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

Telomere dynamics in aging and cancer: exploring therapeutic potential beyond cancer cells

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

This project investigates how aging-induced telomere dysfunction impacts non-cancer cells and contributes to tumorigenesis in aging and cancer.

Telomere dysfunction is a hallmark of aging and a driver of immunosenescence, contributing to impaired T cell function and diminished immune surveillance in cancer. Our recent unpublished work demonstrates that telomeric DNA damage response (tDDR) inhibition by telomeric antisense oligonucleotides (tASO) treatment improves hematopoietic stem and progenitor cell (HSPC) fitness and restores lymphoid and myeloid cell levels in telomerase-deficient (Terc-/-) mice, an accelerated aging model. This treatment is robust and quite long lasting. Building on these findings, this project will explore the broader impact of tDDR inhibition on immune system rejuvenation and cancer progression. In addition to immune cells, we will examine how telomere dysfunction in tumor microenvironment (TME) non-cancer cells, including stromal cells, influences tumor growth. Cancer-associated fibroblasts (CAFs) with telomere shortening and genomic instability promote tumor progression, but the role of tDDR remains unknown. Epigenetic studies will be conducted to investigate the impact on DNA and chromatin modifications of tASO treatment, aiming to understand the long-term effects of this therapy.

We hypothesize that tDDR inhibition can mitigate aging-related cellular dysfunction in the tumor microenvironment, improving overall tissue homeostasis and immune system functionality. To test this, the candidate will evaluate tASO treatment effects on vaccine response in Terc-/- and aged wild-type (WT) mice to assess immune rejuvenation. tASO treatment will be tested in vivo in a murine tumor model to assess its impact on tumor progression and tissue health.

By integrating aging and cancer research, this project aims to provide a comprehensive understanding of how telomere dysfunction impacts immune and stromal cells in the TME, offering novel therapeutic strategies for aging and cancer.

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

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

* Provide up to 3 key words for project:

Telomere biology, Immunosenescence, Aging

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