Single-cell multi-omics for simultaneous detection of SNVs, CNVs and proteins using the Tapestri Platform

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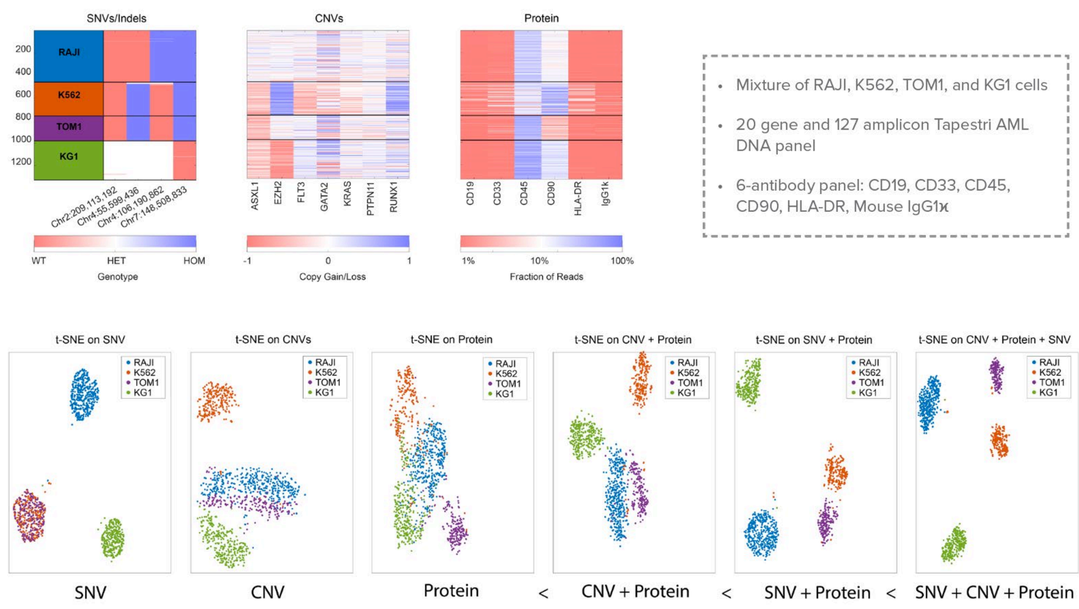
Abstract

Genomics data alone provides only partial insights into the cell's type, state or function. To obtain a more complete picture and reveal the cell's phenotypic character, a multi-omics approach is needed that expands beyond DNA profiling. Here, we demonstrate for the first time, that the Tapestri Platform enables the detection of genomic variants and protein expression simultaneously from the same cell. Genomic variations such as single nucleotide variants (SNVs) and copy number variations (CNVs) are now co-detected with proteins. This novel capability has the power to reveal rare cell populations, subtle cell states, and link genomic variation to protein expression leading to more informed research on disease and therapeutic development.

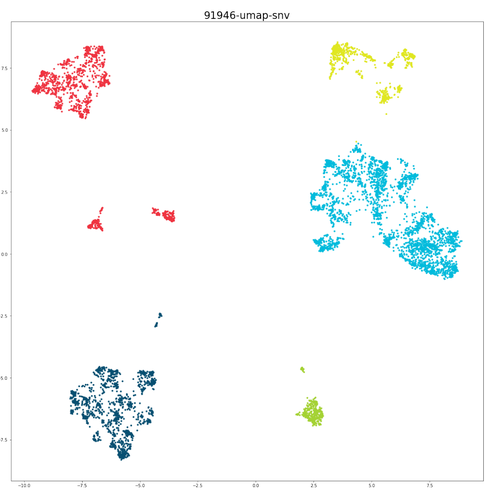
4-Cell Line Mix Using the Tapestri Single-Cell DNA AML Panel and 6 Protein Panel

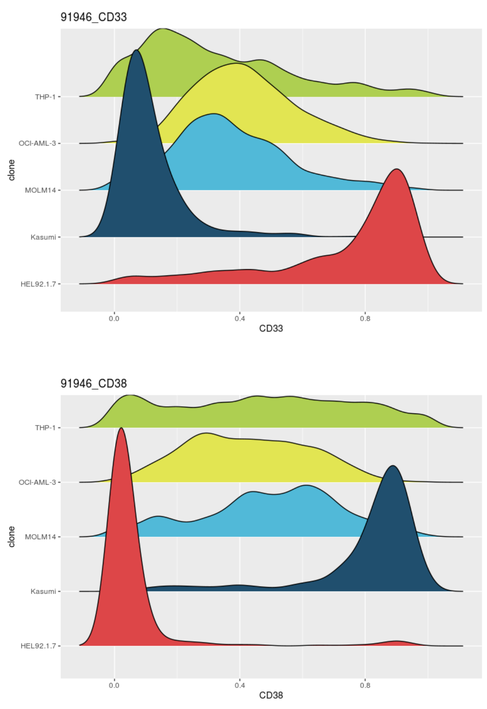


- Mixture of RAJI, K562, TOM1, and KG1 cells
- 20 gene and 127 amplicon Tapestri AML DNA panel
- 6-antibody panel: CD19, CD33, CD45, CD90, HLA-DR, Mouse IgG1κ

Raji, K562, TOM1 and KG1 cells were mixed together at equal ratios and analyzed for SNVs, indels, CNVs and proteins using the Tapestri Platform. Combined SNV, CNV and protein data led to the most distinct resolution of the 4 cell line populations on the t-SNE. This result illustrates the power of using more data from the same cells with a multi-omics approach to gain the greatest resolution between cell types.

