POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Biologia del Mieloma

Novità dal Meeting della Società Americana di Ematologia

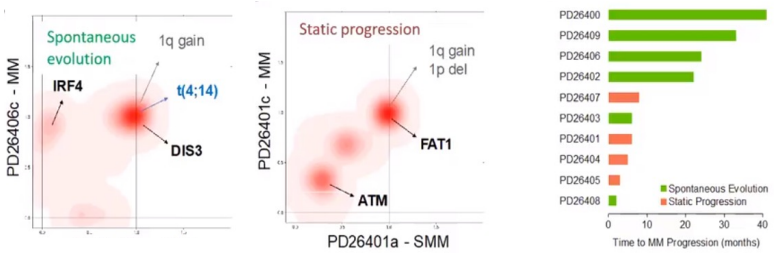
Alessandra Romano

Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

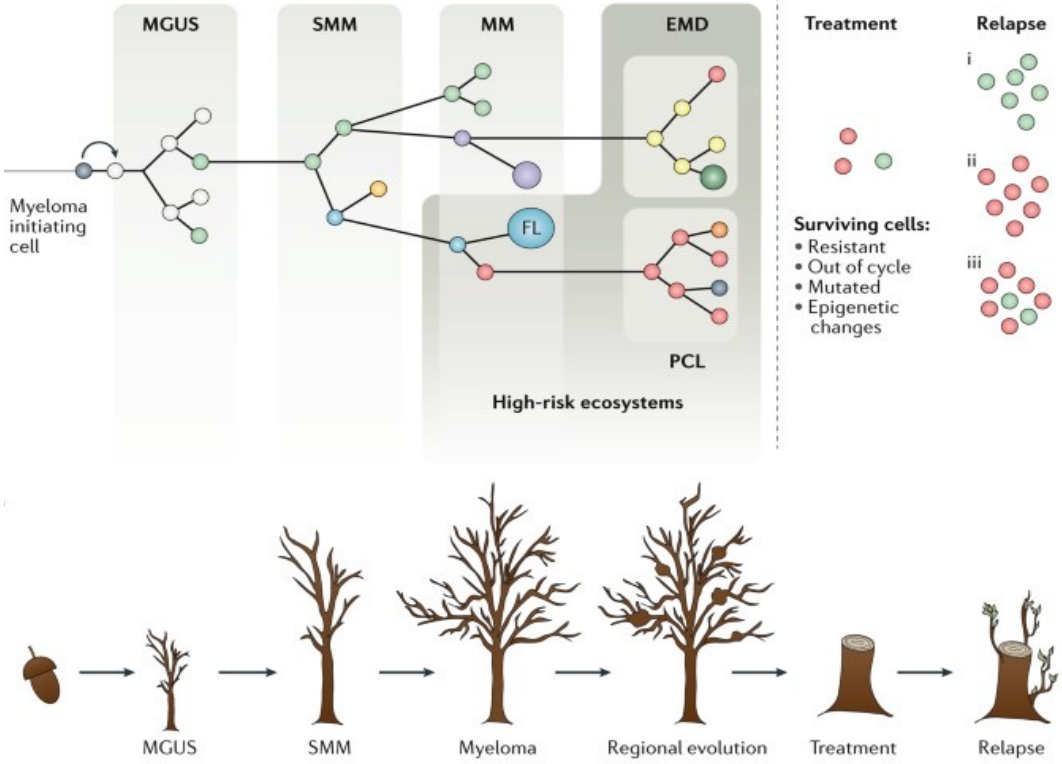
Disclosures of Alessandra Romano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Blueprint			x				
Takeda						x	
Janssen						x	

The complex landscape of Multiple Myeloma evolution

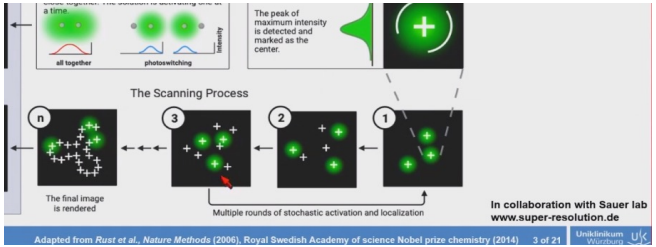


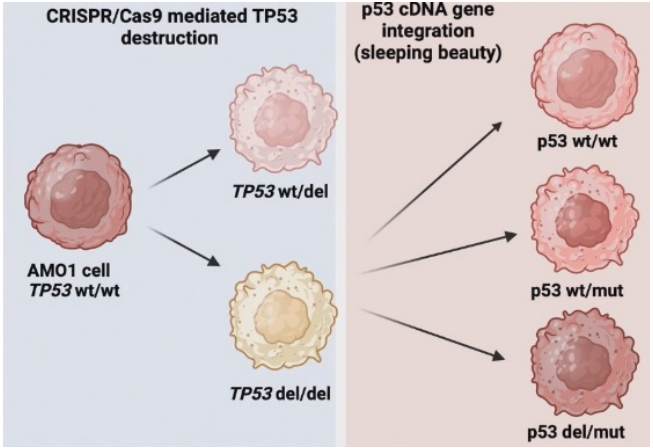
Bolli, Nat. Comm., 2018

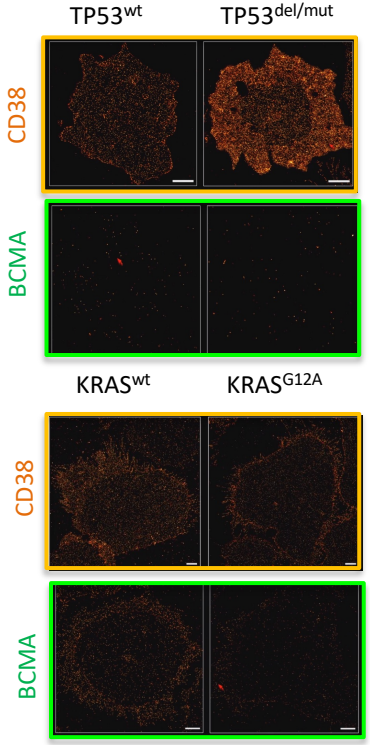


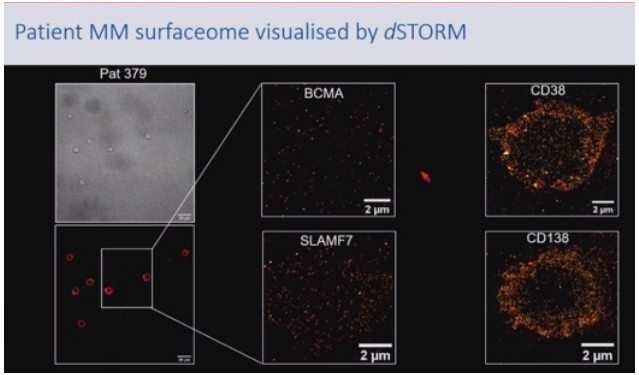
C. Pawlyn, Nat. Rev. Can. 2017

Single genetic lesions impact surface epitope expression, as quantified by dSTORM





