

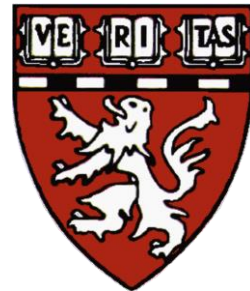
The Role of the Various Monocyte Types in Athero- thrombotic Disease

Protective vs. Detrimental Effects and Therapeutic Implications

Matthias Nahrendorf

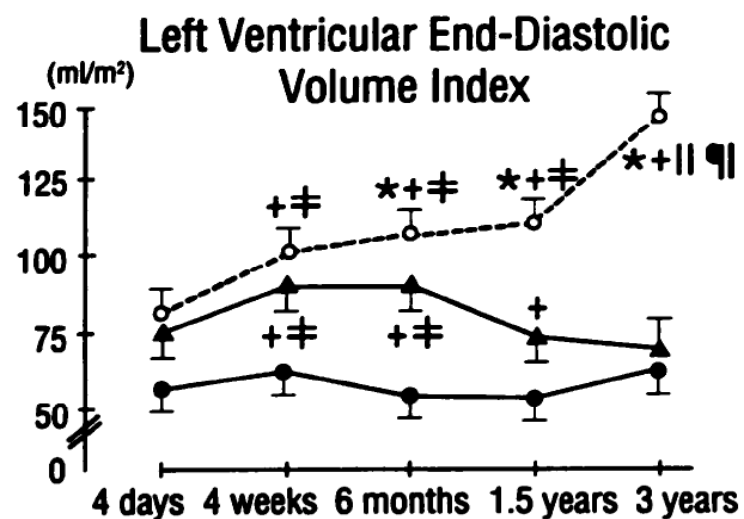
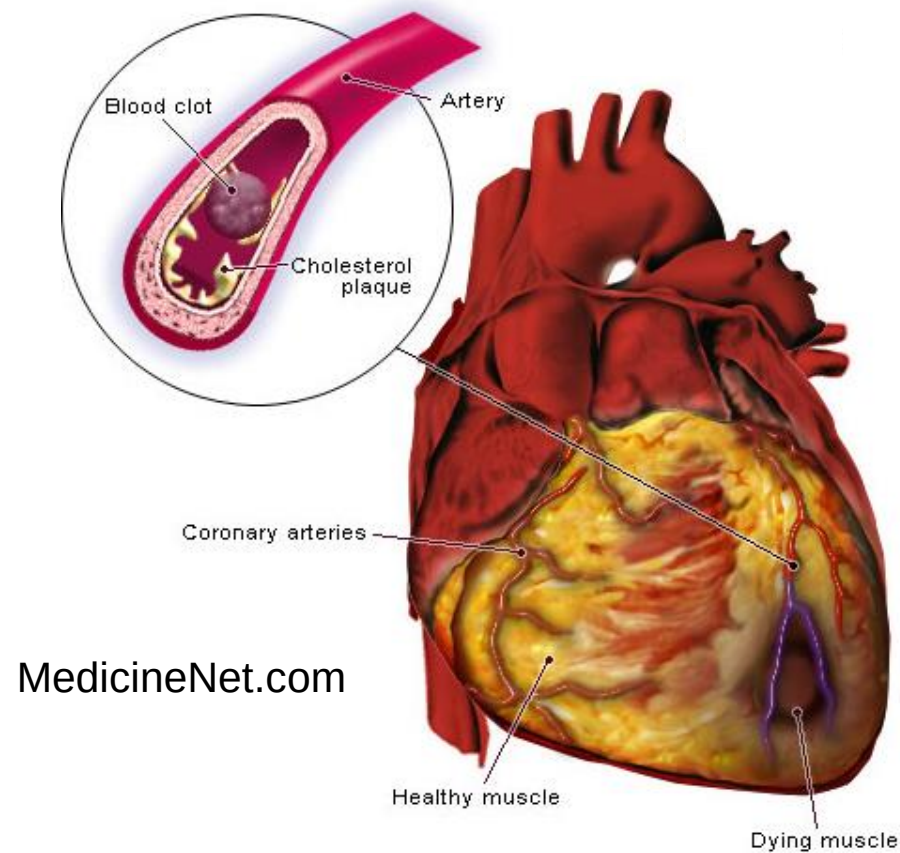
MGH Center for Systems Biology

http://csb.mgh.harvard.edu/investigator/matthias_nahrendorf



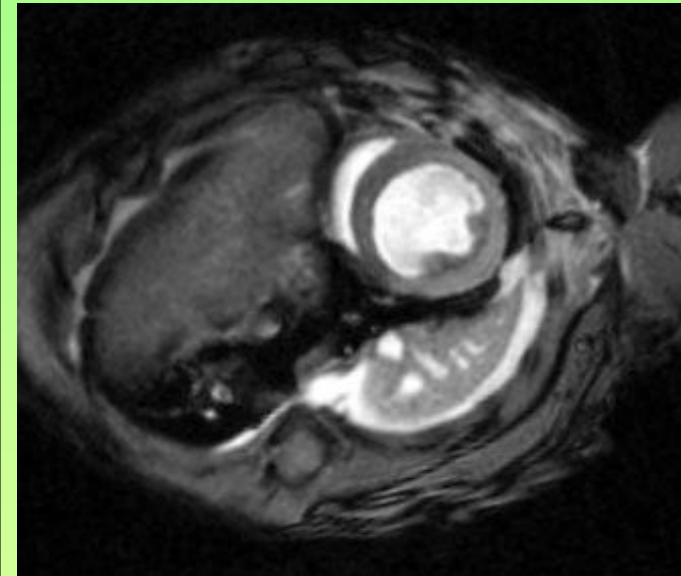
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Healing following myocardial infarction matters



