



POST-NEW ORLEANS 2022

Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI

Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO

Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

Biologia del Mieloma

Alessandra Romano

Università di Catania
AOU Policlinico Rodolico San Marco



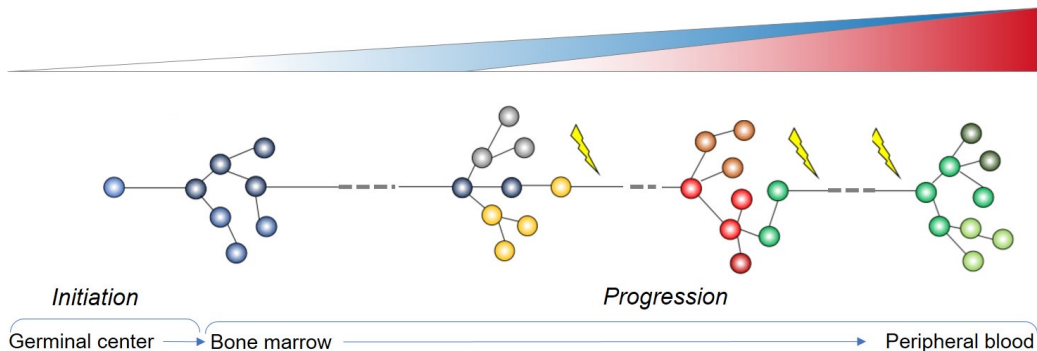


DICHIARAZIONE

Alessandra Romano

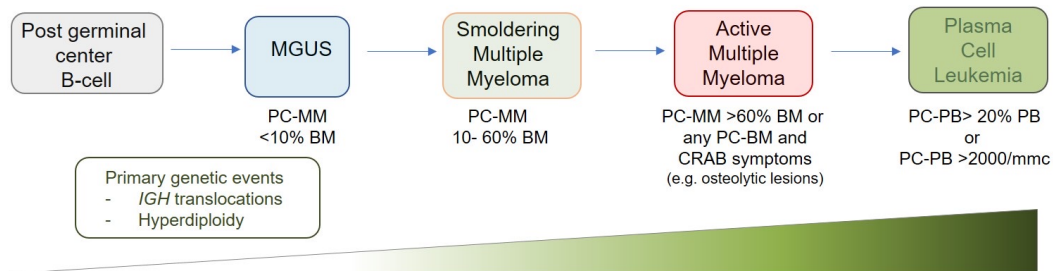
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Takeda, Novartis, Blueprint)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(Incyte)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro



Early/Initiating Driver Events

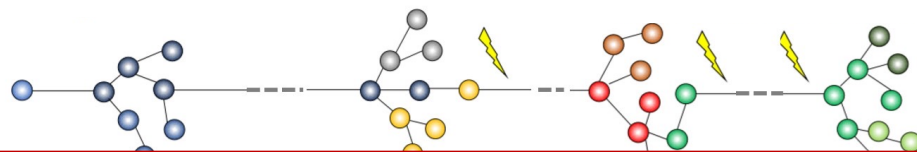
- Hyperdiploidy ($\geq 60\%$ of patients):
 - Trisomies of ≥ 2 odd-numbered chromosomes (3,5,7,9,11,15,19, & 21)
- *IGH* translocations:
 - t(4;14)(*NSD2*;*IGH*)
 - t(14;16)(*IGH*;*MAF*)
 - t(14;20)(*IGH*;*MAFB*)
 - t(6;14)(*CCND3*;*IGH*)
 - t(11;14)(*CCND1*;*IGH*)



Primary genetic events
- *IGH* translocations
- Hyperdiploidy

Secondary genetic events:
Copy number variations, DNA hypomethylation, Acquired mutations
MYC overexpression, TP53 inactivation, NFkB activation

Microenvironment



When and where genetic events occur?

Early/Initiating Driver

- Hyperdiploidy ($\geq 60\%$ of patients)
 - Trisomies of ≥ 2 odd-numbered chromosomes (3,5,7,9)
- *IGH* translocations:
 - t(4;14)(*NSD2*;*IGH*)
 - t(14;16)(*IGH*;*MAF*)
 - t(14;20)(*IGH*;*MAFB*)
 - t(6;14)(*CCND3*;*IGH*)
 - t(11;14)(*CCND1*;*IGH*)

Hyperdiploidy

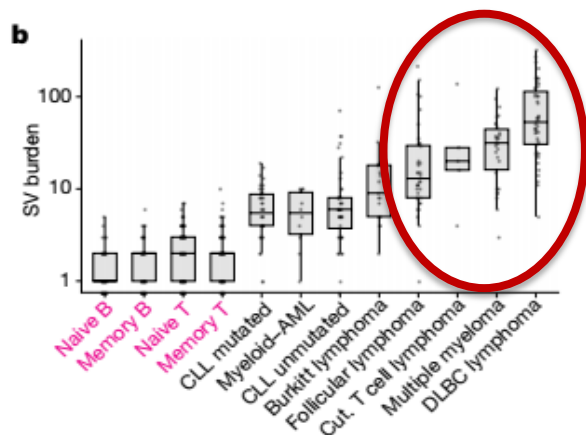
Secondary genetic events:
Copy number variations, DNA hypomethylation, Acquired mutations
MYC overexpression, TP53 inactivation, NF κ B activation

Microenvironment

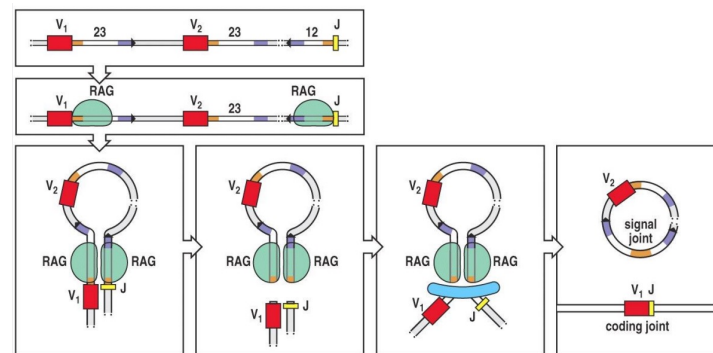


Tracking the Earliest Genomic Events in Multiple Myeloma Life-History

Anthony Cirrincione, Bachisio Ziccheddu, Kylee H Maclachlan, Alexandra M. Poos, Monika Chojnacka, Benjamin Diamond, Eileen M Boyle, Patrick Blaney, Dylan Gagler, Yanming Zhang, Ahmet Dogan, Alexander M Lesokhin, Faith E. Davies, Neha Korde, Marc S Raab, Niels Weinhold, Saad Usmani, Gareth J. Morgan, Ola Landgren, Francesco Maura



