells. EVs=arrow head; multivesicular bodies=dashed black line; MVs=asterisks. Bar = 200 nm

Exosomes and microvesicles. The studies on the extracellular vesicles (EVs), microvesicles (MVs) and exosomes (EXOs), are the most recent research field. The research interest is focused on the extracellular-mediated vesicle communication in some metabolic multifactorial abnormalities, such as hyperglycemia, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, etc., that characterize metabolic diseases, whose progression and pathological features rely on the occurrence of local or systemic inflammation. MVs and EXOs, can transport proteins and nucleic acids to adjacent cells or to distant organs. Currently we are isolating MVs and EXOs from different sources, glioblastoma cells, macrophages, and neuronal stem cells. MVs and EXOs are characterized by cryo-TEM and by SEM and dynamic light scattering (DLS) analysis. The characterization of the cargo of the EVs and the main membrane proteins are exploited as diagnostic markers of brain tumours. Finally the EVs ability to interfere with macrophages polarization and inflammation is studied as well.

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3. Reza M, Dini L, et al. Necrotic, apoptotic and autophagic cell fates triggered by nanoparticles. Autophagy, 2019, 15:14-33

Alessandro
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ORCID

RESEARCH LINES

- m^{6}A RNA modification
- Leukemia

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GRANTS

EU H2020-MSCA-ITN-2018.
PI: Alessandro Fatica

RESEARCH ACTIVITY

Recent studies have uncovered an important role for RNA modifications in gene expression regulation, which led to the birth of the epitranscriptomics field.
It is now acknowledged that RNA modifiers play a crucial role in the control of differentiation of stem and progenitor cells and that changes in their levels are a relevant feature of different types of cancer. One of most studied RNA modifications with a well-define role in gene expression regulation is the N6-methyladenosine (m6A), which is the more abundant internal modification in mRNA, regulating the expression of the latter at different levels, from maturation to translation. Our lab is involved in understanding the cellular processes it regulates, its mechanism of action and its involvement in leukemia.
In particular, our aim is to identify a) the RNA targets (coding and non-coding) of this modification with a potential role in leukemia; and b) specific regulatory proteins of the METTL3 complex in leukemia cells.

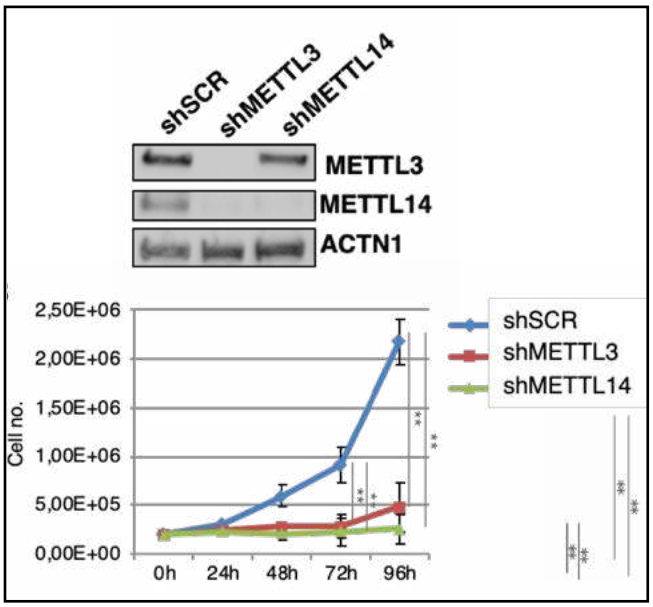

Figure. Upper panel: Western blot analysis of METTL3 and METTL14 levels in the leukemia cell line K562 infected with lentivirus expressing shMETTL3, shMETTL14 and shSCR. Lower panel: Growth curve of K562 infected cells after puromycin selection, n=3.

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2. Ianniello Z, Fatica A. "N6-Methyladenosine Role in Acute Myeloid Leukaemia". Int J Mol Sci. 2018;19. pii: E2345.
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Marco
Fidaleo
Researcher

ORCID

RESEARCH LINES

- Role of cell-derived microvesicles (CMV) in inflammation
- Microbiota and inflammation
- Role of nutrients in cancer
- Interspecies comparison of cancer resistance mechanisms

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GRANTS

GR-2016-02364891 Giovani Ricercatori. "Toward a personalized approach in ulcerative colitis: integrating genetics with microbiota analysis to select therapy and predict individual response"

RESEARCH ACTIVITY

Role of cell-derived microvesicles (CMV) in inflammation. Inflammation is associated with neurodegeneration. In Amyotrophic Lateral Sclerosis (ALS), characterized by selective death of motor neurons in the motor cortex and spinal cord, inflammation plays a crucial role and involves both components residing within the central nervous system (microglia) and immune system cells (monocytes). These can differentiate towards both non-inflammatory or inflammatory types thus contrasting or exacerbating the effects of the disease. In addition to soluble factors, classical mediators, it has been recently established the role of CMV in inflammatory processes linked with neurodegeneration. We are interested in unravelling the complex interaction/communication between cells mediated by CMV that leads to neuroinflammation.

Microbiota and inflammation. The microbiome has a potential role in the development, progression, and treatment of Inflammatory Bowel Disease (IBD). The interaction between bacteria and the intestine barrier and the possible inflammation generated by an imbalance in the microbiome has been a subject of considerable interest and enquiry. Furthermore, the individual genetic background can determine a genetic predisposition. The aim of our research is to understand the link between genetics, microbiota and pathogenesis and to identify the cellular mechanisms involved.

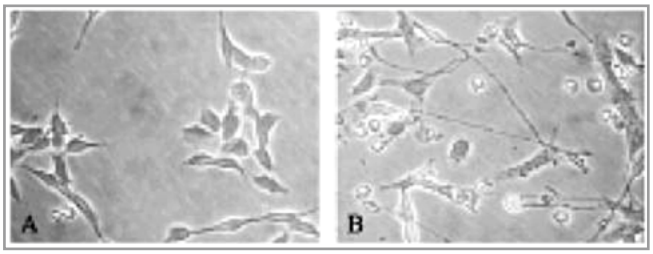

Figure. SH-SY5Y cells untreated (A) and administered with retinoic acid (B). SH-SY5Y are cells isolated from human neuroblastoma and can be prompted to differentiate in motor neurons when treated with retinoic acid. They are used as a model for studying neurodegenerative diseases. Panel A shows undifferentiated cells while panel B shows early-stage differentiated cells.

Role of nutrients in cancer. Cancer cells acquire a specific metabolism that differs from that of the cells they originated from. The transformation affects signal transduction pathways linked to nutrient sensors (such as mTOR) thus altering downstream processes including autophagy. The latter is also linked with inflammatory processes. We have an interest in discovering how altered metabolism can lead to the high resistance observed in cancer and the possible role in its onset.

Interspecies comparison of cancer resistance mechanisms. Peto's paradox states that "the incidence of cancer does not appear to correlate with the number of cells in an organism". Indeed, If the probability of transformation between two different species were the same, this would imply that larger animals, being formed by a greater number of cells, should generate more tumours than smaller animals. Observations do not confirm this hypothesis. Scientific research is highlighting as different species have selected specific mechanisms of resistance to carcinogenesis during their evolution thus opening to a new question about cancer: what does NOT determine tumour onset? Biological diversity allows us to explore systems and mechanisms perfectly adapted in nature. Studying these types of different "perfections" inspires us to unravel the unknown and innovate. Observing and comparing is our method.

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Mauro
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ORCID

RESEARCH LINES

- Role of cyclic nucleotides/ phosphodiesterase isoforms (PDE's) pathway in areas of the central nervous system (basal ganglia) involved in movement disorders (Parkinson, Dystonia)
- In vitro effects of PDE inhibitors in carcinoma cell proliferation;
- Expression, oligomeric assembly and functional role of PDE5A isoforms in various biological systems.

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RESEARCH ACTIVITY

In vitro effect of PDE inhibitors in carcinoma cell proliferation. PDE4 are major members of a superfamily of enzymes (PDE) involved in the modulation of intracellular signaling mediated by cAMP. Recently, a significant body of work has underscored their involvement in different types of cancer, but with no attention paid to liver cancer. The present study investigated the effects of two PDE4 inhibitors, rolipram and DC-TA-46, on the growth of human hepatoma HepG2 cells. Treatment with these inhibitors caused a marked increase of intracellular cAMP level and a dose- and time-dependent effect on cell growth. Results demonstrated that treatment with PDE4 inhibitors affected HepG2 cell cycle and survival, suggesting that they might be useful as potential adjuvant, chemotherapeutic or chemopreventive agents in hepatocellular carcinoma.

Functional role of cyclic nucleotide pathway in a DYT1 dystonia mouse model. DYT1 Dystonia is a movement disorder caused by a 3-bp deletion (Δgag) in the TorsinA gene. Our work using a DYT1 model overexpressing mutated torsinA, demonstrates the opposite changes in the levels of the catabolic cAMP enzyme, PDE10A, occurring in the direct and indirect pathways of the basal ganglia. This imbalance could be responsible for the improper focus of the movements in DYT1 dystonia suggesting the involvement of striatopallidal and striatonigral neuronal subtypes in the pathophysiology of dystonia. We study the changes of the A2a receptor, as a mediator of cAMP synthesis, and of PDE10A levels using a DYT1 knock-in model reproducing the human mutation (Tor1a+/Δgag).The DYT1 knock-in mouse also displayed opposite PDE10A variations and, moreover, the expression of the A2a receptor showed opposite changes in striatopallidal and striatoentipeduncular/nigral circuits, similarly to the alterations in PDE10A. Our data suggest that an alteration of the cAMP pathway in the striatal direct and indirect circuitries can be a general mechanism in the pathophysiology of DYT1 dystonia, and that the activation of adenylate cyclase via the up regulation of the A2a receptor could be a compensatory mechanism.

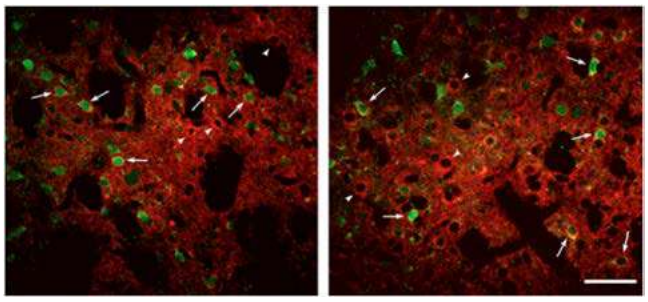

Figure. Confocal laser-scanning microscopy of double-labeled immunofluorescence images for PDE10A and Enkephalin in normal (left) and dystonic mice model (right). PDE10A is visualized by red-Cy3 fluorescence while Enkephaline is in green-Cy2 fluorescence. White arrows show medium spiny neurons positive for both PDE10A and Enkephalin, whereas white arrowheads point to neurons positive for PDE10A, but negative for Enkephaline. Scale bar, 50μm.

The oligomeric assembly of PDE5: A putative role in the regulation of function. PDE5 is the molecular target of several drugs used to treat erectile dysfunction and pulmonary hypertension. Despite its medical relevance, the PDE5 macromolecular structure has only been solved for the isolated regulatory and catalytic domains. The definition of the quaternary structure of the full length PDE5 (MmPDE5A1), produced in large amounts in the yeast Kluyveromyces lactis, could greatly enhance the knowledge on its assembly/allosteric regulation. Small-angle X-ray scattering (SAXS), analytical ultracentrifugation, size exclusion chromatography, native polyacrylamide gel electrophoresis and western blot were used to assess the assembly of PDE5A1. The MmPDE5A1 isoform is a mixture of dimers and tetramers in solution. We also report data showing that dimers and tetramerso coexist in vivo in platelets, containing high levels of PDE5. The assembly of PDE5 in tetramers in platelets, besides the dimers, opens the possibility of alternative assembly/allosteric regulation of this enzyme, as a component of large signaling complexes, in all cellular districts in which PDE5 is present.

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Giuseppe
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ORCID

RESEARCH LINES

- Genetic and epigenetic regulation of neural stem cells
- Molecular mechanisms of neural stem cell aging
- Neural stem cell response to ionizing radiation

STAFF | COLLABORATORS

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Full Professor (Sapienza)
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(Kyushu University, Japan)

GRANTS

2021-23. MAECI Italia - Giappone (PGR01279). The proteoglycan Tsukushi in neural stem cells and hydrocephalus: cellular and pathological mechanisms.

RESEARCH ACTIVITY

Current research in my lab is focused on investigating the molecular mechanisms that regulate neural stem cell fate, using in vitro culture systems of neural stem cells derived from the embryonic and the adult mouse central nervous system.
Over the last few years, we have studied the intrinsic mechanisms controlling neural stem cell identity during neural development, and those underlying the progressive decline of neural stem cell function during aging. This work has led to the identification of transcriptional and epigenetic changes in homeobox genes occurring in neural stem cells and potentially associated with neural stem cell modulation during development and aging. In particular, we have shown that Hox genes are differentially regulated, at the transcriptional and epigenetic level, in neural stem cells of the developing rostral and caudal nervous system.
This differential regulation is stably retained during neural development and in the adult brain, which may be important for the maintenance of neural stem cell fates throughout life[1]. Furthermore, we have found that another homeobox gene, Dbx2, is upregulated, and its epigenetic regulation is altered, in neural stem cells of the aged mouse brain.
Dbx2 overexpression in neural stem cells from young adult mice can phenocopy some of the effects associated with aging, such as the inhibition of neural stem cell proliferation[2].
We are currently investigating the molecular mechanisms regulating Dbx2 expression, and mediating its function, in neural stem cells. We are also interested in studying the response of neural stem cells to extrinsic factors affecting the neural stem cell niche, such as extracellular signaling pathways or aging, and ionizing radiation[3].

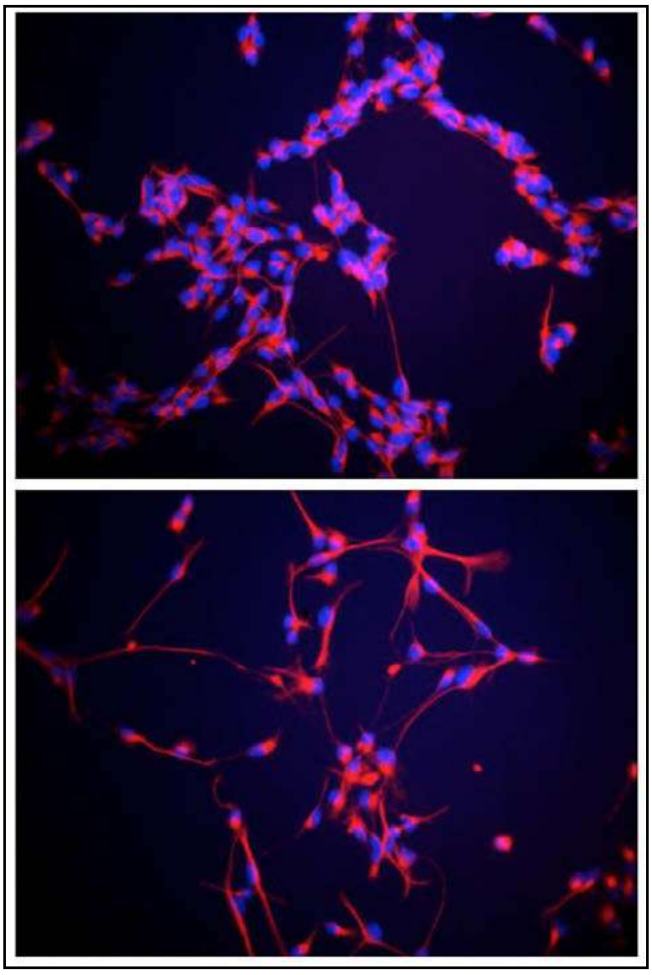

Figure. Transgenic neural stem cultures derived from the young adult mouse brain, which express either the Green Fluorescent Protein as a control (upper panel), or the homeodomain protein Dbx2 (lower panel). Elevated Dbx2 expression levels cause a reduction in the growth of neural stem cell cultures. Red staining shows the expression of the neural stem cell marker Nestin. Blue staining shows cell nuclei.

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Cristina
Mazzoni
Associate Professor

ORCID

RESEARCH LINES

- Study of genes involved in ageing and cell death in the yeast S. cerevisiae
- Heterologous protein production
- Study of molecules of pharmacological interest
- Use of model systems as a tool for the study of the effect of stress on aging and related diseases

STAFF | COLLABORATORS

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Prof. Joris Winderickx,
Functional Biology, (Heverlee, Belgium)

RESEARCH ACTIVITY

Our research activity focused on the use of yeast as a model to study ageing and cell death. Three different types of aging processes can be studied in yeast: RLS (Replicative Life Span), that measures the number of generations performed by a single cell in the life, CLS (Chronological Life Span), which measures cell viability when cells stop dividing (stationary phase) and CILS (Clonal Life Span), which studies the way the colony develops in the absence of other interferences.

The relationships between aging and cell death are far from clear, but it is well known that aged cells accumulate ROS and damaged molecules, show altered mitochondrial morphology and enter Programmed Cell Death. Regulated Cell Death can also be induced by external or internal triggers (Figure, upper panel). Among the internal triggers of cell death and early ageing there are mutations in cellular fundamental processes such as RNA degradation, which is a research topic of our laboratory (Figure, lower panel).

According to the theory of oxidative stress of aging, proposed for the first time in 1954, aging is related to the accumulation of cellular damage triggered by ROS produced during normal cellular metabolism. Therefore, during the aging process, antioxidants decrease, oxidative damage increases and, consequently, the possibility of disease and death. Oxidative stress has been implicated in the progression of age-related diseases.

We exploit the power of yeast molecular genetics to elucidate the molecular basis of both aging and cell death induced by expression of human proteins involved in diseases. The humanized yeast models can help in the identification of molecular pathways and processes contributing to these diseases.

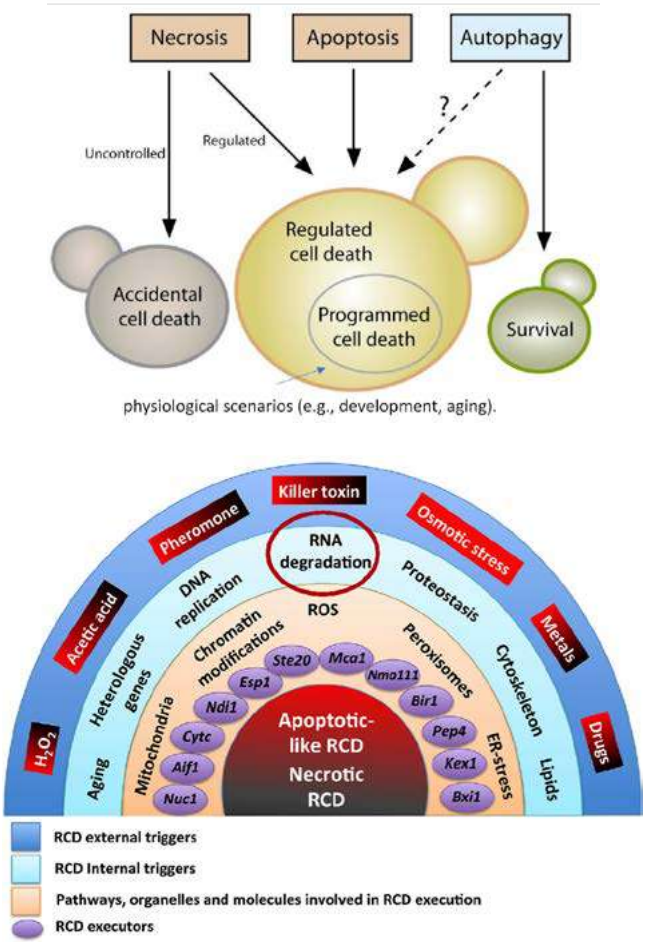

Figure. Upper panel: different scenario leading to cell death. (Carmona et al., 2018 Microbial Cell). Lower panel: External and internal triggers of cell death in yeast. (Falcone and Mazzoni, 2016 Cell Mol. Life Sci)

References

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RESEARCH LINES

- Temporal dynamics of experience dependent plasticity
- Neural circuits underlying memory stabilization

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Researcher (C.N.R. - I.B.F.)

GRANTS

2019. Human Brain Project Infrastructure Voucher Programme Call 2018. Mapping Brain Circuits in Spatial Navigation (MAPS).
P.I. Andrea Mele
2017-2020. NARSAD
The Neurobiological basis of the Spacing effect as a tool to identify new pharmacological targets for cognitive deficits
P.I. Andrea Mele

RESEARCH ACTIVITY

Learning and memory are two of the most important capabilities of our mind. They allow the acquisition of new knowledge and the retention and reconstruction of this knowledge over time. Our group has demonstrated that complex associative learning and memory requires the activation not only of the medial temporal lobe-associated brain structure but also that of different components of the striatal complex (Ferretti et al., 2010).
Using a comparative approach, we investigated molecular processes underlying memory formation in the hippocampus and in the striatal complex demonstrating striking differences between the two brain regions suggesting that memory consolidation depends on molecular processes with complex spatiotemporal dynamics (Capitano et al., 2016a; Capitano et al., 2016b). We are currently working on the functional relationship between the hippocampus and the striatum in learning and memory and how these circuits support different forms of learning.

Future research
We aim to discover the neural circuits and molecular mechanisms that support learning and memory in health and disease. In the long term our findings could help the refinement of theoretical models, and may be insightful for developing new theories on the biological mechanisms underlying learning and memory as well as for the development of new therapeutic strategies for mental illness.

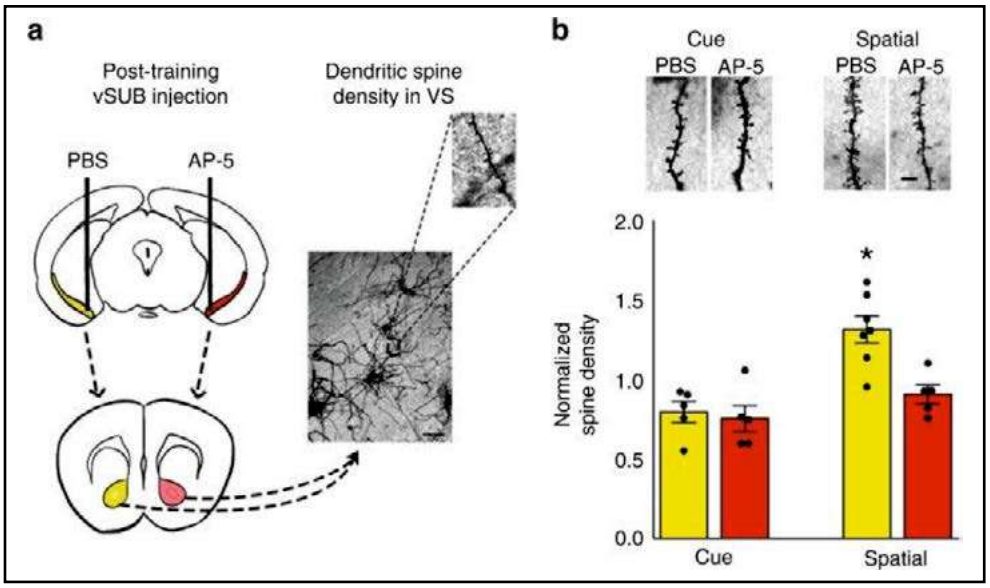

*Figure. Spatial learning-induced increase in VS spine density is vSUB-dependent. a Schematic representation of the experimental design. Scale bar: 50 µm. b Representative microphotographs of dendritic segments of a MSN in the VS for each experimental condition. Mean dendritic spine density/micrometer for cue and spatial trained mice was normalized to naïve mice. Spatial training significantly increased spine density in the VS ipsilateral to the vehicle-injected vSUB as compared to cMWM trained mice. No change was observed in the AP-5 administered hemisphere. Scale bar: 5 µm. Histograms represent mean ± SEM; *p < 0.05 spatial vs cue (Tukey) (modified from Torromino et al., 2019).*

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Maria Elena
Miranda Banos
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ORCID

RESEARCH LINES

- Cellular mechanisms of neurodegeneration FENIB
- Monoclonal antibodies to study alpha-1 antitrypsin

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Full Professor (UCL, UK)
Juan Perez Rodriguez,
Full Professor (Univ. of Malaga, Spain)

GRANTS

Grant Pasteur Institute - Cenci Bolognetti Foundation (Italy),
Cellular pathways involved in the toxicity of neuroserpin polymers that cause dementia FENIB (call 2018, under 45).

RESEARCH ACTIVITY

We study a group of protein conformational diseases caused by polymerisation of mutant serpins (serine proteinase inhibitors), specifically the neuronal protein neuroserpin and the hepatic serpin alpha-1 antitrypsin. The mechanism of inhibition of serpins requires a high molecular flexibility that renders them very sensitive to destabilising mutations. The mutant variants undergo polymerisation within the endoplasmic reticulum of the cell of synthesis, which prevents their normal trafficking and secretion. This leads to disease with both gain- and lack-of-function phenotypes, due to intracellular polymer accumulation and lack of active serpin in the place of action, respectively.
In the case of neuroserpin, polymerisation causes a very rare neurodegenerative condition called familial encephalopathy with neuroserpin inclusion bodies (FENIB), with an onset of disease that correlates to polymerisation propensity of each variant. We have developed a cell culture model consisting in mouse neural progenitor stem cells overexpressing wild type or polymerogenic neuroserpin, which can be differentiated to neurons in vitro. We have shown for the first time that neuroserpin polymers cause oxidative stress and this is balanced by upregulation of antioxidant genes, while pharmacological block of these defences causes apoptosis of neurons containing polymers (1). Our current work also shows that overexpression of polymerogenic neuroserpin causes mitochondrial alterations, changing their cellular distribution and causing a decrease in the inner membrane potential. Mitochondrial mislocalisation is enhanced by prooxidant molecules, is rescued by antioxidants, and correlates with shorter neurites. These results highlight the role of oxidative stress and mitochondrial damage in FENIB.
In alpha-1 antitrypsin deficiency, polymerisation of the mutant protein leads to the lack of active alpha-1 antitrypsin in the lungs, causing emphysema, while polymer retention within hepatocytes causes liver disease. We have developed a set of conformation-specific and functional monoclonal antibodies against alpha-1 antitrypsin that we have used in collaboration to study polymer formation and structure, and the role of these polymers in disease (2, 3).

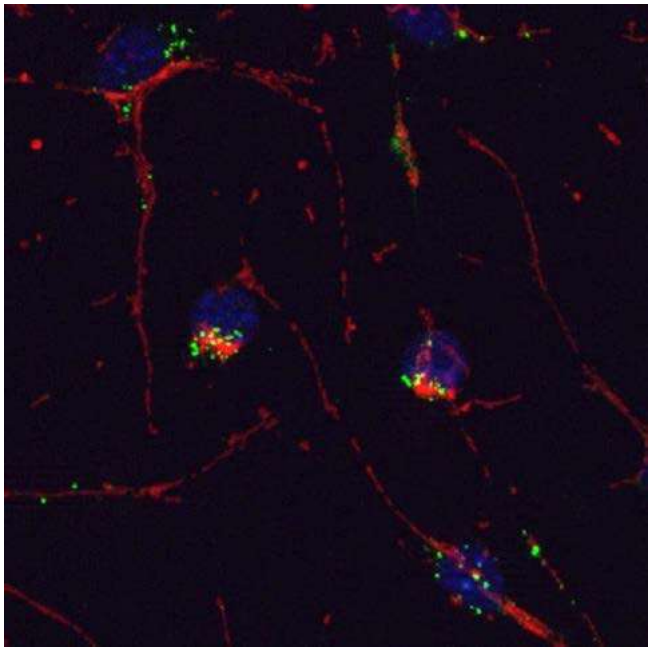

Figure. Mouse neural progenitor stem cells overexpressing mutant G392E neuroserpin, differentiated to neurons in vitro and co-stained for neuroserpin polymers (monoclonal antibody 7C6, green) and mitochondria (anti-Tom20, red). DNA is stained with DAPI (blue).

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Giancarlo
Poiana
Researcher

ORCID

RESEARCH LINES

- Extracellular vesicles in neural stem cell differentiation.
- Transcription factors regulating proliferation and differentiation of neural stem progenitor cells.

STAFF | COLLABORATORS

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Emanuele Cacci,
Assoc. Professor (Sapienza)
Giuseppe Lupo,
Assoc. Professor (Sapienza)

RESEARCH ACTIVITY

Extracellular vesicles in neural stem cell differentiation. Extracellular vesicles (EV), such as exosomes, can play a role in cell-cell communication during neural development, and could influence self renewal and differentiation of neural progenitors, by the transfer of proteins and nucleic acids to target cells. NSPCs from embryonic mouse spinal cords can release EVs among which exosomes are present. We demonstrated that EVs produced by differentiated neural progenitor cells can influence the phenotype of target cells; in particular, they can stimulate differentiation of proliferating NSPCs. Such a treatment drives NSPCs differentiation towards an astrocytic phenotype.

Egr1 and EGF signaling in the regulation of adult neural stem/progenitor cell proliferation and differentiation. Egr1 is an immediate early gene that encodes for a transcription factor that can bind to the promoter of several genes involved in a wide variety of physiological and pathological events. Its activity levels are modulated by several extracellular signals, among which is Epidermal Growth Factor (EGF). As Egr-1 also regulates neuronal differentiation, we studied the role played by Egr1 in controlling proliferation and differentiation of NSPCs from the subventricular zone (SVZ). In the presence of basic fibroblast growth factor (bFGF) and EGF, Egr-1 expression is upregulated and NSPCs are maintained in a proliferative state. EGF is specifically required for Egr-1 upregulation, and its removal from the medium promotes Egr1 downregulation in NSPCS, their exit from the cell cycle and their differentiation towards neuronal and glial differentiation. Egr-1 overexpression can revert cell proliferation decrease determined in NSPCs by EGF removal. This supports the hypothesis that Egr-1 supports cell proliferation of SVZ NSPCs downstream of the EGF-EGF receptor signaling pathway.

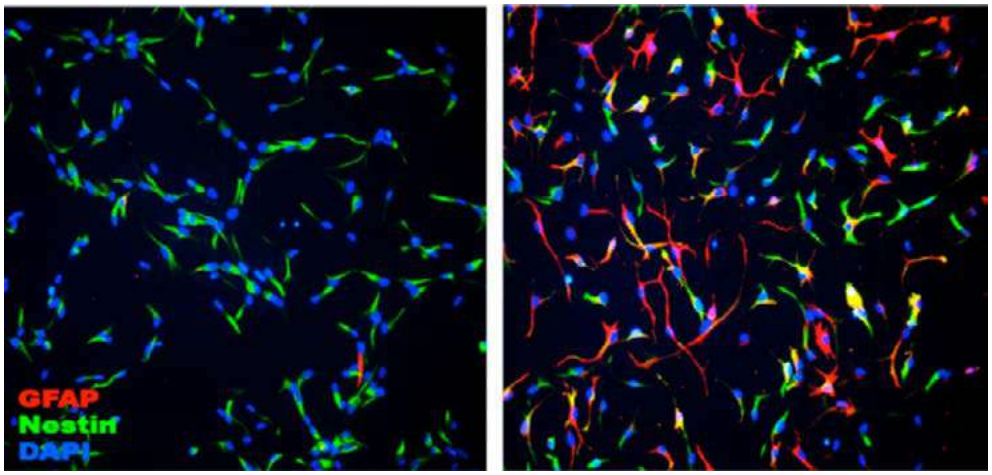

Figure. Neural stem progenitor cells derived from adult mouse brain subventricular zone and maintained in +EGF+FGF culture medium (left) and treated with extracellular vesicles from differentiated NSPCs. Nestin-positive cells (green); glial fibrillary acidic protein-positive cells (GFAP, red); nuclei are counterstained with DAPI (blue).

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RESEARCH LINES

- Neurobiology of the individual response to stress
- Neural circuits of spatial memory

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GRANTS

2019-2020. Human Brain Project (HBP) Voucher Programme. Mapping Brain Circuits in Spatial Navigation (MAPS). Co-PI.
2018 - 2019. ELIXIR-ITA CINECA - 15.000 CPU hours on Cineca High Performance Computing (HPC) platforms for "transcriptome profiling after different kinds of stress in rodents". PI: Arianna Rinaldi

RESEARCH ACTIVITY

Neurobiology of the individual response to stress
Exposure to highly stressful, life-threatening events, that elicit an intense response of fear and helplessness, causes a persistent and exaggerated stress-related reaction in some individuals, known as post-traumatic stress disorder (PTSD). Not all individuals exposed to trauma develop PTSD. It has been estimated that although lifetime trauma incidence in the general population ranges between 40-90%, lifetime prevalence for PTSD is about 7-14%. Although PTSD is one of the few mental disorders whose triggering cause is known, we have a very limited knowledge of the biological mechanisms underlying its development, and what differentiates resilient and susceptible individuals. As a result, no clearly effective pharmacological treatment, nor preventive strategy, or reliable biological markers are currently available.
To study the mechanisms underlying individual differences in stress resilience, we use a multidisciplinary and neural circuit-level approach, combining behavioral analysis, molecular biology, histology, imaging, chemogenetics, and bioinformatics, in preclinical models of stress. Our long-term goal is to understand the neural changes associated with exposure to stress and stress-related disorders, at the molecular and network level, in order to identify novel candidate targets for the prevention or clinical treatment of stress-related disorders, such as PTSD.

