Iniziative PNRR nella Facoltà di Farmacia e Medicina.
Rome Technopole, Centri Nazionali e Partenariati estesi – 16/01/2025

Rome Technopole

- Il contributo del Dip. Fisiologia e Farmacologia
- Il contributo del Dip. Medicina Molecolare
- Il contributo del Dip. Chimica e tecnologie del Farmaco
- Il contributo del Dip. Scienze Biochimiche
- Il contributo del Dip. Scienze e Biotecnologie medico-chirurgiche

PNRR Salute: M6/C2 - Innovazione, ricerca e digitalizzazione del servizio sanitario nazionale

- Presentazione e contributo del Dip. Fisiologia e Farmacologia

PNC Salute/D34 - Health Digital Driven Diagnostics, pronostics and therapeutics for Sustainable Health care

- Il contributo del Dip. Fisiologia e Farmacologia
- Il contributo del Dip. Scienze Anatomiche, Istologiche, Medico-legali e dell'Apparato Locomotore
- Il contributo del Dip. Chirurgia Generale e Specialistica

Centro Nazionale 3 - National Center For Gene Therapy & Drugs Based On Rna Technology

- Presentazione
- Il contributo del Dip. Fisiologia e Farmacologia
- Il contributo del Dip. Medicina Molecolare
- Il contributo del Dip. Chimica e tecnologie del Farmaco
- Il contributo del Dip. Scienze Biochimiche
- Il contributo del Dip. Scienze Anatomiche, Istologiche, Medico-legali e dell'Apparato Locomotore

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Iniziative PNRR nella Facoltà di Farmacia e Medicina:

Dipartimento di Fisiologia e Farmacologia «V. Erspamer».

Rome Technopole, FP7: Metabolomics and biomarker discovery for neurological, neurodegenerative and inflammatory disorders

Foto: Stefania Sepulcri (Stampa e comunicazione)

Department contribution

1) ***C. Babiloni*** *Research, Open Lab Platforms, and High Formation on Neurophysiological Biomarkers of Wake and Sleep Regulations in Neurological Disorders*
2) ***L. Saso*** *CIVIS High Formation on Neurophysiological Biomarkers of Wake and Sleep Regulations in Neurological Disorders*
3) ***G. Esposito, P. Campolongo*** *Advanced and automated innovation labs for diagnostic and therapeutic biopharma solutions*
4) ***S. Gaetani, M. Friuli*** *Study of Oleoylethanolamide as a potential pharmacological target for the treatment of obesity and eating disorders*
5) ***C. Limatola*** *Platform for the study of drug permeability across the blood brain barrier (BBB): focus on gut-brain biomarker discovery in inflammatory/neurodegenerative diseases in preclinical settings*
6) ***D. Ragozzino, B. Basilico*** *Understanding gut brain interactions in preclinical animal models of peripheral inflammation*

Specific aims

Main aim To contrast pathological brain aging with dementia, neurodegenerative diseases with an inflammatory component, brain tumors, eating disorders, and behavioral disorders related to post-traumatic stress.

HOW

Through the creation of **technological platforms**

(integrated with the industry)

Open siesta lab: to validate EEG markers and digital tools for home telemonitoring (Sentech, Sogetel) (https://smartme.cloud.garr.it/).

Smart probiotics: to synthesize neuroprotective lipids in an eco-friendly manner, with therapeutic applications for metabolic and neuropsychiatric diseases

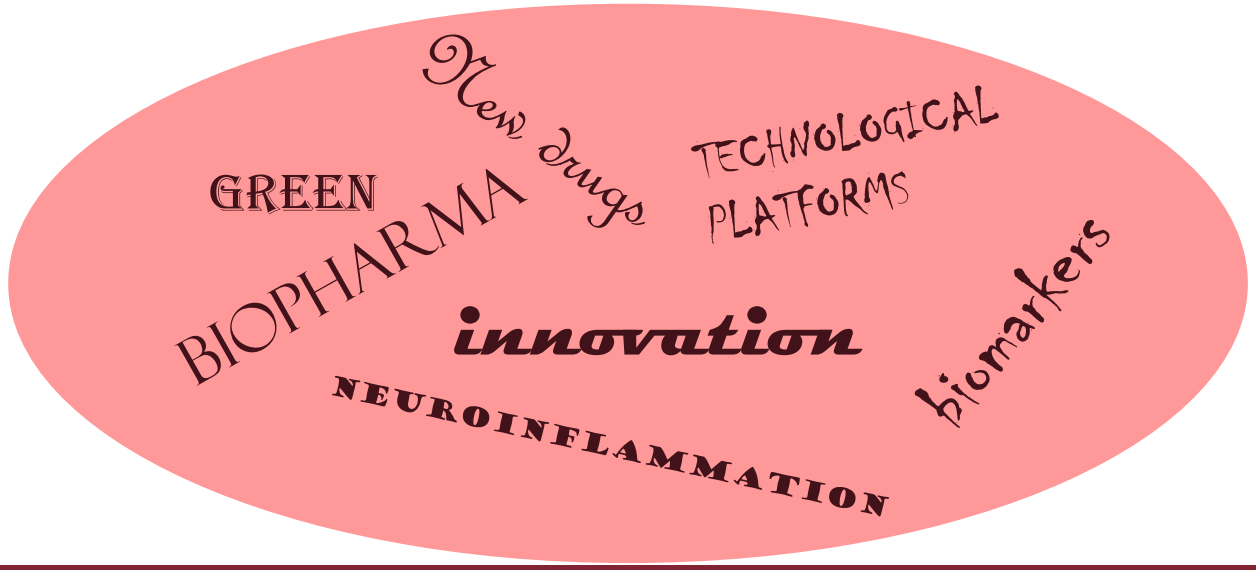
BBB lab: to study new drugs for their effects on the CNS (Takis)

Expected results in line with the PNRR pillars

- Identification of **biomarkers** for the early diagnosis of dementia or cognitive deficits through telemonitoring

- **Produce new drugs** in an eco-friendly way, reducing environmental impact

- Development of a technological platform to **test new drugs** for their effect on the central nervous system



Expected impact and beneficiaries

By the end of the Rome Technopole project (**short-term**)

Creation of multiple permanent nodes in the Lazio biotechnology and bio-pharma innovation ecosystem (**medium-term**)

Increase in knowledge for further therapeutic developments (**long-term**)

Impact on

Citizens (early diagnosis of neurological diseases)

Fragile individuals (telemonitoring)

National Health Service (digitalization and green, targeted care)

Care centers (greater treatment effectiveness)

claudio.babiloni@uniroma1.it
giuseppe.esposito@uniroma1.it
cristina.limatola@uniroma1.it
patrizia.campolongo@uniroma1.it
luciano.saso@uniroma1.it
davide.ragozzino@uniroma1.it
silvana.gaetani@uniroma1.it

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
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Iniziative PNRR nella Facoltà di Farmacia e Medicina.

Realization and application of an innovative CMOS- optical based Biosensor for the Early and Rapid Self- Detection of Cardiovascular Biomarkers of Vital Interest

C.O.S.E.D.H.: CMOS, Optical, Sensor, Early, Diagnostic, Heart)

Prof.ssa Elisa Messina

Foto: Stefania Sepulcri (Stampa e comunicazione)

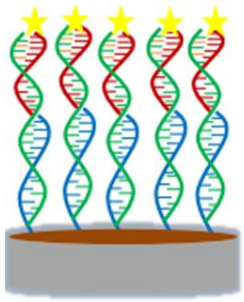
•**Unsolved problem**: Cardiovascular electronic devices (CEDs, implantable or wearable devices), monitoring the cardiac electric activity at **terminal event.**

•With the **hypothesis** that a self-manageable, easily available and costless tool for monitoring strategic **standard biomarkers** in cardiac diagnostics, could capture an **essential biological window of the early stages of an incoming acute heart failure event**, a low cost, point of care device could prevent a huge number of serious cases that, otherwise, cannot be treated effectively,

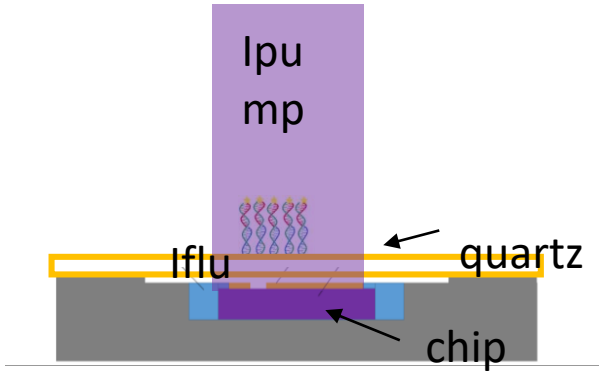
•**our main goal** is to provide accurate and rapid diagnosis through the use of a **costless electronic device**, who's **the innovation lies in the realization of a fluorescence detector coupled to a commercial silicon CMOS technology, elicited by the contact of chip with any easily available biologic fluid (saliva, blood drop), by separating it from the pump radiation, without the need to apply complex and expensive optical filtering systems**.

CMOS Image Sensor

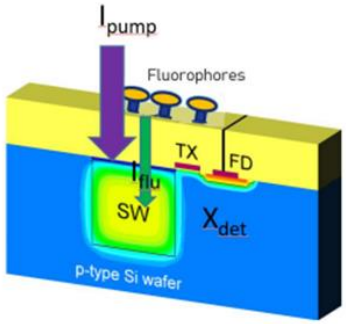
The device is **a lab-on-chip system potentially capable of performing ELISA assays through the specialization of complementary metal-oxide semiconductor (CMOS) Image Sensors (CIS)**. The fluorescence emission is read by the solid state amplified sensor, and the result analyzed. This system should have an **increased sensitivity** (up to 0.1 nM of conjugated streptavidin solution has currently been demonstrated) and **decrease production costs as compared to other available biosensors or standard (ELISA or PCR) techniques**



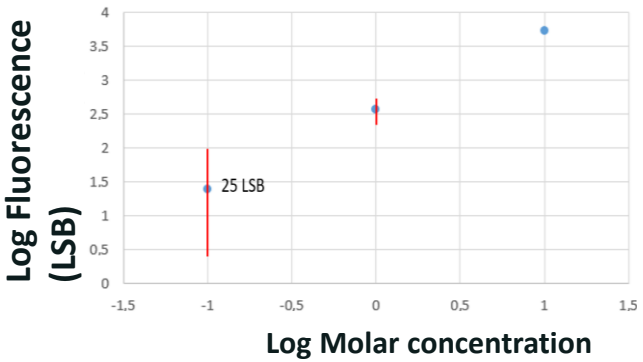
Functionalization on quartz slides to be placed upon the package.



Both the excitation light, and the fluorescence light reach the semiconductor.



The gap between the spectrum of the laser and the emission of fluorescence, permits to design the structure of the semiconductor and dielectric layer on the back end of the CIS such as to capture only proper wavelength arising from the detected sample. The captured light is then converted into current.



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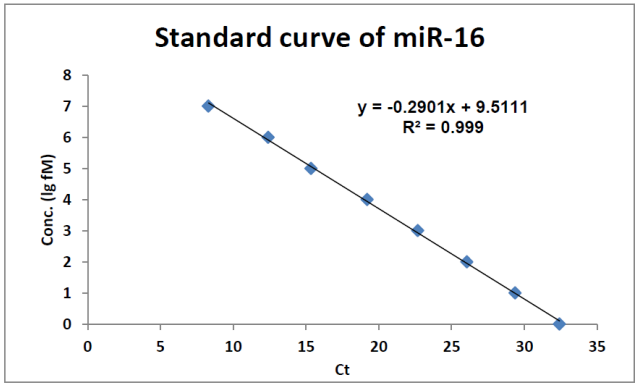

Quartzes functionalized with Qdot 655 have been tested using standard solution samples with fluorophores, 10nM, 1nM, 0.1nM

Use of CMOS Image Sensor as efficient low cost fluorescence detector, F. Palma, F. Michelotti, Eurosensors 2023

Comparison with qRT-PCR Results. The proven sensitivity is equivalent to 15 cycles of PCR. The colored band indicates the concentrations tested

Wei, Hui, et al. "Detection of circulating miRNA levels in schizophrenia." American Journal of Psychiatry 172.11 (2015): 1141-1147.

Applications

- Achieve a new tool for faster biomarker identification and analysis (no sample preparation, high sensitivity without amplification analysis),
- Achieve a new tool centered on personalized biomedical diagnosis (synergy between physicians and biologists, tele-expertise).
- Potential for Multi-Marker Analysis (measuring numerous markers in a single sampling and a single measurement procedure, improving diagnostic power and specificity of rapid clinical intervention and exploiting new mechanistic perspective in the development of critical events on cardiac diseases.

Perspectives

In the presence of know oncoming symptoms of an acute cardiac event, a patient could simply put any easily collectible body fluid directly in contact with the device, thus detecting any kind of biomarker, in particular, those currently considered as gold standard of the routine standard clinical protocols (such as natriuretic peptides (NP), and cardiac troponins, as a proof of concept to figure out further genetic and omics analyses

What needs to be done

The system should be tested with biological fluid-derived molecules to evaluate the detection of real markers. Up to now, the detection has been done using a known amount of fluorophores conjugated to the backend of the circuits.

Ente partner Paese

Sapienza Università di Roma (Coordinatore) Italia
LFoundry Avezzano , CORPORATE HEADQUARTER / MANUFACTURING Italia
Fondazione Rome Technopole Italia
Cardiology UMCU/CMH, Netherlands Heart Institute Netherlands
Microfluidics-Chip Shop, Stockholmer Straße 20, 07747 Jena Germany

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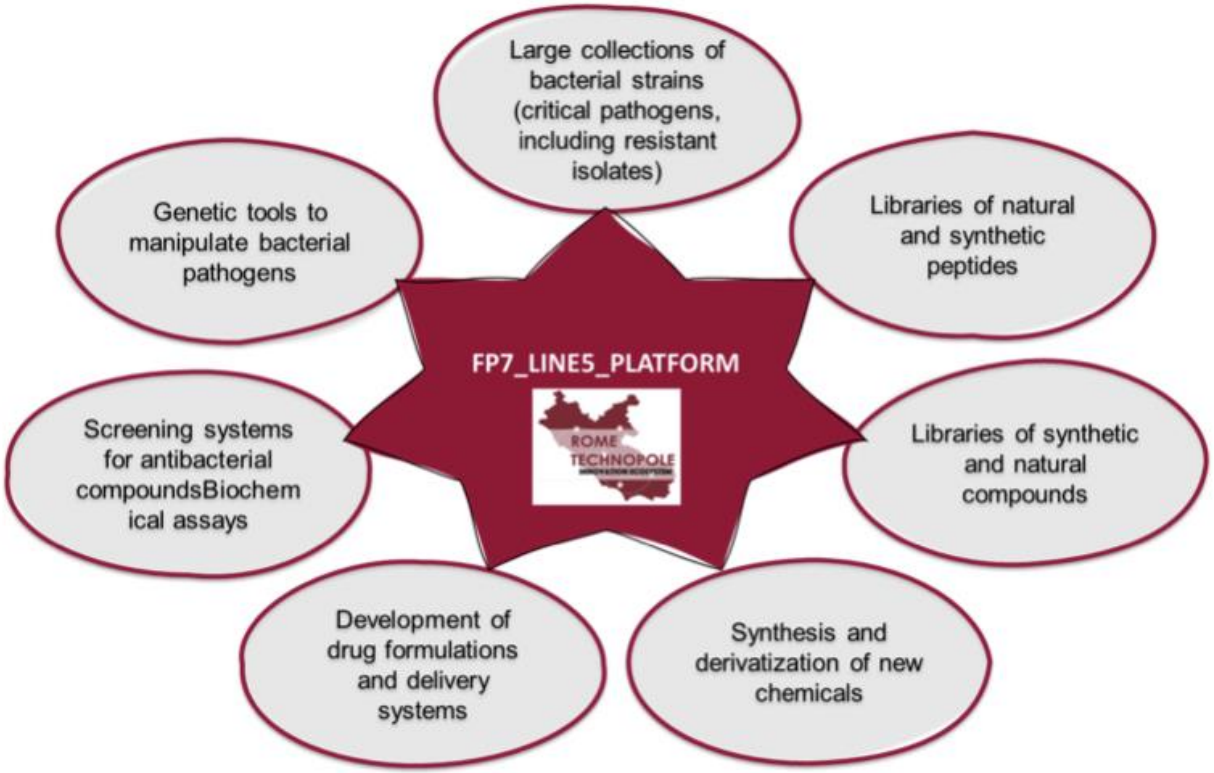
Iniziative PNRR nella Facoltà di Farmacia e Medicina.

Rome Technopole - Progetto Flagship 7

Advanced and automated innovation labs for diagnostic and therapeutic biopharma solutions -

Therapeutic and diagnostic innovation: new bio-active antimicrobials, targeted drug delivery and genomic-based approach to monitor the emergence of drug resistance

Progetto Flagship 7
Advanced and automated innovation labs for diagnostic and therapeutic biopharma solutions



- **Contributo del Dipartimento di Chimica e Tecnologie del Farmaco**

FP7 Therapeutic and diagnostic innovation: new bio-active antimicrobials, targeted drug delivery and genomic-based approach to monitor the emergence of drug resistance

SPOKE 1: Applied Research Technology Development And Innovation.
Identification Of Novel Promising Compounds As Antimicrobial Or Adjuvants Agents Or Adjuvants Agents

Dept. of Chemistry and Technology of Drugs (DP1)

- Structure-based drug design

- Rational design and synthesis of natural compound and their derivatives

-Preparation and characterization of smart nanocarriers for drug delivery and targeting (passive, active and stimuli sensitive);

-Nanocarrier optimization on the basis of way of administration, target site, biological barriers (e.g., mucus, biofilm matrix) and the evaluation of their biological activity.

Dept. of Biochemical Sciences "A. Rossi Fanelli" (DP2),

- Antimicrobial characterization of natural compounds and their derivatives, on Gram-positive and Gram-negative bacteria
- Studies on their synergistic effect with conventional drugs
- Rational design and optimization of antimicrobial peptides.
- Cytotoxicity assays (on different eukaryotic cell lines) of the selected compounds either in the free or incorporated form into designed nanosystems;
- Investigation of the mechanism of antibacterial/antibiofilm activity of hit compounds.

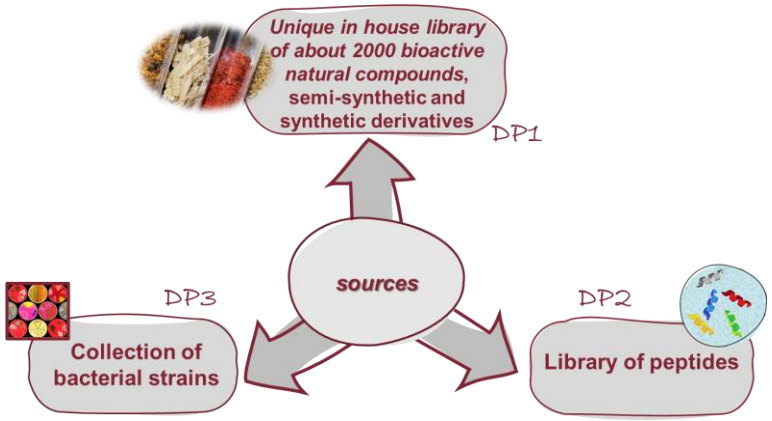
Dept. of Molecular Medicine (DP3)

- Standard panel (reference Gram+ and Gram– bacteria)

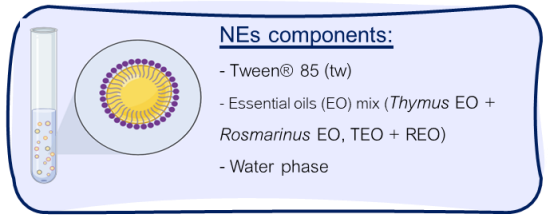
- Disease-based panel (e.g., pneumonia UTI, sepsis)

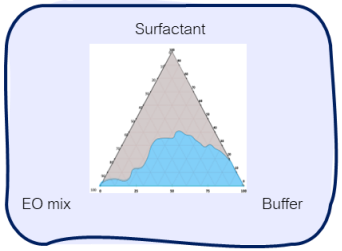
- Updated panel (new/emerging resistances mechanisms)

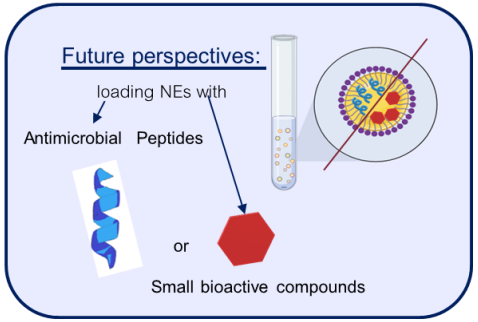
-WGS of reference bacteria



Bio-active TEO-based nanoemulsion for antimicrobial compounds delivery

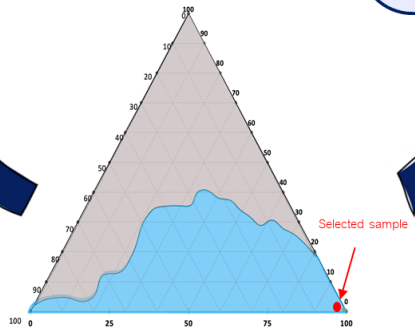


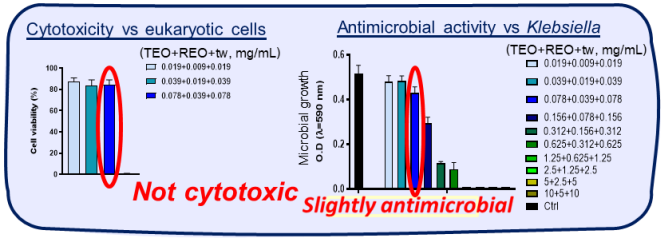




Nebulization Resistance Test

Sample	Z-average ± SD (nm)	PDI ± SD	ζ Pot ± SD (mV)
Before neb	134 ±1.29	0.22 ± 0.01	-34.4 ± 1.07
After neb	109 ± 1.56	0.26 ± 0.01	-31.4 ± 0.29





- **Contributo del Dipartimento di Chimica e Tecnologie del Farmaco**

SPOKE 3. University education, industrial PhD courses, internationalization.

Open calls for undergraduated excellent students
NELL'A.A. 2024-25 BORSE DI STUDIO ROME TECHNOPOLE PER STUDENTI E STUDENTESSE ISCRITTI A LAUREE MAGISTRALI O LAUREE MAGISTRALI CICLO UNICO DELLA FACOLTA'

Spoke 5 - Out-reach, public engagement, lifelong learning

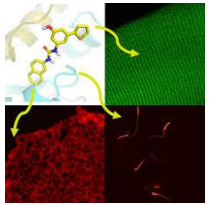
PROGETTO IN VIA DI PERFEZIONAMENTO DI CORSI INTEGRATI PER LIFELONG LEARNING SULL'ANTIOBIOTICO RESISTENZA

ATTIVITÀ DI JOB ORIENTATION, CO-DESIGN DI TRAINING ACTIVITIES CON INDUSTRIE ED ENTI STAKEHOLDERS DI ROME TECNOPOLE.

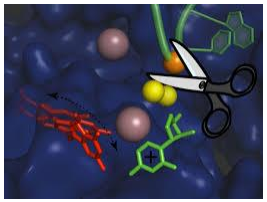
PROMOTION AND FOSTERING, VALORIZATION, DISSEMINATION, AND TRANSFER OF KNOWLEDGE, KNOW-HOW, AND TECHNOLOGIES FOR SOCIAL CHANGES

SETTEMBRE 2024 PARTECIPAZIONE A EVENTO EDUCATIVO PER DIVULGARE IL PROBLEMA DELL'ANTIBIOTICO RESISTENZA

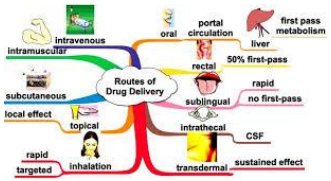
- **Obiettivi Specifici e Risultati Attesi : Linea 4 – FP7 Therapeutic and diagnostic innovation: new bio-active antimicrobials, targeted drug delivery and genomic-based approach to monitor the emergence of drug resistance**



SO1. Identificazione di candidati preclinici e adiuvanti costituiti da piccole molecole di origine sintetica o naturale in grado di ripristinare la sensibilità batterica ai farmaci antimicrobici e/o ostacolare la crescita dei batteri MDR.

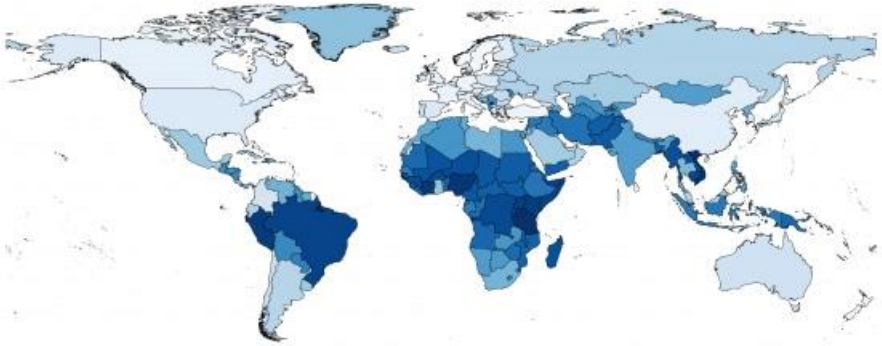


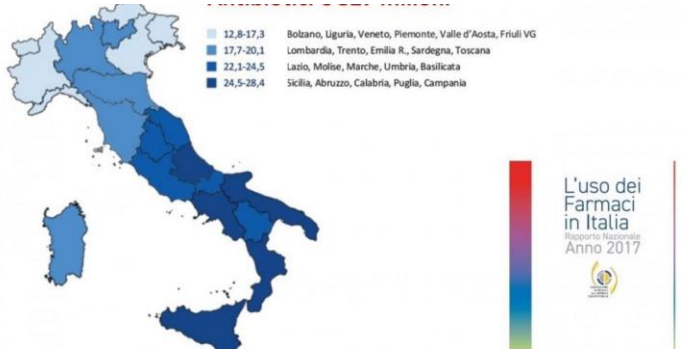
SO2. Comprensione dei meccanismi molecolari e genetici della resistenza ai farmaci a più livelli.



SO3. Sviluppo di nuove strategie di somministrazione di farmaci per ottenere una maggiore efficienza di intrappolamento delle molecole attive e buone caratteristiche fisico-chimiche tenendo conto della modalità di somministrazione.

- **Impatto previsto a breve e lungo termine, su economia, ambiente, società: Linea 4 – FP7 Therapeutic and diagnostic innovation: new bio-active antimicrobials, targeted drug delivery and genomic-based approach to monitor the emergence of drug resistance**





Beneficiari:

- Cittadini
- Studenti universitari coinvolti in tema Salute e Biofarma
- Ricercatori
- Aziende
- Enti di Ricerca

Contatti utili: Informazioni per chi volesse approfondire o collaborare con il Diparimento di Chimica e Tecnologie del Farmaco nell'ambito del progetto FP7

Attività di Spoke 1:

Francesca Ghirga francesca.ghirga@uniroma1.it
Silvia Cammarone silvia.cammarone@uniroma1.it
Carlotta Marianecci carlotta.marianecci@uniroma1.it

Attività di Spoke 3:

Daniela Secci daniela.secci@uniroma1.it

Attività di Spoke 5:

Andrea Calcaterra andrea.calcaterra@uniroma1.it

Foto: Stefania Sepulcri (Stampa e comunicazione)

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Iniziative PNRR nella Facoltà di Farmacia e Medicina.

Rome Technopole - Advanced and automated innovation labs for diagnostic and therapeutic biopharma solutions

Linea Tematica: Therapeutic and diagnostic innovation: new bio-active antimicrobials, targeted drug delivery and genomic-based approach to monitor the emergence of drug resistance

Obiettivi della Linea Tematica

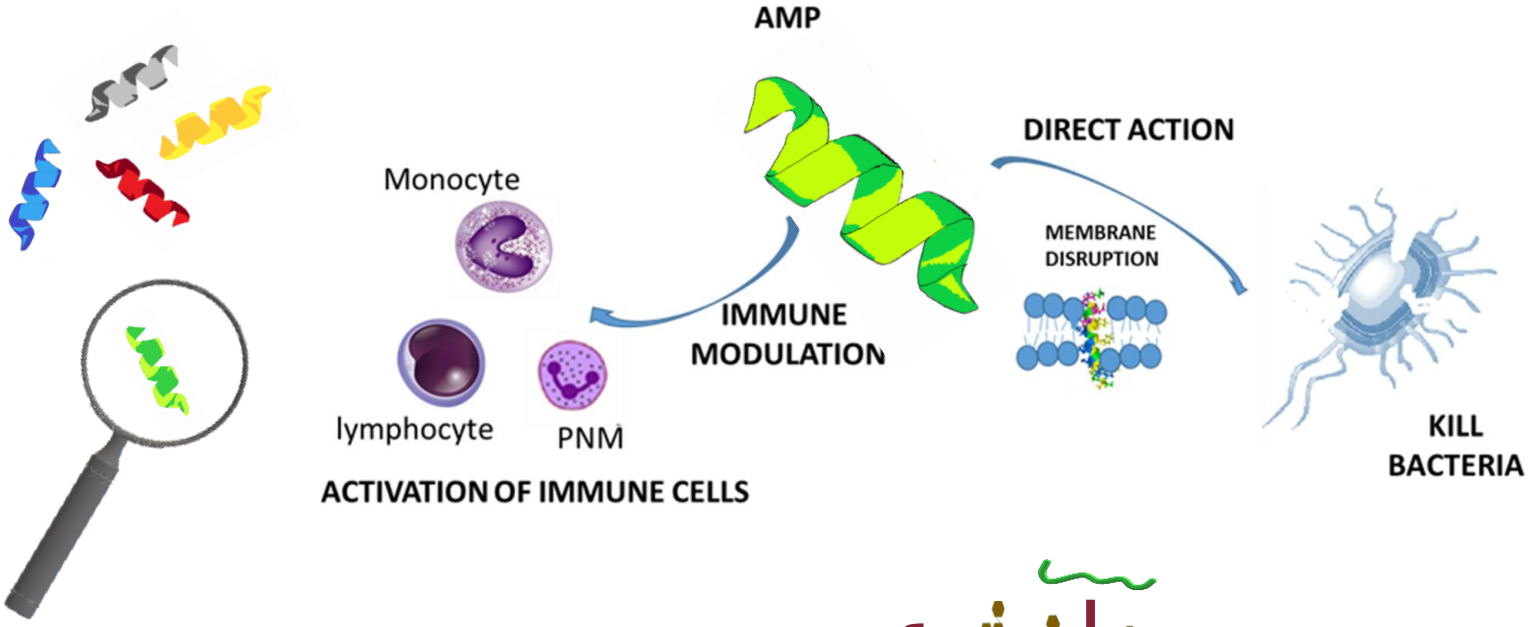
Therapeutic and diagnostic innovation: new bio-active antimicrobials, targeted drug delivery and genomic-based approach to monitor the emergence of drug resistance

1. Identification of pre-clinical candidates and adjuvants from small molecules of synthetic or natural origin capable of restoring bacterial susceptibility to antimicrobial drugs and/or impairing the growth of MDR bacteria

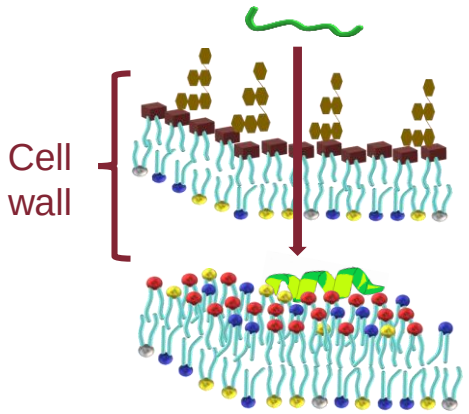
2. Understanding of the molecular and genetic mechanisms of drug resistance at multiple levels.

3. Development of novel drug delivery strategies to achieve higher active molecule entrapment efficiency, good physical chemical features taking into account the way of administration.

Contributo del Dipartimento di Scienze Biochimiche «A. Rossi Fanelli»

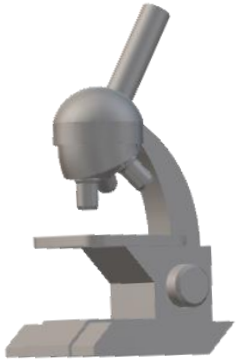


Identification and characterization of antimicrobial peptides



van der Does AM et al, *Adv Exp Med Biol*. 2019;1117:149-171

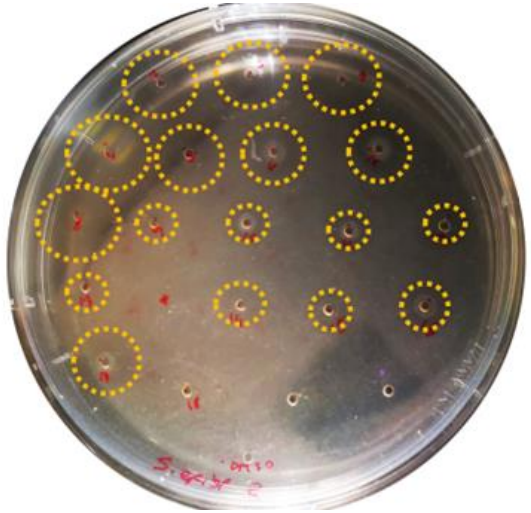
Contributo del Dipartimento di Scienze Biochimiche «A. Rossi Fanelli»



- In vitro screening for

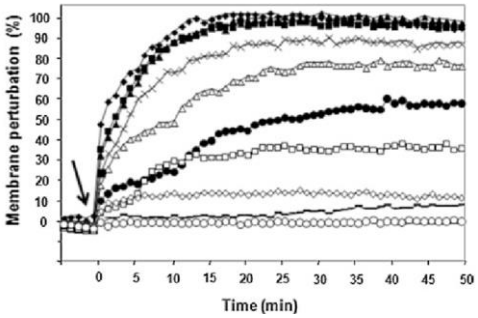
- Antimicrobial activity
- Cytotoxicity
- Mechanism of action

Microbiological assays



Colorimetric assays

Fluorimetric assays



Risultati attesi e impatto previsto

- Discovery of HIT compounds as alternative or adjuvant of conventional antibiotics

- Drug rescue
- New antimicrobial drugs
- New adjuvant drugs

IMPATTO ECONOMICO

IMPATTO SOCIALE

Contatti

- marialuisa.mangoni@uniroma1.it
- bruno.casciaro@uniroma1.it

Partecipanti Dip. Rossi Fanelli, linea tematica:

- **Maria Luisa Mangoni;**
- Bruno Casciaro;
- Beatrice Vallone;
- Francesca Cutruzzolà.

