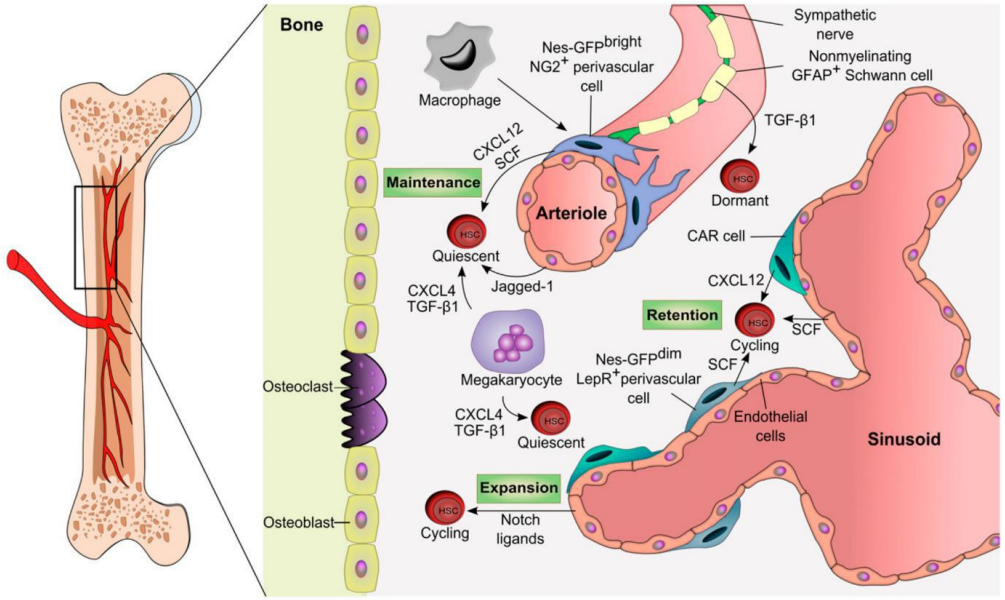
Bone Marrow Mesenchymal stromal cells senescence and alloreactivity after HSCT

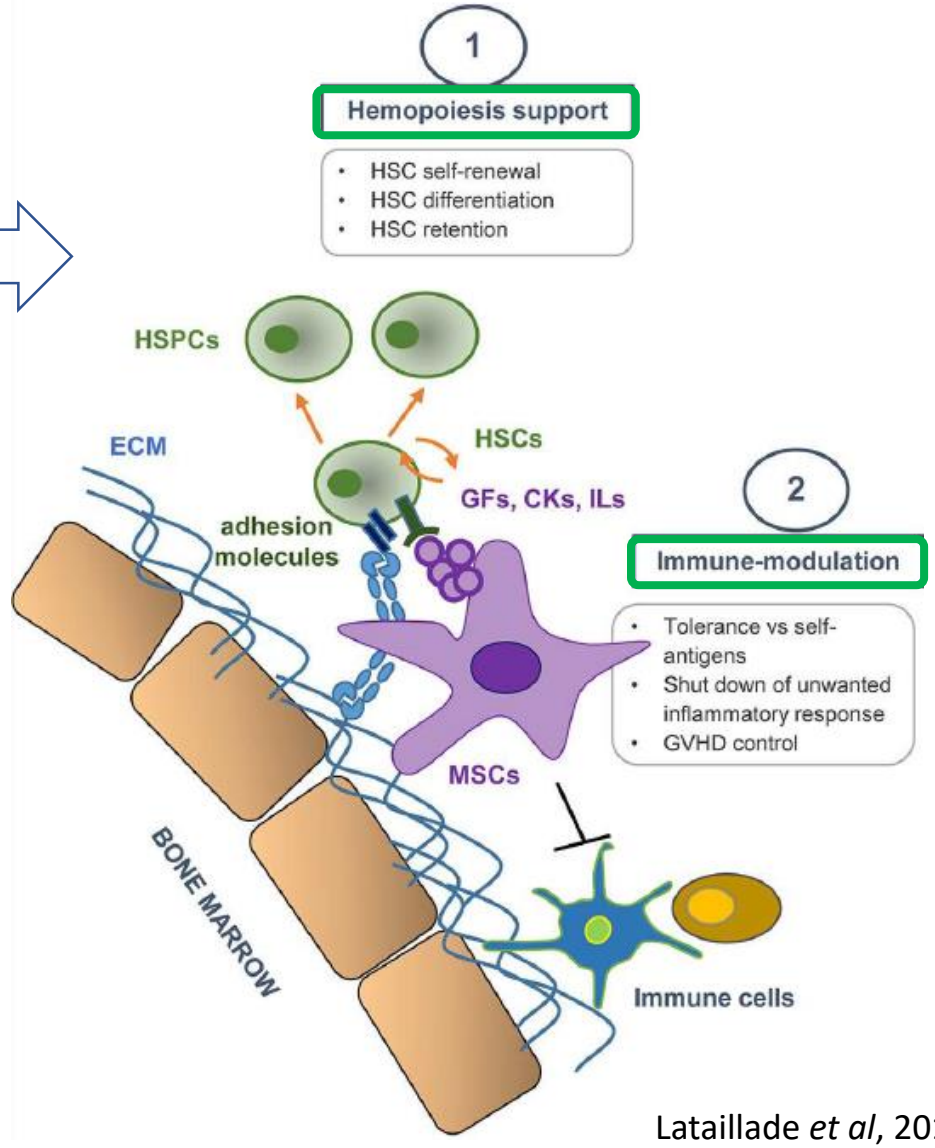
Natalia de Isla

IMoPA (Team 6), CNRS UMR 7365, Université de Lorraine, Nancy

Bone marrow niche

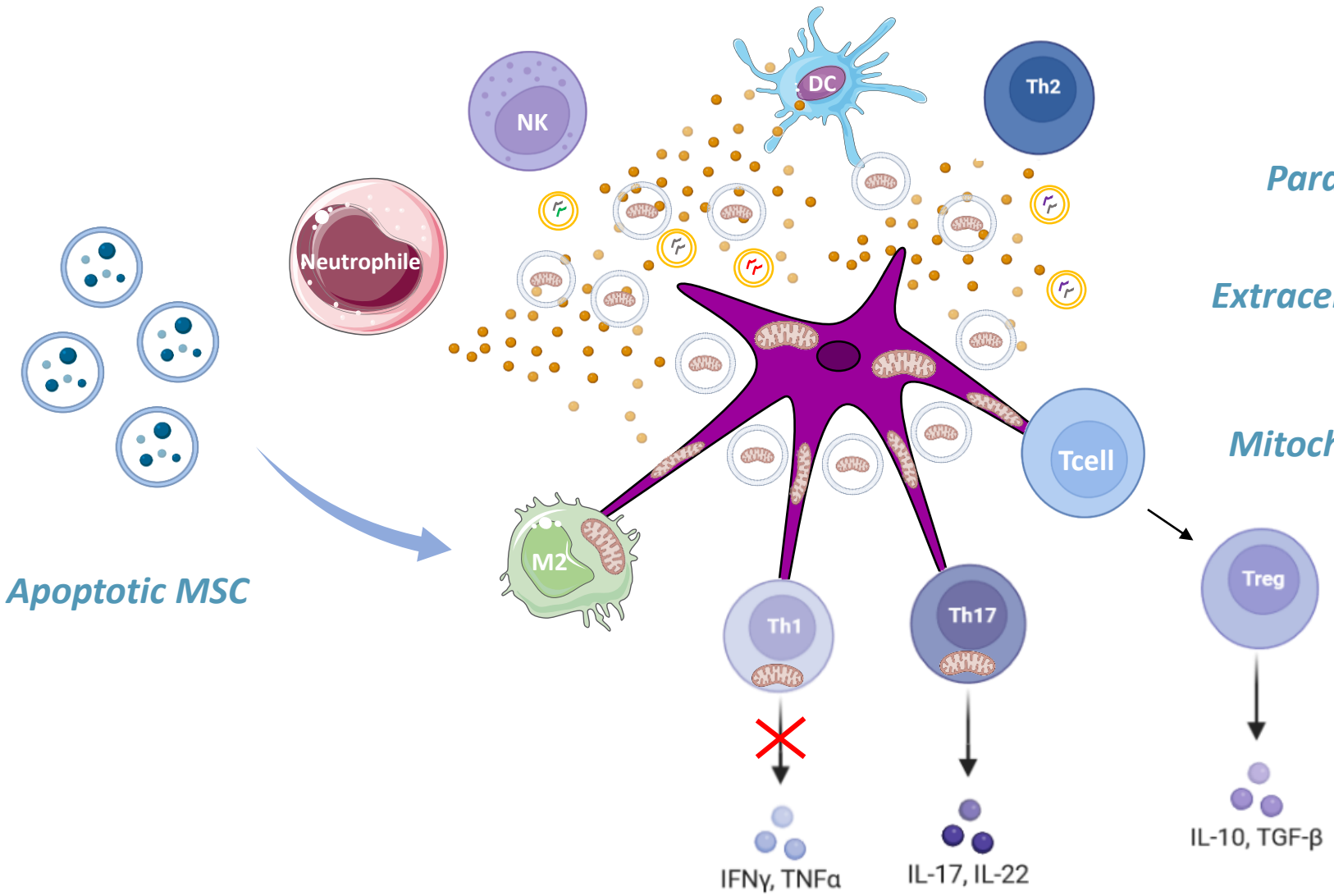


Philip E. Boulais, Paul S. Frenette, Blood, 2015



Lataillade *et al*, 2010

Mesenchymal stromal cells – immunomodulation



Terraza-Aguirre *et al*., *Cells,* 2020
Court *et al*., *EMBO reports,* 2020
Pochon et al, J Cell Mol Med2022

Paracrine factors

Extracellular vesicles (EV)

Mitochondrial transfer

Anti-inflammatory cytokine production

Promotes differentiation in Treg

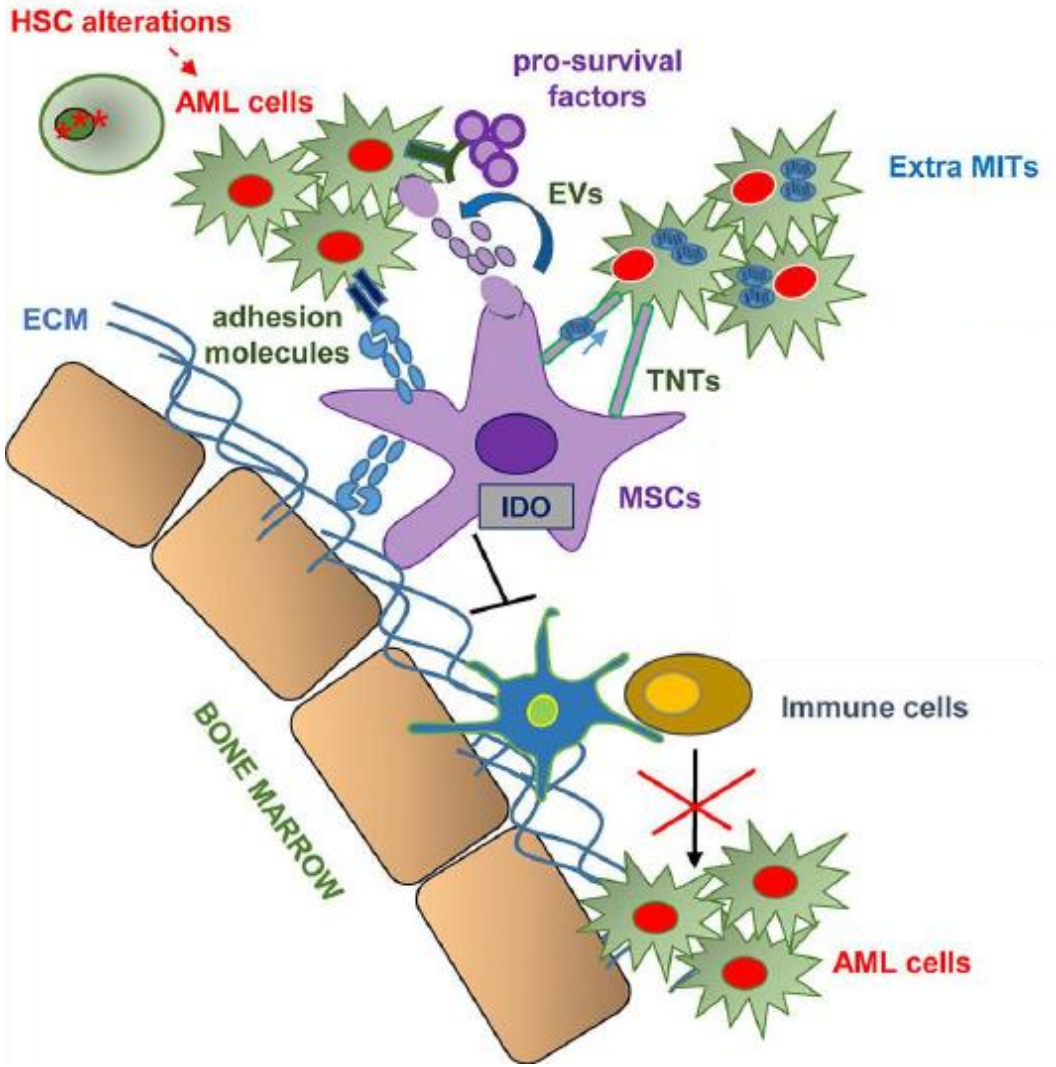
Bone marrow niche – leukemic micro-environment

AML cell support

- AML cell pro-survival mechanisms (soluble factors, adhesion molecules, Evs, …)

