



2nd **BOLOGNA** **WORKSHOP** on **IMMUNOTHERAPY** **FOR ACUTE MYELOID** **LEUKEMIA**

Bologna, Royal Hotel Carlton
September 29-30, 2026

Epithelial-to-Mesenchymal Transition in leukemia: intertwining aggressiveness and immune regulation

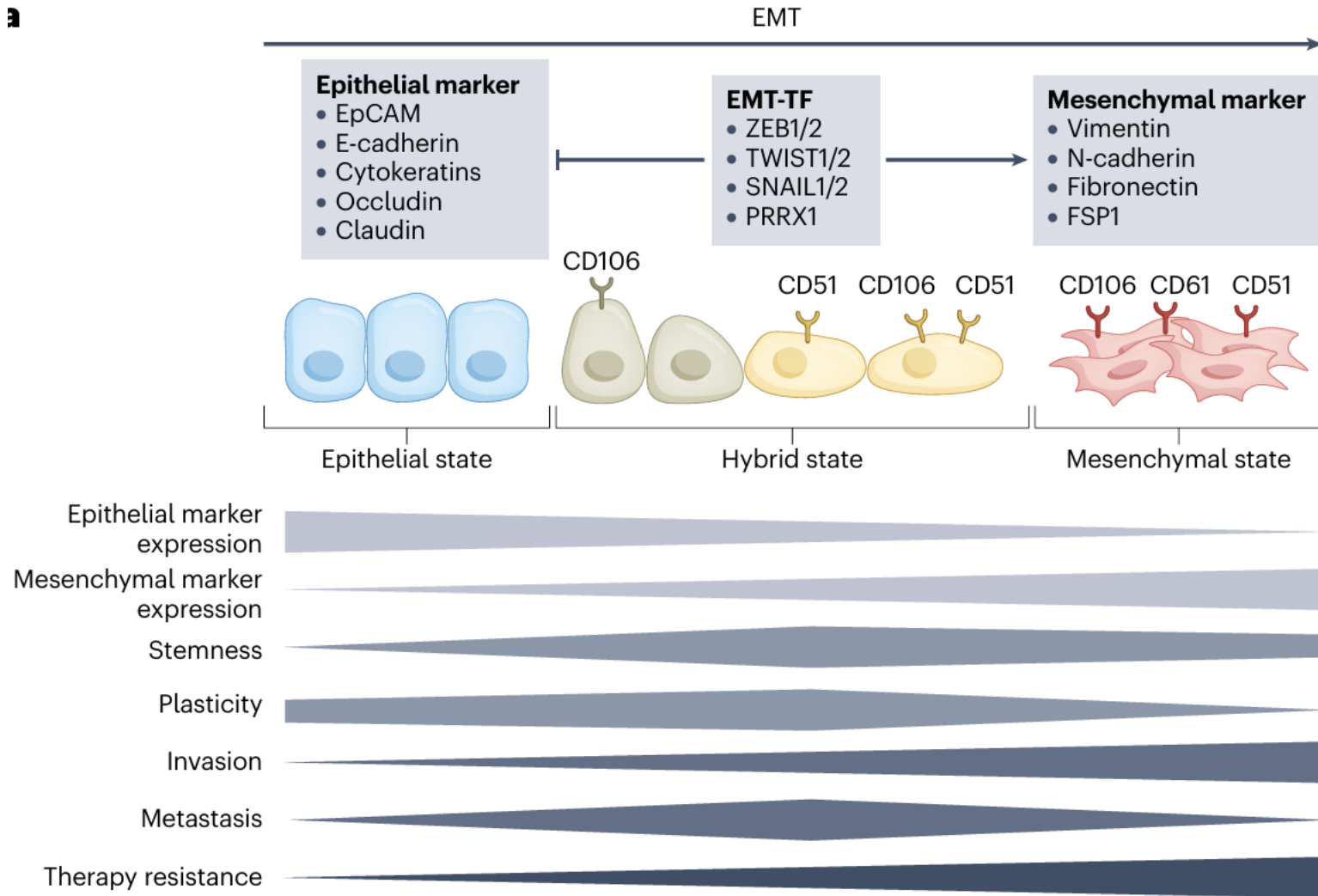
*Sabina Sangaletti,
Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

My disclosure statements

- No conflict of interest to declare

EMT is a paradigm of cellular plasticity

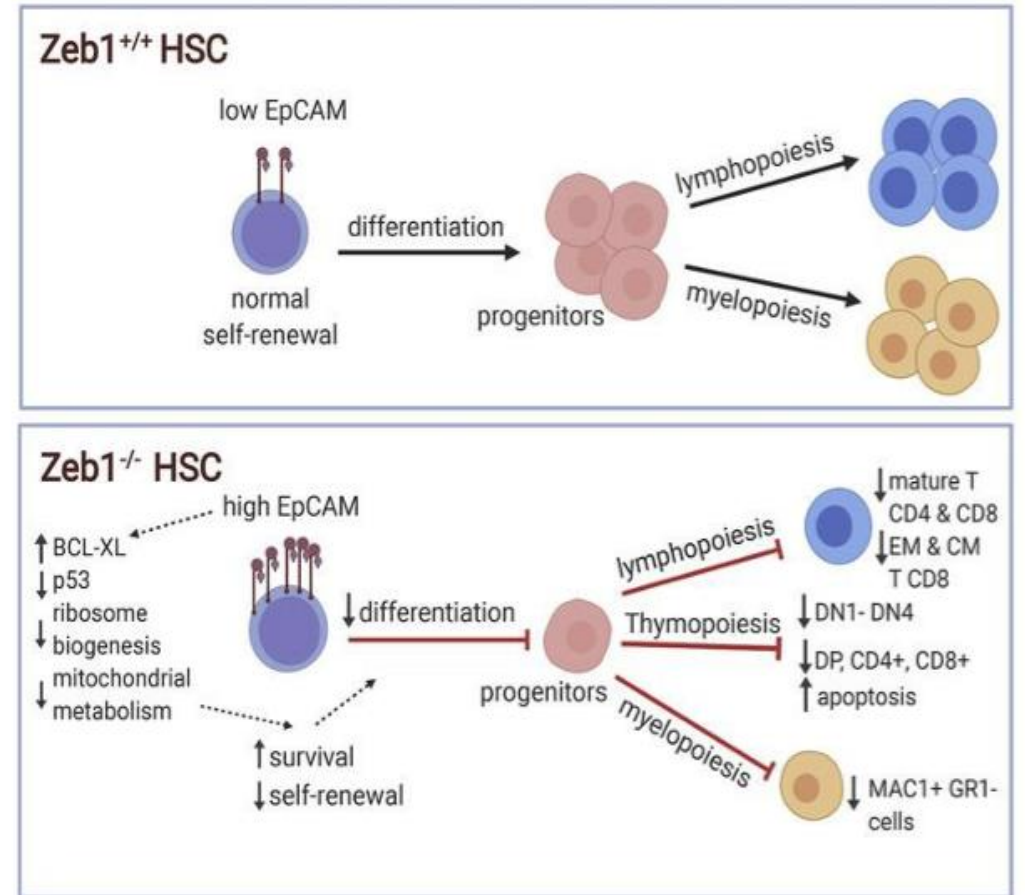
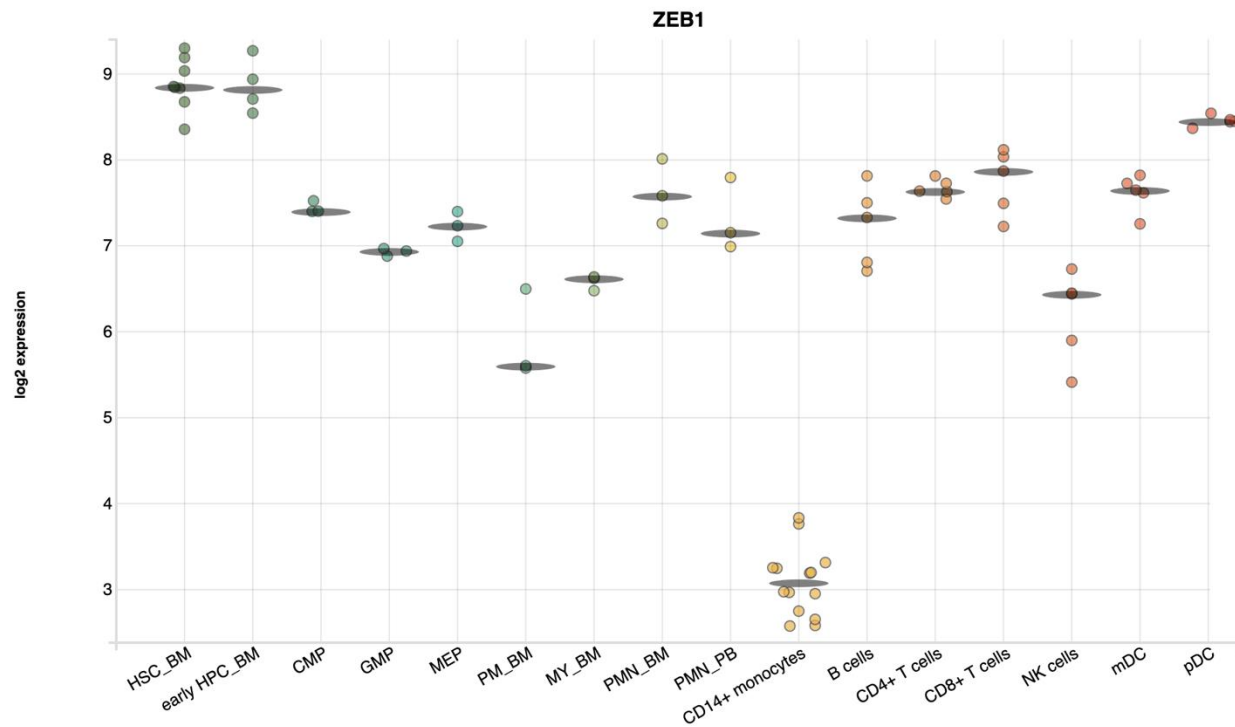
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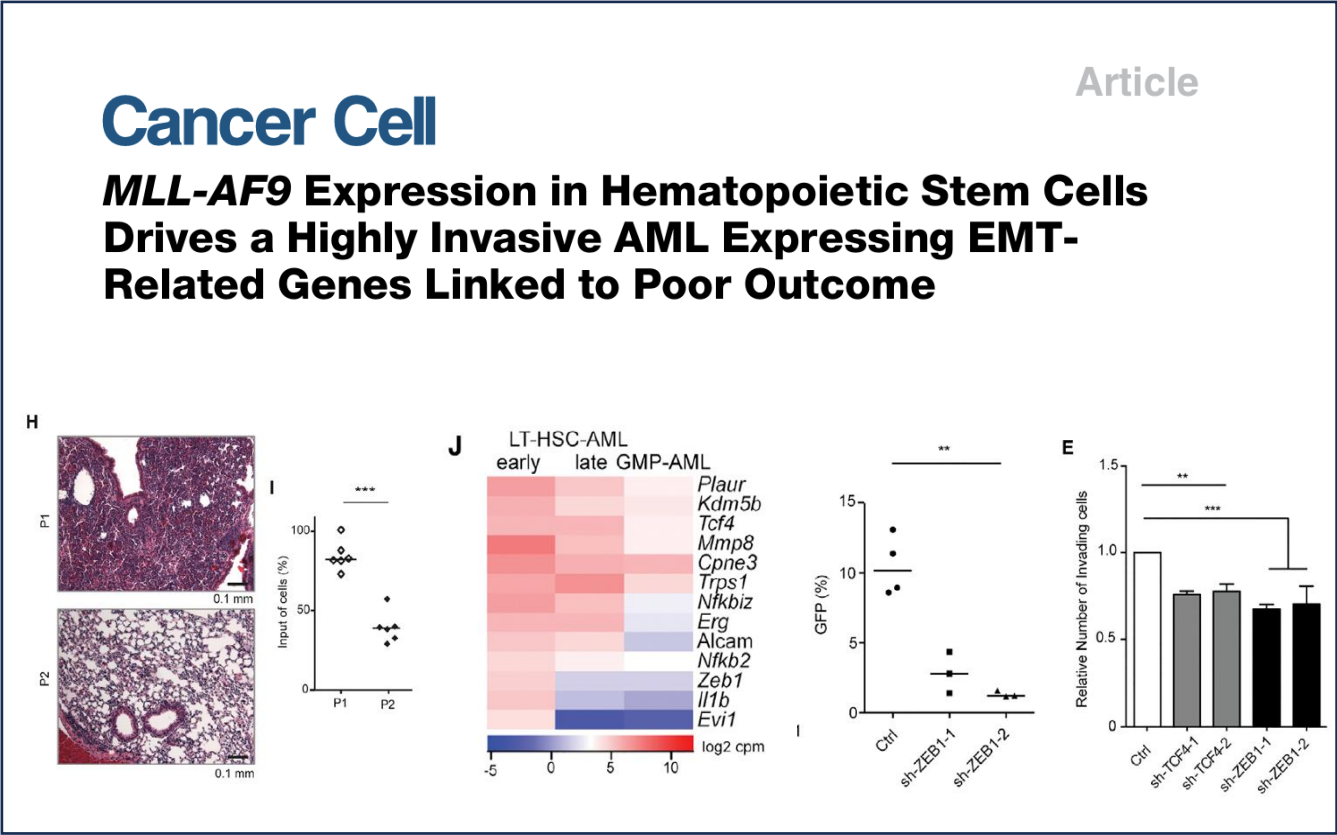
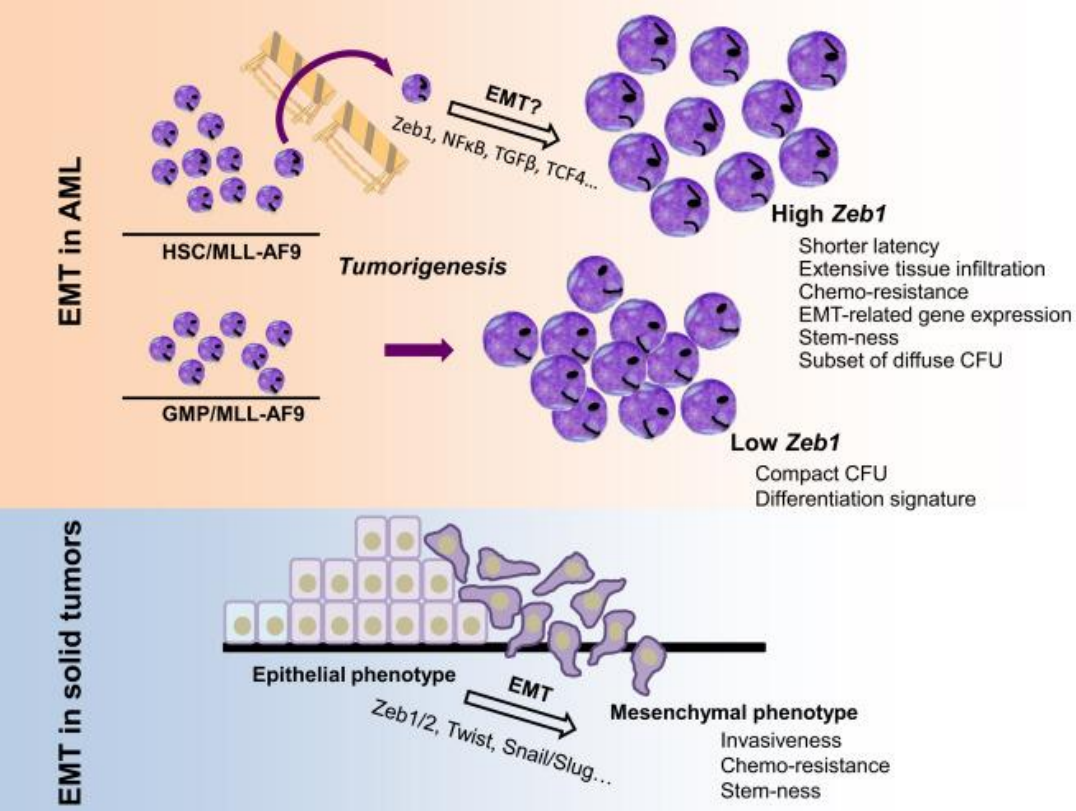
EMT entwined with CSC programs:

