RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Fabrizio d'Adda di Fagagna

* Affiliation IFOM

PHD PROJECT DETAILS

* Title of the proposed project

Targeting ALT-positive tumors with antisense oligonucleotides: telomere biology, mechanisms, and resistance

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

This project aims at uncovering the mechanism of action of a novel anticancer drug based on a telomeric antisense oligonucleotide (ASO) approach. This drug has demonstrated specificity against ALT-positive cancers, a subtype characterized by a specific mechanism of telomere maintenance. Notably, ALT-positive cancers include aggressive tumors such as osteosarcoma and glioblastoma, for which effective therapies are currently lacking. Addressing this unmet clinical need, our research focuses on advancing a targeted therapeutic strategy with the potential for significant impact.

The great attractivity of this project lies in the rich and unpublished dataset from comprehensive genetic, pharmacological, and proteomic screens, that provides an alluring opportunity for in-depth mechanistic studies. The candidate will build on this data to investigate how telomeric ASO exerts its anticancer effects. Using both hypothesis-driven and unbiased strategies, the project will explore molecular pathways and cellular processes modulated by the ASO treatment.

In parallel with mechanistic studies, the project will investigate potential synergistic therapeutic approaches and mechanisms of resistance that may limit the efficacy of the ASO. Leveraging our existing screening data, the candidate will explore combination treatments that could enhance the drug's activity or overcome resistance pathways.

Techniques involved in this project will span molecular biology, cell biology, and advanced omics, progressing to in vivo validation in relevant ALT-positive cancer models.

These findings will inform translational strategies aimed at improving therapeutic options for patients with ALT-positive malignancies.

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

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

* Provide up to 3 key words for project:

Telomere biology, ALT-positive cancer, Antisense oligonucleotide therapy

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

- DNA Damage Response (DDR) mechanisms
- Telomere Biology
- Aging and age-related mechanisms
- Alternative Lengthening of Telomeres (ALT) in cancer
- Non-Coding RNAs in DDR
- Therapeutic Targeting of DDR
- DNA damage and neurodegeneration

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

We study the physiological consequences of DNA damage at the cellular and organismal levels in mammals. Nuclear DNA damage activates the DNA damage response (DDR), a pathway that coordinates cell-cycle arrest and DNA repair. Persistent DDR signaling leads to cellular senescence, a condition in which cells remain alive but stop dividing.

Our research has expanded into the role of non-coding RNAs (ncRNAs) generated at DNA damage sites. These ncRNAs are critical for DDR activation, including signaling and repair (d'Adda di Fagagna, Trends in Cell Biology 2013; Michelini, Chemical Reviews 2018). We found that RNA polymerase II, recruited by the MRE11-RAD50-NBS1 (MRN) complex to DNA double-strand breaks (DSBs), synthesizes damage-induced long non-coding RNAs (dilncRNAs). These dilncRNAs are processed by Drosha and Dicer into shorter DDRNAs, which promote liquid-liquid phase separation (LLPS) of DDR factors at damage sites (Francia, Nature 2012; Michelini, Nature Cell Biology 2017; Pessina Nature Cell Biology 2019). Additionally, the pre-initiation complex (PIC) is recruited to DSBs, similar to canonical transcription initiation (Pessina Nature Cell Biology 2019). DNA:RNA hybrids formed during DSB resection can regulate repair by homologous recombination (D'Alessandro, Nature Communications 2018).

We can modulate DDRNA formation with small molecules (Gioia, Scientific reports 2019), and antisense oligonucleotides (ASOs) targeting dilncRNAs and DDRNAs allow precise DDR inhibition at specific genomic sites (Michelini, Nature Cell Biology 2017).

Short or damaged telomeres trigger DDR and senescence, contributing to aging and related diseases (Rossiello, Nature Cell Biology 2022). We showed that dilncRNA and DDRNA accumulate at dysfunctional telomeres, and using telomere-targeted ASOs (tASOs), we selectively inhibited DDR at telomeres in cells and mice (Rossiello, Nature Communications 2017). tASOs improved cell proliferation in Hutchinson-Gilford Progeria Syndrome (HGPS) patient cells and enhanced tissue homeostasis and lifespan in a mouse model of accelerated aging (Aguado, Nature Communications 2019).

Recently, we demonstrated that tASOs can selectively target DDR at telomeres in ALT-positive cancers, triggering cancer-specific cell death without affecting normal cells or telomerase-positive tumors. This provides a promising new therapeutic strategy for ALT-dependent cancers (Rosso, Nature Communications 2023).

We have additional unpublished data from mouse and fish models confirming the safety and efficacy of tASOs for human conditions caused by telomere dysfunction. We are also exploring targeting recurring DNA damage in cancer cells and investigating DNA damage's role in neurodegeneration.

* Recent bibliography (max 5 references)

- The complex interplay between aging and cancer. Trastus LA, d'Adda di Fagagna F. Nature Aging, 2025. https://rdcu.be/eb9Kq
- Alternative lengthening of telomeres (ALT) cells viability is dependent on C-rich telomeric RNAs. Rosso I, Jones-Weinert C, Rossiello F, Cabrini M, Brambillasca S, Munoz-Sagredo L, Lavagnino Z, Martini E, Tedone E, Garre' M, Aguado J, Parazzoli D, Mione M, Shay JW, Mercurio C, d'Adda di Fagagna F. Nature Communications, 2023
- SARS-CoV-2 infection induces DNA damage, through CHK1 degradation and impaired 53BP1 recruitment, and cellular senescence. Gioia U, Tavella S, Martínez-Orellana P, Cicio G, Colliva A, Ceccon M, Cabrini M, Henriques AC, Fumagalli V, Paldino A, Presot E, Rajasekharan S, Iacomino N, Pisati F, Matti V, Sepe S, Conte MI, Barozzi S, Lavagnino Z, Carletti T, Volpe MC, Cavalcante P, Iannacone M, Rampazzo C, Bussani R, Tripodo C, Zacchigna S, Marcello A, d'Adda di Fagagna F. Nature Cell Biology, 2023
- Colorectal cancer patient-derived organoids and cell lines harboring ATRX and/or DAXX mutations lack Alternative Lengthening of Telomeres (ALT). Falcinelli M, Dell'Omo G, Grassi E, Mariella E, Leto SM, Scardellato S, Lorenzato A, Arena S, Bertotti A, Trusolino L, Bardelli A, d'Adda di Fagagna F. Cell Death & Disease, 2023
- Telomere dysfunction in ageing and age-related diseases. Rossiello F, Jurk D, Passos JF, d'Adda di Fagagna F. Nature Cell Biology, 2022

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

13 members: 3 PhD students, 6 postdocs, 2 staff scientists, 2 technicians.

Institutional page link

https://www.ifom.eu/en/

Lab website link, if any

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

Social media links, if any

https://www.linkedin.com/in/fabrizio-d-adda-di-fagagna-76319b4/
x.com/FdAdF66
fdadf.bsky.social

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

We know why we age – TEDx Talk: https://www.youtube.com/watch?v=yTGj-5BVLXs
La domotica del cancro: https://www.youtube.com/watch?v=Hh9Wy73aZBg
Intervista Elisir Rai3 (min. 1-11): https://www.raiplay.it/video/2025/03/Elisir---Puntata-del-19032025-2b5315c8-9106-4208-babe-482624edf653.html