Resistance Mechanisms to T-cell based Therapies in Myeloma

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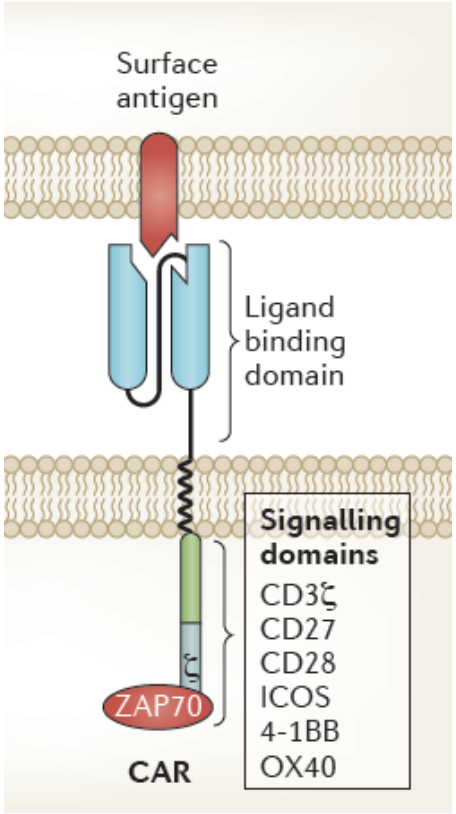
Disclosures of Paola Neri

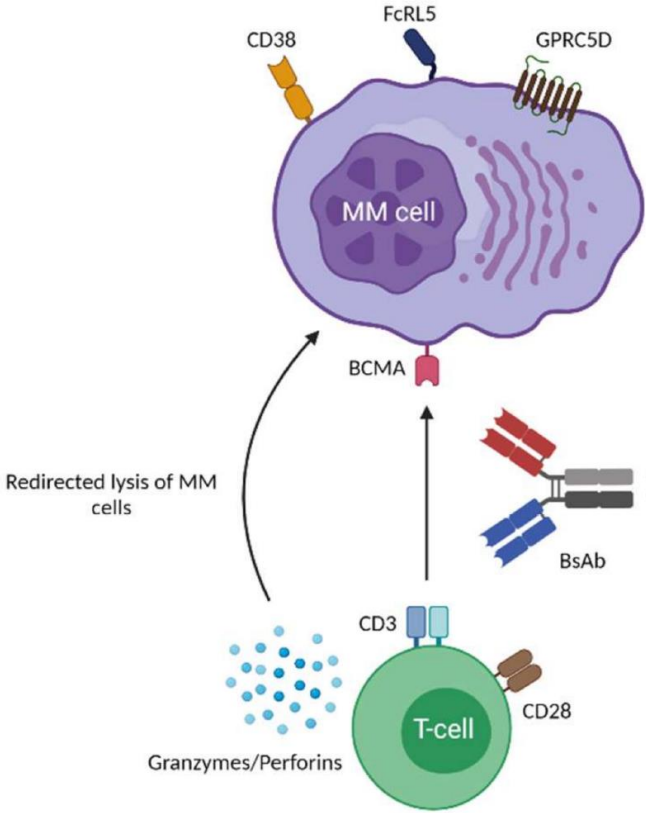
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi			x			x	
Pfizer						x	
Janssen						x	
BMS			x			x	

Chimeric Antigen Receptor T cells (CART) and T cell engagers (TCE)



Fesnak A et al. Nat Rev Cancer 2016

BCMA
GPRC5D
FcRH5
CD38
SLAMF7
BCMA+TACI
BCMA+GPRC5D

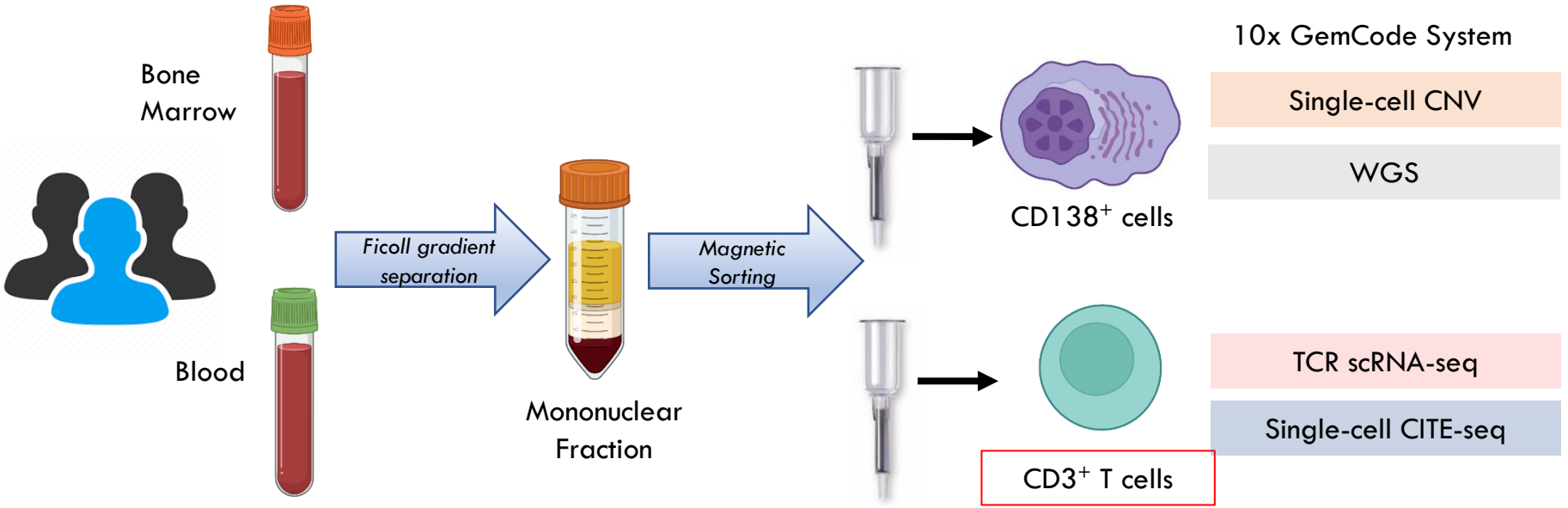


Hosny M et al, Journal of Clinical Medicine 2021

CAR-T and T cell engagers (TCE) have demonstrated unprecedented efficacy in RRMM patients.
However, the cellular and molecular predictors of response as well as the mediators of resistance remain elusive.

Methodology

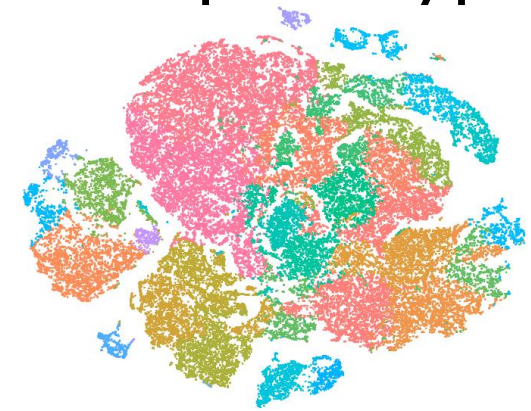
Serial blood samples and BM aspirates have been collected from patients treated with anti-BCMA CAR-T or a BCMAxCD3 T cell engager therapies, prior and post initiation of therapy and/or at time of relapse.