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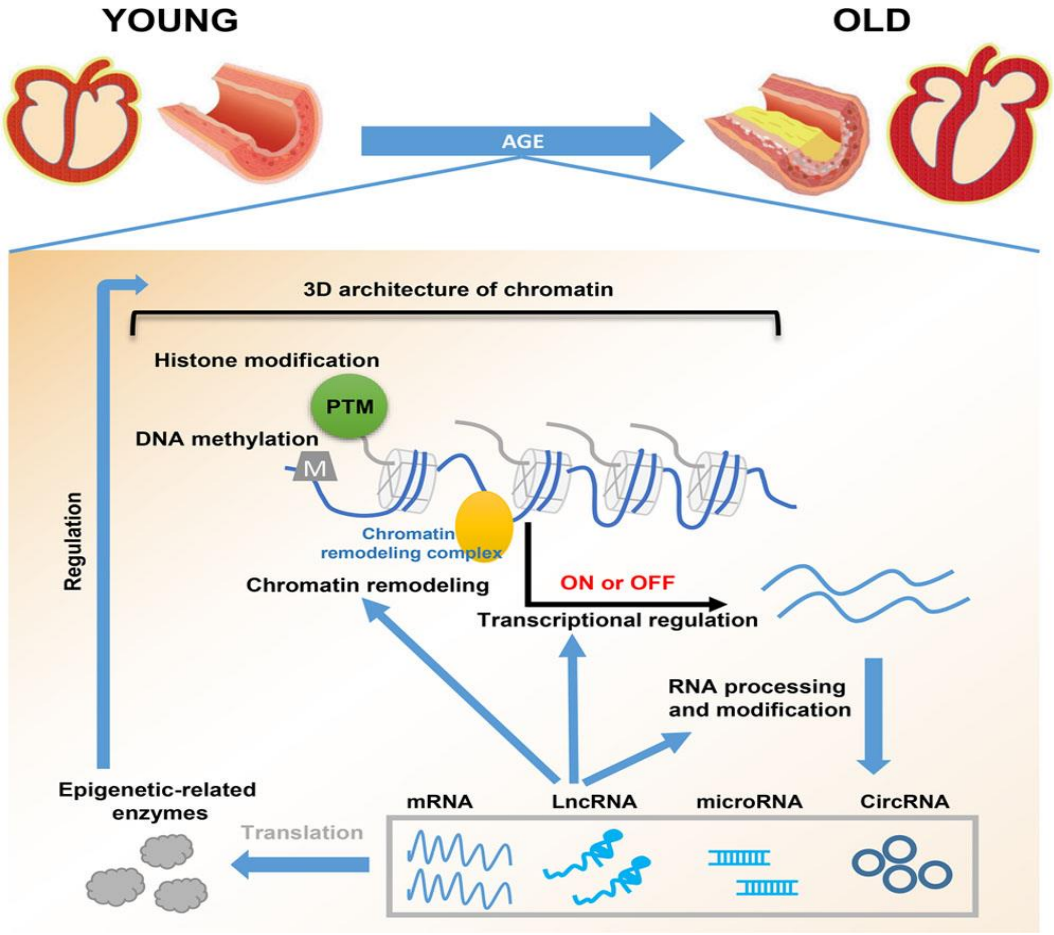
Iniziative PNRR nella Facoltà di Farmacia e Medicina.

Prof. Elena De Falco

Rome Technopole, Flagship 7-Line 3:

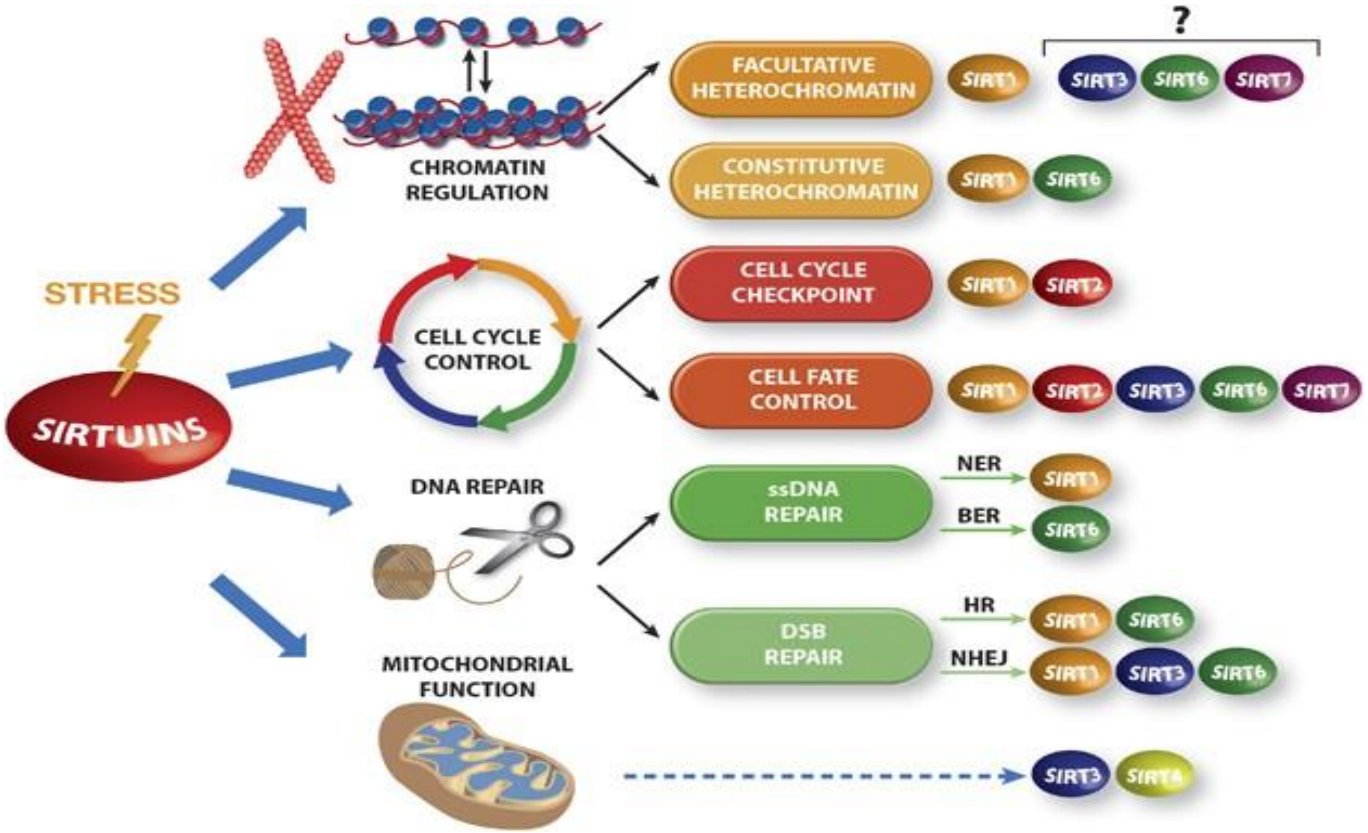
«Targeting autophagy and fibrosis-related Epigenetic Regulators in Cardiovascular Diseases»

Contributo del Dipartimento di Scienze e Biotecnologie Medico-Chirurgiche: «the cardiovascular challenge»



Zhang et al. Circulation Research 2018

Contributo del Dipartimento di Scienze e Biotecnologie Medico-Chirurgiche: «the cardiovascular challenge»



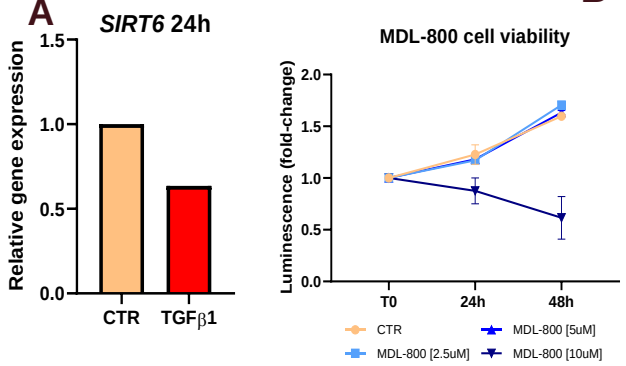
Obiettivi

- **Activity 1 (Spoke 1, Task 1.1):** development of new isoform-selective SIRT1, 2, 3, 5, and 6 modulators and in vitro evaluation on cardiac stromal cells and endothelial cells.
- **Activity 2 (Spoke 1, Task 1.1 and 1.3):** in vivo preclinical testing of the best performing cocktail in a murine model of progressive heart failure.
- **Activity 3 (Spoke 3, Task 3.1 and 3.5):** integration of the novel research topic of epigenetic drugs in cardiovascular medicine in the educational offer of Sapienza University.

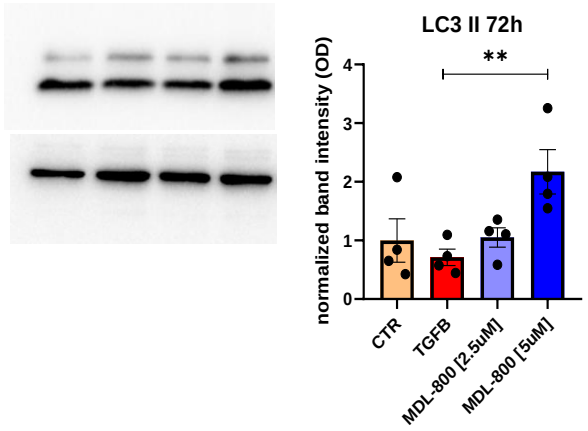
Risultati attesi

Anti-fibrotic effects of the SIRT6-activator MDL-800 in cardiac stromal cells

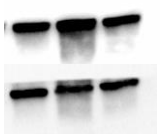
A Preliminary data



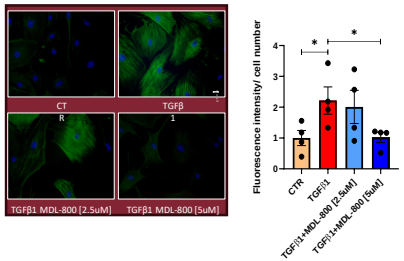
F Autophagy modulation



Protein expression



aSMA Immunofluerescence



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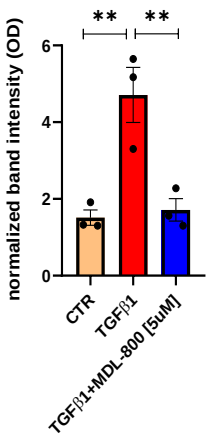

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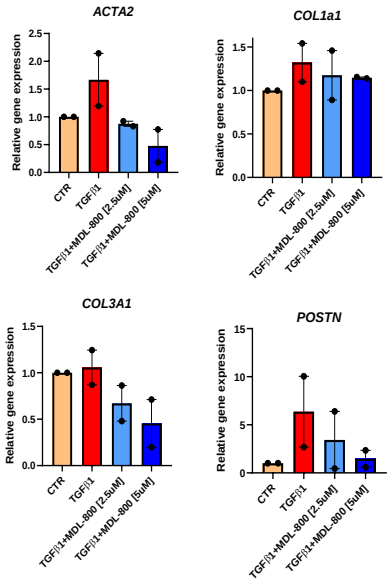
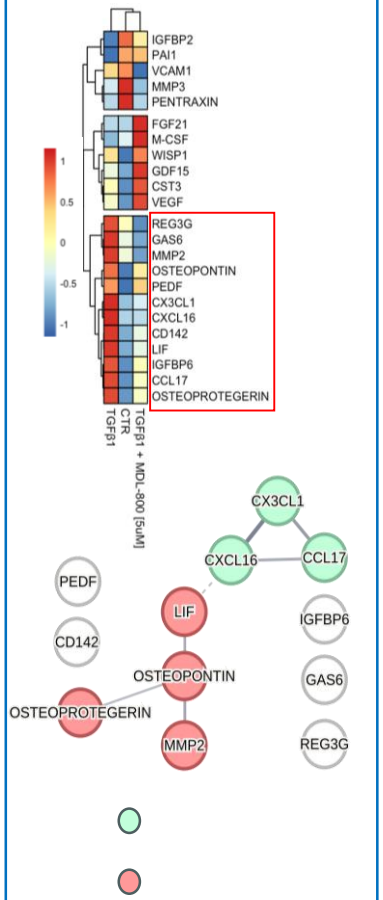
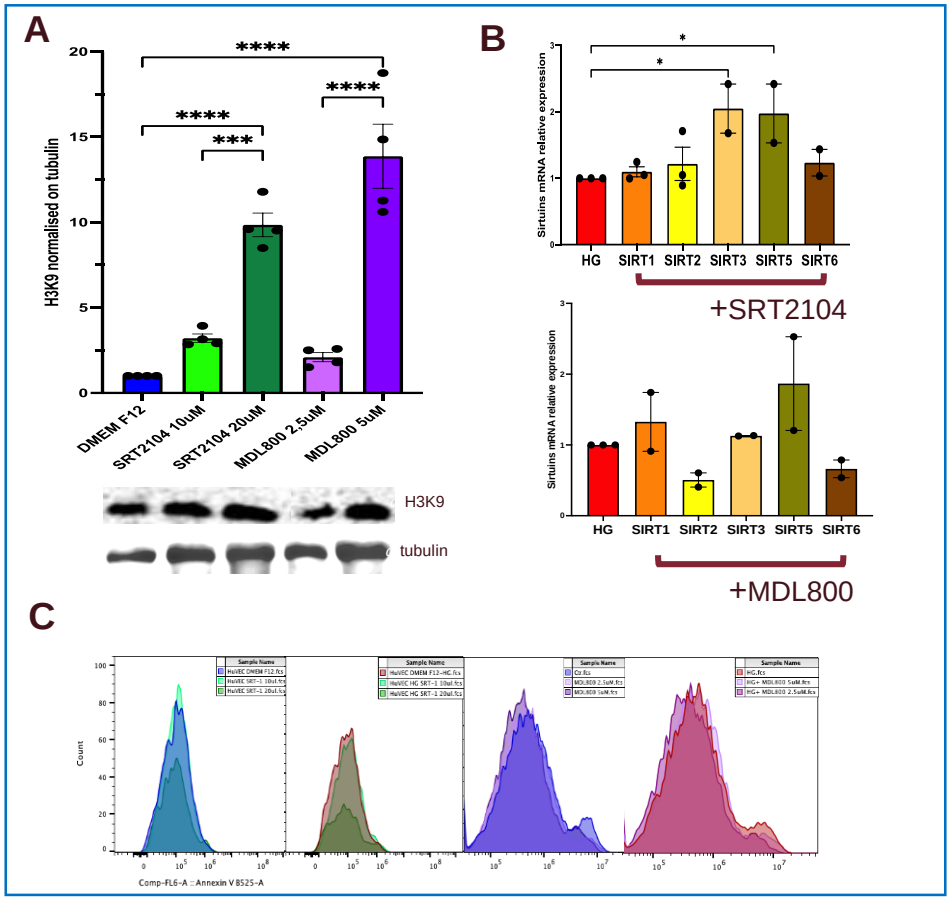


E Paracrine profile



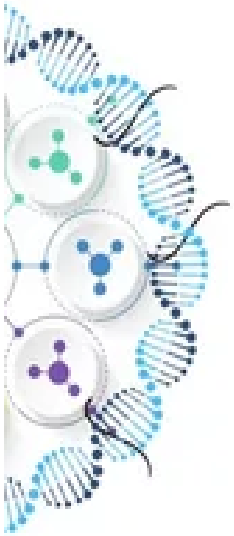
Finanziato dall'Unione europea NextGenerationEU

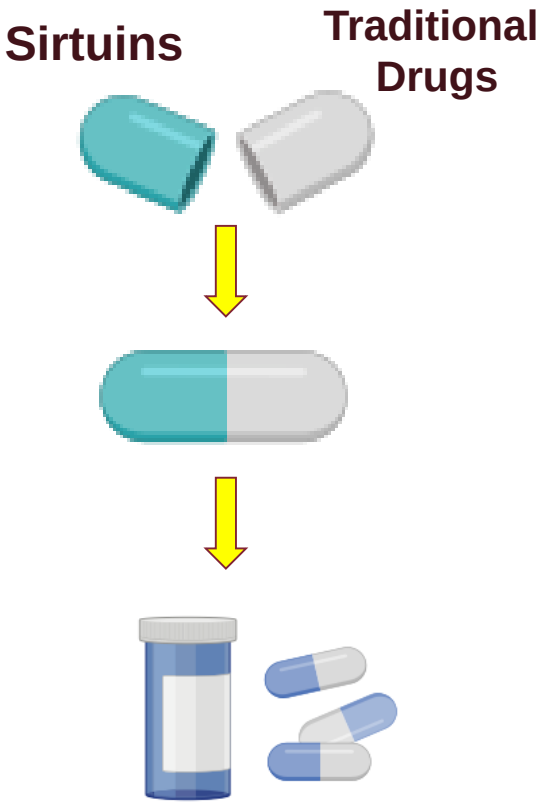
Risultati attesi



Impatto Previsto

Impatto Previsto





Contatti utili

Dip. Scienze e Biotecnologie Medico-Chirurgiche

Prof. Elena De Falco
Prof. Giacomo Frati
Prof. Elena Cavarretta

Dip. di Chimica e Tecnologie del Farmaco

Prof. Antonello Mai
Prof. Sergio Valente
Prof. Alessia Ciogli
Prof. Dante Rotili

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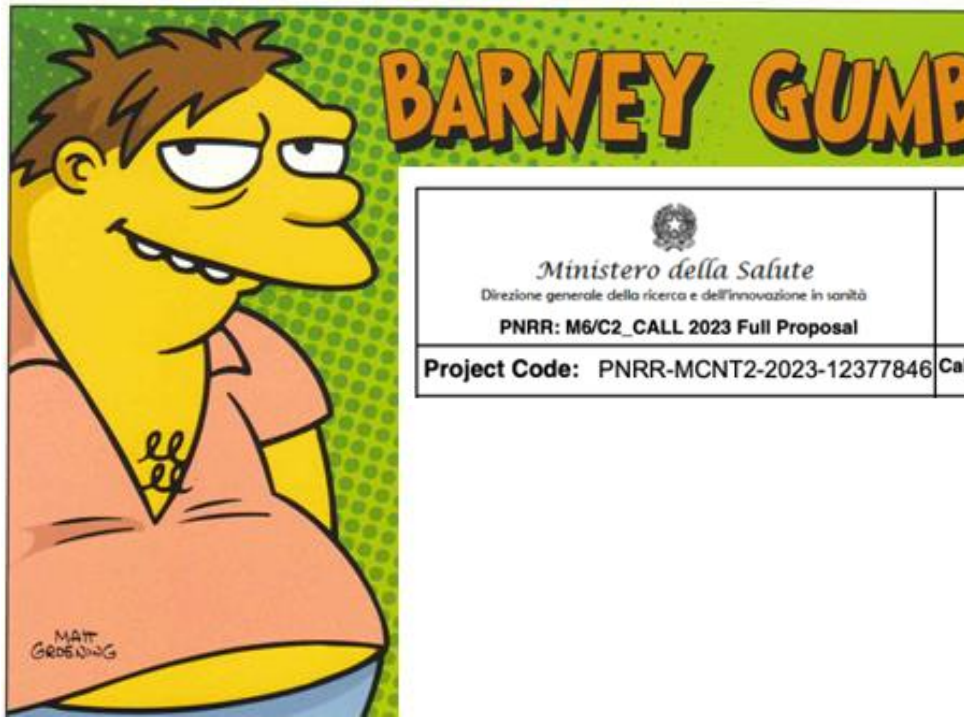
PNRR Salute: M6/C2 Innovazione, ricerca e digitalizzazione del servizio sanitario nazionale

