

Multimodal atlas of paired diagnosis and relapse AML samples enables novel therapeutic targeting of surface antigens

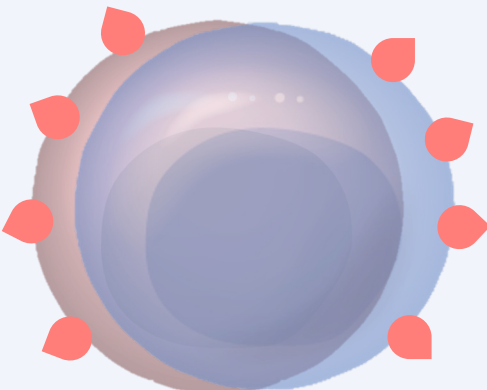
Matthew H. Ung, PhD

Associate Director, Quantitative Biology

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We use genome engineering to make healthy cells invisible to drugs

Problem

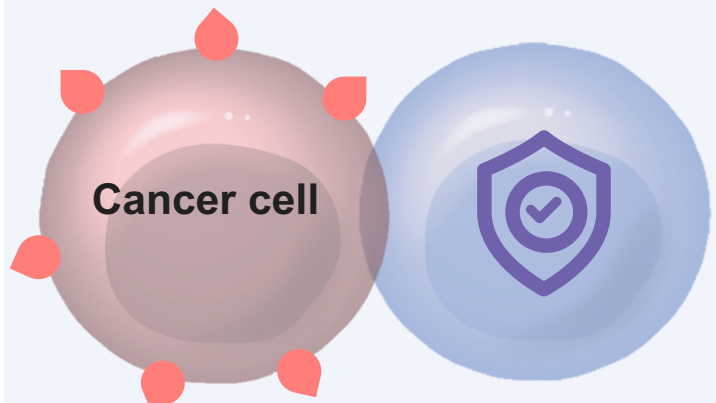


Few unique cancer antigens, so drugs kill both cancer and healthy cells through **on-target toxicity**

The diagram shows a brown cancer cell and a blue healthy cell. Red teardrop-shaped antibodies are bound to antigens on the surface of both cells, illustrating that drugs targeting these antigens will affect both cell types.

Genome engineering

**Vor Paradigm:
Engineered HSCs (eHSCs)**

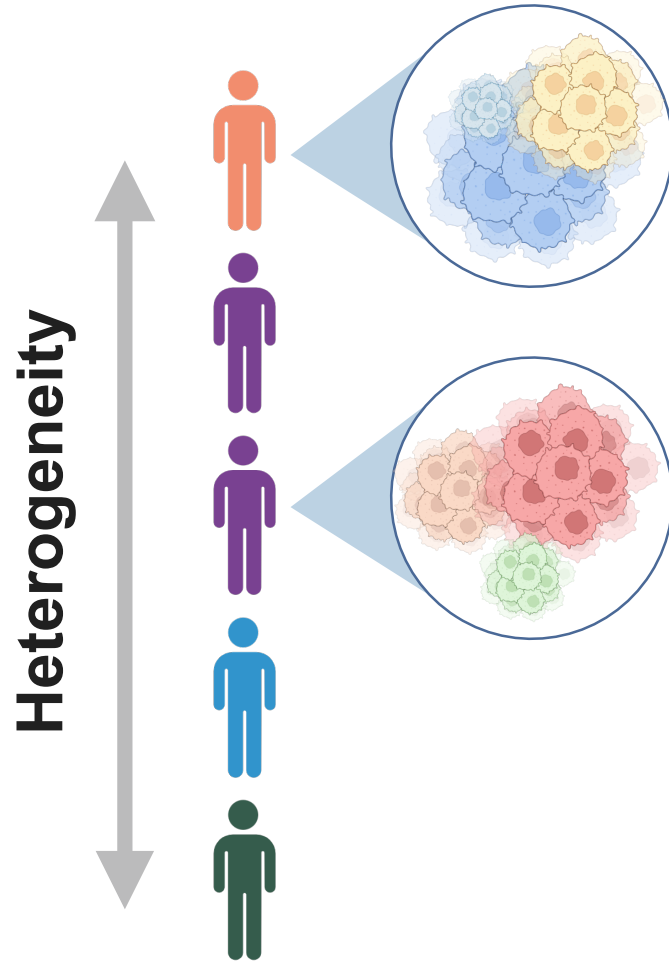


Cancer cell

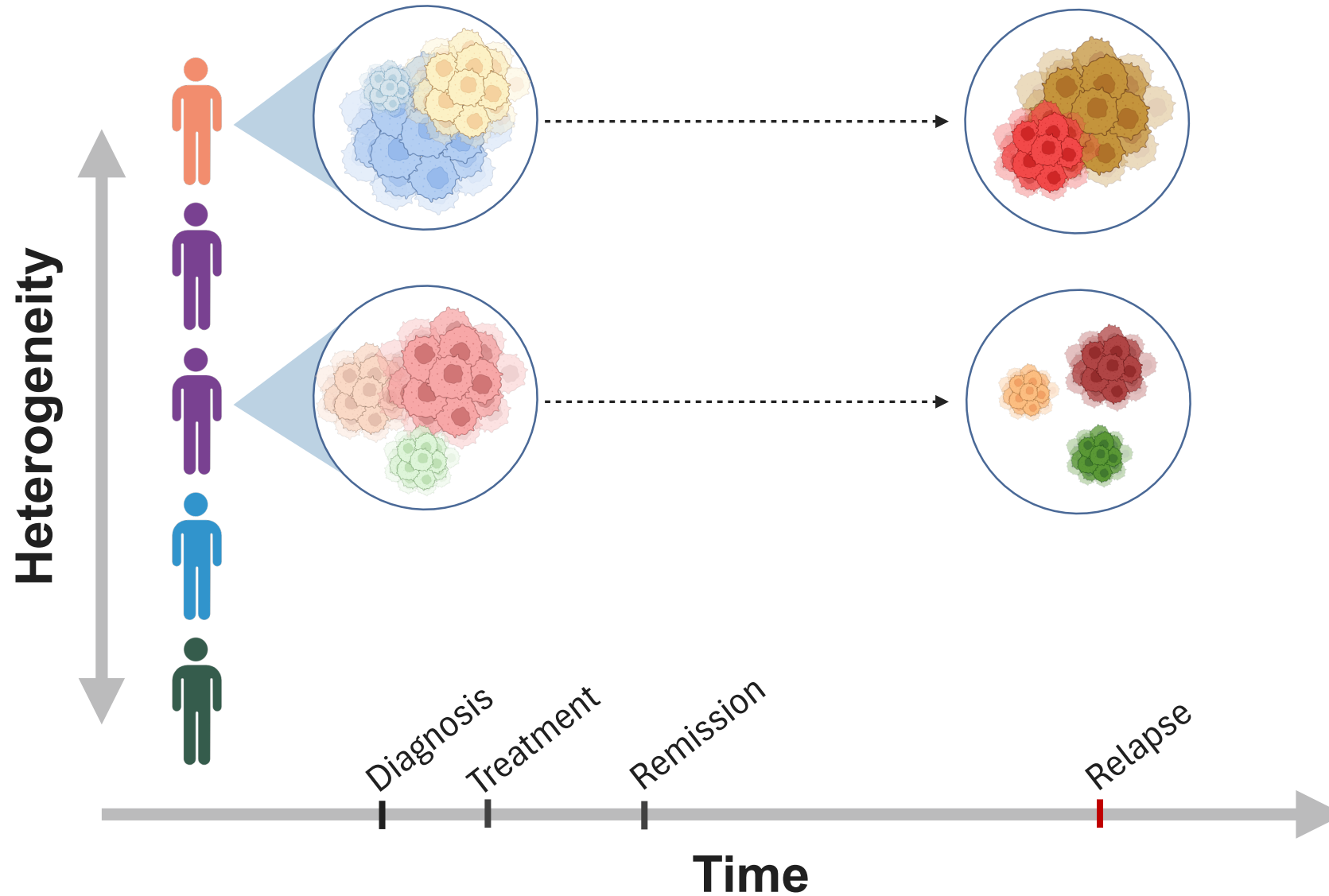
Remove target expression on healthy cells so that killing is **cancer-specific**

The diagram shows a brown cancer cell with red antibodies bound to its antigens. Next to it is a blue healthy cell (eHSC) with a shield icon on its surface, indicating that target expression has been removed from this cell type, making it invisible to the drug.

