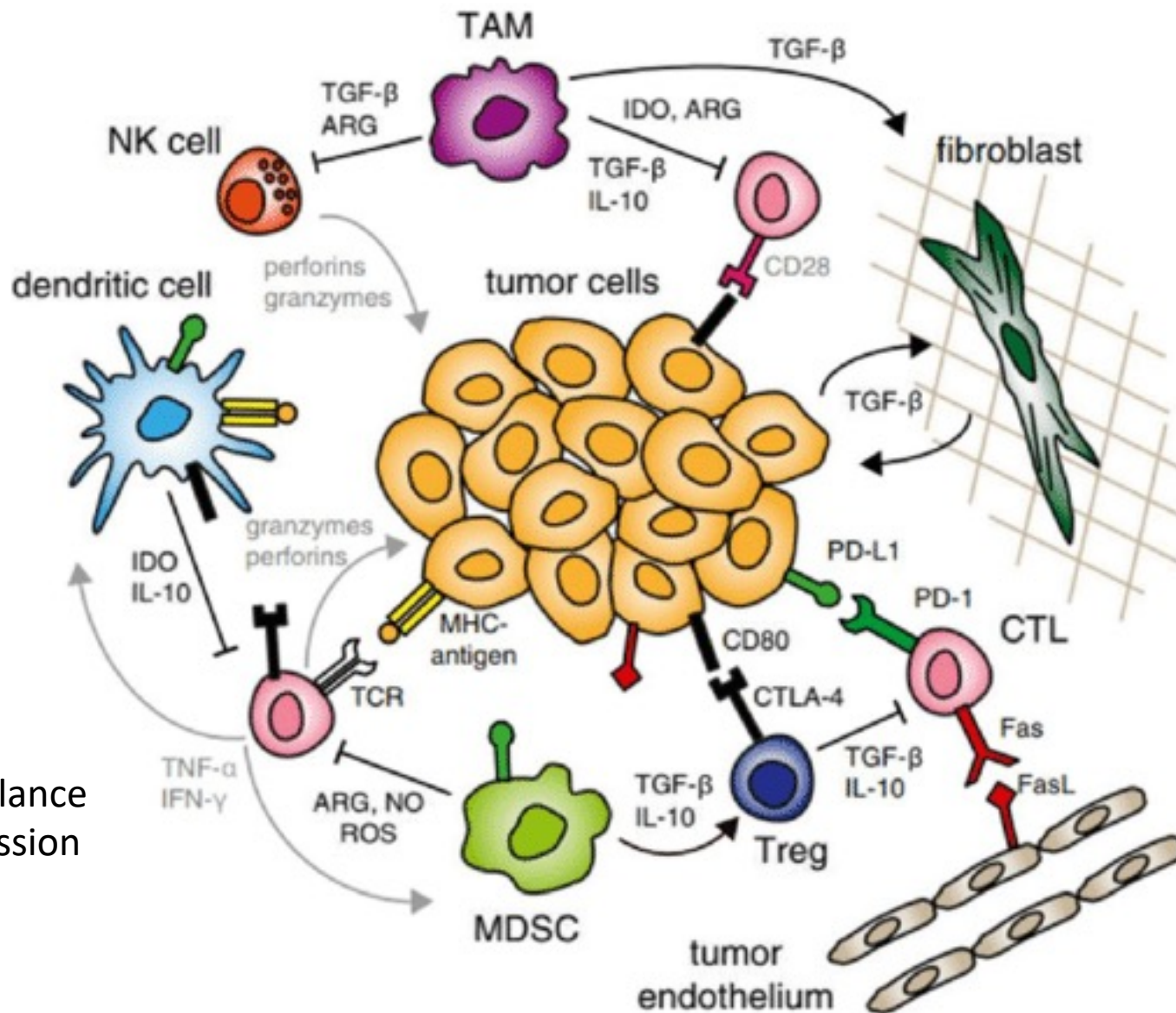


The Role of the Immune System in Multiple Myeloma

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Tampa General Hospital

Torino 2-3 March 2023



- I. Immune surveillance
- II. Immunosuppression
- III. T cell biology

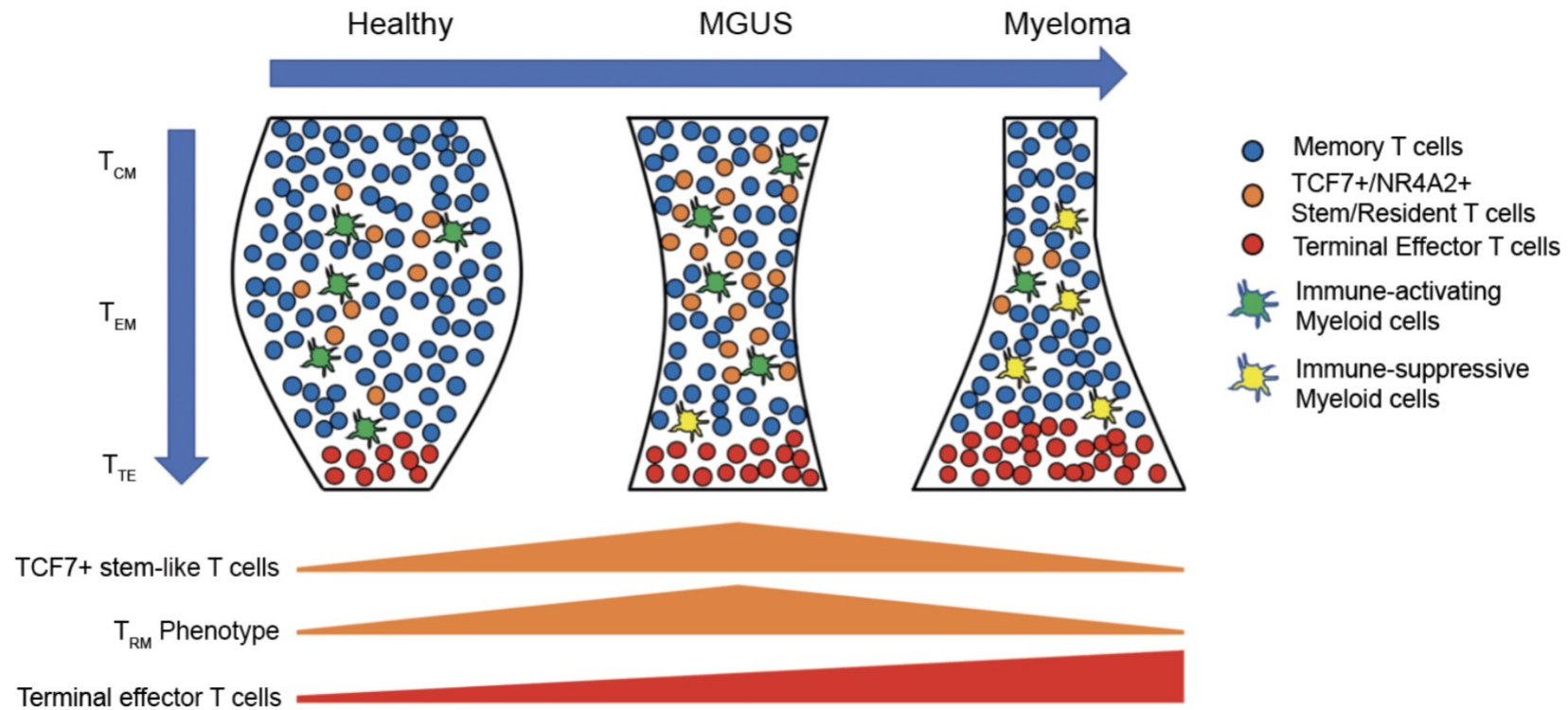
- Immunosurveillance
- Immunosuppression
- T cell biology: Implications for CAR-T and bispecific antibodies