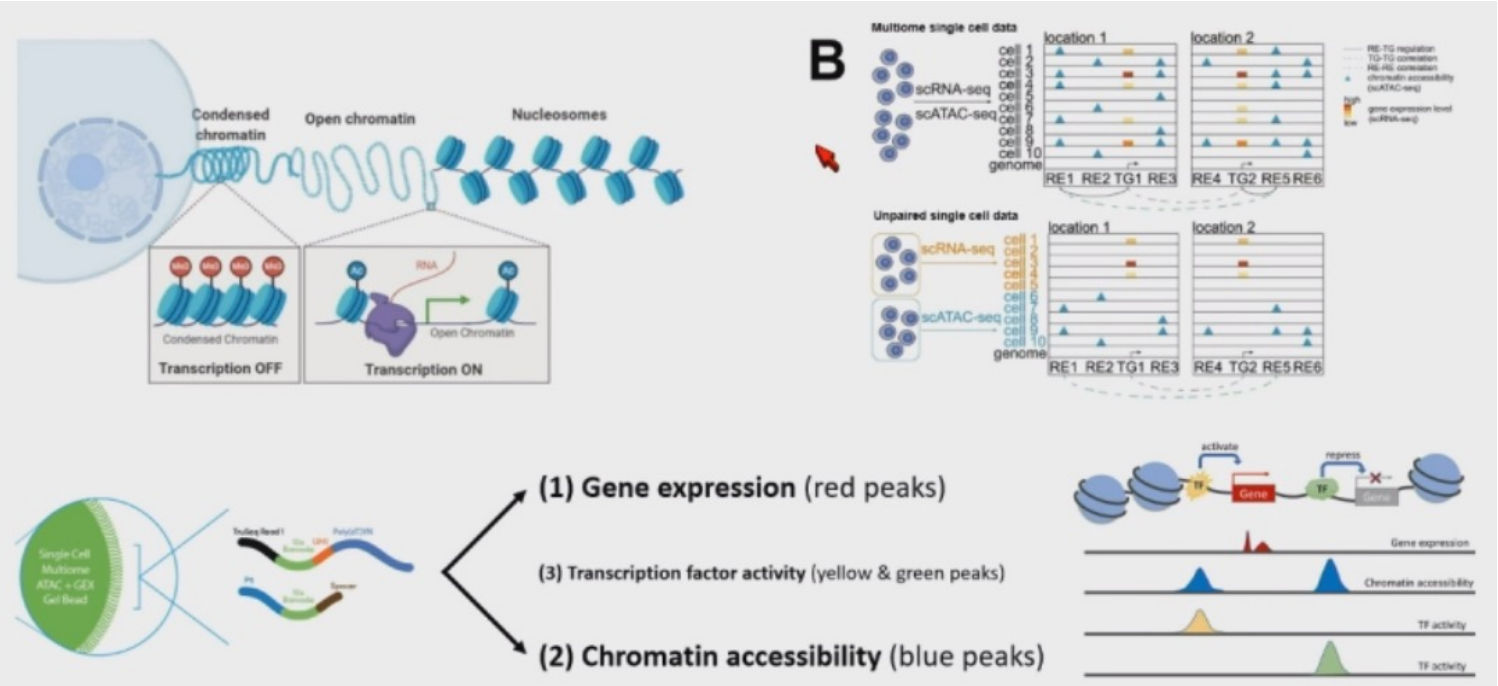




U. Munawar, Abs 451

Single Nuclei Multiomics Analysis of Transcriptional and Chromatin Accessibility of Tumor Cells Uncovers Molecular Signatures and Regulatory Elements of Malignant Clonal Evolution in Multiple Myeloma

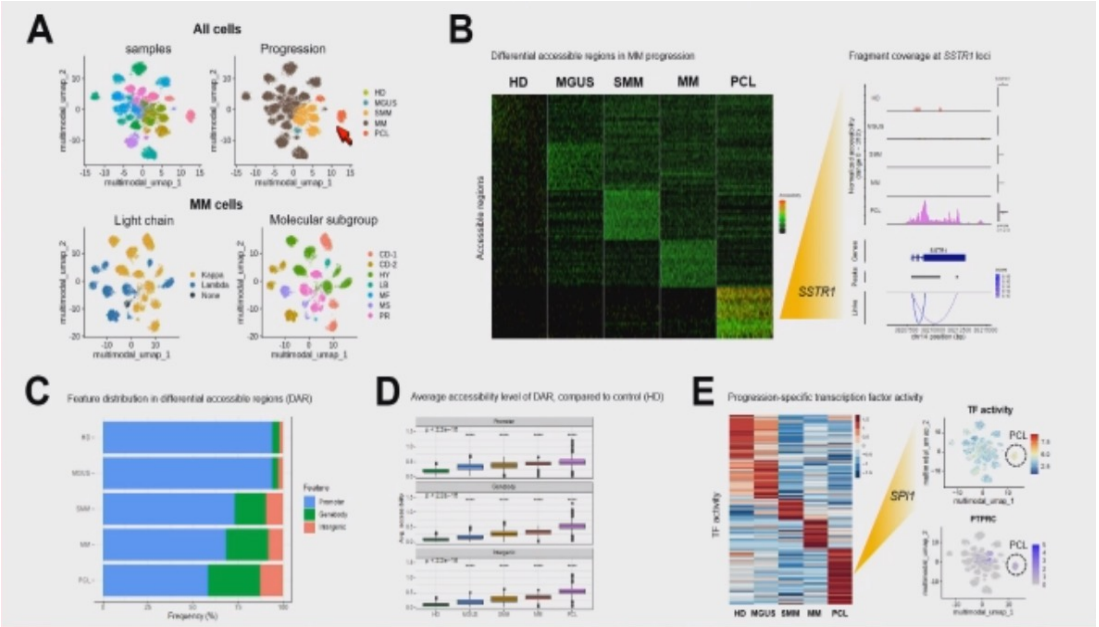
Single nuclei multi-omics analysis reveals unique signature of MM progression

