Il secretoma della nicchia leucemica favorisce l'immunosoppressione mediata da macrofagi M2 nella leucemia mieloide acuta pediatrica

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AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP MEDICI
LECCE, 12-14 ottobre 2026
HILTON GARDEN INN

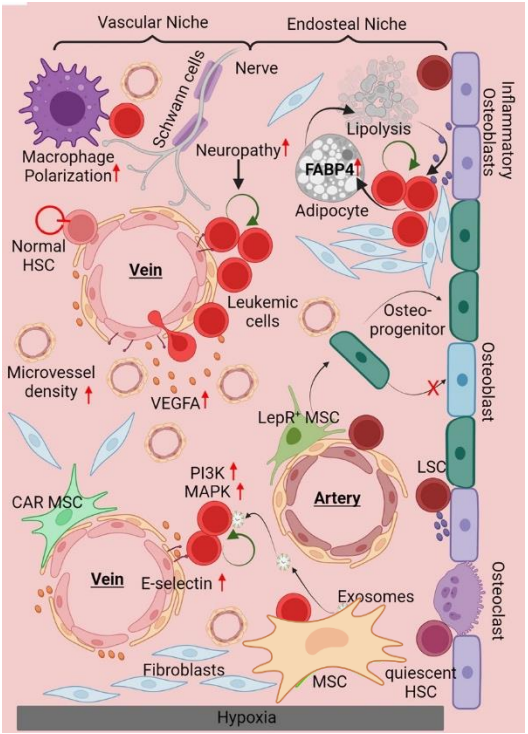
Disclosures of Giorgia Longo

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

AML hijacks the bone marrow niche

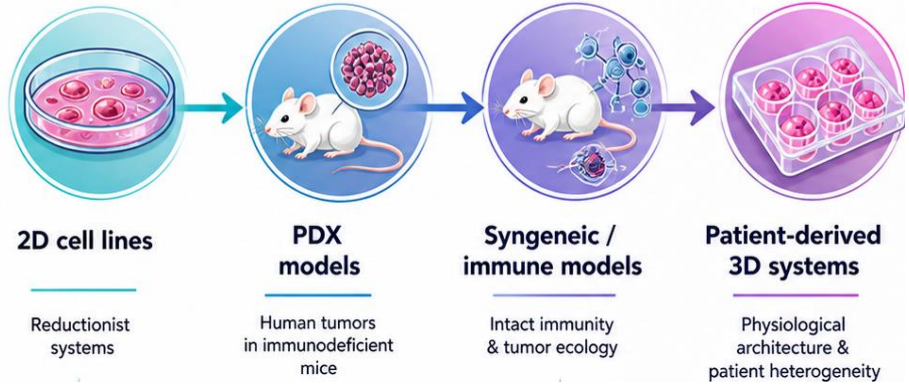
- The leukemic niche: a **complex ecosystem**
- These components form dynamic networks that:

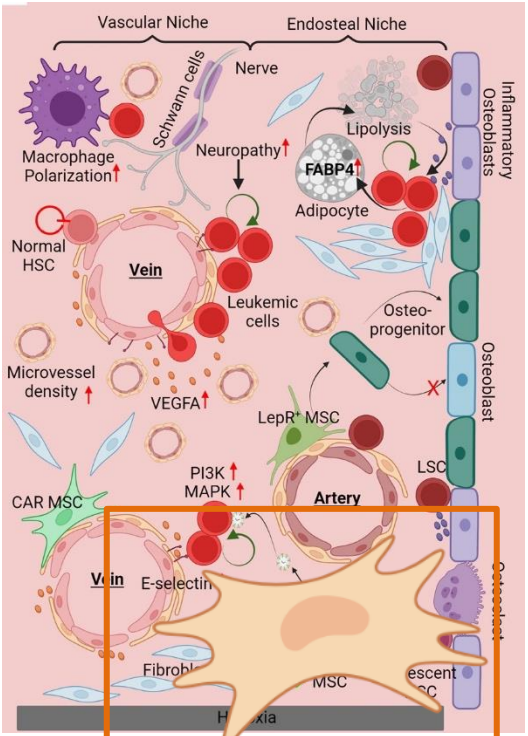
  - Supports leukemic expansion
  - Shapes immune responses
  - Promotes therapy resistance



Adapted from P. Urs et al. , *Ann Transl Med*, 2024

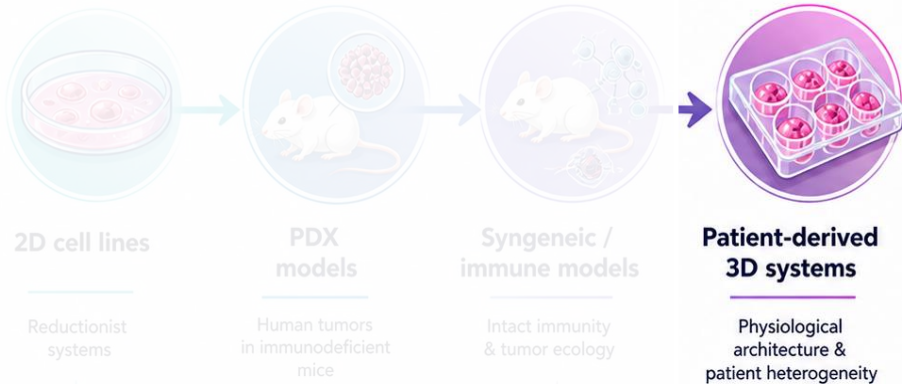
AML hijacks the bone marrow niche



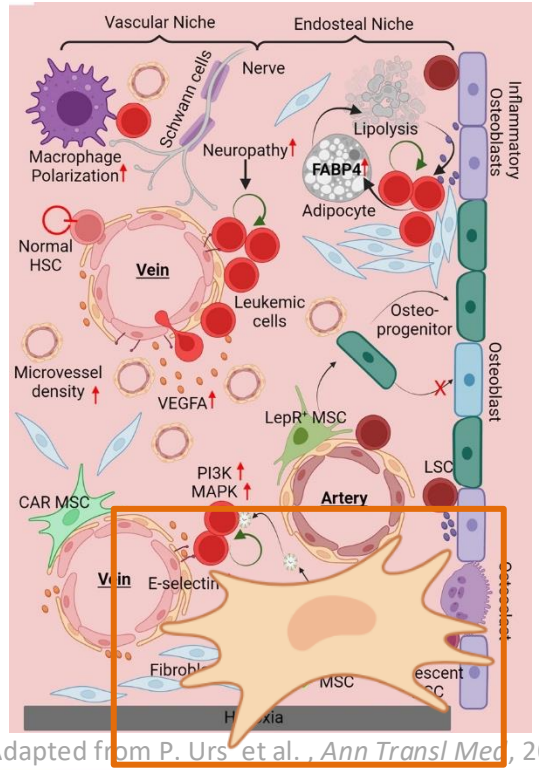


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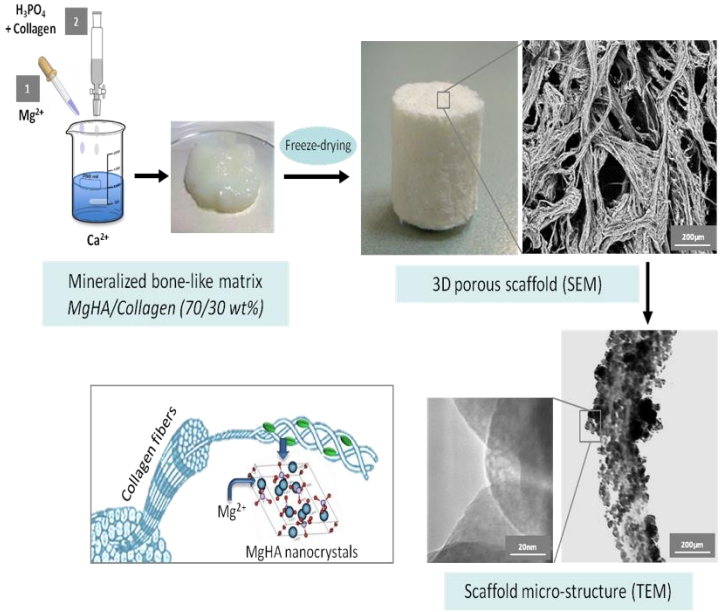


We use 3D models to ask
what works in human context



Adapted from P. Urs et al. , *Ann Transl Med*, 2024

THE PLATFORM (Borella et al., Blood 2021)

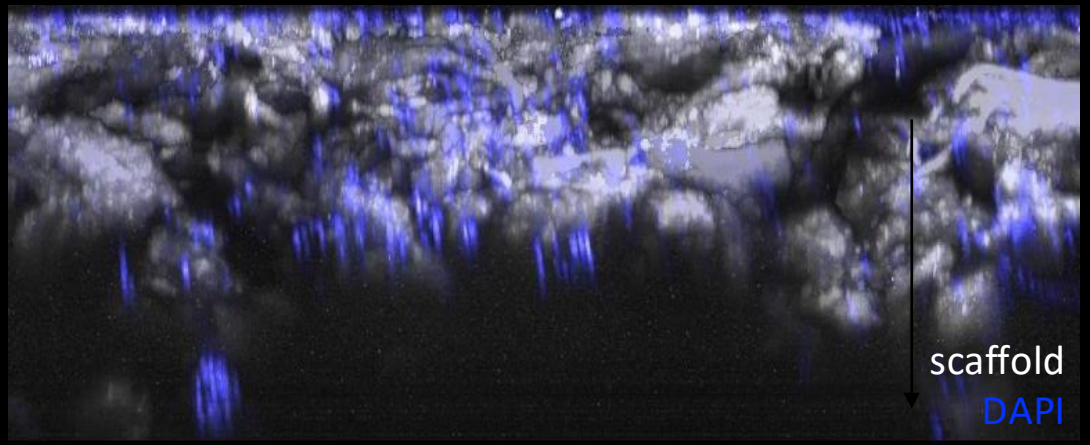


- Magnesium-doped hydroxyapatite-collagen (MgHA/Col)
- Biomineralization process allowing nucleation of biomimetic MgHA nanocrystals on Type I collagen fibers during their self-assembly guided by pH changes.
- High porosity (more than 85%) promoting cell penetration and migration into the scaffold together with suitable nutrients and oxygen diffusion.
- The formation of nanostructured and homogeneously distributed apatite nanocrystals aligned on collagen fibers.
- The weight *ratio* of the MgHA/Col hybrid composite is 70/30, BDDGE crosslinker, a ratio very close to the composition of the natural bone tissue and the mineral phase (MgHA) being characterized by the typical low crystalline pattern due to the presence of magnesium as foreign ion and the presence of collagen as template for the biomineralization.