Foto: Stefania Sepulcri (Stampa e comunicazione)

The GUt Microbiota as a Biomarker and pharmacologicaL target in Epilepsy (GUMBLE Study)



Ministero della Salute Direzione generale della ricerca e dell'innovazione in sanità **PNRR: M6/C2_CALL 2023 Full Proposal**	Finanziato dall'Unione europea NextGenerationEU
Project Code: PNRR-MCNT2-2023-12377846	**Call section:** Malattie Croniche non Trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari

Finanziamento Assegnato

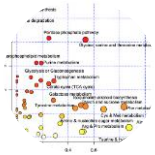
Descrizione Costi	U01 Capofila	U02 Università Federico II Napoli	U03 IRCCS Gaslini Genova	U04 Università La sapienza Roma	totale Budget
CUP	J63C24000260006	E63C24000860006	G33C24000260006	B53C24003000006	
Referente	P.I. Prof. Emilio Russo	prof. Roberto Russo	Prof. Pasquale Striano	prof.ssa Eleonora Palma	
Staff Salary	-	-	-	-	-
Reaserchers' Contracts	240.000,00	80.000,00	80.000,00	80.000,00	480.000,00
equipment (leasing-Rent)	-	-	-	-	-
equipment (buying)	-	-	-	-	-
supplies	39.000,00	131.000,00	80.000,00	86.500,00	336.500,00
Model Costs	-	-	-	9.000,00	9.000,00
Subcontracts	-	-	-	-	-
Patient Costs	-	-	-	-	-
IT services anda data bases	10.000,00	-	10.000,00	-	20.000,00
Travels	8.000,00	4.000,00	4.000,00	2.500,00	18.500,00
Publication coast	8.000,00	10.000,00	6.000,00	6.000,00	30.000,00
Dissemination	10.500,00	7.500,00	6.000,00	6.000,00	30.000,00
Overheads	24.500,00	17.500,00	14.000,00	10.000,00	66.000,00
Coordination costs	10.000,00	-	-		10.000,00
	350.000,00	**250.000,00**	**200.000,00**	**200.000,00**	**1.000.000,00**

Struttura del Progetto

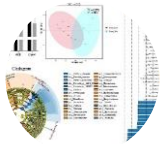
Patients Enrolment

Faecal Samples

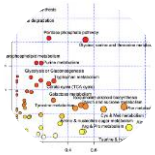
Blood Samples



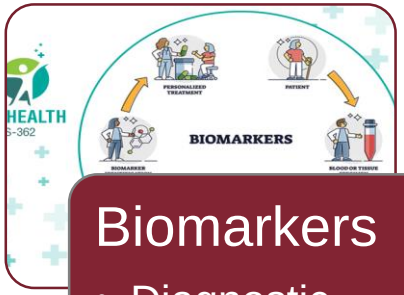
Metabolomic analysis



Metagenomic Analysis

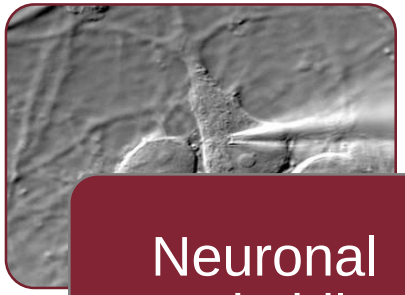


Metabolomic Analysis



Biomarkers

- Diagnostic
- Prognostic
- Safety



Neuronal Excitabilty Evaluation

Novel Therapeutic Targets

Hypothesis and Significance

- **Hypothesis**: Microbiota-gut-brain axis contribute to the development, progression and clinical aspects of epilepsy in patients representing therefore a system by which specific biomarkers can be defined to several purposes

- **Significance**: the definition of clinically relevant biomarkers has an extremely important clinical value in terms of personalised and optimised therapy while also raising the opportunity to define new potential therapeutic targets and develop new therapeutical approaches

Obiettivi

- **Aim 1**: Identification of biomarkers
  - Diagnostic Biomarkers
  - Predictive/prognostic biomarkers
  - Safety Biomarkers

- **Aim 2**: Study of the effects of circulating metabolites belonging to the microbiota-gut-brain axis on neuronal excitability

- **Aim 3**: Creation of a biobank of faecal and blood samples for future studies and integration of data according to potential technological and knowledge advancements

Responsabili del progetto e responsabilità principali

Principal Research Collaborators		
Key Personnel Name	Operative Unit	Role in the project
1 - GAMBARDELLA ANTONIO	University Hospital Dulbecco of Catanzaro	Coordination, adult patients recruitment, clinical evaluation
2 - Striano Pasquale	IRCCS Gaslini Genova	pediatric patients recruitment, clinical evaluation, data interpretation
3 - Russo Roberto	University of Naples Federico II	in vitro sample analysis, data interpretation and integration
4 - Palma Eleonora	University of Rome Sapienza	in vitro evaluation of molecules linked to microbiota brain axis on neuronal excitability
5 - Aviello Gabriella	University of Naples Federico II	in vitro sample analysis, data interpretation and integration
6 Under 40 - MORANO ALESSANDRA	University of Rome Sapienza	patients recruitment, clinical evaluation, data interpretation
7 Under 40 - MUSANTE ILARIA	IRCCS Gaslini Genova	sample analysis, metabolic studies, data interpretation and integration

Responsabili del progetto e responsabilità principali

Emilio Russo
Project Coordinator

Antonio Gambardella
Coordination, adult patients recruitment, clinical evaluation

Pasquale Striano
pediatric patients recruitment, clinical evaluation, data interpretation

Ilaria Musante – U40
sample analysis, metabolic studies, data interpretation and integration

Roberto Russo
in vitro sample analysis, data interpretation and integration

Gabriella Aviello
in vitro sample analysis, data interpretation and integration

Eleonora Palma
in vitro evaluation of molecules linked to microbiota brain axis on neuronal excitability

Alessandra Morano – U40
patients recruitment, clinical evaluation, data interpretation

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Iniziative PNRR nella Facoltà di Farmacia e Medicina.

Progetto «Digital Driven Diagnostics, prognostics and therapeutics for sustainable Health care» **D³ 4 Health – Spoke 3**

Foto: Stefania Sepulcri (Stampa e comunicazione)

Contributo del Dipartimento di Medicina Molecolare: sintesi delle sfide alla base del contributo al progetto

Il gruppo del Prof Fabio Babiloni (Dipartimento di Fisiologia e Farmacologia) sfruttando la consolidata esperienza nell'analisi dei **segnali cerebrali** ed **autonomici** permetterà di fornire **dati neurocognitivi** per la costruzione del **Digital Twin**. Nello specifico il protocollo sperimentale, permetterà di acquisire in presenza e da remoto grazie alla tecnologia acquisita con i fondi PNRR, dati neurofisiologici dei pazienti **in resting state** e **durante task cognitivi ad hoc**.

✓Sistema Mindtooth, indossabile autonomamente, costituito da un avanzato device per EEG, **Mindtooth** ***(Mindtooth Project H2020-EIC-FTI-GA950998)***

mindtooth
one sense more

✓ Research Ring per segnali autonomici (HR, EDA)

BIOPAC Systems, Inc.

Monitoraggio neuroscientifico del paziente per identificare correlati di stati psicofisici spesso compromessi nei pazienti focus del progetto D34H (es. attenzione, stress, affaticamento cognitivo).

Inoltre, una batteria di **questionari psicometrici** somministrati da remoto (Qualtrics) permetterà di effettuare *ongoing* una valutazione cognitiva durante il percorso terapeutico, offrendo un **contributo multifattoriale** alla definizione del Digital Twin.

Obiettivi specifici

Valutare e monitorare in modo innovativo ed interdisciplinare marker neuro-fisio-cognitivi nei pazienti attraverso sia *batterie cognitive* che *analisi di biosegnali* attraverso sistemi intelligenti e non invasivi durante task cognitivi in presenza e da remoto per contribuire alla creazione del gemello digitale il più possibile personalizzato sul paziente:

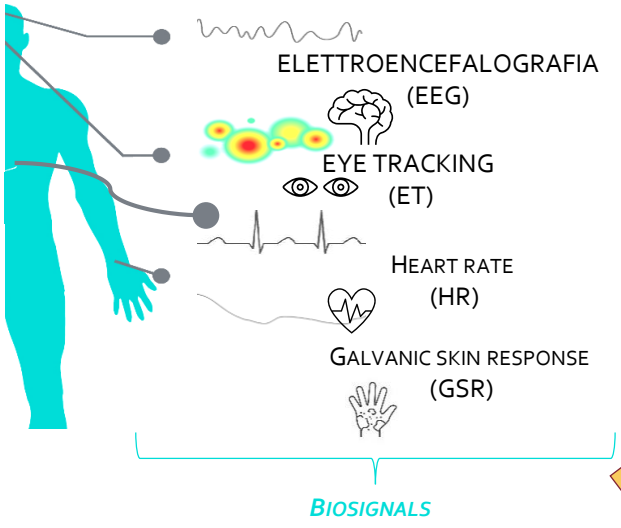
1) Sviluppo delle soluzioni tecnologiche e identificazione dei biomarcatori cognitivi;

2) Validazione delle soluzioni tecnologiche proposte;

3) Contributo al design del gemello digitale - basato su biosegnali e marker cognitivi.

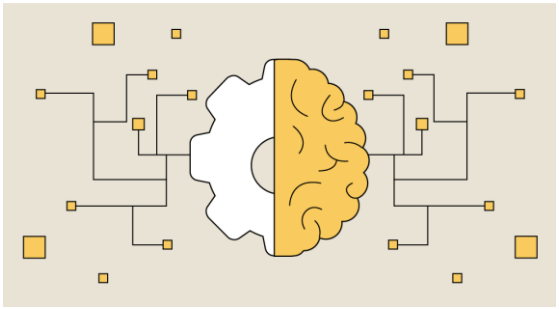
Impiego di **dispositivi medici mini (non)-invasivi** in grado di supportare il processo decisionale clinico, il benessere dei pazienti e la raccolta continua di dati per la progressione/generazione dello sviluppo del gemello digitale.

Nel concreto….



Innovativi Modelli di *Machine Learning*

STATO PSICOFISICO DEL PAZIENTE



Impatto previsto

-**Clinica**: lo sviluppo e la validazione di soluzioni interdisciplinari tecnologiche per la valutazione delle risorse cognitive, permetteranno di promuovere **approcci di cura personalizzati al paziente**, in base ai fattori fisiologici, cognitivi e personologici individuali.

-**Scientifico**: Nuove **evidenze scientifiche innovative** sulla valutazione dello stato cognitivo ed affettivo del paziente, con la definizione di migliori percorsi assistenziali. Progettazione metodologica multidisciplinare innovativa e sperimentazione nella pratica clinica, producendo evidenze per le comunità scientifiche e i decisori politici.

-**Impatto sociale**: Implementazione di approcci innovativi e sostenibili per l'assistenza sanitaria e il benessere, migliorando **l'inclusività sociale**; promuovendo l'accessibilità alla diagnosi clinica ed al monitoraggio; cooperazione con prestazioni ospedaliere con diverse aree di specializzazione in una specifica area patologica.

Prof Fabio Babiloni
fabio.babiloni@uniroma1.it

Dr Bianca Inguscio
biancams.inguscio@uniroma1.it

Dr Giulia Cartocci
giulia.cartocci@uniroma1.it

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Iniziative PNRR nella Facoltà di Farmacia e Medicina.

PNC Salute/D34 - Health Digital Driven Diagnostics, prognostics and therapeutics for Sustainable Health care

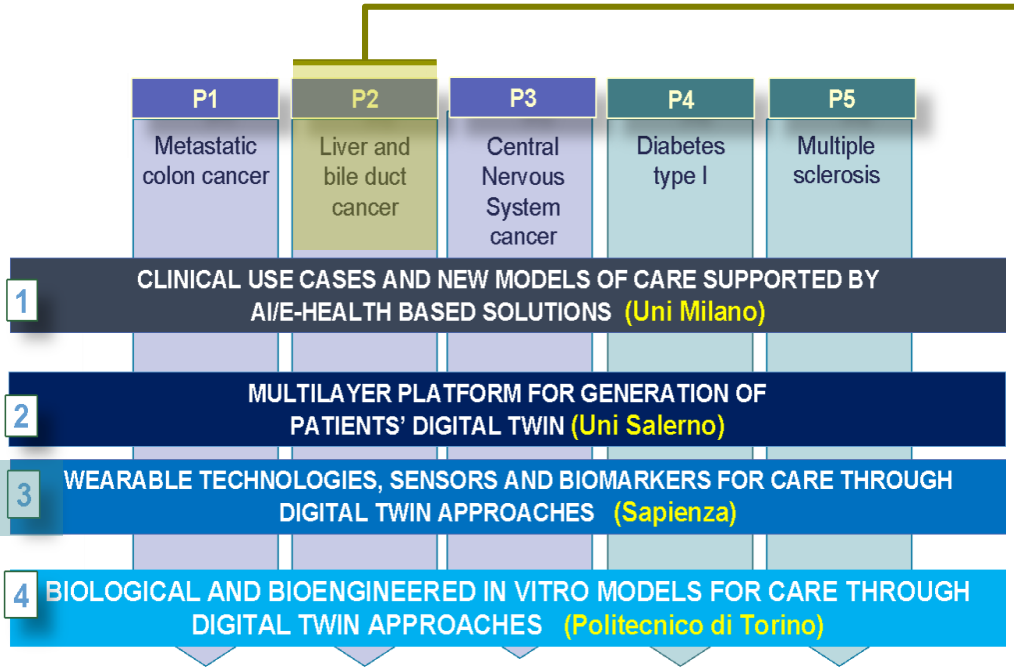
Foto: Stefania Sepulcri (Stampa e comunicazione)

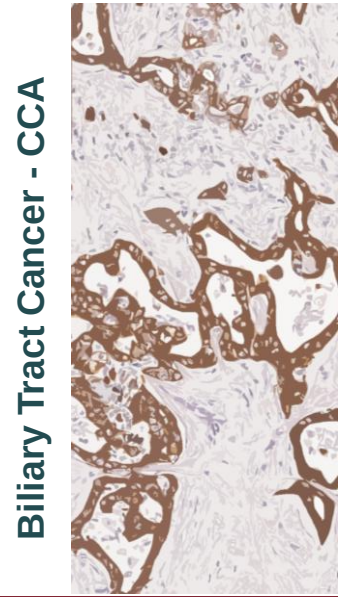
PNC Salute/D34 - Health Digital Driven Diagnostics, prognostics and therapeutics for Sustainable Health care

Contributo del Dipartimento di Scienze Anatomiche, Istologiche, Medico Legali e dell'Apparato Locomotore

N. 3 - Spoke 3 _Task 3.4, 3.6

Title: Digital Twins construction: Advanced **imaging diagnostics** & biomarkers for **tissue characterization**



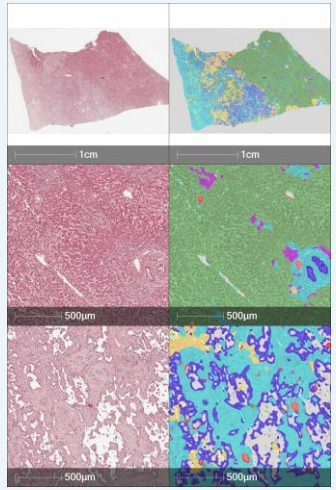


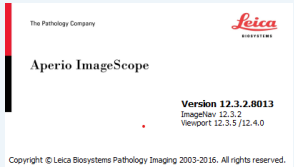
PNC Salute/D34 - Health Digital Driven Diagnostics, prognostics and therapeutics for Sustainable Health care

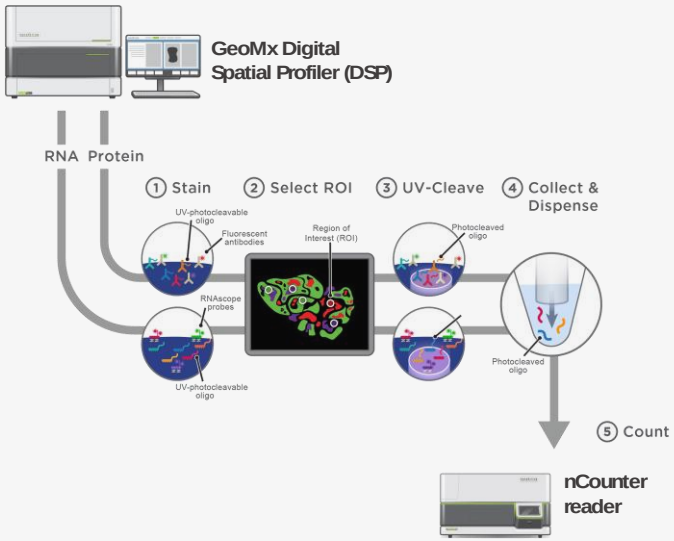
Contributo del Dipartimento di Scienze Anatomiche, Istologiche, Medico Legali e dell'Apparato Locomotore