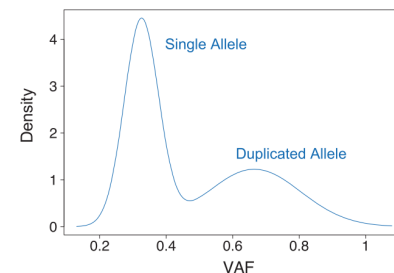
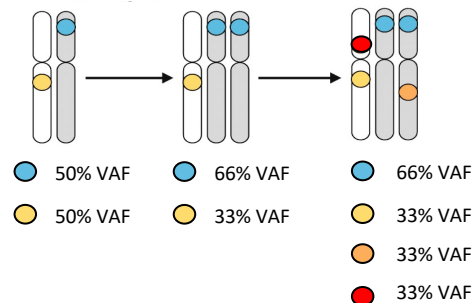
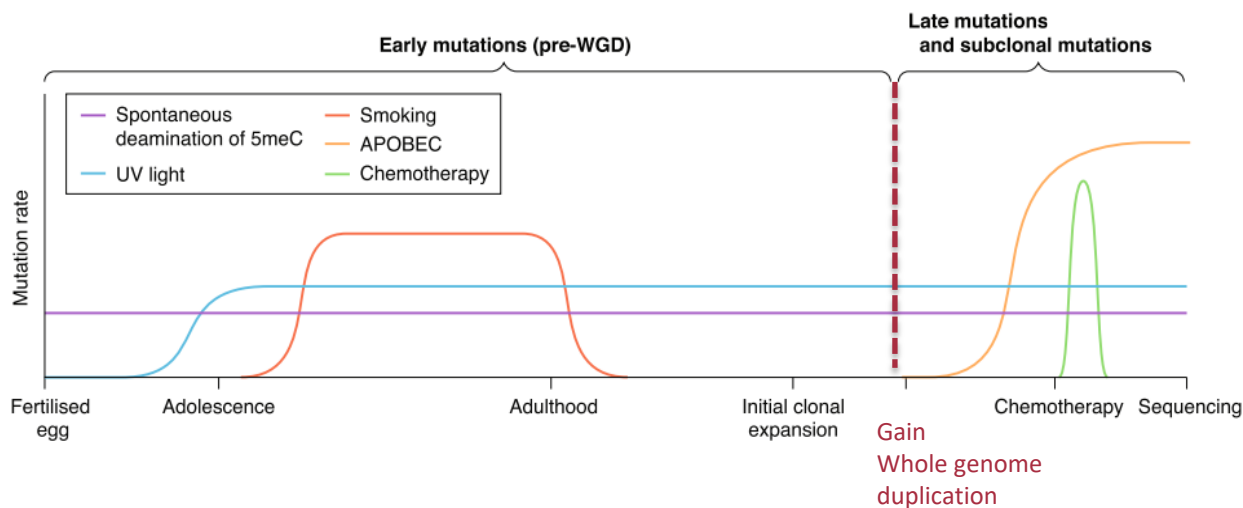
Machado, Nature 2022



Is there any involvement of RAG, a lymphoid-specific endonuclease, participates in V(D)J recombination, which accounts for antigen receptor diversity?



How to define the time windows when driver events are acquired

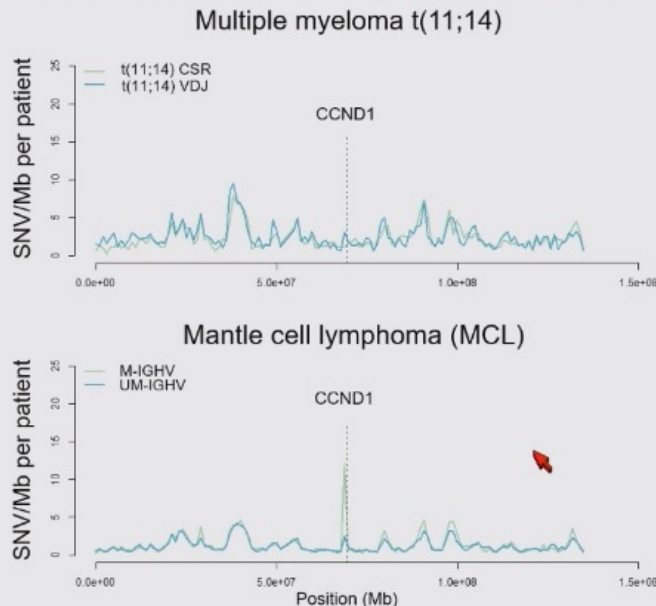
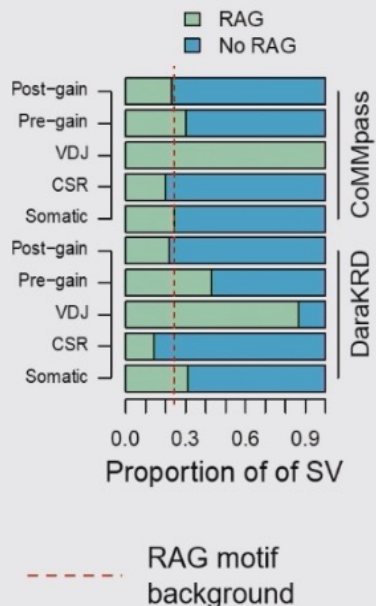


Jolly G., *Gen.Bio.* 2018; Maura F., *Nat. Comm.* 2019; Maura F., *CCR* 2020;
Rustad E., *Nat. Comm.* 2020; Oben E., *Nat. Comm.* 2021



RAG-mediated events are likely not involved in myeloma pathogenesis

RAG Motif Analysis



In post-GC translocations the derivative chromosome is not exposed to somatic hypermutation