Premise

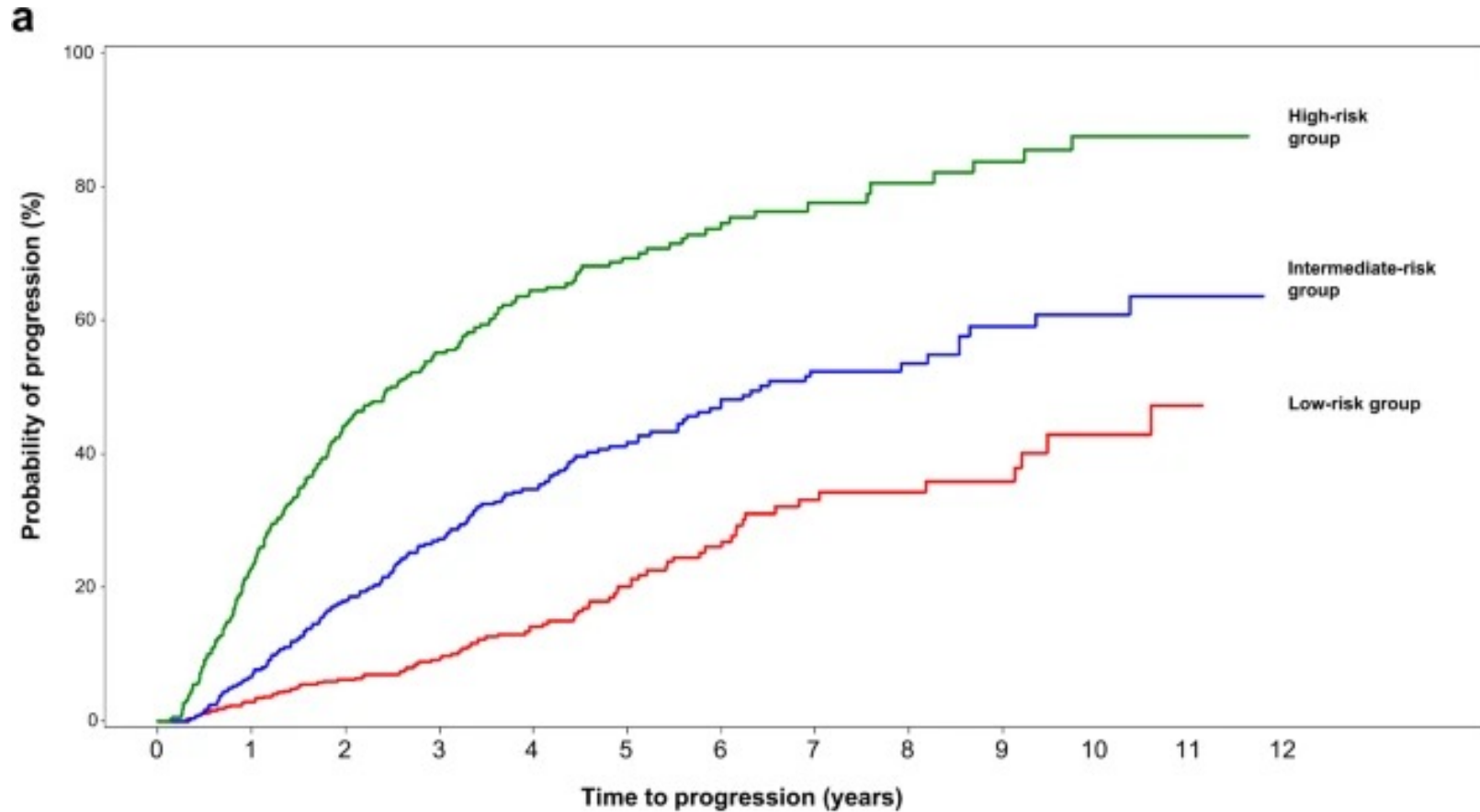
The immune state within the bone marrow microenvironment is a major determinant of the clinical outcomes in myeloma.

It can either promote or control disease

I. Immune surveillance

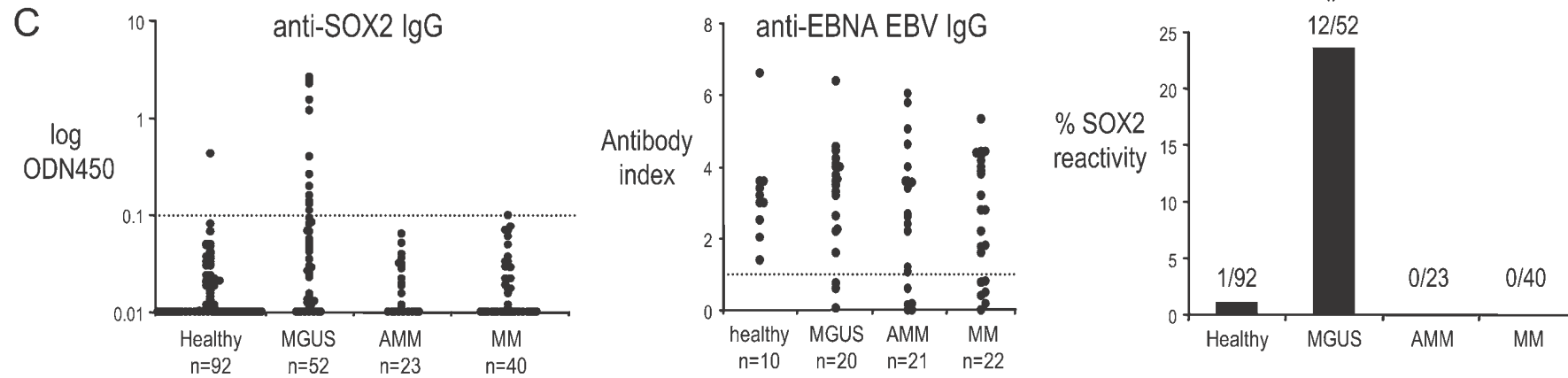


Smoldering Myeloma

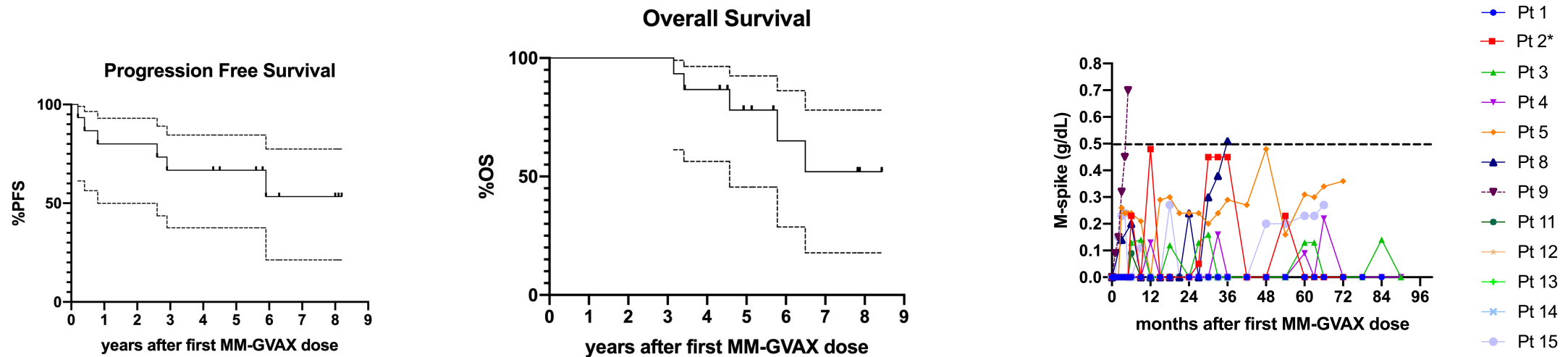


Risk Stratification groups	Number of risk factors	Hazard Ratio (95% CI)	Risk of progression (2 years)	# of patients
Low-Risk	0	Reference	6.2%	522 (38.3%)
Intermediate	1	2.99 (1.97 – 4.54)	17.9%	445 (32.7%)
High	2-3	9.02 (6.15 – 13.2)	44.2%	396 (29.1%)

