RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Paola Scaffidi

* Affiliation - IEO

PHD PROJECT DETAILS

* Title of the proposed project

Epigenetic mechanisms in health and cancer

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

Our laboratory investigates how epigenetic mechanisms regulate basic cell function and how their dysregulation favors cancer development, with a particular focus on chromatin-based mechanisms [1]. By combining experimental and computational approaches, we seek to understand: (i) how chromatin structure and modifications define normal cell behavior (ii) the epigenetic basis of malignant cell phenotypes at various stages of cancer development; (ii) associated vulnerabilities that can be exploited to interfere with the disease. See: https://www.research.ieo.it/research-and-technology/principal-investigators/paola-scaffidi/

By combining genetic CRISPR-based approaches, genome-wide molecular methods and *in vivo* functional assays, we have recently uncovered both tumour-suppressive and tumour-promoting epigenetic mechanisms [2-5]. These findings have both revealed novel therapeutic opportunities and increased our basic understanding of how chromatin regulates gene expression and genome integrity.

The project the student will work on and actively develop will focus on one the following themes:

- Histone modifiers in physiology and cancer
- Epigenetic mechanisms of therapy resistance in cancer
- Functional interactions among epigenetic regulators of diverse molecular functions (e.g. chromatin modifiers, chromatin remodelers, DNA modifiers) and synthetic lethality

Investigation of all areas involves a broad range of techniques including CRISPR-mediated genome editing, microscopy and image analysis, advanced cell biology, genome-wide biochemical techniques (e.g. bulk and single-cell RNA-seq, ATAC-seq, CUT&Run/CUT&Tag, proteomics). Specific approaches include DNA barcoding/lineage tracing and use of mouse models (theme 2), high-throughput microscopy, deep learning-based image analysis and system biology (theme 3).

We are looking from students broadly interested in the research topics we focus on. Specific aspects of the projects will be discussed during the interview.

[1] Wilson T and Scaffidi P, *Trends in Cancer*, 2025
[2] Torres CM et al. *Science*, 2016
[3] Monserrat J et al. *Nature Cell Biology*, 2021
[4] Loukas I et al. *Cancer Cell*, 2023
[5] Chakrabarti AM et al. *Molecular Cell*, 2019

First authors of [1] and [3-5] were PhD students.

* Indicate the main research area for the project described above - Molecular and Cellular Biology

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

* Provide up to 3 key words for project:

Epigenetics, Chromatin, Cancer

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Epigenetic mechanisms in health and cancer

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

The Cancer Epigenetics laboratory investigates biological processes driven by non-genetic mechanisms, focusing on the role of epigenetic regulators in cancer initiation and maintenance.

Findings over the past 30 years have strongly implicated epigenetic mechanisms in cancer development. We now know that alterations in chromatin and DNA methylation patterns are a universal feature of the disease, that epigenetic regulators are among the most mutated classes of genes across malignancies, and that transcriptional intratumour heterogeneity shapes the organisation of many cancer types. Building on epigenomics, genomics and transcriptomics studies that have comprehensively profiled epigenome-related alterations in patients, a major goal of the laboratory is to uncover the functional impact of epigenetic deregulation in cancer and the molecular mechanisms underlying these effects. To do so, we study how epigenetics cooperate with genetics and cell-to-cell signalling in defining cancer cell behaviour at various stages of the disease.

We combine CRISPR-based approaches to model mutations in epigenetic regulators, genome-wide mapping methods to characterize how the epigenome responds to genetic and environmental challenges, single-cell transcriptomics and *in vivo* studies to evaluate the biological consequences of these alterations and explore new therapeutic opportunities.

The laboratory is not directly translational, and a strong interest in basic understanding of cancer and/or gene expression regulation is critical to join the group.

* Recent bibliography (max 5 references)

1. Compromised epigenetic robustness in cancer: fueling evolution, exposing weakness.
Wilson TS, Scaffidi P
Trends Cancer. 2025 Mar 6:S2405-8033(25)00044-5

2. Selective advantage of epigenetically disrupted cancer cells via phenotypic inertia.
Loukas I, Simeoni F, Milan M, Inglese P, Patel H, Goldstone R, East P, Strohbuecker S, Mitter R, Talsania B, Tang W, Ratcliffe CDH, Sahai E, Shahrezaei V, Scaffidi P
Cancer Cell. 2023 Jan 9;41(1):70-87.e14

3. Disruption of the MSL complex inhibits tumour maintenance by exacerbating chromosomal instability.
Monserrat J, Morales Torres C, Richardson L, Wilson TS, Patel H, Domart MC, Horswell S, Song OR, Jiang M, Crawford M, Bui M, Dalal Y, Scaffidi P.
Nature Cell Biology. 2021 Apr;23(4):401-412

4. Target-Specific Precision of CRISPR-Mediated Genome Editing.
Chakrabarti AM, Henser-Brownhill T, Monserrat J, Poetsch AR, Luscombe NM, Scaffidi P.
Molecular Cell 2019

5. The linker histone H1.0 generates epigenetic and functional intratumor heterogeneity.
Torres CM, Biran A, Burney MJ, Patel H, Henser-Brownhill T, Cohen AS, Li Y, Ben-Hamo R, Nye E, Spencer-Dene B, Chakravarty P, Efroni S, Matthews N, Misteli T, Meshorer E, Scaffidi P
Science. 2016 Sep 30;353(6307):aaf1644

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

1 Group scientist, 3 Postdocs, 3 PhD students, 1 Research fellow, 2 Master students.

Institutional page link

https://www.research.ieo.it/research-and-technology/principal-investigators/paola-scaffidi/

Lab website link, if any

Social media links, if any

https://x.com/ScaffidiLab

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

Video_Scaffidi