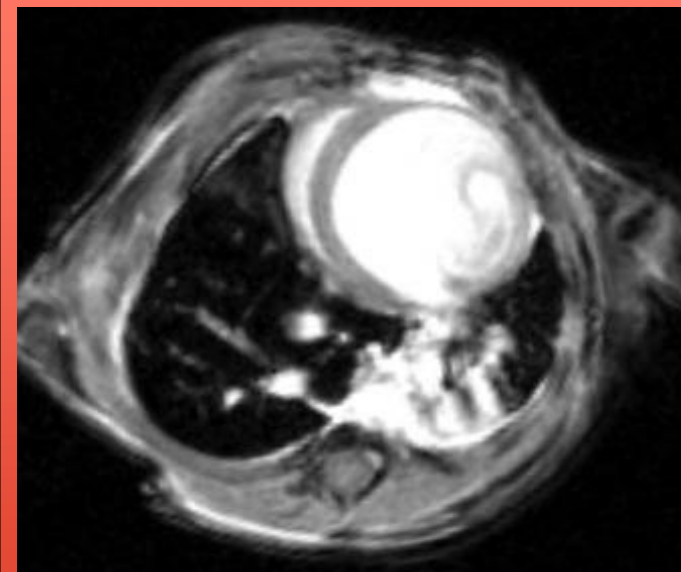
Circulation. 1993 Mar;87(3):755-63

Good healing



Good prognosis

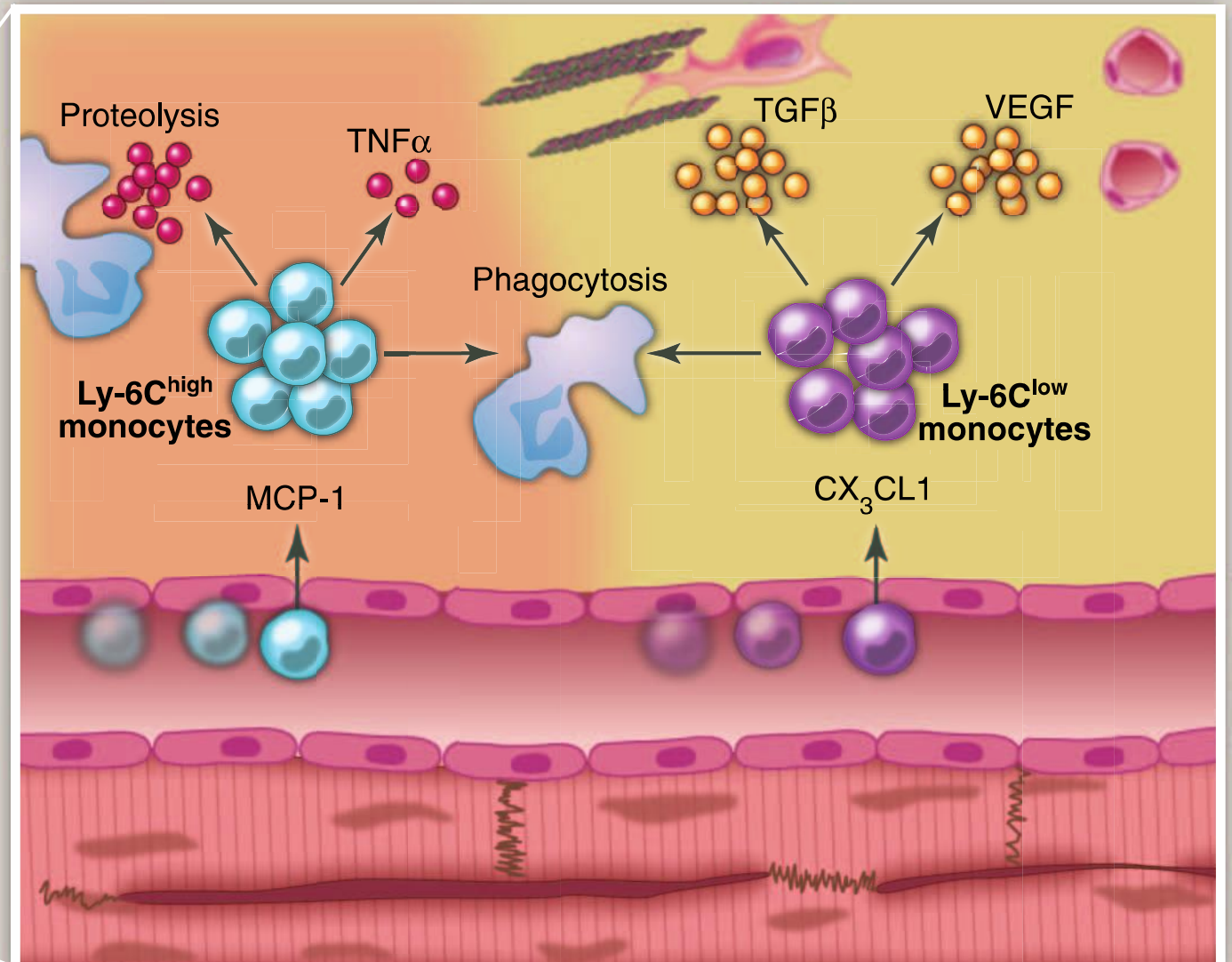
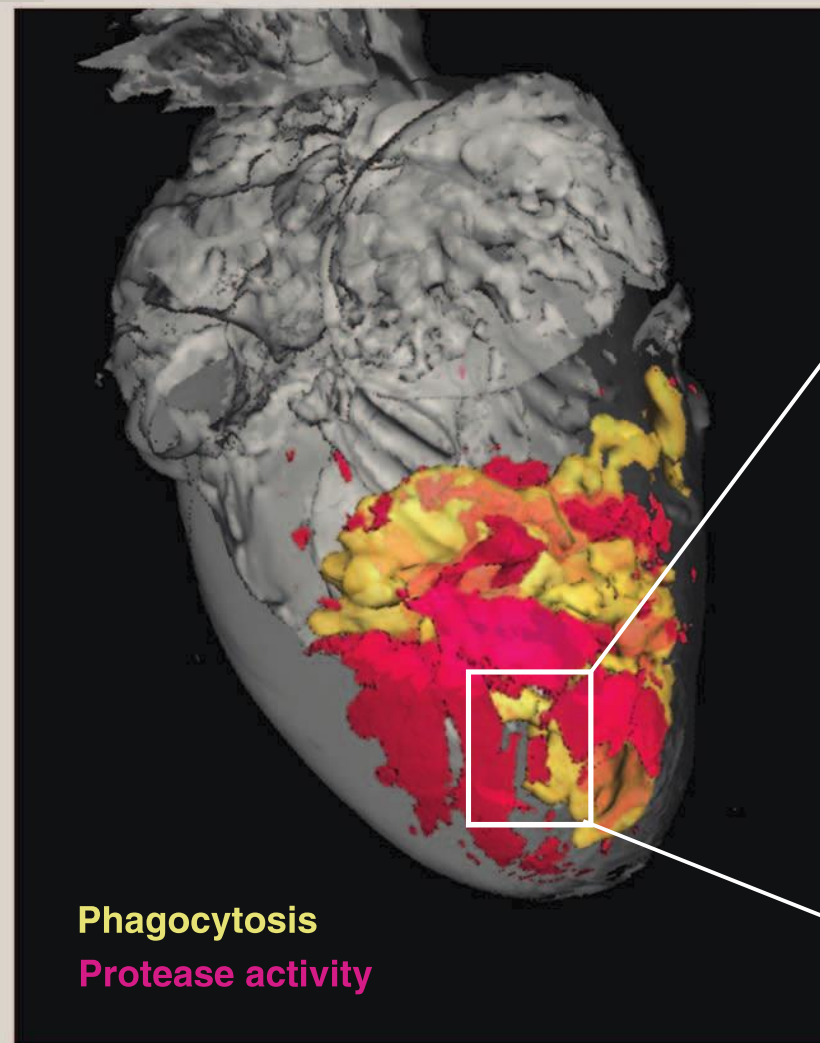
Bad healing



