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Targeting Flt3-resistant Aml: A Combined In Vitro and Zebrafish Model Study

Caterina Ricci [1], Alex Pezzotta [1], Thomas Carzaniga [1], Luca Casiraghi [1]

[1] UNIMI, Milano, Italy

FLT3-mutated Acute Myeloid Leukemia (AML) remains challenging to treat, with FLT3 inhibitor (FLT3i) resistance a therapeutic limiting factor. Histone deacetylase 8 (HDAC8) overexpression has been identified as a primary mechanism of FLT3i resistance, and the therapeutic potential of targeted combination therapies has been hypothesized. This study investigates the synergistic potential of a BCL2 inhibitor and a selective HDAC8 inhibitor to bypass resistance. In vitro testing (FTIR, DSC, DLS, SPR) provides mechanistic insight into drug-drug interactions, and facilitates dosage regimen optimization minimizing unnecessary animal sacrifice. In vivo assessment of an AML zebrafish FLT3-ITD model offers insight into the proliferation and migration of hematopoietic stem and progenitor cells (HSPC). This study provides valuable drug-drug and drug-target interaction knowledge and enables the design of HDAC8-targeted combination therapies for FLT3-mutated AML resistance treatment and clinical efficacy improvement.