1. Regulate stem cell self-renewal
2. EMT-inducing TFs can be stabilized by DNA damage and assist DNA repair response (safeguard the genome of stem cells)

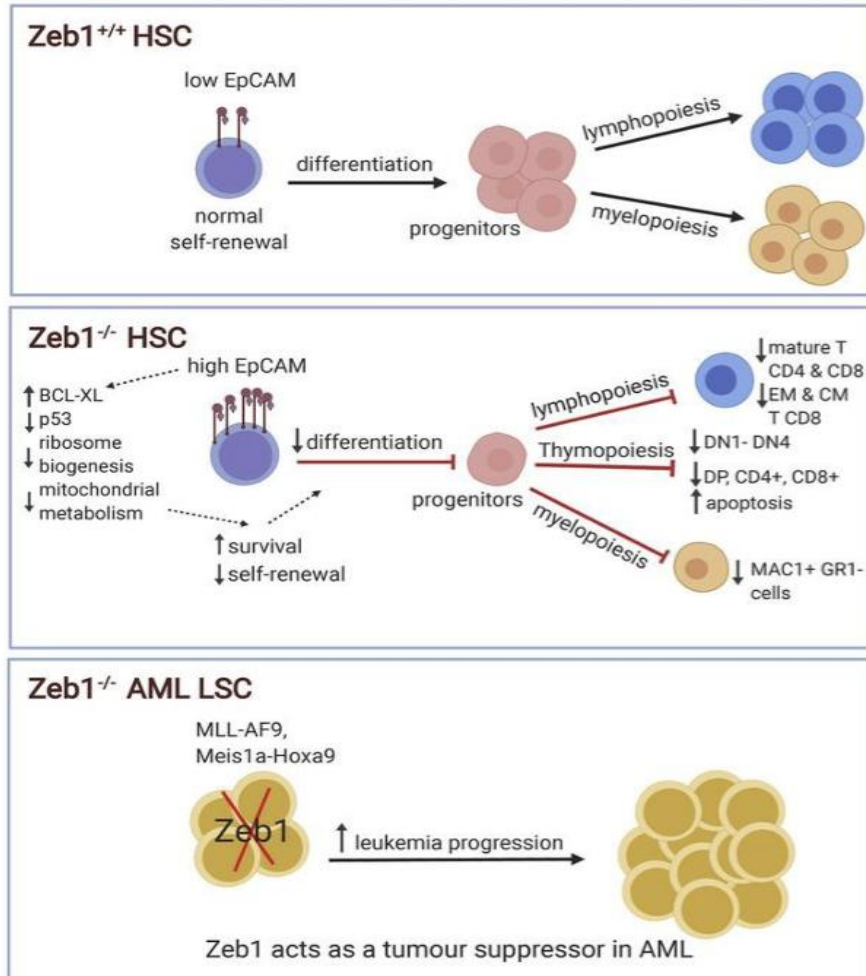
ZEB1 regulates hematopoietic stem-cell fate



The expression of EMT genes reflects more aggressive HSC-derived AML



ZEB1 has context-dependent functions in AML



✔ Tumor-suppressive

ZEB1 preserves HSC/LSC fate and limits leukemic transformation

Altamori et al. J clin Invest, 2021, PMID 33108352

ZEB1 was reduced in AML patients; Zeb1 loss in HSCs/LSCs accelerated MLL-AF9- and Meis1a/Hoxa9-driven AML.

⚠ Pro-leukemic

Invasion · differentiation block · proliferation · immune escape

Stavropoulou et al. Cancer Cell, 2016, PMID 27344946

ZEB1 knockdown reduced blast invasion in aggressive, infiltrative and chemoresistant MLL-AF9 AML.

Bassani et al. Cell Reports, 2024, PMID 38363677

ZEB1 high was associated with shorter survival, Th17 programs, CD8 suppression and extramedullary disease.

Li et al., J Cell Mol Med, 2021, PMID 33960640

ZEB1 high predicted poor prognosis; its depletion induced differentiation and inhibited AML proliferation.

Zhang et al., Appl Biochem Biotechnol, 2025, PMID 40381097

The miR-128-3p-ZEB1-PD-L1 axis promoted AML-cell proliferation and immune escape

Jin et al., Acta Biochim Pol, 2024, PMID 36812496

MALAT1 promoted ZEB1 m6A modification, enhancing AML-cell proliferation, migration and invasion.

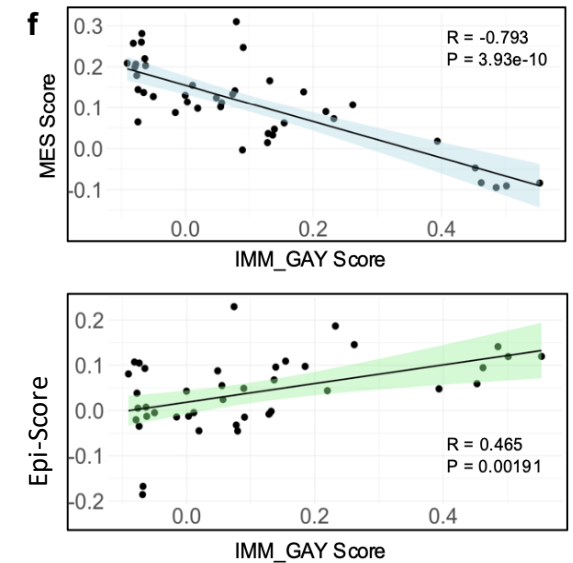
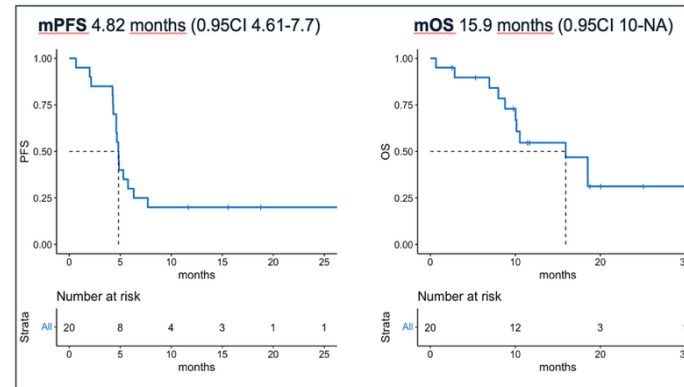
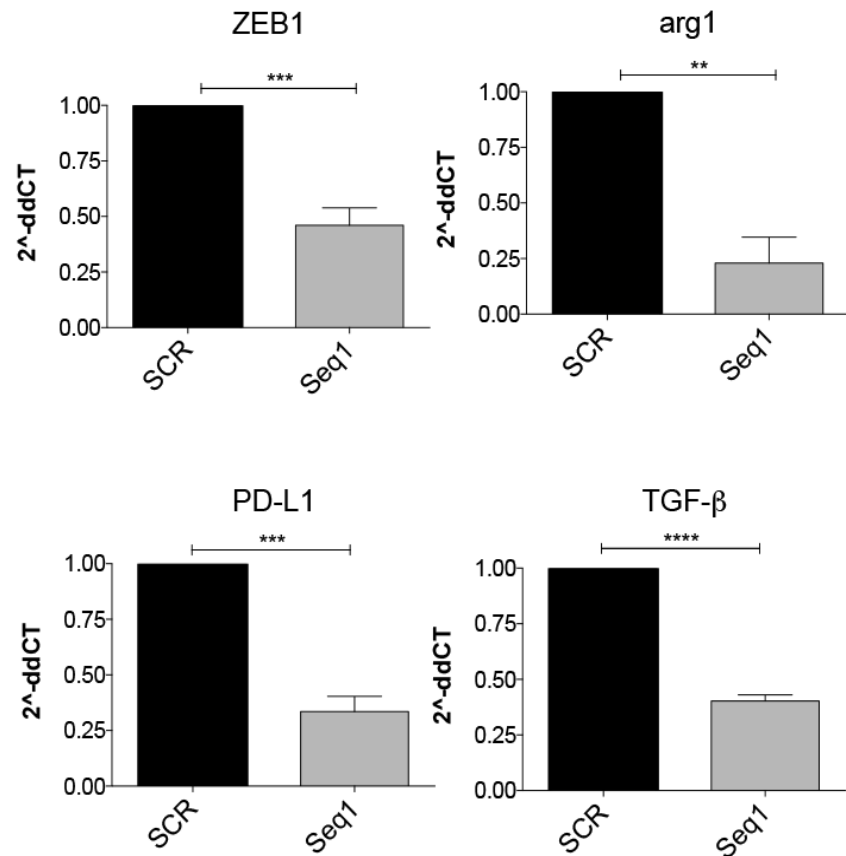
Shi et al., Clinics, 2026, PMID 41863965

The circ-RERE-miR-128-3p-ZEB1 axis enhanced autophagy, PD-L1 expression and immune escape.

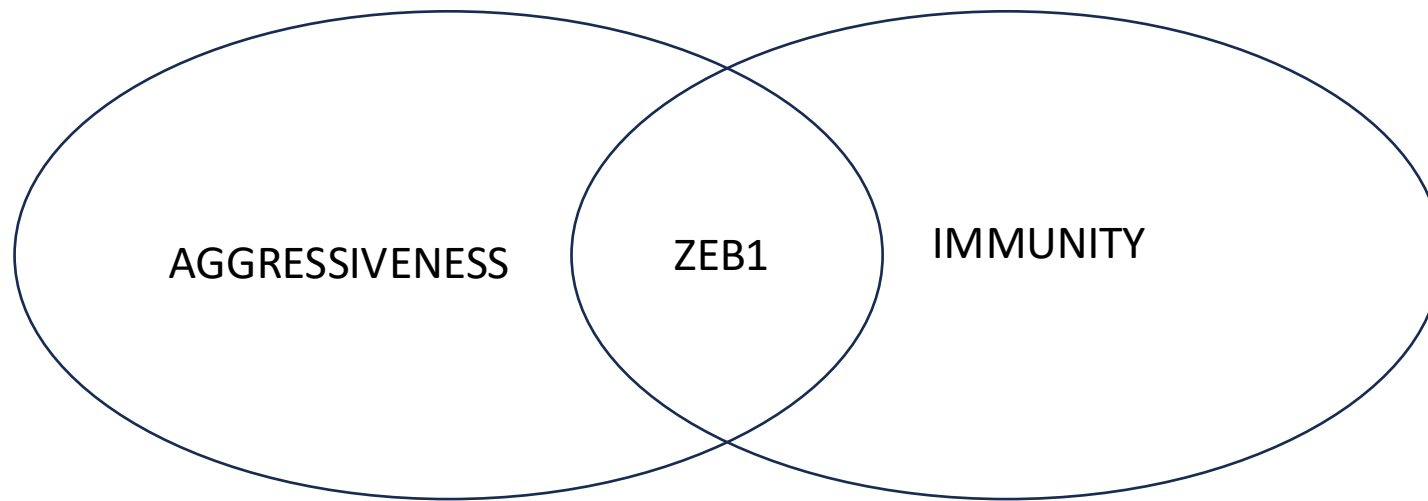
ZEB1 is associated with an immunosuppressive state

1. ZEB1 is expressed in immune suppressive cells

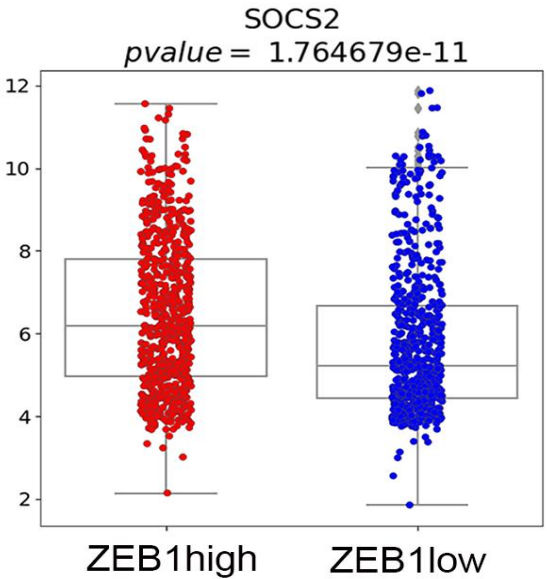
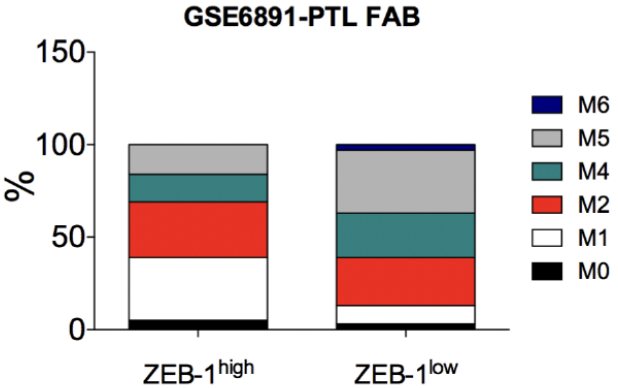
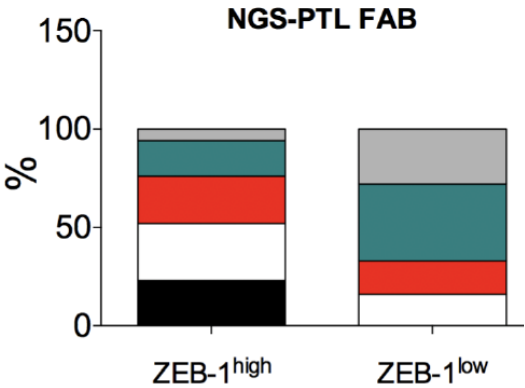
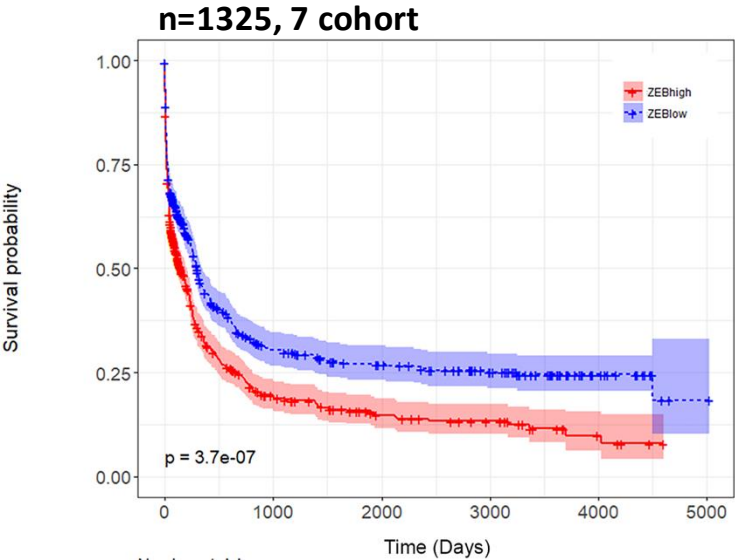
2. In SCLC ZEB1 is negatively correlated with immune cell activation and recruitment



ZEB1 at the intersection of AML aggressiveness and immunity



ZEB1 expression is associated with stemness and aggressiveness

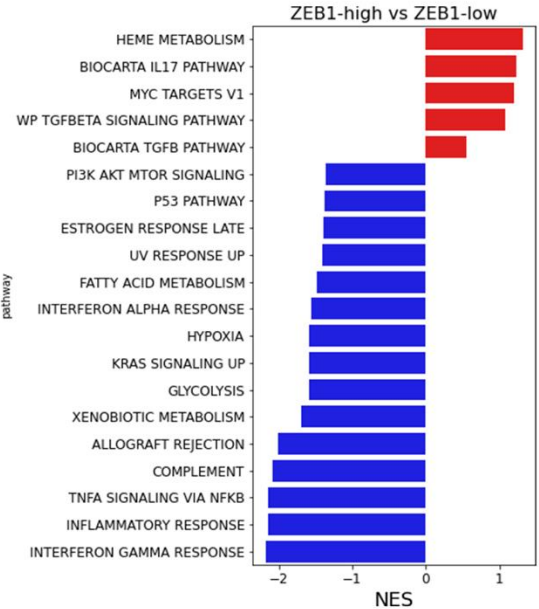


Tumor and Stem Cell Biology

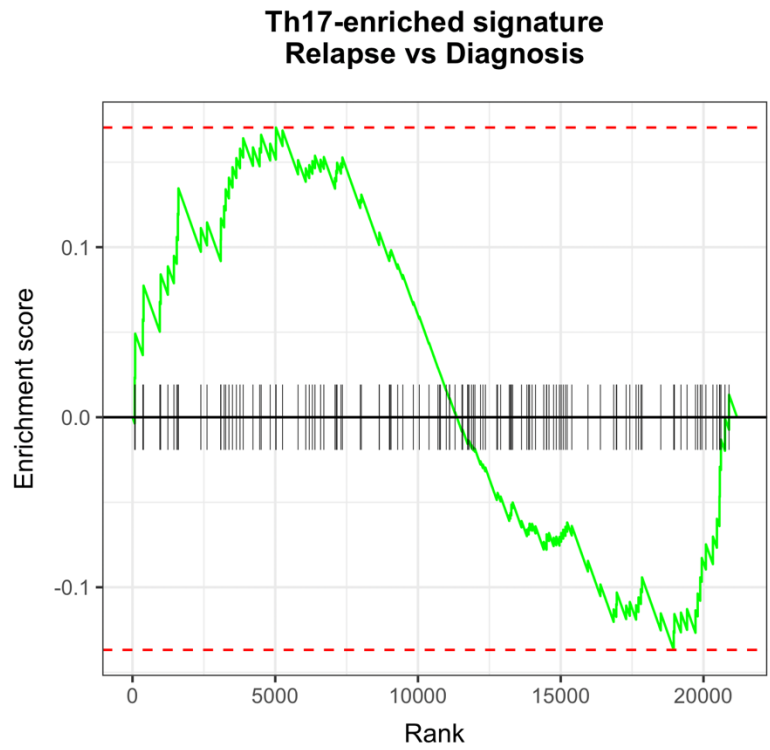
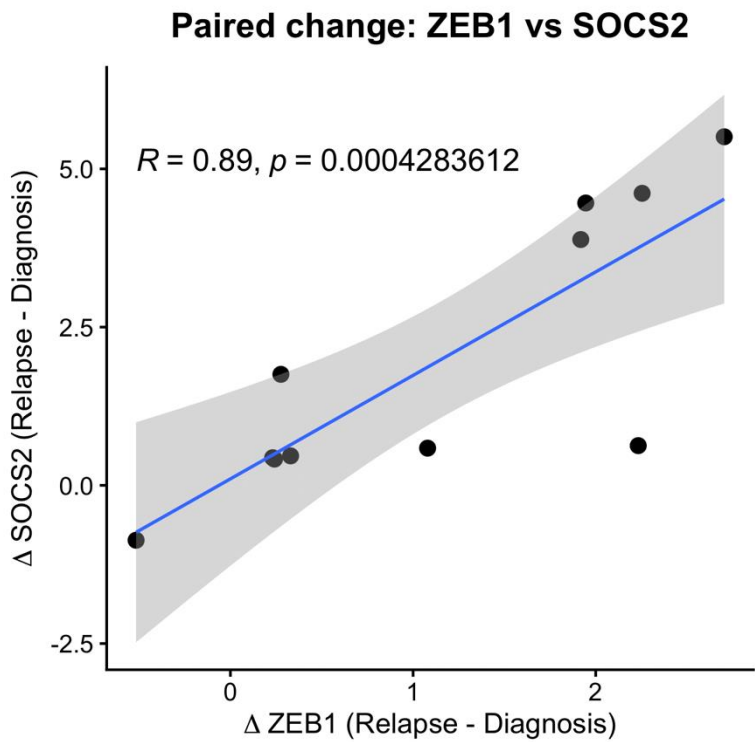
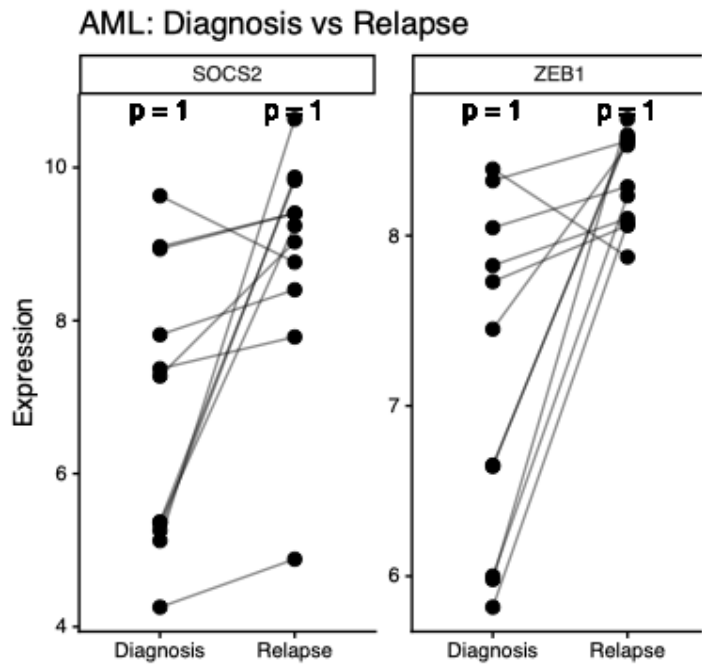
Cancer Research

SOCS2 Controls Proliferation and Stemness of Hematopoietic Cells under Stress Conditions and Its Deregulation Marks Unfavorable Acute Leukemias

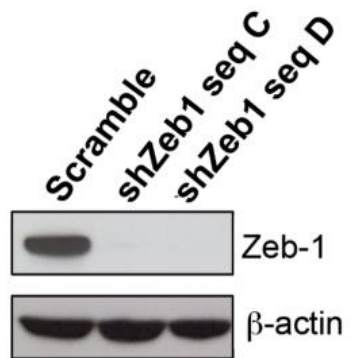
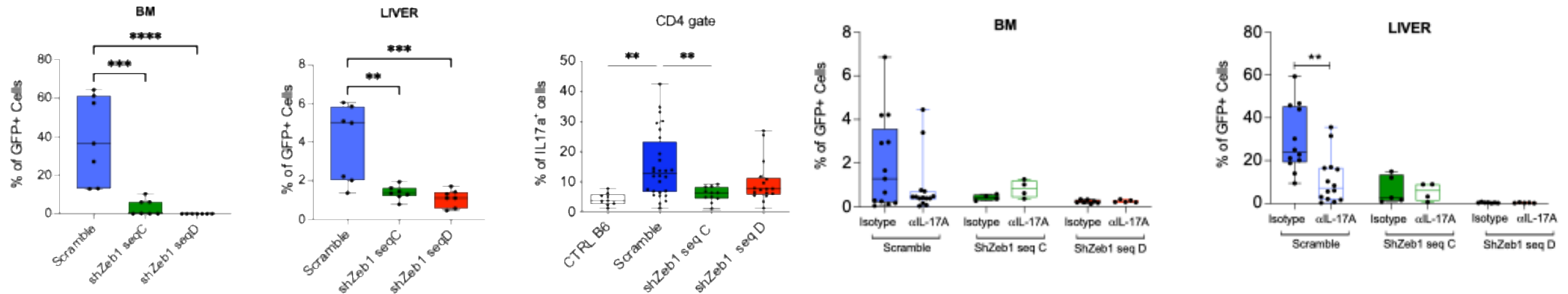
Caterina Vitali¹, Claudia Bassani¹, Claudia Chiodoni¹, Elisa Fellini¹, Carla Guarnotta², Silvia Miotti¹, Sabina Sangaletti¹, Fabio Fuligni³, Loris De Cecco⁴, Pier P. Piccaluga⁵, Mario P. Colombo¹, and Claudio Tripodo²



In AML matched cases: ZEB1 is increased at relapse along with SOCS2 and Th17

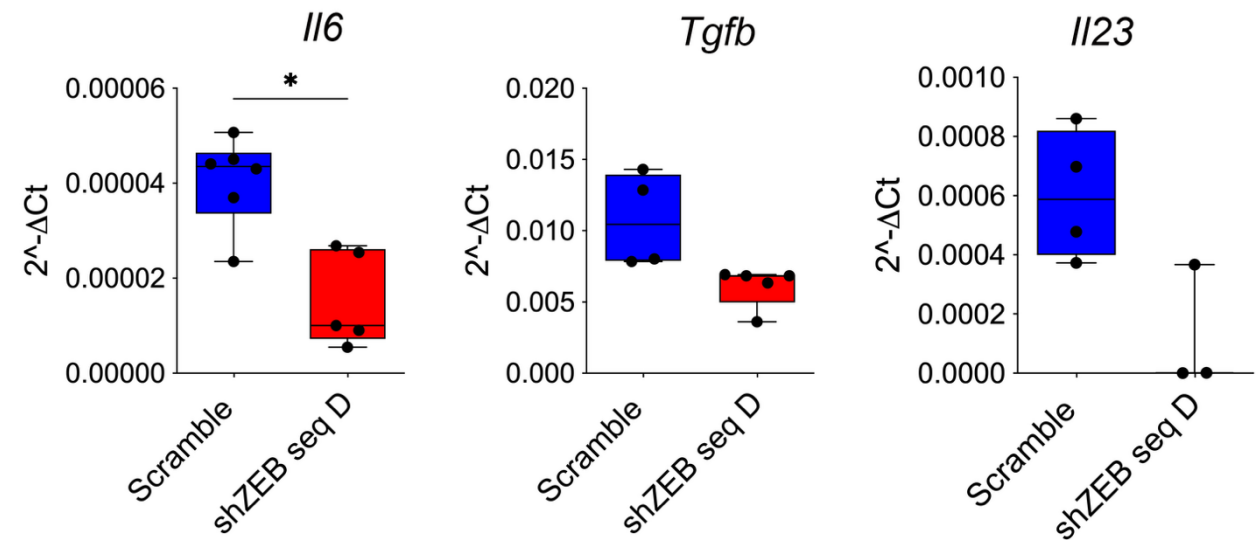


ZEB1 sustains AML cell fitness and promotes extramedullary disease through the expansion of Th17 cells.

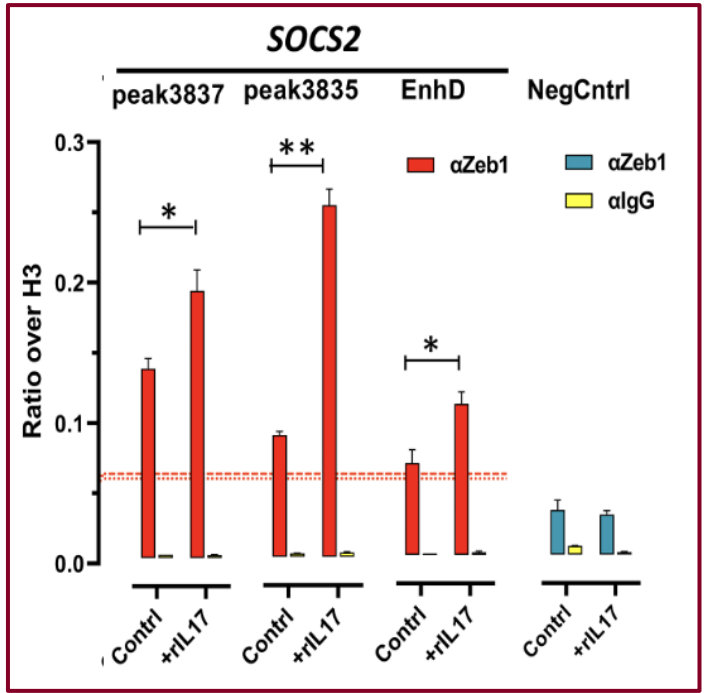
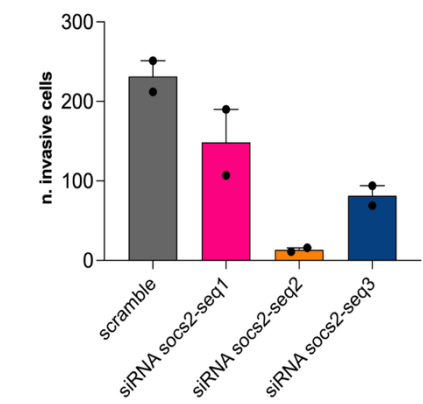
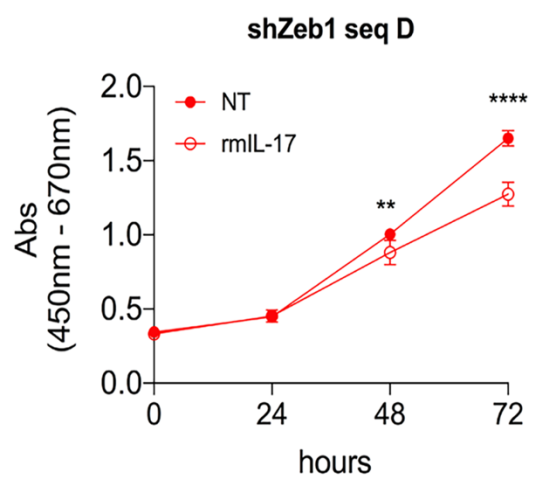
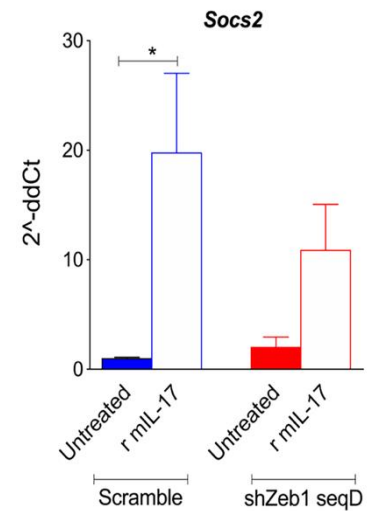
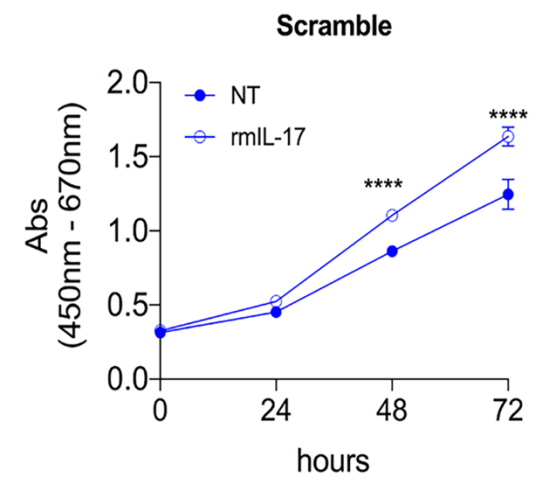


ZEB1 promotes a cytokine program that supports Th17 differentiation

C1498 murine AML

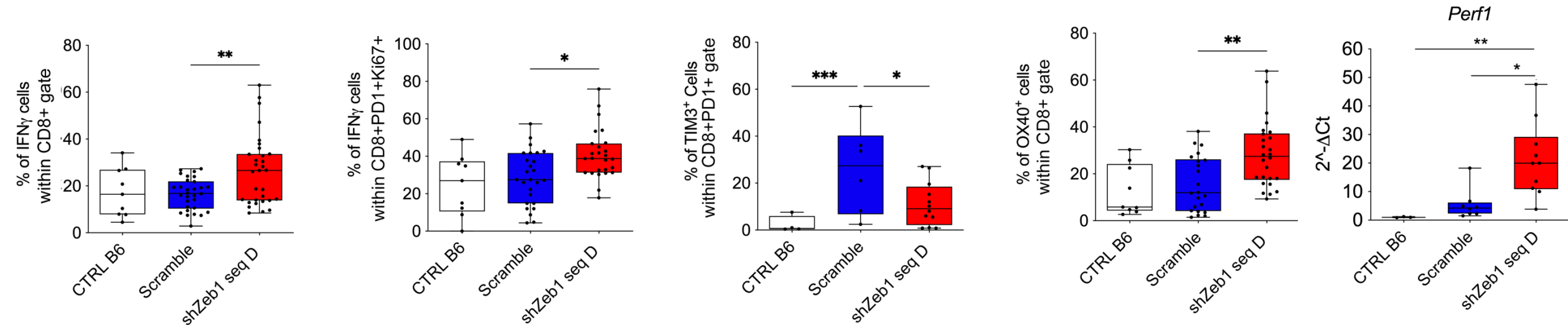


IL-17 sustains ZEB1+ cell proliferation also inducing SOCS2, somehow inducing epigenetic alterations



H3K4m3
H3K27Ac
+ IL-17

Activation of CD8 T cells in the absence of ZEB1



Does ZEB1 loss enhance CD8⁺ T-cell recognition by increasing leukemia immunogenicity/antigenicity?

COULD ZEB1 MODULATE CD8 T-CELL IMMUNESURVEILLANCE?

ZEB1-high AML shows reduced HLA and antigen-processing machinery expression

Genetic and epigenetic modulation of HLA and antigen processing machinery is a mechanism of immune evasion in cancer

Cell

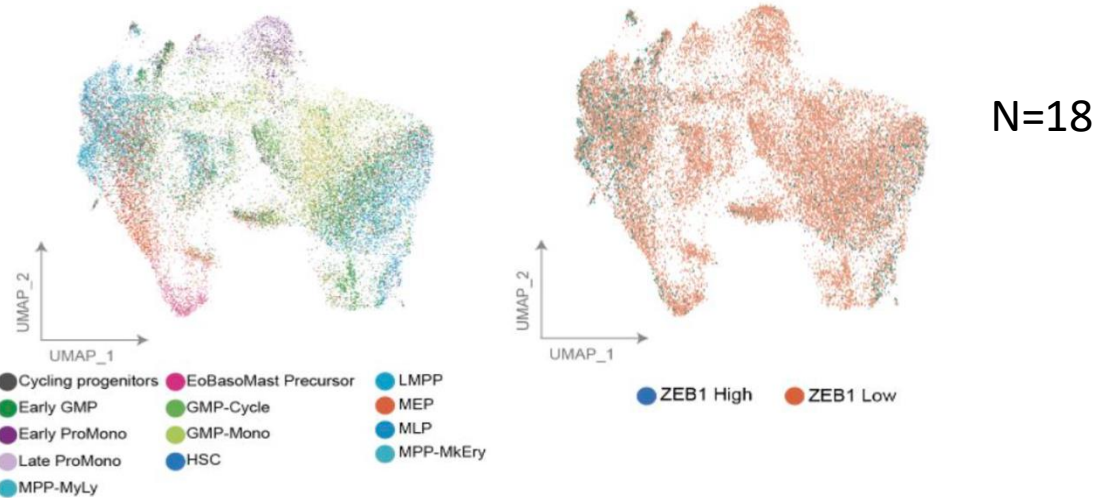
CellPress

Article

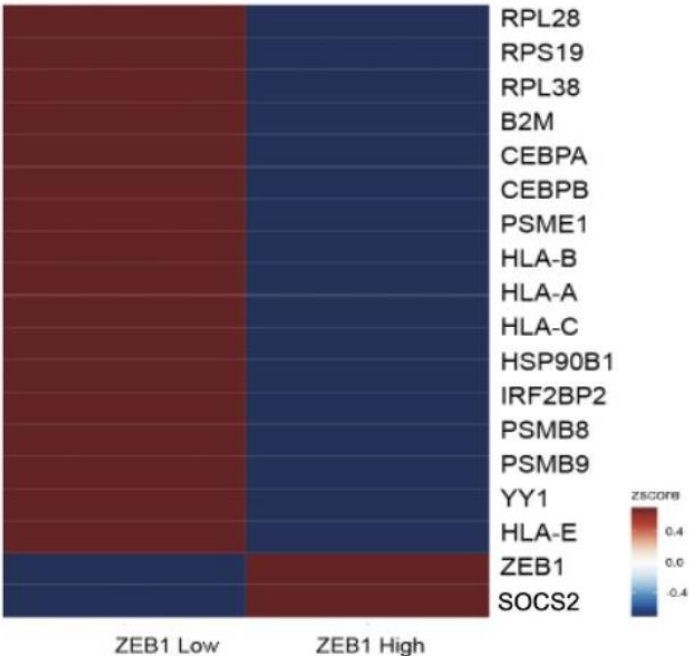
A membrane-associated MHC-I inhibitory axis for cancer immune evasion

Xufeng Chen,^{1,2,11} Qiao Lu,^{1,2,11} Hua Zhou,³ Jia Liu,^{1,2} Bettina Nadorp,^{1,2} Audrey Lasry,^{1,2} Zhengxi Sun,^{1,2} Baoling Lai,⁴ Gergely Rona,^{2,5,6} Jiangyan Zhang,^{1,2} Michael Cammer,⁷ Kun Wang,^{1,2} Wafa Al-Santli,^{1,2} Zoe Ciantra,¹ Qianjin Guo,⁸ Jia You,^{1,2} Debrup Sengupta,⁹ Ahmad Boukhris,^{1,2} Hongbing Zhang,¹⁰ Cheng Liu,¹⁰ Peter Cresswell,⁹ Patricia L.M. Dahia,⁸ Michele Pagano,^{2,5,6} Iannis Aifantis,^{1,2,12,13,*} and Jun Wang^{1,2,12,13,14,*}

Unpublished

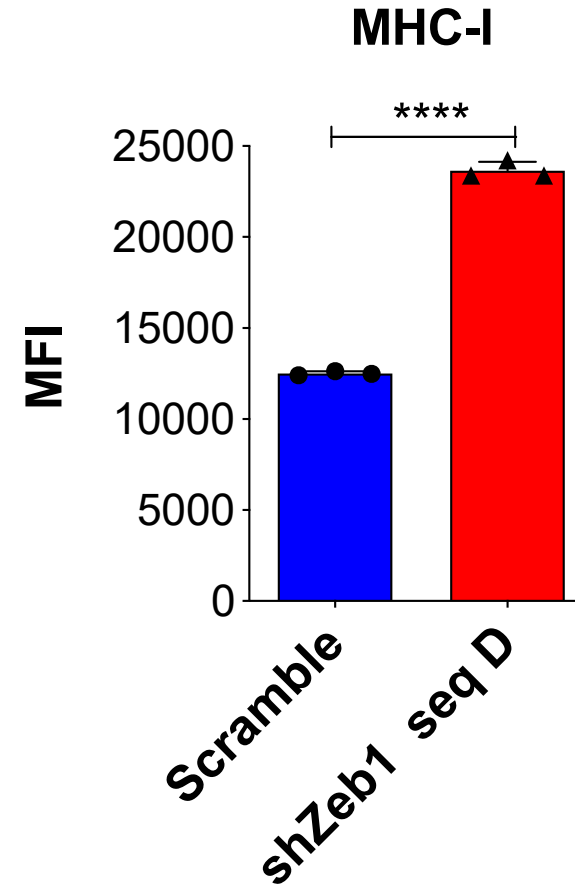
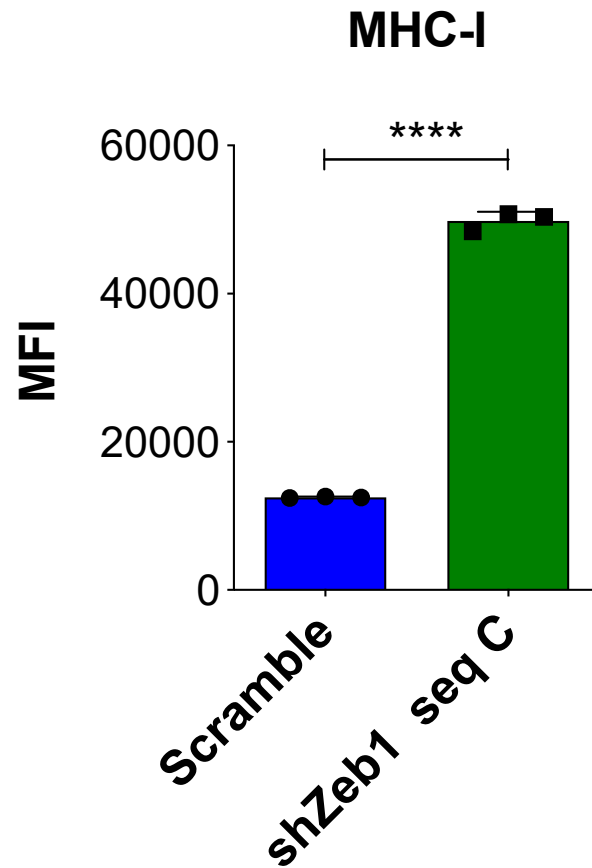


N=18



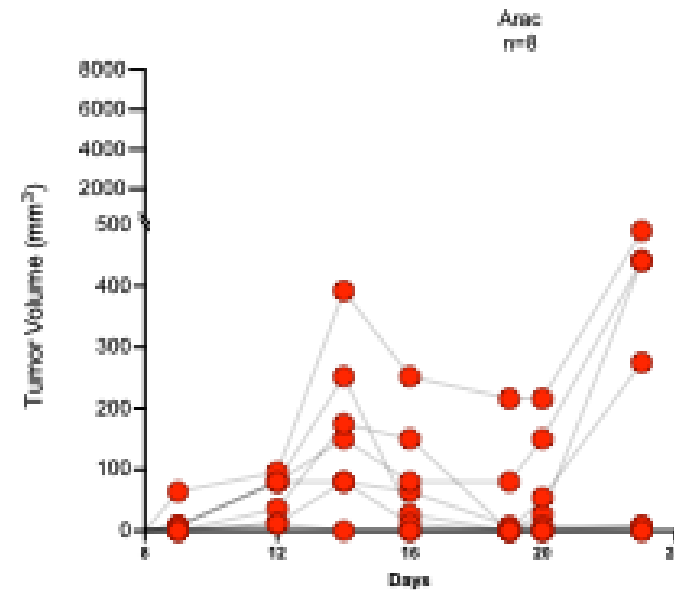
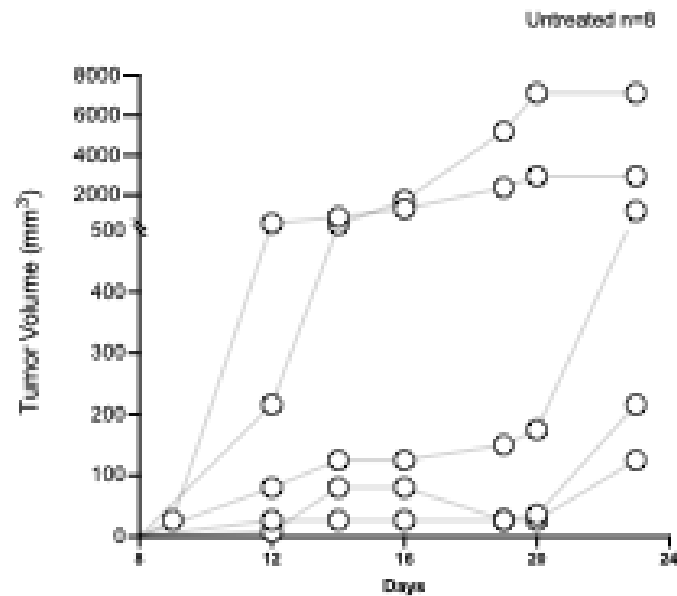
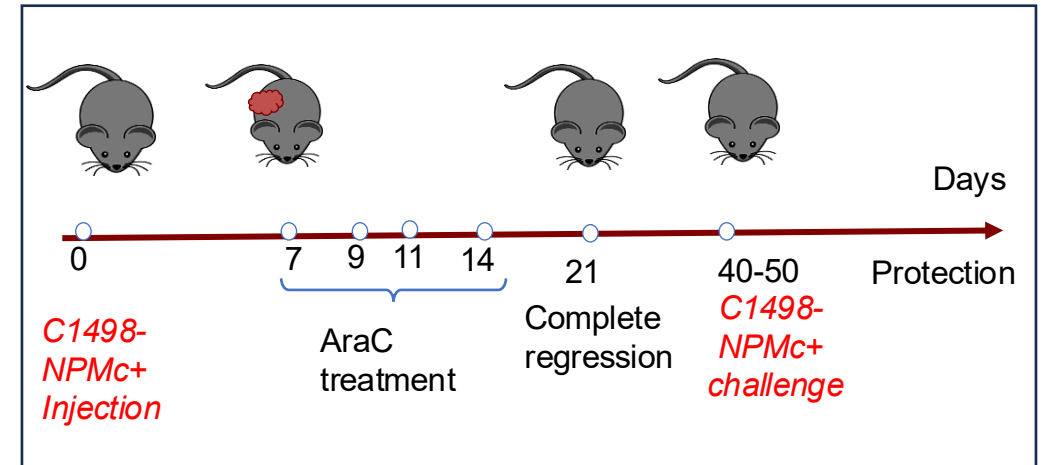
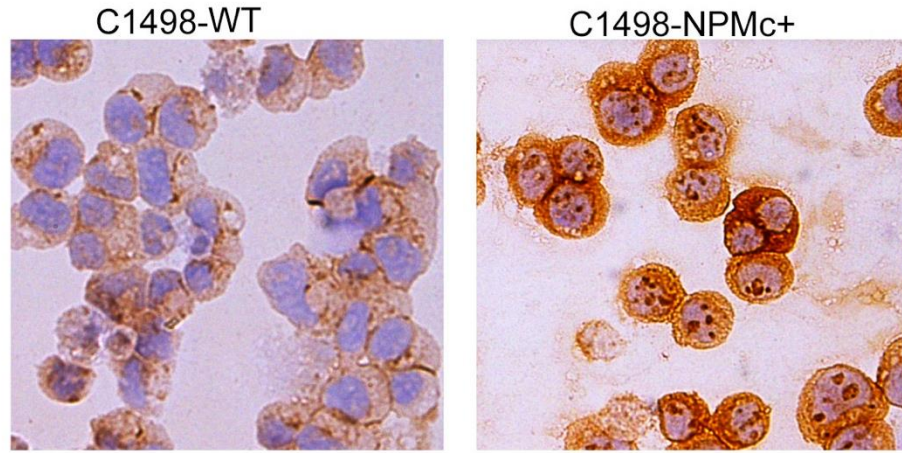
n=18

ZEB1 silencing increases MHC-I/HLA surface expression

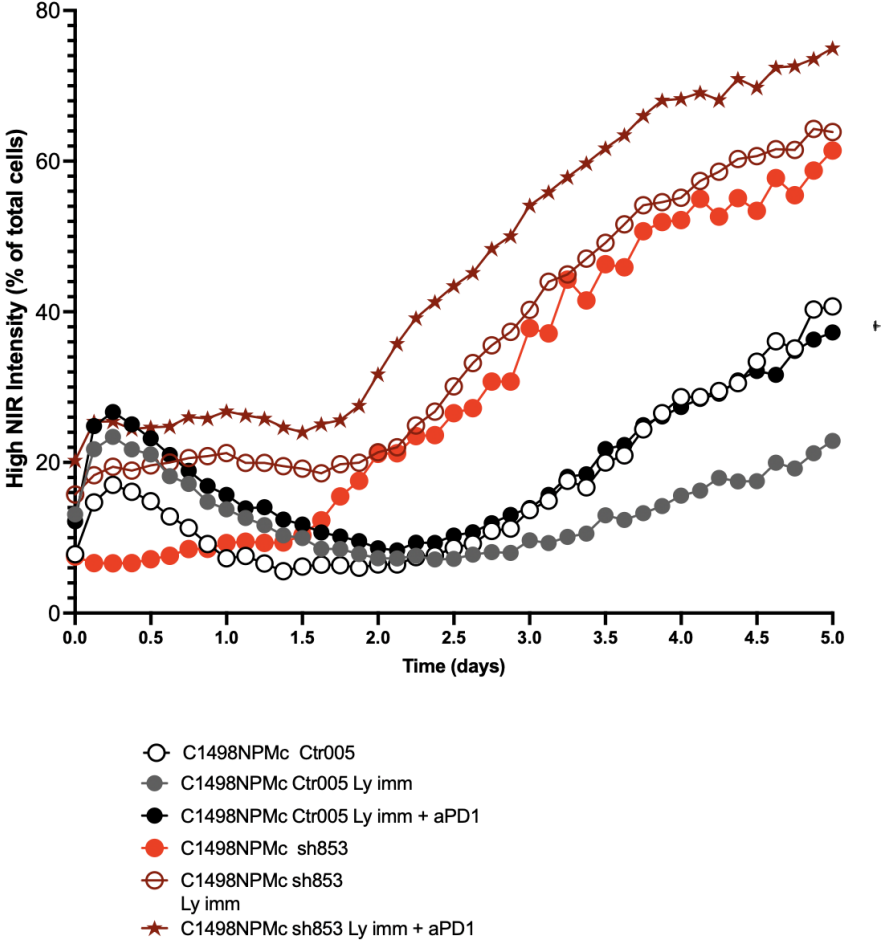
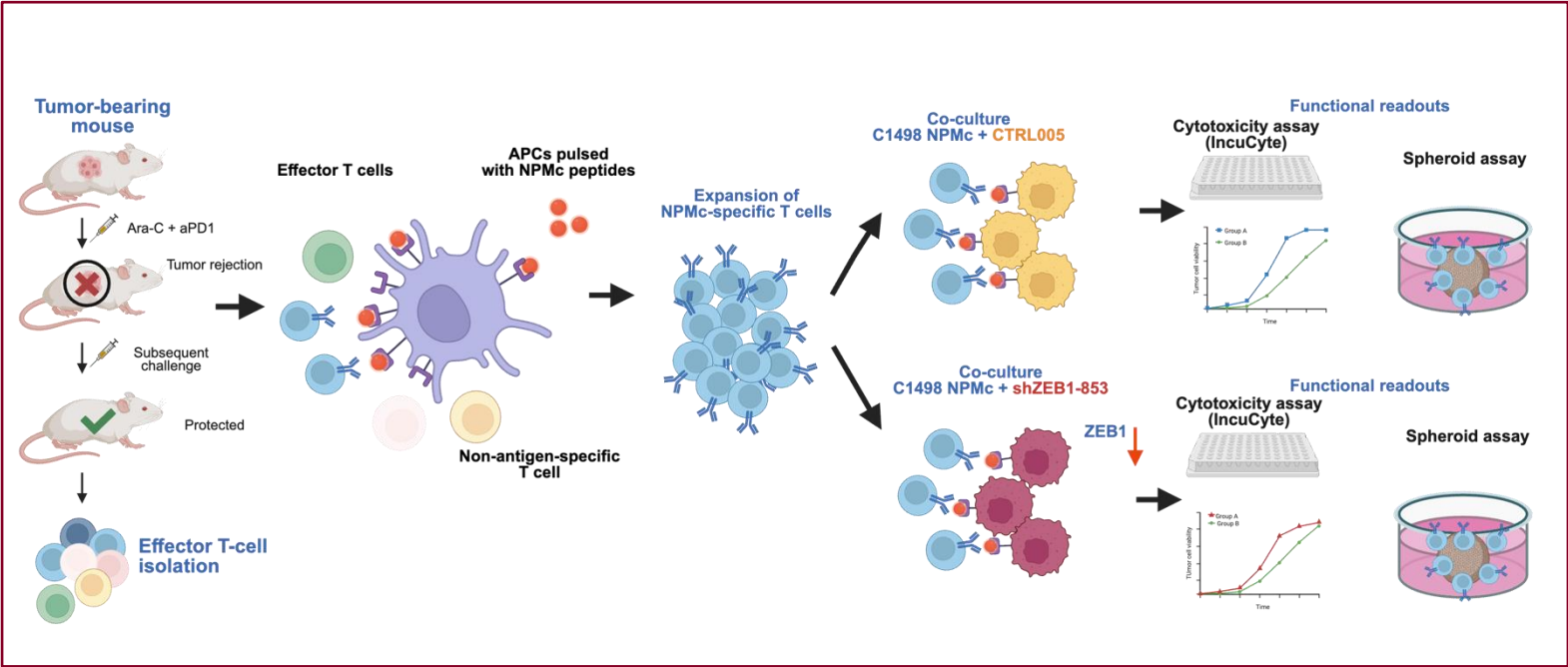


Does this translate into improved CTL recognition?