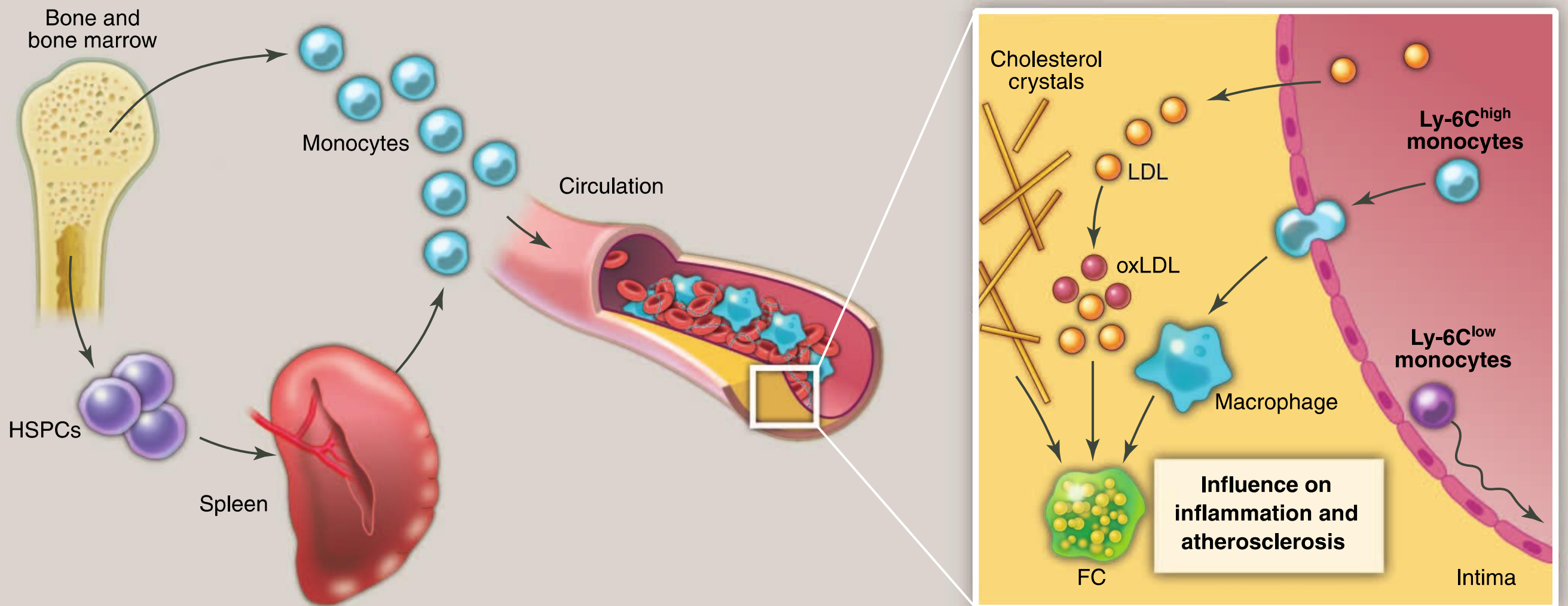
50% chance of death in next

year

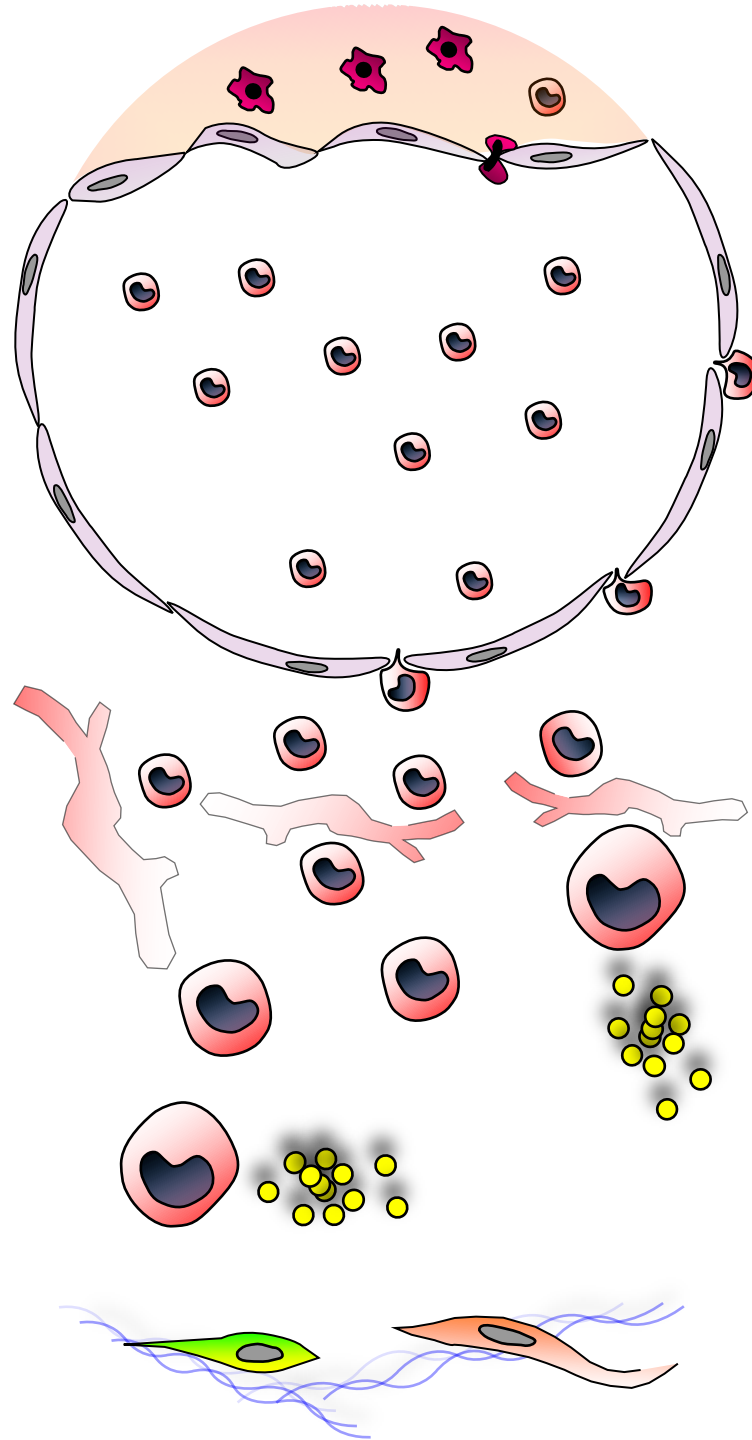
Monocyte/macrophage heterogeneity in myocardial infarction



Monocytes/macrophages in atherosclerosis



Atherosclerosis



Blood monocytes

Recruitment ↑
Ly-6C^{hi}

Inflammatory
cyto/chemokines ↑
(e.g. MPO, TNF-α)

Protease activity ↑
(e.g. MMPs,
cathepsins)

Resolution of
inflammation ↓
(e.g. reduced TGF-β)