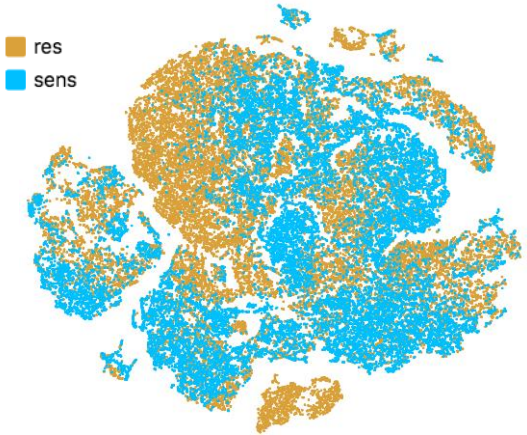


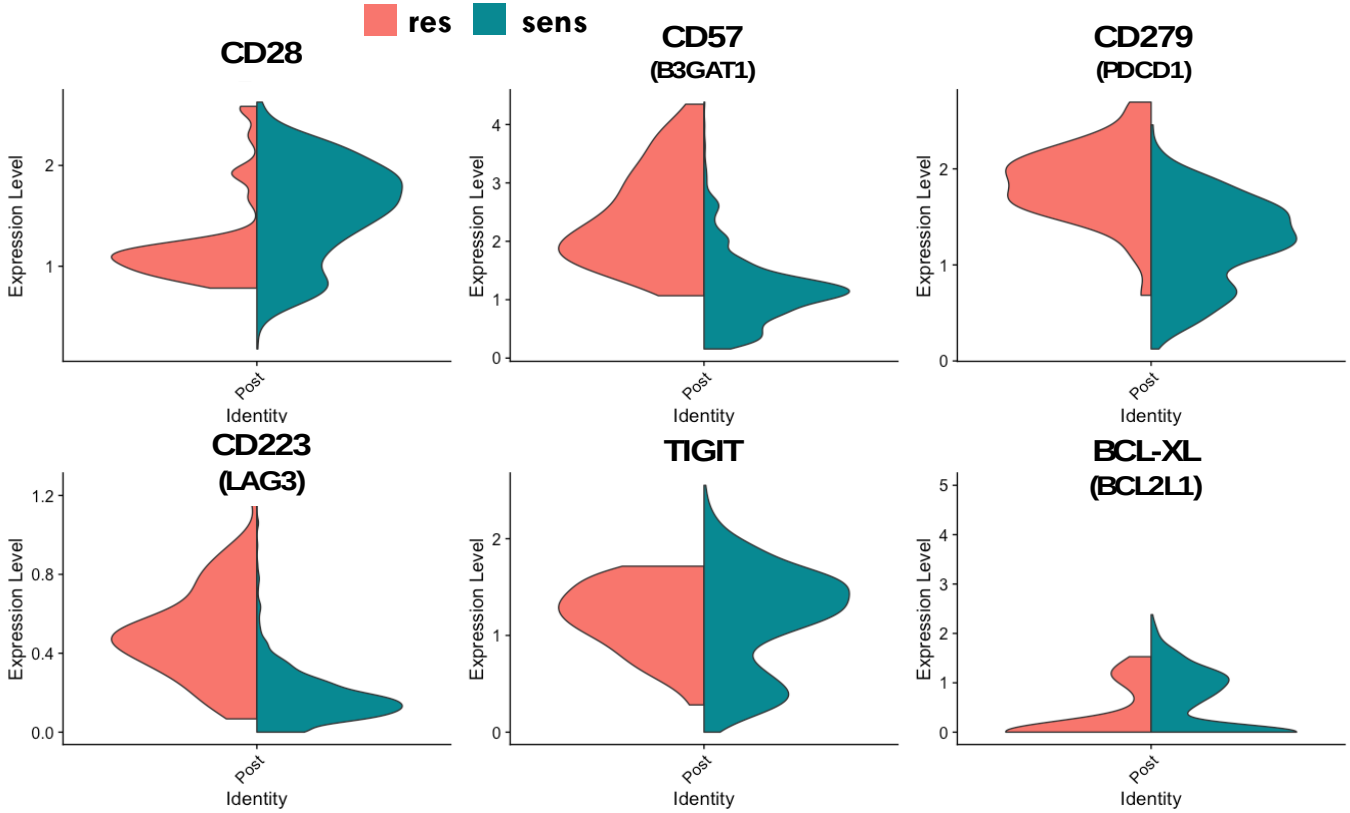
A broad immunophenotypic and transcriptomic characterization of T cells at single cell level using paired TCR sequencing coupled with 5' scRNA and CITEseq. Cell Ranger RNA and VDJ pipeline for sample de-multiplexing, barcode processing and grouping of T cells into clonotypes with shared TCR α/β sequences.

Computational tools: Seurat, scGATE, scPred, scRepertoire, ProjectTILs and Immunarch.

T cell phenotype influences responses to anti-BCMA CAR-T





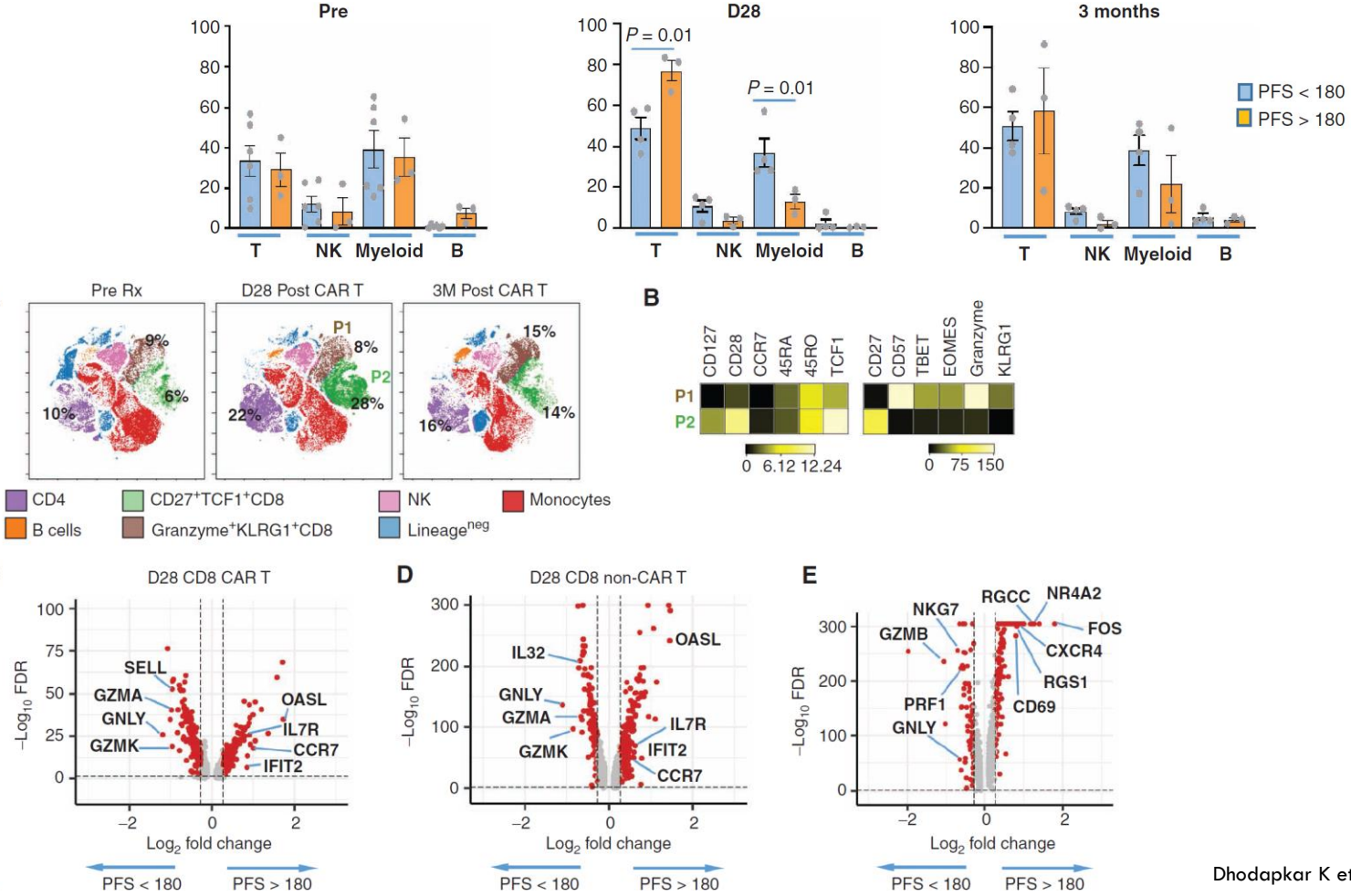


High proportion of $T_{SC/CM}$ ($CD45RA^+$ $CCR7^+$ $CD28^+$) in sensitive patients.

Enrichment of exhausted T cells ($CD45RA^+$, $CD57^+$, PD^+ $TIGIT^+$ $CD28^-$) in resistant patients.

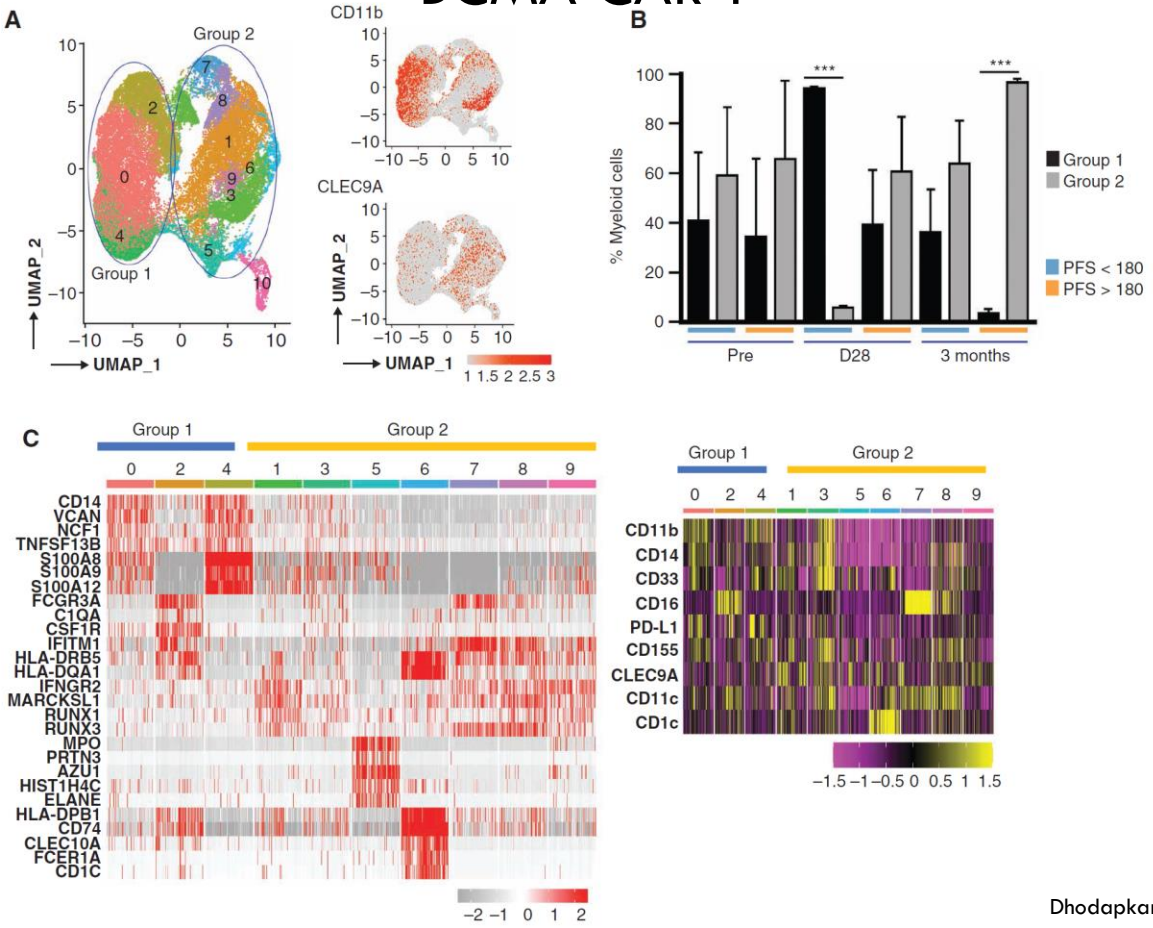
Leblay N et al, Blood 2020, Supp 1,11-12

