

Targeting chromatin regulatory proteins in hematologic malignancies

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VP, Biology

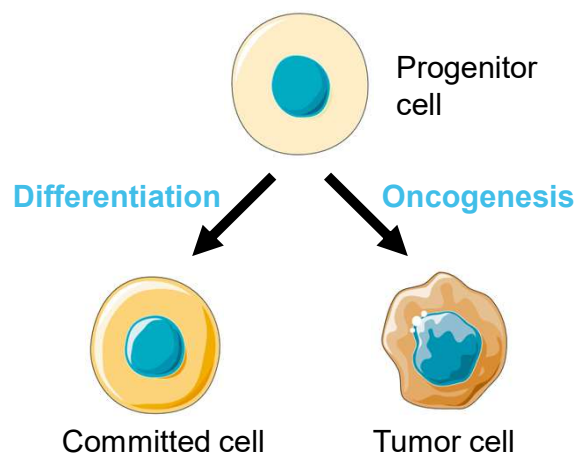


FOGHORN[®]
THERAPEUTICS

Lineage dependence



Tumor cells remain addicted to the lineage specifying genes



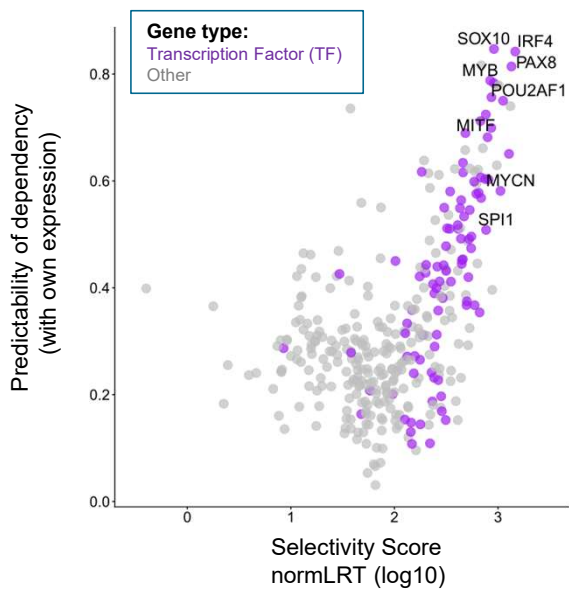
Effect of lineage addiction therapies

↓ normal
cell survival

↓↓↓ tumor
cell survival

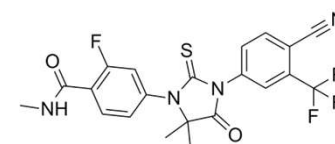
Lineage dependencies are dominated by TFs with selective expression

DepMap vulnerabilities

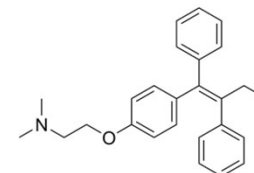


Clinical agents targeting lineage vulnerabilities

Hormone receptor modulators

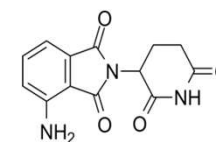


Enzalutamide
(AR)



Tamoxifen
(ER)

Molecular glue degraders

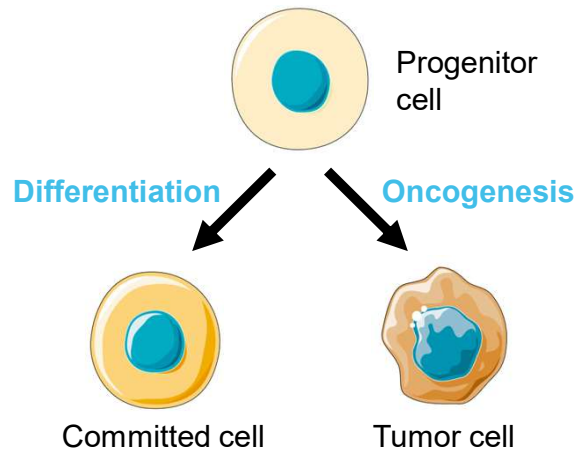


Pomalidomide
(IKZF1/3)

