

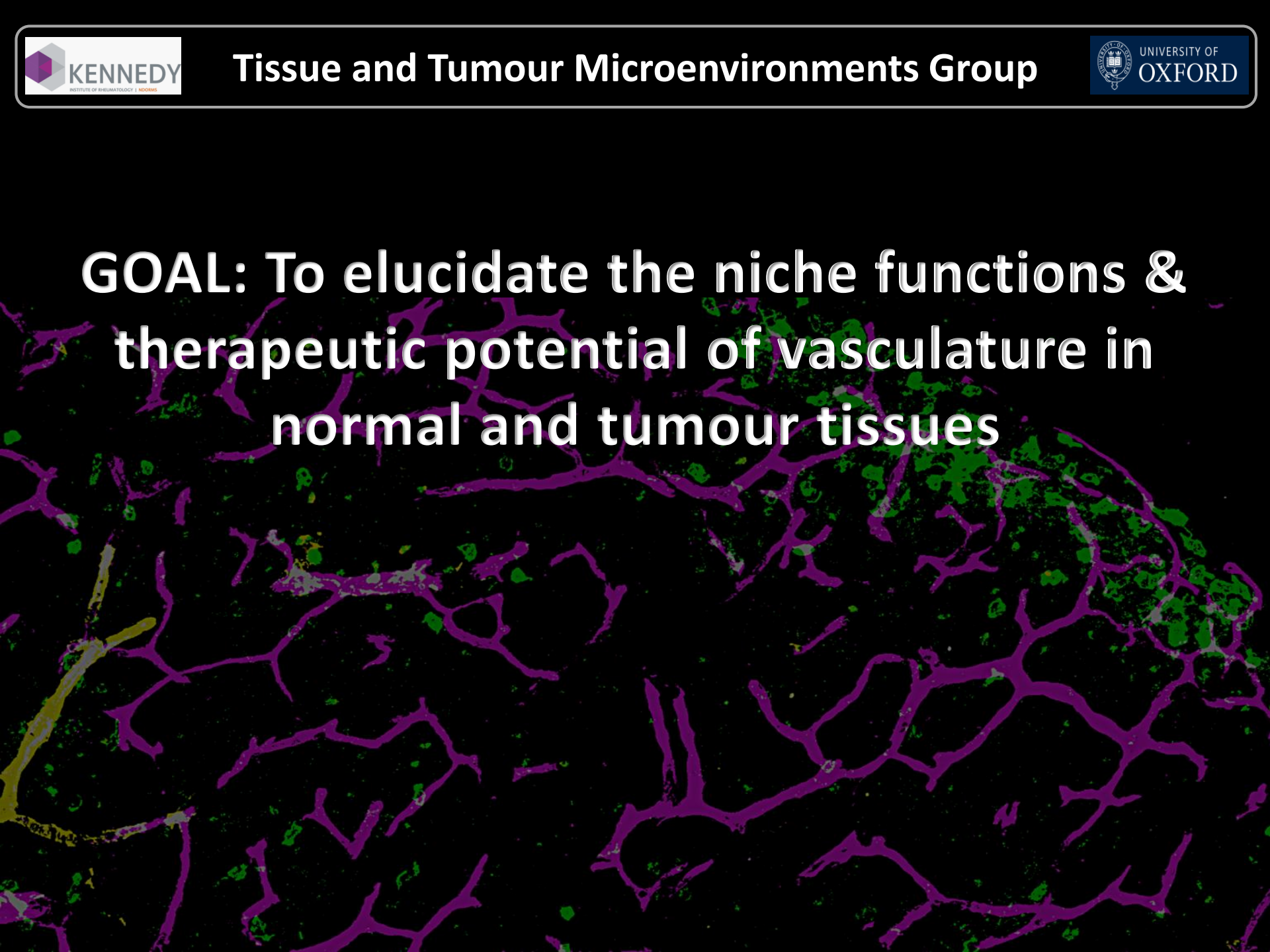
Age-related angiocrine signals in bone homeostasis & disease

ANJALI P. KUSUMBE
University of Oxford



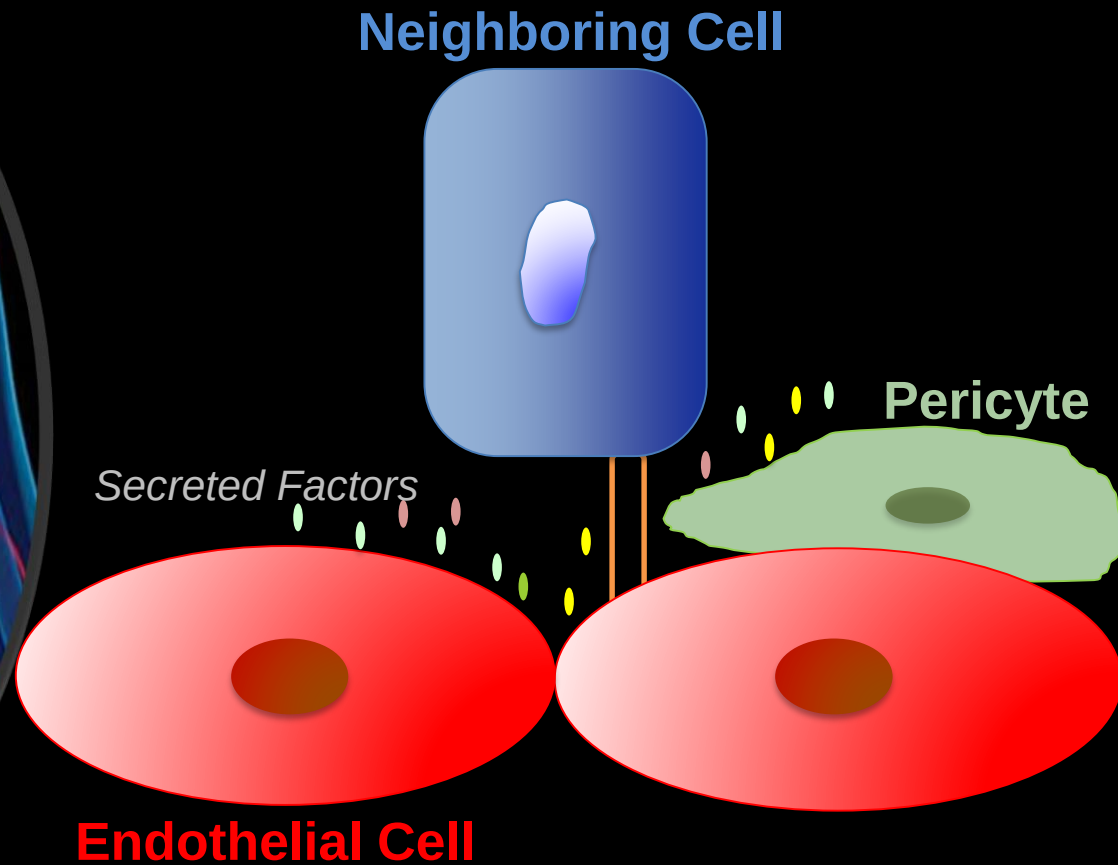
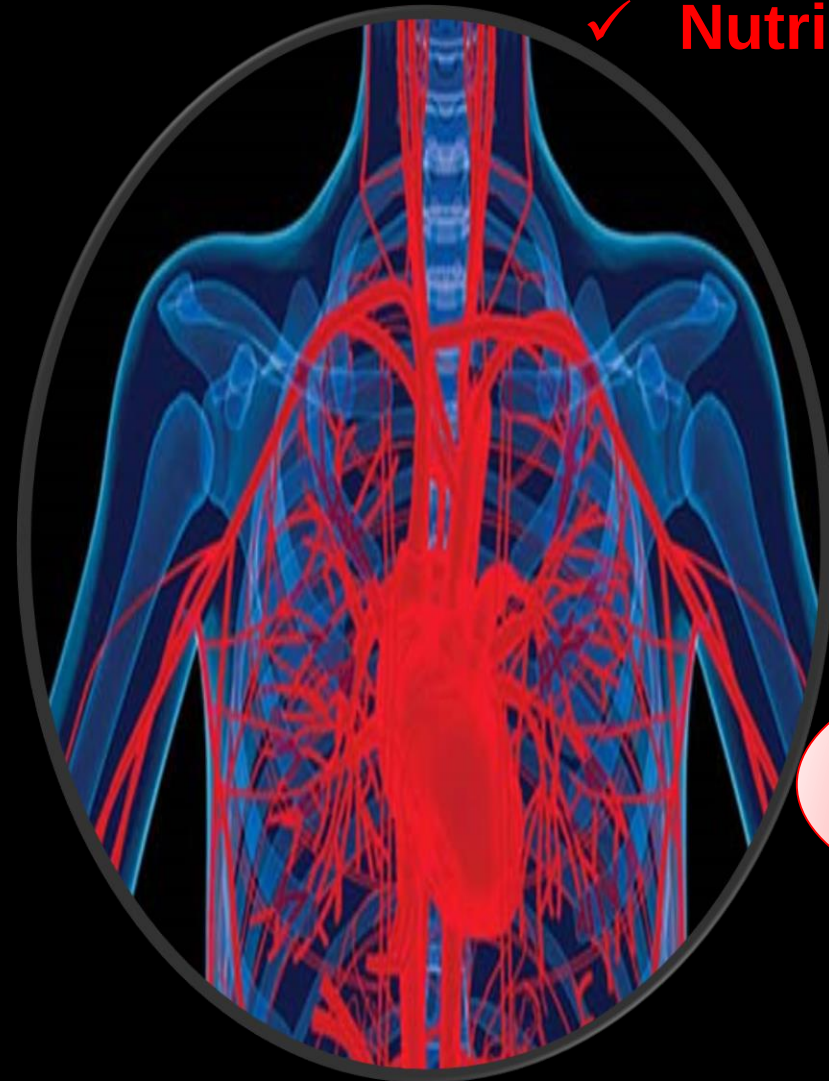
**Oxford Centre for Haematology
Annual Meeting
01.07.2019**

GOAL: To elucidate the niche functions & therapeutic potential of vasculature in normal and tumour tissues



Blood Vessel - Tissue Interactions

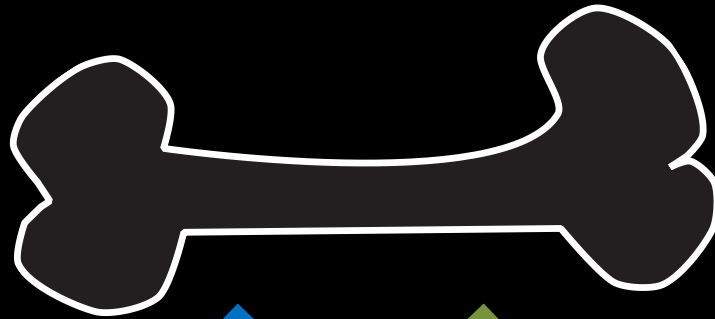
- ✓ Oxygen
- ✓ Nutrients



Juxtacrine/Paracrine/Angiocrine Signaling

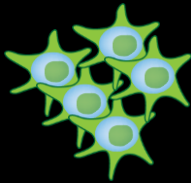
- **Unravel novel interactions between vasculature and tissues**
- **Dissect tissue-specific features of vasculature**
- **Identify dysregulation occurring during ageing and disease**