Cellular composition of the BM and outcome following BCMA CAR T



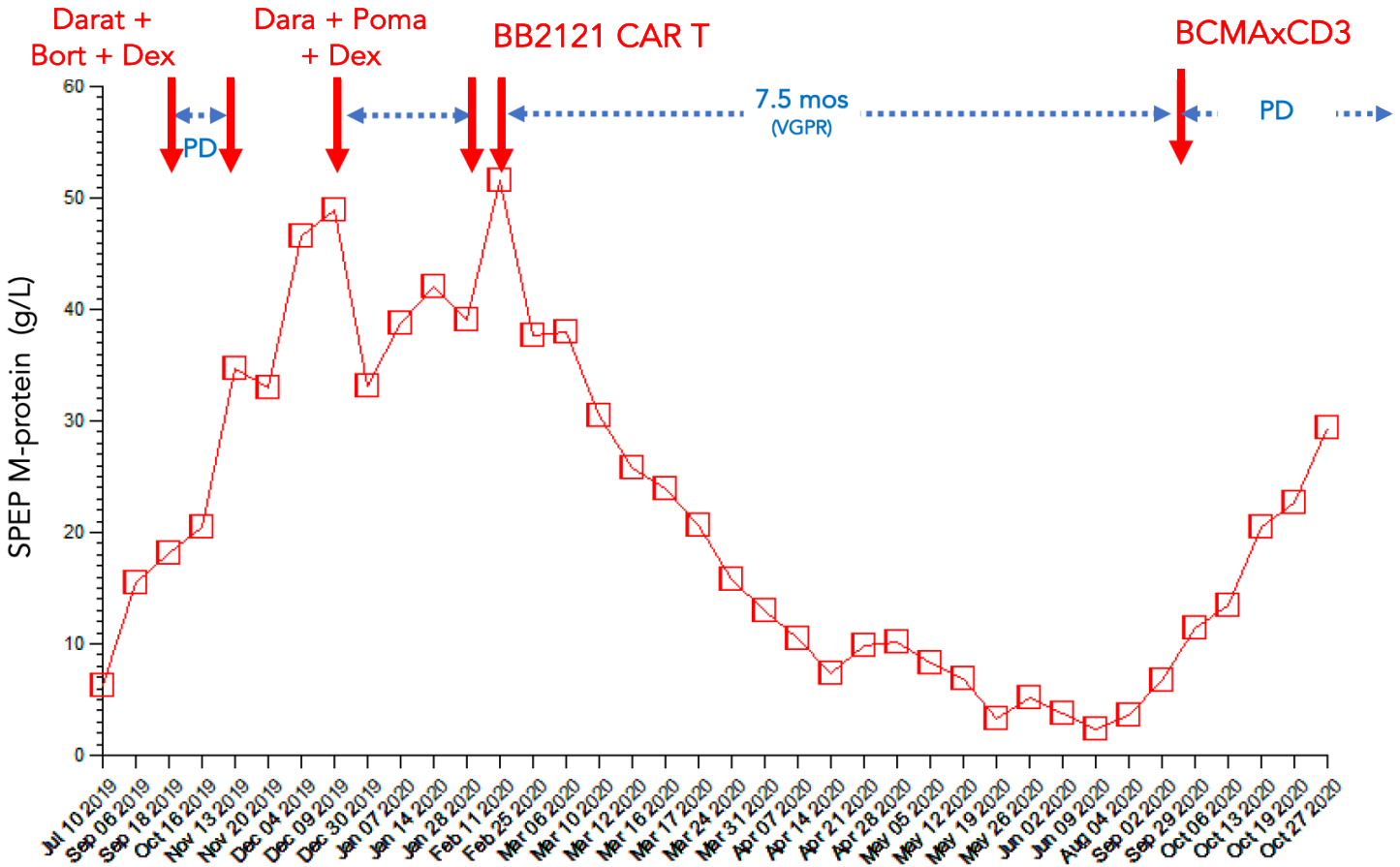
Dhodapkar K et al, Blood Cancer Discovery 2022

Composition of myeloid/DC compartment influences outcome following BCMA CAR T

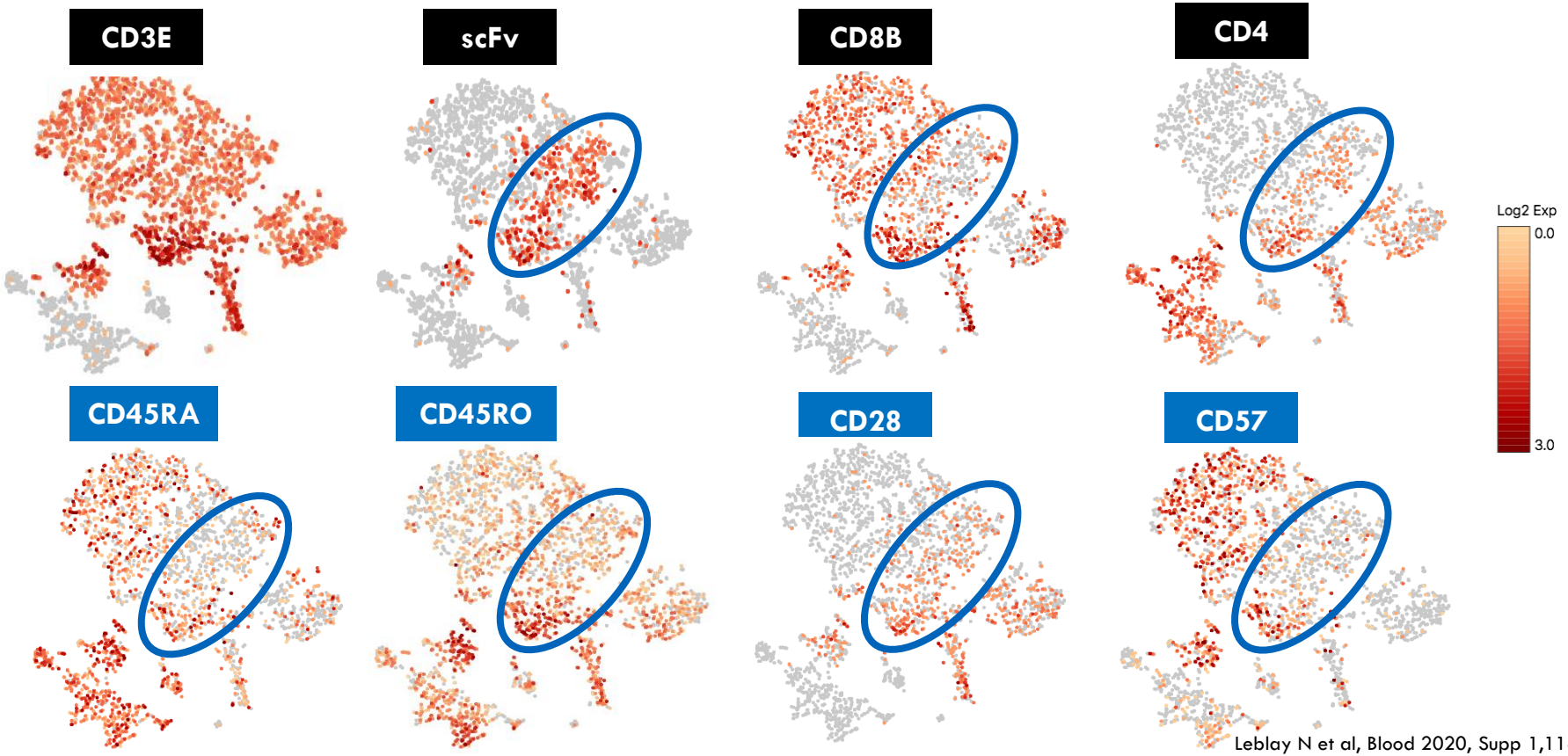


Dhodapkar K et al, Blood Cancer Discovery 2022

CASE 1: Patient relapsed 7.5 months post BCMA CAR-T therapy and failed to respond to BCMA x CD3 TCE