SOX-2 Immunity Maintains Stable Disease

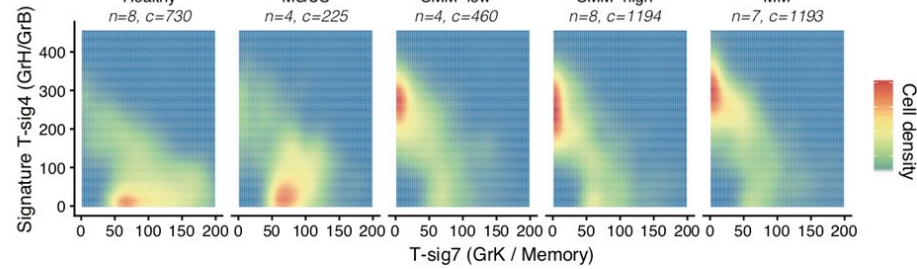
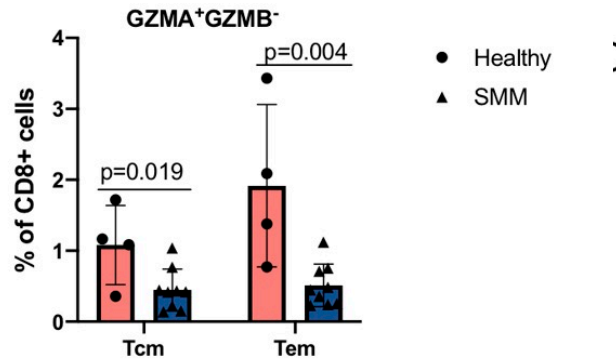


Active immunity can prevent disease progression through immune surveillance

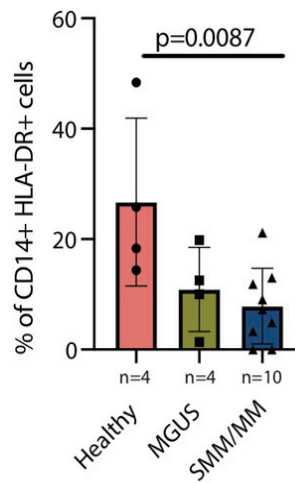


II. Immunosuppression with Myeloma Progression

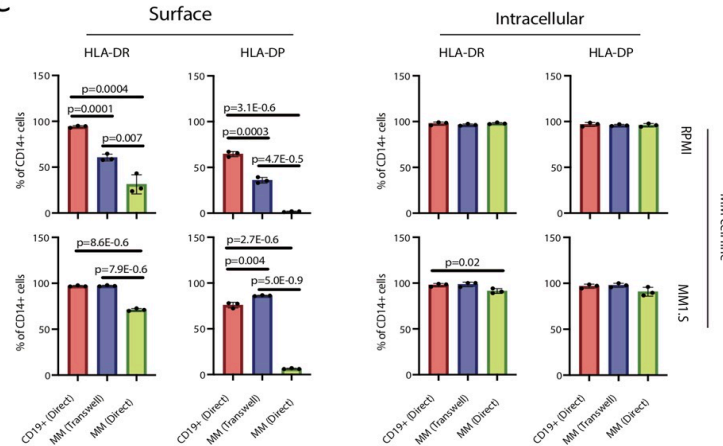
T cells



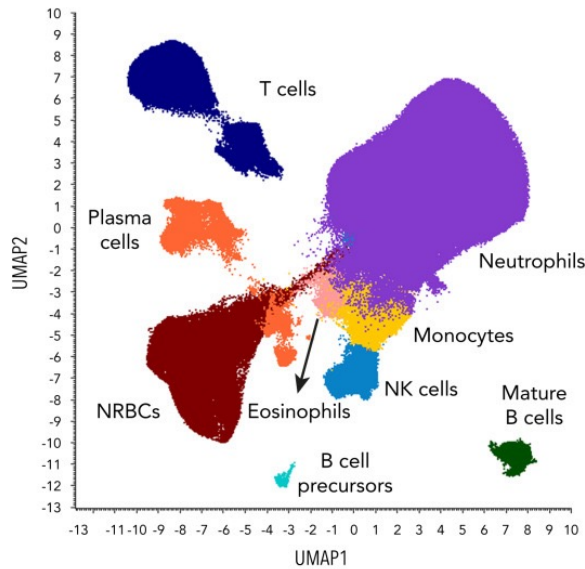
CD14 cells



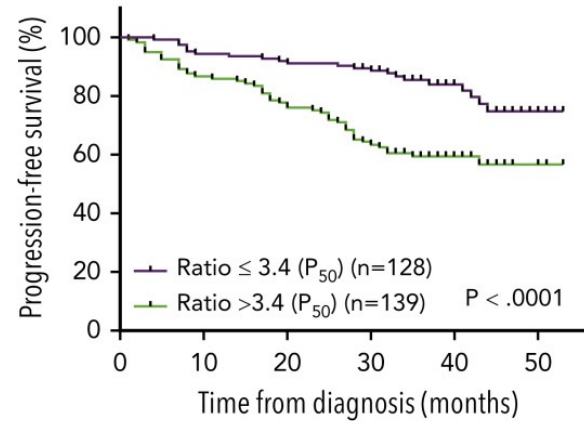
C



G-MDSCs Contribute to Disease Progression



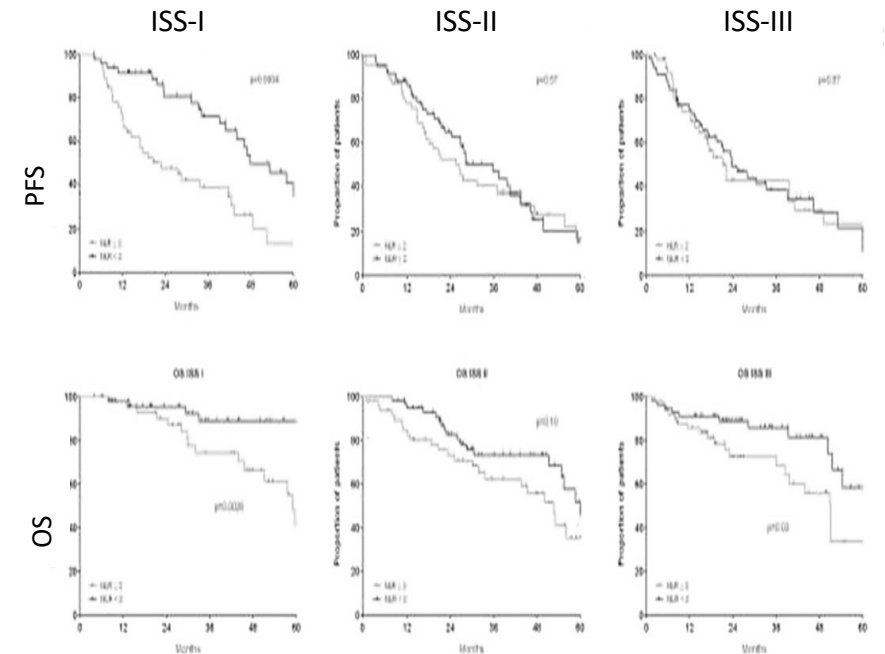
CD11b+, CD13+, CD16+



Number of subjects at risk:

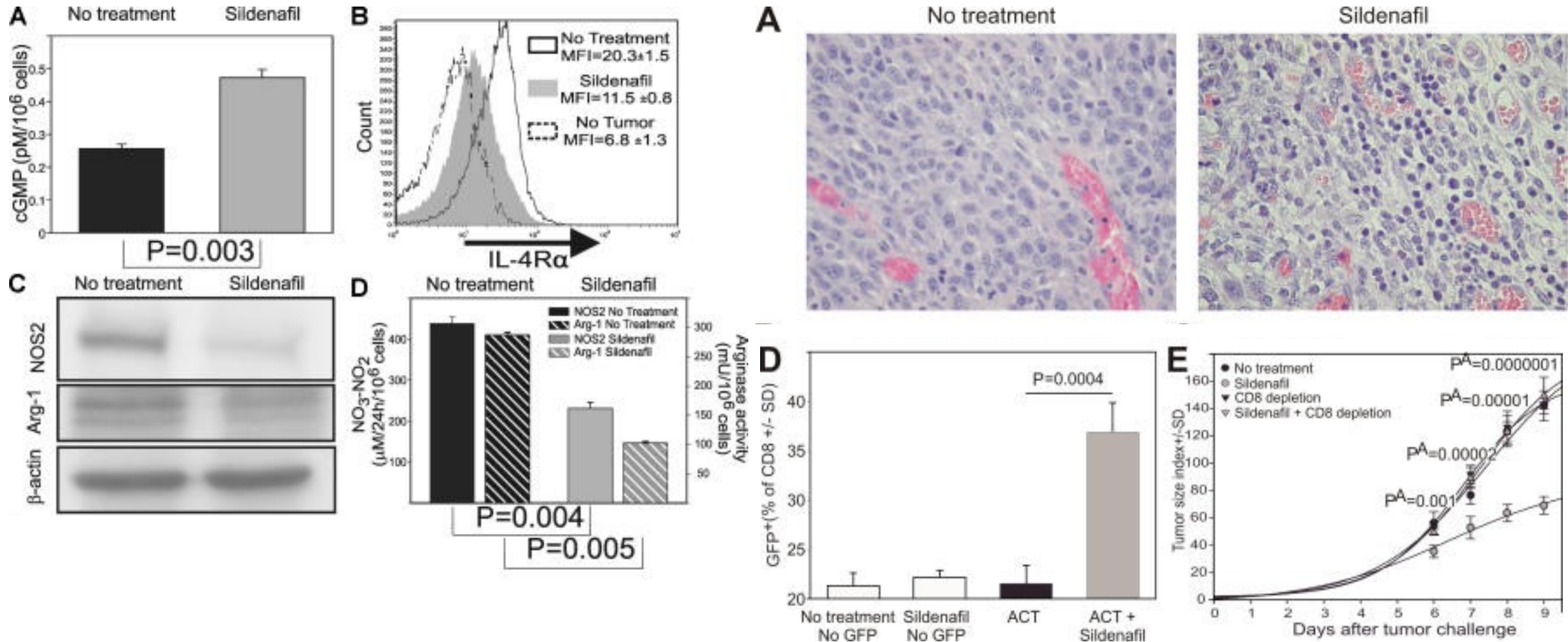
Group ≤ 3.4	134	127	122	117	47	7
Group > 3.4	133	115	102	76	33	5

Clinical Relevance of NLR

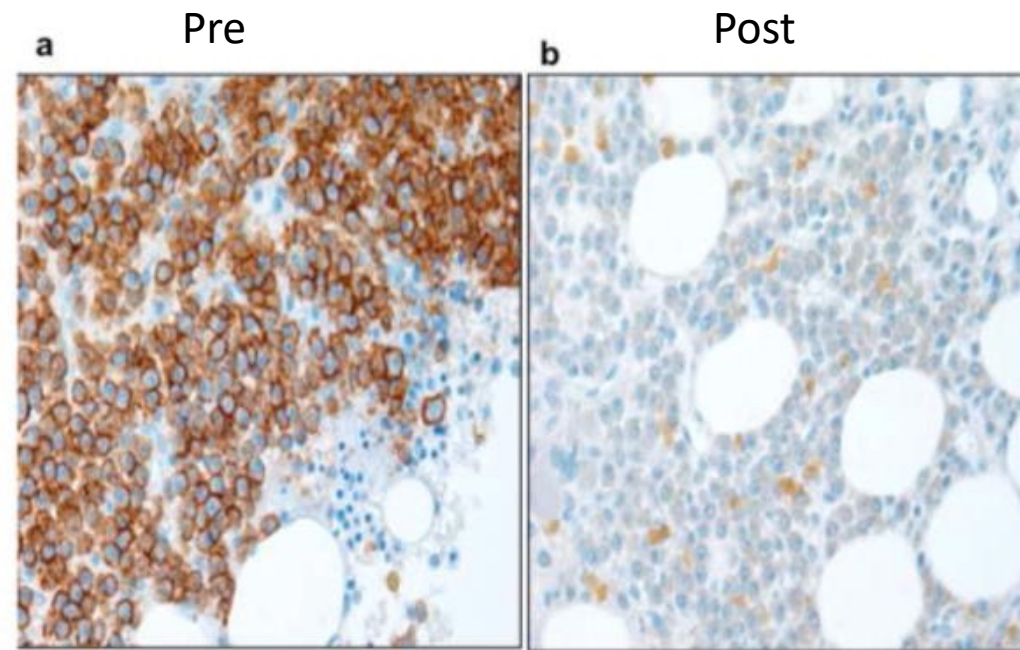
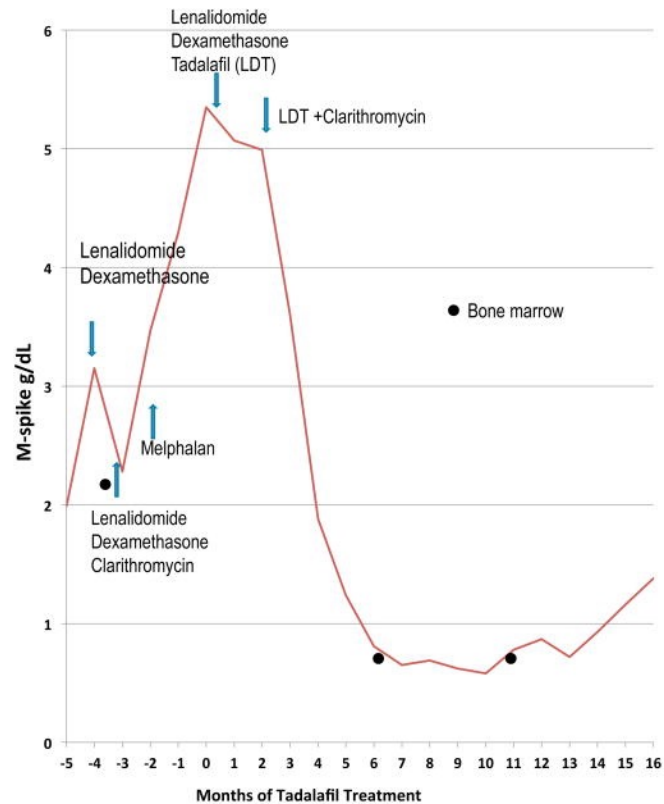


