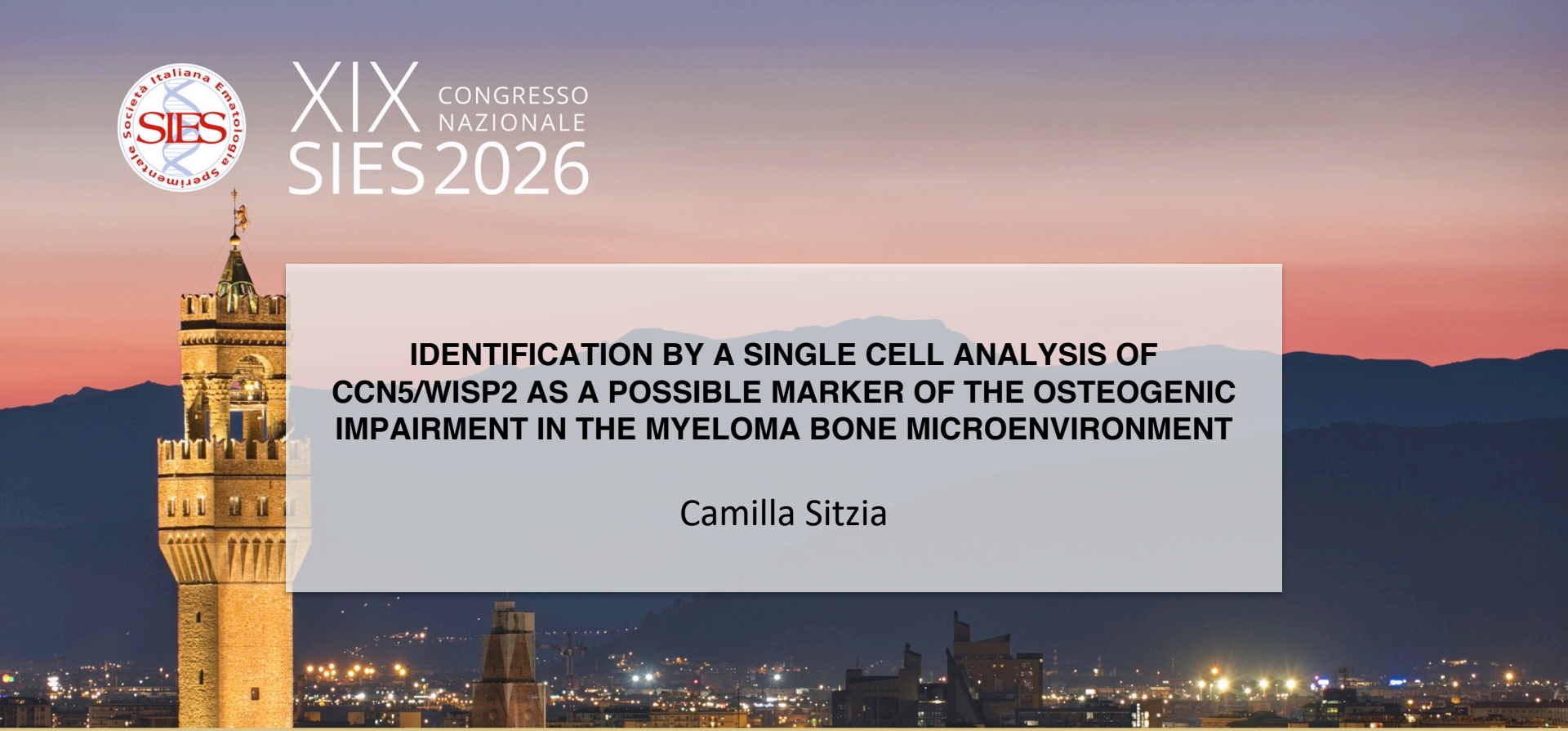


XIX CONGRESSO NAZIONALE SIES 2026

IDENTIFICATION BY A SINGLE CELL ANALYSIS OF CCN5/WISP2 AS A POSSIBLE MARKER OF THE OSTEOGENIC IMPAIRMENT IN THE MYELOMA BONE MICROENVIRONMENT

Camilla Sitzia

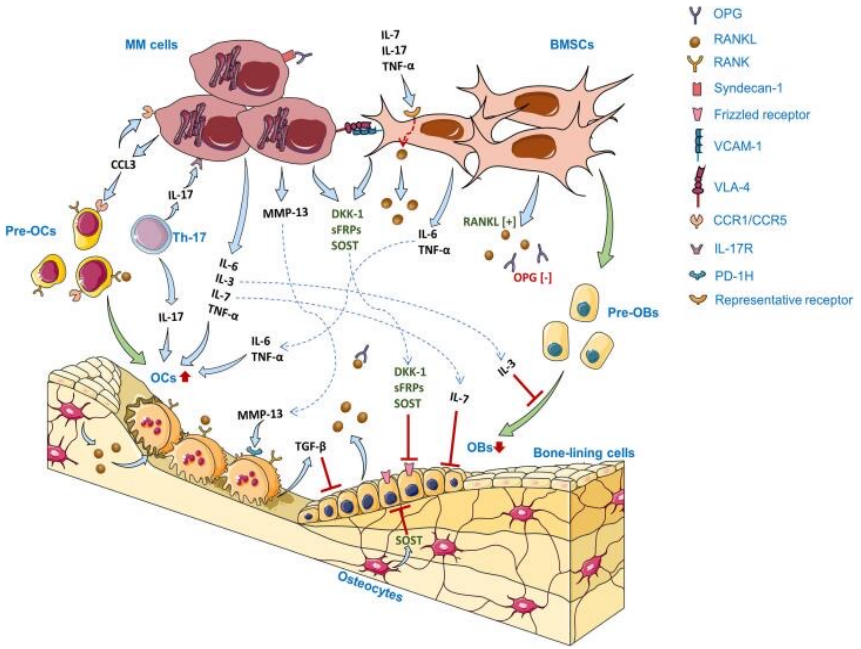
Firenze | 4-6 marzo 2026
Palazzo degli Affari

No conflicts of interest to declare

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

ROLE OF THE BONE MICROENVIRONMENT IN MONOCLONAL GAMMOPATHIES

- Multiple myeloma (MM) is preceded by monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM)[1].
- In MM, mesenchymal stromal cells (MSCs) and osteoblasts (OBs) shape a tumor-permissive bone microenvironment (BME)[2,3].
- Bone remodeling is dysregulated early in MM development[4].
- Progression is associated with remodeling uncoupling: reduced osteoblast function/bone formation and increased bone resorption[5].
- Limited data are available for OBs in MGUS and SMM.