Niche functions of blood vessels in bone

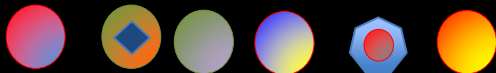


Hematopoietic Stem Cells

Mesenchymal Stem Cells



Blood & Immune cells



Osteoblasts, Adipocytes, Cartilage



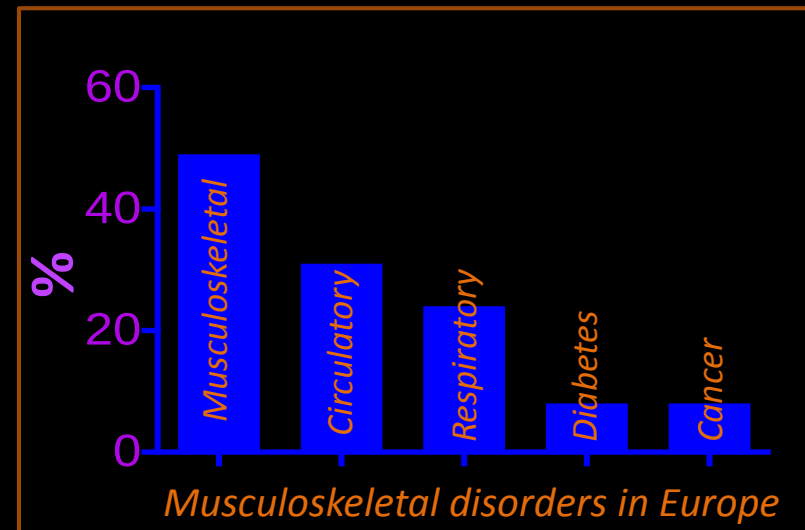


Bone Diseases and Bone Pain

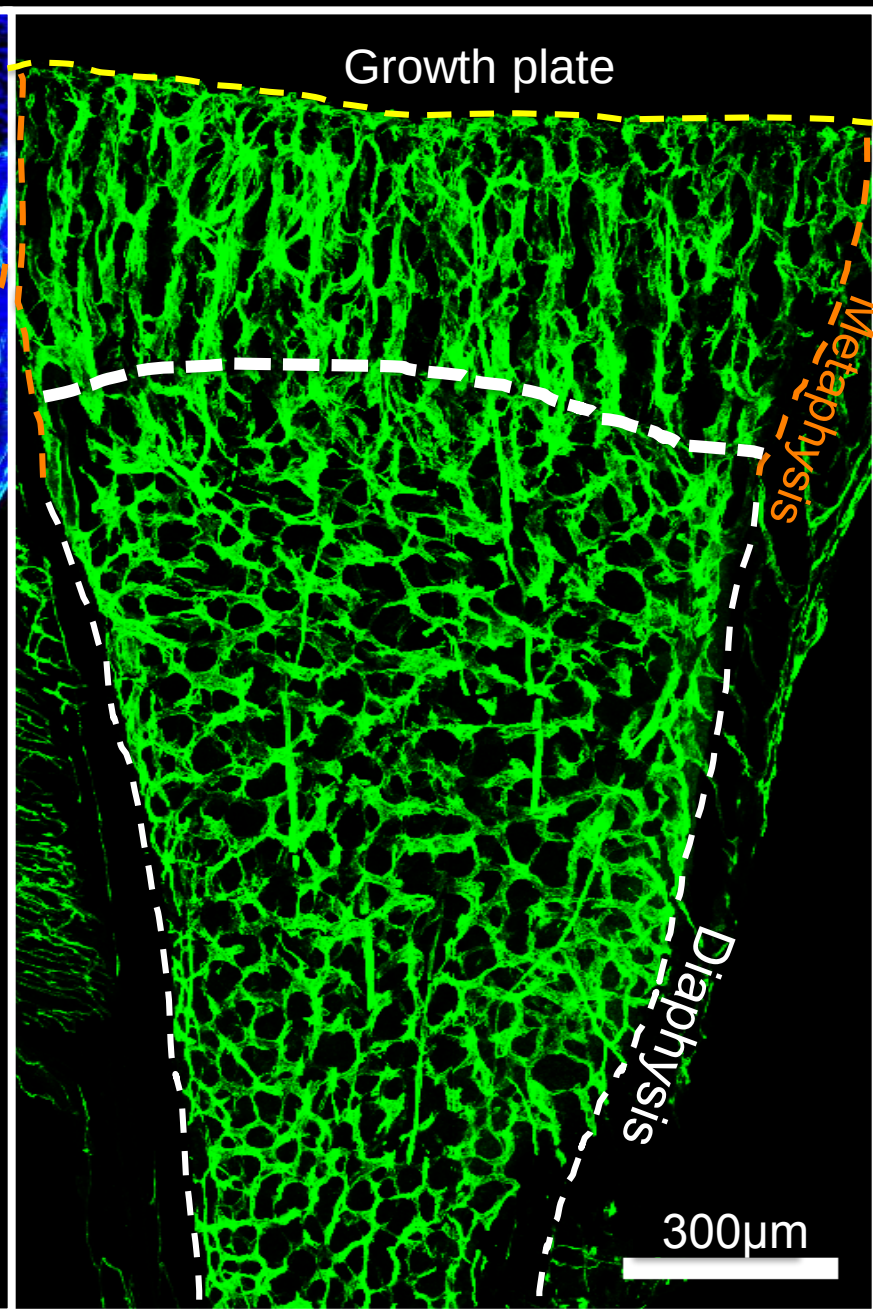
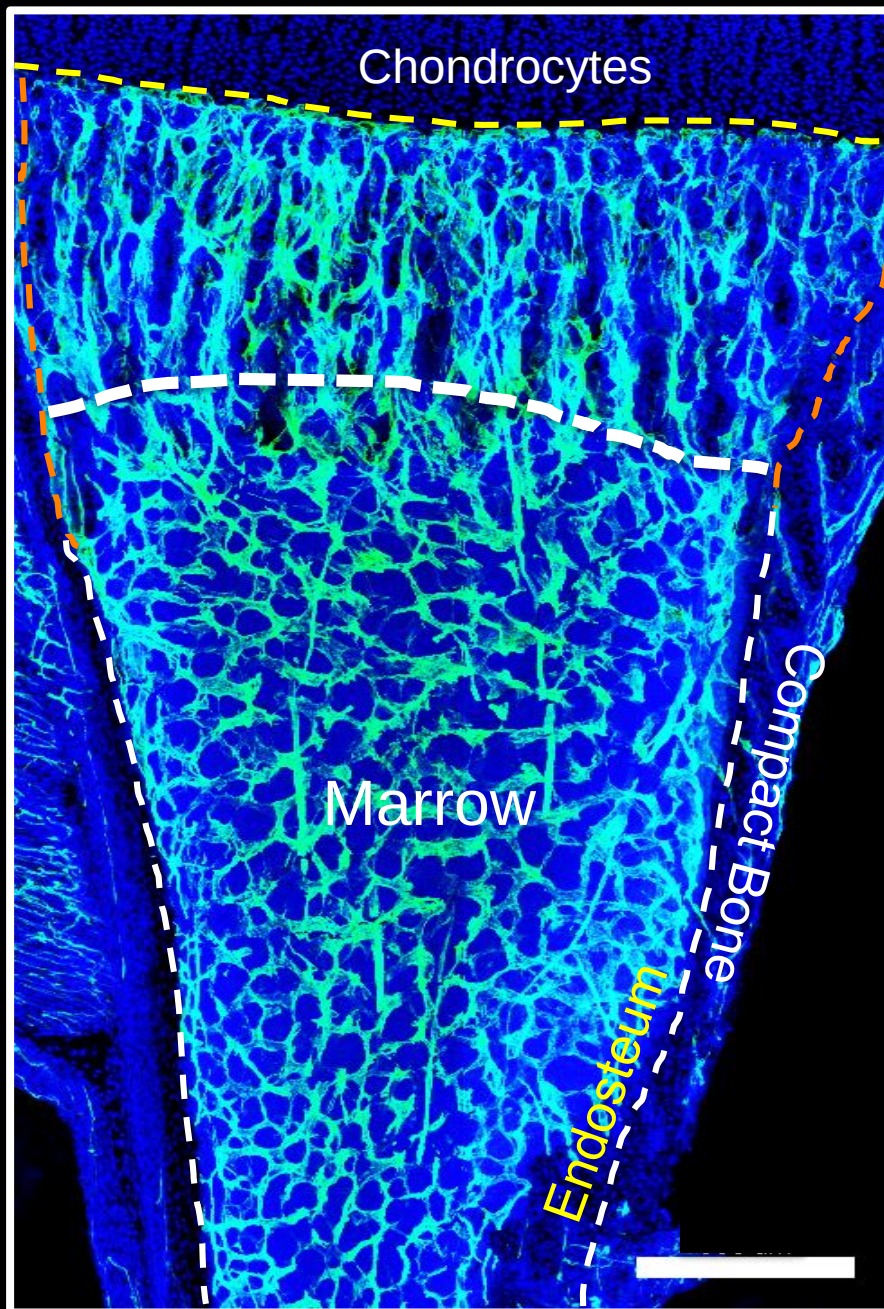


One in two adults report a musculoskeletal condition

This burden will escalate in the next 10-20 years



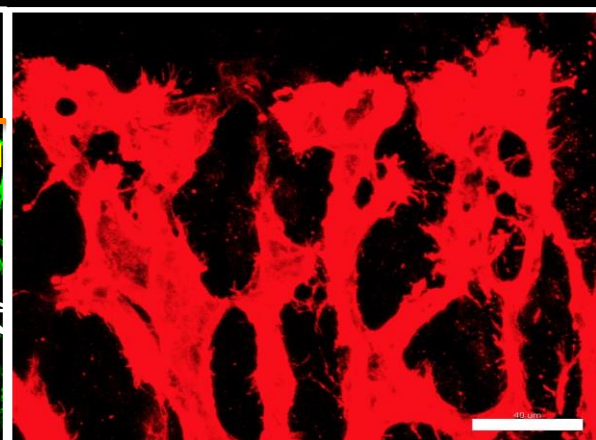
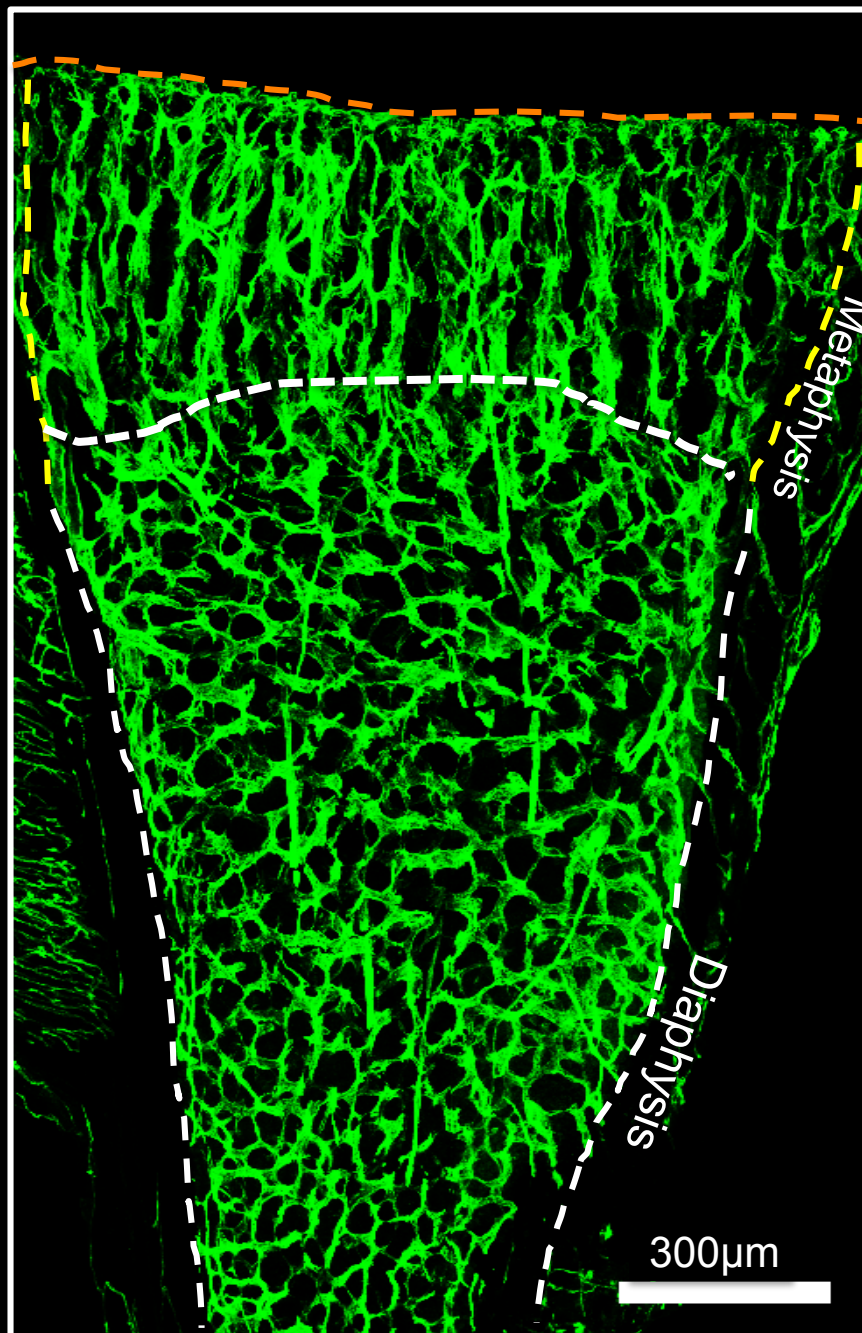
DAPI/VE-Cadherin-GFP



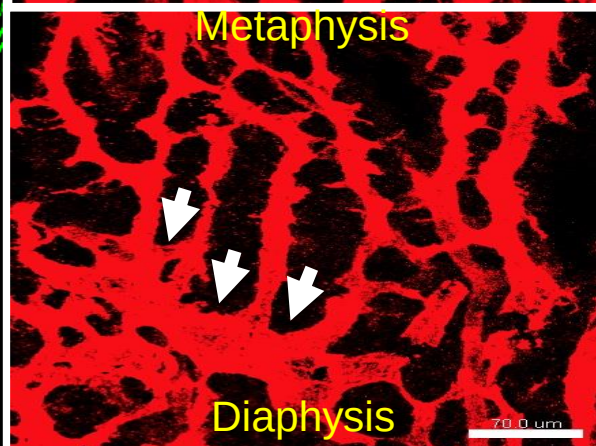
VE-Cadherin-CreERT2 X R26-mTmG

VE-Cadherin-GFP

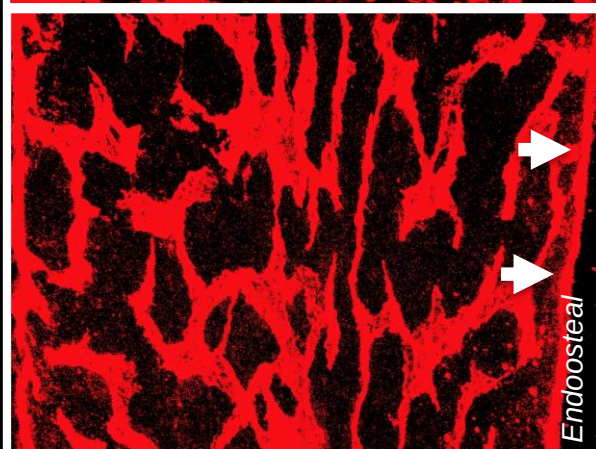
Endomucin



Metaphysis



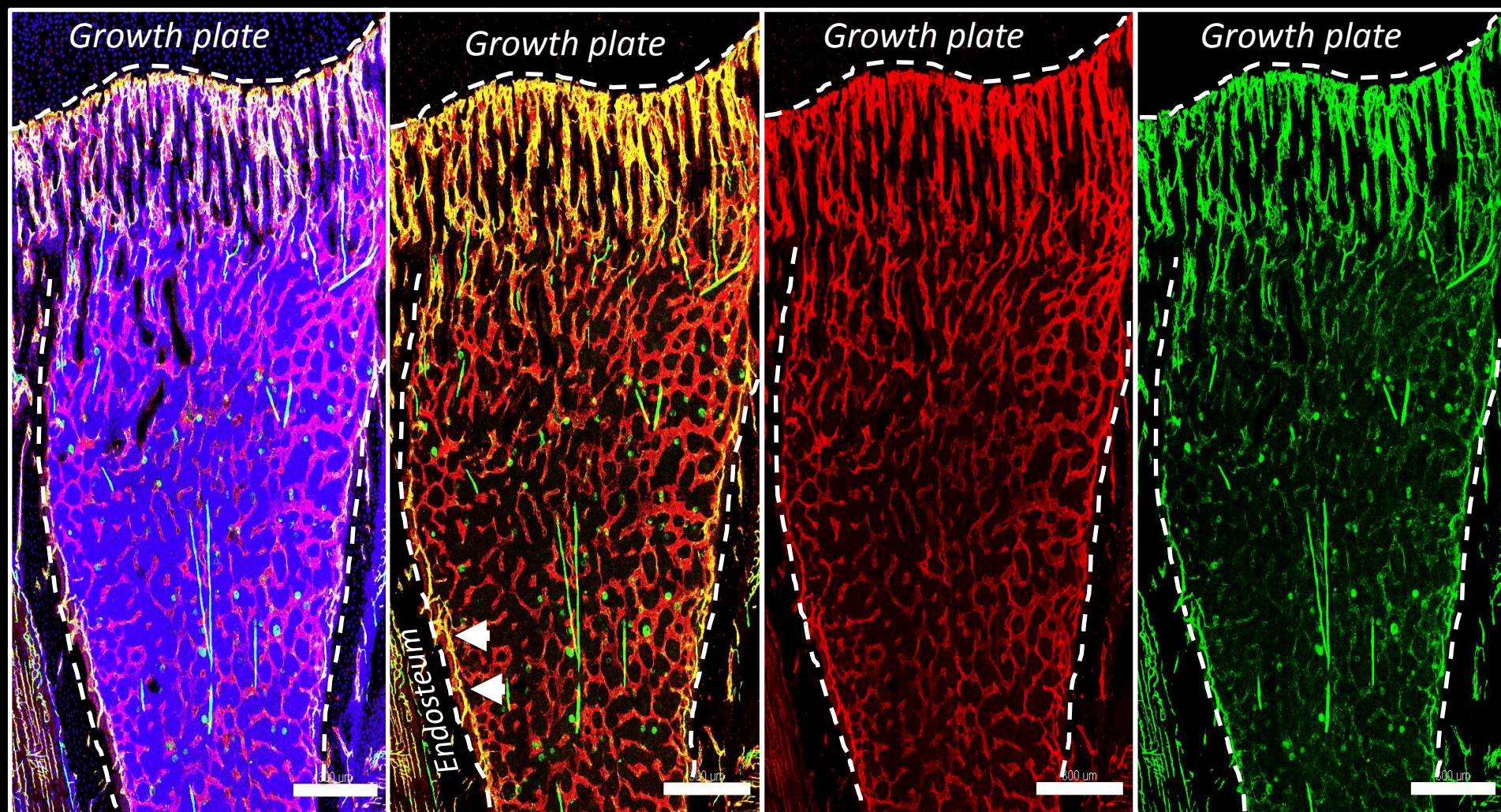
Interface



Diaphysis

Endosteal

CD31/Endomucin expression demarcates spatially and structurally heterogeneous vessels