Ratio > 2

PDE-5 inhibition abrogates MDSC function

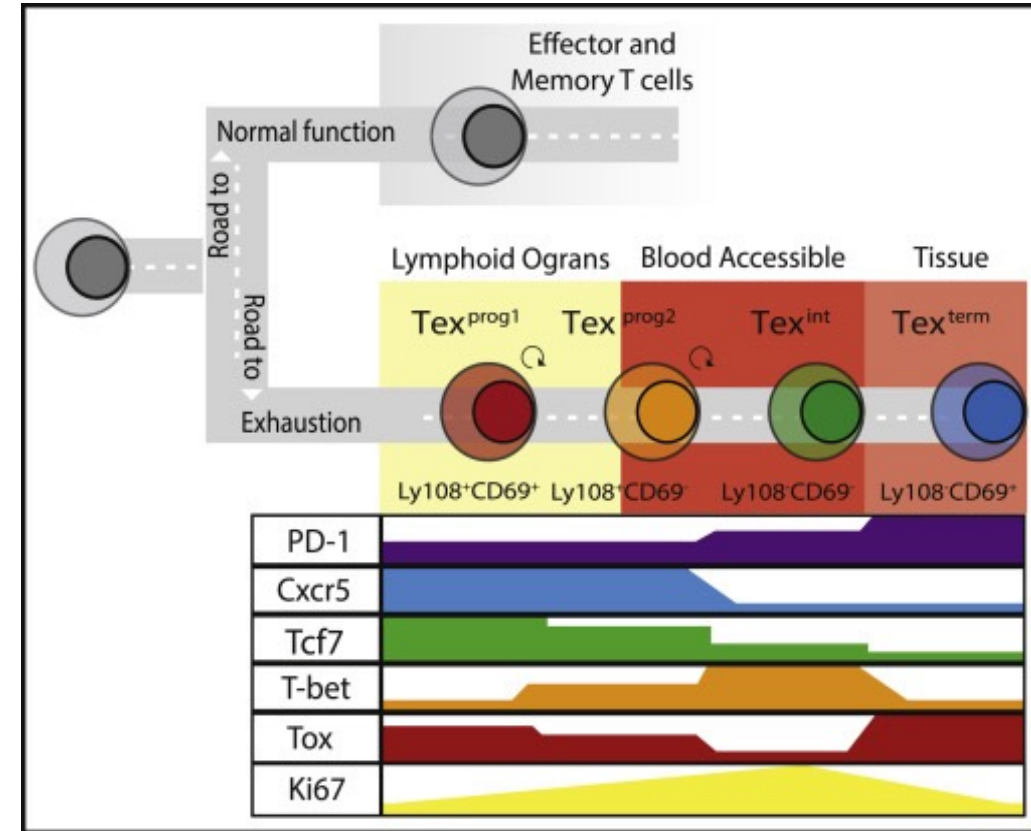
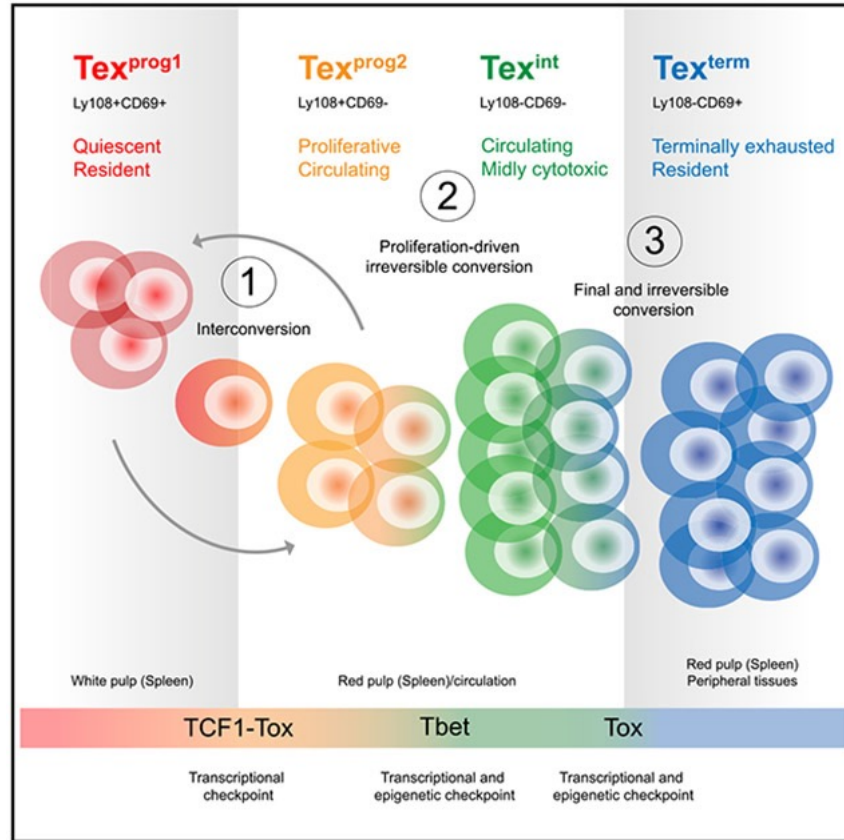


