20TH INTERNATIONAL MYELOMA SOCIETY ANNUAL MEETING AND EXPOSITION

P-369: Single-Cell Multi-Omic Correlation of Single Nucleotide Variants, Copy Number Variation, and Surface Epitopes for Clonal Profiling of Myeloma

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Abstract

Using cryopreserved, human multiple myeloma (MM) patient samples processed on the Mission Bio Tapestri single-cell platform, subclones were simultaneously analyzed for single nucleotide variants (SNV), copy number variants (CNV), and surface protein expression. We show here complex clonal evolution of MM in two patient samples as copy gains and losses were sequentially acquired and correlated with expression changes of MM immunophenotypic markers.

This high-resolution, single cell assay offers a potential new modality for the diagnosis and surveillance of patients with suspected MGUS, SGUS or high-risk MM. We have demonstrated: 1) exceptional results from cryopreserved human specimens, 2) the ability to use genetic lesion profiling to positively identify subclonal MM and, most importantly, 3) correlate cell surface protein expression of potential therapeutic targets with each clonal population.

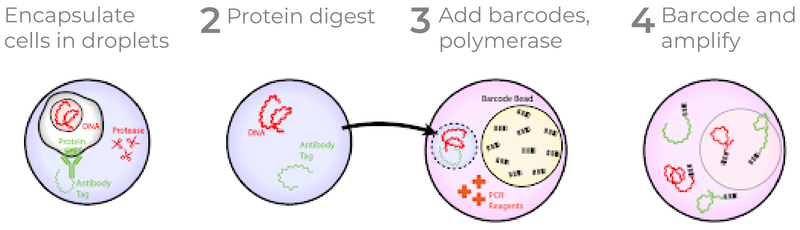
Methods

Samples: Two MM patients, frozen bone marrow, single-time point, CD138+, each mixed with a Raji cell line (Burkitt Lymphoma) control.

Panels: 733-plex DNA primers for genome-wide CNV & MM hotspots. 45-plex antibody panel labeling heme-specific surface markers.

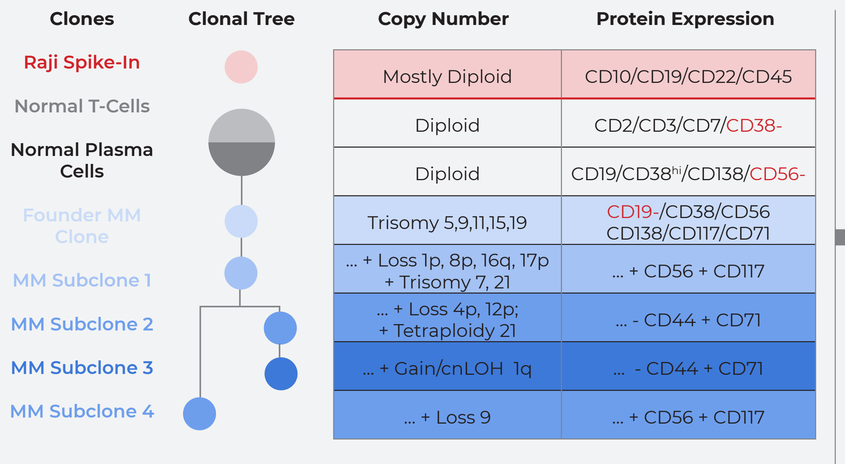
Study: Tapestri DNA+Protein single-cell workflow (below) x two runs.

Kit, instrument, and analysis solutions.