Dr. Monica Sandri, Dr. Elisabetta Campodoni

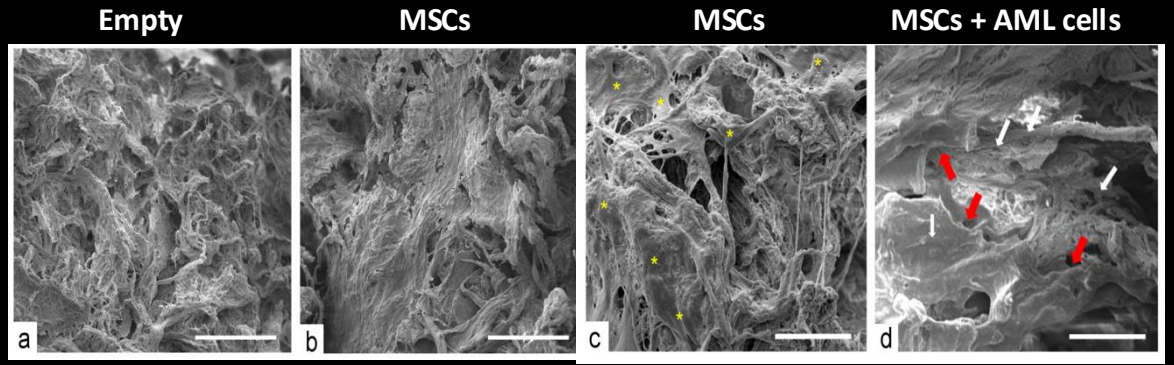
AML cells engraft within the scaffold

2-photon Microscopy:

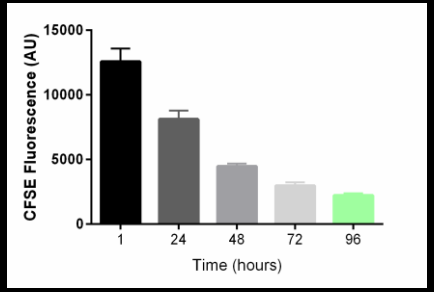


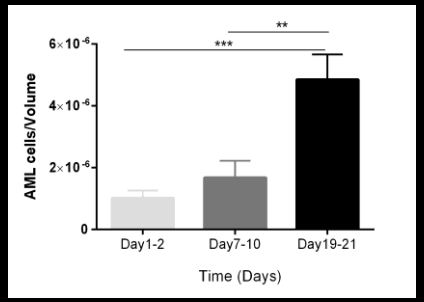
575 µm

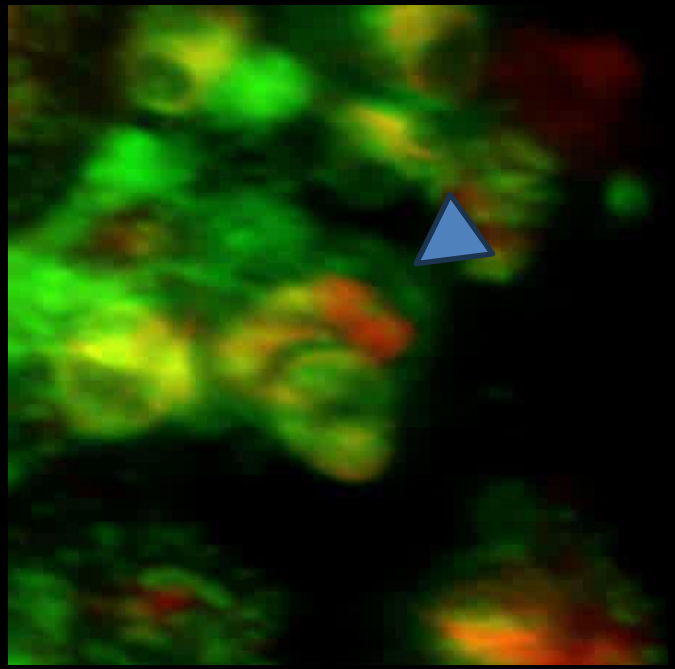
Scansion Electronic Microscopy:



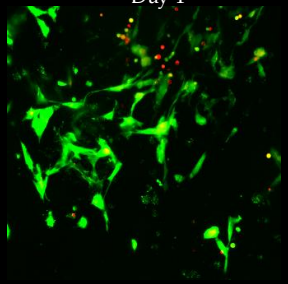
AML cells proliferate for up to 21 days



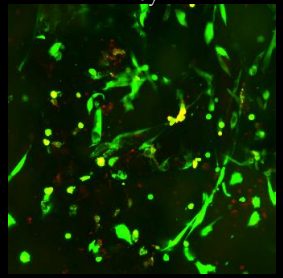




Day 1



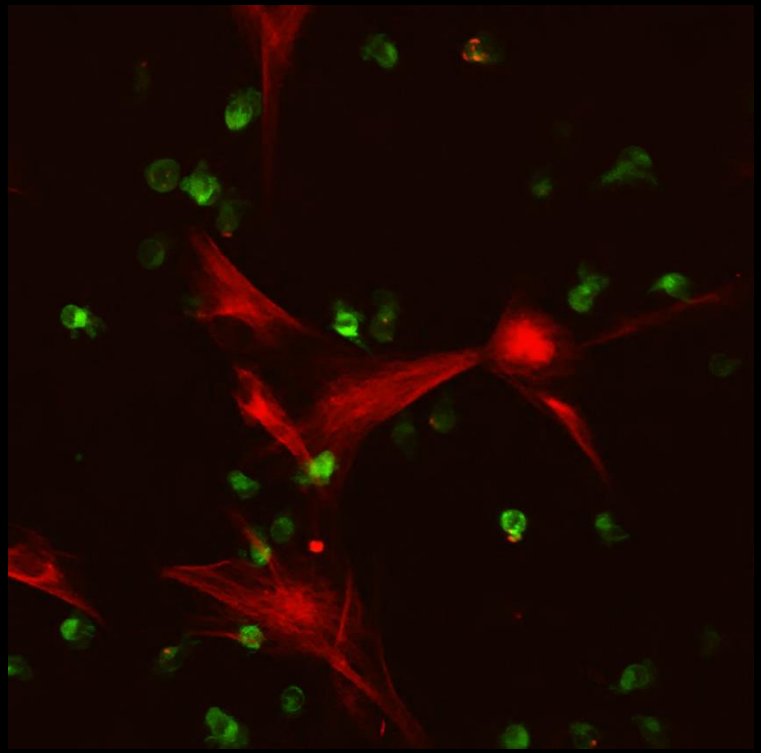
Day 7

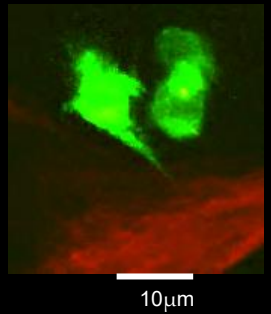


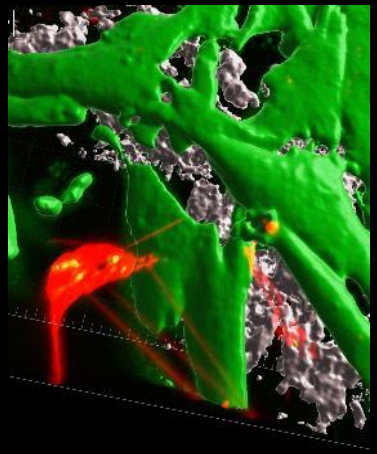
CALCEIN-AM CD45

AML Cells Form Nanotubes to Directly Interact with MSCs

Co-culture AML cells and MSCs
Z-projection of multiple z-stacks

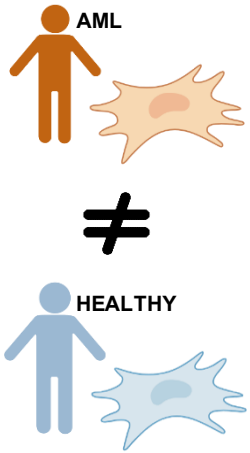




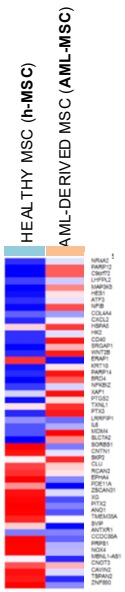


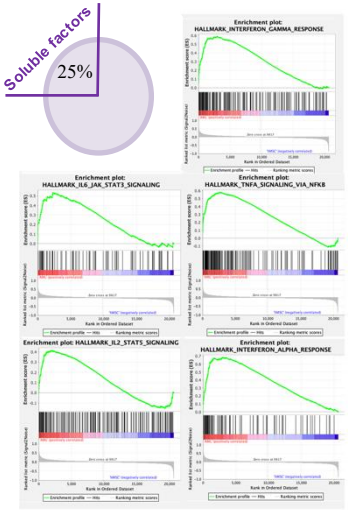
DiO membrane green Tubulin

AML hijacks the bone marrow niche

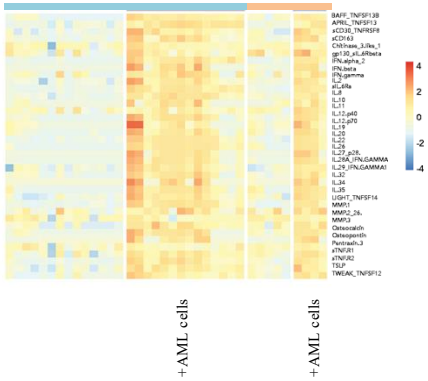


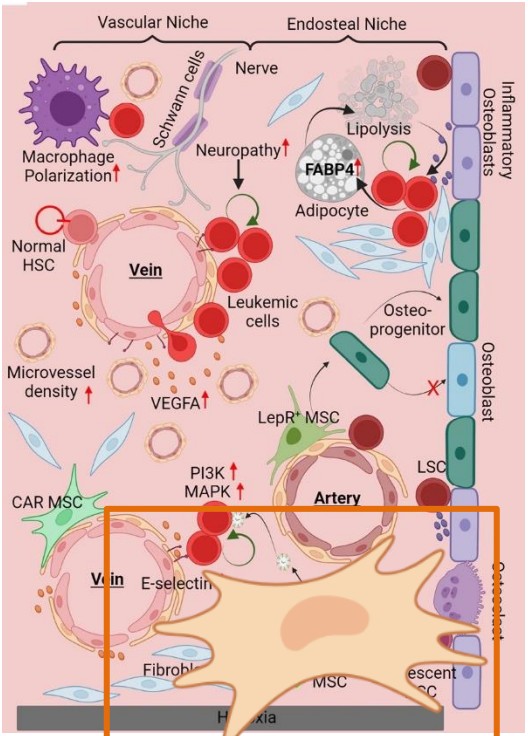
TRANSCRIPTOME





SECRETOME

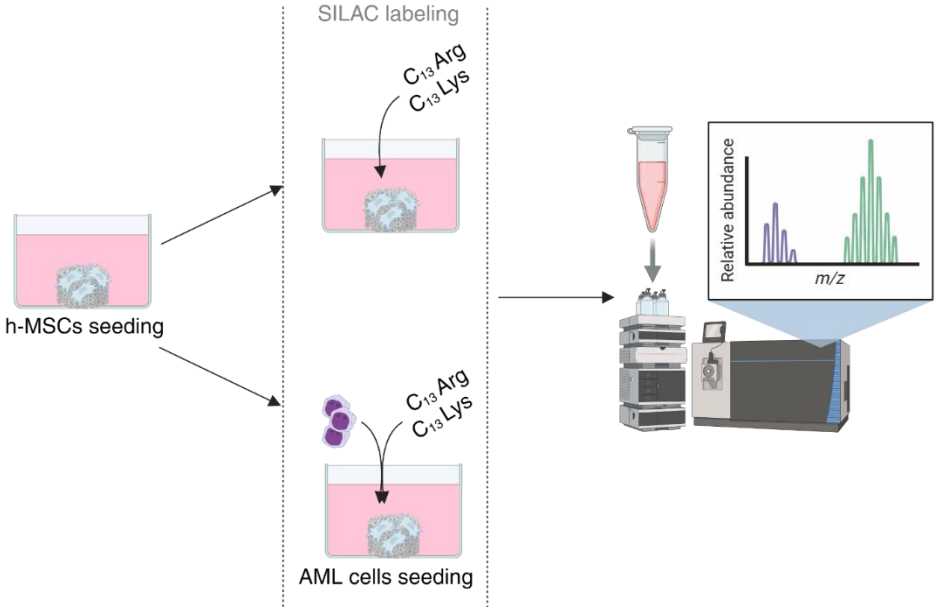




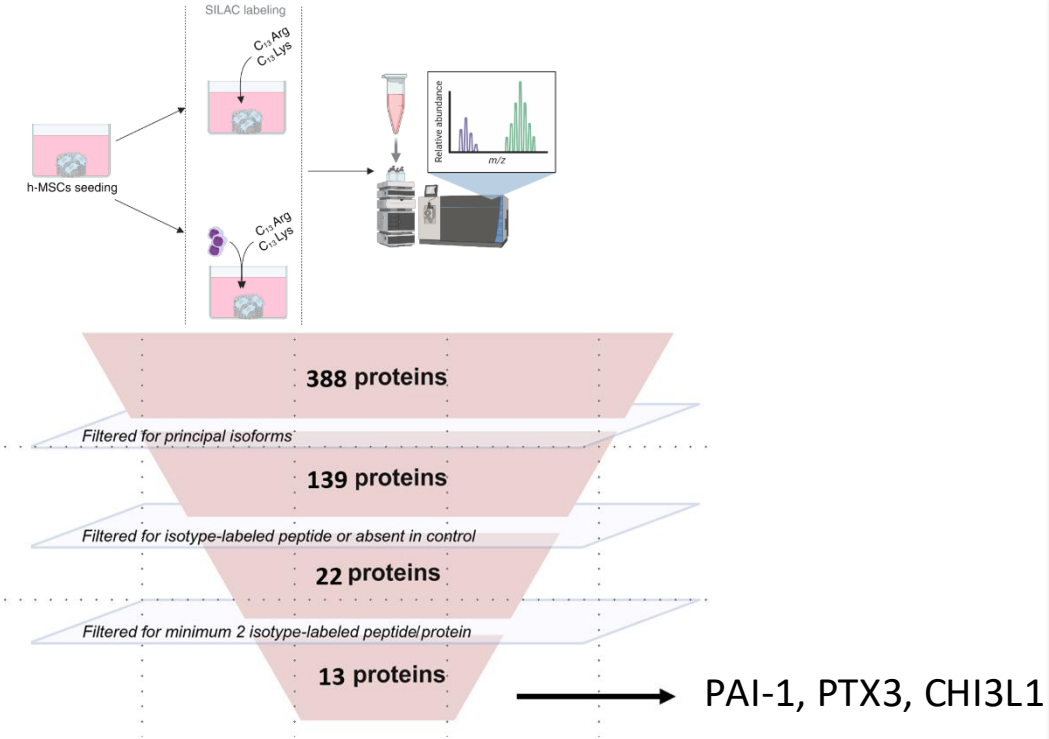
Borella et al. , *Blood* 2021

Adapted from P. Urs et al. , *Ann Transl Med*, 2024

What are the changes in the secretome at leukemia onset?

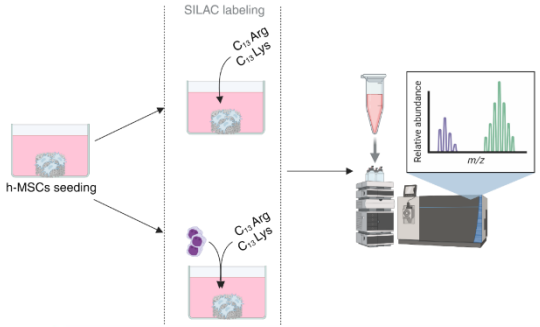


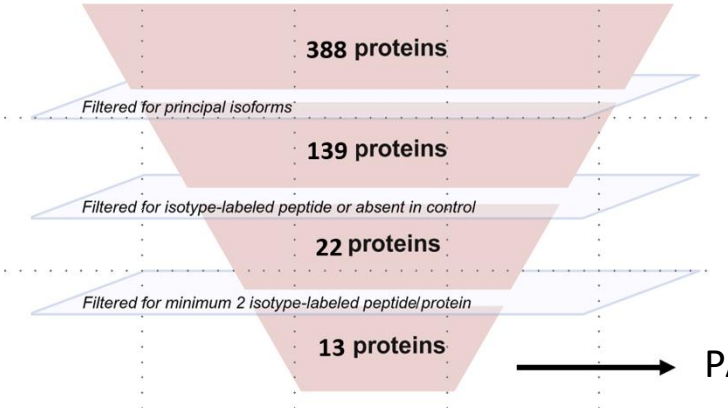
What are the changes in the secretome at leukemia onset?



