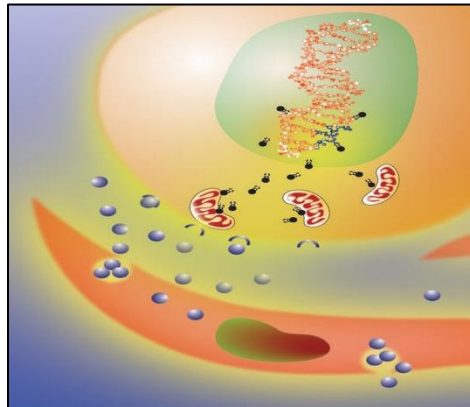


Clonal evolution in myeloid neoplasms and inflammatory stromal remodeling: implications for immunotherapy

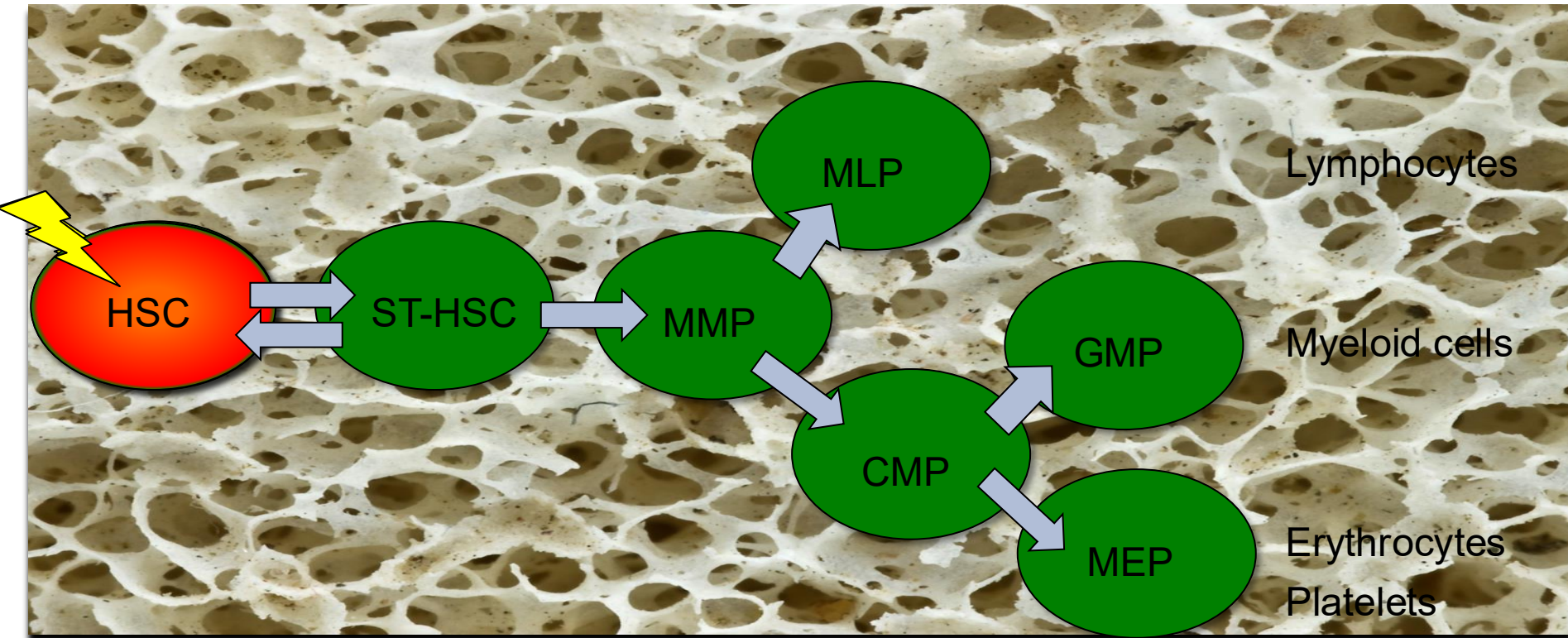
Marc H.G.P. Raaijmakers, M.D., Ph.D.

Erasmus Medical Center Cancer Institute, Department of Hematology Rotterdam
Institute for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm



2d Bologna Workshop on immunotherapy for Acute Myeloid Leukemia
Bologna, September 29-30, 2026

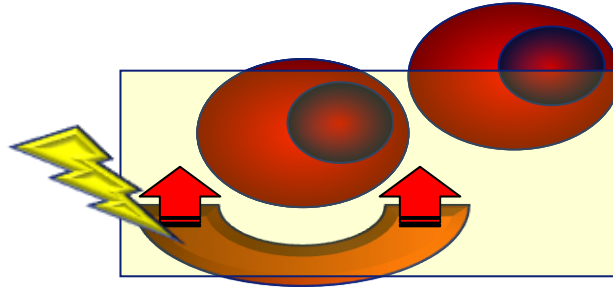
Hematopoiesis and clonal evolution



What drives mutational and epigenetic changes in HSC?
How do mutant clones gain competitive advantage?

Stromal niche contributions to hematopoietic neoplasm

niche-induced/facilitated oncogenesis



Raaijmakers et al, *Nature* 2010 (MDS/AML)

Kode et al, *Nature* 2014 (MDS/AML)

Dong et al, *Nature*, 2016 (JMML/MPN)

Niche-facilitated MDS and AML

Is there a (necessary) contribution of the bone marrow stromal niche to MDS initiation and evolution?

Does the aberrant microenvironment facilitate oncogenesis via induction or selection of mutant clones?

What are the molecular determinants of such contributions?

What is the relevance to human disease?

A comprehensive atlas of HSPC-niche signaling in the human normal and leukemic bone marrow



Lanpeng Chen

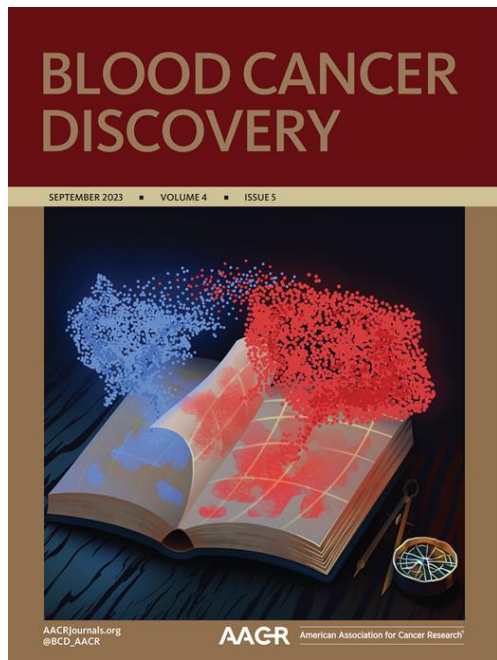
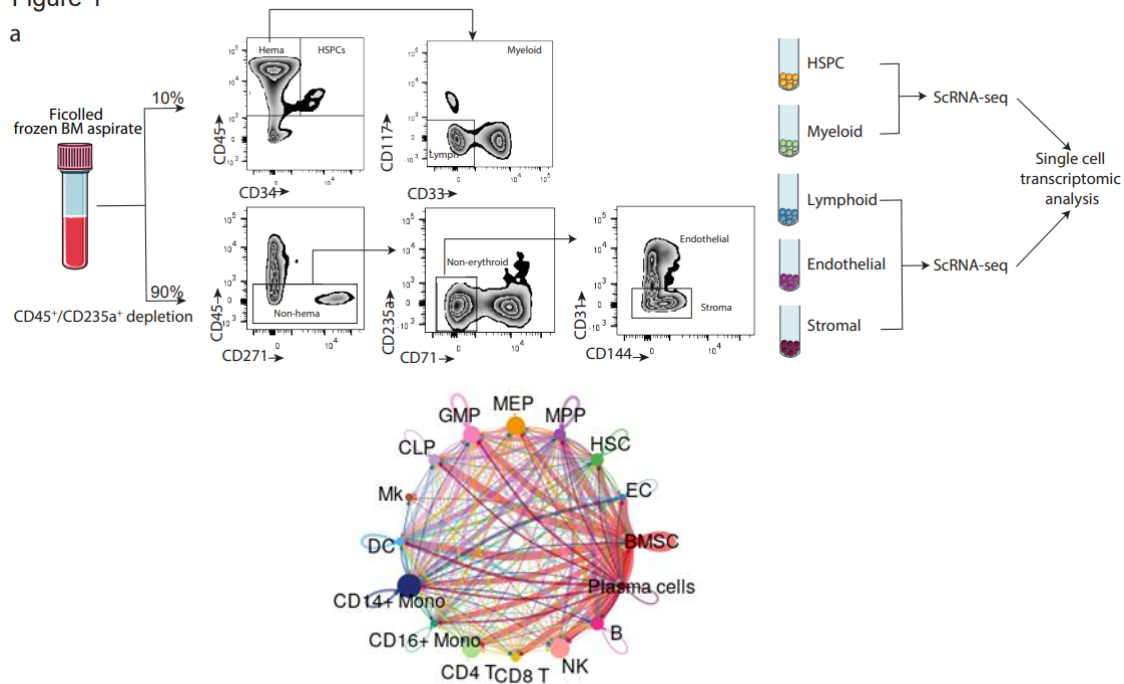