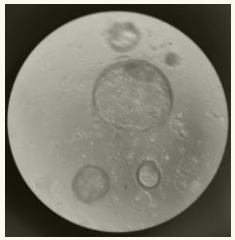
Obiettivi specifici

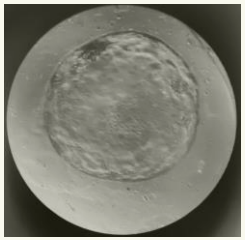
- Istologia Digitale e AI tool
- Profilo molecolare spaziale (Spatial –omics)
- In vitro modelling (2d and 3d)









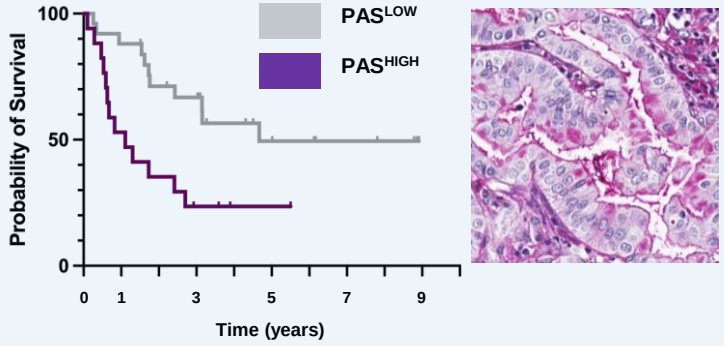


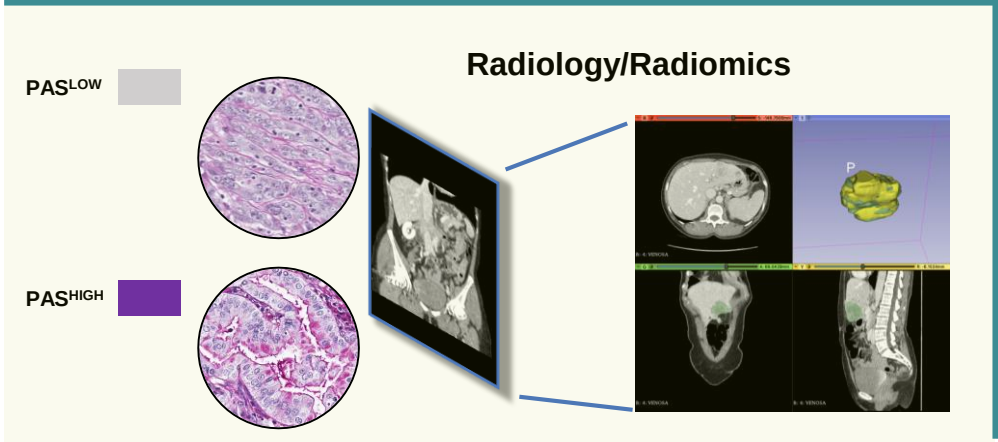
PNC Salute/D34 - Health Digital Driven Diagnostics, prognostics and therapeutics for Sustainable Health care

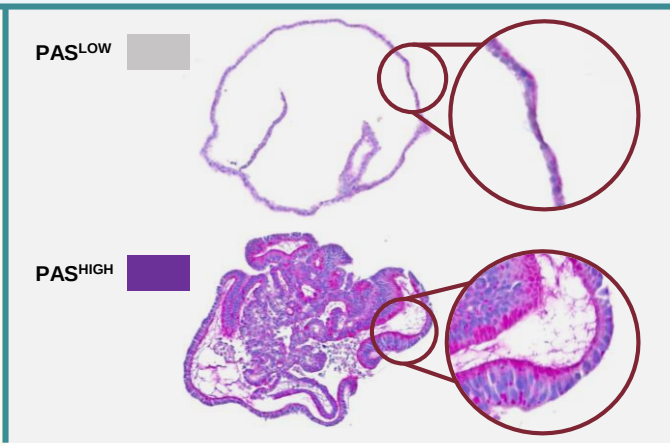
Contributo del Dipartimento di Scienze Anatomiche, Istologiche, Medico Legali e dell'Apparato Locomotore

Risultati attesi in linea con i pilastri del PNRR

- Individuazione di specifici **biomarcatori**
- **AI** per caratterizzazione istologica del CCA
- Caratterizzazione morfo-molecolare spaziale
- **Digital twin**: correlazioni morfologiche, cliniche e radiologiche
- **Biological twin**: modellizzazione *in vitro*







PNC Salute/D34 - Health Digital Driven Diagnostics, prognostics and therapeutics for Sustainable Health care

Contributo del Dipartimento di Scienze Anatomiche, Istologiche, Medico Legali e dell'Apparato Locomotore

Contatti utili

Eugenio Gaudio
eugenio.gaudio@uniroma1.it

Guido Carpino
guido.carpino@uniroma1.it

DIPARTIMENTO DI SCIENZE ANATOMICHE
ISTOLOGICHE
MEDICO LEGALI
E DELL'APPARATO LOCOMOTORE

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PNC SALUTE – D³ 4 Health

Construction of a predictive model of the behavior of primary liver tumors cholangiocarcinoma (CCA) and hepatocarcinoma (HCC) in terms of progression survival and disease recurrence in response to treatments performed.

Prof. Massimo Rossi

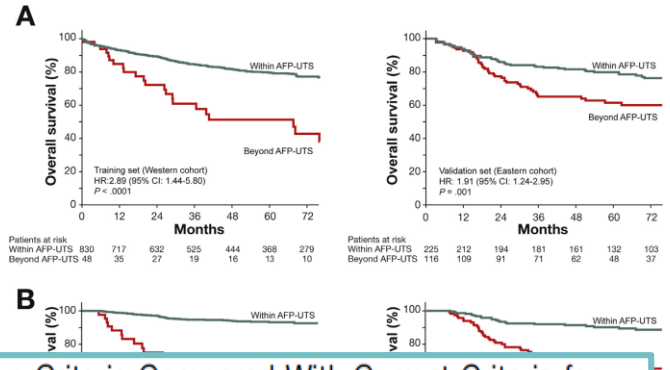
Dott.ssa Manuela Garofalo

Foto: Stefania Sepulcri (Stampa e comunicazione)

TRANSPLANT ONCOLOGY

Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma

Vincenzo Mazzaferro,[1] Carlo Sposito,[1] Jian Zhou,[2,3] Antonio D. Pinna,[4] Luciano De Carlis,[5] Jia Fan,[2,3] Matteo Cescon,[4] Stefano Di Sandro,[5] He Yi-feng,[2,3] Andrea Lauterio,[5] Marco Bongini,[1] and Alessandro Cucchetti[4]



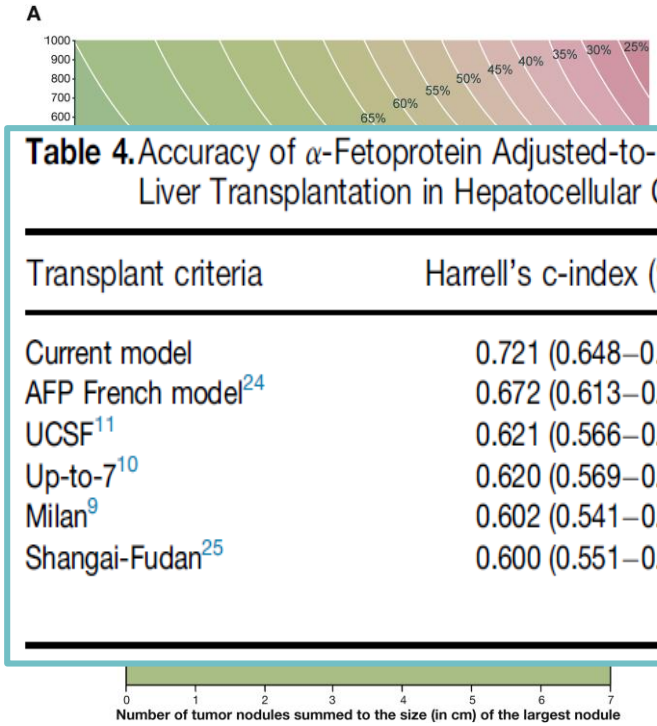


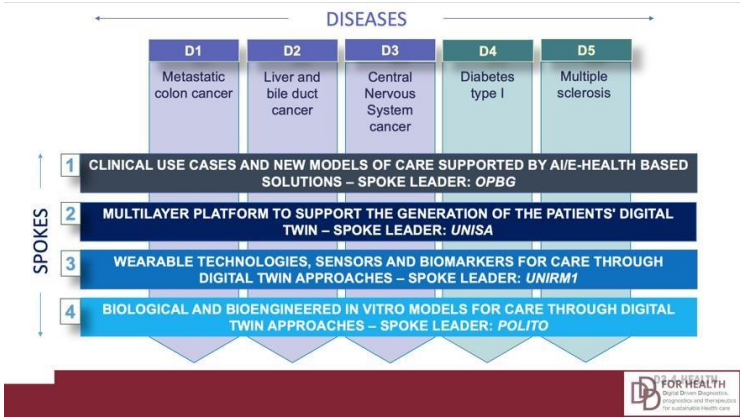
Table 4. Accuracy of α-Fetoprotein Adjusted-to-Hepatocellular Carcinoma Size Criteria Compared With Current Criteria for Liver Transplantation in Hepatocellular Carcinoma Tested in the External Validation Cohort

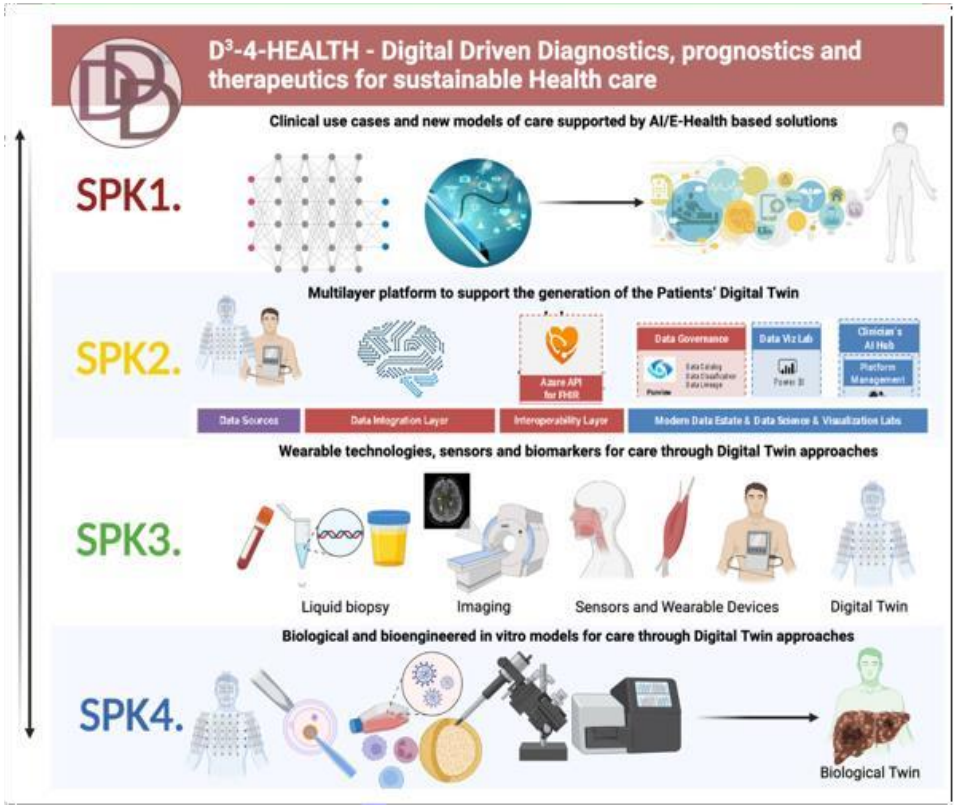
Transplant criteria	Harrell's c-index (95% CI)	*P* value (Harrell's)	Wolbers c-index (95% CI)
Current model	0.721 (0.648–0.793)	—	0.698 (0.640–0.756)
AFP French model[24]	0.672 (0.613–0.731)	.044	0.639 (0.575–0.703)
UCSF[11]	0.621 (0.566–0.676)	.001	0.582 (0.513–0.651)
Up-to-7[10]	0.620 (0.569–0.671)	.001	0.585 (0.517–0.653)
Milan[9]	0.602 (0.541–0.663)	.001	0.558 (0.487–0.629)
Shangai-Fudan[25]	0.600 (0.551–0.649)	.001	0.569 (0.499–0.639)

Figure 2. HCC-specific survival at 5 years after liver transplantation, according to variations in Number of nodules + diameter of the largest nodule and AFP (*A*) with the derived AFP-adjusted-to-HCC-size criteria (*B*). (*A*) HCC-specific survival estimates

www.hcc-olt-metroticket.org.

D3-4-HEALTH


DISEASES
D1
Metastatic colon cancer
D2
Liver and bile duct cancer
D3
Central Nervous System cancer
D4
Diabetes type I
D5
Multiple sclerosis
SPOKES
1 CLINICAL USE CASES AND NEW MODELS OF CARE SUPPORTED BY AI/E-HEALTH BASED SOLUTIONS – SPOKE LEADER: OPBG
2 MULTILAYER PLATFORM TO SUPPORT THE GENERATION OF THE PATIENTS' DIGITAL TWIN – SPOKE LEADER: UNISA
3 WEARABLE TECHNOLOGIES, SENSORS AND BIOMARKERS FOR CARE THROUGH DIGITAL TWIN APPROACHES – SPOKE LEADER: UNIRM1
4 BIOLOGICAL AND BIOENGINEERED IN VITRO MODELS FOR CARE THROUGH DIGITAL TWIN APPROACHES – SPOKE LEADER: POLITO


D3-4-HEALTH - Digital Driven Diagnostics, prognostics and therapeutics for sustainable Health care
Clinical use cases and new models of care supported by AI/E-Health based solutions
SPK1.
Multilayer platform to support the generation of the Patients' Digital Twin
SPK2.
Data Governance
Data Viz Lab
Clinician's AI Hub
Platform Management
Azure API for FHIR
Data Sources
Data Integration Layer
Interoperability Layer
Modern Data Estate & Data Science & Visualization Labs
Wearable technologies, sensors and biomarkers for care through Digital Twin approaches
SPK3.
Liquid biopsy
Imaging
Sensors and Wearable Devices
Digital Twin
Biological and bioengineered in vitro models for care through Digital Twin approaches
SPK4.
Biological Twin

SPOKE 1 (D³-4-HEALTH)
obiettivi principali

- ✓ Creazione di un dataset estratto dall' attività di data mining da una coorte di pazienti affetti da HCC e CCA.
- ✓ Elaborazione di dati clinici, strumentali, di laboratorio e istologici al fine di identificare fattori predittivi per la costruzione di algoritmi che abilitino un percorso di diagnosi e cura più accurato e standardizzato con il supporto dell'intelligenza artificiale (AI).
- ✓ Identificazione delle variabili che definiscono le popolazioni a più alto rischio di recidiva di malattia al fine di ottenere biomarcatori che rendano il follow-up meno invasivo.
- ✓ Impiego delle variabili per la fase di addestramento dei modelli di Machine Learning (ML).
- ✓ Convalida di nuovi modelli di assistenza supportati da soluzioni innovative basate sull'intelligenza artificiale/e-health per garantire una rapida consegna delle evidenze a breve termine.

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Risultati attesi ed impatto

- Realizzazione di modelli predittivi simulati (Digital Twins);
- Personalizzazione terapeutica (schemi immunosoppressivi);
- Maggiore accuratezza prognostica post trattamento (locoregionale o chirurgico);
- Supporto decisionale affidabile, efficace ed efficiente per l'assistenza e la cura del paziente.

massimo.rossi@uniroma1.it
manuela.garofalo@uniroma1.it

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Iniziative PNRR nella Facoltà di Farmacia e Medicina.

CN3 centro nazionale per la terapia genica e farmaci ad RNA

Foto: Stefania Sepulcri (Stampa e comunicazione)

RNA &GENETHERAPY
NATIONAL RESEARCH CENTER

- *PNRR M4C2-Investimento 1.4- CN00000041 ” finanziato dall’Unione europea – NextGenerationEU*
  Finanziamento totale PNRR: Importo assegnato 324 Meuro.

- Meccanismi fondamentali della terapia genica e a RNA e le loro applicazioni terapeutiche per tradurle in prodotti farmacologici.