DAPI/Endomucin/CD31

Endothelial cell heterogeneity in bone

Type H

Type L

➤ **Phenotypic**

CD31^{hi}/Endomucin^{hi}

CD31^{lo}/Endomucin^{lo}

➤ **Spatial**

Metaphysis + Endosteal

Diaphysis

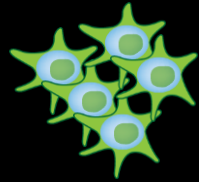
➤ **Structural**

Linear

Branched

Type H endothelium and osteoprogenitors

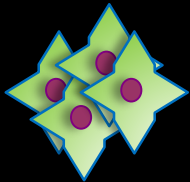
Mesenchymal Progenitors



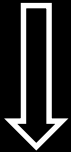
Pdgfr β
Pdgfra



Early Osteoprogenitors



Runx2

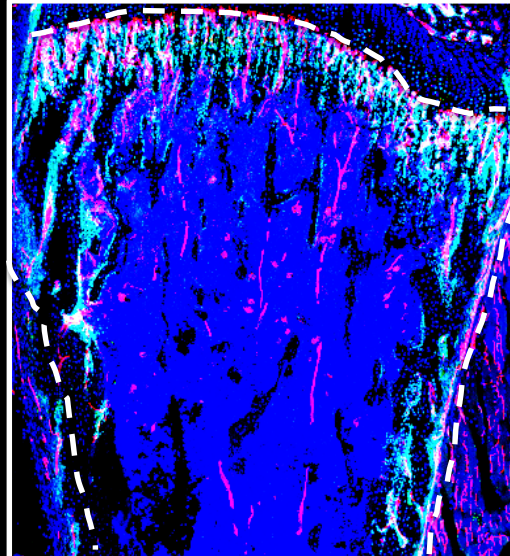


Late Osteoprogenitors

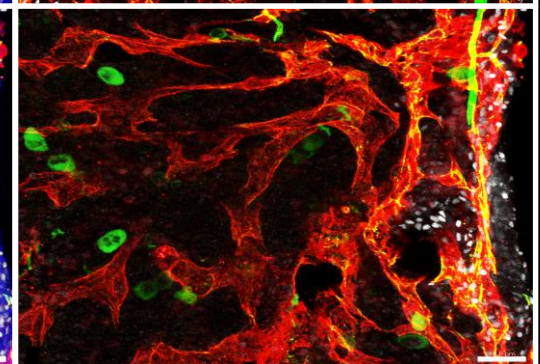
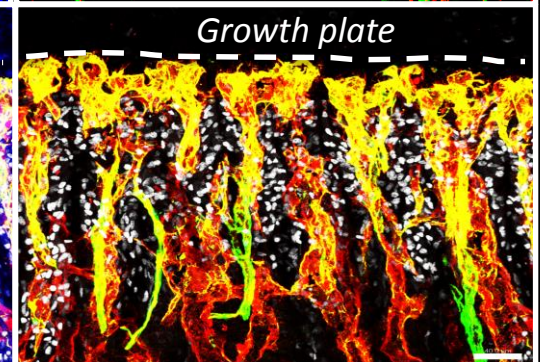
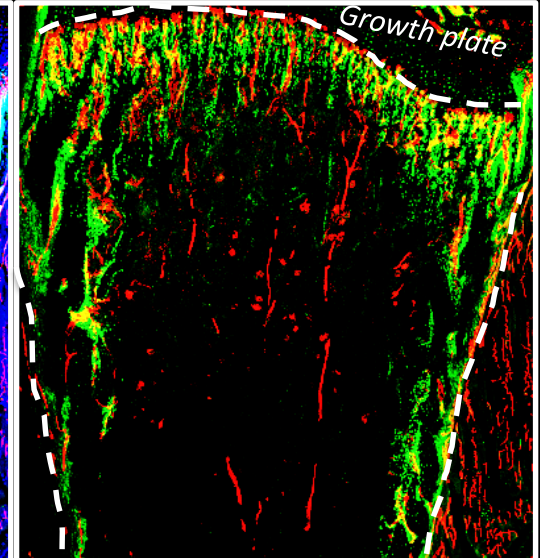
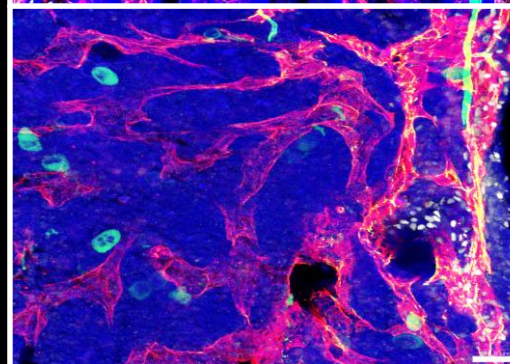
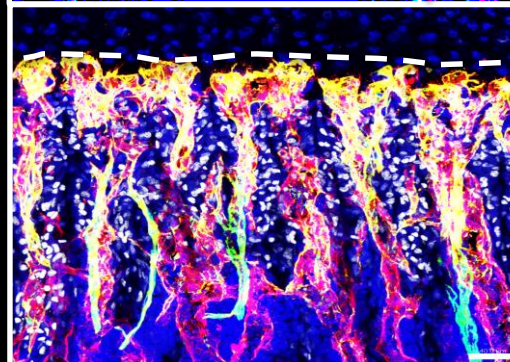


Collagen1 α
Osterix

DAPI/CD31/Osx

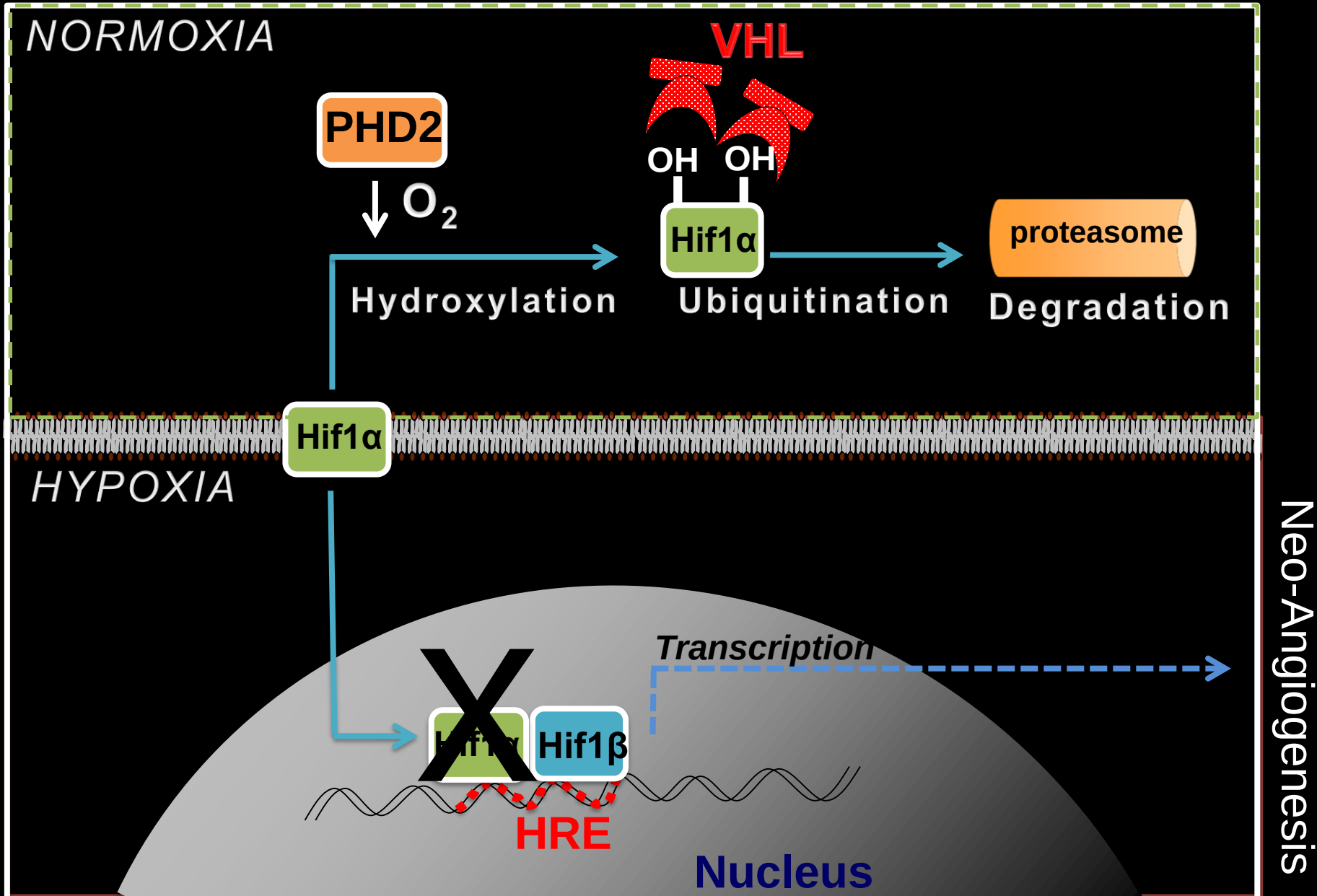


DAPI/Endomucin/CD31/Osx



HIF-1 signaling

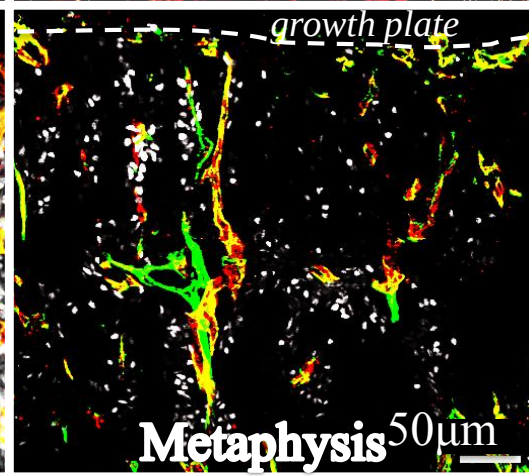
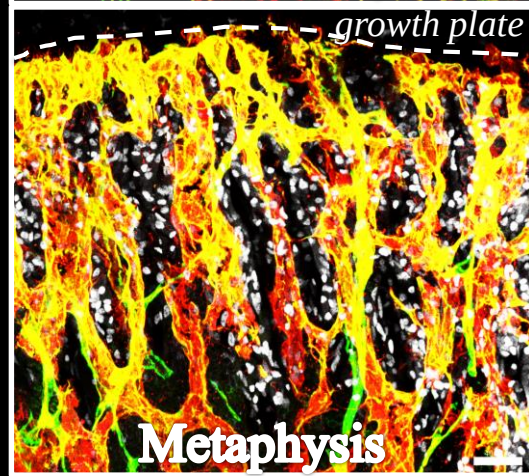
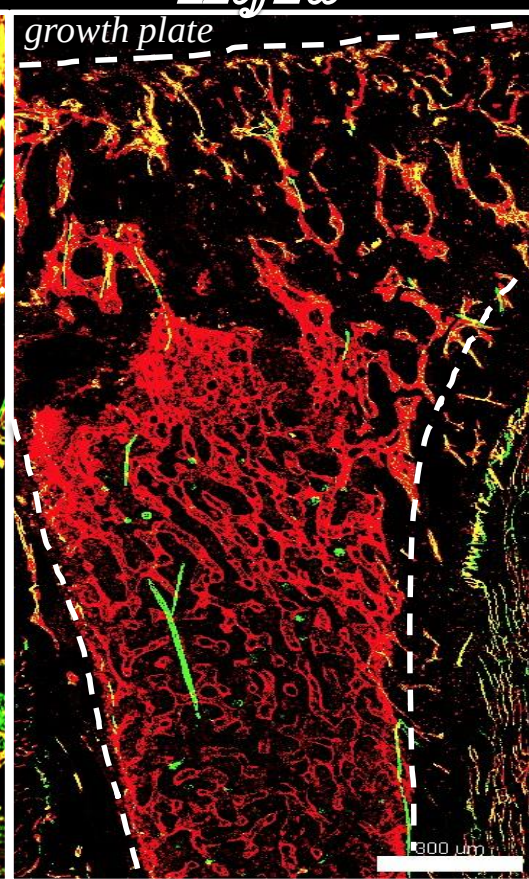
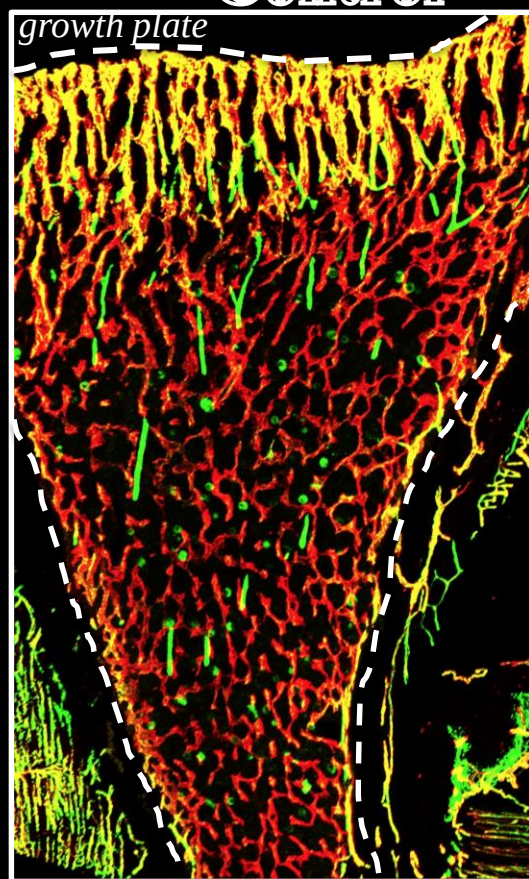
Endothelial Cell