- **SERPINE-1 (PAI-1):** Involved in the inhibition of fibrinolysis and regulation of extracellular matrix degradation. Associated with chronic inflammation, cancer, and tissue remodeling, with pro-tumorigenic effects in various contexts.
- **PTX3 (Pentraxin 3):** Innate immune response protein produced in response to inflammation with both protective and pro-inflammatory roles; involved in infections, tissue damage, and tumor progression.
- **CHI3L1 (YKL-40):** Glycoprotein secreted during inflammation and linked to tumor progression, angiogenesis, and fibrosis; often elevated in cancers and inflammatory diseases.

What are the changes in the secretome at leukemia onset?

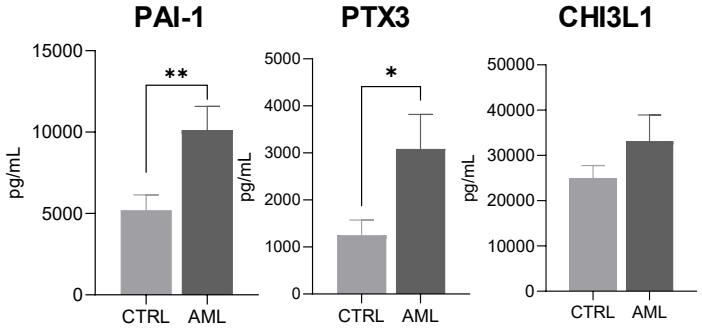




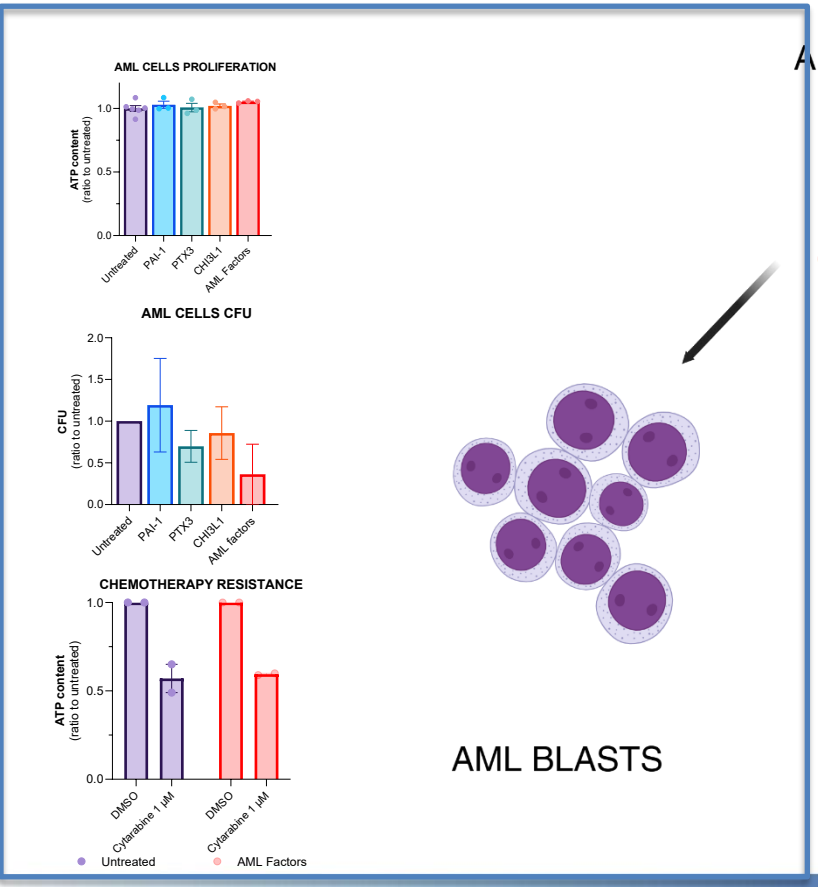
PAI-1, PTX3, CHI3L1

VALIDATION ON BM PLASMA

(n AML=30, ctrl n=9)

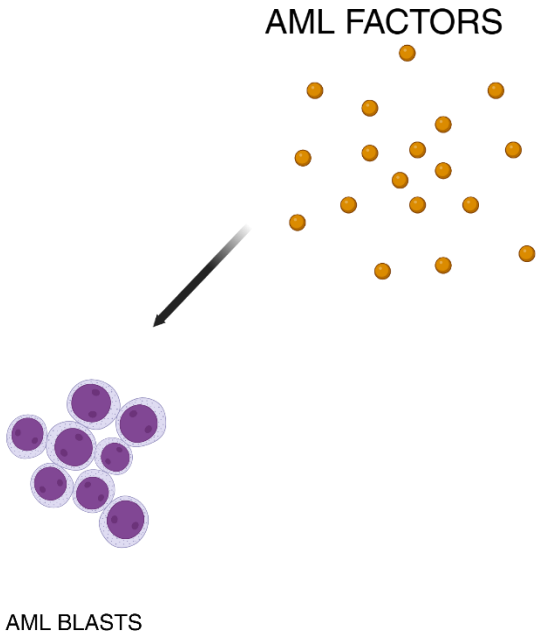


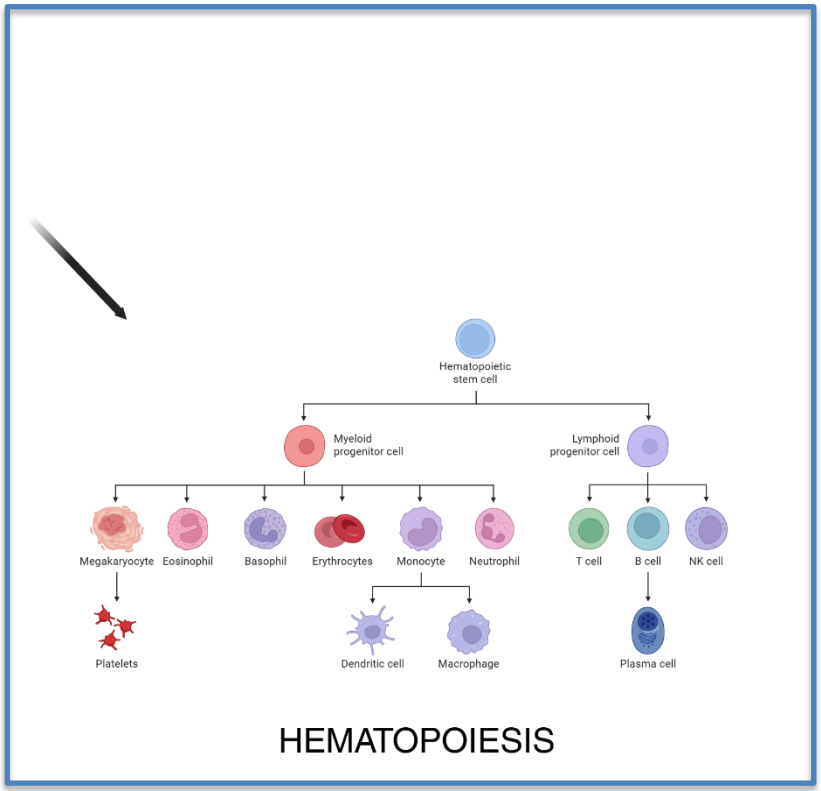
Functional effect of AML factors within the leukemic niche



rPAI-1 + rPTX3 + rCHI3L1 = «AML FACTORS»

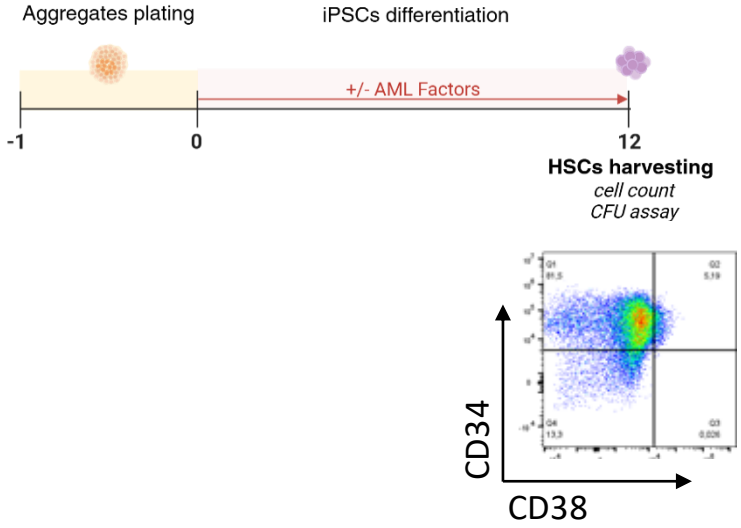
Functional effect of AML factors within the leukemic niche

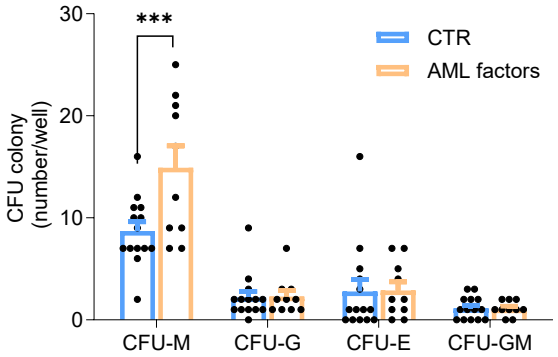




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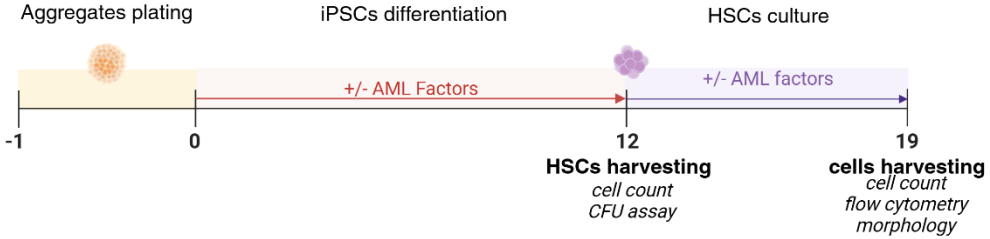
AML factors shape hematopoiesis in iPSC models

