Discovery of the articular cartilage skeletal stem cell

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Disclosures: Bok (N), Yallowitz (N), Cong (Sustain Surgical, Kondral Tech), Niu (N), Cung (N), Xu (N), Debnath (N), McCormick (N), Sun (N), Hu (N), MBG (N)

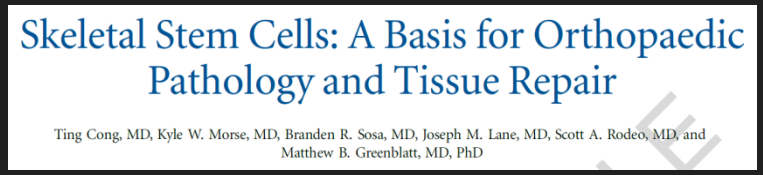
What is a Skeletal Stem Cell?

MSC

- $CD73^{+}CD90^{+}CD105^{+*}$
- Plastic-adherent
- *In vitro* trilineage differentiation

SSC

- $CD45^{-}TER119^{-}CD31^{-}THY^{-}6C3^{-}CD200^{+}CD105^{-*}$
- Homogeneity
- *In vivo* skeletal tissue generation (orthotopic transplantation)
- Apex of differentiation
- Self-renewal (serial transplantation)
- Multipotency*
- Lineage fidelity*


Skeletal Stem Cells: A Basis for Orthopaedic Pathology and Tissue Repair

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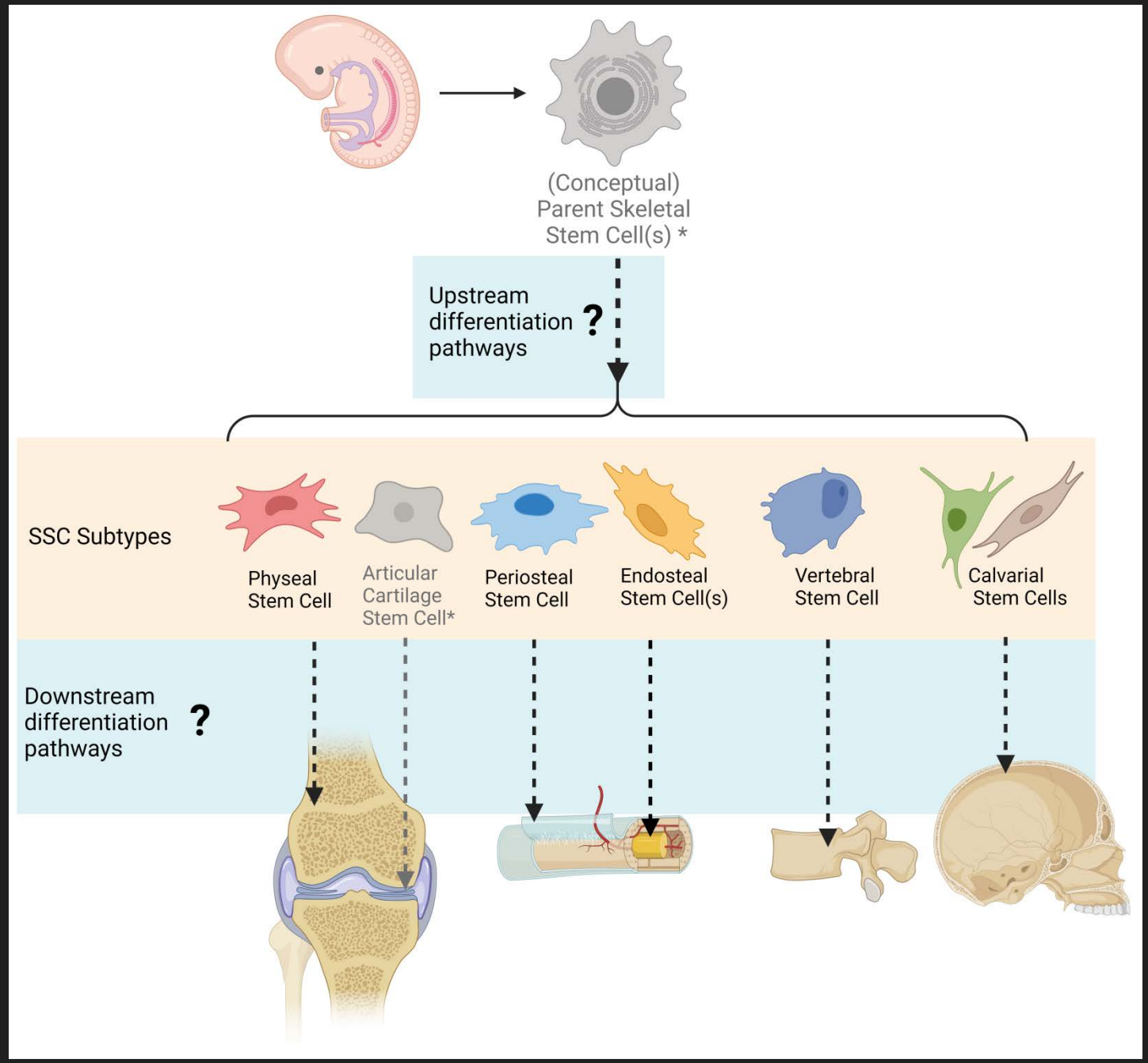
Cong, Greenblatt et al. JBJS 2024



