Fondazione Ri.MED

ANNUAL REPORT 2023

Fondazione Ri.MED

FOUNDING PARTNERS

Presidenza del Consiglio dei Ministri

Regione Siciliana

Consiglio Nazionale delle Ricerche

University of Pittsburgh

UPMC LIFE CHANGING MEDICINE

PARTNER

UPMC | IRCCS ISMETT Palermo

Paolo Aquilanti

PRESIDENT AND CEO

Ri.MED consolidated its activities toward its statutory mission closing successfully 2023, and moving forward important steps for the realization of its goals. I am proud that we have achieved positive results both in terms of research, training and scientific dissemination, as well as in terms of construction of our Biomedical Research and Biotechnology Center, also thanks to the support of our founding partners: the Presidency of the Italian Council of Ministers, the Region of Sicily and the Italian National Research Center (CNR), the University of Pittsburgh (UP) and the University of Pittsburgh Medical Center (UPMC).

Ri.MED keeps on growing: new professionals have been appointed in order to strengthen our research teams, specific technology platforms and projects: during 2023, Ri.MED has hosted 23 fellows, 47 PhD students and 22 trainees. Our commitment to the valorization of the human resources has led the Ri.MED Foundation to implement the Gender Equality Plan, an important tool for promoting equal opportunities, improving work-life balance for our employees, and overcoming all forms of prejudice. Nurturing new talents and training highly qualified resources is one of our missions, which also contributes to increasing local competitiveness.

Ri.MED has been increasingly committed in dissemination and training activities during 2023: with the 11 scientific seminars organized the Foundation disseminated scientific knowledge while at the same time involved and informed people on the construction of the research center. Our 2023 International Symposium on "Pandemic Preparedness" was a successful event, highlighting also the strength of the UPMC-Ri.MED-ISMETT cluster.

Ri.MED carried on its commitment in local schools: at the end of 2023 the Foundation signed an important collaboration protocol with the Regional School Office for Sicily and the Regional Department of Education and Professional Training, in order to structure a widespread calendar of activity. The agreement recognizes the importance of biotechnology and the key role that Ri.MED has – more and more - in the dissemination of scientific culture in Sicilian schools.
Our research network is becoming more and more competitive: 13 agreements were signed in 2023 and today Ri.MED boasts a total 53 agreements for the development of research activities and technological innovation with European and U.S. institutions. Thanks to the outstanding work of our researchers and the Grants office, in 2023 the Ri.MED Foundation awarded 1.760.987 € through national and international grants and has also been a strong effort to submit new grant requests.

Researchers have also created strategic partnerships with small and medium enterprises and start-up businesses for the development of new products, whose tangible outcomes are the 32 patents. At the same time, technology platforms and research areas have been consolidated, with the continuous support of the administrative office.

A recognition to all the people in Ri.MED who, with competence and passion, contribute day after day to the development of our vision: a commitment to excellence and growth of our researchers, the international and multidisciplinary environment and the rich network of collaborations are what make me feel proud to be part of Ri.MED and its mission.

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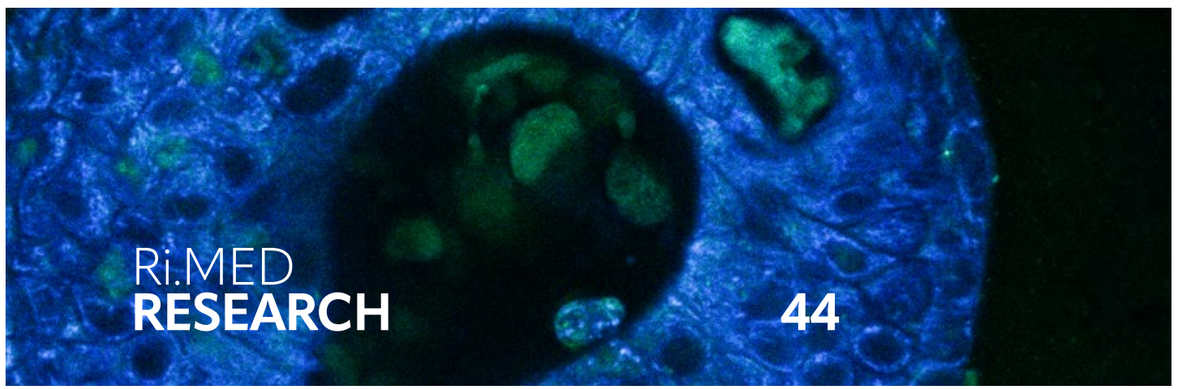


Ri.MED OVERVIEW 2023

Networking

5 active agreements for labs management

54 active scientific collaborations and technology transfer agreements

14 new agreements signed in 2023

Training & employment

HUMAN RESOURCE in 2023

82 employees

62%

38%

23 fellows

47 Ph.D. students

22 trainees

Intellectual property

32 patents portfolio up to 31.12.2023

77 scientific papers published in 2023

Fundings for Research

1.760.987 € awarded through national and international GRANTS in 2023

Scientific knowledge dissemination

4 public engagement events

12 Ri.MED scientific events

80 hours of training provided in local schools

Building the Research Center

17,070 sq m of laboratories

220,000,000€ value of the investment

600 planned occupancy opportunities

HUMAN RESOURCES

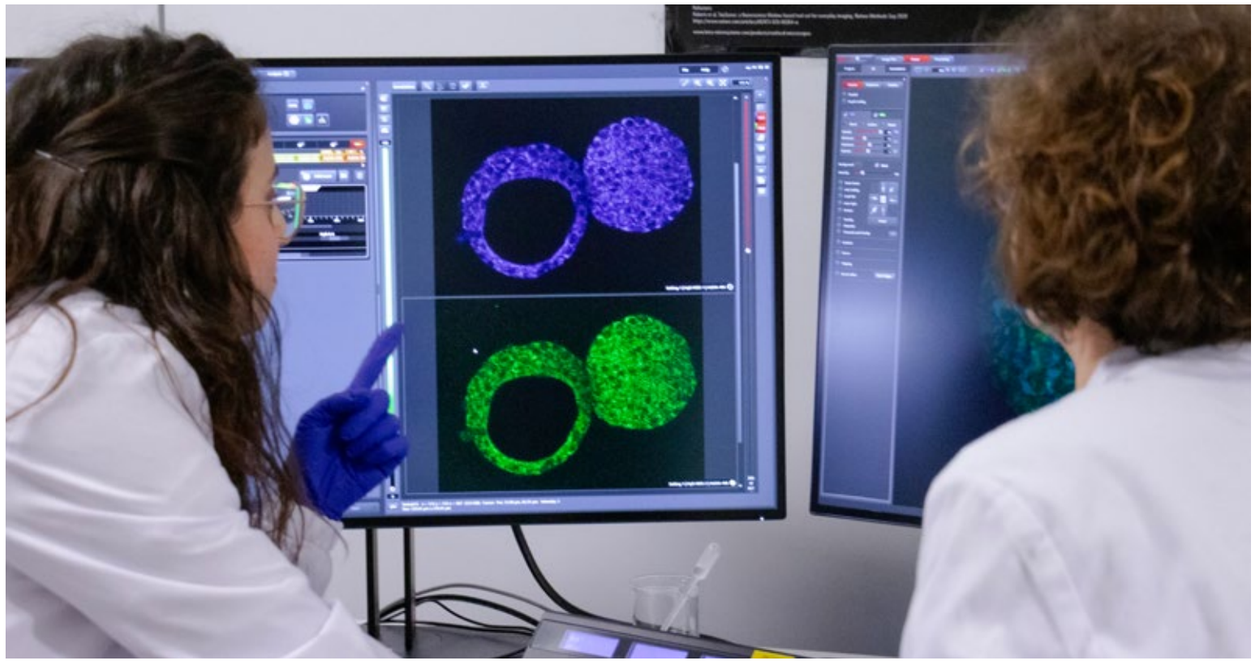
NURTURING NEW TALENTS

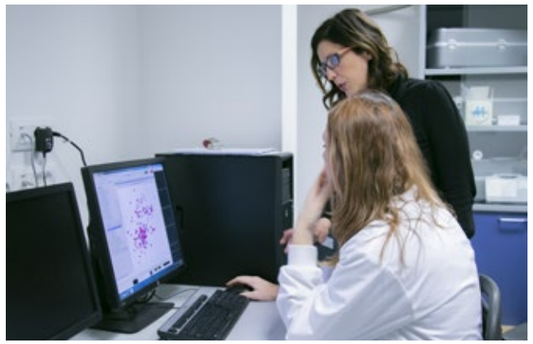
Ri.MED places significant effort in the training of highly-qualified staff, recognizing their key role in accomplishing successful scientific results and guaranteeing the competitiveness and growth of the territory.

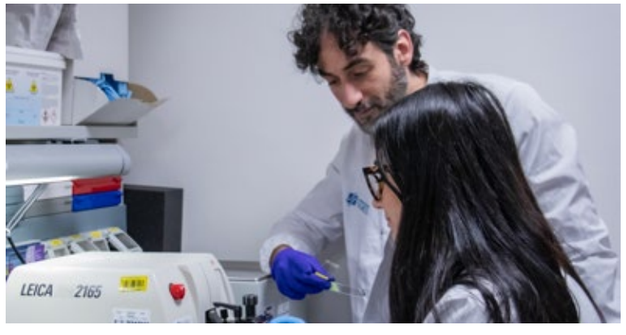
Some of these training programs were implemented in partnership with the University of Pittsburgh, and others activated using EU funds (for example, Horizon 2020 and ERC grants), ministerial funds, and regional calls (including "Chemist", "Obind", "Senso", "Prometeo," and others.)

In 2023, there was an increase in the number of PhD and internship applications at Ri.MED, as a result of the growing interest of young researchers in the Foundation's activities. In 2023, 23 scholarships and 22 internships were activated, and 46 PhD students were hosted, offering over 90 young professionals a unique opportunity to develop new skills.

The fellowships and research grants were awarded to junior and senior researchers wishing to spend part of their career at Ri.MED. The Foundation has become a center of attraction of high scientific value for young promising researchers.







HUMAN RESOURCES

GROWING TOGETHER

As of December 2023, the Ri.MED Foundation has a staff of 126 employees and fellows, of which 98 are researchers. About 20% of the Ri.MED researchers are Sicilians who decided to return to Sicily thanks to the professional opportunities offered by the Foundation. About 11% of researchers arrived from other parts of the world, a further demonstration of the international reputation of the Foundation.

Since last year, Ri.MED hosts researchers from non-EU countries after its inclusion in the list of authorized research institutions issued by the Italian Ministry of University and Research (MUR). While this has increased the Foundation's international reputation, it has always been the strategy of Ri.MED, also thanks to the partnership with the University of Pittsburgh and UPMC (University of Pittsburgh Medical Center), to offer researchers rotations in top scientific institutions, in line with the EU recommendations on mobility of scientific research as a means of developing research networks and consolidating the role of European research at a global level.

In view of the forthcoming opening of the Foundation's new research center in Carini, near Palermo, and thanks to new research funds, in the next coming years Ri.MED's research teams will continue to grow, and the Foundation will become an international host institution.

HUMAN RESOURCES

WOMEN IN SCIENCE & GENDER EQUALITY PLAN

In December 2022, the Ri.MED Board of Directors approved the Gender Equality Plan (GEP), an important tool to ensure recognition and respect of gender equality at all levels. In 2023, the GEP was fully implemented and the training and listening desk services entrusted. The aim was to increase opportunities and enhance skills of employees of any gender and orientation, in line with the European Commission's recommendations. The GEP and its indicators and tasks are designed as a flexible tool that can easily be updated and that includes measurable goals.

Furthermore, scientific dissemination activities focused on gender research are scheduled for the beginning of 2024, with the aim to develop personalized diagnostic and therapeutic solutions taking into account the differences in sex (at a biological level) and gender (at a socio-cultural level) that have an impact on people's health.

Even before the introduction of this tool, however, the Ri.MED Foundation demonstrated the absence of gender bias, selecting over the years a team of researchers composed by 62% of women. This is particularly relevant when analyzed against numbers from European universities where the so-called STEM (Science, Technology, Engineering and Mathematics) studies are still the frontier of the gender equality challenge. We are proud of our brilliant and skilled women, managing important medical and scientific research projects!

HUMAN RESOURCES

HIGHLIGHTS 2023

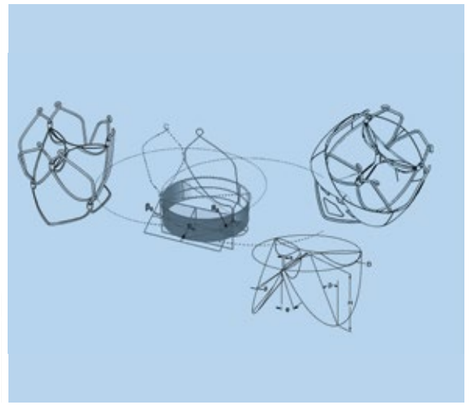
Antonio D'Amore

The only researcher affiliated with an Italian institution to win ERC and NIH funds at the same time

In May 2023, the European Research Council (ERC) announced the winners of the Proof of Concept (PoC) Grant, a competitive translational funding program available only to researchers who already have an ERC award. The PoC Grant fosters new ideas that drive innovation and business innovation, and translate into effective patient care.
In 2023, Antonio D'Amore who already awarded the ERC Consolidator Grant for the Biomitral project in 2020, won the PoC grant with the BioChord project: biomimetic, engineered chordae tendineae for valve repair and regeneration. The project also involves Arianna Adamo, Ri.MED specialist in mechanobiology as leading scientist, and whose research was a key contribution to the development of bioengineered chordae tendineae.

Dr. D'Amore's groundbreaking research on heart valves was awarded over half a million dollars in the United States with the NIH Small Business Technology Transfer (STTR) program, a grant that will support the development of a bioengineered pediatric pulmonary valve. Marzio Di Giuseppe, Ri.MED scientist in numerical methods, a member of Dr. D'Amore's team, worked on the drafting of the project.

"The project focuses on a stentless mitral valve in engineered material able to offer an environment conducive to patient tissue regeneration. Its strong point is biomimicry: the prosthesis has a subvalvular apparatus that copies that of the native valve, a complex system of chordae tendineae, small tendons that connect the valve to the ventricle, keeping it in place during the cardiac cycle," explains D'Amore. "Our work on Biomitral paved the way for the use of bioengineered chordae tendineae also autonomously, hence the idea submitted for the PoC. Chordae tendineae rupture is a frequent cause of valve prolapse. Current surgical repair techniques rely on simple expanded polytetrafluoroethylene (ePTFE) sutures that do not mimic the structure or the mechanics of the native chordae tendineae. In fact, several complications have been observed when using these materials, including rupture and calcification, which strongly impact the patient's life. My laboratory was the first to introduce a bioengineered prosthesis for chordae tendineae repair. BioChord is inspired by the structure and function of the native organ, allowing the growth of the patient's tissue while providing mechanical support to the valve."



Gaetano Burriesci

Intellectual property and successful technology transfer

In July 2023, results were published of the 6-month follow-up on the first patient tested with Sikelia™, the innovative catheter-implantable heart valve designed by Gaetano Burriesci, Ri.MED Group Leader in Bioengineering and Medical Devices, whose entire patent family was acquired by MitrAssist, a multinational cardiovascular company with R&D centers in China, Israel, and Germany.

In the article, the authors review the successful implant of the first polymeric transcatheter aortic valve replacement device in a patient with severe eccentric calcified stenosis of the aortic valve. Compared to conventional valves, this new valve has improved durability, a larger orifice area, and improved morphological adaptability. This successful implantation of the first polymeric TAVR device in humans is described in the article as a significant leap in the history of TAVR technology.

Degenerative aortic stenosis due to senile calcification is the most frequent valve disease in high-income countries, and is escalating due to increasing longevity of the population. However, about one-third of patients have concomitant diseases or previous surgery, which makes surgical replacement of the impaired aortic valve too risky. Transcatheter implantation is an ideal solution, as it allows a percutaneous implant of a prosthetic valve in its anatomical site, avoiding open heart surgery and all associated risks, thereby meeting the needs of patients with comorbidities.

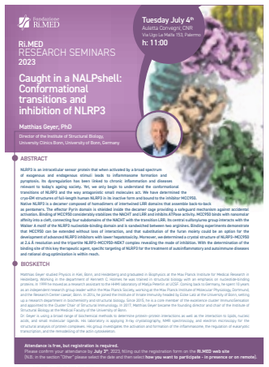
The device was conceived and developed by Gaetano Burriesci, and uses a self-expandable armature in superelastic alloy that supports three leaflets and one polymer sealing cuff, which allows a more precise implant, and extraction and repositioning of the valve after its release. The anchoring system makes the prosthesis particularly suitable for treating congenital valve diseases (e.g., bicuspid aortic valve), and the polymer leaflets are not subject to degenerative calcification. This valve requires significantly lower manufacturing costs compared to current devices, making it potentially suitable for expanding transcatheter treatment to developing countries, where this is not currently sustainable.

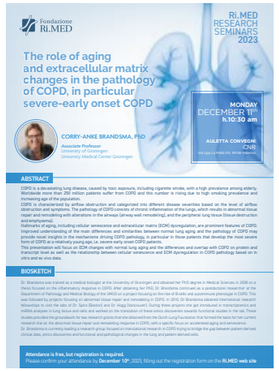
Researchers at Ri.MED Foundation are now working with MitrAssist to facilitate the marketing of Sikelia™.

DISSEMINATION OF SCIENTIFIC KNOWLEDGE

EVENTS

Activities related to scientific dissemination and sharing of research outcomes are part of the Foundation's mission. During 2023, the Ri.MED R&D Coordination Committee organized in Palermo a **series of seminars**: **10 meetings**, between March and December, involving **11 outstanding invited speakers.**





The 2023 Ri.MED Annual Scientific Symposium was held on October 26 and 27. The chairman of the event entitled **"Pandemic Preparedness: from Emergence to Translation"** was Paul Duprex, Director of the Center for Vaccine Research and Professor of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine. The COVID-19 pandemic clearly illustrated how devastating infectious diseases can be on both health and social infrastructure. We hosted leading experts from Italy, Europe, and the U.S. to address the role that current and emerging infectious agents, and the development of effective vaccines and therapies have on next pandemics preparedness.

Year 2023 was also an important time in terms of scientific publications, with close to 80 articles published in peer reviewed journals with relevant impact factors. The role of the Foundation's press office was instrumental to share the main research results to a wider public of non-experts, thus contributing to the dissemination of scientific knowledge.

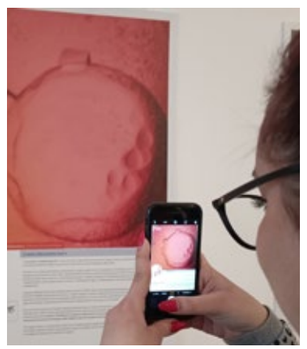
DISSEMINATION OF SCIENTIFIC KNOWLEDGE

PUBLIC ENGAGEMENT

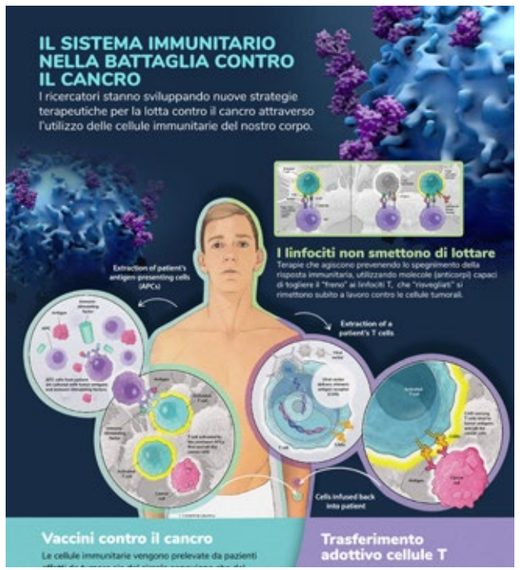
Involving and inspiring a heterogeneous public is one of our priorities, offering a public engagement program for people of all ages, in collaboration with local institutions. We are present in the community with projects to facilitate and promote knowledge, from science and health to investments and employment opportunities, legality, and meritocracy.

In 2023, as usual, Ri.MED took part in **"Sharper - The European Researcher's Night"** - an event that was widely popular among young and older visitors - with the initiative **"Our Match against Cancer."** Our researchers showed the computational models used to design new drug therapies to combat cancer, and illustrated the evolution of the pathology and its regression through simple, highly descriptive representations: laboratory models, illuminated puppets, imaging fluorescence to be observed under the microscope, i.e., everything that can be useful for understanding the mechanisms that regulate the immune system. The youngest participants had fun with simple activities, such as solving a puzzle that represents the attack on tumor cells, building molecules, and even playing five-a-side football in a hypothetical match between good cells and bad cells.

With the event "**SCIENCE UNDER CONSTRUCTION**" at Palazzo Sant'Elia in Palermo, Ri.MED Foundation disseminated scientific knowledge while at the same time involving and informing people on the construction of the BRBC. A selection of photographs of the construction site and the project, the exhibition illustrates the space, projects, materials, surrounding environment and workforce at the BRBC construction site. Furthermore, a series of meetings with schools were organized, during which the students were able to interact with the researchers who spoke about some of Ri.MED's research lines offering insight and advice based on their personal career paths.



Ri.MED took part in the cycle of activities organized in October for the **Centenary of the Italian Research Council**, with the "**The Enchanted Science**," an exhibition of scientific images proposing a striking combination of nature, art, and research." Art is a form of language that interprets the world and creates enchantment. Sometimes rational science can steal the stage from art or merge with nature. These beautiful images were illustrated to all visitors by the Ri.MED researchers.



Moreover, in 2023, Ri.MED carried out scientific dissemination activities in Carini, home of the upcoming research center, with two children's workshops:
"**Molecular biology laboratory: extraction of DNA from fruit,"** organized as part of the Park Art Fest; being able to observe with their own eyes the famous helix-shaped strands of banana DNA was an exciting discovery for the children.
"**The magic of chemistry,**" organized for the "Natale al Parco": a fun exposition of some natural phenomena (such as polarity, density, and lipophilicity), followed by the creation of a lava lamp!

DISSEMINATION OF SCIENTIFIC KNOWLEDGE

SCHOOLS

Throughout 2023 Ri.MED carried on its commitment in local schools. The Foundation entered various agreements with local high schools to activate pathways for transversal skills and guidance. With theoretical and hands-on knowledge, the aim of these programs was to complement the students' curriculum, and enhance their choices for future study or work. Our researchers were asked to conduct sessions for various groups of students.
In addition to the agreements with the schools that requested it, at the end of 2023 the Foundation signed an important collaboration protocol with the Regional School Office for Sicily and the Regional Department of Education and Professional Training in order to create a vast calendar of activity and events. The agreement recognizes the importance of biotechnology and the key role that Ri.MED has in the dissemination of scientific culture in Sicilian schools. The plan involves the creation of courses for transversal skills and orientation (PCTO) on the topics of scientific research applied to health, as well as orientation, promotion, and training activities useful for the growth of the entire school community.

Moreover, Ri.MED took part in DIDACTA ITALIA 2023 - the most important trade fair event dedicated to the world of education and training, presenting two seminars: "Innovative educational paths for future scientific research professionals" by Ugo Perricone, and "The (Ri)- Generation of future scientists" by Giovanna Frazziano and Giampiero Vitale. Our researchers illustrated to teachers and school administrators the process of discovering new drugs, and the path toward development and production of advanced therapies. One of the goals of the seminars was to show which skills to include in the training of future researchers.

The mission of Ri.MED is to gradually increase its presence in the local area, developing new educational programs with schools, and involving the local community.

DISSEMINATION OF SCIENTIFIC KNOWLEDGE

PRESS


Sud

34 ORE

A Carini il polo mondiale per la ricerca e le startup

Lavori in corso. Il nuovo Centro della Fondazione Ri.Med in costruzione a Carini nel palermitano: sarà pronto entro il 2025

Biotecnologia, a Carini un polo mondiale di ricerca e startup


L'Espresso

Da Vienna alla Sicilia: il luminare di biologia molecolare torna in Italia per fare ricerca

Giulio Superti-Furga da direttore del CeMM dell'Accademia Austriaca delle Scienze va a Carini, nel palermitano. Sarà direttore Scientifico della Fondazione Ri.MED e Direttore del Centro per le Biotecnologie e la Ricerca Biomedica in costruzione. «La nostra struttura è unica nel suo genere e promette di diventare un faro di speranza per i pazienti e un motore di crescita economica per la regione»


la Repubblica

Palermo

Giornata donne nella scienza: "Io ricercatrice rimasta in Sicilia ho sconfitto tutti i tabù"


TGR Sicilia

Palermo Catania Messina Trapani Agrigento Caltanissetta Enna

Studiare l'impatto del fumo sui polmoni per scoprire nuovi farmaci

SALUTE

Studiare l'impatto del fumo sui polmoni per scoprire nuovi farmaci

Si celebra la Giornata mondiale senza tabacco. Al Cnr di Palermo l'impegno dei ricercatori della Fondazione Ri.Med guidati da Chiara Cipollina

31/05/2023 Marcello Longo - Montaggio Gerlando Tabone


la Repubblica PALERMO

DATA STAMPA

Rimed, accelerazione sul polo di Carini "Pronti a marzo 2025"

Fondazione e impresa trovano un accordo per la realizzazione del Centro per la ricerca biomedica

di Tullio Filippone

L'investimento è di 200 milioni di euro a regime darà lavoro a circa 600 persone, la gran parte delle quali scienziati tornati in Sicilia o approdati nell'isola da centri di tutto il mondo per la ricerca biotecnologica e genetica e le indagini molecolari su malattie oncologiche.

Lo scheletro della cittadella della ricerca, come un Lego in costruzione, si intravede già dal binario del passante ferroviario che collega l'aeroporto di Punta Raisi a Palermo. E quando sarà completato, dall'alto, avrà una forma di cromosoma, con due cipolle del progetto e l'Upmc di Pittsburgh, colosso sanitario americano da 25 miliardi di fatturato e 90mila dipendenti, che a Palermo dal 1997 gestisce IRCCS, il centro di eccellenza dell'oncologia.

«Quando è nata Rimed e si è deciso di investire per questo centro di ricerca è stata valutata positivamente l'esperienza dell'Ismett — dice Aliquanti — tanto che abbiamo circa 80 ricercatori che lavorano già a Palermo, divisi tra le sedi dell'Università, del Cnr e dello stesso Ismett; il 90 per cento sono siciliani e molti sono rientrati nella loro terra dopo un'esperienza in Italia o all'estero, perché l'obiet


Sanità24

34 ORE

10 OTT 2023

Fondazione Ri.MED e Upmc: Giulio Superti-Furga designato Direttore scientifico

Fondazione Ri.MED e Upmc (University of Pittsburgh Medical Center) annunciano la designazione del Prof. Giulio Superti-Furga a Direttore scientifico della Fondazione e Direttore del Centro per le Biotecnologie e la Ricerca Biomedica (Cbrb) in costruzione a Carini, a pochi chilometri dall'aeroporto di Palermo. La scelta è l'esito di una selezione internazionale tra candidati di elevatissima qualificazione scientifica e gestionale.

