European School of Molecular Medicine

2026 Summer call PhD selections

AVAILABLE POSITIONS

Principal Investigator	Fabrizio d'Adda di Fagagna
Institute of Affiliation	IFOM ETS - The AIRC Institute of Molecular Oncology

PROJECT INFO	
Title of the proposed project:	Targeting Genomic Instability in Neurodegeneration and Brain Cancer: Mechanisms, Interplay, and Therapeutic Opportunities
Short description of the project	Maintenance of genomic integrity is essential for cellular homeostasis, and its progressive decline represents one of several interconnected hallmarks of aging. Aging is a major risk factor for both neurodegenerative diseases and cancer, two conditions that, despite their distinct manifestations, share overlapping mechanisms, including dysregulated DNA damage responses and genomic instability. In neurons, which are post-mitotic and long-lived, the accumulation of DNA damage contributes to functional decline and progressive neurodegeneration. In contrast, in proliferating cells such as cancer cells, defects in DNA damage response (DDR) pathways promote genomic instability, facilitating uncontrolled growth and tumorigenesis. Despite these divergent outcomes, emerging evidence suggests that shared mechanisms involving DNA damage signaling, chromatin remodeling, and transcriptional regulation may underlie both processes. This project aims to investigate DNA damage as a central node linking neuronal dysfunction and tumorigenesis in the brain. A key focus will be placed on how neuronal activity, mediated by NMDA receptor signaling, induces genome-wide DNA damage and shapes transcriptional programs. While this process may support physiological plasticity, its dysregulation could drive persistent genomic instability, contributing to neurodegeneration and potentially influencing tumor–neuron interactions in brain cancers such as glioblastoma. The strength of this project lies in the integration of neuronal and cancer models with advanced genomic and transcriptomic approaches. The project aims to map DNA damage landscapes and associated transcriptional changes using genome-wide techniques. In parallel, the project will explore shared vulnerabilities across neurodegenerative and tumor systems, including potential therapeutic targeting of DNA damage signaling pathways. Mechanistic studies will be complemented by the investigation of combination strategies and factors that may modulate cellular responses to genomic instability. Techniques involved will include molecular and cellular biology, high-throughput sequencing, and functional assays, with the potential to extend findings toward in vivo validation. Ultimately, this work aims to redefine DNA damage as an active regulatory process in brain biology and disease, and to identify novel

	therapeutic targets that can be exploited across both neurodegenerative and oncological contexts.
Main research area for the project	Cancer Biology
Second research area for the project	Neurobiology
3 key words for the project	DNA damage response; neurodegeneration; glioblastoma

LAB INFO	
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 brain disorders
Short description of the lab activity	The laboratory investigates the biological consequences of DNA damage in mammals across multiple contexts relevant to aging and disease. In particular, our research focuses on how DNA damage and the subsequent DNA damage response (DDR) influence cellular fate and genome stability. Persistent DDR signaling leads to cellular senescence, a condition in which cells remain alive but stop dividing. We have extensively characterized multiple forms of senescence, including DNA damage-induced senescence (d'adda di Fagagna, Nature Review Cancer 2008), oncogene-induced senescence (Di Micco, Nature, 2006), and replicative senescence driven by telomere shortening (d'Adda di Fagagna, Nature, 2003). Telomere biology represents a central focus of our work, as telomere dysfunction is a major endogenous source of DNA damage and a primary driver of replicative senescence (Rossiello, Nature Cell Biology 2022). Short or damaged telomeres trigger DDR activation and contribute to aging and related diseases. At the molecular level, we have uncovered a fundamental role for non-coding RNAs (ncRNAs) generated at sites of DNA damage (dilncRNAs), including dysfunctional telomeres, in regulating DDR activation (d'Adda di Fagagna, Trends in Cell Biology 2013; Michelini, Chemical Reviews 2018). Building on these findings, we exploit antisense oligonucleotide (ASO)-based strategies and small molecules to selectively target DNA damage signaling. In particular, ASOs targeting dilncRNAs enable locus-specific modulation of DDR. At telomeres, we have developed telomere-targeting ASOs (tASOs) to selectively inhibit DDR at dysfunctional telomeres in cells and in vivo (Rossiello, Nature Communications 2017). These approaches have shown therapeutic potential in models of premature aging, improving cellular function and organismal homeostasis (Aguado, Nature Communications 2019,), and in ALT-dependent cancers (Rosso, Nature Communications 2023), where targeting telomeric DDR can induce cancer-specific cell

	death. Ongoing work is extending these strategies to additional models, including brain cancer and neurodegeneration. Together, this integrated approach aims to define the mechanisms linking DNA damage, senescence, and genome regulation, and to translate them into novel therapeutic opportunities.
Recent bibliography	- Therapeutic inhibition of telomeric DNA damage response rescues hematopoietic dysfunction driven by telomere shortening and aging. Oppezzo A, Sepe S, Cicio G, Cancila V, Sasso E, Conti A, Marinelli E, Cabrini M, Pallavi R, Iacomino N, Simoni M, Malyshev D, Boggio S, di Lillo A, Rosso I, Tavella S, Trastus L, Rossiello F, Roscia G, Cantaloni P, Manenti A, Cavalcante P, Pelicci PG, Di Micco R, Nicosia A, Tripodo C, d'Adda di Fagagna F. Nature Aging, 2026 - Telomeric DNA damage response mediates neurotoxicity of Aβ42 oligomers in Alzheimer's disease. Sepe S, Rey F, Mancheno-Ferris A, Bigi A, Fani G, Damiani D, Cabrini M, Marinelli E, Aguado J, Contu L, di Lillo A, Boggio S, Tavella S, Rosso I, Gustincich S, Chiti F, d'Adda di Fagagna F. EMBO J, 2025 - The complex interplay between aging and cancer. Trastus LA, d'Adda di Fagagna F. Nature Aging, 2025. - 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
Group composition	9 members: 2 PhD students, 5 postdocs, 1 staff scientist, 1 technician.
Institutional page link	https://www.ifom.eu/en/
Lab website link	https://www.ifom.eu/en/cancer-research/research-labs/research-lab-daddadifagagna.php
Social media links	https://www.linkedin.com/in/fabrizio-d-adda-di-fagagna-76319b4/ x.com/FdAdF66 fdadf.bsky.social

Video link	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