Lineage dependence



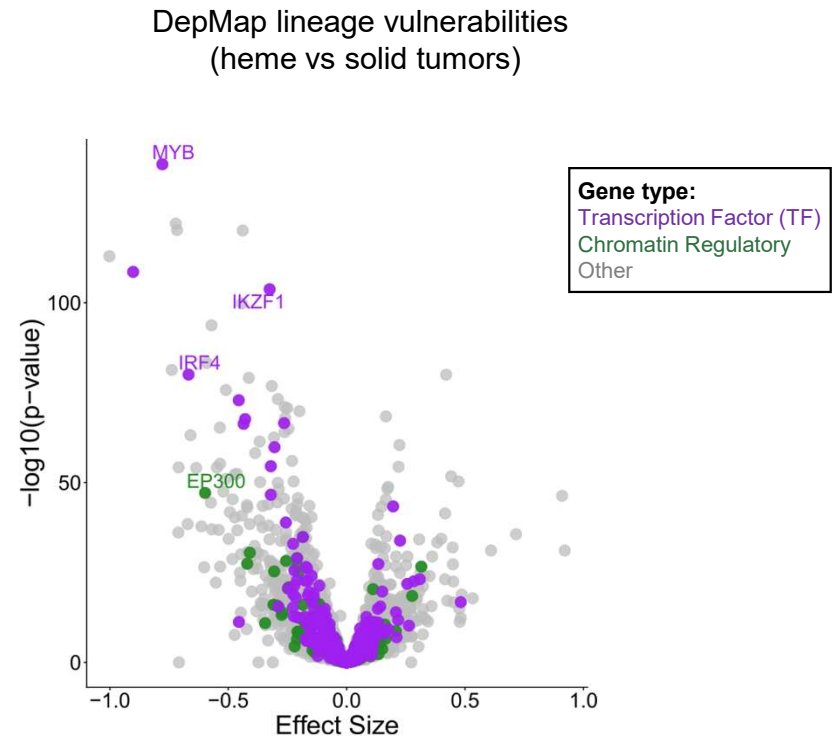
Tumor cells remain addicted to the lineage specifying genes



