European School of Molecular Medicine

RESEARCH ACTIVITY SHEET

2025 PhD selections

YOUR DETAILS

* Name & Surname: Vincenzo Costanzo

* Affiliation IFOM

PHD PROJECT DETAILS

* 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 (up to 300 words)

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 and several other groups (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, and proteomics 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.

* 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:

DNA repair, Cancer therapy, Synthetic lethality

YOUR LABORATORY ACTIVITIES DETAILS

* Main topic/s of the lab

DNA Metabolism and Genome Stability Laboratory

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

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-microscpy** 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 centromeric DNA 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, **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 (max 5 references)

RAD51 protects abasic sites to prevent replication fork breakage.
Hanthi Y, Ramirez-Otero MA, Appleby R, De Antoni A, Joudeh L, Sannino V, Waked S, Ardizzoia A, Barra V, Fachinetti D,
Pellegrini L, Costanzo V
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, Ramirez-Otero MA, De Antoni A, Hanthi YW, Sannino V, Baldi G, Falbo L, Schrempf A, Bernardo S, Loizou J,
Costanzo V. 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, Leuzzi G, Sannino V, Cuella-Martin R, Huang JW, Wu-Baer F, Baer R, Costanzo V, Ciccia A.
Mol Cell. 2021 Oct 7;81(19):4008-4025.e7. doi: 10.1016/j.molcel.2021.08.016. Epub 2021 Sep 10.

Restoration of Replication Fork Stability in BRCA1- and BRCA2-Deficient Cells by Inactivation of SNF2-Family Fork
Remodelers. Taglialatela A, Alvarez S, Leuzzi G, Sannino V, Ranjha L, Huang JW, Madubata C, Anand R, Levy B, Rabadan
R, Cejka P, Costanzo V, Ciccia A.
Mol Cell. 2017 Oct 19;68(2):414-430.e8. doi: 10.1016/j.molcel.2017.09.036.

SAMHD1 acts at stalled replication forks to prevent ssDNA-mediated induction of type I interferons
Coquel F, Silva MJ, Técher H, Zadorozhny K, Sharma S, Nieminuszczy J, Mettling C, Dardillac E, Barthe A, Schmitz AL,
Promonet A, Cribier A, Sarrazin A, Niedzwiedz W, Pasero P. Nature. 2018 May;557(7703):57-61.

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

4 postodcs, 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, if any

Social media links, if any

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