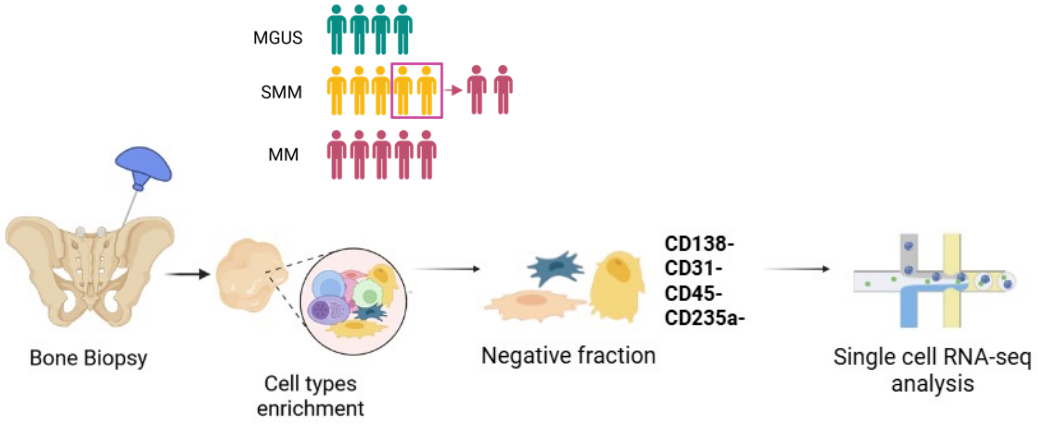


Lungu O. et al, J Bone Oncol., 2025

[1]Van De Donk, N. W. C. J. et al, The Lancet, 2021
[2]Iannozzi NT. et al., Int J Mol Science, 2022
[3]García-Sánchez D. et al, World J. Stem Cells, 2023
[4]Bogun L. et al., Blood Adv., 2024
[5]Lungu O. et al, J Bone Oncol., 2025

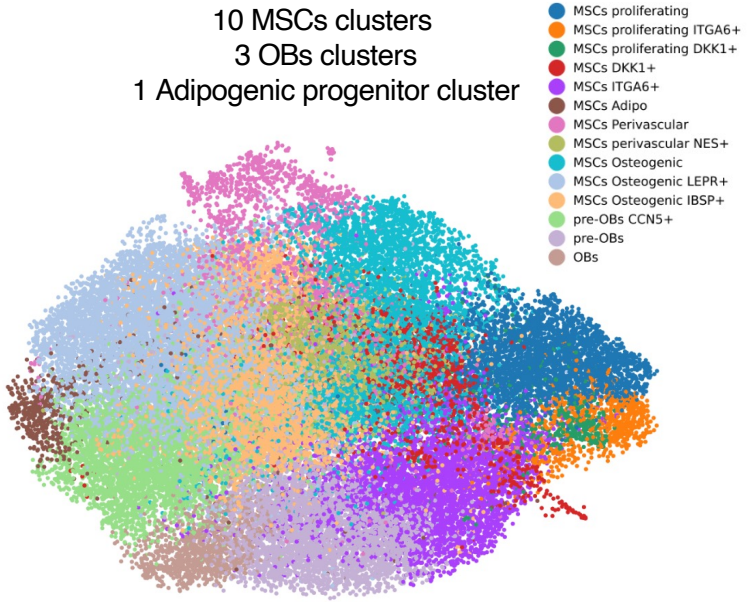
SINGLE-CELL ATLAS OF THE BME: GENERATION AND CHARACTERIZATION

Characterization of the BME across disease stages at single-cell resolution



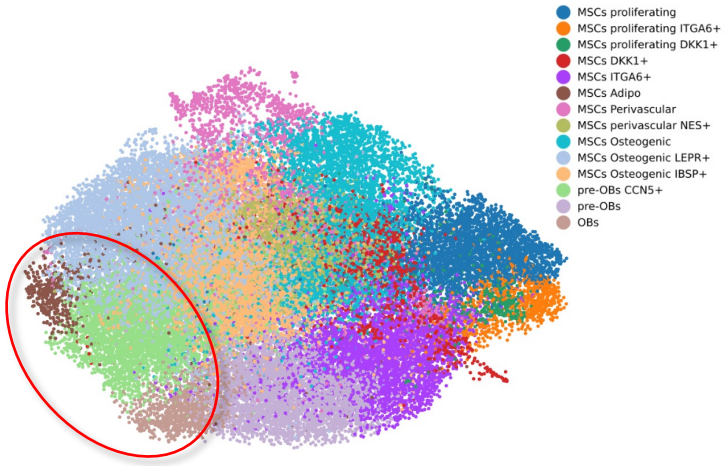
42,823 BME cells divided into 14 BME cell type clusters

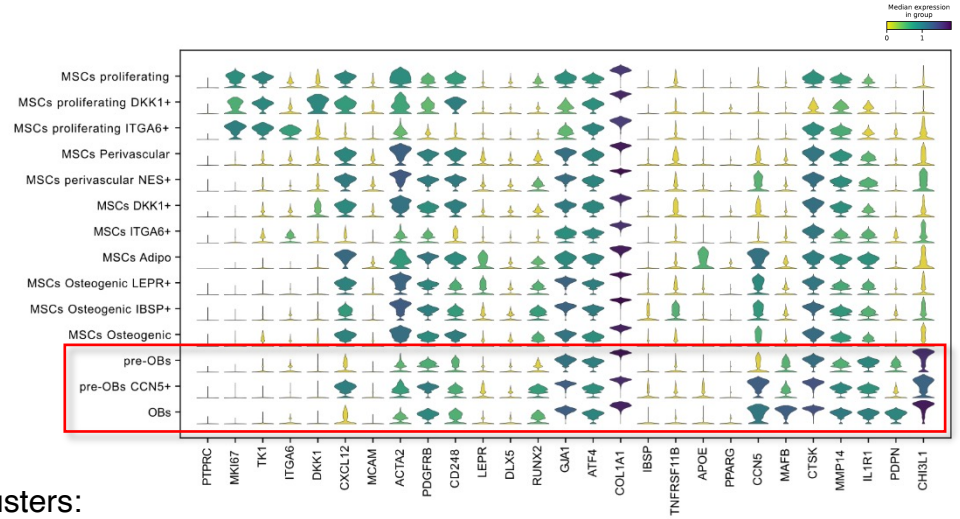
10 MSCs clusters
3 OBs clusters
1 Adipogenic progenitor cluster

