XIX CONGRESSO NAZIONALE
SIES 2026

FROM PRECURSOR DISEASES TO MULTIPLE MYELOMA: REMODELING OF THE OSTEOBLASTIC NICHE AT SINGLE CELL RESOLUTION

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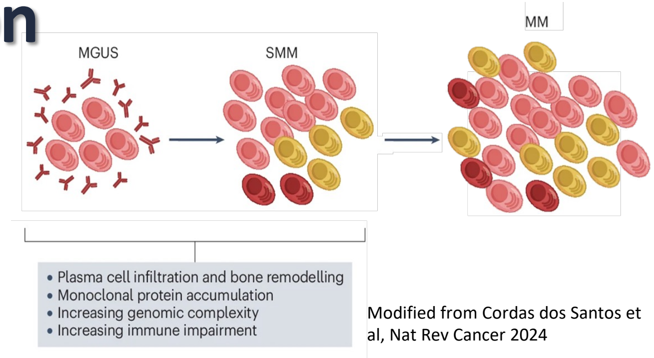
Firenze | **4-6 marzo 2026**
Palazzo degli Affari

Disclosures of Mattia Dessena

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

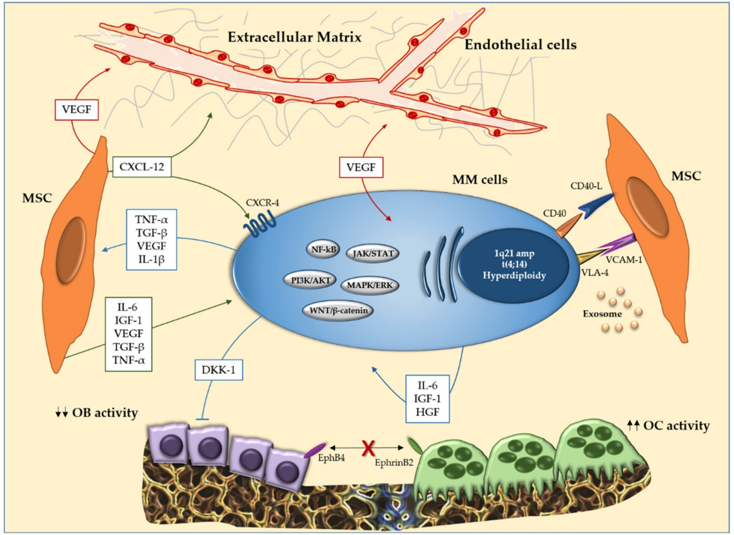
Introduction



- Plasma cell infiltration and bone remodelling
- Monoclonal protein accumulation
- Increasing genomic complexity
- Increasing immune impairment

Modified from Cordas dos Santos et al, Nat Rev Cancer 2024

- ➢ Uncoupled bone-remodelling process characterizes the development of multiple myeloma (MM)-related bone disease, where impaired osteoblastogenesis promotes osteolytic lesions and creates a permissive bone microenvironment (BME) facilitating malignant plasma cell grow. [1]
- ➢ Osteoblasts (OBs) display altered transcriptomic and functional profiles in MM patients compared to healthy subjects. [2,3,4,5]
- ➢ Limited data are available for OBs in monoclonal gammopathy of undetermined significance (MGUS) and smouldering MM (SMM), and existing studies are mainly based on bone marrow aspirates or *in vitro* studies. [5,6]



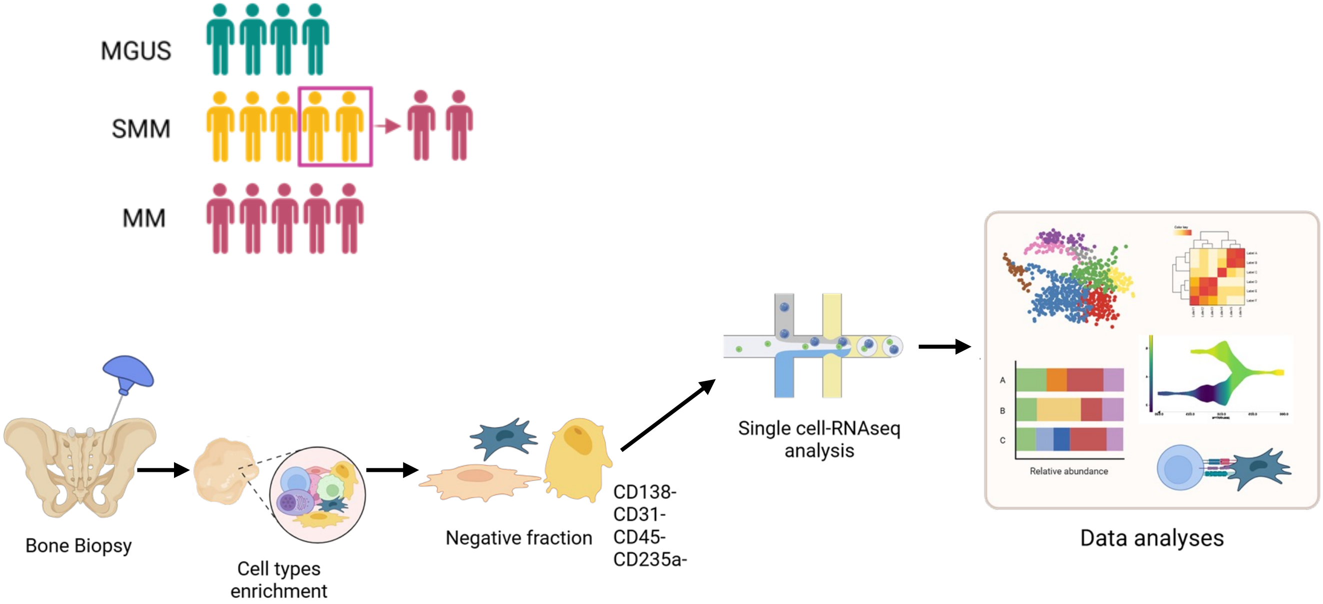
Iannozzi et al, Int. J. Mol. Sci. 2022

1 Lungu et al. J Bone Oncol. 2025
2 Corre J et al. Leukemia 2007
3 Todoerti K et al. Exp Hematol, 2010
4 Alameda et al. Haematologica, 2020
5 Bogun at al, Blood Advance, 2024
6 Carolina Schinke et al. Clin Cancer Res, 2018

Aim

Characterize the **OB population dynamics** at single-cell resolution to identify alterations across MGUS, SMM, and MM.