Osterix **Endomucin/CD31**

Control

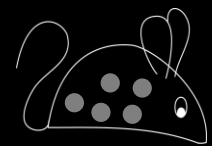
Hif1 α ^{iΔEC}



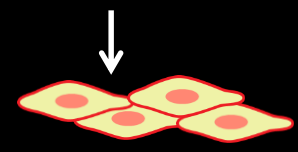
Endothelial Hif1 deletion



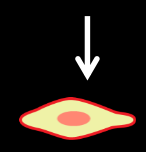
Control



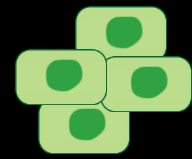
Hif1^{iΔEC}



Type H



Type H

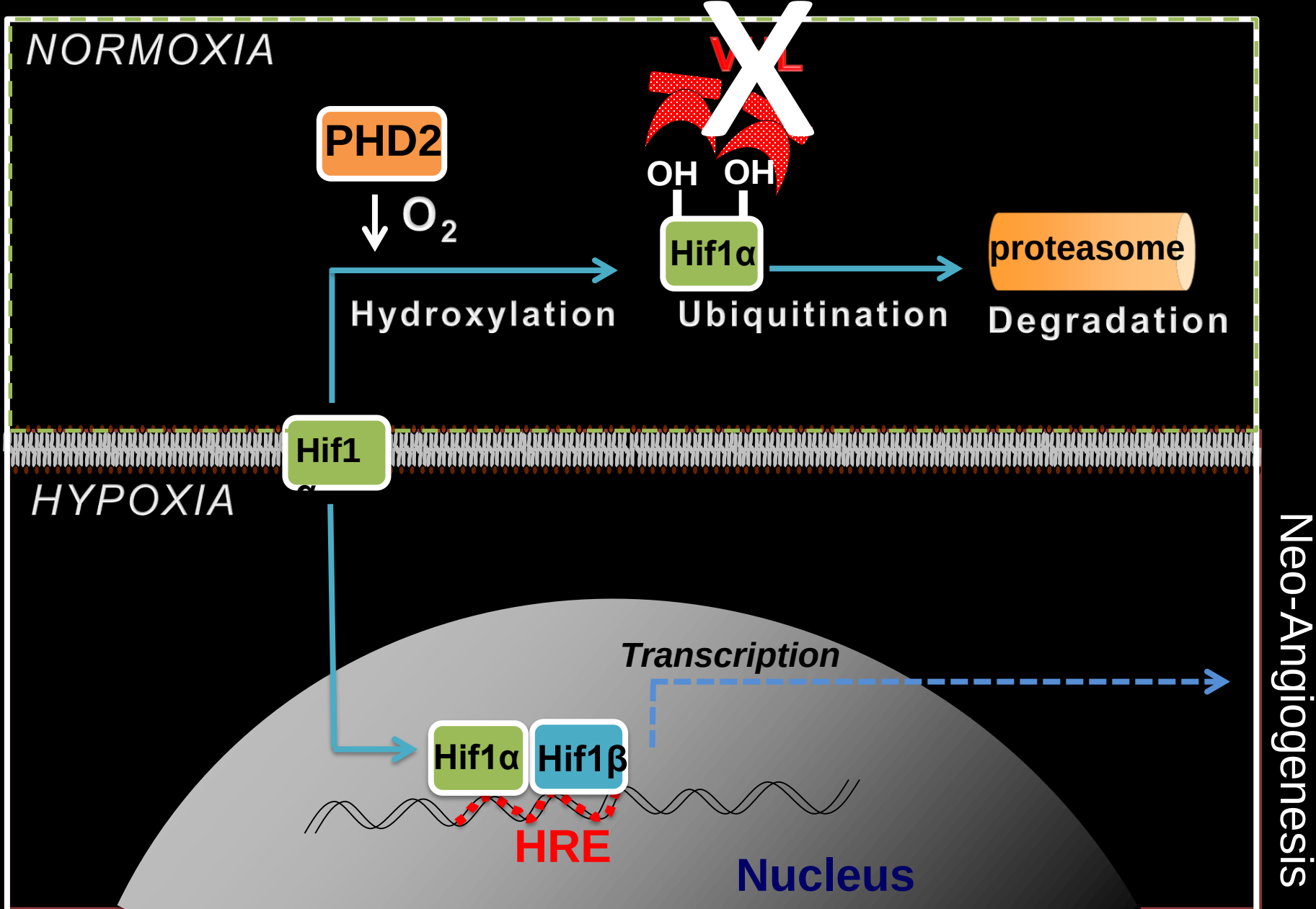


Osteoprogenitors



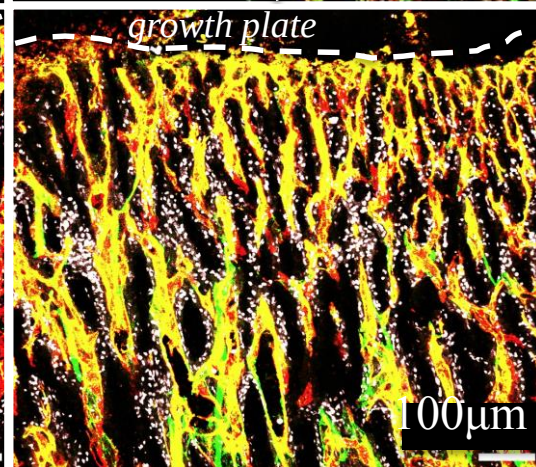
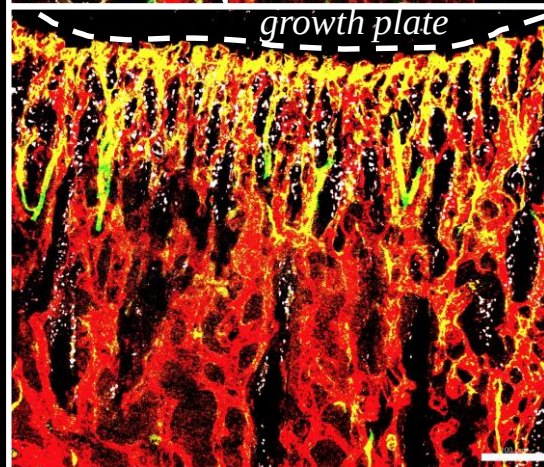
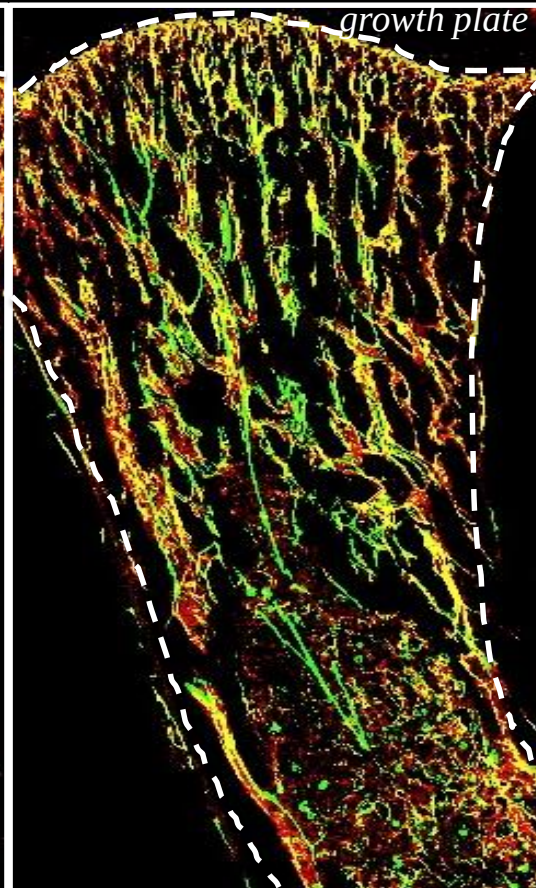
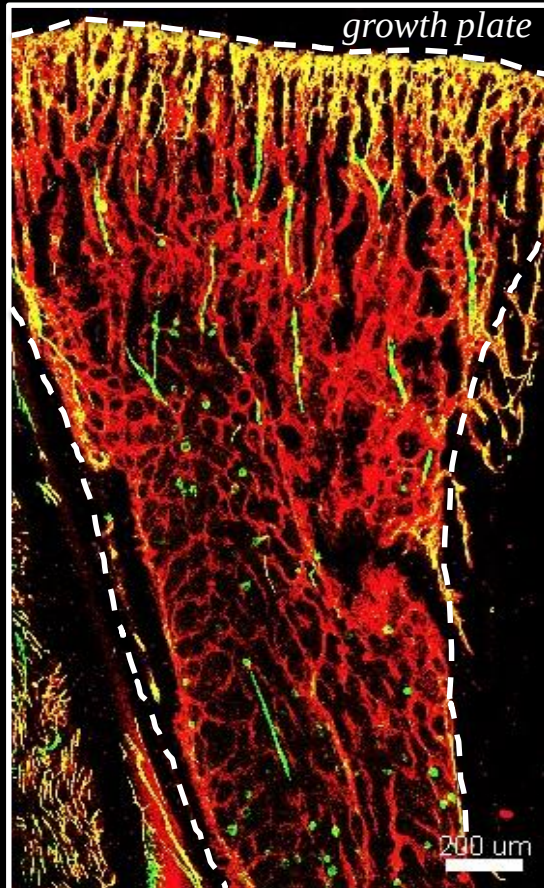
HIF-1 signaling

Endothelial Cell



Control

Vhl^{iΔEC}



Endomucin/CD31

Osterix

Endothelial Hif1 stabilization



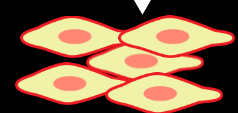
Control



Type H



Vhl^{iΔEC}



Type H



Osteoprogenitors



Bone Mass



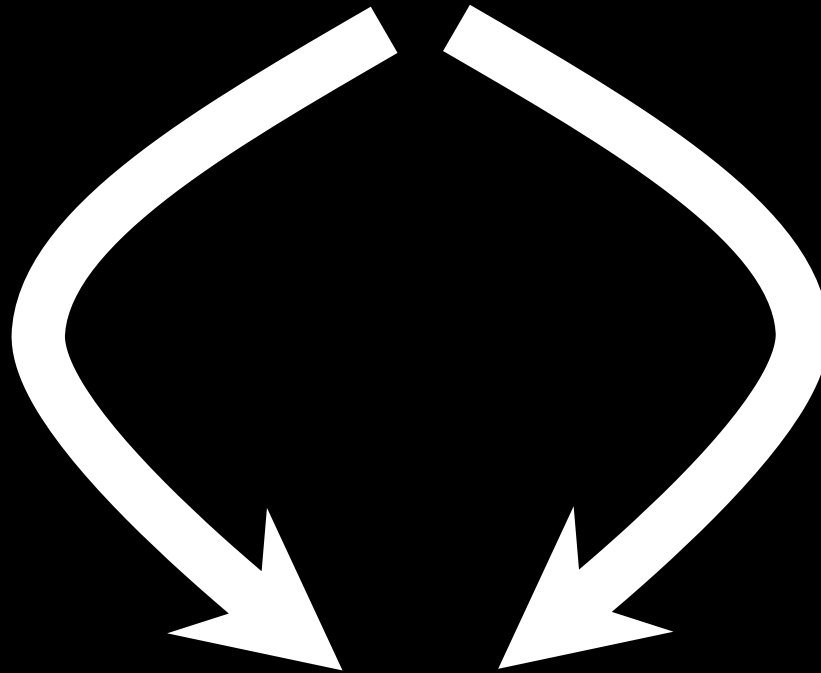
Decline upon Ageing



Type H blood vessels

Associated with
osteoprogenitors

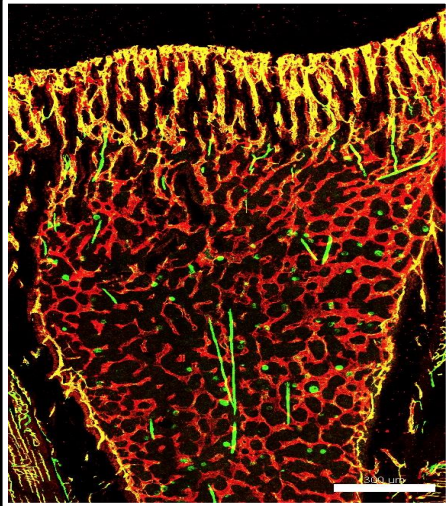
Osteogenic
Factors



Bone Formation

Specialized vessels

TYPE H



(Kusumbe et al. Nature 2014A, Nature 2014B)

Bone Vasculature

Age-dependent changes

YOUNG

TYPE H

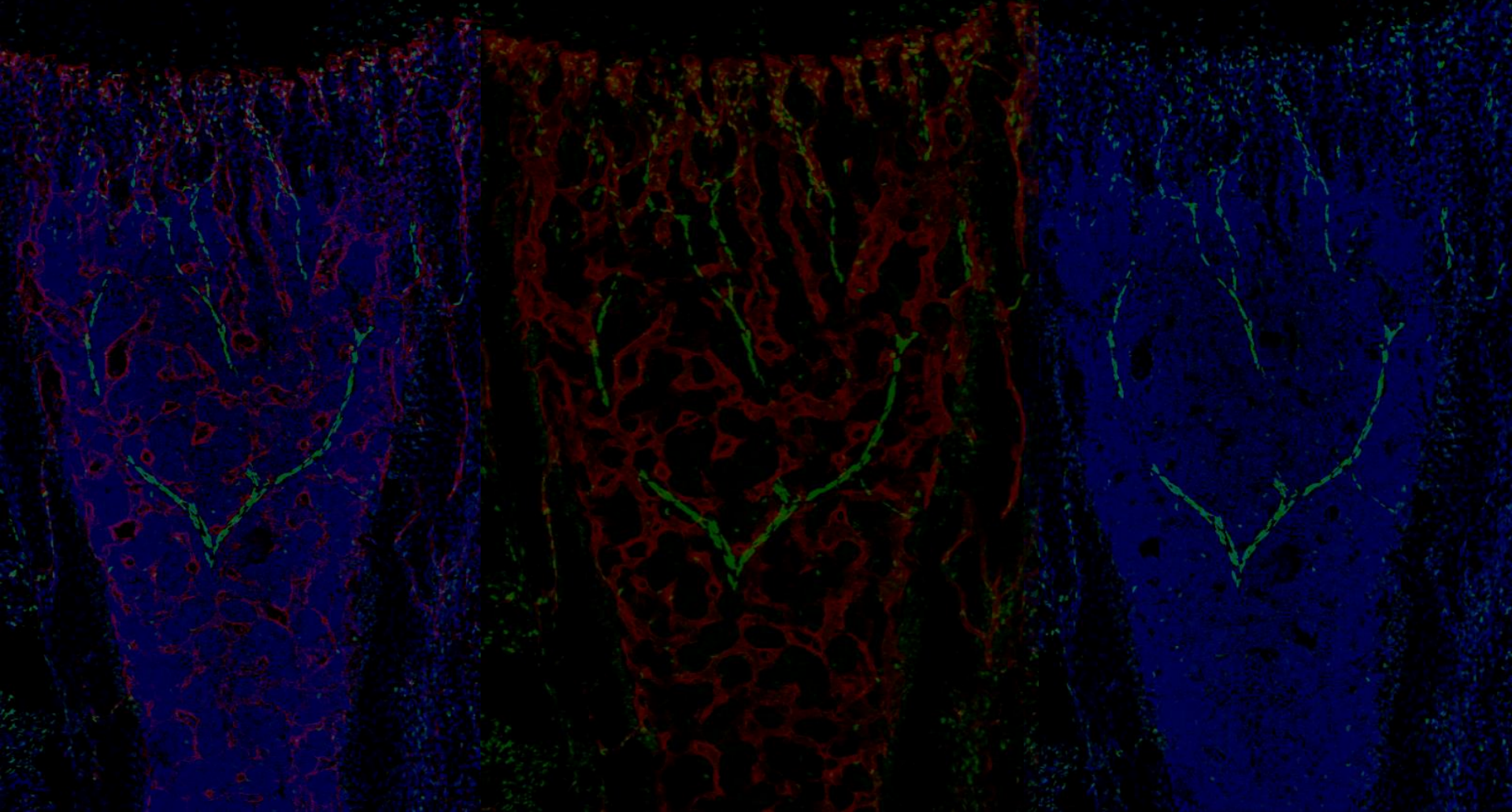


OLD



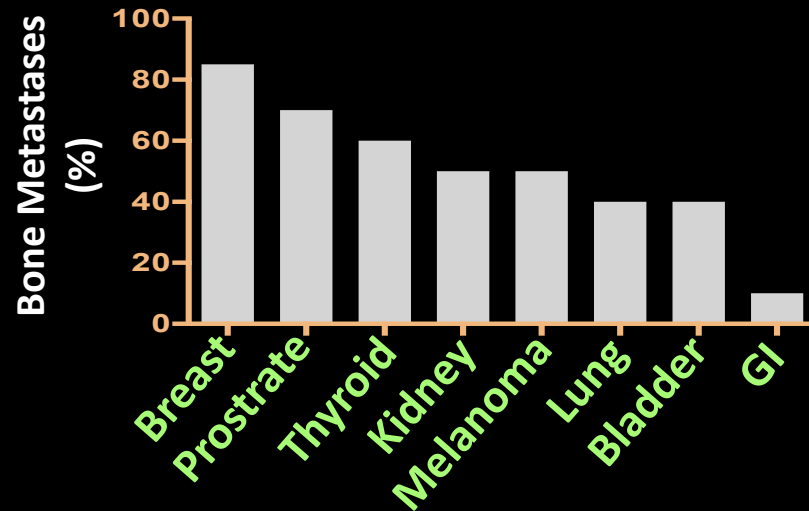
(Kusumbe et al. Nature 2016)

Regulation of bone metastasis by age-associated angiocrine signals

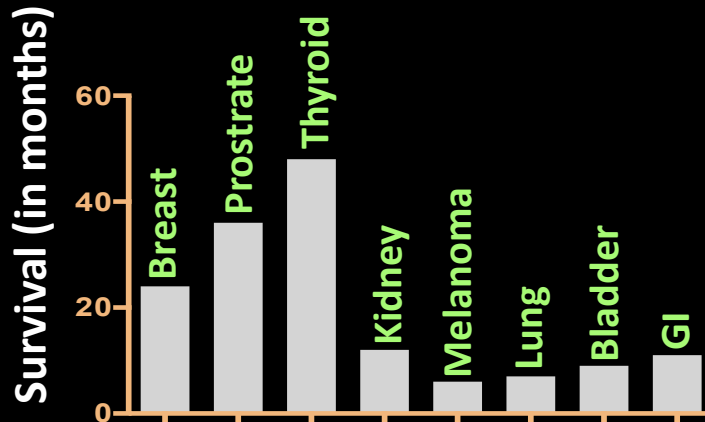


Bone Metastasis

Bone: Most Frequent Site of Metastasis

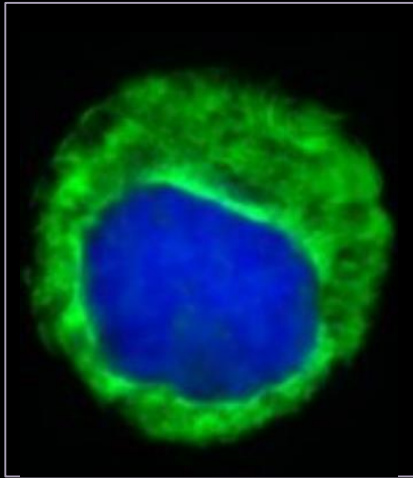


Very Poor Prognosis



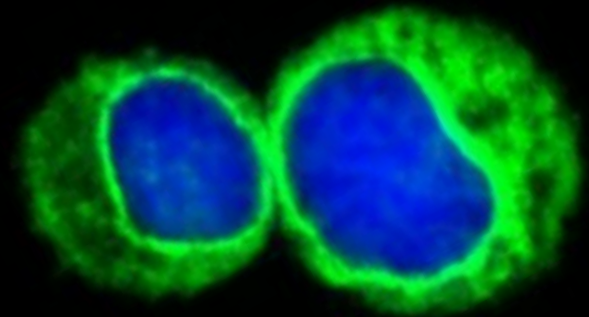
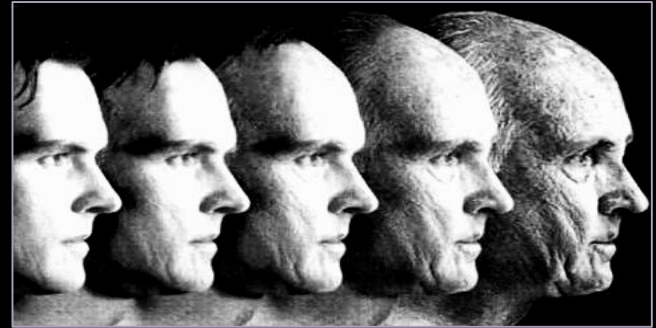
Ageing and bone metastasis

Dormancy



Disseminated Tumor Cell
(DTC)