- AML cell retention/adhesion-mediated quiescence

- Metabolic advantage (extre MiTs, extra nutrients, redox homeostasis



Lataillade et al, 2010
Abdul-Aziz M, et al, Blood, 2019
Griessinger E, Trends Cancer, 2017
I. Morin-Poulard et al., Med.Sci 2014
Ciciarelloet al, Front in Oncol2019

Immune-modulation

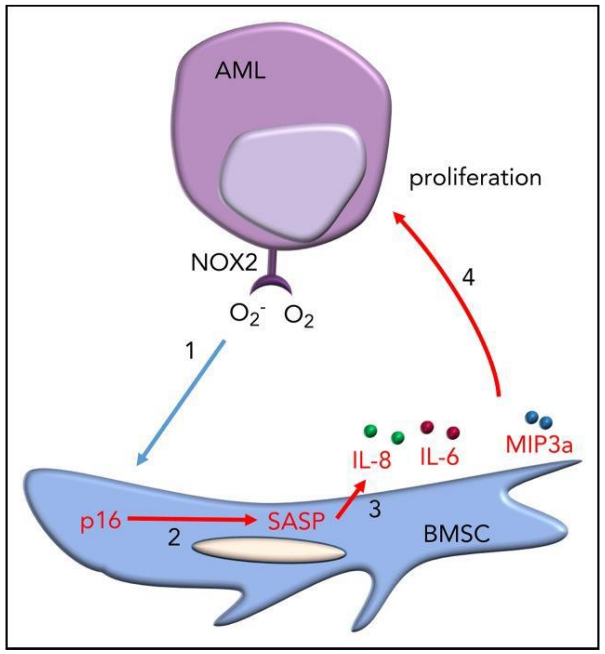
- Tolerance vs tumor cells

- Pro-inflammatory-tumor promoting ME

MSC senescence in the leukemic micro-environment

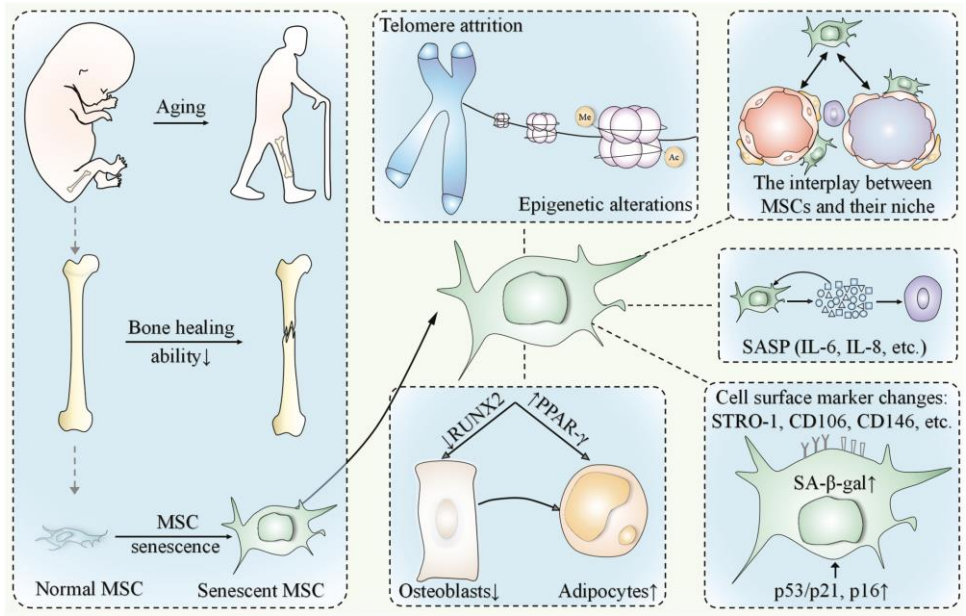
Acute myeloid leukemia induces protumoral p16INK4a-driven senescence in the bone marrow microenvironment

Amina M. Abdul-Aziz,[1,*] Yu Sun,[1,*] Charlotte Hellmich,[1,*] Christopher R. Marlein,[1] Jayna Mistry,[1] Eoghan Forde,[1] Rachel E. Piddock,[1] Manar S. Shafat,[1] Adam Morfakis,[1] Tarang Mehta,[2] Federica Di Palma,[1,2] Iain Macaulay,[2] Christopher J. Ingham,[3] Anna Haestier,[4] Angela Collins,[5] Judith Campisi,[6,7] Kristian M. Bowles,[1,5] and Stuart A. Rushworth[1]



Abdul-Aziz M, et al, Blood, 2019

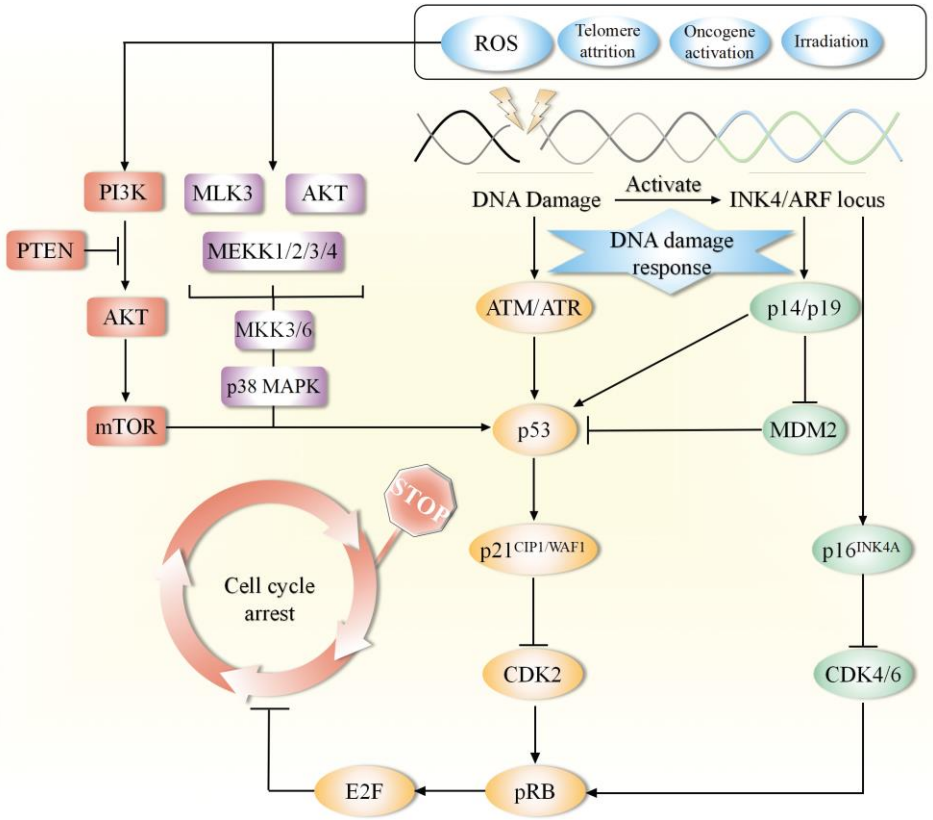
Mesenchymal stem/stromal cell (MSC) senescence is manifested by distinctive phenotypic changes



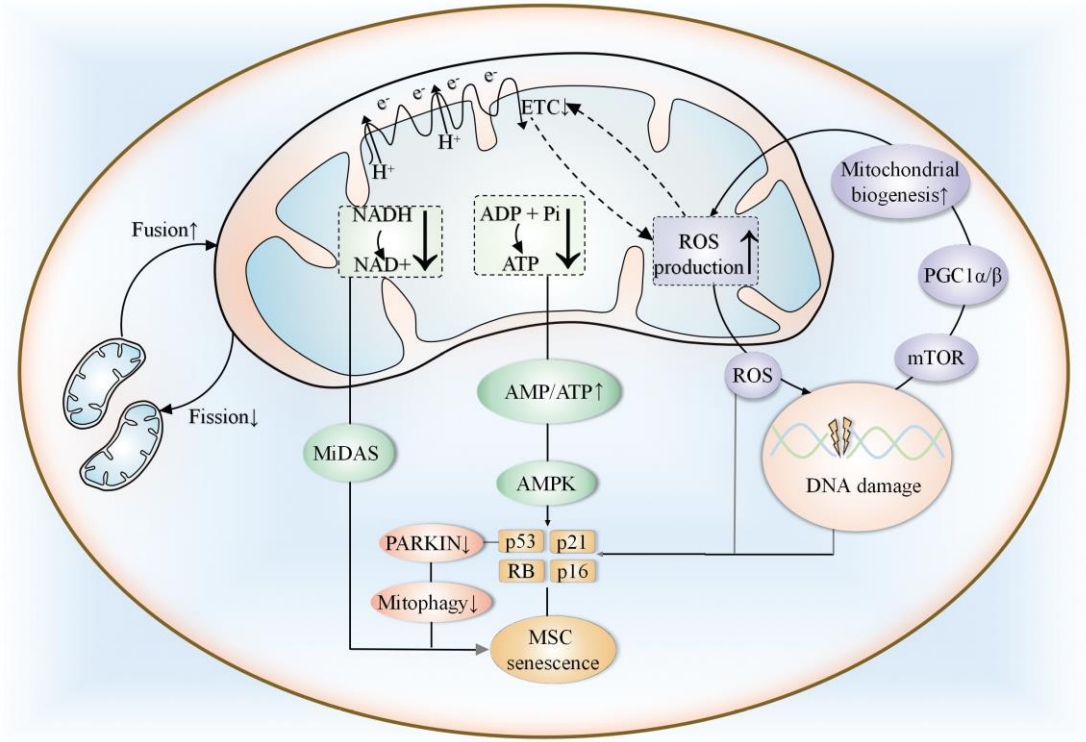
Weng Z et al, Stem Cells Translational Medicine, 2022

MSC senescence

DNA damage response network in MSC cell cycle arrest

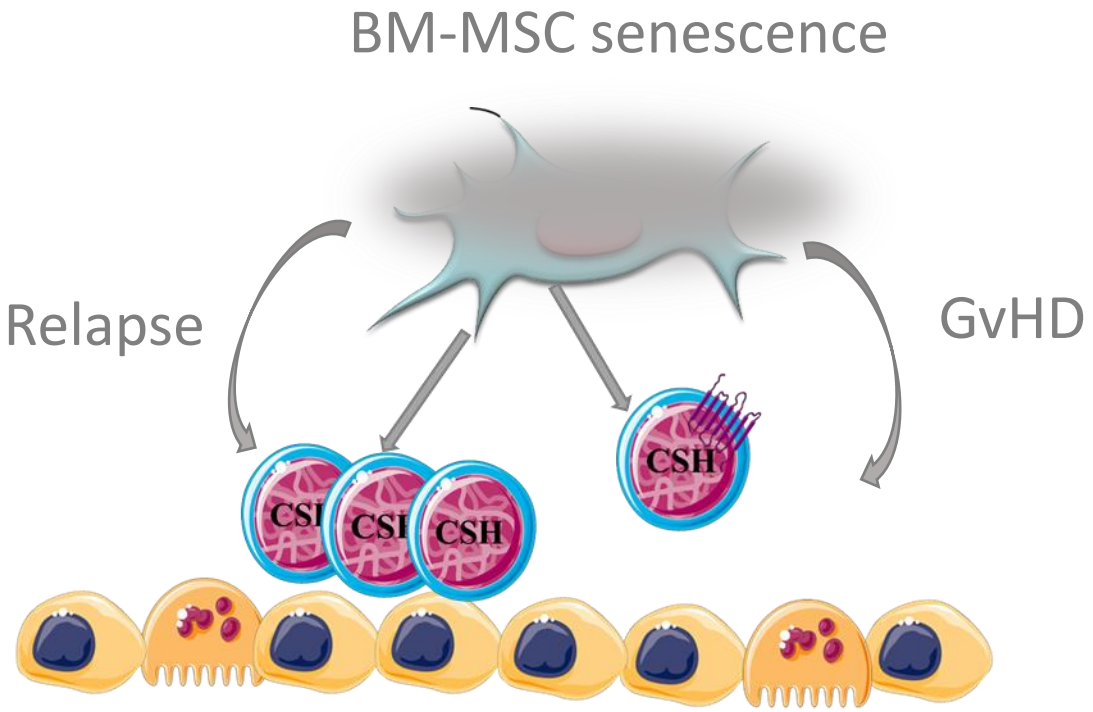


Mitochondrial dysfunction in MSC senescence



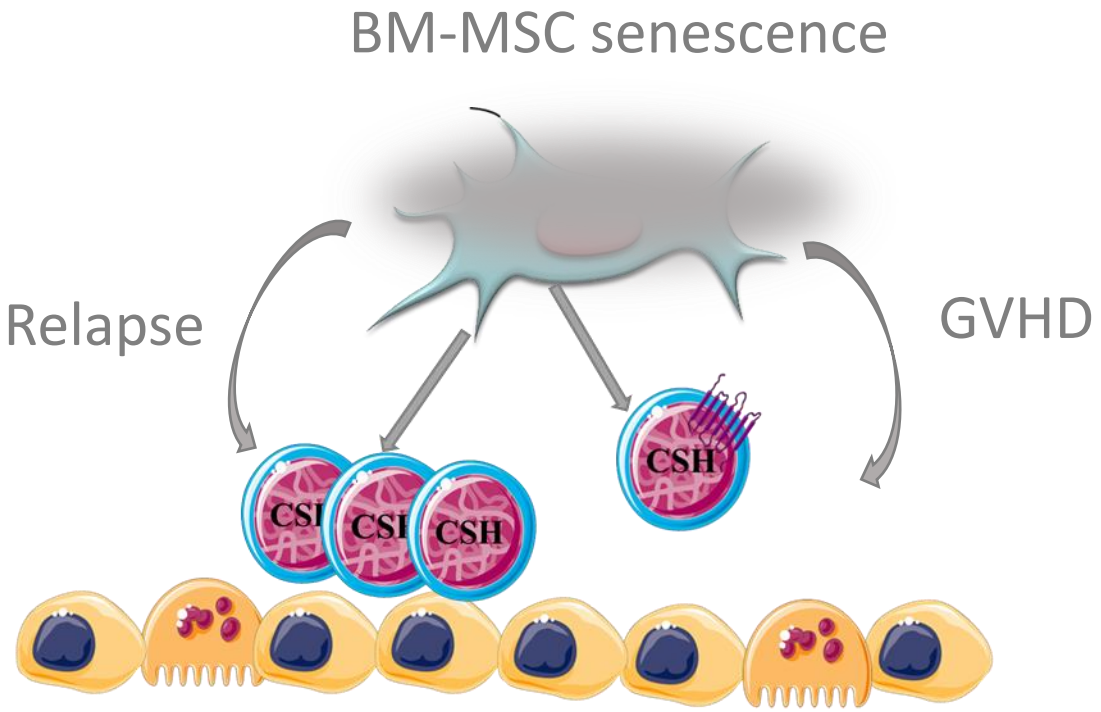
Weng Z et al, Stem Cells Translational Medicine, 2022