Tissue-specific SSCs have defined anatomic functions

They generate skeletal anatomy and maintain skeletal homeostasis

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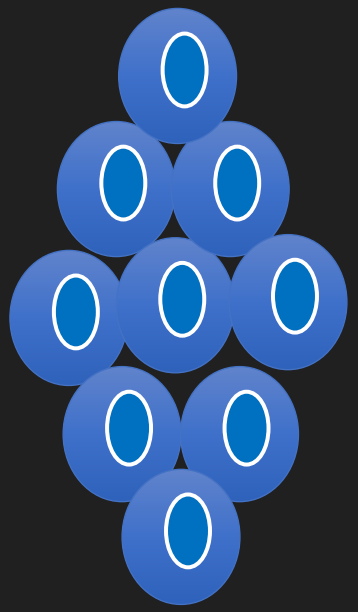
SSC subsets generate MSK tissue subsets

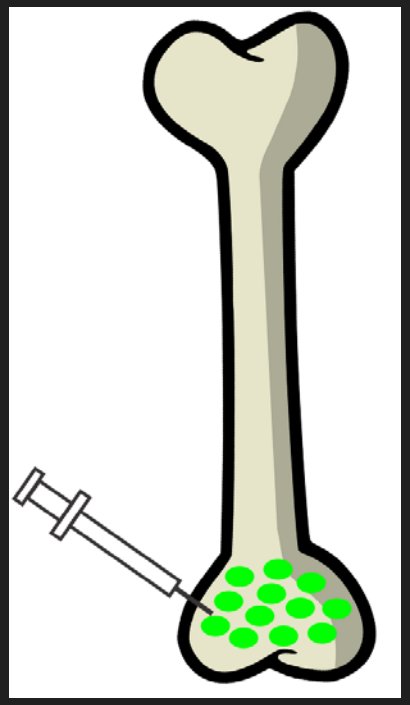
- Focus on skeletal stem cell (SSC) definition
  - Assumed that current SSC definitions (Chan Markers) harbor heterogeneous subsets
  - After screening a panel of additional markers, selected CD24 and CD29
    - Highly upregulated in endochondral ossification

