Single-cell Multiomic Clonal Tracking in Myeloma Identifies SMM Clones that Progress to MM and Low-Frequency MM Clones with Resistance Features Enabling More Precise Application of Targeted Therapies

Poster #: 3227

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Introduction

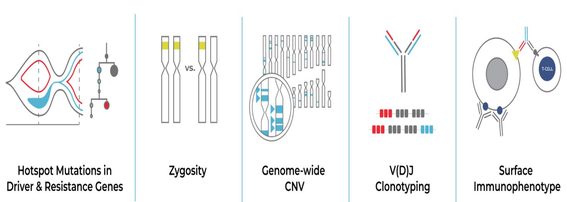
Multiple myeloma (MM) is a cancer of plasma cells with approximately 200,000 new cases/year and a 54% 5-year overall survival rate. Myeloma arises from expansion of pre-existing clonal populations, referred to as either monoclonal gammopathy of uncertain significance (MGUS) or smoldering multiple myeloma (SMM), but only ~1% of individuals with these precursors will develop fulminant MM. As myeloma cells expand, clonal genetic differences lead to relapse due to acquired resistance in nearly 100% of patients, suggesting that initial therapy is inadequate to eradicate the entire disease burden and mandating regular, long-term surveillance. Being able to more comprehensively identify low frequency subclones that may result in frank disease or resistance would enable more direct application of precision therapies. Here, we present proof of concept single cell, multi-omic data identifying the clonal populations that progress to frank myeloma or resistant disease.

Aim

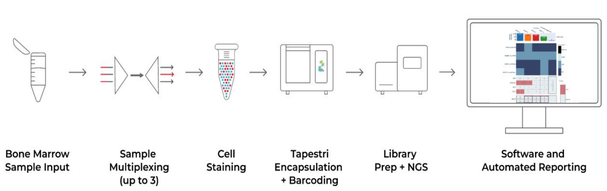
Applying single-cell proteogenomic clonal profiling of MGUS/SMM in matched diagnostic MM samples using Mission Bio's Tapestri platform and analysis tools.

Methods

- **Samples:** 16 matched MGUS/SMM samples with the same patients diagnostic MM sample
- **Assay:** The assay Integrates SNVs, CNVs, VDJ clonotypes and surface immunophenotype assessment in myeloma cells across thousands of individual cells



- **Workflow:** A simple workflow with minimal user touch points, integrating sample multiplexing to reduce cost and increase sample throughput.



Clonal Expansion from SMM to MM

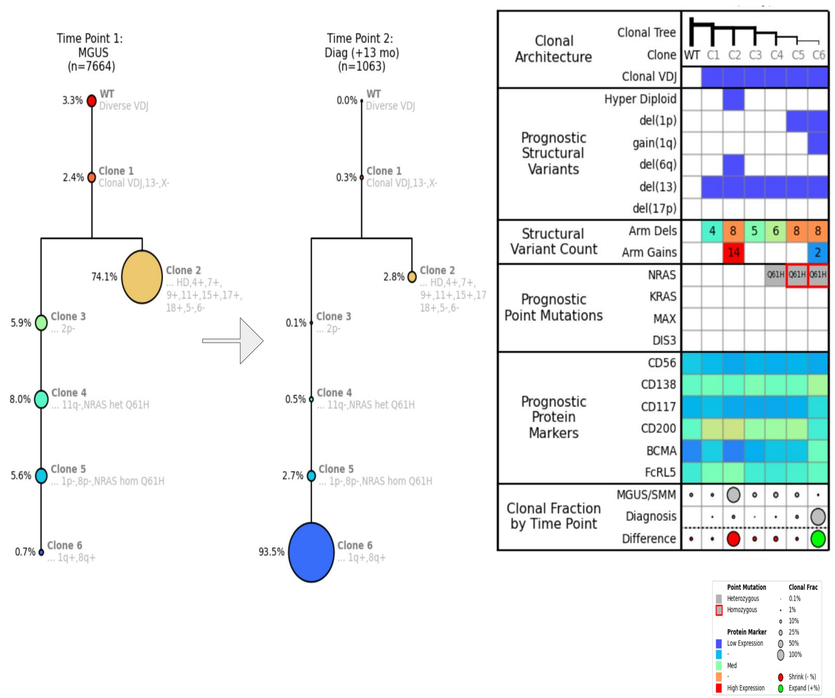


Fig 1: Phylogenetic trees from matched MGUS and diagnostic MM samples collected 13 months apart. In the MGUS sample, clone 2 dominated and clone 6 was only detected at 0.7%. At the time of diagnosis, clone 6 had expanded to 94%, potentially due to the combination of bi-allelic NRAS mutation, 1p loss, and 1q gain. Clones 4 and 5, which lack some of those mutations, are not as proliferative, and clone 2 had diminished to only 2.8%.