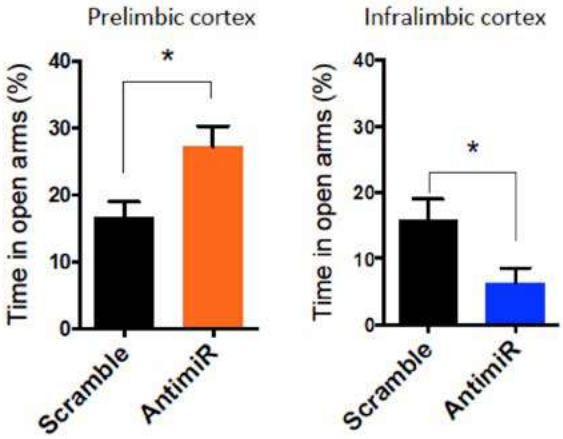

Figure. Inhibition of cluster miRNA-144/451a, in the either the prelimbic or the infralimbic subregion of the medial prefrontal cortex (mPFC) in CD1 mice, induced opposite effects on anxiety-like behavior, measured in the elevated plus maze (Rajendran & Rinaldi).

Neural circuits of spatial memory
Spatial navigation is one of the most common and conserved cognitive functions, as the ability to go from one place to another in a complex environment is essential for the survival of most animals. Spatial memory loss is an early clinical sign of Alzheimer's disease and other types of dementia. Despite the intense research effort poured into this field, we have not yet been able to clearly identify the cause (or causes) nor an effective cure for AD, while the number of people affected is increasing steadily.
We study the neural circuits involved in different types of spatial memory, in order to shed light on network dynamics of memory acquisition, consolidation and storage, in normal and pathological conditions. To this aim, we use behavioural analysis, pharmacology, imaging, chemogenetics and optogenetics.

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RESEARCH LINES

- Ubiquitin-proteasome system and mitochondrial function
- Microbiology and cultural heritage

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RESEARCH ACTIVITY

Our research field is the interplay between the ubiquitin proteasome system and the mitochondrial function in the yeast Saccharomyces cerevisiae. We demonstrated that the S. cerevisiae CSN complex, essential for vitality in multicellular organisms and critical for the turnover of key cellular proteins, is essential for cellular lipid homeostasis. Defects in CSN assembly or activity lead to decreased quantities of ergosterol and unsaturated fatty acids, vacuole defects, diminished lipid droplets size and to accumulation of endoplasmic reticulum stress. We also found that there is a cross talk between the ergosterol biosynthetic pathway and mitochondrial function: a low ergosterol level in the cells results in a loss of mitochondrial DNA with a consequent block of respiration, while a defect in respiration results in a re-localization of Erg27 enzyme, acting as a sensor of the mitochondrial state. We are now investigating the role of the CSN complex in lipid homeostasis and autophagy, using inhibitors of the CSN catalytic enzyme Csn5. We also study the microbiology of cultural heritage. The Etruscan tombs of the necropolis in Tarquinia are a unique hypogeal environment where to have a wider approach to the moonmilk, a nanorods deposition of calcium carbonate. We discovered its presence in the Tomba degli Scudi. Comparing the moonmilk microbial community of five Etruscan tombs, we are studying the microorganisms of these hypogeal environments to shed light on the possible mechanism of moonmilk deposition by this peculiar microbiota. The studies of bacteria able to produce or dissolve calcium carbonate could also have biotechnological applications in the field of biorestoration, biocleaning and biopreservation of cultural heritage objects, such as monuments, sculptures, frescos and paintings.

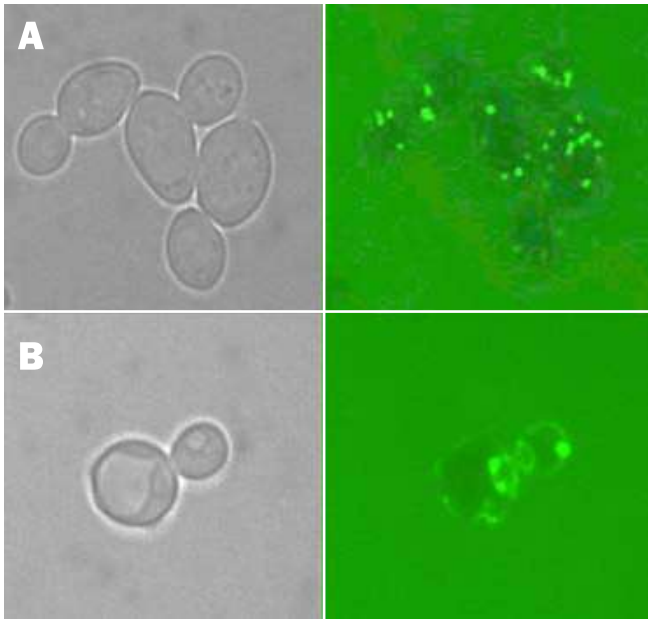

Figure. Upper panel: a protein of the ergosterol biosynthetic pathway in S.cerevisiae is a sensor of a mitochondrial dysfunction. Erg27-Gfp is re-localized from Lipid Droplets (A) to nuclear and cortical Endoplasmic Reticulum (B) following a block in respiration. Lower panel: SEM analysis (A) of moonmilk (B) from Tomba delle Sculture (C)

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RESEARCH LINES

- RNA and RNA-binding proteins
- Human iPSCs for disease modeling
- Neurodegenerative and neurodevelopmental diseases
- Neural development and differentiation

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GRANTS

Istituto Pasteur - Fondazione Cenci Bolognetti "Study of the role of RNA-binding proteins in the neurodegenerative disease Amyotrophic Lateral Sclerosis" 40.000€. PI: A. Rosa
Ricerca Finalizzata 2019 "Dissecting the role of HCN1 in Developmental and Epileptic Encephalopathy by exploiting patient-specific models of cerebral cortex development in vivo and in 3D cortical organoids" 449.500€. PI: S. Lodato; Co-PI: A. Rosa

RESEARCH ACTIVITY

My research goal is elucidating molecular mechanisms that underlie differentiation, development and neurodegeneration, with a particular focus on the role played by non-coding RNA molecules and RNA-binding proteins in these processes. During my PhD at Sapienza University and my post-doc at Rockefeller University (NY, USA), I have studied the function of microRNAs in blood differentiation and embryonic stem cells (a model system to recapitulate the very early stages of embryonic development), respectively. In 2009-2010 was appointed director of the Rockefeller University Stem Cell Derivation Core.

My present research lines are based on human induced Pluripotent Stem Cells (iPSCs), as a model system for the study of molecular mechanisms underlying neurodegenerative diseases in vitro. Human iPSCs are generated by the reprogramming of somatic cells via the ectopic expression of reprogramming factors. These factors are capable of radically changing the gene expression profiles of somatic cells, activating stem cell genes and repressing differentiation genes. In this way, the cells acquire the properties and potential of embryonic stem cells, including the ability to differentiate in vitro and in vivo in various derivatives of the three embryonic germ layers. Notably, iPSCs can be derived from patients carrying disease-linked mutations, modified by gene editing and differentiated into tissues of interest. Thus, they represent excellent model systems for the study of the molecular and cellular basis of genetic diseases.

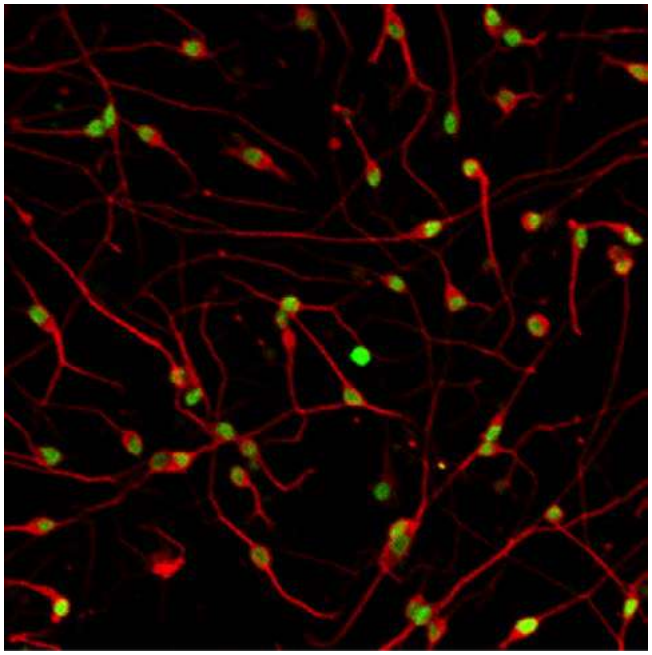

Figure. Immunostaining for the cranial motor neuron marker PHOX2B (green) and the pan-neuronal marker TUJ1 (red) in motor neurons derived from human iPSCs. From De Santis et al., 2018; 10.1016/j.scr.2018.04.012).

In the last few years, my laboratory has generated iPSC-based in vitro models of Amyotrophic Lateral Sclerosis (ALS) and Fragile X-Syndrome (FXS). We have raised a collection of iPSC lines with mutations in RNA-binding proteins (FUS, TDP-43, FMRP) by reprogramming and gene editing. We have also set up protocols for differentiating iPSCs to human motor neurons, cortical neurons and skeletal muscle cells (Figure). We have found that ALS iPSC-derived motor neurons recapitulate disease phenotypes in vitro and reported changes in the transcriptome, microRNA pathway and FUS interactome in ALS motor neurons. Moreover, my laboratory is developing novel tridimensional models of the nervous system by 3D bioprinting of neurons derived from human iPSCs.

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Giovanna
Serino
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ORCID

RESEARCH LINES

- Regulation of the ubiquitin proteasome pathway and its targets during plant development and in response to drought
- Regulation of flower development by light
- Crosstalk between drought and high light stress in plant development

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Qi Xie,
Group leader (CAS, Beijing, China)
Maura Cardarelli,
Researcher (CNR-IBPM)
Paola Vittorioso,
Researcher (Sapienza)

RESEARCH ACTIVITY

The research in my lab aims at understanding how environmental factors affect the molecular mechanisms regulating plant development. We focus on the Cullin-RING class of ubiquitin Ligases (CRLs), which regulate most plant physiological and developmental processes by controlling the half-life of key regulatory proteins. We use Arabidopsis thaliana as a model system because of its small size, fast life cycle, trim genome and easy genetics. We are currently pursuing three different but interconnected research lines:

Regulation of CRLs and their targets during plant development and in response to drought. We have recently discovered that the function of CRLs is differentially regulated during the seed-to-seedling transition, as well as in response to drought. CRLs are activated by the covalent binding to Nedd8 (a small ubiquitin-like protein) and deactivated by Nedd8 removal. Thus, by regulating Nedd8 availability, cells can simultaneously control the activity of >1000 different CRL complexes. Indeed, we have discovered that CRL neddylation increases during seed maturation and returns to a normal level upon seed germination. A similar phenomenon also occurs upon drought stress. We are currently characterizing the physiological relevance and the molecular pathways responsible for this regulation. This research line is in collaboration with Dr. Markus Wirtz.

Regulation of flower organs development by light. While we have a very clear picture of how light regulates flowering time, very little is known on how light affects the growth of flower organs. We have found that light -through the plant hormone auxin- is able to regulate the growth of stamens (the male reproductive organs), using a signaling cascade similar to the one employed by light and temperature to regulate the growth of another organ, the hypocotyl; this suggests that the same signaling module has been recruited multiple times during evolution to translate environmental stimuli into distinct adaptational growth processes. We are currently studying how light interconnects with other hormones such as brassinosteroids in this developmental process. This research line is in collaboration with Dr. Maura Cardarelli.

Crosstalk between drought and high light stress in plant development. CRLs are known to mediate both light and drought stress. As plants, when not grown in the lab, are subjected to a combination of different stresses, we are interested in understanding how plants can integrate signals form the two stresses and translate them in a unique output response through CRLs. This research line is in collaboration with Soyanni Hollness and Dr. Paola Vittorioso.

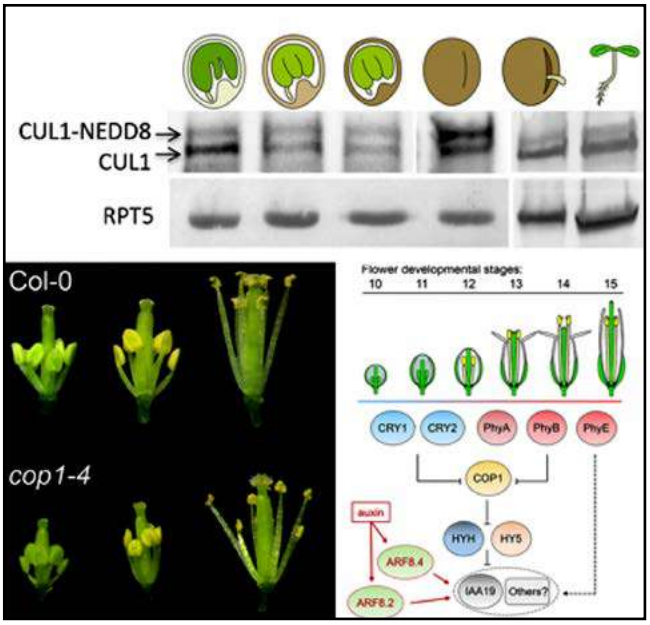

Figure. Upper panel: the neddylation of the typical CRL subunit CUL1 is regulated during the seed to seedling transition. RPT5, loading control. Lower panel: left, mutants of the COP1/SPA CRL ligase (cop1-4) have reduced stamen elongation compared to the wild-type (Col-0); right, model depicting the function of the COP1 containing CRL ligase in regulating stamen elongation downstream to photoreceptors (Phy A, B, and E and CRY 1 and 2) and upstream of the transcription factor HY5 and auxin.

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Gian Gaetano
Tartaglia
Full Professor

ORCID

RESEARCH LINES

- X-chromosome inactivation and phase separation
- RNA molecules prevent aggregation of TDP43
- RNA structure drives interaction with proteins and promotes phase separation
- Predictions of m6A effects on RNA structure
- Networks of the Circadian Rhythm
- Discovery of biomarkers in disease

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Alessio Colantoni,
Post-doc (Sapienza/IIT)
Elias Bechara, *Researcher (IIT)*
Alexandros Armaos, *Post-doc (IIT)*
Elsa Zacco, *Post-doc (IIT)*

GRANTS

ERC/ASTRA, 2.3 million.
PI: Gian Gaetano Tartaglia
H2020/INFORE, 0.5 million.
co-PI: Gian Gaetano Tartaglia
ERC/RIBOMYLOME, 1.5 million.
PI: Gian Gaetano Tartaglia
H2020/IASIS, 0.5 million.
co-PI: Gian Gaetano Tartaglia

RESEARCH ACTIVITY

My main focus is to understand the role played by RNA molecules in protein networks. Characterizing protein-RNA associations is key to unravel the complexity and functionality of mammalian genomes and will open up therapeutic avenues for the treatment of a broad range of human disorders. I aim to discover the involvement of RNA molecules in regulatory networks controlling protein production and I am interested in understanding mechanisms whose alteration lead to aberrant aggregation. We have recently observed that interaction between proteins and mRNAs induce feedback loops that are crucial in protein homeostasis. We also found that specific proteins and RNAs phase separate in the cytosol and nucleus when their abundance is significantly high and we are investigating how formation of large assemblies affects cell function. Examples of our research activity include the following lines:

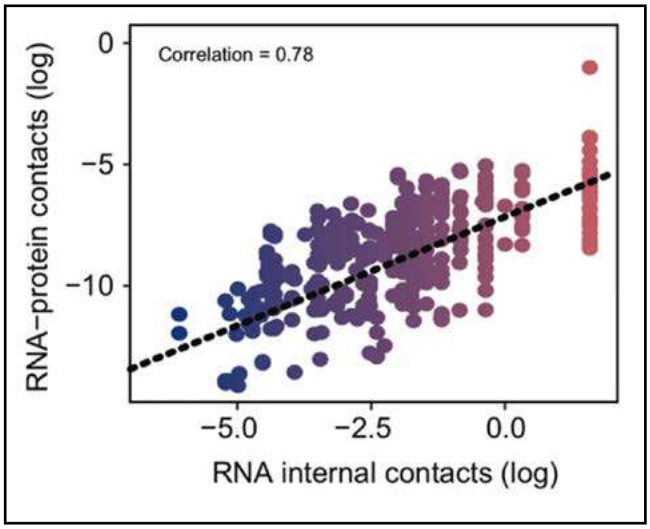

Figure. We observed that the structural content in RNA molecules is correlated to the number of protein interactions. This reveals the existence of a regulation level that directly links RNA to proteins especially for genes that are highly active in cellular processes.

On the Mechanism of Genetic Inheritance Associated with the X Chromosome. We analyzed the process of inactivation of the X chromosome and in particular the role of the RNA molecule called Xist (X-Inactive-Specific-Transcript), its main regulator. We studied the mechanism of action, structure and interactions of the Xist molecule. We observed that Xist acts as a "scaffold", it provides scaffolding and at the same time attracts lots of proteins to organize the "silencing" of the X chromosome. The interaction network is so great that Xist and its partner proteins form a structure that resembles a corpuscle, conceptually similar to a drop of oil in water. Commentary: https://tinyurl.com/Xist-tartaglia

RNA structure drives proteins crazy. We found that messenger RNA could act as a solubilizer, blocking the formation of protein aggregates that are potentially toxic to our organisms. In particular, we observed that the transcript coding for Heat Shock Protein 70 (HSP70) interacts with many proteins and has a strong effect on protein aggregation. We experimentally demonstrated for the first time that, under conditions of stress, HSP70 mRNA has the ability to promote the removal of the protein aggregates that are responsible for serious neuro-degenerative diseases such as Alzheimer's and Amyotrophic Lateral Sclerosis. Commentary: https://tinyurl.com/Structure-tartaglia

Microsatellites and disease. We found observed that non-coding RNAs hold together several proteins, like a sort of scaffolding that encourages their aggregation. We studied which proteins are bound to the CGG repeats in the FMR1 gene and identified in the brain of people with Fragile X Tremor Ataxia Syndome (FXTAS) disease one of these proteins, the TRA2A.TRA2A is involved in RNA splicing, a fundamental process that ensures that the pieces of the genetic code are in the right order and can produce the right protein; since in the pathology examined TRA2A tends to aggregation, it does not perform a correct splicing process, causing the alteration of many RNA that can not function properly. Commentary: https://tinyurl.com/FXTAS-tartaglia

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3. Sanchez de Groot N, Armaos A, Grana-Montes R, Alriquet M, Calloni G, Vabulas RM, Tartaglia GG. "RNA structure drives interaction with proteins" Nature Communications 2019; 10, 3246.

Ada Maria
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ORCID

RESEARCH LINES

- Neuron-glia interaction: cholinergic receptors in the control of myelinating glial cells development
- Cholinergic control of schwann-like adipose-derived stem cell differentiation: implication in peripheral nerve regeneration
- Effects mediated by muscarinic receptors in the glioblastoma cancer stem cells

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GRANTS

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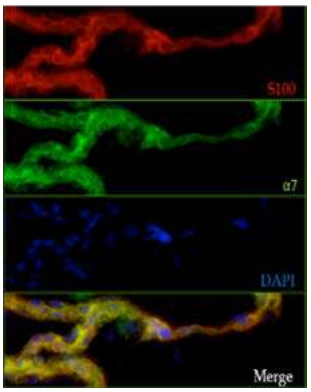
Unit Coordinator, Drugs repositioning and the precision therapy.

RESEARCH ACTIVITY

Neuron-glia interaction: cholinergic receptors in the control of myelinating glial cell development.
The existence of a cross-talk between neurons and glial cells, during development and in adulthood is well documented. Concerning the molecules mediating these cross interactions, neurotransmitters and their receptors have been identified in myelinating and non-myelinating glial cells, suggesting their potential involvement during glial cell development and physiology. Our studies are focused on the functional characterization of cholinergic receptors in myelinating glial cells, (oligodendrocytes and Schwann cells). Previous studies have indicated that muscarinic receptors mediate opposite effects on proliferation and differentiation in oligodendrocyte precursors and in Schwann cells. At least our studies are focused on the effects mediated by α-7 nicotinic receptors on repair Schwann cells, a specific phenotype expressed during peripheral nerve injury, able to mediate peripheral nerve regeneration. α-7 nicotinic receptors are expressed on Schwann cells in particular after axon damage. Using a specific agonist selective for this receptor subtype, we are characterizing the ability of α-7 nicotinic receptors to modulate the pro-regenerative processes.

Cholinergic control of schwann-like adipose-derived stem cell differentiation: implication in peripheral nerve regeneration.
Adipose-derived stem cells (ASCs) can be chemically differentiated towards the SC-like phenotype (dASCs), These cells represent a promising alternative to SCs in the peripheral nerve regeneration therapy. The physiology of these cells can be further modulated pharmacologically by targeting receptors for neurotransmitters such as acetylcholine (ACh). Our studies are focused on the comparison of the cholinergic effects in rat and human dASCs and the respective Schwann cells. Moreover we are studying the cholinergic effects mediated by muscarinic agonists in the modulation of dASC pro-regenerative processes.



Effects mediated by M2 muscarinic receptors in the glioblastoma cancer stem cells.
Glioblastomas (GBM) are the most aggressive form of primary brain tumours in humans. A key feature of malignant gliomas is their cellular heterogeneity. In particular, the presence of an undifferentiated cell population defined Glioblastoma Stem cells (GSCs) has been reported. Increased expression of anti-apoptotic and chemo-resistance genes in GCS subpopulations, favours their high resistance to a broad spectrum of drugs. Our previous studies have demonstrated the ability of M2 muscarinic receptors to negatively modulate the cell growth and survival in GBM cell lines and in the GSCs. The different signalling pathways activated by different M2 muscarinic agonists are at least investigated in order to identify new possible therapeutic targets. Moreover the effects mediated by M2 receptor agonists on drug resistance have also been investigated.

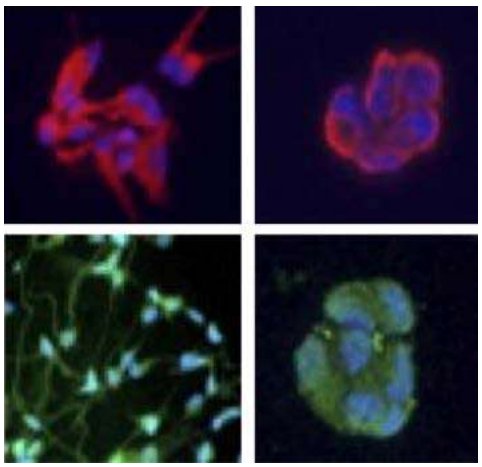


Figure. Upper panel: Sciatic nerve after nerve injury: Schwann cells immunostained for S100 protein (red) and α-7 nicotinic receptors (green). Lower panel: Glioblastoma cancer stem cells in adherent and neurosphere conditions immunolabelled for stemness markers Nestin (red) and Rest (green).

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Maurizio
Trovato
Researcher

ORCID

RESEARCH LINES

- Function of proline in plant growth and differentiation
- Molecular and genetic mechanisms of plant development
- Metabolism of proline in plants
- Drought tolerance in wheat

STAFF | COLLABORATORS

Dietmar Funck,
Researcher
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Faiçal Brini,
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Francesco Sestili,
Assoc. Professor (University of Tuscia)

RESEARCH ACTIVITY

I am a specialist in plant molecular biology with a long-standing experience in various aspects of Agrobacterium rhizogenes-plant interactions, as well as different aspects of the function and regulation of the plant oncogene rolB and rolD.
At present, my current research interests have shifted from the study of the rol genes to that of the amino acids in plants, with particular emphasis on the role of proline in plant development and during abiotic stress. Indeed, besides, to be involved in protein synthesis, the amino acids participate in plant development, signal transduction, energy supply, and tolerance to biotic and abiotic stresses.
Being the only cyclic amino acid, and thanks to its unique chemical-physical properties, proline is especially interesting and has been involved in several biological functions such as compatible osmolyte, ROS scavenger, redox buffer, kosmotropic molecule, and signaling molecule.
A major interest of my research activity is focused on the role of proline in pollen development and fertility. One of the best-known and less-explained facts on pollen composition is the exceedingly large amount of proline found in different plant species, suggesting a special role for proline in pollen development and function.
My research group has recently demonstrated that proline is required for pollen development and fertility, and that is specifically synthesized in the gametophytic tissues of the developing microspores and mature pollen grains. We are currently investigating the molecular mechanism by which proline sustains pollen development and fertility.
In addition to being an essential component of protein biosynthesis in any growing tissue, proline also seems to play a role as a modulator of cell division, especially in the root elongation zone. Indeed, we have recently shown that proline can specifically modulate the size of the root meristem independently from plant hormones, likely controlling the ratio between cell division and cell differentiation.
We are currently studying the molecular and genetic mechanisms that allow proline to fine-tune the growth of the primary root of Arabidopsis. Last but not least, we are currently analyzing different lines of TILLING mutants in durum wheat, and engineering transgenic wheat to hopefully generate drought-tolerant wheat lines with superior grain yield under stressful conditions.

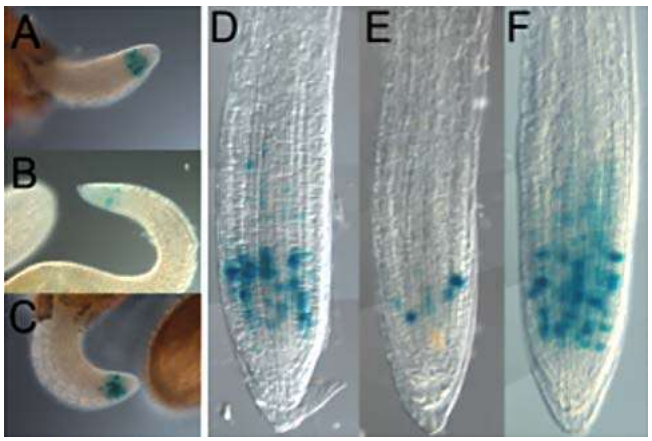

Figure. pCycB1-1::GUS expression in wild type plants (A, D), mutants for the proline biosynthesis genes p5cs1 e p5cs2 (B, E) and wild type plants supplemented with exogenous proline (C, F) a 1 (A, B, C) and 3 (D, E, F) days after germination.

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Daniela
Uccelletti
Associate Professor

ORCID

RESEARCH LINES

- Host-microrganism interactions in the animal model Caenorhabditis elegans
- Nanobiotechnology for biomedical and environmental applications
- C.elegans as environmental biosensor

STAFF | COLLABORATORS

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GRANTS

2020-2023. BIONUTRA
ARS01 - 01166, € 44,000,
Unit Coordinator
2019-2021. INAIL
SenseRisc, € 91,150,
Unit Coordinator
2020-2022. INAIL
Nanobiosan, € 103,000,
Unit Coordinator

RESEARCH ACTIVITY

The research activity is based on the various fields of microbial biotechnology and the use of the nematode C.elegans as a model system to study the host-pathogen interaction processes in order to unveil the mechanisms involved in the innate immunity and in the stress response. Several advantages allow C.elegans to be used as an in vivo infection model. The genome is completely sequenced and it has a defined number of somatic cells which are all visible in the intact living organism under the microscope, making the observation of infection at the level of the organism possible.
It is also an excellent genetic model: it has both hermaphrodite and male sexes and is a premiere organism for the use of RNA interference studies allowing rapid targeted investigation of gene function. Investigations in the lab currently regard the glycosylation's role in pathogen recognition as well as in innate immunity and in the oxidative stress responses. Key signaling pathways involved in pathogen response using several bacterial strains are studied. Dietary sources, such as bacteria, play an important role in the control of C. elegans lifespan; the bacterial biomass indeed represents the worm's food, and although their trophic relationship is different from the synergistic one between mammals and gut microbiota, live bacteria influence the nematode physiology through their metabolites, representing both direct and indirect aspects of a diet (Figure). The nematodes are also utilized to screen for the isolation of potential probiotics deriving from foodborne bacteria. In recent years, our research has also focused on the field of nanotechnology to characterize the antimicrobial properties of nanomaterials utilized in biomedical and cultural heritage fields through multidisciplinary approaches. Specifically, our attention is devoted towards the study of the interactions between the cells and the carbon-based nanostructures to understand how nanomaterials interact with microorganisms. The nematodes are a very sensitive tool to study sublethal responses at the molecular level. The environment directly affects health status and plays a major role in quality of life. In this frame, our research employs C.elegans as a biological model to diagnose environmental quality.

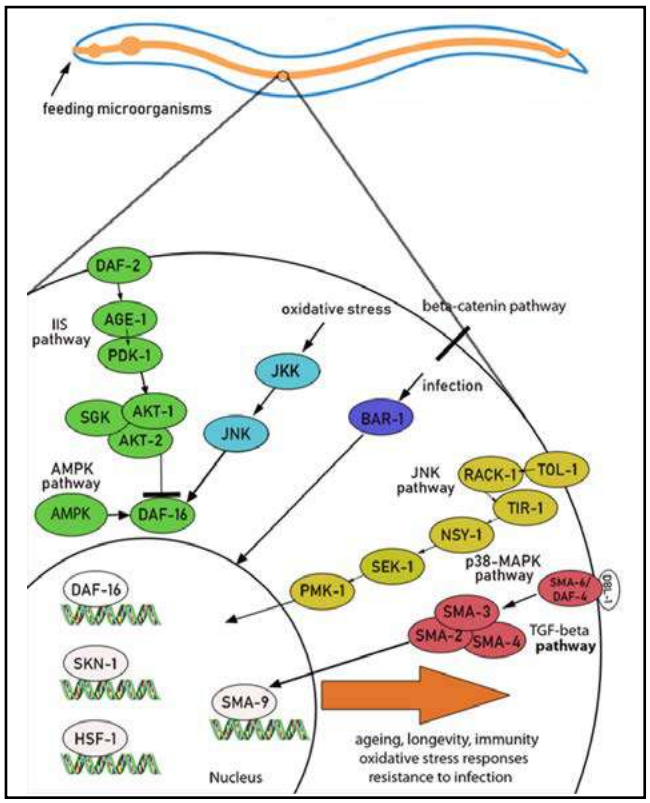

Figure. Schematic representation of the most common signaling pathways influenced by microrganisms employed as a diet in C. elegans studies (Modified from Roselli et al., 2019).

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RESEARCH LINES

- Molecular effects of Quadrato Motor Training

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RESEARCH ACTIVITY

Quadrato Motor Training (QMT) is a specifically structured sensorimotor training, created by Patrizio Paoletti, that involves sequences of movements, developed on the base of a neuroscientific research aimed at finding new means of reducing stress while improving cognition and emotional well-being. It requires standing at one corner of a square and making movements toward different corners in response to verbal instructions. QMT involves enhanced attention to the motor response and cognitive processing for producing the correct direction of movement. It was demonstrated that QMT enhances reflectivity and creativity in healthy subjects, as well as reading skills in dyslexic ones. Electrophysiological studies have shown that QMT significantly increases inter- and intra-hemispheric EEG alpha coherence and cerebellar oscillatory alpha power in dyslexics. In addition, increased neuronal connectivity and arborization following one to three months of daily QMT training was observed by MRI studies. These results imply an ongoing process of neuronal remodeling possibly involving molecular modifications.

Neurotrophins are closely related to neuroplasticity and synaptogenesis, representing valuable candidates as mediators of the QMT driven effects. In addition, they are involved in stress, mental health and well-being. Initially synthesized as precursor proteins (proneurotrophins), they can influence both developing and mature neural circuits. Levels of pro-neurotrophins are considerably changed in neurodegenerative pathologies. In addition, stress was shown to suppress BDNF synthesis, and exogenous administration of BDNF may reverse the stress response in some cases, emphasizing the importance of potentially activating the body's own resources. Our studies demonstrated that salivary proNGF and proBDNF vary following several weeks of QMT practice, their reciprocal variation is positively correlated, and it is also correlated with improved creativity, revealed by specific tests administered before and after the training. Increased salivary pro-BDNF was also correlated with increased white matter volume and inter-hemispheric connectivity by MRI. Therefore, QMT can affect molecular mechanisms that stimulate neuroplasticity in the brain, that are also reflected in periphery. In a recent case study, we observed increased levels of proNGF and proBDNF in a dyslexic adult, correlated with improved reading and creativity. Our results support the idea that QMT is a useful integrated training that may aid in ameliorating well-being, by activating endogenous resources of the mind-body system.

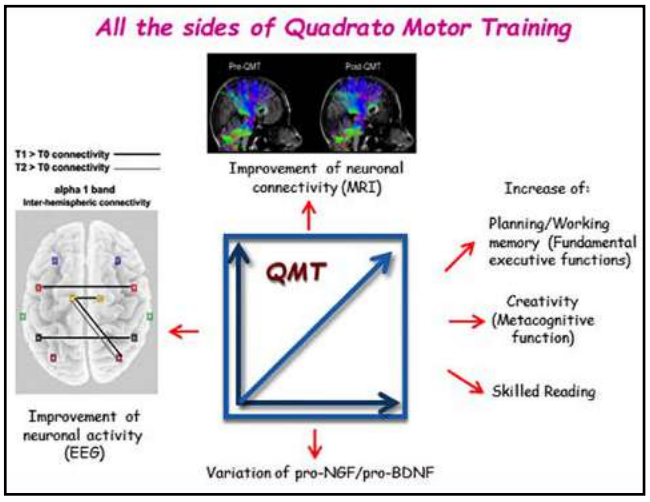

Figure. Summary of the studies and effects related to Quadrato Motor Training (QMT). Scheme of the direction of movements inside the Quadrato space (center). Main electrophysiological effects by EEG (left). Morphological outcomes by MRI (top). Neurotrophin levels (bottom). Cognitive outcomes (right).