No kataegis AID mediated in *CCND1* neither in events involving the CSR nor the one on the VDJ

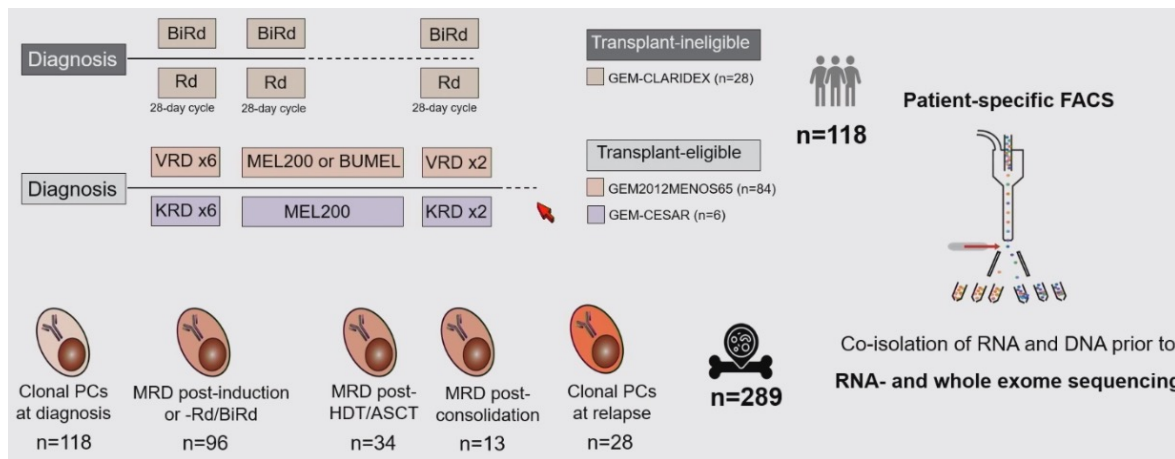
RAG-translocations exposed the derivative chromosome to somatic hypermutation

Kataegis AID mediated in *CCND1* only in M-IGHV MCL



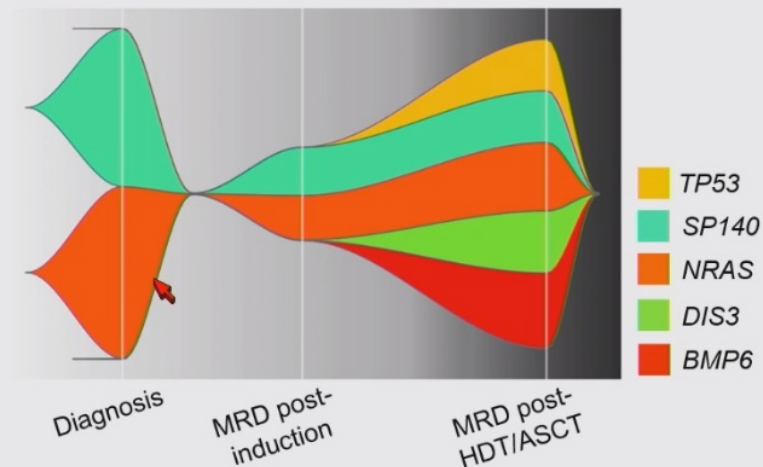
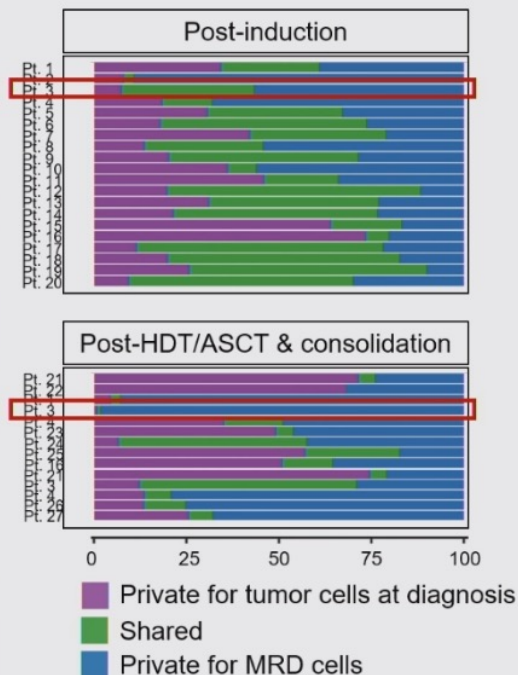
Multomics Profiling of Measurable Residual Disease (MRD) for Understanding the Biology of Ultra-Drug Resistance in Multiple Myeloma (MM)

Camila Guerrero, Noemi Puig, Maria Teresa Cedena Romero, Ibai Goicoechea, Leire Burgos, Diego Alignani, Aitziber Lopez, Sarai Sarvide, María José Calasanz, Ramon Garcia-Sanz, Joaquin Martinez-Lopez, Laura Rosiñol, Esther González Garcia, Albert Oriol, Rafael Rios, Estrella Carrillo-Cruz, Marta Sonia Gonzalez Perez, Carmen Montes Gaisan, Felipe De Arriba, Jose Maria Arguiñano, Josep M Marti, Yolanda Gonzalez-Montes, Antonio Garcia-Guiñon, Juan-José Lahuerta, Joan Bladé Creixenti, Maria-Victoria Mateos, Jesús San-Miguel, Bruno Paiva





MRD cells post-HDT/ASCT present an increase of *de novo* mutations WES of paired tumor cells at diagnosis and MRD

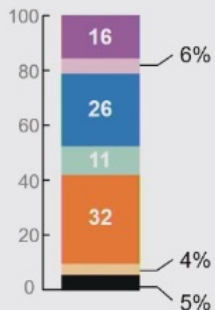


Our results reveal **transcriptional stability during induction** with relative **divergence after HDT/ASCT**, as well as progressive genomic evolution that peaked after HDT/ASCT

