Principal Investigator	Amati Bruno
Affiliation	European Institute of Oncology, Milan
Title of the proposed project:	Unraveling oncogene-drug interactions through computational analysis of transcriptional profiles
Short description of the project	Our research seeks to identify and characterize synthetic-lethal interactions allowing the selective elimination of MYC-driven cancer cells by targeted drug interventions. In this context, essential mechanistic insight is provided by the alterations in mRNA expression profiles elicited by combined MYC activation and drug treatment. In order to map these alterations, we use next-generation sequencing (NGS)-based genomic approaches, such as RNA-seq or ChIP-seq. The successful PhD candidate will be involved in computational analysis of NGS datasets produced in the laboratory, in close collaboration with experimental scientists in the group. He/she will benefit from co-supervision by a computational group leader (Dr. Mattia Pelizzola, Unimib/IIT) as well as from a strong, integrative computational community in our institute. Special attention will be given to MYC and drug-induced alterations in gene expression at both the transcriptional and post-transcriptional levels (e.g. alternative splicing, degradation, translation), which ultimately impact protein production and cell fate. Training and research activities will cover a range of computational genomics approaches for bulk Illumina RNA-seq and Oxford Nanopore single-molecule sequencing, alongside ChIP-seq profiling of transcription factor binding and histone modifications. Analyses employ an extensive set of R/Bioconductor packages—from differential expression to time-courses, pathways and functional enrichment—paired with nf-core and custom, including newly built Nextflow pipelines for automated, reproducible, and scalable workflows. All computation run on the IEO High-Performance Cluster (HPC) with Docker, Singularity, or Conda environments ensuring full reproducibility and portability.
Main research area for the project	Computational Biology
Second research area for the project	Cancer Biology
key words for project:	MYC, transcription, chromatin
Main topic/s of the lab	MYC-driven lymphoma - Synthetic-lethal gene-drug interactions - Transcription - RNA biology - Mitochondrial stress - Integrated Stress Response
Short description of the lab activity	The oncogenic transcription factor MYC is induced by growth-promoting stimuli and drives the activation of biosynthetic and metabolic pathways inherent to proliferating cells. The same pathways are deregulated in MYC-driven tumors where they contribute to cell proliferation and survival, but concomitantly

	elicit multiple stresses, to which cancer cells must adapt during disease progression. Hence, MYC-overexpressing cells depend on a fragile equilibrium between conflicting signals, which creates opportunities to exploit synthetic lethality as a strategy for targeted therapeutic intervention. Our recent work uncovered such opportunities in a variety of different contexts. Drugs inhibiting mitochondrial translation and respiration selectively killed MYC-driven tumor cells with strong anti-tumoral effects in preclinical mouse models of MYC-driven lymphoma. At the mechanistic level these and other drugs converged to elicit oxidative stress and activate the so-called "Integrated Stress Response" (ISR) pathway, which profoundly impacts translational and transcriptional profiles in cells and, depending upon the entity of the stress, can contribute to either cell survival or death. We are currently addressing how MYC sensitizes cells to a series of novel drugs impacting either on mitochondrial dynamics, oxidative stress, ISR signaling, and/or complementary transcriptional programs. In a parallel line of research, we addressed the interplay between MYC and RNA-regulatory mechanisms. Toward this aim, we ran a CRISPR/Cas9 screen targeting RNA-binding proteins (RBPs) in MYC-overexpressing cells. This led to the identification of diverse RBPs as potential MYC synthetic-lethal interactors, pointing to discrete RNA-regulatory pathways as selective MYC-dependent liabilities. Pharmacological targeting of some of these pathways has confirmed their therapeutic potential in MYC-driven lymphoma. The underlying mechanisms are being addressed at present and will be the basis for future developments.
Recent bibliography	1. Donati, G., et al., Oxidative stress enhances the therapeutic action of a respiratory inhibitor in MYC-driven lymphoma. EMBO Mol Med, 2023. 15(6): p. e16910. 2. Donati, G., et al., Targeting mitochondrial respiration and the BCL2 family in high-grade MYC-associated B-cell lymphoma. Mol Oncol, 2022. 16(5): p. 1132-1152. 3. Pellanda, P., et al., Integrated requirement of non-specific and sequence-specific DNA binding in Myc-driven transcription. EMBO J, 2021. 40(10): p. e105464. 4. Tesi, A., et al., An early Myc-dependent transcriptional program orchestrates cell growth during B-cell activation. EMBO Rep, 2019. 20(9): p. e47987. 5. Ravà, M., et al., Therapeutic synergy between tigecycline and venetoclax in a preclinical model of MYC/BCL2 double-hit B cell lymphoma. Sci Transl Med, 2018. 10(426): p. eaan8723.
Group composition	1 PI, 1 Staff Scientist, 3 Postdocs, 3 PhD students, 2 Technicians, 2 Graduate Fellows, 2 Master Interns
Institutional page link	https://www.research.ieo.it
Lab website link	https://www.research.ieo.it/research-and-technology/principal-investigators/bruno-amati/