Work hypothesis - objective



Bone marrow **MSCs Senescence** could be involved in the occurrence of **relapse** or in the modulation of alloreactivity (GVHD) in patients receiving HSC transplantation for hematologic malignancies

Work hypothesis - objectif



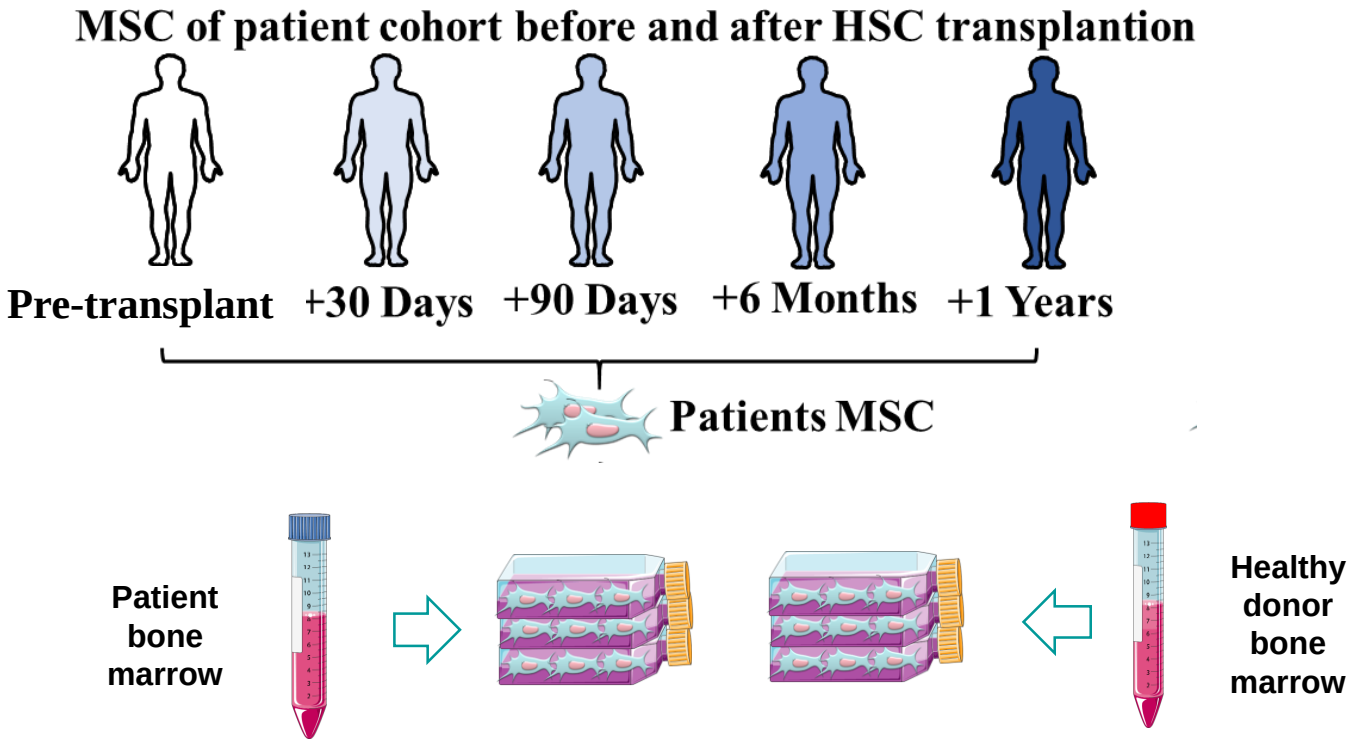
Bone marrow **MSCs Senescence** could be involved in the occurrence of **relapse** or in the modulation of alloreactivity (GVHD) in patients receiving HSC transplantation for hematologic malignancies

Study BM-MSC caracteristics

Patients with hematological malignancies receiving HSCT

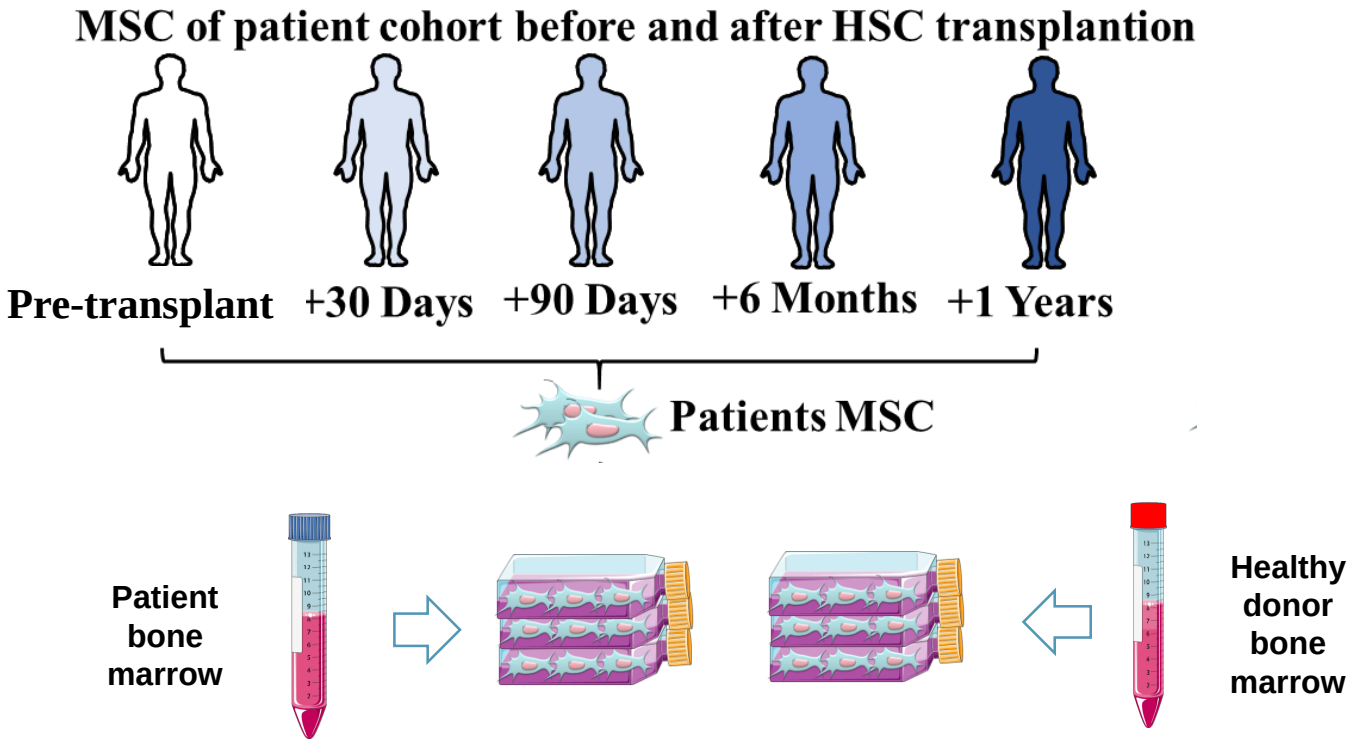
Focus on senescence and MSC-T cell immunomodulation

Experimental design

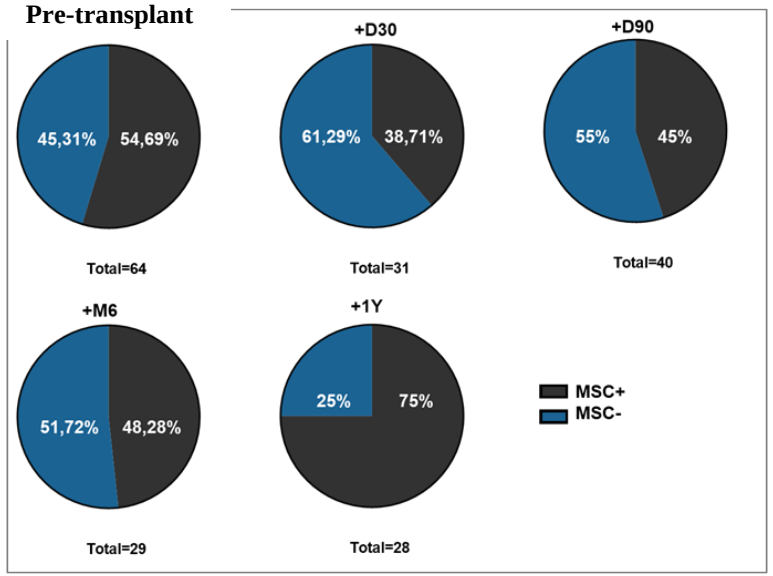


Biocollections: REAL GREFFE, EVADE
(Pr Rubio, Pr D'Aveni, Dr Pagliuca

Experimental design



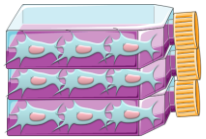
Percentage of samples that allowed MSC isolation



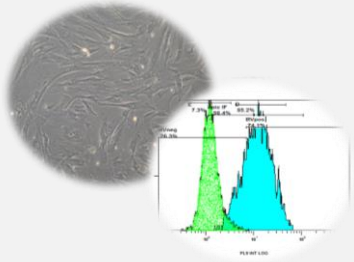
Micro-environment Alterations

Biocollections: REAL GREFFE, EVADE
(Pr Rubio, Pr D'Aveni, Dr Pagliuca

Methodology

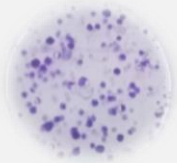


ISCT (Criteria)

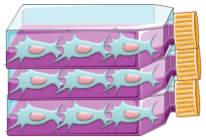


1- Plastic adhesion, 2- (CD73+, CD90+, CD105+, CD44+, CD34-, CD45-, HLADR-)

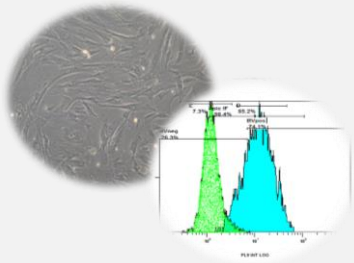
Proliferation
Clonogenicity



Methodology



ISCT (Criteria)



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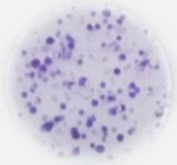
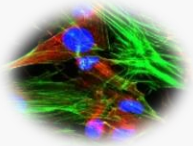
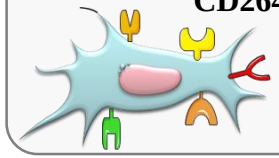
Proliferation Clonogenicity



Fluorescence Microscopy (p16, p21, H2AX, HMGB1)



Specific cell surface proteins : CD157, CD146, CD140b, CD200, CD264

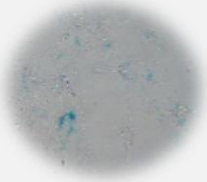


(FCM)

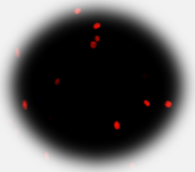
Secreted components of the SASP: IL-1α, IL-6, MMP-3, MMP-9, CCXL-1, CXCL-10, CCL20, CXCL14)

(CBA, ELISA)

