European School of Molecular Medicine

2026 spring call PhD selections

AVAILABLE POSITIONS

Principal Investigator	Vincenzo Costanzo
Institute of Affiliation	IFOM

PROJECT 1 INFO	
Title of the proposed project:	Synthetic Lethality Approaches to selectively kill BRCA1 and BRCA2 Deficient Tumors by targeting DNA replication gaps
Short description of the project	Homologous recombination (HR) repair is defective in more than 70% of human tumors. Among these there are breast, ovaries, prostate and pancreatic tumors. HR-deficient tumors, such as those with BRCA1/2 mutations, exhibit increased reliance on alternative DNA damage tolerance mechanisms, including translesion synthesis (TLS) polymerases and polymerase theta (Polθ) mediated alternative end-joining pathways. Recent studies from the Costanzo's lab (Hanthi et al Mol Cell 2024, Mann et al Mol Cell 2022, Taglialatela et al Mol Cell 2021) indicate that replication gaps linked to the occurrence of abasic sites, rather than double-strand breaks, may be the primary source of genome instability in these cancers, representing a novel therapeutic vulnerability. This project will utilize high-throughput CRISPR-based functional genomics, proteomics, NGS and nanopore DNA sequencing approaches to identify key regulators of replication gap suppression together with advanced DNA electron-microscopy and DNA fiber analysis to validate them. A major focus will be on understanding how ssDNA gaps form and how they are suppressed by tolerance mechanisms. The project will aim at targeting newly identified and known factors such as TLS polymerases (REV1 and Polζ) and Polθ, responsible for the compensatory mechanisms linked to the survival of HR-deficient tumors. By selectively disrupting these pathways, the study aims to exploit synthetic lethality to enhance the efficacy of existing therapies, such as PARP inhibitors, and to identify novel target candidates to eliminate HR-deficient tumors. This is a rare opportunity to train across genomics, proteomics, and genome stability research, using technologies available in only a handful of laboratories worldwide, within the highly collaborative and international environment at IFOM.
Main research area for the project	Cancer Biology
Second research area for the project	Molecular Biology
3 key words for the project	DNA repair, Cancer therapy, Synthetic lethality

LAB INFO	
Main topic/s of the lab	DNA Metabolism and Genome Stability Laboratory
Short description of the lab activity	The DNA Metabolism and Genome Stability Laboratory, led by Prof. Vincenzo Costanzo, investigates the fundamental

	mechanisms that regulate DNA replication, damage response, and repair, with a particular focus on their implications in cancer biology and therapy. The lab studies how cells maintain genome integrity under replication stress, a key driver of tumorigenesis, and explores the role of various DNA repair pathways, including homologous recombination, translesion synthesis, and alternative end-joining. The lab uses cutting edge-technologies based on DNA electron-microscopy for the analysis of DNA replication and repair intermediates that only few groups in world have access to. A major aspect of the research aims to uncover vulnerabilities in tumors with defective DNA repair mechanisms, particularly those associated with BRCA mutations, in order to develop targeted therapeutic strategies such as PARP and polymerase theta (Polθ) inhibitors. Beyond repair mechanisms, the lab also explores the interplay between DNA damage response and cellular metabolism, particularly how the ATM kinase and replication stress-related metabolic rewiring contribute to cancer progression. Another key research direction involves understanding how chromatin architecture and epigenetic modifications influence the cellular response to replication stress. To address these questions, the lab employs a multidisciplinary approach that includes tumor cell based models to study tumor suppressor gene biology, cell-free systems for biochemical reconstitution of DNA repair processes, Cryo-EM, DNA electron microscopy, CRISPR-based functional genomics for gene editing and synthetic lethality screens, and advanced proteomics, transcriptomics, genomics and metabolomics techniques to dissect DNA damage response pathways. High-resolution microscopy and structural biology methods provide insights into replication stress and repair at a molecular level. Additionally, the lab actively engages in high-throughput screening to identify novel cancer therapeutics. Through this integrated research framework, the lab aims to translate fundamental discoveries in genome stability into innovative cancer treatments, ultimately improving therapeutic options for patients with DNA repair-deficient tumors.
Recent bibliography	Replicative gaps in DNA damage tolerance, genome instability, and cancer therapy. Falbo and Costanzo. Mol Cell. 2026 Apr 2;86(7):1200-1216. doi: 10.1016/j.molcel.2026.02.018. RAD51 protects abasic sites to prevent replication fork breakage. Hanthi Y et al. Mol Cell. 2024 Aug 22;84(16):3026-3043.e11. doi: 10.1016/j.molcel.2024.07.004. POLθ prevents MRE11-NBS1-CtIP-dependent fork breakage in the absence of BRCA2/RAD51 by filling lagging-strand gaps. Mann A et al. Mol Cell. 2022 Nov 17;82(22):4218-4231.e8. doi: 10.1016/j.molcel.2022.09.013. REV1-Polζ maintains the viability of homologous recombination-deficient cancer cells through mutagenic repair of PRIMPOL-dependent ssDNA gaps. Taglialatela A et al. Mol Cell. 2021 Oct 7;81(19):4008-4025.e7. doi: 10.1016/j.molcel.2021.08.016.

