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DELLE MARCHE

# AI-powered biochemistry: targeting NAD cofactor essentiality to combat antimicrobial-resistant pathogens

**Supervisor:**
**Prof. Leonardo Sorci**

Department S.I.M.A.U.
Division of Bioinformatics and Biochemistry,
Faculty of Engineering
(https://simau.univpm.it/en/homepage-english/)

**Supervisor:** **Prof. Leonardo Sorci**

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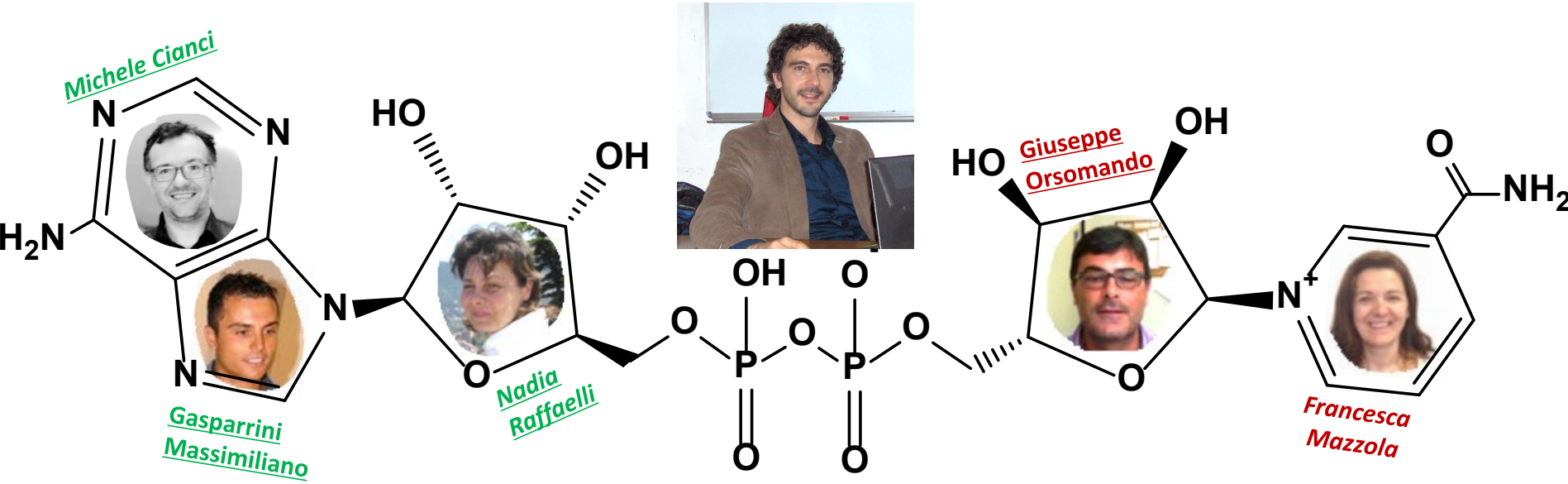
## Research Group Description

**Leonardo Sorci**, Ph.D. in Biomedical Biotechnologies, Associate Professor of Bioinformatics and Biochemistry (*ORCID*, *CV link*, *publications*, H-index 24), former Staff Scientist at Sanford-Burnham-Prebys medical discovery institute, San Diego, California, joins forces with other colleagues at UNIVPM to bring their complementary skills in the area of Biochemistry (**BIOS-07/A Biochemistry)**, sharing their long-term expertise in **NAD cofactor** genomics, metabolism and enzymology.

**Interdepartmental Bioinformatics and Biochemistry lab (IBBL)**

**SIMAU (Bioengineering)**




**D3A (Food Science)**

**DISCO (Medicine)**

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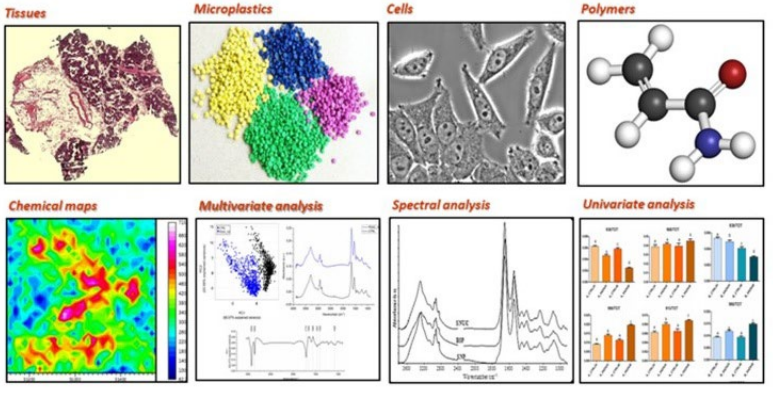
## Department description