La Fondazione Ri.MED condurrà attività di ricerca traslazionale secondo approcci di medicina rigenerativa e immunoterapia, bioingegneria e sviluppo di farmaci e vaccini, avvalendosi di avanzate piattaforme tecnologiche quali quelle di biologia strutturale.


Villaggio Tecnologico Tech4Trade Zampe Libere Switch On InnovArte

TECNOMEDICINA

Home Chi siamo News Informatv Radio Salus Luoghi della Salute Bergamo S

Al via 4 progetti di ricerca congiunti tra Ospedale "F. Miulli" e Fondazione Ri.MED


LA SICILIA Catania

DATA STAMPA

Europa e Stati Uniti puntano sui tessuti bioingegnerizzati

Antonio D'Amore, Arianna Adamo, Marzio Di Giuseppe


la Repubblica

Gli effetti dell'attività fisica adattata su pazienti cronici

Francesca Angelone, Assistente Relazioni Istituzionali Fondazione Ri.MED, Cavilli, referente per l'Ateneo per l'accordo con Ri.MED, Prof. Attilio Parisi, dell'Università degli Studi di Roma "Foro Italico", Cons. Paolo Aliquanti, Pr Fondazione Ri.MED, Avv. Anna Laura Zanzarri, consulente legale Fondazion Ri.Med

Progetto di ricerca congiunto tra Universi degli Studi di Roma "Foro Italico" e Fondazione Ri.MED


About Pharma and Medical Devices

MEDICINA, SCIENZA E RICERCA

LE PROTESI BIOISPIRATE CHE MIRANO A RIVOLUZIONARE IL CARDIOVASCOLARE


TeMi

Impresa Sanità

ARTICOLI WHITE PAPER EVENTI CHI SIAMO/MEDIAKIT LOGIFARMA DIGITAL BAG 2023 PDF MAG SHOP

15th RI.MED SCIENTIFIC SYMPOSIUM

STUDIO E CONFRONTO SULLE EVENTUALI PROSSIME PANDEMIE


LA SICILIA Catania

FONDAZIONE RI.MED

Approvato il Gender Equality Plan

Il Cda di Fondazione Ri.Med ha approvato il Gender Equality Plan, un importante strumento per garantire il riconoscimento e il rispetto della parità di genere a tutti i livelli.

In tutta l'Unione Europea, le donne restano ancora sottorappresentate nei percorsi educativi scientifici. A fronte di una media UE di circa 21 laureati Stem ogni 1.000 giovani tra 20 e 29 anni, le laureate sono solo 14,9. Il dato dei colleghi maschi è quasi doppio: 27,9. In Italia ci sono più donne che uomini iscritte all'università, ma secondo le rilevazioni di AlmaLaurea solo il 18% delle ragazze sceglie corsi Stem.

alla fluidodinamica e non solo), è responsabile dell'area numerica del gruppo Ri.Med di Bioingegneria, dove si occupa di progettazione di valvole cardiache, un settore caratterizzato da importanti prospettive di trasferimento tecnologico. Alessandra è nata e cresciuta a Carini, il comune che ospiterà il Centro per le Biotecnologie e la Ricerca Biomedica della Fondazione Ri.Med, attualmente in fase di costruzione.

Maria De Rosa, a capo del gruppo di Chimica Medicinale, è un esempio del fenomeno di "attrazione di cervelli" innescato da Ri.Med: lacuna di origine, madre e sposata con un ri-


QUOTIDIANO DI SICILIA

A Palermo virologi da tutto il mondo

PALERMO - Gli ultimi tre anni hanno mostrato l'impatto devas

Stenosi sottoglottica nei bimbi, premiato Riccardo Gottardi (Ri.Med)

GIORNALE DI SICILIA

Quotidiano - Dir. Resp.: Marco Romano

Tiratura: N.D. Diffusione: 5126 Lettori: 113000 (0009290)

A Palazzo Sant'Elia

«La scienza in cantiere» Centro Ri.med in mostra

noi lavori al cantiere del Centro e biotecnologie e la ricerca bio- ica a Carini. La realizzazione del us di ricerca terminerà fra due , nella primavera del 2025 e una

scorsi è stata completata la sostitu zione in cavo interrato delle line elettriche aeree e la rimozione dei tra lieci di sostegno, un esempio di mi glioramento dell'impatto paesaggi

NETWORKING

PARTNERSHIPS & COLLABORATIONS

The aim of collaborations is to integrate complementary skills with joint translational research projects, increasing critical mass and potential for success. Ri.MED pays great attention to the ongoing development of its network of scientific collaborations and scientific agreements with centers and institutions operating in its areas of interest: there are currently 54 agreements in place for the development of technological innovation, promotion of research activities, and sharing laboratories and resources with national and international institutions.

Fourteen agreements were signed in 2023.
Ri.MED has Five ongoing agreements for lab hosting: the management of the Regenerative Medicine and Immunology laboratories at ISMETT of strategic importance for integrating basic and clinical research, the Structural Biology and Biophysics labs at ATeN Center, the Bioengineering and Medical Devices lab at the University of Palermo, the Experimental Lung Research lab at CNR, the Preclinical *In vivo* Research Group at Experimental Zooprophylactic and Zootechnical Institutes of Sicily.

Ri.MED Foundation attended the BIO International Convention organized by the Italian Trade & Investment Agency, the governmental agency supporting business development of Italian companies abroad and promoting the attraction of foreign investments in Italy.

GRANTS

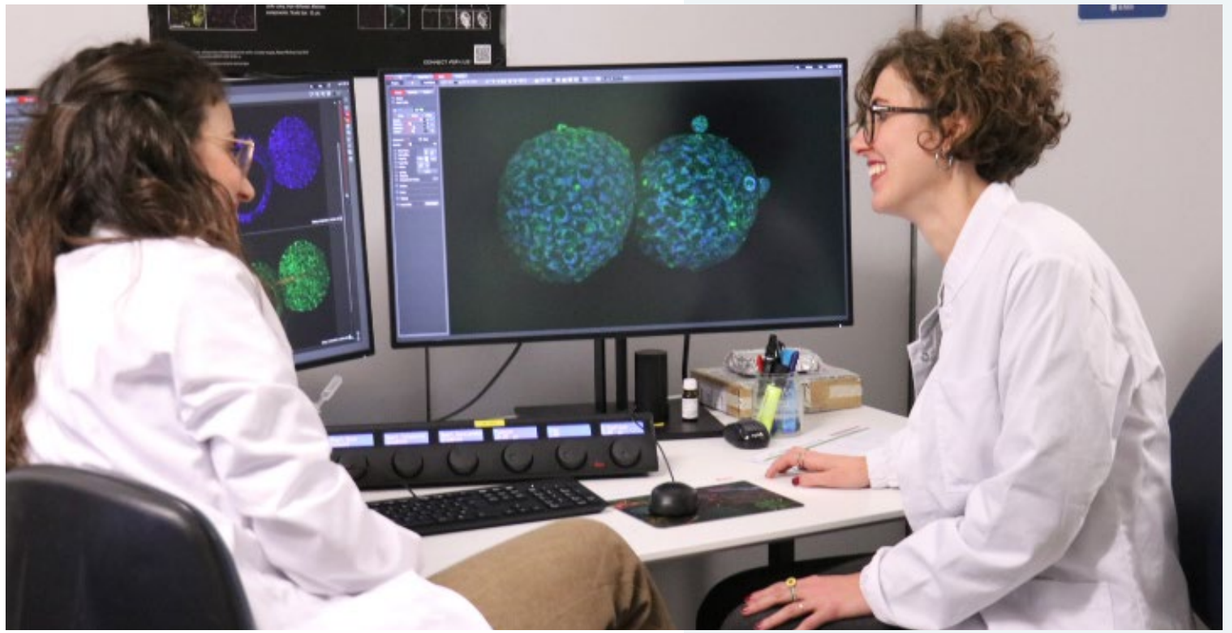
RESEARCH FUNDING

To create new knowledge for contributing to the scientific progress in the biomedical and biotechnological area, Ri.MED Foundation participates in competitive scientific grants funded by public and private financing bodies, at the regional, national, and international level. To achieve this goal, the Grant Area provides technical support to all Ri.MED researchers, from the identification of the most suitable grants, up to the project management and coordination once projects are approved for funding.

In 2023, in addition to the widely known prestigious competitive grants, the new opportunities offered by the National Recovery and Resilience Plan (PNRR), lead Ri.MED Foundation to the submission of more than 40 project proposals.

At this regard, it is worth to mention the Ri.MED participation in the Italian Fund for scientific excellence (FISA - Ministry of Research), and the opportunities offered by the most challenging Italian academic grants (PRIN), financially integrated by the NRRP, allowing the strengthening of the scientific collaboration with Universities.
This year, researchers have also created strategic partnerships with SMEs and start-up, participating in the Ministry of Economics grant, for the development of new products. Moreover, researchers collaborated in the submission of three new proposals, under the NRRP program and managed by the Ministry of Health. To this end, new partnerships with Italian hospitals and excellent research institutes were created, confirming the attractive role of Ri.MED in the Sicilian scientific panorama. Not only collaborative grants, but also individual ones, as the applications submitted according to the prestigious EU ERC Grant and the Italian AIRC Program.

Finally, two excellent researchers, from abroad, applied for the Marie Skłodowska-Curie Actions, selecting Ri.MED as host institution. In 2023, seven new projects have been awarded to Ri.MED Foundation, among them: three funded by the Ministry of Research, two funded by Ministry of Health, one from Versus Arthritis and a PoC funded by the EU ERC.



PhD SCHOLARSHIPS CO-FUNDING

FUNDING AGENCY/PROGRAMME:
National Recovery and Resilience Plan (NRRP) – Mission 4 (Education and Research), Component 2, Investment 3.3 (Ministry decree n.117/2023), with Ri.MED Foundation as both co-financier of PhD fellowships and hosting institution of PhD students (for a period of 6-12 months):

University of Palermo
N. 4 PhD SCHOLARSHIPS IN CHEMICAL, ENVIRONMENTAL, BIOMEDICAL, HYDRAULIC AND MATERIALS ENGINEERING.
Academic Year: 2023/2024 - Cycle XXXIX°
Coordinated by Prof. Giorgio Domenico Maria Micale.

University of Palermo
N. 3 PhD SCHOLARSHIPS IN TECHNOLOGIES AND SCIENCES FOR HUMAN HEALTH.
Academic Year: 2023/2024 - Cycle XXXIX°
Coordinated by Prof. Valeria Vetri.

University of Palermo
N. 1 PHD SCHOLARSHIPS IN BIOMEDICINE, NEUROSCIENCE AND ADVANCED DIAGNOSTICS.
Academic Year: 2023/2024 - Cycle XXXIX°
Coordinated by Prof. Fabio Bucchieri.

University of Palermo.
N. 1 PHD SCHOLARSHIPS IN PHYSICAL AND CHEMICAL SCIENCES.
Academic Year: 2023/2024 - Cycle XXXIX°
Coordinated by Prof. Marco Cannas.

University of Pisa
N. 1 PHD SCHOLARSHIPS IN PHARMACEUTICAL AND BIOACTIVE SUBSTANCES SCIENCES
Academic Year: 2023/2024 - Cycle XXXIX°
Coordinated by Prof. Federico Da Settimo Passetti.

FUNDING AGENCY/PROGRAMME:
National Recovery and Resilience Plan (NRRP) – Mission 4 (Education and Research), Component 2, Investment 3.3 (Ministry decree n.118/2023), with Ri.MED Foundation as host institution of PhD students (for a period of 6-12 months) for targeted scientific activities:

University of Palermo
N. 1 PHD SCHOLARSHIPS IN BIOMEDICINE, NEUROSCIENCE AND ADVANCED DIAGNOSTICS.
Academic Year: 2023/2024 - Cycle XXXIX°, Coordinated by Prof. Fabio Bucchieri.

University of Palermo
N. 1 PHD SCHOLARSHIPS IN MOLECULAR AND CLINICAL MEDICINE.
Academic Year: 2023/2024 - Cycle XXXIX°, Coordinated by Prof. Antonino Tuttolomondo.

FUNDING AGENCY/PROGRAMME:
European Commission HORIZON 2020
ERC Consolidator Grant. A PhD Fellowship totally funded by Fondazione Ri.MED, through the BIOMITRAL project:

University of Palermo
N. 1 PHD SCHOLARSHIPS IN MECHANICAL, MANUFACTURING, MANAGEMENT AND AEROSPACE INNOVATION
Academic Year: 2023/2024 - Cycle XXXIX°, Coordinated by Prof. Giovanna Lo Nigro.

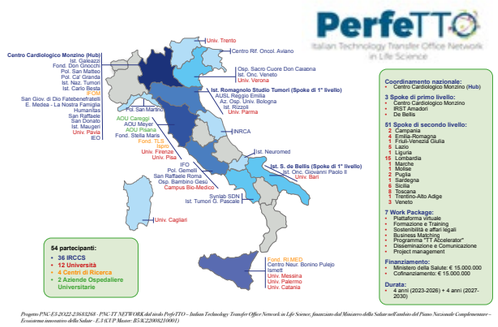
GRANTS

FOCUS ON
PerfeTTO, the first Italian Technology Transfer Office Network in Life Science

In April 2023, Ri.MED Foundation started its activities inside "PerfeTTO", the first Italian Technology Transfer Office Network in Life Science, financed by Ministry of Health (MoH) with a €15 million investment through the Complementary National Plan (PNC). The Project - running from April 2023 to September 2026 - aims to establish a TTO Network which will connect, coordinate and align the network Partners and Stakeholders, while offering world-class services in a collaborative and valuable manner at national and international level. Furthermore, the Project aims to achieve long-term sustainability beyond the reliance on MoH funds by fostering strong and strategic collaborations with market stakeholders, investors and users. All the activities are carried out while adhering to some solid principles such as: Value creation, Inclusiveness and transparency, Sustainability.

The Project combines 54 entities from north to south of Italy, including IRCCS, universities, public and private research entities, organized in Spokes (level I and II), among which Centro Cardiologico Monzino IRCCS acts as HUB Coordinator.

The final goal of the Project is to establish a solid leadership in the Life Science scenario and develop widely available services, tools and resources, which will benefit the partners of PerfeTTO to bridge the gap between research and innovation, encouraging technology development and promoting research valorization.



Progetto PNC-E3-2022-23683268 - PNC-IT-NETWORK dal titolo PerfeTTO - Italian Technology Transfer Office Network in Life Science, finanziato dal Ministero della Salute nell'ambito del Piano Nazionale Complementare - Ecosistema innovativo della Salute - E.I.S.I.P. Master: ECS_00000210001)

FOCUS ON
The EU interest in the innovative potential of Ri.MED scientific outputs

Back in 2021 Prof. D'Amore, Group Leader of Cardiovascular Tissue engineering (CVTE) Lab, was awarded the ERC Consolidator Grant BIOMITRAL - Engineering the mitral valve: bioinspired control of structure and function for enhanced in vivo performance, one of the most competitive and prestigious grants at the EU level.

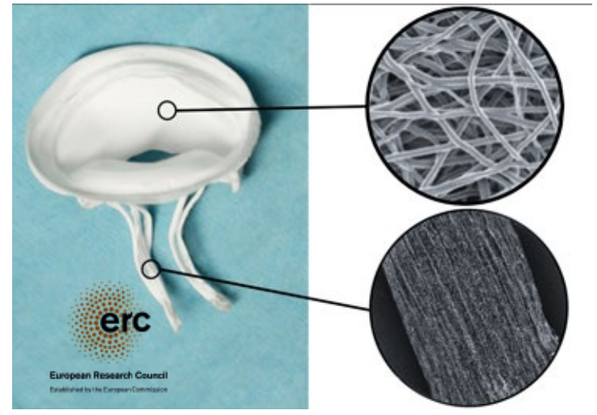
During 2023 the Laboratory of Cardiovascular Tissue Engineering (CVTE) was funded with an ERC Proof of Concept (PoC) grant that aims to progress ERC-funded ideas on the path from ground-breaking research towards innovation. The ERC PoC BioChord – Biomimetic engineered chordae tendineae for valve repair and regeneration involves Prof. Antonio D'Amore as Principal Investigator and Dr. Arianna Adamo as Leading Scientist in bioprocessing and mechanobiology.

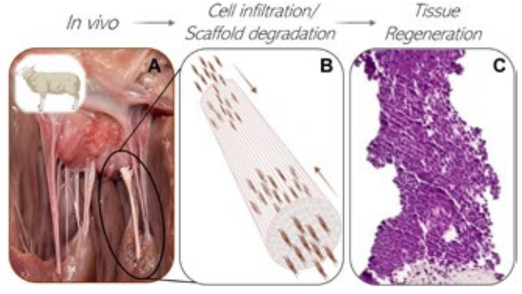
Additionally, both these ERC-funded projects are based on two Ri.MED patented inventions.

Within the BioChord project, in particular, the EU is supporting the Ri.MED CVTE Laboratory in prototyping a new bioengineered chorda tendinea for both open-heart surgeries and minimally invasive repair procedures.

Obtaining another recognition from the European Union validates the high quality of the research conducted in Ri.MED, as well as the reliability of its infrastructures to support excellent scientists engaged in cutting-edge research.

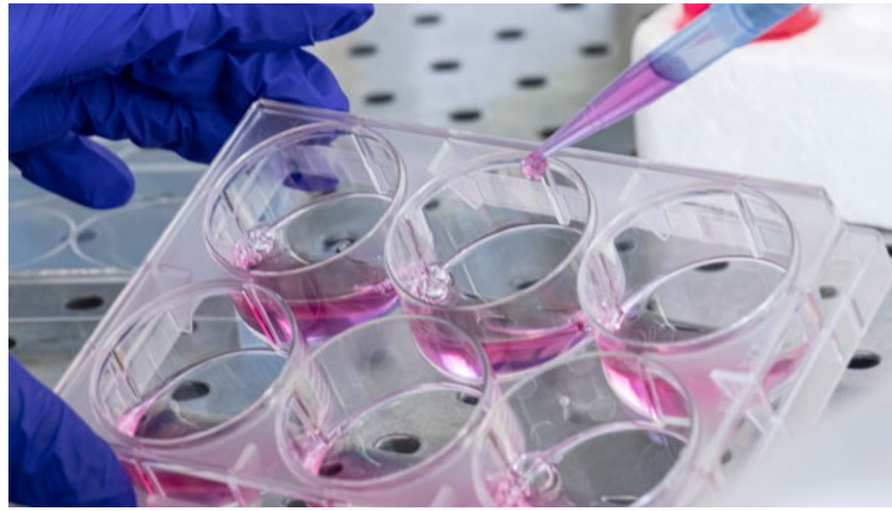
Ri.MED Foundation backs highly innovative, high-impact research, proposing disruptive and market-oriented innovations that could pave the way to critical discoveries and major scientific advancements. In 2023, the EU is confirming once again what already happened in 2021, when Ri.MED was also been identified as a Key Innovator by the European Commission's Innovation Radar.





GRANTS

2023 ONGOING SCIENTIFIC PROJECTS



PROJECTS IN PARTNERSHIP WITH SCIENTIFIC AND/OR HEALTH CARE INSTITUTIONS AND SMEs/BIG ENTERPRISES

National Biodiversity Future Center

Click here for more information

Funding Agency/Programme: National Recovery and Resilience Plan (NRRP) - Mission 4 (Education and Research), Component 2 - Investment 1.4.
Objective: promoting the sustainable management of Italian biodiversity in order to improve the planet's health and return beneficial effects, essential for all people. Specific objective in the health sector is the exploitation of natural products for therapeutic scopes.

National Center for Gene Therapy and Drugs based on RNA Technology

Click here for more information

Funding Agency/Programme: National Recovery and Resilience Plan (NRRP) – Mission 4 (Education and Research), Component 2 - Investment 1.4.
Objective: increasing the technological know-how necessary to design and deliver RNA-based and gene therapy medicinal products and identifying promising candidate drugs/genes in five major areas of human diseases (genetic diseases, cancer, metabolic/cardiovascular diseases, neurodegenerative disorders and inflammatory/infectious diseases).

OBIND

Oncological therapies through Biological Interaction Network Discovery

Click here for more information

Funding Agency/Programme: Sicilian Region. OP ERDF 2014/2020.
Thematic Objective 1: Research, Technological Development and Innovation.
Objective: developing a computerized system in the oncology field which allows for aggregation and analysis of different data sets, focused on studying the interaction between different biological molecules that are found to have changed in tumor diseases and in order to create a rational outline for planning new treatments

SENSO

Development of a miniaturized device for monitoring oxidative stress in cellular systems

Click here for more information

Funding Agency/Programme: Sicilian Region - OP ERDF 2014/2020 - Thematic Objective 1: Research, Technological Development and Innovation.
Objective: creating a nanosensor to detect hydrogen peroxide (H2O2) released *in vitro*/*ex vivo* cellular system culture. To this scope, the expected output is an innovative, robust, reliable, and small-sized lab tool to monitor the H2O2 release within the culture in real time, without affecting the cells' growth conditions.

4FRAILTY

Intelligent sensors, infrastructures and management models for the safety of fragile people

Click here for more information

Funding Agency/Programme: Ministry of Education, University and Research (Italy). NOP "Research and Innovation", 2014-2020. Directorial Decree n. 1735/Rec. (13.06.2017) "Notice for the presentation of Industrial Research and Experimental Development projects in the 12 specialization areas identified by the 2015 - 2020 RNP".
Objective: creating a computational tool able to simulate the sensory platform in its set of sensors and therefore including vital and environmental parameters that will be collected during the clinical work-up phases. The simplicity and versatility of the computational implementation will allow to quickly simulate different virtual scenarios of the possible alterations of the vital and environmental signals associated with a pathological condition.

GRANTS

2023 ONGOING SCIENTIFIC PROJECTS

PROJECTS IN PARTNERSHIP WITH SCIENTIFIC AND/OR HEALTH CARE INSTITUTIONS

Exploiting the power of human induced pluripotent stem cell extracellular vesicles as a new anti- inflammatory drug for lung ischemia reperfusion injury

Click here for more information

Funding Agency/Programme: National Recovery and Resilience Plan (NRRP) – Mission 6 (Health), Component 2 – Investment 2.1.
Objective: assessing technical and commercial feasibility of an innovative cell-free nanomedicine strategy based on extracellular vesicles (EV), human induced pluripotent stem cells and a young cell source such as cord blood. The project is focused on a patent which highlights the strong anti-inflammatory role of EV isolated from cord blood mesenchymal stromal induced pluripotent stem cells.

Life Science TTO Network

Click here for more information

Funding Agency/Programme: Italian Ministry of Health. National Plan for complementary investments to the NRRP – "Innovative Health Ecosystem" Program – Investment E.3.
Objective: establishing and consolidating a nationwide open and sustainable Technology Transfer Office (TTO) Network, which will connect, coordinate and align Network Partners and stakeholders (Research and Care Institutes (IRCCS), Universities, National Health System, Investors, SMEs, Industry, National and International Consortia) as well offer world-class services in a synergistic valuable way at national and international level.

iRhom2

A new therapeutic target in osteoarthritis

Click here for more information

Funding Agency/Programme: Fondazione con il Sud - Bando Capitale Umano ad Alta Qualificazione 2018.
Objective: validating iRhom2 as potential and innovative therapeutic target of osteoarthritis, using state-of the-art proteomics methods and *in vivo* models of the disease, including a study focused on iRhom2 inhibitors.

BIOMITRAL

Engineering the mitral valve: bioinspired control of structure and function for enhanced *in vivo* performance

Click here for more information

Funding Agency/Programme: European Commission HORIZON 2020 – ERC Consolidator Grant
Objective: developing an innovative prototype of a mitral valve by engineering the chordal apparatus and reconnecting the left ventricle with the valve leaflets.

BioChord

Biomimetic engineered chordae tendineae for valve repair and regeneration

Click here for more information

Funding Agency/Programme: European Commission Call ERC-2023-POC (Proof Of Concept).
Objective: to develop better Mitral Valve repair techniques that are simple, effective, and durable, further advancing and validating BioChord, the first ever polymeric bioengineered regenerative Chordae Tendinae, designed to first repair the MV by replacing the diseased CT.

SMART4SCLERO

Smart Injectable Scaffolds for Sclerostin Based Bone Resorption Treatment

Click here for more information

Funding Agency/Programme: Ministry of University and Research - PRIN Call 2022 (Progetti di Ricerca di Rilevante Interesse Nazionale/ Research Projects of Relevant National Interest) on behalf of the project Coordinator Consiglio Nazionale delle Ricerche (Napoli).
Objective: developing an advanced *in vitro* model of joints' disorders dependent from bowel-related pathologies. The model will be based either on native than engineered tissues cultured in static, and dynamic conditions. These latter will be fabricated using the support of the bioprinting, as well as other additive manufacturing technologies.

Green MID-PLACE

Green MIcrofluiDic PLAtform for advanced tissue on a Chip culturEs

Click here for more information

Funding Agency/Programme: Ministry of University and Research - PRIN Call 2022 (Progetti di Ricerca di Rilevante Interesse Nazionale/ Research Projects of Relevant National Interest) on behalf of the project Coordinator Università degli Studi di Palermo.
Objective: to develop an eco-sustainable Organ-on-Chip (OoC) platform for stem cell growth and differentiation.

Complex graphical models for biological network science

Click here for more information

Funding Agency/Programme: Ministry of University and Research - PRIN Call 2022 (Progetti di Ricerca di Rilevante Interesse Nazionale/ Research Projects of Relevant National Interest) on behalf of the project Coordinator Università degli Studi di Firenze.
Objective: collection and pre-processing of omics data and interpretation of results obtained by the novel statistical models developed within the project.

Translating protection of cell-surface receptor LRP1 into potential disease-modifying therapies for osteoarthritis

Click here for more information

Funding Agency/Programme: Versus Arthritis - Bridging fellowship 2023, on behalf of the project Coordinator University of Liverpool (United Kingdom).
Objective: using high-resolution proteomics to identify binding partners of the low-density-liporptoein receptor related protein 1 (LRP-1) in osteoarthritic cartilage. In brief, proteins will be purified from osteoarthritic and normal cartilage, and then applied to an agarose resin coupled with LRP-1 previously purified from placenta. Proteins binding to LRP-1 will be eluted, digested by FASP and analysed by LC-MS/MS.