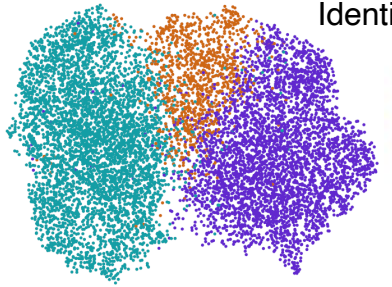


ASH 2024, Dessena M. et al., Supplement 1, Blood, 2024

IDENTIFICATION OF OBs CLUSTERS







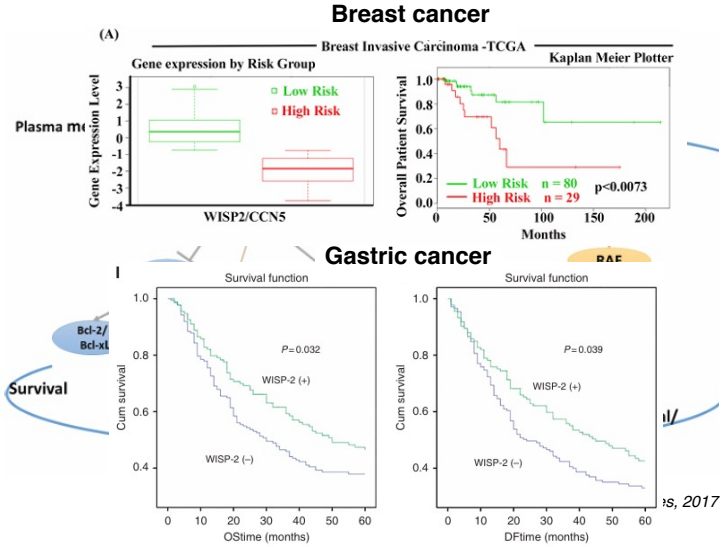
Identification of 3 OBs clusters:

- pre-OBs CCN5+
- pre-OBs
- OBs

ORAL COMMUNICATION C026:
From precursor diseases to multiple myeloma: remodeling of the osteoblastic niche at single cell resolution (Dessena M. et al.)

CELLULAR COMMUNICATION NETWORK FACTOR 5 (CCN5)

- CCN5 is a CCN-family matricellular secreted protein[1].
- First described as a Wnt1-inducible gene (Wnt/β-catenin), CCN5 also interfaces with other signaling pathways, such as TGF-β / SMAD, MAPK/ERK and IGF-1[2].
- CCN5 is expressed in the MSCs compartment and is regulated across osteogenic differentiation states[3].
- Across solid cancers, such as breast and gastric cancer, and in leukemia, CCN5 has been reported to maintain differentiation and restrain tumor progression, with anti-proliferative and anti-invasive effects[4,5].



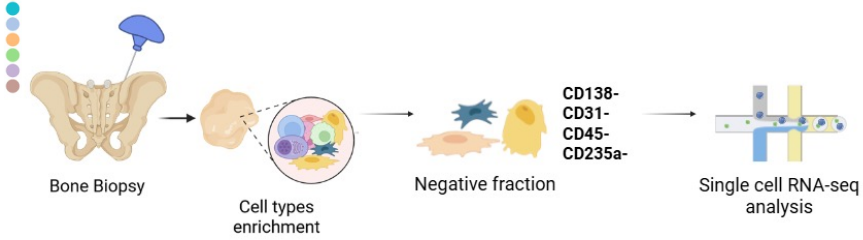
The role of CCN5 in bone non-hematopoietic cells remains largely unknown in monoclonal gammopathies.

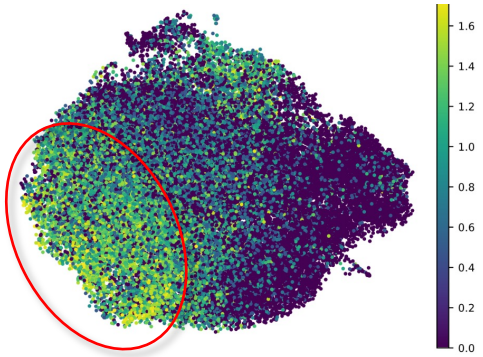
[1]Monsen V., Attramadal H., J Cell Commun Signal, 2023
[2]Liu J. et al, Journal of Diabetes, 2017
[3]Zheng Y. et al., BBA-Molecular Basis of Disease, 2023
[4]Das A. et al., Scientific reports, 2017
[5]Ji J. et al., Br J Cancer, 2015

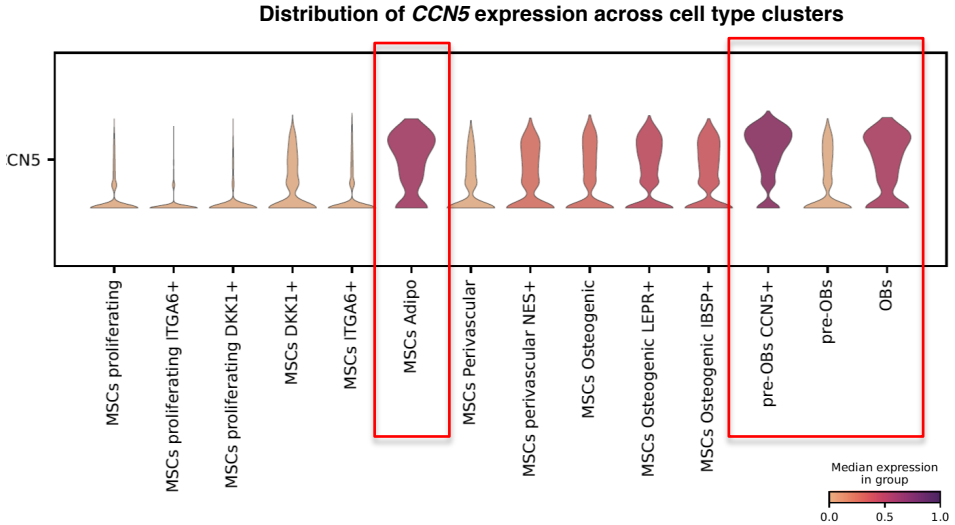
AIM OF THE STUDY

1. To investigate *CCN5* expression across MGUS, SMM and MM.
2. To explore the role of *CCN5* in the bone microenvironment.