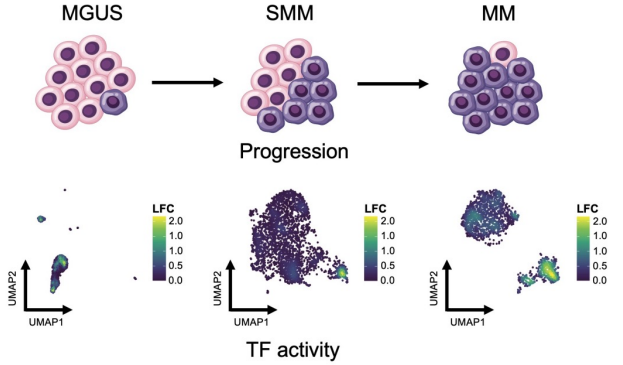


V. Wanchai, Abs 87

Single Nuclei Multiomics Analysis of Transcriptional and Chromatin Accessibility of Tumor Cells Uncovers Molecular Signatures and Regulatory Elements of Malignant Clonal Evolution in Multiple Myeloma

Clonal competition occurrs at the pre-malignant stage, associated to epigenetic dysregulation





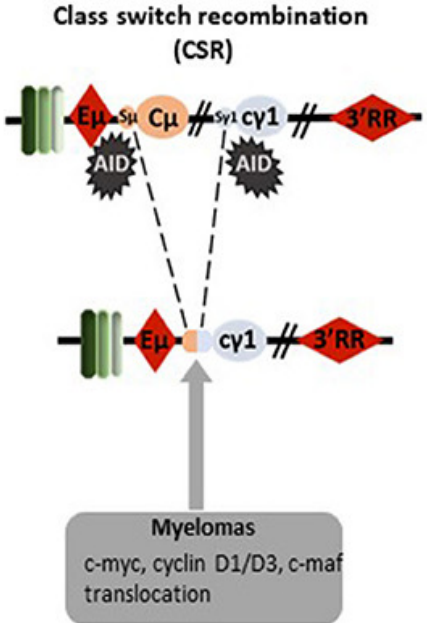
Based on unique clonotypic signature of the immunoglobulin gene rearrangement, the highest NPC in MGUS samples suggests clonal competition at the premalignant stage

Increase of differential accessible regions at intergenic regions implies more complexed long-range gene regulation from cis-regulatory elements during disease progression.

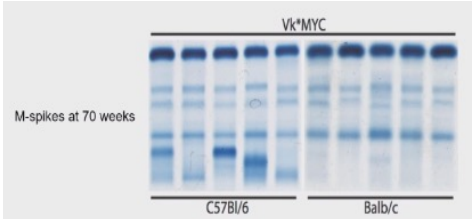
Using the ratio of gene signatures of aggressive disease to determine high-risk cells, the proportion of high-risk cells increase respectively from low to high-risk samples. This expansion of high-risk clonality may contribute to the risk of relapse.

V. Wanchai, Abs 87

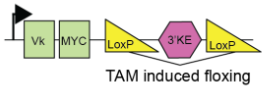
Forced MYC expression in germinal center of Vk*MYC mice leads to MM progression

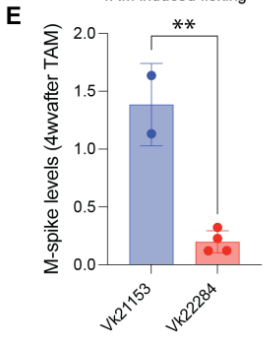


but not disease initiation

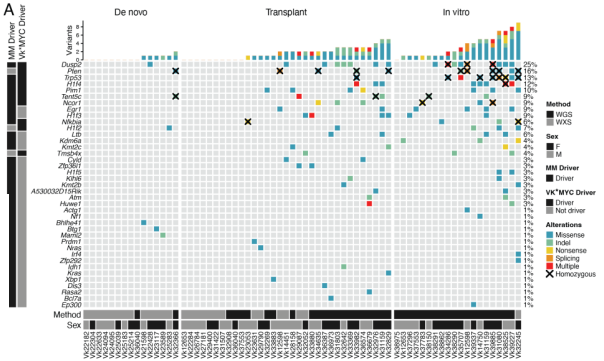


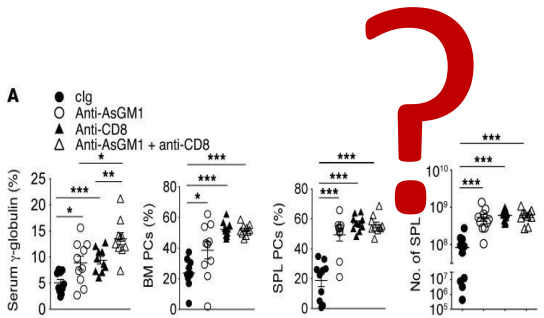
Radl et al. 1978, *Clin. Exp. Immonol*
Chesi..Bergsagel2008, *Cancer Cell*
Affer ..Kuehl 2014, *Leukemia*