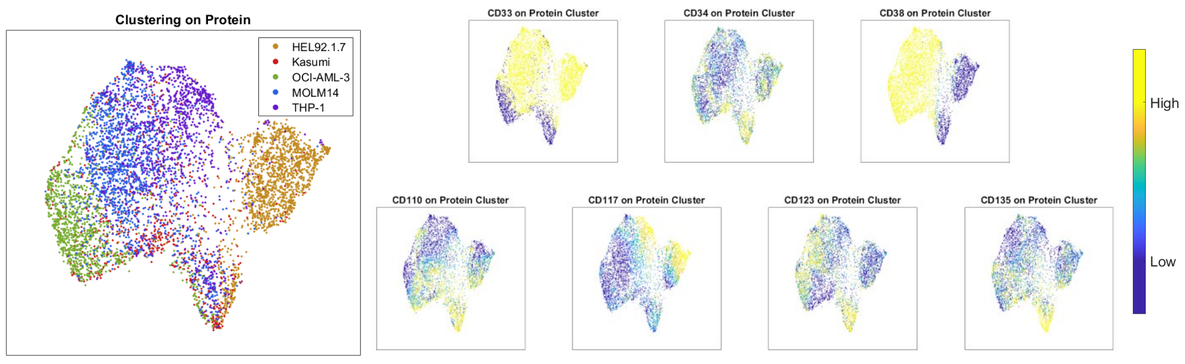
5-Cell Line Mix Using the Tapestri Single-Cell DNA AML Panel a 7 Protein Panel





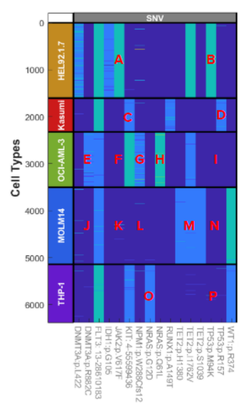
Cell Line	MOLM14	OCI-AML-3	HEL92.1.7	Kasumi	THP-1
CD33	YES	YES	YES	NO	YES
CD38	YES	YES	NO	YES	YES

MOLM14, OCI-AML-3, HEL92.1.7, Kasumi and THP-1 cells were mixed together and projected onto a t-SNE based on their SNV data (left). Protein expression of the two top markers, CD33 and CD38 agreed with known truth for these cell lines and showed broad or bimodal distributions of expression at the single-cell level.

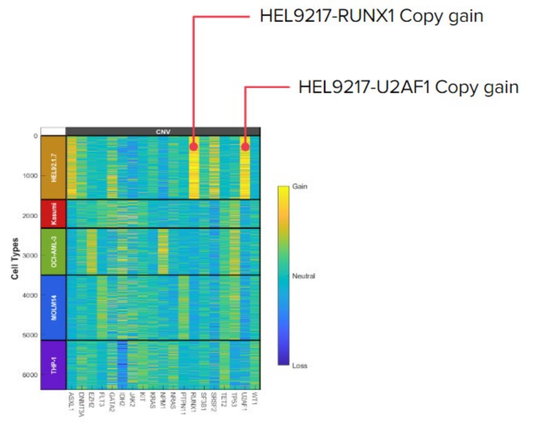


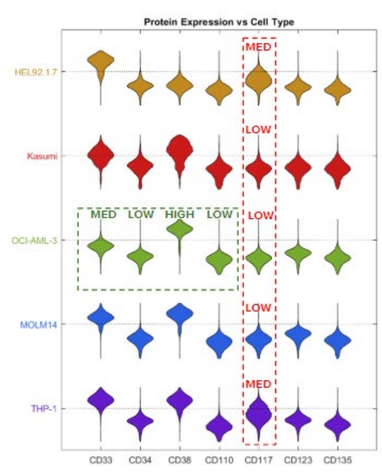
Cells were plotted onto a UMAP projection based on their protein expression data and colored in by their known SNVs (left). Expression of each protein correlates with specific cell lines.