Age-associated Relapse

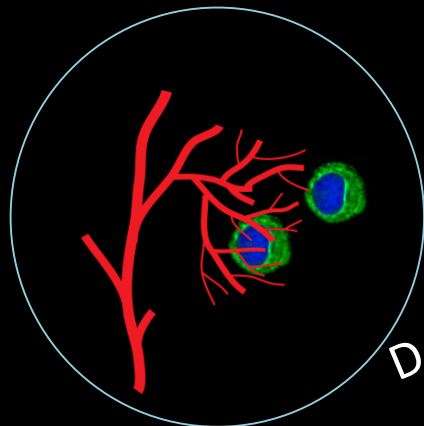


Reactivation

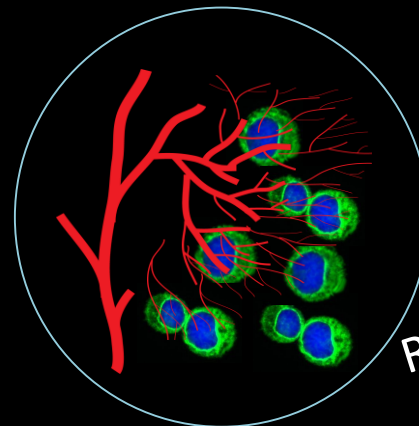
Age-dependent Changes in the Microenvironment May Regulate DTCs



Vascular Microenvironments

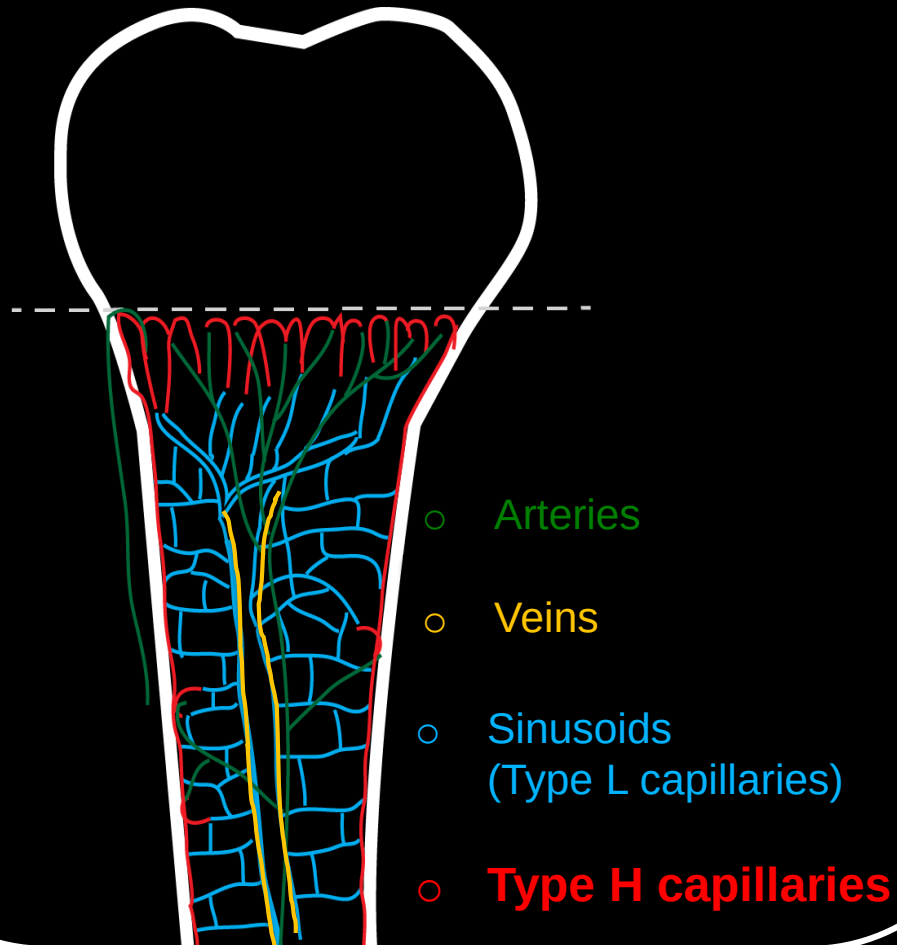


Dormancy

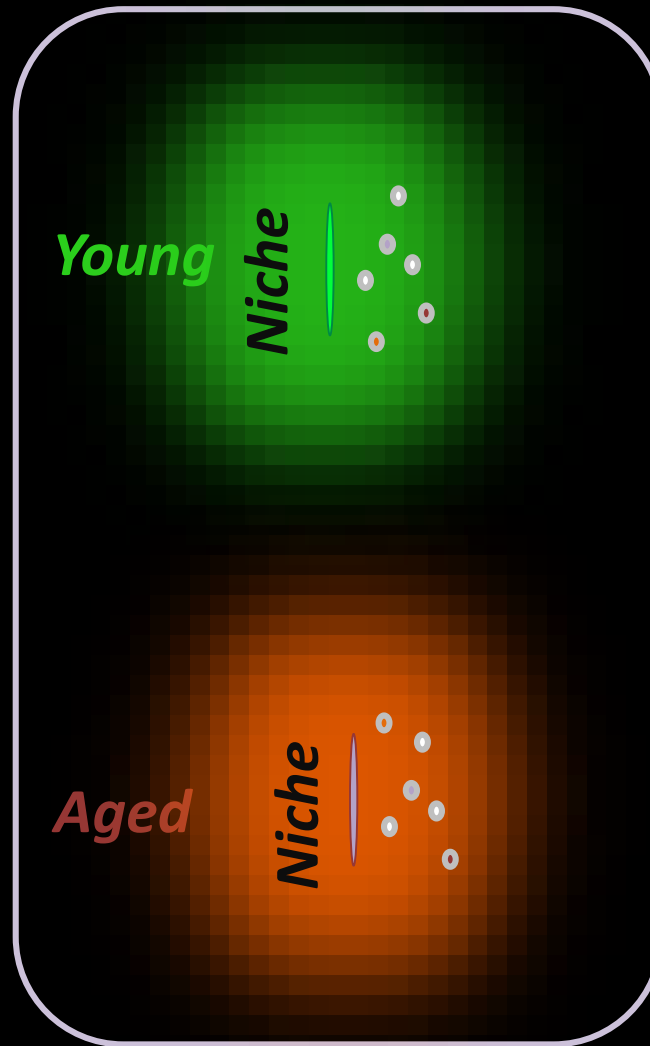


Reactivation

Vascular bed in bone is heterogeneous



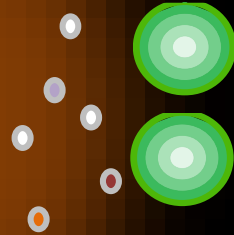
Niche Dependent ?



Impact of the Aged Bone Marrow Microenvironment on Bone Metastasis

Young

Niche

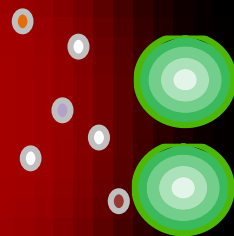


Cancer Cells

?

Aged

Niche



Cancer Cells

Intra Cardiac Injections
Intra Tibial Injections

MDA-MB-231-LUC-GFP
MCF-7-LUC-GFP



Young

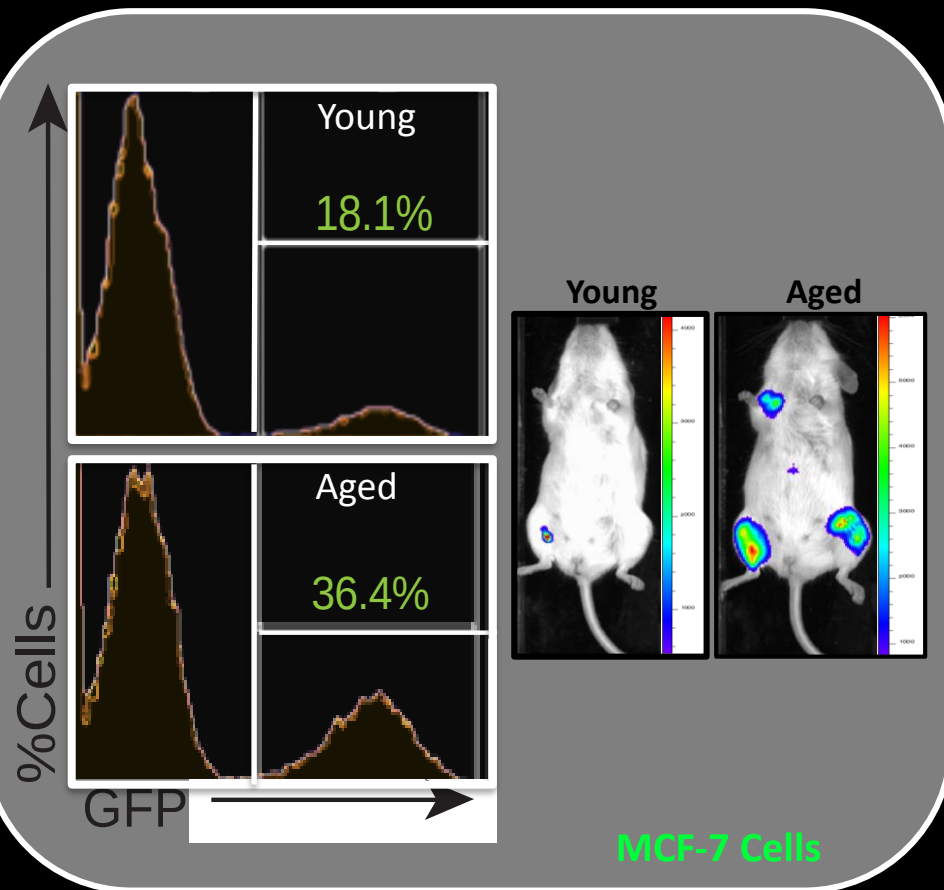


Aged

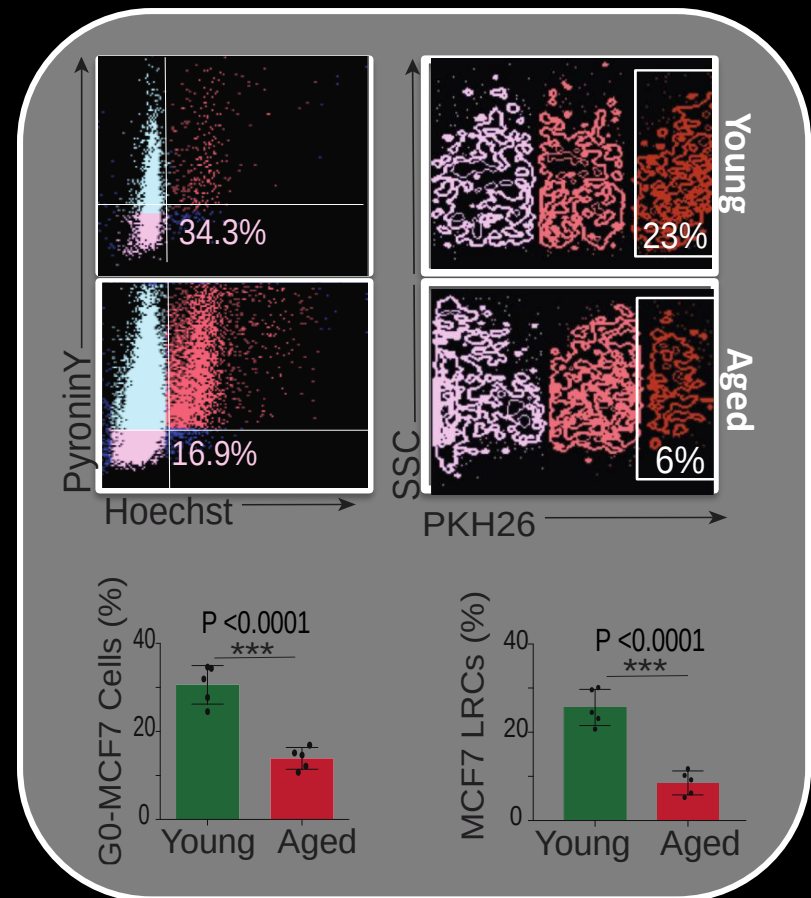
Recipients

The aged bone marrow microenvironment:

Promotes expansion of tumor cells

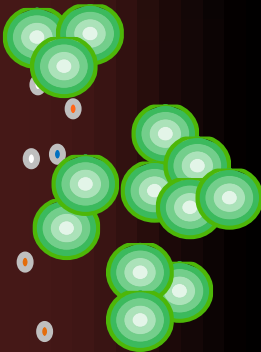


Inhibits cancer cell quiescence



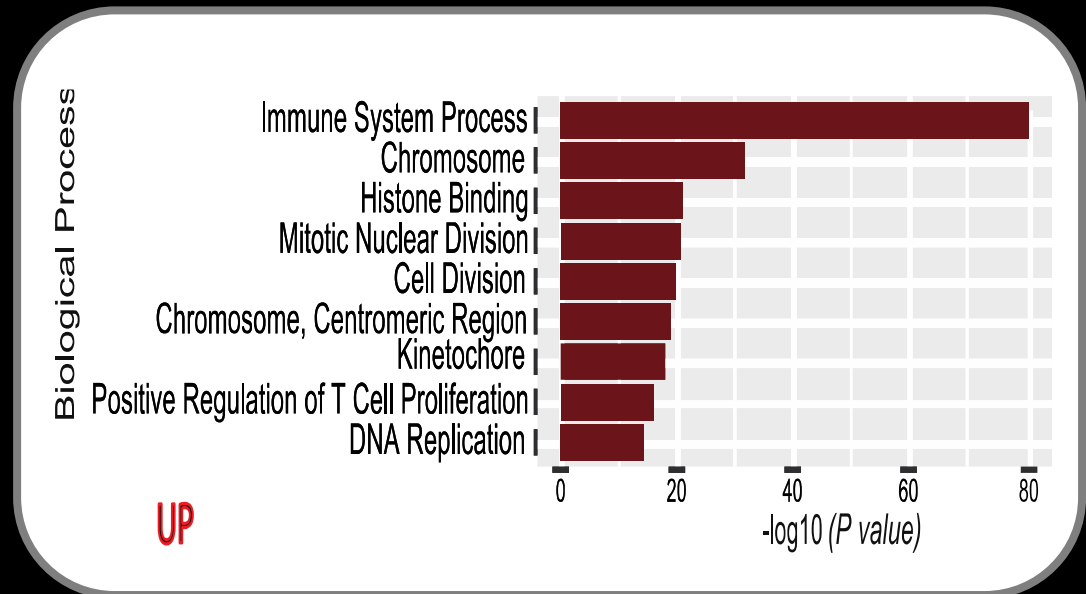
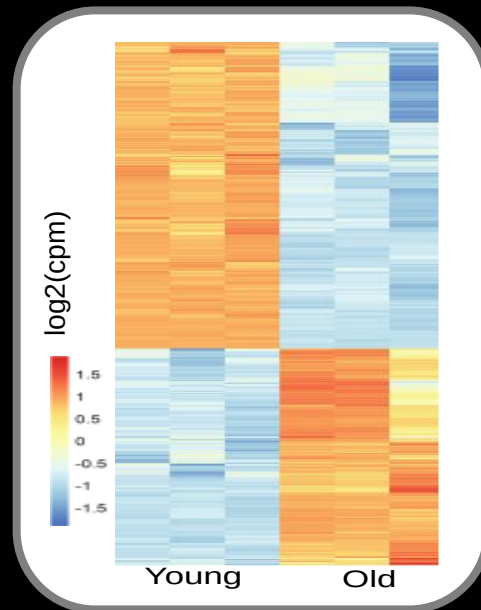
The Aged Bone Marrow Microenvironment