F. Maura and
M. Chesi, in press

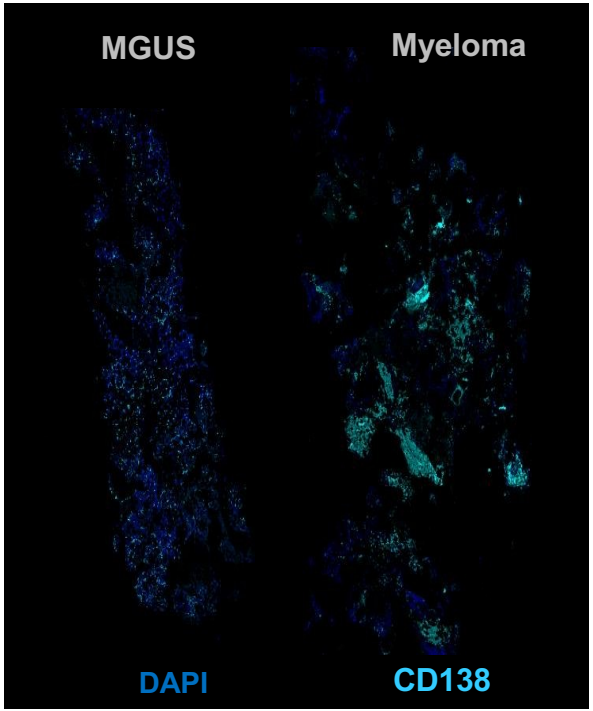




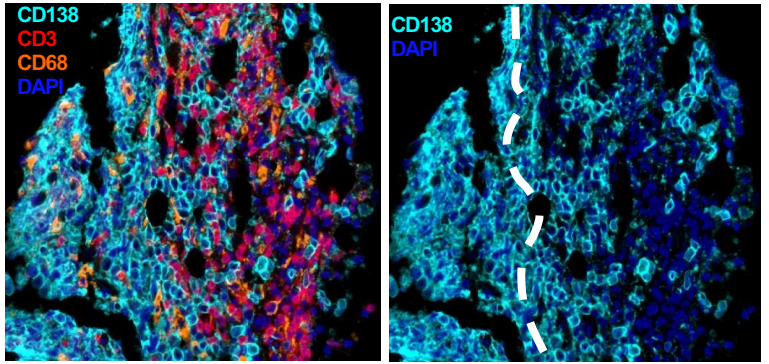
Guillerey et al. JCI
Das et al Nat Med

Clustered growth and immune exclusion are features of malignant transformation

Clustered Pattern in MM Biopsies



Exclusion of T cells

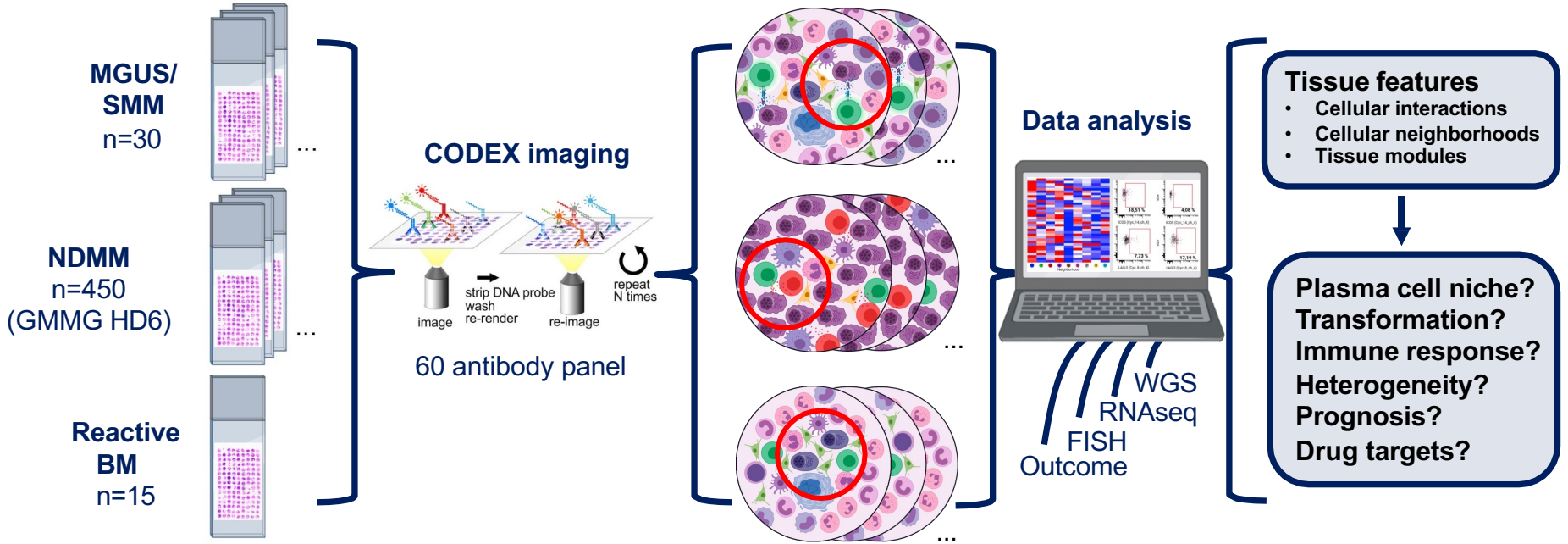


Robinson, Villa et al. JCI 2023

…biology analogous to tissue invasion as hallmark of malignancy in solid tumors?

Spatial Dissection of the Bone Marrow Microenvironment in Multiple Myeloma by High Dimensional Multiplex Tissue Imaging

Multiplexed tissue imaging in bone marrow biopsies



M. Baertsch, Abs 651

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Spatial Dissection of the Bone Marrow Microenvironment in Multiple Myeloma by High Dimensional Multiplex Tissue Imaging

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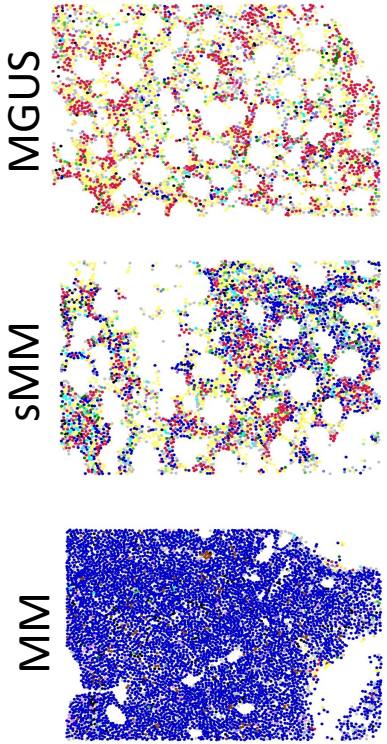
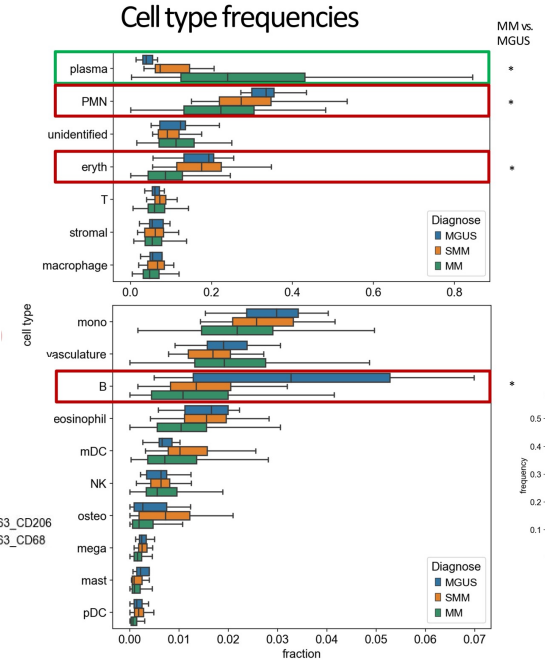
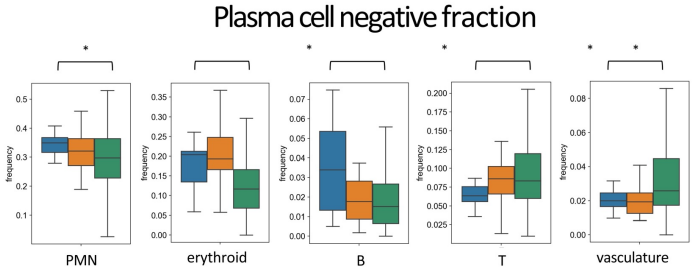
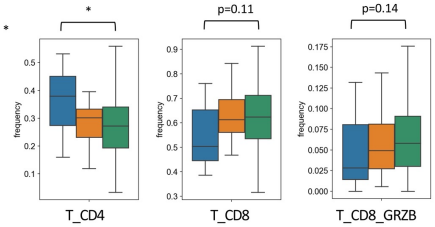
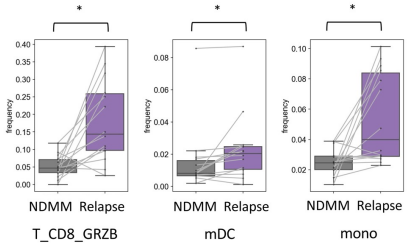
Altered cell type composition in the bone marrow of MGUS, smoldering and multiple myeloma