Greenblatt et al., 2023 preprint PMID 36747839

Assaying CD24+ and CD29+ SSC multipotency *in vivo*



Isolate SSC CD24/CD29 subsets (Lin-THY-6C3-CD200+CD105-) by FACS



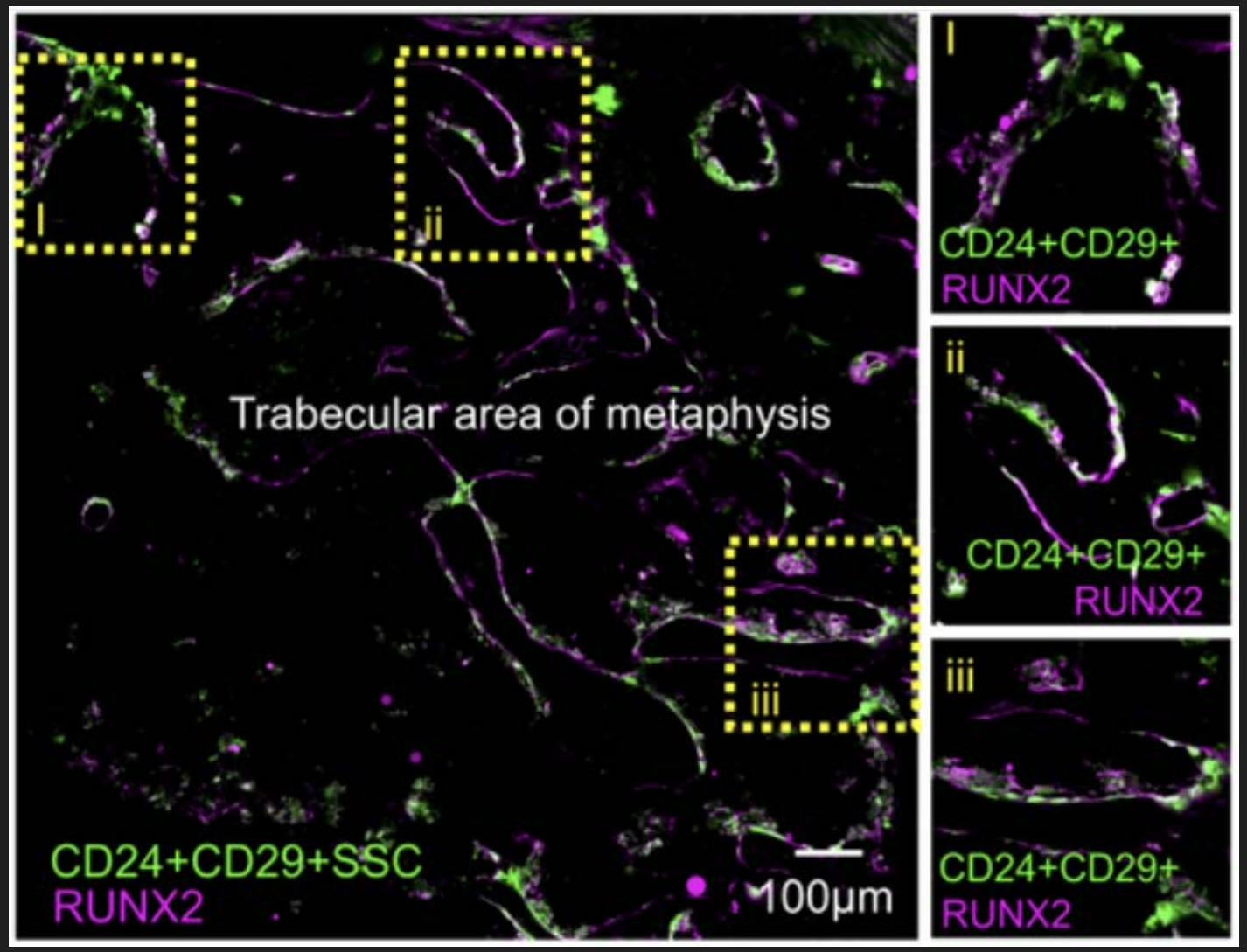
Orthotopic femoral transplantation

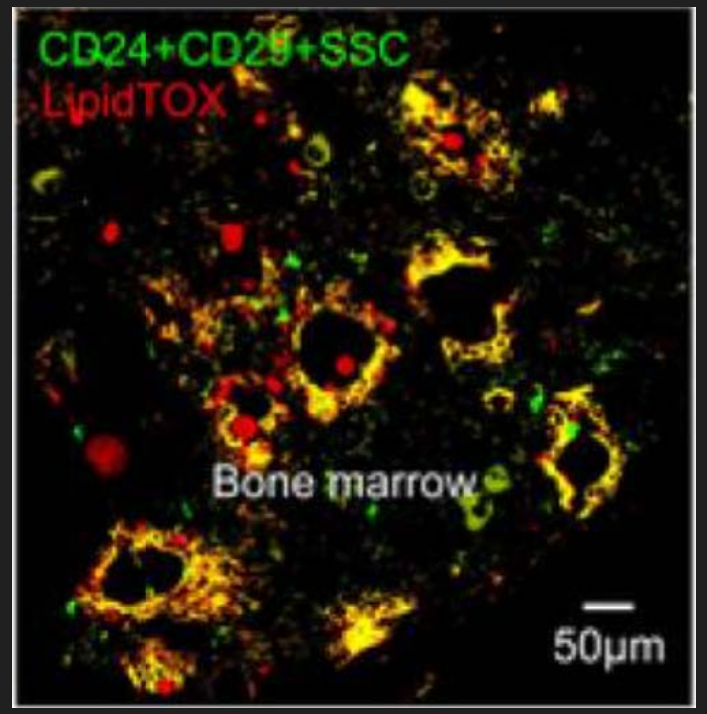
12 wks

Find cells + measure differentiation capacity