Methods



Bone Biopsy

Cell types enrichment

Negative fraction

CD138-
CD31-
CD45-
CD235a-

Single cell-RNAseq analysis

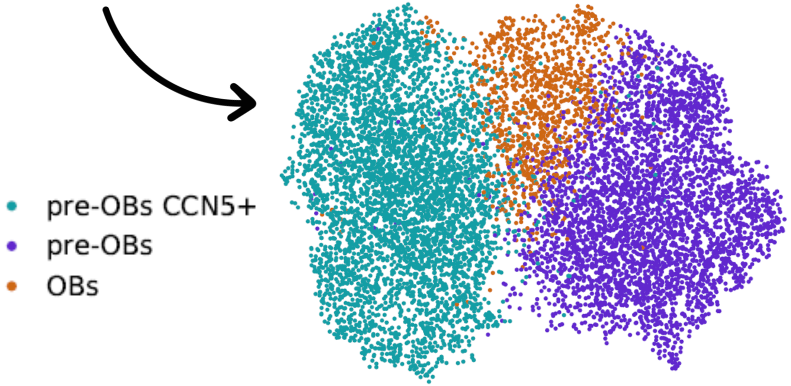
Data analyses

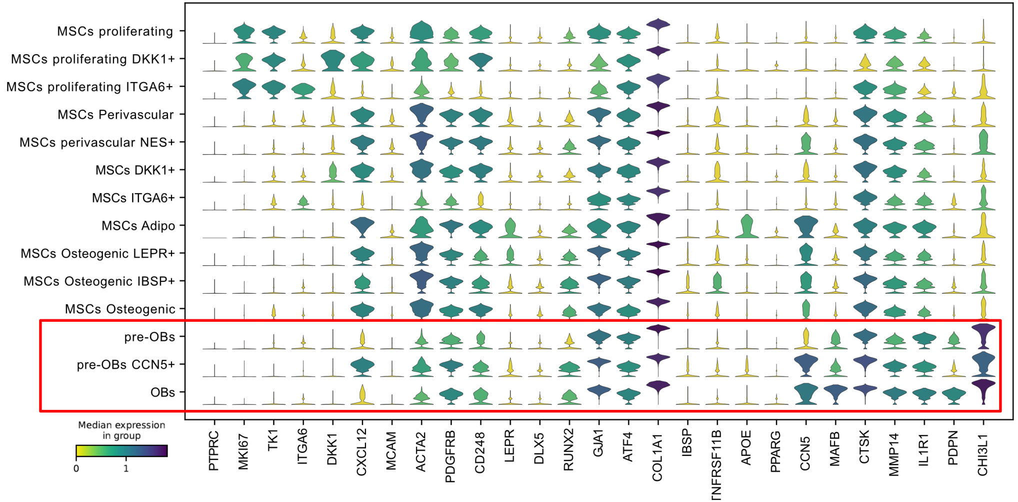
	MGUS	SMM	NDMM
Age (median year)	71	66	63,5
Female gender	40%	60%	33,3%
BM PC%	7%	30%	70%
R-ISS			
I			16,6%
II			33,3%
III			50,0%
Mayo Score			
Low	20,0%		
Low-Intermediate	20,0%		
High-intermediate	60,0%		
High	0,0%		
2-20-20 Score			
Low		20,0%	
Intermediate		40,0%	
High		40,0%	
Bone disease			
Bone disease **(YES)**			66,6%
High bone disease			33,3%
Cytogenetic			
Hyperdiployd	20,0%	80,0%	80,0%
IgH Translocation	0,0%	20,0%	20,0%
High risk (17p and/or t(4:14))	20,0%	40,0%	40,0%
1q21 CNA	0,0%	40,0%	40,0%

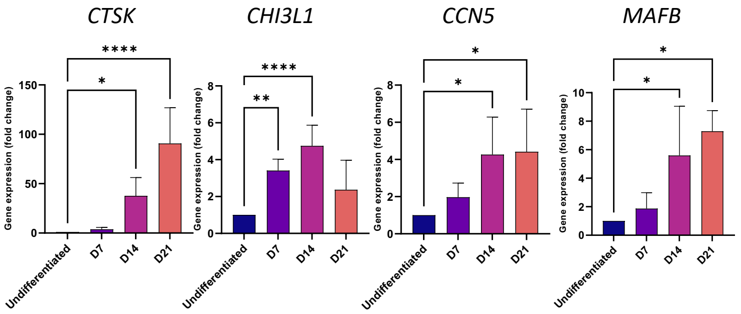
OBs single cell database

BME non-hemopoietic cells

9,565 osteoblastic cells

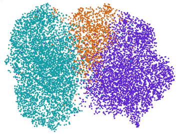


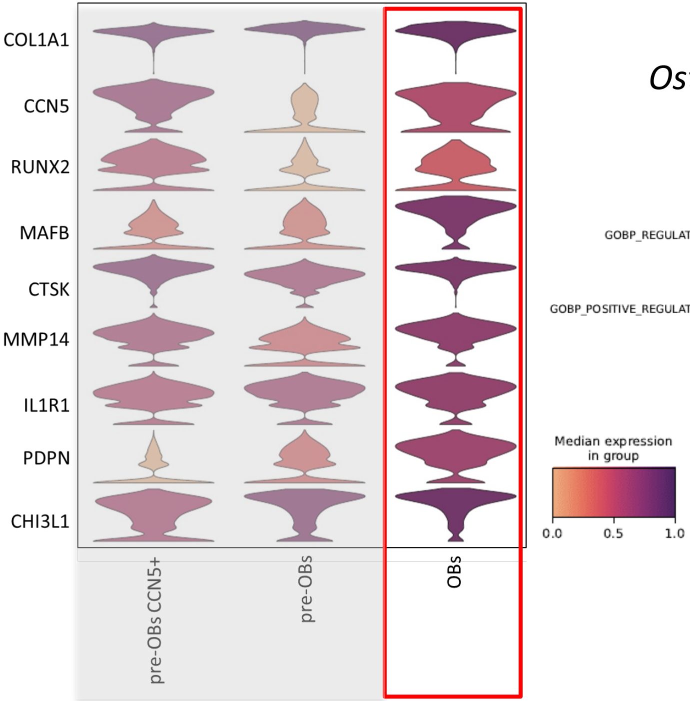




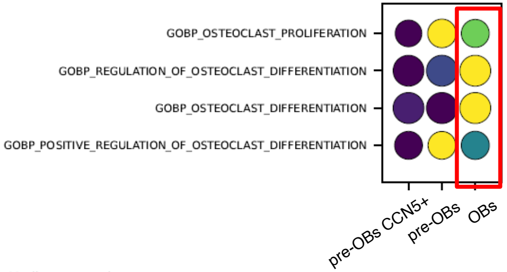
In vitro validation of OB markers in hTERT-MSCs incubated in osteogenic medium (ASC/DEX) for 21 days