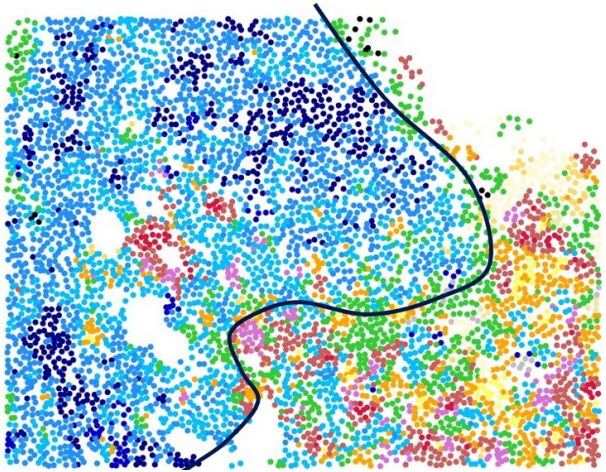


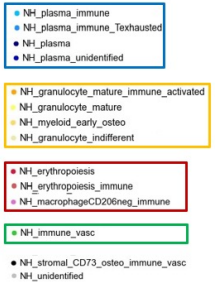


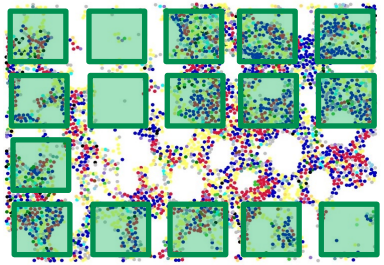
M. Baertsch, Abs 651

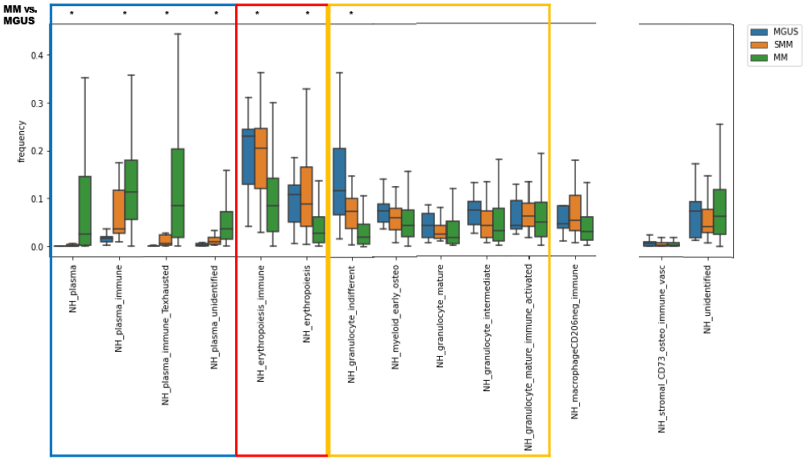
Spatial Dissection of the Bone Marrow Microenvironment in Multiple Myeloma by High Dimensional Multiplex Tissue Imaging

Spatial neighborhoods in the bone marrow changes from MGUS to MM





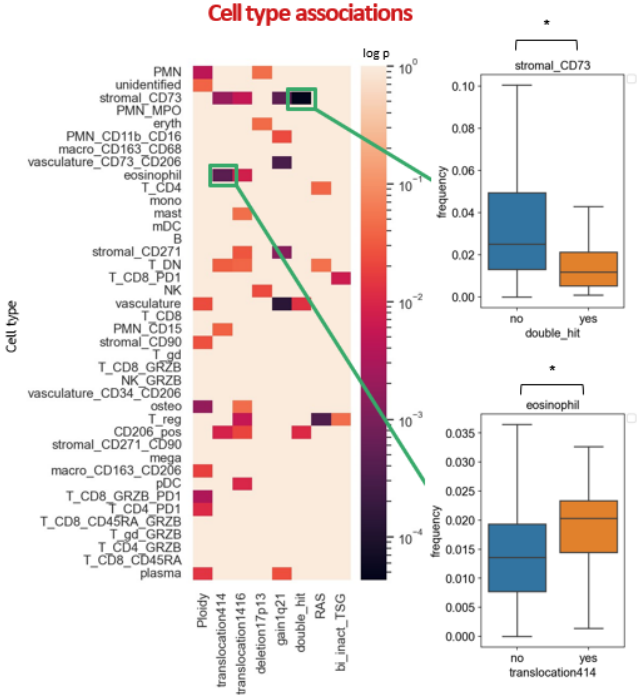


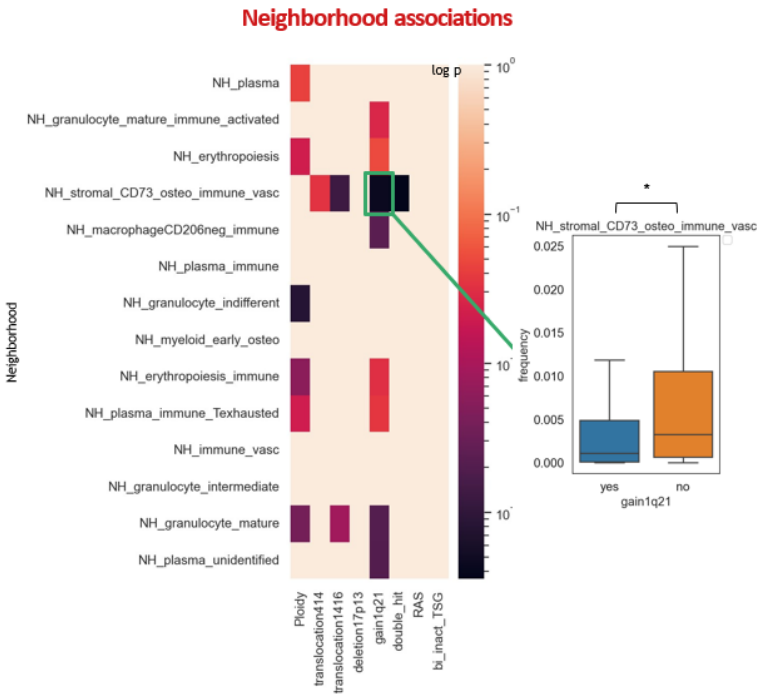


M. Baertsch, Abs 651

Spatial Dissection of the Bone Marrow Microenvironment in Multiple Myeloma by High Dimensional Multiplex Tissue Imaging

