PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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Principal Investigator	Costanzo Vincenzo
Hosting institution	IFOM - Istituto Fondazione di Oncologia Molecolare, ETS
Proposal title	Replication-stress-driven placental-like programme and immune escape in aggressive human cancers
Keywords	DNA repair; DNA damage; DNA replication
PhD project description	We have recently shown that abasic (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 placental proteins linked to immune tolerance and evasion. Starting from these results the proposed project will unravel the connection between AP formation, RS induction, placental mimicry and clinical aggressiveness, and test whether this axis represents a therapeutically exploitable weakness. The project will aim to characterize "born-to-bad" malignancies, prioritizing aggressive gastrointestinal, lung, breast, and gynaecological primaries and their metastases, 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 surgical and 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. Tumor samples will then undergo quantitative assessment of AP lesions and gaps, deep-proteome analysis with Orbitrap-DIA focused on placental peptides and spatial and single-cell mapping of the immune micro-environment. Statistical analysis will link these results with therapy response and survival. Patient-derived organoids will be established to test synthetic-lethal combinations with available drugs that target the pathways unraveled by the proteomic analysis. By combining these multiple approaches, the project aims to demonstrate that RS-driven placental-like 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 oncology service, ensuring continuous feedback between bench discoveries and bedside application.
Main topics of the lab	DNA damage and repair, replication stress, cancer proteomics and basic tumour immune evasion mechanisms
Short description of the	The DNA Metabolism Unit investigates how cancer cells survive the

lab activity	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 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 (Mauri, Santorelli, Marasca et al, in preparation). Thus, checkpoint-sensed genome injury can be a direct molecular bridge between oncogenic RS and the placental-like 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 a trophoblast-like 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.
Main research area	Cancer biology
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 link	https://www.linkedin.com/in/vincenzo-costanzo-a87904147/?originalSubdomain=it
Lab bibliography	SSRP1-mediated histone H1 eviction promotes replication origin assembly and accelerated development. Falbo L, Raspelli E, Romeo F, Fiorani S, Pezzimenti F, Casagrande F, Costa I, Parazzoli D, Costanzo V NAT COMMUN 2020 Mar; 11: 134