Patient to patient heterogeneity presents obstacles to treatment



Evolution of leukemic blasts presents obstacles to treatment



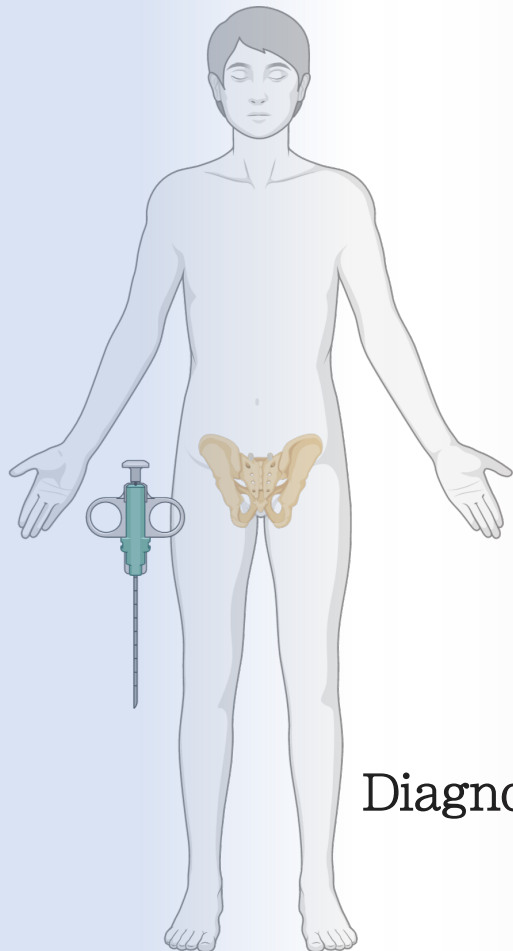


UHN

University Health Network

Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
Michener Institute

Clinical metadata



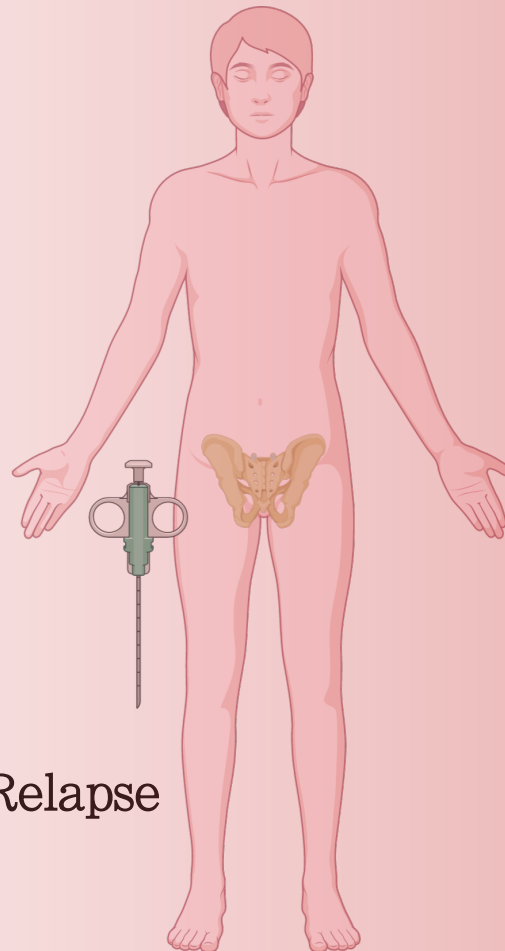
Diagnosis

56

matched AML
bone marrow
samples



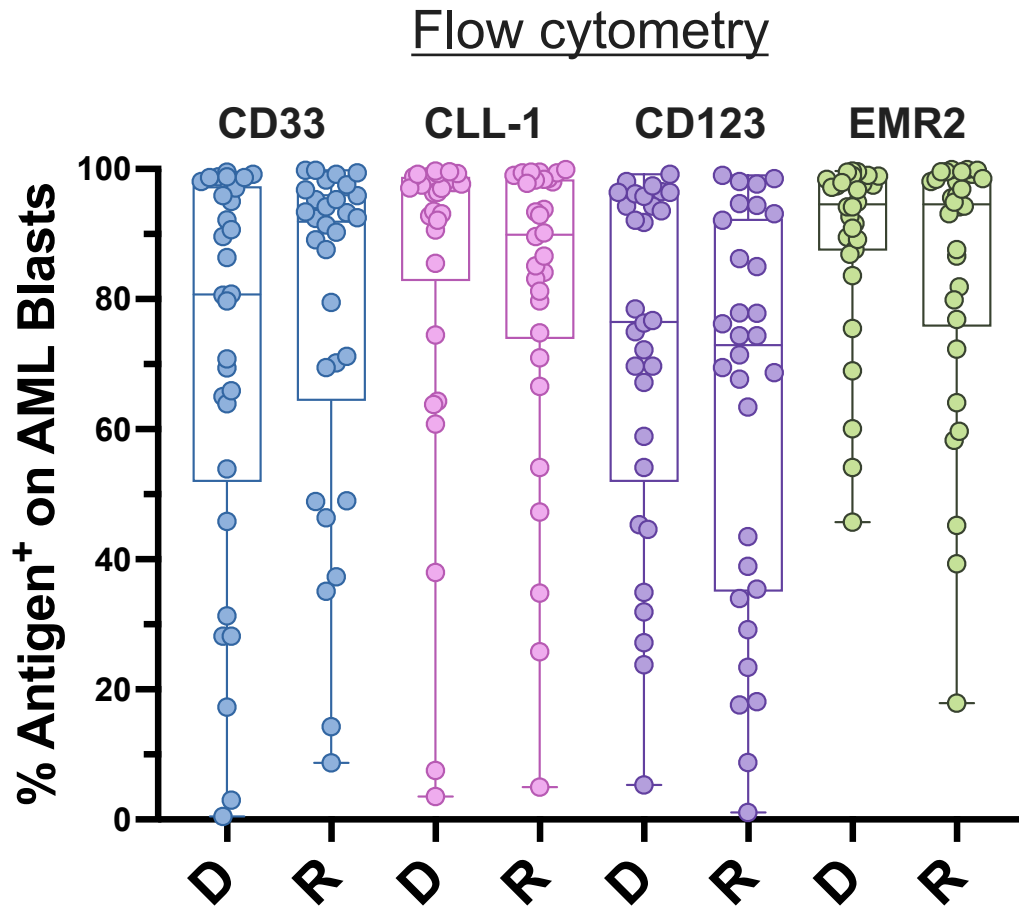
28 patients



Relapse

- ✓ Treatment history
- ✓ Sex
- ✓ FAB subtype
- ✓ Cytogenetics
- ✓ Mutation information
- ✓ Vital status
- ✓ Survival information
- ✓ Time to relapse

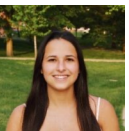
4 myeloid markers are expressed at targetable levels at diagnosis and relapse