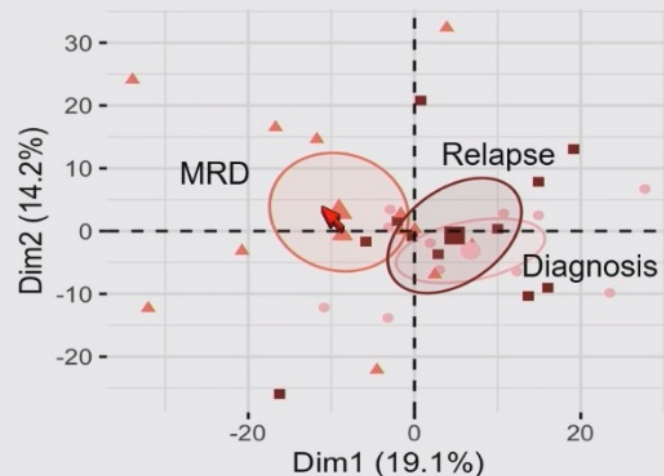
These findings could help explain the **continued responses with longer induction regimens**, and **limited efficacy of consolidation after HDT/ASCT** observed in recent studies



MRD is a singular genomic state between diagnosis and relapse



- Private for tumor cells at **diagnosis**
- Shared between tumor cells at **diagnosis** and **MRD**
- Private for **MRD** cells
- Shared between **MRD** cells and tumor cells at **relapse**
- Private for tumor cells at **relapse**
- Shared between **tumor cells at diagnosis & relapse**
- Shared for **all cells**

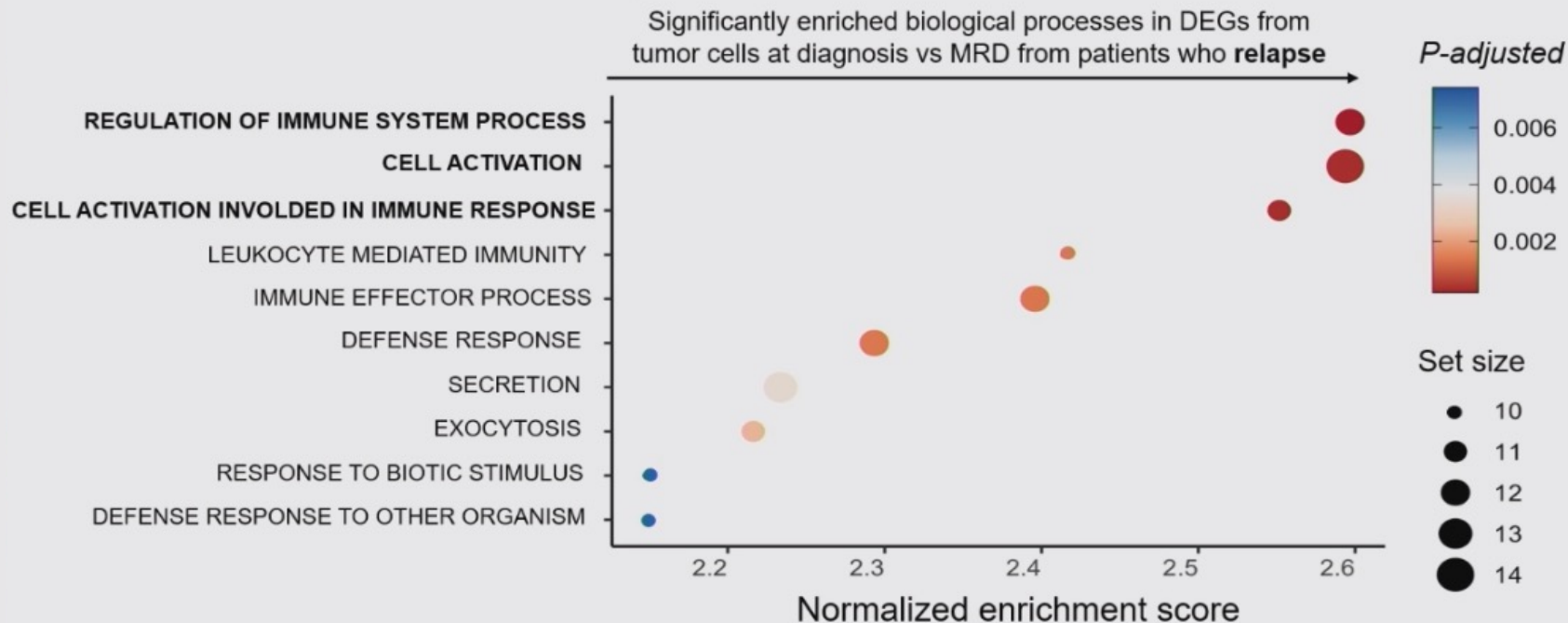


- Tumor cells at diagnosis
- MRD cells
- Tumor cells at relapse



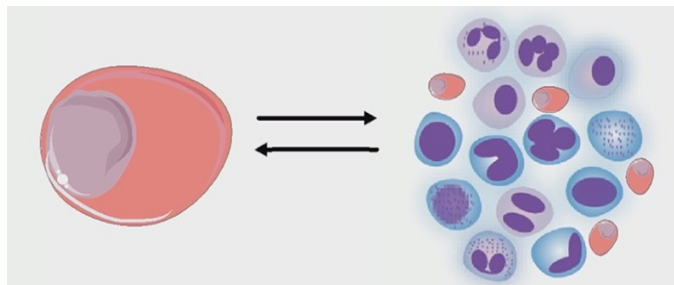
Enriched biological processes in MRD resistance and progression

RNAseq in paired tumor cells at diagnosis, MRD and relapse





How are malignant cells and the tumor microenvironment related in Multiple Myeloma?



- In MM precursors (MGUS, SMM)
- During treatment (MRD cells)
- At relapse
- After exposure to novel immunotherapies

- T-cells (CD4+/CD8+)
- Dendritic cells
- Macrophages
- Others ...