Collagen
synthesis ↓

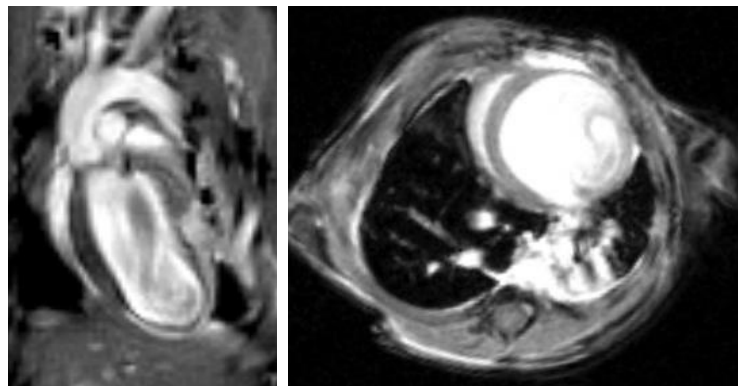
Infarct expansion ↑

LV dilation ↑

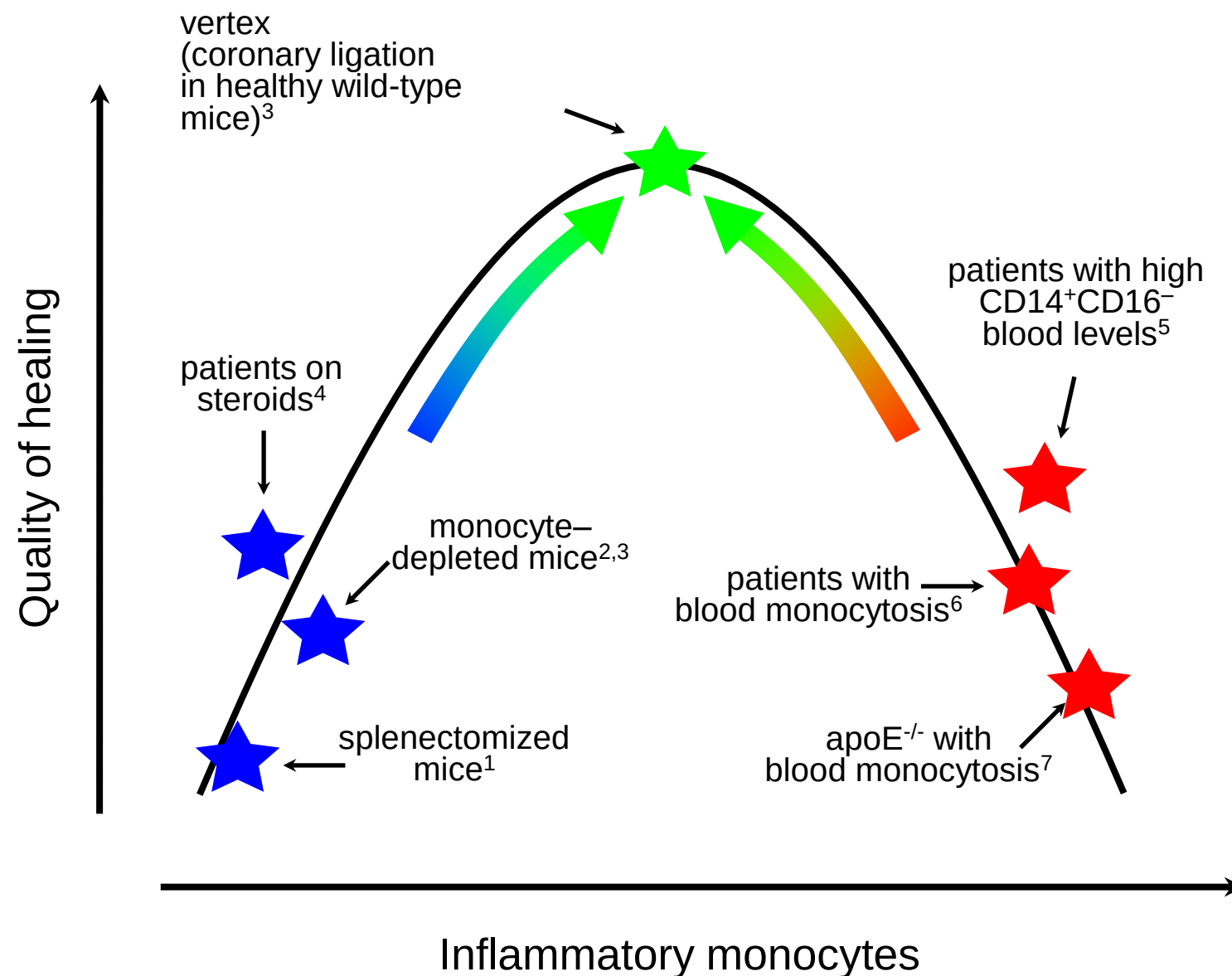
EF ↓

Heart Failure

Impaired infarct healing after plaque rupture



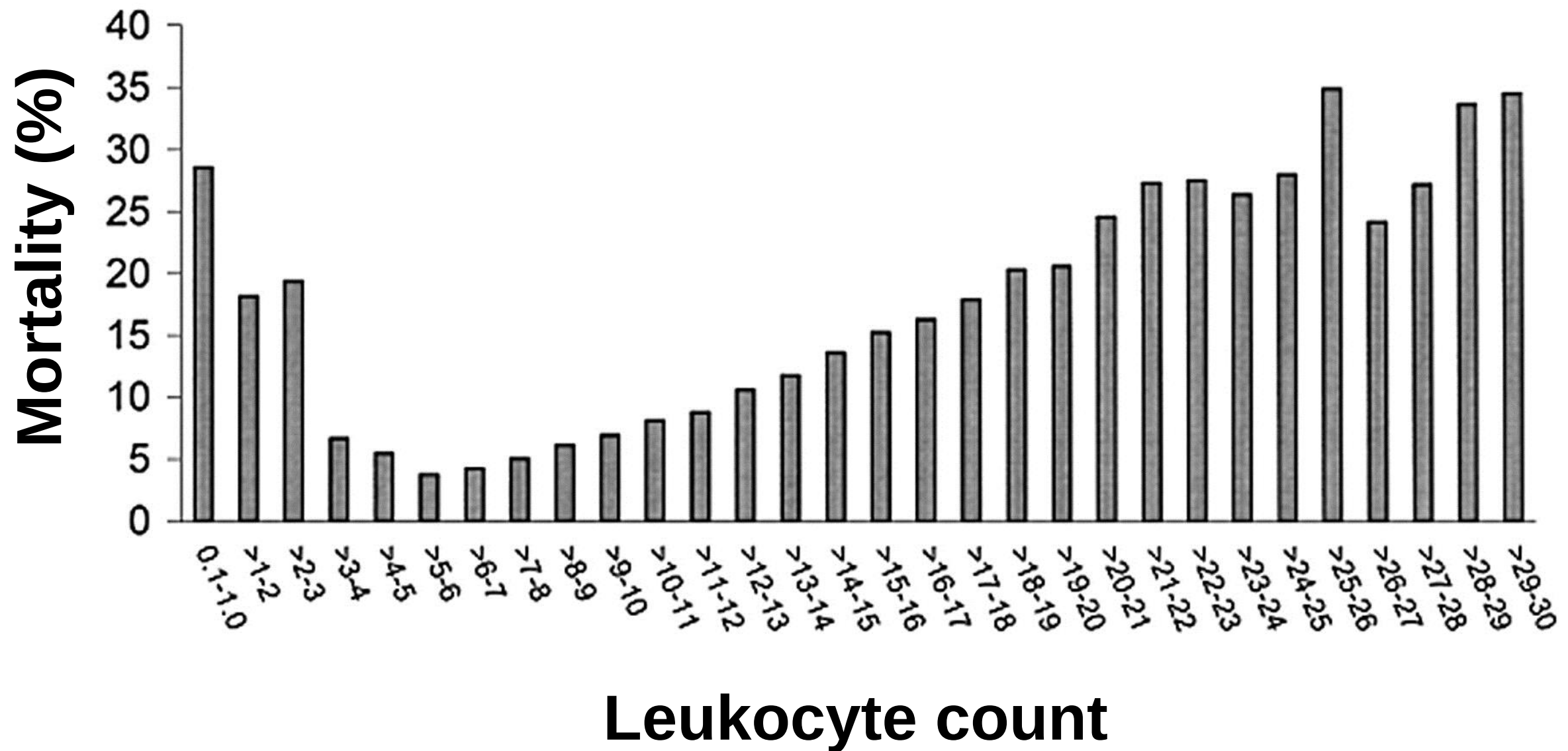
Is there a window of therapeutic opportunity to intervene on inflammation post MI?



1. Swirski & Nahrendorf, Science 2009
2. van Amerongen, Am J Pathol 2007
3. Nahrendorf & Swirski, JEM 2009

4. Roberts, Circulation 1976
5. Tsujioka, JACC 2009
6. Maekawa, JACC 2002
7. Panizzi, JACC 2009

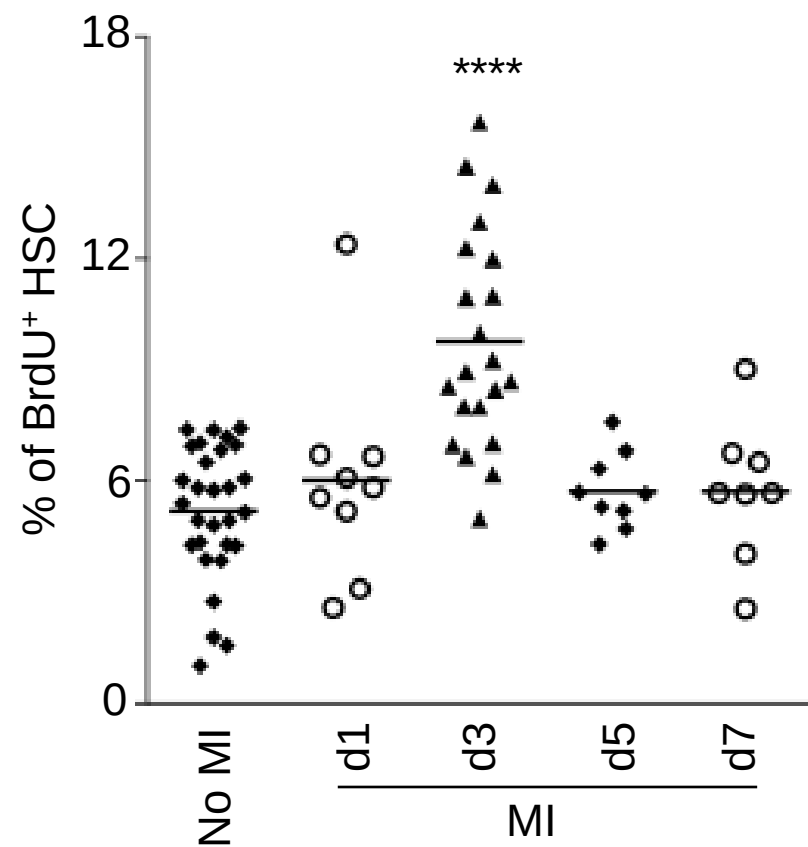
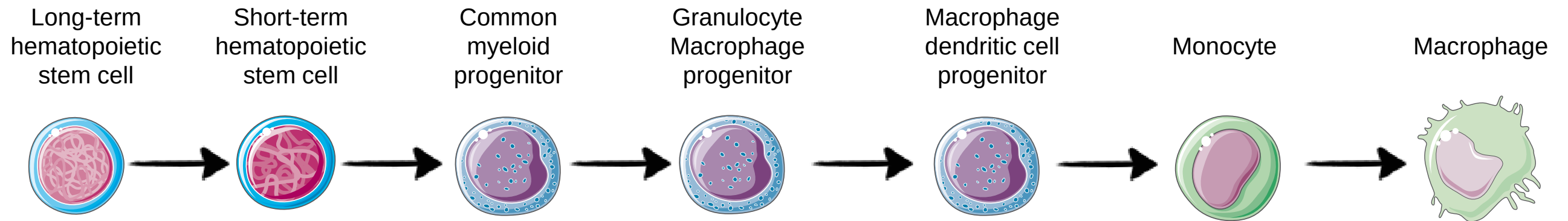
White blood cell count associates with in-hospital mortality in infarct patients (n = 115,000)



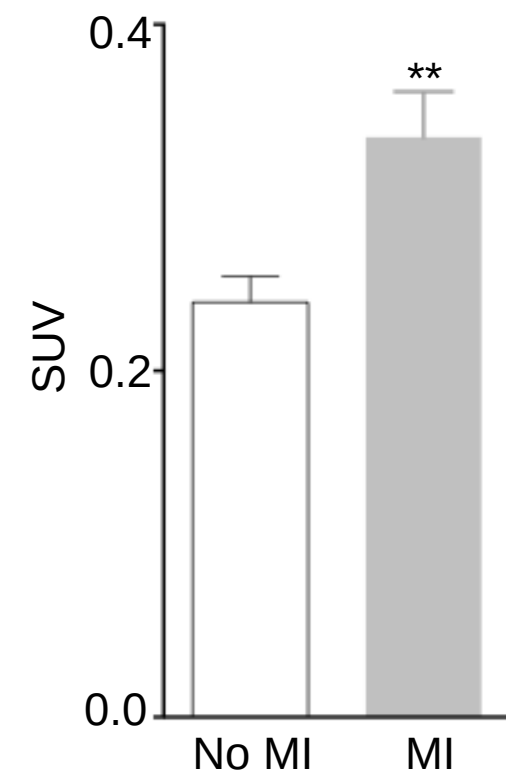
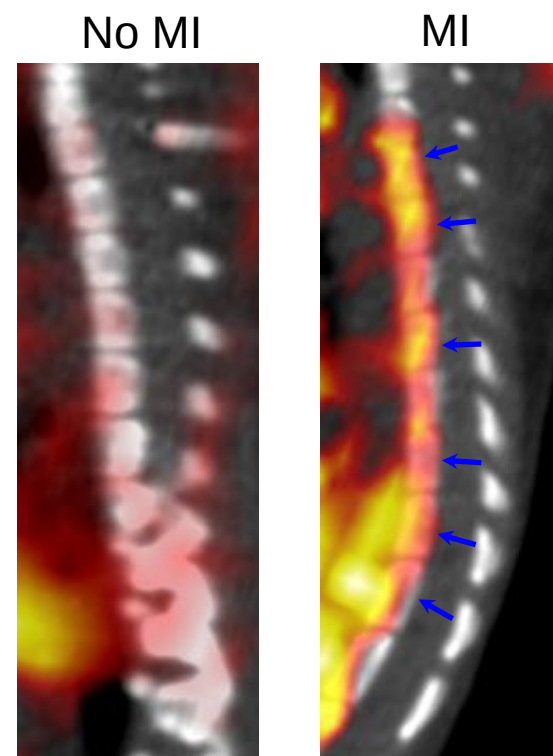
Bone marrow