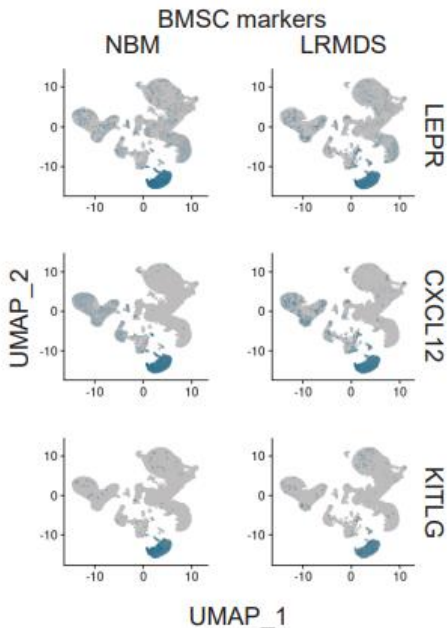
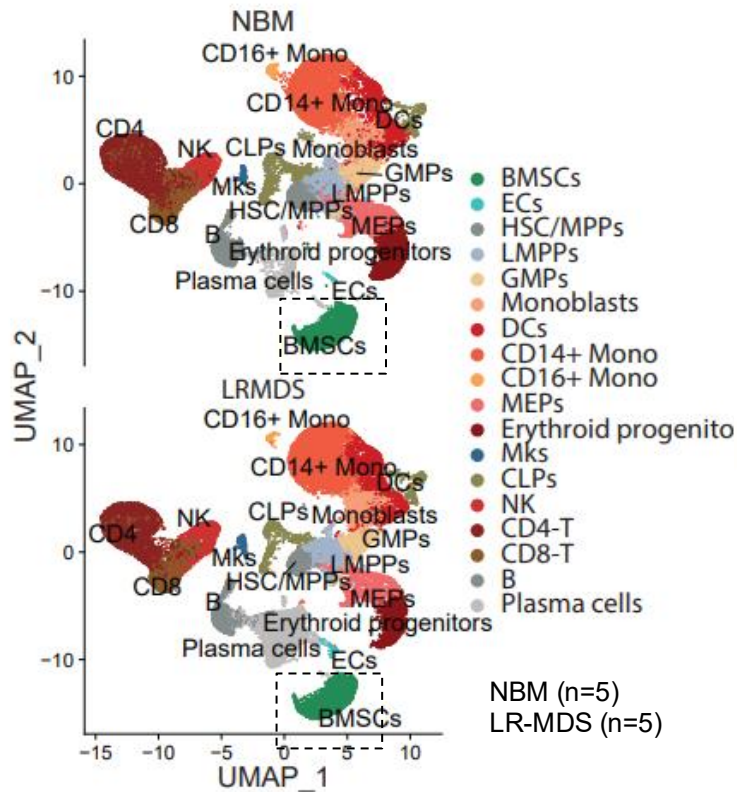
Figure 1

a

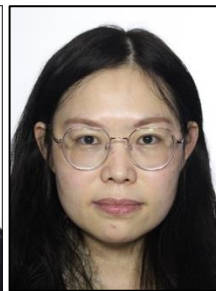


A Single-Cell Taxonomy Predicts Inflammatory Niche Remodeling to Drive Tissue Failure and Outcome in Human AML. Chen L, et al. *Blood Cancer Discov.* 2023 Sep 1;4(5):394-417.

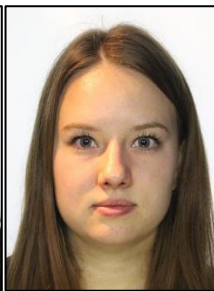
A comprehensive 'tissue map' of human lower-risk MDS