Currently, our direction is focused on the deeper comprehension of the molecular effects of QMT, by studying the possible transcriptional and/or epigenetic mechanisms regulating the differential levels of the pro-neurotrophins. We are investigating RNA levels as well as the promoter DNA methylation levels of the relative genes.

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Paola
Vittorioso
Researcher

ORCID

RESEARCH LINES

- The seed to seedling transition in Arabidopsis thaliana: role of Dof Affecting Germination1
- Seed germination in Cardamine hirsuta: a physiological, genetic and molecular study"
- Light-mediated developmental processes: photomorphogenesis and hypocotyl elongation
- Molecular mechanisms through which germinating seeds sense, respond and adapt to environmental stress: the signaling pathway of the Cold Acclimation response
- Pharmacological approaches to inhibit epigenetic control in seeds and seedlings of Arabidopsis thaliana

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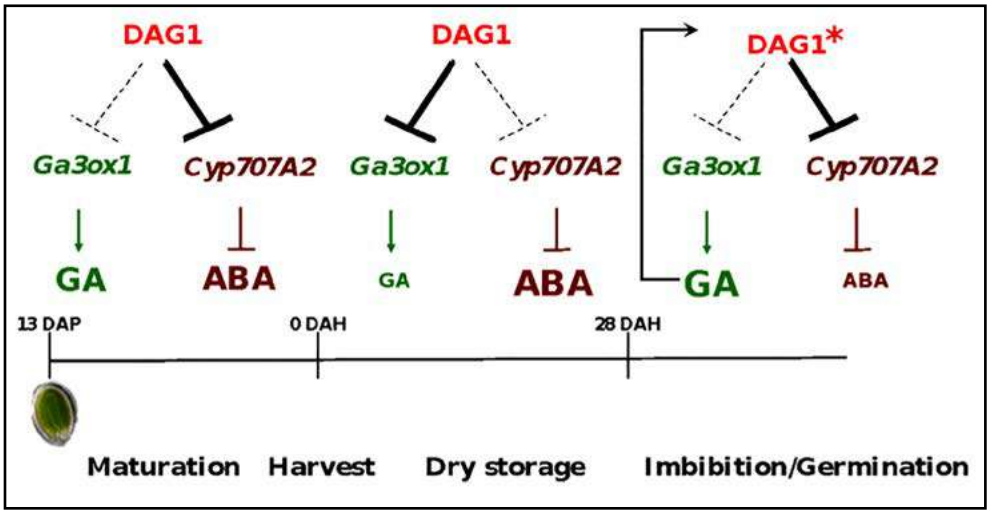
RESEARCH ACTIVITY

The transition from a growth-arrested seed to a germinating seed is a crucial developmental switch in plant life. Arabidopsis seeds develop dormancy during the late stages of their development; abscisic acid (ABA) induces seed dormancy whereas gibberellins (GAs) release dormancy and promote germination. DAG1 is a repressor of the light-mediated seed germination process in Arabidopsis. DAG1 controls the ABA/GA ratio during seed maturation and dormancy by directly repressing GA3ox1 and CYP707A2.



DAG1 mutant seedlings show shorter hypocotyls compared to the WT, suggesting that DAG1 is a negative component of the light-mediated inhibition of hypocotyl elongation. DAG1 promotes hypocotyl elongation acting on ABA, ethylene and auxin signaling. Plants, as sessile organisms, have to survive to changing environmental conditions. ABA has a key role in the adaptation to environmental challenges as in the control of plant development. The response to abiotic stress is mediated by epigenetic reprogramming, which involves the POLYCOMB REPRESSIVE COMPLEX 2 (PRC2). DAG1 is a PRC2 target and is marked by H3K27me3 in seeds and seedlings. Mutations in the catalytic subunit of PRC2 results in a severe phenotype; although the effects of several inhibitors of the PRC2 catalytic subunit (EZH2) have long been tested in animals as anti-cancer therapy, no trial with any inhibitor has ever been reported in plants. Taking advantage of the homology of EZH2 in animals and plants, we assessed the efficacy of a EZH2 inhibitor on Arabidopsis seeds, to provide a powerful tool in studying PRC2 action in plants.

Figure. Upper panel: model illustrating the function of DAG1 during maturation, dormancy and germination of seeds in Arabidopsis thaliana. Lower panel: a new pharmacological approach in Arabidopsis thaliana.

We performed treatments with a compound previously reported as an EZH2 inhibitor in human leukemia cells, and we proved that it is active on the Arabidopsis catalytic subunit of PRC2. Indeed, treatment with the drug reduces the total amount of H3K27me3 in a dose-dependent fashion. The pharmacological approach to inhibit PRC2 is efficient in plants; therefore, this inhibitor could represent a powerful tool to further investigate the effects of the transcriptional control mediated by PRC2 in plants, also in the response to abiotic stresses.

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“GENETICS„

The research activity of the Genetics section of the Department of Biology and Biotechnologies “Charles Darwin” is focused on three main broad areas:

- human population and forensic genetics;
- molecular genetics, gene therapy and cytogenetics of mammalian somatic cells;
- molecular genetics, epigenetics and cell biology of *Drosophila melanogaster*.

These research topics are carried out by Faculty Members in collaboration with researchers of the Institute of Molecular Biology and Pathology (IBPM) of the National Research Council (CNR).

Research on human population genetics traces back to the early times of genetics in Rome, when G. Montalenti and M. Siniscalco used population genetics to study the role of malaria as a selective factor for maintenance of mutant alleles in thalassemia and G6PD genes. There are currently two research groups that exploit human population genetics on ancient and modern samples for studies on human evolution, migrations and the genetics of aging and related diseases. These research activities are also aimed at clarifying the molecular evolution of the human genome and at applying genetic knowledge to address forensic problems and legal proceedings.

Groups currently working on the molecular genetics and cytogenetics of mammalian cells, are mainly interested in development of vectors and strategies for gene therapy, in human telomere and centromere biology and in the control of genome stability, including the structure and origin of chromosomal fragile sites. Current research in human biomedical genetics stems from the human cytogenetics branch set up first by G. Montalenti and then expanded by G. Olivieri.

The research in *Drosophila* genetics, carried out by the Italy’s largest *Drosophila* research pole that was originally founded by two scientifically active emeritus professors, M. Gatti and S. Pimpinelli, embraces different topics. These include the role of transposition in evolution, the epigenetic modifications of chromatin and heterochromatin, the molecular mechanisms of cell division, the analysis of telomere structure and stability, the biological effects of ionizing radiations and the relationship between nutrition, genome integrity and cancer. Some groups also exploit *Drosophila* as a model for different neuromuscular degenerative diseases.

Silvia
Bonaccorsi
Full Professor

ORCID

RESEARCH LINES

- Genetic control of cell division
- Genetic control of genome integrity
- Drosophila as a model system for the study of human pathologies

STAFF | COLLABORATORS

Elisabetta Bucciarelli,
Researcher (CNR-IBPM)
Maria Patrizia Somma,
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GRANTS

MIUR - Drosophila as a model system to study the regulation of centriole length and ciliogenesis,
€ 100.000.
PI: S. Bonaccorsi

RESEARCH ACTIVITY

Since 1995, S. Bonaccorsi research interest has been focused on the genetic control of cell division. Using Drosophila as a model system, she identified and characterized several genes encoding conserved proteins required for cytokinesis that had not previously been implicated in the process including: twinstar, encoding a Drosophila cofilin-like protein; chickadee, encoding the actin-polymerizing protein profilin and fascetto (feo), encoding the Drosophila homologue of human PRC1. Based on the phenotypes elicited by mutations at these loci, S. Bonaccorsi and coworkers proposed for the first time that the central spindle and the acto-myosin-based contractile ring are interdependent structures during the cytokinetic process.
In another group of studies, S. Bonaccorsi analyzed the role of centrosomes and chromosome driven microtubule nucleation in cell division. She showed for the first time that Drosophila mitotic cells devoid of functional centrosomes are able to form anastral mitotic spindles that can mediate normal chromosome segregation. In more recent studies, she showed that failure to produce kinetochore-driven microtubules (MTs) prevents proper formation of a bipolar mitotic spindle. In contrast, meiotic cells of Drosophila males form highly irregular spindles in the absence of functional centrosomes but assemble morphologically normal spindles in the complete absence of chromosomes. Together, these results demonstrate that different centrosome-containing cell types use different modes of spindle assembly.
S. Bonaccorsi and coworkers have also contributed to identify the mitotic role of four conserved Drosophila genes, abnormal spindle, DLkb1, morgana/Chp1 and citron kinase, whose human orthologues are implicated in severe human diseases, providing relevant information on the underlying pathogenetic mechanisms.
More recently, S. Bonaccorsi studied the mechanisms underlying the maintenance of Drosophila genome integrity. She showed that the conserved genes timeless2 (tim2) and topoisomerase II (Top2) are both required for chromosome stability, and that mutations in Top2 produce a highly specific pattern of aberrations.
Finally, S. Bonaccorsi contributed to demonstrate that the Drosophila orthologue of the INT6 onco-protein controls both microtubule growth and kinetochore structure during mitosis and that the conserved splicing factors Sf3A2 e Prp31 play a direct role in the control of kinetochore-MT interaction, independent of their canonical function in transcription, thus representing two novel examples of mitotic “moonlighting” proteins.

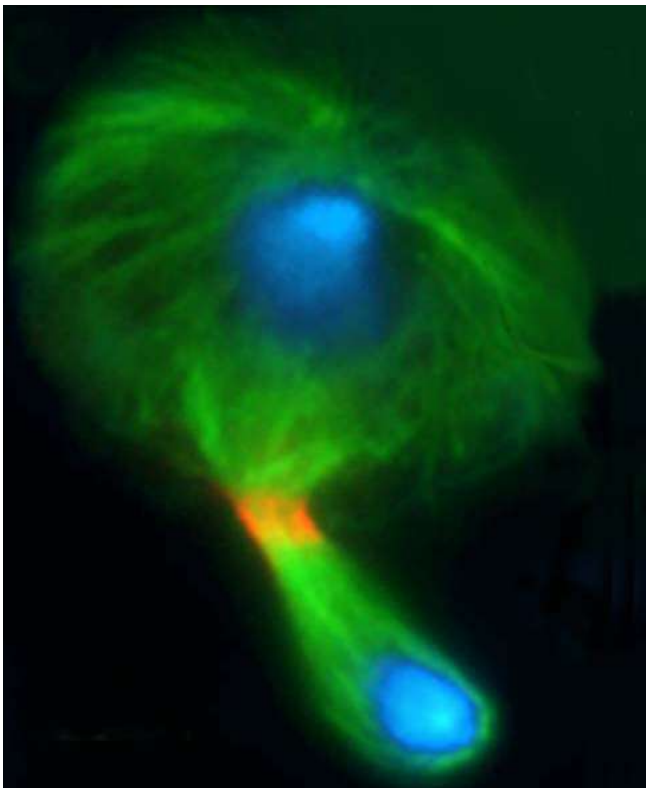

Figure. Telophase of a Drosophila larval neuroblast stained for DNA (blue), tubulin (green) to mark the microtubules and Fascetto (red) to mark the cleavage furrow.

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Rosa Maria
Corbo
Associate Professor

ORCID

RESEARCH LINES

- TELCAD study (TElomer Lenght and Cytokines' expression in Alzheimer's Disease)
- Follow-up study on LTL as biomarker of HD progression
- LTL and different SCA types

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Liana Veneziano,
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RESEARCH ACTIVITY

Over the years, research activity was mainly carried out in the fields of human genetics, genetic epidemiology and evolutionary medicine. The main research lines can be summarized as follows:

1) dissection of the genetic component of complex neurodegenerative diseases of advanced age (Alzheimer's disease);
2) evolutionary medicine studies investigating how some genes are becoming susceptibility factors to complex diseases due to their interactions with modern environment and lifestyles;
3) studies on the genetic basis of human aging and longevity.

In the last years, the activity research was focused on the identification of reliable biomarkers useful to track the disease progression of some complex/mendelian neurodegenerative diseases such as Alzheimer's and Huntigton disease.

The data obtained so far on subjects with sporadic Alzheimer's disease (AD), have shown that the length of leukocyte telomeres (LTL) could be a reliable biomarker to track AD progression from the prodromal states (MCI) to the full-blown AD. Recently we extended the LTL analysis to neurodegenerative monogenic diseases, for which the data on telomeres were very scarce or absent, i.e. Huntington's disease (HD) and some spinocerebellar ataxias (SCA). These are late-onset diseases with monogenic inheritance, caused by CAG trinucleotide repeat expansion, in which clinical onset age varies depending on the CAG number, and on genetic and environmental modifying factors. For these diseases peripheral biomarkers, reliable and easily accessible, could help to identify the time window useful for starting any therapies that may delay the clinical symptom onset. The preliminary results of our HD study indicate that LT shortening seems to be a feature of HD development, from the pre-manifest stage to clinical diagnosis, and could be used to improve the prediction of clinical onset age provided by bio-statistical models based on CAG repeat length.

Two follow-up studies are in progress to evaluate the reliability of LTL as peripheral biomarker to track AD and HD progression.

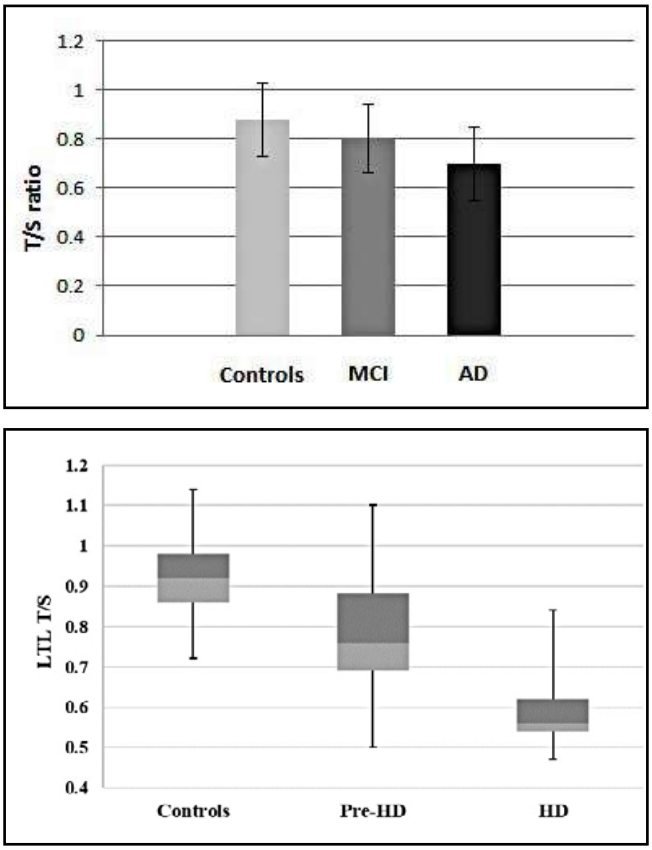

Figure. Upper panel: Mean LTL (T/S ratio) in Controls, MCI and AD patients. Lower panel: Distribution of LTL (T/S ratio) in controls, pre-manifest HD, and HD patients.

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Associate Professor

ORCID

RESEARCH LINES

- Molecular mechanisms underlying the maintenance of chromosome integrity in the model organism, Drosophila melanogaster

STAFF | COLLABORATORS

Francesca Cipressa,
Post-doc (Sapienza)
Antonella Porrazzo,
Post-doc (Sapienza)
Liliana Tullo,
PhD student (Sapienza)
Elisabetta Bucciarelli,
Researcher (CNR-IBPM)

GRANTS

2018-21. Characterization of the role of Separase in the regulation of Lamins and Rad50. Fondazione Cenci-Bolognetti, Pasteur Institute. PI.
2018-20. Role of HP1/Cbx protein ubiquitination in chromatin organization. Programmes Transversaux de Recherche (PTR), Pasteur Institute (France)
Role: Coordinator
2018-20. Functional analysis of separase-dependent lamins' regulation in AD-EDMD.
The French Muscular Dystrophy Association (AFM-Telethon)-France
Role: Coordinator

RESEARCH ACTIVITY

Genetic and molecular regulation of telomere capping. G. Cenci has focused most of his research activity on the identification of proteins required for Drosophila telomere protection. His work has contributed to i) the description of Drosophila telomeres as epigenetically determined structures, ii) the identification of a multi-protein complex, dubbed terminin, which specifically associates with Drosophila chromosome ends; iii) the characterization of non-terminin proteins required for telomere protection that have human counterparts involved in telomere maintenance. These findings unveil the potential of Drosophila as a model system for the study of human telomeres, which are currently object of intense investigations due to their involvement in aging and cancer processes (Cenci et al., Nature Cell Biology, 2003; Musarò et al., Nature Genetics, 2008; Cenci et al., PLoS Genetics, 2015; Cipressa et al., Nat Comm, 2016). G. Cenci lab is currently addressing the role of ubiquitination at chromosome ends and unanticipated functions of centromeric factors in telomere homeostasis (Figure).

Intra-cellular metabolism and genome stability. In 2009 the G. Cenci group revealed that the impairment of citrate efflux from mitochondria, due to loss of the mitochondrial citrate carrier, led to chromosome breakage in both Drosophila and human cells (Morciano et al., Human Molecular Genetics, 2008). This study highlighted for the first time, a link between intermediary metabolism and control of genome stability. The G. Cenci research activity is now focusing on the characterization of additional conserved mitochondrial factors involved in this link.

The biological effects of low dose radiation/low dose rate on genome stability. The G. Cenci laboratory is exploiting Drosophila as a model organism to assess the biological effects of exposure to background radiation that deviate from natural background radiations on a complex organism (Morciano et al., J Cell Physiology, 2017; Morciano et al., Radiation Research, 2018).

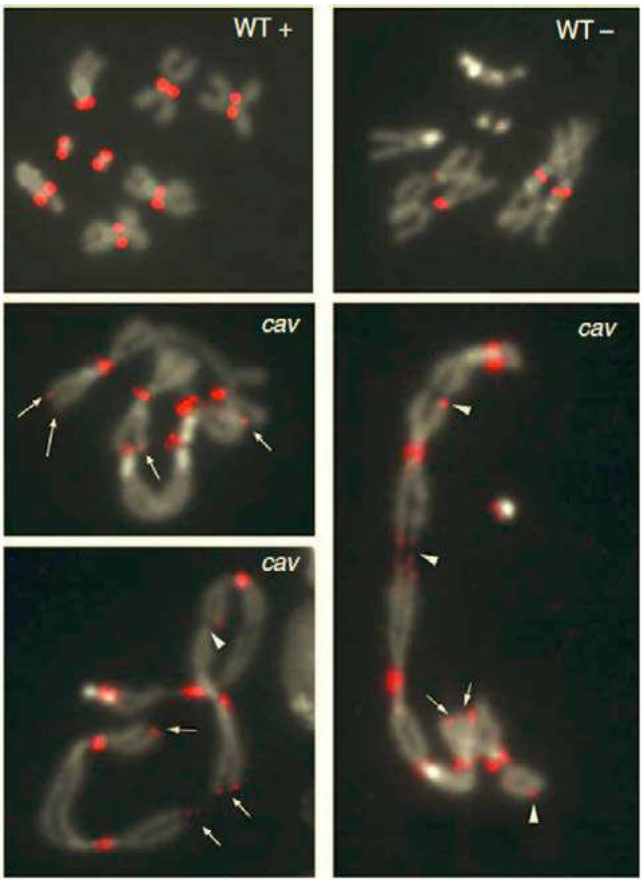

Figure. BubR1 immunostaining in wild-type cells and in cav mutant cells with telomeric fusions. The spindle checkpoint factor BubR1 stains centromeres and localizes also at uncapped telomeres. This suggests that Drosophila uncapped telomeres activate the Spindle assembly checkpoint

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3. Cipressa F, Morciano P, Bosso S, Mannini L, Galati A, Raffa GD, Cacchione S, Musio A, Cenci G (2016). A role for Separase in telomere protection. Nat Comm, 7:10405

Laura
Ciapponi
Associate Professor

ORCID

RESEARCH LINES

- Telomere - DNA damage - Genome stability
- Drosophila as a model system for neuromuscular diseases
- Drosophila as a model system for genetic primary microcephaly

STAFF | COLLABORATORS

Marta Marzullo,
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Gianluca Canettieri,
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Researcher (CNR-IBPM)
Fabian Feiguin,
PI (ICGEB, Trieste)

GRANTS

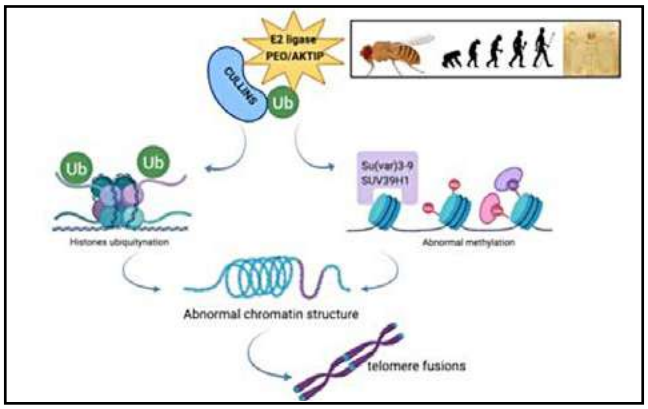
2018-2021. AFM Telethon File number: 21025.
Analysis of the DM2 pathogenic mechanisms using Drosophila as model system.
PI: Laura Ciapponi

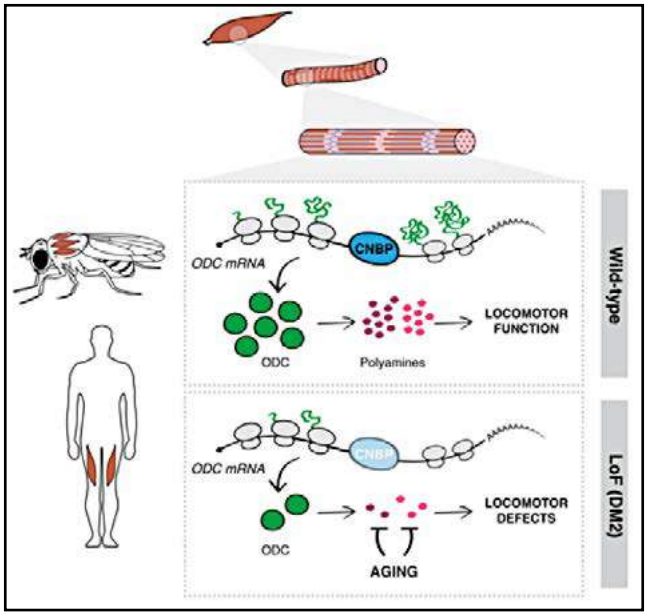
RESEARCH ACTIVITY

I have been working with *Drosophila melanogaster* as a model system since 1997, when I started my postdoc at EMBL, in Heidelberg. My switch to the Drosophila system was a true love at first sight and I am still in love ever since.

Line 1. Telomeres are nucleoprotein complexes that protect the extremities of chromosomes and maintain genome stability. Short or uncapped telomeres lead to chromosomal aberrations and in some cases tumor development. Our current research showed that peo, a *Drosophila* gene that encodes an E2-ubiqutin variant enzyme, plays a crucial role in telomere protection, DNA replication and chromatin maintenance. The Peo human homologue AKTIP mediates proper telomere replication and also has a role in lamin-related processes, including those that govern nuclear architecture. Our current working hypothesis is that loss of peo/AKTIP causes chromatin alterations responsible for telomeric damage, and that this alteration might affect cancer progression.

Line 2. Myotonic Dystrophy 2 (DM2) is a genetic multi-systemic disease, primarily affecting skeletal muscle. It is caused by a CCTGn expansion in intron1 of the CNBP gene. Our studies are aimed at clarifying important and previously unresolved issues concerning the relative contribution of CNBP downregulation, CCUG-repeat toxicity and CCUG-repeat-encoded peptides in DM2. Interestingly, we revealed that depletion of *Drosophila* CNBP in muscles causes locomotor defects due to impaired polyamine metabolism. We found that the levels of ODC and polyamines are reduced upon dCNBP depletion, and most importantly in DM2 patients. Mechanistically, we provide evidence that dCNBP controls polyamine metabolism through regulation of ODC translation.





Line 3. Primary microcephaly is an invalidating condition characterized by a reduced number of neurons, resulting from alterations of the delicate balance between proliferation, differentiation and death. In the developing brain, the proteins encoded by MCPH genes are required for maintaining genome stability, ensuring a precise temporal order of gene expression patterns and maintaining a correct balance in cell fate commitment. We are studying whether DNA damage, apoptosis, altered chromatin organization, abnormal transcription profiles and altered differentiation are consequences of the reduced function of the known MCPH genes, as compared to other genes that have not yet been involved as causal factors.

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3. Bosso G, Cipressa F, Moroni ML, et al. NBS1 interacts with HP1 to ensure genome integrity. Cell Death Dis. 2019.

Fulvio
Cruciani
Associate Professor

ORCID

RESEARCH LINES

- Human population genetics
- Molecular evolution of sex chromosomes
- Forensic genetics

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Maria Bonito,
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Chiara Della Rocca,
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Mogge Hajiesmaeil,
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GRANTS

2017-21. National Geographic. "A great human journey: Peopling and human movements in Africa during the last Green Sahara", $ 30000. PI: Fulvio Cruciani
2018-21. Fondazione Pasteur Cenci Bolognetti. "Dynamics of intra-chromosomal gene conversion between palindrome arms of the human Y chromosome", € 60000. PI: Fulvio Cruciani
2020. Gerda Henkel Foundation. "A window on the Etruscan world", € 12000. Co-PI: Fulvio Cruciani

RESEARCH ACTIVITY

My group is especially interested in studying different aspects of the human genetic diversity and evolution. Our research spans over three major areas: archaeogenetics, sex chromosome molecular evolution and forensic genetics.

Line 1. Archaeogenetics. This is the oldest research line of our group, which has been progressing in parallel with the improvement of technologies and statistical methods for the analysis of molecular diversity. Most of the studies were based on the analysis of the Y chromosome variability, with specific reference to issues related to the origins of our species and to migrations fueled by the cultural evolution and climate changes in the African continent. Among the most relevant results, there are the redefinition of the root of the Y chromosome phylogeny and new evidence for the peopling of the "Green Sahara" during the last humid phase, from 12 to 5k years ago (D'Atanasio et al. 2018). Recently, we have started to analyze high coverage full genomes to unveil past migrations related to the spread of pastoralism in Africa and in the Middle East.

Line 2. Molecular evolution of sex chromosomes. This research line is mainly focused on the role of ectopic gene conversion in the evolution of sex chromosomes. In this decade, we have demonstrated that X-Y ectopic gene conversion is a pervasive phenomenon in the male germline with a role in sex chromosome integrity maintenance (Trombetta et al. 2014). Studies are underway to investigate the impact of intra-chromosomal gene conversion on the diversity of Y chromosome palindromic sequences.

Line 3. Forensic genetics. This is the youngest research line of our group, aimed at evaluating how population structure and demography affect the discrimination power of rapidly mutating Y-STR, used for identification purposes in forensic caseworks. Together with the Reparto di Investigazioni Scientifiche dei Carabinieri, we are also currently exploring new multivariate statistical approaches for the DNA-based inference of biogeographical ancestry, a relevant investigative tool to support law enforcement agencies when no suspects are available for direct comparison and no matches occur through a DNA database search (Alladio et al. 2020).

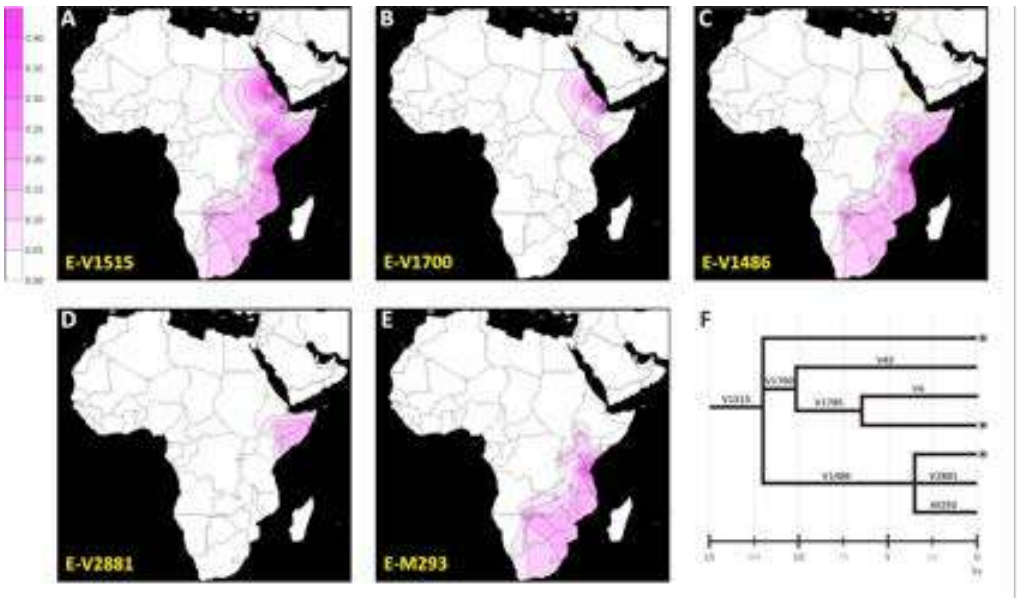

Figure: Phylogeography of E-V1515 haplogroup. The geographic distribution of a series of nested mutations identified through NGS of the Y chromosome marks the route followed by the first pastoralists from eastern Africa to southern Africa (Trombetta et al. 2015)

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Laura
Fanti
Associate Professor

ORCID

RESEARCH LINES

- Formation and organization of heterochromatin
- Transposable elements, environmental stress and evolution
- Circadian rhythms, genomic instability and aging
- Epigenetic regulation of the centromere and telomere

STAFF | COLLABORATORS

Lucia Piacentini,
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GRANTS

Istituto Pasteur - Fondazione Cenci Bolognetti. Circadian Rhythms and Stress: functional role of period gene. PI: Laura Fanti

RESEARCH ACTIVITY

The research activity of Laura Fanti is mainly focused on several aspects of chromosome biology and in particular heterochromatin, using Drosophila melanogaster as a model organism. Heterochromatic regions are a different structural and functional domain with respect to euchromatin, being mostly composed of repetitive DNA.

Heterochromatin, transposable elements and evolution. Among the heterochromatic repetitive sequences, transposable elements (TEs) are relevant components. TEs are mobile genetic elements able to jump in different locations along the chromosomes causing mutations. For this reason, cells evolved mechanisms for TE silencing. In germ cells, the molecular chaperone HSP90 regulates the piwi-interacting RNAs which post-transcriptionally repress TEs. Recently, it was shown that flies exposed to heat stress for some generations during metamorphosis show morphological abnormalities when they become adults (Figure, upper panel). These abnormalities can be assimilated in the genome and become hereditary. The molecular mechanism at the basis of this phenomenon involves the inducible heat-shock protein HSP70 which forms a complex with HSP90, causing TE derepression and their transposition. The discovery of this mechanism that induces hereditary malformations due to TE transposition following environmental stress, allowed us to propose a new evolutionary mechanism, embedded however within a Darwinian framework: transposons are a motor of evolution capable of inducing genetic variability in the populations when strong environmental changes require a rapid adaptation of the organisms. Among the various types of environmental stress, we began to study the effects of circadian rhythm dysfunction to see if they could be considered a form of stress.

Protein composition of heterochromatin and centromeres. In the last years, research has also consisted in the analysis of different chromatin proteins involved in regulating gene expression in Drosophila, to verify their possible function also in heterochromatin. Two important protein groups involved in "cellular memory" have recently been studied, the Polycomb group (Pc-G) and the Trithorax group (trx-G), responsible for respectively maintaining the repressed or active state of homeotic genes during the Drosophila development. The results obtained have unexpectedly shown that Trx-G proteins are associated with specific heterochromatic regions. The most recent results of this work have shown that some of these proteins are important for the functionality of the centromere and in particular for the deposition of the CENP-A protein (Figure, lower panel), a variant of the histone H3 that is a specific component of the centromeric chromatin (3). Finally, an important study that is less recent has been conducted on the Heterochromatic Protein 1 (HP1), known to be abundantly present in heterochromatin. The results of this work have shown, for the first time, that a structural protein, such as HP1, is involved in telomeric capping. In addition, it has been observed that HP1 is also involved in the regulation of euchromatic gene expression.