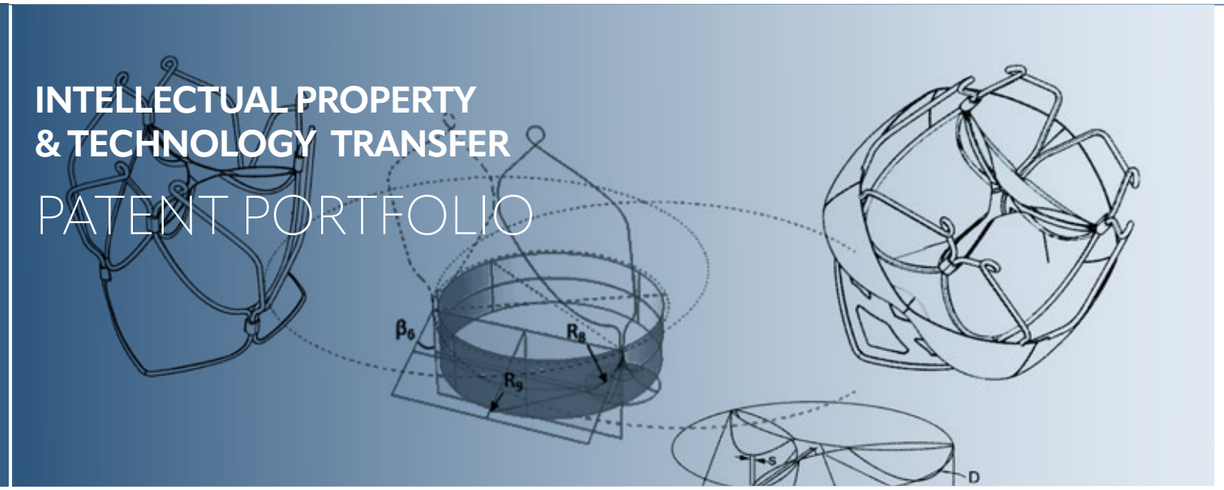
CONTACT CustOm-made aNTibacterical/bioactive/ bioCoated prostheses

Click here for more information

Funding Agency/Programme: PON "Ricerca e Innovazione" 2014-2020, on behalf of a project partner Istituto Ortopedico Rizzoli (Bologna).
Objective: analysis for the identification of biomarkers related to bone remodeling and regeneration, useful for pre-implant diagnosis and post-implant monitoring of the quality of bone tissue for the needs of the Rizzoli Orthopedic Institute.

INTELLECTUAL PROPERTY & TECHNOLOGY TRANSFER

PATENT PORTFOLIO



Research activity of Ri.MED is strongly patient oriented, but in order to ensure that scientific results reach clinical needs, it is necessary to correctly manage the intellectual property generated by our researchers as well as the process of technology transfer which derives from it.
From the laboratories, inventions are translated into patents and then into new solutions for the patients.

The protection of intellectual property is a fundamental value for Ri.MED to develop an innovative model of research sustainability. For this reason, Ri.MED has set up an Intellectual Property and Technology Transfer Office to support, promote and foster the progress of translational research through the enhancement of its application effects: patenting, patent license, industrial sponsorship and creation of technological spin-offs.

Furthermore, in 2021 Ri.MED and a multinational company operating in the cardiovascular area have finalized an important license and collaboration agreement having as object Ri.MED patent family "Triskele" and that is still in full force. This patent family consists of a heart valve prosthesis, a heart valve and their related delivery system and one of the inventors is Gaetano Burriesci, Ri.MED group leader in Bioengineering and Medical devices.

PATENT PORTFOLIO UP TO 31.12.2023

DRUG DISCOVERY

Nitro-oleic acid controlled release platform to induce regional angiogenesis in abdominal wall repair.
WO2019100021
Fondazione Ri.MED - University of Pittsburgh

Novel reversible nitroxide derivatives of nitroalkenes that mediate nitrosating and alkylating reactions
WO2018067709
University of Pittsburgh

REGENERATIVE MEDICINE AND IMMUNOTHERAPY

NK-mediated immunotherapy and uses therefor
WO2018099988
Fondazione Ri.MED - IRCCS ISMETT

Mandrel-less electrospinning processing method and system, and uses therefor
WO2018175234
Fondazione Ri.MED - University of Pittsburgh

Extracts for the regeneration of ligaments
PCT/US2019/019119
Fondazione Ri.MED - University of Pittsburgh

Method of Producing Regulatory Dendritic Cells
US Provisional n. 63/504,494
Fondazione Ri.MED/IRCCS ISMETT/University of Pittsburgh

Kit per la Ricostituzione di un Dispositivo Biomedico Cell-Free ad Uso in Medicina Rigenerativa, Dispositivo Biomedico Così Ricostituito e Relativo Procedimento di Sintesi
ITA N. 102023000019479
Fondazione Ri.MED/IRCCS ISMETT

TISSUE ENGINEERING AND BIOMEDICAL DEVICES

Method and system for the evaluation of the risk of aortic rupture or dissection in an ascending thoracic aortic aneurysm.
WO2018220573
Fondazione Ri.MED - IRCCS ISMETT

Transatrial access for intracardiac therapy
WO2017127682
University of Pittsburgh

Bi-layer extra cellular matrix scaffolds and uses thereof
WO2017044787
University of Pittsburgh

Hybrid Micro Molding-Fiber Deposition Substrate Processing for Cell Biology Manipulation and Local Anisotropy
US 63/091,462
Fondazione Ri.MED - University of Pittsburgh

Double components mandrel for electrospun stentless, multi-leaflet valves fabrication.
WO2016138416
University of Pittsburgh

Retrievable self-expanding non-thrombogenic lowprofile percutaneous atrioventricular valve prosthesis
WO2016138423
University of Pittsburgh

Multi-layered graft for tissue engineering applications
WO2019023447
Fondazione Ri.MED - University of Pittsburgh

Treating soft tissue via controlled drug release
WO2015134770
University of Pittsburgh

Microfluidic Tissue Development Systems
WO2017062629
University of Pittsburgh

A modular, microfluidic, mechanically active bioreactor for 3D, multi-tissue, tissue culture.
WO2015027186
University of Pittsburgh*

Recruitment of mesenchymal stem cells using controlled release systems
WO2014022685
University of Pittsburgh

Osteoarthritis treatment with chemokine-loaded alginate microparticles
U.S. Patent Appl. No. 16/241,112, *continuation application of WO2014022685*
Fondazione Ri.MED - University of Pittsburgh

Organ chip to model mammalian joint.
U.S. Patent Appl. No. 16/193,972)
University of Pittsburgh

Multi-well mechanical stimulation systems and incubators
WO2019079722
Fondazione Ri.MED - University of Pittsburgh

A stentless biopolymer heart valve replacement capable of living tissue regeneration.
WO2018156856
University of Pittsburgh

An expandable percutaneous cannula
PCT/US2018/017795
Fondazione Ri.MED - University of Pittsburgh

Biodegradable metallic - polymeric composite prosthesis for heart valve replacement
WO2019210059
Fondazione Ri.MED - University of Pittsburgh – University of Cincinnati

Processing method and apparatus for micro-structured rope-like material
US provisional Patent Application 62/874,114
Fondazione Ri.MED - University of Pittsburgh

Semi-rigid annuloplasty ring and method of manufacturing
WO2019220365
Fondazione Ri.MED

Heart valve prosthesis
WO2010112844
Fondazione Ri.MED

Prosthesis delivery system
WO2012052718
Fondazione Ri.MED

Prosthetic heart valve
WO2016203241
Fondazione Ri.MED

Implant for heart valve repair
WO/2022/229667
Fondazione Ri.MED - Université de technologie de Compiègne - Centre National De La Recherche Scientifique (CNRS) - Assistance Publique/Hôpitaux De Paris

Cannula Percutanea
ITA n. 102022000027381
Fondazione Ri.MED/ Università degli Studi di Padova

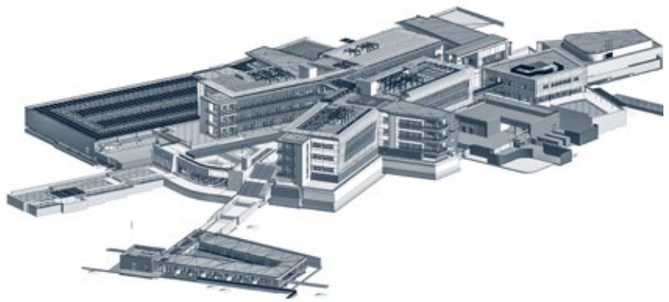
Dispositivo Medico Impiantabile
ITA n. 102023000010848
Fondazione Ri.MED/ University of Pittsburgh

Implantable Composition for Use in Cartilage Defects Repair in Postsurgery Rehabilitation
PCT/EP2023/065364
Fondazione Ri.MED – CHOP (Children's Hospital of Philadelphia)

NOTE:
Also patents where University of Pittsburgh is the only applicant have been co-developed with Ri.MED.

BIOMEDICAL RESEARCH AND BIOTECHNOLOGY CENTER

SOCIO-ECONOMIC IMPACT



The state-of-the-art center that the Foundation is building in Carini, a few miles from Palermo's international airport, will become a reference point for researchers from all over the world, playing a leading role in the scientific and medical industries.

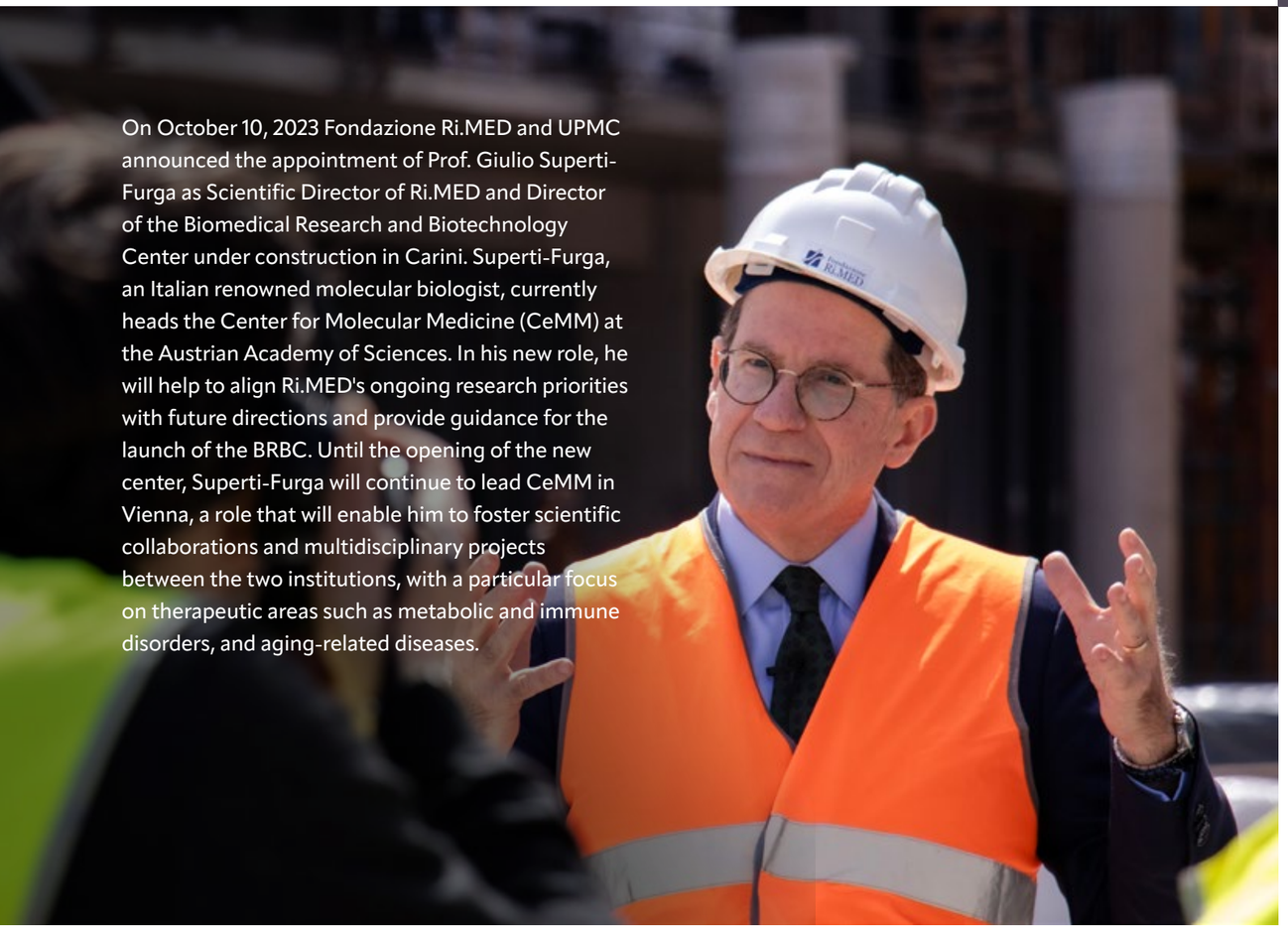
Construction was started in 2020 and, despite unpredictable events, works are now in full swing on the 25,000-square meter area that will host the Biomedical Research and Biotechnology Center (BRBC). The COVID-19 pandemic had a strong impact on the project's timeline, and plans had to be modified along the way to meet restrictions, including a prolonged lockdown, new regulations, and frequent quarantines for entire teams of workers. The 2022 challenge was the ongoing Russian war on Ukraine, impacting Europe and causing a shortage of building materials. However, resilience combined with stubbornness and passion of all the people involved in the project, allowed us to soldier on. Today the layout and elevations are clearly visible in the campus. This project will improve the lives of patients and also open new job opportunities for hundreds of skilled resources, providing a strong economic impact and scientific connotation in the community.

The temporary association of enterprises (ATI) is led by Italiana Costruzioni, while the management of the construction is entrusted to a team led by Progetto CMR, part of the group team awarded the international design competition of the BRBC and led by HOK. The project is inspired by the "village street" model, and provides for an extremely flexible organization of space: 17,070 square meters of laboratories, common areas, meeting rooms, offices, an auditorium, and a guest house.

The BRBC's laboratories and technological platforms will be dedicated to the research and development of innovative vaccines and drugs, cell therapies, organ and tissue engineering for early diagnosis and targeted treatment of terminal organ failure, tumors, infectious diseases and pathologies related to aging, with particular attention to neurological diseases.
Once fully operational, in 2025, the BRBC will employ approximately 600 people creating resources to help innovators break the existing cycle and move their products further and faster through the tech transfer pipeline.

BIOMEDICAL RESEARCH AND BIOTECHNOLOGY CENTER

MEET THE DIRECTOR GIULIO SUPERTI-FURGA



On October 10, 2023 Fondazione Ri.MED and UPMC announced the appointment of Prof. Giulio Superti-Furga as Scientific Director of Ri.MED and Director of the Biomedical Research and Biotechnology Center under construction in Carini. Superti-Furga, an Italian renowned molecular biologist, currently heads the Center for Molecular Medicine (CeMM) at the Austrian Academy of Sciences. In his new role, he will help to align Ri.MED's ongoing research priorities with future directions and provide guidance for the launch of the BRBC. Until the opening of the new center, Superti-Furga will continue to lead CeMM in Vienna, a role that will enable him to foster scientific collaborations and multidisciplinary projects between the two institutions, with a particular focus on therapeutic areas such as metabolic and immune disorders, and aging-related diseases.

Prof. Superti-Furga, you made grow the Austrian Center for Molecular Medicine, founded five biotech companies and led the training of an army of researchers. What kind of new challenge are you planning now?

An epochal challenge: we are building a cutting-edge translational research center here in Sicily! We are looking towards a future in which the relationship between human beings, health and environment will significant change. Our research will embrace a context of environmental medicine based on an integrated perspective, the 'one health' approach, and Sicily is the perfect place to find new solutions between environment, culture and science. It's a generational project born in an era in which opportunities in life sciences and medicine are exploding. A process that can only be understood if you try to address it from very different disciplinary backgrounds.

I am extremely pleased to apply my experience in managing and organizing cutting-edge research institutions to an international project of this magnitude.

We are 3 km from a wonderful Mediterranean beach and we are talking about an international hub for biomedical research. In Southern Italy. Is it a utopia or an epochal opportunity? And why here?

Geographical and historical center of the Mediterranean, place of connections and mixtures between people, with a unique naturalistic heritage, Sicily has the potential to become a major hub of scientific innovation.Here we can investigate how environment affects our health.

Here we can study the incidence of the nutrition, the life near the sea or the solar radiation, better than everywhere else.

We are also interested in history, in how different exposures to migration and the environment have created a unique genomic heritage. Also a unique microbiota.

What will be the focus of the new center's research?

We are evaluating the idea of focusing the research on eight specific organs and the related therapeutic areas: LUNG and respiratory diseases, LIVER, KIDNEY and metabolic diseases, HEART and cardiovascular diseases, and then BRAIN and neurodegenerative diseases, INTESTINE, IMMUNE SYSTEM, and SKIN in all diseases that involve infections and dysbiosis.

A truly translational research: will you also cover clinical trials?

A crucial element in this process is the synergistic collaboration with our main partner, ISMETT, an hospital specializing in transplants and treatment of terminal organ diseases. The objective is to break down barriers to encourage interdisciplinarity, to stimulate innovation and to bring quickly the innovations "from bench to bedside". We also would like to go the other way round and be inspired by real medical observations and challenges, from the hospital.

What are the reasons why an established researcher would like to come and work here?

Our strength will be the excellence. Excellence can attract the best talents from all over the world to Sicily, creating a real pole of attraction of high level and global research. And here there is also the sun and the sea! We will be innovative on all grounds: the way we organize ourselves and work together, the way we value contributions. The way we integrate the science with engineering.

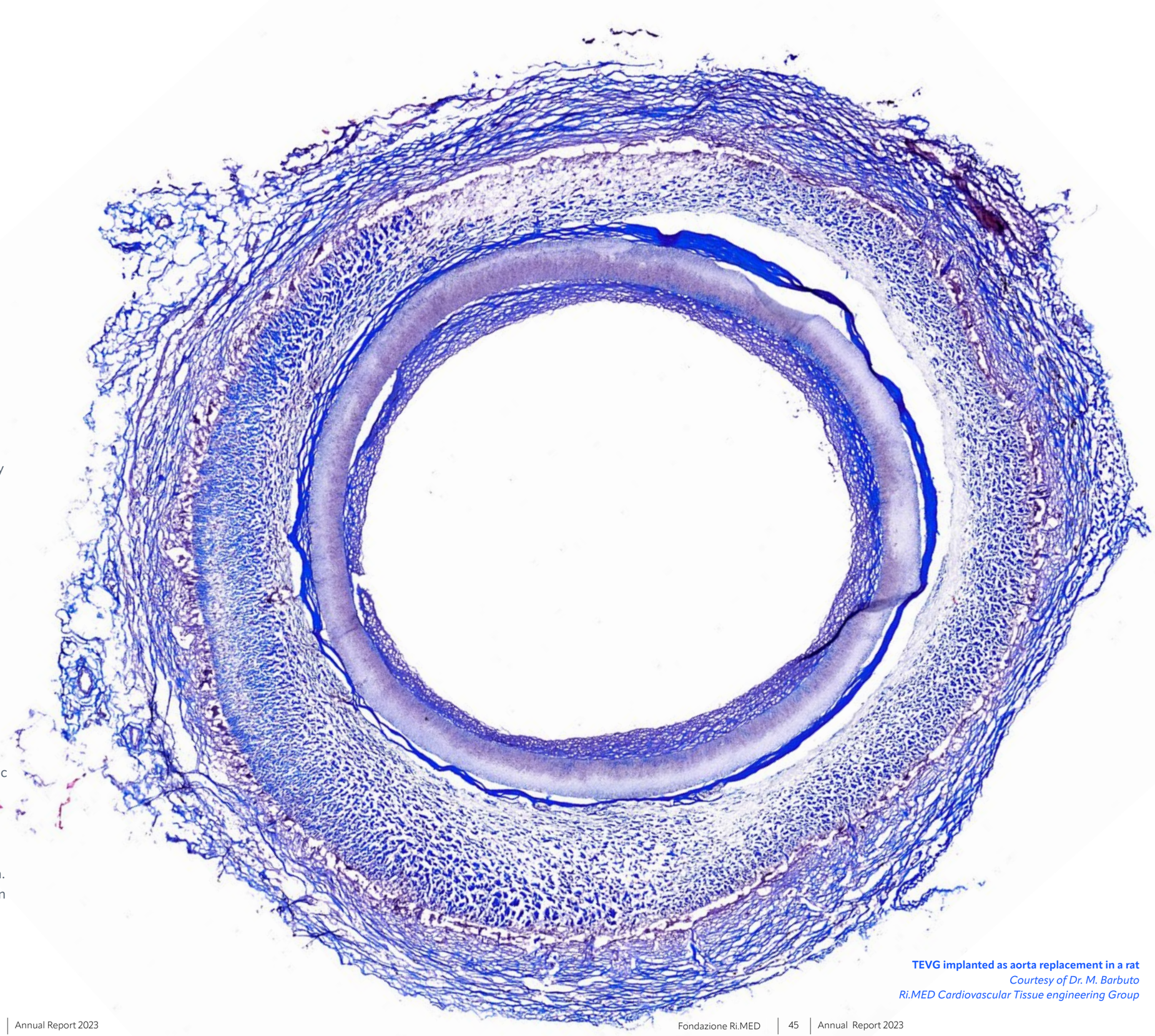
Besides "innovative", which words come to your mind thinking about the research center?

Ultramodern, sustainable, with botanical garden and organic food, own train station, gym, outdoor amphitheater, etc… Next generation center. Finally doing something to understand humanity as part of a bigger something.

Ri.MED RESEARCH

Ri.MED's scientific projects are based on three main areas of interest: regenerative medicine and immunotherapy, aimed at developing advanced therapy medicinal products (ATMP); new drug discovery research; development and tissue engineering and biomedical bioengineering, focused on developing biomaterials, engineered tissues, and medical devices. The activities range from identifying new biologically active molecules to developing cellular products for tissue repair and/or regeneration, and organotypic cultures for regenerative purposes and as models for pharmacology screening, and all the way to simulation of physiological systems and preclinical validation of new generation implantable organs and devices.

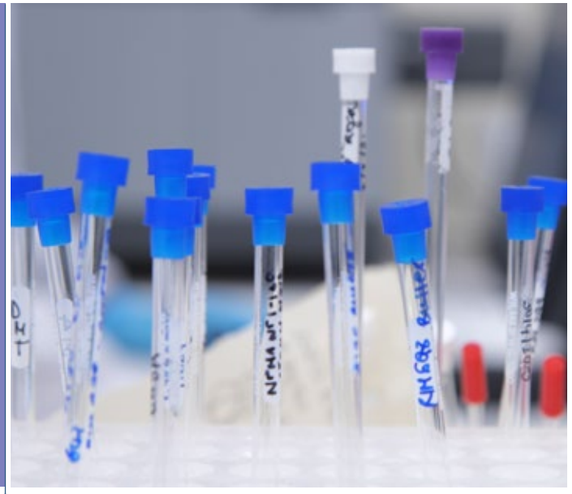
Ri.MED's translational research approach is based on therapeutic needs and developed on multiple levels, including the collaboration with our partners: from basic research and pre-clinical research and development, to clinical trials conducted with IRCCS ISMETT.
Ri.MED has a diversified and balanced project portfolio led by a multidisciplinary team with clear product development goals and a "bench-to-bedside" approach. The translational research engine of Ri.MED Foundation envisages the development of skills and technology platforms supporting scientific projects.

