European School of Molecular Medicine

2025 summer call PhD selections

AVAILABLE POSITIONS

Principal Investigator	Stefano Santaguida
Affiliation	European Institute of Oncology, Milan
Title of the proposed project	Deciphering and exploiting aneuploidy in cancer
Short description of the project	Errors in the process of chromosome segregation result in aneuploidy, where the chromosome count deviates from a multiple of the haploid complement. Aneuploidy is notably linked to developmental abnormalities and is a primary cause of miscarriages. Remarkably, it is strongly associated with cancer, with over 90% of analyzed solid tumors showing an unbalanced chromosome count. While aneuploidy is closely associated with human disease, its effects on cell physiology are only just beginning to be understood. This is because several difficulties are associated with the study of aneuploidy, one of the major ones being the lack of a proper model system in which aneuploidy could have been studied without any other confounders, including chromosomal instability and/or co-occurring mutations. To decipher the multifaceted effects of aneuploidy on cell physiology, we will capitalize on a recently generated collection of human, untransformed and chromosomally stable aneuploid clones. These clones differ from one another only by the presence of a given chromosome without any other confounders, providing a powerful tool to study the consequences of aneuploidy on cell physiology. By combining cell and molecular biology techniques with cutting-edge genome editing, this project will provide a comprehensive molecular characterization of the events deregulated by the aneuploid state.
Main research area for the project	Cancer biology
Second research area for the project	Molecular and cellular biology
3 key words for project	Chromosomal Instability, Aneuploidy
Main topic/s of the lab	Chromosomal Instability, Aneuploidy
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.
Recent bibliography	**1**.Human aneuploid cells depend on the RAF/MEK/ERK pathway for overcoming increased DNA damage. Zerbib J, Ippolito MR, Eliezer Y, De Feudis G, Reuveni E, Savir Kadmon A, Martin S, Viganò S, Leor G, Berstler J, Muenzner J, Mülleder M, Campagnolo EM, Shulman ED, Chang T, Rubolino C, Laue K, Cohen-Sharir Y, Scorzoni S, Taglietti S, Ratti A, Stossel C, Golan T, Nicassio F, Ruppin E, Ralser M, Vazquez F, Ben-David U, Santaguida S. Nat Commun. 2024 Sep 9;15(1):7772. doi: 10.1038/s41467-024-52176-x. **2.**Increased RNA and Protein Degradation Is Required for Counteracting Transcriptional Burden and Proteotoxic Stress in Human Aneuploid Cells. Ippolito MR, Zerbib J, Eliezer Y, Reuveni E, Viganò S, De Feudis G, Shulman ED, Savir Kadmon A, Slutsky R, Chang T, Campagnolo EM, Taglietti S, Scorzoni S, Gianotti S, Martin S, Muenzner J, Mülleder M, Rozenblum N, Rubolino C, Ben-Yishay T, Laue K, Cohen-Sharir Y, Vigorito I, Nicassio F, Ruppin E, Ralser M, Vazquez F, Santaguida S, Ben-David U. Cancer Discov. 2024 Dec 2;14(12):2532-2553. doi: 10.1158/2159-8290.CD-23-0309. **3**.A p62-dependent rheostat dictates micronuclei catastrophe and chromosome rearrangements. Martin S, Scorzoni S, Cordone S, Mazzagatti A, Beznoussenko GV, Gunn AL, Di Bona M, Eliezer Y, Leor G, Ben-Yishay T, Loffreda A, Cancila V, Rainone MC, Ippolito MR, Martis V, Bedin F, Garrè M, Vaites LP, Vasapolli P, Polo S, Parazzoli D, Tripodo C, Mironov AA, Cuomo A, Ben-David U, Bakhoum SF, Hatch EM, Ly P, Santaguida S. to expand our understanding of the biology of aneuploid cells and to identify specific features that can be targeted in cancer therapy. Science. 2024 Aug 30;385(6712):eadj7446. doi: 10.1126/science.adj7446. Epub 2024 Aug 30. **4.**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 11;14(1):1353. doi: 10.1038/s41467-023-37095-7. **5.**Gene copy-number changes and chromosomal instability induced by aneuploidy confer resistance to chemotherapy. Ippolito MR, Martis V, Martin S, Tijhuis AE, Hong C, Wardenaar R, Dumont M, Zerbib J, Spierings DCJ, Fachinetti D, Ben-David U, Foijer F, Santaguida S. Dev Cell. 2021
Group composition	5 total members. 3 Post-docs, 1 PhD Student, 1 Technician

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Institutional page link	https://www.research.ieo.it/research-and-technology/principal-investigators/stefanosantaguida/
Lab website link	https://www.santaguidalab.org