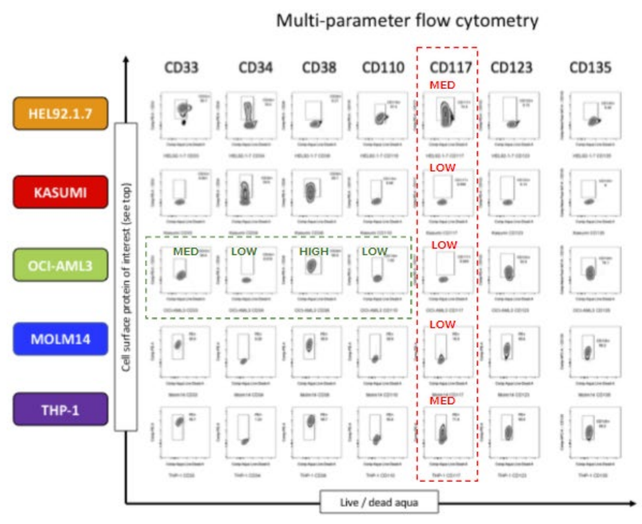
Correlation of SNV, CNV and Protein Data with Orthogonal Methods



	HEL92.1.7	Kasumi	OCI-AML-3	MOLM14	THP-1
DNMT3A R882C			YES[E]	NO[J]	
JAK2 V617F	YES[A]		NO[F]	NO[K]	
KIT N882K		YES[C]			
NPM1 W288C			YES[G]	NO[L]	
NRAS G12D					YES[O]
NRAS Q61L			YES[H]		
TET2				YES[M]	
TP53	YES[B]	YES[D]	NO[I]	NO[N]	YES[P]







In the 5-cell line mix, SNVs agreed with bulk sequencing data (top). CNVs were confirmed to data from the Cancer Cell Line Encyclopedia (middle). Protein expression matched with FACS data (bottom).

Correlations Between Genomic Variants and Protein Expression in AML Patient Samples

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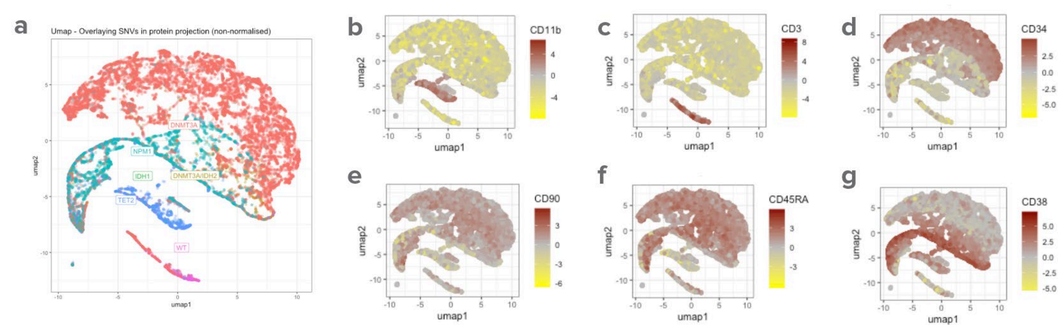
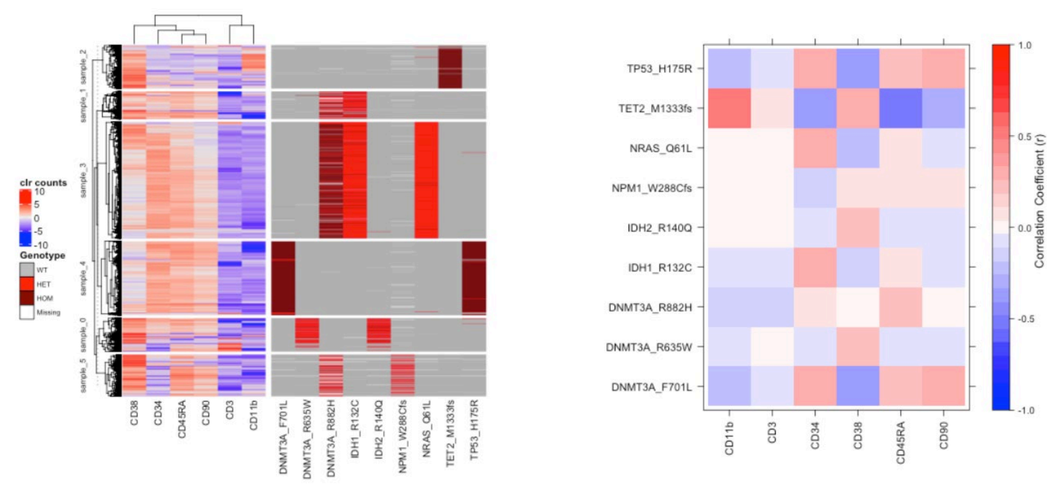


The six protein markers used in this study helped define the phenotypic state of myeloid cells that cause AML, such as stem and progenitor cells versus wildtype T-cells. UMAP projection showed CD3+ T-cells associated with cells that had a wildtype genotype, while the CD34+ and CD38+ stem cells contained cells with mutations. These data show exciting genotype and phenotype information for over 20,000 single cells.



Heat maps (left) showing unsupervised clustering of patient samples based on cell surface proteins and SNVs. We verify the expected correlation between NPM1 W288Cfs mutational status and low CD34 expression. Heat map (right) of correlated expression of cell surface proteins to SNVs, indicating strong correlations between variants and protein levels.

Conclusions

The Tapestri Platform now has new multi-omic capabilities. Using a simple cell staining technique with the standard Tapestri protocol, subtle cell states are determined and genomic variants correlated with protein expression. We present the first commercially available platform that detects proteins, SNVs/indels, and CNVs from the same single cells to unravel genotype to phenotype relationships.