Abstract #470

Genomic Determinants of Resistance in Newly Diagnosed Multiple Myeloma Treated with Targeted-Immunotherapy

Francesco Maura, Eileen Boyle, David Coffey, Kylee H Maclachlan, Benjamin Diamond, Patrick Blaney, Dylan Gagler, Bachisio Ziccheddu, Hussein Ghamlouch, Yubao Wang, James E. Hoffman, Dickran Kazandjian, Hani Hassoun, Emily Guzman, Sham Mailankody, Urvi A Shah, Carlyn Tan, Malin Hultcrantz, Michael Scordo, Gunjan L. Shah, Heather Landau, David J. Chung, Sergio A. Giral, Yanming Zhang, Ahmet Dogan, Alexander M Lesokhin, Dennis Verducci, Faith E. Davies, Saad Usmani, Neha Korde, Gareth J. Morgan, Ola Landgren



Abstract #651

Fc-Mediated Antibody Effector Function, Inflammation Resolution and Oligoclonality on TCR Rearrangements Predict Sustained MRD Negativity in Newly Diagnosed Multiple Myeloma Treated with Immunotherapy Regimens

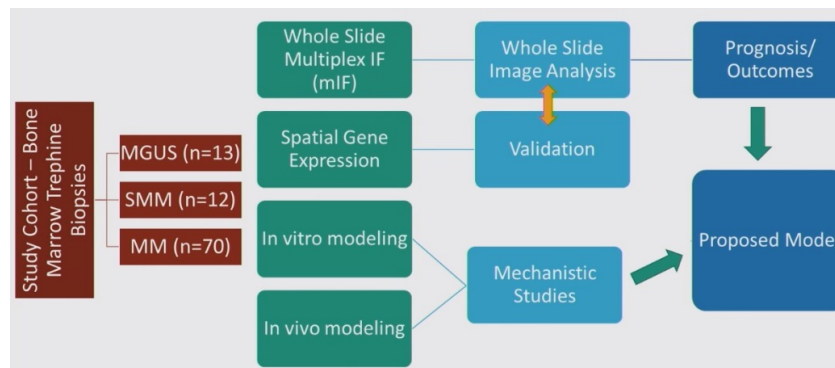
Eileen M Boyle, Francesco Maura, David Coffey, Kylee H Maclachlan, Benjamin Diamond, Hussein Ghamlouch, Dylan Gagler, Patrick Blaney, Bachisio Ziccheddu, Yubao Wang, Emily Guzman, Avital Tenenbaum, Ariel Siegrist, Xiaoyi Chen, Gaurav Varma, James E Hoffman, Dickran Kazandjian, Hani Hassoun, Sham Mailankody, Urvi A Shah, Carlyn Tan, Malin Hultcrantz, Michael Scordo, Gunjan L. Shah, Heather Landau, David J. Chung, Sergio A Giral, Yanming Zhang, Ahmet Dogan, Alexander M Lesokhin, Dennis Verducci, Faith E Davies, Saad Usmani, Neha Korde, Ola Landgren, Gareth J. Morgan





Tumor-Immune Architecture and the Regulation of Antigen-Specific T-Cell Infiltration in Multiple Myeloma and Premalignant Plasma Cell Disorders

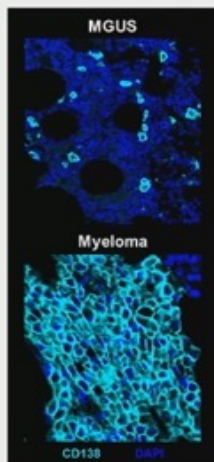
Hope Robinson, Nancy Villa, David L. Jaye, Ajay K. Nooka, Alyssa Duffy, Samuel McCachren, Julia Manalo, Jeffrey M. Switchenko, Ava Horvat, Vaunita C. Parihar, Jingjing Gong, Yan Liang, Geoffrey Smith, Vikas A. Gupta, Lawrence H. Boise, Jonathan L. Kaufman, Craig C. Hofmeister, Nisha Joseph, Sagar Lonial, Kavita Dhodapkar, Madhav Dhodapkar





Clustered growth of tumor cells is a distinct and tumour intrinsic feature of Multiple Myeloma

