PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: SIBMM UNIVERSITÀ DEGLI STUDI DI MILANO

Principal Investigator	**Campaner Stefano**
Hosting institution	Università degli Studi di Padova
Proposal title	Targeting Transcription Replication Pathways in Tumors
Keywords	Transcription; Transcription factors; Genome wide screening/GWAS; Genomic/Genetic instability; Gene regulation
PhD project description	Activation of the oncogene c-Myc-through translocation, amplification or pathway-driven deregulation by Wnt, Notch, RTKs, Ras and others-occurs across many tumour types, making Myc a central hub of oncogenic signalling and a compelling pan-cancer target. Although unchecked Myc increases intrinsic replicative stress, tumour cells survive by engaging safeguard pathways that curb catastrophic genome instability. Our recent work pinpoints CDK12 as an essential protector in this setting, regulating early-S-phase transcription-replication conflicts that would otherwise trigger DNA double-strand breaks. We therefore hypothesise that dismantling CDK12-centred stress-mitigation circuits will expose actionable vulnerabilities in Myc-dependent cancers. To test this, we will map the upstream regulators and downstream effectors of CDK12 through a discovery campaign based on genome-wide CRISPR and RNAi screens to uncover genetic dependencies linked to CDK12 loss, paired to proteomic profiling to identify CDK12-binding partners. High-priority genes will be mechanistically characterised and evaluated for preclinical efficacy in eradicating Myc-driven lymphomas. We anticipate defining a regulatory network that prevents or resolves transcription-replication conflicts alongside CDK12, revealing synthetic-lethal targets and drugs capable of aggravating replicative stress-either alone or in combination with CDK12 inhibitors. Because CDK12 inhibitors are already entering clinical trials, our findings could rapidly inform combinatorial regimens against aggressive Myc-driven malignancies, and may also benefit prostate and ovarian cancers that harbour recurrent CDK12 loss-of-function mutations.
Main topics of the lab	Understanding the function of oncogenic transcription factors
Short description of the lab activity	Our laboratory investigates transcription factors that govern cell growth, proliferation, and identity, aiming to elucidate their roles in both normal physiology and disease. We focus in particular on c-Myc, a basic helix-loop-helix transcription factor that broadly regulates cell growth and metabolism, and YAP/TAZ, two transcriptional coactivators first recognized as key effectors of the Hippo signaling pathway. To dissect their functions, we employ advanced genetic models for both loss- and gain-of-function studies, integrated with genomic approaches based on next-generation sequencing. This allows us to map transcription factor binding genome-wide, analyze epigenetic modifications, assess chromatin accessibility, and explore 3D nuclear

	architecture. These data are further combined with bulk and single-cell mRNA expression profiling to: (i) uncover critical transcriptional programs, (ii) define gene regulatory mechanisms, (iii) map transcriptional networks, and (iv) identify vulnerabilities in cancer cells.
Main research area	Cancer biology
Group composition	1 post-doc 1 PhD stiudent 1 technicians 2 research fellows
Institutional page link	https://www.medicinamolecolare.unipd.it/
Lab website link	https://genomics.iit.it/cancer-biology
Social media link	nan
Lab bibliography	MYC-Induced Replicative Stress: A Double-Edged Sword for Cancer Development and Treatment. Curti L, Campaner S INT J MOL SCI 2021 Jun; 22: