



XIX CONGRESSO
NAZIONALE
SIES 2026

HELLS-driven chromatin remodeling defines transcriptional vulnerabilities in ALK-negative Anaplastic Large Cell Lymphoma

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Translational Research Laboratory, AUSL-IRCCS of Reggio Emilia

Firenze | 4-6 marzo 2026
Palazzo degli Affari



Disclosures of Giulia Gambarelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other



T-CELL LYMPHOMA

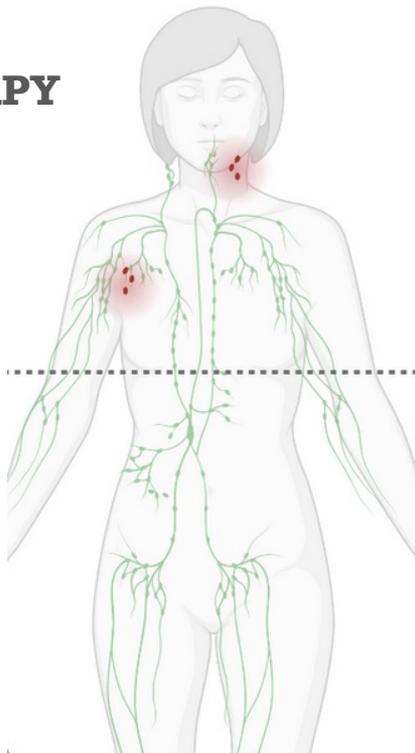
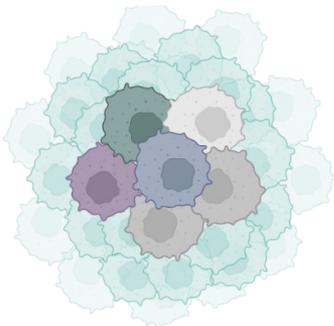


COMPLEXITY

AGGRESSIVENESS

**LIMITED THERAPY
RESPONSE**

RARITY

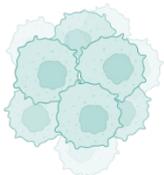
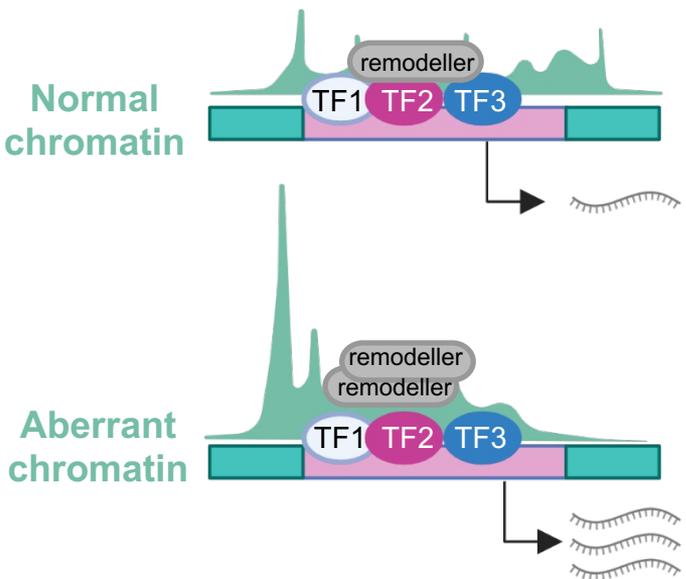


T-CELL LYMPHOMA
(30 different subtypes)

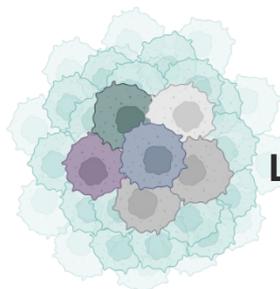
**TARGETED
THERAPY**



CHROMATIN REPROGRAMMING



T-lymphocytes



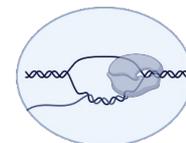
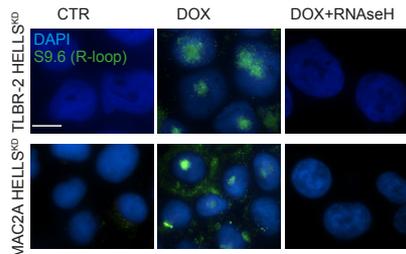
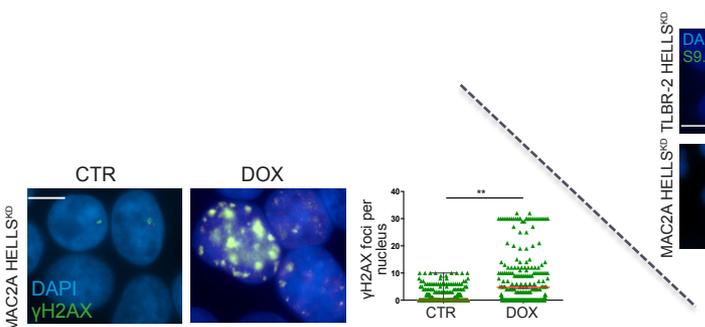
Neoplastic Lymphocytes

Lymphoma progression and aggressiveness

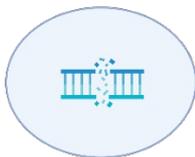
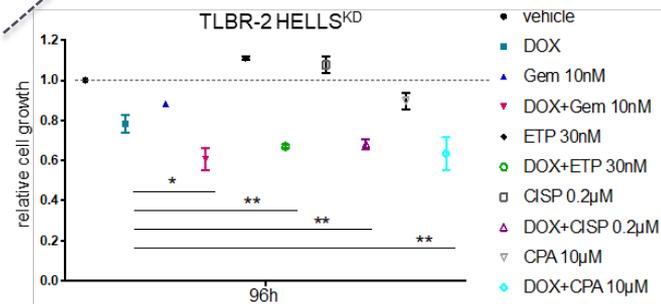
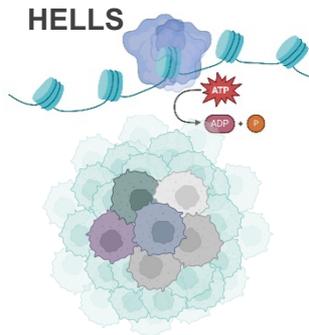
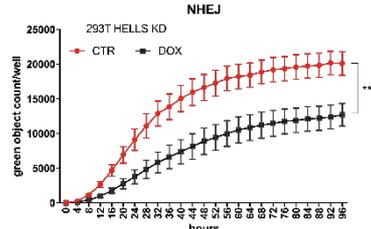
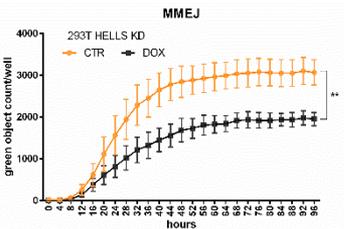
- EZH2**
- KMT2D**
- MLL2**
- DOT1L**
- CBP/p300**
- TIP60**
- KAT6A**
- BETs**
- SWI/SNF**

HELLS

HELLS AT THE CROSSROADS



DNA:RNA HYBRIDS (R-LOOP)



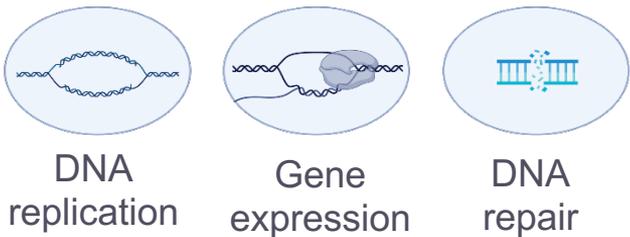
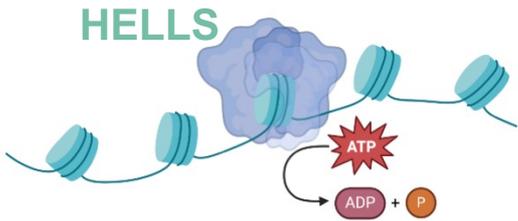
DNA DAMAGE



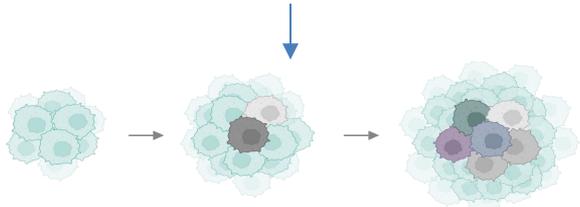
CHEMOTHERAPY EFFICACY

Fragliasso V., *Leukemia* 2020
Mallia S., *NAR* 2024

OUTSTANDING QUESTIONS



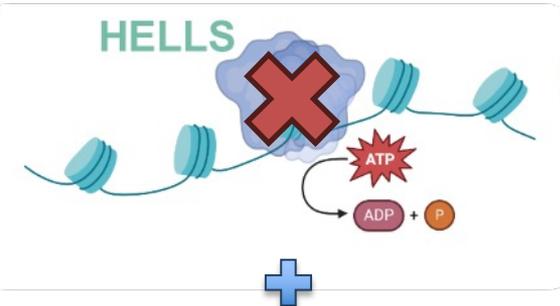
GENOME INSTABILITY



LYMPHOMA PROGRESSION

1. How does HELLIS ensure efficient and adaptable gene expression, ultimately safeguarding genome organization?

OUTSTANDING QUESTIONS



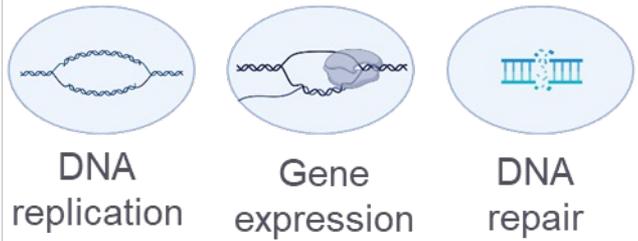
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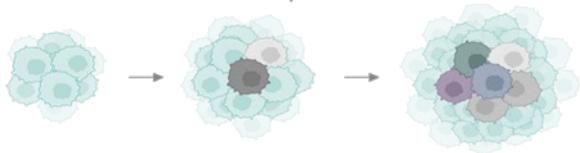
Drug 1

Drug 2

COMBINATORY STRATEGY



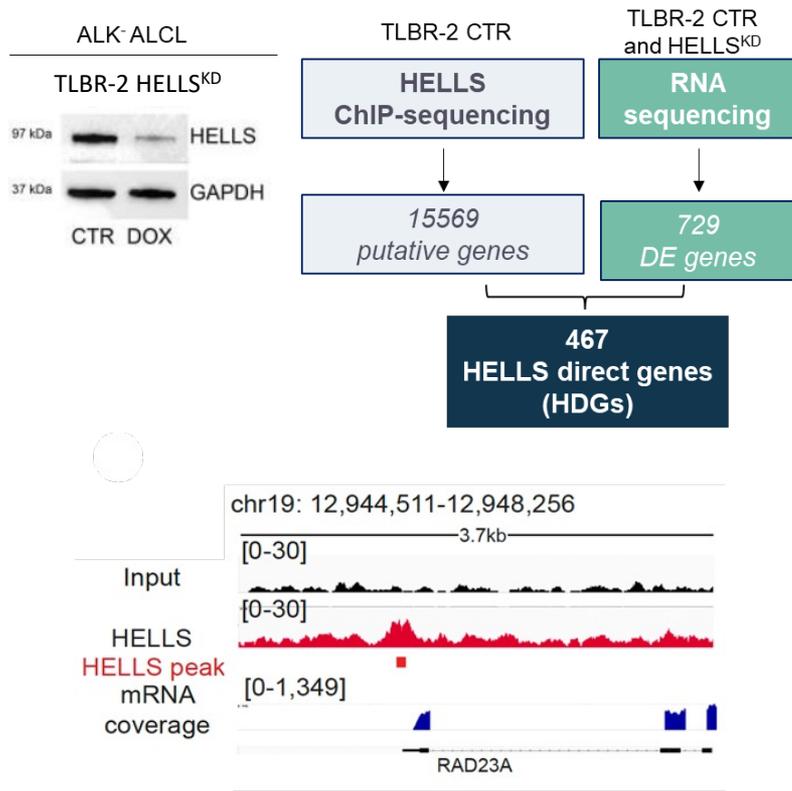
GENOME INSTABILITY



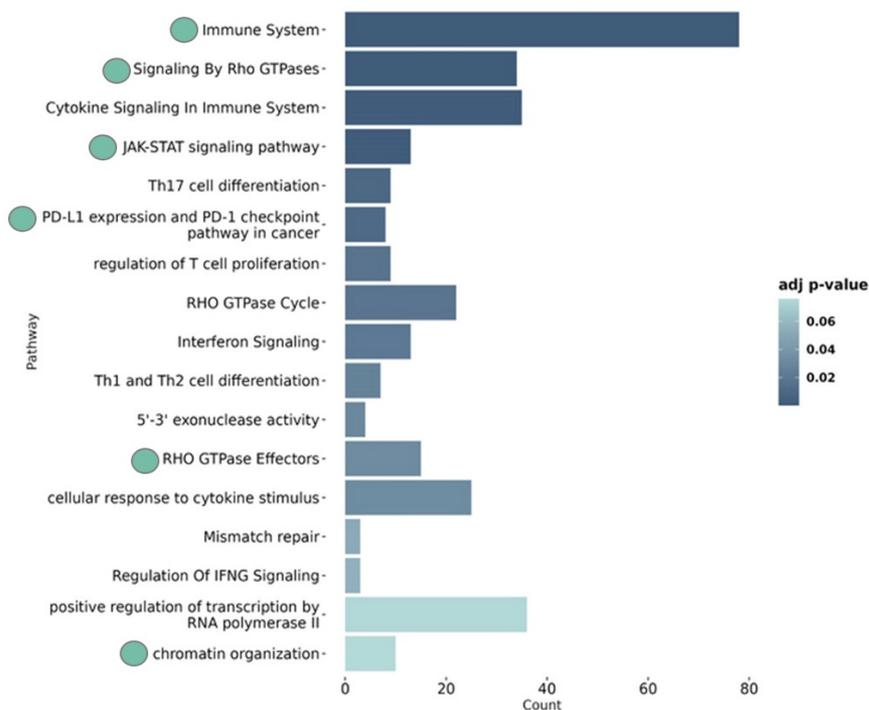
LYMPHOMA PROGRESSION

1. How does HELLs ensure efficient and adaptable gene expression, ultimately safeguarding genome organization?

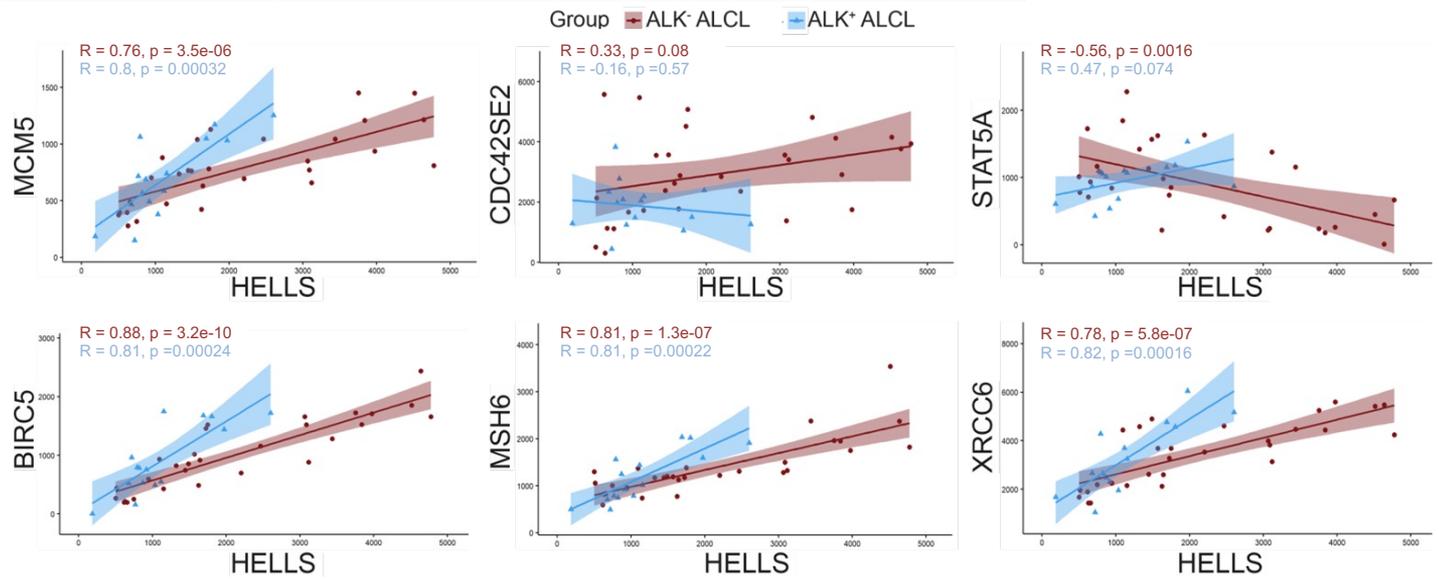
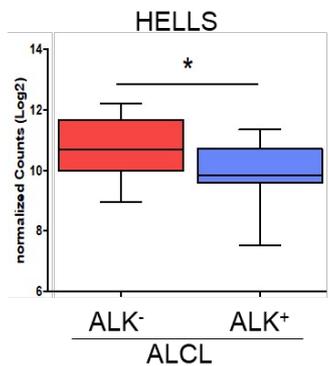
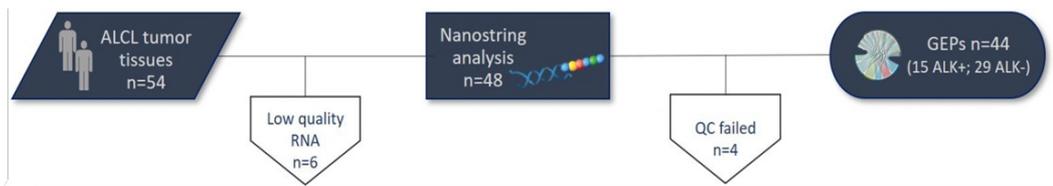
2. What is the potential for HELLs inhibition as a combinatorial therapeutic strategy?



HELLS regulates a unique genes signature

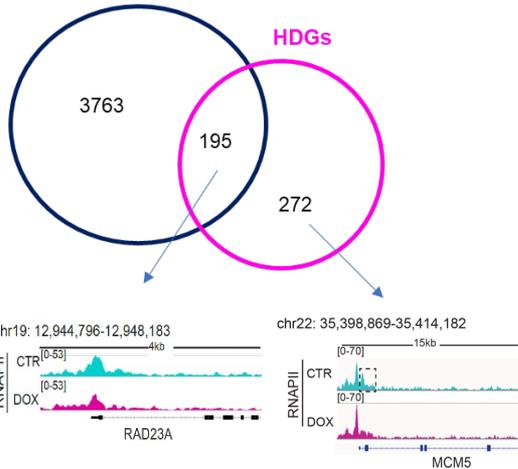


HELLS regulates genes associated with ALK-ALCL aggressiveness

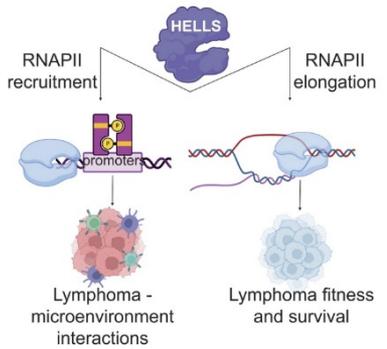
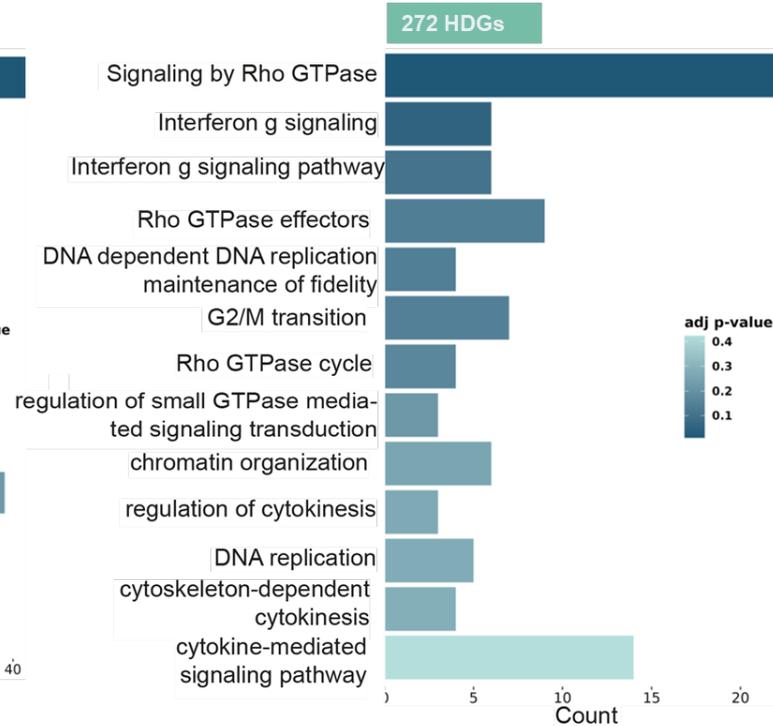
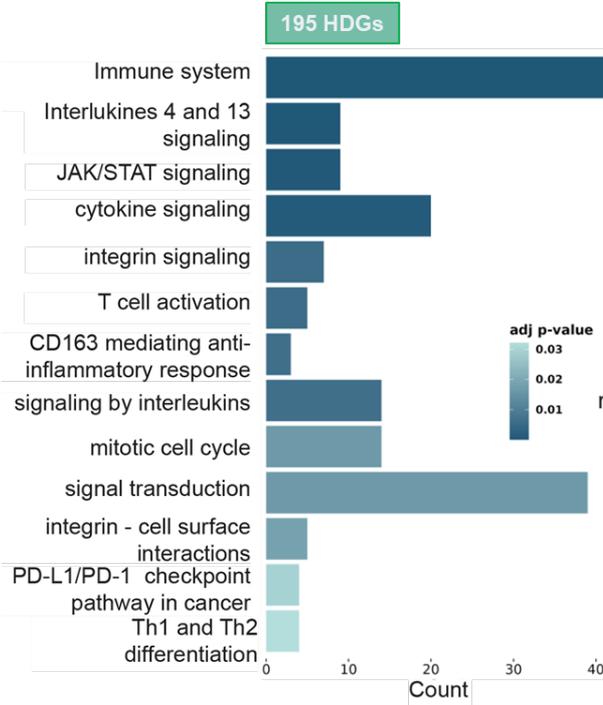


TLBR-2 CTR and HELLS^{KD}

RNAPII ChIP-seq



HELLS regulates RNAPII in a bimodal way



Mallia S., NAR 2024



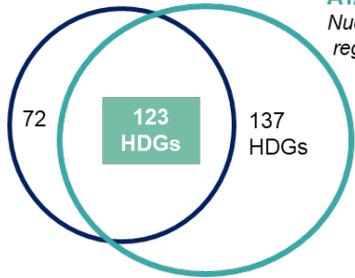
HELLS regulates chromatin accessibility at immune-related genes

TLBR-2 CTR and HELLS^{KD}

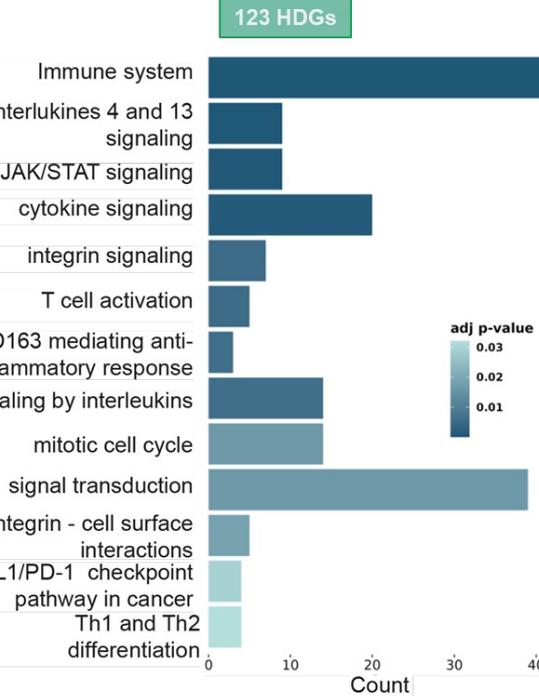
RNAPII ChIP-seq

ATAC-seq

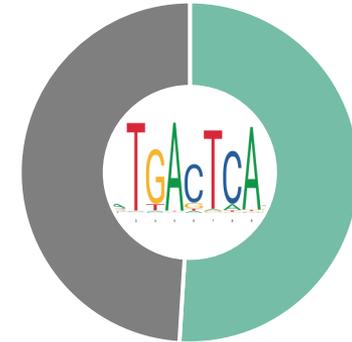
Nucleosome depleted regions



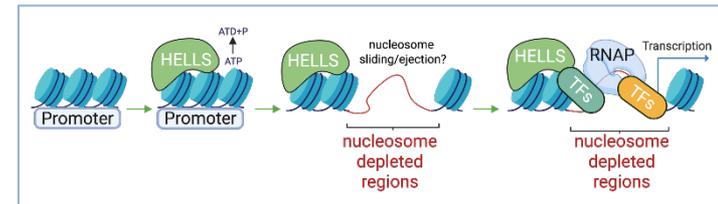
chr1: 167,516,757-167,519,784



103 TFs gained



99 TFs lost



Mallia S., NAR 2024

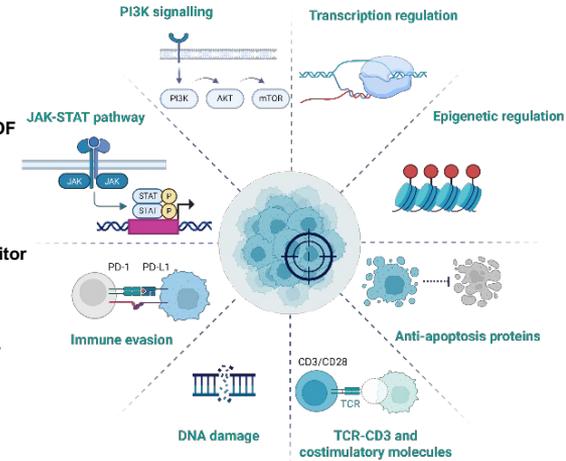
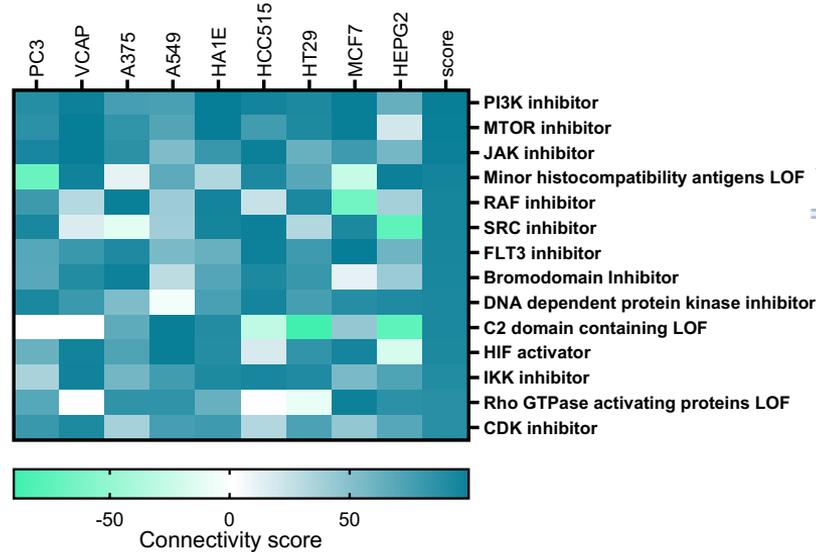
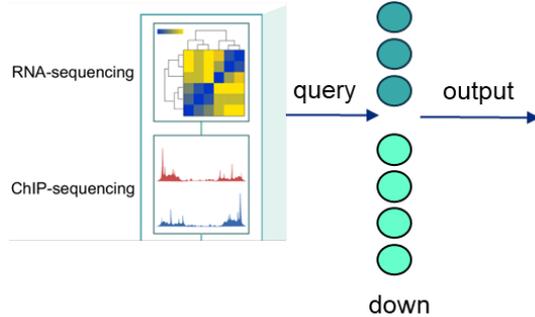
Mallia S., Trends in Cell Biol, 2025

PD-L1 (CD247)

Drug repurposing identified PI3K, JAK/STAT, and DNA-PK as synergistic targets



HELLS gene signature (HDGs)



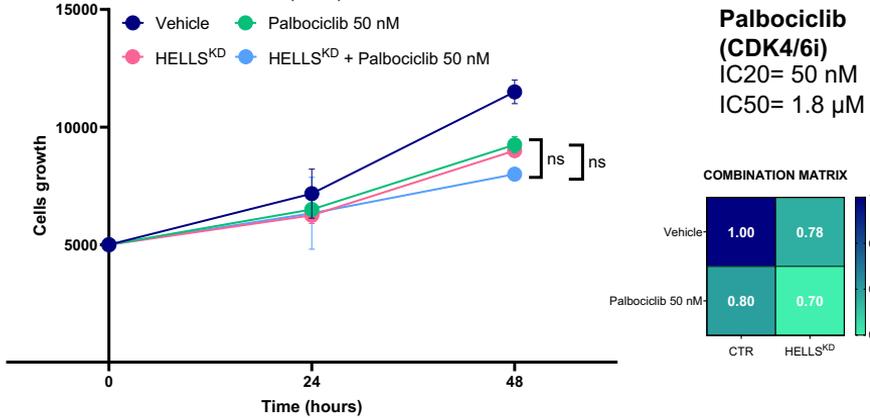
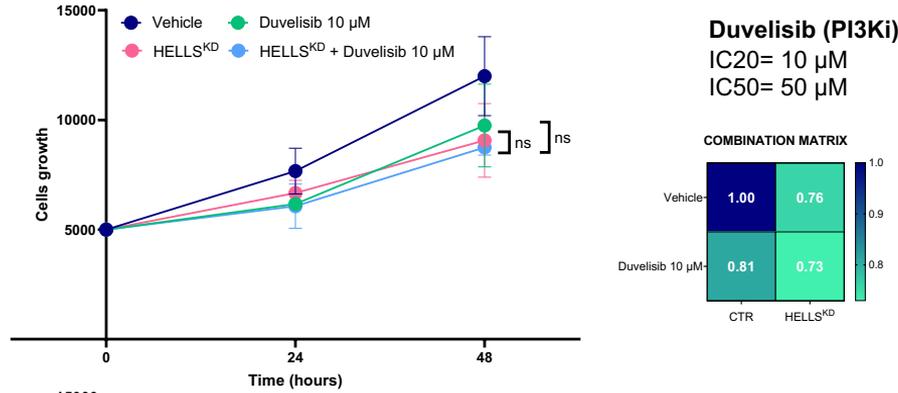
Fiore D., Nat Rev Cancer, 2020

RANK	Targets	Score
1	PI3K	98,71
2	JAK	97,25
3	DNA-PK	91,28
4	CDK	86,00

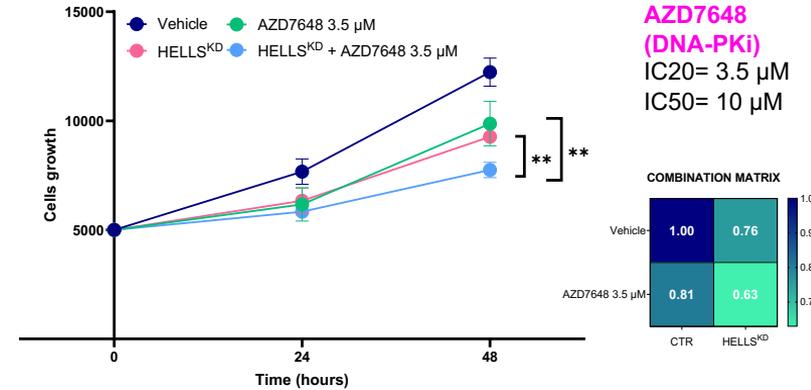
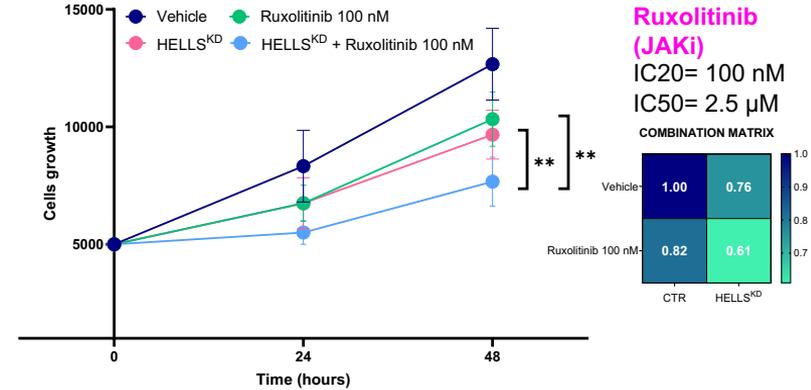
HELLS inhibition drives sensitization to JAK/STAT and DNA-PK inhibitors



TLBR-2 CTR and HELLS^{KD}

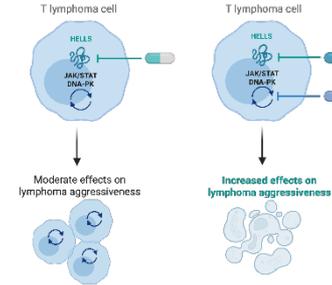
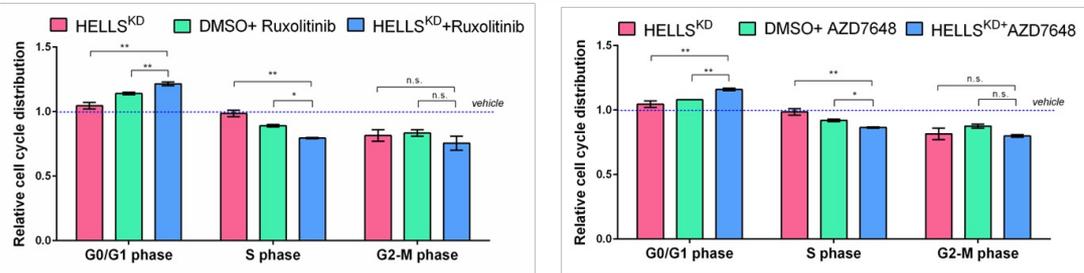


TLBR-2 CTR and HELLS^{KD}

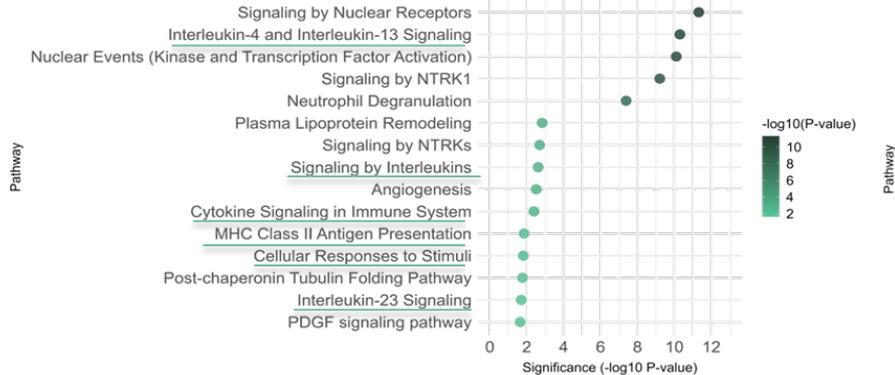


HELLS inhibition drives sensitization to JAK/STAT and DNA-PK inhibitors

TLBR-2 CTR and HELLS^{KD}

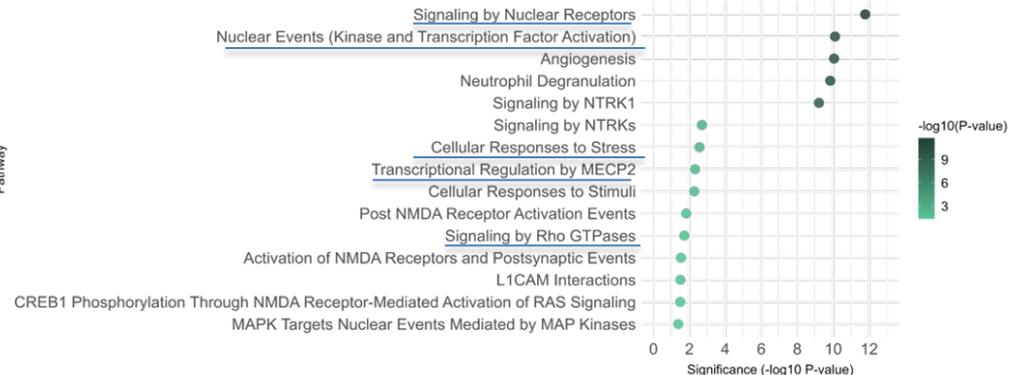


HELLS^{KD} and Ruxolitinib: common pathways



— RNAPII recruitment

HELLS^{KD} and AZD7648: common pathways

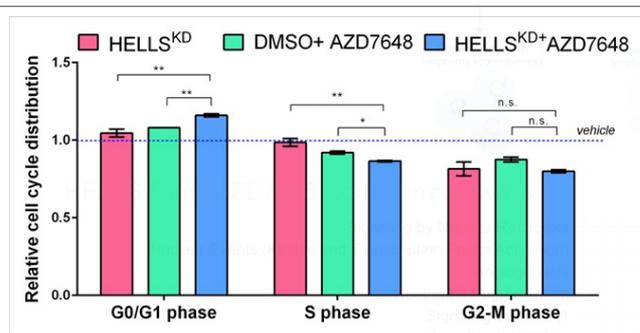
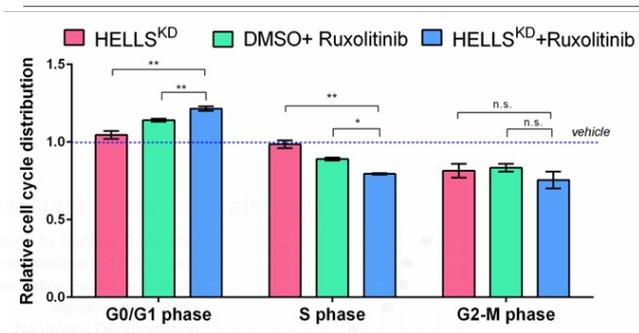


— RNAPII elongation

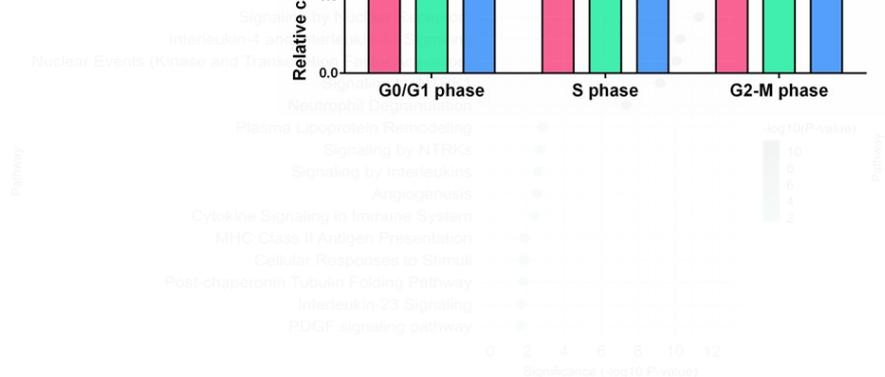
HELLS inhibition drives sensitization to JAK/STAT and DNA-PK inhibitors



TLBR-2 CTR and HELLS^{KD}

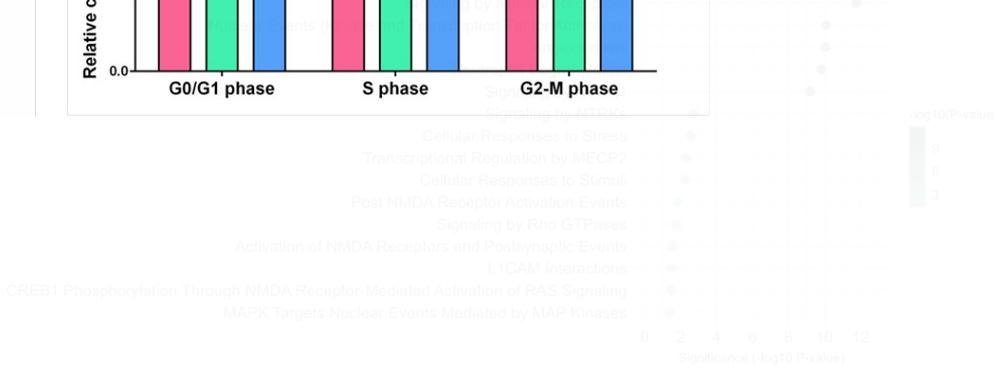


HELLS^{KD} and Ruxolitinib



RNAPII recruitment

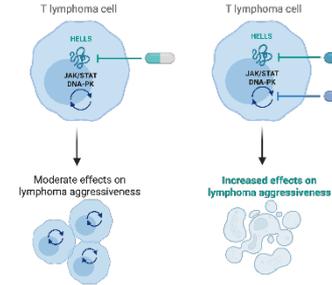
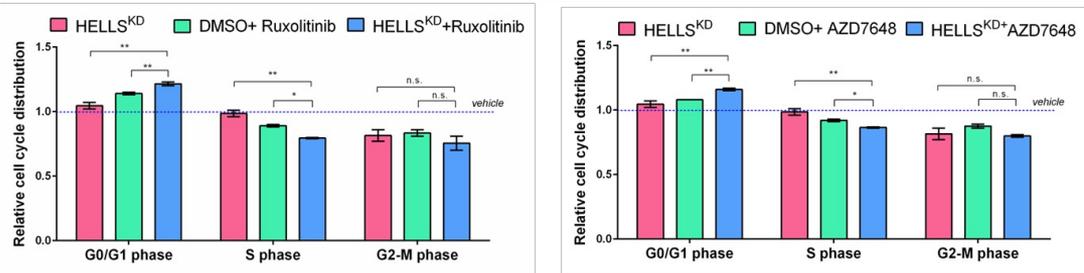
HELLS^{KD} and AZD7648



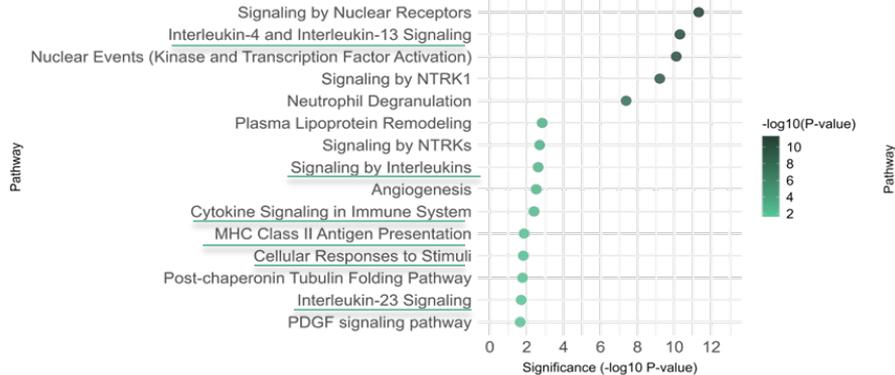
RNAPII elongation

HELLS inhibition drives sensitization to JAK/STAT and DNA-PK inhibitors

TLBR-2 CTR and HELLS^{KD}

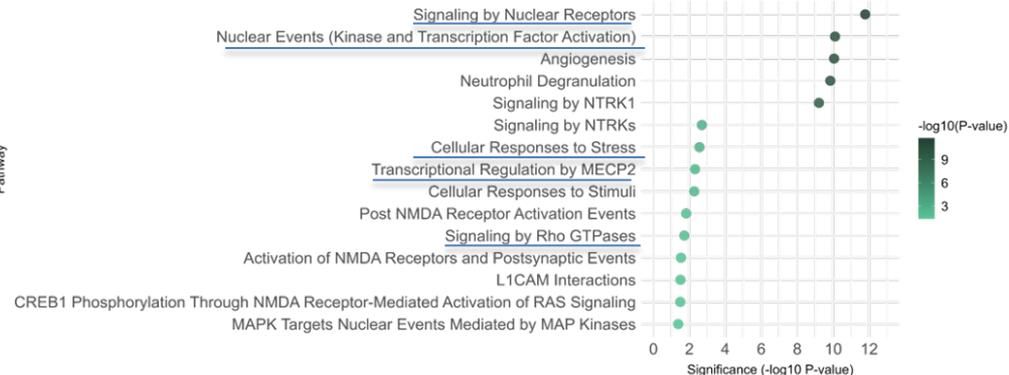


HELLS^{KD} and Ruxolitinib: common pathways



— RNAPII recruitment

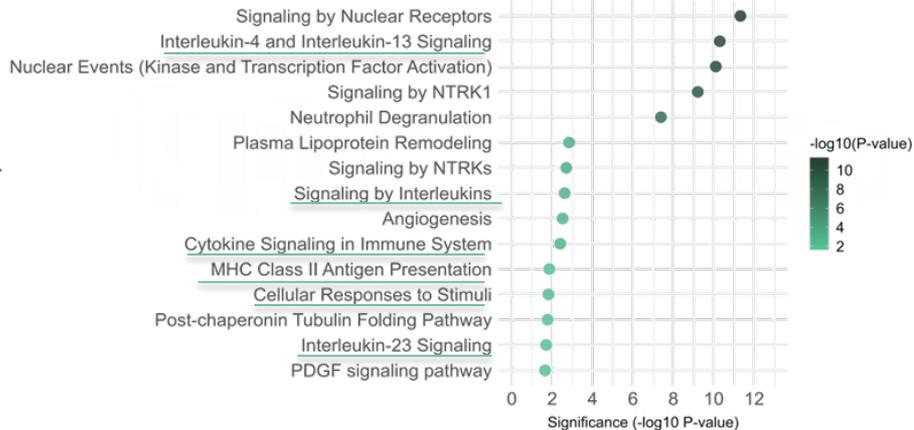
HELLS^{KD} and AZD7648: common pathways



— RNAPII elongation

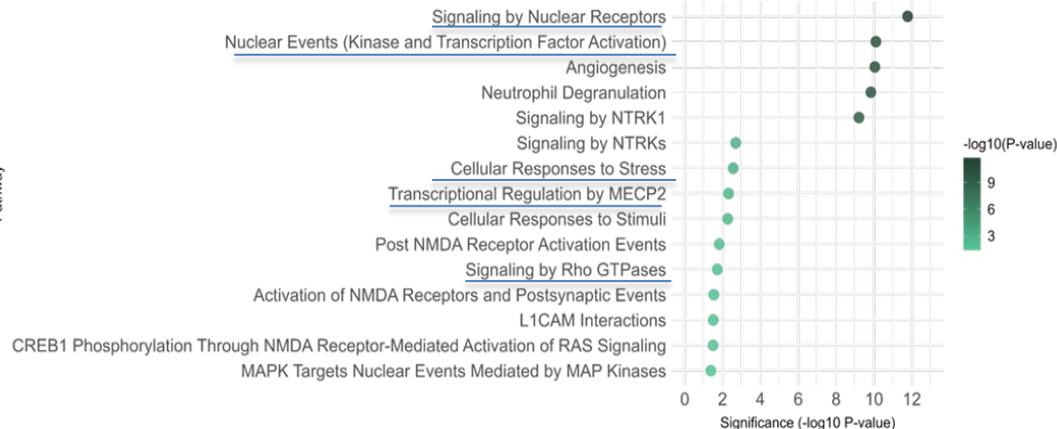
HELLS inhibition drives sensitization to JAK/STAT and DNA-PK inhibitors