Blood
Spleen

Destination
tissue



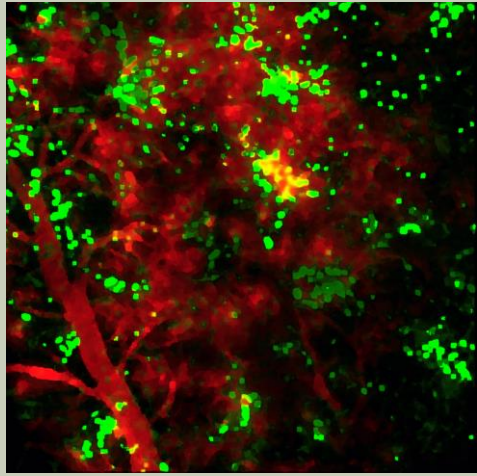
FACS Bone Marrow



¹⁸F-FLT PET

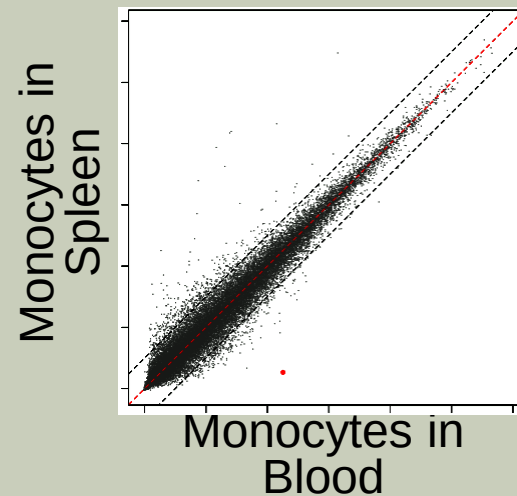
The spleen is a reservoir for monocytes after MI

Organization



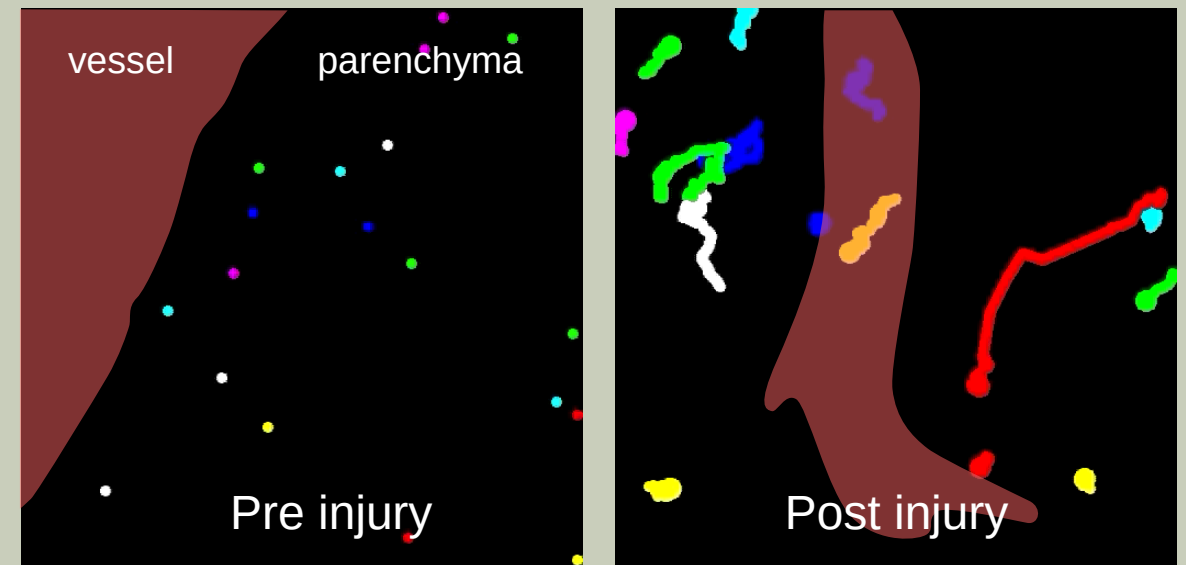
splenic monocytes cluster in the subcapsular red pulp

Expression profile



splenic monocytes resemble blood monocytes (99.998%)

Behavioral activity



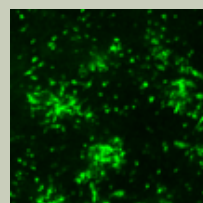
Inflammation mobilizes monocytes in vivo

Release

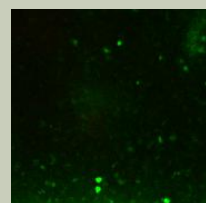


Ang II triggers release of monocytes into peripheral blood

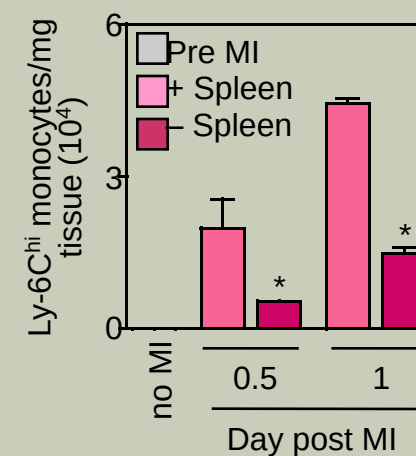
Before



After



Relocation



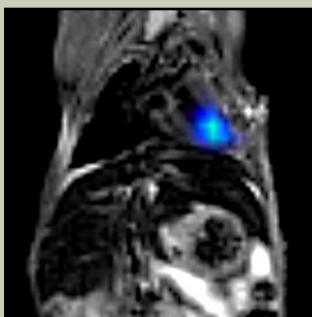
The spleen contributes monocytes in infarct