Tadalafil restores chemosensitivity in end-stage myeloma

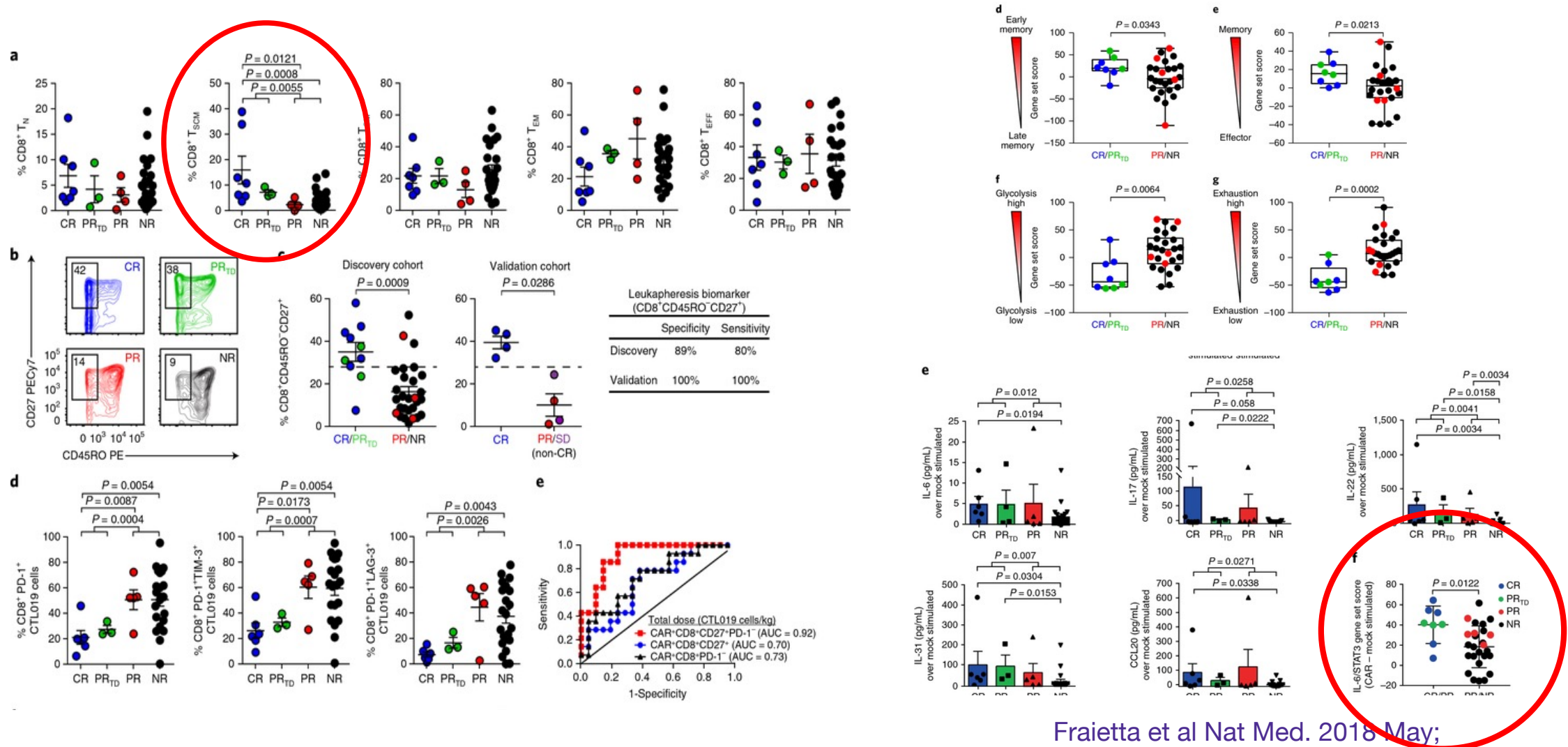


Nitrosylation

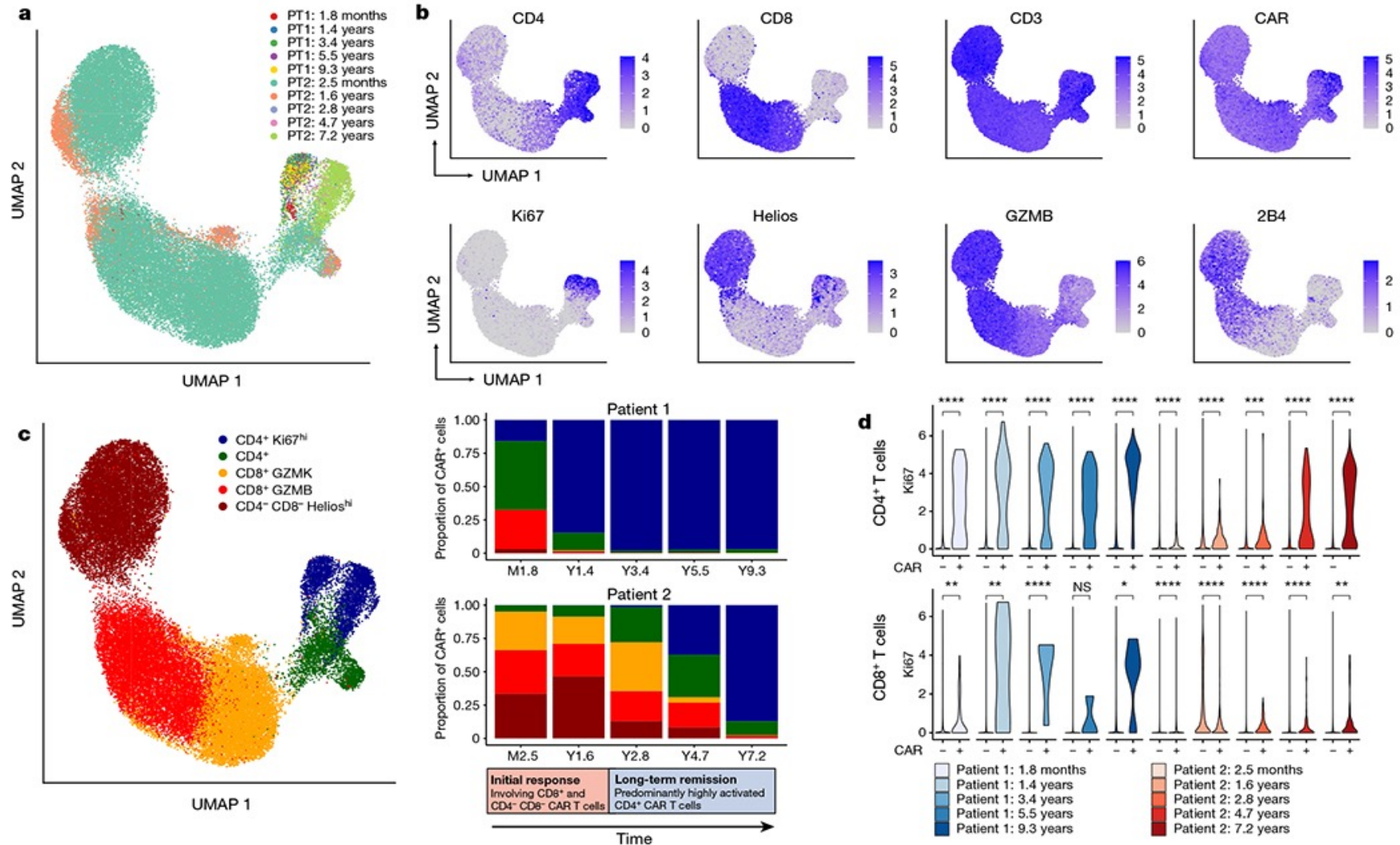
III. T cell exhaustion and adoptive cell therapy