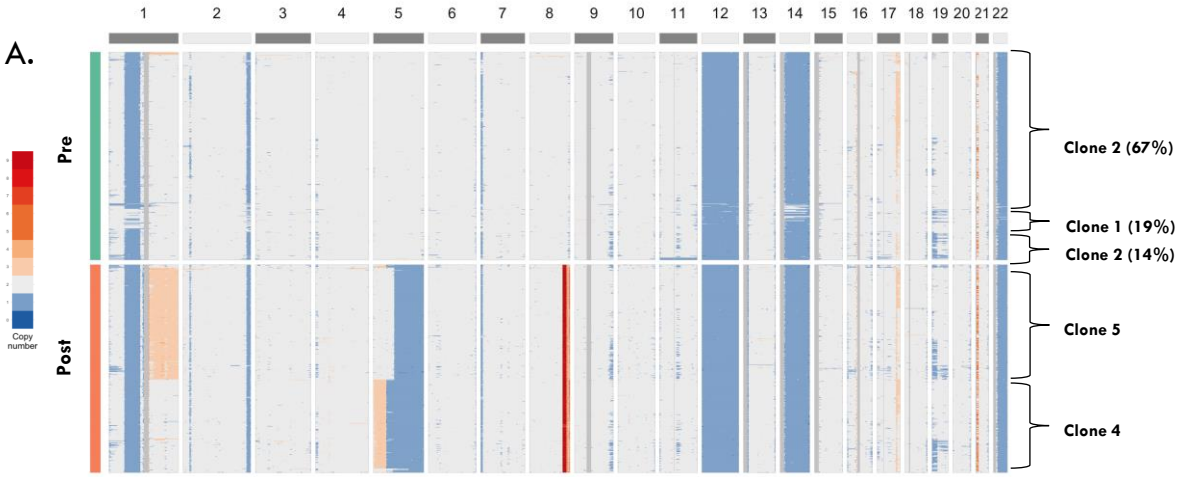
“Fit “ T cells profile of BCMA CAR-T
Why did the patient relapse?



Leblay N et al, Blood 2020, Supp 1,11-12

Acquired focal biallelic loss at TNFRSF17 locus post anti-BCMA CAR T/TCE

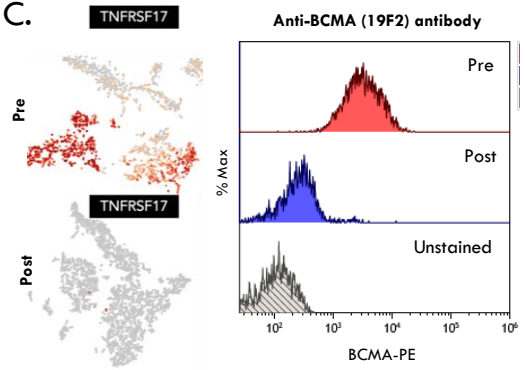
A.



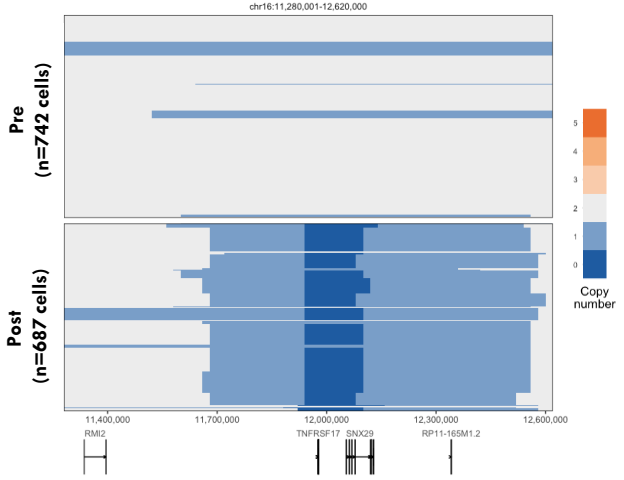
B.

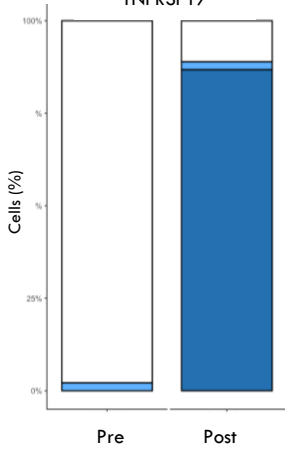
Lee H et al. Nature Medicine 2023

C.



D.



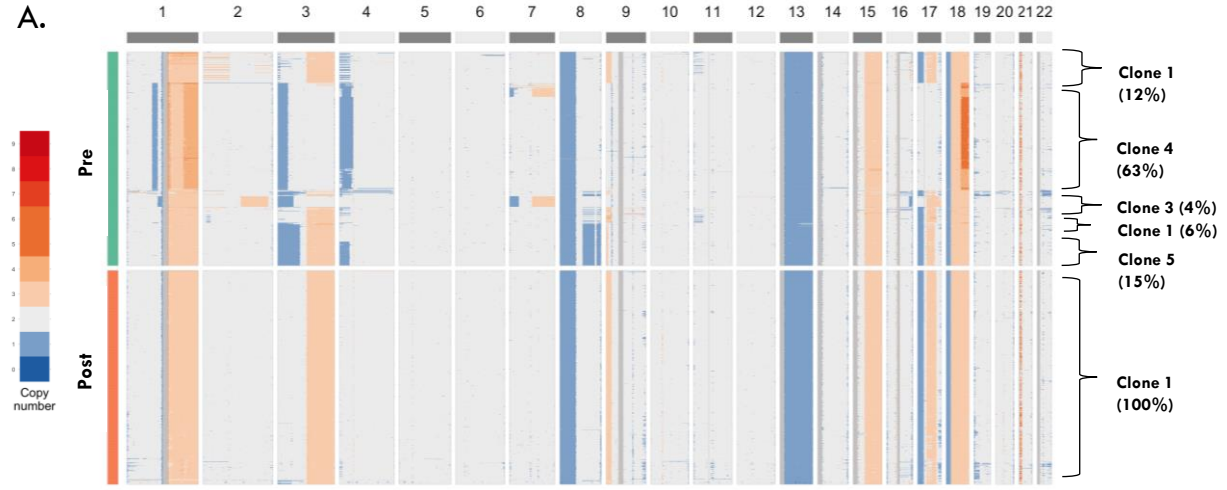


CNV	Pre therapy (%)	Post therapy (%)
2	97.9	11.1
1	2.1	2.1
0	0	86.8

Acquired mono-allelic loss of *TNFRSF17* at progression post BCMAxCD3ε

Case 02
R-ISS III, +t(14;16), del TP53
Therapy: anti BMCAxCD3ε (5th line)
IMWG response: CR; DOR 11 months

A.



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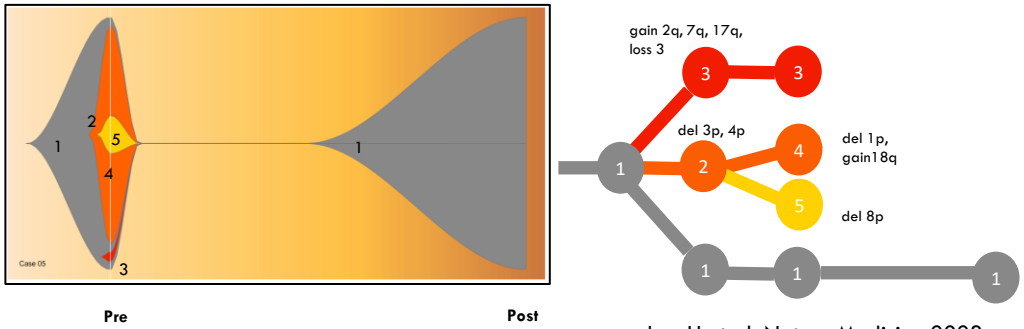
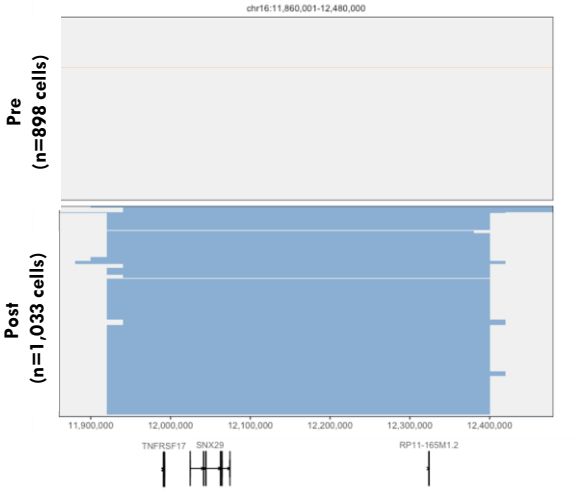
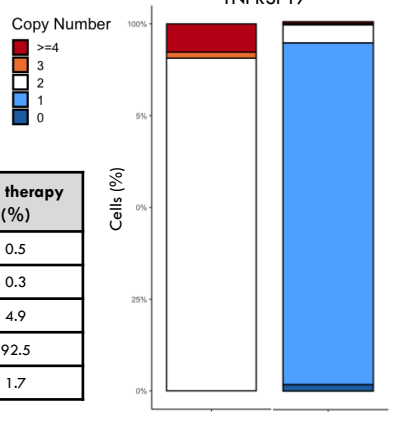