	SAMHD1 acts at stalled replication forks to prevent ssDNA-mediated induction of type I interferons. Coquel F et al . Nature. 2018 May;557(7703):57-61.
Group composition	4 postdocs, 1 staff scientist, 1 technician, 8 PhD students
Institutional page link	https://www.ifom.eu/en/cancer-research/programs/dna-metabolism.php
Lab website link	https://www.ifom.eu/en/cancer-research/researchers/vincenzo-costanzo.php

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Principal Investigator	Vincenzo Costanzo
Institute of Affiliation	IFOM

PROJECT 2 INFO	
Title of the proposed project:	How DNA Repair Proteins Integrate Multiple DNA Metabolism Pathways to Safeguard Genome Stability
Short description of the project	Homologous recombination (HR) proteins, including RAD51, BRCA1, and BRCA2, are essential for maintaining genomic stability. While classically studied in the context of DNA double-strand break repair, our lab has recently uncovered a fundamentally new biochemical function for these factors: using cryo-electron microscopy (cryo-EM) and in vitro reconstitution, we demonstrated that RAD51 directly binds and stabilises abasic (AP) sites during DNA replication, preventing their conversion into lethal replication fork breakage (Hanthi et al., Mol Cell 2024). AP sites are among the most abundant DNA lesions, arising from spontaneous base loss and, notably, from active DNA demethylation during epigenetic reprogramming, where they are generated as obligate intermediates of the TET/TDG/base excision repair (BER) pathway. Despite their frequency, how cells prevent AP sites from derailing the replication machinery has remained a fundamental open question in DNA metabolism. This PhD project will provide a deep biochemical and structural characterisation of this newly discovered HR-AP site axis. The student will employ uniquely biochemical and cellular powerful platforms that recapitulate vertebrate DNA replication and repair to reconstitute AP site recognition, processing, and tolerance at moving replication forks. Cryo-EM structural analysis will resolve how RAD51 engages AP sites at the atomic level and how this interaction differs from its canonical strand-exchange activity. Quantitative mass spectrometry-based proteomics will be deployed to identify the full complement of factors recruited to AP sites during S-phase and to map the protein interaction networks that coordinate BER, translesion synthesis, and HR at these lesions. The project will also investigate how the loss of individual HR components, mimicking BRCA1/2-deficient tumours, and cancer epigenetic alterations rewire impact on cancer cell survival and resistance to therapy, using CRISPR-engineered human cell lines combined with single-molecule DNA electron microscopy to visualise aberrant replication intermediates at nanometre resolution. This is a rare opportunity to train across structural biology, biochemical reconstitution, proteomics, and genome stability research, using technologies available in only a handful of laboratories worldwide, within the highly collaborative and international environment at IFOM.
Main research area for project	Molecular Biology
Second research area for the project	Structural Biology

3 key words for the project	Genome stability, Homologous recombination, DNA replication

LAB INFO	
Main topic/s of the lab	DNA Metabolism and Genome Stability Laboratory
Short description of the lab activity	The DNA Metabolism and Genome Stability Laboratory, led by Prof. Vincenzo Costanzo, investigates the fundamental mechanisms that safeguard genome integrity during DNA replication and repair, with a particular focus on homologous recombination (HR) and its interplay with other DNA damage tolerance pathways. A central strength of the lab is its ability to combine biochemical reconstitution using cell-free systems that faithfully recapitulate vertebrate DNA replication and repair with high-resolution structural approaches, including cryo-electron microscopy (cryo-EM) and single-molecule DNA electron microscopy, technologies available in only a handful of laboratories worldwide. These platforms have recently enabled a breakthrough discovery: the demonstration that the HR factor RAD51 directly binds and stabilizes abasic (AP) sites during DNA replication, preventing their conversion into lethal fork breakage (Hanthi et al., Mol Cell 2024). This finding has opened a new research axis at the interface of base excision repair (BER), translesion synthesis, and homologous recombination, revealing previously unrecognised functions of HR proteins beyond canonical double-strand break repair. The lab also employs quantitative mass spectrometry-based proteomics to map protein interaction networks at sites of replication stress, CRISPR-based functional genomics and advanced DNA sequencing technologies, including nanopore, to dissect synthetic lethal relationships in BRCA1/2-deficient cancer models. A major translational aim is to uncover novel vulnerabilities in tumors with defective DNA repair, guiding the development of targeted therapeutic strategies. Through this integrated, multidisciplinary framework spanning structural biology, biochemistry, proteomics, and cancer cell biology, the lab aims to translate fundamental discoveries in genome stability into innovative cancer treatments.
Recent bibliography	Replicative gaps in DNA damage tolerance, genome instability, and cancer therapy. Falbo and Costanzo. Mol Cell. 2026 Apr 2;86(7):1200-1216. doi: 10.1016/j.molcel.2026.02.018. RAD51 protects abasic sites to prevent replication fork breakage. Hanthi Y et al. Mol Cell. 2024 Aug 22;84(16):3026-3043.e11. doi: 10.1016/j.molcel.2024.07.004. POLθ prevents MRE11-NBS1-CtIP-dependent fork breakage in the absence of BRCA2/RAD51 by filling lagging-strand gaps. Mann A et al. Mol Cell. 2022 Nov 17;82(22):4218-4231.e8. doi: 10.1016/j.molcel.2022.09.013. REV1-Polζ maintains the viability of homologous recombination-deficient cancer cells through mutagenic repair of PRIMPOL-

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