://www.rna-genetherapy.eu

SPOKE 1 | Genetic Diseases
University of Modena and Reggio Emilia

SPOKE 2 | Cancer
Sapienza University of Rome

SPOKE 3 | Neurodegeneration
Italian Institute of Technology

SPOKE 4 | Metabolic and Cardiovascular Diseases
University of Padua

SPOKE 5 | Inflammatory and Infectious Diseases
University of Siena

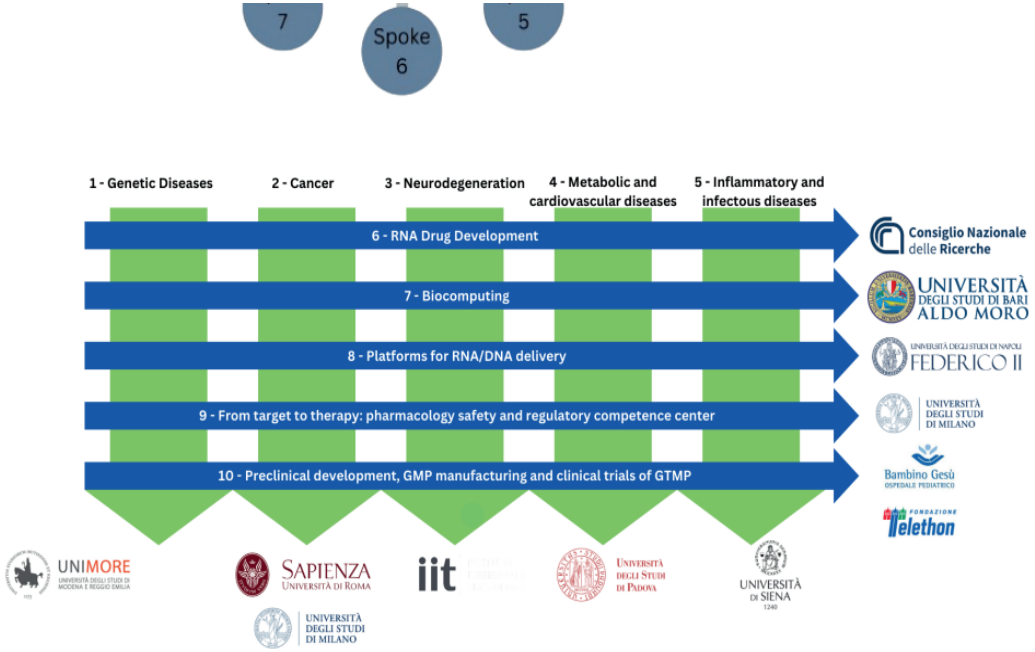
SPOKE 6 | RNA Drug Development
National Research Council of Italy

SPOKE 7 | Biocomputing
University of Bari Aldo Moro

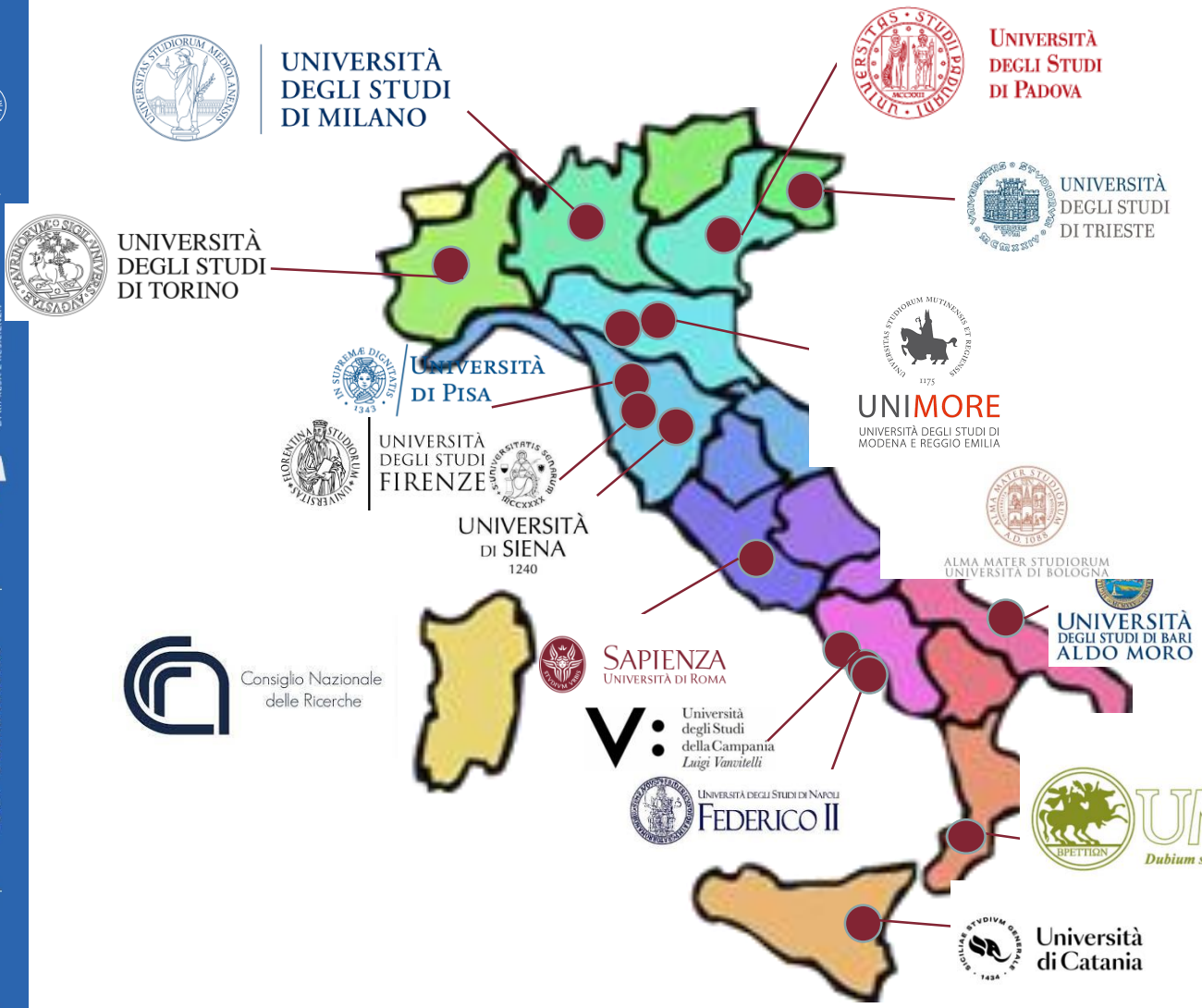
SPOKE 8 | Platforms for RNA/DNA Delivery
University of Naples Federico II

SPOKE 9 | Competence Center on RNA Drug Pharmacology
University of Milan

SPOKE 10 | Pre-clinical Development, GMP Manufacturing and Clinical Trials of GTMP
IRCCS Bambino Gesù Children's Hospital in Rome



CN3 Spoke 2 “ Cancer ”



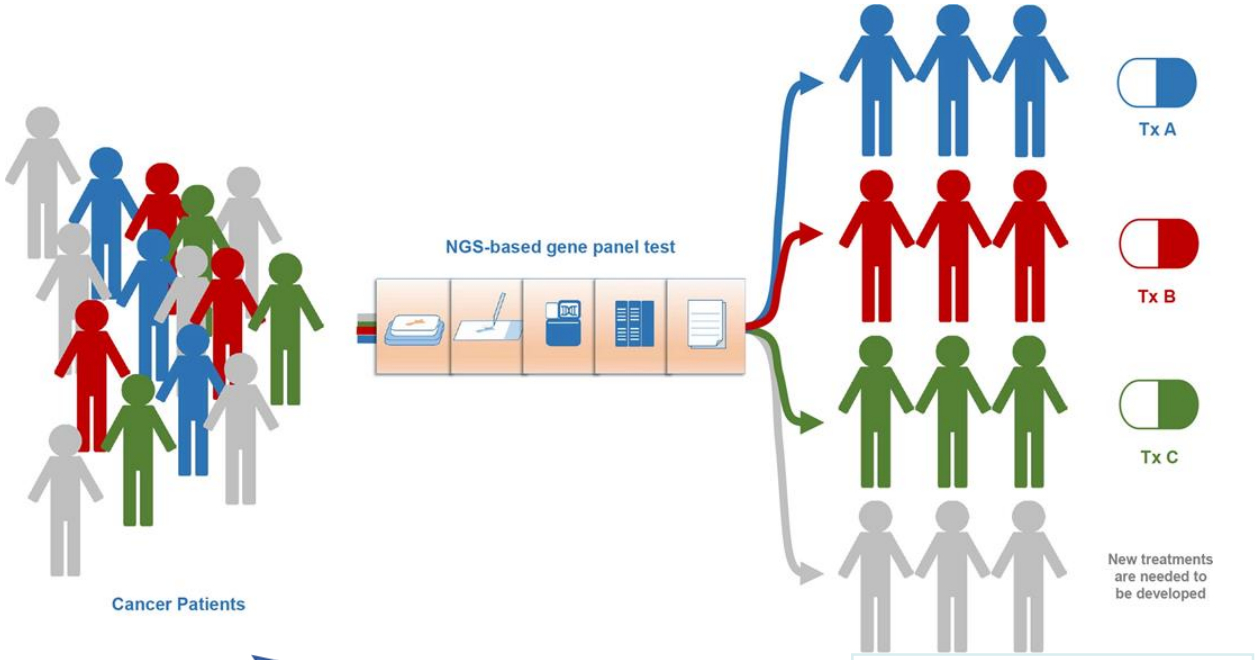
16 UNIVERSITIES (UROM,UNIMI,UMG, UNIPD,UNIBA,UNINA ,UNIPI,UNIBO,UNIFI, UNISI,UNICT,UNITS,U NIBS,UNIMORE,UNIC AMP,UNITO)

2 CNR Institutes (IASI, IEOS)

2 Pharma companies (SANOFI, (IRBM)

1 Financial Institution (Intesa San Paolo).

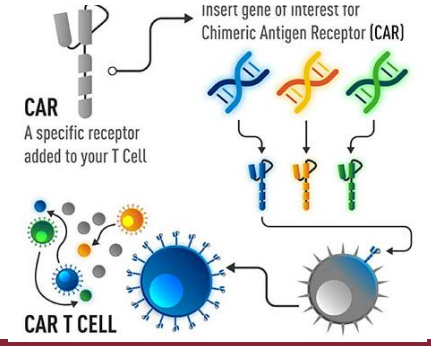
Spoke 2 “ Cancer ” Overview



In cooperation with H-spokes

1. Vaccines
2. ncRNA
3. GTMP

miRNA, siRNA, ASO etc.



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CN3 “SVILUPPO DI TERAPIE GENICHE E FARMACI A BASE DI RNA”– Spoke 2 Cancer

RNA-therapy to target cytotoxic genes in Glioblastoma

CN3 Spoke 2: NOVEL RNA THERAPEUTICS IN TUMORS: FROM DISCOVERY TO PRE-CLINICAL STAGE

4 WORKPACKAGES:

WP1 IDENTIFICATION OF NOVEL TARGETS FOR RNA THERAPEUTICS

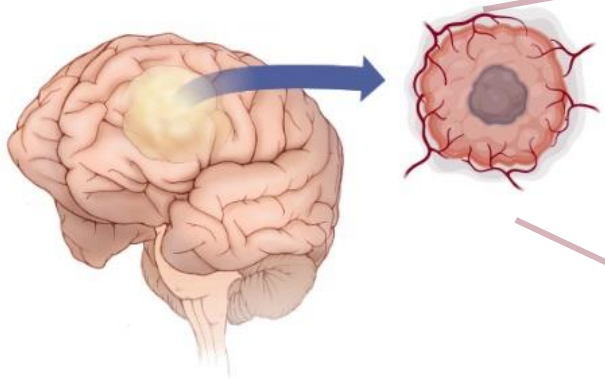
WP2 PRIORITIZATION AND VALIDATION OF TARGETS TOWARDS CLINICAL APPLICATIONS

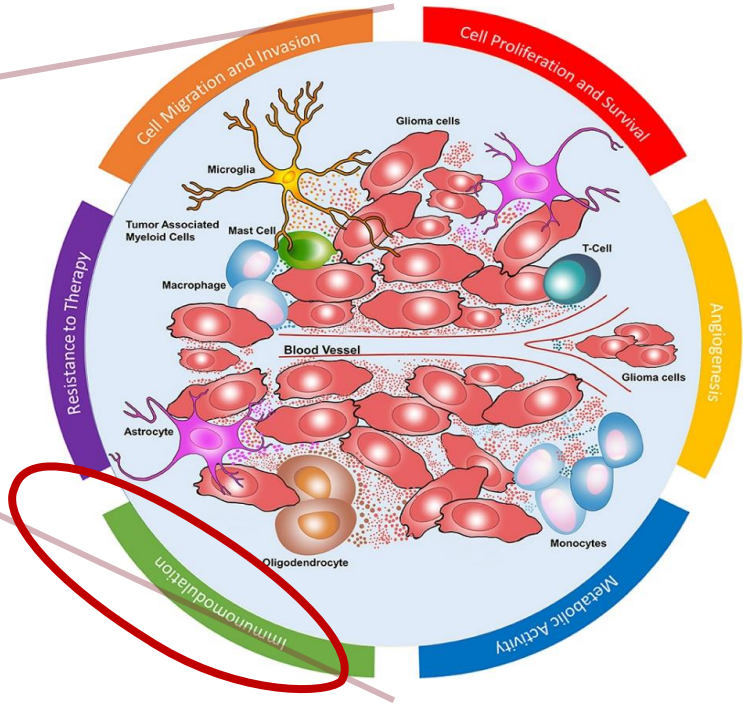
WP3 DISCOVERY OF NOVEL IMMUNE RNA THERAPEUTICS

WP4 MAXIMIZING THE IMPACT

WP2 PRIORITIZATION AND VALIDATION OF TARGETS TOWARDS CLINICAL APPLICATIONS

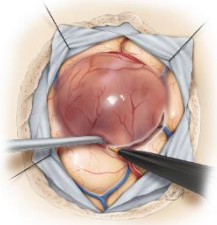
Glioblastoma



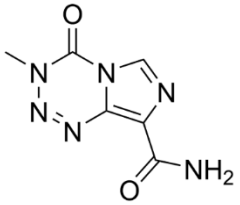


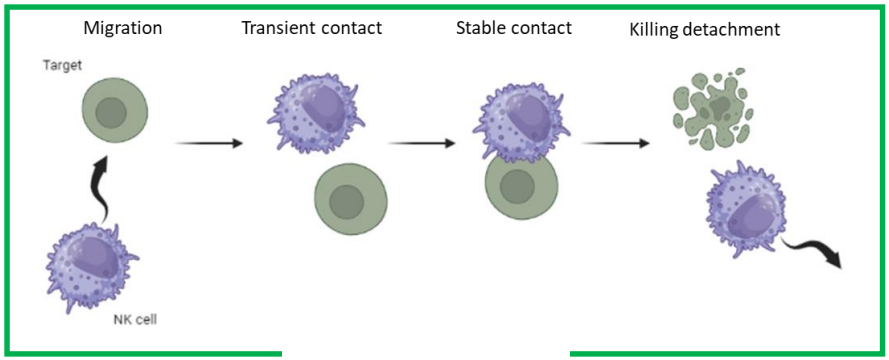
Current treatments

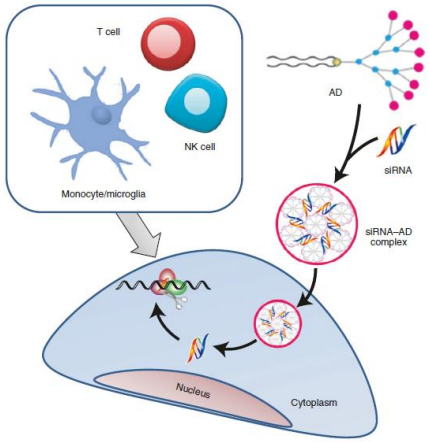
GBM surgery



Temozolomide therapy

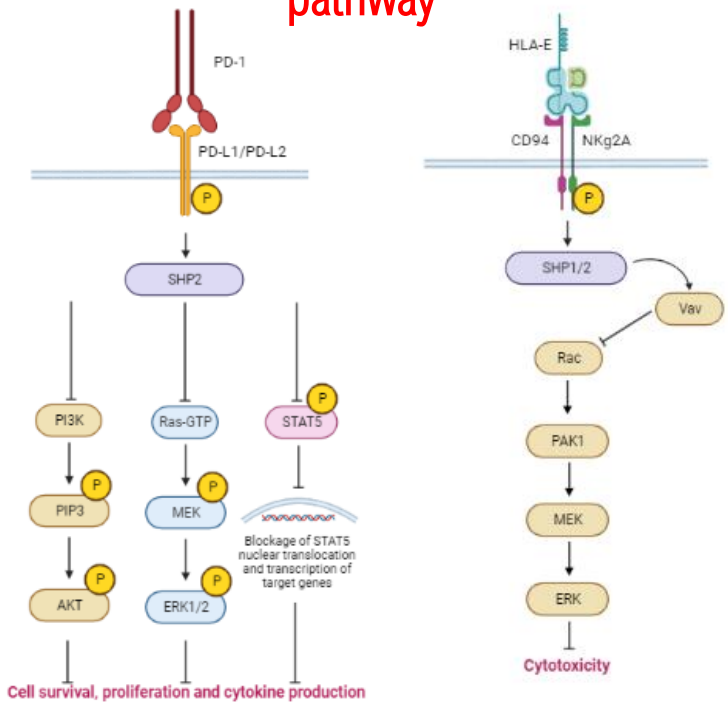






siRNA delivery mediated by the amphiphilic dendrimer

Inhibitory pathway



Main Objective: to modulate target genes and RNA molecules through siRNA.

We aim **to disrupt the GBM immunoescape** by the delivery of siRNA targeting the checkpoint inhibitors NKG2A and PD-1 receptors.

Preclinical animal models

Tasks:

- ***Task 1 Specific shutdown of key proteins, RNA modification and gene editing***
- ***Task 2 In vitro and in vivo efficacy tests and delivery of RNA based therapies***
- ***Task 3 Validation of Diagnostic, Prognostic and Response to therapy biomarkers in preclinical models***

Deliverables:

- Novel gene inactivation protocols; Silencing RNA targeting proteins.
- *In vitro* and in vivo validated therapeutic siRNAs.
- Identification of novel targets for cytotoxic genes in glioblastoma and methods of targeted delivery suitable to further preclinical testing. Assessment and selection of the most effective and powerful targeted nanosystems.