Associations of MM subgroups with cell type- spatial neighborhoods composition





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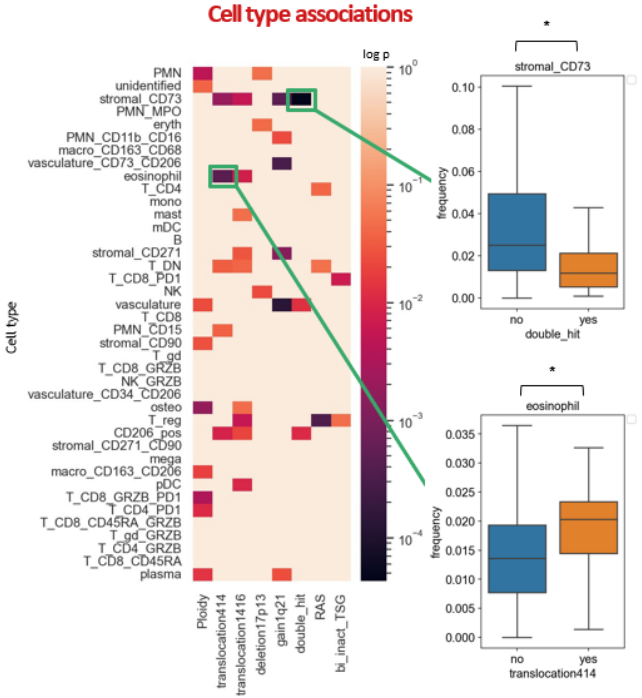
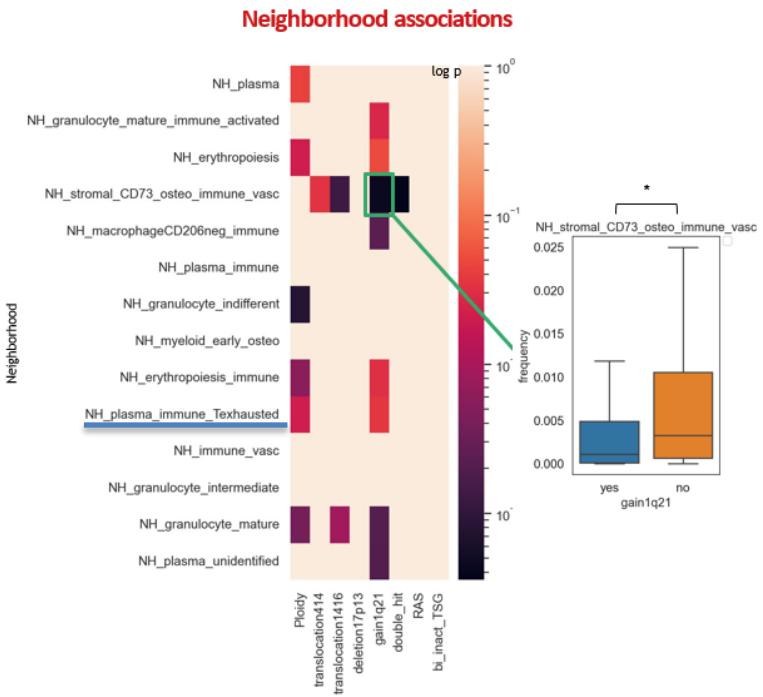
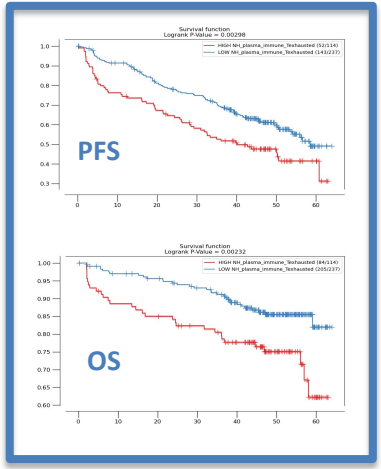
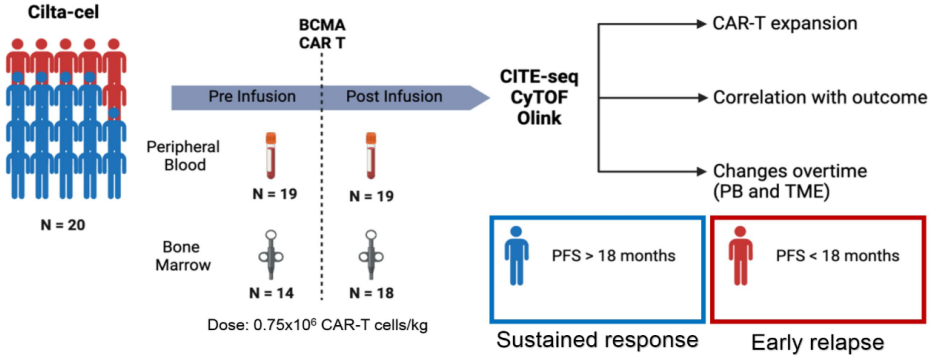


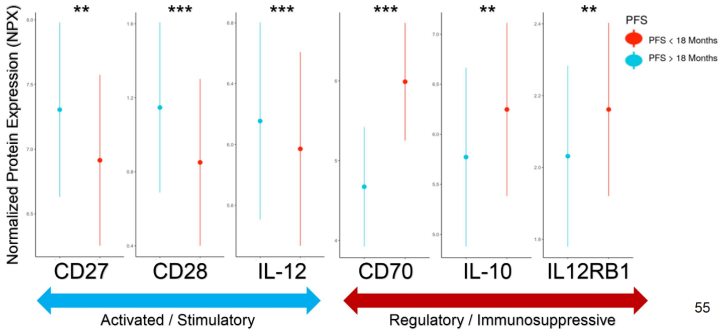


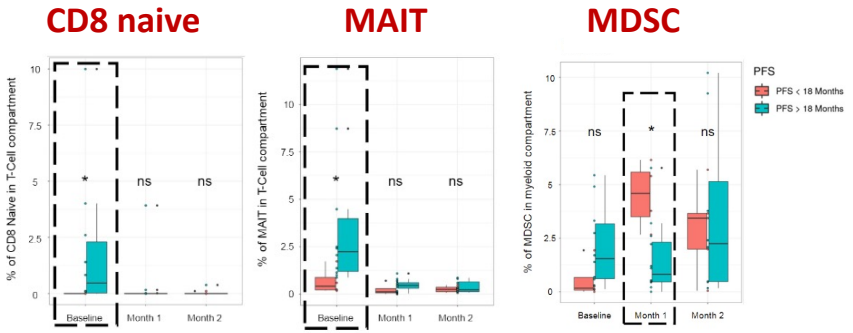


M. Baertsch, Abs 651

CAR-T therapy efficacy is affected by the bone marrow microenvironment composition