Functional Profile of Mature Osteoblasts

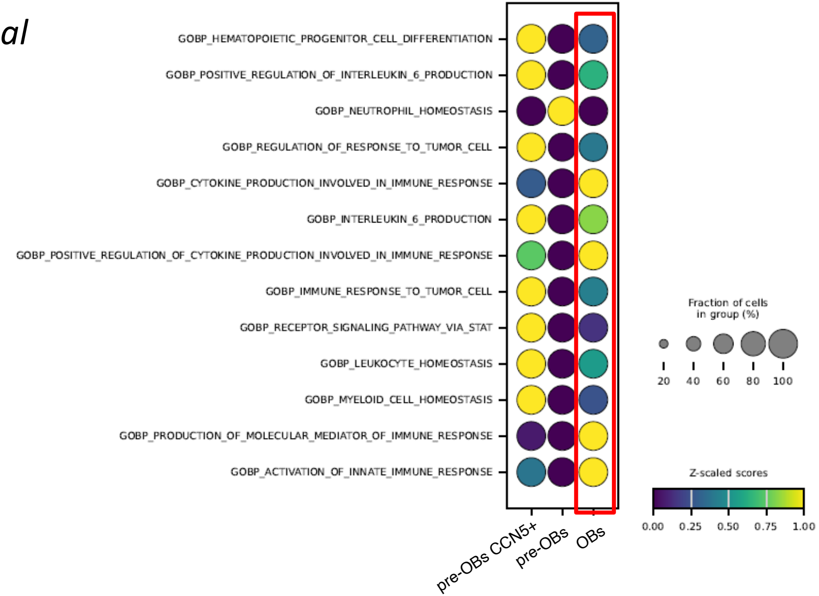




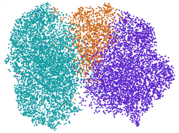
Osteoclast-related biological processes

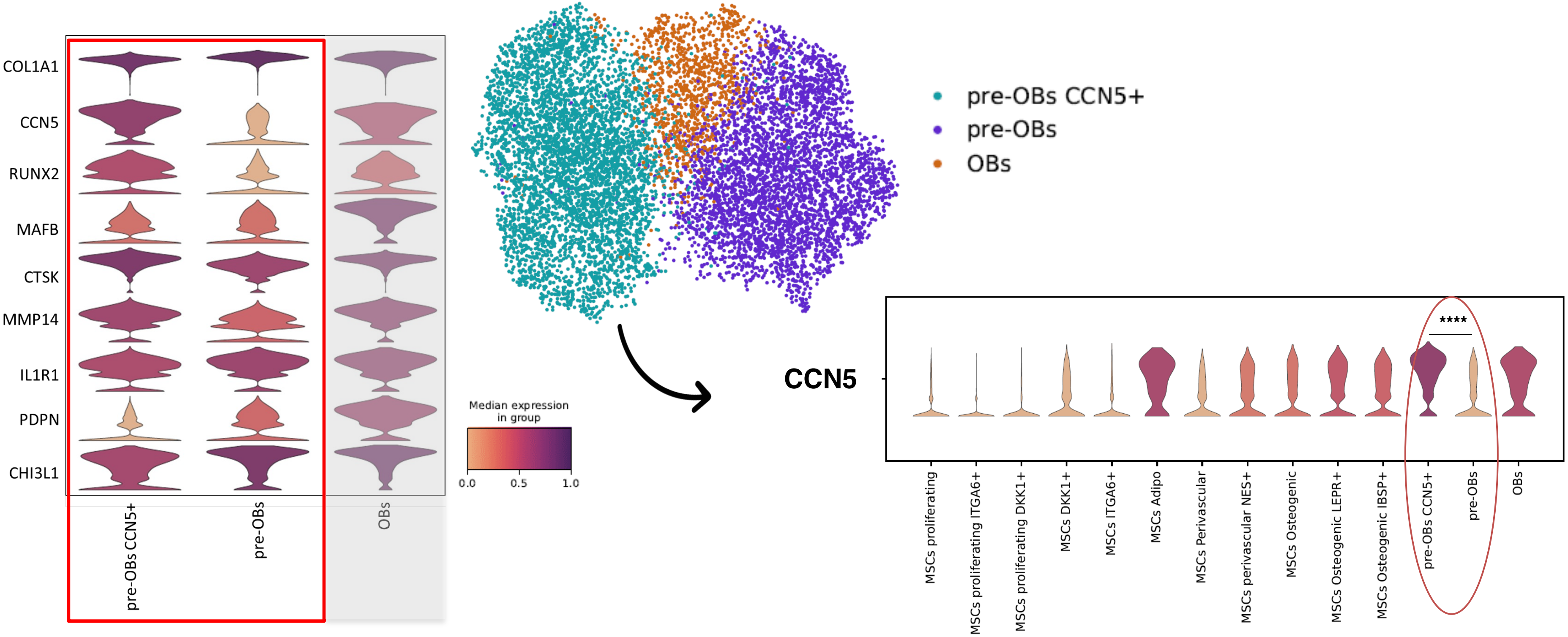


Immune-Related Biological Processes

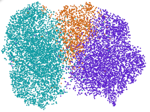


Two different pre-OB clusters

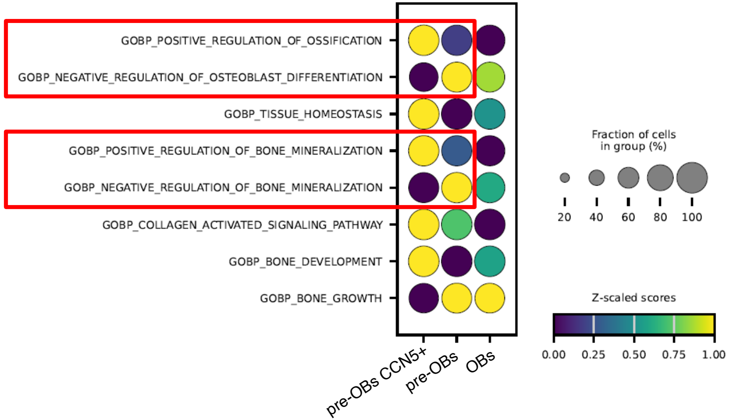




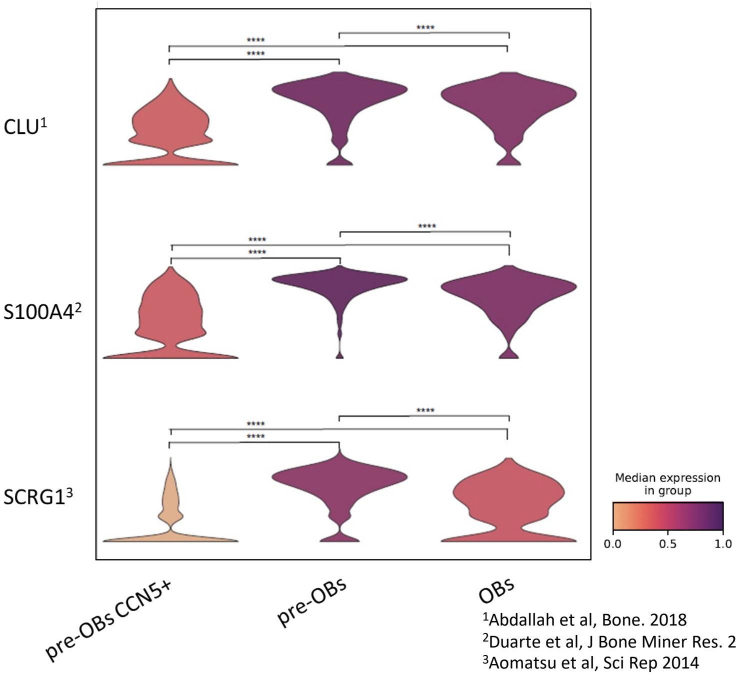
Functional Heterogeneity of Pre-Osteoblast Populations