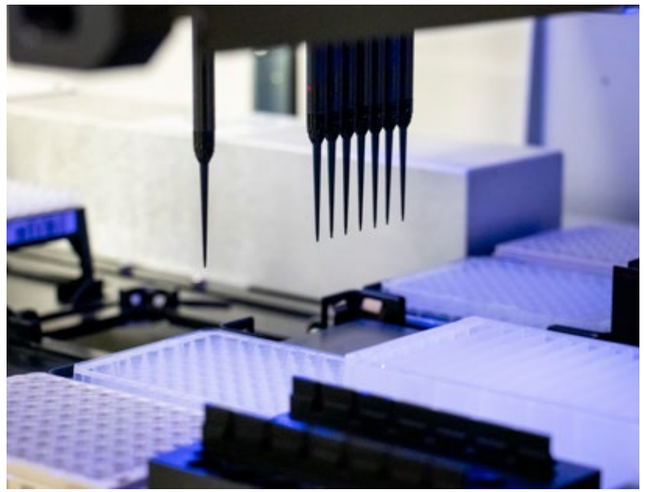


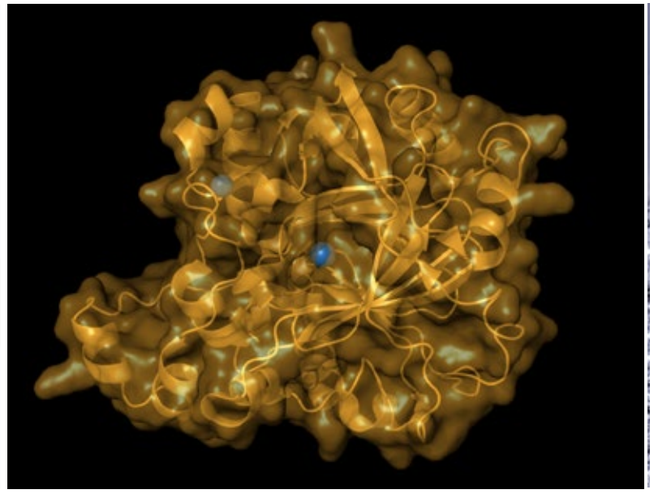
TEVG implanted as aorta replacement in a rat
Courtesy of Dr. M. Barbuto
Ri.MED Cardiovascular Tissue engineering Group

DRUG DISCOVERY

STRUCTURAL BIOLOGY AND BIOPHYSICS
MOLECULAR INFORMATICS
MEDICINAL CHEMISTRY
EXPERIMENTAL LUNG RESEARCH
PROTEOMICS
ADVANCED DATA ANALYSIS
IMAGING AND RADIOMICS







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In silico guided chemical exploration of KDM4A fragments hits
Lombino J, Vallone R, Cimino M, Gulotta MR, De Simone G, Morando MA, Sabbatella R, Di Martino S, Fogazza M, Sarno F, Coronnello C, De Rosa M, Cipollina C, Altucci L, Perricone U, Alfano C
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Rabienezhad Ganji N, Urzì O, Tinnirello V, Costanzo E, Polito G, Palumbo Piccionello A, Manno M, Raccosta S, Gallo A, Lo Pinto M, Calligaris M, Scilabra SD, Di Bella MA, Conigliaro A, Fontana S, Raimondo S, Alessandro R
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1536 Egfl6 induces IL-10 and CXCL2 in tumor associated myeloid cells: link to anti-tumor immunosuppression and resistance to anti-PD-L1 therapy in ovarian cancer
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A Critical Analysis of the Robustness of Radiomics to Variations in Segmentation Methods in 18F-PSMA-1007 PET Images of Patients Affected by Prostate Cancer
Pasini G, Russo G, Mantarro C, Bini F, Richiusa S, Morgante L, Comelli A, Russo GI, Sabini MG, Cosentino S, Marinozzi F, Ippolito M, Stefano A
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Artificial Intelligence for Classifying the Relationship between Impacted Third Molar and Mandibular Canal on Panoramic Radiographs
Lo Casto A, Spartivento G, Benfante V, Di Raimondo R, Ali M, Di Raimondo D, Tuttolomondo A, Stefano A, Yezzi A, Comelli A
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Benfante V, Stefano A, Ali M, Laudicella R, Arancio W, Cucchiara A, Caruso F, Cammarata FP, Coronnello C, Russo G, Miele M, Vieni A, Tuttolomondo A, Yezzi A, Comelli A
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Phenotyping the Histopathological Subtypes of Non-Small-Cell Lung Carcinoma: How Beneficial Is Radiomics?
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Ali M, Benfante V, Stefano A, Yezzi A, Di Raimondo D, Tuttolomondo A, Comelli A
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Radiomics Analyses to Predict Histopathology in Patients with Metastatic Testicular Germ Cell Tumors before Post-Chemotherapy Retroperitoneal Lymph Node Dissection
Scavuzzo A, Pasini G, Crescio E, Jimenez-Rios MA, Figueroa-Rodriguez P, Comelli A, Russo G, Vazquez IC, Araiza SM, Ortiz DG, Perez Montiel D, Lopez Saavedra A, Stefano A
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Matradiomics as a comprehensive radiomics tool to predict high pathological grade in prostate cancer patients undergoing 18f-psma pet/ct
Richiusa S, Russo G, Stefano A, Pasini G, Comelli A, Bini F, Marinozzi F, Cosentino S, Sabini MG, Ippolito M
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Hepatitis C: The Story of a Long Journey through First, Second, and Third Generation NS3/4A Peptidomimetic Inhibitors. What Did We Learn?
Simona Di Martino, Giovanna Li Petri, Maria De Rosa
J. Med. Chem. 2024, 67, 2, 885–921
doi: 10.1021/acs.jmedchem.3c01971

STRUCTURAL BIOLOGY AND BIOPHYSICS

FOCUS

- **Identification of new therapeutic targets**
- **Development of therapeutic proteins with particular emphasis on therapeutic antibodies**
- **Biophysical screening for the discovery of new therapeutic candidates for preclinical studies**
- **Structure determination of proteins and protein complexes**
- **Implementation of NMR-based diagnostic tools**

AIMS

- **Unravel molecular mechanisms behind human diseases**
- **Develop novel preclinical candidates for unmet medical needs**
- **Contribute to define next generation therapeutic treatments**
- **Facilitate the creation and consolidation of local biotech companies**
- **Contribute to consolidate Structural Biology in South Italy and Mediterranean Area**

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- University of Palermo, ITA
- University of Campania "Luigi Vanvitelli", Naples, ITA
- The Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, ITA
- European Brain Research Institute (EBRI) Rita Levi-Montalcini, Rome, ITA
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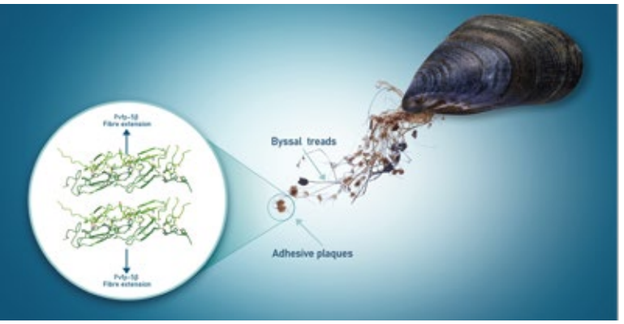
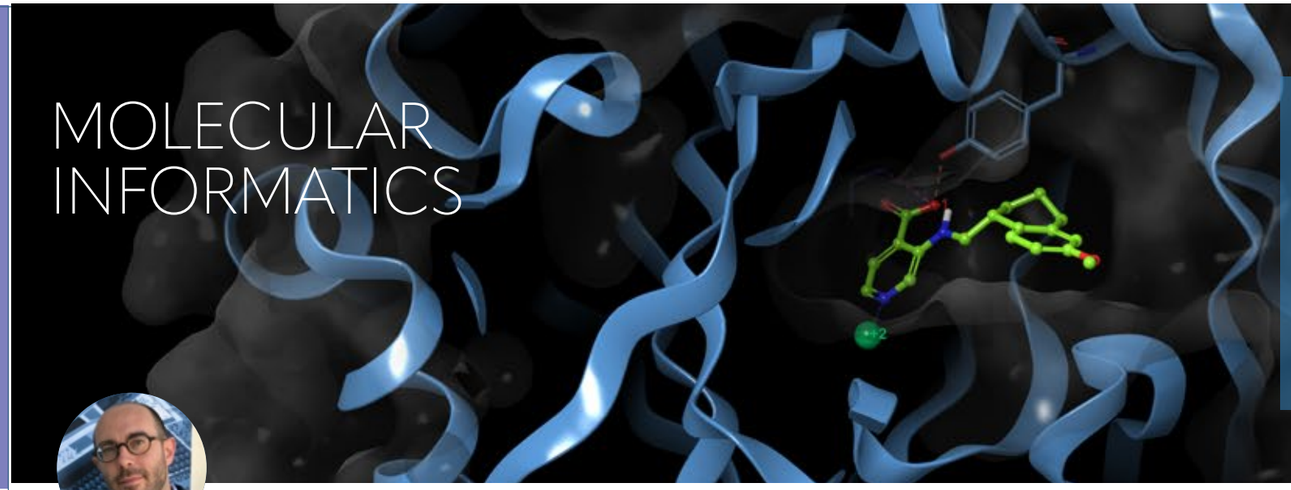


The Structural Biology and Biophysics group provides biophysical and structural information of biological phenomena guided by folding, phase transition, and interaction of proteins with the ultimate goal of understanding the molecular mechanisms underlying serious pathologies. The group is also engaged in small molecules-based drug discovery, and development of protein-based therapeutics with particular emphasis on therapeutic antibodies.

The main focus of the research activities of the group is on neurodegenerative diseases. Neurodegeneration is an increasing threat of our increasingly aging modern society. Current treatments are in the best-case palliative and non-specific, reflecting the fact that the detailed understanding of most of these diseases is still lacking. Our research aims at understanding the molecular mechanisms of protein misfolding and aggregation behind neurodegenerative diseases, and relies on the concept that knowledge of the normal function and of the interaction network of aggregating proteins is a key tool to design molecules which can specifically compete out pathological aggregation. Native protein-protein interactions provide, indeed, important means of altering and controlling the function and assembly of proteins involved in neurodegenerative diseases, and could fulfil a protective role against aberrant aggregation.

In parallel, the group is engaged in the structural and biophysical characterization of Mussel Foot adhesive proteins, which, similar to proteins involved in neurodegenerative diseases, undergo to phase transition and form stable protein aggregates with adhesive features. The final aim of this research is the developing of bioadhesives able to work in wet environments. In the last years, there is a growing interest focusing on the development of novel naturally-derived glues in several areas of clinical applications such as tissue engineering, implantation of medical devices, and regenerative medicine. The big challenge in developing new bio-adhesive molecules is to find molecules able to work in wet and hostile environments and capable of making tissues adhere together in an efficient way. Proteins from sessile animals with natural adhesive properties in water, could overcome these difficulties.

MOLECULAR INFORMATICS



FOCUS

- **Creation of molecular libraries for biological screening**
- **Computer-assisted molecular design for anticancer agents**
- **Biological characterization of air pollutants through computational tools**
- **Study of protein-protein interactions in biological processes**

AIMS

- **Understanding of molecular mechanisms behind different pathologies**
- **Design of chemical or biological therapeutic agents**
- **Creation of predictive *in silico* models to reduce drug discovery process duration**

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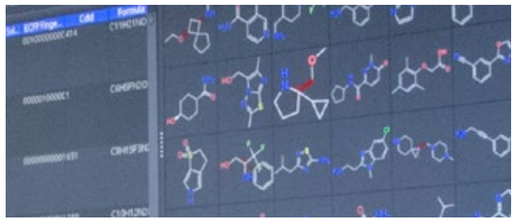
- Université Paris Cité, FRA
- University of Vienna, (Pharmaceutical chemistry department) AUT
- Italian National Council of Research (CNR)



The Molecular Informatics group at Ri.MED Foundation mainly deals with the creation and use of *in silico* tools for the design, identification and optimization of biologically active molecules. The group main focus is the creation of reliable *in silico* prediction models to be used for the understanding of molecular mechanisms behind different pathologies and the subsequent design of chemical or biological therapeutic agents. The approaches used rely on the classical molecular modeling tools for virtual screening as well as modern chemoinformatics tools based on artificial intelligence. Over the years, the team has gained various experiences in the field of medicinal chemistry and computational chemistry.
The expertise acquired by the team members is synergistically exploited for the creation of molecular libraries and to create and validate reliable theoretical models to be used for subsequent virtual ligand screening (VLS).

In recent years, the collaboration with academic groups from University of Palermo and Vienna has strengthen the development of approaches based on the use of deep learning for the activity prediction of small molecules. During 2023 the group has been involved in three main projects:

Design of chronic inflammation disease modulators.
Cutting-edge *in-silico* tools including Artificial Intelligence techniques are used to analyze vast datasets, predict molecular interactions, and uncover hidden molecular patterns related to biological activity. The research combines bioinformatics, molecular modeling, and data analysis to identify novel compounds that can regulate the activity of NLRP3.
During 2023 a hit compound has been discovered and confirmed.

Development of a computational platform for air pollutants characterization and target profiling.
Exploring the intricate link between air pollutants and neurodegenerative diseases, our research aims to provide a comprehensive understanding of environmental factors contributing to neurological disorders. Through advanced *in-silico* profiling techniques, we identify and analyze pollutants with the potential to impact brain health, offering insights for preventive strategies and public health interventions.

Development of an in-house machine learning tool for the prediction of small molecules activity as G quadruplex (G4) stabilizers.
With a specialized emphasis on DNA and RNA G-quadruplex structures, the group strive to develop novel therapeutic interventions. The main focus is leveraging computational models validated through experimental assays to design drugs that can selectively modulate these structures, holding immense potential for treating a variety of diseases, including cancer and viral infections. The group is also in charge to run the compound management platform with the aim of creating molecular libraries suitable for biological screening and draw up screening plate.
The main outcomes for 2023 have been the Completion of the APDB platform (a database on air pollutant characterization and similarity prediction - http://apdb.di.univr.it - doi: 10.1093/database/baad046) and the results of a first application of G4 stabilizers study on Sars-Cov-2 genome - https://doi.org/10.1039/D3SC04004F).

DRUG DISCOVERY

RI.MED RESEARCH

MEDICINAL CHEMISTRY

FOCUS

- Design, synthesis, and structural characterization of new chemotypes
- Identification of hit compounds
- Hit expansion and structure optimization
- Structure-activity relationship (SAR) investigation
- Hit-to-lead optimization
- Planning, set-up, optimization, and scale-up of synthetic routes
- Discovery of novel potential inhibitors of NLRP3 inflammasome

AIMS

- Early drug discovery toward disease therapeutic treatment
- Discovery of new potential target modulators

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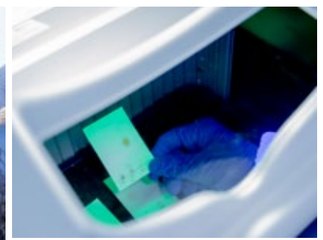
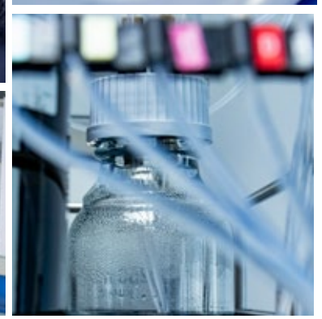
The aim of the Medicinal Chemistry group is to identify new hits toward the therapeutic targets of interest. The design, the synthesis and the structural characterization of novel small molecules are the main expertise and lead to the creation of compounds libraries and building blocks collections. To date, the efforts are focused on the discovery of novel non-covalent inhibitors of NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome. NLRP3 is a validated target for chronic inflammation in age-related diseases (neurodegeneration, autoimmune disorders, etc.). Starting from the structure of the lead compound (MCC950, IC_{50} of 8 nM), we designed novel chemotypes keeping in mind the key interactions within the binding site (pdbs 7PZC and 7ALV). In 2023, we worked on the set-up and optimization of the synthesis of indole structure-based sulfonamides. We managed to assess a short and highly efficient synthetic route which successfully led to a library of nearly sixty compounds, obtained in both high purity grade (>96%) and yields (>80%).
The testing compounds are undergoing the primary assay held by the HTS group. A second project of interest deals with the identification of novel inhibitors of Sirtuin-6 (Sir6), a validated target for the treatment of lymphomas. In collaboration with the University of Palermo and with the Molecular Informatics group, docking studies and structural analysis combined to Molecular Dynamics simulations helped with the selection of the best Sir6 crystal structure, which was used for the rational design of a set of fragments, as novel potential modulators of SIRT6. During the year 2023, the doctoral student worked on the set-up of two alternative synthetic routes for the preparation of these fragments.

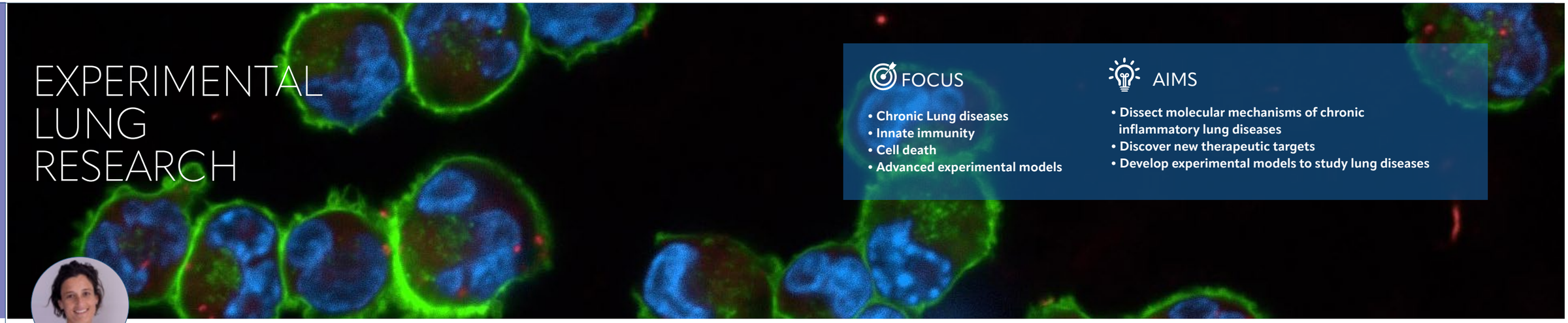




The Medicinal Chemistry group supports the Drug Discovery area during the screening campaigns. The main activities of the platform include the structure confirmation of preliminary hits and the re-synthesis (when not commercially available or in case of purity issues); the hit(s) family expansion and optimization toward the lead compound(s).
During the year 2023, the platform performed the structure confirmation studies of two preliminary actives (NLRP3 inhibitors) retrieved from the screening campaign of December 2022. A set of structural analogues were purchased in order to validate the chemotype. The chemical structure of these compounds was confirmed via NMR spectroscopy and the purity grade (>80%) was assessed via mass spectrometry studies. The compounds will be tested in the primary assay in order to confirm the biological activity.
The Principal Investigator of the team contributed, together with several partners, to the drafting of a proposal for the PNRR-POC 2023 grant. The project was entitled *Early Drug Discovery to identify novel inhibitors of Prenylcysteine oxidase 1 (PCYOX1), a novel target in cardiology and oncology* (waiting for the outcome).

The group prepared and published a peer-review perspective about peptidomimetics developed in the past ten years for the treatment of the hepatitis C infection; and contributed to two scientific peer-review articles in collaboration with the Drug Discovery area.

EXPERIMENTAL LUNG RESEARCH



FOCUS

- **Chronic Lung diseases**
- **Innate immunity**
- **Cell death**
- **Advanced experimental models**

AIMS

- **Dissect molecular mechanisms of chronic inflammatory lung diseases**
- **Discover new therapeutic targets**
- **Develop experimental models to study lung diseases**

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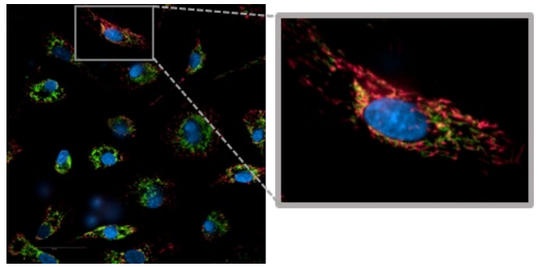
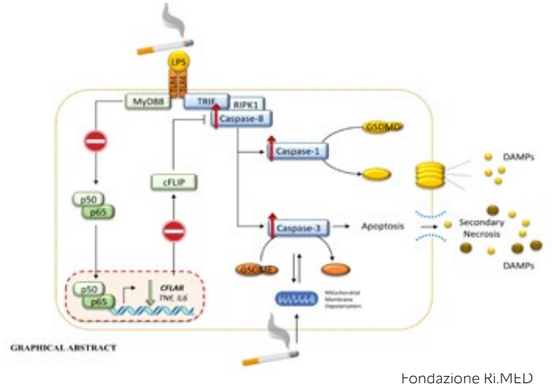
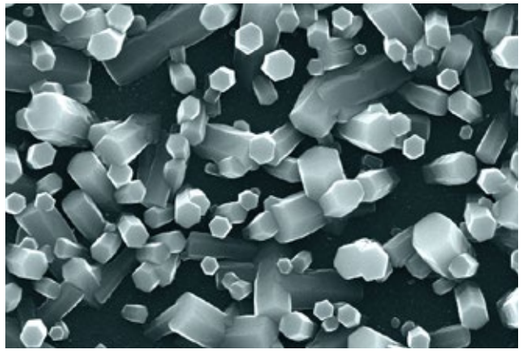
- University Medical Center Groningen, NL
- University of Palermo, ITA
- Institute of Translational Pharmacology (IFT) – National Research Council (CNR), ITA
- Institute for Biomedical Research and Innovation (IRIB) – National Research Council (CNR), ITA
- Insitute for Lung Research, Philipps University Marburg, GER
- Institute of Innate Immunity, University of Bonn , GER

We study innate immunity in lung diseases, both in chronic conditions caused by exposure to external insults such as cigarette smoke as well as in acute settings such as infections. Under homeostatic conditions, alveolar macrophages are the most abundant myeloid cells in the alveolar space and play a key role in orchestrating first line host defenses. Our research focuses on macrophage-associated immune responses. We are particularly interested in studying how inflammasomes, caspases, and regulated cell death participate to inflammatory reactions in health and disease. In this respect, growing evidence suggests that fine-tuning cell death may provide a tool for treating chronic inflammation. In particular, we are interested in studying the impact of the pore-forming proteins gasdermins (GSDMs) on the surrounding inflammatory milieu. GSDMs are activated downstream of inflammasomes and/or apoptotic cell death. Upon their activation, GSDMs promote unconventional secretion of IL-1 family cytokines as well as of small damage-associated molecular patters (DAMPs). We are currently investigating the impact of GSDMs pore formation on the release of cytosolic proteins in human macrophages and how this affect cellular cross-talk.



A key asset of our lab is the availability and the continuous set-up of new experimental models using human primary cells that we isolate from buffy coats and lung resections. These experimental models are also used as a tool for the development and validation of innovative biosensors for monitoring oxidative stress and inflammation within a consolidated collaboration with the Engineering Department at the University of Palermo.
Our Lab is currently hosted by the National Research Council of Palermo and hosts the Screening Lab of the Fondazione Ri.MED Drug Discovery Unit.





PROTEOMICS

FOCUS

- **Use mass spectrometry-based approaches to investigate functions of ADAM17 and its cofactors iRhom1 and iRhom2**
- **Identification of predictive and prognostic biomarkers by high-resolution proteomics**
- **Proteomic characterization of Sicilian food with known nutraceutical properties**

AIMS

- **Identifiy novel functions of ADAM17 and iRhoms, and understand the molecular basis of iRhom-mediated regulation of ADAM17 activity**
- **Identify molecular targets and biomarkers to improve healthcare**
- **Develop proteomic methods to support studies of any size, in health and biotechnology research**

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- University of Palermo, ITA
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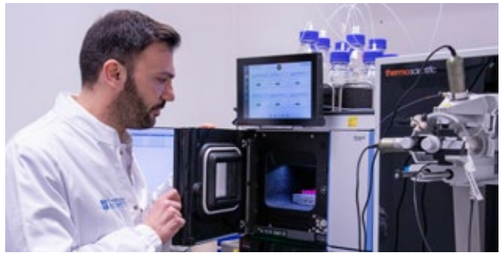
The Proteomics group is focused on elucidating the role of a class of membrane-tethered proteases, called ADAMs (a disintegrin and metalloproteinases), in health and disease. For their ability to release cell surface proteins, ADAMs are involved in a number of cellular processes, including cell-communication, cell-adhesion and molecular transport. The proteomic group uses a synergistic array of proteomic, cell biology, biochemistry and *in vivo* models to identify substrates of ADAMs, validate them by orthogonal methods and uncovering functional consequences of their ADAM-dependent release *in vivo*. One of these is ADAM17, a protease of major pharmaceutical interest as it is responsible for the release of TNF and EGFR ligands, and therefore involved in the development of autoimmune diseases and cancer. We have developed mass spectrometry-based approaches to further characterize functions of ADAM7, and that of its two essential co-factors iRhom1 and iRhom2. iRhom2 specifically regulates the activity of ADAM17 in immune cells. Its genetic ablation in mouse prevents TNF release and it is protective against rheumatoid arthritis.

We have recently found a new function of iRhom2 in stabilizing MHC class I molecules at the cell surface and regulate antiviral responses (3).
We are currently testing whether this mechanism has functional consequences in the recognition of cancer or virus-infected cells by the immune system. Furthermore, we are currently testing the hypothesis that iRhom2 inactivation has beneficial effects on OA progression by a dual role in inhibiting the release of TNF (a proinflammatory cytokine promoting the expression of cartilage catabolic factors) and LRP1, and endocytic receptor that reduces levels of cartilage-degrading proteases. In line, we aim to translate this research into the clinics by developing iRhom2 inhibitors through different biological (phage-display for inhibitory antibodies) and chemical (virtual screening, high-throughput screening of small molecule libraries) approaches. Other examples of our work are the proteomic characterization of ADAM15, a metalloproteinase playing a role in osteoarthritis development and whose substrate repertoire is still limited to few proteins.

The proteomic group has set up methods to analyse plasma proteome and the proteome of liquid biopsies for clinical research. This has allowed to start several research projects in synergy with Ri.MED Foundation's partner ISMETT and Palermo University Hospital, aiming to identify predictive and prognostic biomarkers of different pathological conditions, including cancer and Alzheimer's. Finally, the group has been active in the proteomic characterization of food products with known nutraceutical properties and commonly used in the Sicilian diet, including honey produced by the Sicilian black honeybee and tangerine.



ADVANCED DATA ANALYSIS

FOCUS

- **The molecular aspects of aging, cancer and degenerative diseases**
- **Understanding the role of non-coding RNA (microRNA and long non coding RNA)**
- **Alternative splicing and its modulation**

AIMS

- **Analysis and interpretation of biological big data**
- **Omics data analysis through customized algorithms**
- **Discovery novel biomarkers and pathways**
- **Design of RNA-based therapeutics through machine-learning based approaches**

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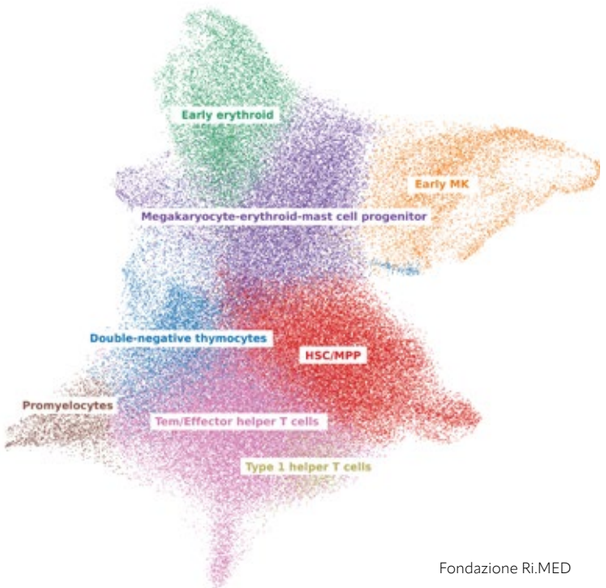
- IRCSS ISMETT, Palermo, Italy
- Università degli Studi di Rome "Foro Italico", Roma, Italy
- IRCSS Policlinico Gemelli, Rome, Italy
- University of Pittsburgh, PA, US



The Advanced Data Analysis group integrates different layers of expertise spanning from wet lab to big data analysis, with the goal of unraveling biological complex systems by developing customized experimental and computational pipelines. In fact, we constantly put at the service of other research groups our expertise on the analysis of biological big data, both leveraging established algorithms and developing new ones, also based on machine learning and deep learning approaches. We actively participate in the Drug Discovery area activities by supporting other groups in high throughput screening experimental design and their data analysis.

Our main interest is in biological regulatory networks. In particular, we study the regulatory role of non-coding RNA, e.g., microRNA and long non-coding RNA, in the context of aging, cancer and degenerative diseases.

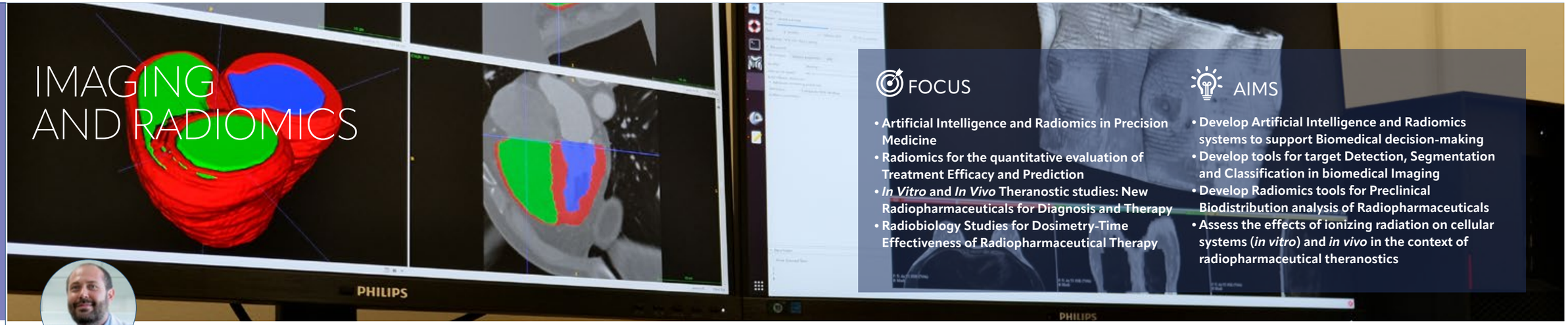
We seek the role of non-coding RNA in gene expression modulation and the occurrence of alternative splicing events, by integrating the analysis of multiple omics data platforms and network analysis methods.