A functional model of treatment-induced AML immunogenicity

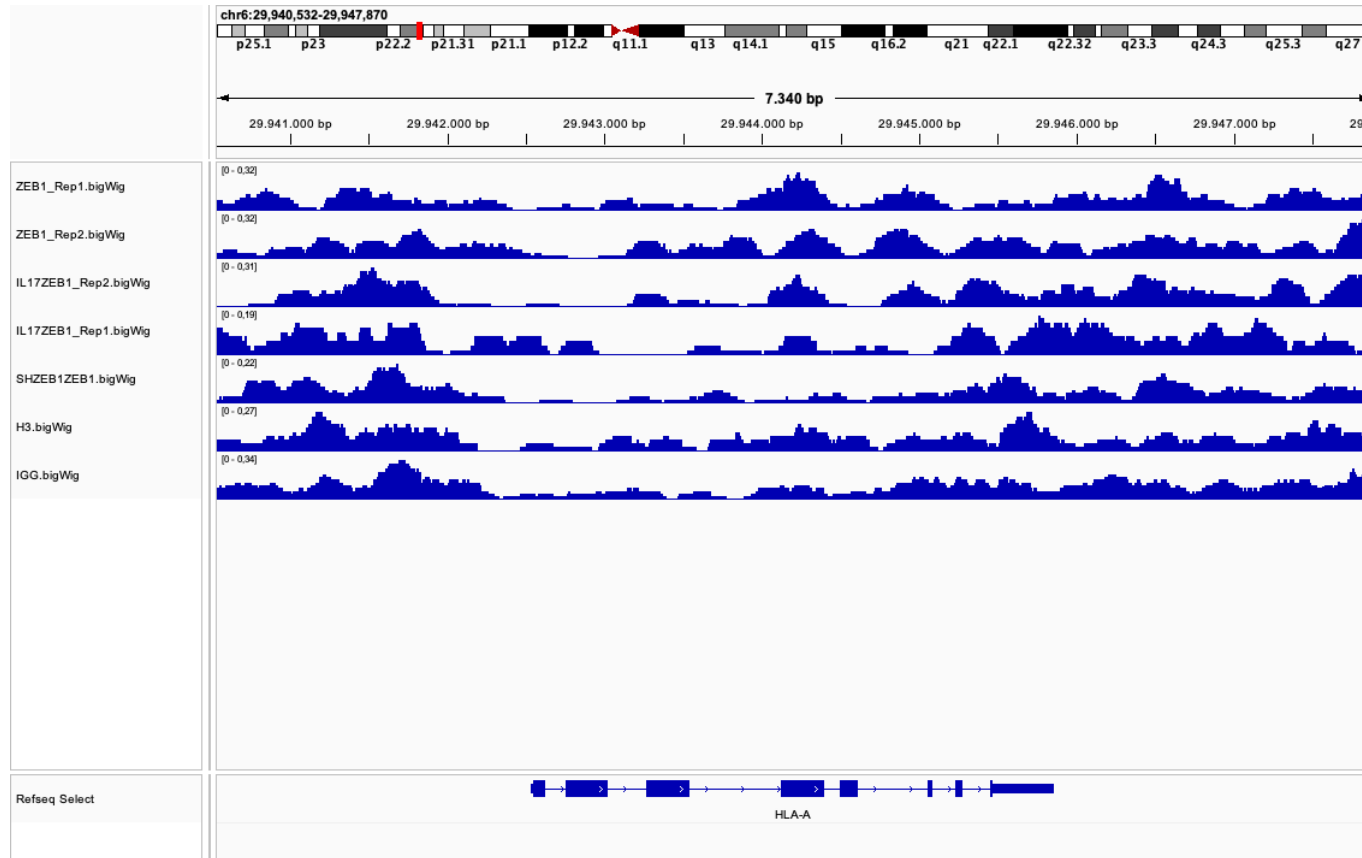


ZEB1 silencing enhances antigen-specific T-cell activity against AML cells



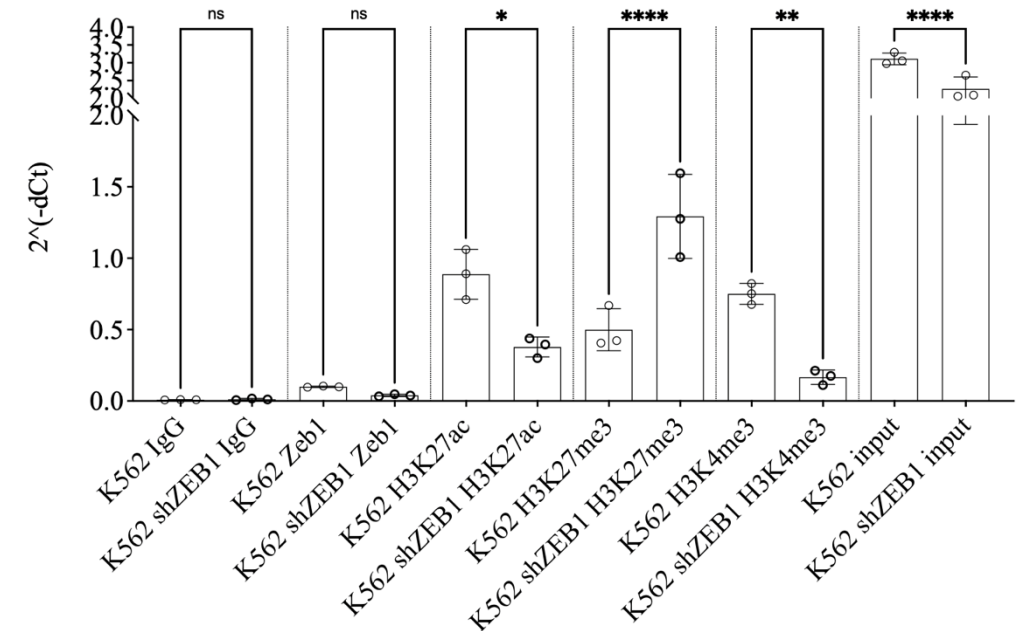
ZEB1 does not appear to directly regulate the HLA-A promoter

Chip-Seq



Chip-qPCR

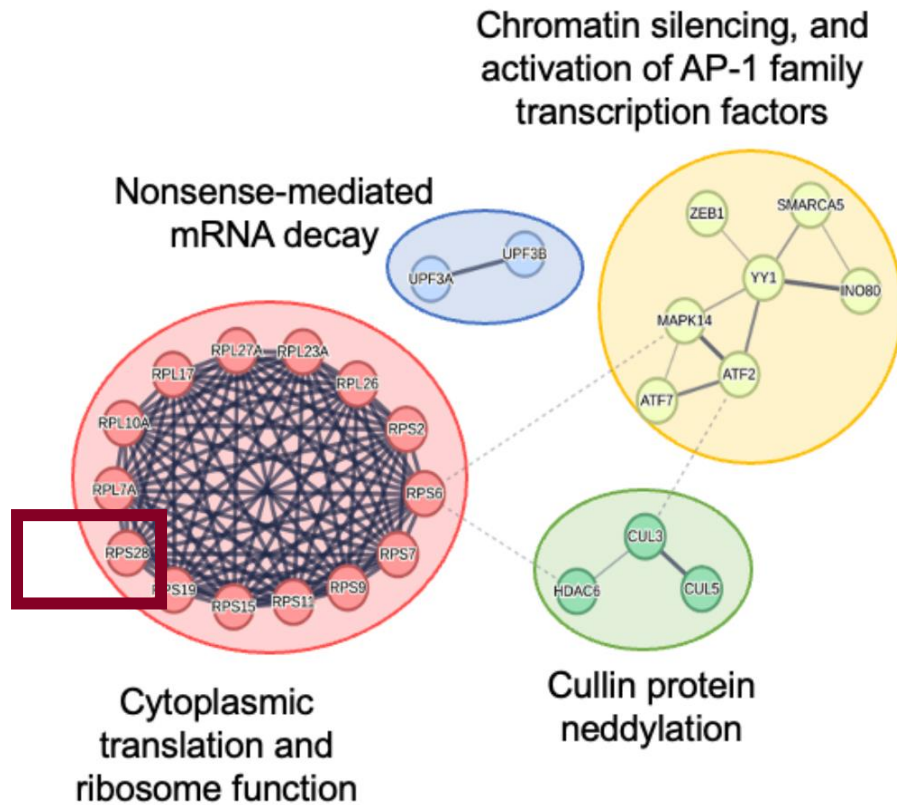
HLA-AE7984P/H3



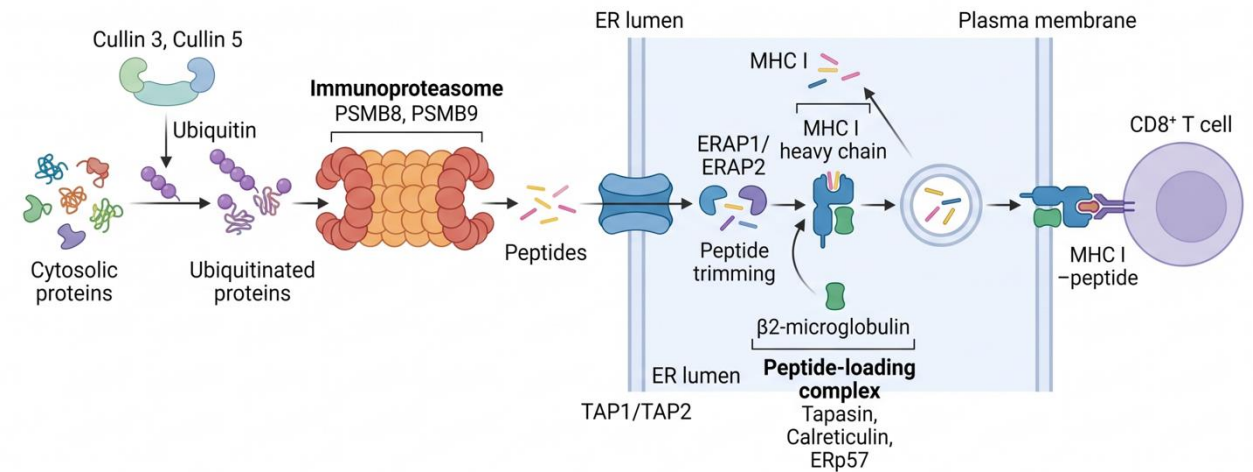
the effect on HLA was unlikely to be explained by simple direct promoter repression.”

DAVID and STRING protein-protein interaction network analysis revealed APM molecules regulated by ZEB1

ChIP-Seq on K562-Scramble and K562shZEB565

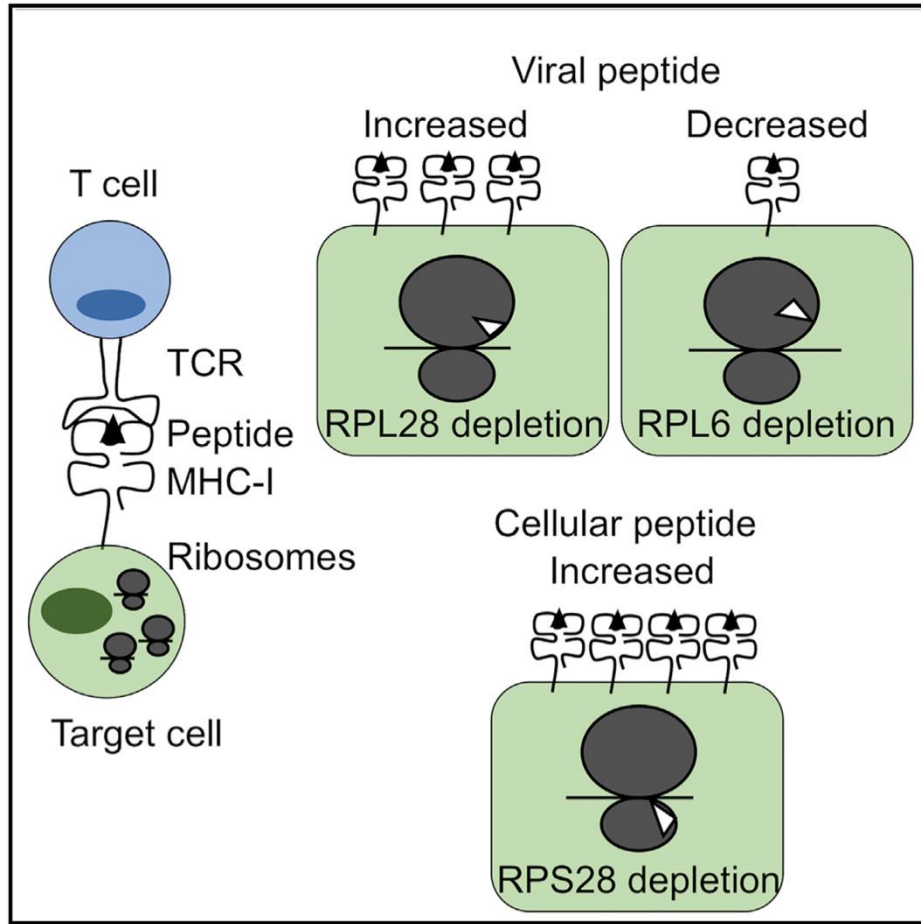


APM pathway (HLA-A)



RPS28 controls MHC-I peptide supply

Graphical Abstract



↓ RPS28 → ↑ non-canonical translation → ↑ DRiPs/cryptic peptides → ↑ peptide loading → ↑ HLA-I stabilization → ↑ CD8 recognition