Lee H et al. Nature Medicine 2023

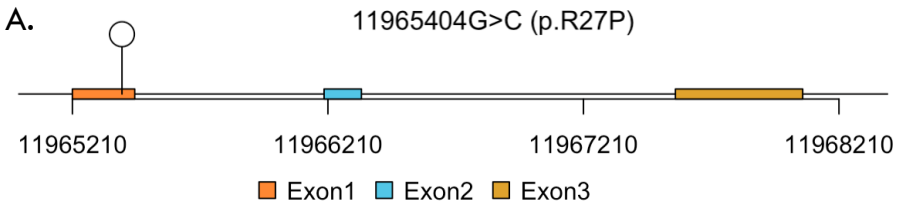
C.

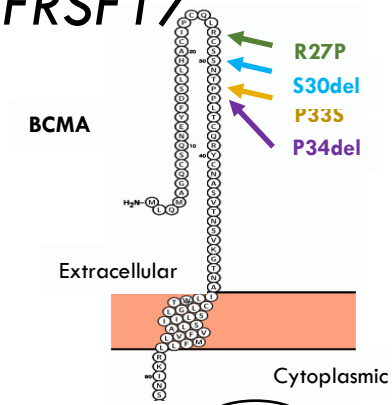


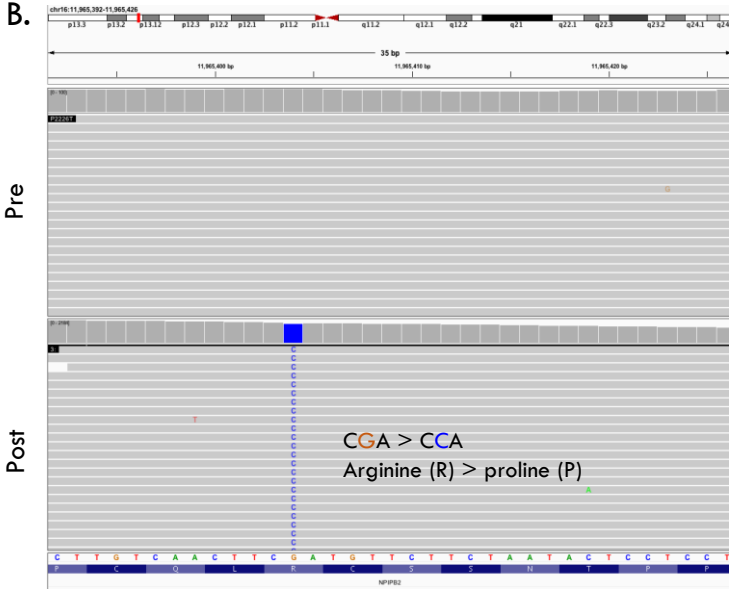


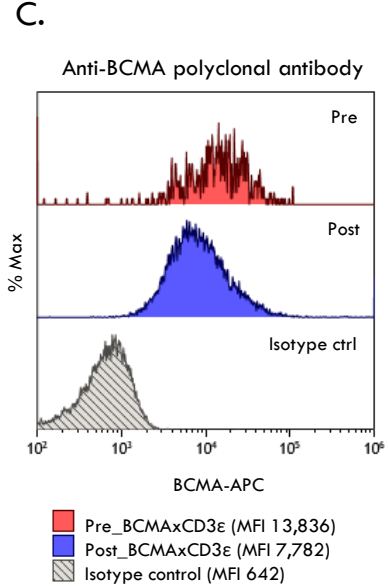
CNV	Pre therapy (%)	Post therapy (%)
4	7.7	0.5
3	1.6	0.3
2	90.7	4.9
1	0	92.5
0	0	1.7

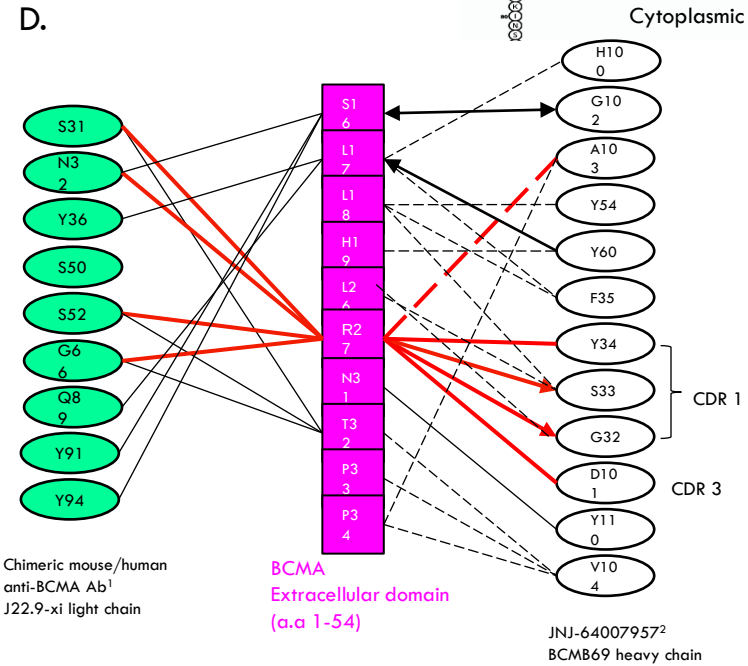
Acquired mono-allelic loss of *TNFRSF17* with mutation in *TNFRSF17* extracellular domain [p. (R27P)]





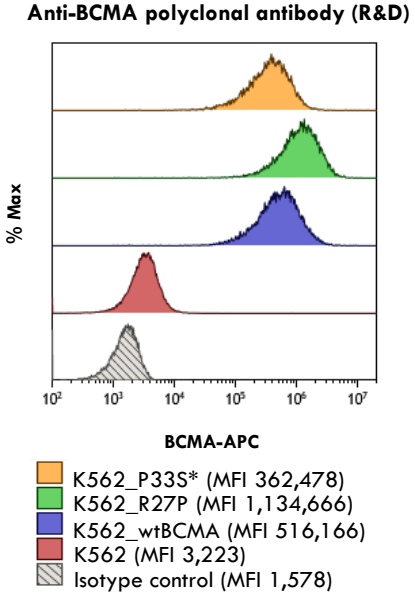


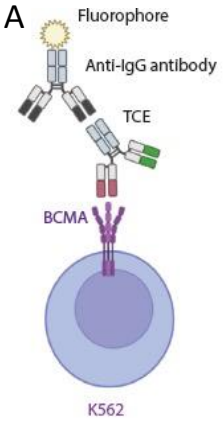


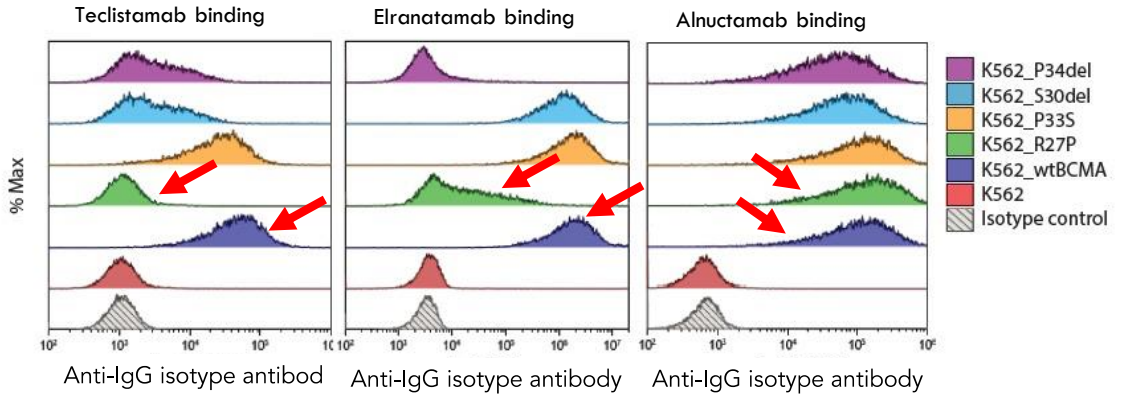


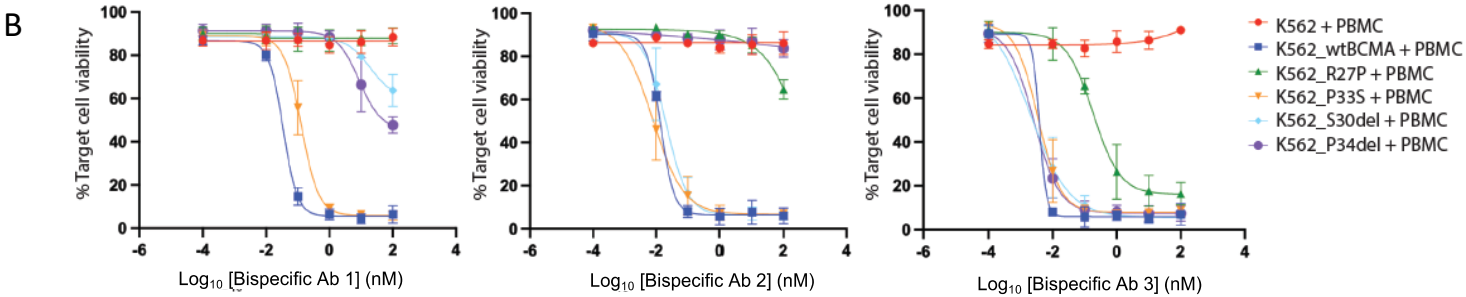
Lee H et al. Nature Medicine 2023

TNFRSF17 extracellular domain mutations differentially affect TCE binding and cytotoxicity