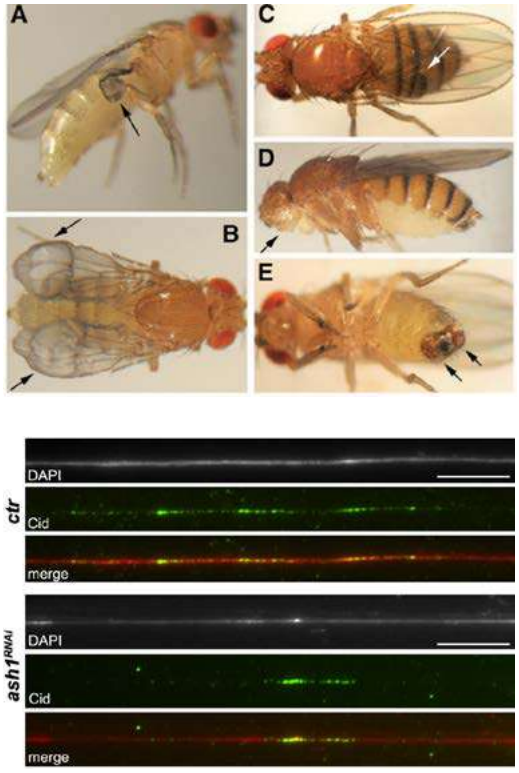

Figure. Upper panel: Morphological abnormalities in heat shocked flies from Fanti, Piacentini et al. Genetics 2017 Lower panel: Extended chromatin fibers colored with DAPI (red) and immunostained with antibodies against CENP-A (green) from Piacentini et al. Chromosoma 2019

References

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3. Piacentini L, Marchetti M, Bucciarelli E, Casale AM, Cappucci U, Bonifazi P, Renda F and Fanti L. 2019. A role of the Trx-G complex in Cid/CENP-A deposition at Drosophila melanogaster centromeres. Chromosoma. 128(4):503-520

Simona
Giunta
Researcher

ORCID

RESEARCH LINES

- Human Centromere Biology
- Repetitive DNA in Human Primary and Cancer Cell Lines
- Genome Stability, Cell Cycle Checkpoints & Repair Pathways
- DNA and Chromosome Structure

STAFF | COLLABORATORS

Elisa Balzano,
Ph.D. student, (Sapienza)
Luca Corda,
Master student, (Sapienza)
Eléonore Perret,
Research Assistant
Edna Cigarroa,
Technician and Lab Admin

GRANTS

2021-2026. AIRC Start-up Grant (€199000 per annum)
2020-2021. Interstellar Early Career Investigator Award NYAS and AMED (Japan) (€20000)
Rita Levi Montalcini Assistant Professorship Award Italian Ministry of Education, University & Research (€216873)
MSCA Marie Curie Reintegration Fellowship - ERC

Giunta Lab Website

RESEARCH ACTIVITY

Human repetitive DNA at centromeres holds a fundamental paradox (Balzano & Giunta, 2020): how is this fast-evolving locus maintained stable to perform its essential and conserved function in chromosome segregation? In the Giunta Lab, we investigate different aspects of centromeres spanning three major areas: genomics, DNA mutagenesis and repair, and chromosome behavior. Altogether our work uses cellular, molecular and structural biology approaches, integrated with cutting edge genomics, high-throughput imaging to bring light into this essential region of the human genome with particular emphasis in understanding its role in tumorigenesis and aging.

Line 1. Centromere genomics. While we celebrated the completion of the human genome project 20 years ago, our DNA still contains large gaps that lack annotation. Human centromeres are defined as “dark regions” in our DNA, representing one of the biggest challenges in completing the genome assembly. We have devised a novel method called Cen-CO-FISH to detect and quantify human centromere DNA repeats (Giunta, 2018) and are validating an innovative CRISPR-based approach to uncover mutational signatures and pathological variants within the repeats.

Line 2. Centromere Stability, Maintenance, Mutagenesis and Repair. We put forward the concept that human centromeres are inherently unstable due to converging vulnerable features commonly associated with fragile sites (Black & Giunta, 2018). We have shown that centromeres recombination is exacerbated in pathological conditions including cancer and cellular aging (Giunta & Funabiki, 2017). Our recent collaborative work with the Institut Curie (France) has highlighted the mechanism for repeats fragility due to generation of mutagenic R-loops during centromere DNA replication (Giunta et al., 2021), that gives raise to complex chromosomal translocations similar to those found in cancer (Figure). Our research currently aims to tease apart mutagenic processes (Balzano, Pelliccia, Giunta, 2020) and the network of factors protecting repetitive DNA from instability using high-throughput bioinformatic and experimental approaches.

Line 3. Chromosomes structure-function relationship. How do changes in DNA translates in alterations in chromosome structure and behavior? We use different types of super-resolution imaging like 3D-Structural Illumination and Expansion Microscopy to image centromeric DNA and its constituents under multiple conditions of stress. We plan to expand our work at nano-scale resolution to study structural alterations of human chromosomes in disease conditions and genetic syndromes (Jenness, Giunta et al., 2018).

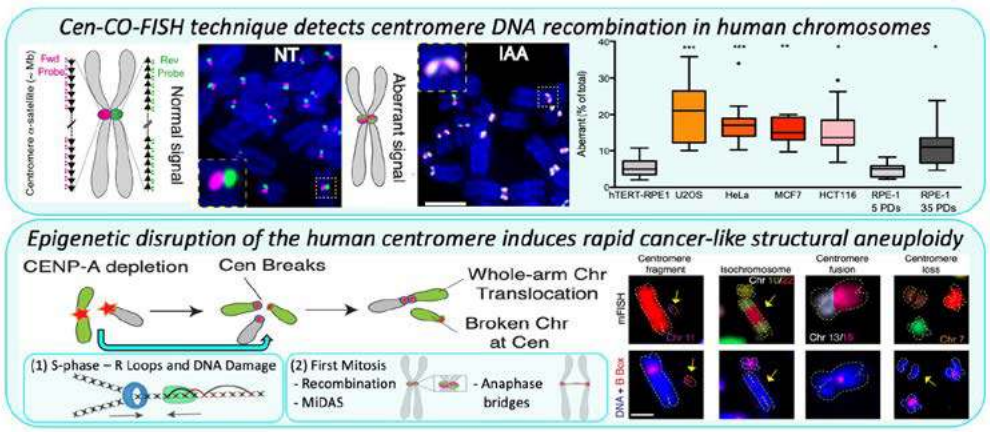

Figure. Centromere instability triggers chromosomal defects seen in solid tumors. *Upper panel: Cen-CO-FISH assay (Giunta, 2018) detects centromere DNA instability quantified in cancer (U2OS – osteosarcoma; HeLa – cervical cancer; MCF7 – breast cancer; HCT116 – colon cancer cell lines) and during cellular aging (35 PDs = population doublings: pre-senescence) (Giunta & Funabiki, 2017). Lower panel: Rapid depletion of centromere-specific histone H3 variant CENP-A via Auxin inducible Degron (AID) system induces R Loops due to transcription-replication conflicts (1) and DNA damage (2) in the first mitosis, with ensuing cancer-like chromosome defects occurring in the following cell cycle (Giunta et al., 2021).*

References

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2. Balzano E, Pelliccia F, Giunta S†. (2020) Semin Cell Dev Biol S1084-9521(19)30132-6.
3. Giunta S† & Funabiki H†. (2017) PNAS 114(8):1928-33 † Corresponding

Valeria Luciana
Palumbo
Researcher

ORCID

RESEARCH LINES

- Analysis of the genetic control of cell division using Drosophila as model system
- Mitotic spindle assembly and microtubule (MT) nucleation
- Consequences of altered Tubulin levels upon mitotic progression

STAFF | COLLABORATORS

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Mara Brancaccio,
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Professor (University of Exeter, UK)

RESEARCH ACTIVITY

Our research activity is mainly focused on deciphering the genetic basis of some aspects of cell division, including mitotic spindle assembly, centrosome duplication and chromosome integrity, aiming to dissect molecular mechanisms and disclose the triggers behind the development of pathological conditions in humans.

Drosophila as model organism for the study of MMYAT disease. misato/MSTO1 gene encodes for a conserved protein sharing structural features common to eukaryotic Tubulins and prokaryotic FtsZ. We have shown that Drosophila Misato is a co-factor of the chaperonin-containing TCP1 complex (CCT/TRiC) and plays an essential role in the Tubulin-folding processes, ultimately controlling the stability and polymerizing competency of α- and β-Tubulin required for proper assembly of spindle microtubules (Palumbo et al., 2015). Importantly, mutations in human MSTO1 has been recently identified as responsible for MMYAT disease (Myopathy, Mitochondrial, and Ataxia; OMIM #617675). The abundance of Misato in the fly CNS, together with the observation that flies develop altered locomotor behavior and reduced lifespan upon pan-neuronal knockdown of misato, suggests that Drosophila could be used as a model for deciphering the pathogenic mechanism underlying the disease.

Role of conserved morgana/CHORDC1 gene in the maintenance of genome stability. We have identified and functional characterized Morgana/CHORDC1, an essential gene that controls multiple aspects of cell division, both preventing centrosome overduplication (Ferretti et al., 2010) and directly stimulating MT polymerization (Palumbo et al., 2020). Our studies reveal that Morgana deregulation predisposes to oncogenic transformation in humans (Ferretti et al., 2010), and is also required for other essential biological functions, currently under investigation.

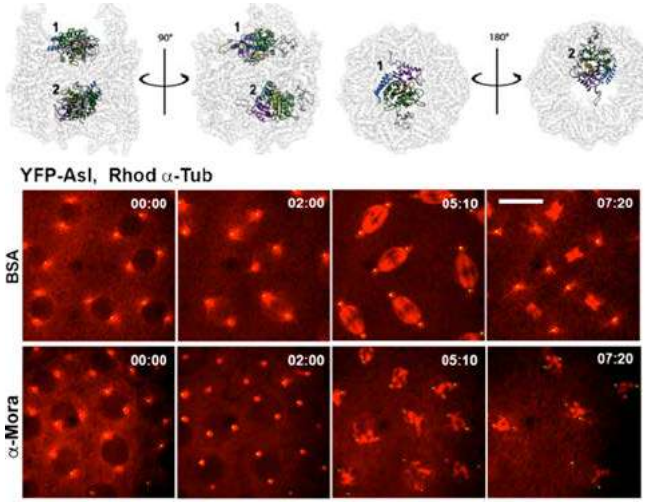

Figure. Upper panel: Superimposition of the Misato model onto the model of bovine Tubulin:TCP-1 complex (from Palumbo et al. (2015). Lower panel: Stills from time-lapse videos of mitosis in Drosophila embryos expressing YFP–Asl (green), simultaneously injected with Rhodamine–Tubulin (red) and either BSA or anti-Mora antibody (from Palumbo et al. (2020).

Analysis of the mitotic progression in response to altered Tubulin cellular levels. We have developed a genetic strategy to progressively deplete Tubulin levels in vivo, leading to mitotic arrest mediated by the Spindle Assembly Checkpoint (SAC) activation. Over time, progressive weakening of SAC promotes mitotic slippage, where cells re-enter interphase without completing cell division, becoming polyploid. Mitotic slippage is thought to be one of the causes of genomic instability, but its molecular mechanism still remains obscure. We intend to exploit our in vivo system and mutant fly strains for genes encoding for diverse SAC proteins, to investigate this phenomenon. As a long-term goal, these notions could potentially have a therapeutic and clinical impact, as microtubule-targeting drugs are among the most effective anticancer agents currently in use.

References

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2. Ferretti, R., Palumbo, V., Di Savino, A., Velasco, S., Sbroggiò, M., Sportoletti, P., Micale, L., Turco, E., Silengo, L., Palumbo, G., et al. (2010). Morgana/chp-1, a ROCK inhibitor involved in centrosome duplication and tumorigenesis. Dev. Cell 18, 486–495.
3. Palumbo, V., Tariq, A., Borgal, L., Metz, J., Brancaccio, M., Gatti, M., Wakefield, J.G., and Bonaccorsi, S. (2020). Drosophila Morgana is an Hsp90-interacting protein with a direct role in microtubule polymerisation. J Cell Sci 133.

Franca
Pelliccia
Associate Professor

ORCID

RESEARCH LINES

- Common Fragile Sites and genome instability:
- Replication timing and molecular characterization of chromosomal fragile sites
- Pathogenesis of Chromosomal Fragile Sites: investigation of relationship between the expression of CFSs and Fanconi Anaemia cells.

STAFF | COLLABORATORS

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Elena Di Tommaso,
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RESEARCH ACTIVITY

The main scientific interest in our laboratory is to investigate, in human cells, the relationship between Common Fragile Sites (CFSs), replicative stress and genome instability.
Molecular characterization and replication timing of Human Chromosomal Fragile Sites. Recent data report that, surprisingly, the sensitivity of specific fragile sites within a cell depends on the tissue or organ from which the cell originates so, in order to analyse the relationship between DNA replication time and fragility in lymphoblasts and fibroblasts we would:

- compare the localization and the frequency of breaks at specific fragile sites in a range of cell types, including the epithelial cells of the lung and lymphoblast, where most human cancers originate.
- visualize DNA-replication dynamics in the fragile and syntenic nonfragile regions on stretched-out DNA strands in lymphoblast and fibroblast in order to investigate the timing of replication of sequences mapping within these sites.

Fragile sequences, early and late replicating control sequences, will be mapped by using fluorescent in situ hybridization (FISH) and BrdU-immunofluorescence on interphase nuclei and stretched-out DNA strands and observed by conventional fluorescence microscopy and confocal microscopy.
Pathogenesis of Chromosomal Fragile Sites. Fragile Sites are also involved in many human diseases. In this regard, we are trying to understand the genetic and molecular implications of these fragile regions in a background such as Fanconi Anaemia (FA) disorder and in cancer cells. Effectively from recent studies, FA repair pathway is fundamental to protect the replication fork and thus to guarantee the chromosomal integrity in peculiar regions, such as of CFSs. Furthermore, the Fanconi Anaemia cells exhibit an higher frequencies of chromosomal aberrations and impairment of replication process with a corresponding stalling of the cell cycle in the transition G2/M phases. Therefore, two isogenic lymphoblastoid cell lines (HSC72 FA-A mutated in FANC A gene; HSC72 FANCA corrected in FANC A gene) will be used to verify the interesting relationship between the CFSs expression in metaphase in a background of mutated FA repair pathway in comparison to a normal condition in lymphocytes from healthy individuals.
In conclusion, further studies on CFSs will allow us to better clarify the biological mechanisms at the basis of this type of chromosomal instability and their involvement in several human diseases.

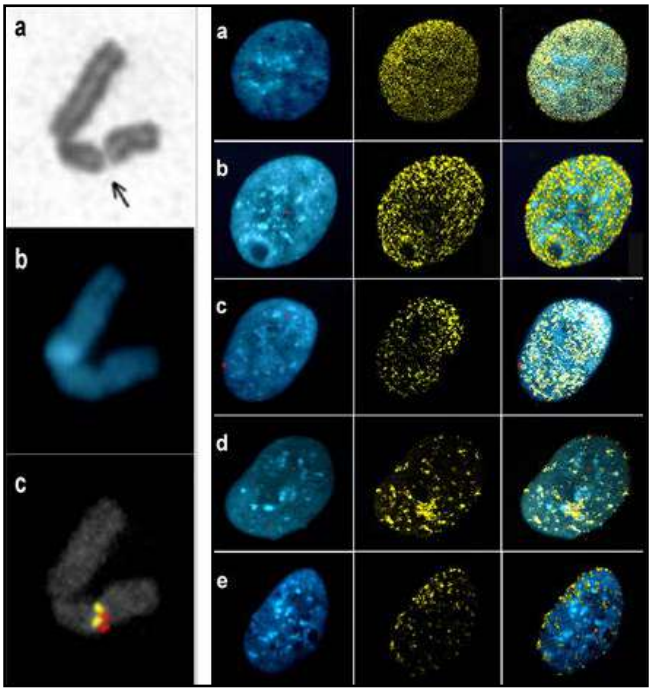

Figure: Left: Identification of the 1p31.1 fragile region. The break on the short arm of chromosome 1 identified with Giemsa staining (a); (b) the same chromosome visualized with DAPI; distal and proximal probes are localized by subsequent FISH staining (c). Right: BrdU replication labelling on interphasic nuclei from first (S1) to last (S5) stage of S-phase. Nuclei stained with DAPI (blue) and FISH (red), BrdU (yellow) and merge (right) showing S1 phase (a), S2 phase (b), S3 phase (c), S5 (d) and S5 phase (e).

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Lucia
Piacentini
Associate Professor

ORCID

RESEARCH LINES

- Transposable elements in stress response and genome evolution
- Transposable elements in neurodegenerative diseases
- Epigenetic regulation of adult stem cell function

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Full Professor (UPO)

GRANTS

OFF Healt s.p.a, Contratto Conto Terzi, Biosintesi di Lanosterolo in E.coli, € 35000. PI: Lucia Piacentini
Fondazione Terzo Pilastro, Drosophila melanogaster as a model to study *in vivo* the functional role of Transposable Elements (TE) in Huntington's disease pathogenesis (HD), € 35000.

RESEARCH ACTIVITY

The research activity is mainly focused on understanding the impact of transposable elements (TEs) in stress response, genome evolution and age-related neurodegenerative diseases. Another major interest of our research is the study of the epigenetic basis of stem cell self-renewal and differentiation.

Transposable elements as environment-sensitive sources of genotypic and phenotypic variability. Transposable elements (TEs) are repetitive mobile genetic elements that represent a large fraction of most eukaryotic genomes and are known to have an important and global impact on genome evolution. TEs are potentially able to modulate host gene expression networks in response to specific environmental stresses thus triggering rapid adaptive phenotypic and genotypic responses. We demonstrated that TE activity can be modulated in response to different types of biotic and abiotic stresses, and identified the Hsp70 chaperone as a key positive regulator of stress-induced transposon mobilization. These results shed new light on our understanding of evolutionary dynamics because they establish that the environment acts not only to select the most suitable physiological traits, but also as an inducer of genetic variability through stress-induced TE activation. Moreover, our studies reveal that genomes can intentionally respond to stress by mobilizing TEs, thus supporting the evocative idea that evolutionary processes may be sped up, potentiated in response to drastic environmental changes. (Figure 1)

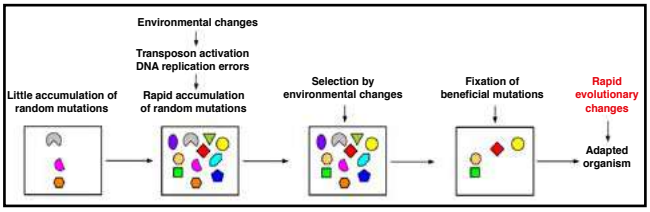

Figure 1. Stress induced transposon activation leads to rapid accumulation of random mutations, generating a new state of 'induced evolutionary plasticity' on which stress selection might act to establish more favourable mutations.

TE activity in neurodegenerative disorders. Given the growing evidence of an association between unregulated TE activation and diseases of the nervous system, another major focus of the lab research is to investigate the molecular mechanisms by which TEs contribute to cellular toxicity in neurodegenerative diseases. In detail, our findings demonstrated that TE expression and mobilization are strongly increased in a Drosophila model of Huntington's disease (HD). Importantly, by inhibiting TE mobilization by Reverse Transcriptase (RT) inhibitors, polyQ-dependent eye neurodegeneration and genomic instability in larval brains are rescued, and fly lifespan is increased, thus suggesting that TE activation may represent an important piece in the complicated puzzle of polyQ-induced neurotoxicity.

Heterochromatin protein 1 (HP1) and epigenetic regulation of germ line stem cell maintenance. Our studies on Heterochromatin organization and function led to the discovery that Heterochromatin Protein 1 (HP1), an evolutionarily conserved epigenetic adapter mainly implicated in heterochromatin formation and epigenetic gene silencing, is also involved in the positive regulation of gene expression by stabilizing RNA transcripts and protecting them against premature and rapid degradation. This novel and unexpected role for HP1 in post-transcriptional regulation of gene expression certainly expanded our understanding about the functional versatility of HP1 in epigenetic regulation, and has allowed us to show another important role for HP1 in Drosophila germ line stem cell proliferation and differentiation. (Figure 2)

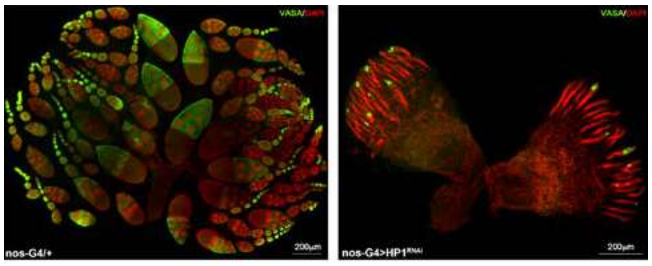

Figure 2. Developing ovaries obtained from newly eclosed females stained for Vasa (green) and DAPI (red)

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Grazia Daniela
Raffa
Associate Professor

ORCID

RESEARCH LINES

- The control of telomere protection in Drosophila melanogaster.
- Regulation of telomerase and telomere homeostasis in human cells.
- The role of 3' end processing of noncoding RNAs in Spinal Muscular Atrophy (SMA)

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Valeria Luciana Palumbo,
Researcher

GRANTS

Telethon - GPP13147-A Drosophila Model for Spinal Muscular Atrophy (SMA), Grazia D. Raffa, € 117.100
Istituto Pasteur - Fondazione Cenci Bolognetti-Programmi di ricerca **2015-2017. "Under 40".**
A Drosophila model for Spinal Muscular Atrophy (SMA): identification and characterization of Smn interactors and phenotypic modifiers. Grazia D. Raffa, € 60.000

RESEARCH ACTIVITY

Lines 1 and 2. We have identified four novel proteins that are essential for preventing telomere fusions in Drosophila, and defined the organization of terminin, the telomere capping complex in flies. We are currently characterizing new terminin interactors, to identify novel telomeric proteins whose human homologs might play a conserved role at telomeres. We have recently found that one of the terminin interactors, the TGS1 hypermethylase, is a negative regulator of telomerase activity and telomere length in human cells (Figure, upper panel). These results show that Drosophila is a powerful system to study conserved mechanisms of telomere maintenance. We are currently investigating TGS1 inhibitors as potential therapeutic treatments for short-telomere syndromes.

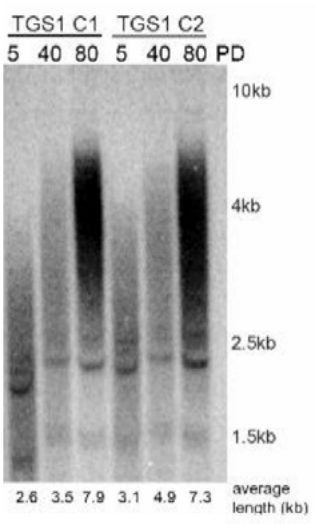

Figure. Deficiency of the Trimethylguanosine synthase TGS1 induces a net increase in telomere length. TRF analysis was performed on TGS1 CRISPR UMUC3 cell lines.

Line 3. Spinal muscular atrophy (SMA) is a severe neurodegenerative disease, characterized by defects in RNA splicing. We recently developed a Drosophila model to identify novel genetic interactors of SMN, the causative factor for SMA. We are currently exploring the functional relationships between SMN and TGS1 in different animal models. We have found that in flies, Tgs1 forms a complex with all the components of the Smn complex in vivo. Depletion of either Tgs1 or Smn by RNAi induces very similar cell death phenotypes in the eye imaginal discs (Figure, lower panel). In addition, expression of fly or human TGS1 can rescue the defects induced by depletion of SMN. We also performed transcriptome studies in CRISPR-derived human cells deficient for TGS1, which led to the finding that TGS1 plays a novel role in the biogenesis of small nuclear RNAs. By combining studies in Drosophila and in human cells, our aim is to explore the functions of SMN, TGS1 and their interactors, to elucidate how perturbations in the transcriptome induce neurological phenotypes relevant for disease.

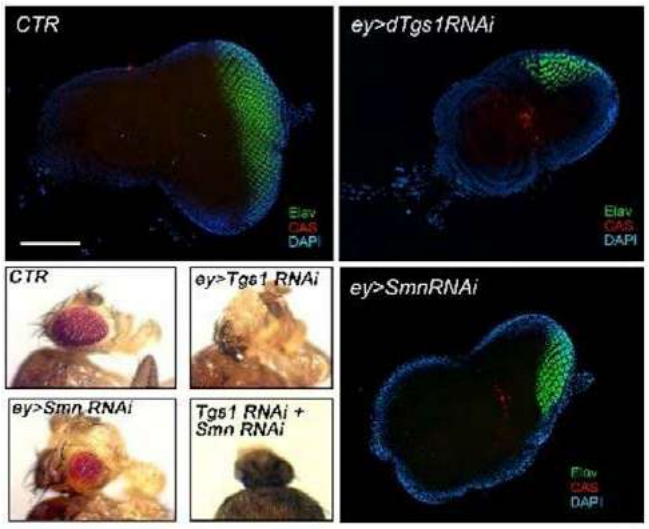

Figure.
Downregulation of dTgs1 or Smn in the eye imaginal discs induces apoptosis of retinal precursor cells and defective eye development. Representative examples of eye-antennal imaginal discs and adult head structures from flies carrying the ey-Gal4 driver (ey) alone (CTR) or in combination with the Tgs1RNAi, the SmnRNAi construct or both.

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Isabella
Saggio
Associate Professor

ORCID

RESEARCH LINES

- Stem cells and gene therapy
- Telomeres, DNA integrity, nuclear envelope and cell homeostasis

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GRANTS

2020-25. AIRC Five Year Investigator Grant: PI: Isabella Saggio
2020. BeForErc
PI: Isabella Saggio
2017-19. Progeria Research Foundation USA
PI: Isabella Saggio

www.saggiolab.com

RESEARCH ACTIVITY

Stem cells and gene therapy. In the course of her scientific career at Sapienza and in association with the laboratories of San Raffaele Science Park, I. Saggio has been involved in the study of stem cells and contributed to unravel the characterization of stem cell progenitors as organizers of the hematopoietic microenvironment (Sacchetti et al Cell 2007; Sacchetti et al Stem cell reports 2016). In addition, the I. Saggio laboratory has experience in vectors for gene and stem cell therapies, including lentiviral, adenoviral and humanized phages (patented WO 02/24934). For oncological purposes I. Saggio developed growth factor antagonists, and expressed them with adenoviral vectors as proof of principle studies of customized tumor gene therapy (Saggio et al Gene therapy 1997; Di Marco et al PNAS 1996; and patent on viral vectors WO 98/13383).

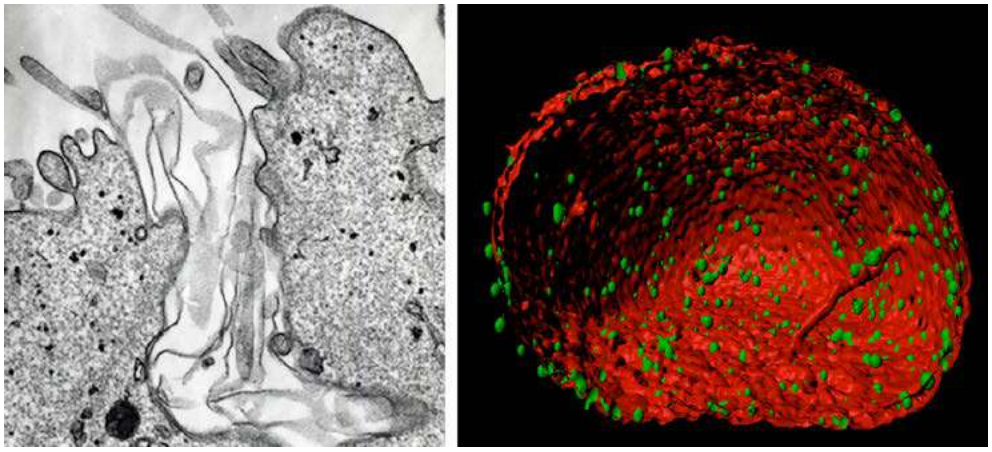

Figure. Left: Electron microscopy image of humanized bacteriophages. Right: Super resolution microscopy images of AKTIP (green) at the nuclear envelope.

Telomeres, DNA integrity, nuclear envelope and cell homeostasis. I. Saggio identified the first human telomere-associated factor linked with the nuclear envelope. Telomere dysfunction is a cancer driver, thus the identification of new factors associated with telomeres contributes to the dissection of molecular mechanisms in cancer (Burla et al Plos Genetics 2015; Cenci et al Plos Genetics 2015; Burla et al Open Biology 2016; La Torre et al Aging Cell 2018, Chen et al. Cell Reports 2019). Moreover, building on the link between telomeres and the nuclear envelope, I. Saggio developed new research focusing on the interconnection between chromatin structure and nuclear integrity in aging and cancer. These studies were recognized internationally and funded by the Progeria Research Foundation USA and by AIRC.

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Beniamino
Trombetta
Associate Professor

ORCID

RESEARCH LINES

- Human genetic diversity
- Molecular evolution
- Y chromosome phylogeography
- Ancient DNA

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GRANTS

2020. Gerda Henkel Foundation (co-PI; € 12000) "A window on the Etruscan world"

RESEARCH ACTIVITY

I have always worked in the field of population and computational genomics. The main research activity carried out in my lab concerns the study of human genetic variation with different approaches and aims. My lines of research branch out in three main directions.

Line 1. Archeogenetics: This line of research is based on the study of ancient DNA (aDNA). By using next generation sequencing (NGS) technologies, we analyse ancient genomes to reconstruct the cultural and genetic heritage of central Italy. We focused our attention on the Piceni: a pre-Roman population, whose culture was absorbed by the Roman society after the III cent. BC. We also intend to clarify the genetic legacy of the Roman expansion and understand the possible genetic continuity between ancient and modern populations within the same geographic area. To reach this goal, we scan several ancient and modern samples at the level of WGS. The former include pre-Roman populations settled in central Italy, such as Piceni, Latini and Umbri, from necropolises of the Iron Age and Romans; the latter are autochthonous subjects from all the administrative provinces of the same area. We will also have the possibility to analyse Neolithic and Eneolithic samples belonging to populations living in the same area of the Piceni.

Line 2. Human evolutionary genetics and Y chromosome phylogeography: Phylogeography is the study of past demographic processes that shaped the genetic diversity of one species. By analyzing autosomal and Y chromosome human genetic variation, we are able to reconstruct the evolutionary history of modern human populations. In many years of research, we focused our attention on African populations and we identified several fundamental demographic processes ranging from the first human movements within the African continent to more recent migrations across the Sahara desert.

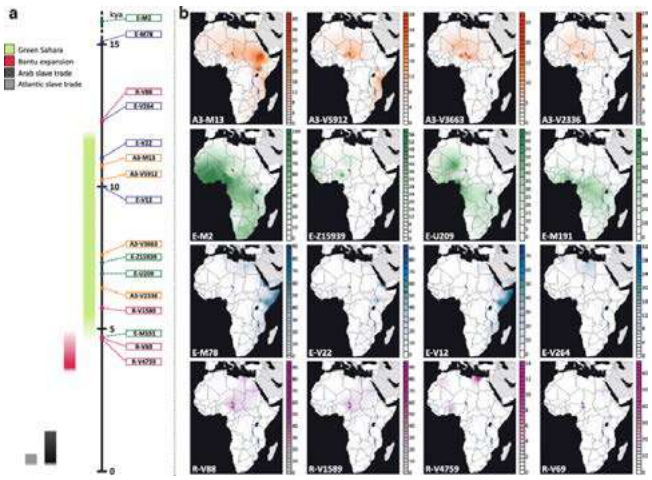

Figure 1: Time estimates and frequency maps of the four trans-Saharan haplogroups and major sub-clades (from D'Atanasio et al. 2018).

Line 3. Molecular evolution of the human genome: The standard approaches of NGS might not be suitable for the analysis of variation in Segmental Duplication (SD) due to the disproportion between the length of NGS reads and the greater length of SD in the human genome. Generally, each read deriving from different highly similar repeats could be not-univocally mapped within the reference genome. We elaborated new computational methods to analyze genetic variation within SD and accurately described the evolutionary dynamics (mutation and gene conversion) of the segmental duplications associated with the human Y chromosomes.

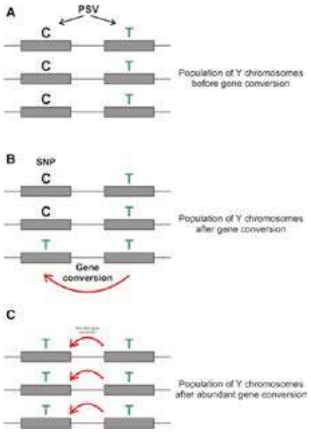

Figure 2: effect of mutation and gene conversion on the diversity of SDs associated with the human Y chromosome (from Trombetta and Cruciani 2017).

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Fiammetta
Vernì
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ORCID

RESEARCH LINES

- Vitamin B6 diabetes and cancer
- Diabetes and DNA damage

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RESEARCH ACTIVITY

Our research activity aims to elucidate the relationship between vitamin B6, diabetes and cancer using Drosophila as a model organism. Vitamin B6 active form, pyridoxal 5'-phosphate (PLP), is produced by the enzymes pyridoxal kinase (PDXK) and pyridoxine 5'-phosphate oxidase (PNPO), that recycle B6 vitamers taken from food, such as pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM). PLP is involved as a cofactor in more than 150 metabolic reactions and elicits antioxidant effects.

We provided evidence that vitamin B6 plays a role in genome integrity maintenance and glucose homeostasis in flies. Mutations in the gene encoding pyridoxal kinase (dPdxk) as well as the depletion of PNPO cause chromosome aberrations (CABs) and increase the glucose content in larval hemolymph. We demonstrated that hyperglycemia and CABs are correlated when PLP levels are low and proposed a model according to which PLP deficiency increases glucose content that, in turn, elicit the formation of Advanced Glycation End products (AGEs) which are responsible for CAB formation as their metabolism is associated to ROS production.