PROGRESSIVE *CCN5* UPREGULATION ACROSS THE OSTEOGENIC LINEAGE

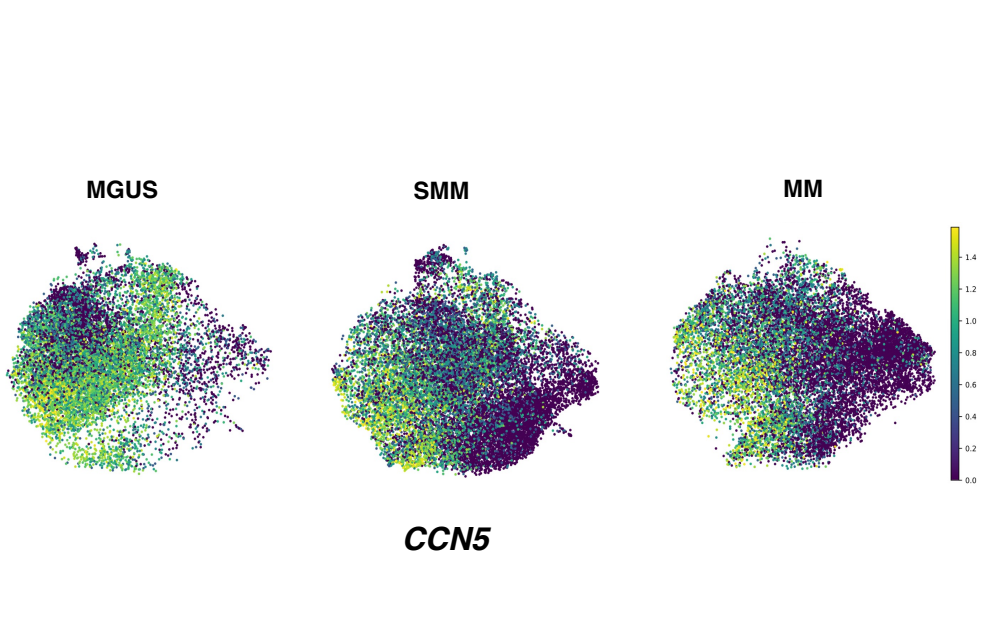


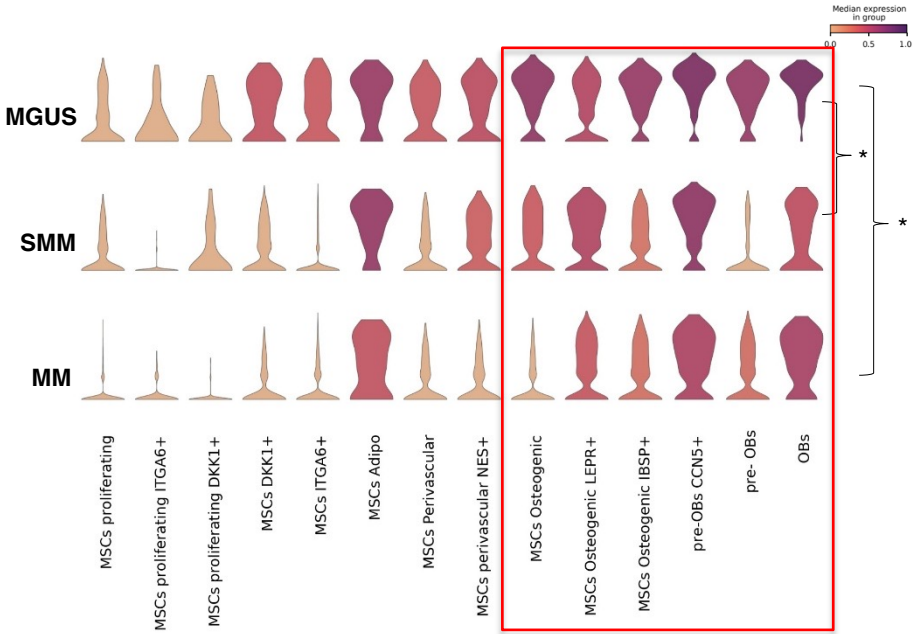




Enriched *CCN5* expression in pre-OBs CCN5+, pre-OBs and OBs clusters.

CCN5 EXPRESSION DECLINES FROM MGUS TO MM



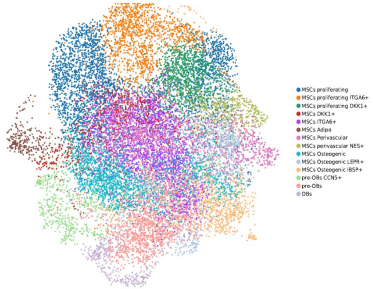


CCN5 levels progressively decline from pre-malignant stages to MM.