Useful contacts:

Information for those who would like to learn more or collaborate

Prof. Stefano Garofalo
mail: stefano.garofalo@uniroma1.it

Main REFERENCES:

- Mormino A, et al., Histone-deacetylase 8 drives the immune response and the growth of glioma. Glia. 2021 Nov;69(11):2682-2698.
- Chen J, et al., Synthesis and use of an amphiphilic dendrimer for siRNA delivery into primary immune cells. Nat Protoc. 2021 Jan;16(1):327-351.
- Garofalo S, et al., Natural killer cells modulate motor neuron-immune cell cross talk in models of Amyotrophic Lateral Sclerosis. Nat Commun. 2020 Apr 14;11(1):1773.

siRNA Targets:

1. NK cell lectin-like receptor subfamily C member 1 subtype A – **NKG2a**
2. Programmed cell death protein 1 – **PD1**

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PNRR CN3_spoke 2 Cancer

National Center for Gene Therapy and Drugs based on RNA Technology

Foto: Stefania Sepulcri (Stampa e comunicazione)

NextGenerationEU DD. 3175/2021 E DD. 3138/2021 CN_3:
National Center for Gene Therapy and Drugs based on RNA Technology

Codice Progetto CN 00000041

Responsabile progetto:

PI: Alberto Boffi

Co-PI: Lucia Di Marcotullio

Personnel

RTDA: Francesca Bufalieri

PhD Student: Gennaro Adabbo

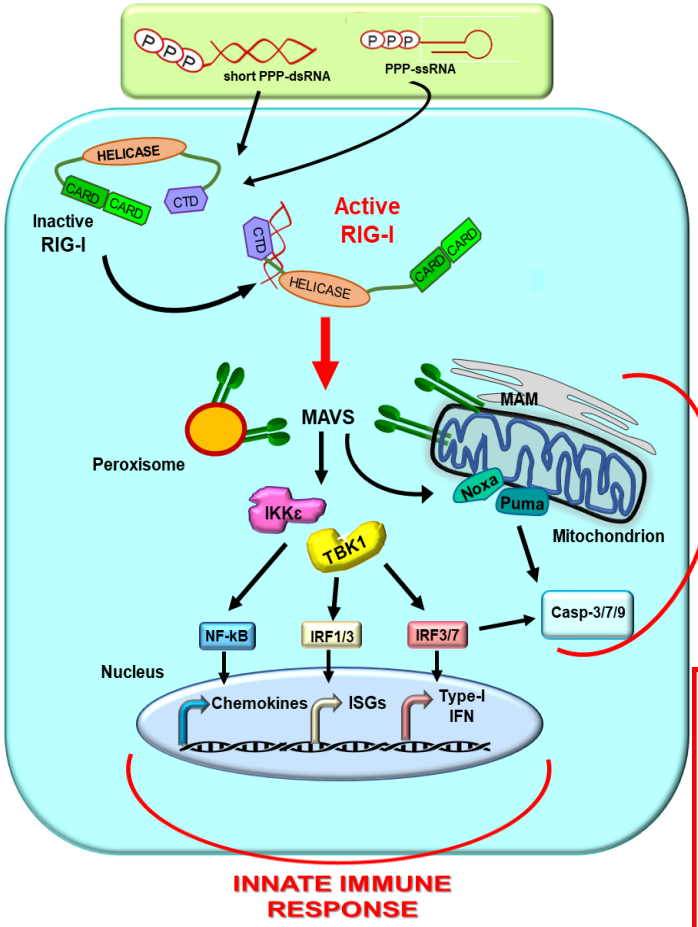
Collaborators

Luca D'Angelo, Giulio Caracciolo, Clara Nervi

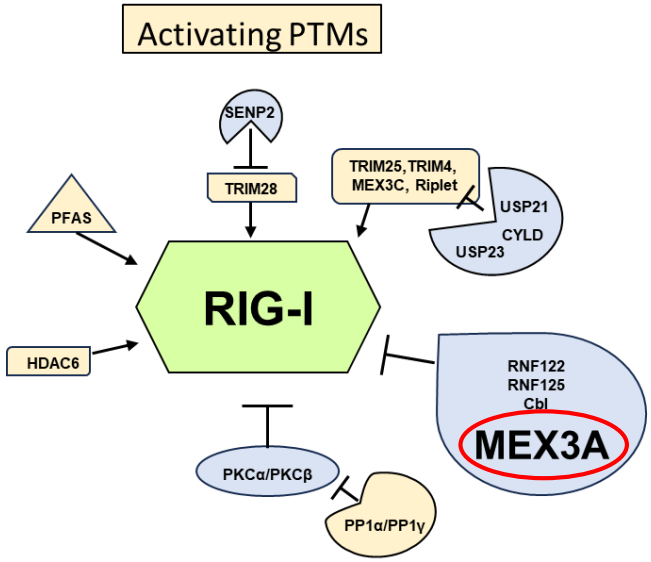
Amount

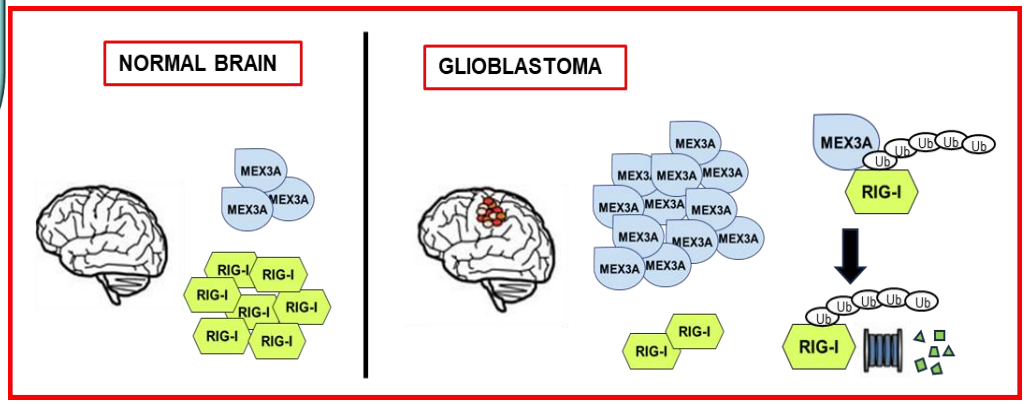
€155.310,00

Acid Nucleic Sensing Pathway: the relevance of RIG-I

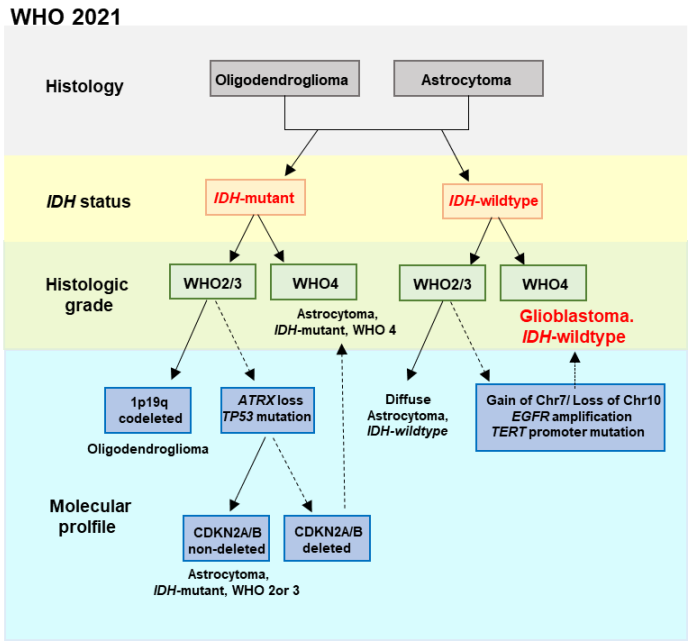


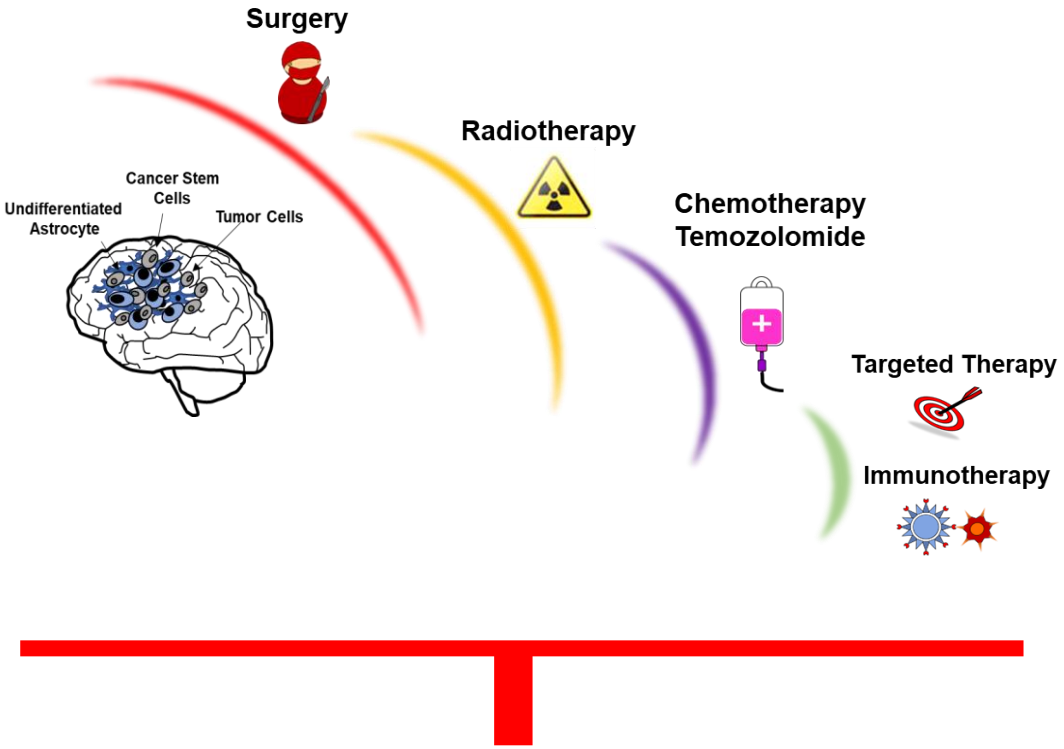
APOPTOSIS





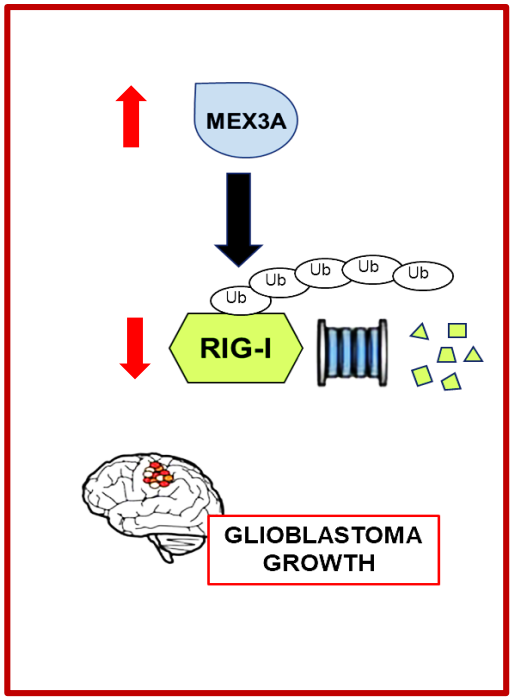
Glioblastoma

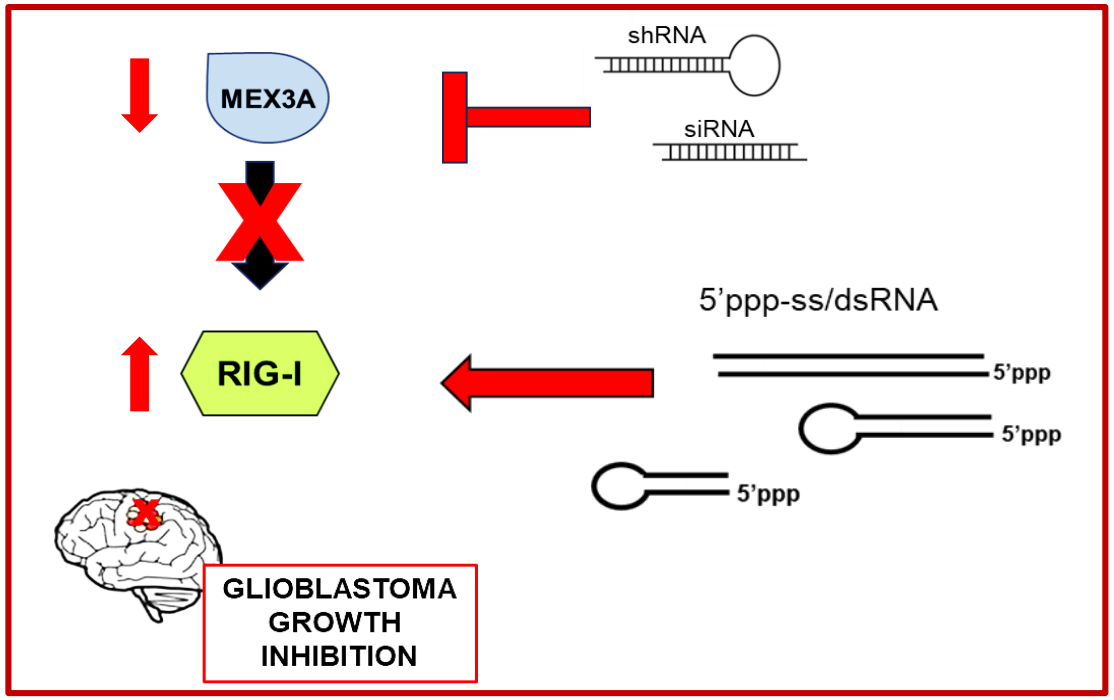




Residual GB cells
Tumor heterogeneity
Immunosuppressive TME

Project strategy





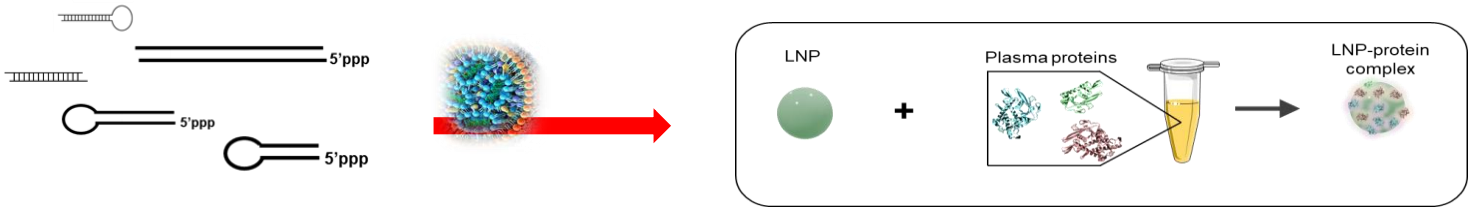
AIM1 → **Design and synthesis of small synthetic RNA molecules to restore the expression and/or to activate RIG-I**

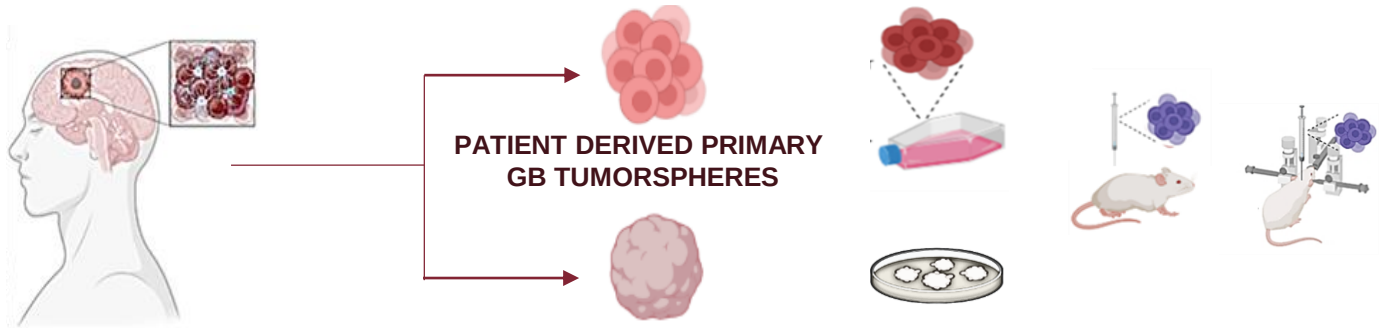
AIM2 → ***In vitro* efficacy and delivery strategies of RNA-based agonists**

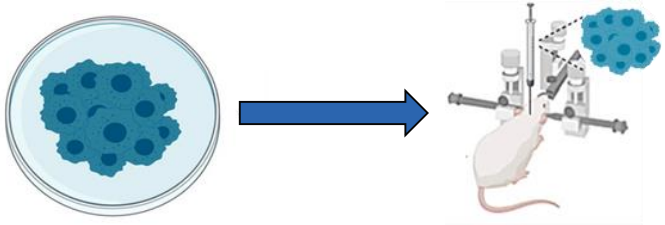
AIM3 → **Evaluation of the immune-mediated anti-tumor effect of selected RIG-I agonists in *in vivo* preclinical models**