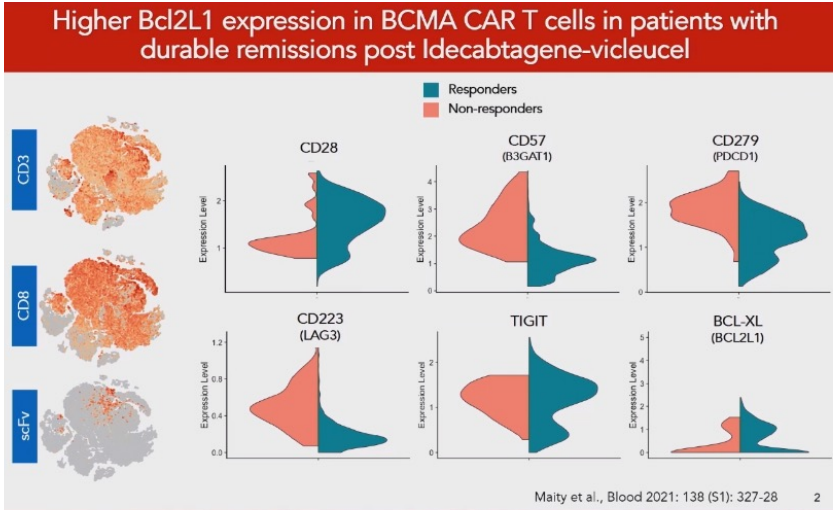


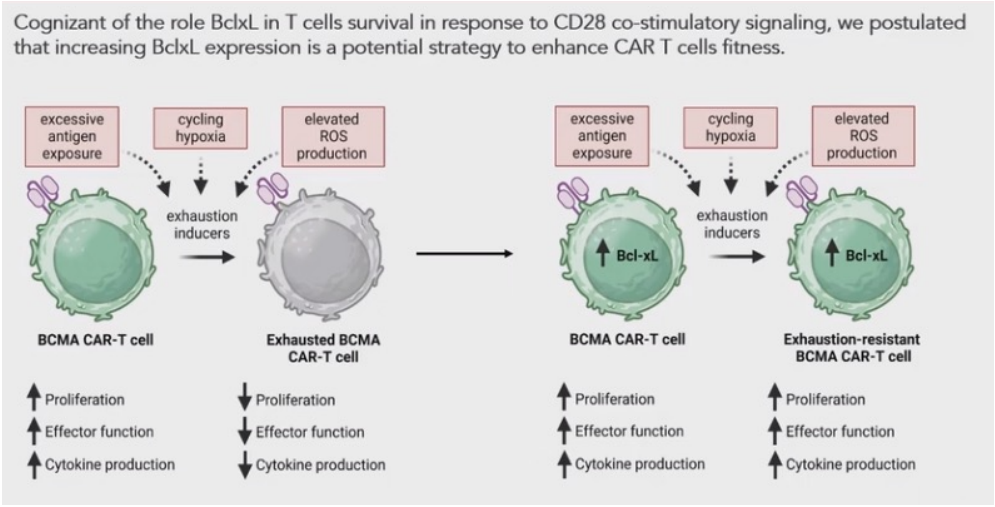




J.Vieria dos Santos, Abs 93

CAR-T cells armored with BCL2L1 can eliminate more efficiently myeloma cells

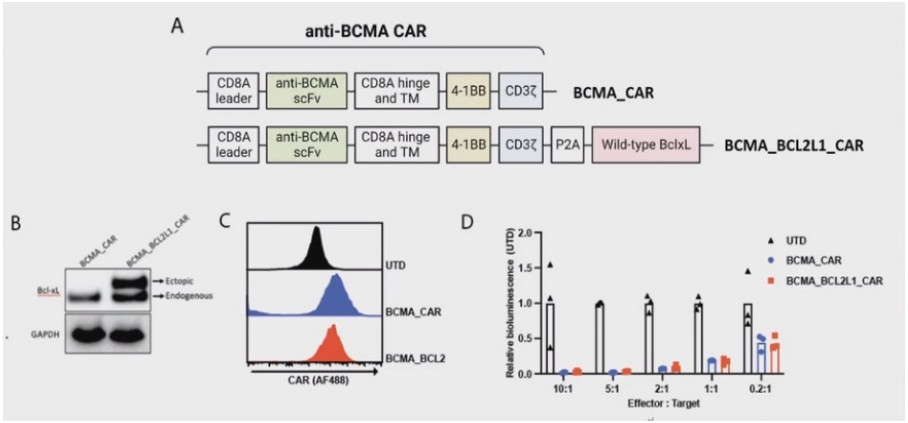


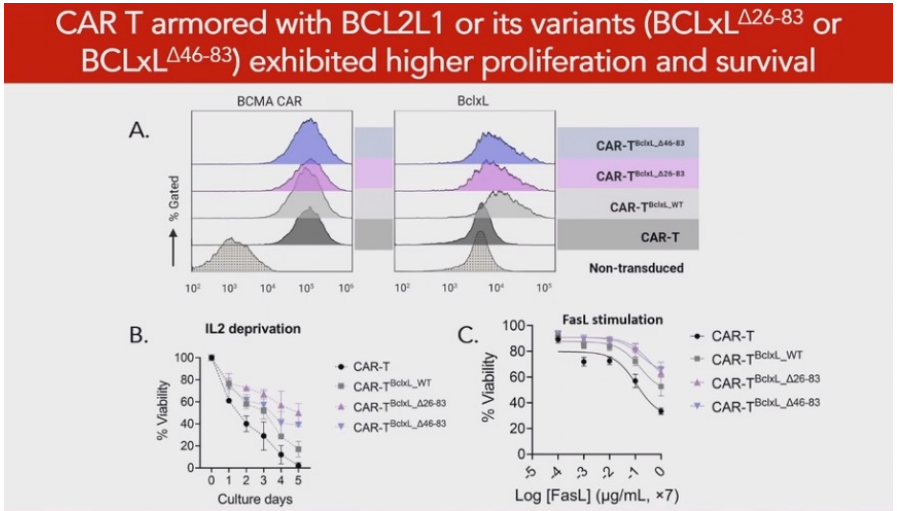


M. Poorebrahim, Abs 454

Bclxl Prevents Progressive Exhaustion in BCMA CAR T Cells with Maintenance of High TCF1 Expressing T Cells

