RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Ylli Doksani

* Affiliation IFOM

PHD PROJECT DETAILS

* Title of the proposed project

Unraveling the Mechanisms of eccDNA Formation

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

Extrachromosomal circular DNA (eccDNA) represents a unique form of genetic material that exists outside chromosomal DNA. These circular elements are increasingly recognized for their role in genome plasticity, particularly in cancer, where they contribute to oncogene amplification, drug resistance, and tumor heterogeneity. Despite their biological significance, the precise mechanisms governing eccDNA formation and maintenance remain largely unknown.

Recent findings from our laboratory have identified a mechanism by which eccDNA is generated at repetitive elements—regions of the genome known for their susceptibility to instability and rearrangement. These discoveries suggest that specific genomic features and molecular processes drive the formation of eccDNA, raising fundamental questions about its regulation and function in both normal and disease states.

This project aims to uncover the molecular mechanisms underlying eccDNA generation and persistence, focusing on the role of repetitive elements in this process. The study will integrate advanced molecular biology, genetics, and genomics approaches to dissect the pathways involved. CRISPR-based genome editing will be used to manipulate key genomic loci and assess their contribution to eccDNA formation, while high-throughput sequencing and computational analyses will characterize the composition and dynamics of eccDNA populations. Additionally, chromatin and protein interaction assays will be employed to explore the regulatory factors that influence eccDNA stability and function.

By elucidating the fundamental mechanisms of eccDNA formation, this research will provide new insights into genome stability and its implications in cancer and other diseases. The project will contribute to a deeper understanding of how the genome reorganizes itself through circular DNA elements, with potential implications for future therapeutic strategies targeting eccDNA-driven genomic alterations.

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

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

* Provide up to 3 key words for project:

Extrachromosomal circular DNA (eccDNA), Genome instability, Repetitive elements

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

DNA replication stress, genome instability, telomere metabolism, eccD

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

Our lab investigates how cells cope with DNA replication stress and maintain genome stability, with a particular focus on telomeres—the protective caps of chromosomes—and extrachromosomal circular DNA (eccDNA). We study how DNA damage accumulates at fragile genomic regions and explore the structural changes that occur at telomeres during replication and repair.
Using unique tools developed in our lab, we have discovered that DNA damage at telomeres can trigger the formation of intramolecular loops (i-loops), which may be excised as circular DNA. We have also uncovered a novel role for telomerase in processing reversed replication forks at telomeres, providing new insights into telomere maintenance.

To dissect these mechanisms, we combine molecular and cellular biology with state-of-the-art methodologies, including advanced imaging, electron microscopy, and genomics approaches. In particular, we leverage third-generation nanopore sequencing to map structural variations and characterize eccDNA, but also monitor replication stress at an unprecedented resolution. Beyond telomeres, we are exploring whether similar mechanisms drive genome instability and eccDNA formation at other repetitive elements. By integrating these cutting-edge techniques, we aim to uncover fundamental principles of genome integrity with important implications for cancer and aging.

* Recent bibliography (max 5 references)

1. Huda, A., Arakawa, H., Mazzucco, G., Galli, M., Petrocelli, V., Casola, S., Chen, L. & Doksani, Y. The telomerase reverse transcriptase elongates reversed replication forks at telomeric repeats. Sci Adv 9, eadf2011 (2023). 36947627
2. Mazzucco, G., Huda, A., Galli, M., Piccini, D., Giannattasio, M., Pessina, F. & Doksani, Y. Telomere damage induces internal loops that generate telomeric circles. Nat Commun 11, 5297 (2020). 33082350
3. Mazzucco, G., Huda, A., Galli, M., Zanella, E. & Doksani, Y. Purification of mammalian telomeric DNA for single-molecule analysis. Nat Protoc 17, 1444-1467 (2022). 35396546
4. Pessina, F., Romussi, A., Piccini, D., Mazzucco, G, Varasi, M. & Doksani, Y. Enrichment of DNA replication intermediates by EdU pull down. Methods in Cell Biology (2022).
5. Zanella, E. & Doksani, Y. In the Loop: Unusual DNA Structures at Telomeric Repeats and Their Impact on Telomere Function. Cold Spring Harb Perspect Biol (2025). 40097153

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

One staff scientist, two postdocs, two PhD students, one research fellow and one undergraduate student.

Institutional page link

https://www.ifom.eu/en/cancer-research/research-labs/research-lab-doksani.php

Lab website link, if any

Social media links, if any

https://bsky.app/profile/doksanilab.bsky.social;
https://sciencemastodon.com/@DoksaniLab;
https://x.com/doksanilab?lang=en

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