Consequence

+ Spleen

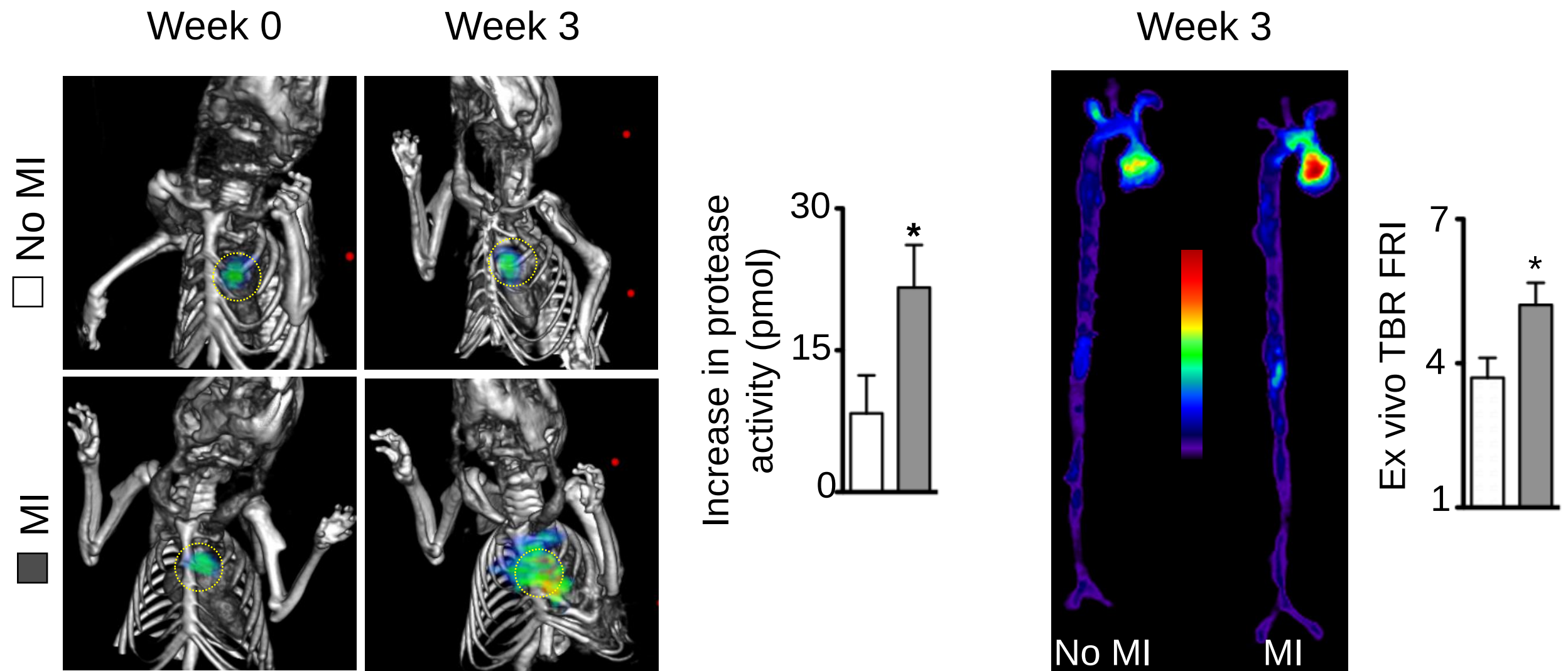


- Spleen

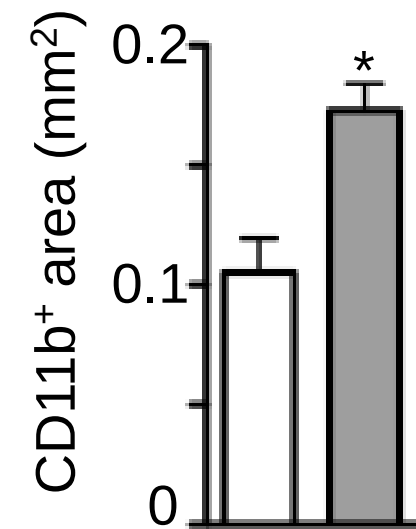
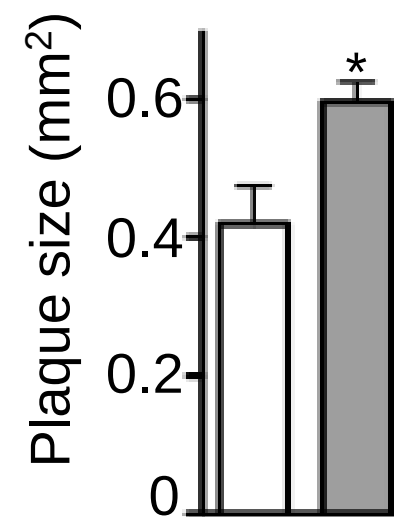
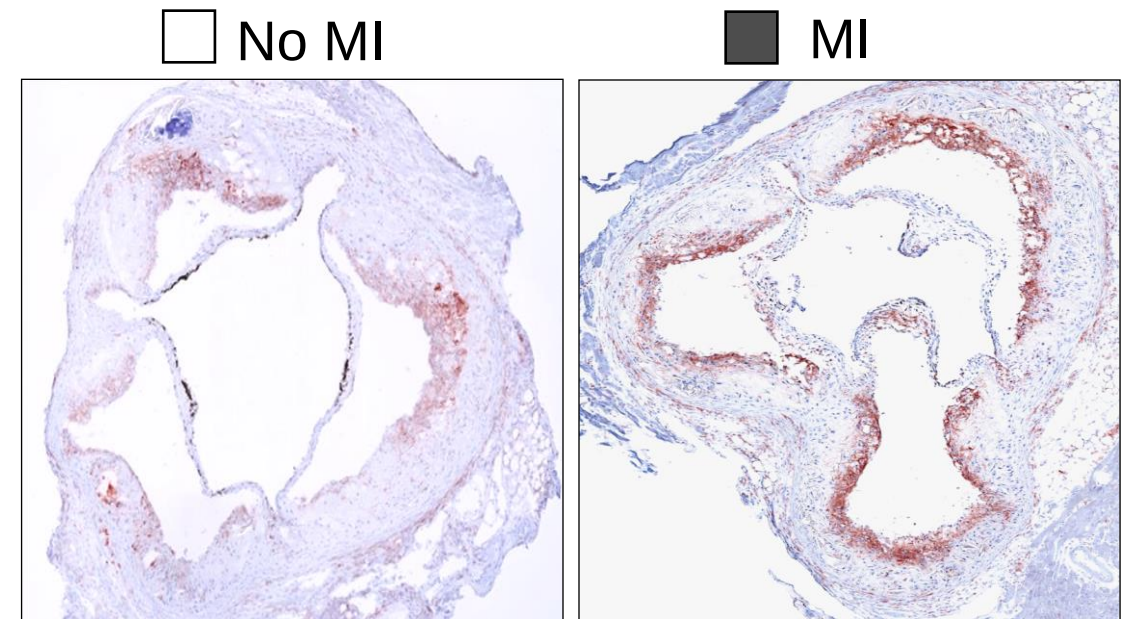
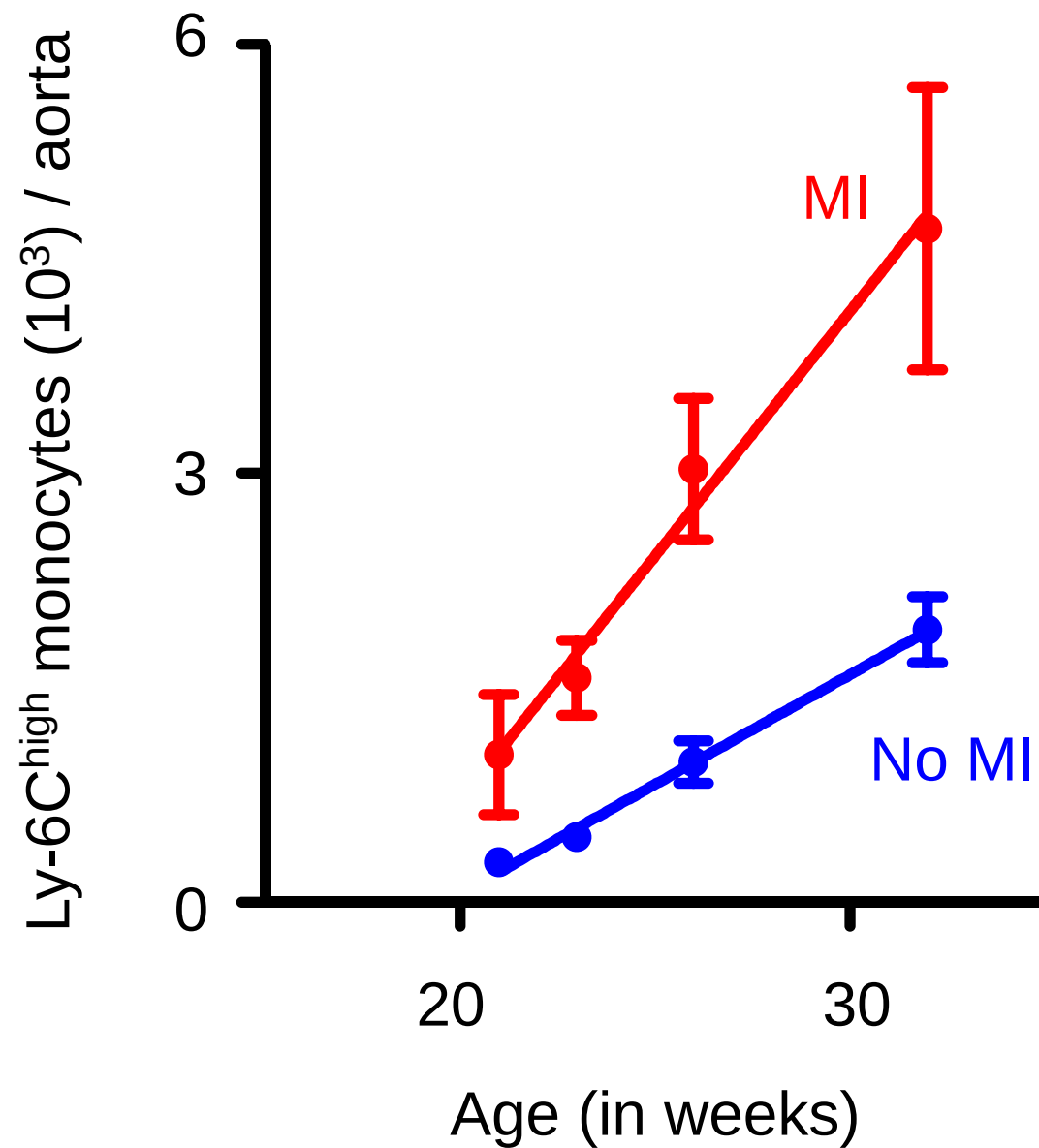