Julia Etchin



Amanda Halfond



Julia DiFazio

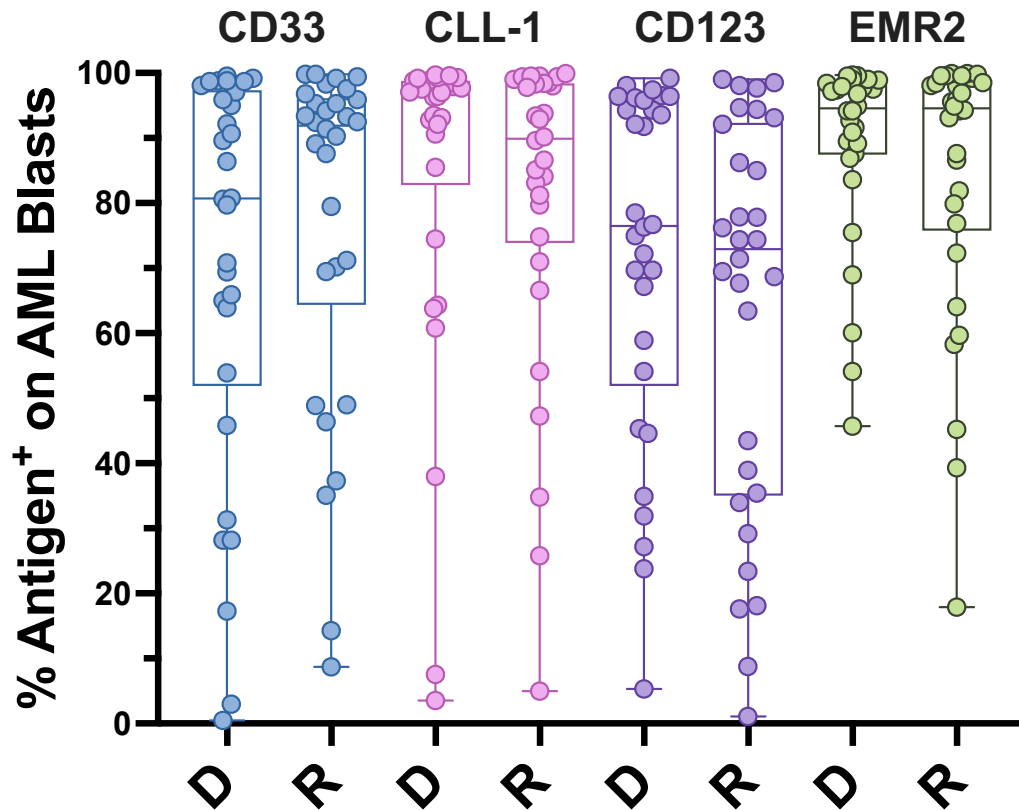


Yonina Keschner

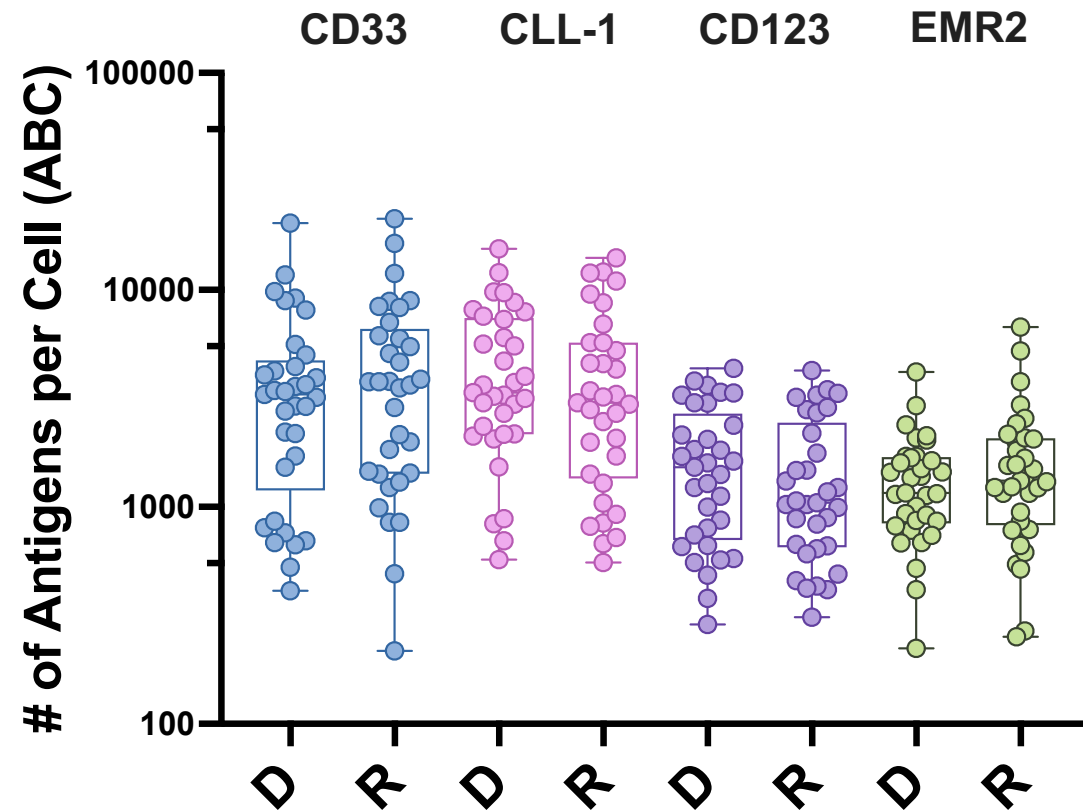
D = Diagnosis R = Relapse

4 myeloid markers are expressed at targetable levels at diagnosis and relapse

Flow cytometry



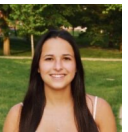
Flow cytometry with QuantiBRITE



Julia Etchin



Amanda Halfond



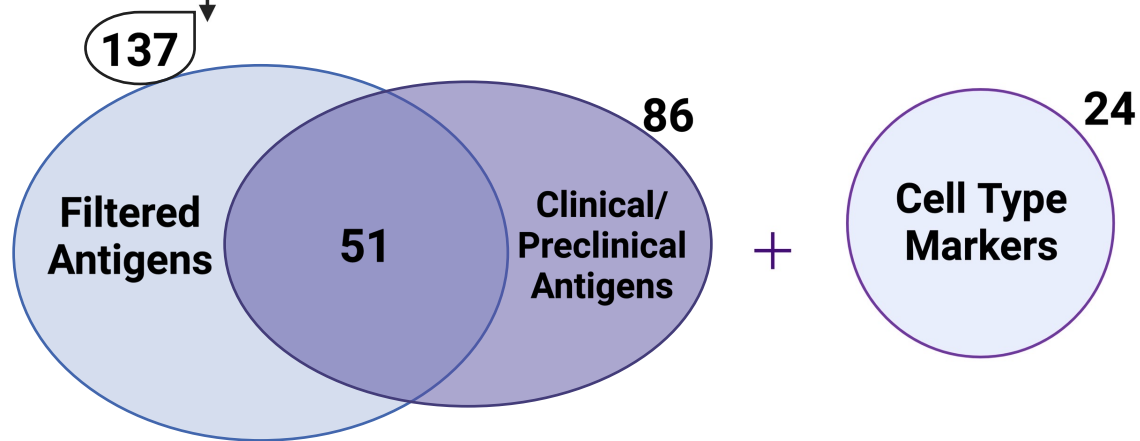
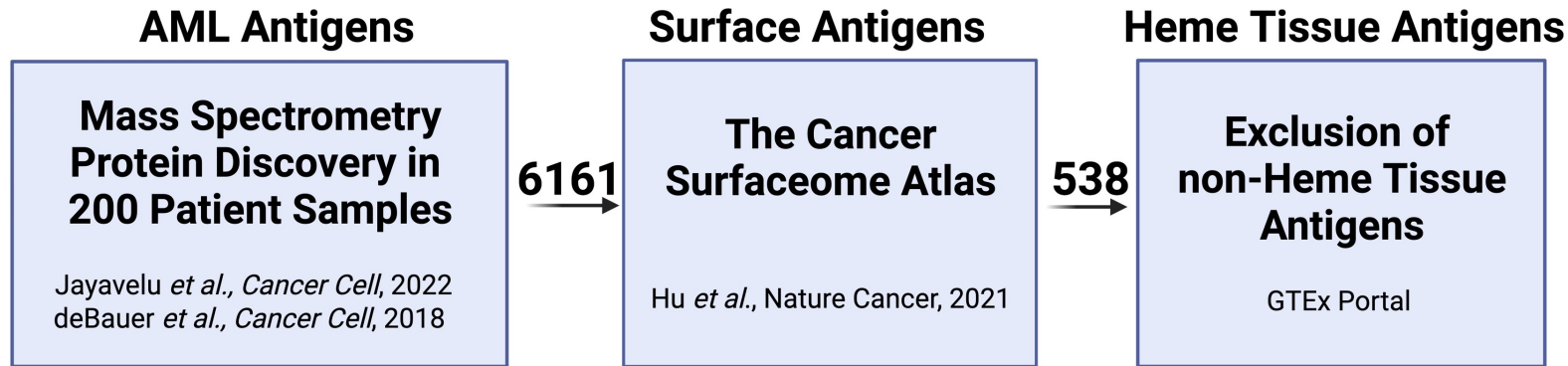
Julia DiFazio



Yonina Keschner

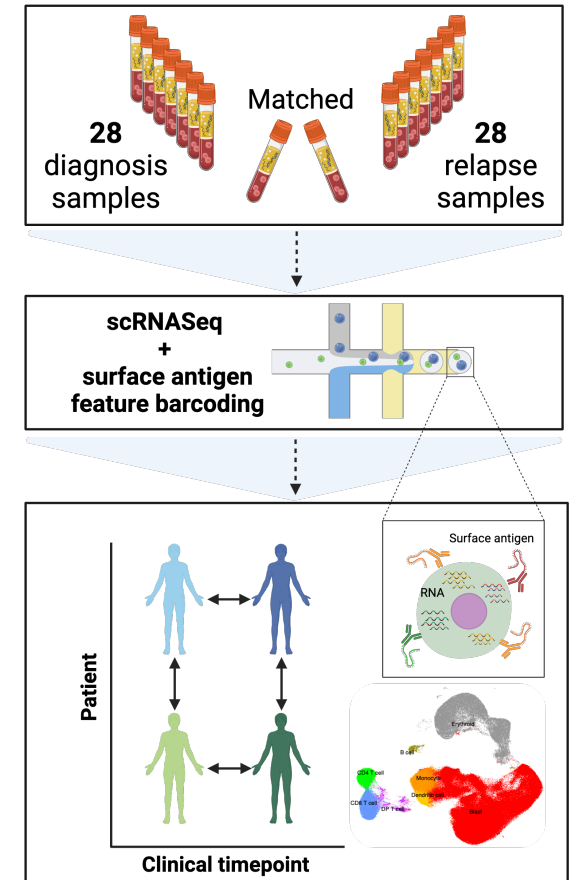
D = Diagnosis R = Relapse

Single cell RNA sequencing of matched AML samples with feature barcoding of 81 surface antigens