(https://simau.univpm.it/en/homepage-english/)

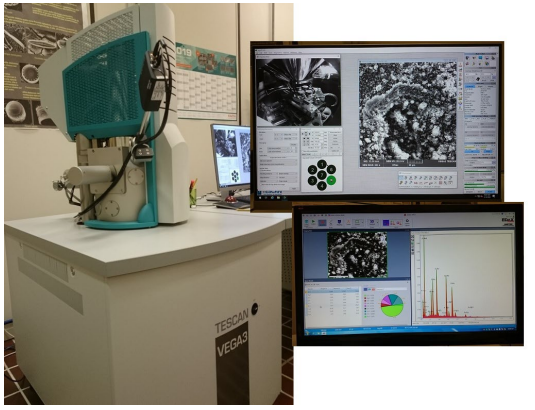
The **Department of Science and Engineering of Materials, Environment and Urban Planning** (**SIMAU**) is a structure in which the **confluence of different expertises** yield high-level teaching and high-profile international research in the field of **Science of Matter** and **Earth Sciences** with a special focus toward the **Environment**.

It operates within the **Engineering Faculty** offering teachers specialised in the so-called «hard sciences» (**Chemistry** and **Physics**) as well as teachers involved in more «applicative» fields, such as **Materials Engineering**, **Geotechnics**, **Geology**, **Environmental Engineering** and **Urban Planning**.

- **TECHNICAL ARCHITECTURE**
- **BIOINFORMATICS AND BIOCHEMISTRY**
- **ECOLOGY**
- **ECONOMICS AND MARKETING**
- **EXPERIMENTAL PHYSICS**
- **CHEMICAL FOUNDATION OF TECHNOLOGIES**




**Research Areas**




- **APPLIED GEOLOGY AND HYDROGEOLOGY**
- **ENVIRONMENTAL AND SANITARY CHEMICAL ENGINEERING**
- **GEOTECHNICAL ENGINEERING**
- **MATERIALS SCIENCE AND TECHNOLOGY**
- **URBAN PLANNING TECHNIQUES**

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# Lab skills/expertise: wet-lab approaches relevant to antimicrobial research

## 1

GENE OR DNA OF INTEREST

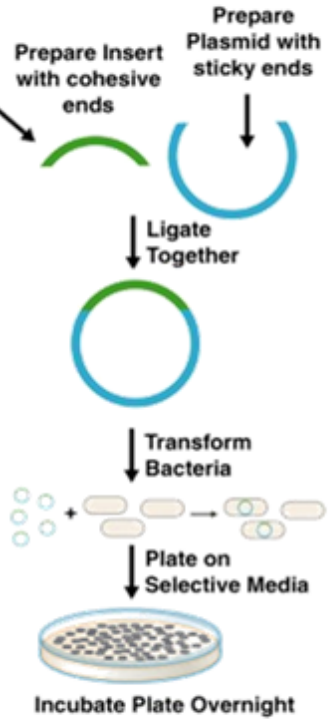
i) isolation

ii) amplification

iii) synthesis

## 2

### GENE CLONING

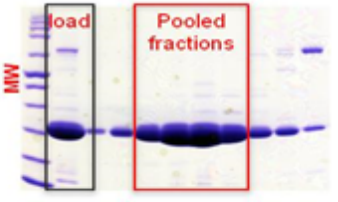



## 3

### PROTEIN EXPRESSION

### PROTEIN PURIFICATION

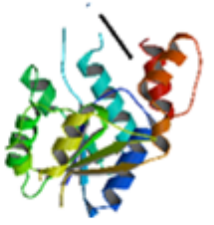
Column Chromatography



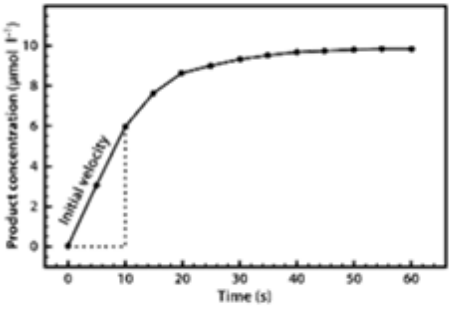

## 4

### PROTEIN CHARACTERIZATION

- Bioch properties
- Bioassay
- Kinetics
- 3D Structure



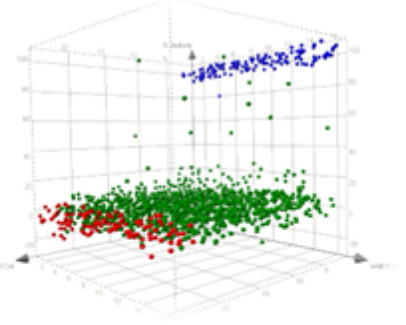
NMN+ATP ➡ NAD+PPi ?