Regulatory interactions that have been computationally predicted are validated in wet lab, e.g., with luciferase assays for microRNA-target interactions. For completeness, we are growing expertise with the OXFORD Nanopore technology, which provides a complete picture of the samples at transcriptomics level, useful for our investigations on gene expression and alternative splicing occurrences.

Unraveling cellular senescence was our main focus in 2023. In this concern, we continued to work on SMART and SUNFOX project, funded by PNRR through the National Center for RNA-based Therapeutics, born in 2022. The two projects are focused on finding new approaches for the gene expression regulation of two targets, LMNA and FOXO4 respectively, both involved in senescence pathway. In addition, in collaboration with two department of the University of Palermo, i.e., DiFC and DSEAS, we started new projects focused on classifying senescence cells by single cell's morphological or transcriptomic information, with the aim of detecting time course behavior and contagion effects.

Finally, in 2023, we started setting up a new laboratory, with cellular and molecular biology equipment, useful to develop experimental approaches to validate the predictions obtained by novel bioinformatics algorithms developed by the group itself. The experimental activity will be initially focused on microRNA target validation and anti-sense oligonucleotide's application for gene expression and alternative splicing modulation.

IMAGING AND RADIOMICS



FOCUS

- **Artificial Intelligence and Radiomics in Precision Medicine**
- **Radiomics for the quantitative evaluation of Treatment Efficacy and Prediction**
- ***In Vitro* and *In Vivo* Theranostic studies: New Radiopharmaceuticals for Diagnosis and Therapy**
- **Radiobiology Studies for Dosimetry-Time Effectiveness of Radiopharmaceutical Therapy**

AIMS

- **Develop Artificial Intelligence and Radiomics systems to support Biomedical decision-making**
- **Develop tools for target Detection, Segmentation and Classification in biomedical Imaging**
- **Develop Radiomics tools for Preclinical Biodistribution analysis of Radiopharmaceuticals**
- **Assess the effects of ionizing radiation on cellular systems (*in vitro*) and *in vivo* in the context of radiopharmaceutical theranostics**

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- The Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, ITA
- Department of Agricultural, Food and Forests Sciences University of Palermo, Palermo, ITA

The Imaging and Radiomics Group is a multidisciplinary team united by multimodal imaging research. A synergy of transversal expertise is the basis of this team; in particular, the group is made up of Computer Scientists, Biotechnologists, specialized Medical Doctors and Engineers from different sectors. The focus of the group is twofold. Part of the research concerns the development of Artificial Intelligence (Machine Learning and Deep Learning algorithms) and Radiomics applied to Multispectral and Biomedical Images (Cellular, Preclinical and Clinical) to support Biomedical decision-making. Additionally, this research group utilizes new innovative and translational approaches to support Nuclear Medicine and Precision Medicine through *in vitro*, *ex vivo*, and *in vivo* studies in the fields of radiopharmaceutical therapy, nanoparticles, and biodiversity.

Preliminary experiments were conducted in collaboration with the Georgia Institute of Technology (GIT) during 2023 with the aim of synthesizing and functionalizing nanoparticles that have plasmonic effects for applications in cancer precision therapy; In addition, the Imaging and Radiomics group has maintained and strengthened the GIT collaboration in radiomic analysis of magnetic resonance angiography of mice suffering from a particular type of anemia. As a third line of research in collaboration with the GIT, biodistribution studies of novel radiopharmaceuticals were carried out on preclinical PET models in light of the discovery of new PET ligands and neurological receptors, transporters and enzymes. As part of their collaboration with Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR, Cefalù and Milan), the group is conducting preclinical PET and MRI studies to detect neuronal degeneration early in Parkinson's disease. In addition the group has conducted the following research lines in preclinical and clinical molecular imaging with positron emission tomography (PET):

- Analysis of the Robustness of Radiomics to Variations in Segmentation Methods in 18F-PSMA-1007 PET Images of Patients Affected by Prostate Cancer;
- Radiomics Tool to Predict High Pathological Grade in Prostate Cancer Patients Undergoing 18F-PSMA PET/CT
- Overview of *In Vitro* Assays of 64Cu-, 68Ga-, 125I-, and 99mTc-Labelled Radiopharmaceuticals Using Radiometric Counters in the Era of Radiotheranostics;

Clinical research activities in Magnetic Resonance Imaging included:

- Grading and Staging of Bladder Tumors Using Radiomics Analysis in Magnetic Resonance Imaging
- PET and MRI for Early Assessment of Neuronal Degeneration in a Transgenic Mouse Model of Parkinson's Disease;

Additionally, the group was involved in the development of:

- Radiomics Analyses to Predict Histopathology in Patients with Metastatic Testicular Germ Cell Tumors before Post-Chemotherapy Retroperitoneal Lymph Node Dissection;
- Artificial Intelligence for Classifying the Relationship between Impacted Third Molar and Mandibular Canal on Panoramic Radiographs;
- Phenotyping the Histopathological Subtypes of Non-Small-Cell Lung Carcinoma using Radiomics Approach;
- Anti-arthritic and anti-cancer activities of polyphenols: A review of the most recent *in vitro* assays;

Several research studies were conducted by the group in the field of:

- Radiomics and radiogenomics in oncology: artificial intelligence and deep learning application.

REGENERATIVE MEDICINE AND IMMUNOTHERAPY

EXPERIMENTAL IMMUNOTHERAPY
HEPATOBILIARY REGENERATIVE MEDICINE
REGENERATIVE MEDICINE - CELLULAR THERAPIES
GMP CELL FACTORY
PRECLINICAL *IN VIVO* RESEARCH

Ri.MED RESEARCH

(Human Umbilical Vein Endothelial Cells, HUVEC)
Courtesy of the Hepatobiliary Regenerative Medicine Group

PUBLICATIONS

Two Sides of The Same Coin: Normal and Tumoral Stem Cells, The Relevance of *In Vitro* Models and Therapeutic Approaches: The Experience with Zika Virus in Nervous System Development and Glioblastoma Treatment
Tinnirello R, Chinnici CM, Miceli V, Busà R, Bulati M, Gallo A, Zito G, Conaldi PG, Iannolo G
Int J Mol Sci. 2023 Aug 31;24(17):13550
doi: 10.3390/ijms241713550

Oncolytic Effect of Zika Virus in Neuroendocrine Pancreatic Tumors: New Perspectives for Therapeutic Approaches
Cocco MM, Carcione C, Miceli V, Tinnirello R, Chinnici CM, Carbone C, Zito G, Conaldi PG, Iannolo G
Int J Mol Sci. 2023 Dec 8;24(24):17271
doi: 10.3390/ijms242417271

3D Culture and Interferon-γ Priming Modulates Characteristics of Mesenchymal Stromal/Stem Cells by Modifying the Expression of Both Intracellular and Exosomal microRNAs
Bulati M, Gallo A, Zito G, Busà R, Iannolo G, Cuscino N, Castelbuono S, Carcione C, Centi C, Martucci G, Bertani A, Baiamonte MP, Chinnici CM, Conaldi PG, Miceli V
Biology (Basel). 2023 Jul 28;12(8):1063
doi: 10.3390/biology12081063

Building Basic and Clinical Research Around Lung Transplantation
Miceli V, Bertani A, Pagano V, Centi C, Conaldi PG
Contemporary Lung Transplantation, Organ and Tissue Transplantation,2023 edited by Springer
doi: 10.1007/978-3-319-20788-9_48-1

Impact of T Lymphocytes Isolated from Liver Perfusate of Deceased Brain Donors on Kidney Transplantation: Preliminary Evidence and Future Directions
Pagano D, Badami E, Zito G, Conaldi PG, Vella I, Buscemi B, Amico G, Busà R, Salis P, Li Petri S, Di Francesco F, Calamia S, Bonsignore P, Tropea A, Accardo C, Piazza S, Gruttadauria S
J Clin Med. 2023 Jul 20;12(14):4786
doi: 10.3390/jcm12144786

EXPERIMENTAL IMMUNOTHERAPY

FOCUS

- **Engineering of CAR-NK cells for the treatment of liver cancer**
- **Increasing the anti-tumoral fuction of NK cells by *ex vivo* activation with specific cytokines**
- **Understanding the role of dendritic cells in tolerance induction**
- **Development of GMP-compliant protocols for large scale cell production for clinical applications**
- **Production of Tolerogenic Dendritic Cells**

AIMS

- **Treatment of patients affected by liver cancer with innovative CAR-NK cells engineered to have enhanced specificity to hepatocellular carcinoma**
- **Early weaning off immunosuppressive therapy of Solid Organ Recipient using Tolerogenic Dendritic Cells**
- **Development of "off-the-shelf" cellular products**

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Laboratory Technician

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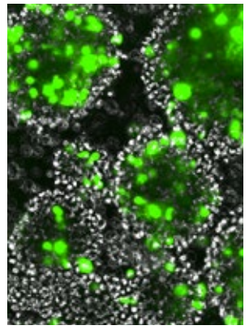
- Thomas E. Starzl Transplantation Institute, University of Pittsburgh School of Medicine, USA
- University Of Pittsburgh Medical Center (UPMC)
- The University of Pittsburgh, McGowan Institute of Regenerative Medicine (MIRM), USA
- Experimental Zooprophylactic Institutes of Sicily (IZS Sicily), IT
- National Research Council (CNR), ITA



Our research is focused on the development of cell-mediated therapies aiming at increasing the life expectancy of patients in solid organ transplantation and cancer. During 2023 we focused our research on novel treatment to improve the prognosis of hepatocellular carcinoma (HCC), such cell-mediated immunotherapy. A second project developed in our lab investigates the role of tolerogenic Dendritic cells in the induction of operational immune tolerance in solid organ recipients. HCC is a malignant epithelial tumor arising from hepatocytes. Treatments for HCC include hepatectomy, liver transplant or chemotherapy which are not always effective for advanced forms of HCC and the risk of recurrence is high. Therefore novel treatment strategies are urgently needed. Natural killer (NK) cells play an important role in the innate host immune response against viruses and tumors.
The frequency and function of NK cells in the peripheral blood and liver are associated to the recurrence and survival rates of patients with resectable HCC. Thus, hepatic NK cells are thought to play an important role in mediating the immune function of the liver. We have patented a method to isolate high numbers of viable NK cells from an alternative source such as the liquid perfusate of the liver of deceased donors. We have also optimized a protocol to expand these cells obtaining clinically relevant cell concentrations. We have recently demonstrated that NK cell conditioning with cytokines such as interferon-alpha (IFN-α) significantly increase their anti-viral an anti-tumor response both *in vitro* and in preclinical studies *in vivo*. Having therefore performed all the proof-of-concept studies, our cellular product is ready to move on to the clinic. ISMETT is equipped with a Cell Factory which will support the production of this cellular product for downstream clinical applications.
Genetic modification techniques have been developed to improve the specificity and efficacy of NK cell cytotoxicity to tumor cells. For example, the approach using Chimeric Antigen Receptor (CAR) engineering for NK cells has enhanced the specificity and efficacy of NK cell therapy. In our laboratory we are investigating the use of a novel CAR construct to engineer NK cells with specificity for a tumor antigen described in HCC and known as Glypican-3 (GPC3). The 4th generation lentiviral construct is designed to also secrete soluble cytokines such as interleukin-15 (IL-15), known to sustain NK cells proliferation, function and survival, and IFN-α. The vector we designed also expresses the suicide gene Epidermal Growth Factor Receptor in a truncated form (EGFRt) as safety switch. In close collaboration with the researchers at ISMETT, we have optimized the protocol of transduction of liver derived NK cells, obtaining about 35-40% of CAR-expressing cells. We have demonstrated that these CAR-NK specifically recognize GPC3-expressing tumor target cells and that release IFN-α upon engagement of the CAR receptor. Further, we have shown the correct function of the suicide gene. The experimental protocol for the preclinical studies is currently under evaluation by the Istituto Zooprofilattico Sicilia (IZS), our partner for the *in vivo* experimentation.
Lately, we are exploring the role of the ADAM-17 in the NK-mediated innate response to cancer by knocking out the expression of this metalloproteinase, which is involved in the stabilization of the surface protein CD16 that concurs to NK cell killing of target cells.
Our lab is also interested in developing a cell-based approach to induce operational tolerance in liver/kidney using tolerogenic Dendritic cells. One major caveat of organ transplantation is graft rejection. Accordingly, immunosuppressive therapy is provided for life to transplanted patients, though it is accompanied by severe side effects such as kidney failure. The use of cellular therapies such as the administration of donor derived tolerogenic Dendritic Cells for early weaning of liver transplanted patients is a novel strategy to prevent graft loss. Our strategy in the use of the liver perfusate from deceased donors as source of DCs precursors.

HEPATOBILIARY REGENERATIVE MEDICINE

FOCUS

- **Development of implantable bioartificial biliary ducts**
- **Establishment of a viable source of cells for biliary regenerative medicine**

AIMS

- **Endow our tissue-engineered CBD with endothelial cells**
- **Investigate safety of our tissue-engineered CBD *in vivo***
- **Advance three-dimensional organotypic culture models of biliary cells**

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Mattia Pasqua, PhD
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Claudio Catalano
ITS Academy student (01/03/2023 – 30/09/2023)

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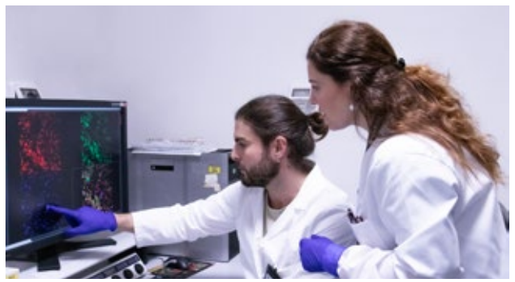
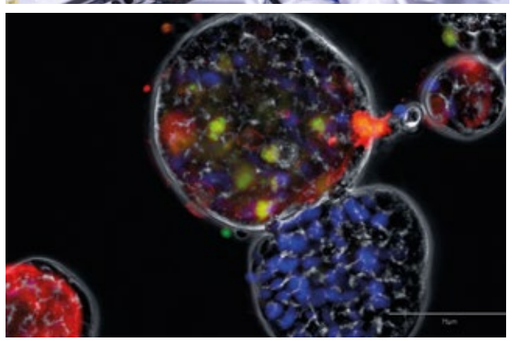
- University of Pittsburgh, PA, USA
- McGowan Institute for Regenerative Medicine (MIRM), PA, USA

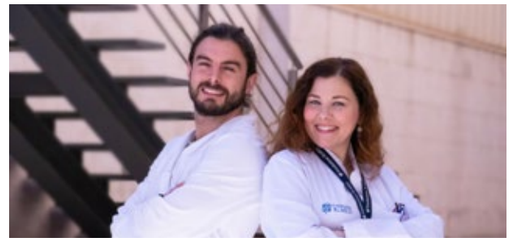


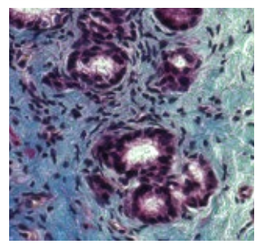


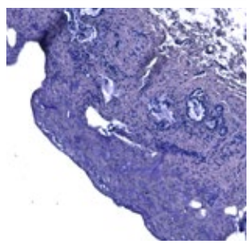
The Hepatobiliary Regenerative Medicine group led by Maria Giovanna focuses broadly on regenerative medicine strategies for the treatment of cholangiopathies, a diverse group of diseases targeting the biliary tree.

Current efforts aim to address the need to develop therapies to treat still incurable structural abnormalities of the common bile duct (CBD). These include biliary atresia, choledochal cysts, distal cholangiocarcinoma, and injuries resulting from liver transplantation or other surgical procedures performed on the biliary tract (e.g. laparoscopic cholecystectomy), stomach and duodenum. Without early recognition and appropriate treatment, these diseases, which are frequent causes of hospital admissions and surgical interventions, may lead to biliary tract obstruction or stricture, inflammatory response, cholestatic liver failure, and ultimately, they might require liver transplantation. The past several decades saw the development and evolution of different biliary stent technologies for the management of bile duct obstruction. However, biliary stenting is not flawless, and this has directed efforts towards fabricating bile duct substitutes by means of tissue engineering techniques. Nevertheless, none are yet available for clinical use. Our group aims to fill this therapeutic gap.

Over the past three years, we have therefore worked hard towards a clinically-relevant tissue-engineered CBD. Using molding and electrospinning techniques, we have fabricated a multiphasic tubular structure of a size similar to the human native CBD. Our artificial CBD contains two biocompatible biomaterials and biliary cells. One such biomaterial was used to support biliary cell growth; the other one, was used to provide the structure with mechanical properties. Through a multidisciplinary characterization, which included histological and ultrastructural analyses, mechanical testing, biochemical assays, and mass spectrometry-based proteomics, we demonstrated the generation of a viable and functional biliary-like epithelium, as well as homogeneity, stability, mechanical strength, handleability, suturability, and leak-free property of our artificial CBD. These characteristics position it as a promising tool for future endeavors in biliary tissue regenerative medicine. The possibility to include other cell types like endothelial cells is currently being investigated, and a pre-clinical assessment will hopefully follow in the near future. Should safety and effectiveness of our device be proven *in vivo*, this could bring new treatment options for CBD-associated diseases, and help reduce hospital admissions and high health care expenditures. In the meantime, we are in the process of filing a patent application to protect our invention. In parallel, efforts are also being directed to advancing biliary cell culture techniques and establish three-dimensional organoids for applications in regenerative medicine.







REGENERATIVE MEDICINE: CELLULAR THERAPIES

FOCUS

- **Identifying the best therapeutic agent by comparing secretome/EVs of different sources**
- **Creation of master cell banks according to GMP standards**
- **Manufacturing of secretome/EVs according to GMP standards**
- **Design and production of secretome/EV-laden biomaterials**
- **Selection and validation of anti-fibrotic microRNAs**
- ***In vivo* preclinical tests of efficacy and safety**

AIMS

- **Developing treatment options for chronic skin wounds**
- **Developing treatment options for NAFLD/NASH**
- **Improving the efficacy of secretome/EV therapeutics by providing scaffold biomaterials**

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Annalisa Martorana
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Paolo Accardo
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Claudia Carcione
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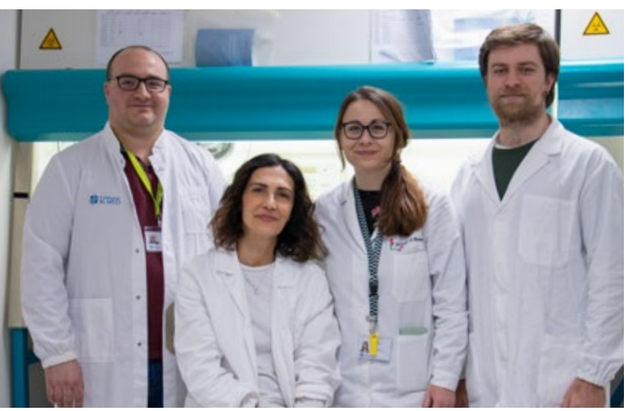
- Fondazione IRET, Tecnopolo di Bologna, ITA
- Lab of Translational Research, Dept of Medical Sciences, University of Turin, ITA
- National Center for Gene Therapy and Drugs based on RNA Technology, University of Padova, ITA

The Regenerative Medicine - Cell Therapy group is engaged in developing strategies focusing on the use of therapeutic cells, such as mesenchymal stromal cells (MSCs) and their secreted factors to restore/improve organ function after a damage. In this scenario, the role of secretome as a new booster for regenerative medicine is crucial. Bioactive molecules of secretome include a wide range of soluble proteins and nucleic acids (e.g., microRNAs) with anti-inflammatory, anti-oxidative and anti-fibrotic effects. Alternatively, bioactive molecules of secretome are also packed into extracellular vesicles, nanosized particles with the capacity to bring their cargos into target cells. MSC-derived secretome and extracellular vesicles recapitulate therapeutic features of parental cells with equal or even better efficacy, to the point that they are considered next generation therapeutics (cell-free therapy).



We seek to develop treatment options for chronic skin wounds, and for acute and chronic liver diseases. In particular, patients with cirrhosis complications or with an increased risk of developing liver fibrosis, such as those with obesity, type 2 diabetes and/or metabolic syndrome, could benefit from MSC-based therapeutics. Furthermore, improving the efficacy of cell-free therapy by polymer-based delivery systems is a central research topic. Delivery systems might preserve the stability of soluble agents by providing protection from clearance and from *in vivo* enzymatic degradation. Delivery systems will also sustain the release of soluble agents to target organ/cells. These systems can be fabricated either as sponges for topical application, or as injectable hydrogels and polymer-coated extracellular vesicles for systemic administration.
The main research activities of our group are listed below:

1. Selecting the appropriate quality control parameters for a GMP-compliant production of MSC-based therapeutics.
2. Releasing cells and secreted products according to the principles of manufacturing and quality control (QC) described in the guidelines for ATMP/biological therapeutics.
3. Design and synthesis of secretome/extracellular vesicle-laden biomaterials, such as injectable or 3D porous hydrogels, and polymer-coated extracellular vesicles.
4. Implementing *in vitro* approaches to evaluated the tuning of biomaterials with cell secreted factors.
5. Implementing *in vitro* approaches to evaluate the efficiency of extracellular vesicle delivery inside target cells.
6. Preclinical studies of efficacy and safety.

REGENERATIVE MEDICINE AND IMMUNOTHERAPY

Ri.MED RESEARCH

GMP CELL FACTORY

FOCUS

- **Cell based therapies for end stage organ failure (e.g. based on MSCs)**
- **Immunotherapies, e.g. Multivirus specific T lymphocytes**

AIMS

- **Contribute to translational medicine, providing new ATMPs to patients**
- **ATMPs release for Phase I studies and single patient use**
- **Optimization/automation of production processes and Quality Control (QC) tests**

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Salvatore Pasqua
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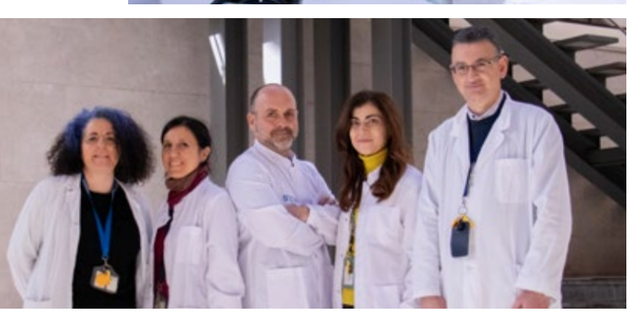
- ISMETT-IRCCS Ospedale Galeazzi- Sant'Ambrogio, ITA
- University of Pittsburgh, USA



The Cell factory group is developing Advanced Therapy Medicinal Product (ATMP) that use polyclonal multivirus specific T cells (MVT-cells) for autologous and allogeneic applications. Our protocol is based on the stimulation of T lymphocytes with a mix peptides of derived from Epstein-Barr virus (EBV), Cytomegalovirus (CMV), BK polyomavirus (BKV) and Adenovirus (ADV). The main goal is to generate multivirus-specific T cell clones capable of containing or treating virus related post transplant complications (i.e. primary infections or virus reactivation). We tested innovating closed culture systems, the G-Rex 10M devices, to enhance T cells expansion, and obtained a rapid and remarkable improvement in cellular yield, with minimal manipulation, demonstrating also the optimal quality of the final products (phenotype and specific cellular activity).

The production group, in collaboration with ISMETT infectious disease specialists and biologists research groups, is also actively involved in a clinical study aimed to define new tools to monitor and finely predict the clinical outcome (and potential neoplastic complications) of solid organ transplantation recipients after Human Herpesvirus-8 (HHV-8) primary infection or virus reactivation. HHV-8 infection can lead to the development of neoplastic pathologies such as Kaposi's Sarcoma (KSHV), Castelman's Disease and Prymary's Effusion Lymphoma, as well as non-neoplastic pathologies including KICS syndrome (KSHV-associated inflammatory cytokine syndrome), diseases, for which there are no international guidelines nor therapies with a 100% success rate.

More specifically, the production group is involved in the patient immunologic monitoring, analyzing the specific T cell response (IFN-gamma secretion quantified by ELISPOT assay) following HHV-8 latent and lythic antigens stimulation (K8, K12, LANA, GB viral peptides). Patients' T cell specific viral response is currently used to integrate clinical evidences during the follow-up of transplanted patients.

In 2023, the Quality Control group investigated the growth performance of iFA BacT/Alert culture bottles for the detection of nosocomial Aspergillus in clinical matrices, such as blood and bronchoalveolar lavage (BAL) and developed a new protocol to recover aspergillus conidia from positive culture bottles in order to overcome the loss during subculture procedure, in relation of addition of different concentrations of TWEEN 20 and agitation duration.

Addition of 0,5% Tween 20 and vigorous agitation of the bottles for 60 seconds significantly enhanced the recovery of Aspergillus spp., with ranges from 90 to 100%. The recovery rate of the Aspergillus isolated from bottles processed with lower Tween 20 concentrations and shorter agitation times was more variable, compared to previuos experimental condition, with range from 70 to 80%. Vigorous agitation for 15, 30 or 60 seconds alone resulted in 40, 60 and 80%, respectively.

These results support the routine use of the iFA aerobic vial for the detection of Aspergillus in blood and BAL samples, proposing an efficient alternative method for culturing and isolating Aspergillus spp from blood culture bottles.

Moreover, QC Staff collaborated with RiMED Proteomic Group to analyze Honey produced by different species of endemic sicilian bees. The Identification of microbial species, in honey samples, showed microorganisms that are currently used as probiotics and that are able to produce metabolites that alleviate inflammatory response.