Lanpeng Chen

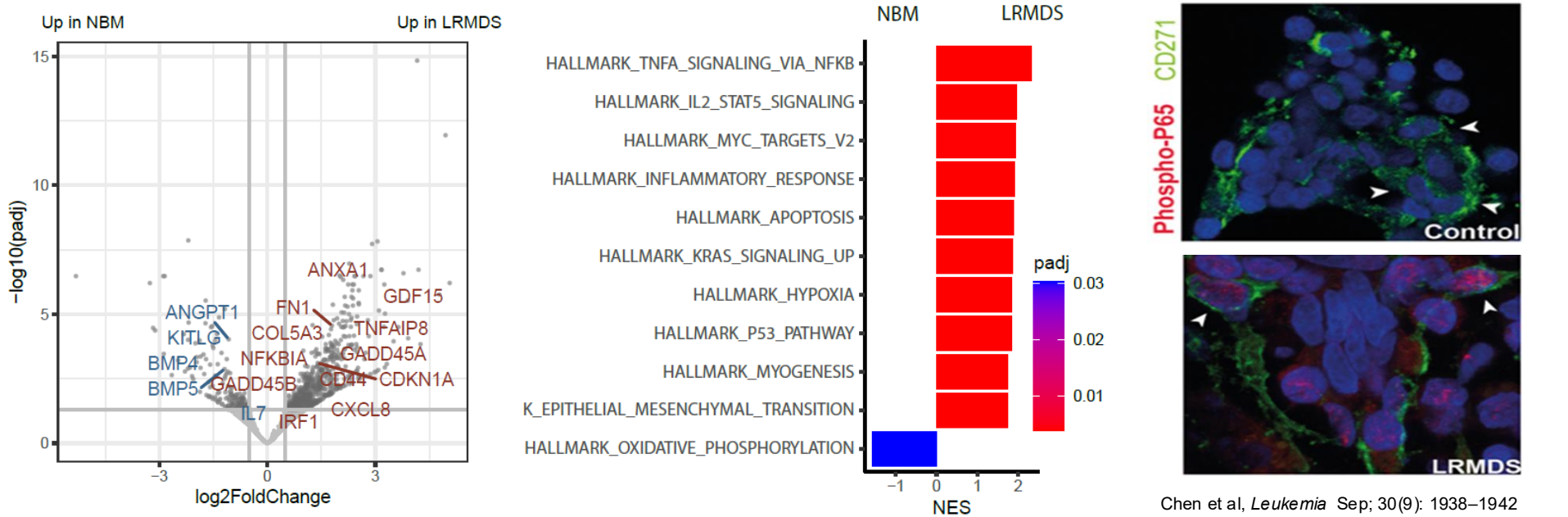


Yujie Bian



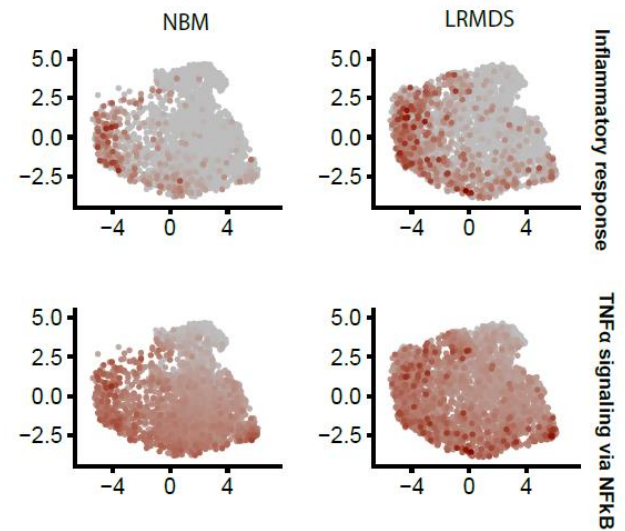
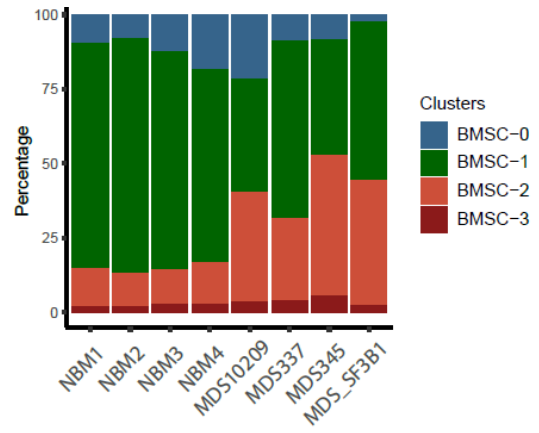
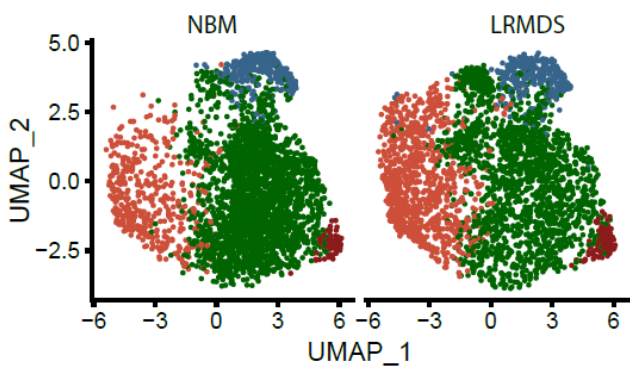
Claire van Dijk

Activation of NFkB signaling and inflammatory ligands with predicted negative impact on hematopoiesis in bone marrow stromal cells in LR-MDS

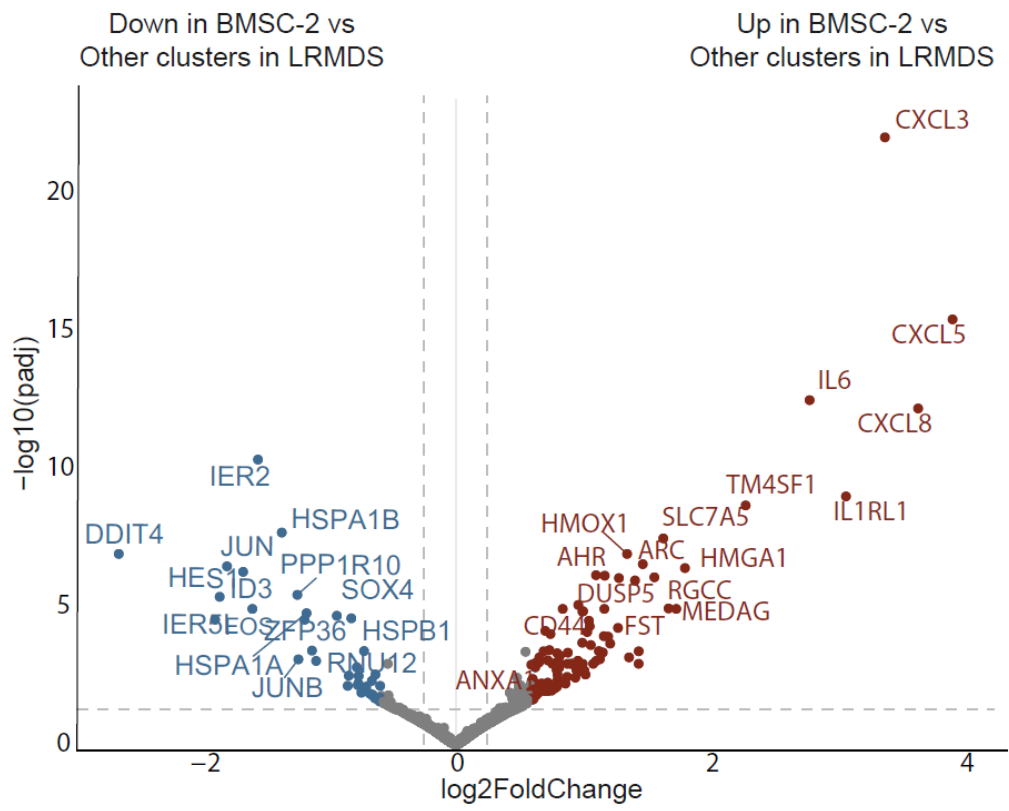


Chen et al, *Leukemia* Sep; 30(9): 1938–1942
 Ping Z, Chen S, et al. *Leukemia*. 2019 Feb;33(2):536–541.

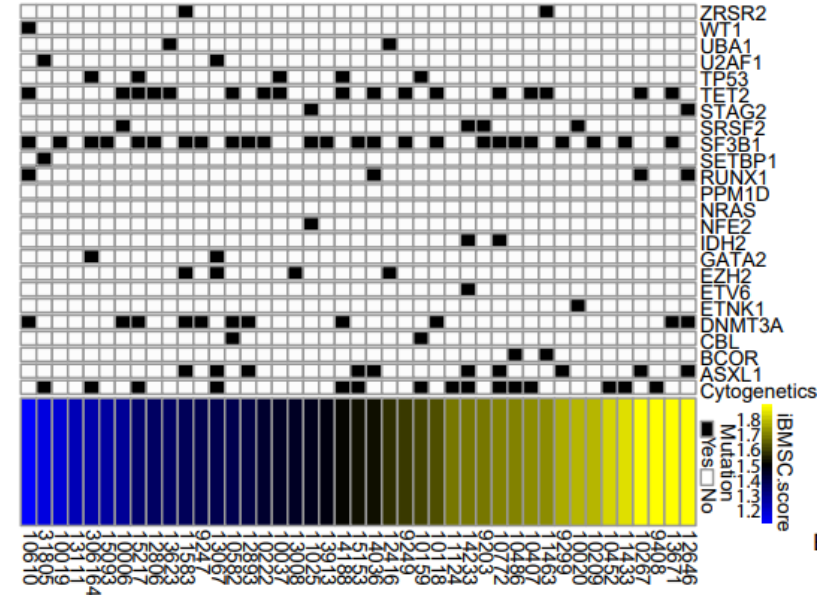
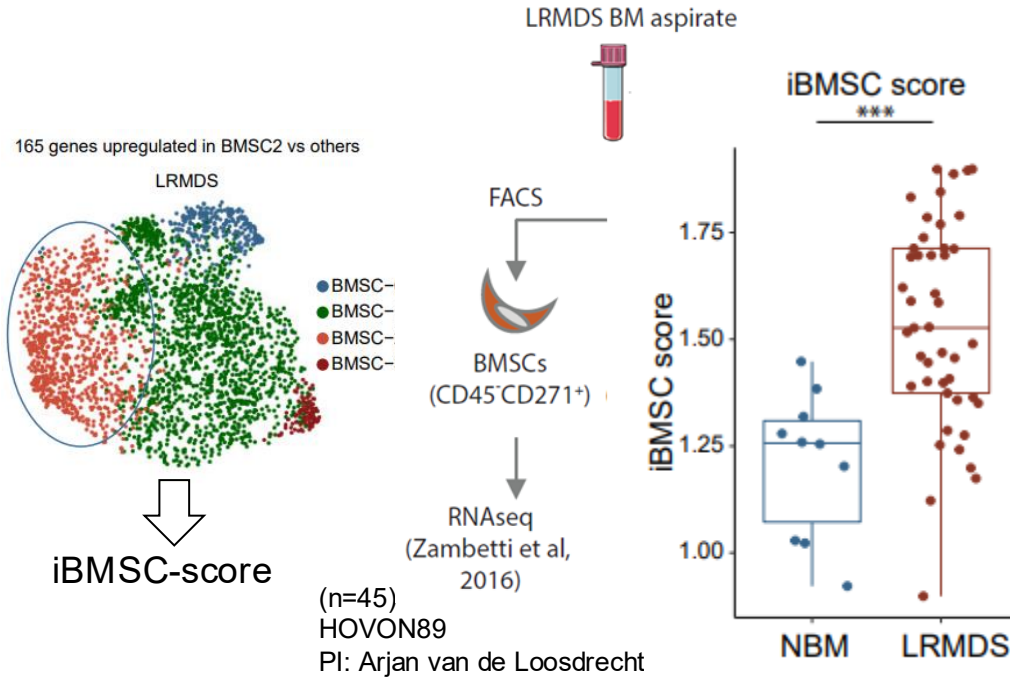
Inflammatory remodeling of bone marrow stromal cells in LR-MDS