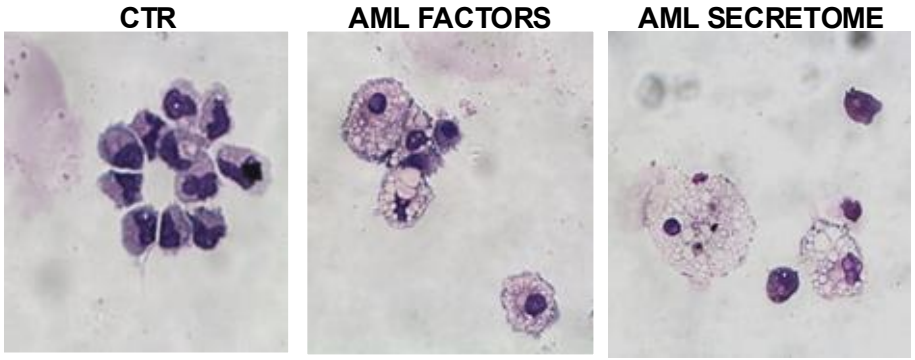


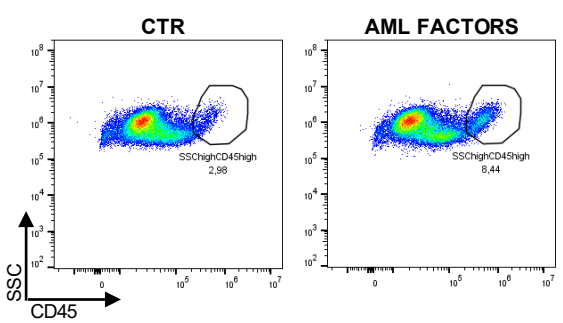


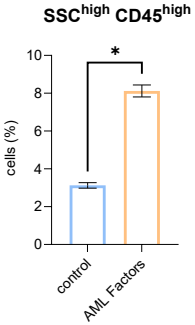
>80% OF CD45+/CD34+/ CD38- CELLS

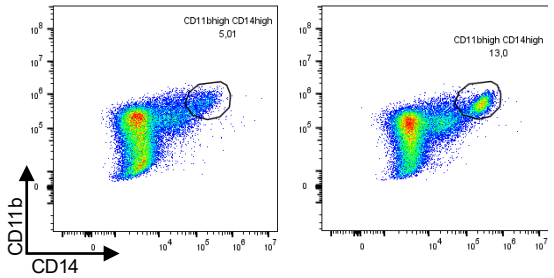
AML factors promote HSC differentiation into a monocyte/macrophage-like lineage

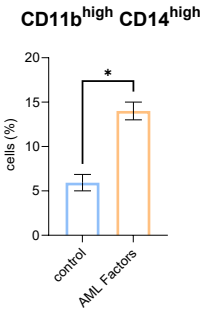






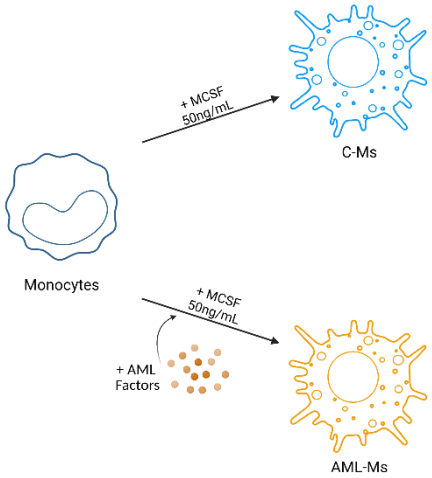


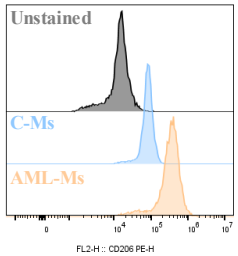


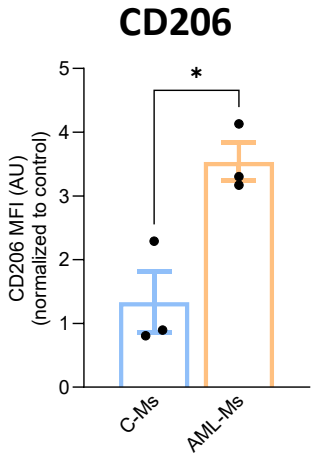


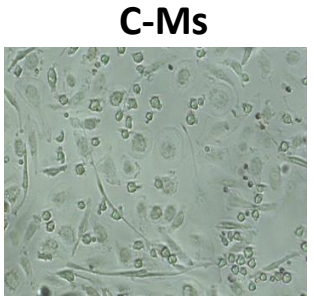
AML factors polarize macrophages toward CD206+ phenotype

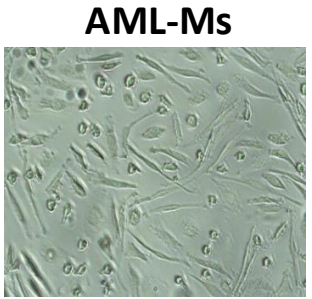
PBMCs-derived monocytes:

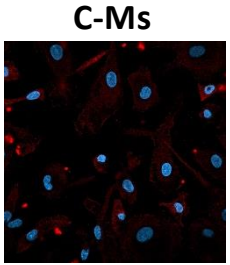


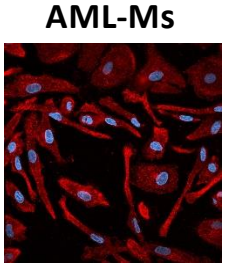


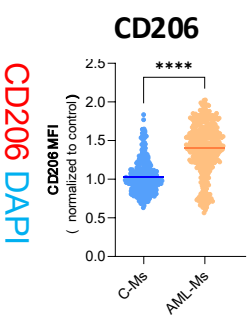


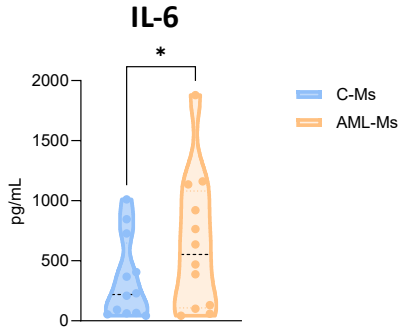






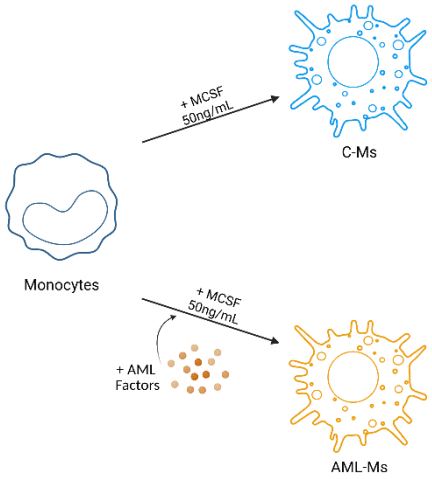


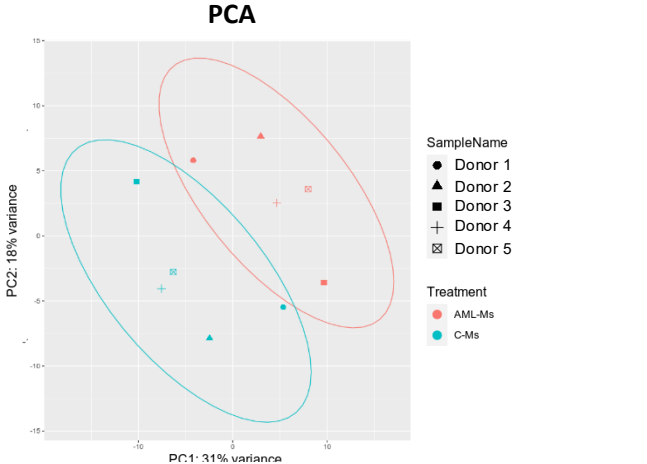


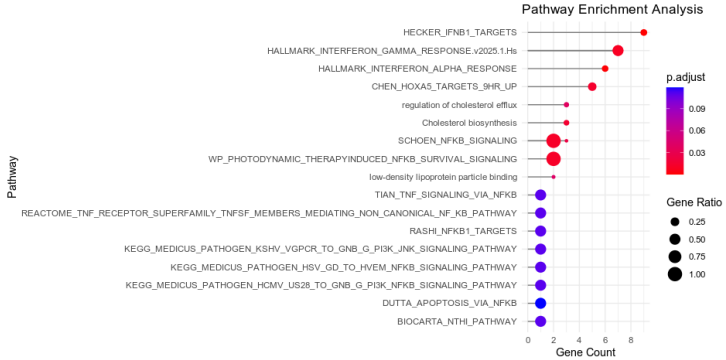


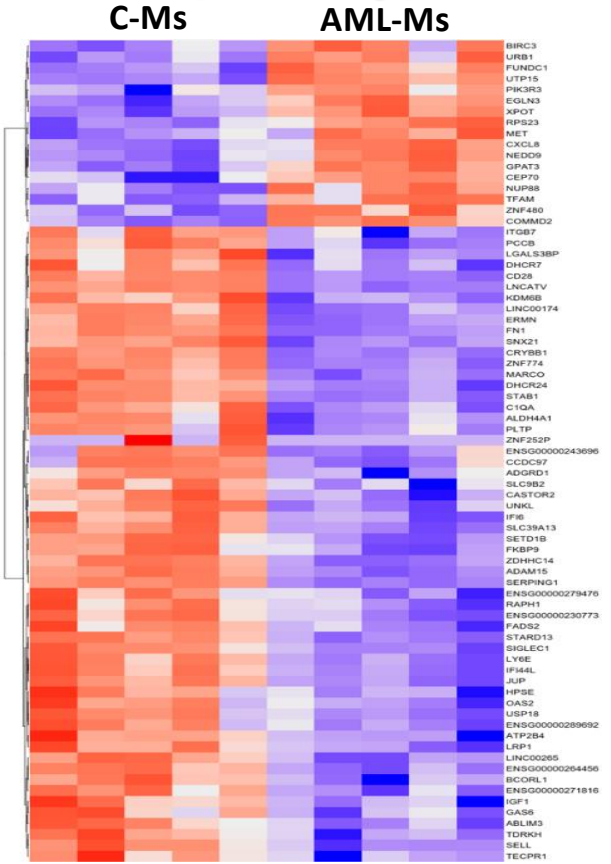
AML factors polarize macrophages toward CD206+ phenotype

PBMCs-derived monocytes:



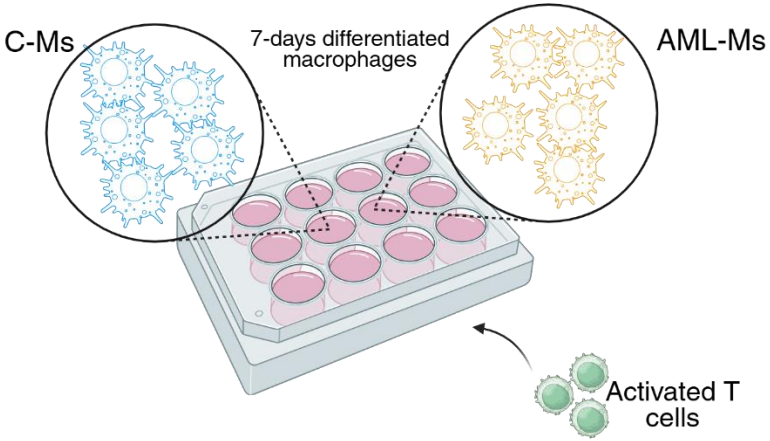




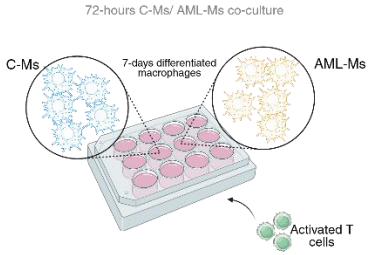


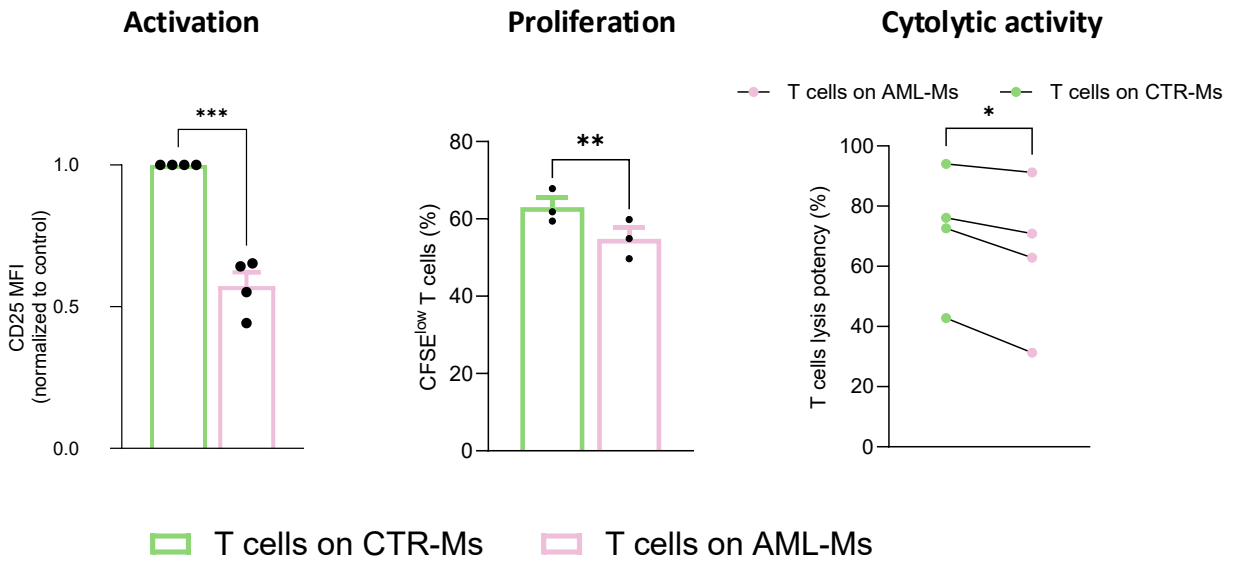
Functional effects of AML-Ms in the leukemic niche

72-hours C-Ms/ AML-Ms co-culture



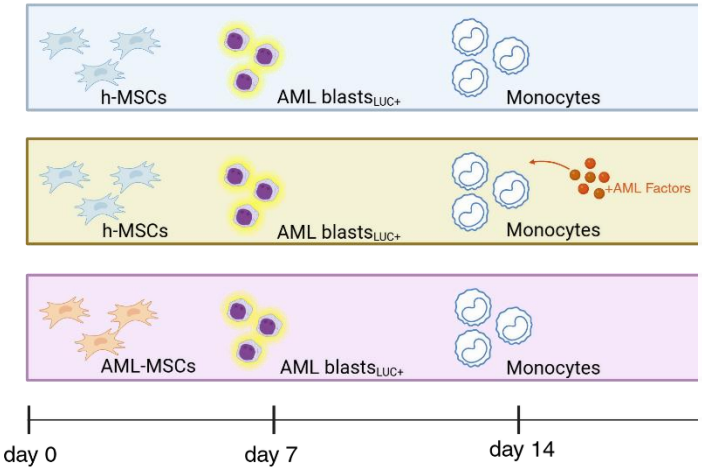
Functional effects of AML-Ms in the leukemic niche



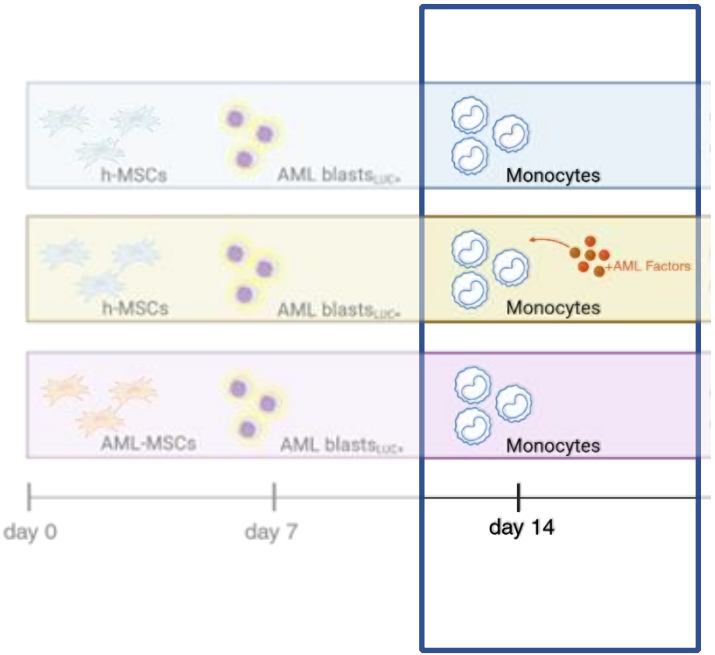


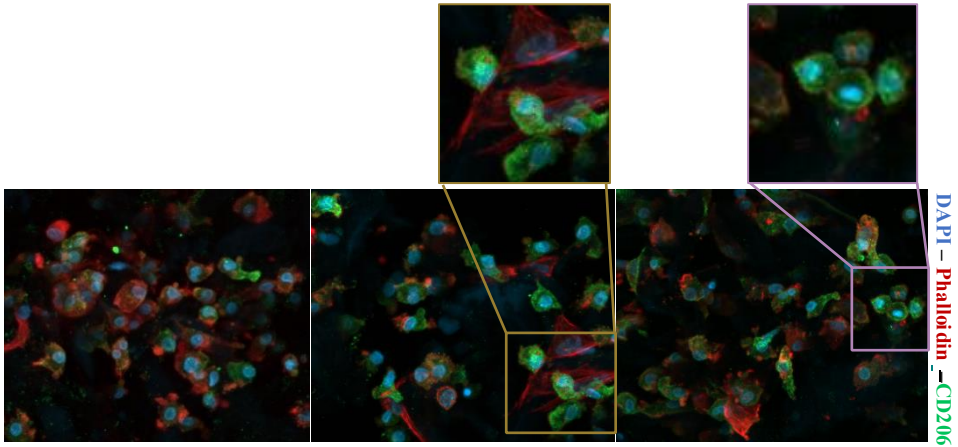
AML-Ms exert immunosuppressive effects on T cells