Lee H et al. Nature Medicine 2023

Since these mutations confer distinct sensitivities toward different anti-BMCA therapies their recognition is key for optimal design and selection of targeted immunotherapy.

Tumor-Intrinsic Mechanisms of resistance to anti-GPRC5D T-cell based Therapies

GPRC5D biallelic loss

- Post TCE:

Clonal convergence → 5 cases of MM relapse with biallelic genomic events on GPRC5D (biallelic deletions or monoallelic deletion and mutations) [1,2].

Epigenetic silencing: 2 patients with loss of chromatin accessibility at GPRC5D gene locus[2].

- Post anti-GPRC5D CAR T:

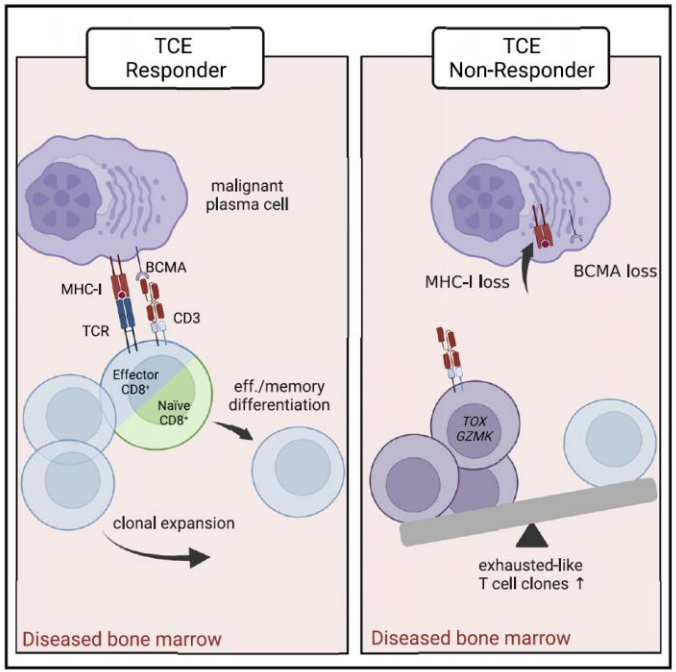
GPRC5D loss or reduction of surface antigen expression in 6/6 patients post anti-GPRC5D CAR T[3,4].

1. Lee H et al. Nat Med. 2023;29:2295-2306
2. Derrien J et al. Nat Cancer 2023; 4: 1536-1543
3. Mailankody S et al N Engl J Med 2022; 387:1196-1206
4. Mi X et al. N Engl J Med 2023; 389:1435-1437

Cancer Cell

The pre-existing T cell landscape determines the response to bispecific T cell engagers in multiple myeloma patients

Graphical abstract



Authors

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Correspondence

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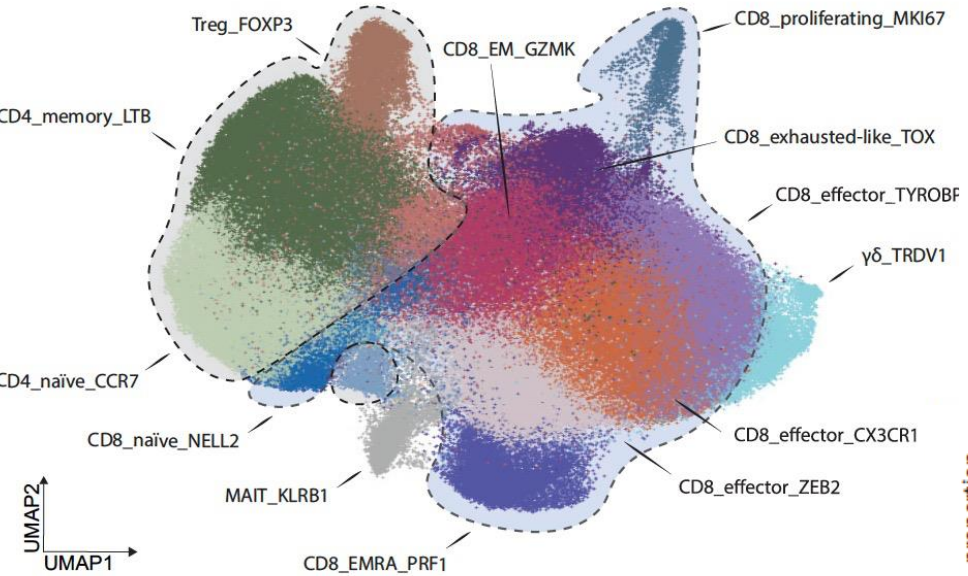
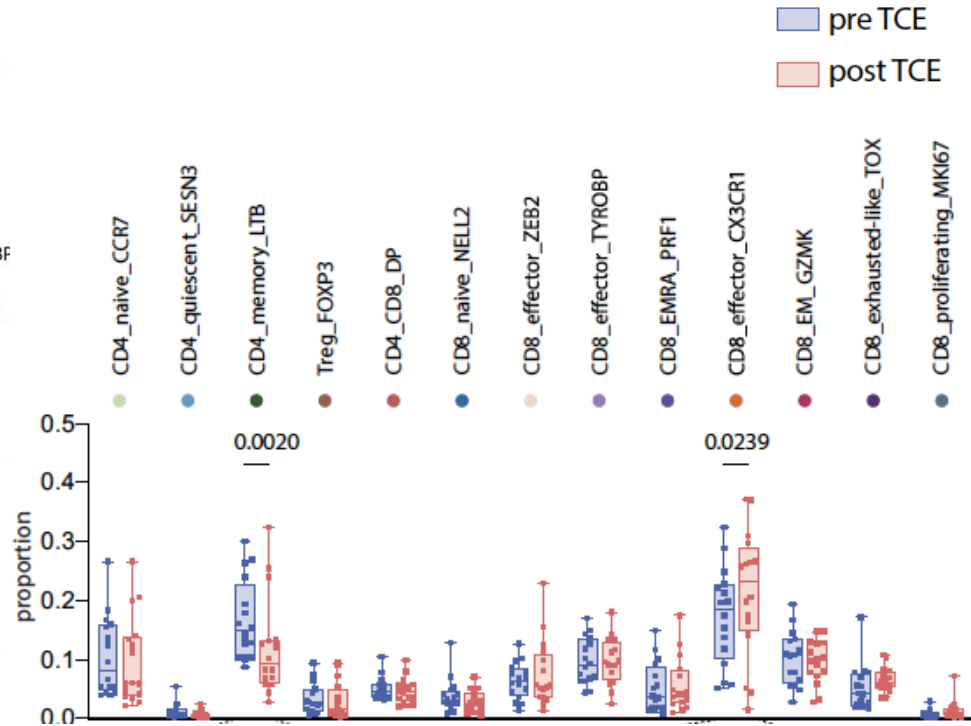
In brief

Bispecific T cell engagers (TCEs) have shown promise in the treatment of various cancers, but their mode of action in humans is elusive. Providing new insight into immunological mechanisms, Friedrich et al. identify how T cells in multiple myeloma patients respond to TCEs according to their cell state and link inter-individual differences in the immune repertoire to clinical response.