Released splenic monocytes participate in inflammation

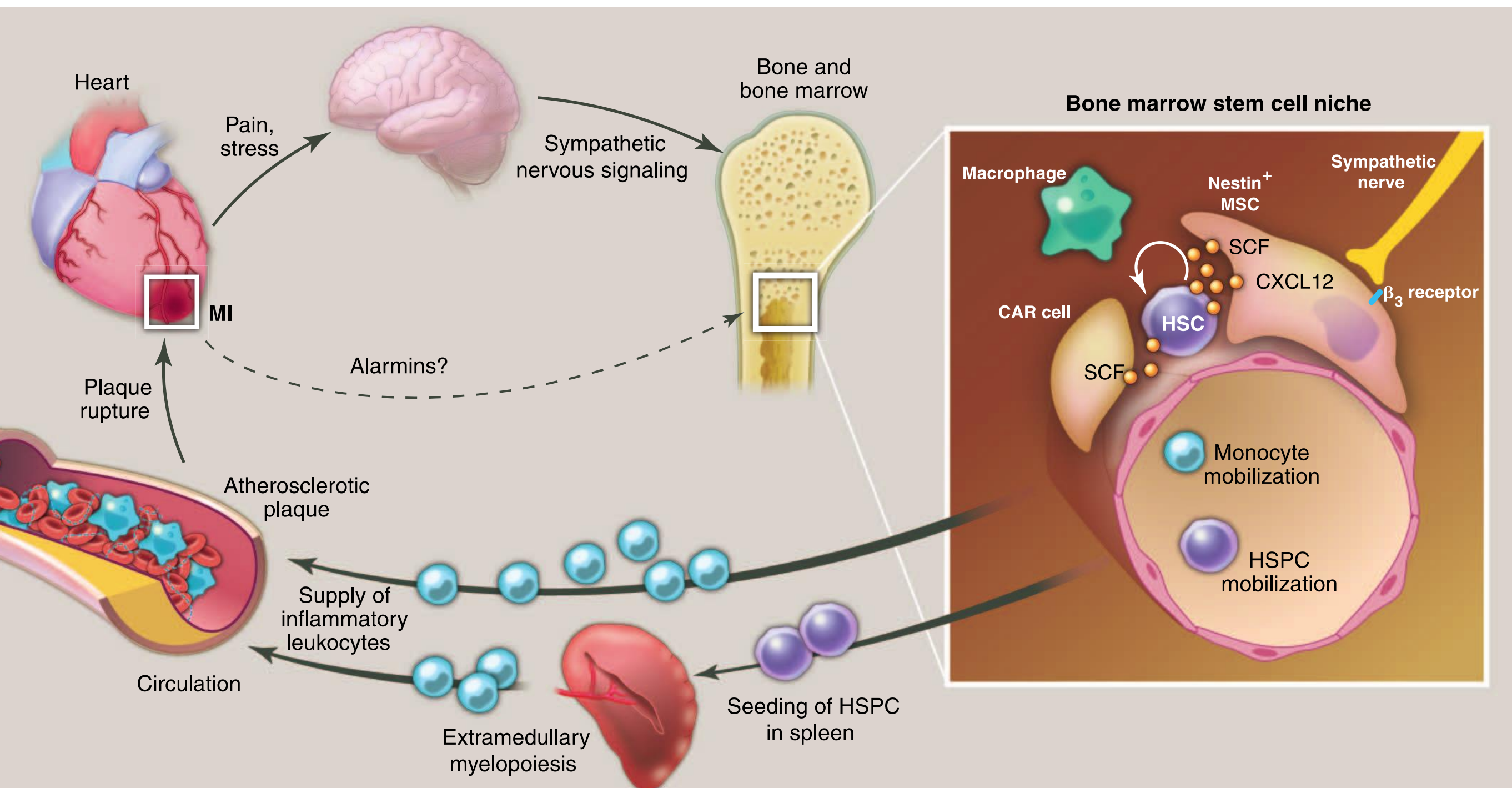
MI enhances protease activity in plaque



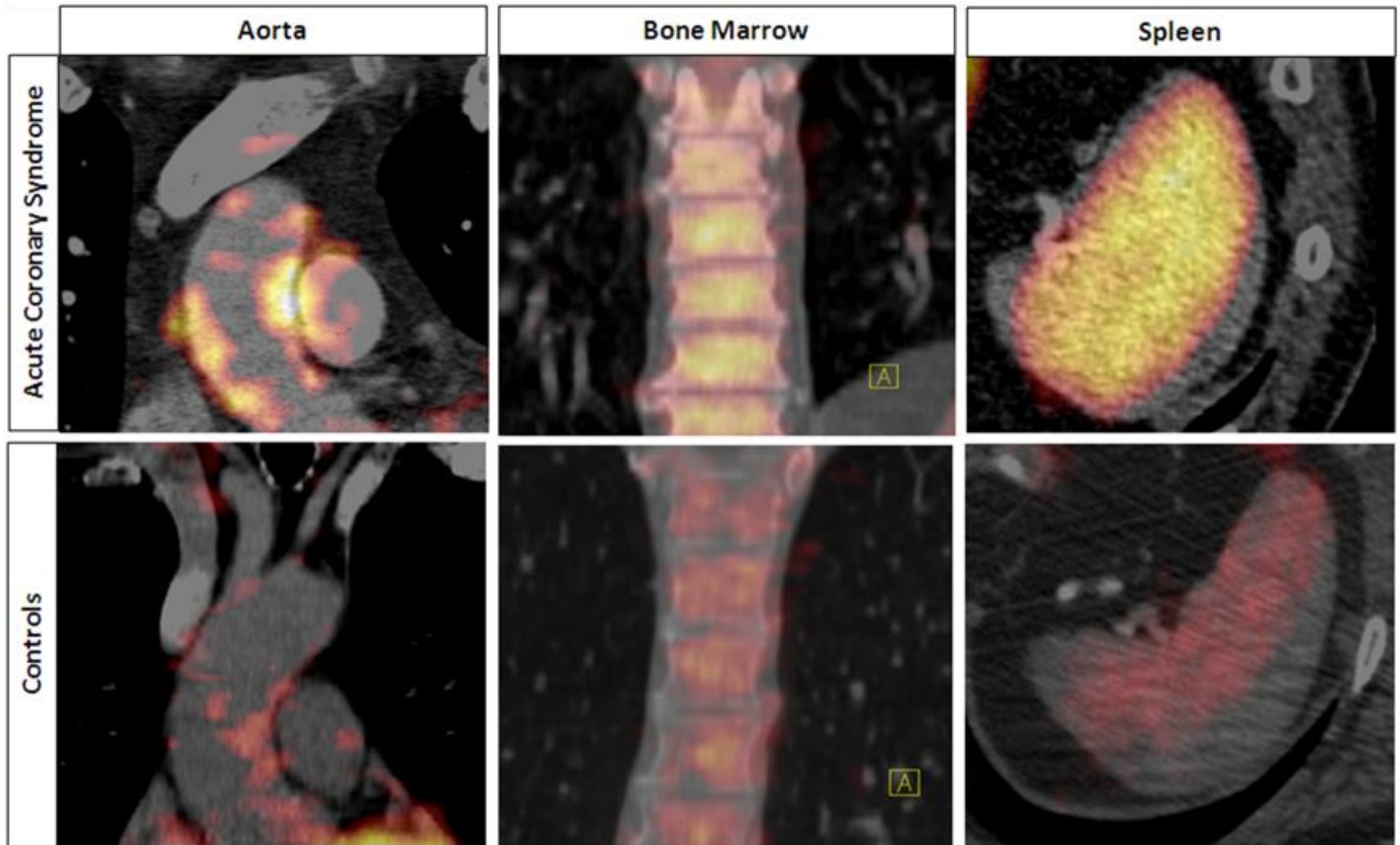
MI enhances monocyte/macrophage numbers in plaque