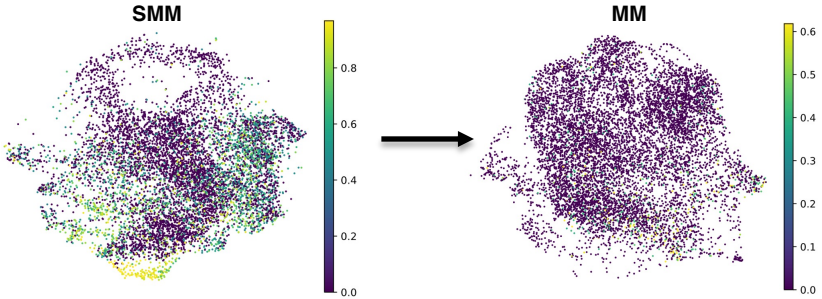
LONGITUDINAL CHARACTERIZATION OF *CCN5* IN PROGRESSED-SMM PATIENTS

Negative fraction of progressed-SMM patients

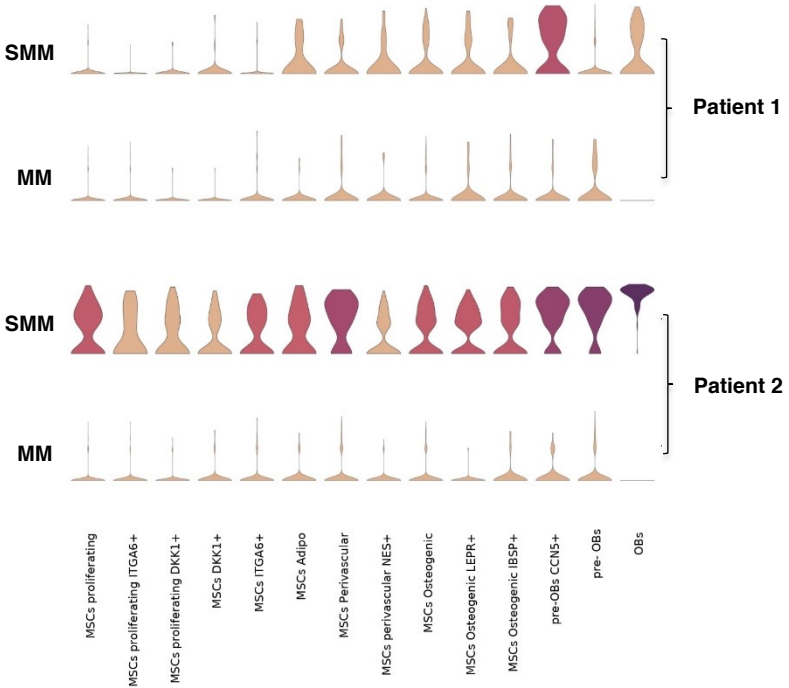
17,257 BME cells



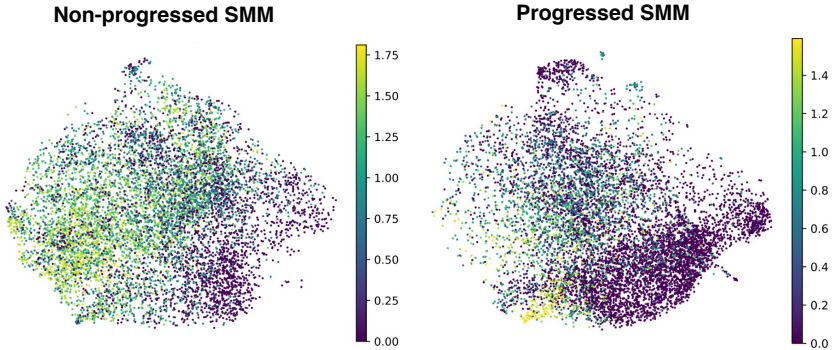
Feature plot of *CCN5* expression from SMM to MM