In vitro and *in vivo* validation in pre-clinical models

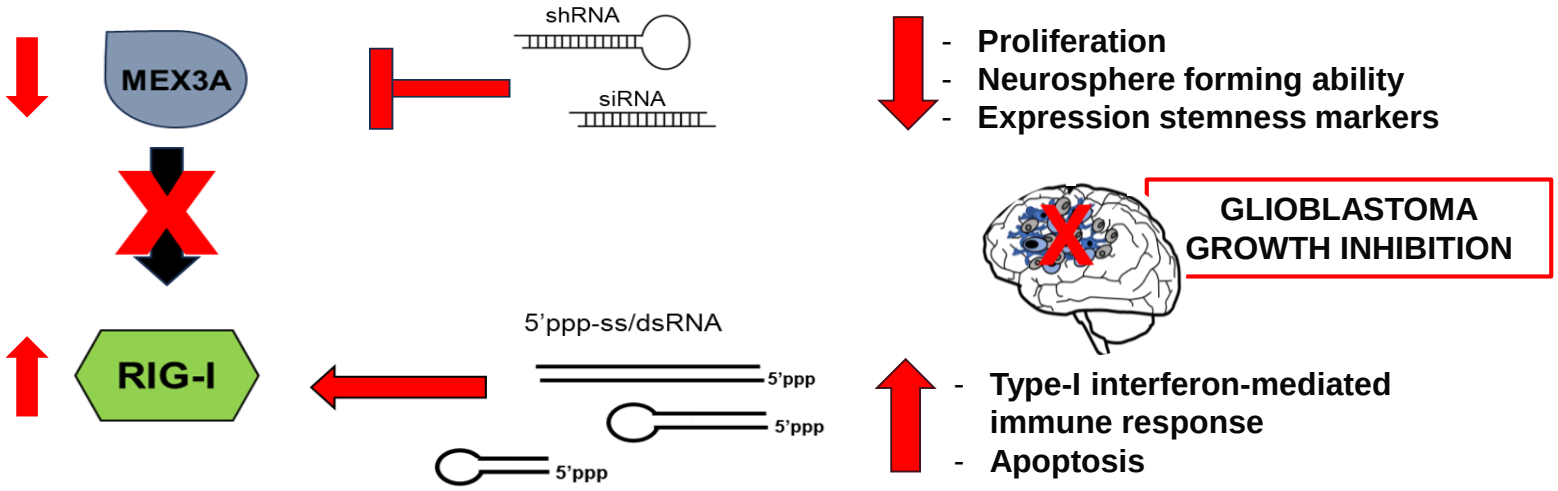
RNA-based molecules delivery

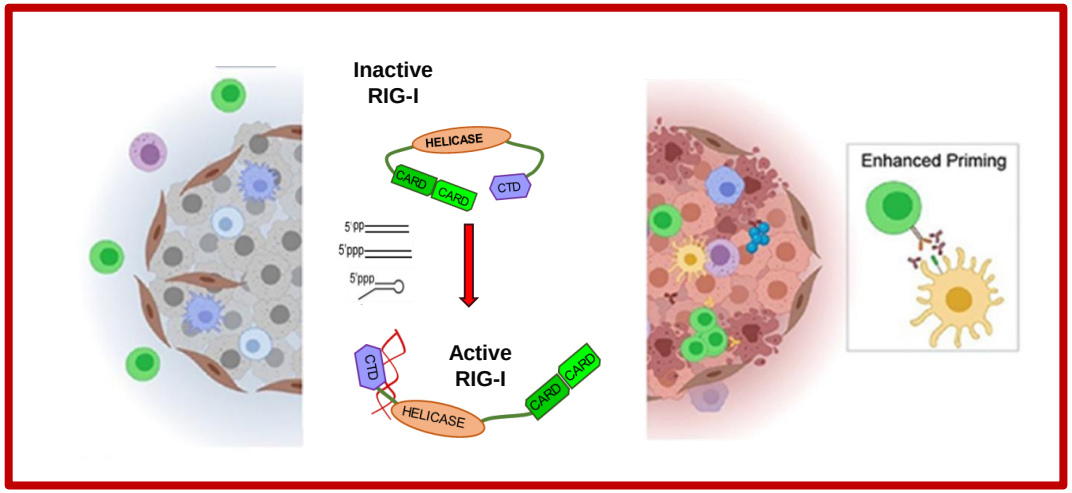






Expected results





Thanks

for your attention

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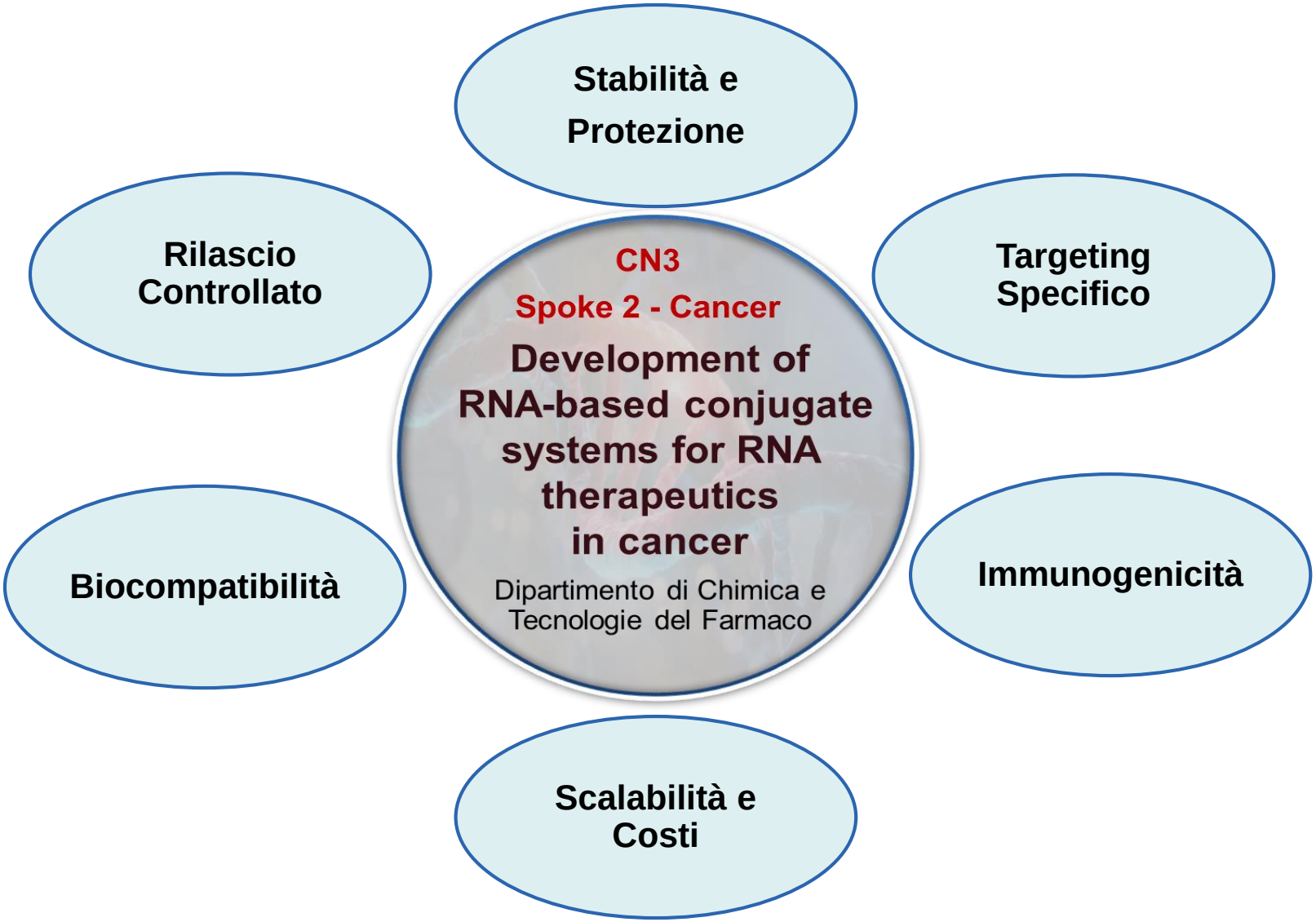
Iniziative PNRR nella Facoltà di Farmacia e Medicina.

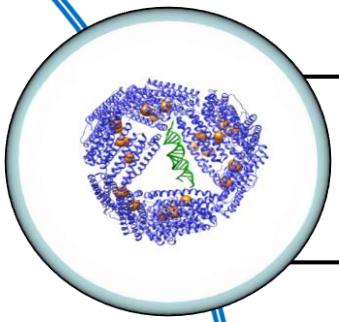
Centro Nazionale 3 - National Center for Gene Therapy & Drugs Based on RNA Technology

Foto: Stefania Sepulcri (Stampa e comunicazione)

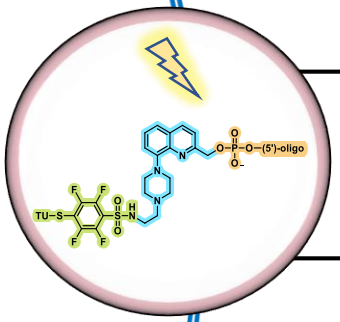
Sfide nello Sviluppo di Bioconiugati per RNA Terapeutici



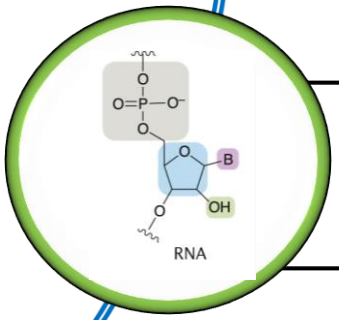
Obiettivi specifici



Sviluppo di bioconiugati basati su molecole policationiche lineari o cicliche per migliorare l'affinità degli RNA terapeutici per la cavità interna di proteine



Sviluppo di bioconiugati sensibili alla luce nel vicino infrarosso (NIR), che permettono un rilascio controllato di RNA terapeutici



Sviluppo di analoghi strutturali di RNA terapeutici attraverso l'esplorazione dello spazio chimico dei nucleosidi e dello scheletro fosfato

Risultati attesi in linea con i pilastri del PNRR

- Avanzamenti scientifici e tecnologici
- Formazione avanzata

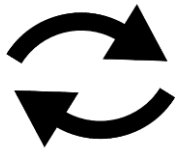
- Accesso universale a trattamenti avanzati
- Applicazioni in ambito sanitario

- Terapie mirate
- Promozione della salute e della qualità della vita

- Innovazione nel settore industriale
- Digitalizzazione dei processi

Impatto previsto

	A breve termine	A lungo termine
Impatto Economico	Crescita dell'industria biotecnologica	Riduzione dei costi per il trattamento dei tumori
Impatto Ambientale	Impatti minimi rispetto a trattamenti tradizionali	Miglioramento della sostenibilità nella produzione di bioconiugati
Impatto Sociale	Miglioramento delle opzioni terapeutiche per i pazienti	Maggiore accesso a terapie innovative



Contatti utili: Dott.ssa *Deborah Quaglio*, RTDB, Dipartimento di Chimica e Tecnlogie del Farmaco, e-mail deborah.quaglio@uniroma1.it

Iniziative PNRR nella Facoltà di Farmacia e Medicina.

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National Center for Gene Therapy and Drugs based on RNA Technology –Spoke 2- Cancer (PNRR M4C2-Investimento 1.4-CN00000041 " finanziato dall'Unione europea – NextGenerationEU

Francesca Cutruzzolà
Dipartimento Scienze Biochimiche A.Rossi Fanelli

RNA &GENETHERAPY

Foto: Stefania Sepulcri (Stampa e comunicazione)

Identification, validation of non-coding RNAs as therapeutic tools in cancer metabolism and delivery

RATIONALE

- Metabolic reprogramming is a hallmark of cancer (**health pillar**)
- Explore the Druggability of RNA Binding Metabolic Enzymes (RBME)

We aim to develop:

- Novel modulatory RNAs targeting RBMEs in cancer metabolism
- Novel delivery methods

The Department of Biochemical Sciences

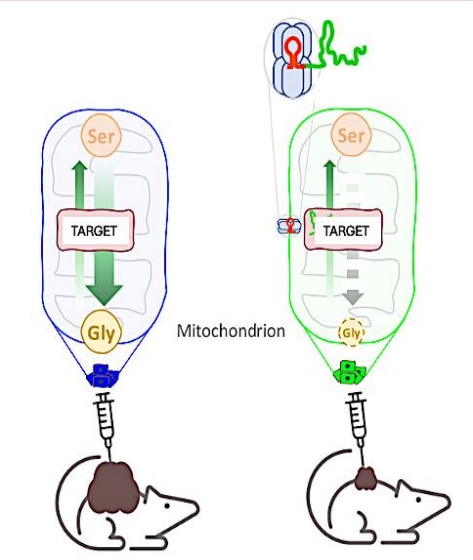
Advanced expertise/instruments on

- Protein biochemistry
- Protein: protein interactions
- Protein:RNA interactions
- Structural Biology
- Mitochondrial biochemistry
- Cancer metabolism

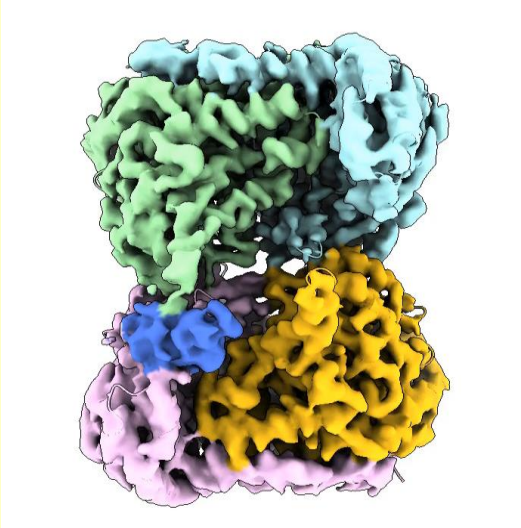
- Protein based nanoparticles and novel delivery methods

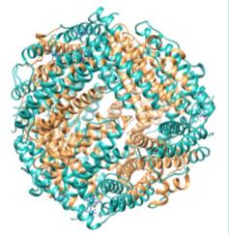
SCIENTIFIC RESULTS AND ADVANCES

Research4health
Translational results



Research4Education
Knowledge





Research4Economy
Technology transfer

Nanoparticles

BENEFICIARIES

Research4health
Citizen

Research4Education
University

Young scientists in STEM

Research4Economy

Research Infrastructure
(RNA formulation lab)

Enterprises

Finanziato dall'Unione europea NextGenerationEU

Ministero dell'Università e della Ricerca

Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA

SAPIENZA UNIVERSITÀ DI ROMA

RNA &GENETHERAPY

GROUP AND CONTACTS

Cutruzzolà Francesca
Boffi Alberto
Rinaldo Serena
Arese Marzia
Paone Alessio
Giardina Giorgio
BaioccoPaola

Sara Di Russo
Chiara Di Lucente
Roberta Piacentini

Sharon Spizzichino
Federica Di Fonzo
Francesca Romana Liberati

Francesca.cutruzzola@uniroma1.it

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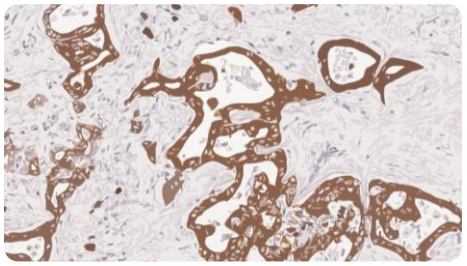
PNRR-CN3_Spoke 2

Definition of RNA therapeutic targets and molecular pathways in Cholangiocarcinoma and Acute Myeloid Leukemia

Foto: Stefania Sepulcri (Stampa e comunicazione)

Definition of RNA therapeutic targets and molecular pathways in Cholangiocarcinoma



PNRR-CN3_Spoke 2

WP2.1 – Sapienza. Co-PI: Prof. E. Gaudio

Task 2.1.1. Identification of Novel RNA targets.

Objective #1. Identification of overexpressed miRNA in cholangiocarcinoma (CCA) to target with miRNA inhibitors and their identification of novel RNA and molecular (SHH, Notch) targets in the CCA (*proff. Gaudio, Carpino, Cardinale*).

Objective #2. Human carbonic anhydrases IX and XII (hCA IX and hCA XII) isoforms as targets for cancer treatment (*prof. Secci*).

Objective #3. Modulation of MIR Oncosuppressor (204-5p, 199b-5p, 579-3p) or Oncongene (miR-4443 and miR-4488) using LNP-miRNA (*prof. Mancini*).

Task 2.1.4. Identification of diagnostic, prognostic, response to therapy biomarkers

Objective #4: Definition of novel RNA therapeutic targets and biomarkers for predicting the therapeutic responsiveness in CCA and their identification in the tumor microenvironment (*proff. Gaudio, Carpino, Cardinale*).

Definition of RNA therapeutic targets and molecular pathways in Acute Myeloid Leukemia

PNRR-CN3_Spoke 2

WP 2.1 - Identification of novel targets for RNA-based therapeutics and biomarkers

WP 2.2 - Prioritization and validation of targets toward clinical applications

In the past decade tremendous progress has been achieved in the development and clinical application of molecular targeted therapies for Acute Myeloid Leukemia (AML). However, **drug resistance** and **relapses** are still major issues rendering the rate of cure unsatisfying. This is mostly due to clonal selection and the **protective effect** of the **leukemic bone marrow microenvironment.**

We previously developed a strategy based **on a combination of drugs inducing proteotoxic and oxidative stress**. We demonstrated that it efficiently leads to cell death of AML cell lines and primary leukemic stem cells (LSCs) bearing the mutation FLT3-ITD, both *in vitro* and *in vivo*.

However, **bone marrow stromal cells** (BMSCs**) protect AML cells by** reducing the amount of oxidative stress generated by the treatment in a co-culture system, where the cells are in direct contact.

Specific Objectives

Our main focus is to investigate the **mechanisms contributing to the protective abilities of the BMSCs.** Furthermore, aiming to **optimize the combination of drugs** to increase its translational potential, we are evaluating the efficacy of combining induction of **proteotoxic stress** with different drugs that are at the cutting edge in clinical trials for AML, among which the **BCL-2 inhibitor Venetoclax**.

- Identification of the **molecular pathways involved in the cross-talk** between Acute Myeloid Leukemia (AML) cells and bone marrow stromal cells (BMSCs) that by cell-cell contacts protect AML cells by reducing the amount of oxidative stress generated by the anti-leukemia treatments.

- Once characterized the molecular pathways modulated in BMSC the specific contribution of the identified pathways will be evaluated, by using **shRNA, siRNA, miRNAs, circRNAs or CRISPR-CAS9 technology**, to assess the capability of BMSC to still protect AML cells to treatments.

- Optimization of the RNA-based therapeutic strategy through an established technology based on autoassembling **ferritin nanoparticles**.

Expected results and impact

Definition of the **mechanotransduction molecular network** as a possible RNA-based therapeutic target to sensitize AML cells to treatments.

Improvement of the **efficacy of a new combined therapeutic strategy** based on proteotoxic stress and the inhibition of the antiapoptotic protein BCL-2.

Reduction of toxic off-target effects by the combination of RNA-based therapeutic strategy and low doses of anti-leukemic drugs

Reduction of healthcare costs and **definition of novel targets** for precision therapies.

Contacts

eugenio.gaudio@uniroma1.it

guido.carpino@uniroma1.it

francesco.fazi@uniroma1.it

silvia.masciarelli@uniroma1.it

claudia.tito@uniroma1.it