- Transplant 10-30k cells: retrograde injection into femoral shaft

In vivo tissue generation capacity of CD24+CD29+ SSCs





CD24+CD29+ SSCs repopulate osteoblasts and adipocytes in marrow

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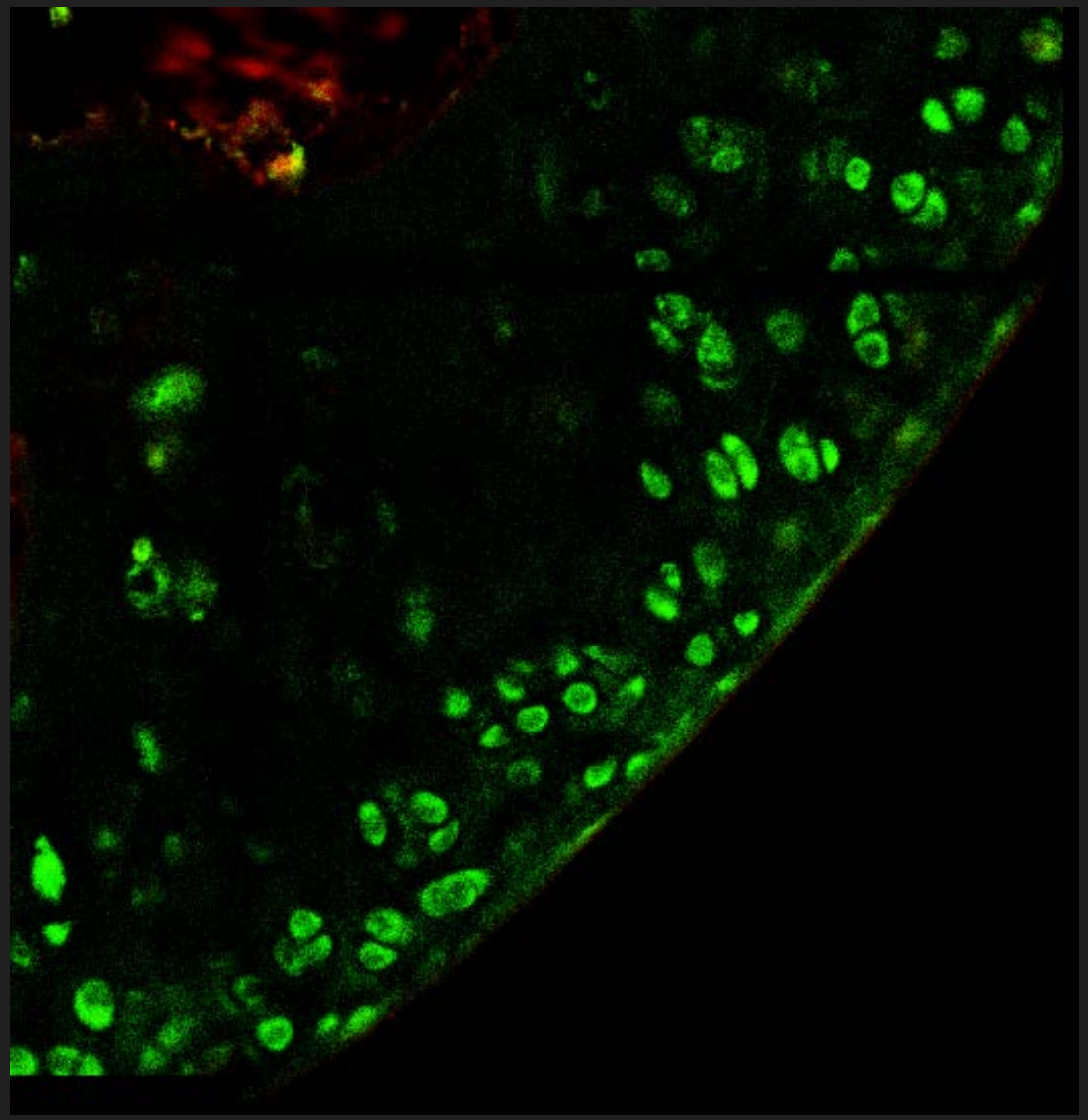
A surprising result: CD24+CD29+SSCs also repopulate articular cartilage