CAR-T cells armored with BCL2L1 can eliminate more efficiently myeloma cells



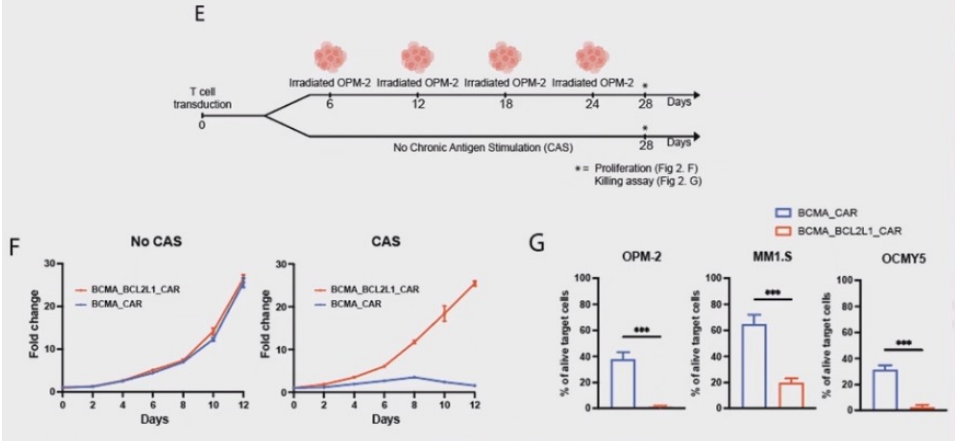


M. Poorebrahim, Abs 454

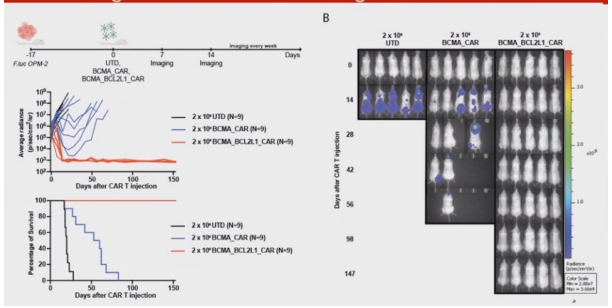
Bclxl Prevents Progressive Exhaustion in BCMA CAR T Cells with Maintenance of High TCF1 Expressing T Cells

CAR-T cells armored with BCL2L1 can eliminate more efficiently myeloma cells

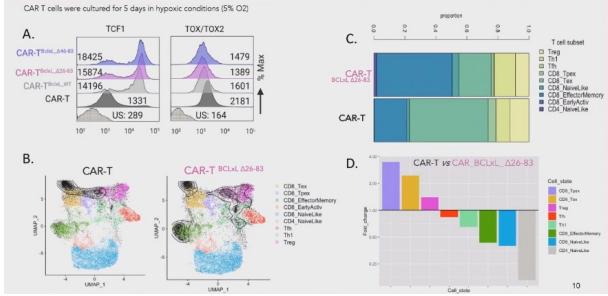
Under Chronic Antigen Stimulation (CAS) conditions BCL2L1 armored CAR T have superior proliferative and cytotoxic activity



BCL2L1 armored CAR have enhanced antitumor activity in a xenograft model of MM with high disease burden



Under hypoxia, CAR T cells armoring with BCL2L1 significantly reduced terminally exhausted cells (T_{EX}) with higher TCF1⁺ cells ($T_{SCM/CM}$)



M. Poorebrahim, Abs 454

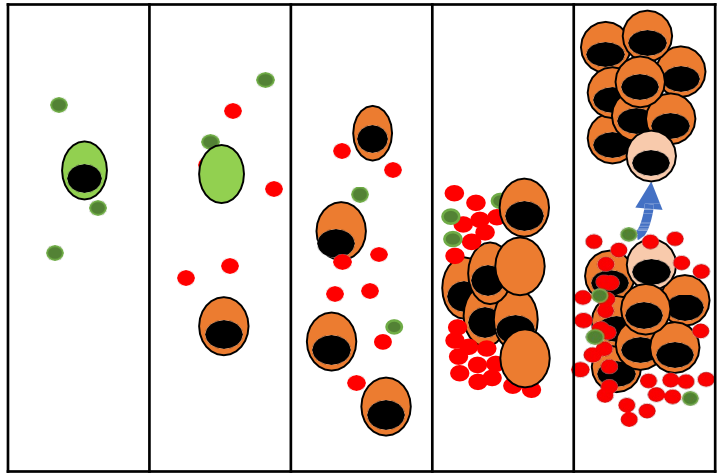
Conclusions

The fertile soil in myeloma:
the contribution of the microenvironment

MGUS precedes all MM but not the first step.

There is an increasing role for non-immune compartment

CAR-T therapy can be affected by immune cell composition



	Normal	pre-MGUS	MGUS	Early MM	MM
Underlying triggers	?	+	+	+	?
Immune recognition			+	+	+
Immune dysfunction		?	+	+	+
Immune exclusion				+	+

Conclusions

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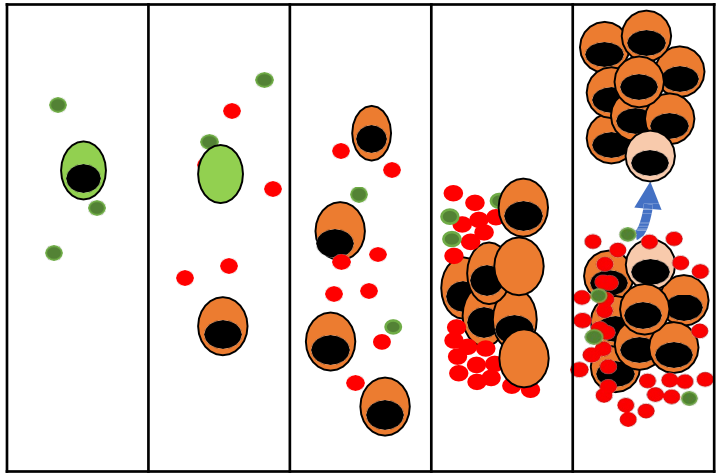
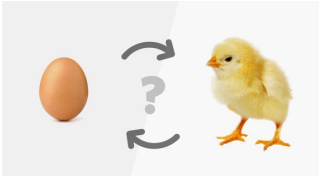


		Normal	pre-MGUS	MGUS	Early MM	MM
Underlying triggers	?	+		+	+	?
Immune recognition				+	+	+
Immune dysfunction		?		+	+	+
Immune exclusion					+	+



Some Questions:
What is the impact on biology of immune recognition?
Reversibility? Impact on Survival?

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