Aged Niche

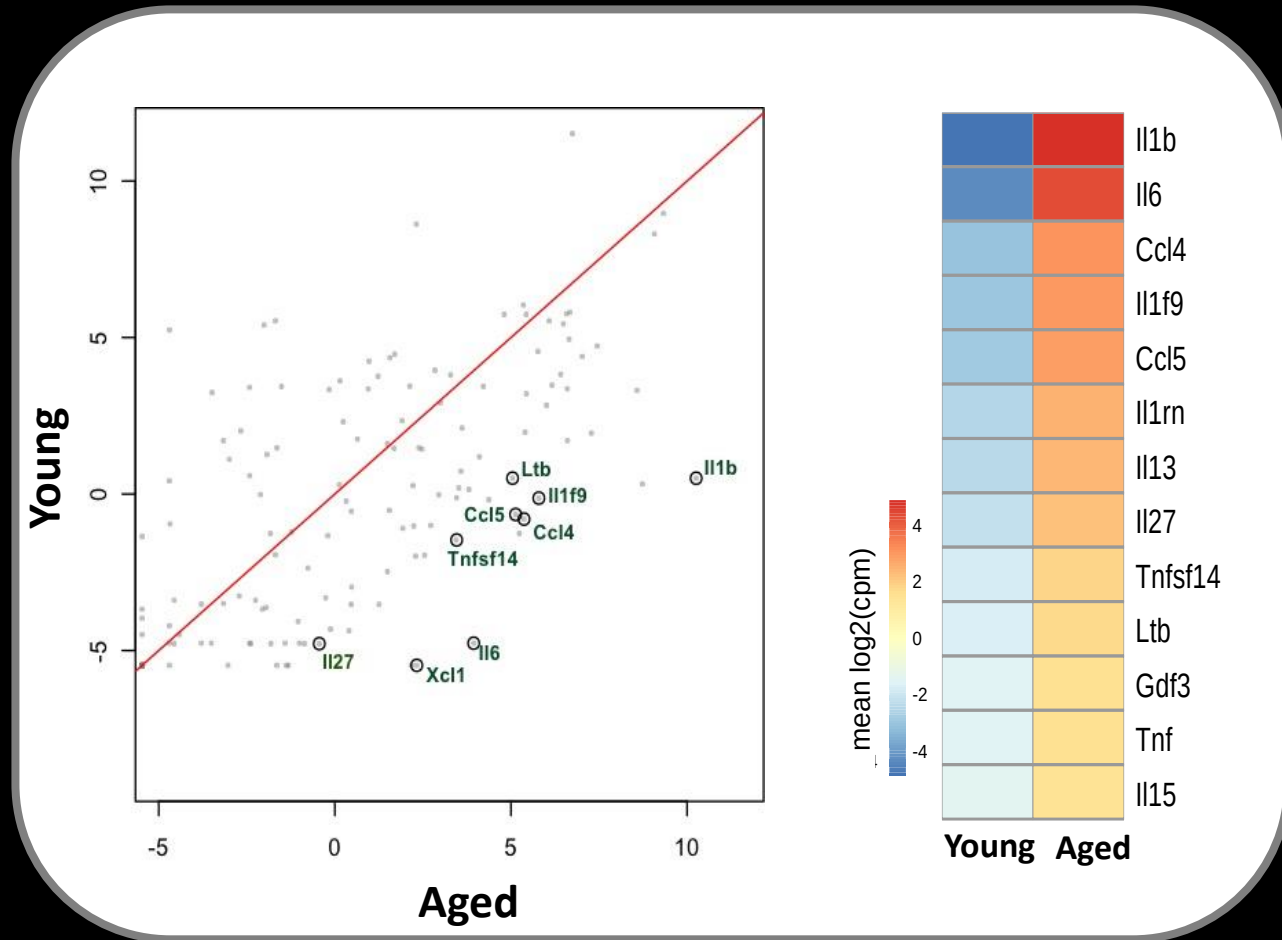


- 1. Promotes Expansion**
- 2. Inhibits Quiescence**

Enrichment of Cell Proliferation Genes in the Aged Bone Marrow

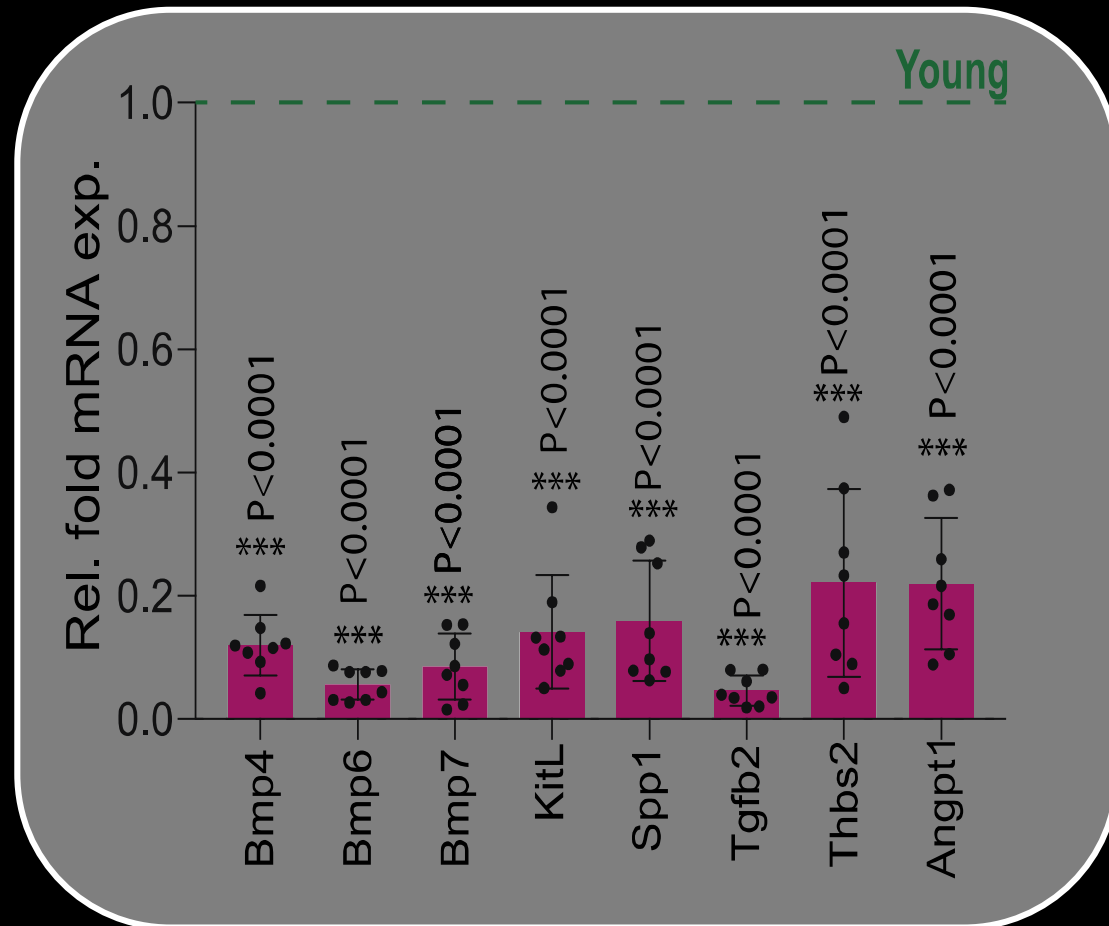
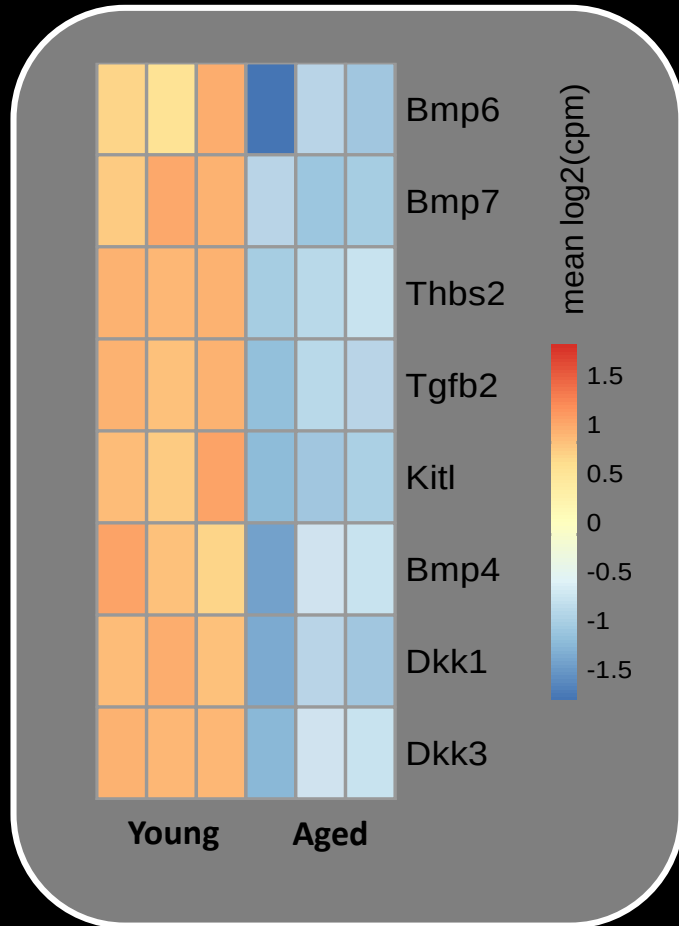


The aged bone marrow :



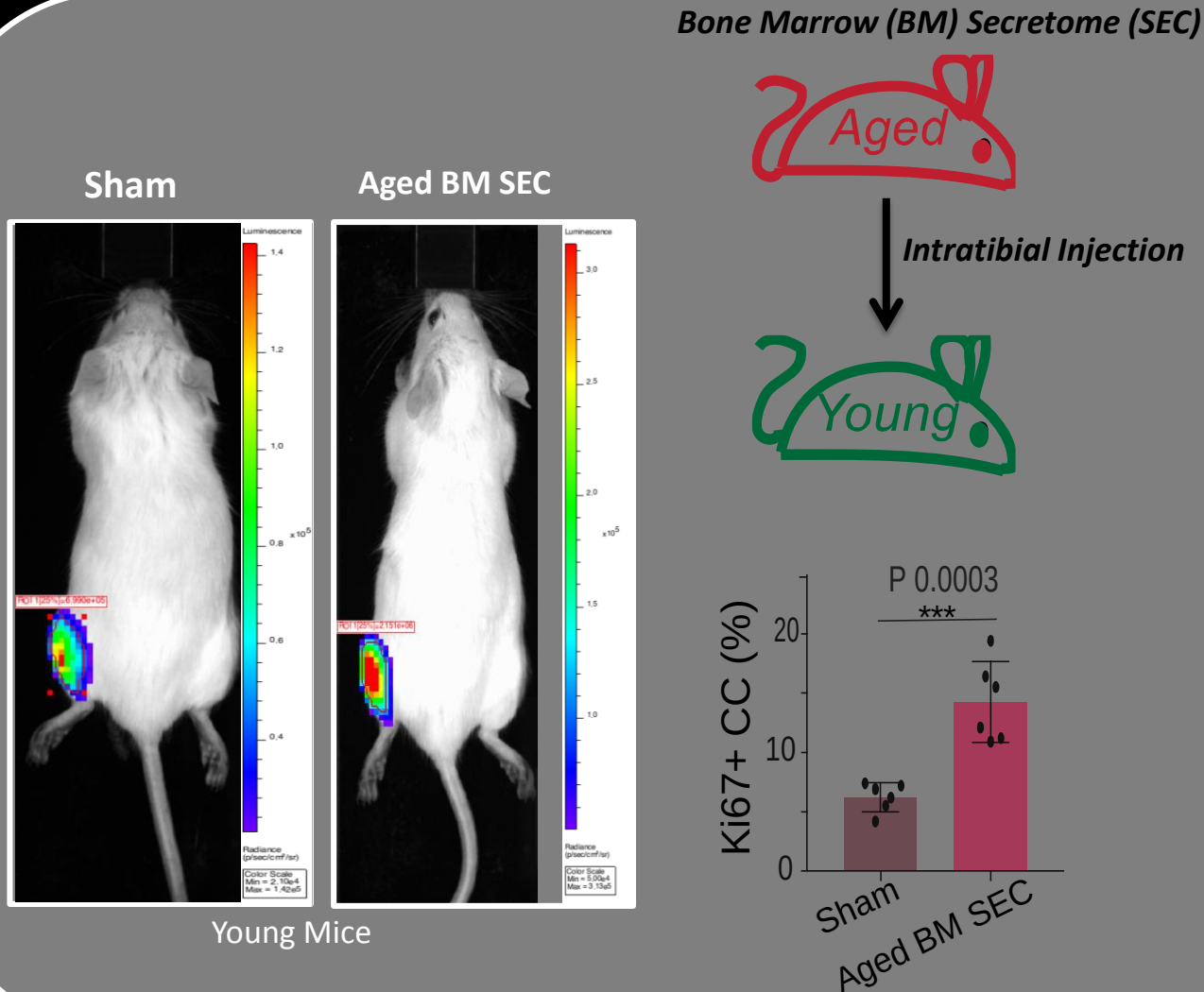
proliferation promoting cytokines increase

Decline of quiescence inducing factors in the aged bone marrow microenvironment

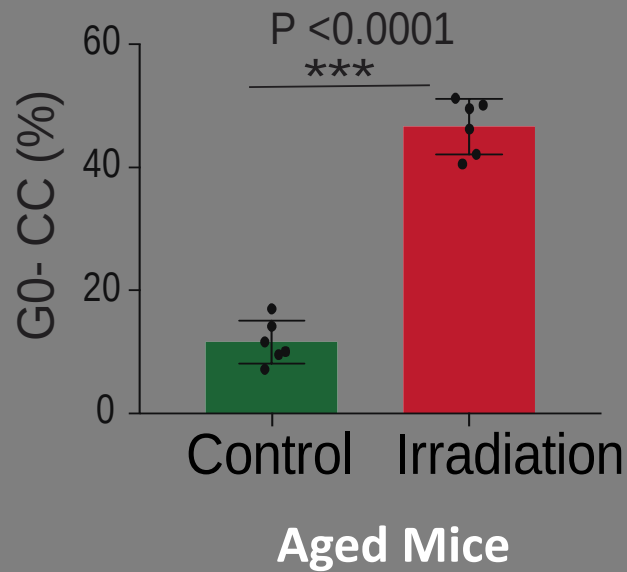


Validated by ELISA in bone marrow supernatants

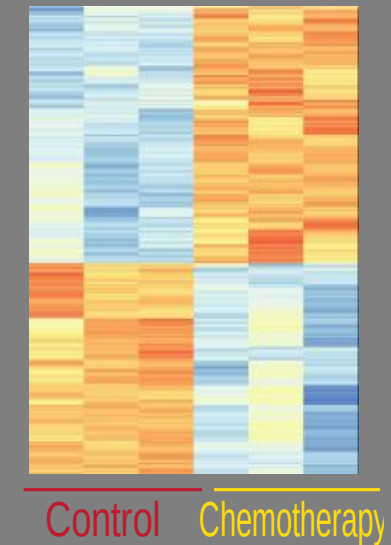
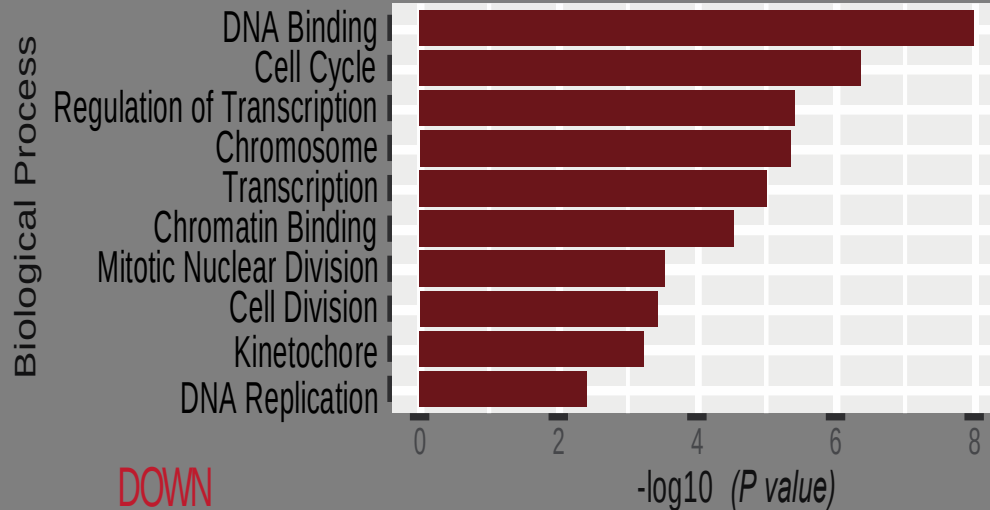
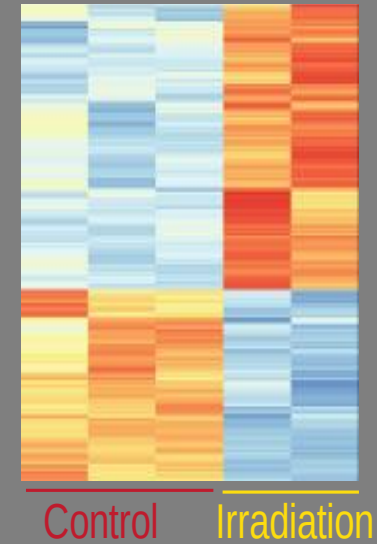
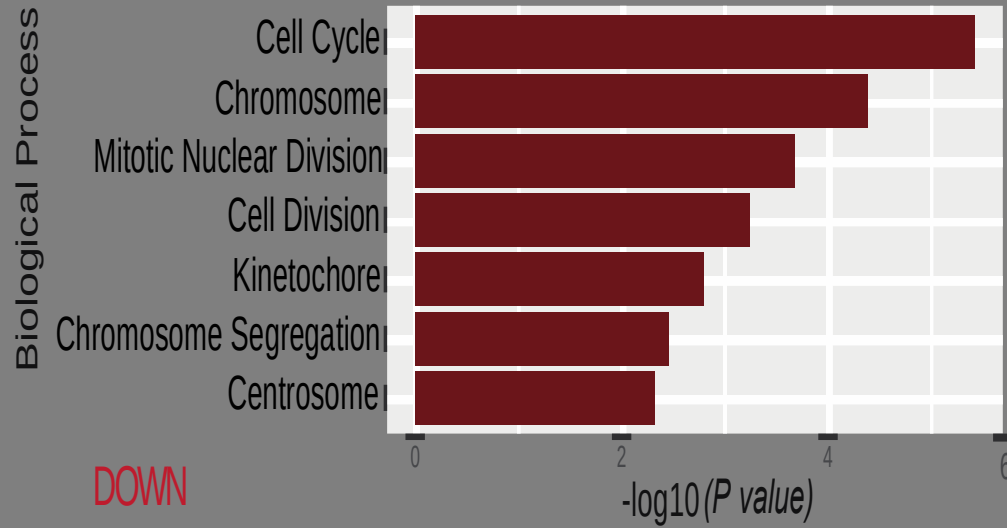
The aged bone marrow secretome stimulates proliferation of cancer cells