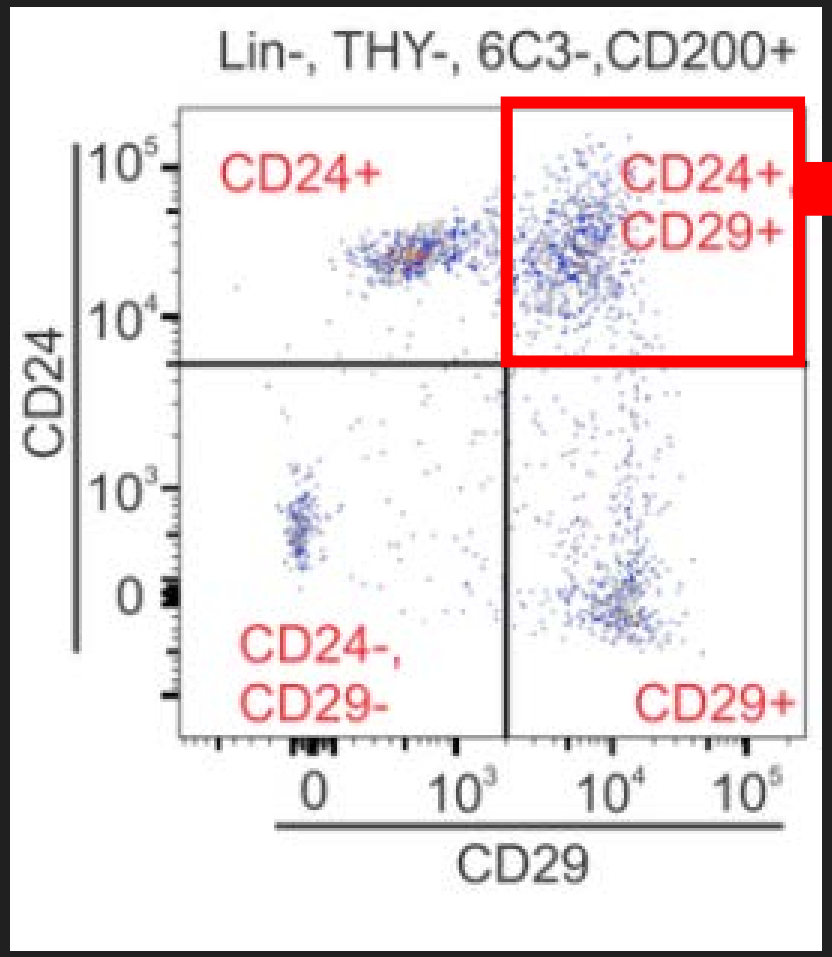


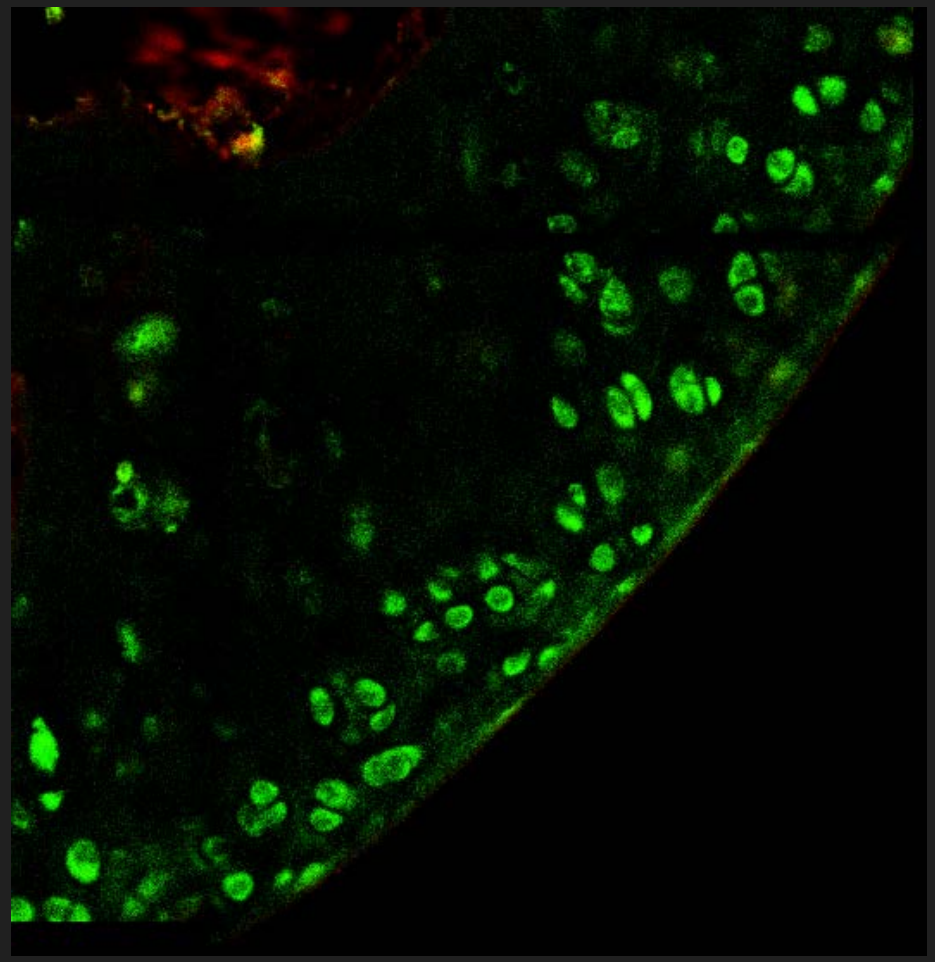
acSSCs also reconstitute articular cartilage when transplanted into secondary hosts!

So: CD24+CD29+ SSCs may represent the articular cartilage skeletal stem cell (acSSC).

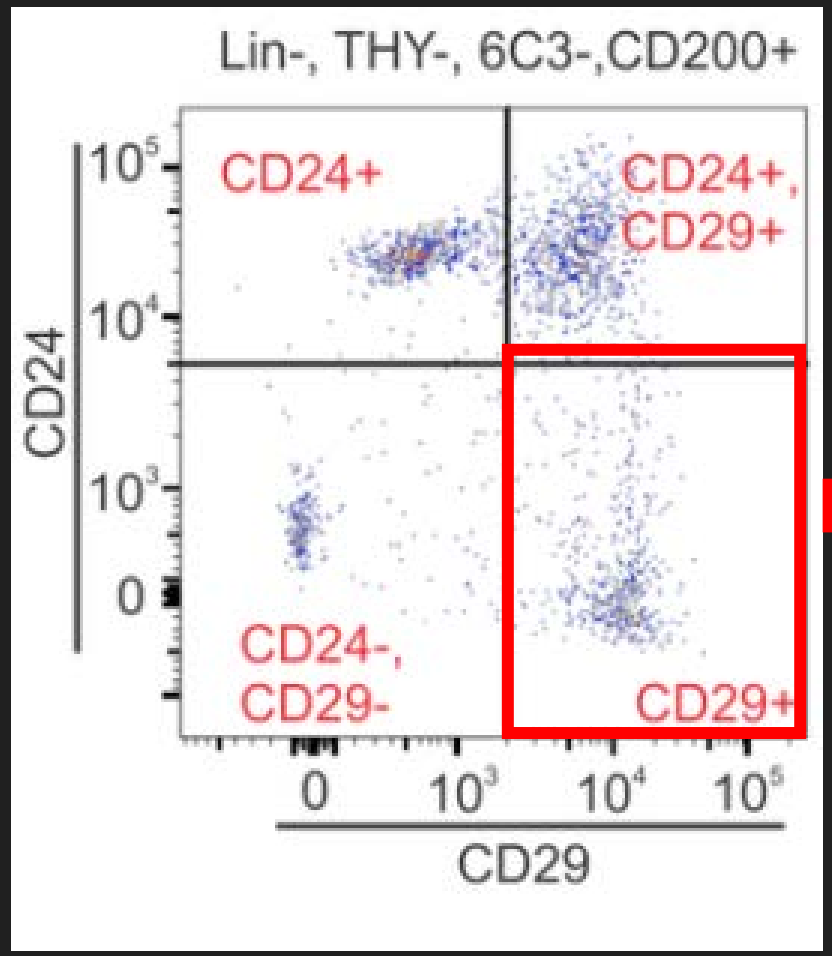
- What are the key points of lineage commitment along its differentiation path?
- Why don’t these cells regenerate injured cartilage in adults?