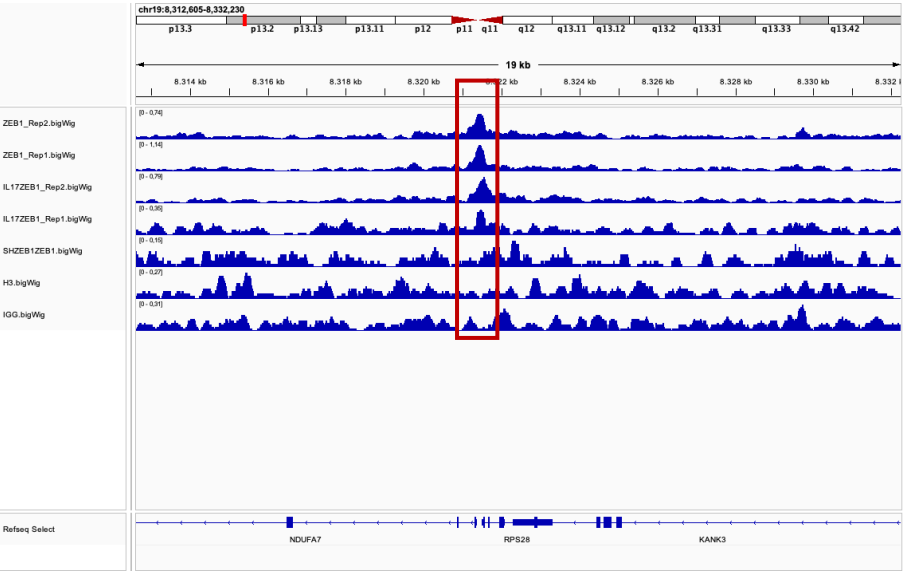
Mol Cell. 2019 March 21; 73(6): 1162–1173.e5. doi:10.1016/j.molcel.2018.12.020.

Ribosomal Proteins Regulate MHC Class I Peptide Generation for Immunosurveillance

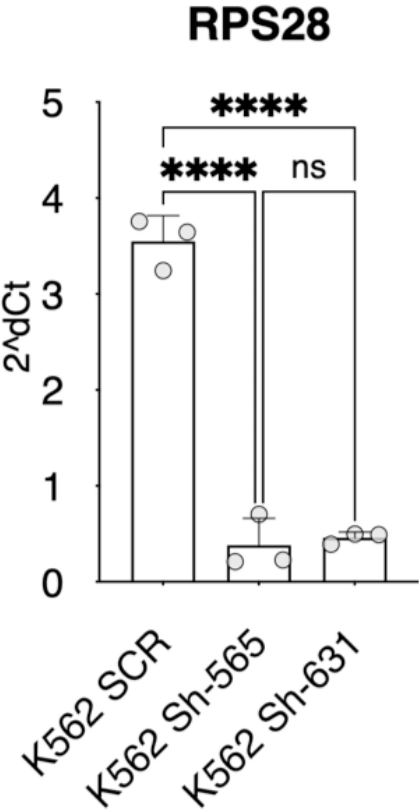
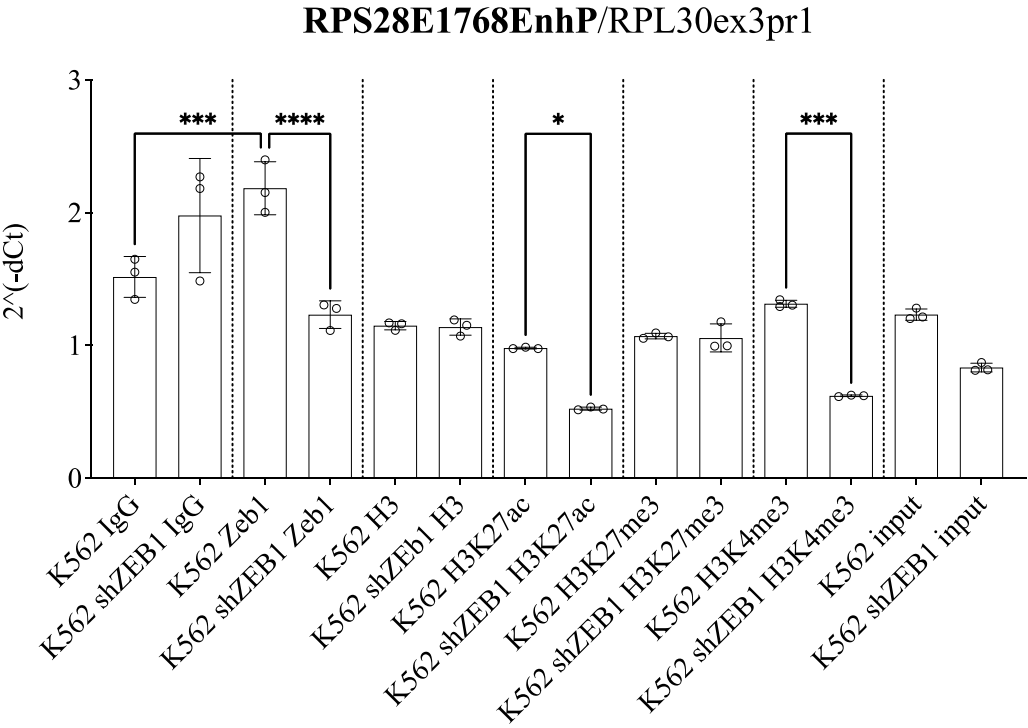
Jiajie Wei^{1,*}, Rigel J. Kishton², Matthew Angel¹, Crystal S. Conn³, Nicole Dalla-Venezia⁴, Virginie Marcel⁴, Anne Vincent⁴, Frédéric Catez⁴, Sabrina Ferré⁵, Lilia Ayadi^{6,7}, Virginie Marchand^{6,7}, Devin Dersh¹, James S. Gibbs¹, Ivaylo P. Ivanov⁸, Nathan Fridlyand⁹, Yohann Couté⁵, Jean-Jacques Diaz⁴, Shu-Bing Qian³, Louis M. Staudt¹⁰, Nicholas P. Restifo^{2,11}, Jonathan W. Yewdell^{1,*,\$}

ZEB1 is recruited to an RPS28 regulatory element

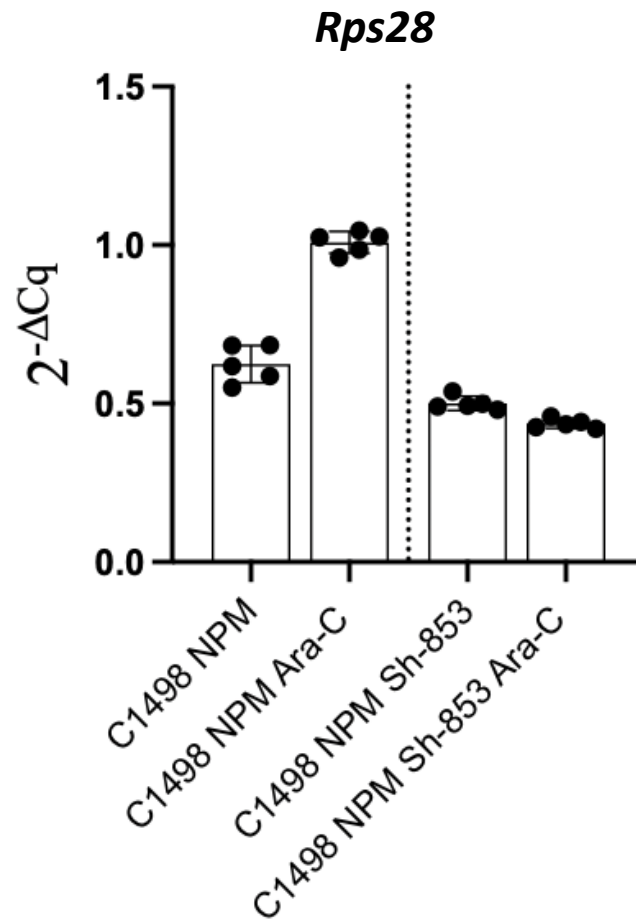
Chip-Seq



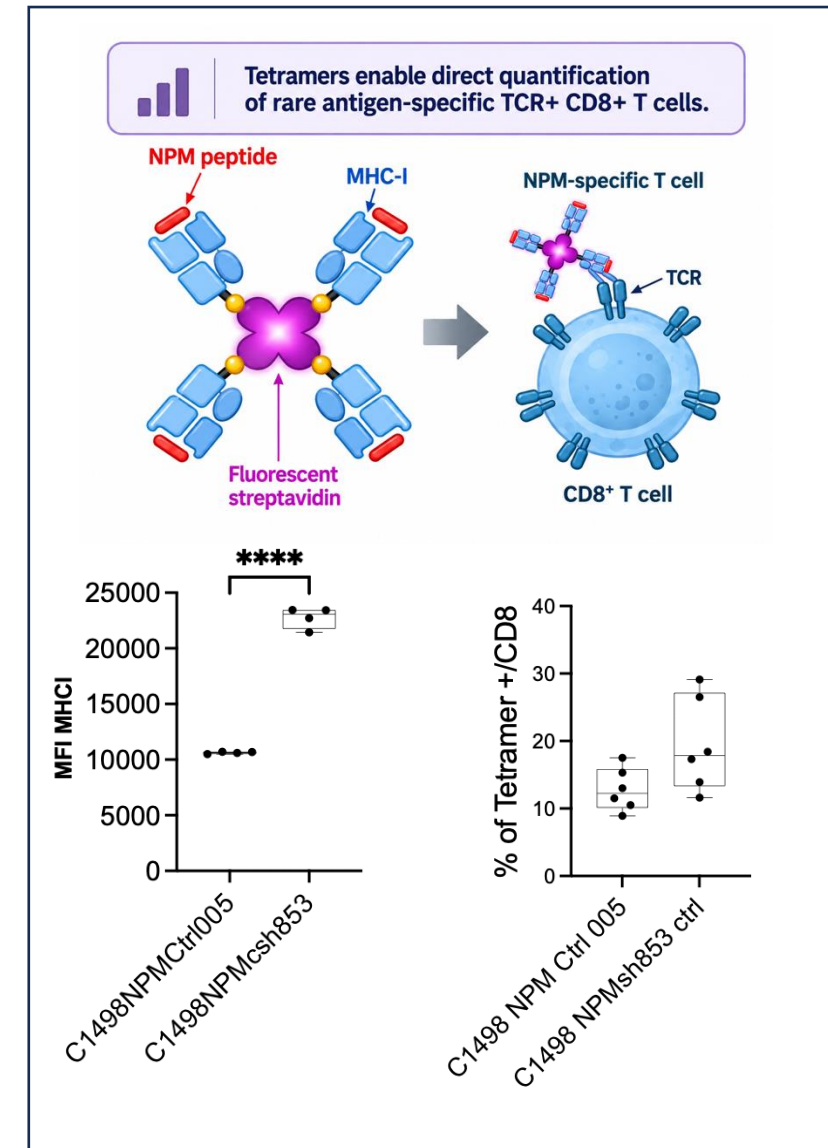
Chip-qPCR



ZEB1 is required for cytarabine-induced RPS28 upregulation



ZEB1 protect from the generation of immunogenic peptides (under stress conditions)



Conclusions:

1. ZEB1 marks less immature and undifferentiated AML
2. ZEB1 couples AML aggressiveness to immune regulation.
3. ZEB1 shapes both the Th17-rich microenvironment and leukemia-cell antigenicity.
4. The ZEB1–RPS28 axis may connect therapy-induced stress to reduced MHC-I immunosurveillance.

ZEB1 does not only regulate how aggressive AML is but it also regulates how leukemia interacts with, and is seen by, the immune system

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Ministero della Salute