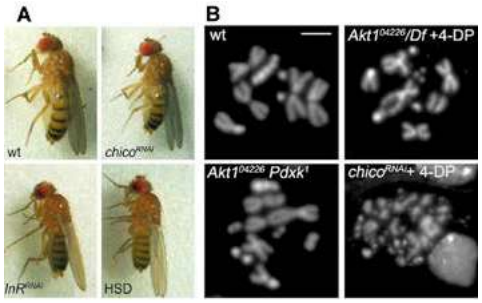

Figure.
A. Examples of body size reduction (a hallmark of diabetes in flies) observed in In^{RRNAi}, $chico^{RNAi}$ and HSD fed flies compared to wild type control.
B. Examples of complex rearrangements and metaphases with multifragmented chromosomes observed in chicoRNAi and $Akt1^{04226}$/Df neuroblasts from larvae fed with 4-DP (a PLP inhibitor) and from $Akt1^{04226}$ $dPdxk^{1}$ double mutant larvae (Scale bar 5 μm).

Moreover we showed that the expression of the human PDXK gene in dPdxk1 mutant flies rescues CABs and hyperglycemia, while, in contrast, the expression of four human PDXK variants in dPdxk1 mutant flies failed to rescue both chromosome damage and hyperglycaemia. We also demonstrated that low levels of vitamin B6 are much more genotoxic in diabetic flies than in non-diabetic individuals, indicating that vitamin B6 deficiency may represent a cancer risk factor for diabetic patients. Currently, we are investigating whether reduced PLP levels can impact on cancer onset and/or progression in Drosophila.

Although it is well known the role of vitamin B6 in cancer, underlying mechanisms remain to date unknown. We already collected encouraging results indicating that low PLP levels increase the malignancy of both Ras and Ras/Src. Next step will be understand whether DNA damage plays a role in this process and also to understand whether vitamin B6 impacts on cancer as antioxidant molecule or as cofactor of enzymes involved in DNA metabolism such as SHMT or GDC.

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“SAN LORENZO”

The RM024 building is a former brewery built at the beginning of the 20th century in the heart of Rome’s San Lorenzo district. It was first known as the Paszkowsky and later as the Wuhrer building. Like many of the former factory buildings nearby (Vetreria Sciarra, ufficio direzionale delle poste, etc), it was acquired by Sapienza University to face the huge increase in the student number during the years.

Today, the building hosts three University Departments and several research groups from CNR-IBPM (Institute of Molecular Medicine and Pathology) in the framework of an agreement to constitute a joint research collaborative structure between Sapienza and CNR. A section of the Department of Biology and Biotechnologies is located on floors 1, 2 and 3 of the building, where many research groups are studying biological processes in a variety of model organisms. Virology, Immunology, Microbiology, Genetics, Neurobiology, Plant Biology, Epigenetics and RNA metabolism are among the research topics.

On the third floor are three laboratories (Microbiology, Molecular Biology and Cellular Biology) which are considered among the best equipped in Sapienza and are used for practical work training by a large number of students from many different academic Courses.

In collaboration with CNR, which shares a part of the laboratories, the building hosts a “State of the Art” Microscopy Center, inserted in the Microscopy Network of National Interest, that is heavily used by many research groups of Sapienza. Other noteworthy technological infrastructures available in the building include: a transcriptomic platform equipped with two microarrays laser-scanners (Packard) and a hybridization facility (Agilent); a proteomics facility equipped with an FT-Orbitrap mass analyzer; cytofluorimeters; temperature-controlled growth chambers for bacteria and various model organisms; and temperature and light-cycle controlling phytotrons.

A small library is located on the first floor. And a classroom on the second floor is dedicated to the memory of Franco Tatò, an unforgettable brilliant microbiologist.

Fiorentina
Ascenzioni
Associate Professor

ORCID

RESEARCH LINES

- Microbicidal mechanisms of phagocytes and the bacterial defense pathways in macrophage and Pseudomonas aeruginosa interaction
- Molecular mechanisms of antibiotic resistance and identification of drugs that inhibit resistance
- Biofilms as targets for the selection of antimicrobial drugs

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GRANTS

2019. Pharmacological inhibition of colistin resistance in gram-negative cystic fibrosis pathogens, 2 years multicenter project, italian cystic fibrosis research foundation, PI.

RESEARCH ACTIVITY

Cystic Fibrosis, the most common life-limiting genetic disease, is the main focus of my research since many years. CF is caused by mutations in the CFTR gene, which can be targeted by gene therapy, and for which we have developed non-viral vectors for the delivery of the wild type CFTR to CF cells. More recently, we are investigating the molecular mechanisms that make these patients particularly susceptible to lung infections by opportunistic pathogens, such as *Pseudomonas aeruginosa*. For the first time we have identified a defective microbicidal activity of the human macrophages from CF patients against *P. aeruginosa*. On the basis of this study, and to identify the molecular pathway/s underlaying this defect, we moved our attention to the oxidative mechanisms that contribute to counteract bacterial infection. We are investigating the interplay between the oxidative burst and the ROS scavenger activity of *P. aeruginosa*. In particular, we are studying the role of the *P. aeruginosa* superoxide dismutases, SOD, to counteract the macrophagic microbicidal mechanisms (Figure).
Antibiotic resistance, in particular resistance mechanisms, is a more recent research subject of my group. We are focusing on "highest priority critically important antimicrobials" (World Health Organization) which are associated to high risk of resistance. Colistin is one of these, being the last-resort therapeutic option against multi-drug-resistant Gram-negative pathogens. By targeting the most prevalent colistin resistant mechanism in *P. aeruginosa* we have identified specific inhibitors of ArnT, a key enzyme of resistance, that restore colistin activity in otherwise resistant strains. We are presently working on drug optimization and development of specific delivery systems for both planktonic bacteria and biofilms.

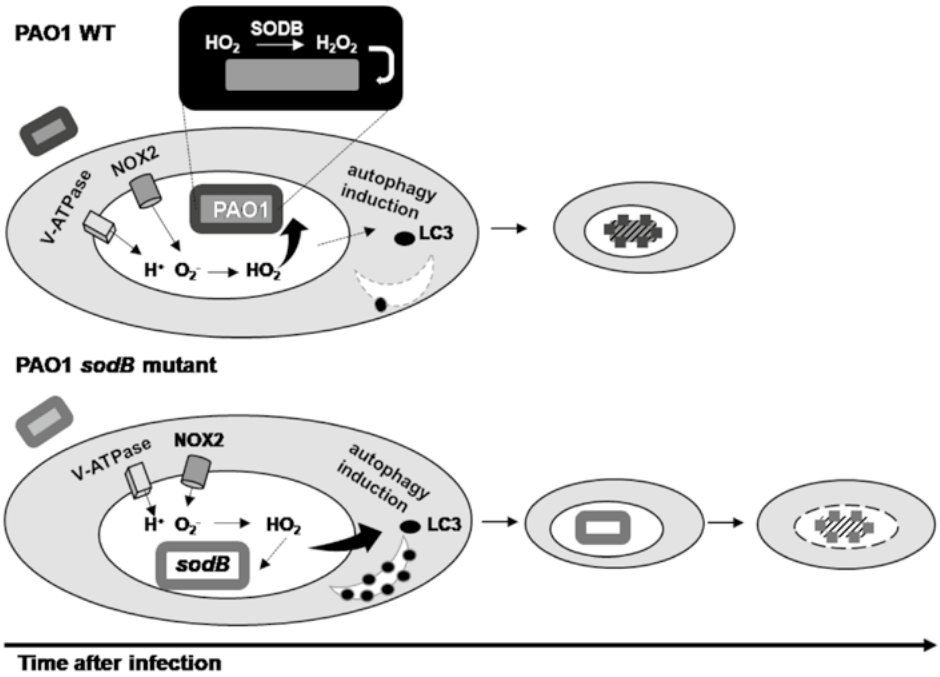

Figure. The role of SODB in P. aeruginosa killing by macrophages, a working model. The NOX2, NADPH oxidase, pumps superoxide radicals (O_2^-) into the phagosome lumen. Here, the protonated form of O_2^- (HO_2) can pass into the engulfed bacteria or the host cytosol. The bacterial SODB activity (PAO1 WT) dismutates HO_2 within its periplasm into H_2O_2 which is lethal for the bacterium itself. Of note the bacterial SODB contributes to O_2^- depletion from phagosome. In the absence of SODB activity (PAO1 sodB mutant), the phagocytic HO_2 is mainly transferred to the macrophagic cytosol, where it promotes autophagy induction, which in turn improves bacterial killing at the later stages following infection.

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Daniela
Bellincampi
Full Professor

ORCID

RESEARCH LINES

- Cell wall in plant resistance to pathogens: biochemical characterization, regulation and physiological role of cell wall proteins (enzymes and inhibitors)
- Agricultural By-products into valuable Assets for Sustainable Agriculture

STAFF | COLLABORATORS

Laura Vittozzi,
PhD student (Sapienza)
Daniela Pontiggia,
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M.Manuela Rigano,
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M.Rosaria Fullone,
Assist. Professor (Sapienza)
Thierry Giardina,
Full Professor (AixMarseille University)

GRANTS

2018. LazioINNOVA, PROGETTI - GRUPPI DI RICERCA. "Agricultural By-products into valuable Assets for Sustainable Agriculture. prot. n 85-2017-15080 - CUP: B81G18000770002 €150.000.

RESEARCH ACTIVITY

One research line aims at providing new knowledge in order to improve plant resistance to fungal disease and move towards sustainable agriculture. Botrytis cinerea and Fusarium graminearum are important fungal necrotrophs that cause serious pre- and post-harvest damage to plant organs including leaves, fruits and spikes of dicot and monocot species respectively. Pectin integrity alteration, pectin methylesterification status and pectin methylesterase (PME) activity can impact on plant disease resistance.
Currently the knowledge on molecular mechanisms underlying PME-mediated immunity is limited. A reverse genetics approach combined with biochemical studies and plant molecular biology is utilized in the Arabidopsis model plant to identify the functional role of pathogen-responsive PME isoforms and of PME inhibitors (PMEI) induced in response to pathogens.
Efforts are devoted to defining the three-dimensional structure of the single proteins and complexes (in collaboration with Institute of Molecular Biology and Pathology-National Research Council, Biochemical Sciences Department of Sapienza University and AIX Marseille University-FR) to provide insight into the specificity of plant PMEs towards PMEIs.
The identification of molecular factors triggering PME expression and regulating PME activity during infection is another important task of this research. Dynamics of cell wall changes during infection are monitored with advanced analytical platforms (glycome profiling). The identification of new genetic determinants underlying pectin integrity maintenance will be useful for obtaining plants with improved resistance to pathogens.
Another research line aims to recover, through advanced membrane Tangential Filtration technologies (in collaboration with ENEA-National Agency for new technologies, energy and sustainable economic development), value-added biomolecules such as oligosaccharins and phenols, present in the oil waste, to be reused in agriculture, as biopesticides, photoprotectors and to utilize fractions rich in mineral salts as soil biofertilizers.
This in the view of a circular economy for the recovery of plant products with high added value to be reused in agriculture.

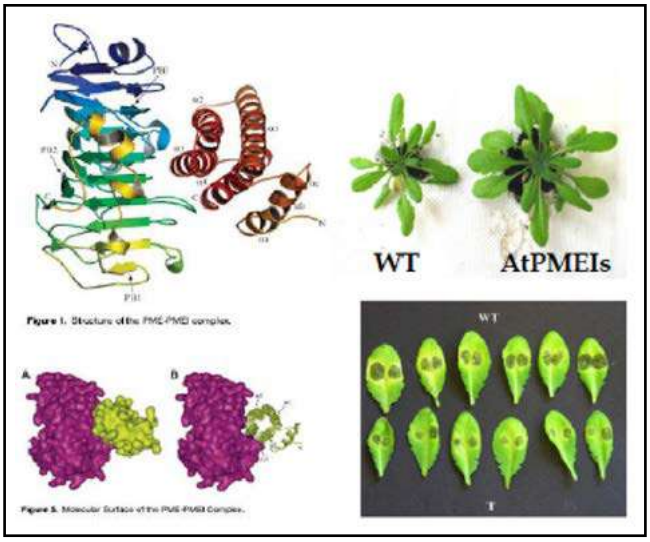

Figure. Left panel, Structure and molecular surface of the PME/PMEI-complex. Right panel, phenotype and reduced susceptibility to B.cinerea of Arabidopsis plants overexpressing PMEI (T) respect to the Control (WT).

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Maria Lina
Bernardini
Associate Professor

ORCID

RESEARCH LINES

- Study of the interaction between host response and bacterial infection. A special interest has been dedicated to bacterial vaccine development and pre-clinical studies.

STAFF | COLLABORATORS

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RESEARCH ACTIVITY

Cellular Microbiology and innate immunity. My research activity have been focused on the mechanisms underlining the interplay between pathogenic bacteria and host cell response. My attention was mainly focused on the invasion process of the enteropathogen Shigella flexneri. I have also supplemented these studies with the assessment of the innate immune responses to bacterial MAMPs (Microbial Associated Molecular Patterns), with a special interest to lipopolysaccharide (LPS) and peptidoglycan (PGN). This approach led to the analysis of the role played by LPS of various pathogens and commensals in their strategies to survive in the host.

Shigella vaccine development. Over the years, I also opened a research line aimed at the design and development of a *Shigella* vaccine, in the framework of various projects funded by the EU commission and WHO. In collaboration with a veterinary team at the University of Camerino we settled animal models to test the Shigella vaccines. Finally, on the basis of this expertise, in the last year I acted as principal investigator in the preclinical studies in the *Shigella* vaccine development.

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Bianca
Colonna
Full Professor

ORCID

RESEARCH LINES

- Regulation of MDR efflux pumps in response to intracellular stimuli
- Molecular events in the evolution of Shigella

STAFF | COLLABORATORS

Gianni Prosseda,
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Giulia Fanelli,
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Marco Coluccia,
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Frederic Barras,
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GRANTS

2020-22. MAECI Italia - Giappone (PGR07208) Combination therapies for fighting antibiotic resistant bloodstream infections in cancer patients.
2017-22. MIUR PRIN (20177J5Y3P) Next-generation antibacterials: new targets for old drugs and new drugs for old targets.

RESEARCH ACTIVITY

Regulation of MDR efflux pumps in response to intracellular stimuli. Efflux pumps (EPs) represent an important and large group of transporter proteins found in all organisms. The importance of efflux pumps resides in their ability to extrude a wide range of antibiotics, resulting in the emergence of multidrug resistance (MDR) in many bacteria. MDR EPs are able to export a large variety of molecules and are emerging as relevant elements in interactions with other bacteria and with plant or animal cells. We have recently analysed the contribution of MDR EPs during the intracellular life of two groups of pathogenic E. coli, *Shigella* and Adherent Invasive E. coli (AIEC), characterized by their ability to invade the host cells. The results indicate that the expression of MDR EPs is differentially modulated during the intracellular life of the bacterium and that the MFS-type EmrKY efflux pump of *Shigella* and the RND-type MdtEF efflux pump of AIEC contribute significantly to bacterial survival in the harsh macrophage environment. Currently we are addressing the following issues: how relevant are MDR EPs for the intracellular life of *Shigella* and AIEC in epithelial cells? Which regulatory networks allow the activation of specific MDR efflux pumps in response to intracellular environments?

Molecular events in the evolution of *Shigella*. It is well known that *Escherichia coli* is not only a harmless commensal of the human and animal intestine but also a major cause of morbidity and mortality. The evolution of *E. coli* towards pathogenic phenotypes has been determined, as in many other bacterial pathogens, mainly by two mechanisms: the acquisition of virulence genes by horizontal gene transfer as parts of plasmids, phages or pathogencity islands, and the silencing of genes of the core genome. In *Shigella*, currently regarded as an invasive pathogenic *E.coli*, the critical event towards a pathogenic life-style has been the acquisition a large plasmid (pINV) containing the genes required for invasion, intracellular survival and spreading through the intestinal mucosa. The ample gain in virulence determinants has been counteracted by a substantial loss of functions that, although important for the survival in the environment, are redundant or even deleterious for survival inside the host. We have contributed to the characterization of novel antivirulence loci mainly related to the polyamine metabolism (*cad, speG*). Currently we are investigating whether other housekeeping genes of *Shigella* have been disrupted or lost to increase the bacterial fitness in the host.

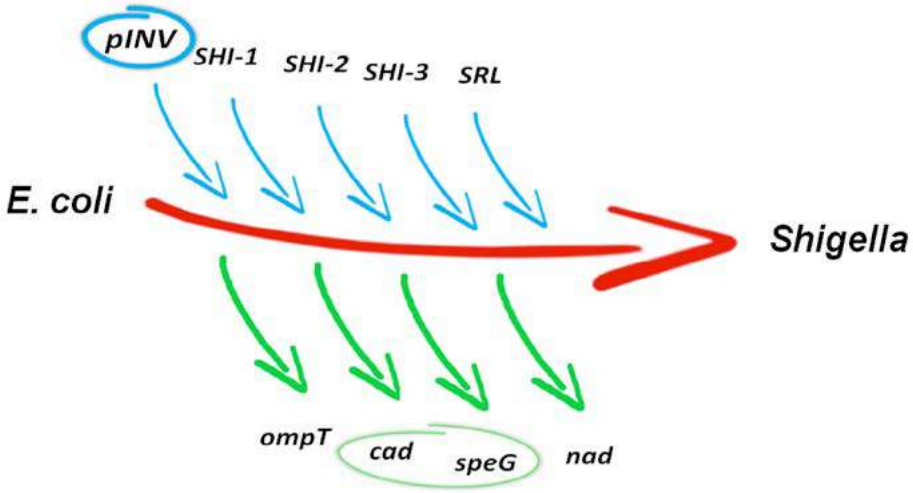

Figure. Genetic events contributing to the evolution of Shigella from ancestral commensal E. coli. The acquisition of the virulence plasmid (pINV) by horizontal gene transfer is a major evolutionary event towards pathogenicity. This has been flanked by the acquisition of the SHI-1, SHI2, SHI 3, and SRL pathogenicity islands. The loss of the antivirulence genes ompT, nad, cad, and speG has contributed to the optimization of the virulent phenotype

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Giulia
De Lorenzo
Full Professor

ORCID

RESEARCH LINES

- The interplay between plant immune and developmental processes induced by cell wall-derived DAMPs
- Homeostasis of cell-wall derived DAMPs

STAFF | COLLABORATORS

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Assist. Professor (Sapienza)
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Assoc. Professor (Sapienza)
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Benedetta Mattei,
Full Professor (Università dell'Aquila)
Charles Melnik,
Assist. Professor (Swedish University of Agricultural Science)
Carlos Labate,
Full Professor (University of Saõ Paulo, Piracicaba, Brazil)

GRANTS

2017. MIUR PRIN - ZBBYNC
€ 206.843 (PI)
2017. MIUR PON "ORIGAMI";
€ 203.000 (participant)

RESEARCH ACTIVITY

When challenged by biotic stresses, plants rely on their innate immune system, which can be activated by Microbe-Associated and Damage-Associated Molecular Patterns (MAMPs and DAMPs). Activation of immunity is accompanied by a down-regulation of growth (growth-defense trade off). Several oligosaccharide fragments that act as DAMPs are released from the plant cell wall (CW) during pathogenesis by microbial or plant-derived enzymes. Known CW-derived DAMPs are the oligogalacturonides (OGs), released upon degradation of homogalacturonan (HGA), and the products of cellulose breakdown, i.e. cellodextrins (CDs). In animals, hyaluronan, a linear negatively-charged polysaccharide can be considered the vertebrate counterpart of HGA and is a molecule with critical roles in homeostasis as well as onset, progression, and recovery or decline of diseases. Although OGs are the first DAMP ever discovered, much is unknown about their biology due to the complexity of their mediated signaling and the difficulty of isolating mutants defective in specific or general responses to OGs. By exploiting unique tools and expertise developed over many years, the laboratory aims at disentangling the interplay between plant immune and developmental processes played by OGs and CDs. Moreover, mechanisms for the homeostasis of these signals that rely on specific oxidases are a special focus of our studies. Acquired knowledge will be crucial for breeding- and biotechnology-based strategies aimed at reducing crop losses caused by diseases.

Line 1. Plants [OG-machine (OGM) plants] have been obtained capable of generating elicitor-active OGs on command in planta. Exaggerated OG levels lead to inhibition of growth and eventually plant death, reflecting a growth-defense trade off. The pathways involved in the hyper-immunity response caused by high OG levels is under dissection using plants expressing the OGM in backgrounds mutated in immune-related transduction/response elements. The role of changes of ROS and Ca2+ flux triggered by OGs and CDs in immunity and development will be elucidated with a special focus on the root. Evidence suggests the involvement of PCAP1, a PM cation-binding protein, ANPs, MAPKKKs that plays a role in the oxidative burst induced by OGs, and type 2b plasma membrane (PM) Ca2+-ATPases (ACAs) in both OG and CD signaling. The role of these elements is being investigated.

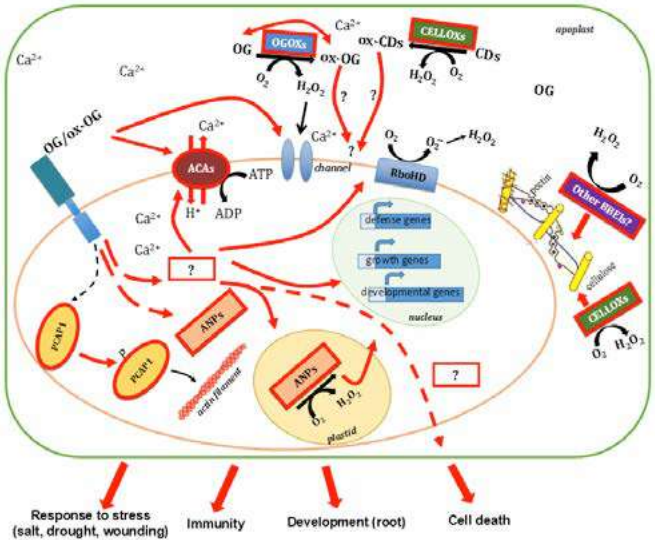

Figure. Mechanisms and processes investigated in the laboratory are indicated with red frames and arrows. Broken arrows indicate multiple still uncharacterized steps.

Line 2. We have discovered a novel mechanism that likely controls the homeostasis of OGs and CDs, and prevents the deleterious effects of their accumulation. It relies on H2O2-generating FAD-dependent oxidases (OGOXs and CELLOXs) that belong to the large subfamily of berberine-bridge enzyme-like (BBEl) proteins that inactivate OGs and CDs. This novel research area addresses the control of DAMP-triggered immunity to avoid deleterious effects and aims at defining if CW-derived DAMPs act in concert and their oxidation merely dampens the immune response or modulates it for a finely tuned output. Evidence indicates that these oxidases are important in developmental processes and also this role is being investigated. Moreover, we hypothesize that the BBEl family represents a general oxidation machinery for CW substructures, and other BBEl members are being studied to assess if they can oxidize other types of CW-oligo/polysaccharides.

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Raffaele
Dello Ioio
Researcher

ORCID

RESEARCH LINES

- Asymmetric Cell Division
- Evolution and Development
- Plant Science
- Stem cells

STAFF | COLLABORATORS

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Research director (Max Planck Institute for Plant Breeding)
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Researcher (University of Milan)
Riccardo Di Mambro,
Assoc. *Professor (University of Pisa)*

RESEARCH ACTIVITY

Our general interest is to uncover the molecular mechanisms governing anatomical diversity among species. One classic example of this diversity resides in root cortical layer number variability, that can span from one to several according to the plant species. The cortex is among the root tissues that contributes most to plant adaptive potential. For example, in plants living on wet soils, such as rice, secondary growth of the cortex gives rise to the aerenchyma, a tissue controlling the air/water ratio, whereas in plants living in unfavourable conditions, such as turnip, the cortex originates storage parenchyma, a tissue where carbohydrates such as starch are stored. Hence, the study of the molecular and genetic basis governing root cortical layer number variability has both conceptual and biotechnological outcomes. On the conceptual point, this system allows the study of the genetic mechanisms giving rise to functional, morphological and anatomical differences; on the biotechnological point manipulation of cortical layer number will enable an increased crop performance in hostile soils. To discover those genetic and molecular networks at the basis of root cortical layer number variability, my group utilizes a comparative development approach between the roots of the well-known plant model system Arabidopsis thaliana (one cortical layer) and of its close relative Cardamine hirsuta (two cortical layers). Since root cortical layer/s derive from the asymmetric cell division of a set of stem cells, our research largely involves the temporal and spatial in vivo tracing of molecular factors that govern cell cycle and control proper cell fate acquisition. We also aim to expand the acquired knowledge to phylogenetically distant plant species showing multiple cortical layers such as turnip, rice and tobacco to generate crops with higher adaptive potential to disturbed conditions such as dry or wet soils.

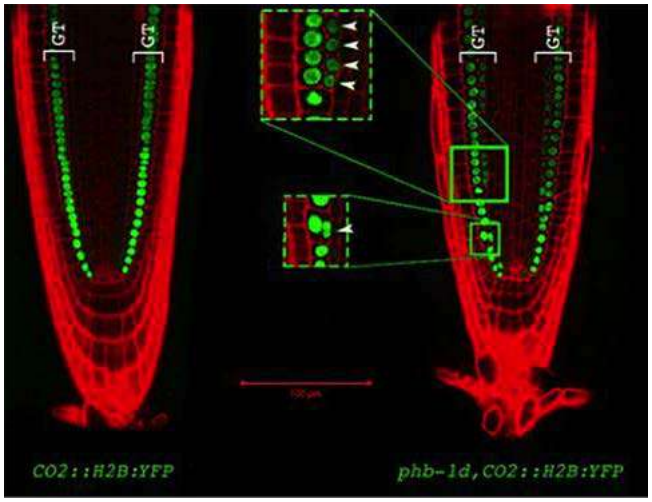

Figure: Confocal images of 4 days post-germination root meristems of Wt Arabidopsis (on the right) and the double cortical layer mutant phb-1d (on the left) harbouring the cortex specific promoter CO2 driving the expression of the nuclear localize fluorescent reporter VENUS (CO2::NLS3xVENUS).Please note that in Arabidopsis VENUS signal is present in only one tissue layer, whereas in phb-1d in two. Blow up: Asymmetric cell divisions occurring in the cortex layer of phb-1d mutants. Scale Bars: 50 µm.

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Paola
Del Porto
Associate Professor

ORCID

RESEARCH LINES

- Study of the interplay between host immune response and viral infections (HCV, HPV)
- Role of the cystic fibrosis transmembrane conductance regulator (CFTR) in innate immune cells

STAFF | COLLABORATORS

Fiorentina Ascenzioni,
Assoc.Professor (Sapienza)
Anna Rosa Garbuglia,
Researcher (Laboratory of Virology, 'Lazzaro Spallanzani', National Institute for Infectious Diseases, IRCCS, Rome, Italy)

RESEARCH ACTIVITY

My research activity is focused on the study of the interaction between the host immune response and microbial infections. In particular in the past, I have investigated the mechanisms employed by the hepatitis C virus to escape the host adaptive immune response demonstrating that the chronic evolution of the disease is associated with the emergence of escape mutations in cytotoxic T cell epitopes.
An additional scientific interest has been to investigate the expression and the role of the cystic fibrosis transmembrane conductance regulator (CFTR) in human monocyte/macrophages. In this context we demonstrated that human macrophages express CFTR and that dysfunctional CFTR is associated with defective bactericidal activity in such cells. More recently, we performed miRNA profiling in macrophages from cystic fibrosis (CF) individuals to determine whether miRNA dysregulation underlies the functional abnormalities of macrophages carrying dysfunctional CFTR.
We demonstrated that CF macrophages display increased miR-146a and that inhibition of miR-146a significantly increases IL-6 protein and mRNA levels in CF macrophages compared to controls.

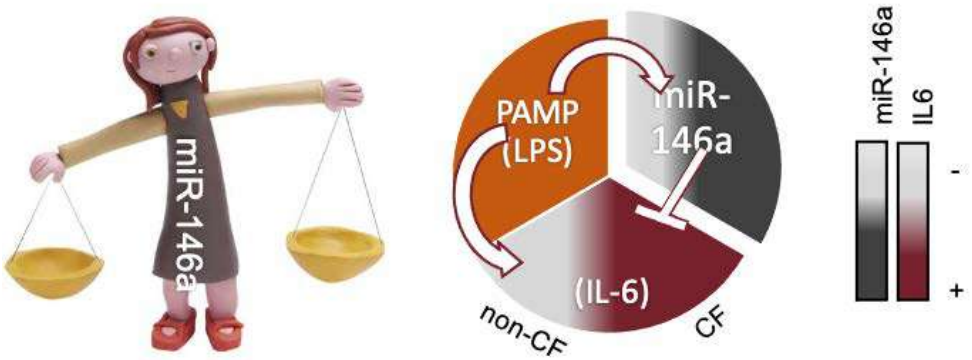

Figure. Model explaining the role of miR-146a in controlling the inflammatory response of macrophages carrying dysfunctional CFTR. image).

References

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3. Lévêque M, Le Trionnaire S, Del Porto P, Martin-Chouly C. The impact of impaired macrophage functions in cystic fibrosis disease progression. J Cyst Fibros. 2017 Jul;16(4):443-453.

Patrizio
Dimitri
Full Professor

ORCID

RESEARCH LINES

- Roles of ATP-dependent chromatin remodeling proteins in mitosis and cytokinesis.
- Generating cellular models to reproduce the genetic defect found in the human syndrome Floating-Harbor.
- Chromatin remodeling complexes and the regulation of gene expression in pericentromeric heterochromatin.

STAFF | COLLABORATORS

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Master degree-host
Maria Virgina Santopietro,
Master student (Sapienza)
Merve Sali,
Master student (Sapienza)

GRANTS

2019-2022. PRIN Project:
"Microtubule and centrosome dynamics, from Omics to neurodevelopmental disorders of Central Nervous System".
PI Patrizio Dimitri.

RESEARCH ACTIVITY

An early focus of my lab was on identifying and demonstrating genetic functions of constitutive heterochromatin, at a time at where the latter was considered mainly as "junk" DNA. This has been possible by developing and implementing an original combination of classical genetics, molecular biology and high-resolution cytogenetics methods in Drosophila. The results are discussed in various papers and reviews (Dimitri et al, PNAS, 1997; Dimitri and Junakovic, Trends in Genetics, 1999; Dimitri et al, Molecular Biology and Evolution, 2003; Dimitri et al, Bioessays, 2005; (Hoskins et al, Science, 2007; Rossi et al, Genetics, 2007; Andreyeva et al, PNAS, 2007; Yeh et al, PNAS, 2012; Hoskins et al, Genome Research, 2015, Caizzi et al, Plos Genetics, 2016). The findings have contributed to modify the concept of heterochromatin, which is now recognized to be of crucial importance to genome function, with roles in cell differentiation, diseases, and cancer onset and progression at various levels. Recently, we have proposed a new functional view of constitutive heterochromatin (Marsano et al, Trends in Genetics, 2019). Our current work is focused to the study of different aspect of chromatin biology, using a combination of classical genetics, forward genetics, cell and molecular biology. Chromatin organization is highly dynamic and subject to epigenetic changes mediated by histone modifying enzymes and ATP-dependent chromatin remodeling complexes. These complexes are multi-protein molecular devices able to slide or displace nucleosomes, thus making DNA more accessible to specific binding proteins that control essential cellular processes, such as transcription, replication and DNA repair. Mutations in genes which encode the epigenetic regulators controlling chromatin configuration can promote human developmental disorders and cancer.

Main research projects of the lab are:

1) Elucidating the role of ATP-dependent chromatin remodeling proteins in mitosis and cytokinesis, using as model systems Drosophila melanogaster and human cell lines (Messina et al., bioRxiv, 2020).
2) Generating cellular models to reproduce the genetic defect found in the rare genetic syndrome Floating-Harbor (see the review by Messina et al, Journal of Medical Genetics, 2016).
3) The role of chromatin remodeling complexes in the regulation of gene expression in pericentromeric heterochromatin.

Figure. A "pop art" style interpretation of an heatmap of Drosophila melanogaster *heterochromatic genes. Cover of Trends in Genetics, 35: 615-631. https://www.cell.com/trends/genetics/issue?pii=S0168-9525(18)X0010-9*

References

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3. R.M. Marsano, E. Giordano, G. Messina and P. Dimitri (2019) A new portrait of constitutive heterochromatin: lessons from Drosophila melanogaster. Trends in Genetics. 35: 615-631. Image selected for the cover https://www.cell.com/trends/genetics/issue?pii=S0168-9525(18)X0010-9

Simone
Ferrari
Associate Professor

ORCID

RESEARCH LINES

- Regulation of elicitor-induced defense responses in plants.
- Impact of cell wall modifications on plant growth and defense.
- Biotechnological approaches to exploit lignocellulosic sugars.

STAFF | COLLABORATORS

Riccardo Lorrai,
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PhD student (Sapienza)
Francesca Angelini,
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Nora Hidasi,
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Christiane Nawrath, *Full Professor (University of Lausanne)*
Stephen Mayfield,
Professor (UC San Diego)

GRANTS

2017. MIUR PON "ORIGAMI
Integrated biorefinery for the production of biodiesel from microalgae";
€ 203.000; PI: Simone Ferrari.