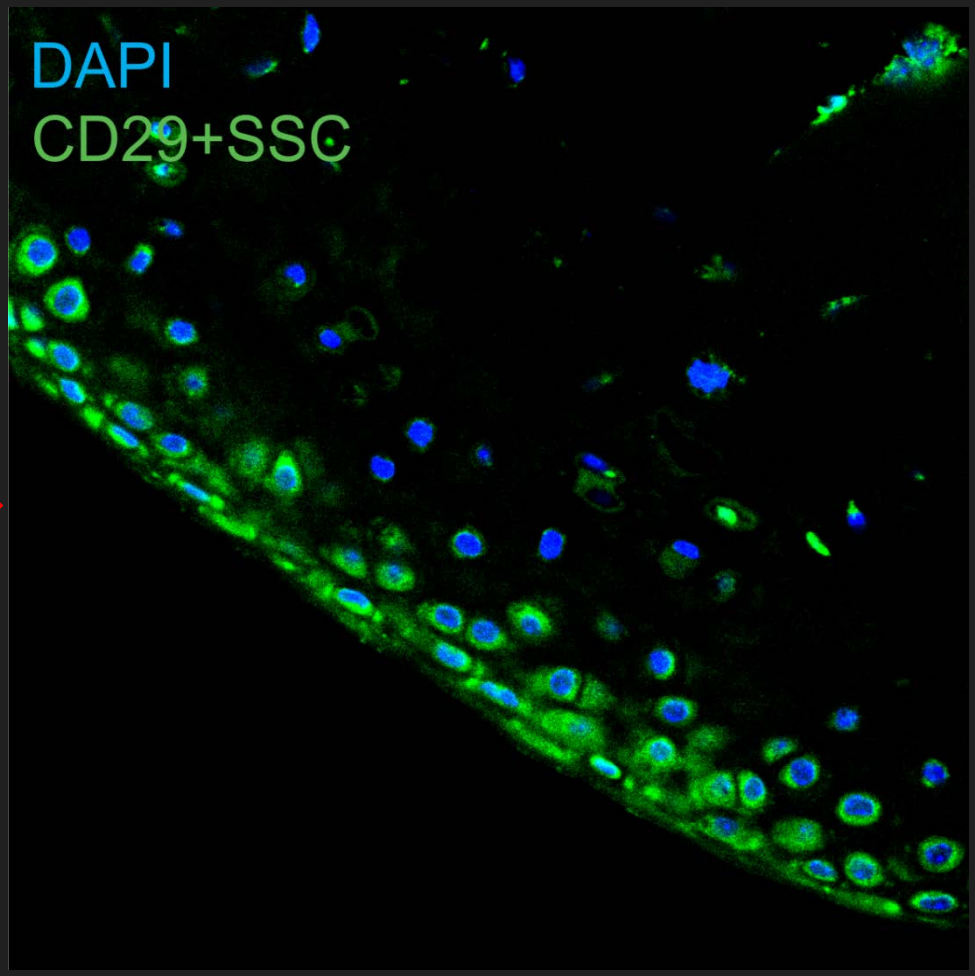
Where do CD24+CD29+SSCs (acSSCs) diverge from other skeletal lineages?