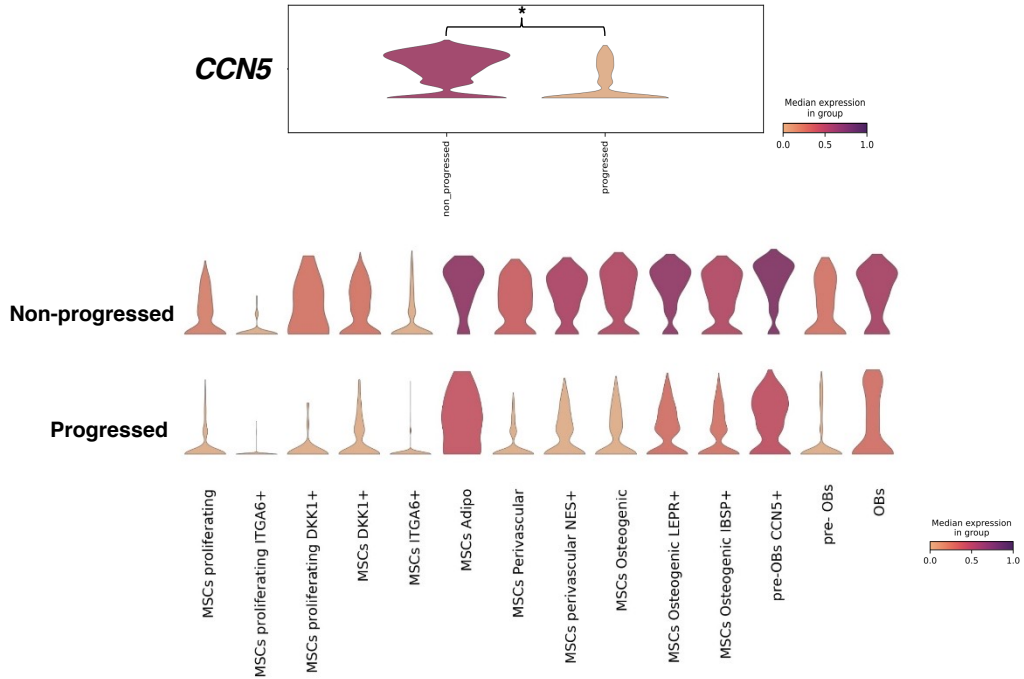


CCN5

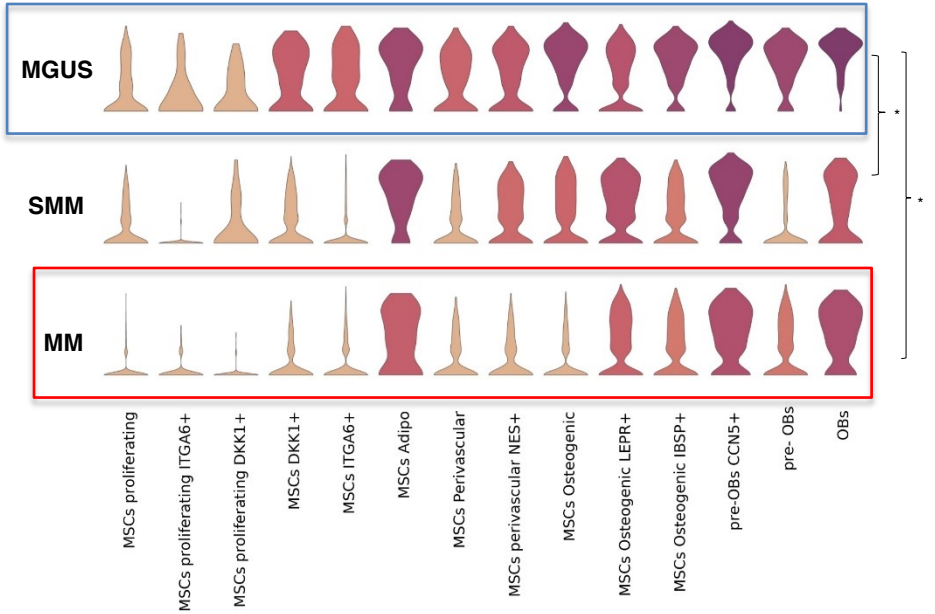


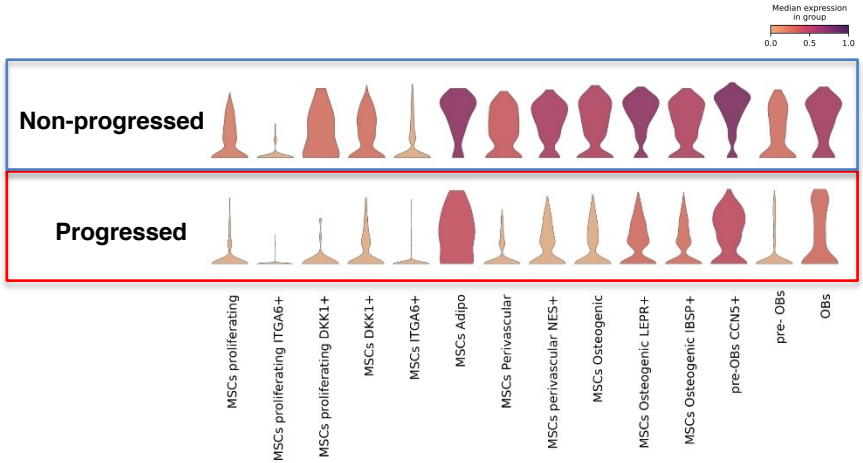
DIFFERENTIAL *CCN5* EXPRESSION IN NON-PROGRESSED *vs* PROGRESSED SMM PATIENTS





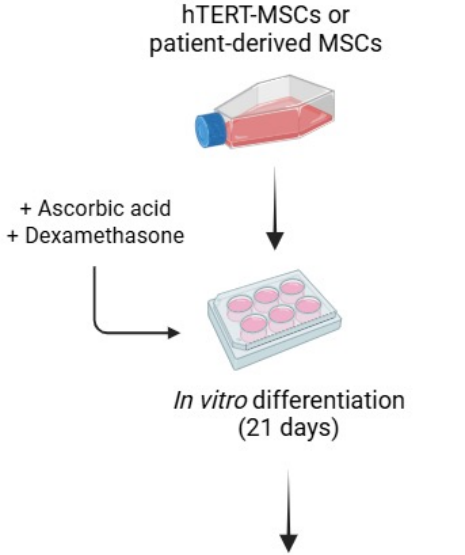
DIFFERENTIAL *CCN5* EXPRESSION IN NON-PROGRESSED *vs* PROGRESSED SMM PATIENTS

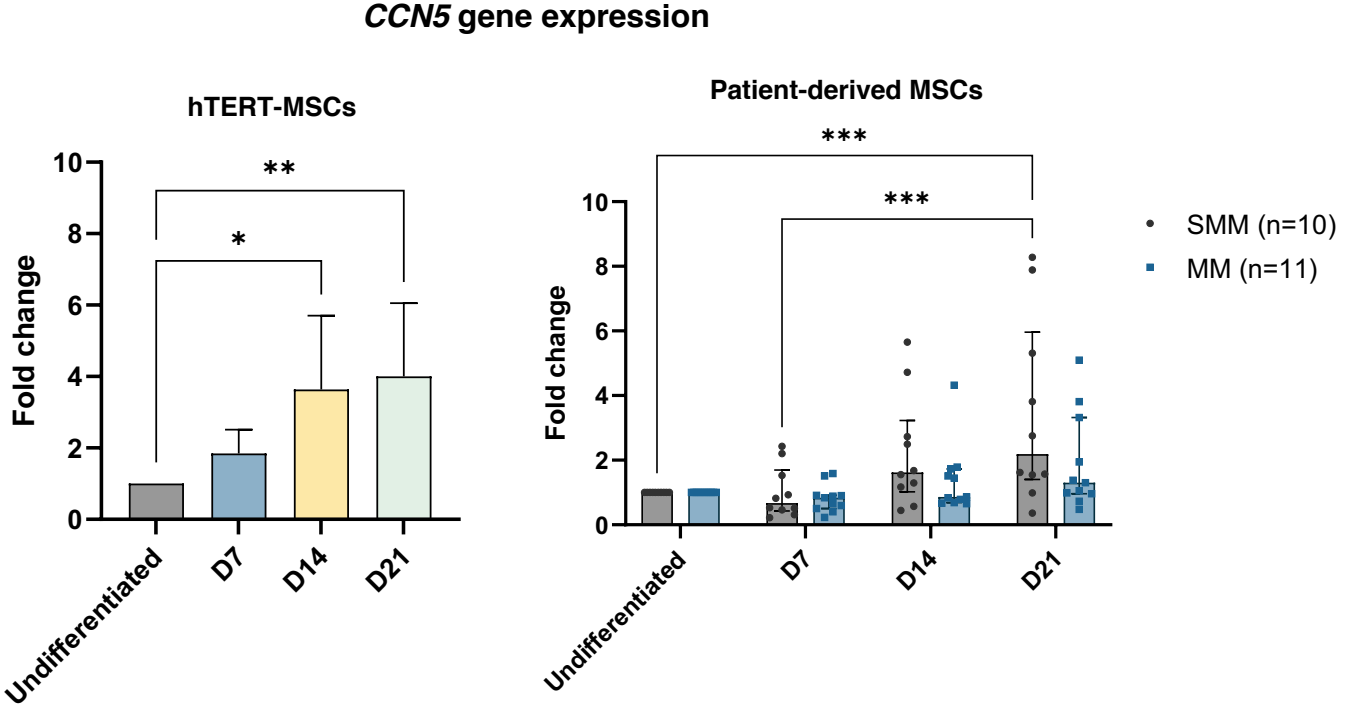




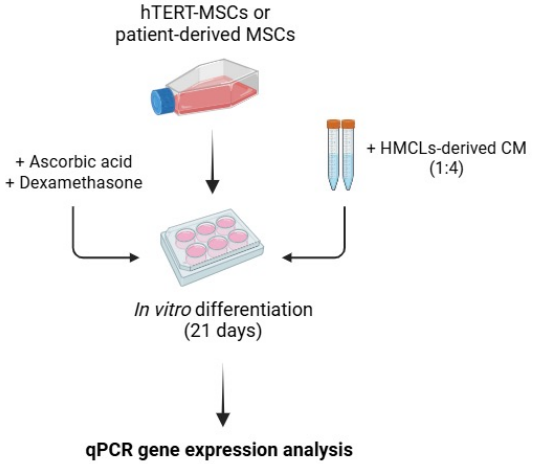
Non-progressed SMM show a MGUS-like *CCN5* expression pattern,
while progressed SMM show a MM-like expression pattern.