Bone-related biological processes



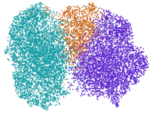
Osteoblast dysfunctional genes



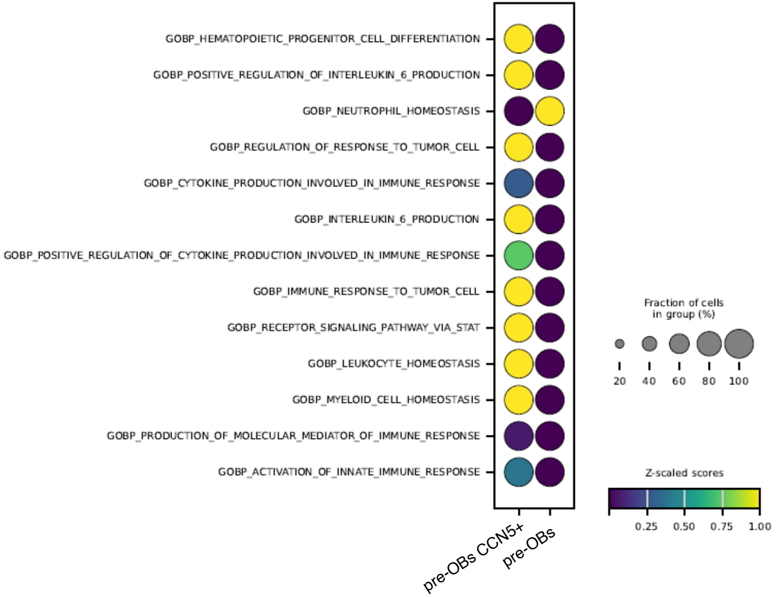
- *Pre-OBs CCN5+*: characterized by enhanced osteoblastogenesis activity and bone mineralization programs.
- *Pre-OBs*: associated with osteoblast dysfunction, expressing genes such as CLU, SCRG1, and S100A4, showing reduced regulation of bone growth and osteoblast differentiation processes

[1] Abdallah et al, Bone. 2018
[2] Duarte et al, J Bone Miner Res. 2003
[3] Aomatsu et al, Sci Rep 2014

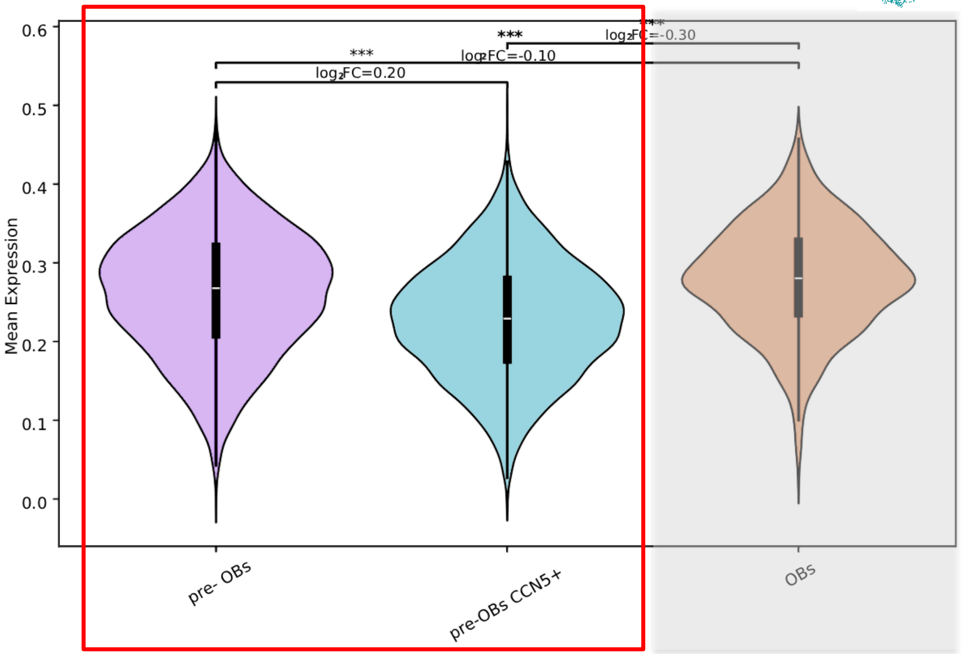
Functional Heterogeneity of Pre-Osteoblast Populations



Immune-Related Biological Processes



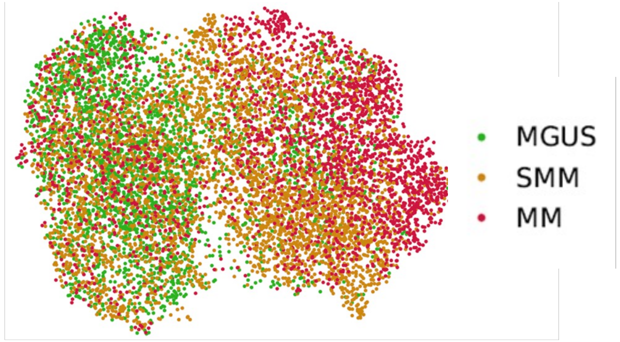
Immunosuppression signature

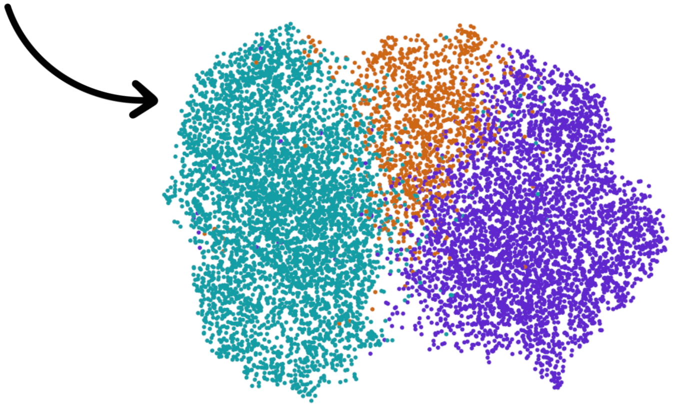


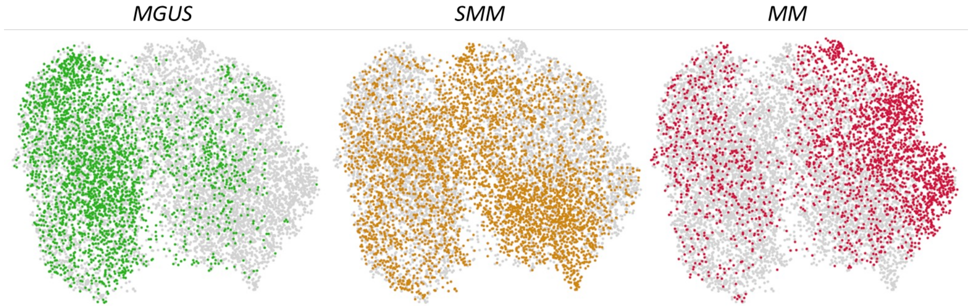
Distribution of OB populations in MGUS, SMM and MM