Total: 196

Total Antibody-Derived Tags (ADT) in CITE-seq: 81*

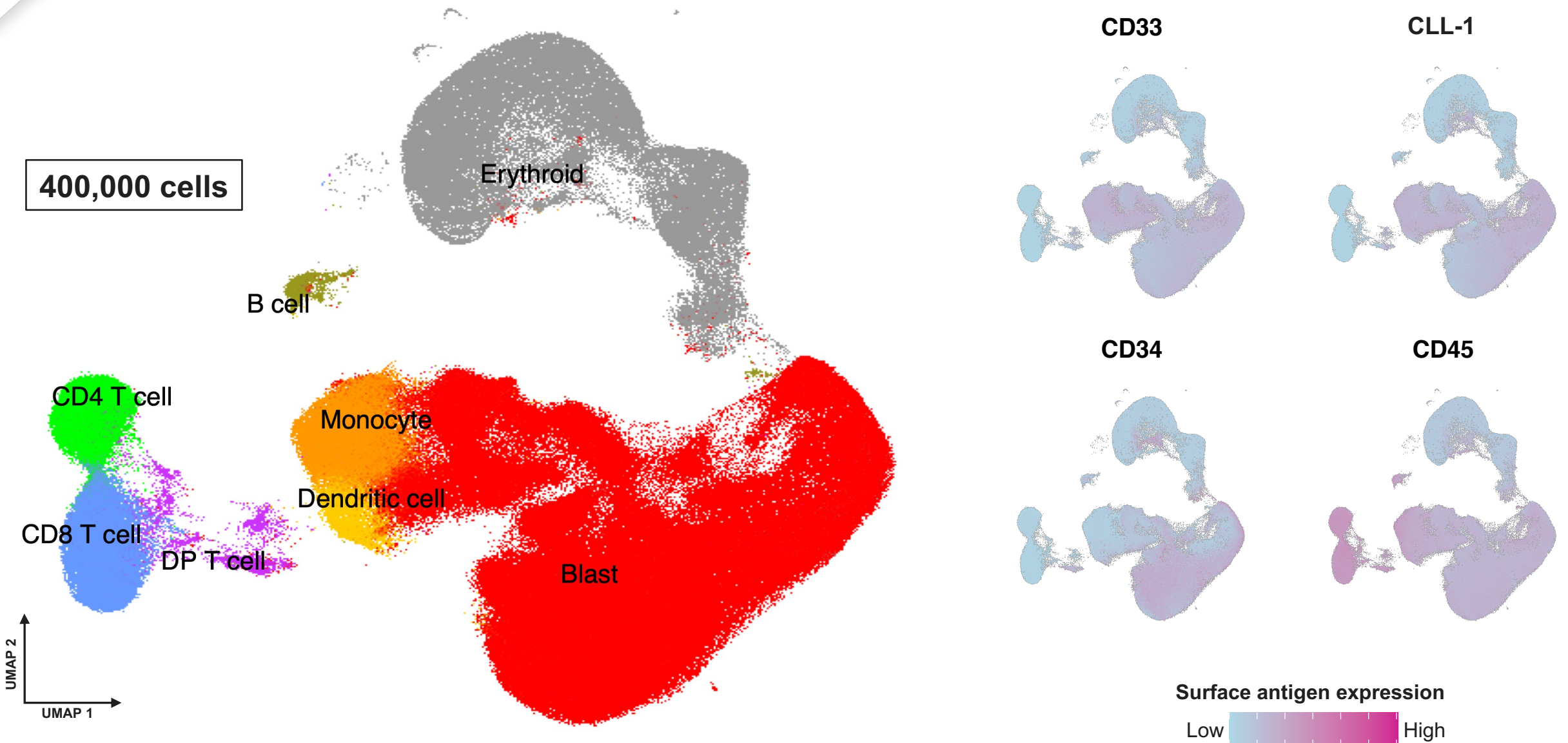


Created with BioRender.com

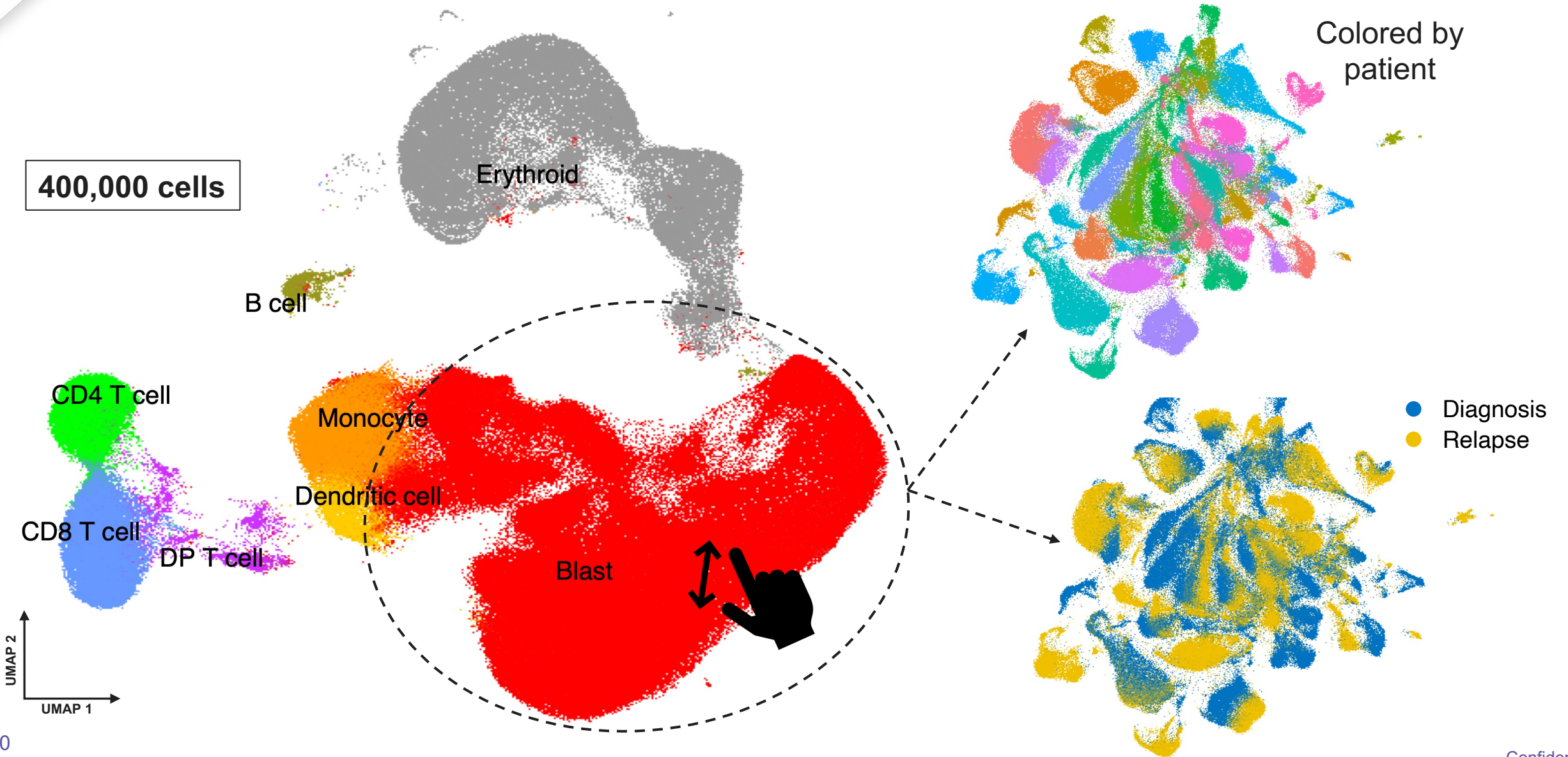
*Commercially Available or Custom Conjugated ADT



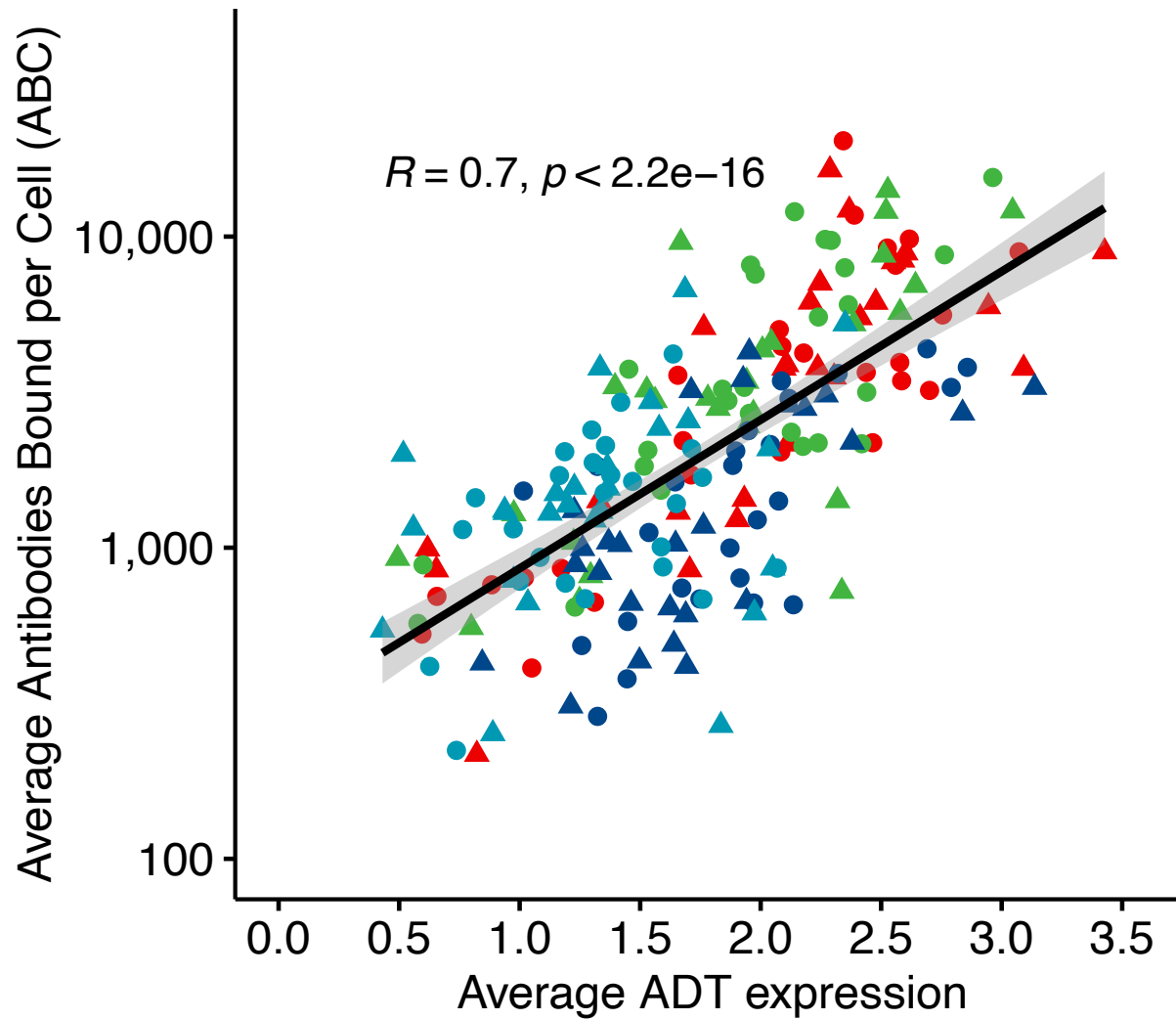
Multimodal atlas of AML reveals distinct cell populations