Senescence/ Proliferation

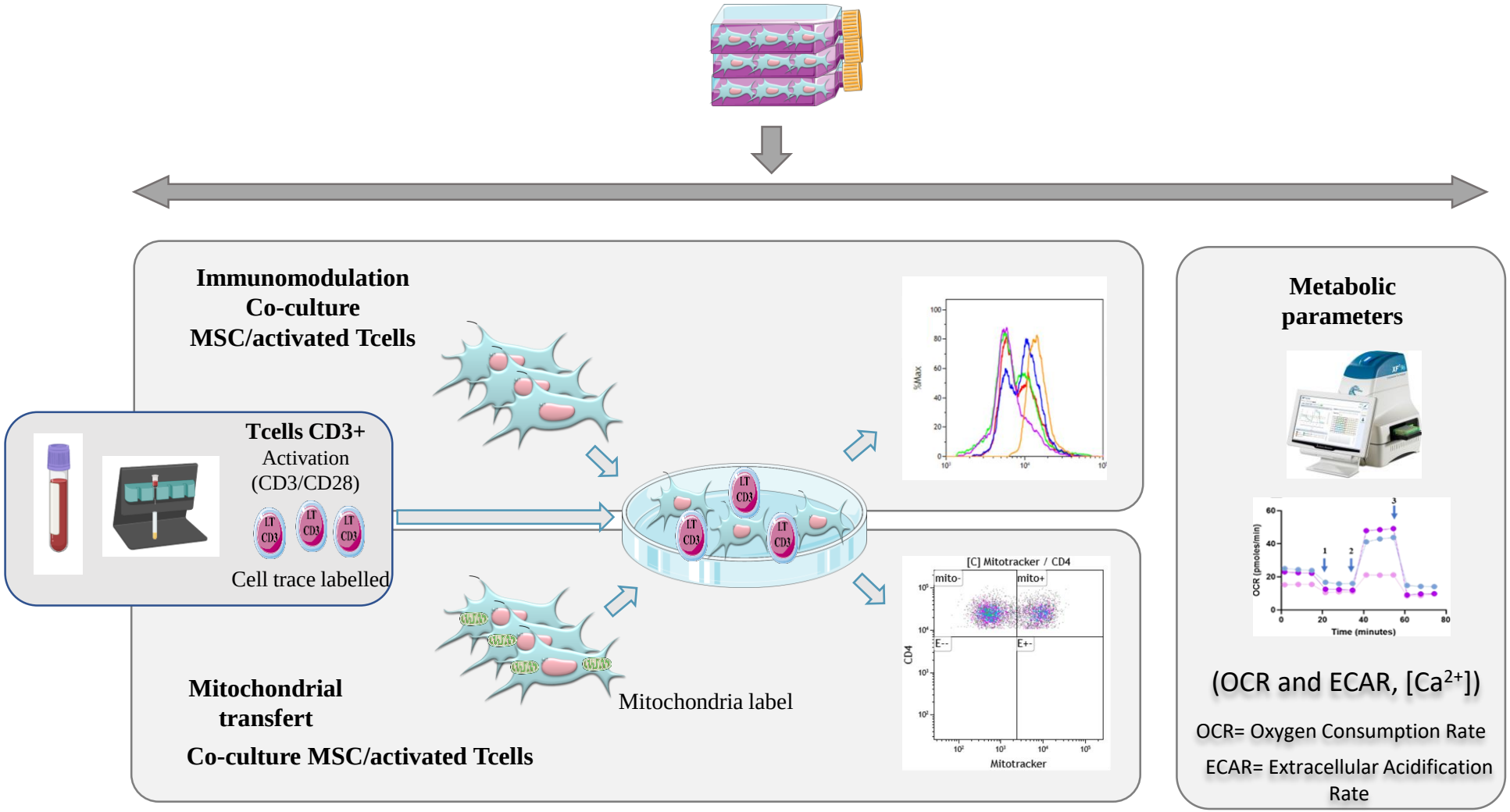


Xgal- sénescence



EdU Proliferation

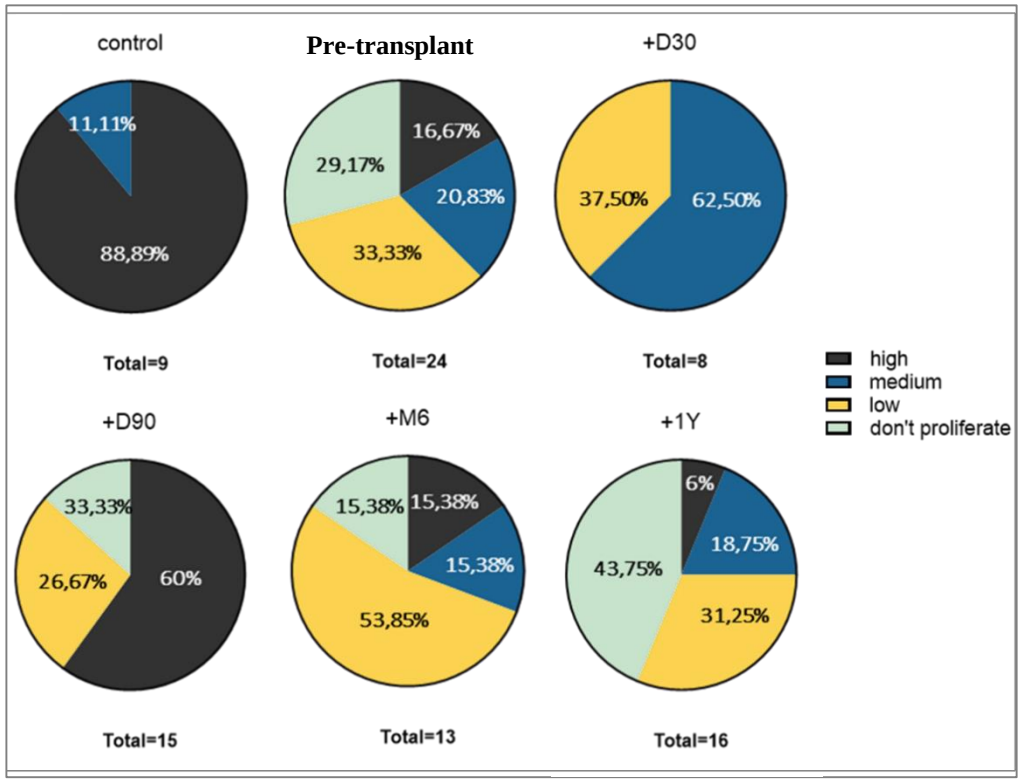
Methodology



BM-MSC Proliferation

High : DT > 4, medium : DT >7, low : DT > 13

Proliferation capacity related to time

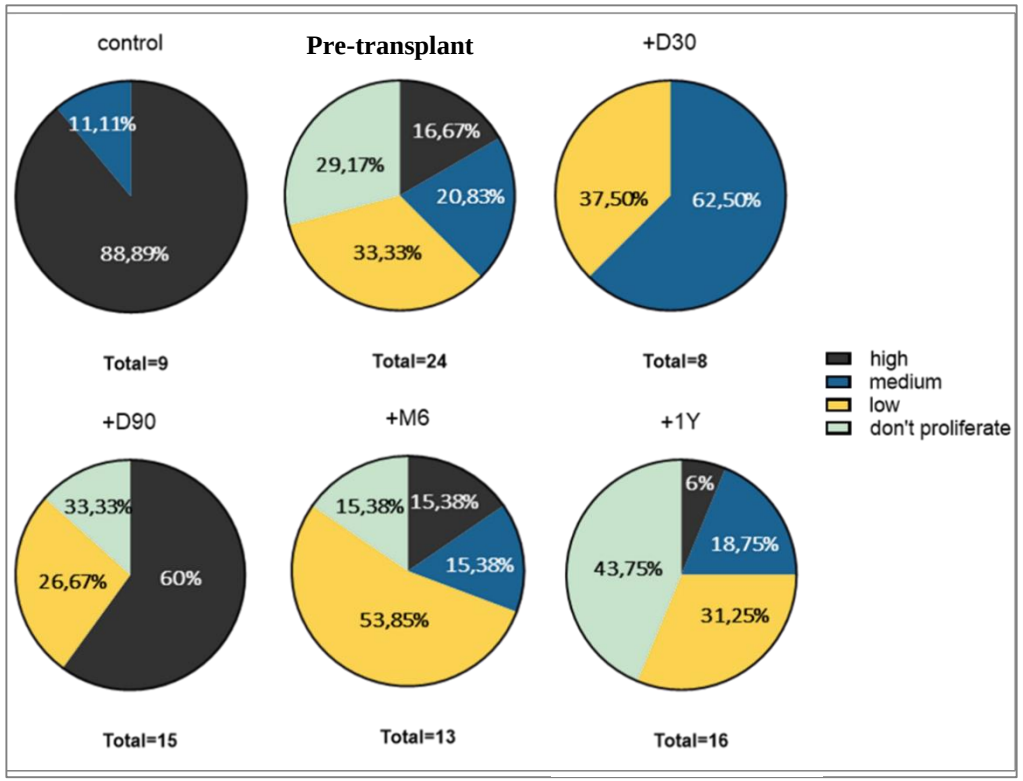


Alteration on cell proliferation

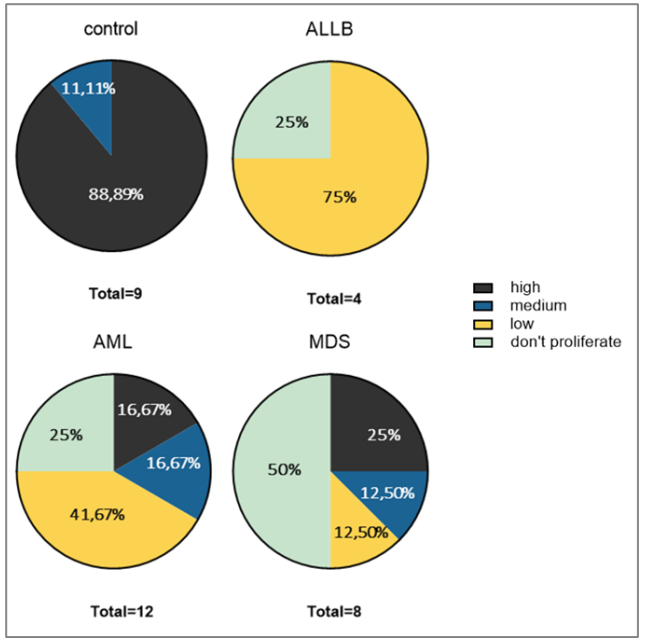
BM-MSC Proliferation

High : DT > 4, medium : DT >7, low : DT > 13

Proliferation capacity related to time



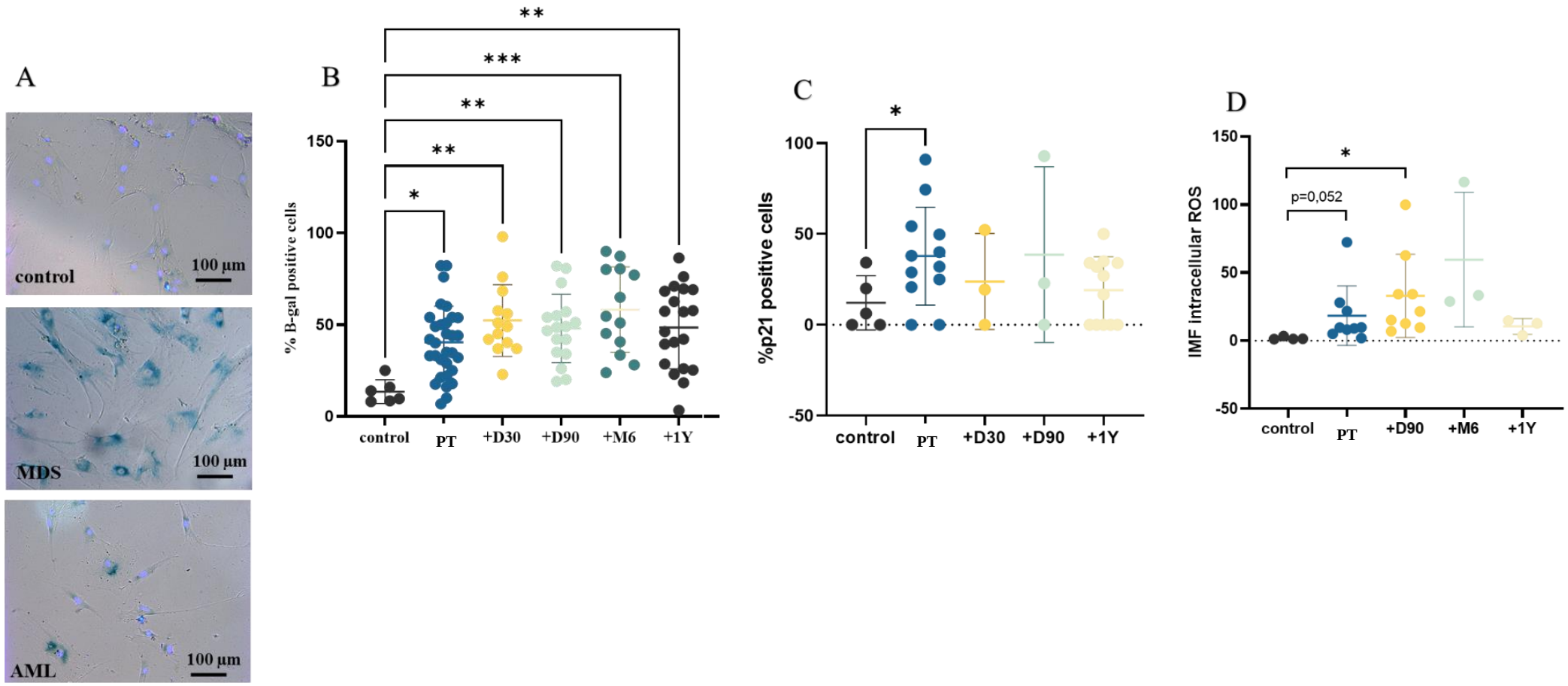
Related to Hemopathy