Inflammatory remodeling of bone marrow stromal cells in LR-MDS



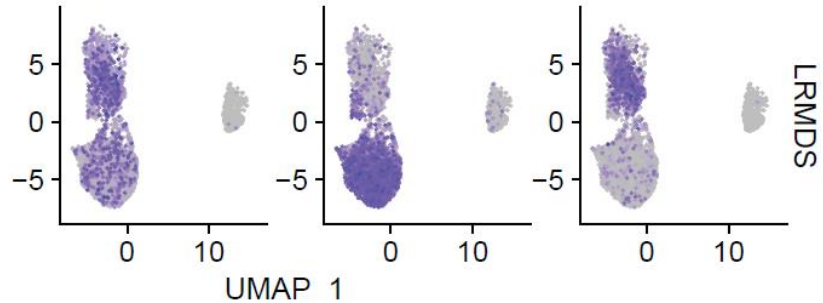
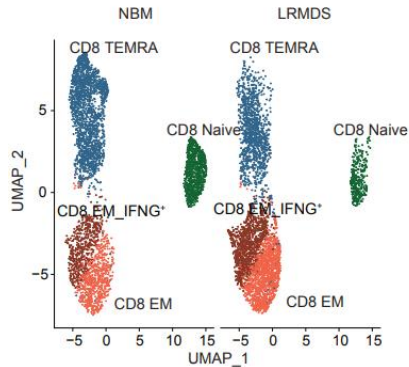
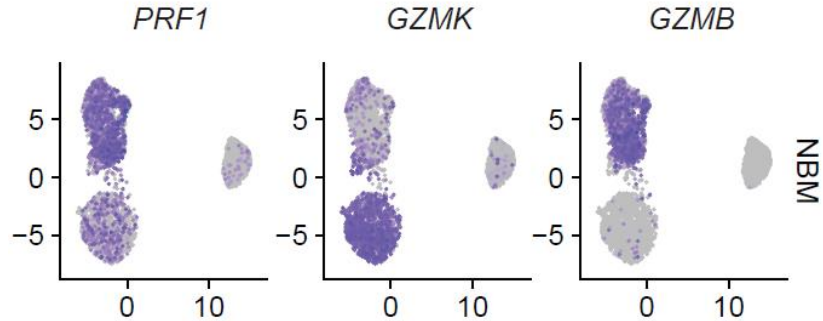
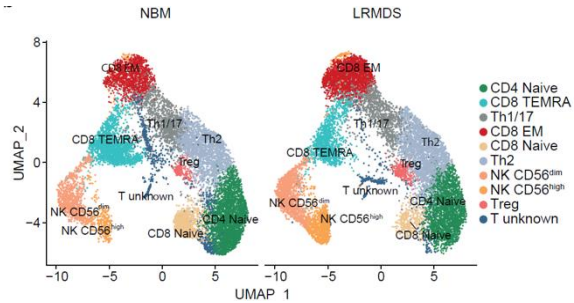
Inflammatory activation of stromal niche cells is a biologic commonality in LR-MDS, independent of genetic background



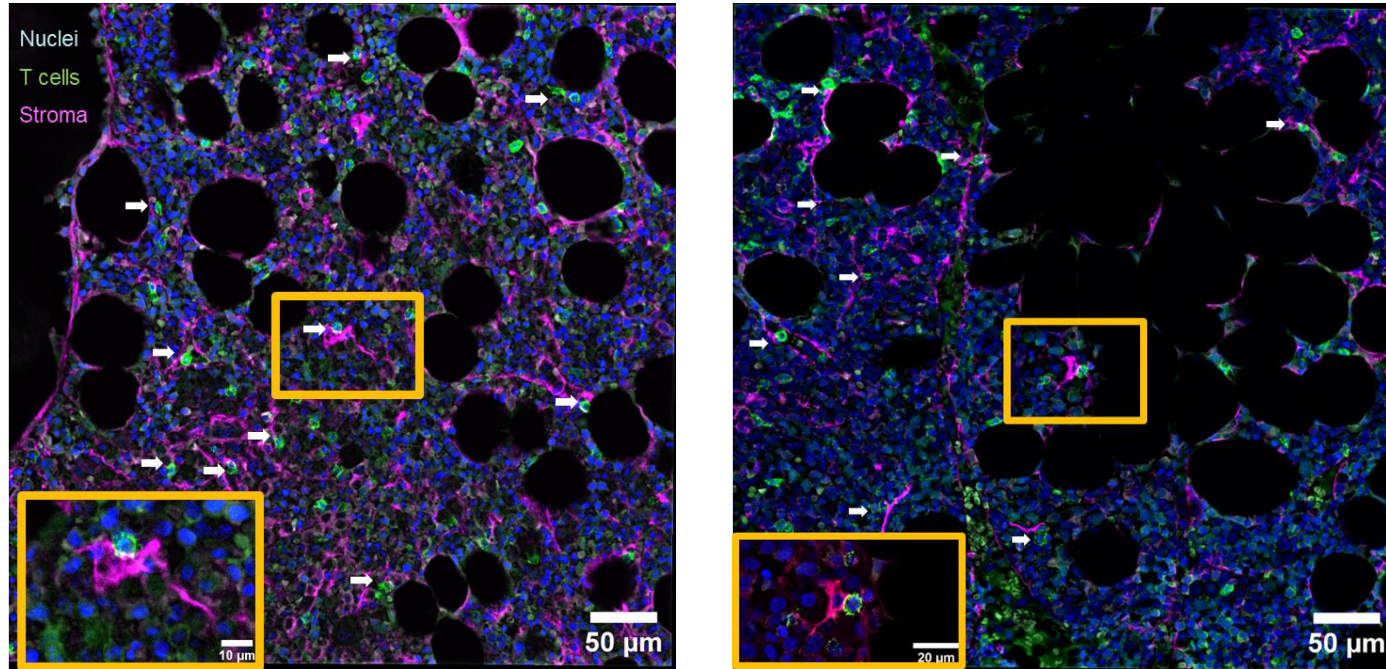
Downloaded from <http://www.sagepub.com> at NANYANG TECH UNIV LIBRARY on June 11, 2015