Effect of lineage addiction therapies



Ample opportunities for targeting lineage vulnerabilities

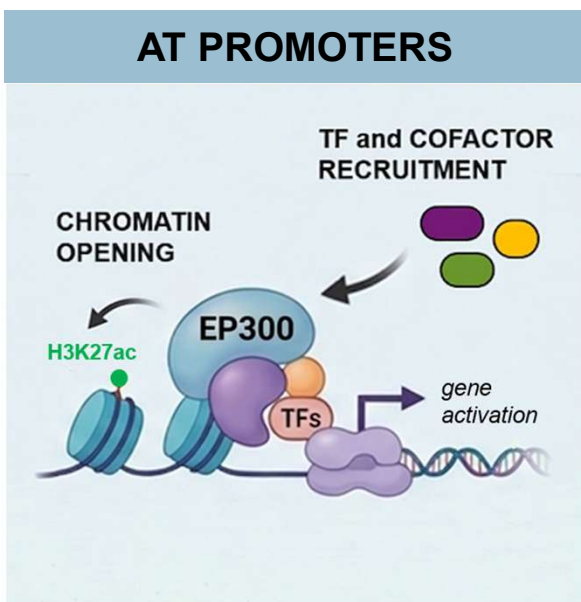


EP300 – a critical regulator of gene expression

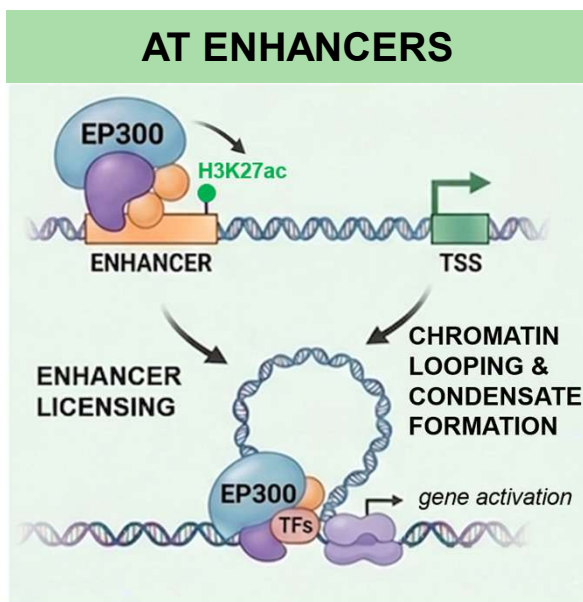


Role in gene regulation

AT PROMOTERS

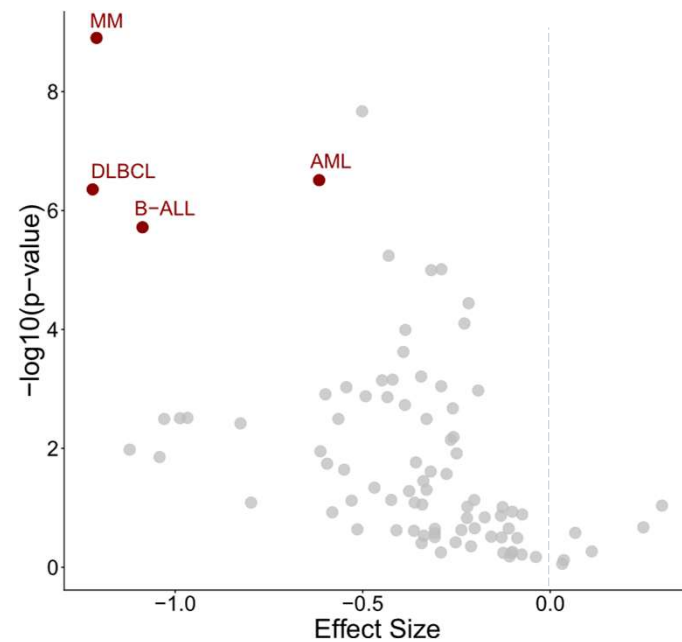


AT ENHANCERS

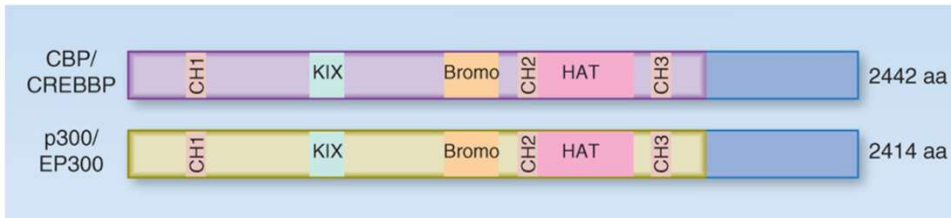


Target dependence in oncology

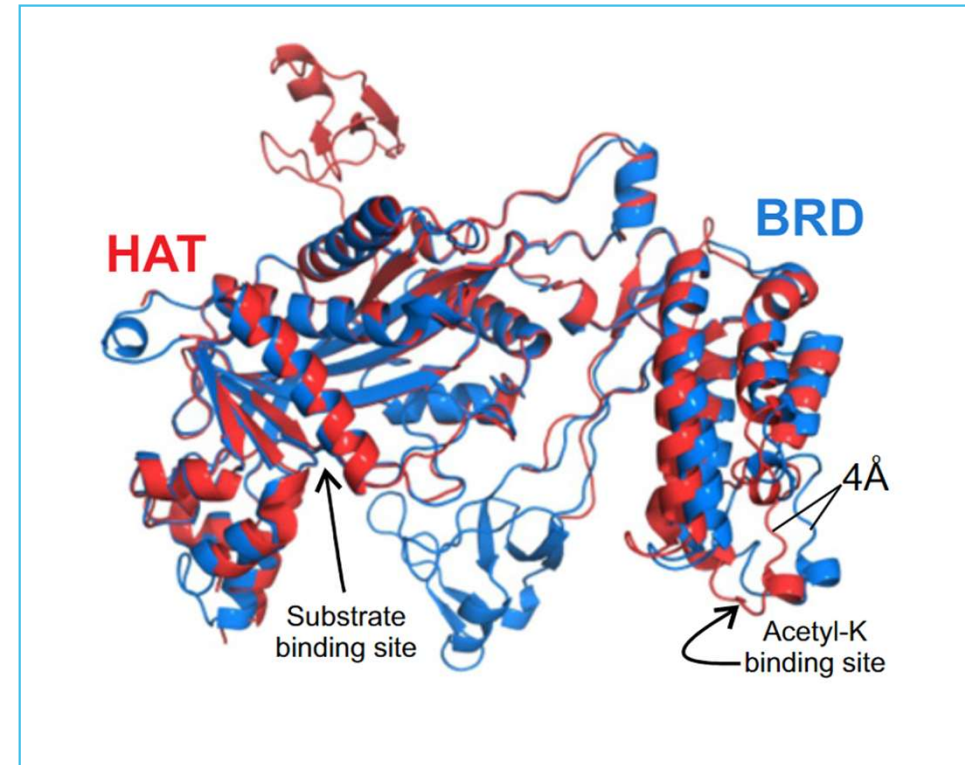
EP300 DepMap sensitivity (by lineage)



Historical development of specific drugs targeting EP300 has been hampered by the high degree of homology with CBP



- CBP and EP300 are highly homologous
 - 59% identity and 68% similarity
 - HAT domains are 88% identical
 - Bromodomains are 97% identical
- Vast majority of known binders/inhibitors are not selective
- Treatment with dual CBP/EP300 bromodomain inhibitors results in thrombocytopenia