Alteration on cell proliferation

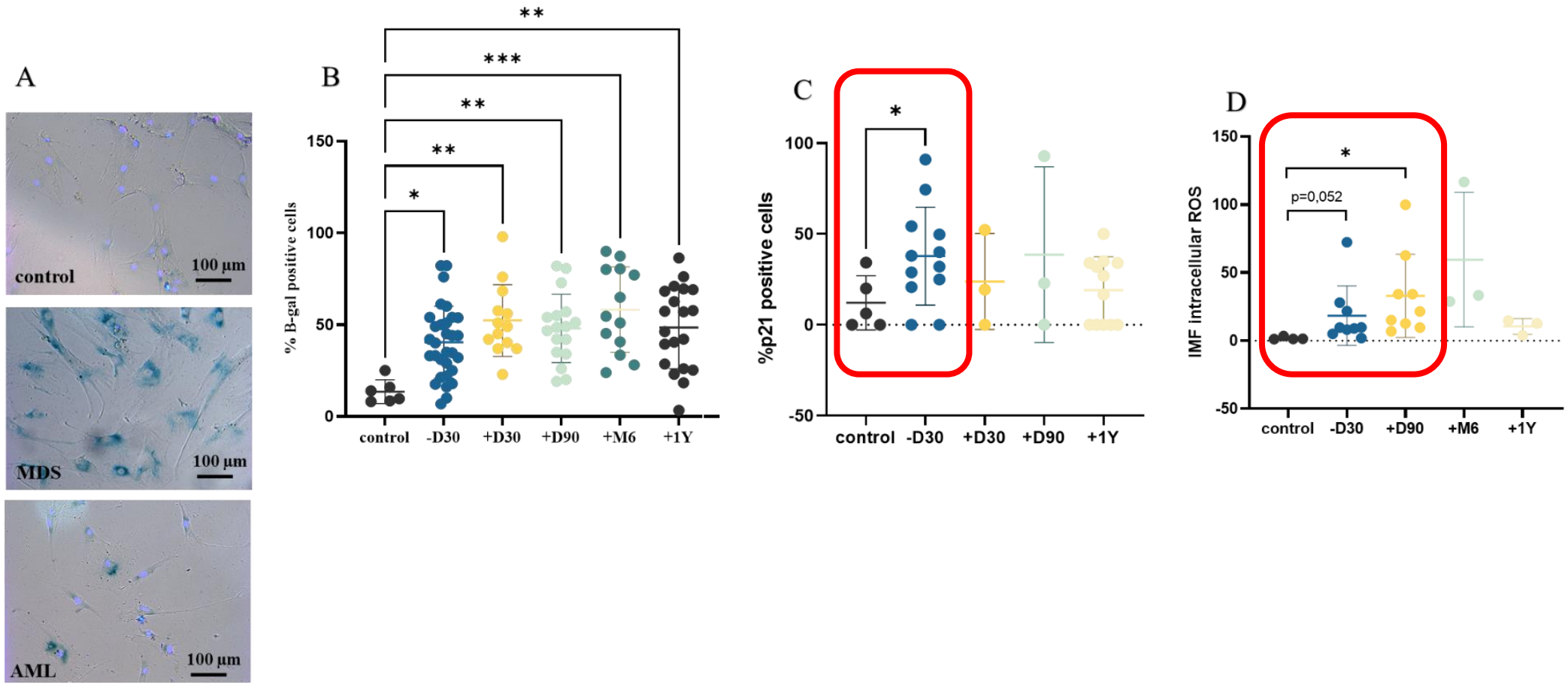
AML >> MDS

BM-MSC Senescence – time after HSCT



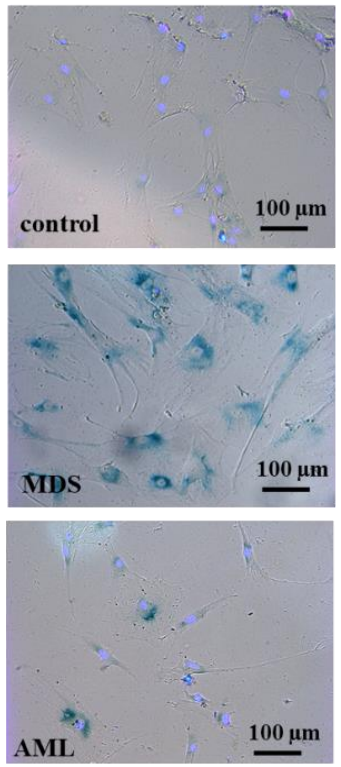
PT : pre-transplant MSC

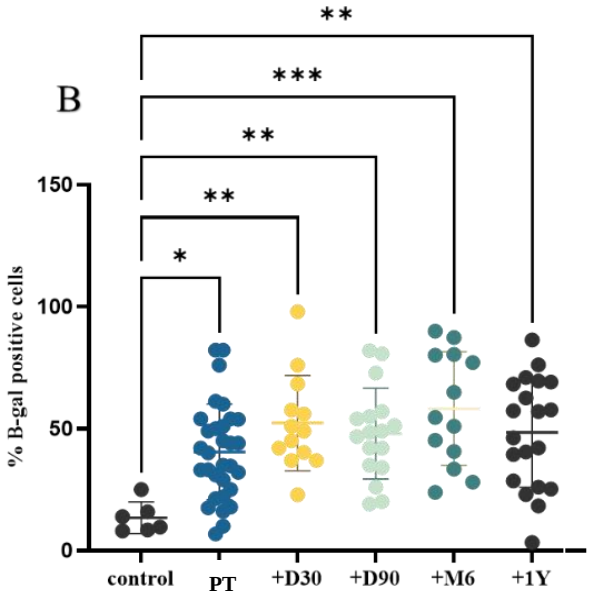
BM-MSC Senescence – time HSCT

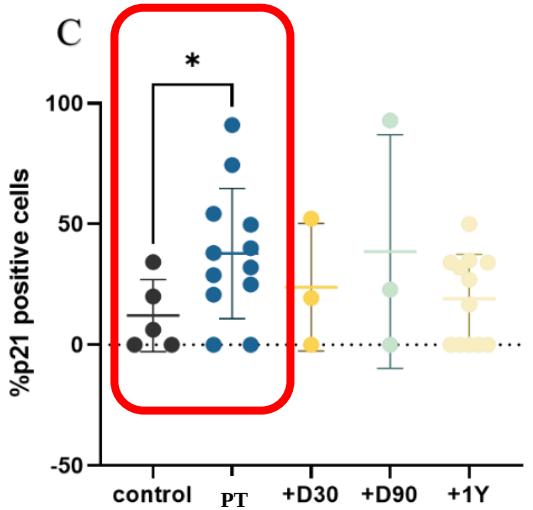


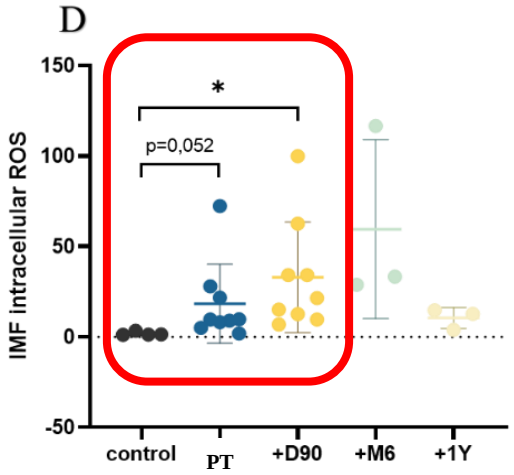
PT : pre-transplant MSC

BM-MSC Senescence – time HSCT





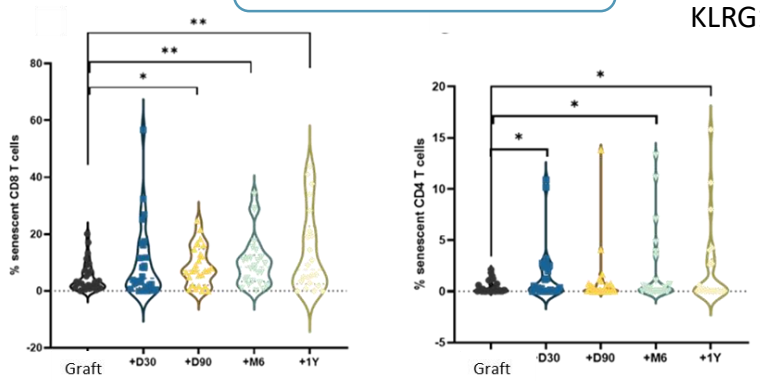




MSCs obtained from patients have a significant increase in senescence-associated *β*-galactosidase activity

