European School of Molecular Medicine

RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Alessio ZIppo

* Affiliation UNITN

PHD PROJECT DETAILS

* Title of the proposed project

Computational Epigenetics in cancer progression

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

Tumor relapse and metastasis formation rely on the capability of cancer cells to adapt to hostile microenvironments once disseminated on distal sites. The project is centered on determining the contribution of epigenetic rewiring in promoting tumor progression and metastasis formation. While the occurrence of epigenetic modifications as drivers of tumorigenesis is widely documented, the contribution of chromatin topology rearrangements and its interplay with genomic alterations is far from being understood. By combining epigenome profiling with graph-based methodologies to solve genome topology hierarchy, the herein program aims to gain insights on epigenetic heterogeneity and its impact on cancer cell adaptation to hostile conditions encountered at distant sites. With this project, the PhD candidate will develop and apply graph-theoretical approaches, including contrast subgraph mining, community detection, and centrality analysis to identify topological features linked to tumor progression and metastasis formation. Indeed, we have already developed a novel computational approach to interrogate the 3D genome topology across scales, which permits to weight the relevance of chromatin interactions in defining the multiscale levels of genome topology. Additionally, we aim to investigate the effect of cancer genomic alterations on chromatin organization, with a specific emphasis on copy number variations. Finally, the integration of chromatin interaction data with epigenomic and transcriptomic profiles at single cell level will allow the PhD student to uncover multi-layered regulatory circuits supporting metastasis. The project will involve the development of a reproducible, open-source software toolkit for chromatin topology analysis, with the opportunity to work at the interface of computational biology, cancer genomics, and machine learning. This position offers a unique training environment in quantitative cancer biology, supported by strong collaborations with experimental labs and exposure to state-of-the-art epigenomics technologies.

* Indicate the main research area for the project described above Computational biology

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

* Provide up to 3 key words for project:

Computational Biology, 3D chromatin organization, multi-omics data analyses

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 architecture. 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