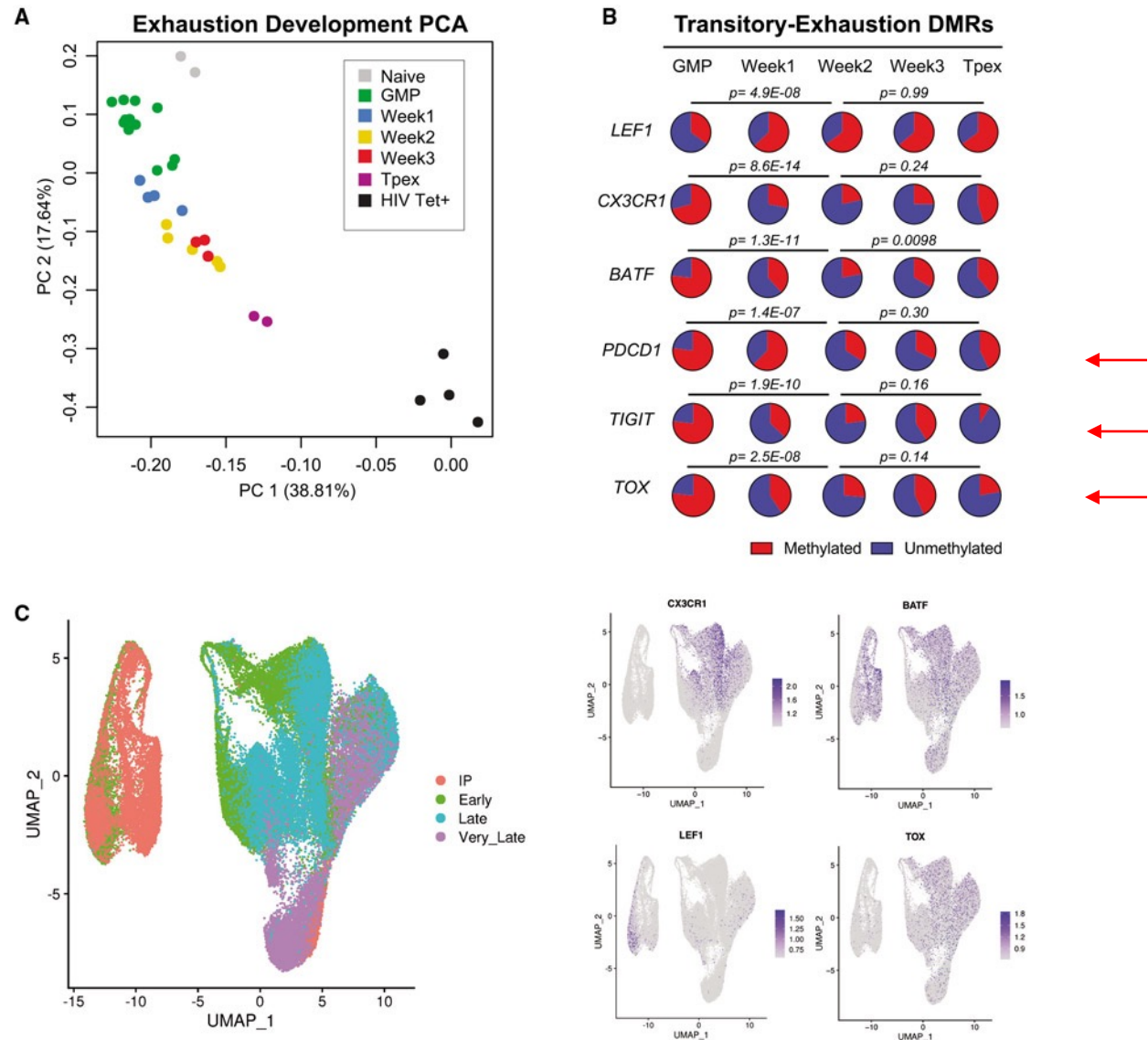
Baseline Predictors of CAR-T Responses



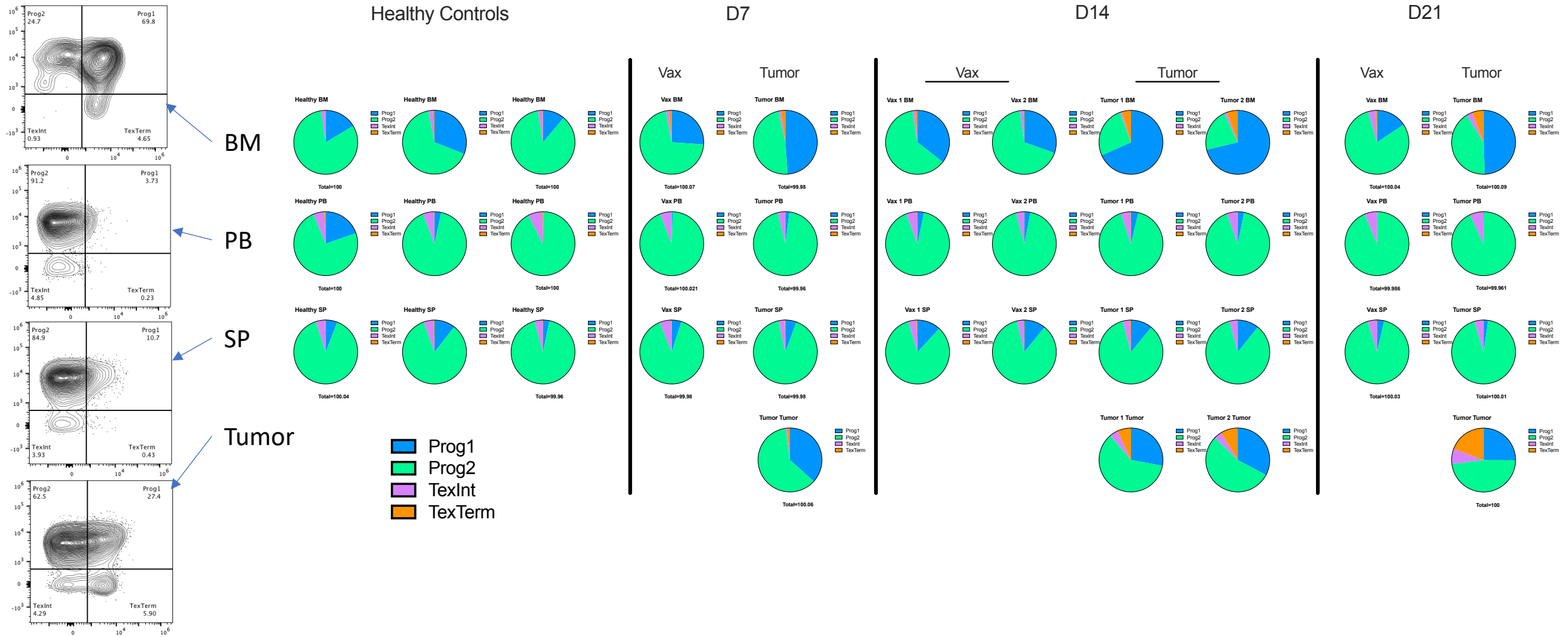
Long-term Persistence of CD4+ CAR-T



CD8⁺ CD19-CAR T cells transition into an exhaustion developmental path post-infusion

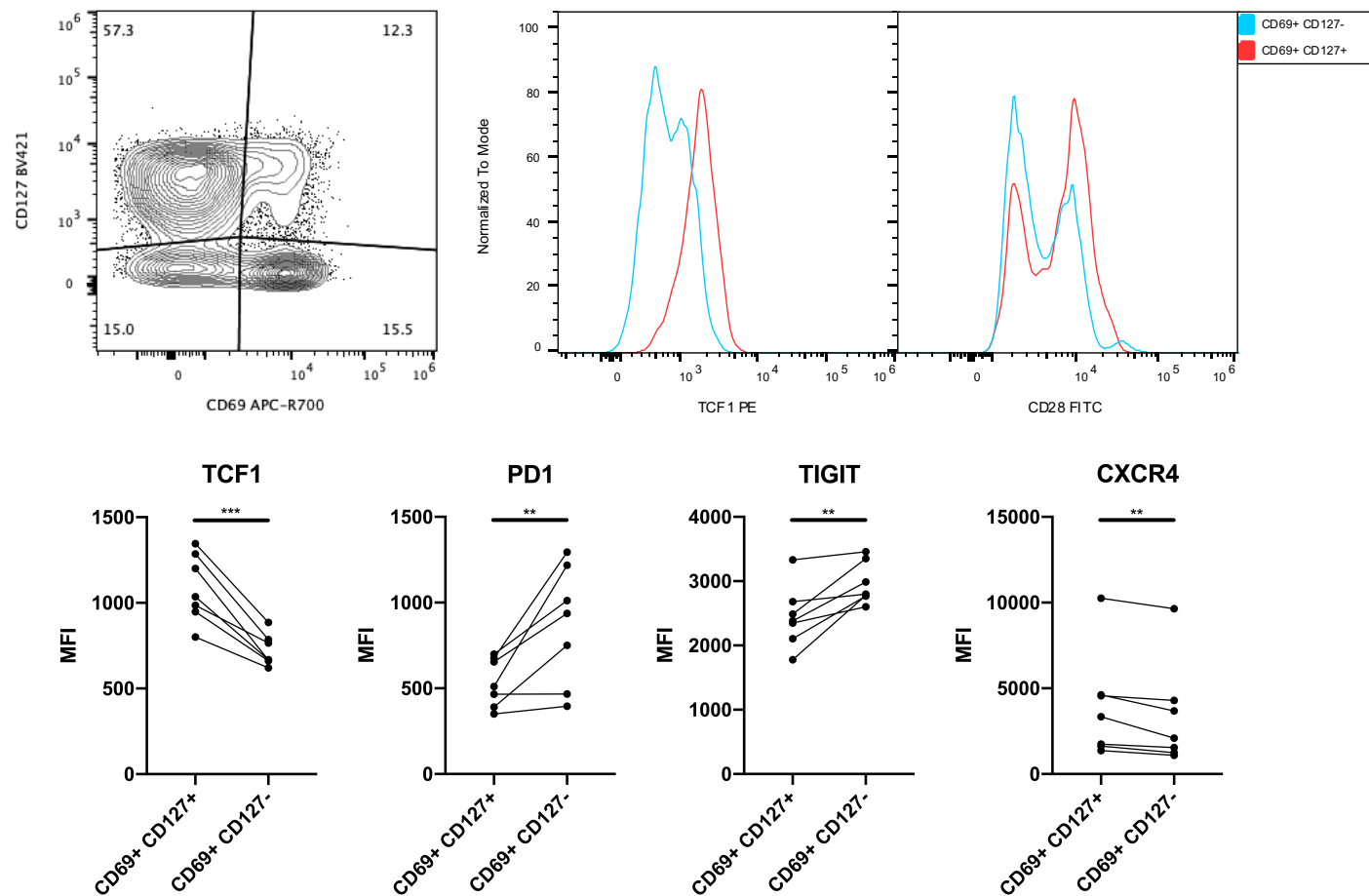
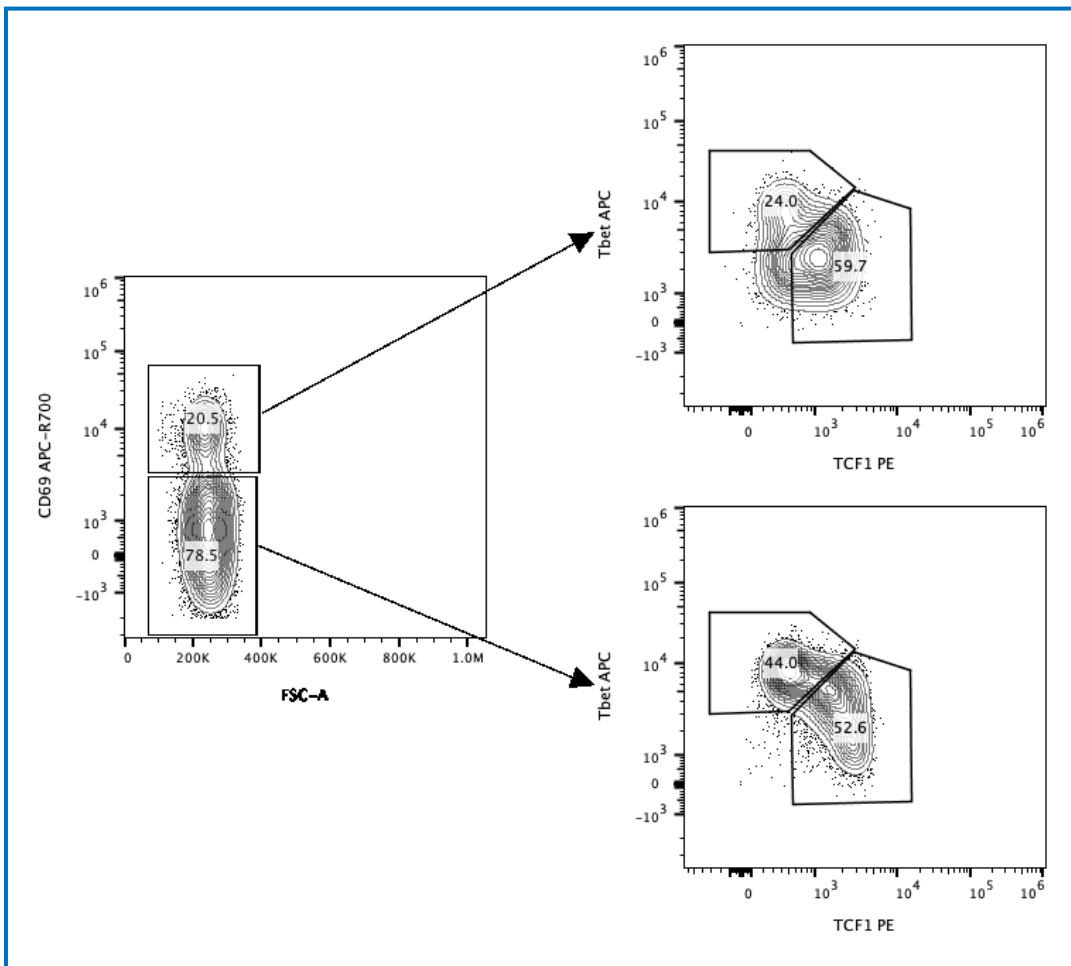