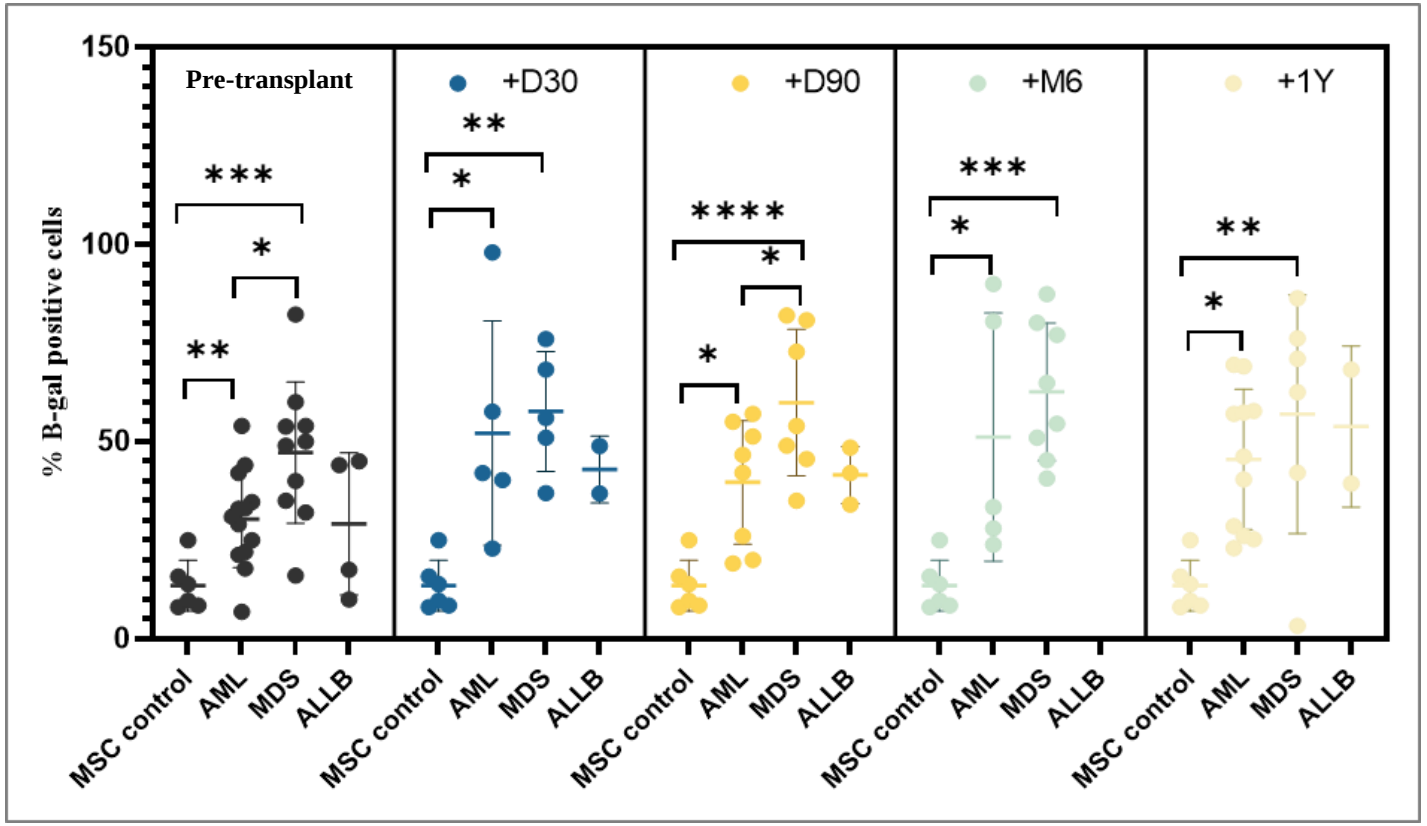
Tcell Senescence

TEMRA CD28-, CD27-, CD57+, KLRG1+

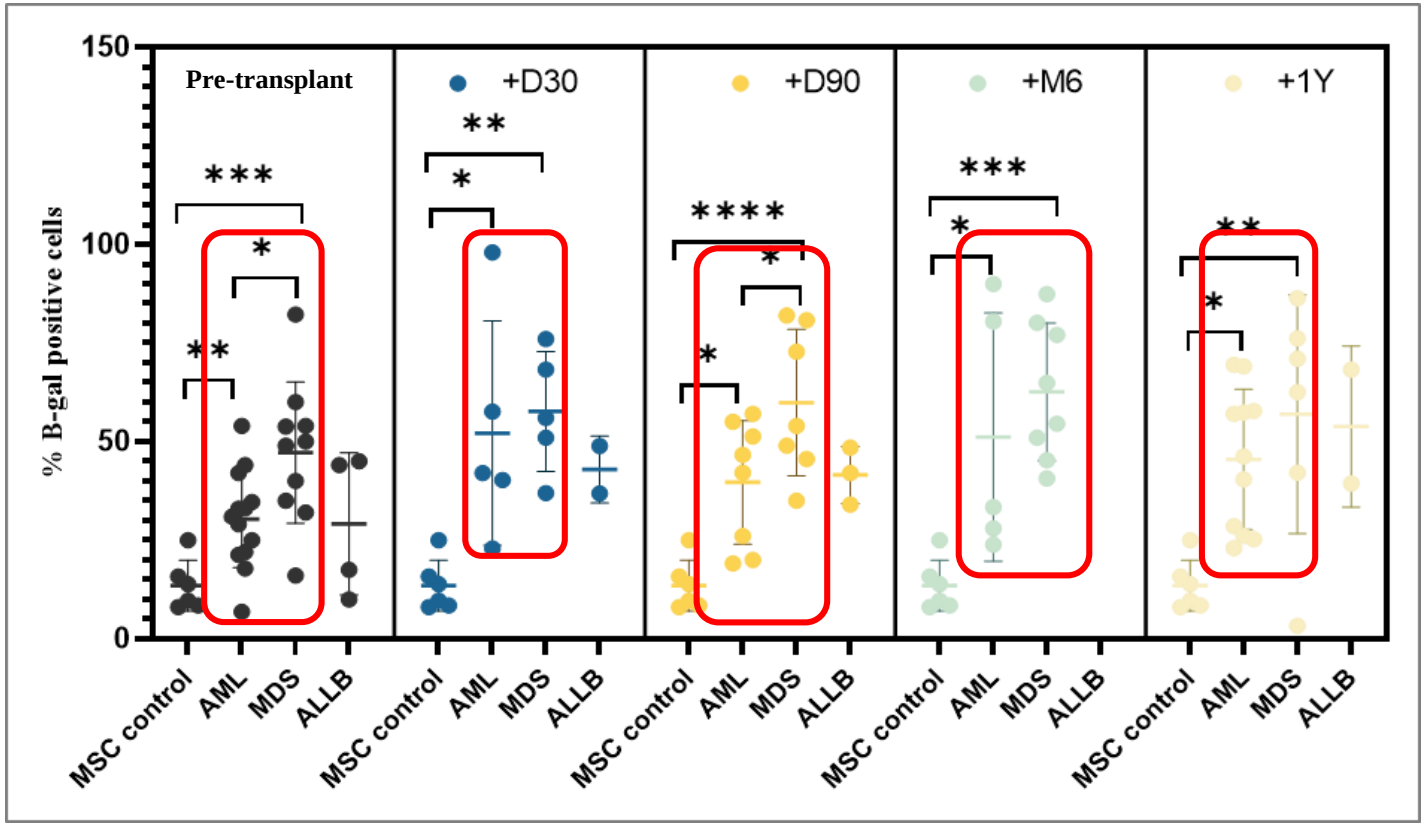


PT : pre-transplant MSC

BM-MSC Senescence - hemopathy

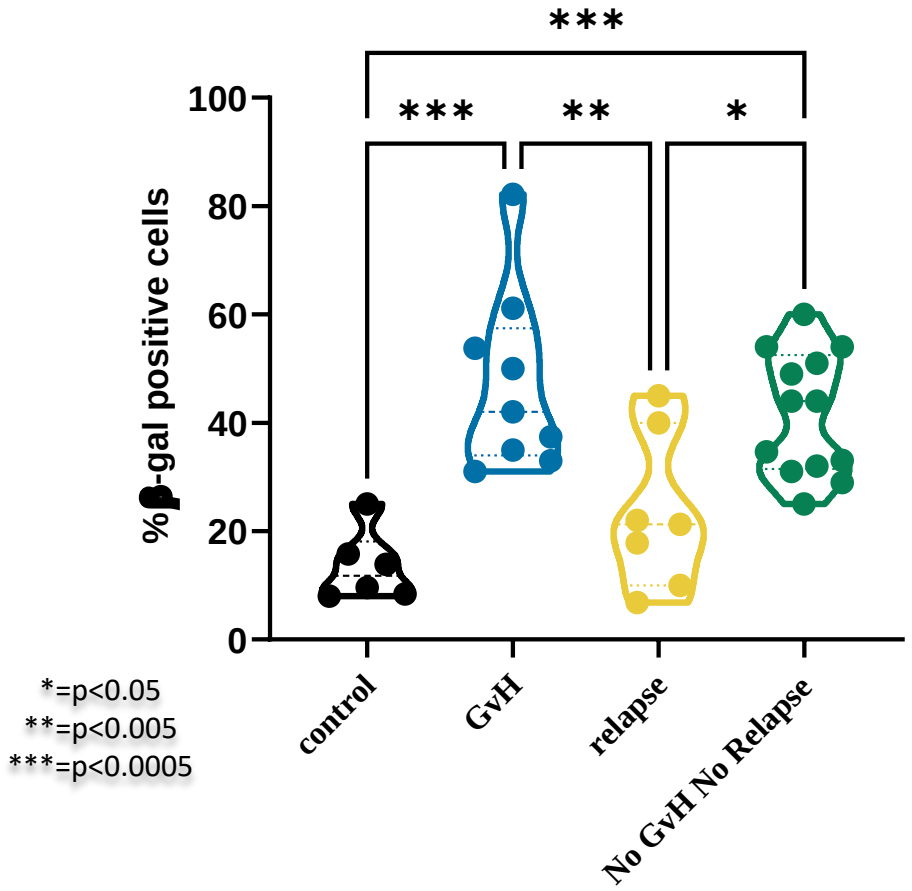


BM-MSC Senescence - hemopathy



MDS senescence >> AML senescence

Pre-transplant BM-MSC Senescence – patients outcome



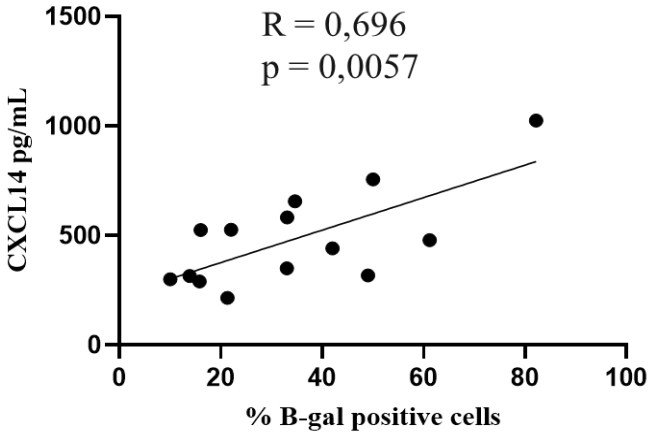
Patients outcome at 1-3 months

↑ Senescence ⇨ GvHD

↓ Senescence ⇨ Relapse

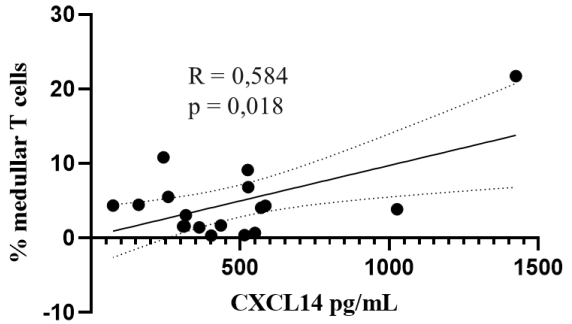
BM-derived MSCs' senescence correlates with CXCL14 and BM Tcell infiltration

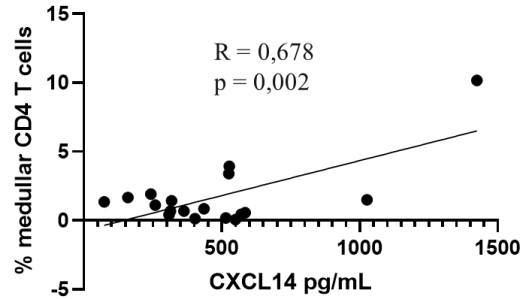
Correlation between MSC's senescence and BM concentration in CXCL14

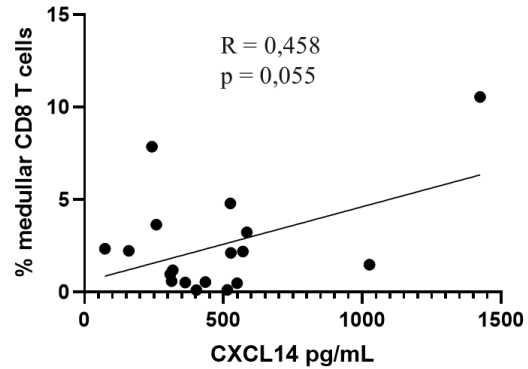


No significant correlation with IL6, IL8, IL1b…

Correlation between BM concentration in CXCL14 and BM infiltration by T cells



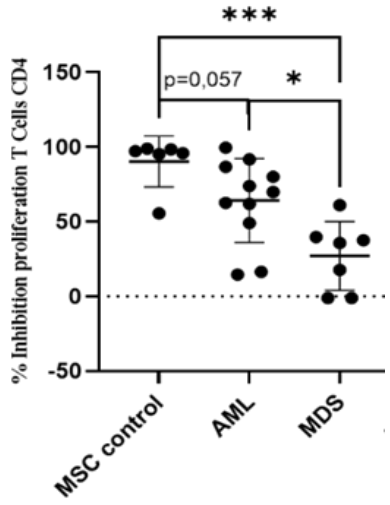


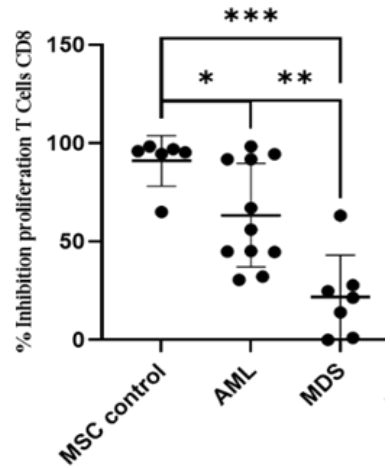


No correlation with Tregs, Monocytes, inflammatory monocytes, granulocytes

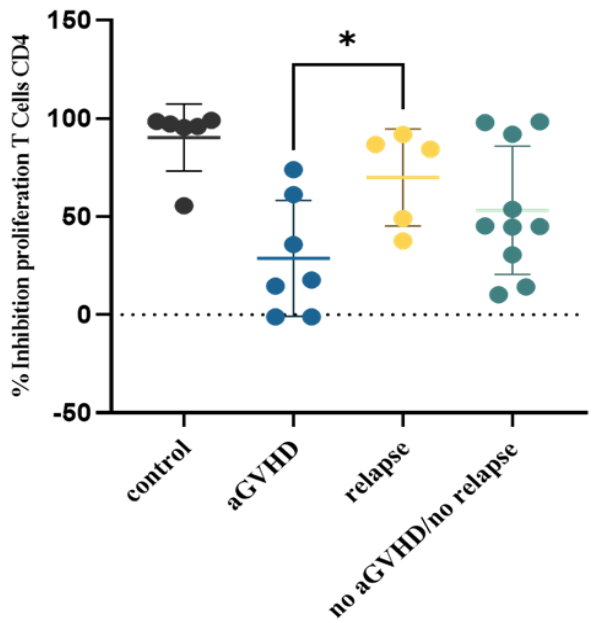
PhD : Meriem EL Ouafy, manuscriptin preparation