Transcriptional characterization of the IFNG⁺ EM CD8⁺ T-cells in LR-MDS

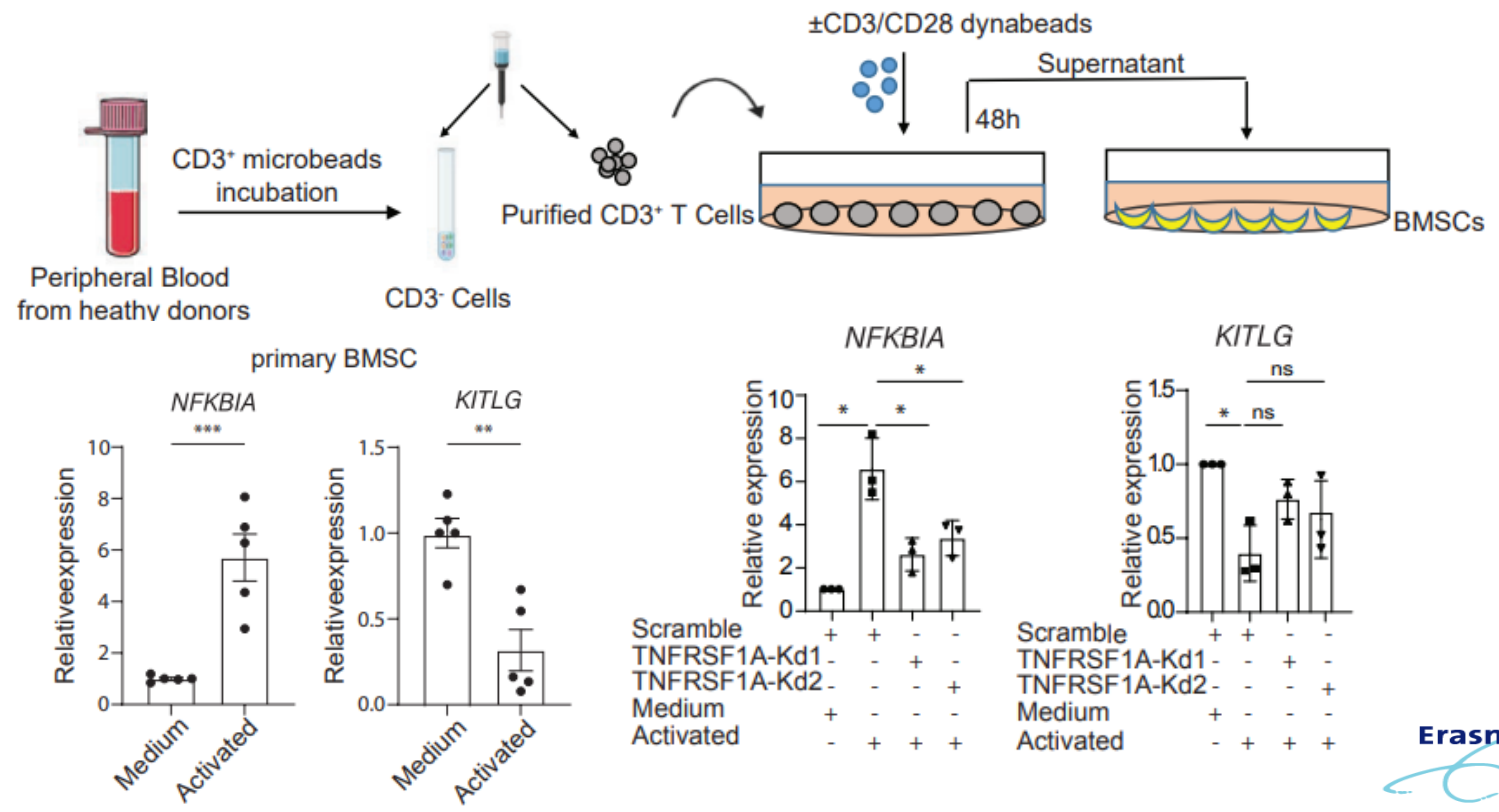


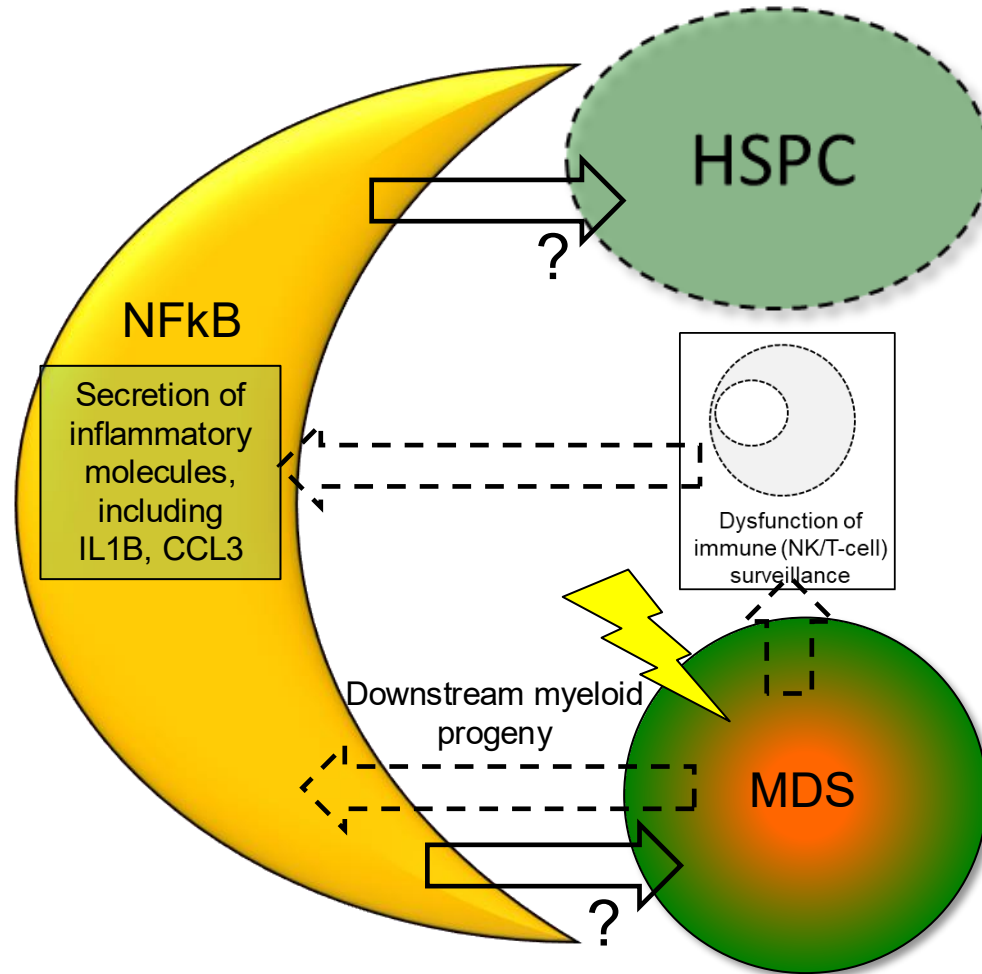
A substantial subset CD8-T cells resides directly adjacent to stromal cells in the human SF3B1m MDS bone marrow



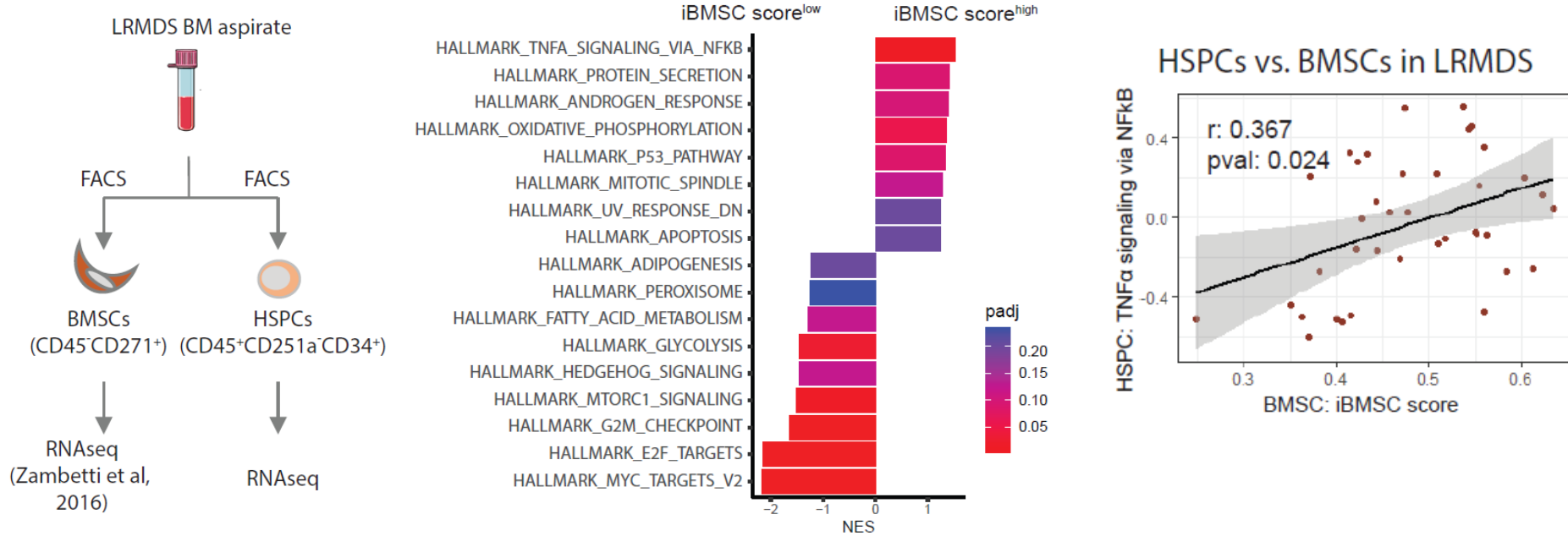
20-30% of CD8⁺ T-cells in close contact with body of CD271⁺ stromal cell