9,565 osteoblastic cells

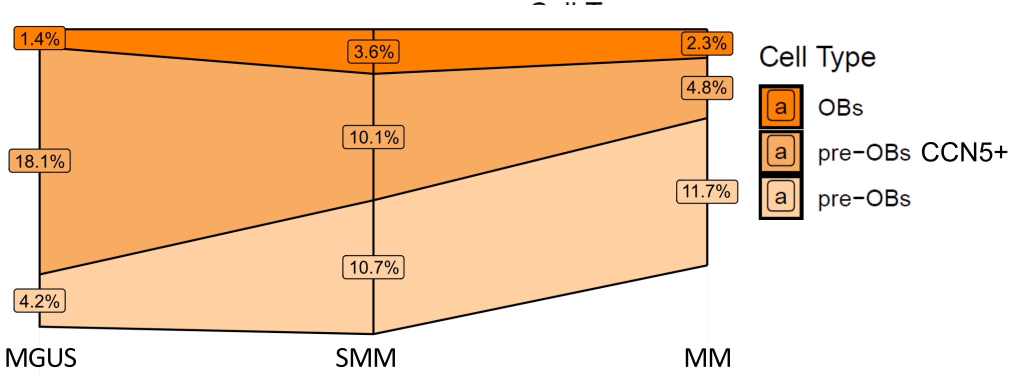
2,841 MGUS
4,082 SMM
2,642 MM

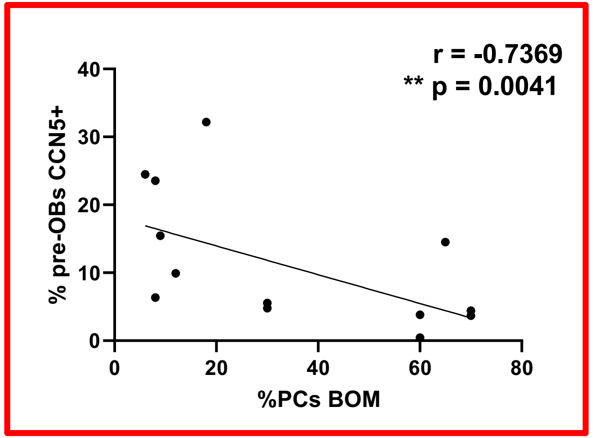


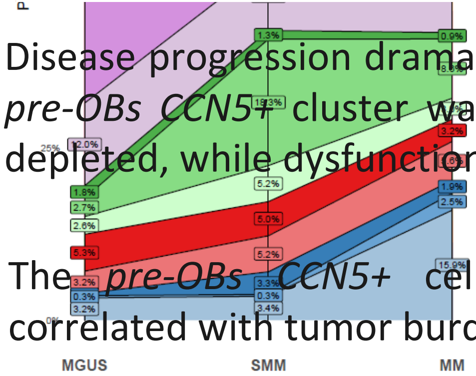




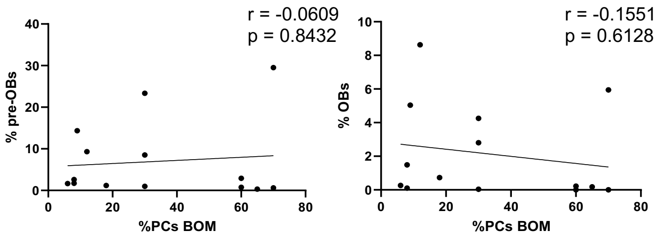
Switch of the 3 OB clusters proportions from MGUS to MM



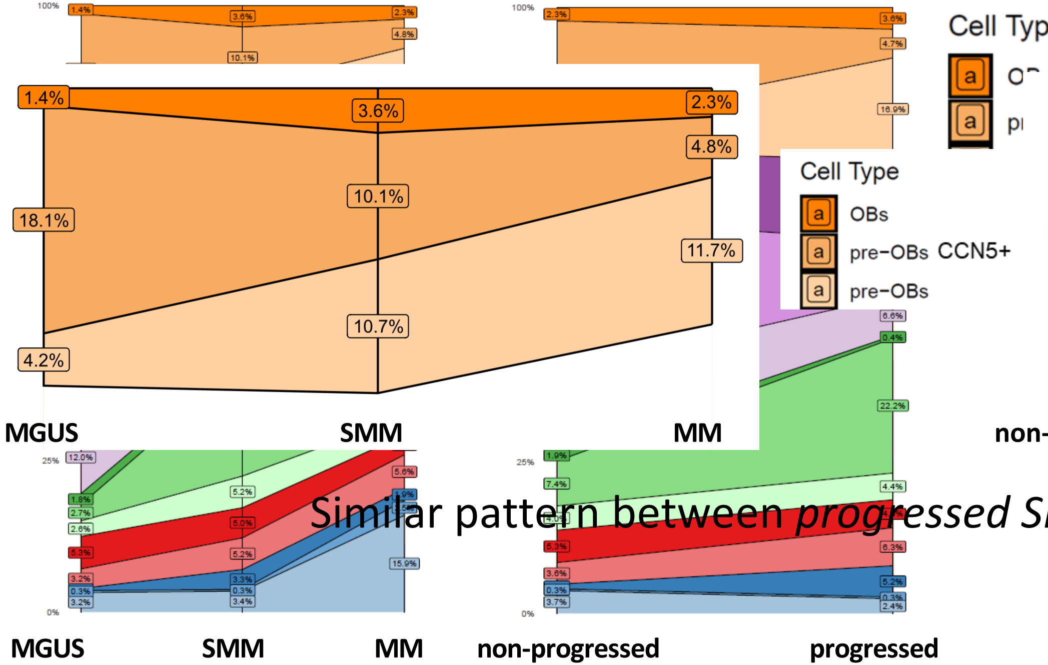


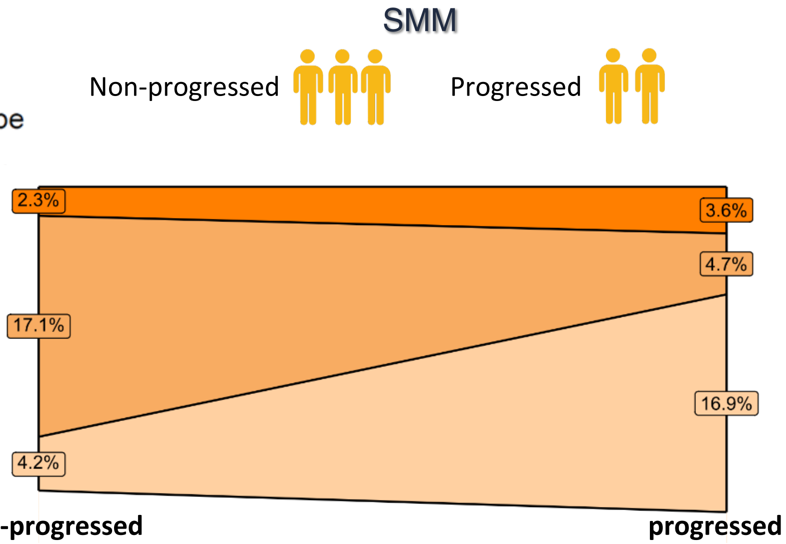


- ➢ Disease progression dramatically altered OB dynamics: *pre-OBs CCN5+* cluster was significantly progressively depleted, while dysfunctional *pre-OBs* were expanded.
- ➢ The *pre-OBs CCN5+* cell proportion inversely correlated with tumor burden.