Table 1: The same patient as Fig 1. A detailed evaluation of disease evolution; clones from left to right, features/biomarkers top to bottom:

(1) architecture and clonotype,
(2) prognostic structural variants,
(3) arm-level CNV counts,
(4) prognostic mutations,
(5) prognostic protein expression
(6) clonal fraction/expansion.

Cohort Analysis

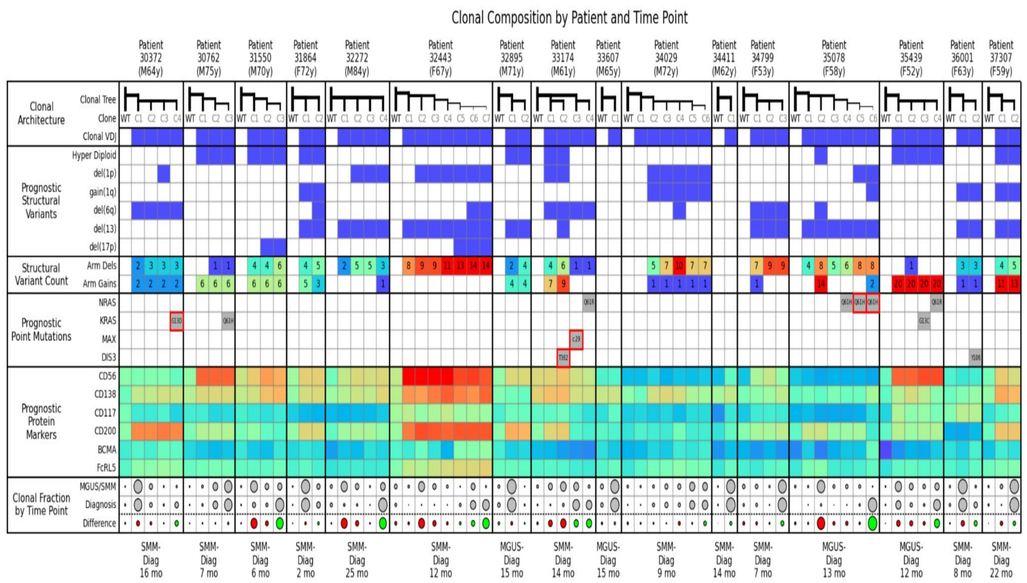


Table 2: 16 matched MGUS/SMM samples with the same patient's diagnostic MM sample

(1) In 8 of 16 (50%) cases, the dominant clone at the MGUS/SMM time point was not the dominant clone observed at diagnosis. In these cases, the average clone size at diagnosis was 11.1% (range: 0.7-28.5%).
(2) Bi-allelic RAS mutations were common in expanding clones, but typically coupled with CNVs
(3) Surface protein expression of immunophenotyping and therapeutic targets was variable across clones/subclones.

Takeaways:

(1) The oligoclonal variability of MGUS/SMM and fulminant MM lead to the high rate of relapse, treatment failure and mortality associated with the disease.
(2) Bulk genomic measurements lack the resolution to identify these clonal differences.
(3) More sensitive, single-target assays typically fail to provide therapeutic guidance.

Conclusions

- MGUS/SMM is an oligoclonal proliferation marked by dynamic genomic and proteomic variability that can best be quantitatively characterized using single cell proteogenomics, which **enables the simultaneous measurement of CDR3 clonotyping, CNVs, SNVs and surface protein expression.**
- In this cohort, Tapestri identified the MGUS/SMM clone that would expand to dominance at the time of MM diagnosis with an average lead time of **15 months prior to diagnosis**.
- In addition to identifying features associated with clonal expansion, Mission Bio's Single-Cell Myeloma Multiomics Solution includes putative therapeutic targets (e.g. BCMA, RAS, CD200), **which could be potentially used to guide treatment.**
- Clones with bi-allelic RAS loss would **not** be expected to respond to RAS inhibition therapy (Ref 1).

References

1. Schavgoulidze A et al.; **"RAS/RAF landscape in monoclonal plasma cell conditions."** *Blood* 2024, Apr 21:blood.2023022295. doi: 10.1182/blood.2023022295. PMID: 38643494.
2. Sciambi A et al.; **"Single cell correlation of SNVs, CNVs and surface epitopes for clonal profiling in myeloma."** International Myeloma Society 2023 Annual Meeting, Athens, Greece (abstract).

Acknowledgements

Thank you to Cedric Dos Santos of Genentech and Herve Avet-Loiseau of IUCT Oncopole for their generous support and guidance.

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