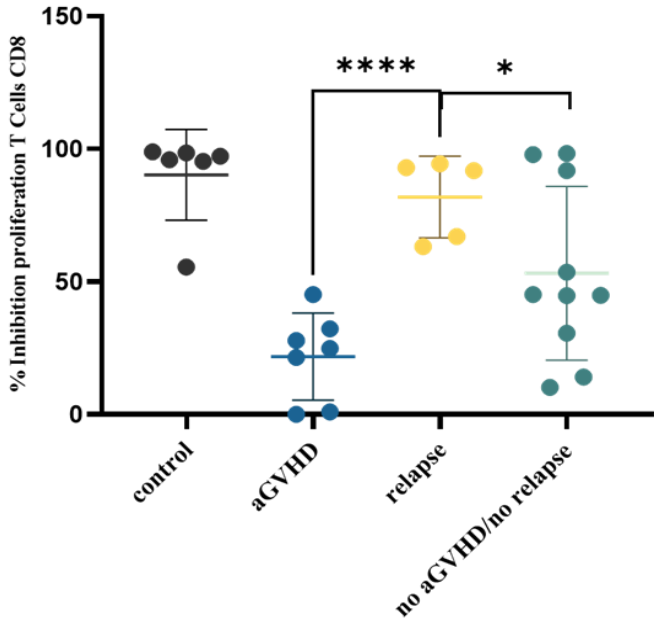
Pre-transplant BM-MSC immunomodulation





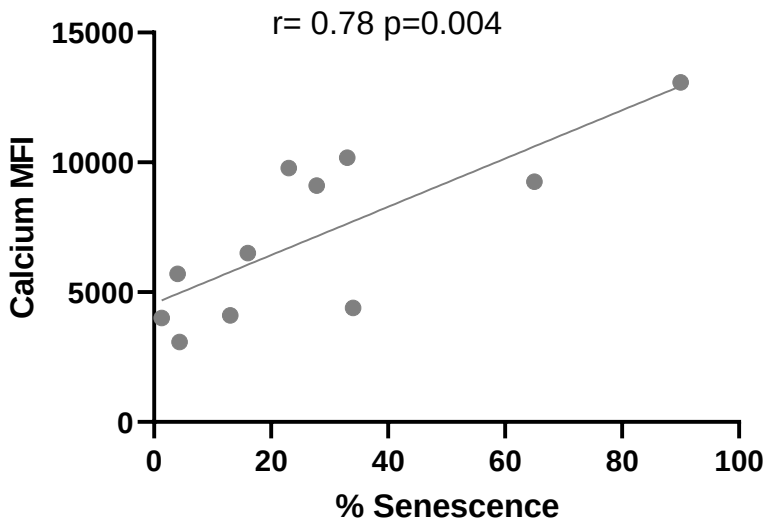
Control >>AML >>MDS



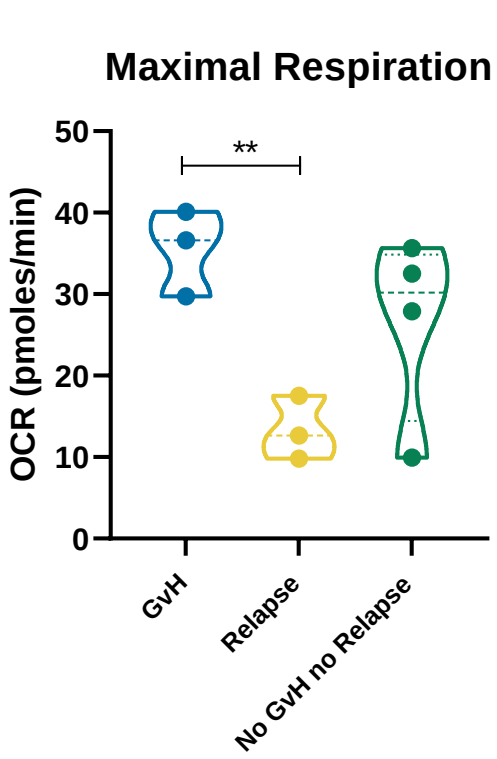


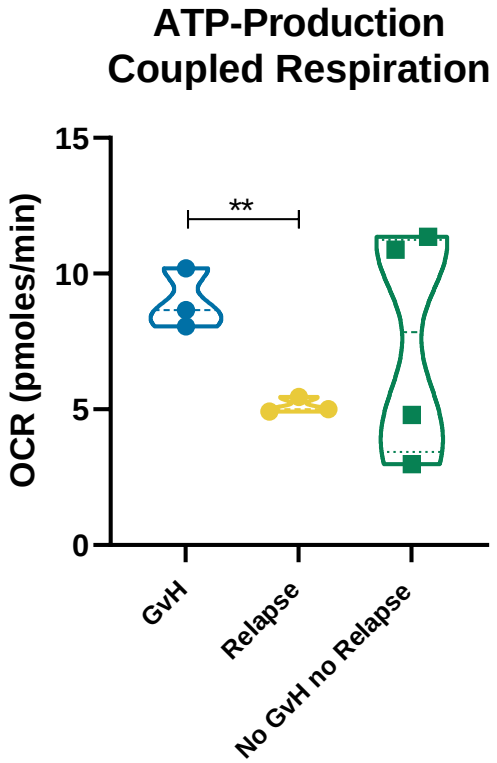
Control ≅ relapse >> GvHD

Pre-transplant BM-MSC metabolism



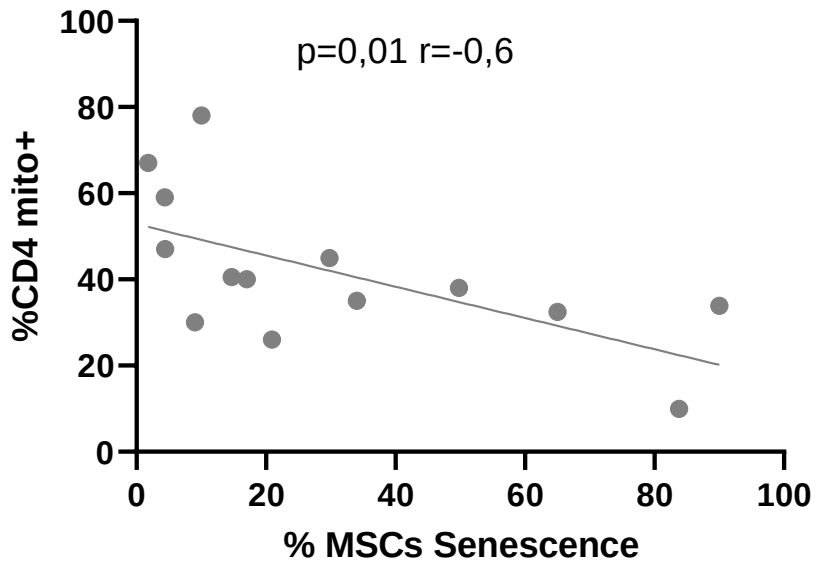
[Calcium] ↑ in senescent MSC





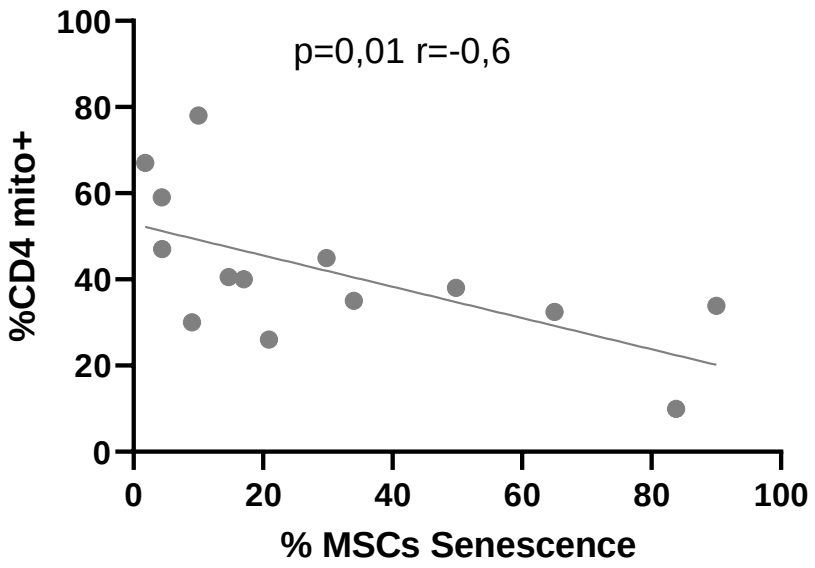
MSCs' Metabolic alteration related to patient outcome

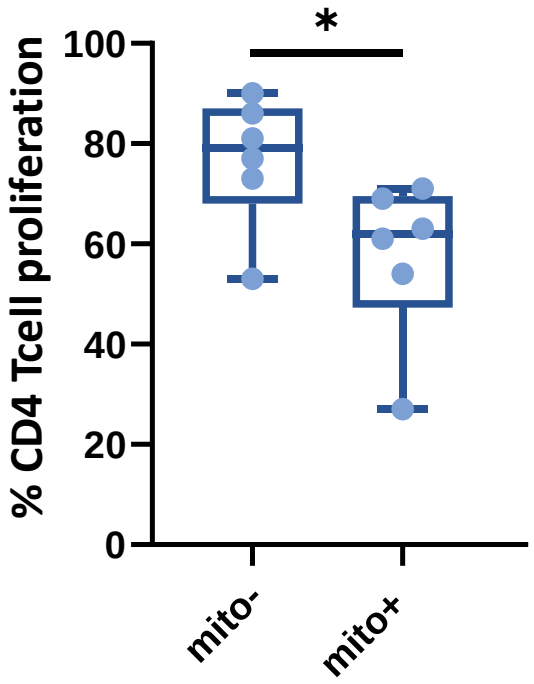
Pre-transplant BM-MSC mitochondrial transfer to Tcells



Senescent MSC have decreased mitochondrial transfer capacity

Pre-transplant BM-MSC mitochondrial transfer to Tcells

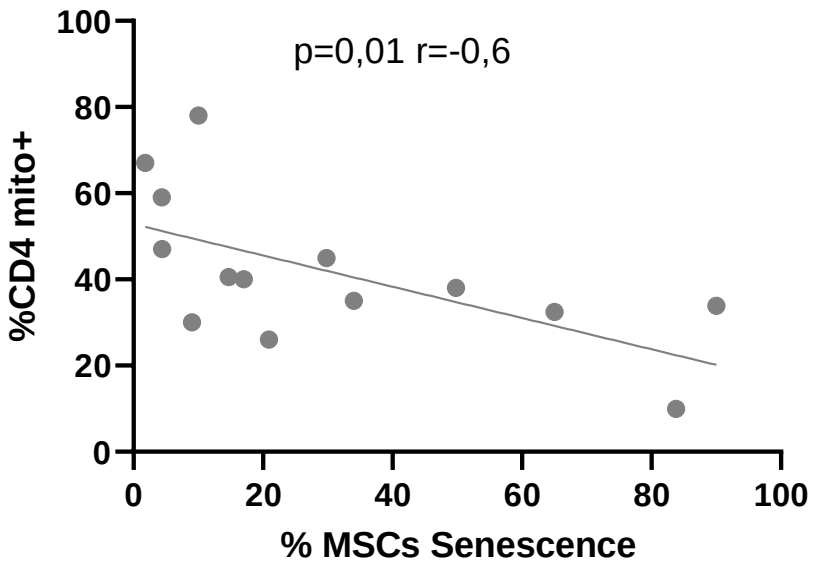




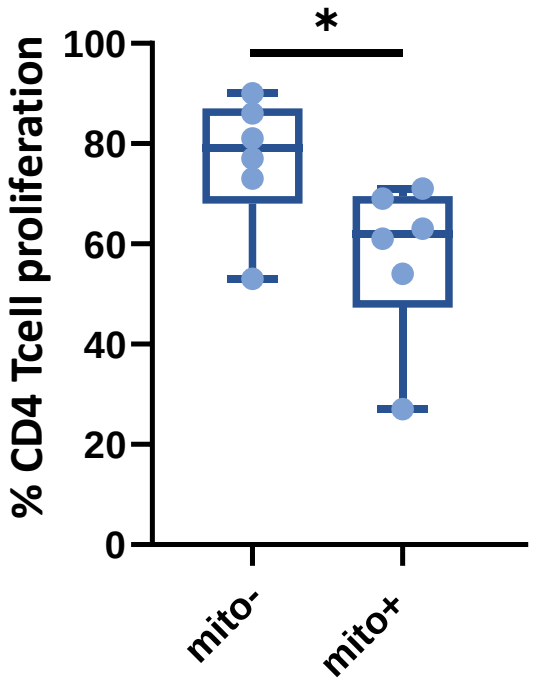
Senescent MSC have decreased mitochondrial transfer capacity

Decreased proliferation for mito+

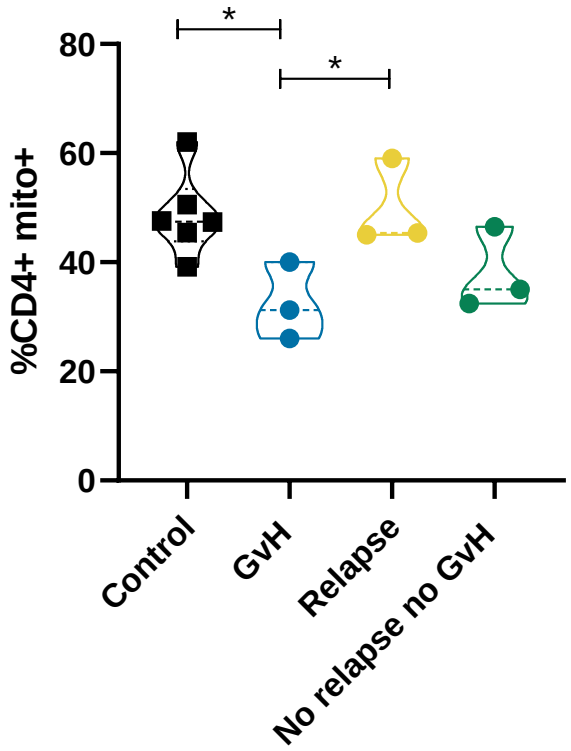
Pre-transplant BM-MSC mitochondrial transfer to Tcells



Senescent MSC have decreased mitochondrial transfer capacity

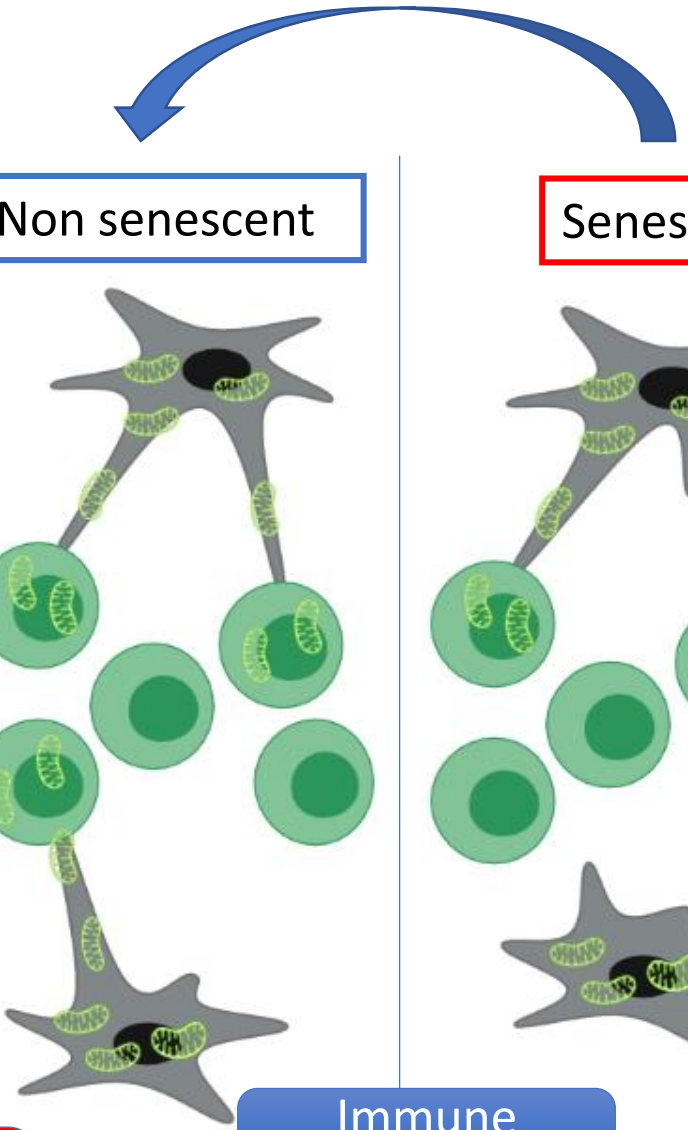


Decreased proliferation for mito+



Decreased mitochondrial transfert - GvHD

Summary (1)