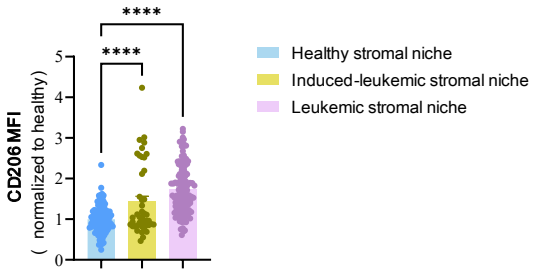
Functional effects of AML-Ms in the leukemic niche



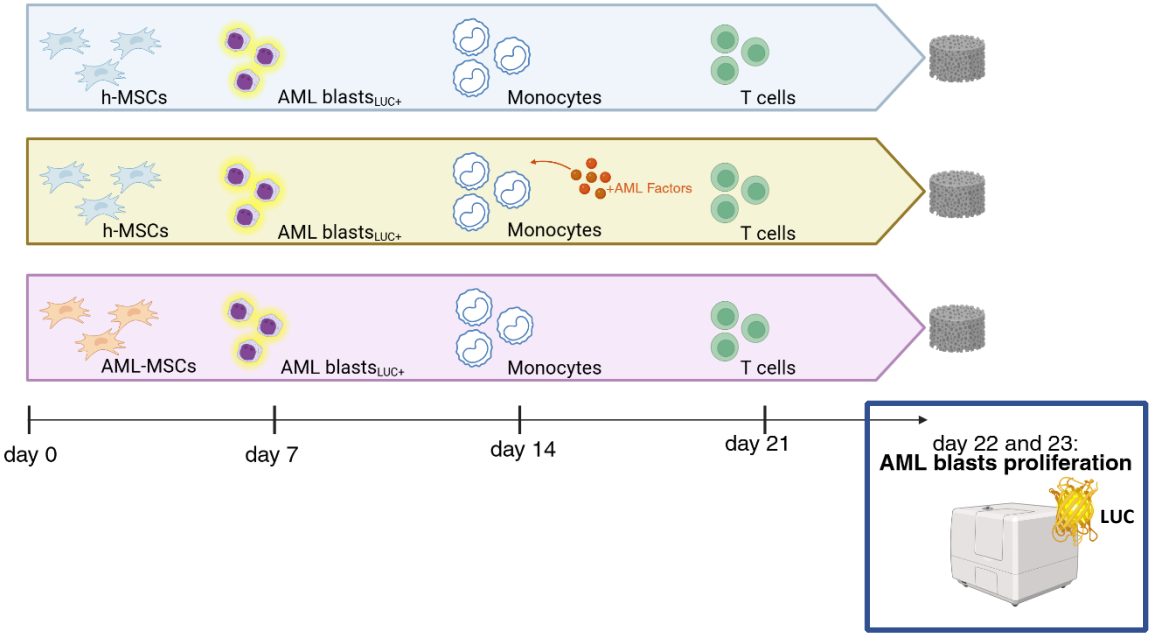
Functional effects of AML-Ms in the leukemic niche



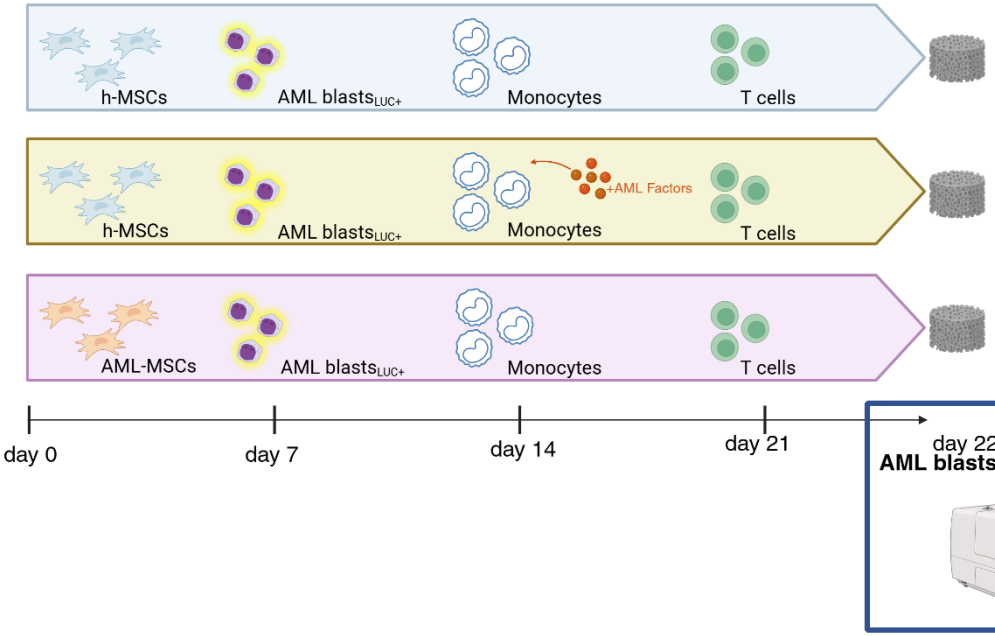


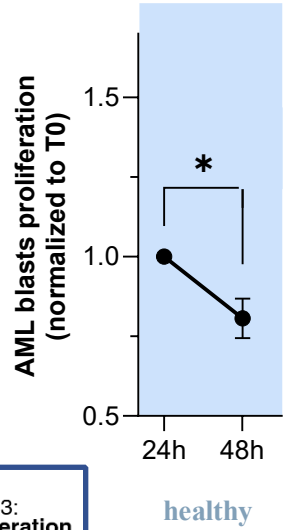


Functional effects of AML-Ms in the leukemic niche

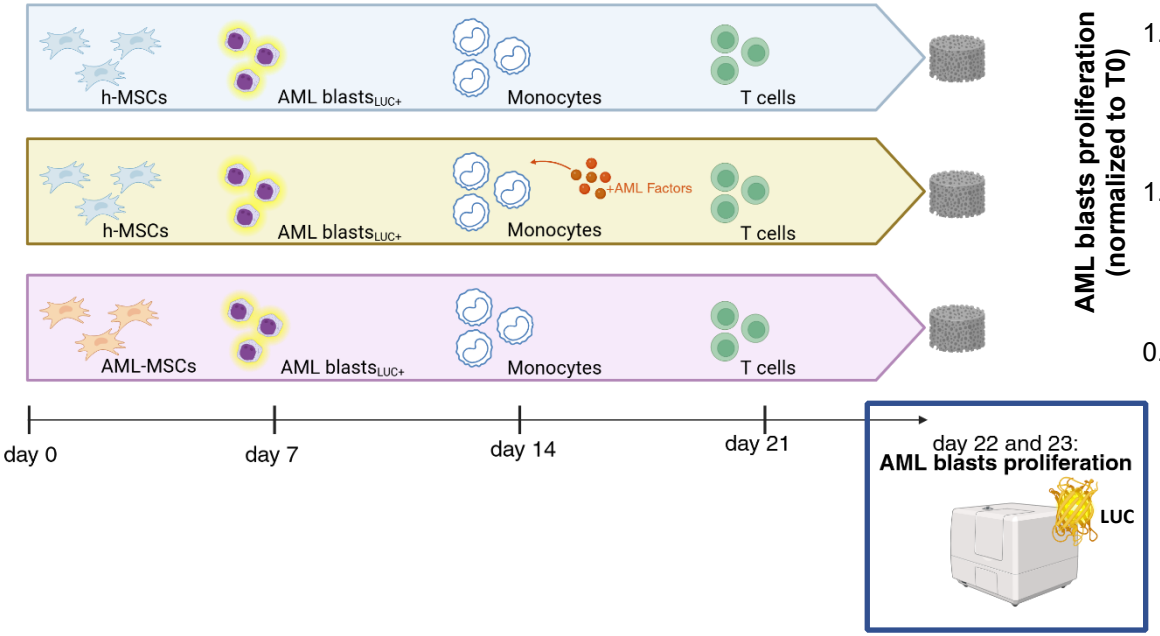


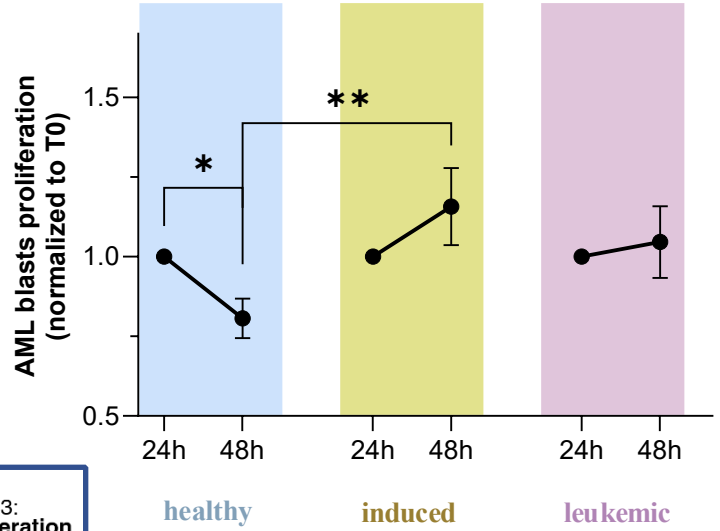
Functional effects of AML-Ms in the leukemic niche