Multimodal atlas of AML reveals distinct cell populations



Cell surface antigen density can be estimated for each blast by incorporating QuantiBRITE information



Antigen

- CD33
- CLL-1
- CD123
- EMR2

Timepoint

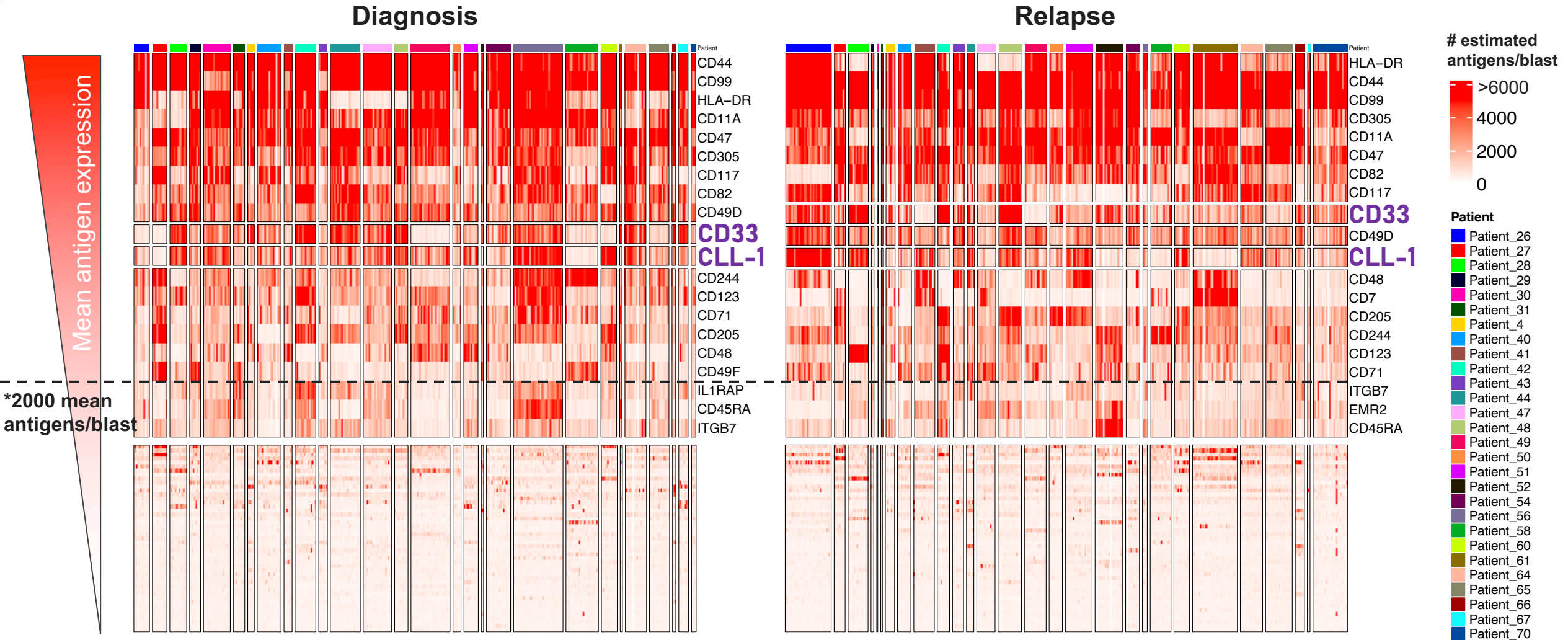
- Diagnosis
- ▲ Relapse

Feature barcoding



QuantiBRITE

Estimated blast surface antigen density reveals targetable antigens across patients at diagnosis and relapse



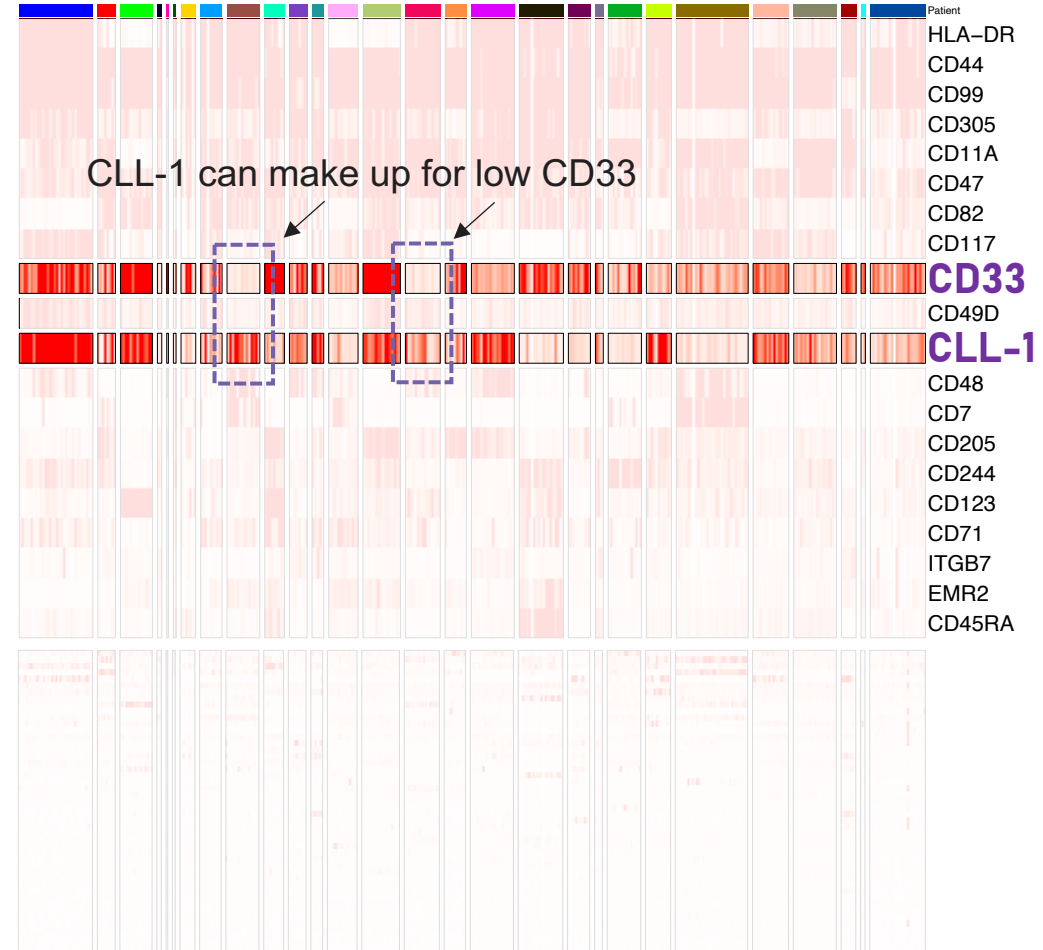
Estimated blast surface antigen density reveals targetable antigens across patients at diagnosis and relapse

