XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026 Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P004

New technologies and multiomics analysis

GENOMIC AND FUNCTIONAL CHARACTERIZATION OF THE MURINE ACUTE MYELOID LEUKEMIA CELL LINE C1498 AS A PRECLINICAL MODEL OF VENETOCLAX/AZACITIDINE RESISTANCE

M. Ghetti[1], I. De Santis[2], D. Tolomeo[3], F. Ruggieri[1|4], C. Bracci[1], M.T. Bochicchio[1], M. Paganelli[1], A. Ferrari[1], S. Sangaletti[5], C. T. Storlazzi[3], G. Simonetti[1]

[1]Biosciences Laboratory, IRCCS Istituto Romagnolo per lo Studio dei Tumori IRST "Dino Amadori"; [2]Unit of Biostatistics and Clinical Trials, IRCCS Istituto Romagnolo per lo Studio dei Tumori IRST "Dino Amadori"; [3]Department of Biosciences, Biotechnology and Environment, University of Bari Aldo Moro; [4]Department of Medical and Surgical Sciences DIMEC, University of Bologna; [5]Molecular Immunology Unit, Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale Tumori.

Introduction: The murine leukemia cell line C1498, derived from a C57BL/6J mouse, induces a lethal acute myeloid leukemia (AML)-like disease in immunocompetent hosts. Given its widespread use in preclinical studies of AML pathogenesis, tumor-host interactions and therapeutic responses, a comprehensive molecular characterization is crucial to fully define its translational relevance.

Methods: We performed an integrated genomic and molecular cytogenetic characterization of C1498 cells through whole-genome sequencing (WGS; median coverage 70×) and multicolor fluorescence in situ hybridization (M-FISH). Variants were annotated by mouse and human ortholog databases as OncoKB, and filtered against population references (Mouse Genomes Project, Ensembl). Drug sensitivity to the venetoclax/azacitidine (ven/aza) combination was assessed by in vitro dose–response assay.

Results: WGS (Figure A) identified 2,075 variants in the coding genome, absent from population databases. Among 1,800 mutated genes, 1,632 had human orthologs, with 155 variants in 133 cancer-related genes, including 17 mutations in 14 AML-associated genes (*Asxl2*, *Bcor*, *Crebbp*, *Flt3*, *Gnas*, *Idh1*, *Kit*, *Kmt2d*, *Nf1*, *Notch1/2*, *Setbp1*, *Tet2*, *Trp53*). High-impact lesions included stopgain mutations in *Bcor* and *Tet2*, nonsynonymous alterations in the NADP-dependent domain of *Idh1*, the RAS-GAP domain of *Nf1*, and the DNA-binding site of *Trp53*. Pathway analysis showed enrichment of mutated genes in transcriptional regulation, signaling and epigenetics.

M-FISH and WGS revealed a highly rearranged karyotype (37–42 chromosomes, Fig.B) with complex translocations, deletions, and amplifications. Copy number variant analysis identified 81 high-confidence calls, with amplifications involving Stk32b and Bub1 kinases. Notably, deletion events involved *Trp53*, *Brca1*, *Stag1/2*, *Pds5b*, and *Rad50*, while *Myc* was tandemly duplicated. Among structural variants, 239 overlapped with cytogenetic rearrangements and 27 translocations involved at least one cancer-related gene, including the previously described *E2f3::Cdkal1* fusion. Data integration revealed double-hit events including mutations co-occurring with deletions of tumor suppressor genes (*Trp53*, *Nf1*, *Recql4*) and amplifications of oncogenes (*Idh1*, *Ccnd3*, *Ret*, *Gnas*, *Ntrk3*). Drug testing showed that C1498 cells were resistant to ven/aza (Fig.C), with IC_{50} values of 9.85 µM ven/98.5 µM aza at 48h and 3.16 µM ven/31.6 µM aza at 72h, in line with the presence of Trp53 mutation and recent prognostic AML signatures.

Conclusions: C1498 cells display a complex genomic landscape characterized by *Trp53* and *Tet2* mutations, *Myc* amplification, and cohesin gene deletions. Its limited sensitivity to ven/aza mirrors the *TP53*-mutated AML resistance phenotype. This integrated molecular profile provides a robust framework for the rational use of C1498 as a preclinical model to study AML biology and evaluate novel therapeutic and immunologic strategies.

Acknowledgements: AIRC MFAG 2023 (29381).

