ANTI-CANCER ACTIVITY OF POTENT AND SELECTIVE EP300 DEGRADATION IN HEMATOLOGICAL MALIGNANCIES

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Abstract

E1A binding protein (EP300) and CREB binding protein (CBP) are highly homologous acetyltransferase paralogs with demonstrated roles as transcriptional co-activators. Dual inhibition of EP300 and CBP has been reported to have anti-proliferative effects in several cancer types. However, it has also been reported to elicit thrombocytopenia, a toxic reduction in the number of platelets in the blood (Nicosia et al., 2023). Hematological malignancy lineages are particularly susceptible to EP300 loss (DepMap, Broad 2024), therefore, developing chemical matter that selectively targets EP300 has the potential to broaden the therapeutic window and improve tolerability. Historically, selectivity has been difficult to engineer due to the high sequence similarity between EP300 and CBP. Using the targeted degradation approach, we have developed a potent and selective heterobifunctional degrader of EP300 with biological activity in hematological malignancy. We observed that selective degradation of EP300 has anti-proliferative activity in a broad range of hematological malignancies in vitro, including diffuse large B-cell lymphoma, multiple myeloma, and follicular lymphoma. We also achieved in vivo efficacy in a Karpas422 GCB-DLBCL xenograft model. Importantly, an investigational safety study was performed in mice at efficacious doses, and no thrombocytopenia was observed. Therefore, leveraging targeted protein degradation to achieve selective EP300 degradation shows promise to be a well-tolerated and effective treatment strategy for advanced hematological malignancies.

Key results

1) Heme lineages are dependent on EP300

2) Combo with SoC in DLBCL and MM is highly synergistic

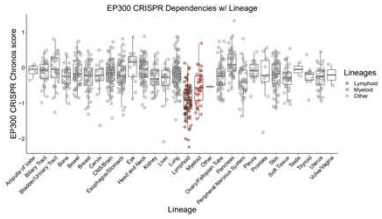
3) EP300 degradation is effective in IMiD-resistant MM cell lines

4) EP300 degradation in MM CDX model shows complete tumor regression

Conclusions and Next Steps

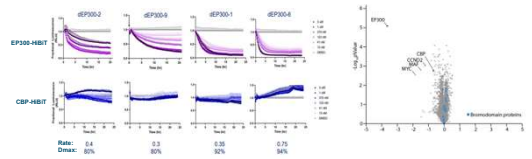
- Selective EP300 degradation inhibits growth of heme cell lines
- Combinations with SoC in both DLBCL and MM are highly synergistic in vitro
  - *Next steps: Confirm combos identified in screen in additional cell lines, and in vivo CDX/PDX models*
- Selective EP300 degradation is effective in IMiD-resistant MM cell lines
  - *Next steps: Generate additional IMiD-resistant MM cell lines. In vivo studies with resistant CDX models with single agent and in combo with SoC*
- CDX models of DLBCL and MM are responsive to dEP300 in vivo. MM shows complete tumor regression.
  - *Next steps: Test additional models with single agent and in combo with SoC*

EP300 Dependency in Hematological Malignancy

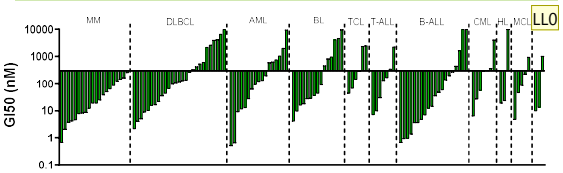


◀ Negative EP300 dependency scores are most enriched in the lymphoid and myeloid lineages (highlighted in plot). Within these heme lineages, MM and DLBCL are the most sensitive.