Mean antigen expression

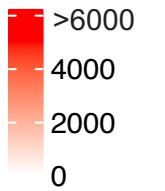
Diagnosis



Relapse



estimated antigens/blast



Patient

- Patient_26
- Patient_27
- Patient_28
- Patient_29
- Patient_30
- Patient_31
- Patient_4
- Patient_40
- Patient_41
- Patient_42
- Patient_43
- Patient_44
- Patient_47
- Patient_48
- Patient_49
- Patient_50
- Patient_51
- Patient_52
- Patient_54
- Patient_56
- Patient_58
- Patient_60
- Patient_61
- Patient_64
- Patient_65
- Patient_66
- Patient_67
- Patient_70

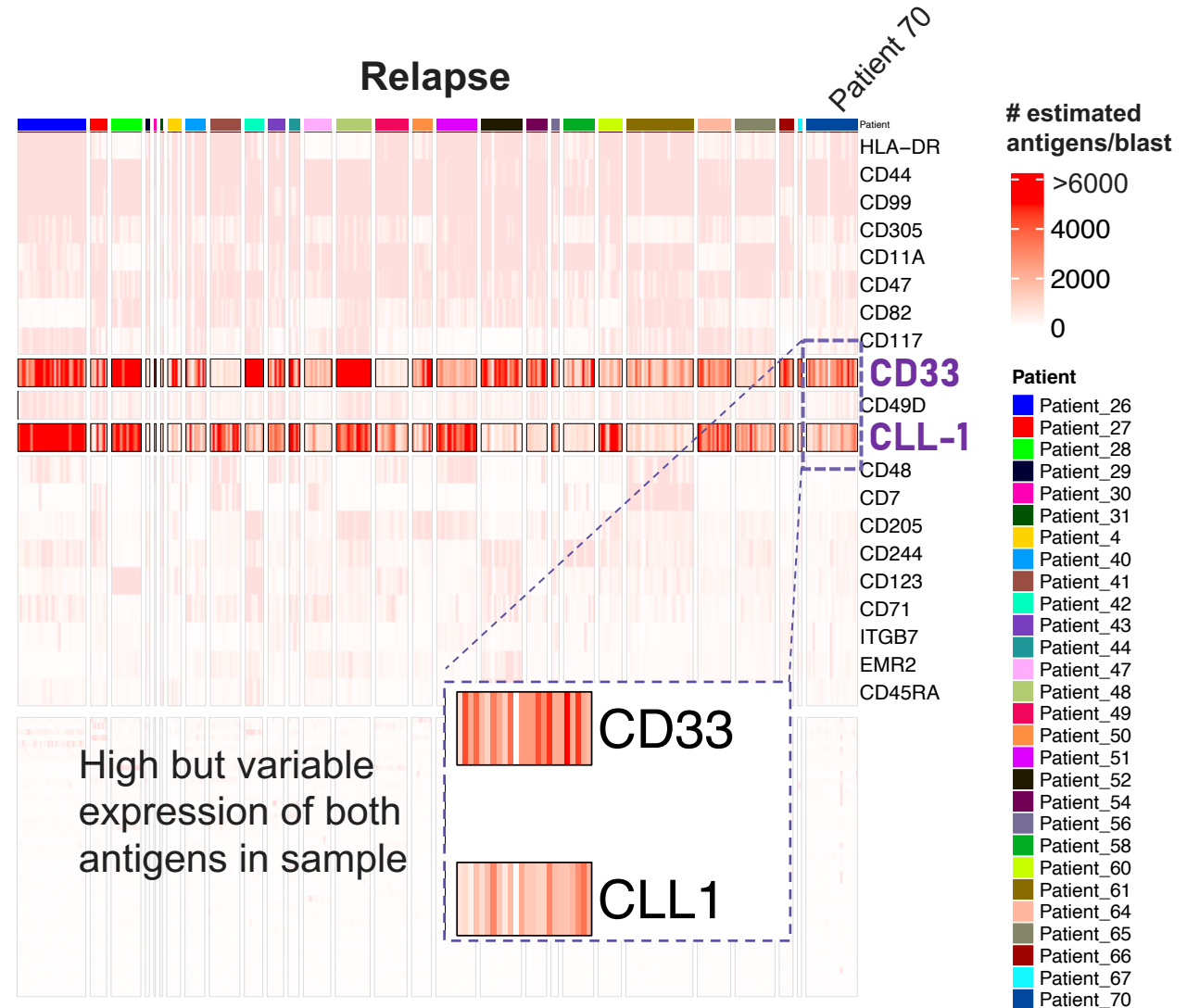
Estimated blast surface antigen density reveals targetable antigens across patients at diagnosis and relapse

Mean antigen expression

Diagnosis

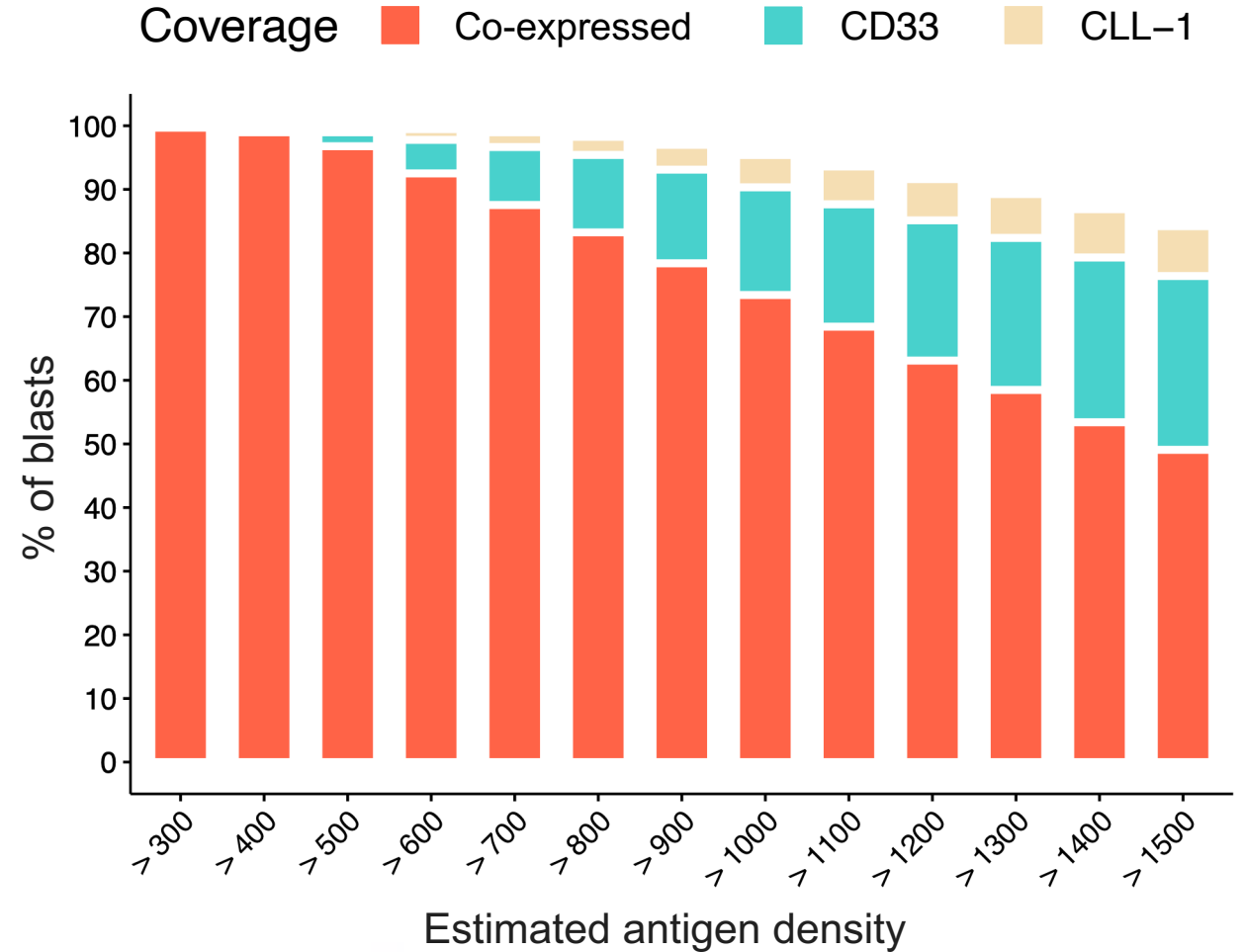
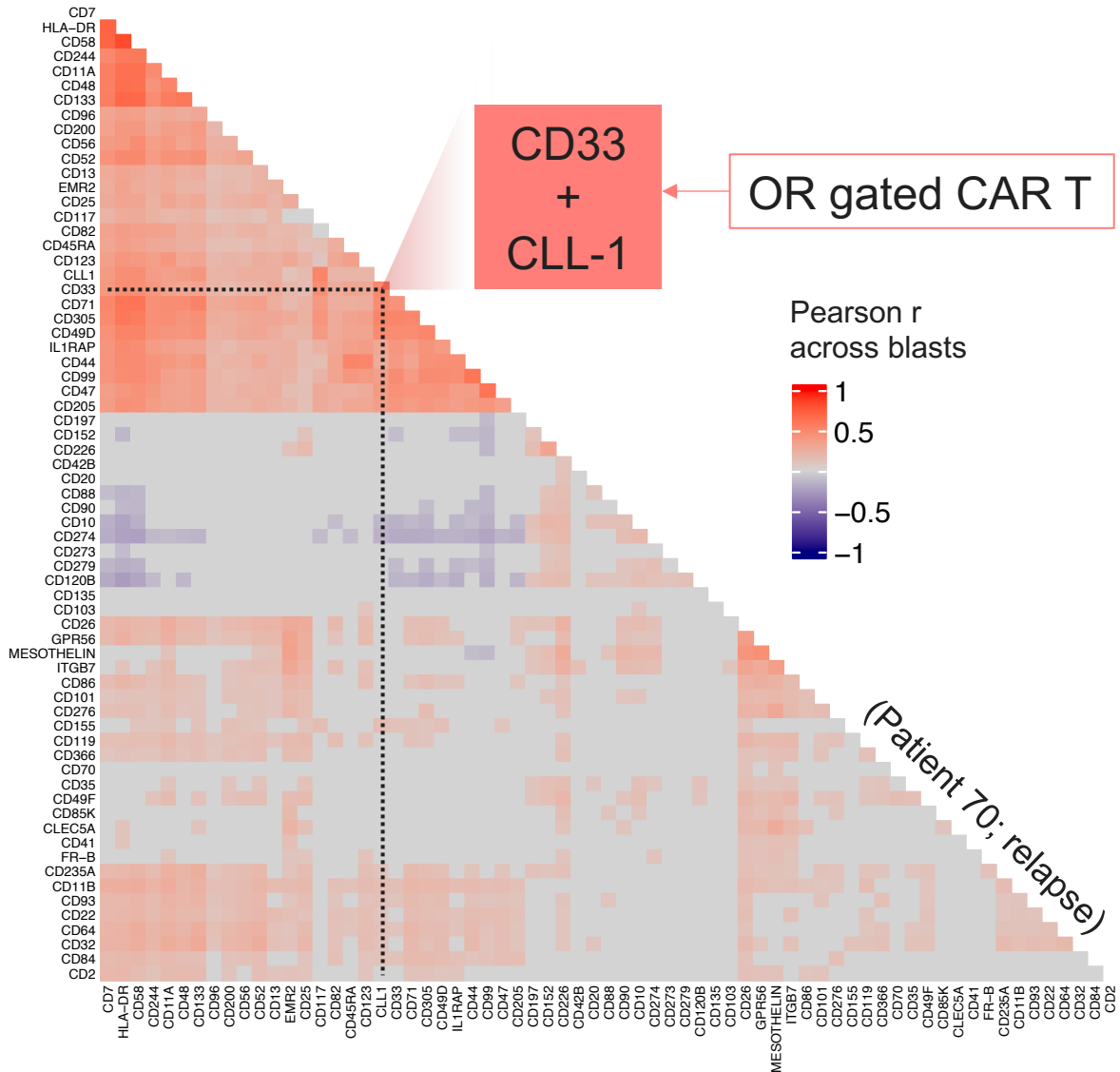