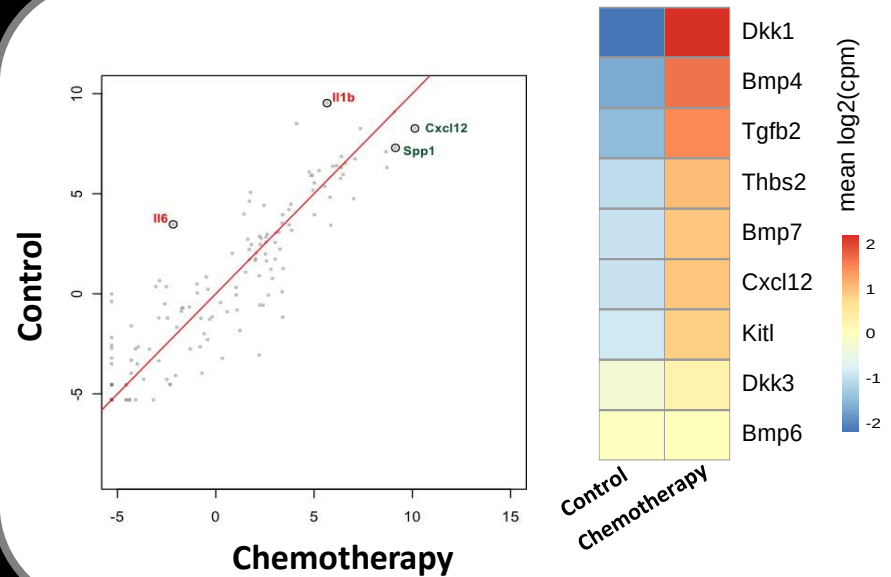
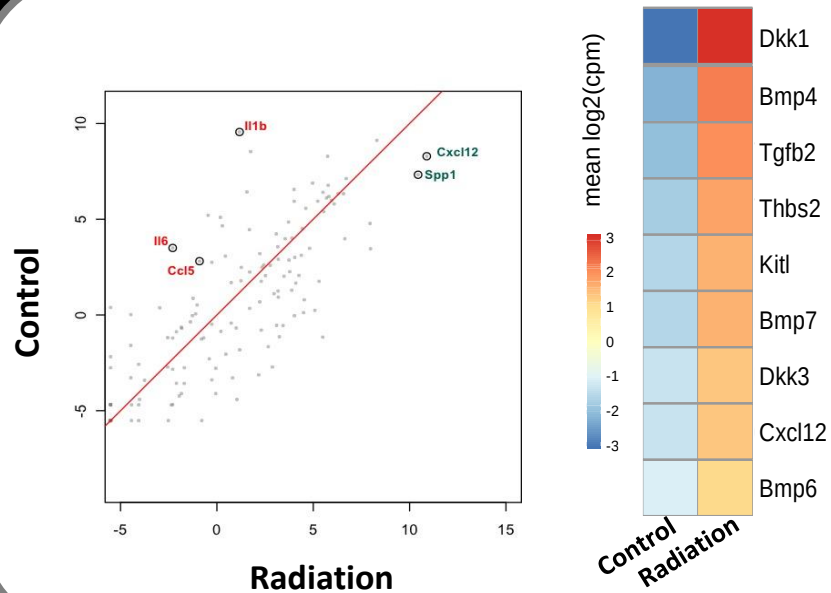
Radiation leads to increase in quiescent cancer cells in aged mice



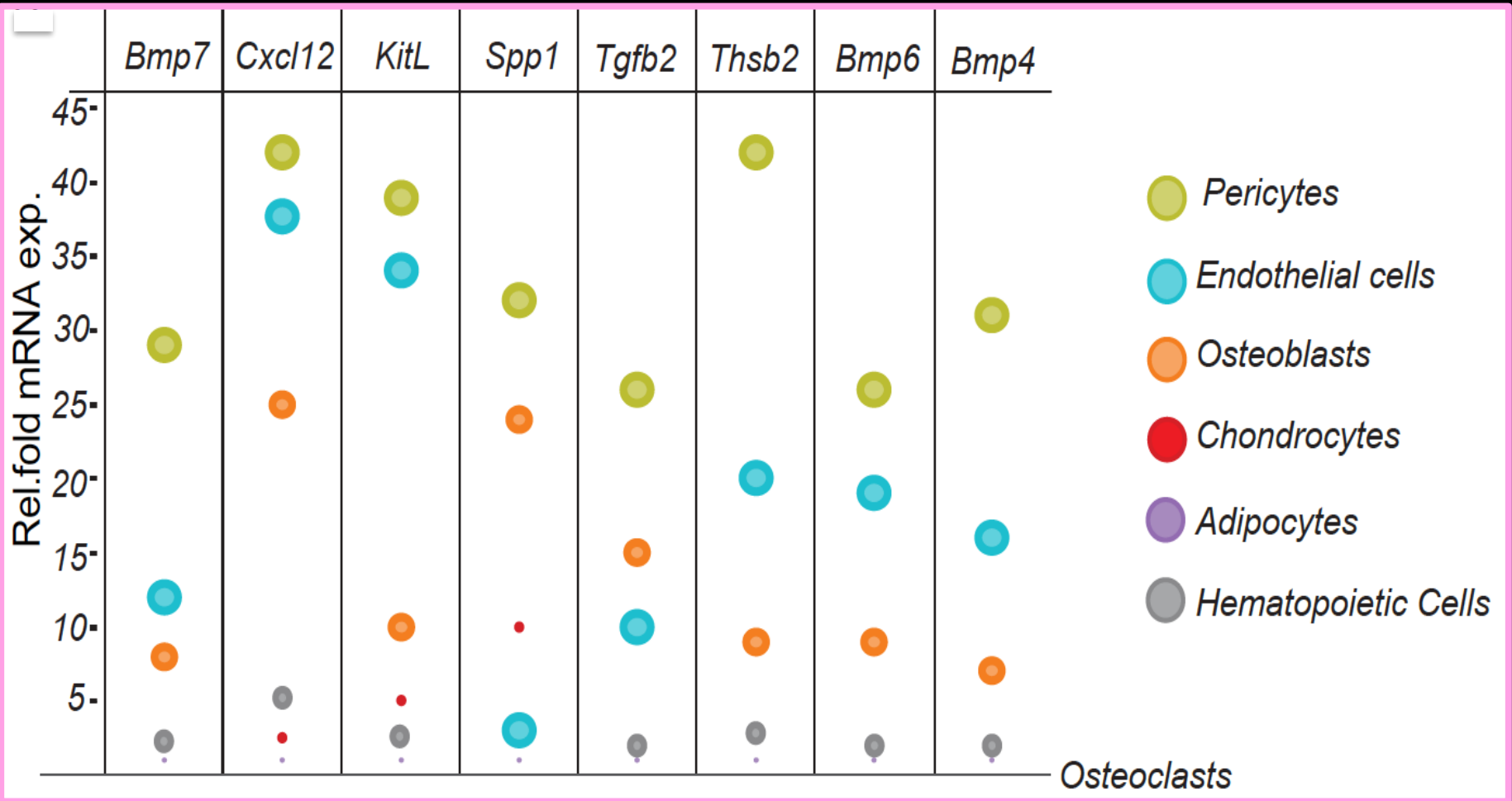
Down-regulation of cell proliferation genes