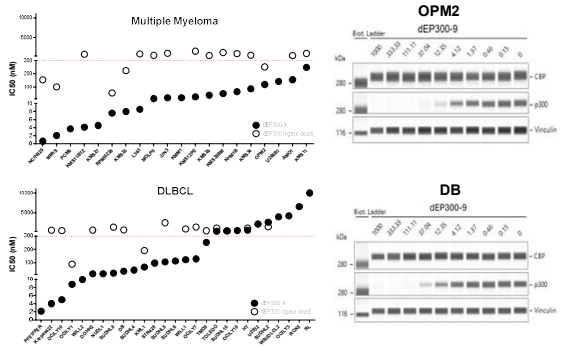
EP300 shares 59% overall and 97% bromodomain identity with its paralogue CBP, making selective degradation of either paralogue challenging. Kinetic experiments show improvement on depth and rate of EP300 degradation while maintaining selectivity over CBP and other bromodomain-containing proteins. ▼



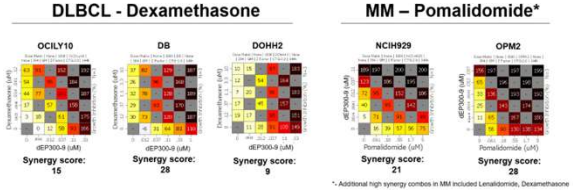
Broad sensitivity across a panel of heme malignancy cell lines treated with dEP300-9. ▼



Panel of MM and DLBCL cell lines are sensitive to selective EP300 degradation. Treatment with a ligase dead version of EP300-9 (does not bind to E3 ligase but still binds target) is significantly less potent across cell lines (left). EP300 degradation with dEP300-9 is dose dependent, without off target degradation of CBP (right). OPM2 and DB cell lines shown as exemplars. ▼



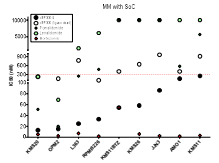
Combining dEP300 with SoC in DLBCL and MM



*- Additional high synergy combos in MM included Lenalidomide, Dexamethasone

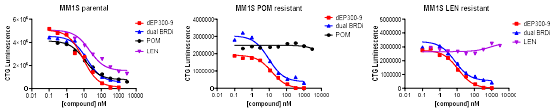
▲ 3 DLBCL cell lines (DB, DOHH2, and OCILY10) and 2 MM cell lines (OPM2, NCIH929) were treated with dEP300-9 and ~30 combination agents for 5 days to assess potential synergistic pairs. Standards of care (SoC) in heme malignancies showed very strong synergy with dEP300 across cell lines. Additionally, >100% growth inhibition (cell death), was observed at several concentrations of dEP300-9 in combination with Pomalidomide in both multiple myeloma cell lines.

IMiD-resistant MM cell lines are sensitive to dEP300



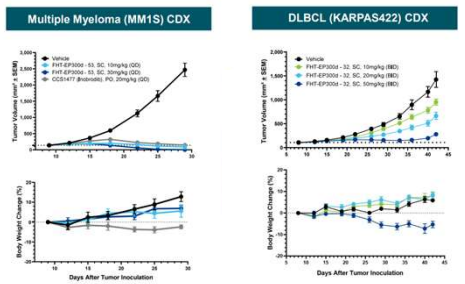
◀ Treatment with dEP300-9 remained effective in a panel of MM cell lines that included cell lines with complete resistance to Pomalidomide and Lenalidomide.

MM1S multiple myeloma cell lines with acquired resistance to Pomalidomide and Lenalidomide remained sensitive to dEP300-9 ▼



CDX of MM and DLBCL are sensitive to dEP300

MM1S multiple myeloma CDX model and KARPAS422 DLBCL CDX model show dose responsive sensitivity to dEP300, without significant loss in body weight. The MM1S CDX model showed complete tumor regression at highest dose. ▼



References

DepMap, Broad (2023). DepMap 23Q4 Public. Figshare+. Dataset.

Nicosia L ET AL., Therapeutic targeting of EP300/CBP by bromodomain inhibition in hematologic malignancies. Cancer Cell. 2023 Dec 11;41(12):2136-2153.e13.