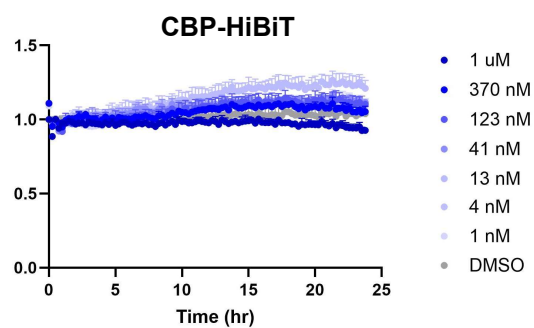
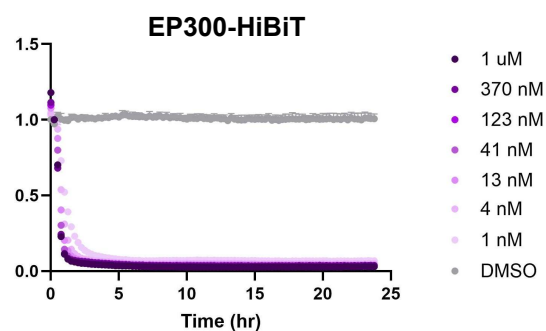
Park S, et al., PNAS (2017)

Development of selective EP300 degraders



Kinetic experiments reveal remarkably efficient and selective degradation

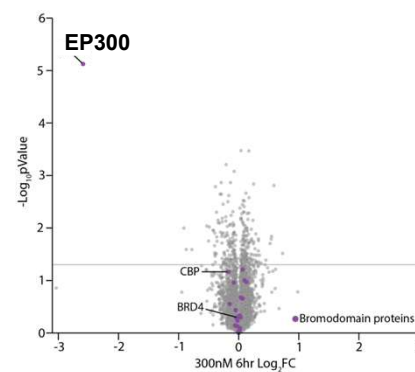
dEP300-9
Dmax: 96%
Rate: 2.5 μ /hr
DC₅₀: 3 nM