PRECLINICAL *IN VIVO* RESEARCH

FOCUS

- **Test surgical, pharmacological, metabolic, gene and immunological therapies on animal models that mimic terminal organ failure**
- **Safety ed efficacy of scaffold**
- ***In vivo* Proof-of-concept**
- **Training for MD and DVM**

AIMS

- **Welfare of Laboratory animals**
- **Drafting of the protocol**
- **Standardization of animal model**
- **3R Application (Reduction, Replacement and Refinement)**
- **Training modules for researchers and personnel who perform procedures (function A), take care of animals (function C), euthanize animals (functionD) and design procedures and projects (function B)**

Valeria Pagano, DVM PhD LAMS
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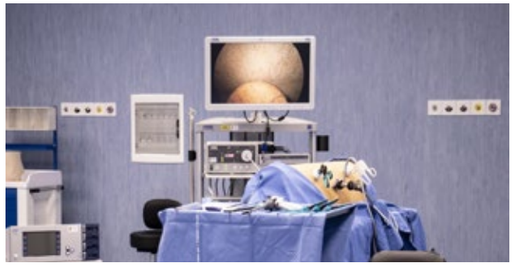
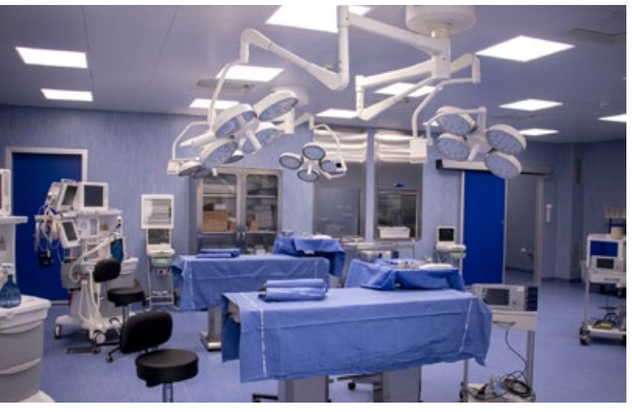
Nazareno Costa
Animal Care

COLLABORATIONS
- The Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), ITA
- University of Palermo, Palermo, ITA
- Experimental Zooprophylactic Institutes of Sicily (IZS Sicily) Palermo, ITA
- Experimental Zootechnical Institute for Sicily (ISZS) Palermo, ITA





Our research is focused on the development of animal pathological models, the improvement of housing conditions based on specie's needs and their microbiological condition and experimental refinement procedures, in order to improve animal wellbeing, and to standardize protocols to obtain robust data.
To date, as the Ri.MED Foundation does not have its own animal facility, the preclinical *in vivo* group uses animal facilities of our institutional partners (such as IZS Sicilia and ISZ) and acts as an interface between Ri.MED research groups and Competent Authorities to carrying out the *in vivo* projects and to obtain the mandatory authorization .

In the course of 2023 we have concentrated our activities giving support to the researchers, supporting them for the drafting of the necessary documents for the Ministerial authorizations and the experimental protocols *in vivo,* by dealing with the application of 3R (refinement replacement and reduction) and obtaining the necessary authorisations for the import, removal and use of organs and tissues for *ex vivo* testing.

In addition, the Preclinical group is following the authorization path of the ISPEMI large animal facility to the Ministry of Health, a structure consisting of an operating room, a pre-surgery and intensive care area and a long-stay area for sheep and pigs.

Moreover, our group has been included in educational projects in local schools, with the aim of offering the means to understand the need for preclinical research *in vivo*, the progress that research has achieved thanks to the conscious use of the animal, assessing them by criticizing them or supporting them, with a critical spirit free from prejudices.

Furthermore, our group takes care of training external and internal personnel for functions a) b) c) d) of the directorial decree on training pursuant to art. 23 Legislative Decree 26/14.

BIOENGINEERING AND TISSUE ENGINEERING

BIOENGINEERING AND MEDICAL DEVICES
CARDIOVASCULAR TISSUE ENGINEERING
MUSCULOSKELETAL TISSUE ENGINEERING

RI.MED RESEARCH

Assembly process of a biphasic bioreactor used for 3D multi-tissue *ex vivo* cultures in dynamic conditions.
Courtesy of the Ri.MED Musculo-Skeletal Tissue Engineering (MSTE) Group.

PUBLICATIONS

Compliant Aortic Annulus Sizing with Different Elliptical Ratios Through a Valvuloplasty Balloon Catheter
Yao J, Bosi GM, Burriesci G, Wurdemann H
IEEE Transactions on Biomedical Engineering, 70(12): 3469-3479
doi: 10.1109/TBME.2023.3289300

Biological equivalence of genetically engineered porcine pericardium for biological heart valve manufacture: a randomized 150 day blind study in sheep
McGregor CG, Salmonsmith J, Burriesci G, Byrne G
Transplantation 107(10S2):p 24
DOI: 10.1097/01.tp.0000993852.97979.3a

Finite element and fluid-structure interaction modelling of a balloon catheter
Yao J, Salmonmith J, Bosi GM, Burriesci G, Wurdemann H
IEEE Transactions on Medical Robotics and Bionics (TMRB)
doi: 10.1109/TMRB.2023.3332434

Valvulogenesis of a "living", innervated pulmonary root induced by an acellular scaffold
Yacoub M, Tseng YT, Kluin J, Vis A, Smail H, Sarathchandra P, Aikawa E, El-Nashar H, Chester A, Shehata N, Nagy M, El-sawy A, Burriesci G, Salmonsmith J, Romeih S, Latif N
Communications Biology 6: 1017
doi: https://doi.org/10.1038/s42003-023-05383-z

Hydrodynamic ex-vivo analysis of valve sparing techniques: assessment and comparison
Di Leonardo S, Vella D, Grillo CS, Martorana C, Torre S, Argano V, Burriesci G
European Journal of Cardio-Thoracic Surgery 63(3): ezad040
doi: https://doi.org/10.1093/ejcts/ezad040

Modelling of thrombus formation using smoothed particle hydrodynamics method
Monteleone A, Viola A, Napoli E, Burriesci G
Plos One 18(2): e0281424
doi: https://doi.org/10.1371/journal.pone.0281424

Elastic properties of 2D Auxetic Honeycomb structures - A review
Montgomery-Liljeroth E, Schievano S, Burriesci G
Applied Materials Today 23, 101722
doi: https://doi.org/10.1016/j.apmt.2022.101722

A bioengineered in situ ovary (ISO) supports follicle engraftment and live-births post-chemotherapy
Buckenmeyer MJ, Sukhwani M, Iftikhar A, Nolfi AL, Xian Z, Dadi S, Case ZW, Steimer SR, D'Amore A, Orwig KE, Brown BN
J Tissue Eng. 2023 Nov 17:14:20417314231197282
https://doi.org/10.1177/20417314231197282

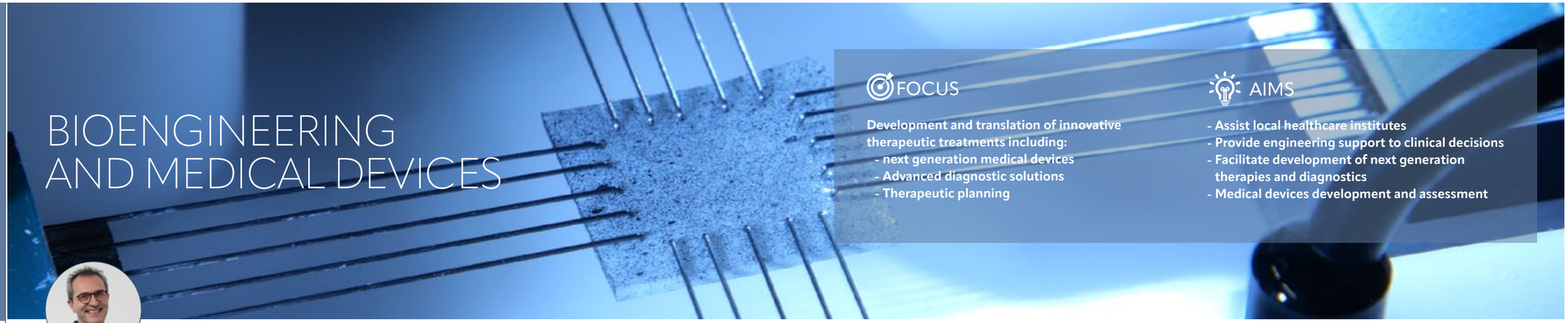
Creating and Transferring an Innervated, Vascularized Muscle Flap Made from an Elastic, Cellularized Tissue Construct Developed In Situ
Sato H, Kohyama K, Uchibori T, Takanari K, Huard J, Badylak SF, D'Amore A, Wagner WR
Adv Healthc Mater. 2023 Nov;12(29):e2301335
doi: 10.1002/adhm.202301335

Cardiac valve scaffold design: Implications of material properties and geometric configuration on performance and mechanics
Pedersen DD, Kim S, D'Amore A, Wagner WR
J Mech Behav Biomed Mater. 2023 Oct:146:106043
doi: 10.1016/j.jmbbm.2023.106043

Polyester urethane urea (PEUU) functionalization for enhanced anti-thrombotic performance: advancing regenerative cardiovascular devices through innovative surface modifications
Rodríguez-Soto MA, Suárez Vargas N, Ayala-Velásquez M, Aragón-Rivera AM, Ostos C, Cruz JC, Muñoz Camargo C, Kim S, D'Amore A, Wagner WR, Briceño JC
Front Bioeng Biotechnol. 2023 Sep 20:11:1257778
doi: 10.3389/fbioe.2023.1257778. eCollection 2023

Dynamical modeling reveals RNA decay mediates the effect of matrix stiffness on aged muscle stem cell fate.
Hettinger ZR, Hu S, Mamiya H, Sahu A, Iijima H, Wang K, Gilmer G, Miller A, Nasello G, D'Amore A, Vorp DA, Rando TA, Xing J, Ambrosio F
bioRxiv. 2023 Mar 2:2023.02.24.529950
doi: 10.1101/2023.02.24.529950

BIOENGINEERING AND MEDICAL DEVICES



FOCUS

Development and translation of innovative therapeutic treatments including:
- **next generation medical devices**
- **Advanced diagnostic solutions**
- **Therapeutic planning**

AIMS

- **Assist local healthcare institutes**
- **Provide engineering support to clinical decisions**
- **Facilitate development of next generation therapies and diagnostics**
- **Medical devices development and assessment**

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Giulio Musotto, PHD
Post Doctoral Researcher in Cardiovascular Engineering

Valentina Pinto
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Alessia Viola, PhD
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Anna Maria Lo Presti
PhD Student

COLLABORATIONS
- Adeka, Japan
- Erasmus MC, The Netherlands
- Harvard Medical School, USA
- Imperial College London, UK
- ISMETT- IRCCS, Palermo, ITA
- Magdi Yacoub Foundation, Egypt
- Mitrassist Lifesciences, PRC
- Università degli Studi di Palermo, ITA
- Università degli studi di Padova, ITA
- Université de Technologie de Compiègne, FRA
- University College London, UK
- University of Amsterdam, the Netherlands
- University of Bristol, UK
- University of Minnesota, USA
- University of Pittsburgh, USA
- University of Pittsburgh Medical Centre, USA

The Bioengineering group applies engineering principles and physical science to the analysis of biological systems and the design new generation biomedical technologies. The group operates mainly in the cardiovascular field, contributing to the conception and optimisation of advanced diagnostic solutions, support tools for therapeutic planning and new generation medical devices based on innovative approaches. The group is rapidly consolidating as a reference for regional healthcare, for the local academic institutions, and for the small and medium enterprises in the geographic area. The group's researchers offer solid skills in numerical modelling, fluid-structural analysis, and medical device design and development. They are continuously expanding their portfolio of medical device technologies, which already includes a number of innovative technologies for surgical and minimally invasive heart valve repair and replacement. In collaboration with clinical and industrial partners, they are facilitating the introduction of these technologies into clinical practice to maximise their positive impact on patients' quality of life.

In 2023, the group has strengthened the intellectual property of the foundation and accelerated clinical translation. Another US patent for a novel medical device was granted, and collaborations with global partners to bridge the gap between research and patient care were intensified through several meetings and in person visits. The group's has published seven new scientific papers in leading peer-reviewed journals, highlighting the diversity of our research in both fundamental and applied cardiovascular engineering. Their work on genetically modified porcine pericardium (alpha-Gal free), in collaboration with UCL, UK and the University of Minnesota, USA, has demonstrated that the use of this tissue for surgical or transcatheter heart valves could increase prostheses durability by mitigating calcification. Another collaborative study (involving Imperial College London, UK; Magdi Yacoub Foundation, Egypt; Erasmus MC, The Netherlands; the University of Amsterdam, the Netherlands; Harvard Medical School, USA; and UCL, UK) has resulted in a novel synthetic scaffold inducing a rapid process of morphogenesis, through the control of the material characteristics, design and "morphodynamism". Working with the School of Medicine and Surgery at the University of Palermo, Italy, an *in vitro* analysis of different valve-sparing surgical techniques has demonstrated that the use of aortic conduits replicating the presence of the Valsalva sinuses establishes more physiological operating conditions. New intra-operative methods for determining the dimension of the aortic annulus and to simplify balloon valvuloplasty have been proposed in collaboration with UCL, UK. A meshless computational approaches have been developed together with the University of Palermo, Italy, to allow the simulation of thrombus formation though a novel single-physics approach. Finally, with UCL, UK, we have deepened the understanding of auxetic metamaterials, attempting to establish a systematic and coherent classification of these structures.

CARDIOVASCULAR TISSUE ENGINEERING

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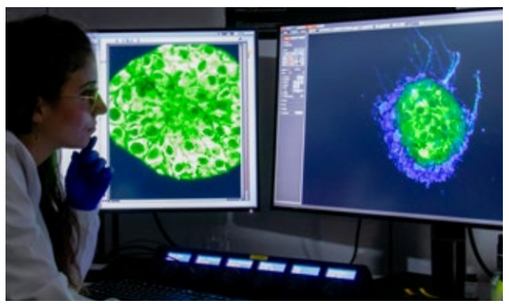
Federica Cosentino, PhD
Scientist in Numerical Models
Marzio Di Giuseppe, PhD
Scientist in Numerical Models
Viktor Balashov, PhD
Post Doctoral Researcher in Tissue Engineered Heart Valves



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Pietro Terranova, PhD
Scientist in Tissue Engineering
Marianna Barbuto, MS
PhD Student in Technologies and Sciences for Human Health
Patrizia Caruso, MS
PhD Student in Mechanical, Manufacturing, Management and Aerospace Innovation
Elisa Lanzalaco, MS
PhD Student in Chemical, Environmental, Biomedical, Hydraulic and Materials engineering
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Ignazio Niosi, MS
PhD Student in Mechanical, Manufacturing, Management and Aerospace Innovation
Luca Di Nino
MSc Università degli Studi di Palermo
Beatrice Di Caccamo
MSc Politecnico di Torino
Anne Bouwens
MSc Eindhoven University of Technology

FOCUS

- **Tissue-engineered heart valves**
- **Tissue-engineered vascular grafts**
- **Tissue-engineered cardiac patches**
- **Bioreactors for enhanced extracellular matrix elaboration**
- **Native/engineered tissue image-based structural and histopathological analysis**
- **Native/engineered tissue numerical models for mechanics and tissue growth**

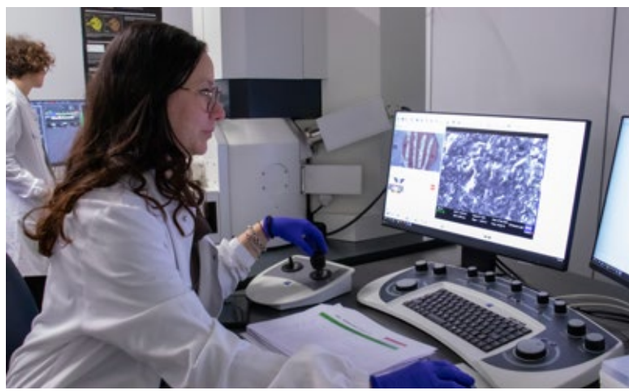
AIMS

- ***In silico*, *in vitro*, and *in vivo* models**
- **Quantitative histology and biomaterial micro-structure image-based analysis**
- **Structural modelling for cardiovascular tissue engineering**
- **Mechanical and topological conditioning to duplicate native tissue properties**
- **Endogenous tissue growth, vascular grafts, and engineered heart valves.**

COLLABORATIONS

- University of Palermo, Palermo, Italy
- Advanced Technologies Network Center (ATeN Center), Palermo, ITA
- McGowan Institute for Regenerative Medicine (MIRM), Pittsburgh, USA
- University of Pittsburgh Medical Center (UPMC), Pittsburgh, USA
- The Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy
- Universidad Abierta Interamericana (UAI), Buenos Aires, Argentina
- Neoolife, Pittsburgh, USA
- TELEA BioTech, Sandrigo, Italy
- Columbia University Irving Medical Center (CUIMC), New York, USA
- Technical University of Munich, (TUM), Munich, Germany
- University of California Irvine (UCI), Irvine, USA
- Eindhoven University of Technology, Netherland
- Politecnico di Torino, Italy

The D'Amore's Cardiovascular Tissue Engineering group aims to integrate a mechanistic understanding of scaffold – host interaction with the development of novel biomaterials and tissue engineering strategies. The focus of our research is upon unmet clinical needs in cardiovascular diseases. Recent areas of interest include: quantitative histology and biomaterials micro-structure image-based analysis, structural modeling strategies to guide tissue engineering scaffold fabrication, mechanical and topological conditioning for tissue elaboration, development of cardiac restrain devices, vascular grafts and engineered heart valves. Our multidisciplinary research team, currently 21 people strong, includes biomedical, mechanical, and structural engineers as well as biotechnologists, biologists, clinicians in addition to a number of interns and Master of Science's degree students. The RiMED laboratory, established in 2020 and graciously hosted by the Departments of: Chimica e Fisica, and STEBICEF, University of Palermo (UNIPA), includes 100 m^2 of fully equipped, independent lab space and 300 m^2 of office and numerical lab space located in buildings 16 and 18 of the UNIPA campus. Two major technology platforms have been developed since 2020 covering material processing, characterization, imaging and histology. Additional laboratory space is also provided at the McGowan Institute, University of Pittsburgh and includes ~70 m^2 of fully equipped lab space, cubicles and office space.



MUSCULOSKELETAL TISSUE ENGINEERING

FOCUS

- **Cartilage and bone pro-regenerative technologies**
- **Bioactive materials stimuli-responsive**
- **Tendon/ligament-like scaffolds**
- ***Ex vivo* tissue culturing**
- **Reliable musculoskeletal diseases modeling**

AIMS

- **Biofabrication of active scaffolds for the cartilage focal lesions repair**
- **Production of engineered tendon-like constructs supporting the surgical tendon/ ligament reconstruction**
- **Set-up of advanced *in vitro* models of musculoskeletal diseases**
- **Use of macrofluidic bioreactor for the *ex vivo* culturing of biphasic tissues**

DIRECT COLLABORATION

Riccardo Gottardi, PhD
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Bioengineering and Biomaterials Lab.
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Roberto Di Gesù, PhD
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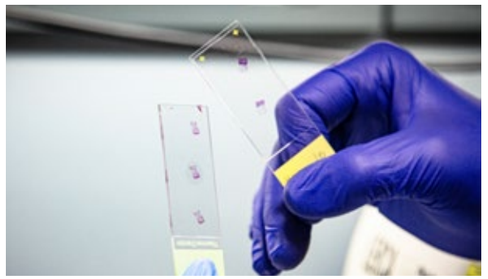
Francesca Romano
PhD student



COLLABORATIONS

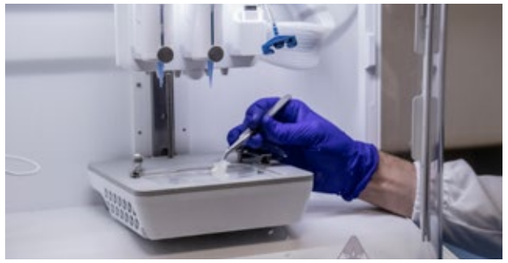
- The Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), ITA
- University of Pittsburgh Medical Center (UPMC), USA
- University of Bologna (Alma Mater Studiorum), ITA
- Buccheri la Ferla clinic (ITA)
- University of Palermo (UNIPA) (ITA)
- The Children Hospital of Philadelphia (CHOP), USA

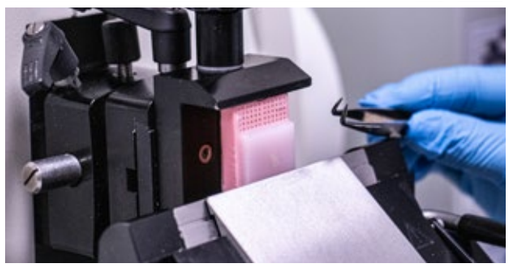
The MusculoSkeletal Tissue Engineering (MSTE) group is dedicated to pursuing as a main objective the advancement of groundbreaking strategies for the treatment of various pathologies that affect ligaments, tendons, cartilage, bone, and muscles.

In order to achieve this goal, the MSTE group employs a wide range of innovative approaches relying on tissue engineering technologies. These approaches are based on the most advanced techniques of biofabrication, including but not limited to 3D printing, electric-field induced biofabrication, and bioprinting. Notably, the MSTE research is developed jointly with the Bioengineering and Biomaterials Laboratory at the Children's Hospital of Philadelphia (CHOP, PA - USA) led by prof. Riccardo Gottardi.
The primary focus of the MSTE group is to fabricate bioactive scaffolds able to provide pro-regenerative cues for cells that are either seeded onto or embedded within these kinds of 3D supports. Following this approach, we aim to support reconstructive surgery after tendons/ligaments injuries promoting the regeneration of functional tissue in the mid-term. Analogously, our activity aims to restore the functionality of joints affected by focal chondral defects developing functional scaffolds stimuli-responsive, with a vision toward a clinical translation in the near future. In addition, the MSTE group is leading several projects aimed to the development of highly realistic *ex vivo* models of pathologies affecting the musculoskeletal system. Such an activity is supported by the employment of a proprietary technology based on macro-fluidic bioreactors for the culturing of biphasic tissues in native-like conditions.

The MSTE group is actively involved in numerous collaborations with international partners, which allow the design and management of different interdisciplinary projects. These collaborations serve as a fertile ground for the exchange of knowledge, expertise, and resources, enabling the MSTE group to push forward the boundaries of innovation. In this direction, we are developing engineered models of muscle tissue with a specific focus on fill the gap in the knowledge of the intricate interplay between the pathologies affecting the nervous system and the musculoskeletal apparatus.

This groundbreaking research provides a deeper insight into the mechanisms underlying various neuromuscular disorders and facilitates the exploration of innovative therapeutic approaches.





TECHNOLOGY PLATFORMS

With its strongly oriented translational approach, Ri.MED strategy provides for the development of skills and technological platforms, significantly enhanced in recent years, also thanks to the funding provided by the Sicilian Region and by the Dipartimento "Casa Italia" of Presidency of the Council of Ministers.

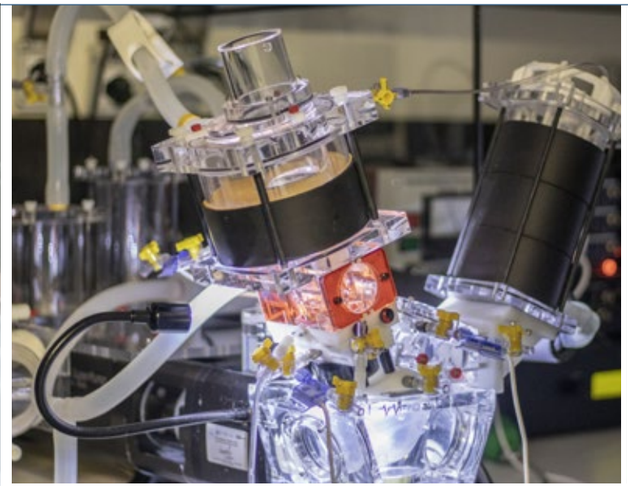
Some example are the automated system implemented for the storage and manipulation of molecule libraries for the **Screening laboratory**; the cardiac simulator and instrumentation supplied to the **Bioengineering Platform** for the characterization of biomaterials and medical devices; an 800 MHz magnetic resonance spectrometer at the **Biophysics and Structural Biology** platform, while the **Biomedical Imaging and Radiomics** platform uses 3T and 7T spectrometers and employs skills for the analysis of multimodal data and images, predictive diagnosis of pathologies and relapses.

The **Tissue Engineering Platform** allows the mechanical and structural characterization of native and bioengineered tissues and the *in vitro* and *in vivo* study of de novo tissue development; it also has software for the elaboration of predictive numerical models for tissue growth and regeneration and instruments for the development of engineered heart valves through the use of a six-degrees-of-freedom robotic arm. The **Bioinformatics** and **Molecular Informatics** groups integrated hardware and software with a virtual screening speed of 5,000 molecules per minute, with proprietary algorithms to study molecular interactions at the cellular level, and with the infrastructure for analyzing chemical-physical properties.

The **Medicinal Chemistry** Platform allows for the structural validation of primary hits and expansion of the chemical family, as well as the structural optimization of biologically promising molecules, up to the identification of small molecules that will enter the preclinical development phase. At IRCCS ISMETT, the **Proteomics** group supports the identification of new pharmacological targets and biomarkers, as well as the study of potential side effects of particular therapeutic molecules, while the **Cell factory** allows for the production of ATMP.

- BIOENGINEERING
- BIOINFORMATICS
- CELL FACTORY
- IMAGING AND RADIOMICS
- MEDICINAL CHEMISTRY
- MOLECULAR INFORMATICS
- PROTEOMICS
- SCREENING
- STRUCTURAL BIOLOGY AND BIOPHYSICS
- TISSUE ENGINEERING

Bioengineering
PLATFORM



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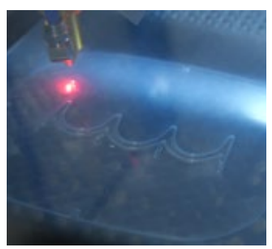
- Policlinico Giaccone, Palermo, IT
- Università degli Studi di Palermo, IT
- Institute Foundation G. Giglio, IT
- Università degli studi di Padova, IT
- Université de Technologie de Compiègne, FR
- Barts Heart Centre at St Bartholomew's Hospital, GB
- Great Ormond Street Hospital for Children, GB
- University College London, GB
- Queen Mary University of London, GB
- University of Bristol, GB
- University of Leeds, GB
- University of Pittsburgh, US
- University of Alabama at Birmingham, US
- MitrAssist, CN
- Adeka, JP

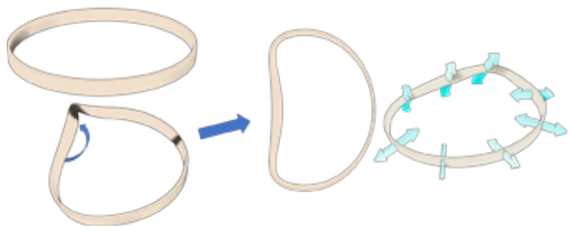
The Bioengineering Platform provides the treatment and characterisation of biomaterials, the numerical simulation of complex physiological systems, and the preclinical validation of medical devices of the different classes (from class I to class III).

Our research team offers solid expertise in numerical modelling, fluid-structure analysis, design optimisation of medical devices, and pre-clinical evaluations complying with regulatory requirements and good practice. The platform is consolidating as a reference for healthcare providers, academic groups and small and medium-sized enterprises in the region, contributing to stimulate the implementation of clinical innovations emerging from the local excellence and providing the necessary professional training to generate new technical and business competencies in the field.