RESEARCH ACTIVITY

Regulation of elicitor-induced defense responses in plants. Plants can detect invading microbes by perceiving elicitors, called Pathogen- and Damage-Associated Molecular Patterns (PAMPs and DAMPs), that trigger PAMP-Triggered Immunity (PTI). Examples of PAMPs and DAMPs are chitin in fungal cell walls and oligogalacturonides (OGs), pectin fragments released from the plant cell wall by fungal polygalacturonases (PGs), respectively. We have characterized the main components of the signalling pathways linking OG perception to downstream responses. Moreover, we have investigated the role of LysM-containing receptor-like kinases in modulating defense responses and demonstrated that chimeric PAMP receptors can be engineered to obtain plants more resistant to infections. Activation of PTI is costly and, in the absence of pathogen pressure, might reduce fitness. On the other hand, plants treated with elicitors acquire a "primed" status and respond more efficiently to subsequent infections. Current research aims to characterize the mechanisms underlying this phenomenon and the trade-off between defense and growth in plants.

Impact and mode of action of cell wall modifications on plant growth and defense. Plant cell walls are the first line of defense against pathogen attack and regulate growth under physiological and stress conditions. Plant cells constantly monitor wall integrity to adjust growth and modulate defenses. We have shown that plants with altered pectin composition constitutively express defense responses and are more resistant to infections, but are severely impaired in growth. This growth defect is dependent on apoplastic peroxidases that cause the accumulation of reactive oxygen species (ROS). Current research focuses on the elucidation of the interactions between cell wall damage, ROS production cell wall damage and resistance to pathogens.

Biotechnological approaches to exploit lignocellulosic sugars. Lignocellulosic biomass is a promising source of sustainable biofuels and chemicals, but its use is hampered by its recalcitrance to enzymatic deconstruction. Current research in the lab aims to find biotechnological solutions to improve conversion of biomasses into simple sugars, both modifying the plant cell wall composition and searching for novel sources of degrading enzymes. We are also studying the use of lignocellulosic sugars to grow microalgae with the aim of producing biodiesel and nutraceuticals.

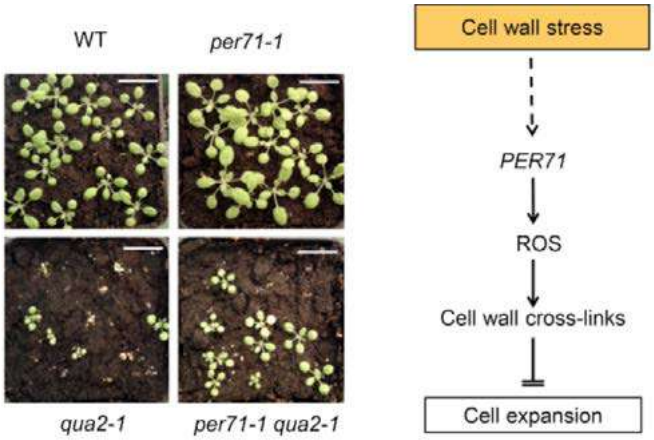

Figure.
Loss-of-function mutations in the Arabidopsis peroxidase gene PER71 partially restores growth in a pectin-deficient mutant (qua2-1), indicating its role in mediating cell wall stress-induced growth inhibition (modified from Raggi et al. 2015).

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Maria Teresa
Fiorillo
Associate Professor

ORCID

RESEARCH LINES

- Molecular mechanisms of autoimmune disorders
- Role of HLA-B27 alleles in Spondyloarthritis
- CD8+ T cell biology in immune-mediated diseases

STAFF | COLLABORATORS

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Post-doc (Sapienza)
Giorgia Paldino,
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Fabiana Paladini,
Assistant Professor (Sapienza)
Alberto Cauli,
Full Professor (University of Cagliari)
Arie Admon,
Full Professor
(Israel Institute of Technology, Haifa)

GRANTS

2019. "HLA-B27 AND ANKYLOSING SPONDYLITIS", Ceschina Foundation Grant, € 255.000.
PI: Sorrentino R. and Fiorillo M.T.

RESEARCH ACTIVITY

Mechanisms underlying autoimmune disorders remain largely elusive. Hence, the need to improve our knowledge to find suitable molecular targets for personalized new therapeutic approaches. In this context, our research project has been focused on the study of genetic predisposing factors associated with a group of rheumatic, chronic inflammatory diseases named Spondyloarthritis (SpA) of which Ankylosing Spondylitis (AS) is the prototype.
Much of our efforts have been devoted to dissect the pathogenic role of HLA-B27 which represents the most strongly associated gene for this group of disorders. Starting from the discovery of an allelic variant of HLA-B27 found in Sardinia and not predisposing to AS, we conducted our analysis by a comparative approach between risk and non-risk HLA-B27 alleles. Several studies combining T-cell antigen presenting functions with peptidome characterization by mass spectrometry, biophysical methods and computational analysis have disclosed a higher flexibility of the disease-associated HLA-B27 allele.
This confers the ability to bind and present a wider peptide repertoire extended to atypical viral antigens and self-peptides thus eliciting virus-specific and autoreactive CD8+ T cell responses. We are currently studying how the antigen presenting functions of HLA-B27 molecules could be modulated by allelic variants of ERAP1 and ERAP2 aminopeptidases which are other strong risk factors in AS and related SpA. Genome wide association studies (GWAS) have identified more than 100 genes contributing to the AS-susceptibility and many of them are involved in development, differentiation, function and count of CD8+ T cell justifying a specific interest for this lymphocyte subset in the SpA.
Accordingly, we are now carrying out a study to correlate the immune-phenotype and metabolic properties of CD8+ T cells with their migratory properties in patients with SpA compared to healthy controls and patients with other immune-mediated diseases.

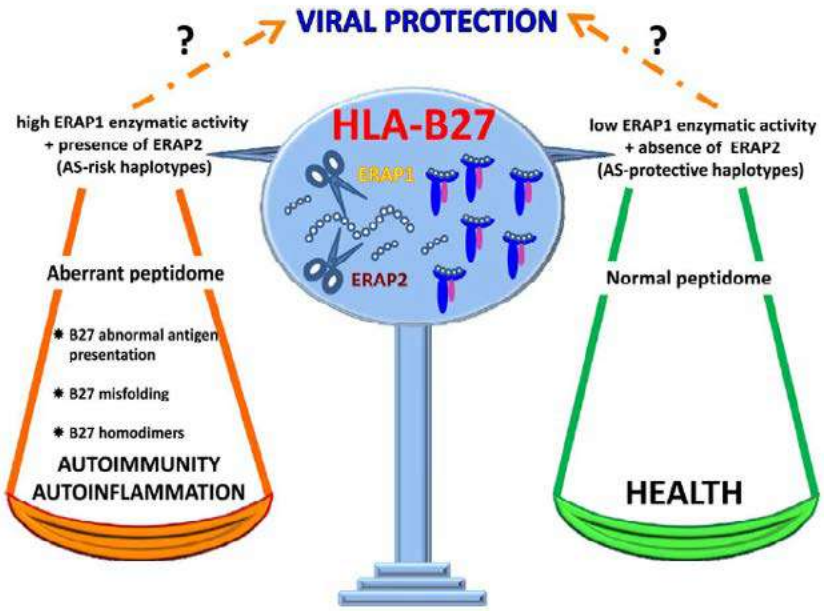

Figure. Cartoon illustrating the possible interaction between HLA-B27, the strongest risk factor for Ankylosing Spondylitis, and the aminopeptidases ERAP1 and ERAP2 in shaping a normal or an aberrant peptide repertoire in a context of autoimmunity/autoinflammation or antiviral defence.

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2. Vitulano C, Tedeschi V, Paladini F, Sorrentino R, Fiorillo MT. (2017) The interplay between HLA-B27 and ERAP1/ERAP2 aminopeptidases: from anti-viral protection to spondyloarthritis. Clin Exp Immunol. 190:281-290.
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Milena
Grossi
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ORCID

RESEARCH LINES

- Role of polyamines in the intracellular life of Shigella
- Inhibitors of efflux pump expression for fighting incoming bacterial infections in cancer patients

STAFF | COLLABORATORS

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Gianni Prosseda,
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Ryutaro Utsumi,
Full Professor
(Osaka University, Japan)

GRANTS

2020-22. MAECI Italia -Giappone (PGR07208) Combination therapies for fighting antibiotic resistant bloodstream infections in cancer patients (participant).

RESEARCH ACTIVITY

Role of polyamines in the intracellular life of Shigella. Polyamines are small polycationic molecules associated with a broad range of biological functions: translation, gene regulation, stress resistance, cell proliferation and differentiation. in eukaryotic as well as prokaryotic cells. In recent years it has become increasingly evident that, in addition to core physiological functions, polyamines are crucial also to the virulence phenotype of many bacterial pathogens, including *Shigella*. *Shigella* is an intracellular pathogen, belonging to the *E. coli* species, causing bacillary dysentery. During the adaptation to an intracellular lifestyle, *Shigella* evolution included the loss of "housekeeping" functions, redundant or deleterious for life in the new environment. Among these, loss of *speG*, encoding spermidine acetyltransferase (SAT), leads to abnormal intracellular spermidine accumulation, which makes *Shigella* more resistant to oxidative stresses and increases its survival inside macrophages, an essential step of the *Shigella*' invasive process. Present studies aim at elucidating whether spermidine accumulation, as a consequence of *speG* loss of function, represents a defensive weapon for the bacterium to counteract the host cell response, and/or an offensive weapon against the host cell aimed at destabilizing the homeostasis of the polyamine content. Recently, we have identified an efflux pump, MtdJI, involved in the extrusion of polyamines and highly expressed upon host cell infection. We are investigating whether activation of MtdJI or other transporters favours the release of spermidine or its precursor putrescine causing an alteration of the expression of enzymes involved in the host cell polyamine metabolism.

Inhibitors of efflux pump expression for fighting incoming bacterial infections in cancer patients. Infections with antibiotic-resistant pathogens are a major threat to the lives of cancer patients, causing 10% of death. Classical anticancer therapies create conditions favouring microbial infections. Most of drugs target dividing cells, and among the most important side effects are impairment of the immune system and weakening of the intestinal barrier. The latter can be responsible of increased bacterial translocation. Functioning as DNA damage agents, anticancer drugs can also work on bacterial DNA leading to both unbalance of microbiota composition and onset of multidrug-resistant pathogens. Our research is focused on: i) the identification of bacterial efflux pumps involved in multidrug resistance whose expression is activated by anticancer drugs; ii) the characterization of their regulatory network iii) the identification of inhibitors affecting those regulatory systems.

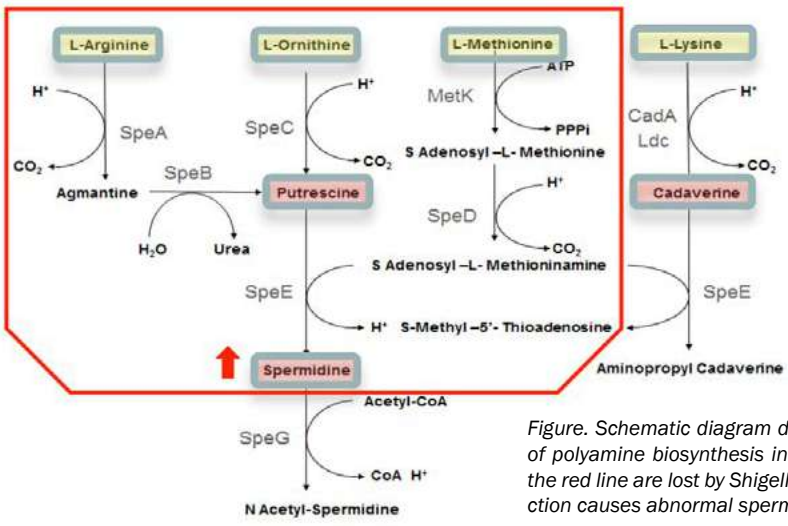

Figure. Schematic diagram depicting the pathways of polyamine biosynthesis in E. coli. Steps outside the red line are lost by Shigella. Lack of the SAT function causes abnormal spermidine accumulation.

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Valerio
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RESEARCH LINES

- Role of the histone demethylases and its isoforms in cancer
- Transcriptomics
- Bioinformatics tool development

STAFF | COLLABORATORS

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RESEARCH ACTIVITY

Precise regulation of gene expression is critical for almost all biological processes. Although the human genome has only nearly 20,000 protein-coding genes, the unique isoforms generated from each gene can be more than ten times the number (Djebali et al., 2012). In the last years since the advent of RNA-seq technology and computational biology tools has produced tremendous growth in the amount of human transcriptome data and have led transcriptome-wide studies at a new level of resolution (Pan et al., 2008). With the rise of long-read sequencing with the third generation of sequencers such as Oxford Nanopore the ability to investigate the transcriptome landscape of the cell will increase.
In particular, very little attention has been paid to alternative isoforms of chromatin modifying proteins. Misregulation of alternative intronic promoters is frequently associated with various developmental defects and diseases including cancer, and it is becoming increasingly clear that this phenomenon deserves more attention.
In collaboration with prof. Negri's lab we are investigating the role of different isoforms of the H3K4 histone demethylase KDM5B/JARID1B in cancer. Recently, it has been proposed that the relative abundance of different KDM5B isoforms may contribute to tumor progression in melanoma (Kuźbicki Ł, 2017). Previously, we demonstrated that KDM5B is involved in the response of cells to genotoxic damage and its expression is regulated by two specific miRNAs.
As a bioinformatician, my work is also focused on the development of bioinformatics tools. The last one is MIENTURNET (MicroRNA ENrichment TURned NETwork) (Figure) developed in collaboration with prof. Paci's group (ref. 1), an easy-to-use web application freely available at http://userver.bio.uniroma1.it/apps/mienturnet/ without any login requirement. The whole web tool was developed based on the open source shiny package from RStudio (http:// shiny.rstudio.com), that allows to create an interactive web interface for sharing analysis and graphics from R.

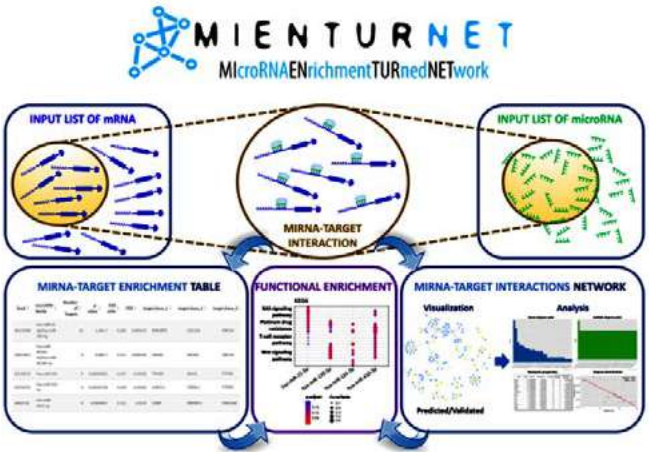

Figure. Sketch of MIENTURNET input/output files. MIENTURNET looks for miRNAs targeting an input list of mRNAs (top-left) or mRNAs targeted by an input list of miRNAs (top-right) and it performs a statistical analysis for over-representation of miRNA-target interactions (bottom-left) together with a network-based visualization and analysis of the resulting enriched interactions (bottom-right).

MIENTURNET receives in input a list of miRNAs or mRNAs and tackles the problem of prioritizing miRNA-target interactions by performing a statistical analysis followed by a fully featured network-based visualization and analysis that can be filtered, explored, and customized interactively, besides it offers also the possibility to perform a functional enrichment analysis of the targets of selected miRNAs, in order to gain insight into understanding the biological processes underlying the target gene activity.
Currently, MIENTURNET supports the choice of six organisms for which both predicted and experimentally validated miRNA-target interactions were available.

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RESEARCH LINES

- Plant Biology
- Plant Physiology
- Plant Cell Wall
- Plant-Microbe interaction
- Plant Immunity

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William Willats,
Full Professor
(Newcastle University)

GRANTS

2019. Progetto "Torno subito" - Regione Lazio.
In vivo imaging of the plant cell wall proteins at the plant-pathogen interface.
2019. Progetti gruppi di ricerca Lazio Innova Regione Lazio.
Agricultural byproducts into valuable Assets for Sustainable Agriculture.

RESEARCH ACTIVITY

Dr. Lionetti has a proven track record in the field of plant-pathogen interactions. He is an expert in the dynamic modifications of the composition and structure of the cell wall polysaccharides during pathogen infection. Cell Wall Degrading Enzymes (CWDEs) are expressed by pathogens during host invasion to penetrate the cell wall barrier and colonize the tissue. Plants evolved the ability to sense loss of cell wall integrity and trigger defence responses leading to an improved resistance to disease (Figure). Dr. Lionetti has contributed to understanding the molecular bases of plant defence to biotic stresses. He demonstrated that the modulation of the expression of CWDEs or their inhibitors in planta represents a useful tool to improve plant resistance to pathogens and to investigate the role of an altered structure and integrity of wall polysaccharides in plant-pathogen interactions. Moreover, he demonstrated that alterations of pectin esterification impact on cell wall degradability and on plant susceptibility to pathogens. Dr. Lionetti, by applying his competence in the glycomics of cell wall polysaccharides, uncovered specific cell wall components remodelled to resist against fungal necrotrophs. He is considered an international expert on the modification of pectin methyl esterification in the plant-pathogen interaction. He also proposed biotechnological applications of the CWDEs and their inhibitors to improve saccharification of cell wall polysaccharides and protoplast isolation.

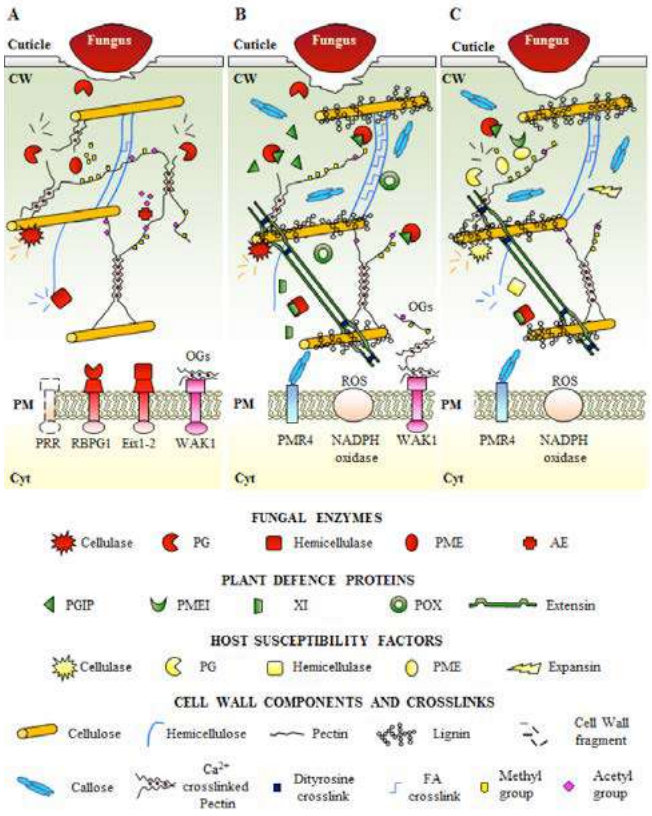

Figure. Cell wall dynamics during necrotrophs invasion. (A) Necrotrophic fungi secrete CWDEs to degrade cell wall polymers (B) As defense, plants produce CWDE inhibitors to hinder degradation. (C) Necrotrophs force plants to cooperate in disease exploiting plant susceptibility factors.

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Lucia
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ORCID

RESEARCH LINES

- Regulation of defense responses in plants.

STAFF | COLLABORATORS

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Daniela Pontiggia,
Research assistant (Sapienza)

RESEARCH ACTIVITY

Plants are able to perceive, transduce and integrate multiple signals from the environment, allowing them to adapt correctly to environmental disturbances. They have therefore evolved a series of complex mechanisms that mediate the activation of the adaptive response which gives plants the ability to survive in adverse conditions. The improvement of agricultural production has always been one of the greatest challenges for human beings. To achieve this goal, we should try to use pesticides and fertilizers as little as possible, which despite their benefits, can contaminate aquifers and springs as well as the surrounding land, becoming dangerous for both humans and the environment.
My research work is focused on the molecular mechanism involved in plant defense against pathogens, with the aim of improving and monitoring agricultural production without the use of pollutants.
Plants have evolved the ability to activate immune responses against invading organisms that involve cell-surface receptors named pattern-recognition receptors (PRRs), which recognize Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs).
DAMPs that are well-characterized include o ligogalacturonides (OGs), oligomers of α-1,4–linked galacturonic acid generated by the hydrolysis pectin which belongs to the plant cell wall. The accumulation of OGs in vivo is favored by the interaction of the pathogen polygalacturonase (PG) with a plant inhibitor polygalacturonase-inhibiting protein (PGIP). We have previously generated Arabidopsis thaliana transgenic plants named OG-machine (OGM) expressing a chimera consisting of a fungal PG fused with a gene encoding a plant polygalacturonase-inhibiting protein (PGIP) under the control of a β-estradiol–inducible promoter. In these plants, OGs can be released on command. These plants show increased resistance against pathogens. However elevated levels of expression of the chimera cause reduced growth and eventually lead to plant death, consistent with the current notion that a trade-off occurs between growth and defense.
My work is aimed to investigate the key aspects that underlie the growth-defense trade-off mediated by OGs. Therefore, to genetically dissect the pathways involved in the responses to OGM, we generated plant lines that express the chimera in the genetic background defective in key elements involved in immunity (e.g. mpk-3, mpk-6, ndr1-1, eds1-2, mpk6, rbohD, NahG). The uncoupling of the effects of the accumulation of OGs on growth and defense is a final aim of this study, to obtain plants more resistant to pathogens and normal growth.

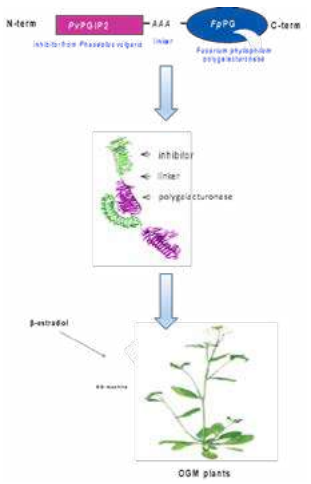

Figure. β-estradiol expression of the PGIP–PG chimera induces defense responses causing reduced growth.

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2. Redwan M, Spinelli F, Marti L, Bazihizina N, Azzarello A, Mancuso S, Masi E (2017) "Investigation of root signaling under heterogeneous salt stress: a case study for Cucumis sativus L." Environ. Exp. Bot.
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Rodolfo
Negri
Full Professor

ORCID

RESEARCH LINES

- Role of histone demethylases in transcription and genome integrity
- Transcriptional response of mammalian cells to genotoxic damage
- Transcriptional response of mammalian cells to gravity alteration

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Romano Sivestri,
Full Professor (Sapienza)
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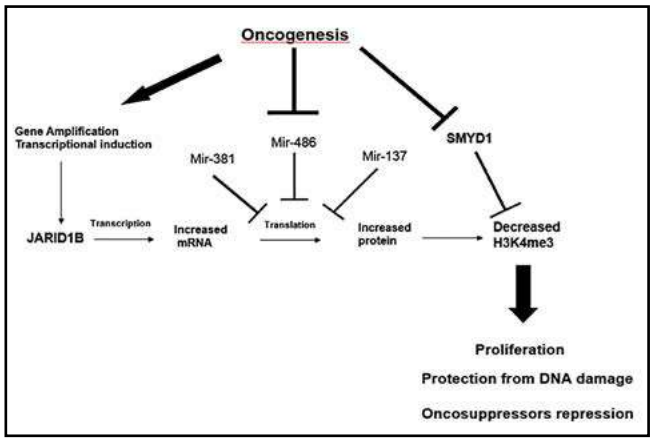
Full Professor (Haifa University)

GRANTS

2019-21. ASI-MARS-PRE-40000.
PI: Rodolfo Negri
Progetto strategico regionale
2019-22. GENOMEUP - POR FESR
Lazioinnova AdS Scienze della Vita
progetto prot. n°A0320-2019-28186
-2020-2022/283000.
PI: Rodolfo Negri

RESEARCH ACTIVITY

The main focus of the research work in the lab is on the influence of chromatin structure on transcription regulation in the yeast S.cerevisiae (Costanzo et al., 2001; Negri et al., 2001; De Sanctis et al., 2002; Del Vescovo et al.,2004, Gufanti et al., 2006, Del Vescovo et al., 2008). In the last years we analyzed the influence of regulatory elements of protein homeostasis (notably COP9 signalosome) on transcription regulation and lipid metabolism (Licursi et al., 2014; Cirigliano et al., 2016; Cirigliano et al., 2019). We have also been studying the role of the NuA4 and SWR complexes Yaf9 in the response of S.cerevisiae to salt stress (Casagrande et al., 2009; Del Vescovo et al., 2008, Piccinni et al., 2011) and the effect of the histone demethylase Jhd2 on chromatin structure and gene regulation (Licursi et al., 2020 in preparation). We also set up an in vivo screening system for H3K4 histone demethylase inhibitors in yeast and mammalian cells (Mannironi et al., 2014). We then characterized the regulation of H3K4-specific histone demethylase KDM5B by specific miRNAs in human breast cancer cell lines. Using constructs overproducing these miRNAS and chemical inhibitors of the catalysis, we could recently show that KDM5 histone demethylases are deeply involved in the response of breast cancer cells to genotoxic damage (Mocavini et al., 2019; Pippa et al., 2019). We are now studying the different isoforms of this protein and their putative roles in regulation in cancer cell lines.
Finally, an independent line of research in the lab is traditionally devoted to the study of the transcriptional response of human cells and of organized tissues to irradiation.



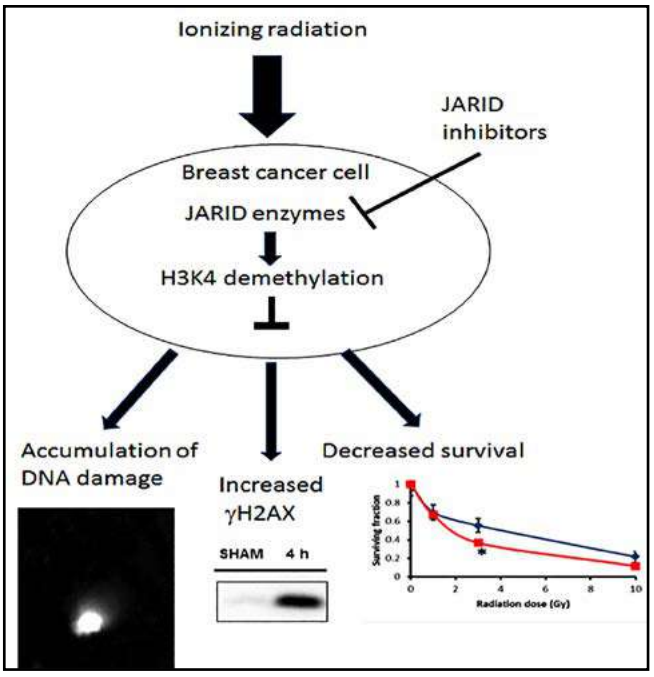


Figure. Regulatory circuits involving H3K4 methylation in breast cancer cells

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2. Pippa S, Mannironi C, Licursi V, Bombardi, L, Colotti G, Cundari E, Mollica A, Coluccia A, Naccarato V, La Regina G, Silvestri R, Negri R. "Small molecule inhibitors of KDM5 histone demethylases increase the radiosensitivity of breast cancer cells overexpressing Jarid1b." MOLECULES, 2019; 24: 1420-3049.
3. Mannironi C, Proietto M, Bufalieri F, Cundari E, Alagia A, Danovska S, Rinaldi T, Famiglini V, Coluccia A, La Regina G, Silvestri R, Negri R. "An High-Throughput In Vivo Screening System to Select H3K4-Specific Histone Demethylase Inhibitors". PLoS One. 2014; 9:e86002.

Carlo
Presutti
Associate Professor

ORCID

RESEARCH LINES

- mRNA stability
- ncRNA in ASD (Autism Spectrum Disorder)
- miRNA in cancer

STAFF | COLLABORATORS

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Alessandro De Santis,
Master student (Sapienza)
Cecilia Mannironi,
Researcher (IBPM/CNR)

GRANTS

2018-2019. Life2020 Regione Lazio
PI: Carlo Presutti
2019. Progetto Finalizzato Sanità
PI: Carlo Presutti

RESEARCH ACTIVITY

Our lab's research is focused on the functions of non-coding RNAs (ncRNAs) in different cellular processes.
It is now acknowledged that in mammalian cells ncRNAs play a fundamental role in regulating gene expression at different levels.
We are currently analyzing the complex relationship between miRNA, mRNA and RBPs (RNA Binding Proteins) on different mRNA coding for transcription factors crucial for the development of skin cancer (melanoma).
The role of ncRNA in ASD is another research project carried out in the lab. In this regard we are characterizing the expression and the role of specific ncRNAs (miRNA, lncRNAs and circRNAs) in different mouse models for the pathology.

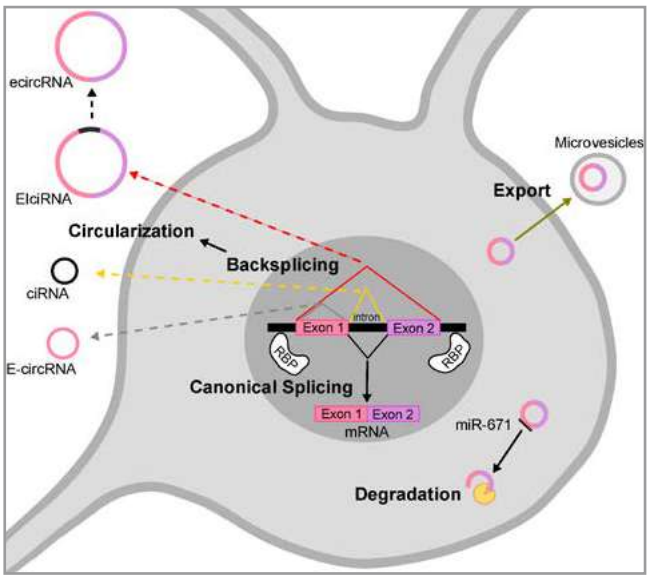

Figure.
Biogenesis and removal of circRNAs. On the left, circular RNA molecules originating from back-splicing events: E-circRNA from exon1- gray arrow; ciRNA from intron- yellow arrow; EIciRNA from pre-mRNA- red arrow. On the right, known pathways of circRNA elimination from cells: degradation through an almost perfect complementarity with a miRNA (i.e., miR-671) and export through microvesicles and exosomes. E-circRNA: exonic circRNA; ciRNA: intronic circRNA; EIciRNA: exonic-intronic circRNA; ecircRNA: exonic circRNA originating by splicing of EIciRNA; RBP: RNA-Binding Protein.

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Gianni
Prosseda
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ORCID

RESEARCH LINES

- Study of the regulation of the main activator in the Shigella virulence system
- Analysis of the Shigella/EIEC virulence plasmid integration
- Influences of the intestinal metabolites on the virulence of enteropatogens.

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RESEARCH ACTIVITY

Study of the regulation of the main activator in the Shigella virulence system. *Shigella* spp. are highly adapted human pathogens that cause bacillary dysentery (Shigellosis). The sophisticated infectious strategy of *Shigella* is supported by a coordinated expression of several genes located on the chromosome as well as on a virulence plasmid (pINV) organized in a cascade manner. At the top of this regulatory structure is the VirF protein, responsible for the activation of the virulence system in *Shigella*. This role imply a complex and multifactorial regulation that has been unveiled by our studies at transcriptional and post transcriptional (Figure). This research line evolves in the study of the post translational control of the VirF protein activity focused on the identification of cell and environmental cofactors responsible of its activation or inhibition. The identification of these compounds may open up new therapeutic approaches to the treatment of Shigellosis.

Analysis of the Shigella/EIEC virulence plasmid integration. Occasionally, pINV plasmid can naturally integrates into *Shigella* and EIEC (Enteroinvasive *E. coli*) nucleoid. This integration event results in the loss of virulence. This process can revert leading to the restoration of the invasive *Shigella*/EIEC phenotype. This research line is focused on the study of the relevant steps in the integration process and of the mechanisms responsible for silencing of virulence.

Influences of the intestinal metabolites on the virulence of entero-patogens. The human gut microbiota contributes to the physiology, function and development of the immune, nervous and digestive systems. It is also involved in the defence of the host from allogeneic microorganisms. This protective action is carried out by direct competition for nutrient sources as well as by the production of molecules by the microbiota or intestinal mucosa. However, entero-pathogenic bacteria have learned to harness a panel of these molecules to modulate their virulent potential. This line of research is dedicated to the identification of these compounds and to the study of the mechanisms they use to program the virulence of *Shigella* and other entero-pathogens.