Radiation & chemotherapy leads to enrichment of quiescence inducing factors

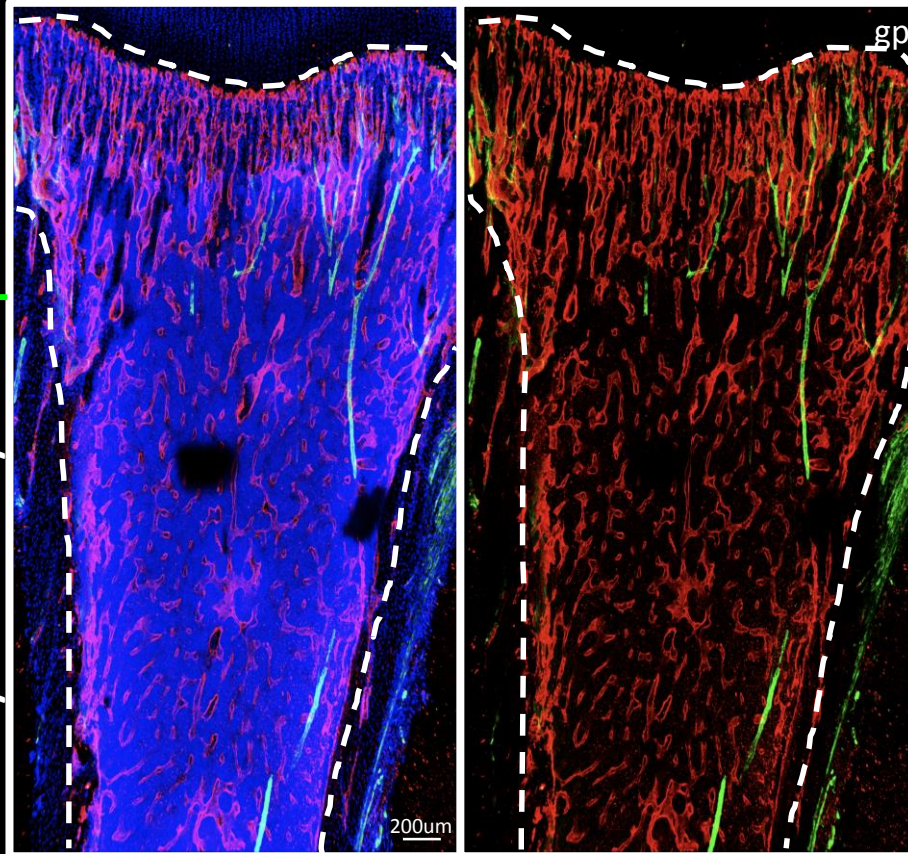


Pericytes & endothelial cells exhibit high levels of quiescence factors

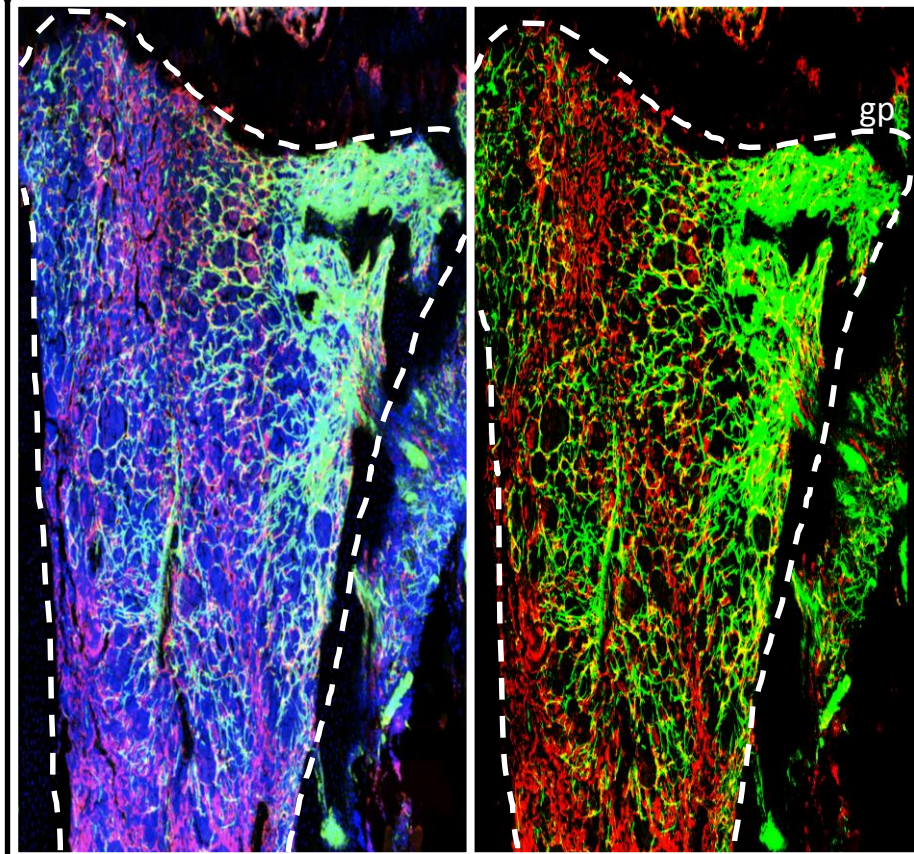


Expansion of pericytes post-radiation

Control



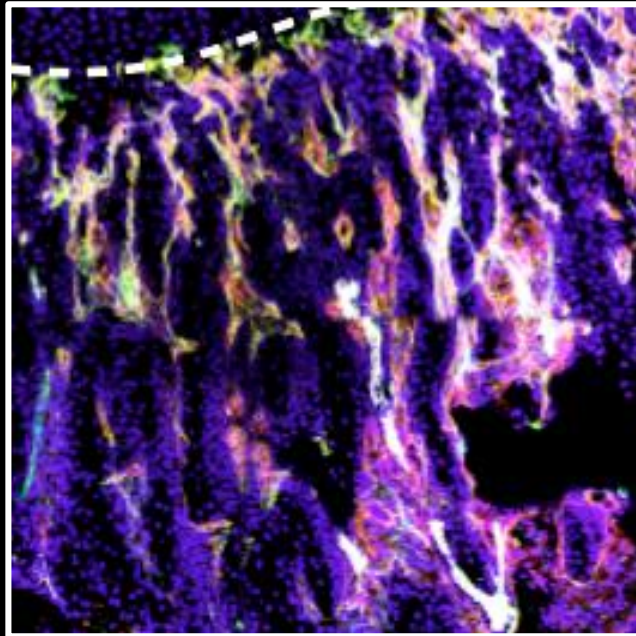
Radiation



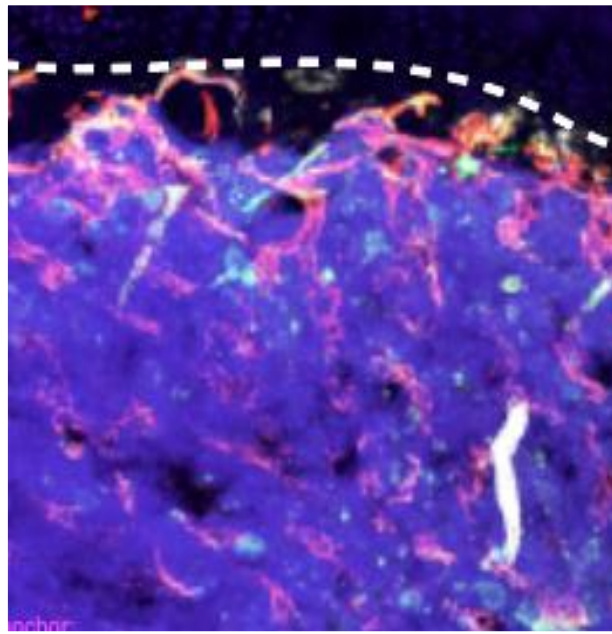
DAPI/Endomucin/ α SMA

Expansion of pericytes post-radiation in aged mice

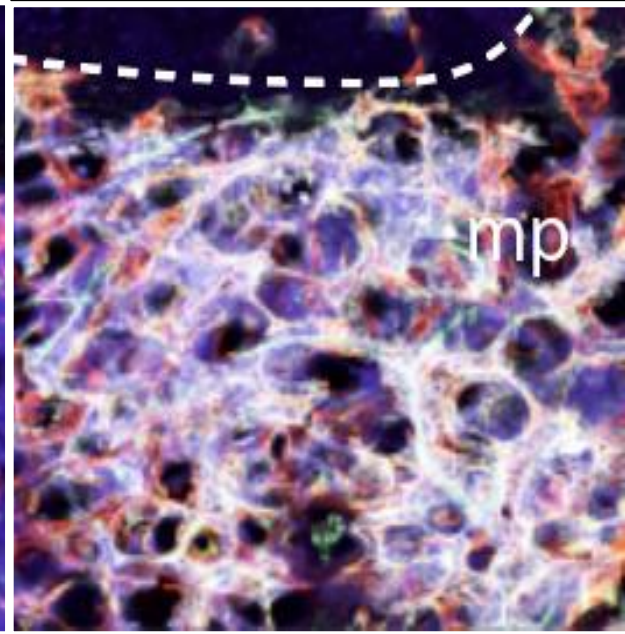
DAPI/CD31/Endomucin/PDGFR- β



Young

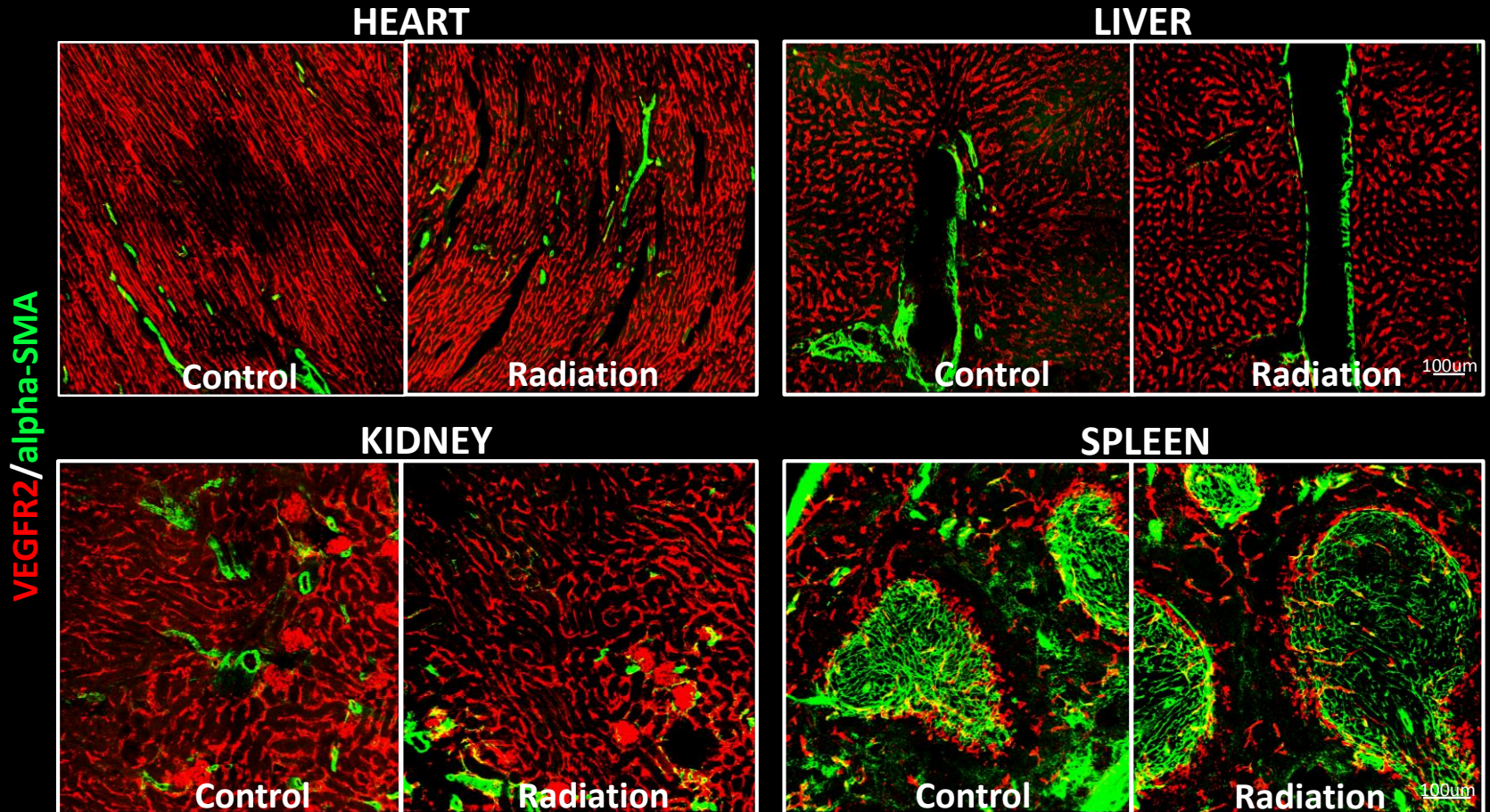


Aged



Aged
(radiation)

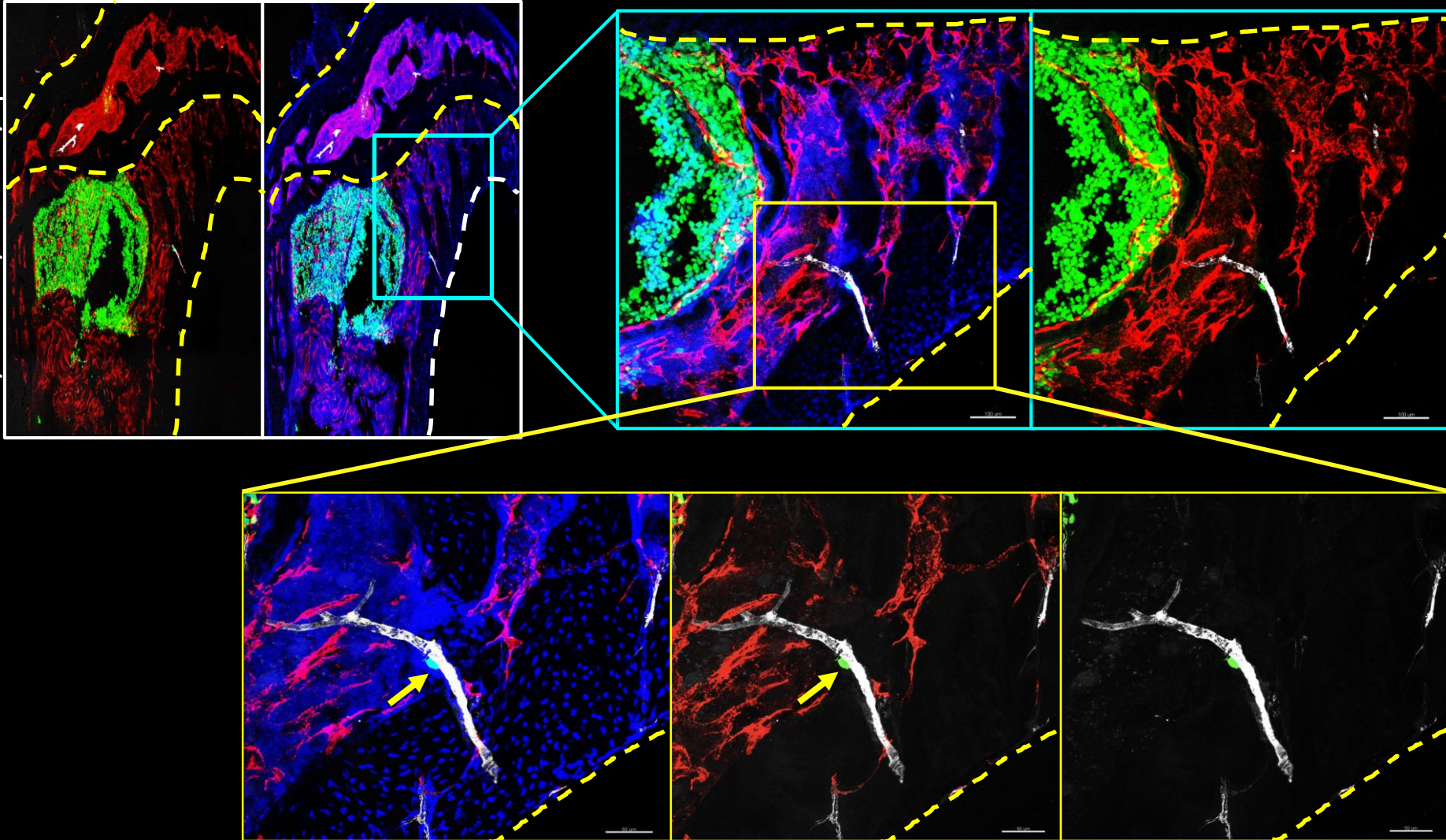
Bone provides specialized quiescent microenvironments



Expansion of pericytes in response to radiation or chemotherapy is bone-specific

Quiescent cancer cells are peri-arteriolar

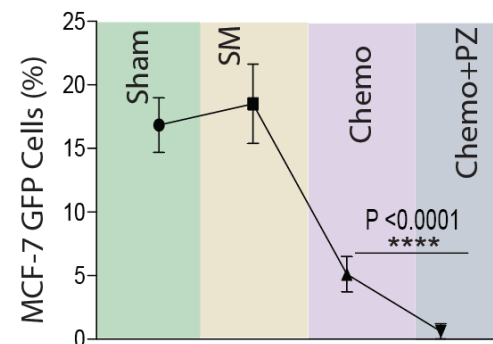
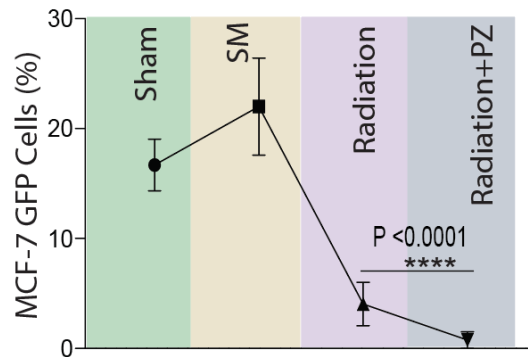
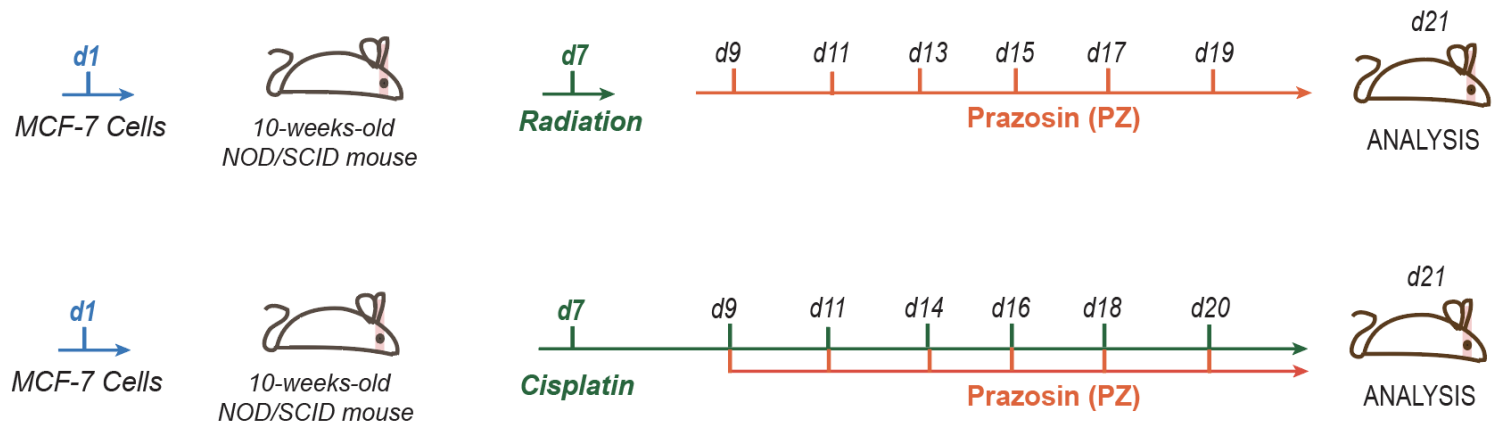
DAPI/MCF7-GFP/Endomucin/alpha-SMA



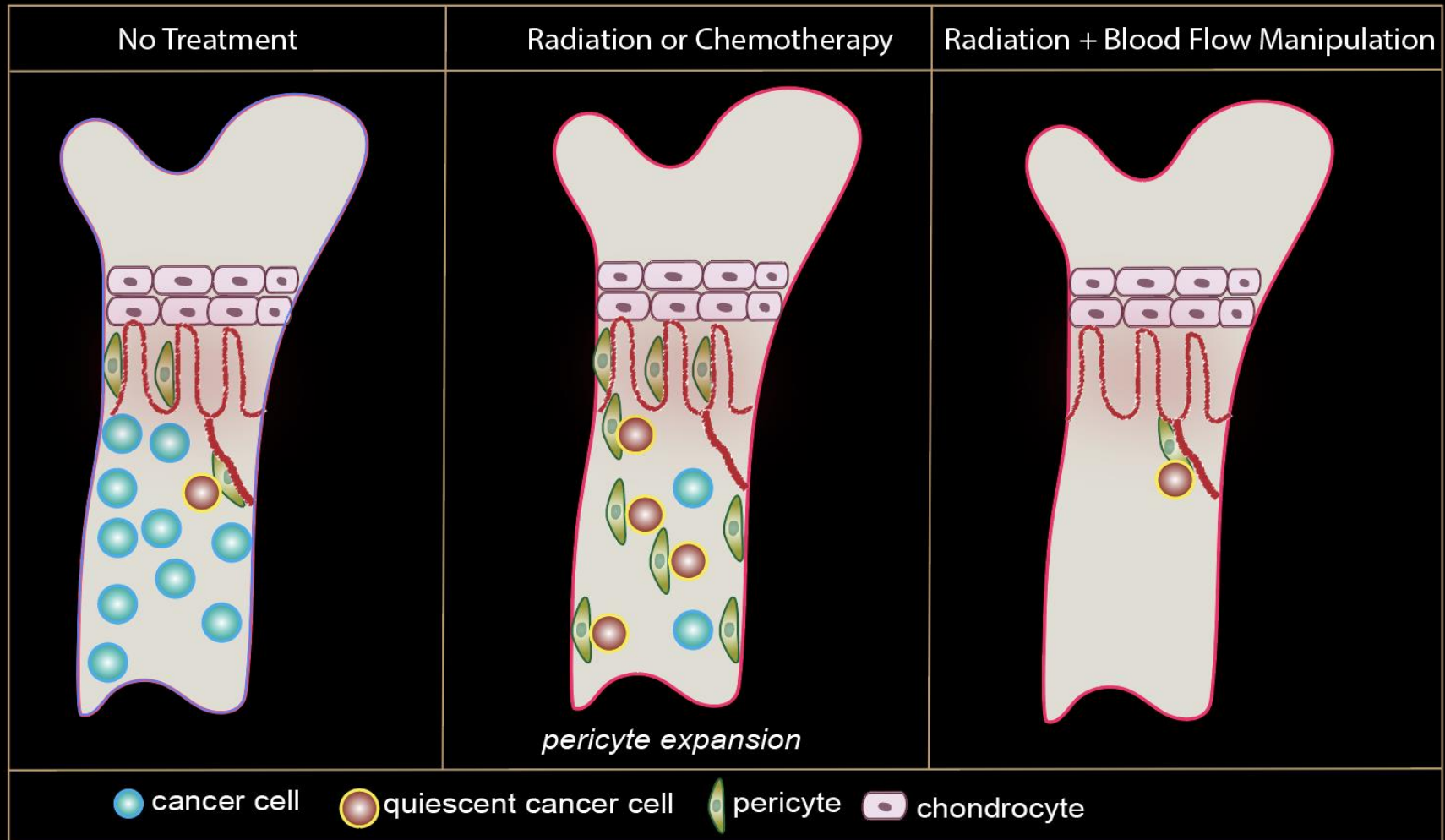
Type H Endothelial Cells



Decreasing blood flow renders cancer cells susceptible to existing therapies



Blood flow manipulation renders quiescent cells susceptible to conventional therapies



Kusumbe Lab

Amit Singh
Junyu Chen
Rossella Labella
Jessica De Angelis
Vimal Veeriah
Unnikrishnan Sivan
Luciana Lippo

THANK YOU!

PhD Studentship Available