## 5

### LEAD DISCOVERY

- HTS screening
- Cheminformatics artifact filter
- Hit confirmation and selection
- Dose response (IC50, Ki)
- Inhibition mechanism
- Counterscreen



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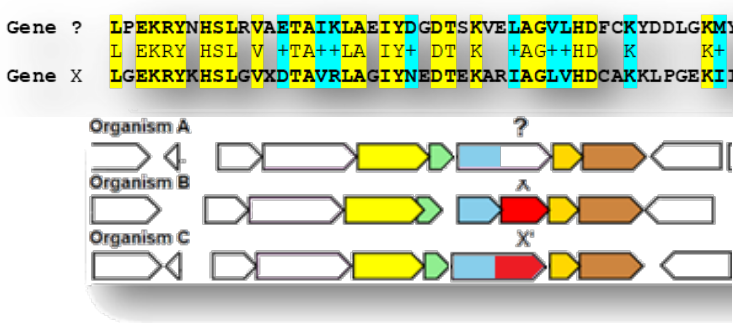
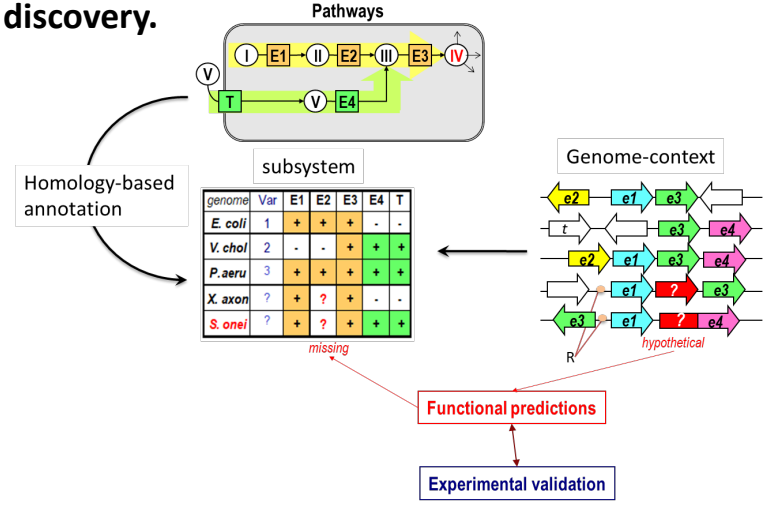
# Lab skills/expertise: in silico and AI-powered approaches relevant to antimicrobial research

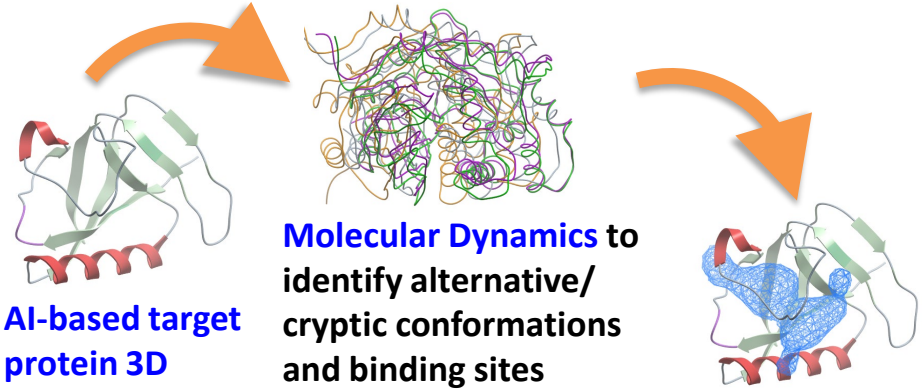
Gene/protein identification and prediction by sequence (*homology*) and comparative genomics (*gene-fusion, clustering, co-regulation*) approaches




Genomics and network-based, including emerging graph-neural networks and trasformer models to identify unexplored target genes for antimicrobial discovery.