BM is enriched for vaccine and tumor-specific T_{Prog1}



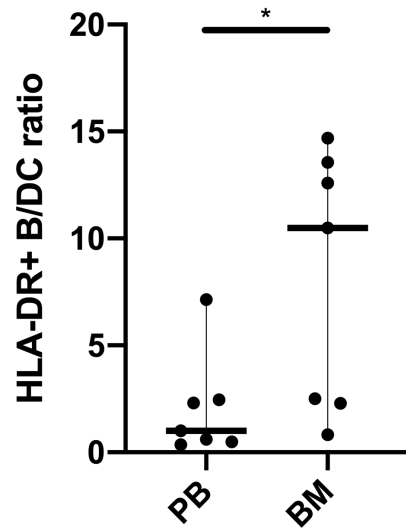
D14
representative data

TCF1⁺ CD8 T cells are present in the bone marrow of cancer patients

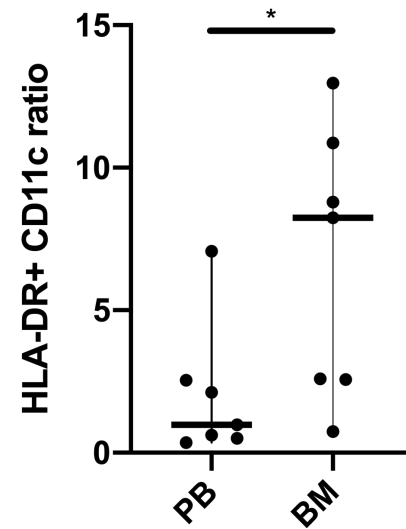


BM APCs may support differentiation and maintenance of MILs

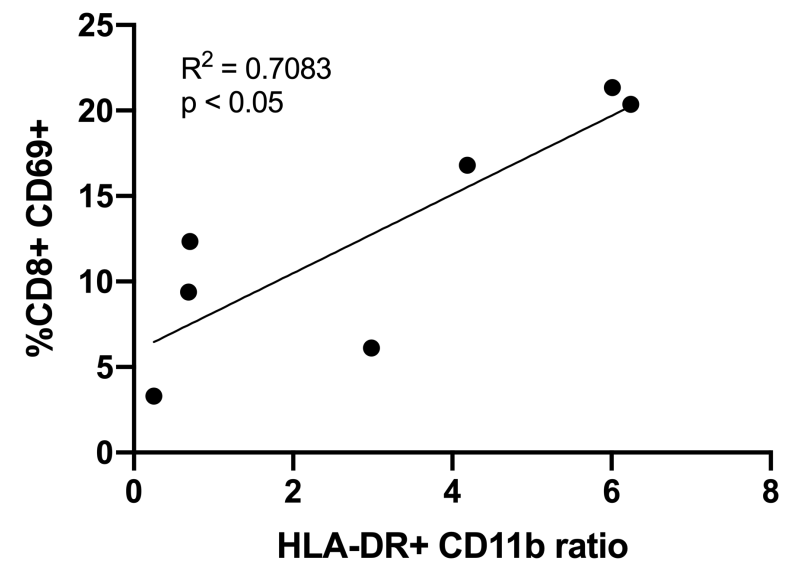
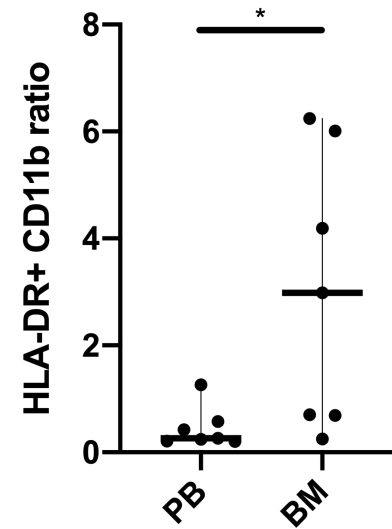
HLA-DR+ B to DC ratio



HLA-DR+ CD11c ratio



HLA-DR+ CD11b ratio



Conclusions

- Immunotherapy plays an important role in myeloma therapy
 - Active treatment: CAR-T, bispecific antibodies
 - Immunosurveillance: Vaccines
- Immunosuppression involves numerous mechanisms which must be understood to best select patients and develop targeted effective therapies
- Effective immunotherapy requires an understanding of the immune status
 - T cell exhaustion
 - MDSCs
 - Immune status in specific organs
- Baseline immune status predicts responses: Tscm, IL-6
- Not all patients benefit from immunotherapy or the same therapy
- Different disease states require different approaches

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