Activated human T-cells can ‘inflamm’ bone marrow stromal niches via TNF α signaling



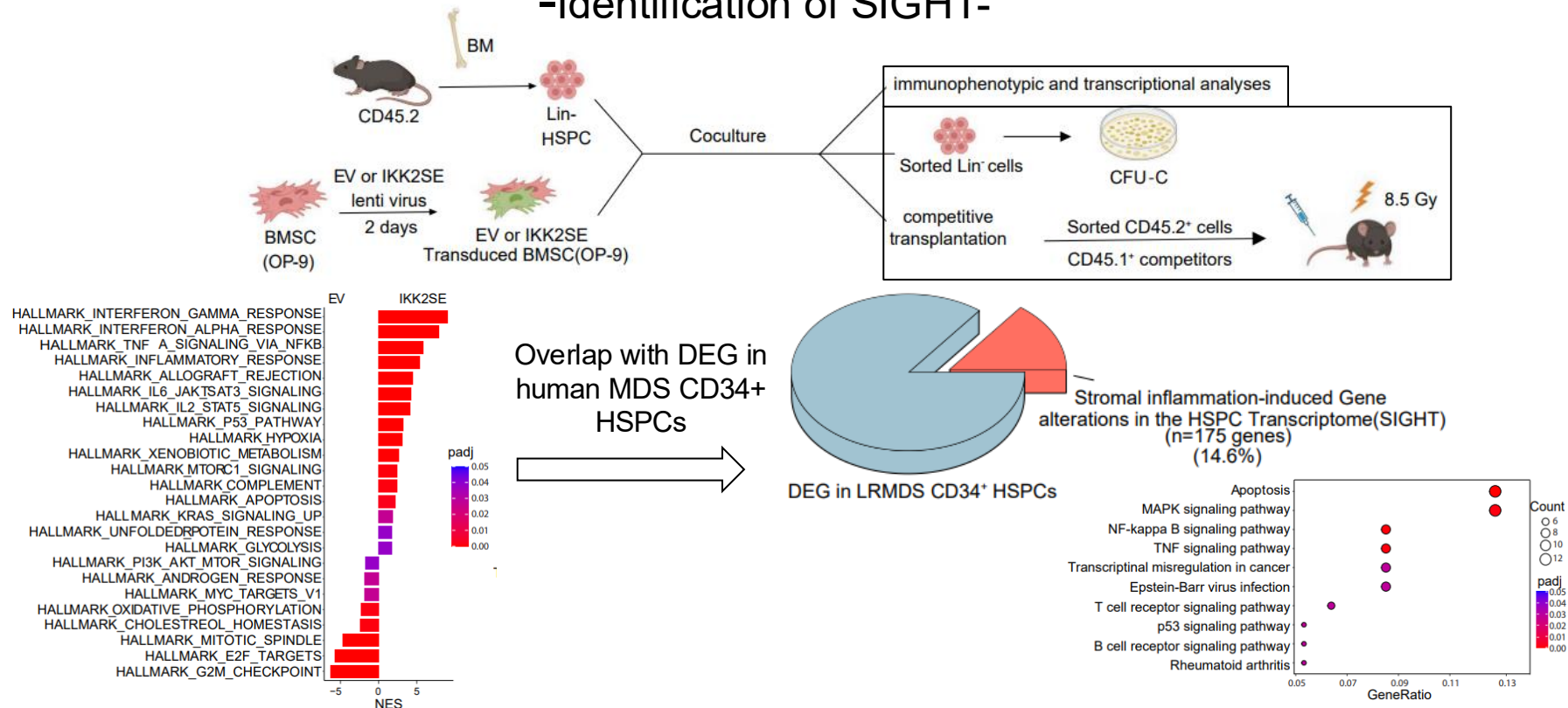


Stromal inflammation is reflected in the transcriptional wiring of hematopoietic stem/progenitor cells in LR-MDS

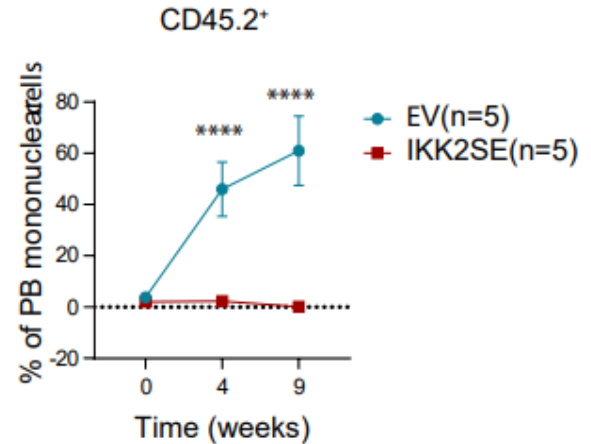
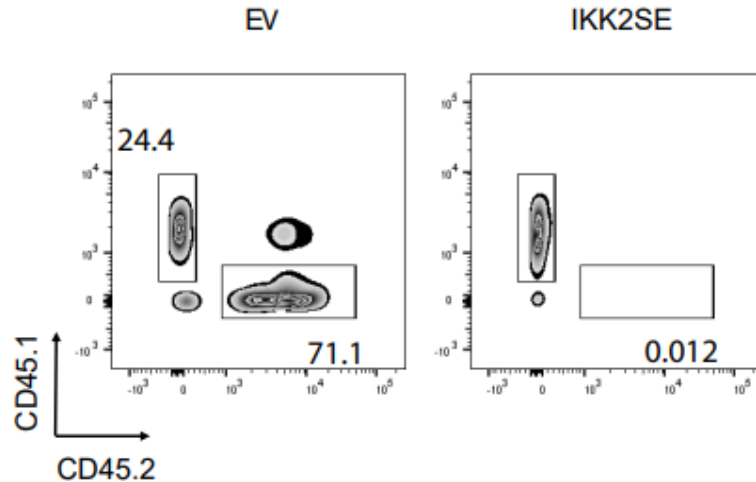
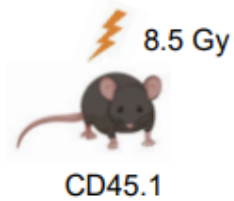
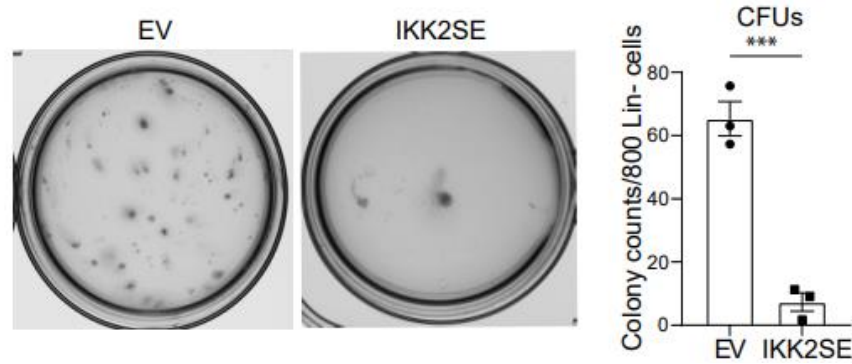