Switch of the 3 OB clusters proportions between non-progressed and progressed SMM

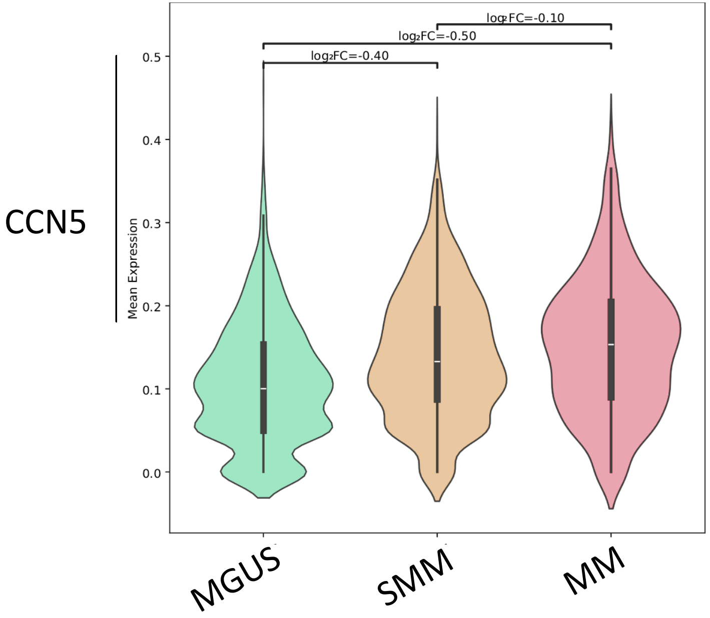




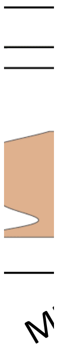
Similar pattern between *progressed SMM* and *MM*

pre-OBs CCN5+ acquire a Senescence-Associated phenotype and less pro-bone features in MM