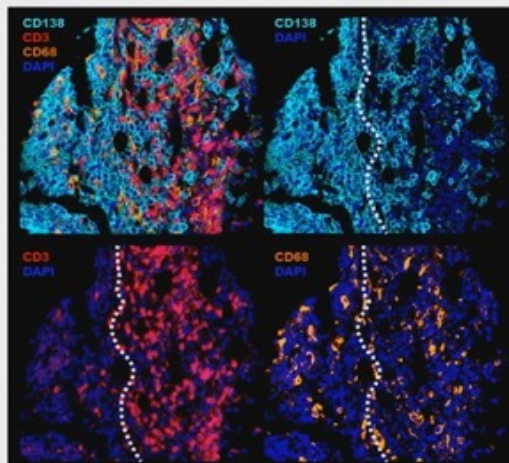
Clustered Tumor Growth



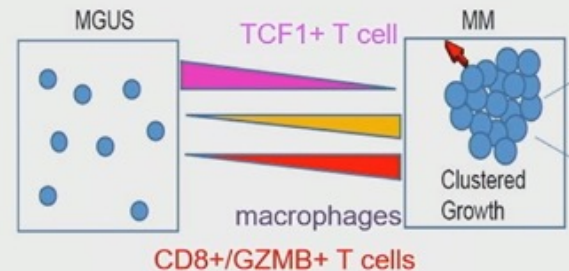
Humanized models



Immune Exclusion with MM



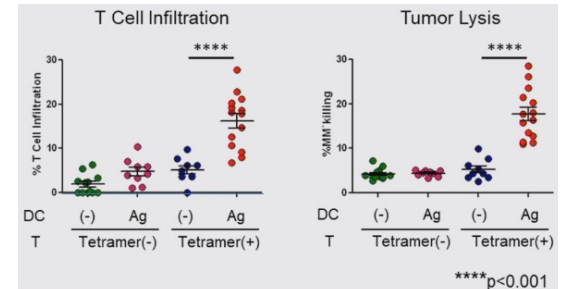
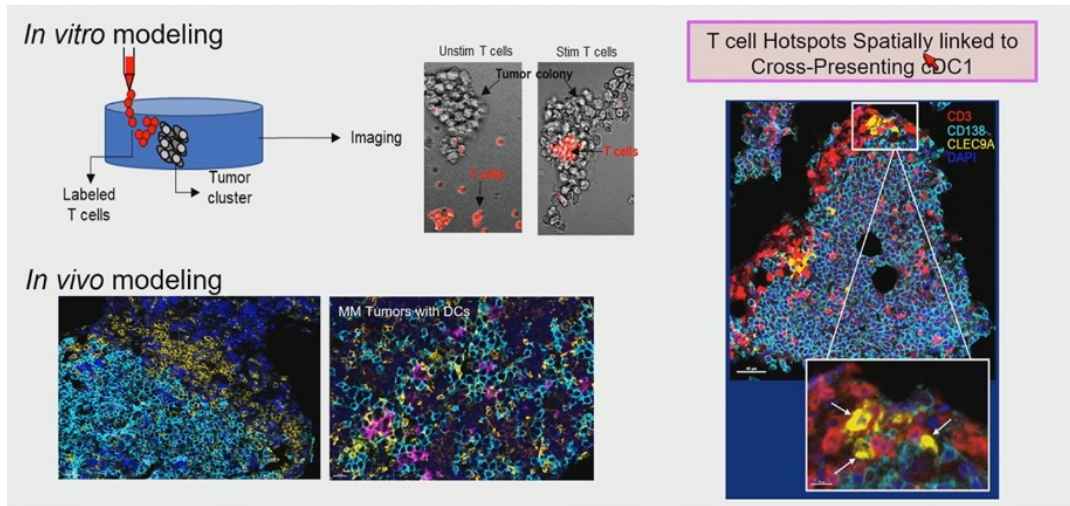
Intra-lesional heterogeneity



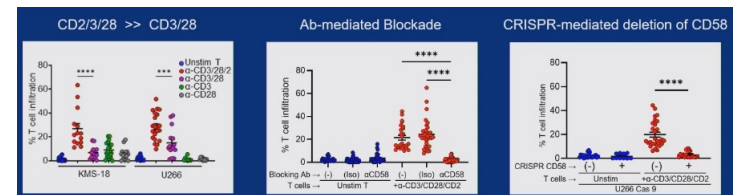


T-cell hotspots are spatially linked to cross-presenting cDC1, T-cell gradients and immune activation nodes

DC-mediated in situ stimulation

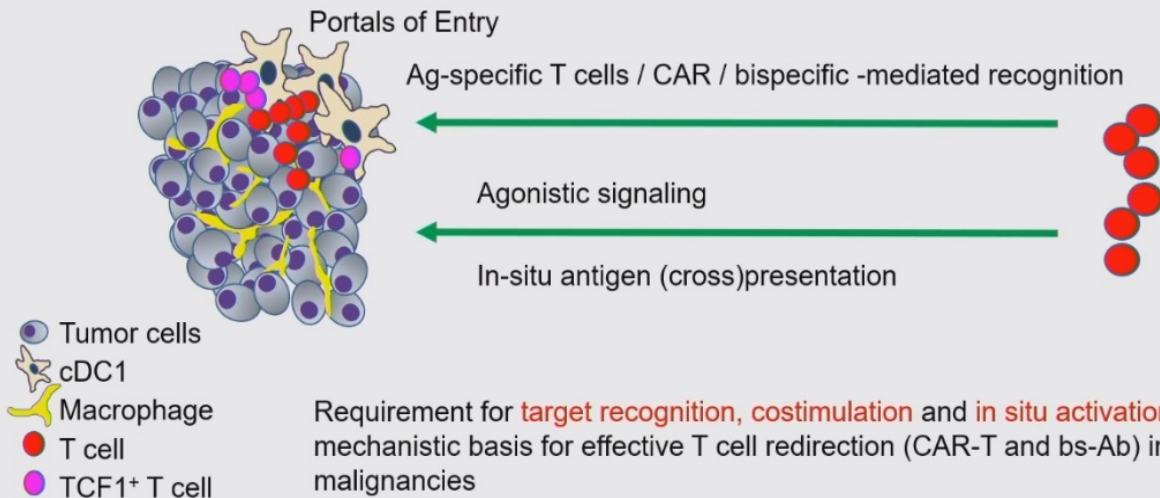
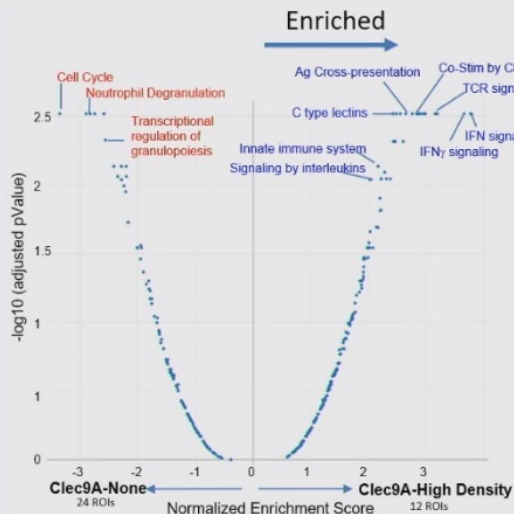


co-stimulation (CD2/CD58 axis)





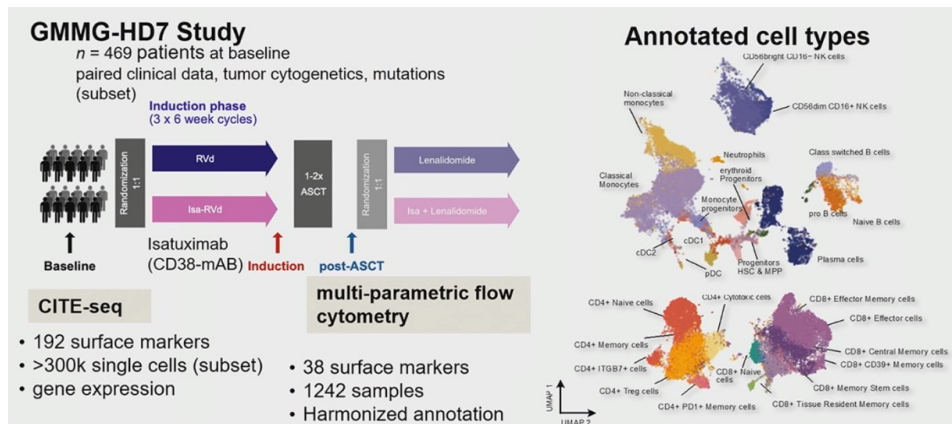
Mechanisms regulating entry of antigen-specific T cells into MM tumours