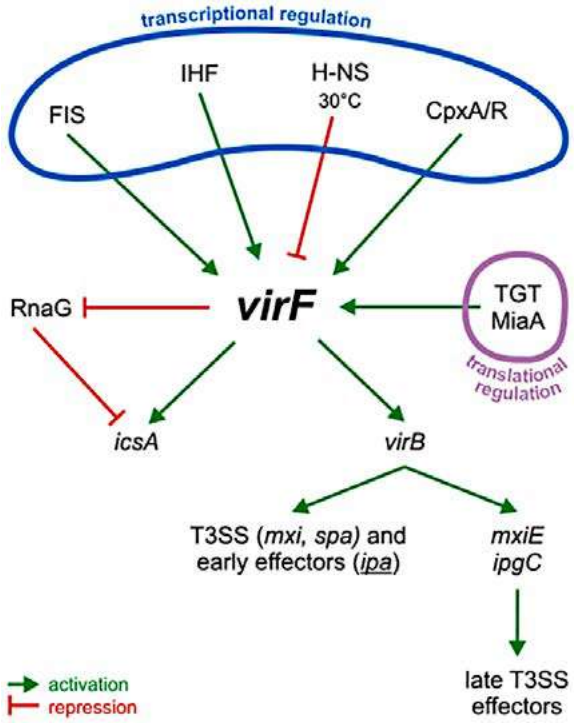

Figure.
Centrality of VirF in the pINV regulatory cascade of Shigella. Factors involved in virF regulation are indicated. VirF protein activates the icsA and virB genes and represses the synthesis of the sRNA RnaG. VirB, activates the downstream element of Shigella virulence system.

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2. Expression Profile of Multidrug Resistance Efflux Pumps During Intracellular Life of Adherent-Invasive Escherichia coli Strain LF82.Fanelli G, Pasqua M, Colonna B, Prosseda G, Grossi M. Front Microbiol. 2020 Aug 17;11:1935.
3. One Gene and Two Proteins: a Leaderless mRNA Supports the Translation of Shorter Form of the Shigella VirF Regulator. Di Martino ML, Romilly C, Wagner EG, Colonna B, Prosseda G. mBio. 2016 Nov 8;7(6):e01860-16.

Sabrina
Sabatini
Associate Professor

ORCID

RESEARCH LINES

- Role of mechanical forces during organogenesis
- Molecular mechanisms that balance cell division with cell differentiation
- Developmental boundary specification

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GRANTS

2020. CDA Mid-Career GRANT PROGRAM of the Giovanni Armenise-Harvard Foundation,
200.000 US $.
PI: Sabrina Sabatini

RESEARCH ACTIVITY

Major questions in developmental biology involve how organs expand and subsequently stabilize when reaching a functional size. By combining molecular genetics with computational modeling and using the root organ of Arabidopsis thaliana as a model system we aim to understand the basic principle of these patterning processes.
At the end of embryogenesis the root consists of a stem cell niche only. Stem cell activation and spatiotemporally coordinated decisions of individual cells section the root into distinct zones, in which cells either divide or differentiate.
These zones first expand and then stabilize when root maturation is completed. We first demonstrated how the developmental boundary that keeps these zones separated, the transition zone, is maintained.
This depends on the antagonistic activities of two plant hormones: cytokinin and auxin. A computational model showed that cytokinin shapes in the root a graded distribution of auxin, positioning an auxin minimum at the transition zone. Dividing cells upon sensing this auxin minimum, stop dividing and start differentiating.
Thus in plants the graded distribution of a hormone is used as a positional signal to trigger cell differentiation. We also showed that changes in cell size are a necessary trigger for cell differentiation.
Cytokinin first establishes the position of the auxin minimum, and subsequently induces changes in the cell's volume that is the functional trigger for differentiation. These findings provide an elegant example on the importance of mechanical forces during organogenesis.
Recently combining computational modelling and experiments we also identify an auxin/PLTs/ARRs regulatory network controlling expansion and stabilization of the division and differentiation zone of the root.

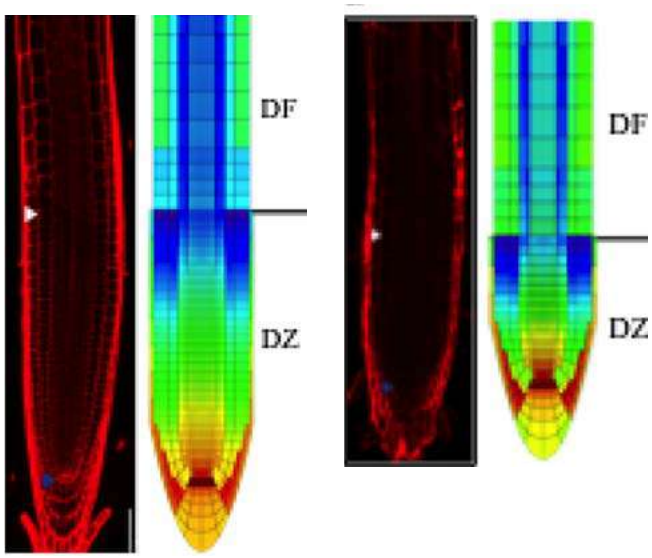

Figure.
Left panel: Arabidopsis thaliana root confocal image and the layout of a root computational model where a simulation predicts the formation of an auxin minimum (in blue) separating the division zone (DZ) from the differentiation zone (DF).

Right panel: Simulation in which changes in gene expression predicts changes in the auxin minimum position and thus in root size. Changes in root size have been verified in vivo identifying the relative mutants (confocal

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Rosa
Sorrentino
Full Professor

ORCID

RESEARCH LINES

- HLA genes and function
- Mechanisms of antigen presentation
- Effects of gene variations in autoimmunity
- Myeloid cell differentiation

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GRANTS

2019-21. Fondazione Ceschina.

RESEARCH ACTIVITY

Antigen presentation is a crucial step in mounting the immune responses against foreign antigens and cancer. This response however can also be directed against normal components of the tissues and in this case autoimmunity can occur. While some degree of autoimmune reactivity is well tolerated, there are cases where it can unleash a pathogenic response leading to autoimmune diseases, among which a group associated with the presence of some HLA class I alleles, so called MHC-I-opathies.
In the last years our group has focused on:

1) Identification of genetic variations in genes associated with MHC-I-opathies.
2) Functional outcome of some of the variations identified.
3) Evolutionary and functional analysis of the aminopeptidases that refine the HLA-antigen repertoire and influence self-reactivity.
4) Monocytes to macrophages differentiation: variations in gene expression and function.

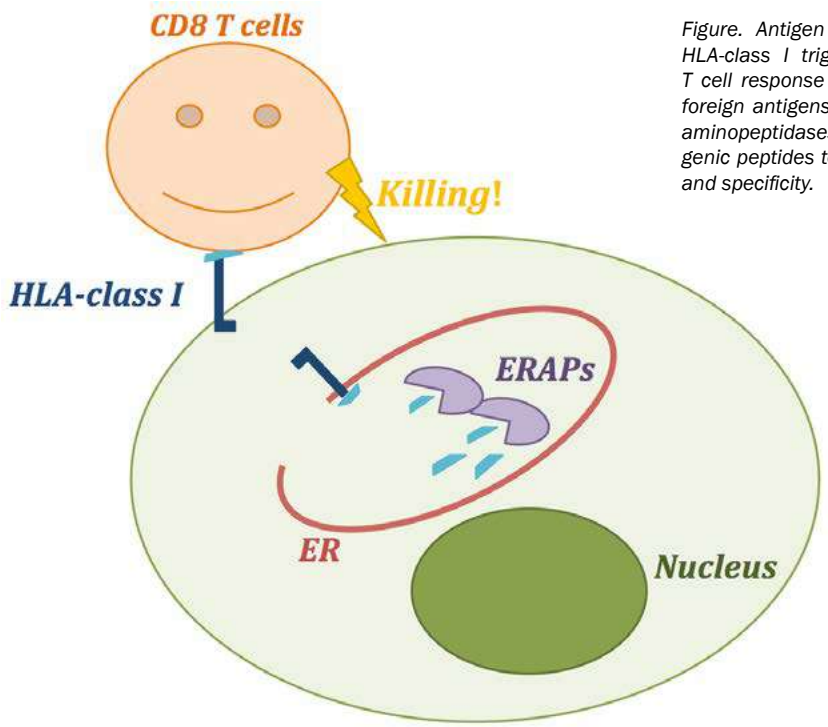

Figure. Antigen presentation by HLA-class I triggers a cytotoxic T cell response against self and foreign antigens. The ERAPs (ER aminopeptidases) refine the antigenic peptides to the right length and specificity.

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Loretta
Tuosto
Associate Professor

ORCID

RESEARCH LINES

- Characterization of the signalling molecules and cellular metabolic programs regulating CD28 pro-inflammatory functions
- Characterization of the signalling motifs of human CD28 involved in the lethal inflammatory responses to bacterial superantigen toxins

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GRANTS

Istituto Pasteur Italia - Fondazione Cenci Bolognetti, "Anna Tramontano" Project 2019. "Characterization of the signalling molecules and cellular metabolic programs regulating CD28 pro-inflammatory functions"
PI: Loretta Tuosto

Vigevani Foundation Research Project 2020. "Control of intracellular signalling through CD28: key to preventing lethal inflammatory responses to infectious pathogens".
PI: Loretta Tuosto and Raymond Kaempfer.

RESEARCH ACTIVITY

Our research activity is aimed at characterizing the mechanisms and molecules regulating T lymphocyte functions in health and disease, by characterizing the pro-inflammatory signals elicited by CD28 costimulatory molecule[1].
We were among the first to evidence that human CD28 engagement in the absence of TCR activates, in primary T lymphocytes, a non-canonical NF-κB2-like cascade leading to the expression of several NF-κB target genes including survival and inflammatory genes in Multiple Sclerosis (MS) and type 1 diabetes (T1D). These studies also contributed to the identification at a cellular and molecular level of distinct signalling abilities between human and mouse CD28, thus emphasizing the essential need to pay attention to molecular details when transferring results from preclinical models to the bedside[2].
More recent studies of our laboratory clarify the pivotal role of class 1A PI3K (phosphatidylinositol 3 kinase) in the regulation of both glucose metabolism and inflammatory functions of CD28 in T lymphocytes from MS patients[3], thus suggesting class 1A PI3K as a therapeutic target to dampen the pro-inflammatory functions of specific T cell subsets in MS. Actually, in collaboration with Prof. Raymond Kaempfer (The Hebrew University of Jerusalem), we are working on the characterization of the intracellular signalling events elicited by CD28 in response to bacterial superantigens and its control by CD28 dimer interface mimetic peptides that have been demonstrated to dampen inflammatory cytokine production and, in vivo, to protect mice from toxic shock induced by bacterial superantigen toxins and from pandemic H1N1 and avian H5N1 influenza A virus infection.

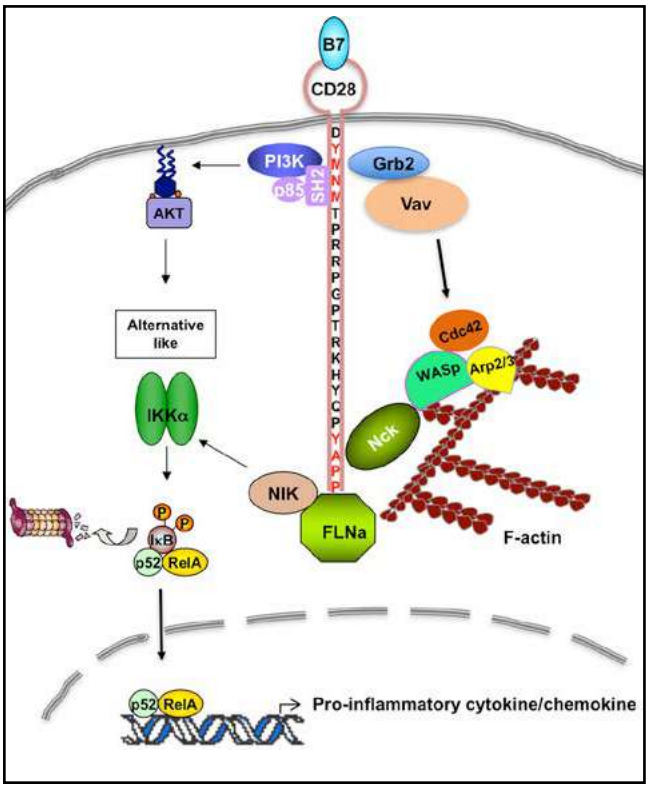

Figure. Following engagement of human CD28 by B7, tyrosine phosphorylated YMNM binds the class 1A PI3K and Grb2/Vav, while C-terminal YAPP binds Nck, filamin-a (FLNa) and associated NIK. Vav and Nck cooperate to induce actin cytoskeleton reorganization. Class 1A PI3K generates phospholipids that favour the recruitment and activation of Akt that in turn cooperates with NIK to activate IKKα and non-canonical NF-κB2 pathway, thus leading to pro-inflammatory cytokine expression.

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“ ZOOLOGY ”

During the ‘70s of the XX century, the zoologists of Sapienza moved to their current location, a beautiful Liberty-style building on the campus edge. The diversity of expertise spans several taxonomic groups and a variety of methodological and theoretical approaches, carried out at the main location and at the ***Museum of Zoology***.

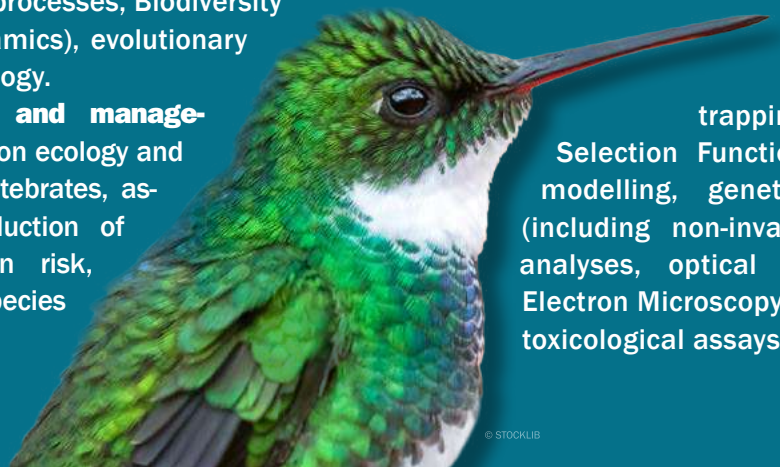
The research lines can be summarised under the following headings:

- **Evolutionary Biology** of insects (Coleoptera and Diptera), molluscs, and vertebrates, with a focus on: Integrative Taxonomy, Phylogeny, Biogeography, Population genetics/genomics (spatial patterns of variation, divergence rates), Molecular evolution (biochemical and ecological drivers of evolution), Microevolutionary processes, Biodiversity (patterns and dynamics), evolutionary developmental biology.
- **Wildlife ecology and management**, with a focus on ecology and conservation of vertebrates, assessment and reduction of mammal extinction risk, and modelling of species distribution.

Ecotoxicology. Global change and biodiversity from species, to communities, to wilderness areas, including forecast of scenarios of global change for both native and invasive vertebrates.

Applications of zoological research include: bioprospecting, development of monitoring methods, conservation planning, conflict mitigation, integration of biodiversity conservation with other societal goals (food production, climate change mitigation, improved human well-being).

Methods employed include: field observations and sampling in terrestrial and aquatic (marine and freshwater) habitats, VHF- and GPS-telemetry, camera-trapping, scat-analysis, Resource Selection Functions, population and habitat modelling, genetic and genomic analyses (including non-invasive genetics), phylogenetic analyses, optical stereomicroscopy, Scanning Electron Microscopy, histological techniques, ecotoxicological assays.



Paolo
Audisio
Full Professor

ORCID

RESEARCH LINES

- Taxonomy and biogeography of beetles
- Phylogeny and molecular evolution of insects
- Population and conservation genetics
- Conservation Biology of insects
- Molecular evolution of phytophagous insects
- Ecology and evolution of aquatic beetles
- Applied entomology

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Marco Alberto Bologna,
Full Professor (Roma Tre)

GRANTS

EU LIFE + Project "Monitoring of Insects with Public Participation". PI: Paolo Audisio
Circeo N.P. Project "Monitoraggio presenza e consistenza artropodi di interesse comunitario Parco Nazionale Circeo" PI: Paolo Audisio

RESEARCH ACTIVITY

My research activities are carried out through field collections, study of Museum collections, morphological and cladistic investigations, ecological investigations, genetics/genomics methods, and fauna monitoring techniques. These activities are all framed in the vast fields of the evolutionary biology, biodiversity, ecology, and conservation biology of insects.
My main research lines aim to: 1) outline the phylogeny, taxonomy and biogeography of insects (mostly Coleoptera) by integrating morphology, ecological information, DNA barcoding and conservation genetics, 2) unravel the biological factors favouring - and maintaining over time - the interactions among phytophagous insects and their host plants by taking into account their parallel evolution, their ecological shifts, and their microbiome component, 3) unravel the biological factors involved in the interactions among aquatic beetles and their habitats, with particular emphasis on running waters and terrestrial salt waters, 3) improve our knowledge on European saproxylic forest beetle communities, with particular emphasis on Conservation Biology of flagship species listed in the in EU Habitat Directive, and on new tools for monitoring the biological quality of forest habitats, based on beetle biodiversity.
Other research activities pertain to applied evolutionary entomology and aim to: 1) outline the evolutionary relationships of the phytophagous insects associated with alien and invasive weeds, potentially able to be used as biological control agents, 2) outline the evolutionary relationships of some beetle species associated with beehives, with particular emphasis on the alien invasive small hive beetle (SHB) *Aethina tumida* (Coleoptera, Nitidulidae).

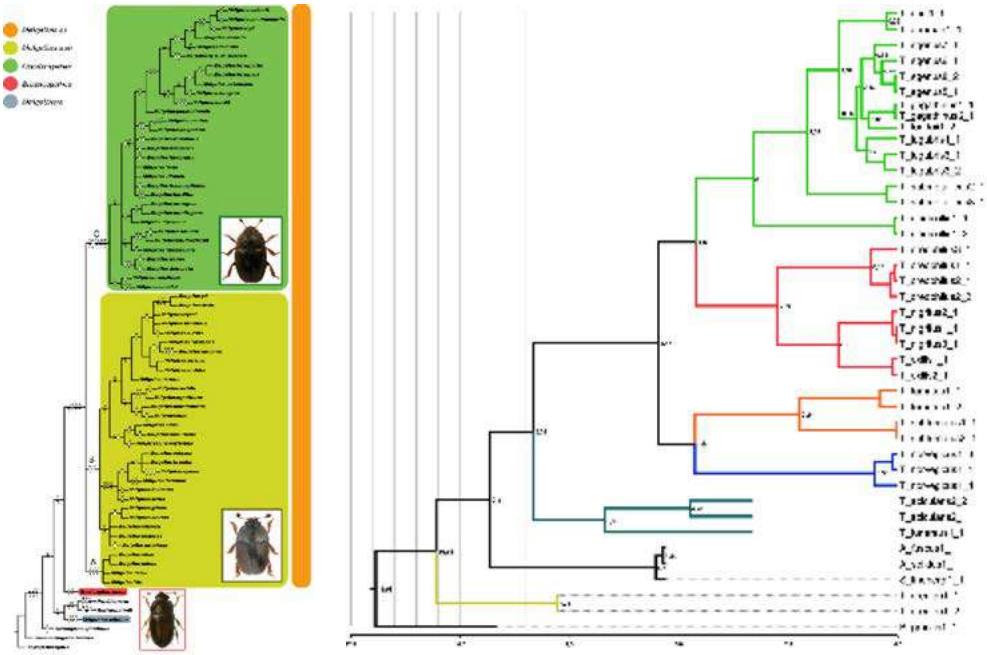

Figure. Left panel: One of the most parsimonious trees based on morphological data (tree length = 160, C.I. = 0.42, R.I. = 0.83) in Meligethes s.l., a group of anthophagous Nitidulidae Meligethinae. Numbers in boxes under branches indicate Bremer support values. Apomorphic and plesyomorphic character states are indicated with black and empty squares, respectively (modified from Liu et al., Frontiers in Zoology, 2021, in press). Right panel: Ultrametric tree of members of the genus Thymogethes (Coleoptera, Nitidulidae, Meligethinae) obtained by BEAST with the mitochondrial sequences data. Numbers at nodes refer to million years obtained with 3.54% of sequence divergence per My calibration (modified from Sabatelli et al. 2020, Zoologica Scripta, 49: 28-46).

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Pierfilippo
Cerretti
Associate Professor

ORCID

RESEARCH LINES

- Systematics and phylogeny
- Parasitoid community structure and diversity
- Insect diversity inventories, catalogues, checklists
- Museology, zoological collections, type material, curatorial activities

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Technician (Sapienza)

RESEARCH ACTIVITY

Since 2001 I have focused much of my research activity on Diptera systematics, phylogeny and evolution, with the Oestroidea (blow flies, flesh flies and relatives) as my main target clade. My ongoing studies are aimed at elucidating the phylogenetic relationships and key character evolution of oestroid flies using morphological and molecular approaches. A robust reconstruction of the phylogenetic history of this lineage is the first step to both developing a more stable, predictive classification that can be applied on a world scale and reconstructing the evolution of a diverse array of key traits (e.g. reproductive strategies, host associations) of these economically important flies.
Recently I extended my research interest to the phylogeny and evolution of Neuroptera (lacewings) and relatives (Figure). Lacewings are a relatively minor insect group, not reaching by several orders of magnitude the diversity of other Holometabola such as the related Coleoptera. Nonetheless they are characterized by unusual morphologies and life styles, besides being a relatively ancient lineage.
In addition, I hold a deep interest in the basic task of documenting and understanding insect diversity. The effects on biodiversity of the conversion of natural ecosystems into agricultural farming and human settlements are of significant concern in Europe. I have been developing new research lines in collaboration with several ecologists for studying the effects of climate change, habitat loss and fragmentation on the higher trophic levels represented by insect predators and parasitoids.
Combined approaches and tools I employ in my studies of insect parasitoids and predators are broad, including field surveys and experiments, molecular and morphological phylogenetics, DNA-taxonomy, collection-based research and statistical modelling.

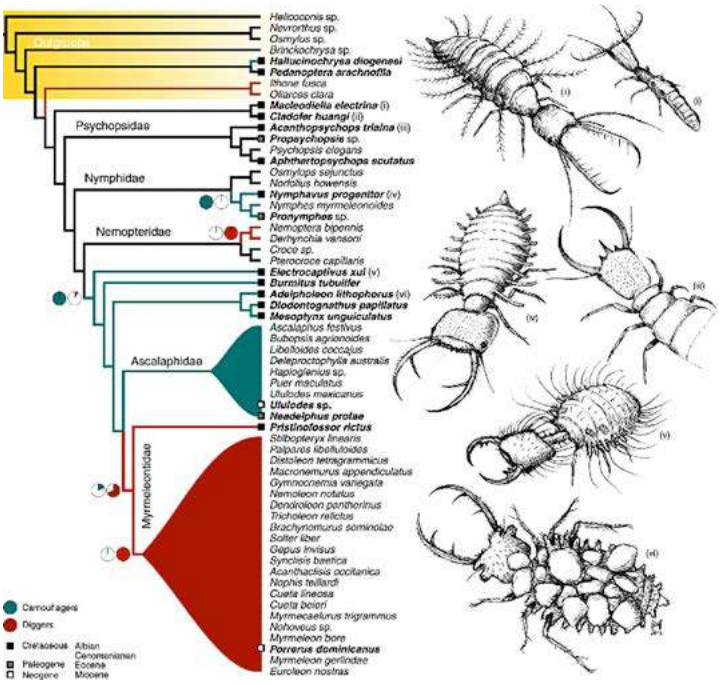

Figure. Phylogeny of Myrmeleontiformia, including fossils, based on larval morphology. The cladogram is a strict consensus tree of the four equally parsimonious trees obtained under implied weighting (k = 9.219). Pie charts near nodes represent the proportional likelihood of digging and camouflaging behaviour across the Myrmeleontidae + Ascalaphidae clade calculated through ancestral state reconstruction. Terminal taxa marked in bold indicate amber-embedded specimens from mid-Cretaceous Burmese amber. Main extant families are collapsed. Drawings by Maurizio Mei.

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Claudio
Chimenti
Researcher

ORCID

RESEARCH LINES

- Development of the adrenal gland in low vertebrates
- Study of the consequences on the internal organs of various types of stress on invertebrates
- Cerebral proliferation in anamia after thermal shock

STAFF | COLLABORATORS

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GRANTS

2019-22. Horizon 2020 CollectionCare Innovative and affordable service for PC monitoring of individual Cultural Artefacts during display, storage, handling and transport. Great agreement N° 814624.

RESEARCH ACTIVITY

Particular attention was paid to the study of the development of the adrenal gland in various species of teleosts such as Dicentrarchus labrax (sea bass). The development of the adrenal gland of reptiles, in particular Chelonians adrenal gland, was well studied, comparing it with the development of lizards adrenal gland; in all cases the development of the kidney, directly connected to the development of the adrenal gland, was taken as a reference. Figure 1 was chosen for represent the aim of the volume: Recent advances in non-mammalian adrenal gland researches.
More recent research has concerned the study of crustaceans that can be used as bioindicators for the control of pollution of inland waters. In this perspective, research on the crustaceans, that inhabit the cave environment, is also interesting.
Other researches have concerned the study of amphibians and reptiles nerve cells during the various phases of the life cycle.

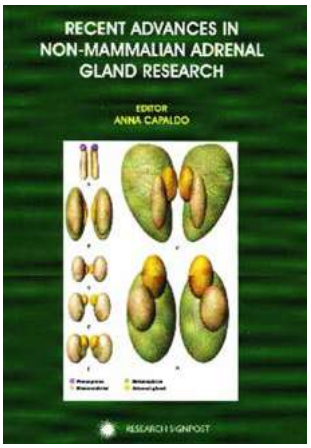

Figure 1. Sketches of the position of the adrenal gland relative to that of the kidneys during embryogenesis in turtles (a-c) and in chicken (d-g). The sketches are not to scale. 5a - Yntema's stage 18 (middle part of the turtle embryonic development). The interrenal blastema, about as long as the mesonephros, lies on the medial surface of this kidney. At this stage the pronephros persists cephalically. The metanephros has not yet differentiated. 5b - Yntema's stage 26 (hatching) - The blastema of the adrenal gland is shorter than the mesonephros and is in contact with the dorsal-medial surface of the mesonephros and the ventral-medial surface of the metanephros, now in an advanced state of differentiation and longer than the mesonephros. 5c - One month a.h.: the

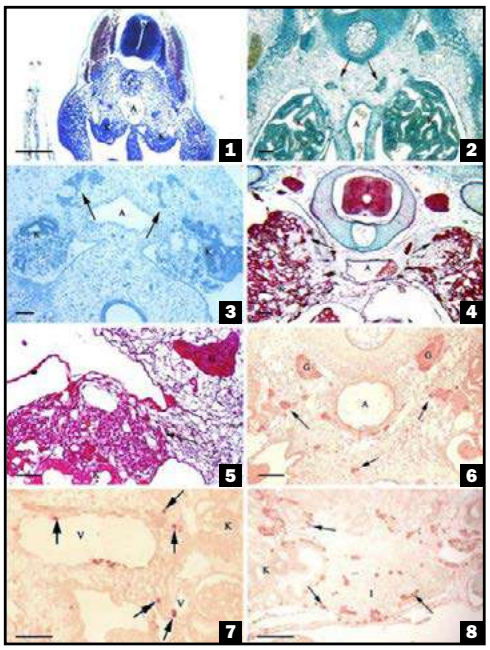

Figure 2: (1) Histological section of stage 9 embryo: neural tube (N), notochord (C), dorsal aorta (A) and the pronephric anlagen (K). Giemsa. Bar: 400 µm (2) Histological section of stage 12 embryo; presumptive chromaffin cells form two small masses (arrows) at both sides of dorsal aorta (A). K mesonephric kidneys. Mallory. Bar: 200 µm (3) Thick section of stage 12 embryo; chromaffin cells (arrows), dorsal aorta (A), kidneys (K). Methylene blue. Bar: 100 µm (4) Histological section of stage 20 embryo; the adrenal gland (arrows) is arranged on the medial edge of the mesonephric kidney (K). A: dorsal aorta. Mallory. Bar: 200 µm (5) Magnification of the previous figure. The gland (arrow) is in deep contact with the mesonephric kidney (K). A ganglion (G) is embedded in the connective tissue. Mallory. Bar: 100 µm (6) Immunohistochemical localization of DßH at stage 18. Positive chromaffin cells (arrows) and ganglia (G) are localized at both sides of dorsal aorta (A). Bar: 100 µm (7) Immunohistochemical localization of PNMT at stage 18. Few positive adrenaline cells (arrows) are localized near the blood vessels (V) and kidney (K). Bar: 50 µm (8) Immunohistochemical localization of DßH at stage 26. Positive chromaffin cells (arrows) are localized both around the interrenal cells (I) and the kidney (K). Bar: 100 µm

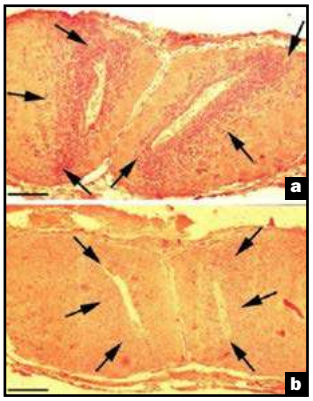

Figure 3. In the olfactory bulbs of an adult Triturus carnifex stem cells are visible in the ependyma, sub ependymal grey matter and internal granular layer (arrows): a) specimen exposed to cold shock; b) normal specimen. Transverse sections, PCNA immunocytochemistry without nuclear counterstaining.

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Paolo
Ciucci
Associate Professor

ORCID

RESEARCH LINES

- Wildlife Ecology, Management, and Conservation
- Animal movement, space-use patterns, resource selection and feeding ecology
- Species-habitat relationship and species distribution models
- Sampling, assessment and monitoring of vertebrate populations

STAFF | COLLABORATORS

Matteo Falco,
Post-doc (Sapienza)
Luigi Maiorano,
Assoc. Professor (Sapienza)
Nina Santostasi,
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University of Montpellier
Anna Loy,
Full Professor (University of Molise)
Gianluca Mastrantonio,
Researcher (Politecnico of Turin)

GRANTS

2018-21. Edmund Mach Foundation,
€ 70.800. PI Sapienza: P. Ciucci.
2020-21. Regione Lazio,
€ 35.750. PI: P. Ciucci.
2020-21. Parco Nazionale d'Abruzzo Lazio e Molise,
€ 30.000. PI: P. Ciucci.

RESEARCH ACTIVITY

My main research interests center on wildlife ecology, including the estimation of biological and ecological parameters of wildlife populations. The main focus of my research is on the ecology of large carnivores, including applications for management and conservation. Research activities range from the assessment of wildlife population, to behavioural ecology studies of large carnivores, to dietary and predation studies, and investigations of species-habitat relationships to develop habitat modelling and assist conservation planning. Field and lab work entails a diversity of wildlife techniques (live-trapping, VHF- and GPS-telemetry, GPS-cluster checking, scat analysis, stable isotope analysis, non-invasive genetic sampling and hormonal essays, camera trapping, genome sequencing, 3D morphometry), and data are used to make inference at the demographic, ecological, taxonomic, genetic, and genomic domains.
Recent research has focused on the behavioral ecology of wolves and brown bears in different national parks, investigating space-use patterns, dispersal, territorial behavior, activity, feeding ecology, prey use and selection, predation, and conflict with human activities. Special interest rests in unveiling habitat-mediated behavioral strategies that these species adopt to co-occur with humans in human-modified landscapes such as Italy. In particular, species-habitat relationships have been investigated at multiple scales to detect how anthropogenic factors affect changes in ecological domains of large carnivores, revealing trade-offs in resource selection both at the landscape and the home range scales.
In the past few years, I coordinated the first formal assessment of the relict brown bear population in the central Apennines to inform conservation planning. Other recent investigations, conducted by my PhD students, regard the risk of anthropogenic hybridization, the role of animal culture in the maintenance of complex animal societies and its relevance for conservation, the relative effects of ecological vs anthropogenic factors as drivers of large ungulates migrations. Research results have often informed practical management, entailing the production of guidelines and management action plans for local (e.g., National Park Authorities), regional, national (Ministry of the Environment) and international (European Union) wildlife management authorities.