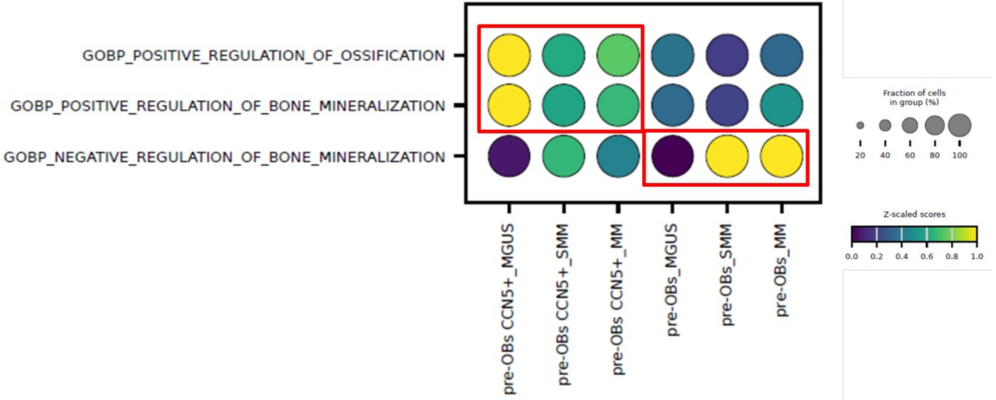
pre-OBs CCN5+ iSASP signature



s diagnosis

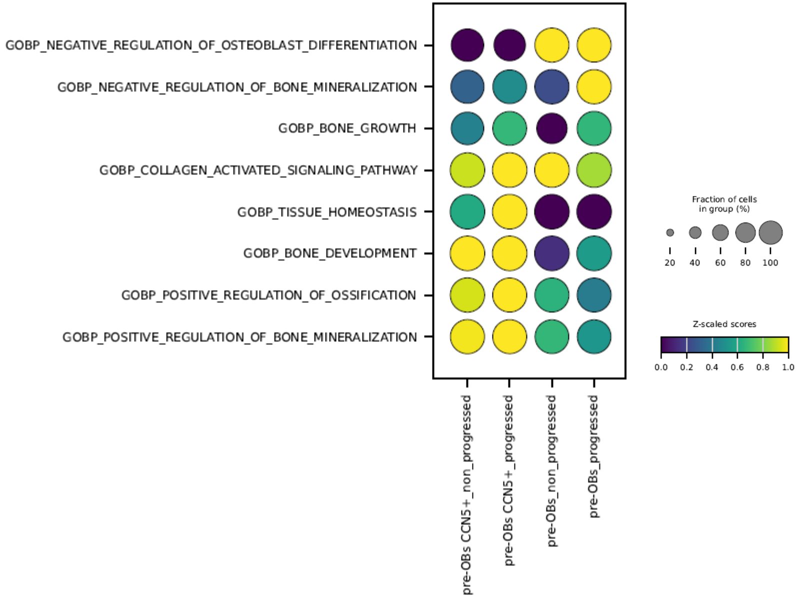


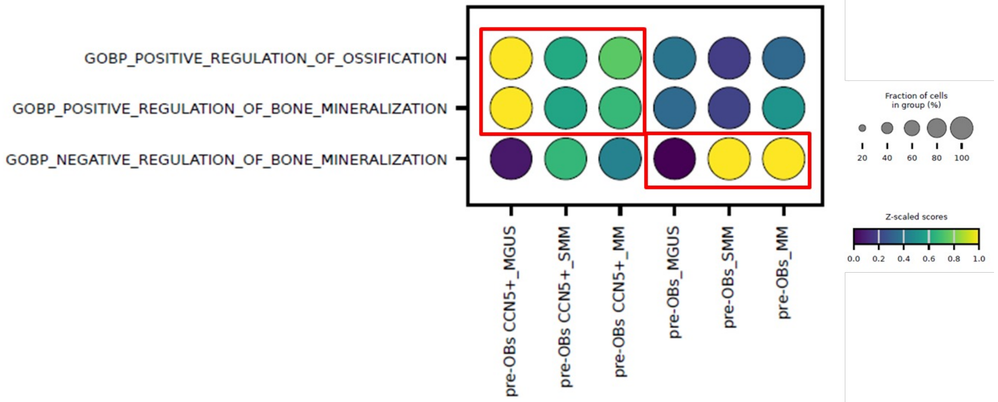
Bone-related biological processes



Pre- osteoblastic clusters acquire MM-like features in progressed SMM

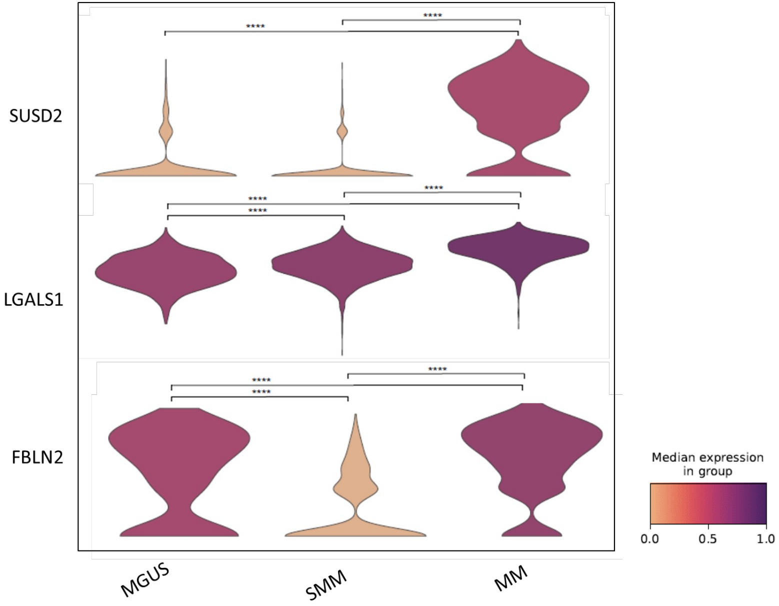
Bone-related biological processes



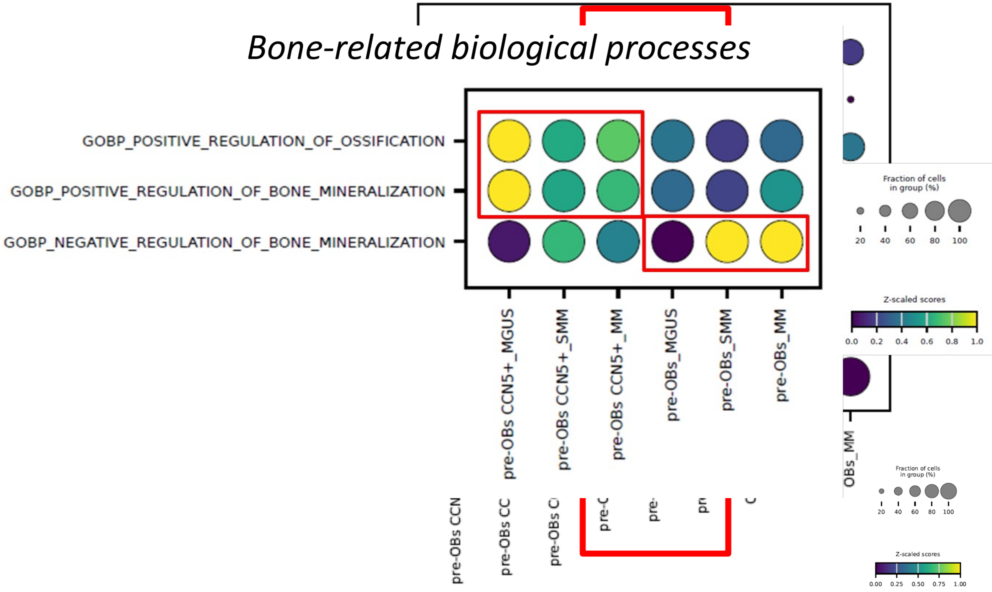


Expanded *pre-OBs* Undergo Functional and Immunometabolic Reprogramming from MGUS to MM

pre-OBs genes expression across diagnosis



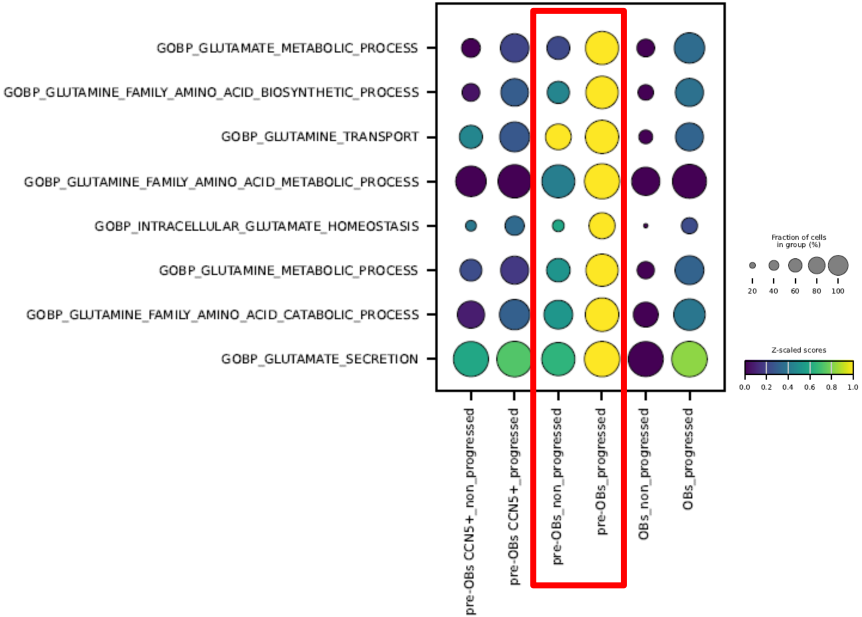
Glutamine/Glutamate-Related Biological Processes

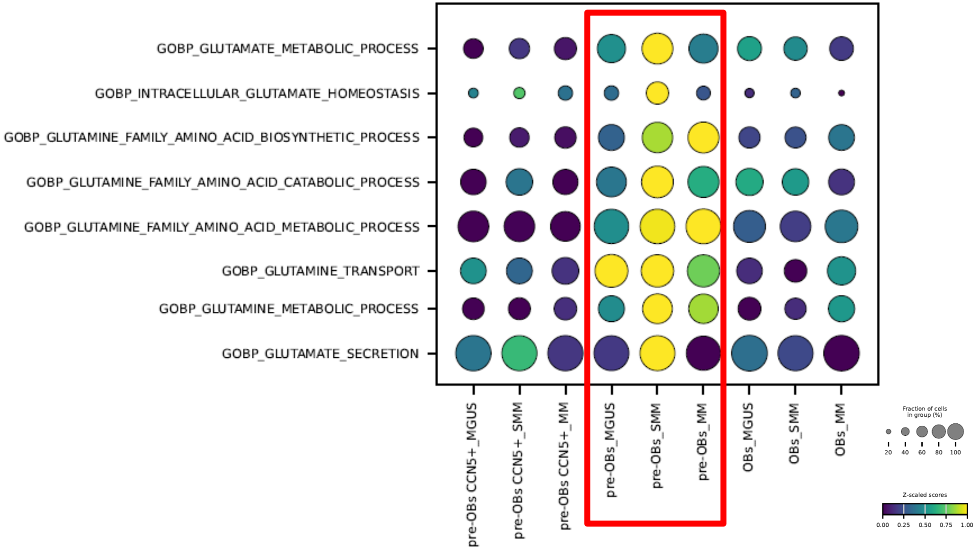


Bone-related biological processes

Expanded *pre-OBs* Undergo Functional and Immunometabolic Reprogramming from MGUS to MM

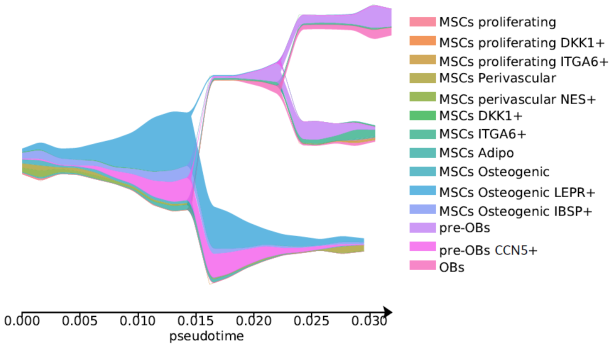
Glutamine/Glutamate-Related Biological Processes