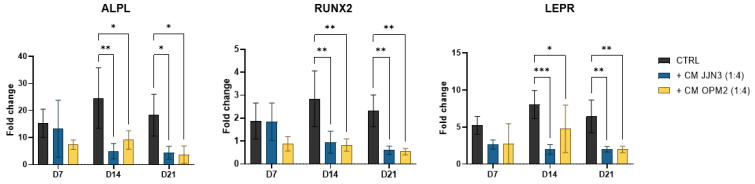
CCN5 GENE EXPRESSION INCREASES DURING OSTEOGENIC DIFFERENTIATION IN hTERT-MSCs AND SMM PATIENT-DERIVED MSCs



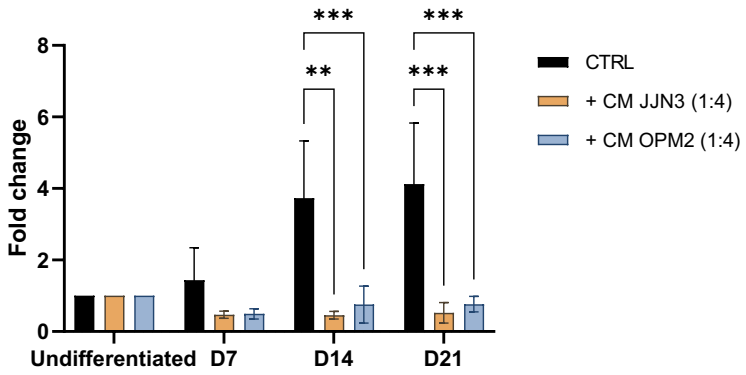


CONDITIONED MEDIA (CM) FROM HUMAN MYELOMA CELL LINES (HMCLs) SUPPRESS *CCN5* IN hTERT-MSCs AND SMM OBs, BUT NOT IN MM-DERIVED OBs

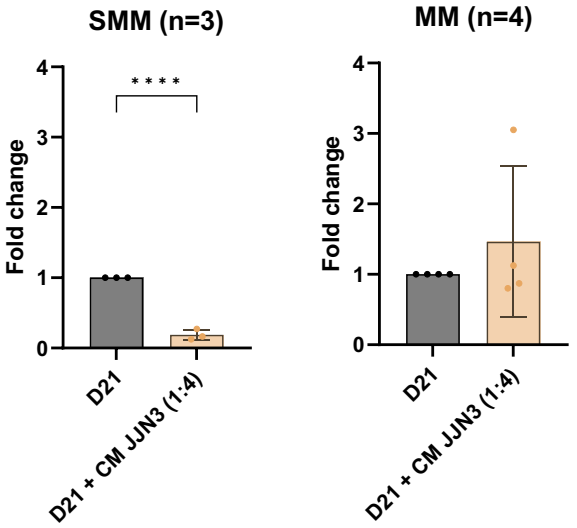




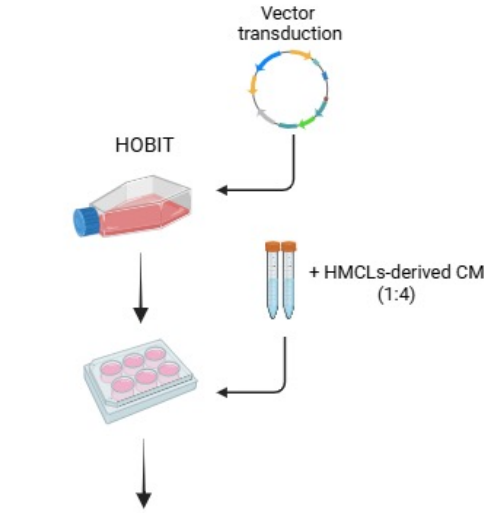
***CCN5* gene expression in hTERT-MSCs with HMCLs-CM**



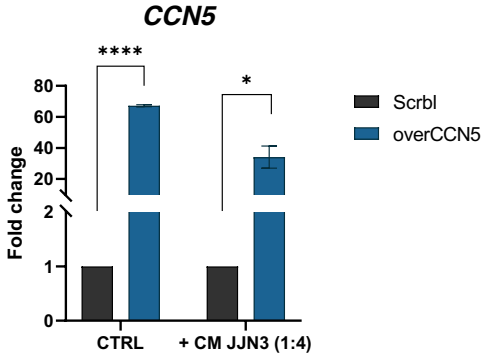
***CCN5* gene expression in patient-derived OBs with HMCLs-CM**

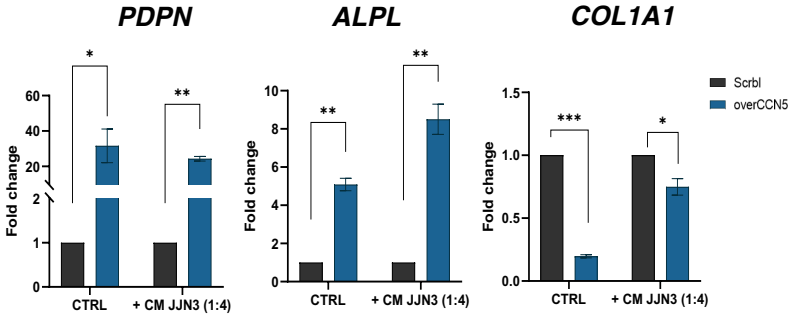


CCN5 OVEREXPRESSION IN OB-LIKE CELLS (HOBIT) ENHANCES OSTEOGENIC MARKERS AND OVERCOMES HMCLs-CM–MEDIATED INHIBITION



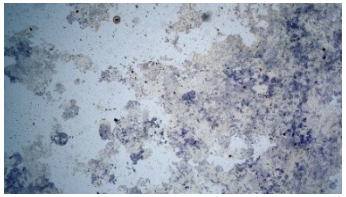
- qPCR gene expression analysis
- ALP activity assay