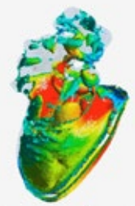


EXPERTISE
- Mechanical and thermo-mechanical and rheological characterisation of biomaterials and biofluids
- Numerical simulation of physiological systems and their interaction with medical devices (by means of structural, fluid dynamic and fluid-structure interaction analyses)
- Development of numerical codes for the study of cardiovascular problems (e.g. simulation of thrombosis)
- Development of support tools for therapeutic planning;
- Development of advanced diagnostic solutions
- Design of medical devices
- Hydrodynamic and structural *in vitro* characterisation of physiological systems and cardiovascular implants

TECHNOLOGY PLATFORM
- Codes for the numerical simulation of complex physiological systems (developed in house and commercial)
- Equipment for the treatment and characterisation of biomaterials and biofluids
- Tools for the basic manufacturing of components and prototypes
- Instruments for the preclinical validation of cardiovascular medical devices

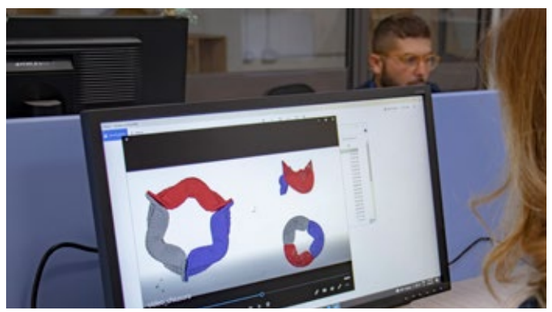


Structural analysis of contracting left atrial appendage.

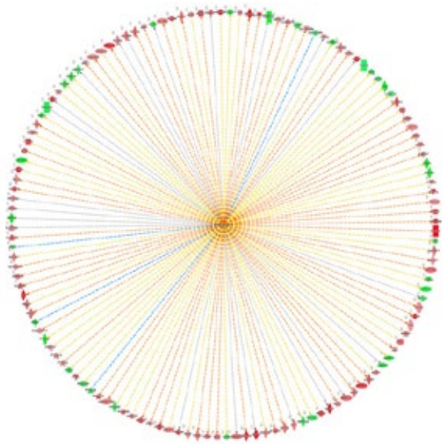


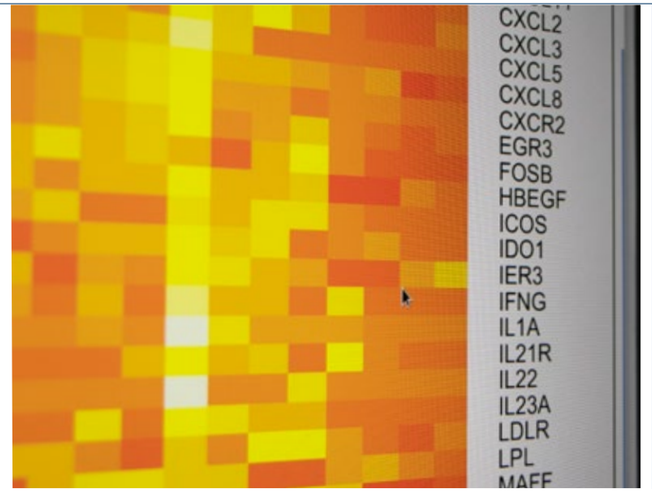
FSI vorticity analysis of a left atrial appendage.

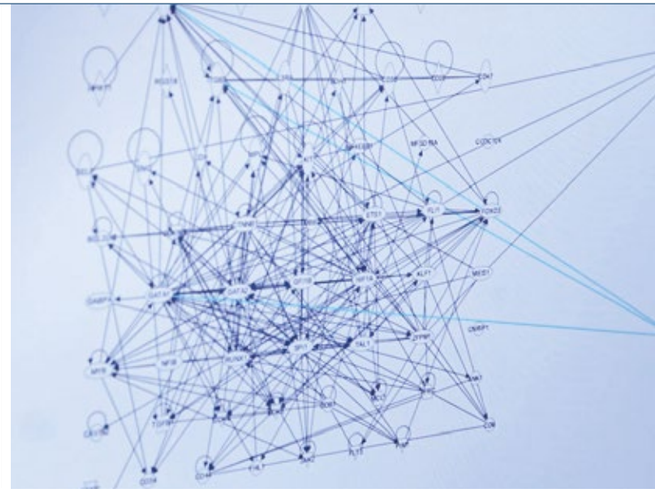
Clot formation in atrial fibrillation predicted with our code.



Bioinformatics
PLATFORM







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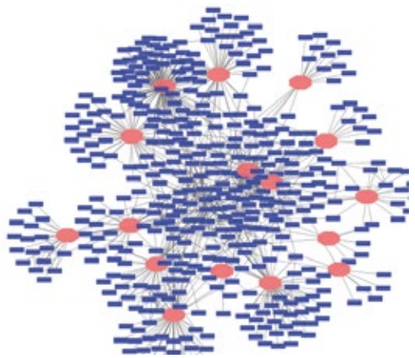
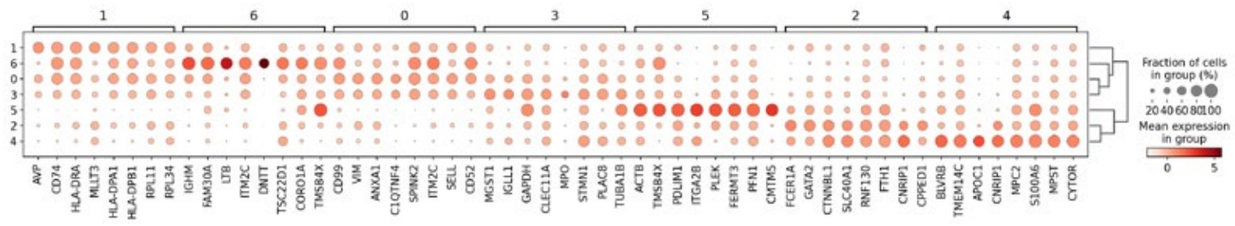
- National Research Council (CNR), ITA
- IRCSS ISMETT, Palermo, Italy
- Università degli Studi di Roma "Foro Italico", Roma, Italy
- IRCSS Policlinico Gemelli, Roma, Italy
- University of Pittsburgh, PA, US

Bioinformatics platform is devoted to support Ri.MED researchers and collaborators to retrieve the most amount of information from their data, with a particular interest on Biological Big Data. For instance, it supports the Drug Discovery Unit in high throughput screening experimental design and data analysis. It performs standard high-throughput data analysis, applied on a wide range of data source technologies, e.g., microarray or next generation sequencing data, integrated with clinical data if available.

Very often, the biological questions of interest and the associated experimental designs cannot be analyzed by the commercial software available to the scientific community. In this case, the expertise on computer programming and big data management for analyzing high-throughput data in a customized way. The main scientific interest of the group is the study of biological interaction networks, analyzed by integrating many sources of data. For instance, the project is dedicated to describe the regulatory interaction network of the endogenous microRNA in a specific tissue of interest, by analyzing its microRNA and gene expression profiles.





EXPERTISE
- Molecular biology, Genetics, Systems biology.
- Bulk and single cell RNAseq data analysis, Genomics, Epigenomics, Transcriptomics, Metagenomics.
- Statistics, Bioinformatics, Machine Learning, Complex Systems, Network analysis.
- Long-read Next Generation Sequencing (Oxford Nanopore Technologies).
- Programming with R, Python, Matlab, Galaxy.

TECHNOLOGY PLATFORM

Software

Our scripts for data analysis are realized with open-source language, i.e., Python, R and Bioconductor libraries. Visualization of interaction network is performed with the software Pajek or Cytoscape. In order to better satisfy the collaborators needs we are able to enrich our analysis results by comparing them with the results obtained with the software Ingenuity Pathway Analysis.

Hardware
- Server - CPU: 2x Xeon Gold 6152 2.10 GHz 22 Cores RAM: 128GB
- Server - CPU: 2x AMD Epyc 7402 24 Cores 2.8GHz RAM: 256GB HDD: 3x 480GB SSD GPU: 2x Nvidia A100 40GB

Wet Lab equipment
- cellular and molecular biology equipment
- MinION Mk1C, portable and real-time device for DNA and RNA sequencing, Oxford Nanopore Technologies.
- Biotek Synergy H1, multimode plate reader
- Agilent AriaDx, Real-Time PCR System

ACTIVE RESEARCH PROJECTS

SUnFox - *Senescence Undoing by FOXO4 knock down. This project is funded by National Center for Gene Therapy and Drugs based on RNA Technology" (CN3 – Spoke 4)*
Abstract: This is a project that studies a novel senolytic approach for the treatment of aging-associated diseases and senescence-associated diseases. The aim is inducing the apoptotic death of the senescent cells by knocking down FOXO4 via systemic and local delivery of specific ASO/siRNA.

SMART: *(Splicing Modulation by Advanced RNA Technologies)*
Abstract: The project aims to study *in silico* and *in vitro* RNA-based approaches to manipulate pathological splicing events. Classical *in vitro* assays will be supported by imaging and omic studies. Splicing modulation can be obtained by means of i) canonical ASO (that inhibit selected splicing site by occupancy), ii) bifunctional ASO (targeted bifunctional oligonucleotide enhancer of splicing - TOES) and iii) engineered Cas13.

Cell Factory

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PARTNERSHIPS AND COLLABORATIONS

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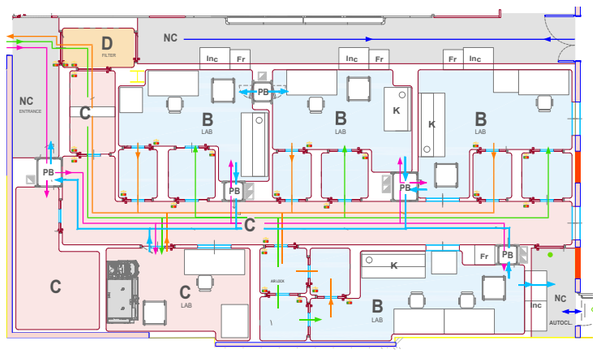
- ISMETT- IRCCS policlinico San Matteo, Pavia, IT
- ISMETT-IRCCS Ospedale Galeazzi- Sant'Ambrogio, IT
- University of Pittsburgh, US

The new cell factory guarantees flexibility in the type of production and functionality of the different areas. The design of production and quality control layouts for advanced therapies (gene therapy, cell therapy, tissue engineering and combined ATMPs) was approved by AIFA during a Scientific Advice meeting. There are 4 class B laboratories, one of which allows for a higher containment and has an autoclave for waste treatment.

The other 3 class B laboratories can be used in a totally independent way, for the simultaneous preparation of three different products. Alternatively, they can be connected two by two. In the last case, part of the operations can be performed in one lab and other manipulations can be performed in the second lab, passing the intermediate product through a pass box.



GMP Facility Layout, with personnel and material flows

An additional class C room is used for cell preparation in specific closed systems. Maintenance can be performed without access to the production rooms, as the engines of the equipment protrude into technical areas.

The Quality Control laboratories are equipped to conduct all the tests on raw materials, intermediates and final products required for product release. These labs can receive and adequately store reagents, materials and products according to GMP. Production areas and QC labs are equipped with a remote monitoring system.

EXPERTISE

- Set up of a GMP compliant Quality Assurance System
- Definition of GMP production protocols
- Development of Quality Control Methods
- Validation of environment, equipment, products
- GMP Training

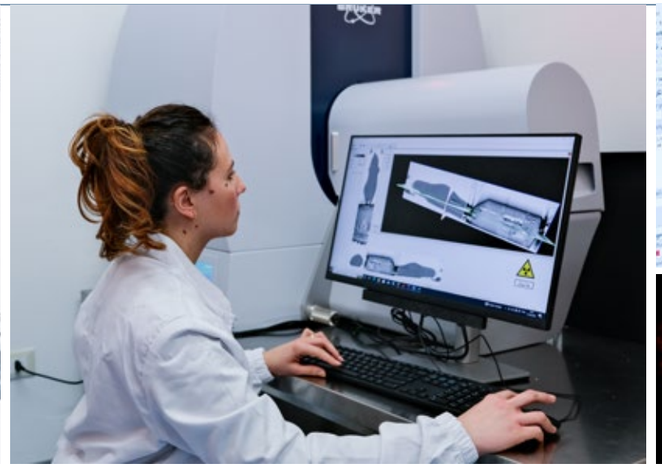
ACTIVITIES

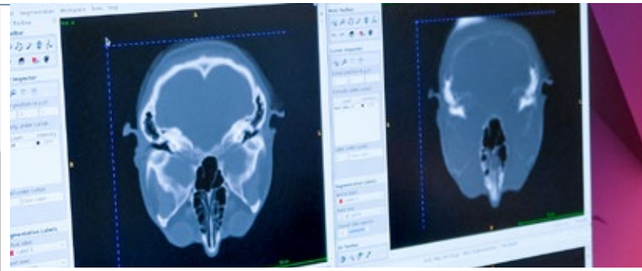
The facility is being qualified. The cell factory staff will carry out the validation of fundamental general processes (gowning validation, sanitization and clean hold time, passage of materials, etc.). Once the necessary development/ technology transfer data of the first advanced therapy products (adoptive immune therapies) are available, specific validation activities for the production process and related quality control methods will be carried out.

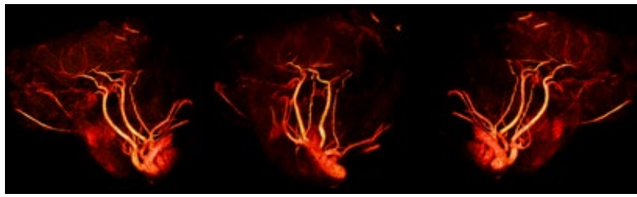
A complete dossier on the first advanced therapy product and its intended clinical use will be submitted as an integral part of the manufacturing authorization application of the new facility. Novel culture methods allowing minima operators' intervention and automatic QC tests are being tested.

Continuous activities include the maintenance of the GMP compliant Quality Assurance system and the periodic training of internal and external staff.

Imaging and Radiomics
PLATFORM







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PARTNERSHIPS AND COLLABORATIONS

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- Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Cefalù and Milan, ITA
- Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, (PROMISE) University of Palermo, Palermo, ITA
- Department of Biomedicine, Neuroscience and Advanced Diagnostics, (BIND)University of Palermo, Palermo, ITA
- University Hospital Agostino Gemelli IRCCS, Rome, ITA
- University of Catania, Catania, ITA
- Ospedale Generale Regionale "F.Miulli", Bari, ITA
- Nuclear Medicine, University of Messina, Messina, ITA
- Biomedical Campus University of Rome, Rome, ITA
- Medical Physics Unit, Cannizzaro Hospital, Catania, ITA
- Nuclear Medicine Department, Cannizzaro Hospital, Catania, Catania, ITA
- La Maddalena Hospital, Palermo, ITA
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The Biomedical Imaging and Radiomics Platform is primarily focused on oncology and neuroscience research. The Platform supports *in vitro*, *ex vivo*, and *in vivo* experiments, aiming for translation into the clinical application. Image analysis, artificial intelligence and radiomics tools are the driving forces of the platform, which are the basis for the entire workflow. The staff, which is currently increasing, is now comprised of scientific figures who possess transversal skills suitable for supporting the entire translational workflow, including experiments using cellular models and phantoms, scaffolds, tissues and organs within the RadioTheranostics and Biodiversity field. The scientific personnel on this platform are also trained in working with small animal models (mice and rats).
During 2023 the platform was enriched with the creation of the radiobiology laboratory (at Corso Calatafimi 414). The radiobiology laboratory has been authorized to process experiments using the following radionuclides such as Tc-99m, F-18, Cu-64, Ga-68, Lu-177, Ag-111, Zr-89 for research purposes. Moreover, along with the Gamma Counter, it is also equipped with all radioprotection equipment, a dose calibrator, an EVOS M5000 microscope, a ChemiDoc MP Imaging System, a chemical hood, a biological hood, centrifuges, and everything else required for biological cell line cultivation.

ACTIVE RESEARCH PROJECTS

Synthesis and functionalization of nanoparticles with plasmonic effects for applications in cancer precision therapy in collaboration with the GIT.

Radiomic analysis of magnetic resonance angiography of mice suffering from a particular type of anemia in collaboration with the GIT.

Biodistribution studies of novel radiopharmaceuticals on preclinical PET models in light of the discovery of new PET ligands and neurological receptors, transporters and enzymes in collaboration with the GIT.

Preclinical PET and MRI studies to detect neuronal degeneration early in Parkinson's disease in collaboration with IBFM-CNR (Cefalù and Milan).

In vitro radiobiology studies on innovative radiopharmaceuticals through pharmacokinetic, trafficking and cell viability assays (ISOLPHARM project) in collaboration with IBFM-CNR (Cefalù).

In vivo biodistribution studies for the evaluation of the efficacy of the treatment of site-directed radiopharmaceuticals on a preclinical mouse model in diagnosis and theranostics (ISOLPHARM project) in collaboration with IBFM-CNR (Cefalù).

EXPERTISE

- Image Processing Models (MR/PET/CT/IVIS, Microscopy and histological), 3D Segmentation, Deep Learning and Machine Learning to Extract, Classify and Delineate Tumor Volumes and Radiomics Features for Predictive Diagnosis of Pathologies (eg. Tumor, COVID19) and Relapses and Medical Decisions Support.
- Magnetic Resonance Imaging (T1, T2, DP, DWI, ADC and DCE)
- Positron Emission Tomography/Computer Tomography (PET/CT).
- Spectroscopy on phantoms, *in-vivo* and *ex-vivo* samples.
- *In Vitro* and *In Vivo* Radiobiology: Radiopharmaceuticals and Radio-labeled Chelators.
- Biodistribution analysis of Radiopharmaceuticals: Preclinical Molecular Imaging.
- PET/CT, MRI, HRCT, IVIS, Gamma Counter.
- Python, Matlab, CUDA.

TECHNOLOGY PLATFORM

At Imaging and Radiomics Lab – Via Marini 14 :

- **Hardware:** two workstations featuring 16-core Xeon CPUs, 128 GB RAM, 1x1TB HD SSD, 4x2TB HDs, and two Nvidia RTX8000 GPUs; one laptop with an Intel Xeon W-11955M CPU, 64 GB RAM, 1x2TB HD SSD, 3x2TB HDs, and two Nvidia A6000 GPUs.
- **Software:** PMOD, TopSpin, Paravision 6.1, Jmrui, Tarquin, Horos, 3DSlicer.

At Radiobiology Lab – Corso Calatafimi 414 :

- Cell cultures and imaging: Incubator 37°C 5%CO2, Biohazard laminar flow biological hood equipped with UV for cells, Thermostated bath, electrophoresis cells for sds page, transblot machine, inverted digital microscope, cell counter, 2 centrifuges with adapters, fluorescence 4-color/transmitted light and color applications, ChemiDoc MP Imaging System with accessories. Other small laboratory equipment (e.g. scales, aspirator, sonicator,..).
- Radioprotection and radioactivity detection: Chemical hood with edge for shielded vision and cabin for acids, bases and flammables, Comecer safe for radiopharmaceuticals, Plexiglass screen for Comecer beta emitters, Geiger counter, WIZARD 2470 gamma counter with 10 PerkinElmer detectors.
- Cryopreservation: FRIDGE +4 °C, FREEZER -20°C, FREEZER -80°C.

At Istituto Zooprofilattico Sperimentale:

- Bruker Pharmascan 70/16 (7 Tesla).
- IVIS Spectrum Advanced pre-clinical optical imaging.
- microCT Skyscan 1276 CMOS Bruker.

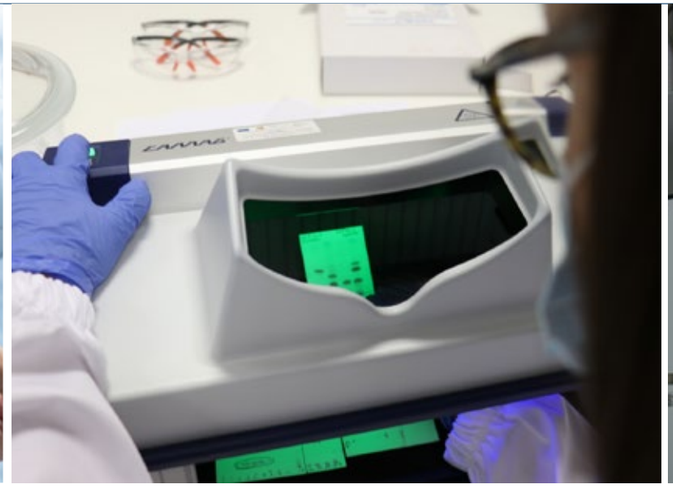
At IRCSS ISMETT

- GE DISCOVERY MR 750 W 3 Tesla High-Field Magnetic Resonance.

At Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR):

- PET/CT Clinical and Preclinical.

Medicinal Chemistry
PLATFORM



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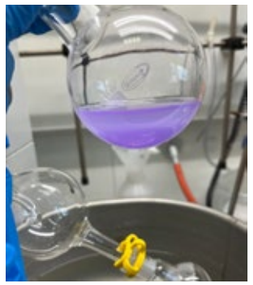
PARTNERSHIPS AND COLLABORATIONS
- University of Palermo, Palermo, IT

The Medicinal Chemistry platform supports the early drug discovery campaigns, with the hit structure confirmation, hit re-synthesis, hit series expansion and optimization, hit-to-lead activities.

The main expertise covers the design, planning and the optimization of the synthetic routes, the purification, isolation, and the analytical characterization of the newly synthesized compounds. Furthermore, structure-activity-relationship (SAR) studies allow to explore the chemical space of the hits to better define the *in vitro* biological profile. The platform is fully equipped for reactions set-up, work-up and purification of complex mixtures; and for the isolation, structure characterization, and standard purity grade assessment of the title compounds.



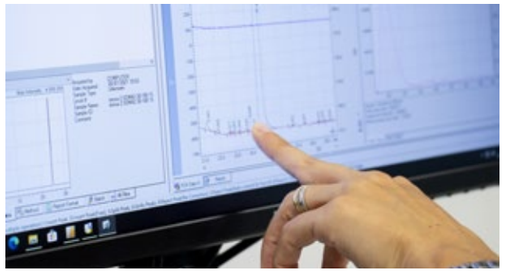
EXPERTISE
- Drug design.
- Synthetic routes planning, development and optimization.
- (Microwave-assisted) organic chemistry.
- Purification of complex mixtures on normal and reverse phase.
- Isolation of title compounds.
- Structure elucidation and analytical characterization.
- Purity grade assessment.

TECHNOLOGY PLATFORM
- Milli Q-3, Merck: Water purifier system for the production of pure and ultra-pure water needed for analytical applications.
- Isolera One, Biotage: Flash chromatography apparatus for the isolation (on normal and reverse phase) of the compounds of interest, starting from complex reaction mixtures.
- Nexera, Shimadzu: High-performance liquid chromatography (HPLC) platform for semi-preparative applications and purity grade assessment.
- LC-MS 2020, Shimadzu: Liquid chromatography-mass spectrometry platform for reactions monitoring and analysis of complex mixtures.
- Discover 2.0, CEM: Microwave reactor for homogenous and heterogenous catalytic transformations.
- Lyovapor L-200, Büchi: Lyophilizer for in vacuo drying, preserving the stability and integrity of the samples.

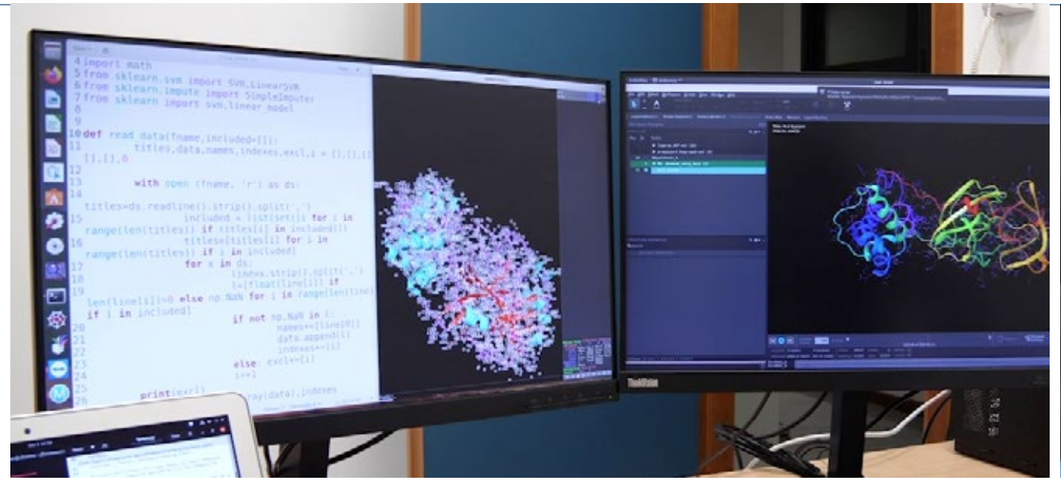
Implementation:
- H-Cube Mini-Plus, StepBio: Flow reactor for catalytic hydrogenations, able to safely generate high-pressure hydrogen via the electrolysis of water.
- Glass oven B-585 drying, Buchi: Benchtop equipment for removal of traces of solvents, combining the use of mild temperatures and vacuum, preserving the integrity of the samples.

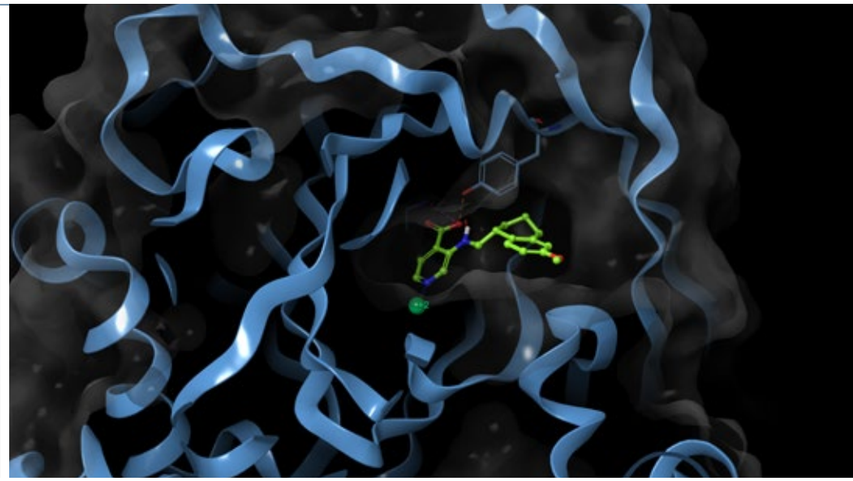
ACTIVE RESEARCH PROJECTS
Development of selective inhibitors of NOD-like receptor family, pyrin domain containing 3 (NLRP3), as potential anti-inflammatory compounds.

Design and synthesis of new Sirtuin-6 (Sir6) inhibitors, a validated target for lymphoma treatment.