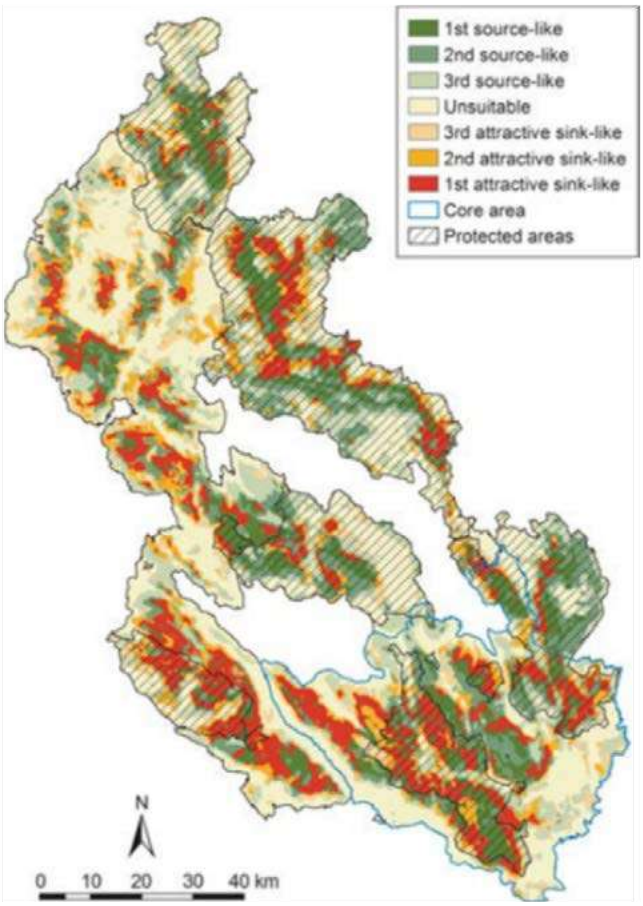

Figure. Two dimensional habitat model for brown bears in the central Apennines (Italy), developed by integrating an occurrence model (1399 bear occurrence points, 1999–2006) and a mortality risk model (37 human-caused bear fatalities, 1980–2007). A limited amount of source-like habitat appears highly fragmented by ecological traps (from Falcucci et al., J Appl Ecol 2009 46:600).

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2. Mancinelli, S., M. Falco, L. Boitani, P. Ciucci. Social, behavioural and temporal components of responses by wolves to anthropogenic landscape features in the central Apennines, Italy. J Zool, 2019; 309:114.
3. Ciucci, P., L. Boitani, M. Falco, L. Maiorano. Hierarchical, multi-grain rendezvous sites selection by wolves in southern Italy. J Wildl Manage; 2018 82:1049.

Alessio
De Biase
Associate Professor

ORCID

RESEARCH LINES

- Evolutionary systematics and zoogeography of insects
- Population genetics/genomics and Phylogeography of insects
- Evolutionary biology of phytophagous insects

STAFF | COLLABORATORS

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Researcher (Biotecnology and Biological Control Agency)
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Matteo Montagna,
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Giulia Magoga,
Post-doc (Universiy of Milan)
Massimo Cristofaro,
Researcher (ENEA, La Casaccia)
Lincoln Smith,
Researcher (USDA-ARS, Albany, USA)

GRANTS

2009-20. Fondazione Biotechnology and Biological Control Agency; Genetic characterization of populations of phytophagous insects for the implementation of biological control programs against invasive plants; € 86000,
PI: Alessio De Biase.

RESEARCH ACTIVITY

I'm interested in the taxonomy and systematics of groups of species or higher taxa, of beetles of the families Curculionidae, Nitidulidae, Phalacridae, Scarabaeidae, Hydraenidae and Endomychidae, from Palaearctic and Afrotropical areas. The disentangling of taxonomic and phylogenetic issues is the main prerequisite for studying these beetles from a biogeographic and evolutionary perspective, this being my main interest. I use morphological and molecular approaches to study these insects in a modern cladistic framework in order to infer the phylogenetic relationships among the taxa under study. From a biogeographic and phylogeographic perspective my research is mainly focused on the analysis of the beetle fauna of the above-cited families in Euro-Mediterranean and Afrotropical areas. The reconstruction of palaeo dynamics of colonization events and the identification of homogeneous geographical areas (zoogeographic regions or districts), are the main goals. More recently and following a genetic approach, I started to study the biological invasion of the Red Palm Weevil that was introduced in the Mediterranean basin with the trade of plants grown for food and ornamental purposes. The main goal is the detection of the colonization routes as a contribution to the development of a management strategy for this biological invasion. I'm also interested in evolutionary topics regarding the insect-plant relationships and the adaptive meaning of genetic polymorphisms of some groups of phytophagous beetles (Weevils; Curculionidae). I'm studying the relationships between the genetic variability and the breadth of diet (monophagy to polyphagy) of species strictly related to the weevil Trichosirocalus, by integrating data on ecology, phylogeny and genetic structure of natural populations. As of 2002, in light of these studies, I have been responsible for a research project, in collaboration with the European Biological Control Laboratory (EBCL) of USDA (United States Department of Agriculture) and the Biotechnology and Biological Control Agency (BBCA, Rome, Italy), focused on the biological control of weeds. I'm characterizing several natural populations of phytophagous insects from a genetic point of view, in order to evaluate them as putative agents of biological control against weeds. The insect populations are biotypes associated with the weeds of interest that could eventually be used as a source for the release of agents for the biological control of that weed. The project is therefore strongly based on the integration of genetic and ecological data in order to plan the release of these insects in nature. Some results of this project have triggered a research program to shed light on a) the genetic divergence associated to the use of alternative host plants by strictly related species of leaf beetles (Psylliodes spp.; Chrysomelidae) and weevils (Trichosirocalus spp.; Curculionidae) and b) supposed hybridization phenomena between host races of these beetles.

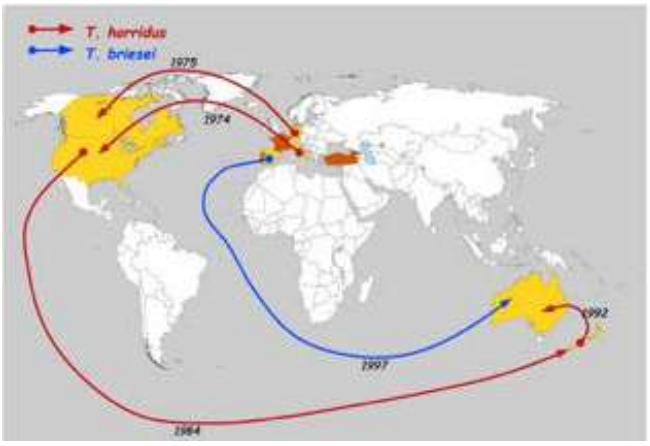

Figure: Map showing the introductions of Trichosirocalus horridus sensu lato to Canada, USA, New Zealand and Australia. Yellow countries were involved in translocations. Orange countries were included in the sampling to get more data on biological variation of the species complex. All coloured countries were sampled for the genetic characterization of introduced populations.

I have published more than 80 scientific papers primarily on insects. I have participated and organized many trips to collect biological samples in European and African countries
Summary bibliometrics: (Scholar) 87 publications; 1920 citations; H-index 19; (Scopus): 38 publications; 566 citations; H-index: 13.

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1. De Biase A., Smith L., Brunetti M., Belvedere S., Primerano S., Antonini G., La Marca A., Audisio P., Biondi M., Cristofaro M. (2019). Three prospective agents instead of one? Cryptic diversity of the biological control agent Psylliodes chalcomera. Biological Control, 136: 103998.
2. De Biase A.*, Colonnelli E., Belvedere S., La Marca A., Cristofaro M., Smith L. (2016). Genetic and morphological studies of Trichosirocalus species introduced to North America, Australia and New Zealand for the biological control of thistles. Bulletin of Entomological Research, 106: 99-113.
3. Smith L., Cristofaro M., Bon MC., De Biase A., Petanović R., Vidović B. (2018). The importance of cryptic species and subspecific populations in classic biological control of weeds: A North American perspective. BioControl, 63: 417-425.

Moreno
Di Marco
Researcher

ORCID

RESEARCH LINES

- Biodiversity Conservation
- Global Change Biology
- Sustainable Development
- Climate Change

STAFF | COLLABORATORS

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Victor Cazalis, *Postdoc (Germany)*
Juan Pablo Ramirez-Delgado, *PhD student (UNBC, Canada)*
Bonnie Mappin, *PhD student (Australia)*

GRANTS

2021-22. Global Wildlife Conservation "Testing automated approaches to prioritiseIUCN Red List reassessments" Co-PIs: L. Santini e M. Di Marco, € 25,703.
2021-23. German Centre for Integrative Biodiversity Research iDiv "Accelerating IUCN Red List assessments for rapid and effective biodiversity monitoring (Working Group)". Co-PIs: L. Santini & M. Di Marco, € 38,200 plus a fully funded 2-yrs postdoc
2020-23. MIUR Rita Levi Montalcini "Identifying areas of universal biodiversity importance to inform conservation action and sustainable development under rapid global change". PI: M. Di Marco, € 199,874

RESEARCH ACTIVITY

I am a conservation biologist with a passion for addressing the challenges that global change poses to biodiversity. I am especially interested in developing quantitative techniques for addressing large-scale conservation problems and evaluate how the solution to these problems interact with the achievement of other societal goals (such as food production, climate change mitigation, improved human well-being). I received a PhD in Ecological Sciences in 2013, and have published 60 scientific articles since 2011, collaborating with >270 researchers worldwide (source Scopus). Since 2009 I've worked for Universities, NGOs, and GOs across Europe and Australia. I am currently a Research Fellow at Sapienza University of Rome (Italy) and I also have adjunct roles, such as Honorary Senior Research Fellow at the University of Queensland, and Handling Editor for the journal Conservation Biology.
After completion of my PhD, I contributed to the definition of a new global Standard for the identification of Key Biodiversity Areas (KBA). I led a consultancy for the International Union for Conservation of Nature (UK), to demonstrate the value of complementing KBA identification with conservation planning techniques. This new Standard is highly influential to inform protected area targets and monitoring. I then moved to the University of Queensland (Australia) where I was part of the team unveiling the global distribution and decline of wilderness areas in 2016, resulting in an article entering the top-100 Altmetric list of media attention. Important debate followed that publication about the need for an international wilderness retention target, which allowed me to lead a research project at CSIRO (Australian's national science agency) where we demonstrated the importance of wilderness areas for biodiversity, resulting in a Nature article. At CSIRO I also led the development of future scenarios of plant biodiversity decline using compositional turnover modelling, which contributed to important international initiatives such as the 2019 Global Assessment Summary for Policymakers of the IPBES. More recently at Sapienza University of Rome (Italy) I published an opinion piece on PNAS relating unsustainable development practices to the risk of emerging zoonotic diseases, which has attracted substantial attention, due to the COVID-19 outbreak.

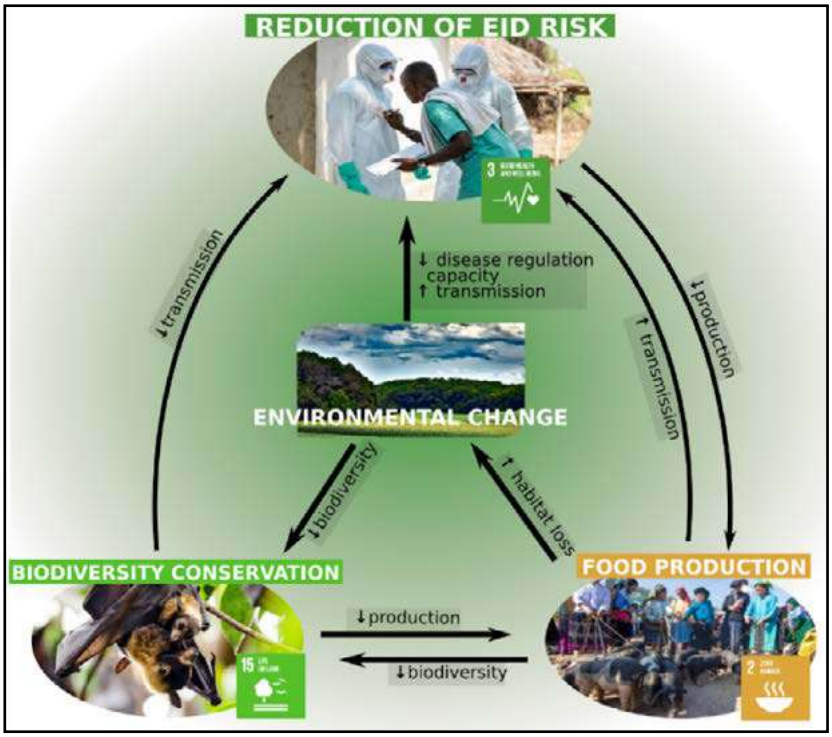

Figure. Risk of emerging infectious diseases (EIDs) is a key component of sustainable development planning. UN Sustainable Development Goals 2, 3, and 15 are linked through the shared influence of environmental change. These interactions increase (↑) or decrease (↓) key elements of the systems underpinning the achievement of each goal.

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2. Di Marco, M., S. Ferrier, T. Harwood, et al. Wilderness areas halve the extinction risk of terrestrial biodiversity. Nature 2019; 573:582.
3. Di Marco, M., O. Venter, H.P. Possingham, J.E.M. Watson. Changes in human footprint drive changes in species extinction risk. Nature Comm 2018, 9:4621.

Luigi
Maiorano
Associate Professor

ORCID

RESEARCH LINES

- Macroecology
- Biogeography
- Global Change Biology
- Conservation Biology

STAFF | COLLABORATORS

Paolo Ciucci,
Assoc. Professor (Sapienza)
Moreno di Marco,
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Full Professor (Sapienza)
Daniele Canestrelli,
Full Professor (University of Tuscia)
Wilfried Thuiller,
Researcher (CNRS, Grenoble)
Niklaus E. Zimmermann,
Researcher (WSL, Zurich)

GRANTS

2018. PRIN HYBRIND: global changes, hybridization, and the tyranny of the golden mean, € 820,757.
2019-20. AtlantECO: Atlantic Ecosystems assessment, forecasting and suystainability. H2020-BG-2019-2, € 10,925,660.
2019. FutureWEB: climate and land use change threat to the vertebrate food web structure and functioning. BiodivScen, € 1,269,532.

RESEARCH ACTIVITY

My research aims at exploring the patterns and processes that shape species distribution in space and time, going from local to continental/global scales. I focus on various systems, considering both animals and plants, marine and terrestrial, being particularly active with terrestrial vertebrates in the Mediterranean basin. My research activities are in the field of macroecology, focusing particularly on assessing the impacts of past and future global changes on biodiversity. I'm also interested in conservation biology and wildlife management, always considering the spatial components of complex research problems. I'm currently involved in research projects spanning the macro-ecology of trophic interactions for terrestrial vertebrates in Europe, the impact of climate change and forestry practices on the distribution and the conservation of the Abruzzo brown bear, and ecosystem services in the Atlantic Ocean.

Figure. Interspecific hybridisation between the common toad (Bufo bufo) and the green toad (Bufotes balearicus) in the wild. As a consequence of global changes, two species separated by 30 million years of evolution get in sympatry and form hybrid pairs. All tadpoles were heavily malformed, and none survived until metamorphosis. Photo: M. Zampiglia.

Recently, I have been exploring more and more the evolutionary component of biodiversity, focusing on the contribution of macroecology to macroevolution as well as on the impact of climate change on species hybridization. In particular, I'm working with a PhD project in an international collaboration on the detection of evolutionary trends in mammalian carnivores worldwide using 3D-morphometry of current and fossils species. On the other side I'm using hybridization to explore the paradox of the tyranny of the golden mean. In many areas of the life sciences differences between individuals, although ubiquitous in natural populations, are commonly summarized within descriptive statistics. This blurs the role played by non-average individuals, potentially biasing our appreciation of the process under study. In a collaborative study, I will address this gap by focusing on the role of inter-individual differences in hybridization dynamics. Hybridization in a perfect window to study this paradox, since it is at the same time a fundamental step of major evolutionary processes, a consequence of global changes, and one of the main triggers of their outcomes.

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2. Araújo M.B., R.P. Anderson, A.M. Barbosa, C. Beale, C. Dormann, R. Early, R. Garcia, A. Guisan, L. Maiorano, B. Naimi, B. O'Hara, N.E. Zimmermann, C. Rahbek. 2019. Towards a golden age in biodiversity assessments. Science Advances 5: eaat4858.
3. Maiorano L., Amori G., Montemaggiori A., Rondinini C., Santini L., Saura S. and L. Boitani. 2015. On how much biodiversity is covered in Europe by national protected areas and by the Natura 2000 network: insights from terrestrial vertebrates. Conservation Biology 29: 986-995.

Emiliano
Mancini
Researcher

ORCID

RESEARCH LINES

- Phylogeny and biogeography of insects
- Population and conservation genetics
- Molecular evolution
- Evolutionary parasitology

STAFF | COLLABORATORS

Paolo Audisio,
Full Professor (Sapienza)
Alessandra della Torre,
Assoc. Professor (Sapienza)
Marco Pombi,
Assoc. Professor (Sapienza)
Marco Alberto Bologna,
Full Professor (Roma Tre)

GRANTS

2019-21. Regione Lazio - Progetti Gruppi di ricerca: Conoscenza e Cooperazione per un Nuovo Modello di Sviluppo "Cantharidin: from biodiversity to biotechnology", € 149,826.
PI: Prof. M. Bologna;
Co-PI; E. Mancini

RESEARCH ACTIVITY

My research activities - carried out through field collections, fauna monitoring techniques, morphological/ecological investigations, genetics/genomics methods - deal with some of the main themes of evolutionary biology and are all framed in the field of entomology.

Current research lines aim to:

1) outline the phylogeny and biogeography of insects (coleoptera and hymenoptera) by integrating ecological monitoring, DNA barcoding and conservation genetics;
2) unravel the biological factors favouring - and maintaining over time - the interaction among phytophagous insects and their host plants by taking into account their parallel evolution and microbiome component;
3) understand - through chemical ecology and transcriptomics - the ecological role and metabolism of cantharidin, a defensive terpene of blister beetles owning a great potential in medicine and crop-protection.

Other research activities pertain to evolutionary parasitology and medical entomology and aim to:

1) outline the evolution of Anopheles mosquito genetic traits (in reproduction and immunity) mostly influencing the transmission of malaria in Sub-Saharan Africa;
2) detect the genetic/genomic consequences on malaria transmission of the hybridization process occurring in West Africa between the two main malaria mosquito vectors (A. gambiae and A. coluzzii);
3) examine the evolution of emerging insecticide resistance mechanisms in mosquito populations (Anopheles and Aedes) to tackle their possible consequences on the spread of vector-borne diseases.

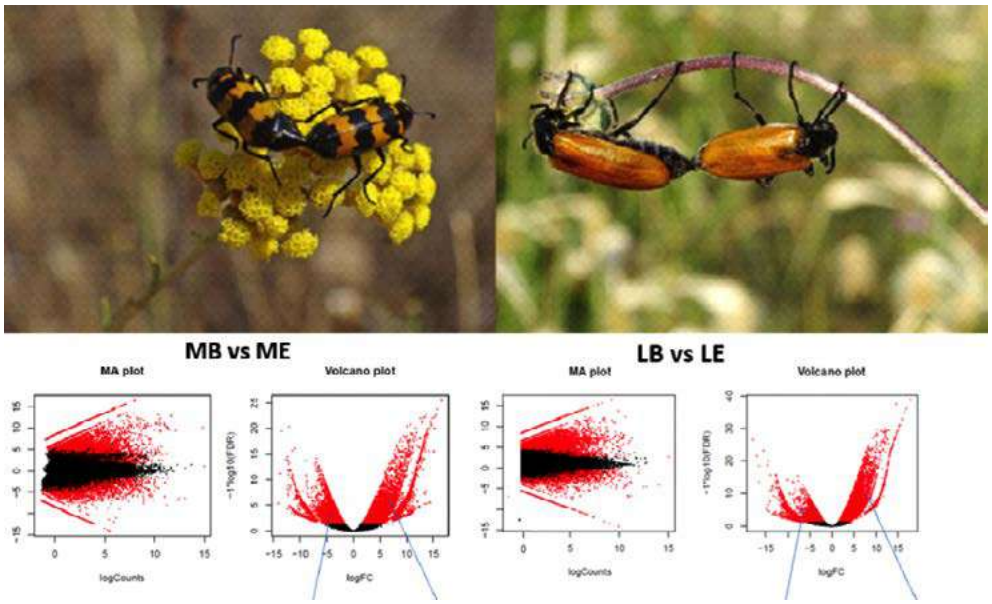

Figure. Upper panel: Mylabris variabilis (left) and Lydus trimaculatus (right) feeding and copulating on their host plants. Lower panel: "volcano plots" from transcriptomic analyses showing the number of differentially expressed genes in the exuded haemolymph containing the toxic terpene cantharidin in Mylabris variabilis (left, ME UP) and Lydus trimaculatus (right, LE UP).

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Marco
Oliverio
Full Professor

ORCID

RESEARCH LINES

- Taxonomy, systematics and biogeography of molluscs
- Population genetics/genomics
- Microevolutionary processes and larval ecology of marine invertebrates
- Animal associations
- Molecular Evolution

STAFF | COLLABORATORS

Elisa Nocella,
PhD (Sapienza)
Giulia Fassio,
Post-doc (Sapienza)
Maria Vittoria Modica,
Research Scientist (Stazione Zoologica Anton Dohrn, Napoli)

GRANTS

2016. EU-LIFE-LIFE-EUROTURTLES
€ 400,000, Draško Holcer (Zagreb)

RESEARCH ACTIVITY

My whole research activity is bound by the fil-rouge of the evolutionary perspective. This results in a primary interest in the Evolutionary Biology of molluscs, with a focus on: Integrative Taxonomy, Phylogeny, Biogeography, Population genetics/genomics (spatial patterns of variation, divergence rates), Molecular evolution (biochemical drivers of evolution), Microevolutionary processes, Biodiversity (patterns and dynamics), evolutionary developmental biology.

I am currently focused on the evolutionary biology of Neogastropoda, with a special emphasis on the phylogeny of this group, on the Integrative Taxonomy of some families (Muricidae, Columbellidae, Raphitomidae, Colubrariidae, Mitridae), and on the diversification of the trophic specializations at the various levels (ecological, anatomical, biochemical). In particular, I am using transcriptomic comparative approaches to address the role of biochemical drivers in the evolution of haematophagous and corallivorous groups (Colubrariidae; Coralliophilinae), with remarkable bioprospecting outputs.

I am also interested in the role of the ecological associations between different species of animals (mutualistic and parasitic symbioses), in shaping the current patterns of biodiversity in the involved groups. I am currently studying gastropods parasitically associated to cnidarians (Calliostomatidae; Ovulidae; Epitoniidae; Coralliophilinae; Architectonicidae), echinoderms (Eulimidae), other molluscs (Capulidae), ascidians (Velutinidae).

Since genetic connectivity plays a crucial role in shaping the geographic structure of species, I am studying marine gastropods as excellent models for testing the influence of pelagic larval dispersal on genetic structure. In gastropods the developmental type (long v. short pelagic phase) can be inferred from the morphology of the embryonic and larval shells. I am contrasting closely related species with opposite larval development, in several families, to test the hypothesis that long lasting dispersal yields higher connectivity over long distances, and short dispersal produces isolation-by-distance patterns.

I have published over 160 scientific papers (mostly on molluscs, but also on insects and vertebrates). I have participated in and/or organized dozens of collecting expeditions at many distinct localities (from the SW Pacific to the Indian Ocean, from the Mediterranean Sea to the Antarctic) shore-based and onboard international research vessels, logging more than 2000 SCUBA dives.

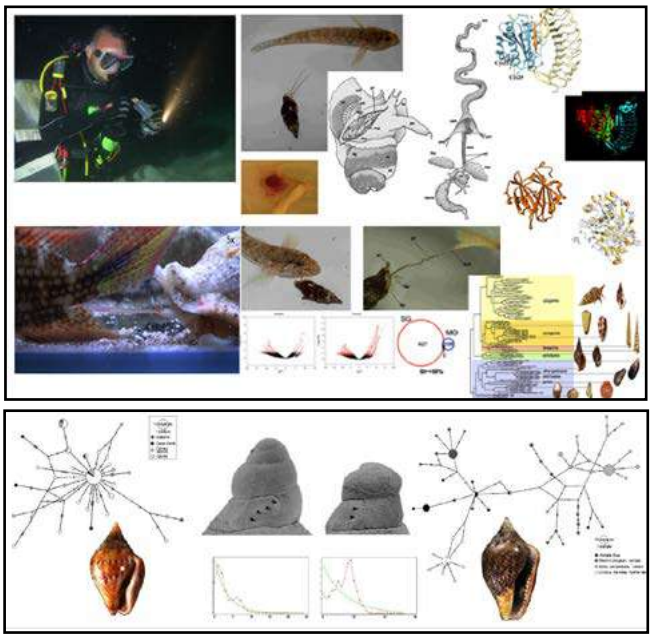

Figure. Upper panel. The vampire snail Cumia reticulata and its biochemical weaponry. From sampling specimens, to the study of the molecules in its venomous cocktail, their evolution and physiological role.
Lower panel. Genetic connectivity in two species with opposite larval development: left, Columbella adansoni, with long lasting pelagic larva; right, C. rustica, with short dispersing larva. Haplotypes (COI) networks and spatial PCA showed significant differences, with isolation-by-distance and a global structure in C. rustica vs high connectivity and no geographic structure in C. adansoni.

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RESEARCH LINES

- Global species distributions
- Global species extinction risk
- Global biodiversity scenarios

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GRANTS

2020. Horizon Marie Skłodowska-Curie Actions International Training Network Inspire4Nature.
€ 3,950,859 (€ 1,032,245 at Sapienza). Project Coordinator Dr. Ana Rodrigues, CNRS, Sapienza PI C. Rondinini.

RESEARCH ACTIVITY

Research at the Global Mammal Assessment (GMA) lab focuses on species distribution, extinction risk, conservation priority setting and biodiversity scenarios. We model the distribution of terrestrial vertebrates, including mammals, amphibians and birds from the regional to the global scale based on the concept of the Area of Habitat, the habitat available to a species within its range (Brooks et al. 2019).
In partnership with the IUCN (International Union for Conservation of Nature) we coordinate the program that monitors the risk of extinction of all mammals globally. This involves working with thousands of mammal experts organized in 35 Specialist Groups to assess the extinction risk of each of the World's mammals and publish it on the IUCN Red List, to produce policy-relevant indicators used by Multilateral Environmental Agreements (e.g., the Convention on Biological Diversity, CBD, and the Intergovernmental science-policy Platform on Biodiversity and Ecosystem Services, IPBES).
We identify priority conservation sites and actions, based on spatial data on the distribution of biodiversity and threats (e.g. Hanson et al. 2020). We have developed the InSiGHTS scenario modelling framework (Visconti et al. 2016) to assess the effects of socio-economic development pathways and policies on biodiversity.
This research line includes spatially-explicit models of future Area of Habitat based on policy-relevant scenarios of land-use and climate change, studies of expected species responses to global change, and investigations on present and projected effects of biological invasions.

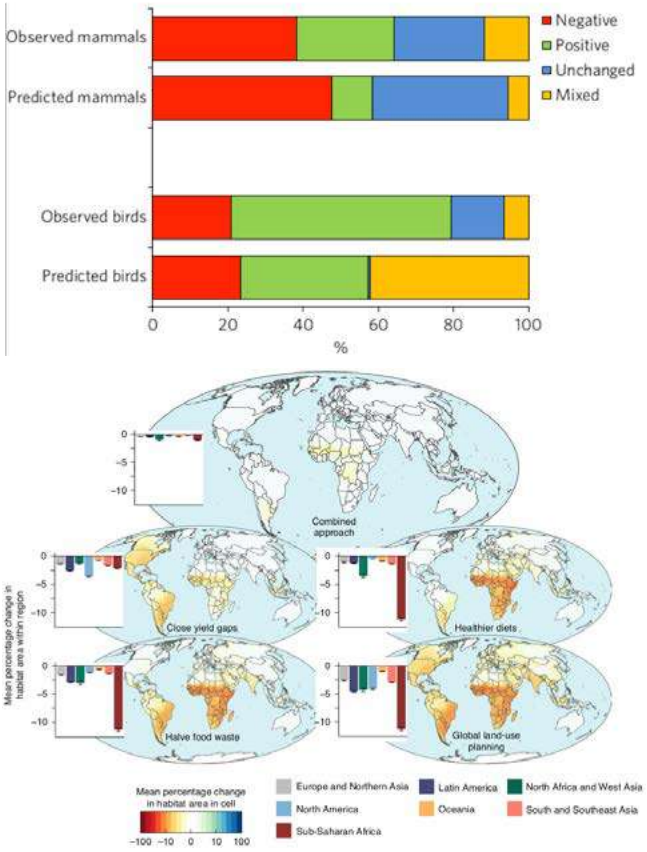

Figure. Upper panel: observed and projected response of mammals and birds to climate change. Red bars show the percentage of species whose populations were documented to have had, or are predicted to have had, a negative response to climate change in the study period (studies spanned from 1858 to 2010); green bars represent the percentage of species with a positive response; blue bars indicate the percentage of species with no response; yellow bars show the percentage of species with mixed responses (from Pacifici et al. 2017 Nature Climate Change, 7:205-208). Lower panel: projected changes in mean Area of Habitat for terrestrial vertebrates from 2010 to 2050 under alternative scenarios of agricultural expansion. Maps show the mean change for all species of all taxa in a cell, with values on a log 10 scale. Insets show the mean change in habitat area for all species within a region, error bars show s.e.m (from Williams et al. 2020 Nature Sustainability, https://doi.org/10.1038/s41893-020-00656-5)

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RESEARCH LINES

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- Functional ecology
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GRANTS

2020-22. Global Wildlife Conservation (USA) "Testing automated approaches to prioritise IUCN Red List reassessments" PI: L. Santini ($31,153)
2020-23. German Centre for Integrative Biodiversity Research iDiv (Germany) "Accelerating IUCN Red List assessments for rapid and effective biodiversity monitoring (Working Group)". PI: L. Santini (€38,200)
2020-23. MIUR Rita Levi Montalcini (Italy) "Automatizing extinction risk assessments for efficient biodiversity monitoring".
PI: L. Santini (€185,181.44)

RESEARCH ACTIVITY

My research focuses on ecological patterns and processes across large (spatial, temporal and taxonomic) scales in order to derive general principles that explain how life on earth is distributed and structured. A recurrent theme in my research is unravelling how such patterns and processes have been altered by anthropogenic pressures, to estimate natural baselines and get a deeper insight on the ongoing reorganization of biotic systems. I'm particularly interested in macroecological patterns of abundance across vertebrate species, and processes underlying them. To this end, I have created the TetraDENSITY database, which includes tens of thousands of dated and georeferenced population density estimates from the literature. Important applicative sides of my research consist in the integration of macroecological and biogeographical principles into biodiversity and conservation assessments, with the ultimate goal of reducing our dependency on species-level information by focusing on general ecological principles and species functional differences. Specifically, by understanding biodiversity patterns and their causes, I attempt to use existing biodiversity knowledge to infer missing information on poorly known species and areas that are relevant for conservation assessments and planning. A practical example is the development of automatized approaches to assess species conservation status in a rapid and cost-efficient manner. I am currently leading a large network of scientists working toward this goal (sRedList project). I believe in the potential of big data to deepen our knowledge beyond the specifics of local case studies, and I rely on a variety of statistical, machine learning, and meta-analytical approaches, and to address both theoretical and applicative questions. I strongly support "predictive ecology", not only as an important tool for conservation biology, but also as a proof of concept of our understanding of ecological dynamics.
I also make a large use of ecological simulations in order to explore ecological mechanisms, test methodological approaches on virtual species, and assess possible outcomes of human actions. I'm also passionate about animal ecology and behaviour, and to a lesser extent I also research the behavioural and spatial ecology of mammals, with a particular interest on how they are altered by anthropogenic pressures and the influence species' intrinsic vulnerability to different anthropogenic threats.

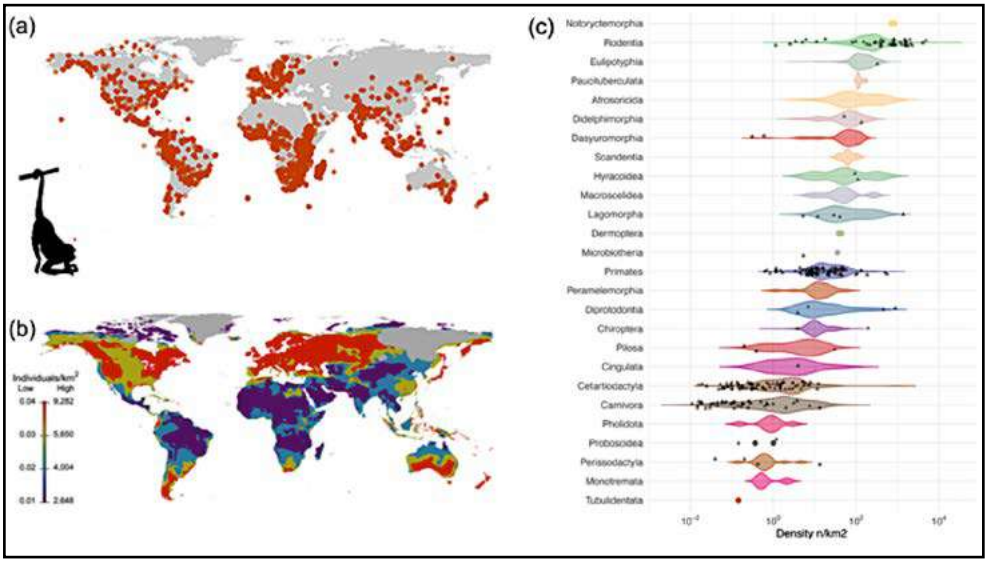

Figure. (a) Distribution of population density estimates for terrestrial mammals from the TetraDENSITY database (Santini et al. 2018a Glob Ecol Biogeog 10.1111/geb.12756); (b) Global prediction of how average population density in mammals scales with climatic conditions (Santini et al. 2018b Glob Ecol Biogeog 10.1111/geb.12758); (c) Distribution of population density predictions for all mammal orders (Santini et al. in prep).

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