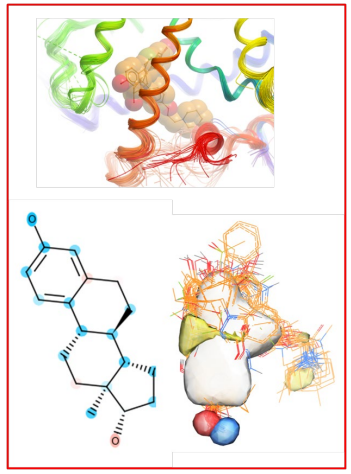

As an integration of, or when experimental 3D structure of the target is unavailable…

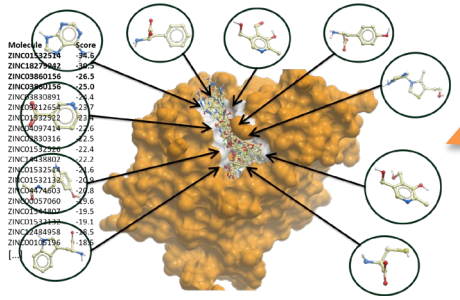


AI-based target protein 3D prediction (includes oligomerization)

Molecular Dynamics to identify alternative/ cryptic conformations and binding sites

Identification of *orthosteric* and *allosteric* binding sites (pocket finder AI-tools)





High quality 2D fingerprint and 3D pharmacophore models used to lead discovery

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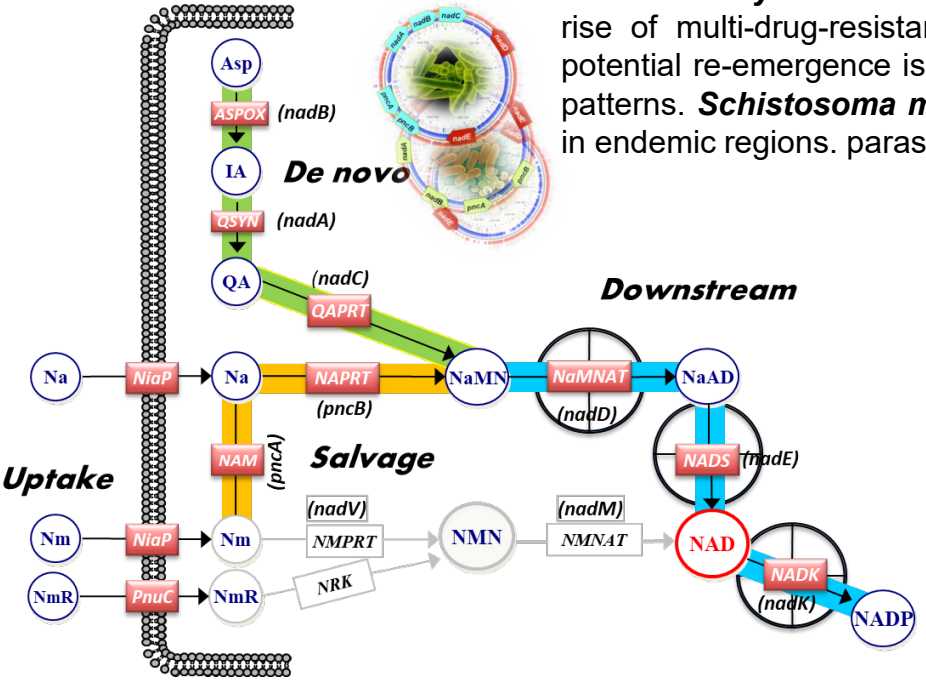
# Project Idea: AI-powered biochemistry: targeting NAD cofactor essentiality to combat antimicrobial-resistant pathogens

**Background**: NAD cofactor metabolism, which is essential for all pathogens, contains several promising drug targets–specifically, between two and five key enzymes that could be exploited to combat infectious diseases. This approach is especially valuable for addressing bacterial infections, given the growing crisis of multidrug resistance. Since bacteria and other pathogens have not yet evolved defenses against them, new NAD-based antibiotics are expected to remain effective for decades to come.

**Objectives**: By combining advanced AI-driven biochemistry and drug discovery with our deep expertise in NAD enzymology and structural biology, we aim to develop novel drug candidates targeting pathogens most prone to antibiotic resistance, thus addressing a critical public health challenge. Our target pathogens include, but are not limited to:

***Acinetobacter baumannii*** and other gram-negative enterobacteria, which represent an active and growing threat in Europe due to their high propensity for developing antibiotic resistance. ***Mycobacterium tuberculosis***, a re-emerging deadly pathogen driven by the rise of multi-drug-resistant strains. ***Plasmodium species (malaria parasites***), whose potential re-emergence is linked to climate change, increased global travel, and migration patterns. ***Schistosoma mansoni***, a parasitic flatworm causing significant disease burden in endemic regions. parasite (flatworm)




## Supervisor's curated publications pertinent to the project.

PNAS, 2008

Chemistry & Biology, 2009

Journal of Biological Chemistry 2010

mBIO, 2014

ACS Chemical Biology, 2019

PLOS Pathogens, 2020

Frontiers in microbiology, 2021

Pharmaceuticals, 2024