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Institute of Affiliation	IFOM - Istituto Fondazione di Oncologia Molecolare, ETS
Title of the proposed project:	Replication-stress-driven re-programming and immune escape in aggressive human cancers
Short description of the project	<p>We have recently shown that a basic (AP) sites, among the most frequent DNA insults, induce replication stress (RS) by promoting single-stranded DNA gap formation in cancer cells (Hanthi, Mol Cell-2024). We have also demonstrated that RS in stem cells activates trophoblast-placental-like programs that support immune escape and tissue invasion (Atashpaz, Elife-2020). In agreement with these findings, preliminary analyses of aggressive tumors revealed high AP sites and gap densities that track with RS markers and expression of embryonic proteins linked to immune tolerance and evasion (Mauri, Santorelli et al Research Square 2025). Starting from these results the proposed project will unravel the connection between AP formation, RS induction and clinical aggressiveness, and test whether this axis represents a therapeutically exploitable weakness. The project will aim to characterize aggressive tumors and their metastases, including solid malignancies and advanced hematological cancers depending on availability and agreements with the clinical partner. During the first year the physician-scientist will secure ethical approval for a prospective biobanking protocol, collect pathology samples and implement case-report forms capturing treatment outcomes. These activities will confer Good Clinical Practice competence, embedding laboratory effort in a clinical framework. Samples will then undergo quantitative assessment of AP lesions and gaps, deep-proteome analysis, RNA- and DNA-seq profiling, and single-cell mapping. Statistical analysis will link these results with therapy response and survival. Patient-derived cells and organoids will be established to test synthetic-lethal combinations with available drugs that target the pathways unraveled by the multi-omics analyses. By combining these diverse approaches, the project aims to demonstrate that RS-driven reprogramming is a unifying, targetable vulnerability across diverse aggressive cancers. Majority of fellow's effort will be devoted to laboratory work at IFOM, with the remaining time embedded in the partnering service, ensuring continuous feedback between bench discoveries and bedside application.</p>
Main research area for the project	Cancer biology
5 key words for the project	DNA repair, DNA damage, DNA replication
LAB INFO	
Main topic/s of the lab	DNA damage and repair, replication stress, cancer proteomics and basic tumour immune evasion mechanisms

Short description of the lab activity

The DNA Metabolism Unit investigates how cancer cells survive the relentless RS imposed by endogenous DNA damage, high proliferation and DNA repair defects. The laboratory combines in vitro biochemistry, single-molecule imaging, quantitative proteomics and tumor-oriented translational studies to reconstruct the molecular choreography that from DNA damage accumulation and the loss of replication-fork integrity to the development of human tumors, exposing vulnerabilities that can be therapeutically exploited. Using this approach the group discovered that homologous-recombination factors RAD51 and BRCA2 safeguard forks by preventing nascent-strand degradation and by suppressing single-stranded DNA gaps induced by AP sites, thereby laying the conceptual foundations of “fork protection” biology. The group also made fundamental observation for the field of molecular oncology by showing that RS leading to hyper-activation of the ATR–CHK1 checkpoint in stem cells induces trophoblast-like programs promoting a switch in cell fate that when occurring in somatic cells is probably important for the acquisition of several cancer features. Cells that experience this DNA-damage signal begin to express placental and embryonic markers, including ERV retrotransposons, Zscan, Syncytin, HLA-G, PLAC1 and others and can colonise extra-embryonic tissues. Aggressive tumors exploit an analogous route: chronic RS induced often induced by abasic DNA lesions, engages ATR and resurrects the same placental programme by inducing trophoblast and placental proteins that dampen immune surveillance as confirmed by our recent unpublished work on human colon cancer. Thus, checkpoint-sensed genome injury can be a direct molecular bridge between oncogenic RS and the embryonic re-programming that underlies immune-evasive, therapy-resistant features of aggressive human cancers. These studies from our laboratory provide the first direct evidence that DNA damage and RS can act as developmental cues, funnelling stem cells towards an aggressive tumor cell fate. By linking genome-integrity surveillance to cell-lineage decisions, it opens conceptual and therapeutic perspectives that expand the our knowledge in molecular oncology and precision medicine.

Recent bibliography

- POL#952; prevents MRE11-NBS1-CtIP-dependent fork breakage in the absence of BRCA2/RAD51 by filling lagging-strand gaps.
MOL CELL 2022 Nov; 82: 4218
- A high-throughput screening identifies MCM chromatin loading inhibitors targeting cells with increased replication origins.
Iscience 2024 Aug; 27: 110567
- RAD51 protects abasic sites to prevent replication fork breakage.
MOL CELL 2024 Aug; 84: 3026
- Targeting the FNIP2-SERCA2b axis improves metabolic and mitochondrial defects in Ataxia Telangiectasia.
CELL DEATH DIS 2026 Mar; 17:

	- Replicative gaps in DNA damage tolerance, genome instability, and cancer therapy. MOL CELL 2026 Apr; 86: 1200
Group composition	14 members: 1 PI, 3 senior post-docs, 7 PhD students, 1 technician, 1 bioinformatician and 1 staff scientist
Institutional page link	https://www.ifom.eu/it/ricerca-cancro/ricercatori/vincenzo-costanzo.php
Lab website link	https://www.ifom.eu/it/ricerca-cancro/ricercatori/vincenzo-costanzo.php
Social media links	https://www.linkedin.com/in/vincenzo-costanzo-a87904147/?originalSubdomain=it