Stromal niche inflammation induces inflammatory alterations in normal HSPCs

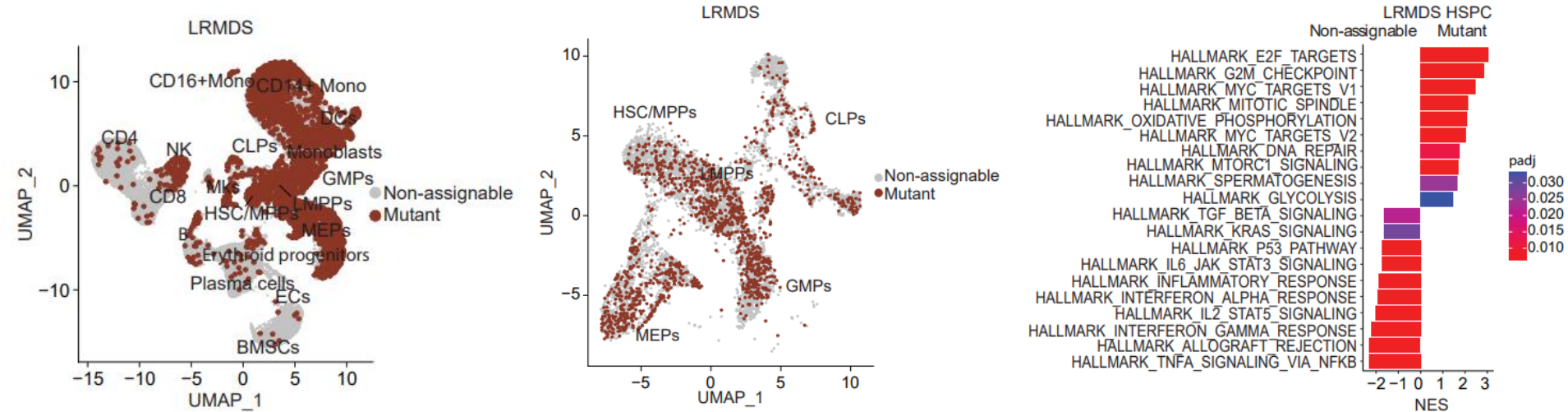
-Identification of SIGHT-



Stromal inflammation suppresses normal hematopoiesis



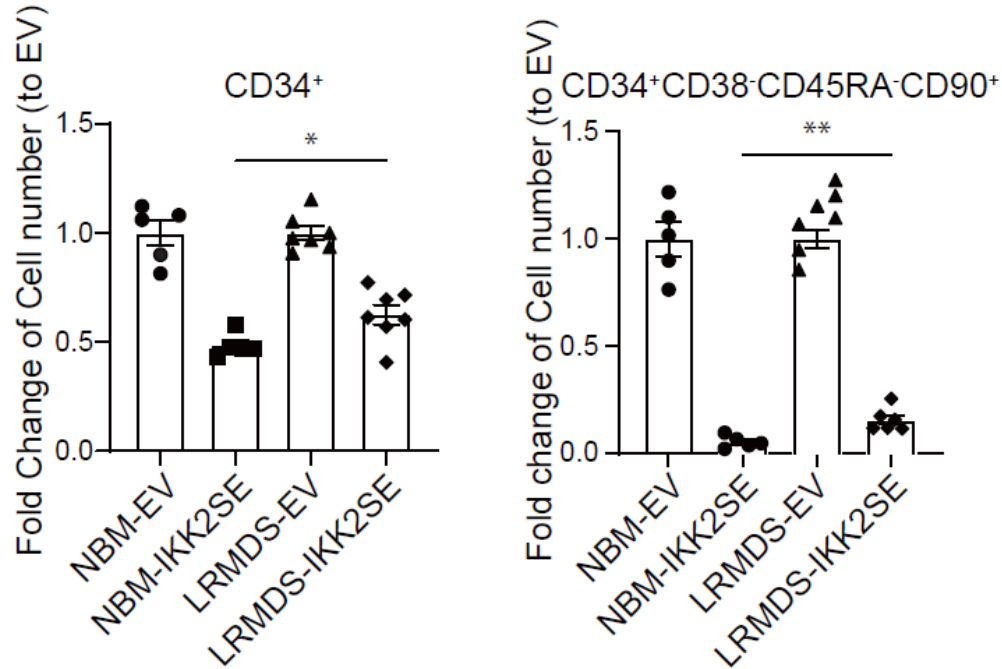
The inflammatory stress induced by inflamed niches is mitigated in clonal cells



SF3B1-mutated LR-MDS (n=5)

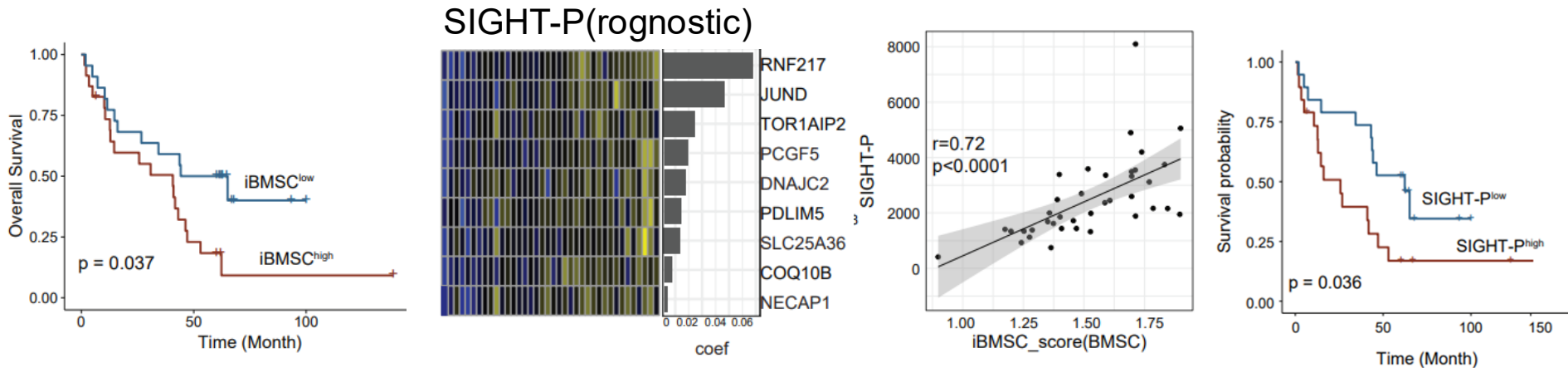
- ☐ 10xscRNAseq
- ☐ RaCH-seq
- ☐ Computational modeling (SpliceUp)

Human *SF3B1*-mutated HSPCs are relatively resistant against stromal inflammation induced repression

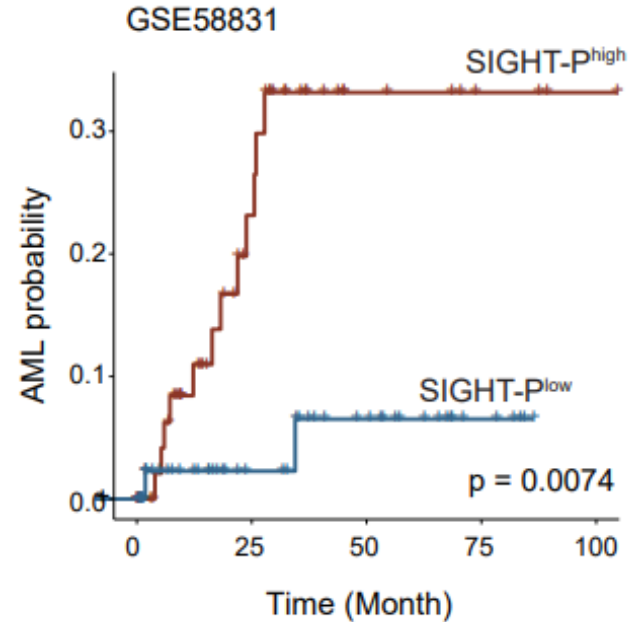
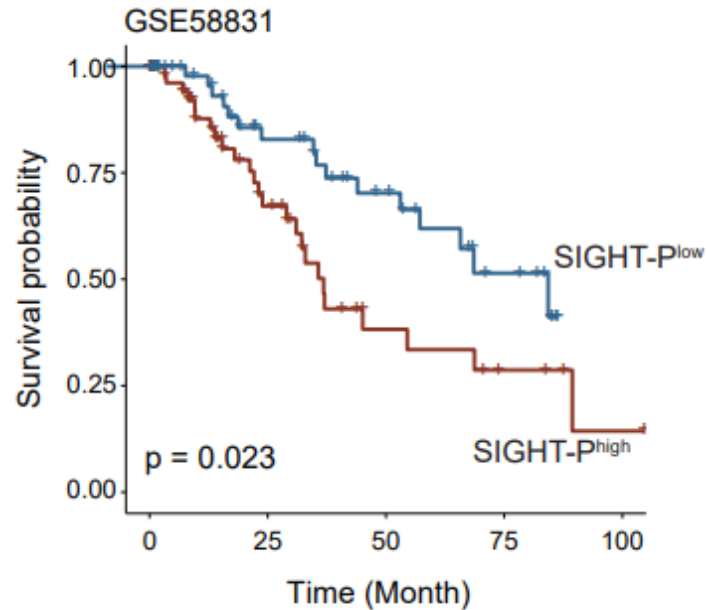