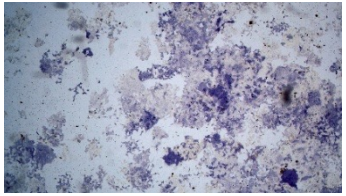


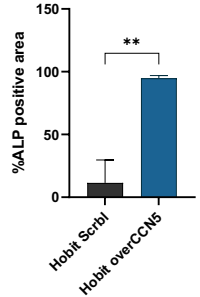
ALP activity assay

HOBIT Scrbl



HOBIT overCCN5

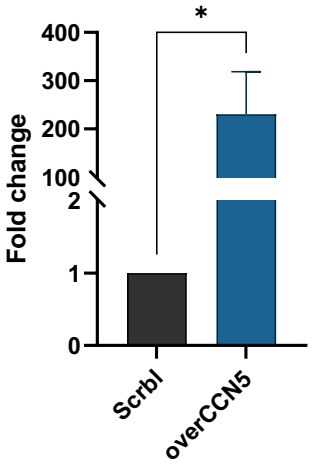


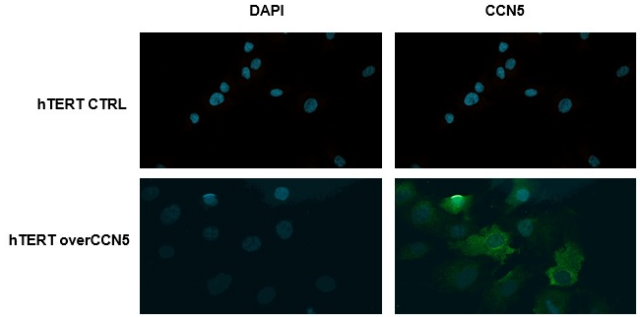


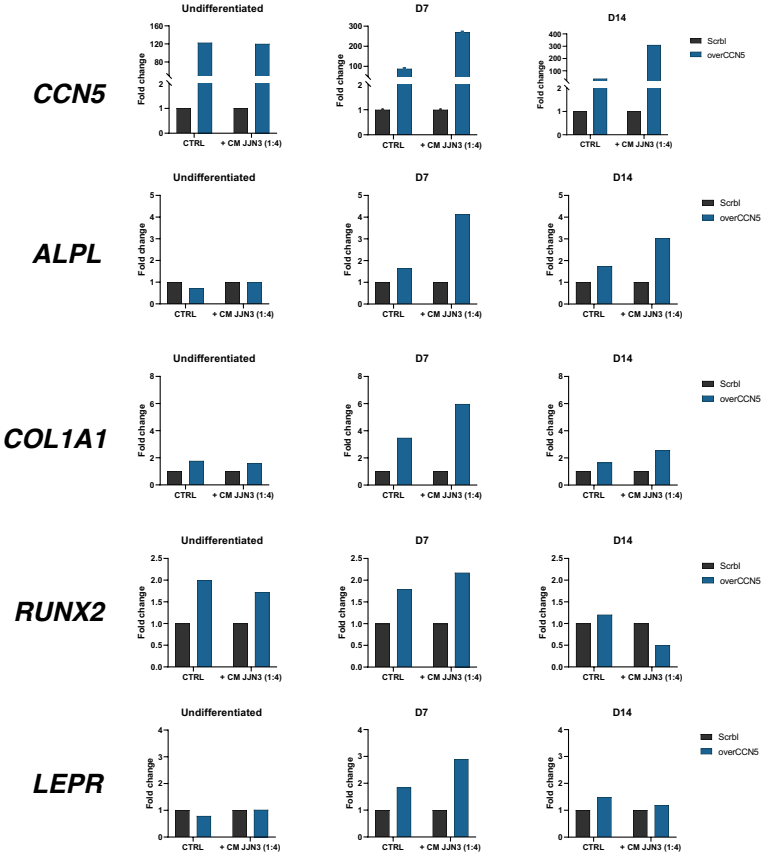
ONGOING…

mRNA and protein expression of *CCN5*

hTERT-MSCs

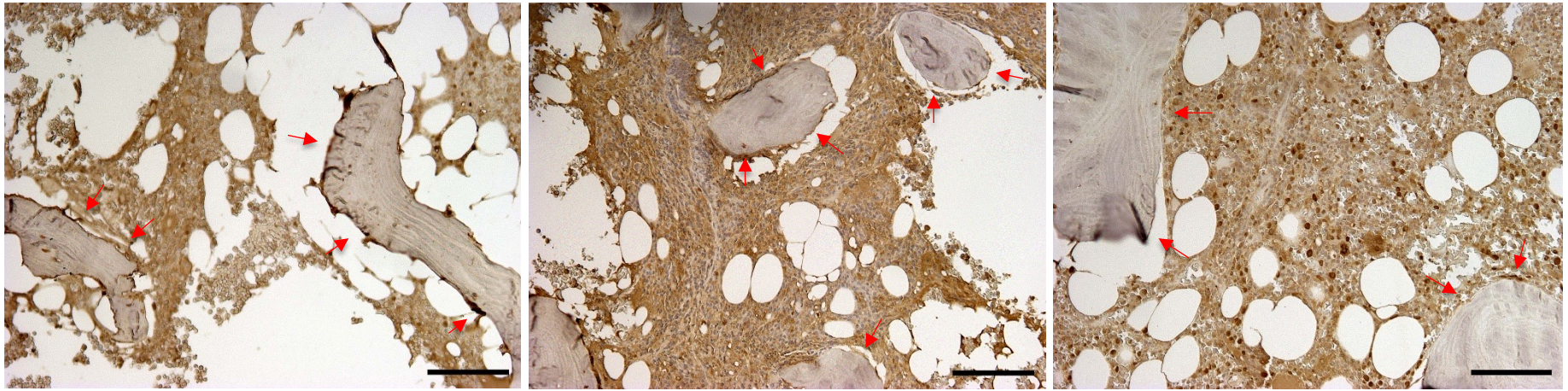






ONGOING…

MGUS | **SMM** | **MM**



10x

SUMMARY AND CONCLUSIONS

- *CCN5* expression declines from MGUS to MM.
- Paired longitudinal analysis of SMM progressors to-MM confirm the overall progression pattern of *CCN5* expression.
- Notably, within the SMM group, non-progressors show higher *CCN5* expression than progressors.
- *CCN5* expression during osteogenesis is suppressed by HMCLs-CM in hTERT-MSCs and SMM-derived OBs, but not in MM-derived OBs.
- *CCN5* overexpression increases osteoblast-lineage markers and attenuates the inhibitory effect of HMCLs-CM on osteogenic differentiation.

CCN5 expression is progressively downregulated from pre-malignant monoclonal gammopathies to MM being involved in MM-induced osteoblast suppression.

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