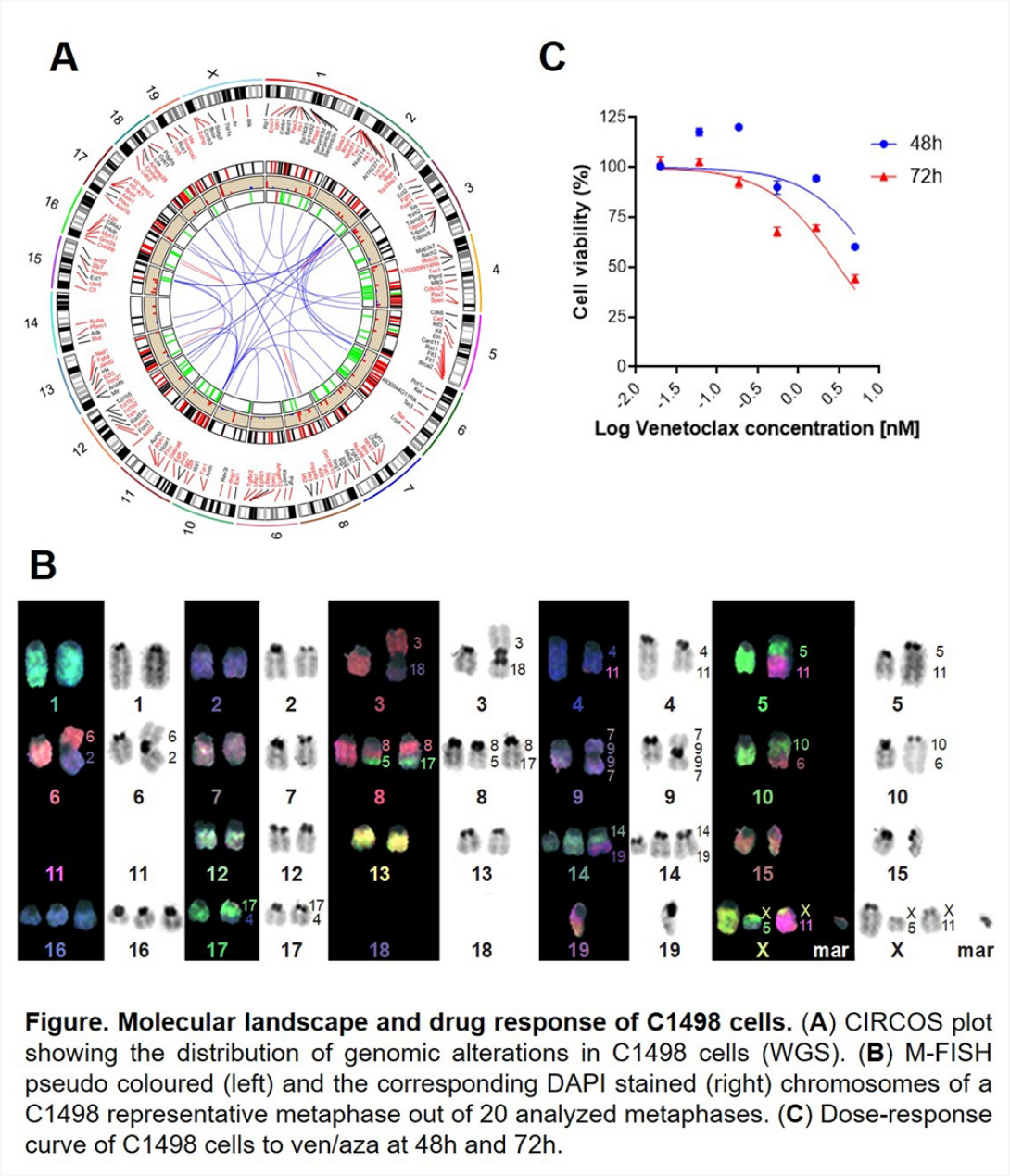

Figure. Molecular landscape and drug response of C1498 cells. (**A**) CIRCOS plot showing the distribution of genomic alterations in C1498 cells (WGS). (**B**) M-FISH pseudo coloured (left) and the corresponding DAPI stained (right) chromosomes of a C1498 representative metaphase out of 20 analyzed metaphases. (**C**) Dose-response curve of C1498 cells to ven/aza at 48h and 72h.