Non senescent

Healthy mitochondrial network

Mitophagy/
Mitochondrial renewal

Mitochondrial transfer

[Ca^{2+}] deacreased

High immunosuppressive capacity
Immunosuppressive context

Senescent

Mitochondrial Dysfonction

High mitochondrial mass

Reduction in mitochondrial transfer

High [Ca^{2+}]

Decreased immunosuppressives capacity
Pro-inflammatory Context

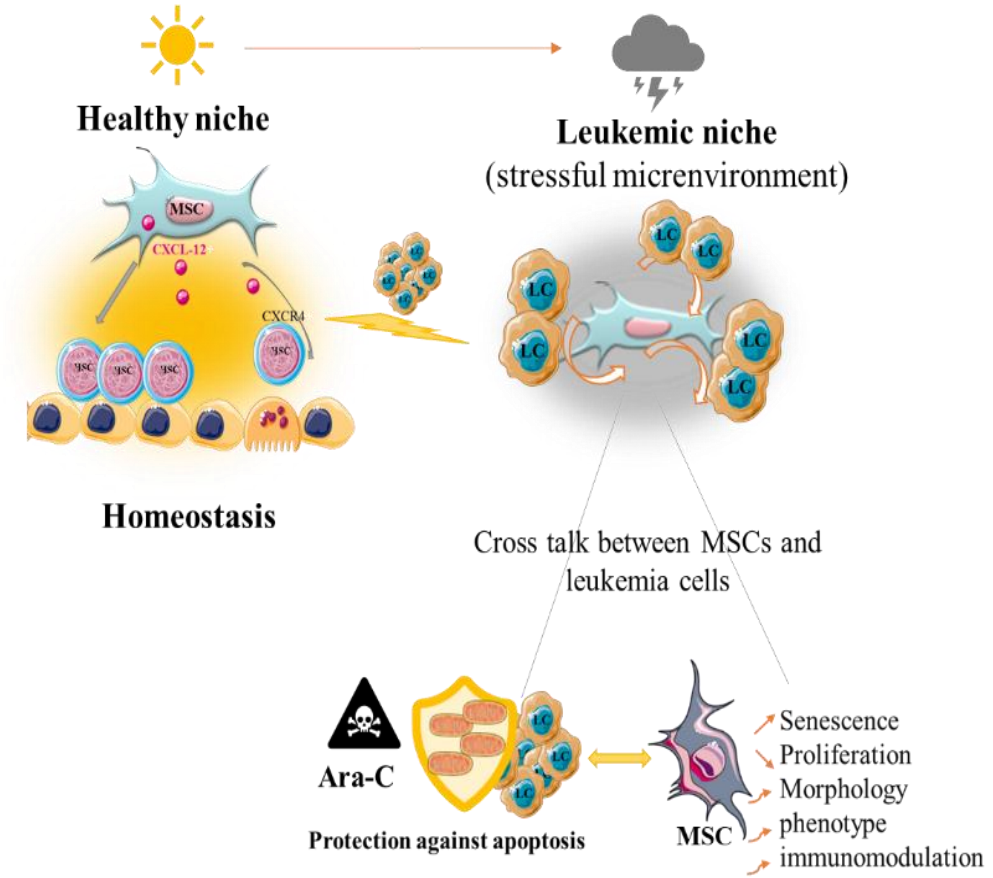
Relapse

Immune reconstitution

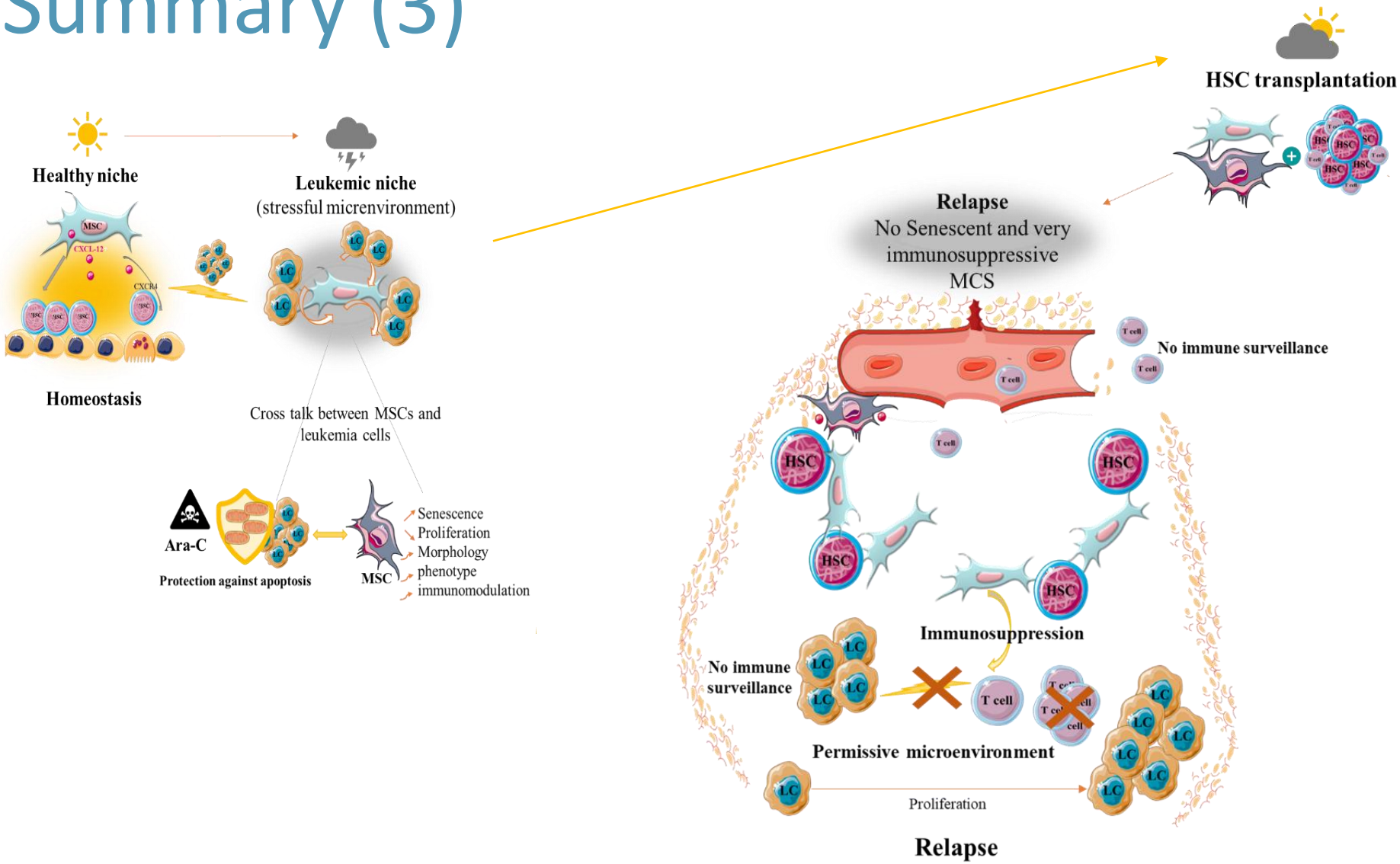
Graft versus leukemia (GvL)

Graft Versus Host Disease (GvHD)

Summary (2)


Healthy niche
Leukemic niche
(stressful micrenvironment)
MSC
CXCL-12
CXCR4
LC
Homeostasis
Cross talk between MSCs and
leukemia cells
Ara-C
Protection against apoptosis
MSC
Senescence
Proliferation
Morphology
phenotype
immunomodulation

Summary (3)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HSC
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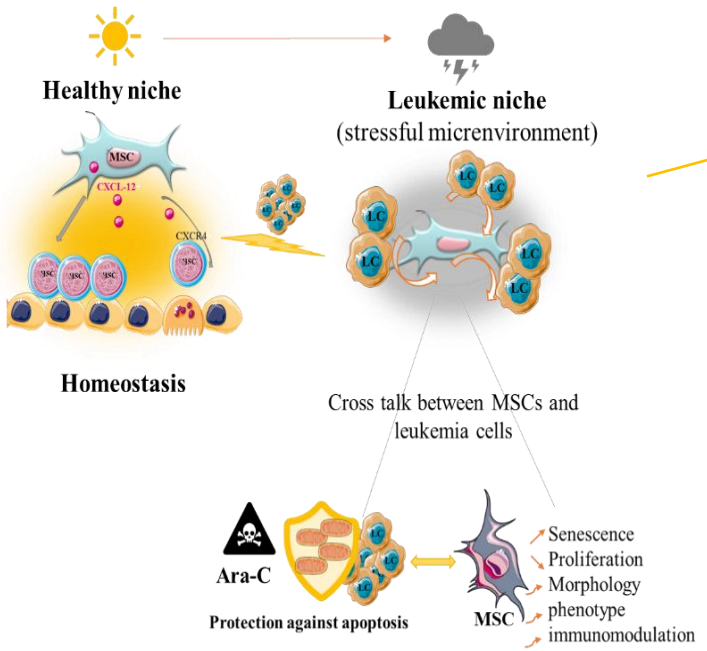
Ara-C
Protection against apoptosis
MSC
Senescence
Proliferation
Morphology
phenotype
immunomodulation
HSC transplantation
Relapse
No Senescent and very
immunosuppressive
MCS
T cell
No immune surveillance
HSC
Immunosuppression
No immune
surveillance
Permissive microenvironment
Proliferation
Relapse

Summary (4)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phenotype
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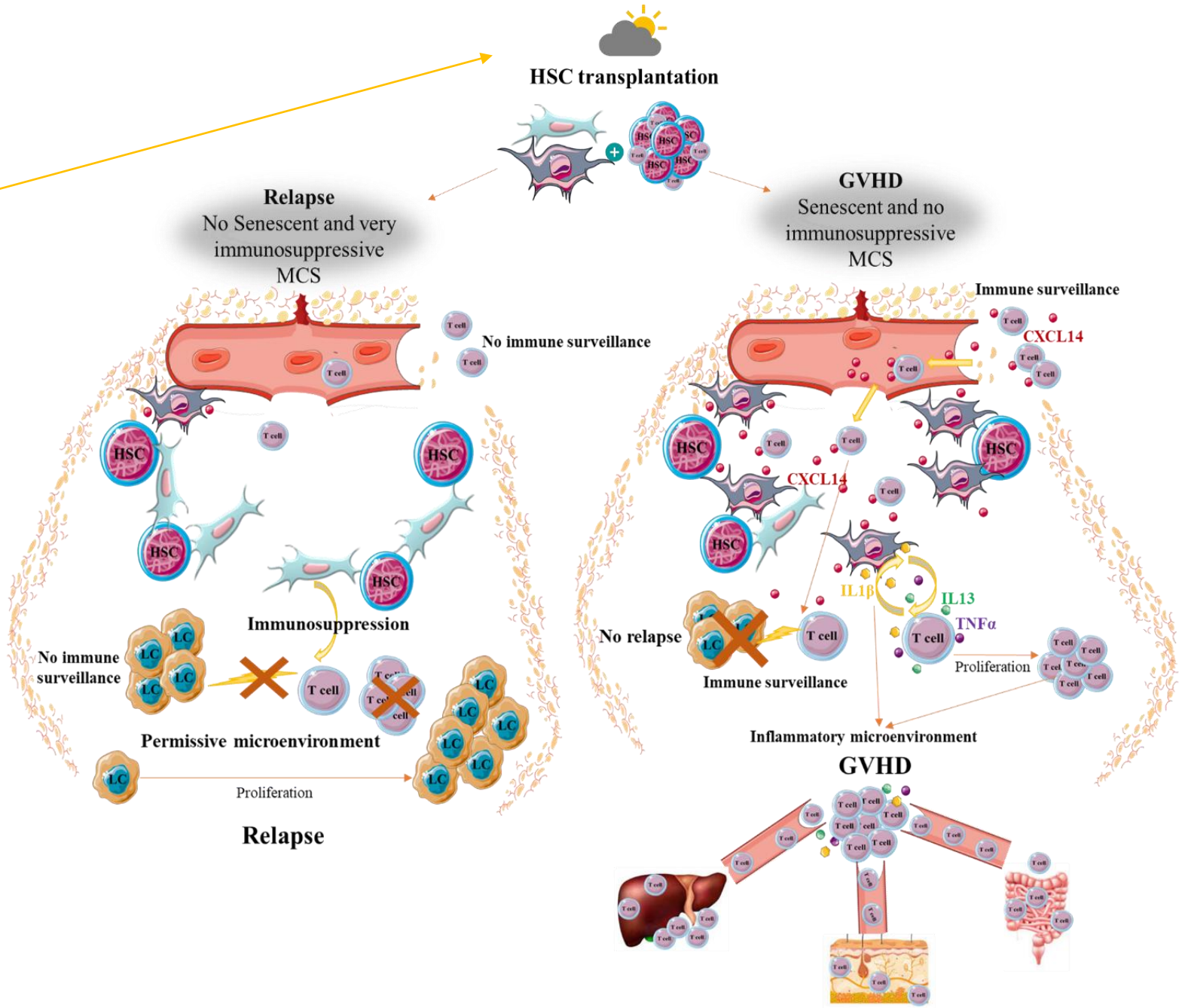
HSC transplantation
Relapse
No Senescent and very immunosuppressive MCS
GVHD
Senescent and no immunosuppressive MCS
No immune surveillance
Immunosuppression
No immune surveillance
T cell
Permissive microenvironment
Proliferation
Relapse
Immune surveillance
CXCL14
CXCL14
IL1β
IL13
TNFα
No relapse
Immune surveillance
Proliferation
Inflammatory microenvironment
GVHD

Team 6

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Thank you for your attention

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- Romain Perouf
- Alexandra Guelton

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Muriel Barberi-Heyob
Valérie Jouan-Hureaux
Alicia Chateau

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