TCE response is driven by CD8+ effector cells

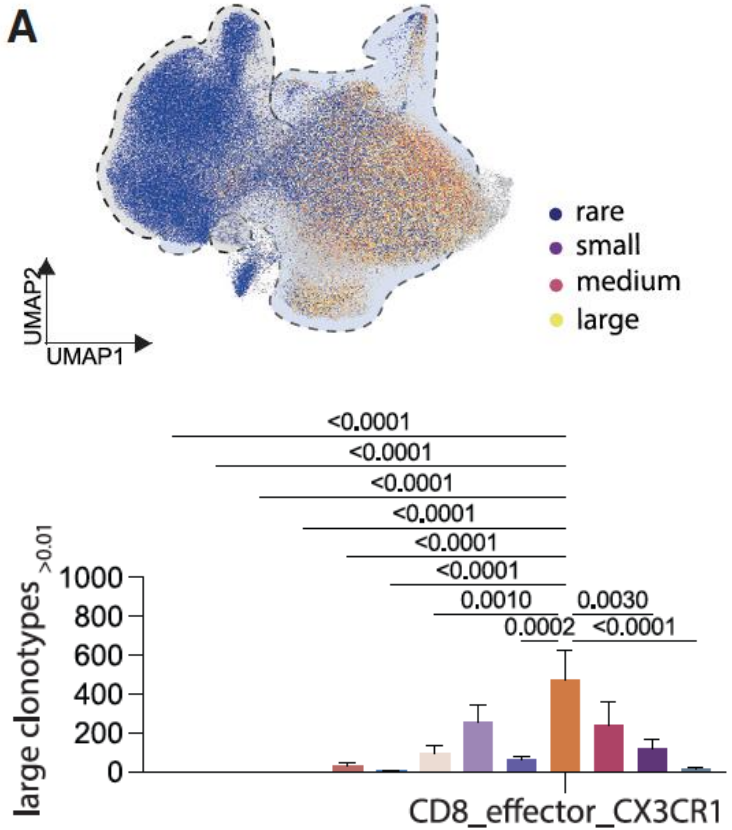


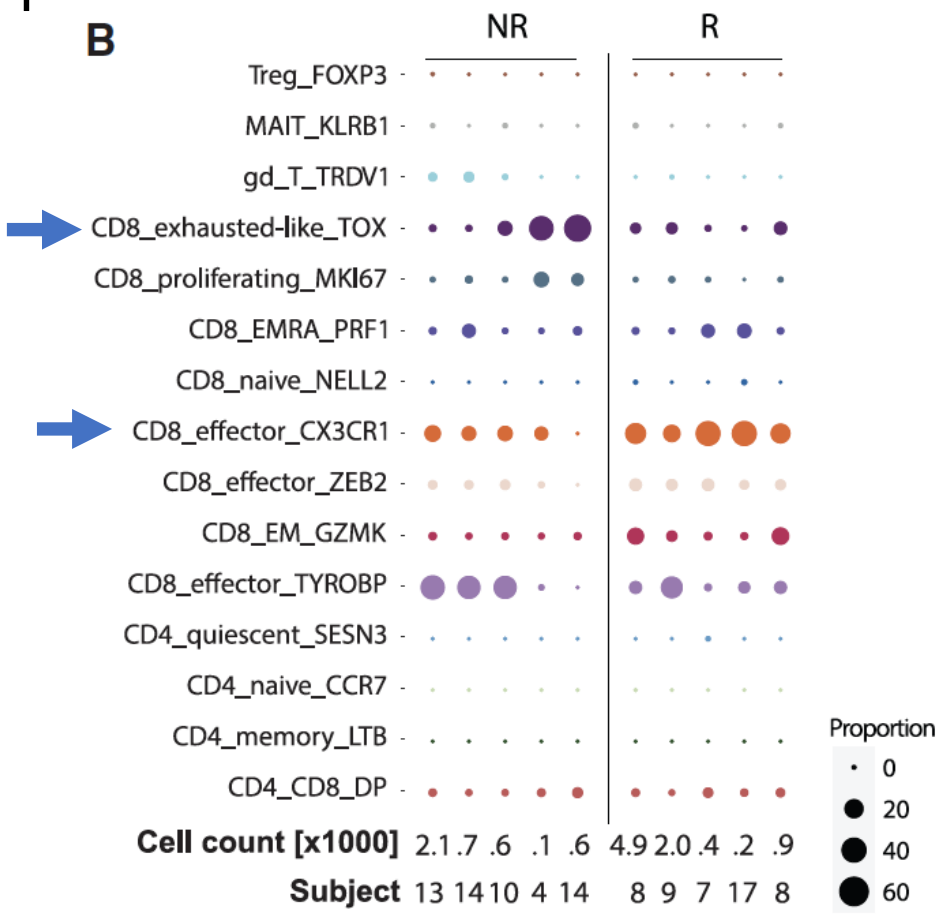


Friedrich, Neri et al., 2023, Cancer Cell 41, 1–15

Longitudinal tracking of clonotypic T cells during TCE treatment reveals preferential expansion of cytotoxic CD8$^+$ cells

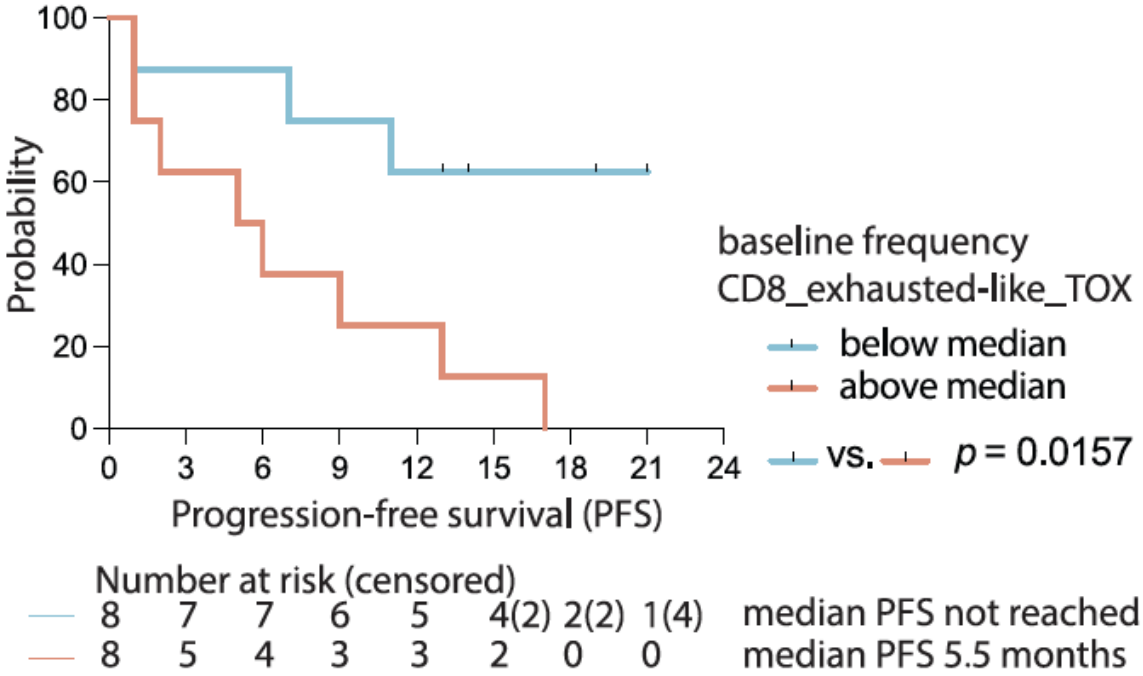
Abundance of exhausted-like T cell clones is associated with clinical response failure

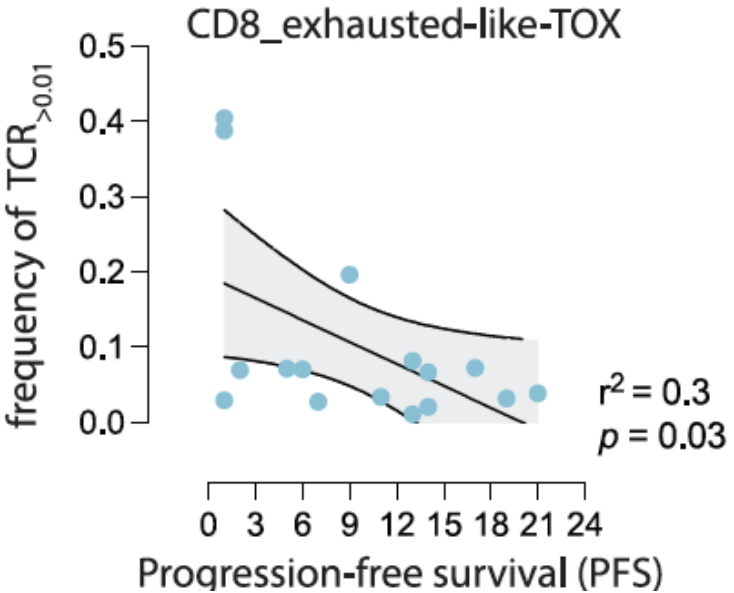




Friedrich, Neri et al., 2023, Cancer Cell 41, 1–15

Proportion of pre-existing exhausted CD8+ clonotypes pre-therapy is significantly increased in BCMAxCD3 TCE non-responder patients