HELLS^{KD} and Ruxolitinib: common pathways



— RNAPII recruitment

HELLS^{KD} and AZD7648: common pathways

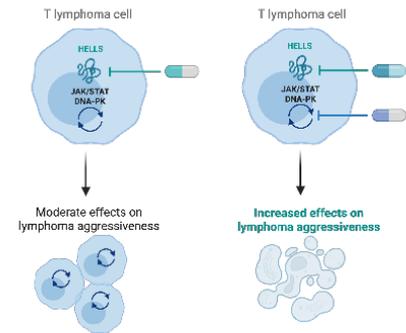
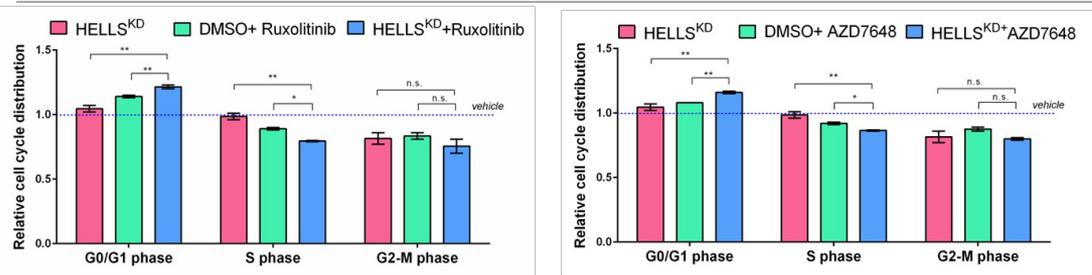


— RNAPII elongation

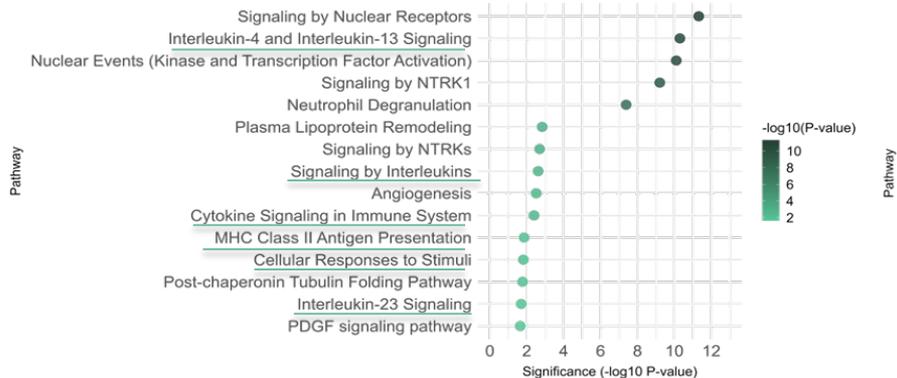


HELLS inhibition drives sensitization to JAK/STAT and DNA-PK inhibitors

TLBR-2 CTR and HELLS^{KD}

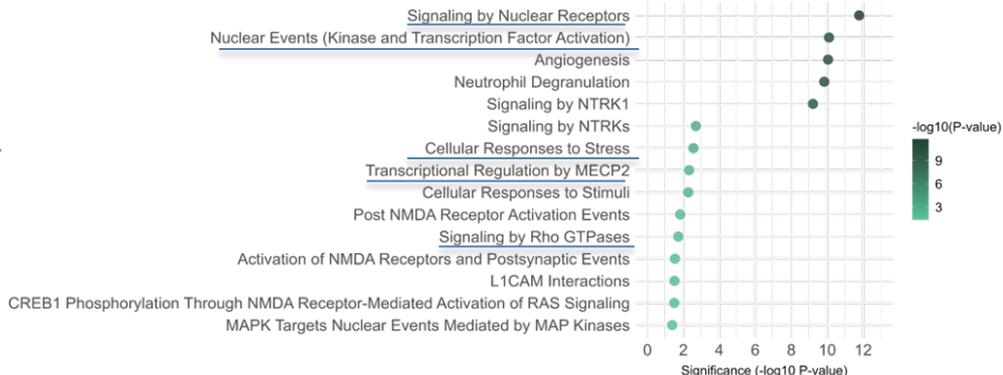


HELLS^{KD} and Ruxolitinib: common pathways

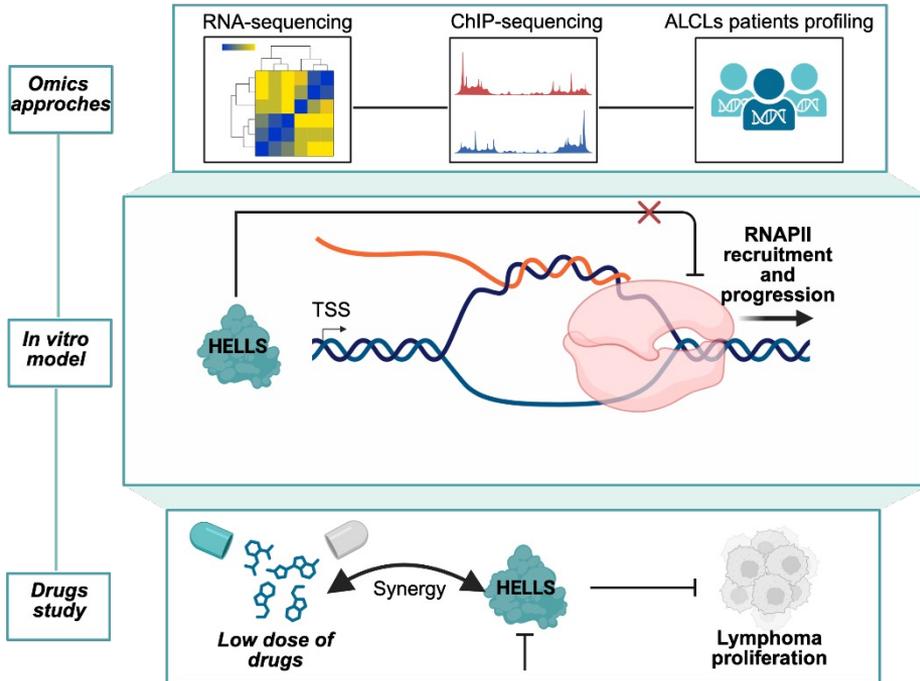


— RNAPII recruitment

HELLS^{KD} and AZD7648: common pathways



— RNAPII elongation



HELLS functions as a bi-modal regulator of gene expression, controlling both the loading and elongation phases of RNAPII.

The bi-modal function of HELLs can be exploited to enhance the response of lymphoma cells to low doses of approved targeted agents.

The development of selective HELLs inhibitors can expand the therapeutic portfolio for patients with T-cell lymphoma.



Translational Research Laboratory

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Dr. Alessia Ciarrocchi

Prof. Antonino Neri

All the members of the Lab

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Funders



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Dr. Marco Pizzi



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Dr. Danilo Fiore





XIX CONGRESSO
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SIES 2026