Bone Marrow Immune Signatures in Multiple Myeloma Are Linked to Tumor Heterogeneity and Treatment Outcome

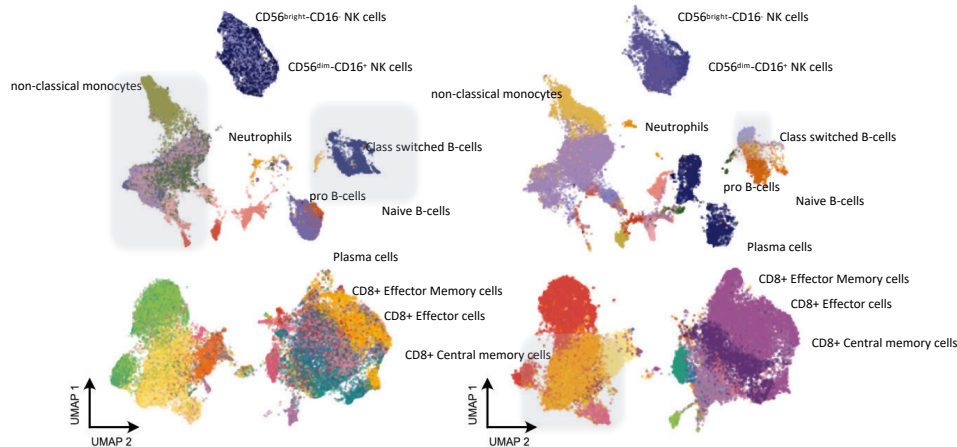
Simon Steiger, Raphael Lutz, Nina Prokoph, Subarna Palit, Stephan M Tirier, Philipp Reichert, Anja Baumann, Nadine Hefner, Sabrina Schumacher, Dominik Vonficht, Florian Grünschläger, Alexandra M Poos, Lukas John, Laleh Haghverdi, Jan-Philipp Mallm, Elias K Mai, Mirco Friedrich, Katharina Kriegsmann, Mohamed H.S. Awwad, Anna Jauch, Uta Bertsch, Diana Tichy, Carsten Müller-Tidow, Roland Schroers, Hans Salwender, Britta Besemer, Roland Fenk, Katja Weisel, Hartmut Goldschmidt, Stefanie Huhn, Michael Hundemer, Karsten Rippe, Simon Haas, Niels Weinhold, Marc S Raab





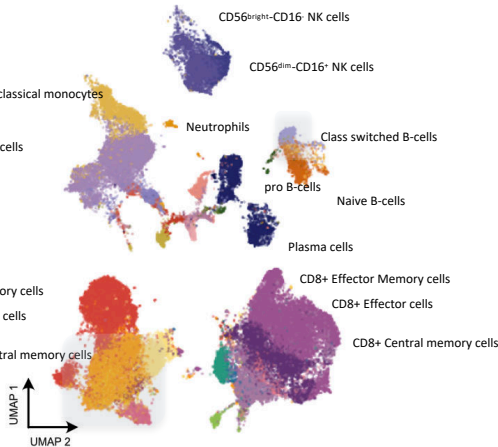
Dynamic changes of immune cells with therapy

