RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname	Angela Bachi

* Affiliation -IFOM

PHD PROJECT DETAILS

* Title of the proposed project

Unveiling the dark proteome of cancer: Defining the Existence and Therapeutic Potential of Noncanonical ORFs in Cancer

* Short description of the project (up to 300 words)

Recent data indicate that cancer cells express **proteins that are not derived from known open reading frames** as well as **proteins with alterations in amino acid sequences without corresponding DNA mutations**. Current technical advances have revealed the existence of a previously underexplored layer of the human proteome, named the **Dark Proteome**, which consists of small, noncanonical proteins encoded by open reading frames (ncORFs) that were largely overlooked in traditional gene annotation pipelines. These ncORFs, typically found in untranslated regions (UTRs), long noncoding RNAs (lncRNAs), pseudogenes, and transposable elements, are often shorter than canonical proteins, typically producing **miniproteins** (<100 amino acids). However, these short proteins have been increasingly recognized as biologically active, regulating critical cellular functions, signaling pathways, and contributing to the pathophysiology of diseases such as cancer. While ribosome profiling (Ribo-Seq) has been invaluable in identifying the translation of these short peptides, the **direct identification and characterization of these miniproteins** remain a significant challenge due to their small size, low abundance, and the inherent technical limitations of conventional proteomics techniques. This project aims to employ **high-resolution mass spectrometry (MS)** for deep proteome sequencing to systematically identify and characterize expressed miniproteins derived from **noncanonical ORFs** in cancer cells, with a focus on identifying tumor-specific miniproteins that can serve as potential therapeutic targets or tumor-associated antigens.

By systematically characterizing the translation and functional roles of **ncORF-derived miniproteins**, this project will not only expand our understanding of the dark proteome but also provide new insights into tumor-specific vulnerabilities that could lead to **novel strategies targeting miniproteins** for potential therapeutic applications in cancer.

a) * Indicate the main research area for the project described above -Cancer Biology- Fundamental Biological Mechanisms

If needed indicate a second research area for the project described above -

Bioinformatics

* Provide up to 3 key words for project:
Dark proteome, Deep proteomics sequencing, Cancer

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Cancer microenvironment interactions, Proteomics

* Short description of the lab activity (up to 500 words)

Our group is interested in understanding how tumors tame the microenvironment to facilitate growth and spreading. To address this issue we exploit quantitative proteomics, cell and molecular biology to characterize novel cancer vulnerabilities.

* Recent bibliography (max 5 references)

- Tamburri S, Zucchelli C, Matafora V, Zapparoli E, Jevtic Z, Farris F, Iannelli F, Musco G, Bachi A**.** SP140 represses specific loci by recruiting Polycomb Repressive Complex 2 and NuRD Complex. Nucleic Acids Res. 2024 Dec 24: gkae1215. doi: 10.1093/nar/gkae1215.
- Rospo G, Chilà R, Matafora V, Basso V, Lamba S, Bartolini A, Bachi A, Di Nicolantonio F, Mondino A, Germano G, Bardelli A. Non-canonical antigens are the largest fraction of peptides presented by MHC class I in mismatch repair deficient murine colorectal cancer. Genome Med. 2024 Jan 19;16(1):15. doi: 10.1186/s13073-023-01275-3.
- Farris F, Elhagh A, Vigorito I, Alongi N, Pisati F, Giannattasio M, Casagrande F, Veghini L, Corbo V, Tripodo C, Di Napoli A, Matafora V, Bachi A. Unveiling the mechanistic link between extracellular amyloid fibrils, mechano-signaling and YAP activation in cancer. Cell Death Dis. 2024 Jan 11;15(1):28. doi: 10.1038/s41419-024-06424-z
- Jevtic Z, Matafora V, Casagrande F, Santoro F, Minucci S, Garre' M, Rasouli M, Heidenreich O, Musco G, Schwaller J**,** Bachi A. SMARCA5 interacts with NUP98-NSD1 oncofusion protein and sustains hematopoietic cells transformation. *J Exp Clin Cancer Res* 2022 24;41(1):34. doi: 10.1186/s13046-022-02248-x

* Group composition: total members, and roles distribution (PhD, postdoc, technician, etc.)

1 staff scientist
1 post doc
4 PhD students
2 undergraduate students

Institutional page link

https://www.ifom.eu/en/cancer-research/programs/functional-proteomics.php

Lab website link, if any

Social media links, if any

If you prepare a video to promote your lab/project, please include the link below