UNIVERSITÀ
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DELLE MARCHE

Exploring the role of vitamin B3 metabolism in inflammation

Supervisor: Prof. Nadia Raffaelli

Department D3A - **https://www.d3a.univpm.it/**

UNIVERSITÀ POLITECNICA DELLE MARCHE

Supervisor Prof. Nadia Raffaelli

Research Group Description – the Supervisor

Full Professor of Biochemistry at the Department of Agriculture, Food and Environmental Sciences, and member of the Interdipartimental Biochemistry Lab at the Marche Polytechnic University, Ancona.

More than 100 peer-reviewed research articles with about 4,000 citations received, h-index = 37 according to Scopus (ORCID, CV). More than 30 years experience in the **enzymology of nucleotides metabolism**, with special focus on how the various metabolic pathways leading to **NAD biosynthesis from vitamin B3** are affected depending on the cell-type and metabolic status, and how alteration of the intracellular NAD pool impacts on **energy metabolism and inflammation**.

For more than 10 years academic collaborator for TES Pharma (Perugia, Italy), a company focusing on **drug discovery against key targets in metabolic diseases and oncology**, providing expertise in Biochemistry and Enzymology.

Active research collaborations with national Universities (Genova, Piemonte Orientale, Firenze, Camerino, Milano) and International Institutes (University of Cambridge, University of Liège, University of Oslo, Sunford Barnham Preys in USA).

MOST RELEVANT RESEARCH SUPPORT IN RECENT YEARS

- 2018-2020 - "Understanding and targeting the extracellular NADome in inflammation" (PI), Application 2017CBNCYT, PRIN-MIUR. *The goal of this project was to characterize the enzymes and the metabolites of the NAD biosynthetic pathways which are active in the extracellular environment.*
- 2020-2023 - "Structure-based insights into the inflammatory functions of extracellular NAD biosynthetic enzymes" (PI) – Bando Ricerca Scientifica di Eccellenza 2018, Fondazione Cariverona. *The goal of this project was to structurally characterize the interaction between extracellular NAD biosynthetic enzymes capable of triggering an inflammatory response and their receptor.*

MOST RELEVANT PUBLICATIONS IN RECENT YEARS

- Rosell AL et al, The NAD+ precursor NMN activates dSarm to trigger axon degeneration in Drosophila. ***eLife***, 11, e80245, DOI: 10.7554/ELIFE.80245, 2022
- Gasparrini M et al. Molecular insights into the interaction between human nicotinamide phosphoribosyltransferase and Toll-like receptor 4. ***Journal of Biological Chemistry*** 298(3), 101669, DOI: 10.1016/j.jbc.2022.101669, 2022
- Managò A e al. Extracellular nicotinate phosphoribosyltransferase binds Toll like receptor 4 and mediates inflammation. ***Nature Communications*** 10 (4116), DOI: 10.1038/s41467-019-12055-2, 2019
- Buonvicino D et al. Identification of the Nicotinamide Salvage Pathway as a New Toxification Route for Antimetabolites. ***Cell Chemical Biology*** 25 (4), 471-482, DOI: 10.1016/j.chembiol.2018.01.012, 2018
- Katsyuba E et al. De novo NAD synthesis enhances mitochondrial function and improves health. ***Nature*** 563 (7731) 354- 359, DOI: 10.1038/s41586-018-0645-6, 2018

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Research Group Description – the Group

D3A - DIPARTIMENTO DI SCIENZE AGRARIE, ALIMENTARI E AMBIENTALI

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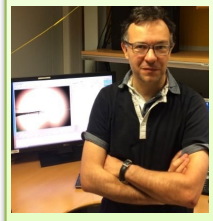
Michele Cianci


Massimiliano Gasparrini


Nadia Raffaelli

Role of vitamin B3 in inflammation, enzymes structure-function, Targeting enzymes for drug development

The **Interdepartmental Biochemistry lab (IBL)** comprises biochemists, molecular biologists, bioinformatics and structural biologists from three UNIVPM departments working together to study the structure, function and dynamics of enzymes.

https://simau.univpm.it/

SCIENZE INGEGNERIA MATERIA AMBIENTE URBANISTICA

DIPARTIMENTO DI SCIENZE E INGEGNERIA DELLA MATERIA, DELL'AMBIENTE ED URBANISTICA


Leonardo Sorci

Computer based modeling of protein structures, protein-protein interactions, AI in protein science

https://disco.univpm.it/

DISCO

DIP. DI SCIENZE CLINICHE SPECIALISTICHE E ODONTOSTOMATOLOGICHE


Giuseppe Orsomando


Francesca Mazzola

Enzymology of NAD metabolism in neurodegerative diseases and cancer

Lab expertise and facilities

- **Gene-to-Protein**
  - *gene cloning*
  - *protein expression (in E.coli, yeasts, baculovirus mediated systems, mammalian cells)*
  - *protein purification*
  - *3D structure resolution through X-ray and Cryo-EM*
- **Enzymatic mechanisms**
- **Metabolites analysis**
- **Bioinformatics and computing**

The lab offers facilities in biochemistry and molecular biology, HPLC, UV-VIS and fluorescence spectroscopy, X-ray crystallography, computational modelling, mamalian cell cultures.

In collaboration with clinical chemists, cell biologists and clinicians, we focus on identifying molecular drivers of human diseases, discovering prognostic and predictive biomarkers and novel therapeutic strategies fighting, among others, cancer and antibiotic resistance.

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Project Idea: Exploring the role of vitamin B3 metabolism in inflammation

BACKGROUND - The coenzyme NAD is critical in cellular bioenergetics and regulatory processes. It is produced from the different forms of vitamin B3 through various metabolic pathways which are controlled by key regulatory enzymes. Unexpectedly, the enzymes controlling NAD biosynthesis from nicotinamide and nicotinic acid (NAMPT and NAPRT in the figure) can be secreted into the extracellular space where they act as cytokines (eNADBEs). With a still unknown mechanism, eNADBEs trigger intracellular signaling pathways that result in a wide range of different effects, like increased aggressiveness in cancer cells and proinflammatory effects in immune cells. Basal levels of circulating eNADBEs can be detected in healthy subjects, and they markedly increase in cancer and inflammatory diseases. **We aim at clarifying the mechanism of action of eNADBEs** with the ultimate goal of controlling the induced inflammatory response.

Project OBJECTIVES

- ***Set up a cellular model to elucidate the molecular mechanisms responsible of the pro-inflammatory effects of NADBEs by using the recombinant purified enzymes***
- ***Identify the receptor(s) of NADBEs and the triggered-signaling pathways***
- ***Characterize the interaction between NADBEs and their receptors at molecular level***
- ***Study the molecular and structural properties of eNADBEs to compare them with the intracellular enzymes***