A scalable pan-cancer antigen target discovery platform for precision oncology

Abstract 1915 E. Fox[1], G. Appe[1], A. Behdenna[1], L. Meunier[1], A. Nordor[1], S. Weill[1], C. Marijon[1]. [1]Epigene Labs, Paris, France

AACR American Association for Cancer Research

Introduction

- With the emergence of precision oncology as a new paradigm in cancer care, there is an urgent need to develop tools capable of mining the **massive amounts of rich omic data generated** every year.
- To support target discovery programs at scale, we developed a pan-cancer bioinformatics platform combining **patient data with extensive biological and pharmaceutical knowledge** for the identification and prioritization of novel antigen targets.
- Our platform was first validated with the discovery of antigen targets amenable to chimeric antigen receptor (CAR)-T therapy for relapsed/refractory multiple myeloma[1].
- Here, we are systematically stratifying and analyzing **7 cohorts of patients selected from our pan-cancer omic data lake[2]** (Fig. 1), and deep diving into Acute Myeloid Leukemia (AML) results.

Methods

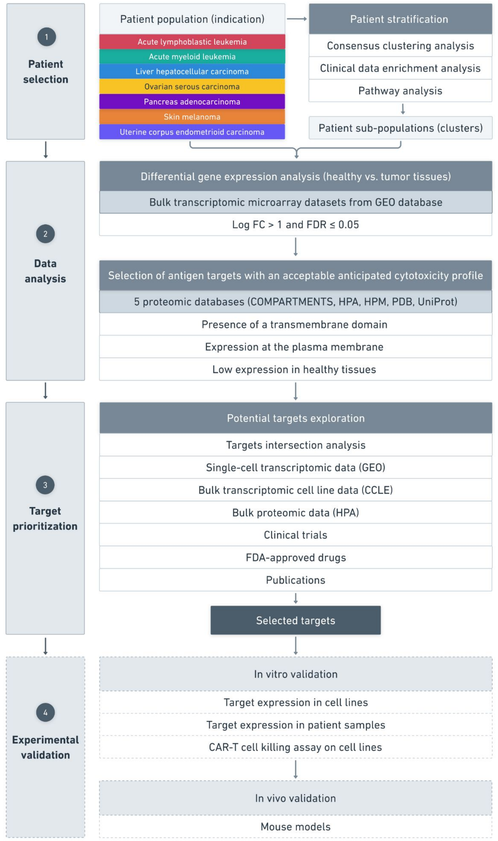

Figure 1: Epigene Labs' antigen target discovery platform
(Log FC = Log Fold Change, FDR = False Discovery Rate, HPA = Human Protein Atlas, HPM = Human Proteome Map, PDB = Protein Data Bank, GEO = Genome Expression Omnibus, CCLE = Cancer Cell Line Encyclopedia, FDA = Food and Drug Administration)

Pan-cancer analysis

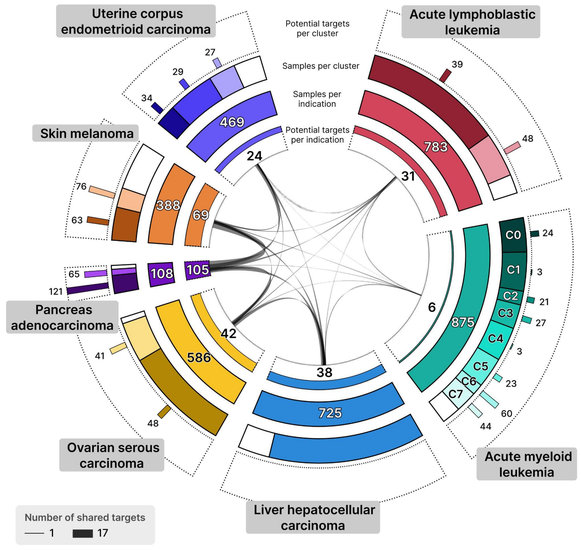

Figure 2: Overview of our pan-cancer antigen target discovery analysis in 7 indications
Patient cohorts and corresponding clusters are represented by the 2 middle circles. Numbers of targets matched with each cohort and cluster are represented, respectively, by the inner circle and outer bar plot. Numbers of targets shared between indications 2 by 2 are represented by the inner links.

Key results

- Stable clusters identified in 6 indications out of 7 (Fig. 2)
- All clusters found to be **associated with at least one clinical data element and/or one relevant biological pathway** (*e.g.* poor overall survival, metastasis-related pathway)
- Potential antigen targets identified for all 7 indications and 19 clusters, including CD19 in acute lymphoblastic leukemia
- In all indications, **higher numbers of targets following stratification**, with values ranging from 1.2x to 20x → reducing the cohort heterogeneity effectively increases the potential antigen target discovery rate
- 57 targets matched to 2+ indications and 221 targets matched to 2+ clusters → **tissue-agnostic potential** (Fig. 3)
- Shared targets between clusters displaying similar dysregulations

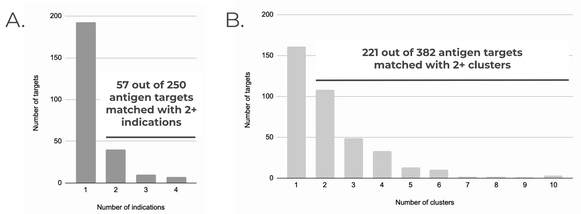

Figure 3: Tissue-agnostic potential of identified antigen targets
Number of shared targets between indications (A.) and clusters (B.)