Patient 1 Clonal Architecture

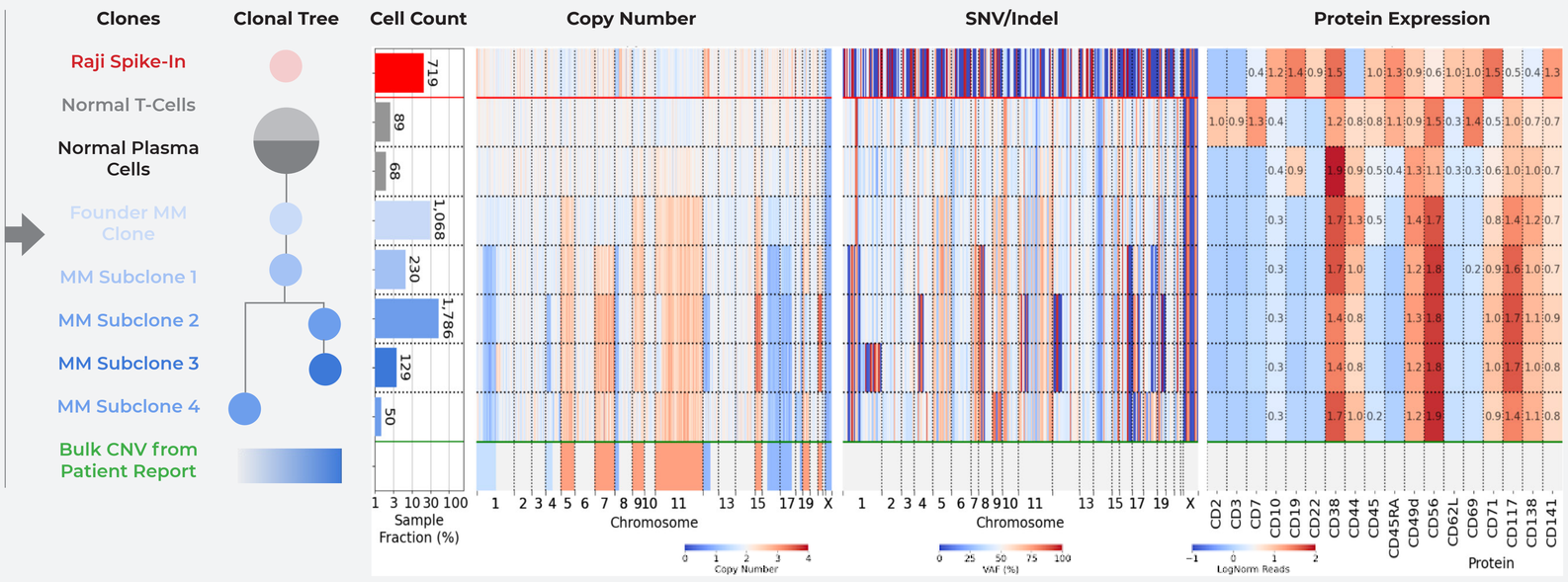
Clonal analysis of MM patient 1 sample from one single-cell Tapestri run. Shown is the sequential/branched acquisition of copy changes (table, left), from healthy t-cell/plasma cells to highly mutated MM cells (top/gray to bottom/dark blue). Also shown is the cell line control (red). The platform correlated copy number with multiple protein markers that tracked with MM progression (table, right).



Copy Number	Protein Expression
Mostly Diploid	CD10/CD19/CD22/CD45
Diploid	CD2/CD3/CD7/CD38-
Diploid	CD19/CD38^{hi}/CD138/CD56-
Trisomy 5,9,11,15,19	CD19-/CD38/CD56 CD138/CD117/CD71
… + Loss 1p, 8p, 16q, 17p + Trisomy 7, 21	… + CD56 + CD117
… + Loss 4p, 12p; + Tetraploidy 21	… - CD44 + CD71
… + Gain/cnLOH 1q	… - CD44 + CD71
… + Loss 9	… + CD56 + CD117

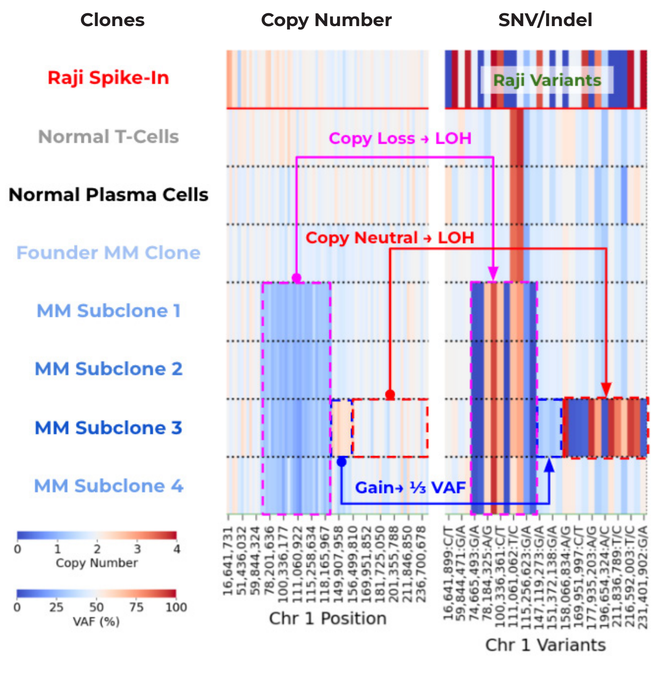
Patient 1 Clonal Details

Analyte heatmaps used for the previous summary figure. Each row represents one patient clone (plus rows for control and bulk) averaged across single-cells for four analytes (cell count, copy number, SNV/Indel, protein expression). Disease progression of MM is visualized by the loss/gain of chromosomal copies (left), corresponding loss/gain of heterozygosity (middle), and expression changes of typical myeloid markers (right). Normal cells (T-cells/plasma cells) in the sample show a CNV/SNV profile with fewer features.