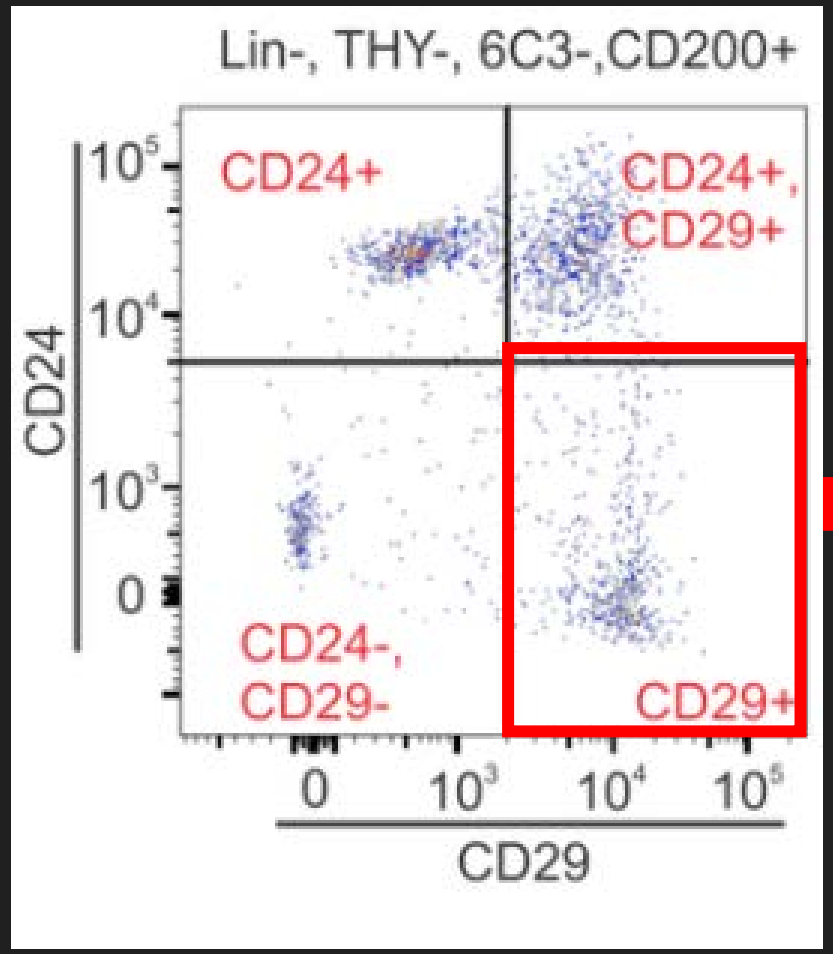


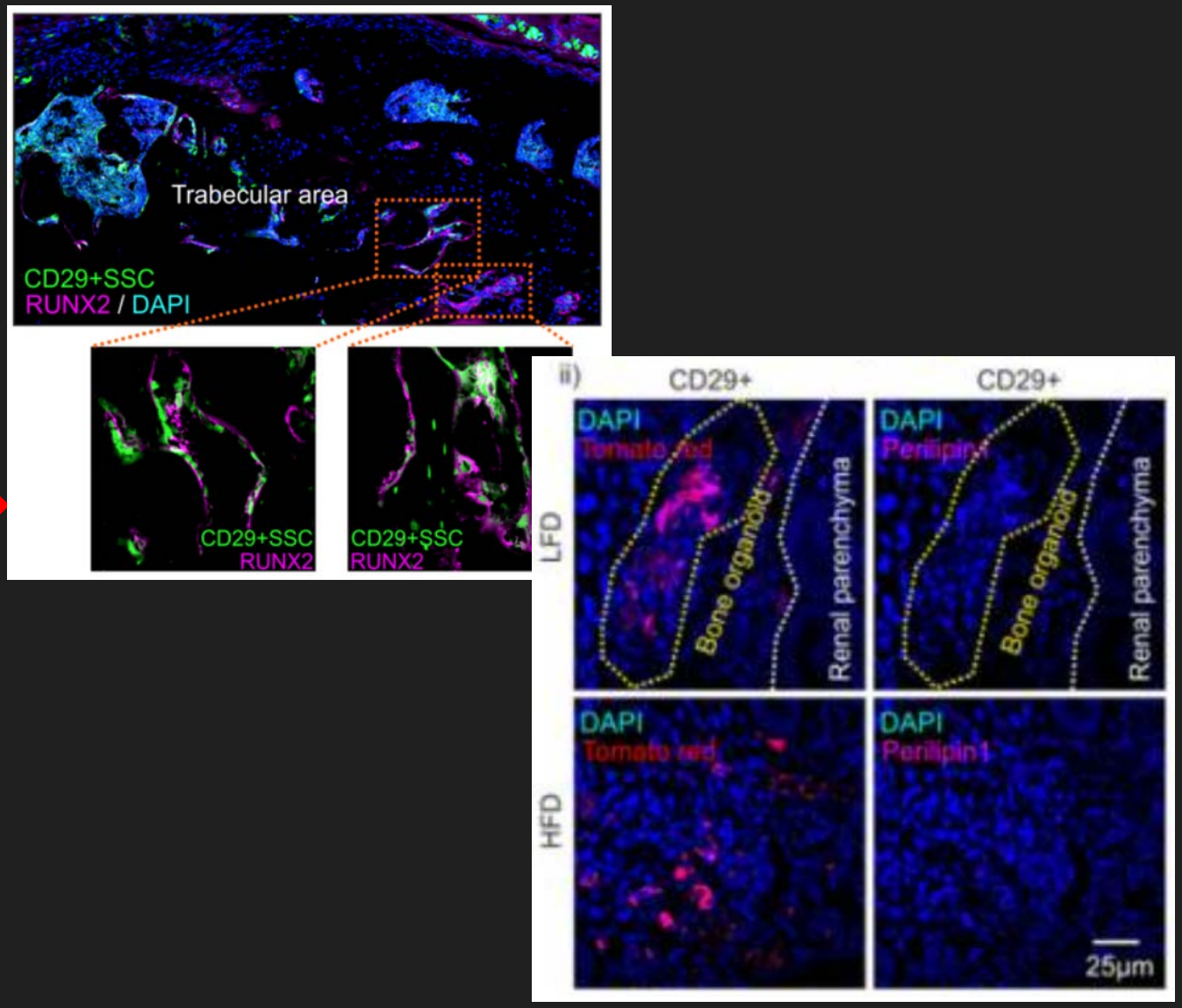
CD29+ progenitors also form articular chondrocytes