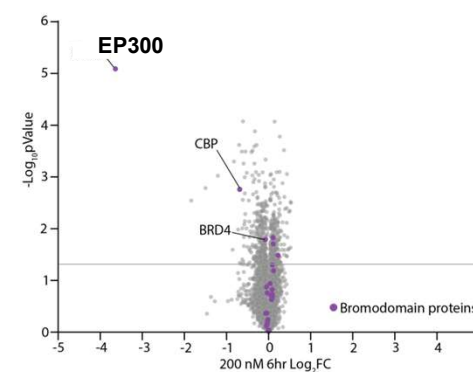
U2OS cells

Selectivity of EP300 degraders

U2OS (CBP/EP300 WT)
6hrs – 300nM



MM1.S (CBP/EP300 WT)
6hrs – 200nM

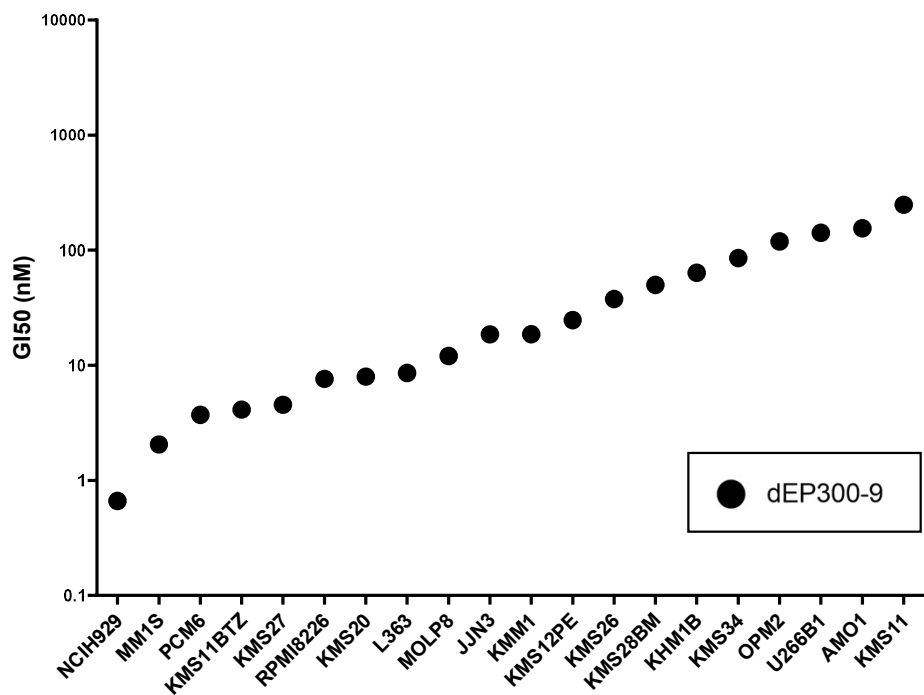


dEP300-9 tool compound

All multiple myeloma cell lines tested are sensitive to dEP300-9

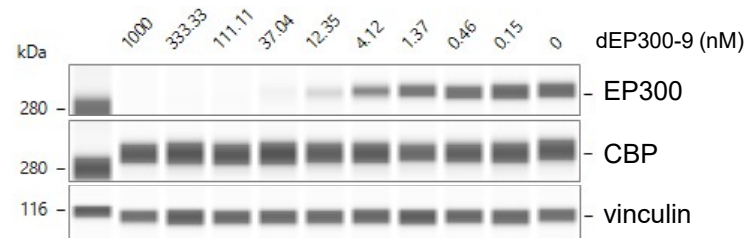


Cell sensitivity data



Selective EP300 degradation

OPM2



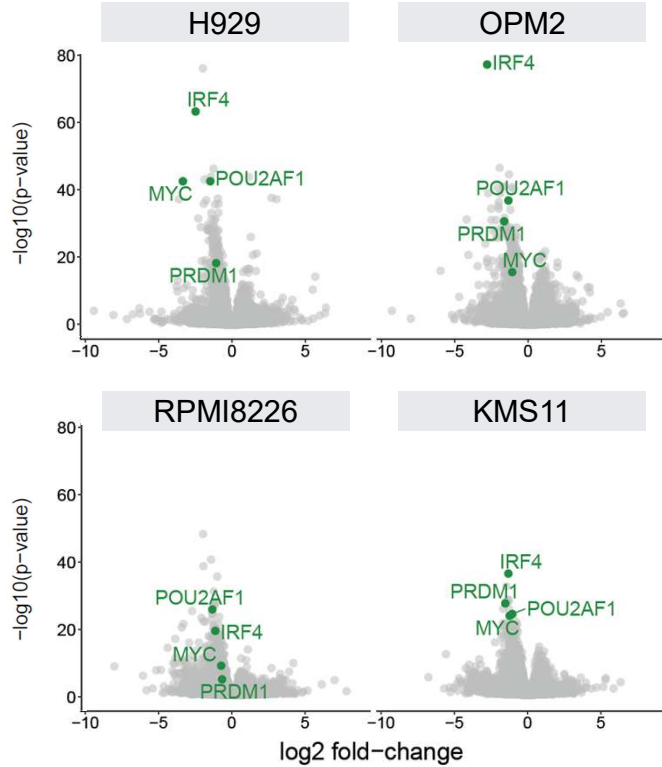