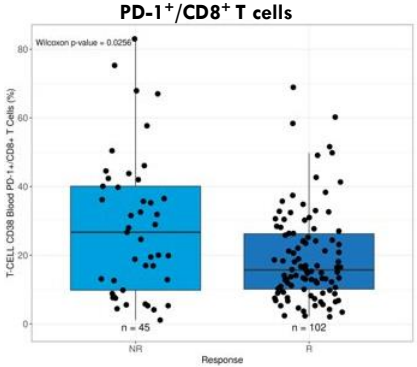


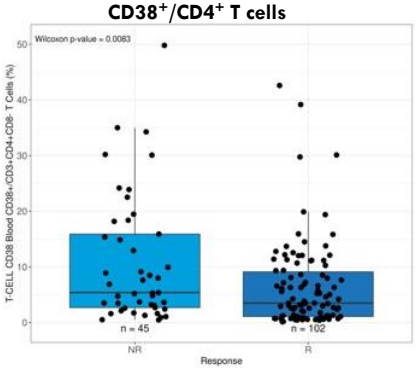


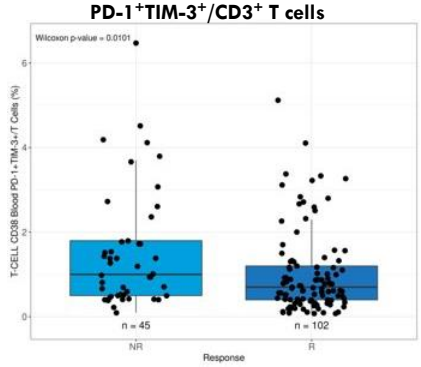
Friedrich, Neri et al., 2023, Cancer Cell 41, 1–15

Non-responders Show Higher Frequency of T Cells Expressing PD-1, TIM-3, and CD38 in Blood and Bone Marrow at Baseline

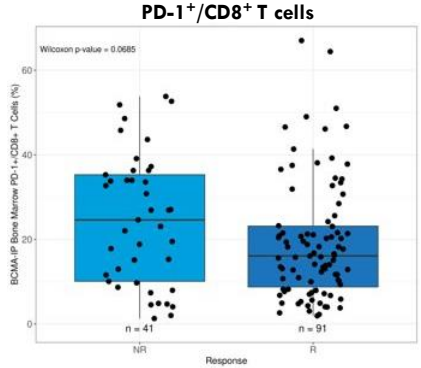
Peripheral Blood

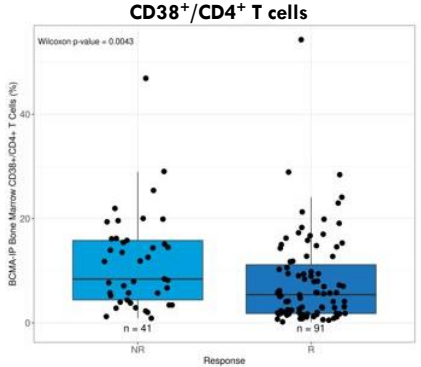


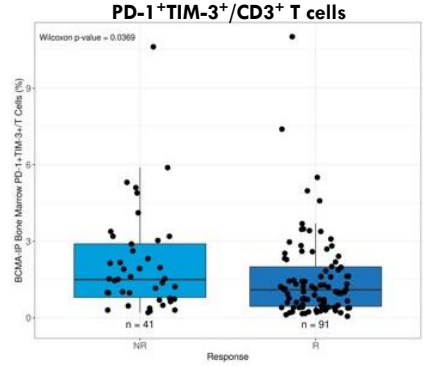




Bone Marrow





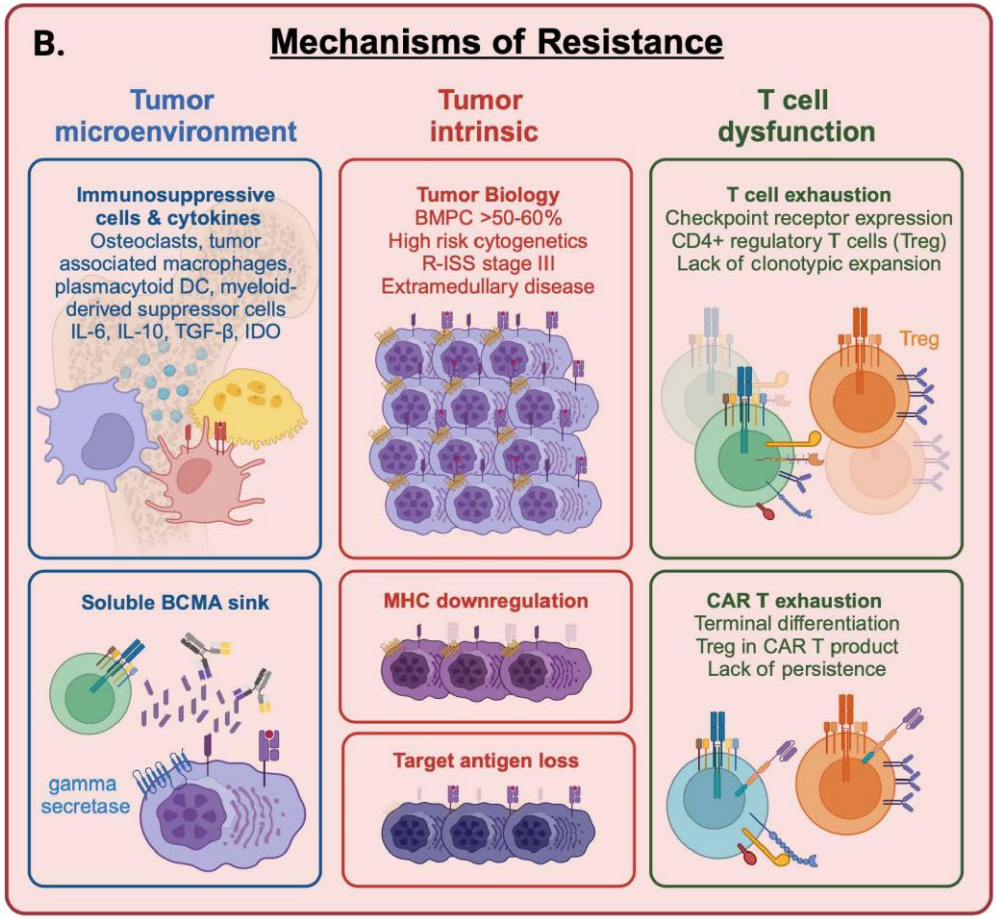


PD-1, TIM-3 and CD38 markers can be associated with T cell exhaustion or dysfunction

Peripheral T cells of non-responders are enriched for Tregs, which are key regulators of immune response

Cortes-Selva D et al , *Blood* 2022; 140: 241–243

Summary



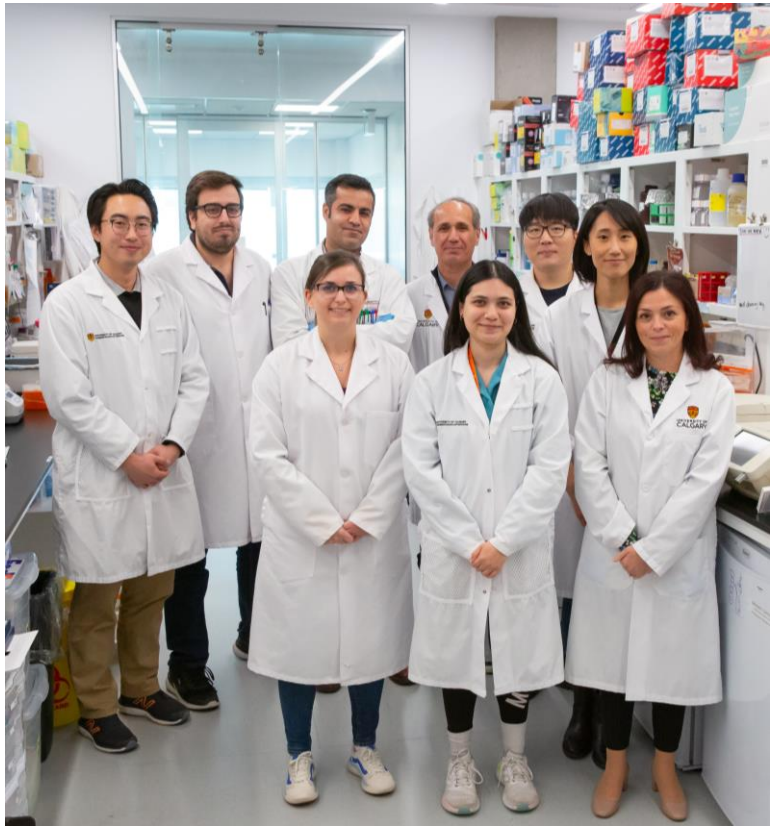
Lee H, Neri P et Bahlis N, Blood January 9, 2024

Acquired resistance to T-cell based therapies:
→ Predominantly driven by target antigenic loss post BCMA or GPRC5D CART and TCE
→T cell exhaustion.

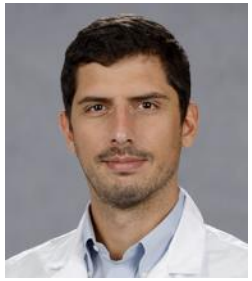
Primary resistance to T-cell based therapies: :
→ High serum soluble BCMA
→ High disease burden and EMD
→ Pre-existing T cell exhaustion ($CD8^+$ TOX^+)
→ Composition of myeloid/DC compartment

A comprehensive genomic analysis of the tumor together with the study of the immune cell repertoire can help to identify patients with the highest likelihood of respond to these therapies and lead to the development of more effective strategies.

Acknowledgements



Our Patients & their families



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