PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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Principal Investigator	Santaguida Stefano
Hosting institution	Istituto Europeo di Oncologia I.R.C.C.S. S.r.l.
Proposal title	Molecular and clinical characterization of micronuclei in chromosomally-unstable tumors
Keywords	Cell cycle; Genomic/Genetic instability; Aneuploidy; Mitosis
PhD project description	Background Chromosomal instability (CIN) generates micronuclei (MNi), promoting genomic instability and metastasis via micronuclear envelope collapse. In our recent publication (Martin et al., Science 2024), we identified the autophagic receptor p62/SQSTM1 as a key regulator of micronuclear stability. Hypothesis Given the strong correlation between p62 levels, micronuclear rupture, and chromothripsis, we hypothesize that p62 might serve as a prognostic marker in chromosomally-unstable tumors, such as breast and ovarian cancers. Furthermore, the identification of the molecular mechanisms regulating p62's micronuclear localization can potentially lead to the identification of therapeutic targets that could prevent micronuclear envelope rupture and thus inhibit tumorigenesis. Experimental design We will build upon our recent publication (Martin et al., Science 2024) and we will analyze p62 protein levels in breast and ovarian cancer samples as well as identify proteins regulating p62's micronuclear localization. This will be achieved through cutting edge techniques, such as genome editing, mass-spectrometry, super resolution microscopy. Expected results This research will be the first to assess p62 levels in breast and ovarian cancers, testing the hypothesis that high p62 levels correlate with poor prognosis in CIN-high tumors. We will also identify key regulators of p62 activity to enable the development of novel inhibitors. Impact on cancer This research will assess p62 as a prognostic marker in CIN-high tumors, such as breast and ovarian cancers, potentially improving risk stratification, guiding treatment decisions, and survival. It will also identify novel therapeutic targets for these malignancies, contributing to earlier and more effective interventions, thus improving patient outcomes and survival rates.
Main topics of the lab	Genome Integrity
Short description of the lab activity	Genome integrity is maintained through faithful chromosome segregation at each cell division, in which one copy of a duplicated chromosome is deposited in each daughter cell. Errors in this process lead to aneuploidy, a condition in which cells carry an abnormal karyotype. Aneuploidy is the most common chromosome aberration in humans and is a widespread feature of solid tumors. To shed light on how aneuploidy contributes to tumorigenesis, it is crucial to determine how this condition impacts normal cells and to determine the immediate consequences of an imbalanced karyotype on cellular functions. Our work seeks to decipher how aneuploidy affects cell physiology by identifying and characterizing the pathways deregulated

	in human cells following chromosome segregation errors. To tackle this biological question, we use a combination of cell biology, molecular biology and genome editing techniques. Our goal is to expand our understanding of the biology of aneuploid cells and to identify specific features that can be targeted in cancer therapy. Over the last few years, we have made several contributions to the molecular understanding of the loss of genome integrity on cell physiology, briefly summarized below: Micronuclei Integrity Regulation: Identified p62/SQSTM1, an autophagy component, as crucial for maintaining micronuclei integrity. p62's localization relies on oxidation-driven homo-oligomerization induced by reactive oxygen species (ROS). It influences micronuclear integrity by inhibiting ESCRT-III-dependent envelope repair. For more details see Martin et al. Science 2024. Aneuploidy and Genome Instability: Demonstrated that the acquisition of unbalanced karyotypes directly contributes to short-term genome instability, leading to diverse karyotypic landscapes. Aneuploidy leads to CIN and more aneuploid daughter cells. In the first S-phase, aneuploid cells fire dormant replication origins and complete replication via mitotic DNA synthesis (MiDAS). For more details see Garribba, De Feudis et al., Nature Communications 2023. Chemoresistance: Showed that aneuploidy-induced genome instability facilitates the acquisition of resistance to chemotherapy. Survival under selective pressure involves expanding karyotypic heterogeneity and converging onto specific karyotypes. For more details see Ippolito et al., Developmental Cell 2021. Immune Clearance of Aneuploid Cells: Found that aneuploid cells signal for their elimination by Natural Killer (NK) cells. Activation of NF-κB pathways in aneuploid cells causes NK cell-mediated immunogenicity. For more details see Wang et al., EMBO Reports 2021. Aneuploidy-Selective Vulnerabilities: Discovered that aneuploid cells exhibit elevated RAF/MEK/ERK pathway activity and are more sensitive to drugs targeting this pathway. For more details see Zerbib, Ippolito et al., Nature Communications 2024. Global Attenuation of aneuploidy-induced cellular stresses: Aneuploid cells experience increased transcription. Interestingly, more genes were downregulated than upregulated in the highly-aneuploid clones, indicative of buffering mechanisms at play to decrease mRNA levels. The highly aneuploid clones exhibit elevated dependency on the nonsense mediated decay (NMD) pathway, the miRNA pathway. For more details see Ippolito, Zerbib et al., Cancer Discovery 2024.
Main research area	Cancer biology
Group composition	5 in total: 3 Post-docs, 1 PhD Student, 1 Technician
Institutional page link	https://www.research.ieo.it/research-and-technology/principal-investigators/stefano-santaguida/
Lab website link	https://www.santaguidalab.org
Social media link	nan
Lab bibliography	Short-term molecular consequences of chromosome mis-segregation for genome stability. Garribba L, De Feudis G, Martis V, Galli M, Dumont M, Eliezer Y, Wardenaar R, Ippolito MR, Iyer DR, Tijhuis AE, Spierings DCJ, Schubert M, Taglietti S, Soriani C, Gemble S, Basto R, Rhind N, Foijer F, Ben-David U, Fachinetti D, Doksani Y, Santaguida S NAT COMMUN 2023 Mar; 14: 1353