RPMI8226



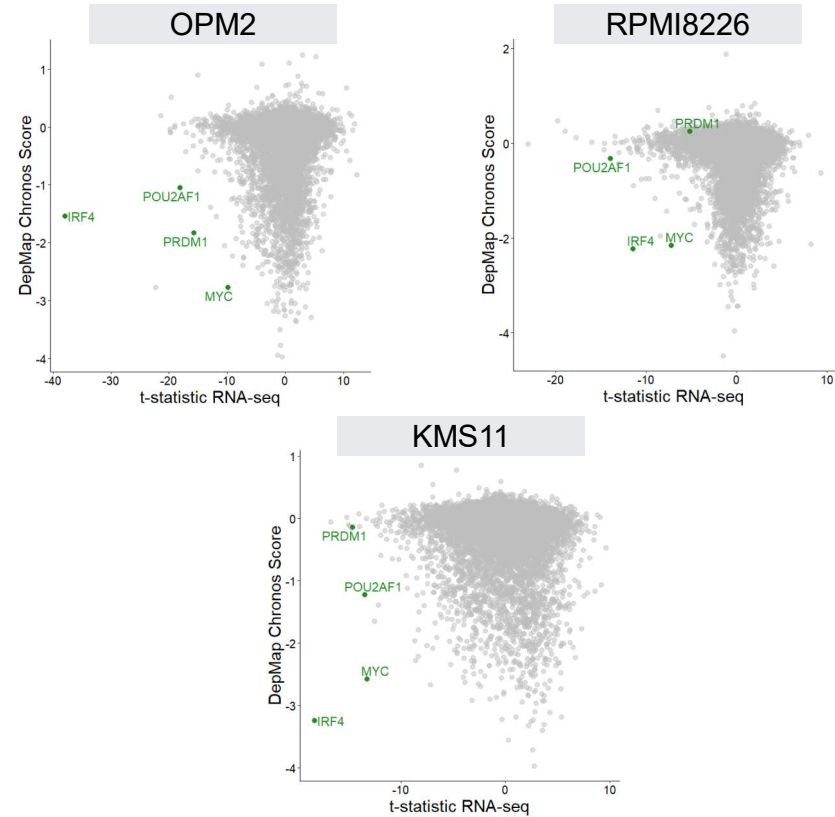


EP300 degradation effects on MM cell lines

EP300 degradation downregulates the expression of several transcription factors



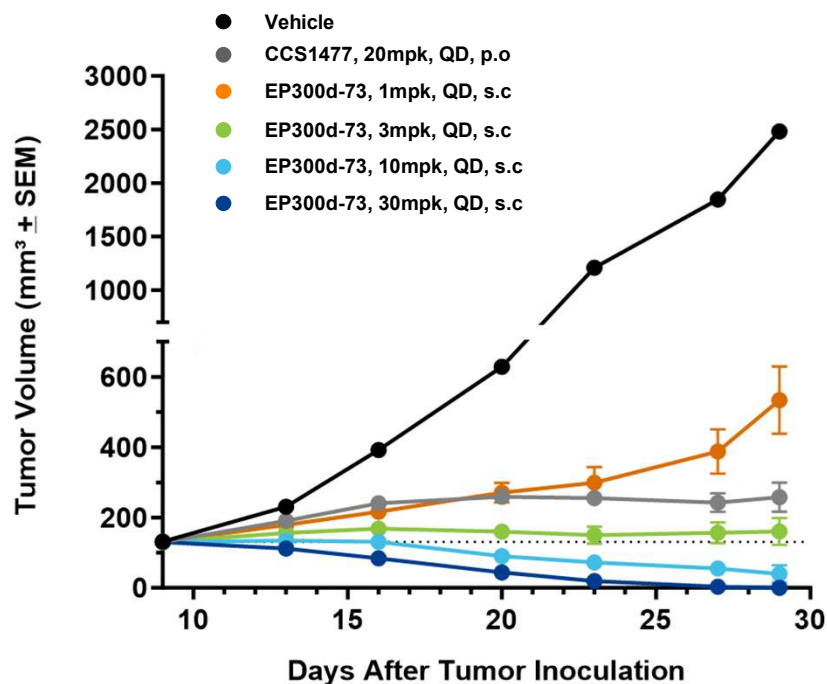
Lineage dependence of EP300-regulated transcription factors



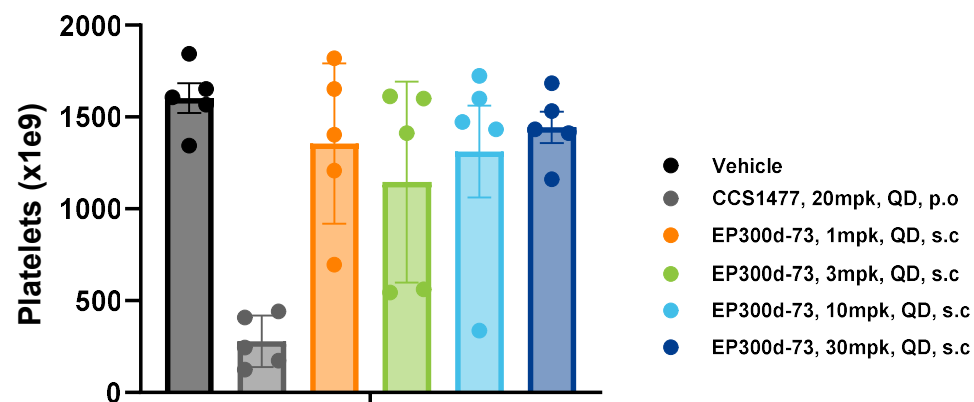
Selective EP300d shows robust efficacy and tolerability in MM1S model