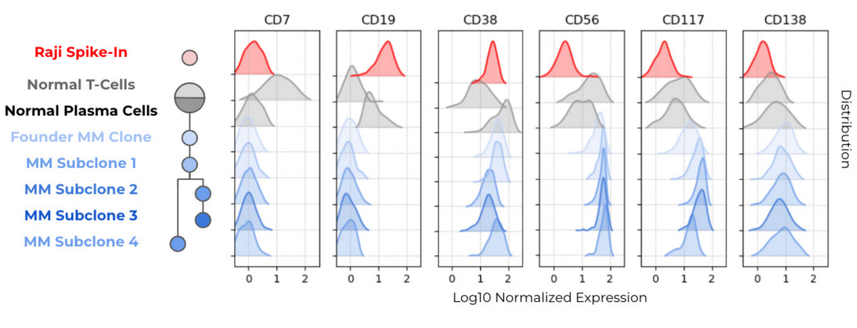
CNV-SNV Correlation in Patient 1

Heatmap close-up of Chr 1 showing CNV-SNV correlation: copy loss matches loss of heterozygosity (LOH), and copy gain sees atypical variant allele frequency (VAF). Also seen is copy-neutral LOH.



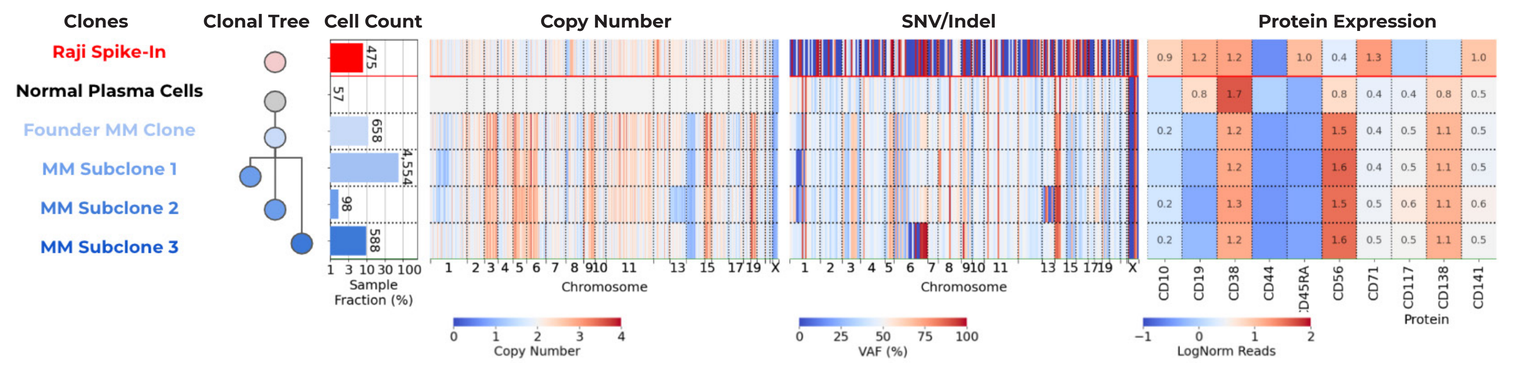
Patient 1 Protein Distributions

Single-cell expression by clone/ marker. Low noise expression data reveal patient's MM progression has higher CD117, lower CD38, and equivalent CD56 for the right clonal branch. Normal plasma cells show CD19+ and CD38hi, low CD56.



Patient 2 Clonal Details

Multi-analyte heatmaps from a different patient, showing a three-way branching architecture by CNV/SNV from the founding MM clone. Normal plasma cells were detected but no T-cells. Unlike the previous patient, myeloid markers were very consistent across MM subclones.



Conclusions

- Study demonstrates high MM clonal resolution, detailed by CNV, SNV, and protein.
- Next: process more samples and timepoints, as well as add therapeutic MM targets (e.g. BCMA, GPRC5D) and associated resistance mutations.

Mission Bio Tapestri References

- Miles, LA, et al. "Single cell mutation profiling delineates clonal trajectories in myeloid malignancies." Nature 587, 477 (2020).
- Ren, AA, et al. "PIK3CA and CCM mutations fuel cavernomas through a cancer-like mechanism." Nature 594, 271 (2021)
- Zhao, Y, et al. "Diverse alterations associated with resistance to KRAS(G12C) inhibition." Nature 599, 679 (2021).

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