Functional effects of AML-Ms in the leukemic niche





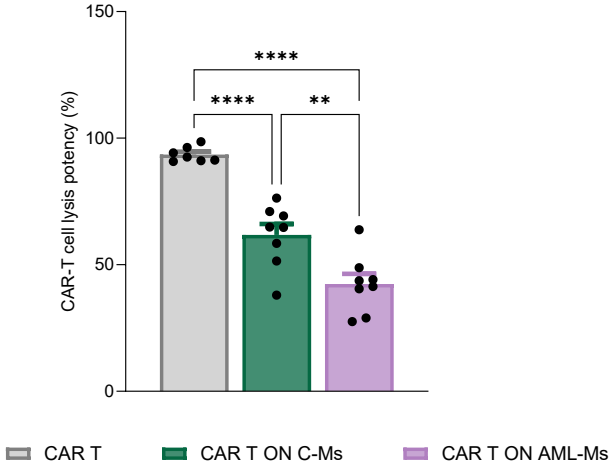
N=5

Preliminary results: AML-Ms reduce anti CAR-T cells activity

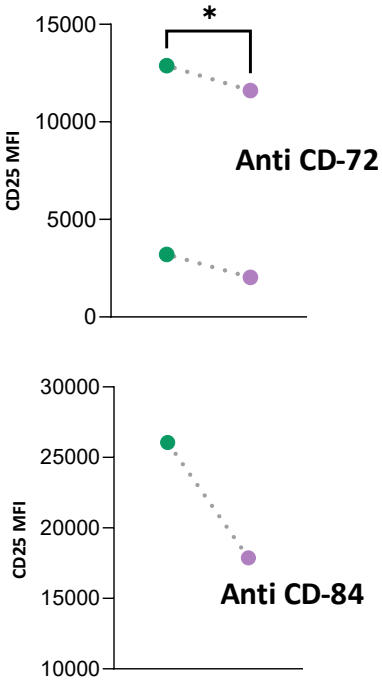
ALHENA SCIENCE towards curative medicine

CAR-T program;
Prof. A. Biffi - Prof. M. Pigazzi

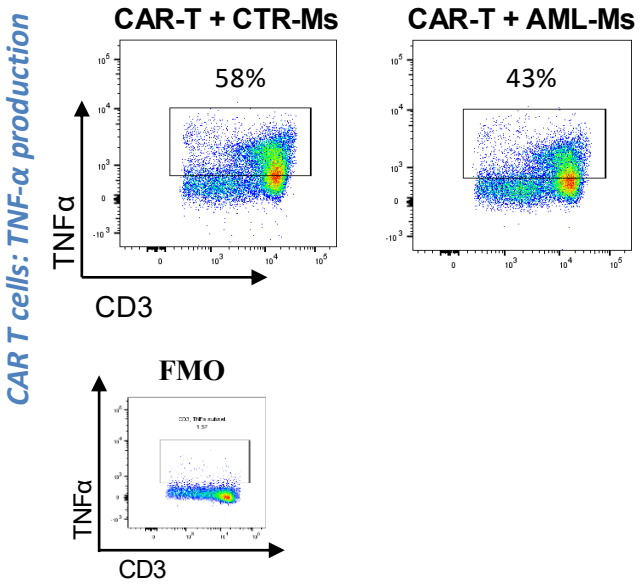
CAR T cells: Lysis potency



CAR T cells: Late activation



CAR T cells: TNF-α production



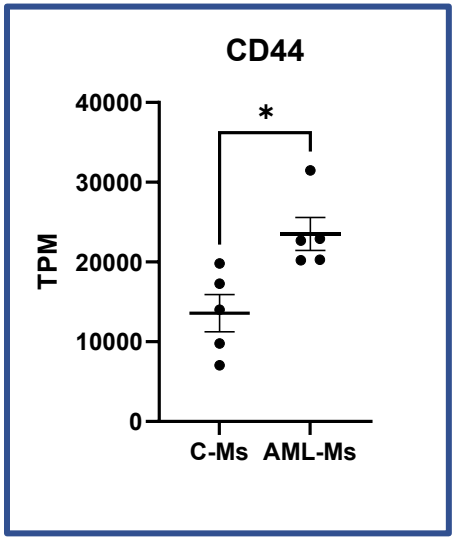
Conclusions

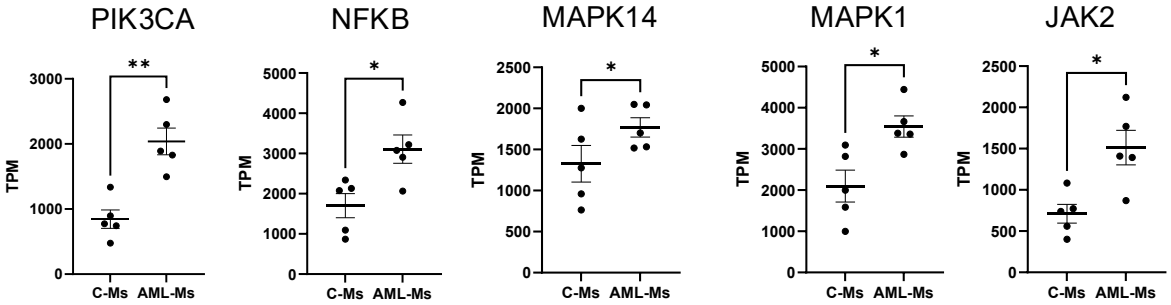
1. The AML secretome shapes **macrophage polarization** within the BM niche, with a key contribution from PAI-1, PTX3, and CHI3L1.

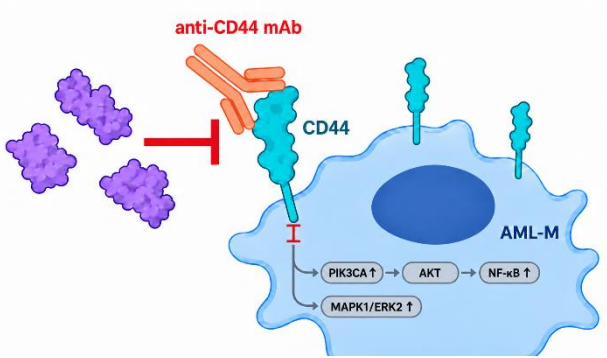
2. AML-educated macrophages acquire an **immunosuppressive phenotype**, leading to impaired T cell proliferation, activation, and effector function.

3. We identify **3 main factors** that may represent a key determinant of patients' response to **immunotherapy** and a potential therapeutic target.

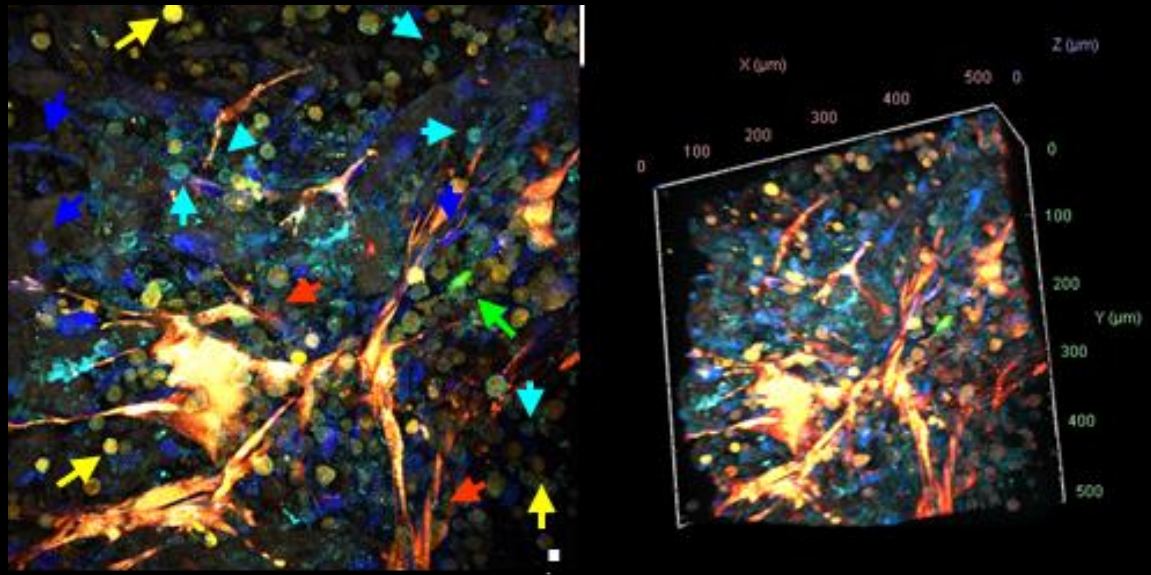
AML-Ms display signaling profile consistent with CD44-associated pathway activation







FUTURE PERSPECTIVEs:
study immunosuppression and novel therapies in an advanced 3D BM model



MSCs HUVEC Schwann cells monocytes AML T cells

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