RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Alessio Zippo

* Affiliation UNITN

PHD PROJECT DETAILS

* Title of the proposed project

Epigenetic mechanisms in cancer dormancy

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

After dissemination from the primary tumor, disseminated tumor cells (DTCs) encounter hostile conditions at distant sites, including immune surveillance and growth-restrictive cues from the microenvironment. DTCs can enter a reversible dormant state, enabling them to withstand these challenges for extended periods before reactivating to form overt metastases. We have recently shown that this ability to persist in a non-proliferative state relies on active, adaptive mechanisms, including transcriptional memory, a process by which past environmental signals are epigenetically encoded to shape future gene expression responses. Despite its relevance, the epigenetic regulators underlying transcriptional memory and their role in dormancy remain largely unexplored, representing both a critical knowledge gap and a potential therapeutic window to prevent relapse. With this project, the PhD student will characterize the epigenetic state of quiescent DTCs and identify chromatin factors that support transcriptional memory and enhances their fitness under stress. This project aims to:

- Identify epigenetic changes supporting transcriptional memory in quiescent DTCs.
- Determine whether a primed chromatin landscape facilitates dormancy induction and maintenance.
- Characterize the chromatin factors that preserve dormancy and contribute to metastatic reawakening.

To tackle these questions, the PhD candidate will combine epigenetic profiling with CRISPR-based functional screening, targeting quiescent cancer cells. This interdisciplinary approach will integrate wet-lab techniques and computational analysis, offering a comprehensive training in quantitative cancer biology. Overall, this project offers a unique opportunity to advance our understanding of metastatic dormancy and inform future therapeutic strategies.

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

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

* Provide up to 3 key words for project:

Cancer Dormancy, Epigenetics, transcriptional memory

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

Chromatin Biology, Epigenetics, Biomolecular Condensates, Cancer Biology

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

At the Chromatin Biology & Epigenetics Lab, hosted within the vibrant and international CIBIO Department at the University of Trento, we explore how epigenetic mechanisms drive cellular plasticity in both physiological and pathological contexts. Our overarching goal is to understand how chromatin dynamics and transcriptional regulation support adaptation to environmental cues, with a focus on stem cell biology, cancer progression, and rare genetic diseases.

Our lab pursues three interconnected research lines:

1. Epigenetic Reprogramming and Cancer Plasticity:

We study how epigenetic alterations support tumor progression, metastasis, and dormancy. Using pre-clinical models of aggressive cancers such as triple-negative breast cancer, we investigate how chromatin regulators promote transcriptional memory, a mechanism by which past stimuli are epigenetically encoded to influence future cell states. By combining epigenomic profiling, 3D genome architecture mapping, and CRISPR-based epigenome editing, we uncover how epigenetic plasticity enables disseminated tumor cells to evade immune surveillance and adapt to foreign microenvironments. Our work has revealed that enhancer-mediated transcriptional memory is key to preserving dormancy and we are dissecting the specific contribution of chromatin regulators in this process. More recently, we are implementing the live imaging methodologies to dissect the role of mitotic bookmarking in preserving the epigenetic state at other cis-regulatory elements, ensuring entry into quiescence upon mitotic exit.

2. Oncogene-induced epigenetic reprogramming and replicative stress**:**

In a newly established line of research, we explore how deregulated chromatin factors contribute to genome instability in cancer. IN this respect, a major area of interest is the role of oncogene-induced replicative stress and transcription-replication conflicts (TRCs) in promoting genome instability. Our recent work reveals that the chromatin remodeler ANP32E, often co-upregulated with MYC in breast cancer, drives H2A.Z turnover and alters RNA polymerase II processivity. This disrupts transcription dynamics, causing R-loop accumulation at TRC-prone loci and triggering ATR-dependent DNA damage responses. These insights position ANP32E as a critical mediator of chromatin-induced genomic fragility, with direct implications for therapy: ANP32E-overexpressing tumors display a synthetic vulnerability to ATR inhibition, offering a targeted strategy to suppress their progression.