Induction

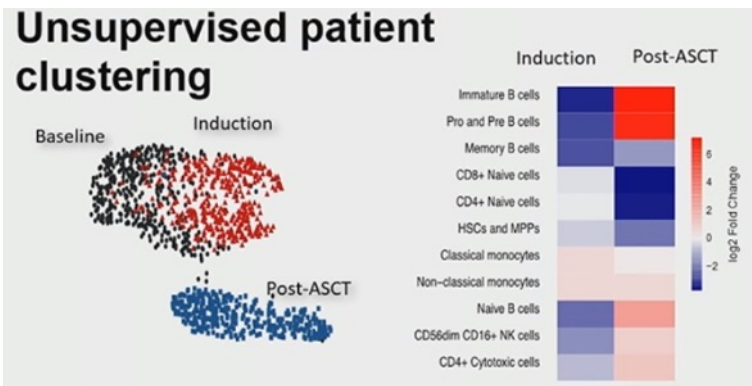


B cell lineage ↓
Monocytes ↑

Post ASCT



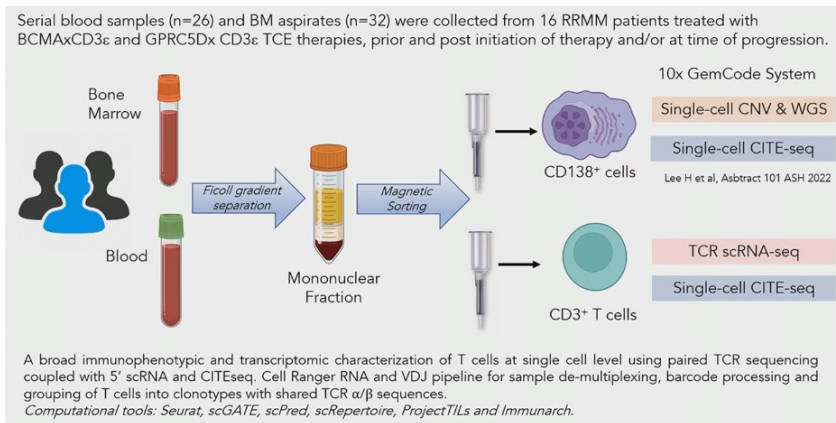
Naïve T & HSC/MPP ↓
B lineage ↑





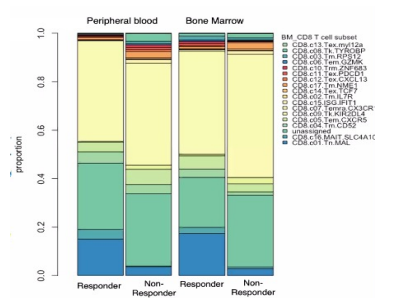
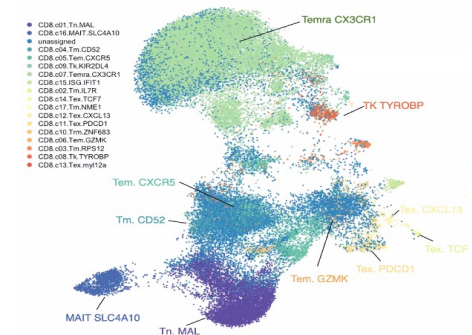
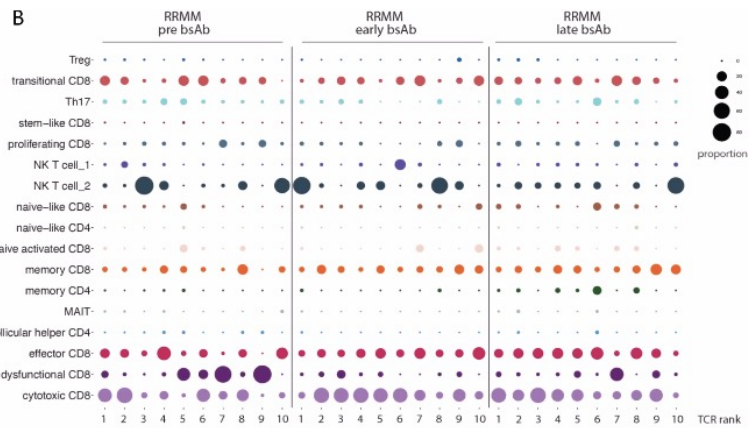
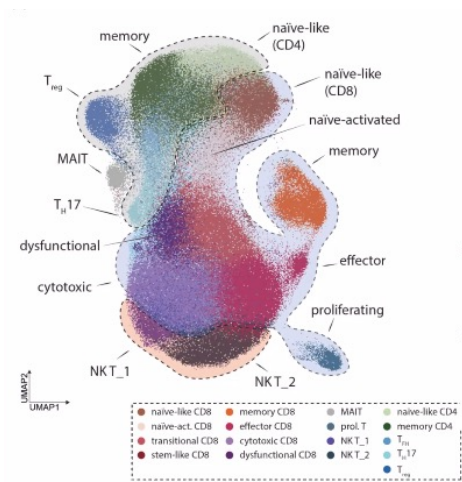
Dysfunctional Hyper-Expanded Clonotypes and Lack of TCR Clonal Replacement Predict Resistance to T Cell Engagers in Multiple Myeloma

Paola Neri, Sungwoo Ahn, Holly Lee, Noemie Leblay, Mirco Friedrich, Ranjan Maity, Rémi Tilmont, Elie Barakat, Marc S Raab, Nizar Jacques Bahlis





T-naive CD8 cells are enriched in responders with higher proportion of Tex in non responders

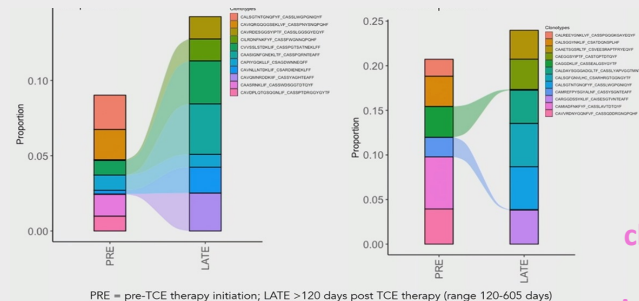
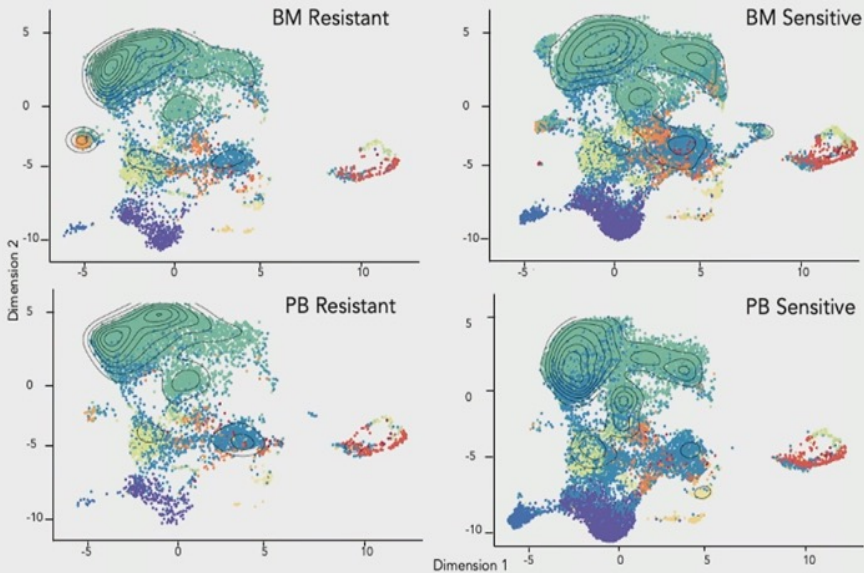




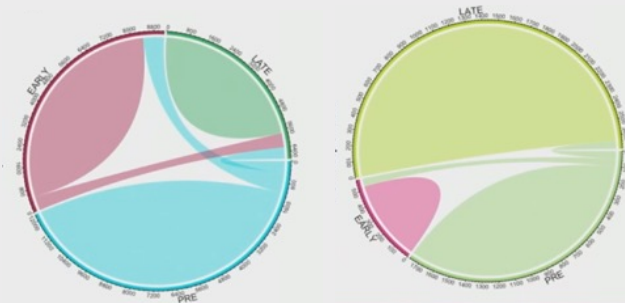
BM TCR clonal replacement by non-exhausted PB TCRs mediates response to TCE

Top clonotypes persist and expand in TCE responders

Top clonotypes contract in TCE non-responders



PRE = pre-TCE therapy initiation; LATE >120 days post TCE therapy (range 120-605 days)



due to lack of spatial overlap and temporal persistence of hyper-expanded CD8 clonotypes in non responders



Conclusions

- ❑ *MACRO*-effects of the *micro*-environment
- ❑ Microenvironment determinants have a role in MM relapse in MRD+ cases
- ❑ T-cell fitness and engagement are crucial for MM (*clustered*) growth and treatment
- ❑ Emerging escape mechanisms to TCE in RRMM: global exhaustion of both PB and BM T-cell clonotypes
- ❑ What to treat rather than when based on genomics **AND** microenvironment composition