Deep dive into AML

Key results

- **8 stable patient clusters identified and characterized** with clinical data, pathway enrichment analyses, and a review of the relevant literature (Fig. 4)

3 well-characterized AML subtypes
- C0 = core-binding factor (CBF)-AML
- C1 = acute erythroid leukemia (AEL)-AML (FAB M6)
- C6 = acute promyelocytic leukemia (APL)

2 clusters with **upregulated immune system pathways**

Other clusters of interest defined by:
- **specific gene mutations**
- **sequence alterations**
- **enriched pathways**

- **20x more targets identified following patient stratification**

AML cohort
6 targets → **AML clusters**
118 targets identified across all clusters
- 26 targets per cluster in average
- maximum of 60 targets for C6

- Thanks to our methodology, we identified interesting patient sub-populations and potential antigen **targets specific to one or multiple patient subgroups,** as well as a few targets applicable to the full indication.
- Additional exploration is required in order to identify patient subgroups with unmet clinical needs, thereby enabling the customization of therapeutic strategies based on their molecular profiles.

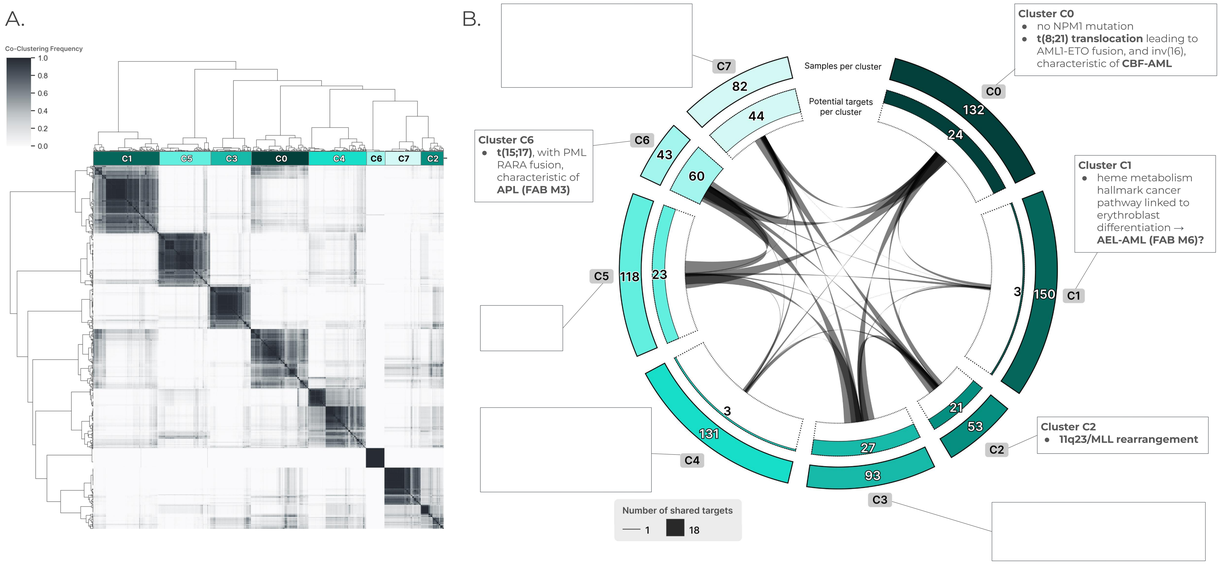

Figure 4: Focus on the AML cohort stratification and analysis
A. Consensus clustering matrix of the 802 primary samples of the AML cohort divided in 8 clusters. Patients are represented in the columns and genes in the rows. The co-clustering frequency is represented by the grey gradient. B. Cluster-level clinical data enrichment, pathway and antigen target discovery analysis. Clusters are represented by the outer circle. Numbers of targets matched with each cluster are represented by the inner circle. Numbers of targets shared between clusters 2 by 2 are represented by the inner links. A summary of the clinical data and pathway enrichment analyses is provided in the boxes surrounding the circos plot. MSigDB hallmark gene sets (H), curated gene sets (C2), ontology gene sets (C5) and oncogenic signature gene sets (C6) collections were used as reference gene sets in the pathway analysis on all clusters, as well as the immunologic signature gene sets (C7) collection to further explore cluster 4 and 7.

Conclusion

- Developing scalable pipelines will be instrumental in the advent of precision oncology.
- Combining **unbiased data-driven tools with cancer biology-driven** approaches, our state-of-the-art platform can be used for **any cancer type and antigen-targeting modality**, including CAR-T and antibody-based therapies.
- The present study illustrates the potential of our platform when applied to 7 cancer types.
- Leveraging our large and unique patient cohorts, we are not only able to **detect relevant subgroups of patients, but also identify novel antigen target candidates** for these specific populations.
- Broader studies addressing other cancer indications, including breast, lung, and head & neck cancer, are underway.

References

1. A. Talbot et al. Integrating Transcriptomics and Proteomics for the Discovery of Novel Antigen Targets on Surface of Malignant Plasma Cells Amenable for Chimeric Antigen Receptor-T (CAR-T) Cell Approach in the Treatment of Patients with Relapsed/Refractory Multiple Myeloma. Blood 2022; 140 (Supplement 1): 7094–7095.
2. **Poster #6209** - L. Meunier et al. From data disparity to data harmony: A comprehensive pan-cancer omic data collection. **AACR 2024.**

Contact
Akpéli Nordor, PharmD, PhD (akpeli@epigenelabs.com).
The authors have no conflict of interest to declare.

CHECK US OUT!

European Innovation Council
Co-funded by the European Union