Molecular Informatics
PLATFORM





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PARTNERSHIPS AND COLLABORATIONS
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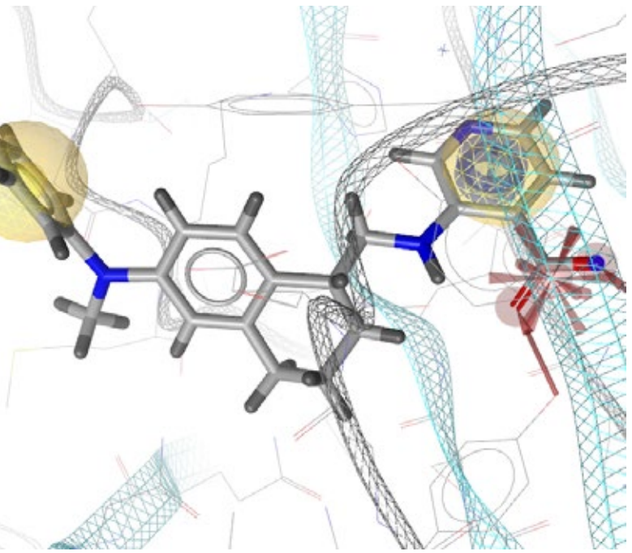
- Italian National Council of Research (CNR)
- University of Verona
- University of Paris Citè
- University of Palermo



The Molecular Informatics platform mainly deals with the identification and optimization of biologically active molecules through the use of *in silico* techniques.
The approaches used range over classical molecular modeling techniques for virtual screening to the combination of modern chemoinformatics in house developed tools.
The expertise acquired by team members is synergistically exploited for the creation of molecular libraries, creating and validating reliable theoretical models to be used for subsequent virtual screening of ligands (VLS). The molecular informatics platform is also involved in the exploration and enrichment of the chemical space to create the most suitable molecular libraries to be used for biological screening campaigns. In recent years, the collaboration with different academic groups from University of Palermo and Vienna allowed the development of approaches based on the use of deep learning for the activity prediction of small molecules. The compound management system, a part of the Molecular informatics platform, allow to automatically prepare screening plates starting from a list of in-house molecular libraries based on the virtual screening campaigns.

ACTIVE RESEARCH PROJECTS
- Development of selective inhibitors of NOD-like receptor family, pyrin domain containing 3 **(NLRP3)**.
- Machine learning-based drug repurposing of **Kinases** inhibitors.
- Design of protein-protein interaction modulators
- Role of Air pollutans in neurodegenerative diseases
- Computer-aided molecular design of DNA and RNA G-quadruplexes stabilizers.

EXPERTISE
- Structure based virtual screening (Docking and Pharmacophore).
- Ligand Based virtual screening (pharmacophore, molecular descriptors based models, QSAR and 3D QSAR).
- Molecular Dynamics.
- Dynamic pharmacophore (hybrid technique based on the use of pharmacophores from the molecular dynamics trajectory).
- Chemical Database creation and management .
- Chemical data mining.
- Machine Intelligence in Drug Design.
- Compound Management (plates design and preparation).

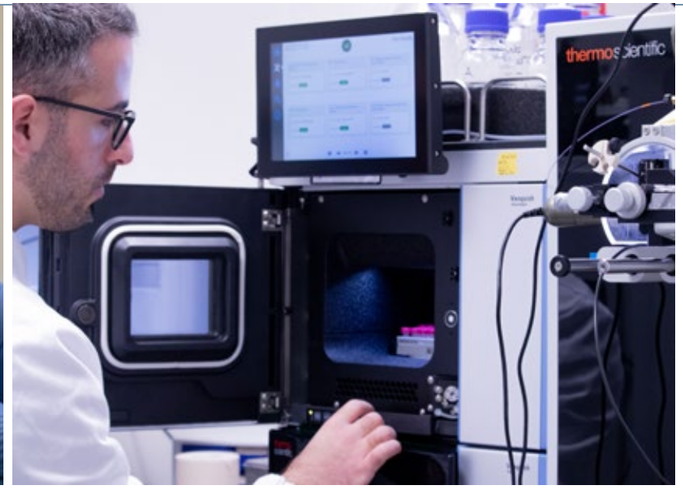
TECHNOLOGY PLATFORM
Software
- Schrödinger suite for small molecule drug discovery
- Schrödinger suite for biologics drug discovery
- LigandScout expert suite
- Autodock and Autodock Vina
- AlvaDesc/AlvaModel
- DESMOND (OPLS2005 and OPLS3e, OPLS4)
- AMBER
- NAMD
- VMD
- GROMACS
- KNIME

Hardware
- 6 Workstations
- Server: 80 cores e 2 x NVIDIA Tesla K80
- Server: 96 cores e 2 x NVIDIA A100
- Hamilton compound storage (up to 80K compounds)
- Hamilton liquid handler for plates preparation

Calculation capability:
- Library optimisation → ~ 6,000 molecules/min
- Virtual Screening HTVS → ~ 5,000 molecules/min
- Virtual Screening SP → ~ 1,500 molecules/min
- Molecular Dynamics → ~ 200 ns/day/Card (on 40,000 atoms system)

Integrated in Silico Platform
The group is actually working at the creation of an integrated platform for molecular network analysis in collaboration with the Bioinformatics group.

Proteomics
PLATFORM



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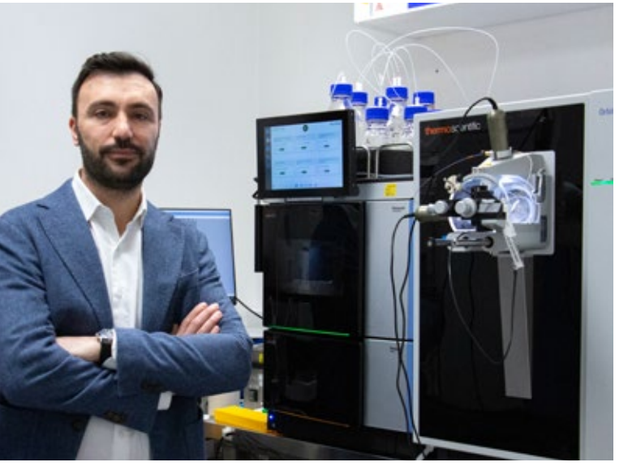
- University of Surrey, UK
- St. George's, University of London, UK
- University of Nottingham, UK
- Università di Udine, IT
- University of Padova, IT
- University of Palermo, IT
- IRIB-CNR, Palermo IT



The proteome is the entire set of proteins that is expressed by a cell, tissue or organism. The systematic high-throughput analysis of proteomes, known as proteomics, enables the identification of proteins and their relative content within biological samples. Furthermore, proteomics allows quantification of differentially regulated proteins across multiple conditions. Proteomics has broken through over the past decade with the evolution of several approaches, mainly mass spectrometry-based technologies for large-scale study of proteins. Proteomic applications in preclinical and clinical research are numerous. They span from identification of novel potential drug targets, to discovery of disease-associated biomarkers and prediction of drug-dependent side-effects.

Ri.MED has established a state-of-the-art proteomic platform, comprising a full-equipped laboratory for biochemistry and molecular biology, tissue culture facilities and a Vanquis Neo uHPLC system connected to an Orbitrap Exploris 480 mass-spectrometer, and an UltiMate 3000 RS LCnano System on-line coupled to a Q-exactive mass spectrometer, that allow top-level quantitative proteomic analysis. In details, this technology allows the chromatographic separation of different peptides derived from the proteolytic digestion of complex protein mixtures, electrospray ionization of such peptides and their fragmentation into a number of ions with a specific pattern of different mass/charge ratios, called mass spectra, that are a unique signature of each peptide. Mass spectra get computationally analyzed to infer each single protein contained in the starting mixture. Moreover, Ri MED instruments and the dedicated software allow quantitative proteomics, by which is not only possible to identify the unknown proteins of a biological samples, but also to quantify levels of the same protein in different biological samples.

In addition to support the forefront scientific research at Ri.MED, our proteomic platform aims to provide high-standard quantitative proteomic analysis for external research groups on collaborative basis, thus becoming a benchmark for the whole scientific research in the area.

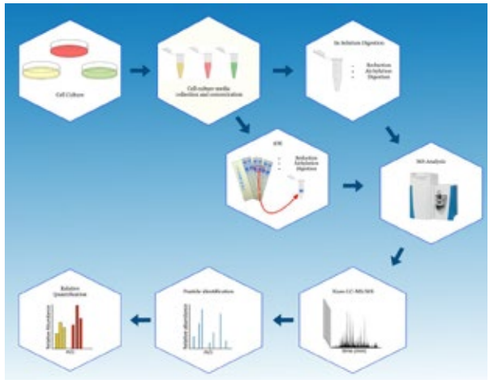
EXPERTISE
- Structure based virtual screening (Docking and Pharmacophore)
- Protein concentration from conditioned media
- Spectrophotometric Measurement (Bradford, BCA, micro BCA)
- Precipitaion and sample chemical processing
- In solution and in gel proteolysis
- Filter-aided sample preparation (FASP)
- STAGE (STop And Go Extraction) TIPS sample desalting
- Sample CleanUp
- pH fractionation
- Secretome protein enrichment with click sugars (SPECS)
- Label free quantitative proteomics
- Western Blot
- SDS-PAGE
- Quantitative and qualitative analysis of predicted and / or annotated proteins by liquid chromatography tandem mass spectrometry (LC-MS / MS) with Bottom Up and Shot-gun approaches.

Generalized mass spectrometry based proteomic workflow

TECHNOLOGY PLATFORM
The unit is equipped with:

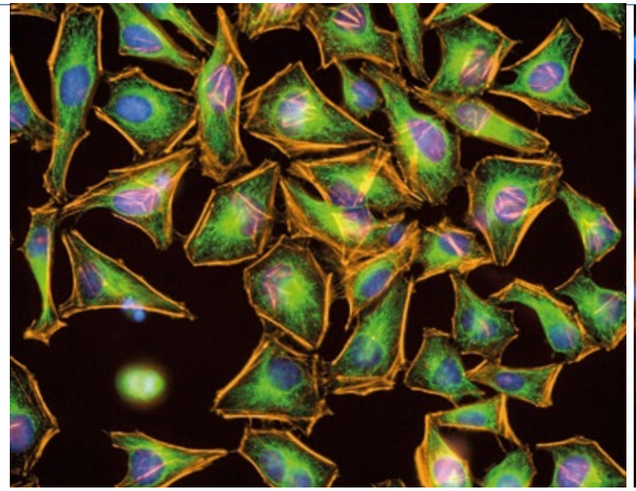
Hardware devices:
- Ultra-High Performance Liquid Cromatography: Vanquish Neo uHPLC, UltiMate 3000 UHPLC RSLC-nano System (Thermo Scientific).
- Mass Spectrometers: Exploris 480 and Q-Exactive (Thermo Scientific)

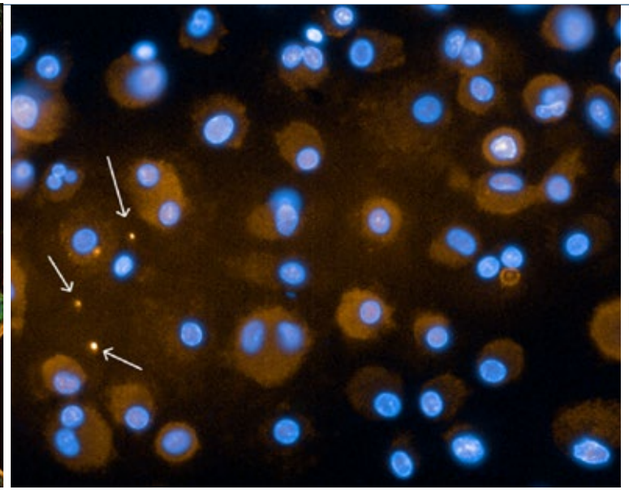
Software devices:
- Chromeleon
- Xcalibur
- Proteome Discoverer
- MAX QUANT
- DIANN
- Perseus for statistical analysis

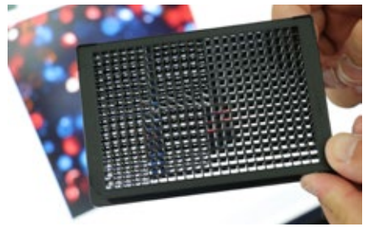


Screening

PLATFORM







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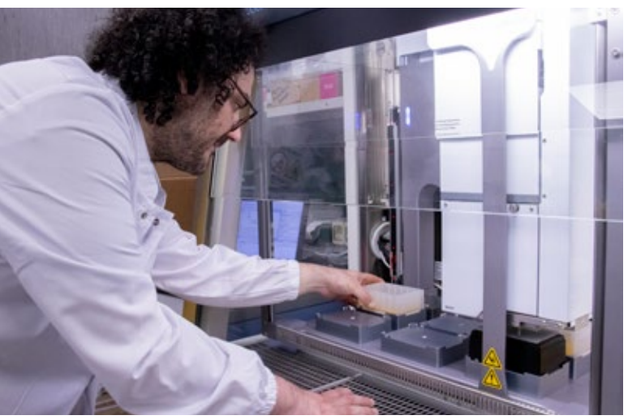
PARTNERSHIPS AND COLLABORATIONS

- Institut de la Vision, Parigi, FR
- University of Campania "Luigi Vanvitelli", IT
- University of Bologna, IT
- National Research Council (CNR), IT

The screening platform provides labs and expertise for the development, miniaturization and validation of biochemical and cellular assays for the screening of libraries of small molecules. Our instrumentation allows the setup of flexible and partially automated protocols using a variety of readouts including absorbance, luminescence, fluorescence, TR-FRET, and imaging. Our lab is equipped with a high-content screening (HCS) system combined with software for image analysis and data evaluation. The platform supports Drug Discovery projects by performing both primary screening as well as dose-response curves, orthogonal and secondary assays.

ACTIVE RESEARCH PROJECTS

Discovery of selective inhibitors of the NOD-like receptor protein 3 (NLRP3) inflammasome for the treatment of chronic inflammatory diseases.

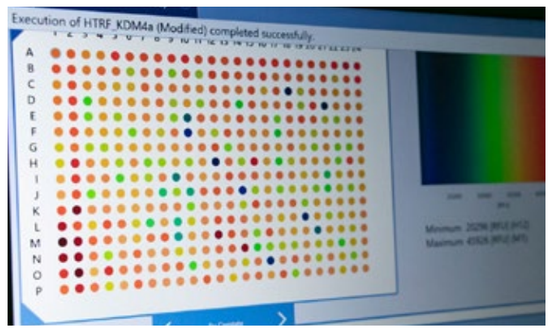


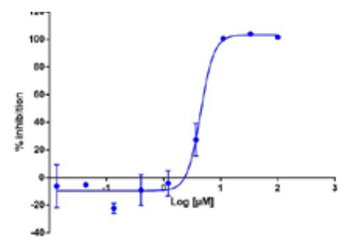
EXPERTISE

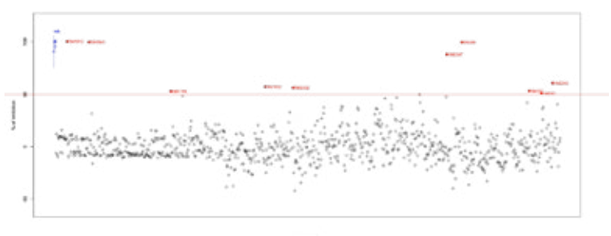
- Set-up and validation of primary assay (cell-free and cell-based);
- Different readouts possible including absorbance, luminescence and TR-FRET;
- Assay miniaturization (384-well plates);
- High-content imaging (HCI);
- Screening/high-content screening (HCS);
- Data analysis and primary active selection;
- Orthogonal and secondary assays;
- Toxicity tests.

TECHNOLOGY PLATFORM

- Wet lab for cell and molecular biology;
- In-Hood-Bravo (Agilent) - liquid handling system;
- Spark (Tecan) - multimode microplate reader;
- Incucyte® S3 (Sartorius) Live-Cell Analysis System;
- EL406 (Biotek) – automatic microplate washer/dispenser;
- Aquamax 4000 (Molecular Devices) – automatic microplate washer for gentle cell washing;
- Operetta-CLS (Perkin Elmer) –high-content imaging (HCI) system;







Structural Biology and Biophysics
PLATFORM

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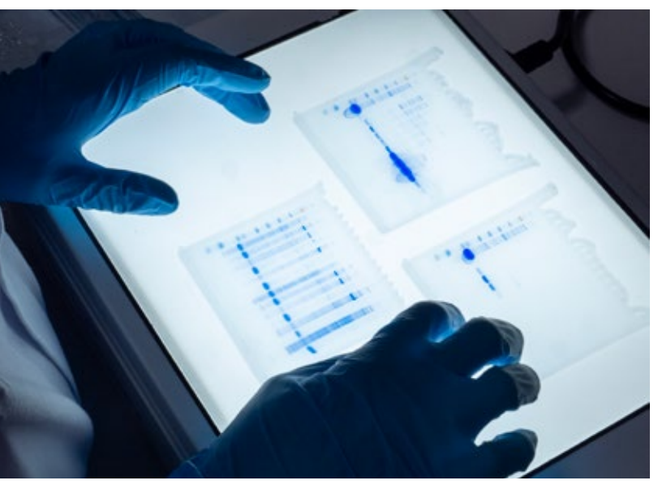
PARTNERSHIPS AND COLLABORATIONS

- King's College London
- European Brain Research Institute Rita Levi-Montalcini, Roma, IT
- Università degli studi della Campania "Luigi Vanvitelli", Naples, IT
- University of Palermo, IT
- Institute of Biophysics of the Italian National Research Council (IBF-CNR), Palermo, IT
- International Covid-19 NMR Consortium

The Structural Biology and Biophysics Platform provides support for target identification, small molecules-based drug discovery, and development of protein-based therapeutics with particular focus on therapeutic antibodies.

The platform is supplied with cutting-edge equipment that allow a multi-techniques approach, such as nuclear magnetic resonance, circular dichroism, calorimetry, and interferometry. The available technologies allow elucidating of the structure/function relationship of proteins, as well as structural, kinetic and thermodynamic studies of protein-protein and protein-ligand interactions.

The Platform supports several research projects in several therapeutic area such as Neurodegenerative diseases, Cancer, and Infectious diseases. The diversity of all the active research projects well represents the potential of the Platform which can be used for basic research as well as translational science and can support transversally several research activities.



EXPERTISE

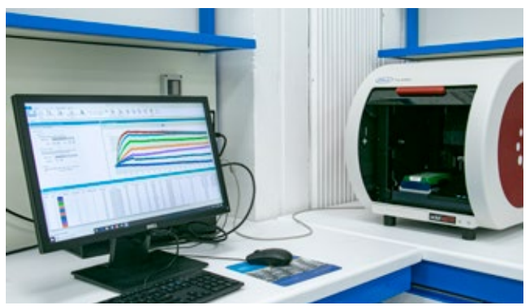
- Proteins Production: from cloning to purified and characterized proteins.
- Determination of size, structure and stability of macromolecules.
- Structural, kinetic and thermodynamic studies of protein-protein and protein-ligand interactions.
- BLI-based and NMR-based fragments screening.
- Development and application of customed analytical assays.

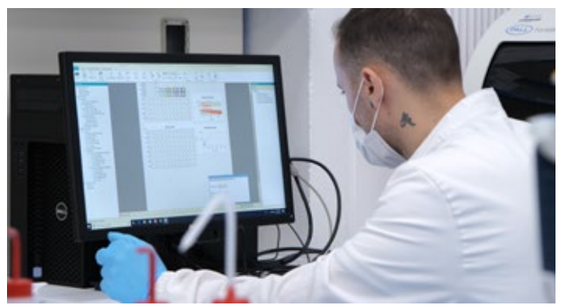
TECHNOLOGY PLATFORM

- Molecular biology laboratories for the production of recombinant proteins according to the most modern cloning, expression and purification techniques.
- AVANCE NEO 800 MHz NMR spectrometer equipped with cryo-probe – Bruker.
- MicroCal PEAQ_ITC – Malvern Panalytical.
- Bio-Layer Interferometer Octet Red96 – Sartorious.
- CD Spectropolarimeter J-1500 – JASCO.
- Multi-mode high-performance Microplate Reader CLARIOstar Plus – BMG Labtech.

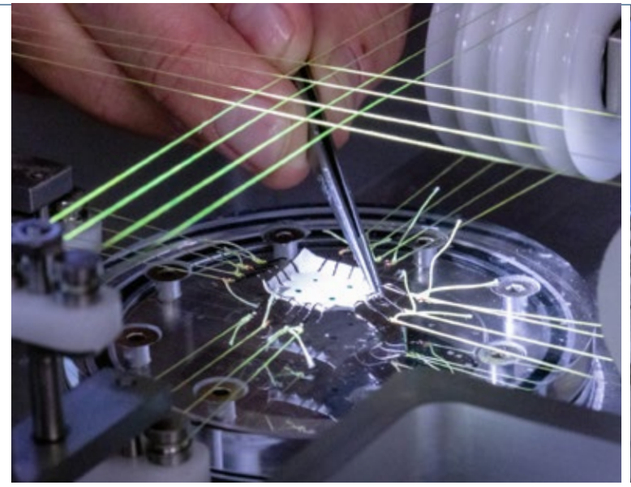
ACTIVE RESEARCH PROJECTS

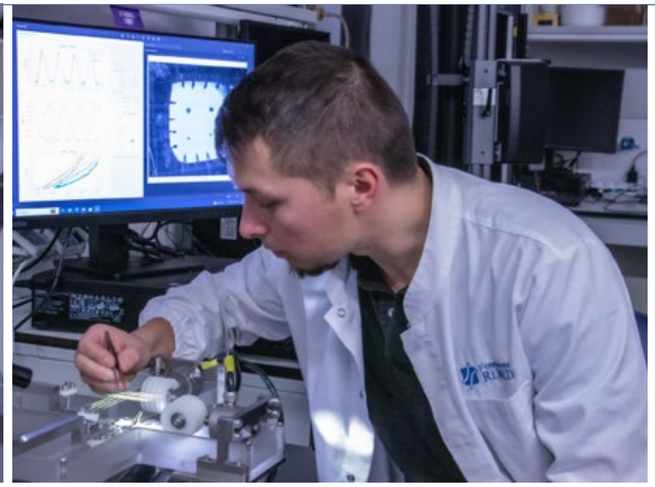
- Characterization of selective inhibitors of NOD-like receptor family, pyrin domain containing 3 (NLRP3).
- Identification of KDM4A inhibitors.
- BLI- and NMR-based fragment screening.
- Biophysical and structural characterization of antigen-antibody interaction.
- Identification and characterization of interactions among SARS CoV-2 RTC and host proteins.
- Molecular mechanisms of protein misfolding diseases.
- Development of nontoxic bio-adhesives for wet environments.





Tissue Engineering
PLATFORM





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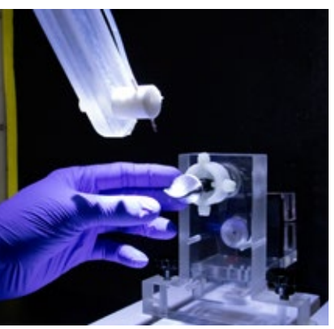
PARTNERSHIPS AND COLLABORATIONS

- University of Palermo, Palermo, Italy
- Advanced Technologies Network Center (ATeN Center), Palermo, Italy
- McGowan Institute for Regenerative Medicine (MIRM), Pittsburgh, USA
- University of Pittsburgh Medical Center (UPMC), Pittsburgh, USA
- The Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT-IRCCS), Palermo, Italy
- Universidad Abierta Interamericana (UAI), Buenos Aires, Argentina
- Neoolife, Pittsburgh, USA
- TELEA BioTech, Sandrigo, Italy
- Columbia University Irving Medical Center (CUIMC), New York, USA
- Technical University of Munich, (TUM), Munich, Germany
- University of California Irvine (UCI), Irvine, USA
- Eindhoven University of Technology, Netherland
- Politecnico di Torino, Italy

The Tissue Engineering Platform aims at establishing a world class and financially sustainable tissue engineering program at Ri.MED with a focus on clinical translation. The interest of this research platform is upon clinical applications where few effective solutions exist, with an emphasis upon unmet clinical needs in cardiovascular diseases. The bioprocessing and tissue engineering core platform, in the process of being developed, offers disruptive tools for prototyping and assessing advanced scaffolds and biomaterials for tissue engineering applications.

The platform aims to address a broad spectrum of needs within the IRCCS-ISMETT, UPMC Italy and Ri.MED cluster as well as it aims to push forward collaborative efforts with investigators at the McGowan Institute, and Pitt departments of bioengineering and surgery.



EXPERTISE

- Advanced bio-fabrication.
- Polymer Synthesis.
- Decellularization of organs and tissues.
- Mechanical, physical, and chemical characterization of native and engineered tissues.
- Qualitative and quantitative histological evaluation of native and engineered tissues.
- Formulation and characterization of controlled drug release medical devices.
- *In silico* and *in vitro* mechanobiology models.
- Structural deterministic models for tissue growth and scaffold degradation.
- Pre-clinical evaluation in small and large animal models.
- Numerical simulation of physiological systems and their integration with medical devices.
- FDA class II and III medical devices prototyping.

TECHNOLOGY PLATFORM

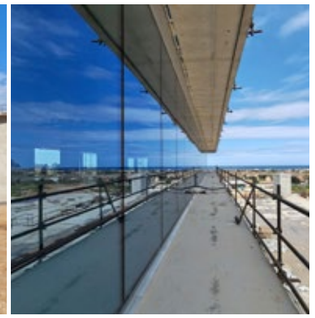
- Extraction of ExtraCellular matrix from organ and tissue to produce bio-hybrid medical devices such as cardiac patches, esophageal and vascular grafts.
- Numerical codes for the development of simulation models of physiological and predictive systems.
- Numerical models to predict de novo tissue growth, native tissue remodeling, and polymeric degradation.
- Numerical simulation of physiological systems and their integration with medical devices.
- Software for quantitative histology analysis.
- Software for qualitative and quantitative analysis of microstructure from scanning electron microscopy and multi-photon images.
- Innovative methods of morphological analysis of micro and nanostructured materials.
- Bio-assembly Robot for the development and optimization of engineered heart valves.
- Electrodeposition equipment with and without mandrel.
- Design and development of bioreactor.
- Prototyping unit with Plastic and Metallic 3D Printers.
- Mechanical characterization of the tissue engineered prosthesis including cardiac patches, vascular grafts, and heart valves.

ACTIVE RESEARCH PROJECTS

- Design and development of a minimally invasive cardiac patch implantation system.
- Design of a prototype esophageal graft.
- Development and evaluation of conductive cardiac patches.
- Manipulation of the scaffold microarchitecture in collaboration with the company Telea Biotech.
- Study of the tissue growth, native tissue remodelling and polymeric degradation.
- Redesign electrospun scaffold microarchitecture.
- Development of a bioengineered chordal apparatus for heart valve repair.
- Development of a 3-layer vascular graft to limit hyperplasia of the intima and promote re-endothelialization.

WORK IN PROGRESS






BRBC

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