PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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| Principal Investigator | Amati Bruno |
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| **Hosting institution** | Istituto Europeo di Oncologia I.R.C.C.S. S.r.l. |
| **Proposal title** | Exploiting synthetic-lethality toward targeted therapeutic development against MYC/BCL2-driven B-cell lymphoma |
| **Keywords** | Mitochondria; Lymphomas; RNA binding proteins; bcl2 family; Myc |
| **PhD project description** | Our research seeks to identify synthetic-lethal interactions allowing the selective elimination of MYC-driven cancer cells by targeted drug interventions. The PhD candidate will be involved the discovery and characterization of such interactions, followed by development of novel targeted therapies against aggressive MYC-driven malignancies, with a focus on MYC/BCL2 "double-hit" B-cell lymphoma (DHL) [1, 2]. As exemplified in previous studies [3-6] select gene-drug and drug-drug interactions will be characterized at the phenotypic and molecular levels in cultured cells, followed by preclinical assessment of their therapeutic potential in animal models. An important outcome of this research lies in the discovery of new indications for existing drugs, paving the way for their combinatorial repurposing in oncology - as suggested for tigecycline and venetoclax for the treatment of DHL [5]. Important emphasis will be placed on the analysis of mechanisms-of-action, involving the use of advanced cellular and molecular biology tools, such as genomic engineering, -omic technologies, etc... For example, where applicable, short- and long-read RNA-seq technologies will be combined to address the consequences of MYC activation and drug treatment on mRNA processing and expression profiles. In turn, the mechanisms and pathways uncovered by these studies may provide new leads for targeted intervention, which may then be pursued and characterized on their own right. For example, alongside other studies, our work on mitochondrial inhibitors led to the identification of the integrated stress response (ISR) pathway as a common therapeutic effector [2, 4], a connection that we are now extending to other drugs and studying in detail in the laboratory. The PhD student may carry out his/her clinical duties in the Clinical Haemato-Oncology Division of the European Institute of Oncology, Directed by Dr. Enrico Derenzini. https://www.ieo.it/en/About-Us-old/Our-Organization/Clinical-Divisions/Clinical-Haemato-Oncology-EMADV/ https://www.ieo.it/it/CHI-SIAMO/Come-siamo-organizzati/Le-divisioni/Oncoematologia/ References: Listed below in the Laboratory Activities section. |
| **Main topics of the lab** | MYC-driven lymphoma; Synthetic-lethal gene-drug interactions; Transcription; RNA biology; Mitochondrial stress |
| **Short description of the lab activity** | The emergence of B-cell lymphomas is associated with chromosomal translocations that activate proto-oncogenes, such as MYC or BCL2 [1]. A subset of cases accumulates concurrent translocations of both genes, giving rise to high-grade tumors commonly known as “double-hit” |

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| | lymphoma (DHL) that show dismal prognosis with current therapeutic regimens. In normal cells, MYC is induced by growth-promoting stimuli; its protein product, the MYC transcription factor, drives biosynthetic and metabolic pathways required for cell growth and proliferations. The same pathways are deregulated in MYC-driven tumors where they contribute to unscheduled cell proliferation, but concomitantly elicit oncogenic stress and apoptotic cell death, which cancer cells must bypass for disease progression. One example is provided by BCL2, which antagonizes MYC-induced apoptosis, explaining the strong cooperativity between the two oncogenes and the aggressive nature of DHL. While adapting to oncogenic stress, 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 [2]. For example, MYC sensitizes cells to drugs targeting mitochondrial translation or respiration [3, 4]. Most importantly, the same drugs synergize with a BCL2 inhibitor (venetoclax) in killing DHL cells, allowing strong anti-tumoral effects in preclinical mouse models [4, 5]. At the mechanistic level these drugs converge to elicit oxidative stress and activate the so-called "Integrated Stress Response" (ISR) [4, 6], an adaptive pathway previously shown be required for tumor progression. Hence, in response to drug-induced stresses, the ISR can be subverted from its pro-tumoral action to elicit anti-tumoral, therapeutic effects [2]. We are currently addressing how MYC sensitizes cells to novel drugs impacting either mitochondrial dynamics, oxidative stress, ISR signaling and/or a series of complementary pathways. In a parallel line of research, we study 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, which identified several RBPs as new MYC synthetic-lethal interactors (unpublished data). We hypothesize that these RBPs, as well as the specific RNA-regulatory pathways in which they are involved, may constitute new therapeutic targets in MYC-driven lymphoma. Pharmacological inhibition of two of these pathways in cultured cells supports this prediction, paving the way to further preclinical and mechanistic studies. 1. Bisso A et al. MYC in Germinal Center-derived lymphomas: Mechanisms and therapeutic opportunities. Immunol Rev (2019) 288, 178-197. 2. Donati G and Amati B. MYC and therapy resistance in cancer: risks and opportunities. Mol Oncol (2022) 16, 3828-3854. 3. D'Andrea A et al. The mitochondrial translation machinery as a therapeutic target in Myc-driven lymphomas. Oncotarget (2016) 7, 72415-72430. 4. Donati G et al. Targeting mitochondrial respiration and the BCL2 family in high-grade MYC-associated B-cell lymphoma. Mol Oncol (2022) 16, 1132-1152. 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, eaan8723. 6. Donati G et al. Oxidative stress enhances the therapeutic action of a respiratory inhibitor in MYC-driven lymphoma. EMBO Mol Med (2023) 15, e16910. |
| **Main research area** | Molecular Therapy |
| **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 |

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| **Lab website link** | https://www.research.ieo.it/research-and-technology/principal-investigators/bruno-amati/ |
| **Social media link** | |
| **Lab bibliography** | Cooperation between MYC and b-catenin in liver tumorigenesis requires Yap/Taz. Bisso A, Filipuzzi M, Gamarra Figueroa GP, Brumana G, Biagioni F, Doni M, Ceccotti G, Tanaskovic N, Morelli MJ, Pendino V, Chiacchiera F, Pasini D, Olivero D, Campaner S, Sabò A, Amati B HEPATOLOGY 2020 Oct; 72: 1430 |