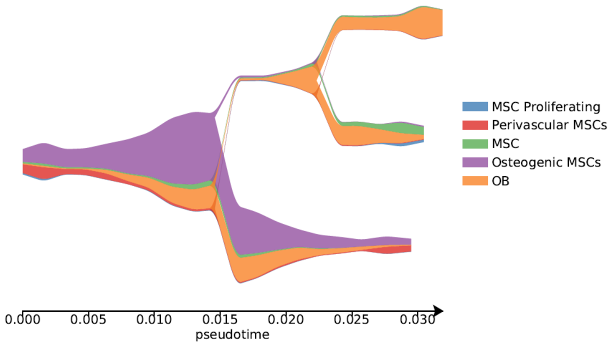




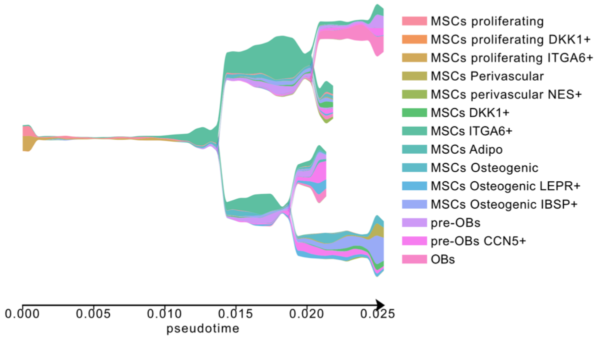
Cellular Trajectories and Gene Expression Dynamics Across Progression

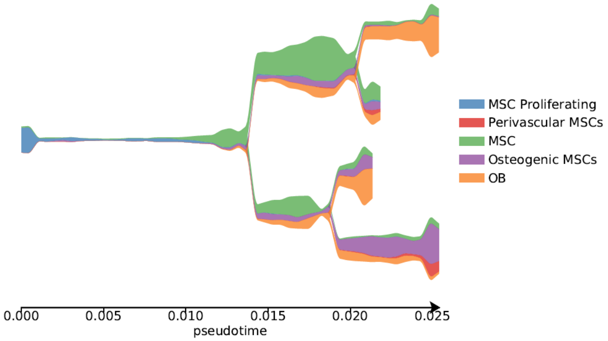
MGUS



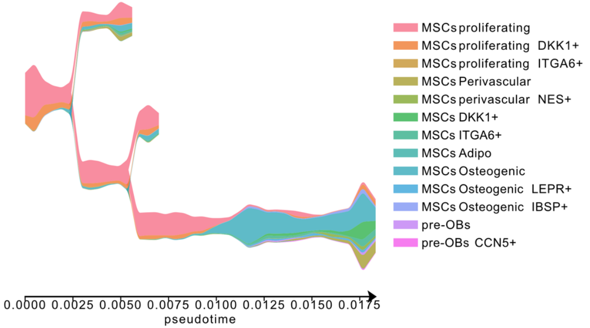


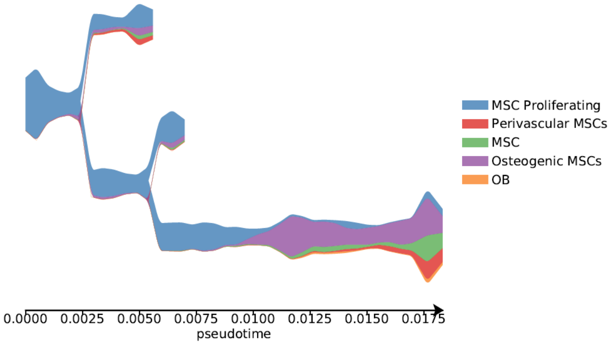
SMM



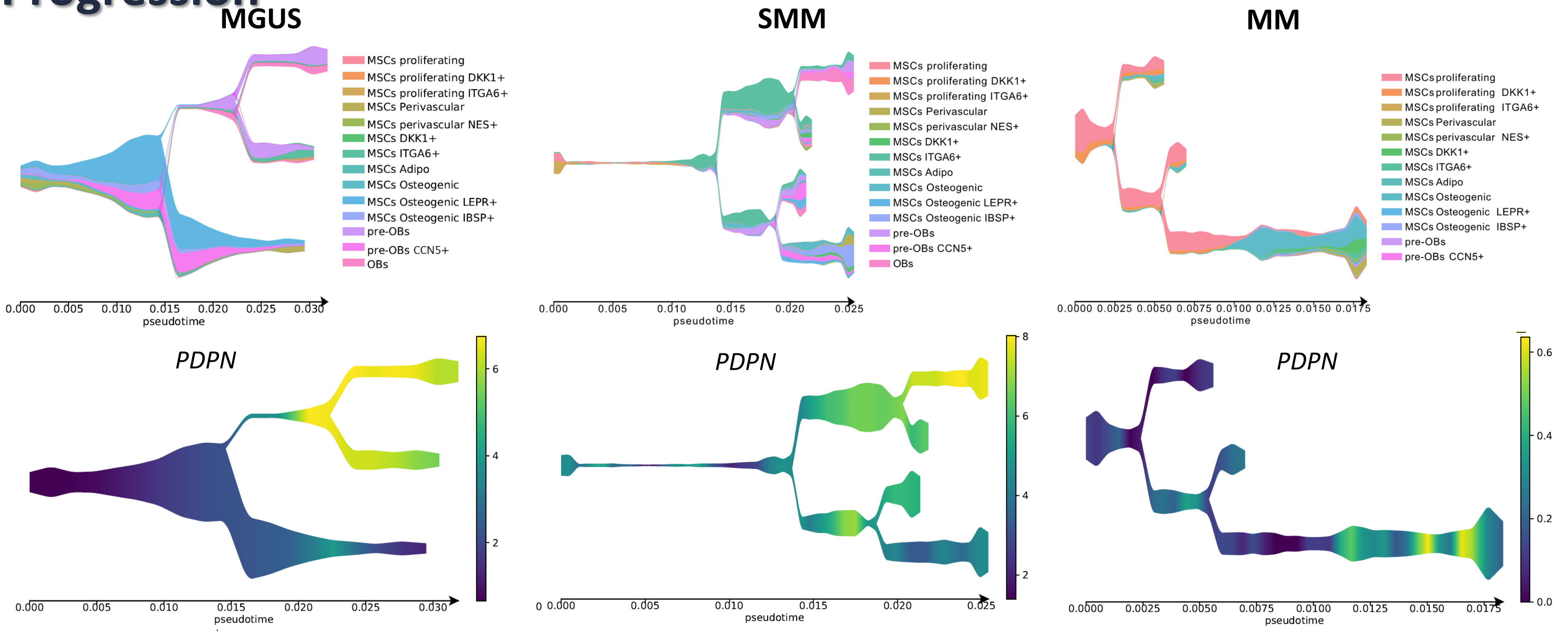


MM





Cellular Trajectories and Gene Expression Dynamics Across Progression



Summary and conclusion

- Two functionally distinct pre-osteoblastic clusters were identified: a pro-osteogenic CCN5+ cluster supporting mineralization and hematopoietic niche functions, and a dysfunctional cluster characterized by impaired differentiation and immunosuppressive features that segregate along bifurcating branches of the pseudotime-inferred trajectory.
- A depletion of pro-osteogenic *pre-OBs CCN5+* and an expansion of pre-Obs were observed from MGUS to MM .
- *pre-OBs CCN5+* cluster inversely correlates with disease burden, while expanded and dysfunctional *pre-OBs* may be involved in the immunosuppressive, pro-tumoral BME of MM patients.
- Early remodeling of the pre-osteoblastic compartment was identified, with alterations characteristic of MM already detectable in SMM that subsequently progressed.

Our single cell analysis on bone biopsies of patients with monoclonal gammopathies deciphers the OB populations complexity, overcoming the incomplete view derived from in vitro/bulk approach.

Thank you for the attention…

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