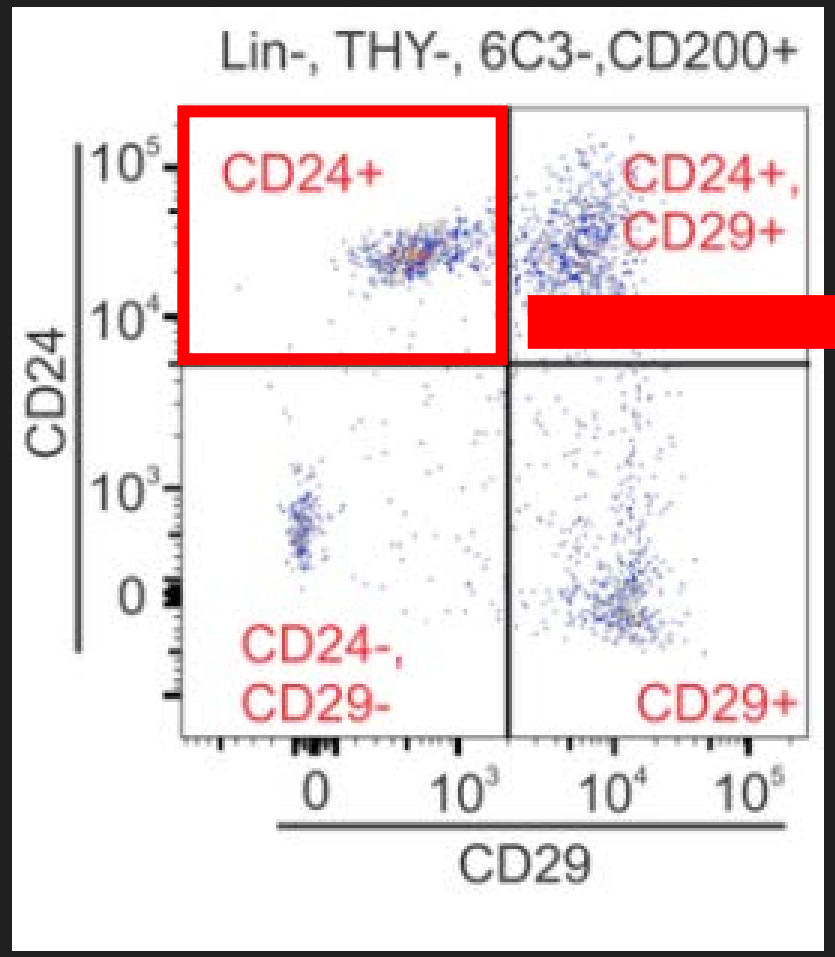


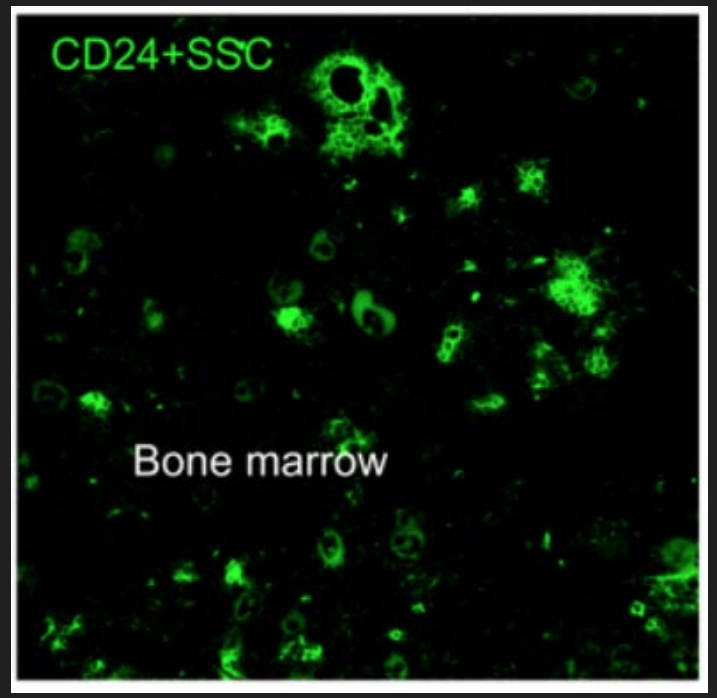
CD29+ progenitors form osteoblasts but not adipocytes

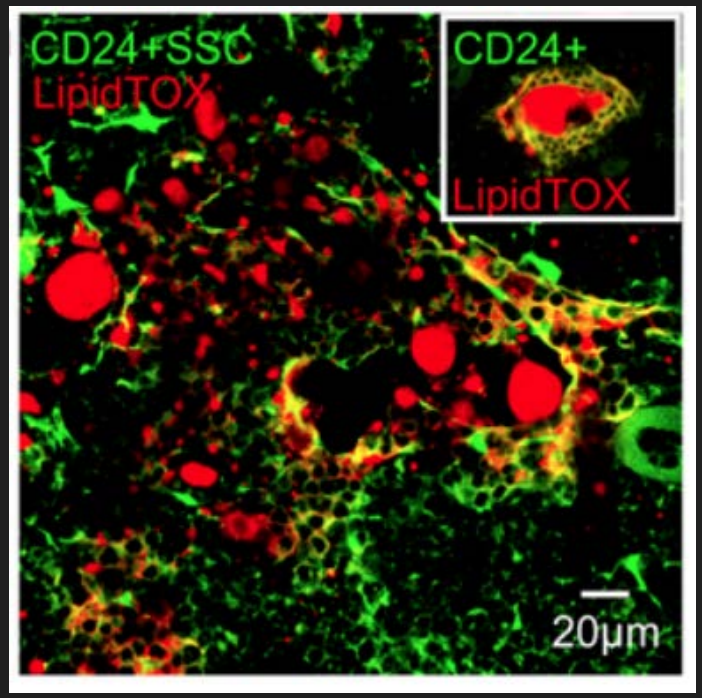




CD24+ progenitors only form adipocytes







Working model of articular cartilage differentiation sequence