Relapse



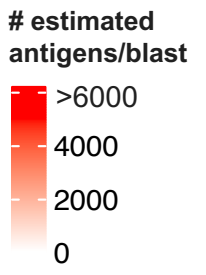
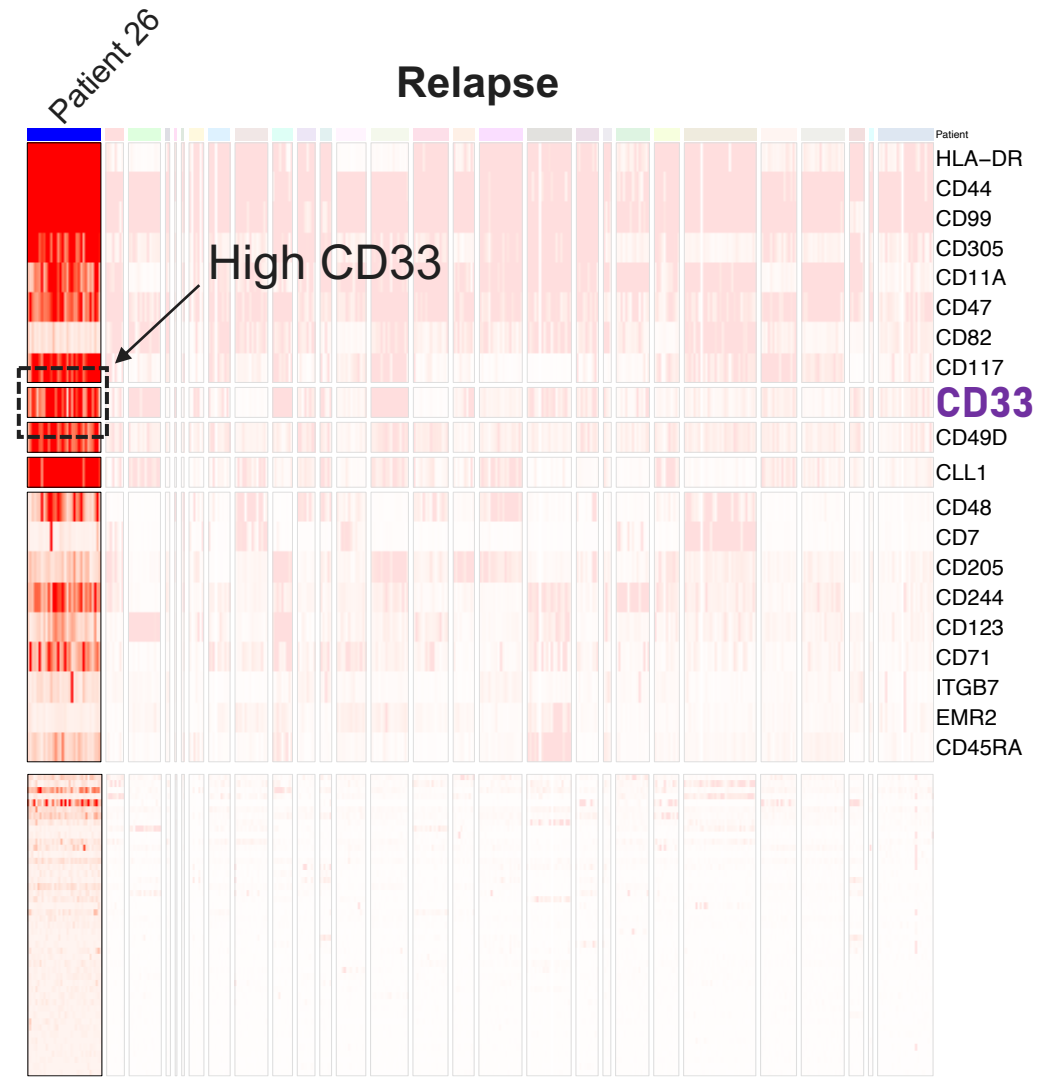
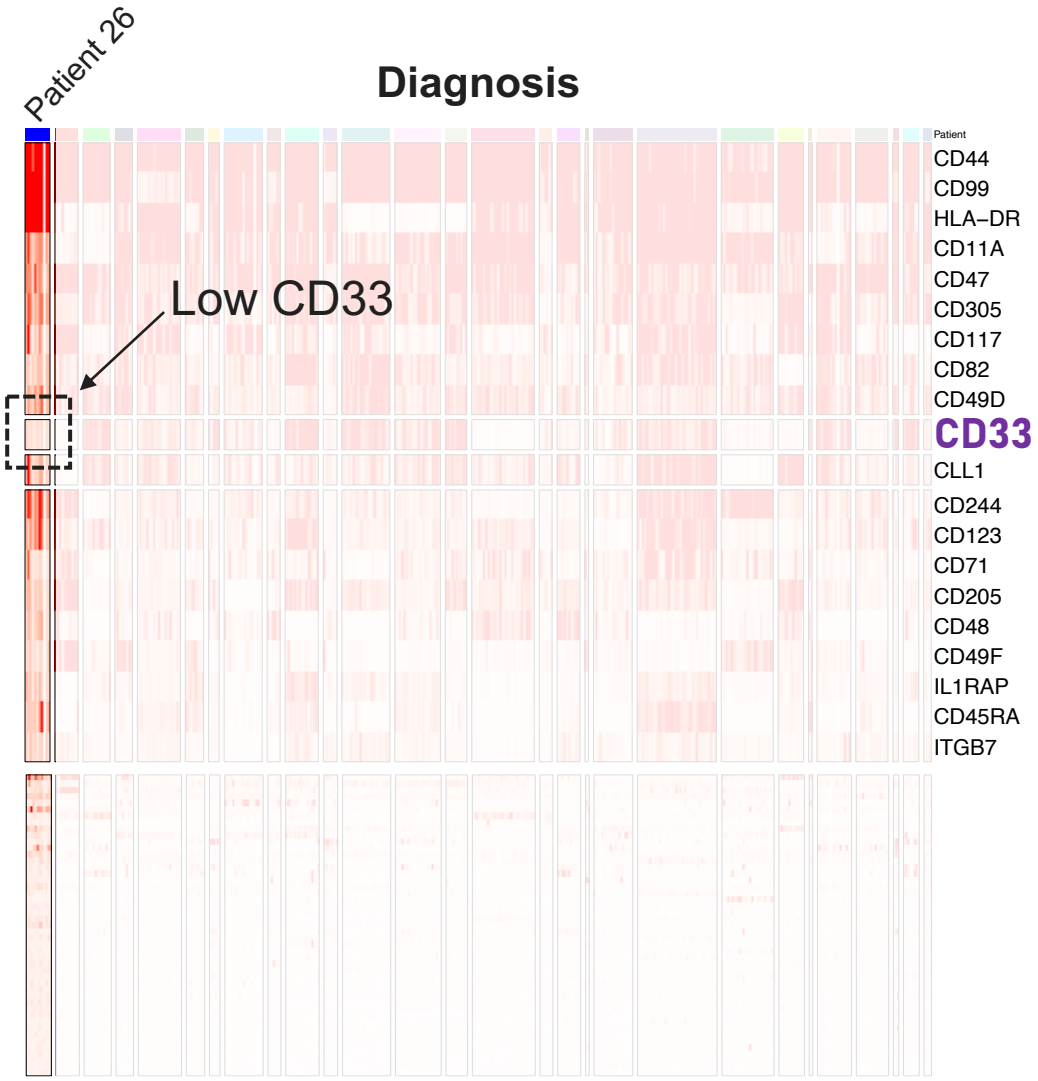
Patient 70