EP300d-73 demonstrates dose-responsive efficacy, including complete responses



Selective EP300 degrader spares platelets

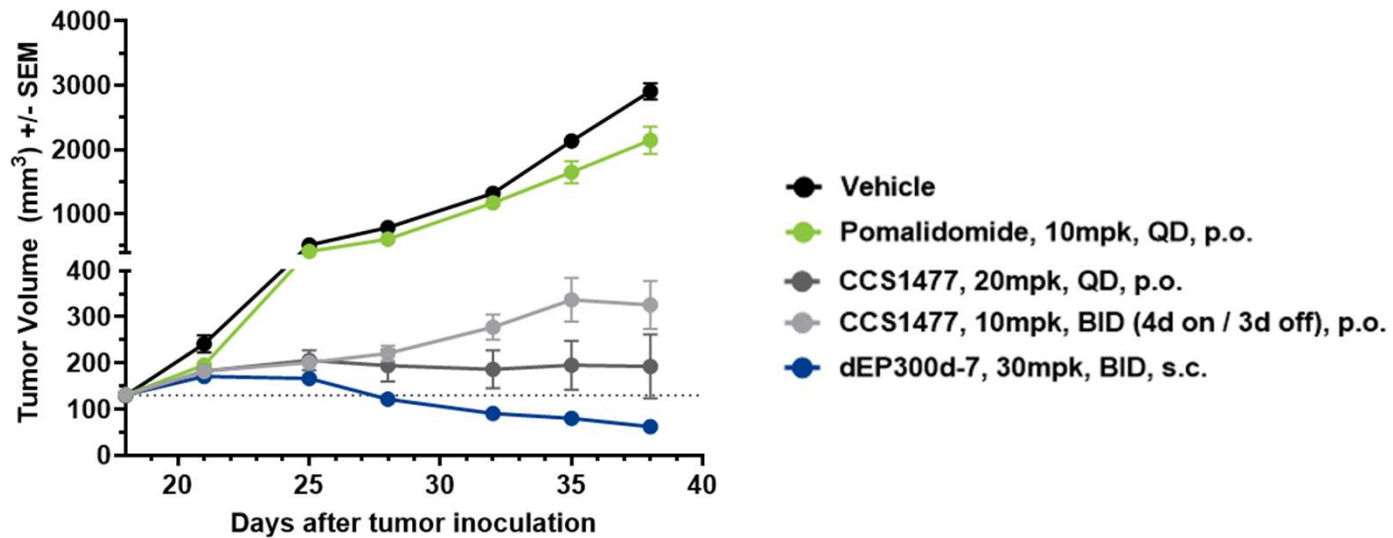


No reductions in WBCs, RBCs or neutrophils were observed at any dose level for either compound

Selective EP300d shows robust efficacy an IMiD-resistant MM model



Pomalidomide-resistant MM model (MM1S-PomR) treated with dEP300-7

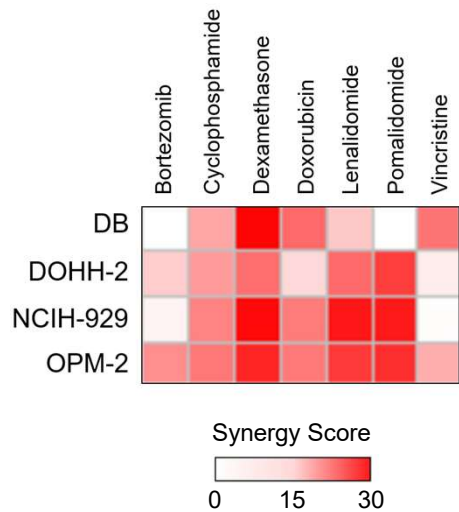


- Selective EP300 degrader achieves deeper responses (regressions) in a pomalidomide-resistant MM model
- Selective EP300 degrader with improved therapeutic window enables sustained target coverage and improved efficacy



dEP300 combinations converge on key lineage transcription factors

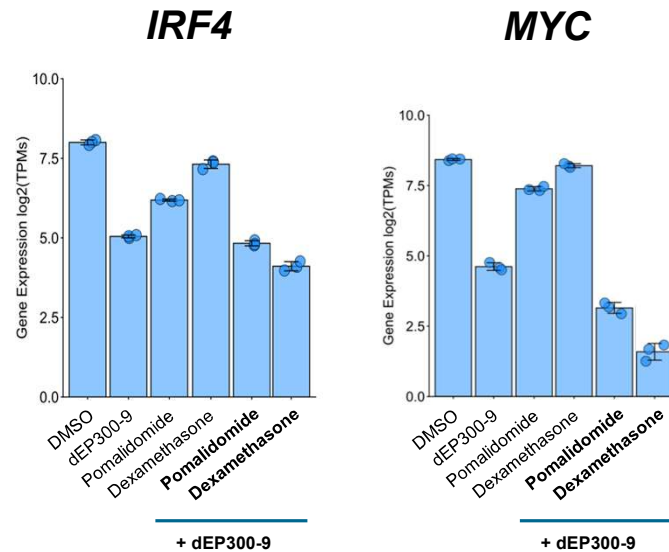
Combination therapy opportunities for EP300d



dEP300-9 combination screen details:

- 2 DLBCL, 2 MM cell lines
- 34 compounds screened
- 6-day CTG assay
- optimized 5x5 dose matrix

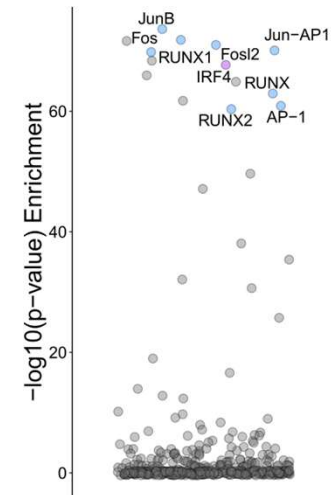
dEP300 combinations regulate multiple key TFs