Bead-selected CD34⁺ cells from *SF3B1*m LR-MDS (VAF appr. 40%) vs.
CD34⁺ cells from NBM co-cultured on IKK2SE vs. EV-transduced stromal cells

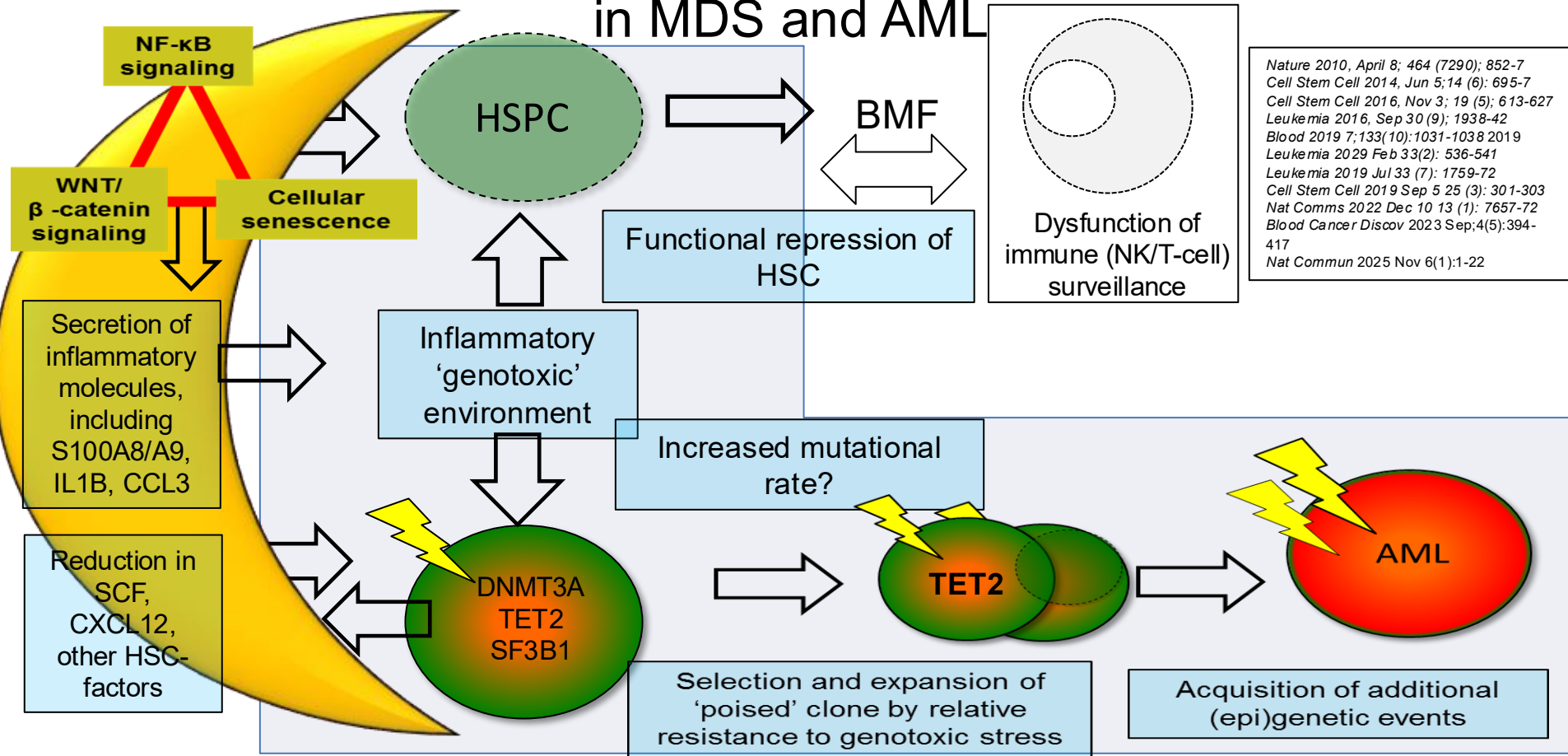
Inflammatory remodeling of stromal niches and related transcriptional HSPC signatures are associated with leukemic progression and reduced survival in MDS-1



Inflammatory remodeling of stromal niches and related transcriptional HSPC signatures are associated with leukemic progression and reduced survival in MDS-2



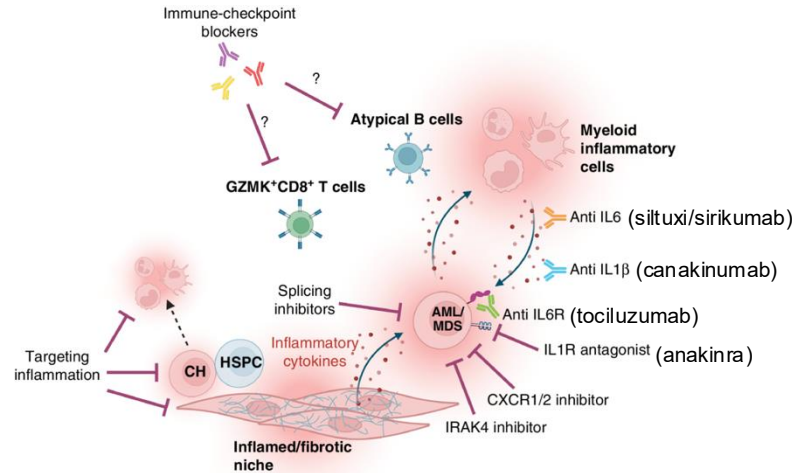
A model of 'stromal niche inflammation-facilitated' clonal evolution in MDS and AML



Therapeutic implications

I

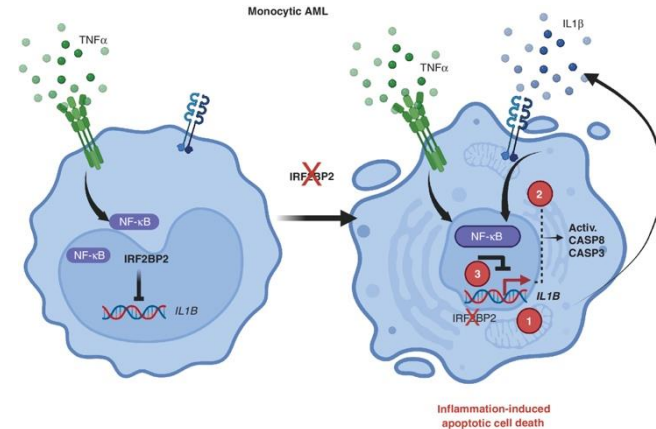
Inhibiting inflammation
(to delay disease progression)



Balandrán et al. Blood Cancer Discov. 2023 Jul 5;4(4):254-266.

II

Inhibit resistance to
inflammation of clonal cells



Ellegast JM et al. Cancer Discov. 2022 Jul 6;12(7):1760-1781; Puissant & Medyouf. Cancer Discov. 2022;12(7):1617-1619

Acknowledgments

ErasmusMC Hematology

Noemi Zambetti

Zhen Ping

Si Chen

Keane Kenswil

Claire van Dijk

Eline Pronk

Lanpeng Chen

Paola Pisterzi

Jacqueline Feyen

Martijn Ernst

Tim van Tienhoven

Yujie Bian

Joke Zink

Tom Cupedo

Ruud Delwel

Els Mansell

Matthijs Sanders

Ivo Touw

Peter Valk

Karolinska Institutet Center for Hematology and Regenerative Medicine

Pedro Luis Moura

Sadaf Fazeli

Eva Hellström Lindberg

UMC Radboud

Joop Jansen

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HOVON and HOVON-SAKK-Nordic Leukemia Working Group