Multi-targeting strategies can enhance blast killing: Example from a single patient sample

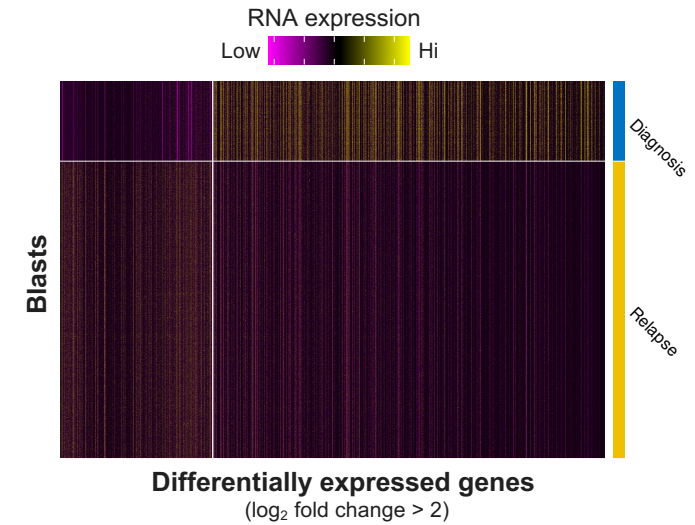
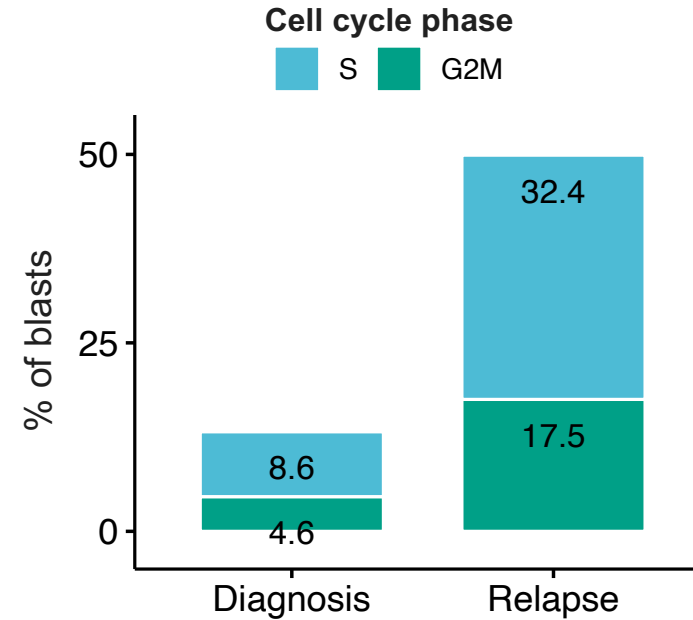
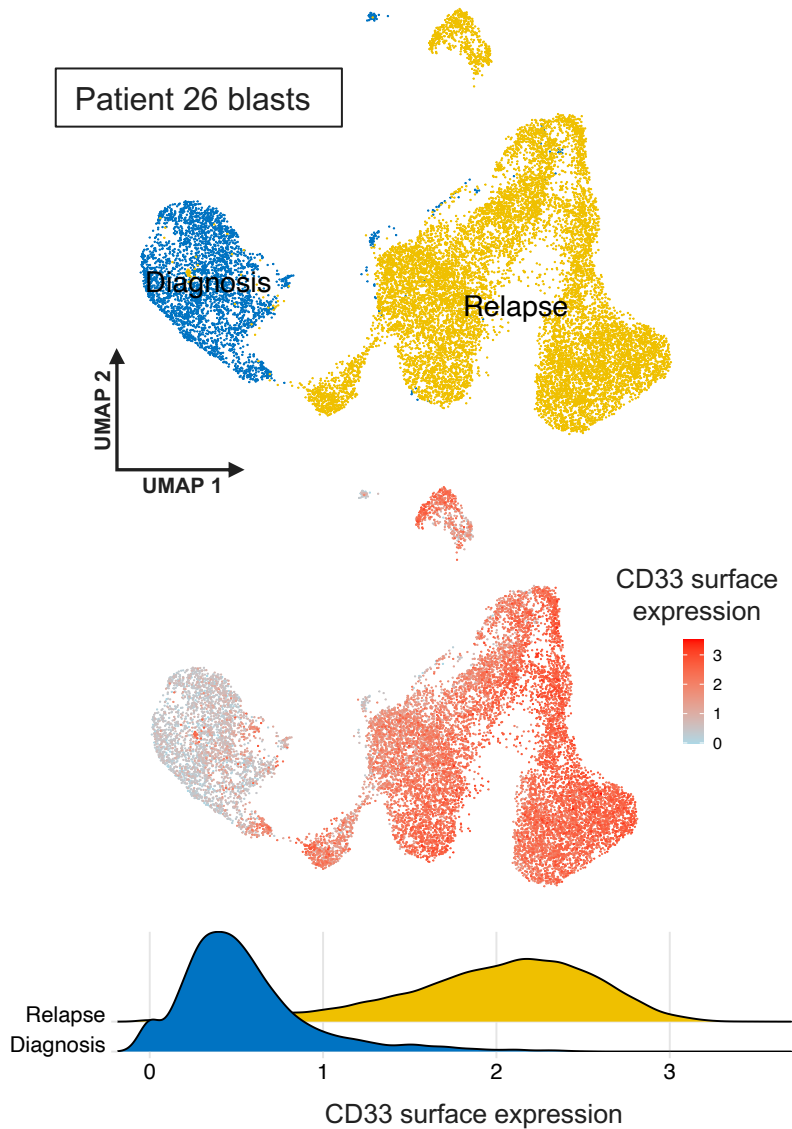


CD33 expression is higher in relapse blasts: Example from another patient

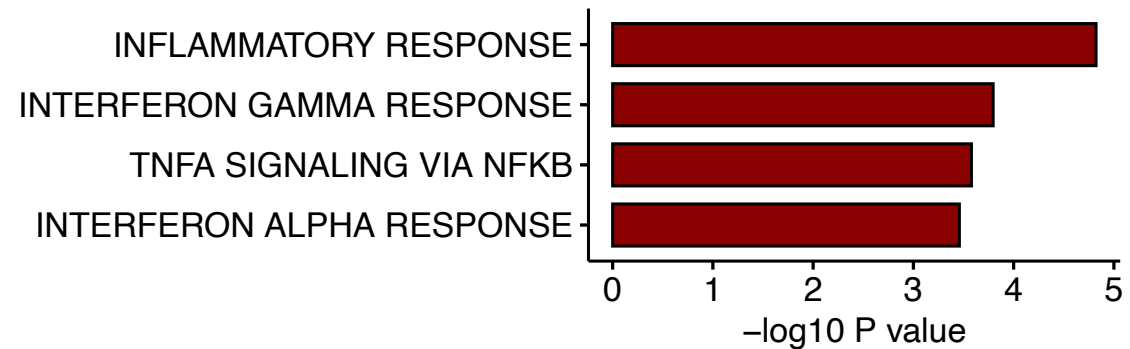
Mean antigen expression



CD33 upregulation on cell surface is associated with proliferation and downregulation of cell-intrinsic inflammation in the patient



Downregulated Hallmark pathways in relapse S/G2M blasts (FDR < 0.01)



Summary

- ✓ Vor's AML atlas enables extensive characterization of inter- and intra-patient blast heterogeneity
- ✓ CD33 and CLL-1 are among the highest expressed antigens across entire cohort
- ✓ Transcriptomic information identified downregulation of inflammatory pathways in CD33-high relapse blasts from a single patient
- ✓ Analysis of surface antigen density supports multi-targeting strategies that enhance blast destruction and guard against antigen escape

Acknowledgement

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The patients and their families and caregivers

