USING ARTIFICIAL INTELLIGENCE TO OVERCOME RESISTANCE TO CAR-T THERAPY IN MANTLE CELL LYMPHOMA

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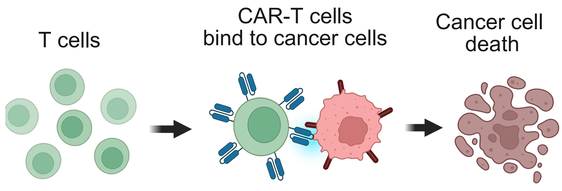
Introduction

Mantle cell lymphoma (MCL)

- aggressive subtype of non-Hodgkin B-cell lymphoma[1]

Chimeric antigen receptor (CAR) T therapy

- approved by FDA for relapsed MCL[2,3]



Current challenge

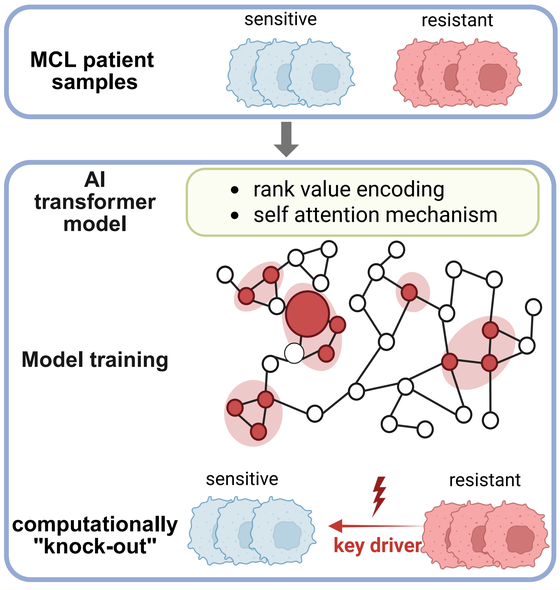
- **Resistance with poor outcomes**
- high patient heterogeneities

Aim

To leverage **AI transformer model** to identify **targets** to **overcome CAR-T resistance** in MCL

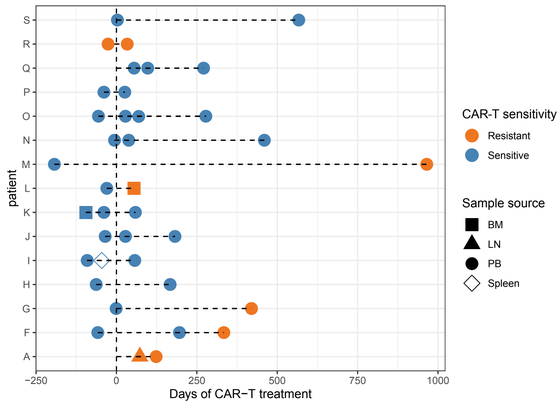
Methods

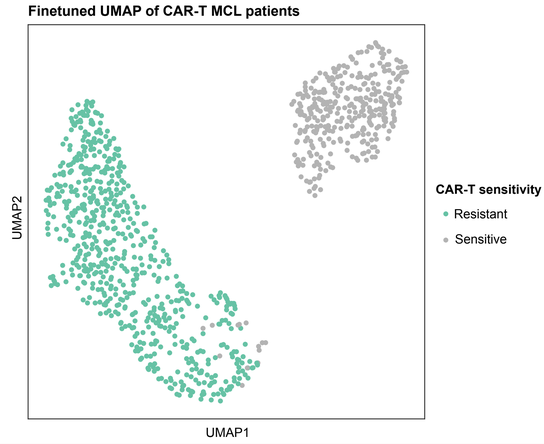
- PBMC samples from MCL patients pre- and post-CAR-T therapy were analyzed using scRNA-seq.
- A pretrained transformer model was fine-tuned on this MCL dataset to classify resistant and sensitive cell populations.
- In silico perturbation analysis simulated gene knockdown experiments to predict transitions of resistant cells to sensitive states.
- Top-ranked regulators are undergoing experimental validation.



Results

- Our scRNA-seq data contains a total of 39 samples, collected from 15 MCL patients both before and after CAR-T cell therapy.
- Fine-tuning the transformer model effectively resolved patient-specific batch effects, achieving accurate classification of resistant and sensitive cell clusters.
- **In silico perturbations** identified two distinct gene sets:
  - ➢ **(1) resistance-reversing genes**, whose loss reprogrammed resistant cells toward sensitivity
  - ➢ **(2) sensitivity-promoting genes**, whose loss disrupted the sensitive phenotype and induced resistance.
- CD19, the direct target of CAR-T therapy, ranked top among the top sensitivity-promoting genes. Its in silico deletion will induce resistance, consistent with clinical observations linking CD19 loss to relapse.





Summary

- Through transformer-based model and in silico perturbation, we identified novel targets that may overcome CAR-T resistance in MCL.
- Further validation is needed to translate these findings into clinical applications.

Discussion

This study demonstrates the power of transformer-based deep learning models to uncover drivers of therapy resistance in hematologic malignancies.

References

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3. Jain P, Nastoupil L, Westin J, Lee HJ, Navsaria L, Steiner RE, et al. Outcomes and management of patients with mantle cell lymphoma after progression on brexucabtagene autoleucel therapy. Br J Haematol. 2021;192(2):e38-e42.