3. Mechanobiology of Chromatin Condensates: impact on 3D genome organization and integrity

We examine how mutations in chromatin regulators disrupt nuclear organization and genome topology, in the pathological context of rare genetic disorders. A major focus is on Kabuki Syndrome, caused by loss-of-function mutations in MLL4. We develop in vitro disease models to study how MLL4 loss affects the balance between transcriptional and Polycomb condensates, leading to abnormal nuclear mechanics and impaired mechano-responsiveness. We found that MLL4 condensates sense and respond to mechanical stress, safeguarding the nuclear archtecture. We are now investigating how this chromatin-based buffering system contributes to genome surveillance and how its failure drives pathology in developmental syndromes. Using super-resolution imaging, optogenetic tools, and engineered in vitro disease models, we aim to define how nuclear architecture and chromatin mechanics intersect to safeguard genomic integrity.

Our multidisciplinary approach integrates molecular biology, epigenomics, single-cell imaging, computational modeling, and biophysics. The lab is composed of a dynamic and diverse team of researchers, fostering a collaborative and stimulating environment. PhD students in our lab benefit from hands-on training in state-of-the-art techniques and access to a broad scientific network across multiple fields.

* Recent bibliography (max 5 references)

Lago S., Poli V, Fol L, Botteon M, Fasciani A, Turdo A, Gaggianesi M, Todaro M, Ciani Y, D'Amato G, Demichelis F, **Zippo A.**
ANP32E drives vulnerability to ATR inhibitors by inducing R-loops-dependent Transcription Replication Conflicts in Triple Negative Breast Cancer
Nat Commun. 2025, accepted

Zippo A*, Beyes S*.
Molecular mechanisms altering cell identity in cancer.
Oncogene. 2025 Feb 26.
* Co-senior Authors

Michelatti D, Beyes S, Bernardis C, Negri ML, Morelli L, Bediaga NG, Poli V, Fagnocchi L, Lago S, D'Annunzio S, Cona N, Gaspardo I, Bianchi A, Jovetic J, Gianesello M, Turdo A, D'Accardo C, Gaggianesi M, Dori M, Forcato M, Crispatzu G, Rada-Iglesias A, Sosa MS, Timmers HTM, Bicciato S, Todaro M, Tiberi L, **Zippo A.**
Oncogenic enhancers prime quiescent metastatic cells to escape NK immune surveillance by eliciting transcriptional memory.
Nat Commun. 2024 Mar 19;15(1):2198.

Fasciani A, D'Annunzio S, Poli V, Fagnocchi L, Beyes S, Michelatti D, Corazza F, Antonelli L, Gregoretti F, Oliva G, Belli R, Peroni D, Domenici E, Zambrano S, Intartaglia D, Settembre C, Conte I, Testi C, Vergyris P, Ruocco G, **Zippo A.**
MLL4-associated condensates counterbalance Polycomb-mediated nuclear mechanical stress in Kabuki Syndrome
Nature Genetics, 2020 Dec;52(12):1397-1411

Poli V, Fagnocchi L, Fasciani A, Cherubini A, Mazzoleni S, Ferrillo S, Miluzio A, Gaudioso G, Vaira V, Turdo A, Gaggianesi M, Chinnici A, Lipari E, Bicciato S, Bosari S, Todaro M, Zippo A.
MYC-driven epigenetic reprogramming favors the onset of tumorigensis by inducing a stem cell-like state
Nature Communications, 2018 March 9;9(1):1024.

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

12 members: 4 Postdocs, 5 PhD, 2 undergraduate students, 1 Lab Manager

Institutional page link

https://www.cibio.unitn.it/

Lab website link, if any

https://www.cibio.unitn.it/675/laboratory-of-chromatin-biology-epigenetics

Social media links, if any

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