RNA-seq analysis, MM1S cells
24h time treatment

EP300 regulates specific chromatin sites

Motifs enriched in closing ATAC-seq sites after EP300d treatment



ATAC-seq analysis, MM1S cells
30nM dEP300-9, 72h time treatment

Conclusions and ongoing efforts



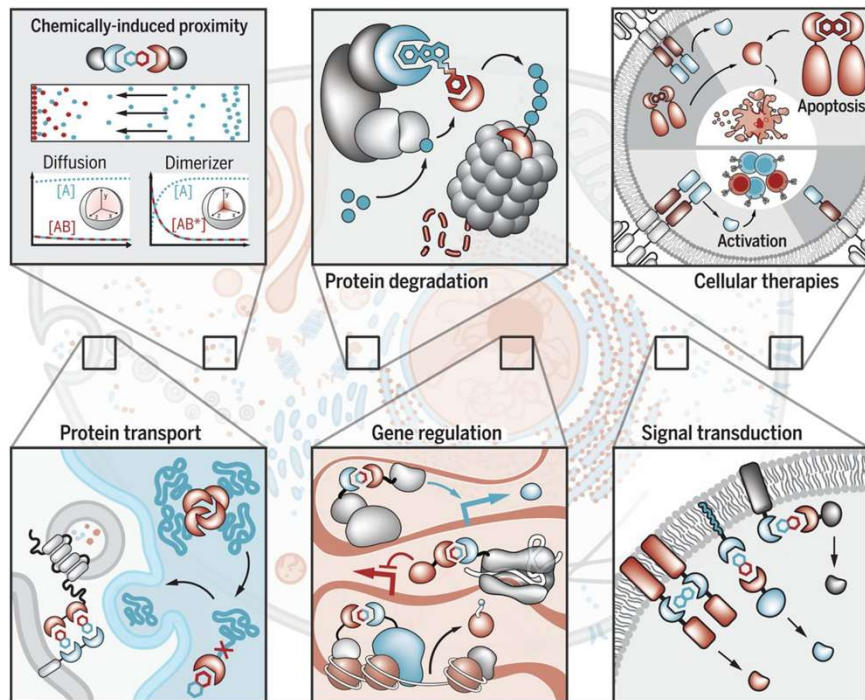
- Selective EP300 degradation has the potential to be a well-tolerated and effective treatment strategy in multiple indications, including multiple myeloma
- Robust activity in the context of IMiD-resistant MM cell lines
- EP300 controls the expression of critical transcription factors for MM lineage
- Promising combination potential of dEP300, converging on key lineage mechanisms in MM
- Identifying the dEP300 clinical candidate molecule

Expanding the induced proximity toolbox to target lineage dependence

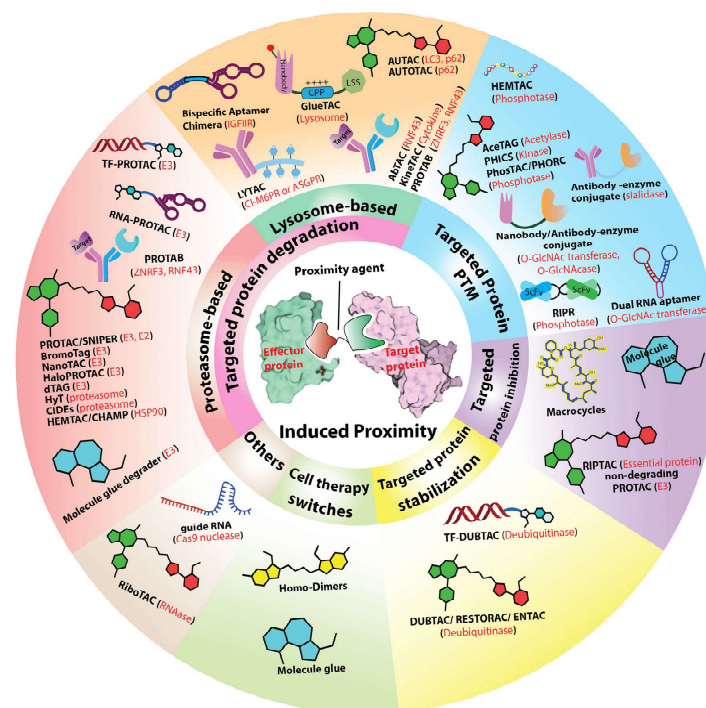


Induced proximity in controlling biological processes

Rapidly growing array of therapeutic approaches



Stanton BZ, et al., *Science* (2018)



Liu X, et al., *ACS Cent Sci* (2023)

Acknowledgements



Biology

Laura La Bonte
Qianhe Zhou
Claudia Dominici
Mark Zimmerman
Hafiz Ahmad
Ketaki Adhikari
Darshan Sappal

Pharmacology/DMPK

Mei Yun Lin
Brandon Antonakos
Brian Ethell

Drug Discovery

Marina Nelen
Julie Di Bernardo
Elizabeth Wittenborn

Computational Biology

Dave Lahr
David Mayhew

Protein Degradation

Danette Daniels
Karolina Mizeracka
Benjamin Adams
Grace Werosta

Chemistry

Kevin Wilson
Wesley Austin
Shawn Schiller
Solymar Negretti
Nihan Ucisik
Thomas Dixon
Md Imran Hossain
Paige Monsen