MI enhances atherosclerosis

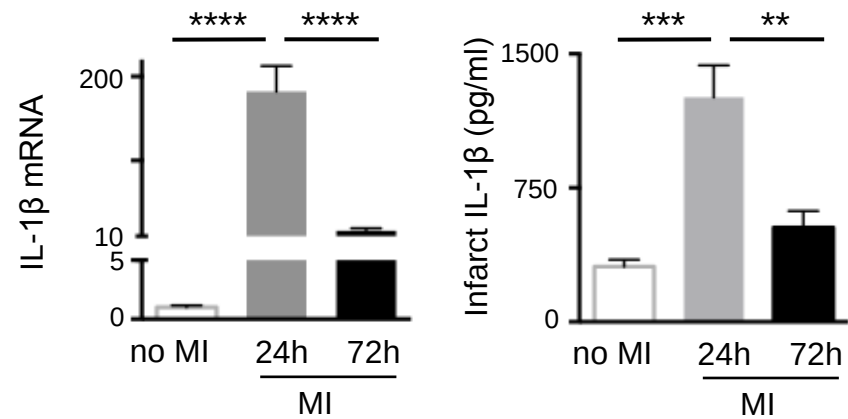


^{18}F -FDG uptake increases in atheroma, bone marrow, and spleen during acute MI

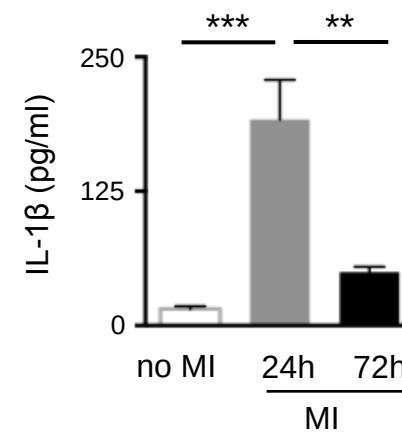


Danger signals: IL-1 β

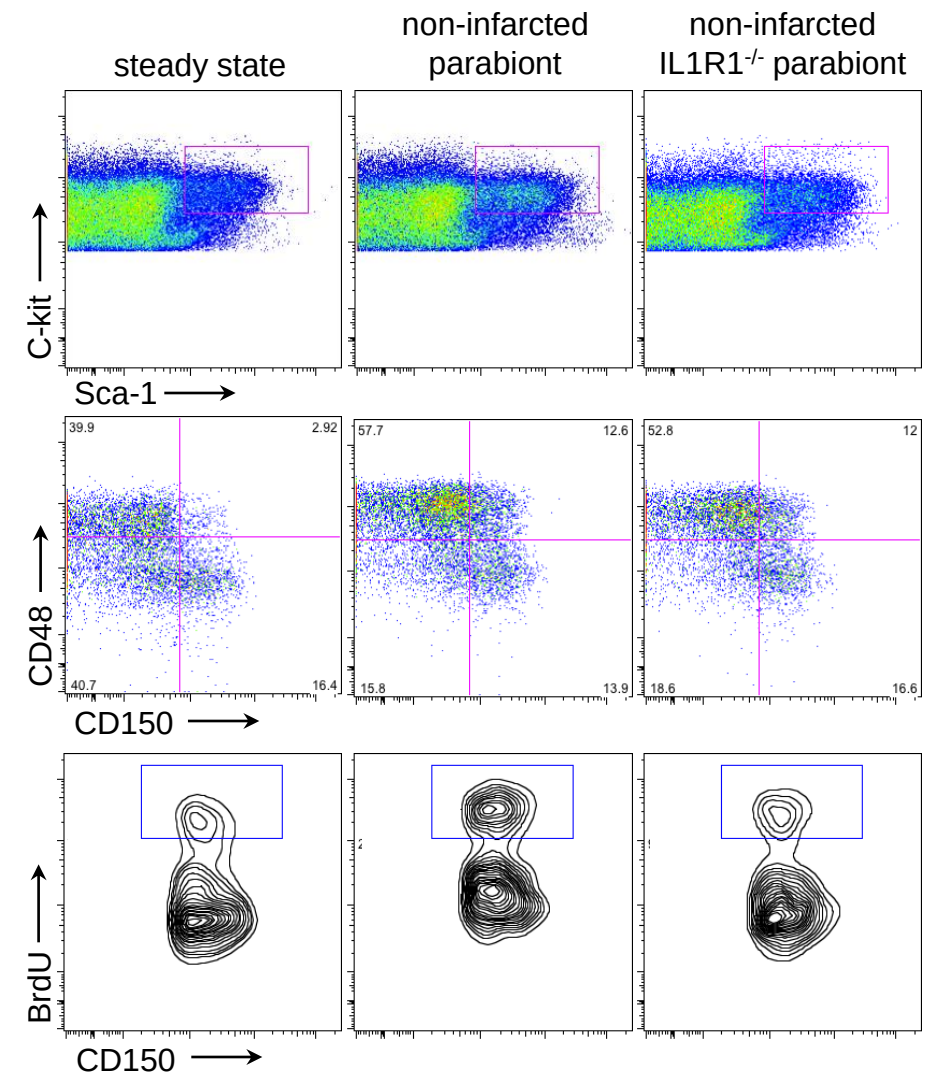
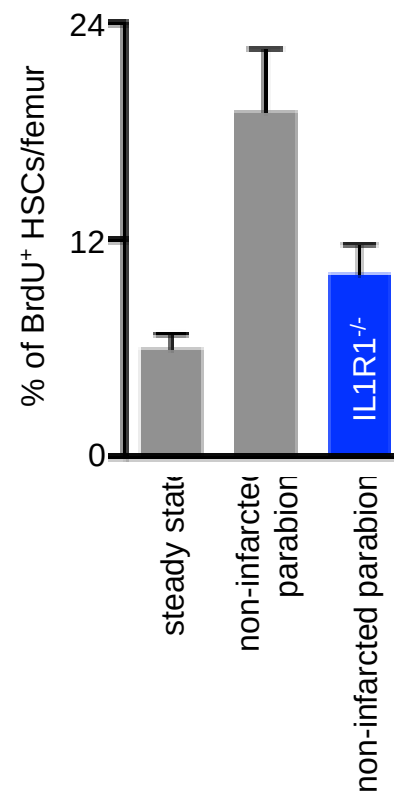
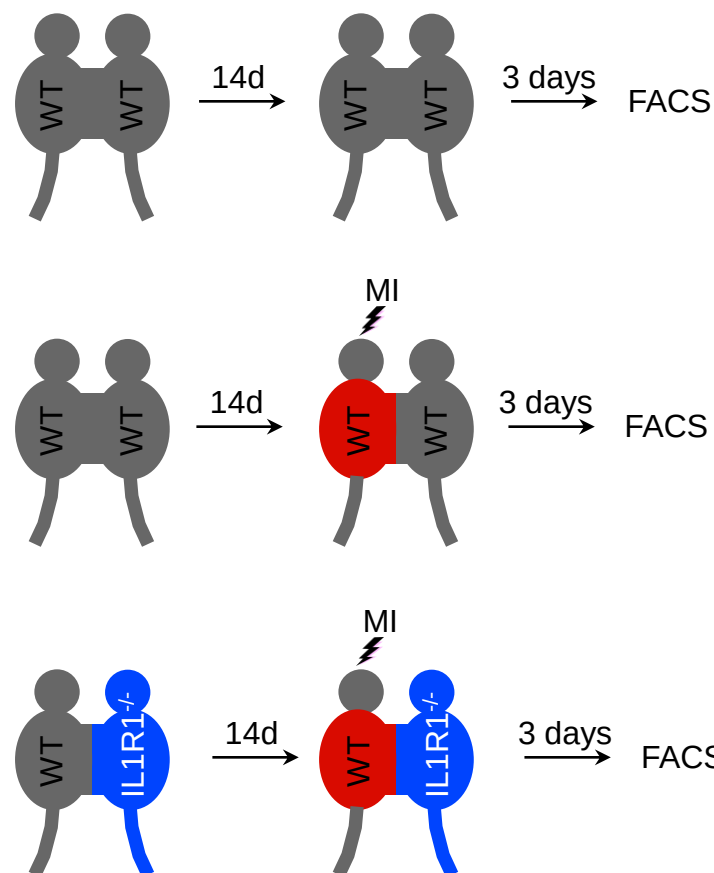
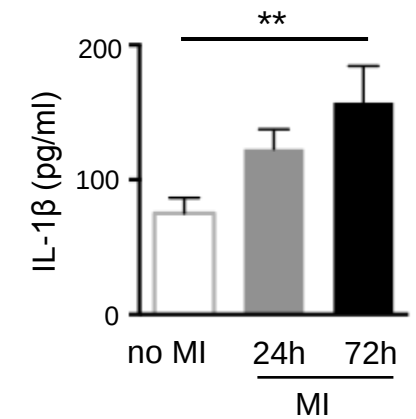
Heart



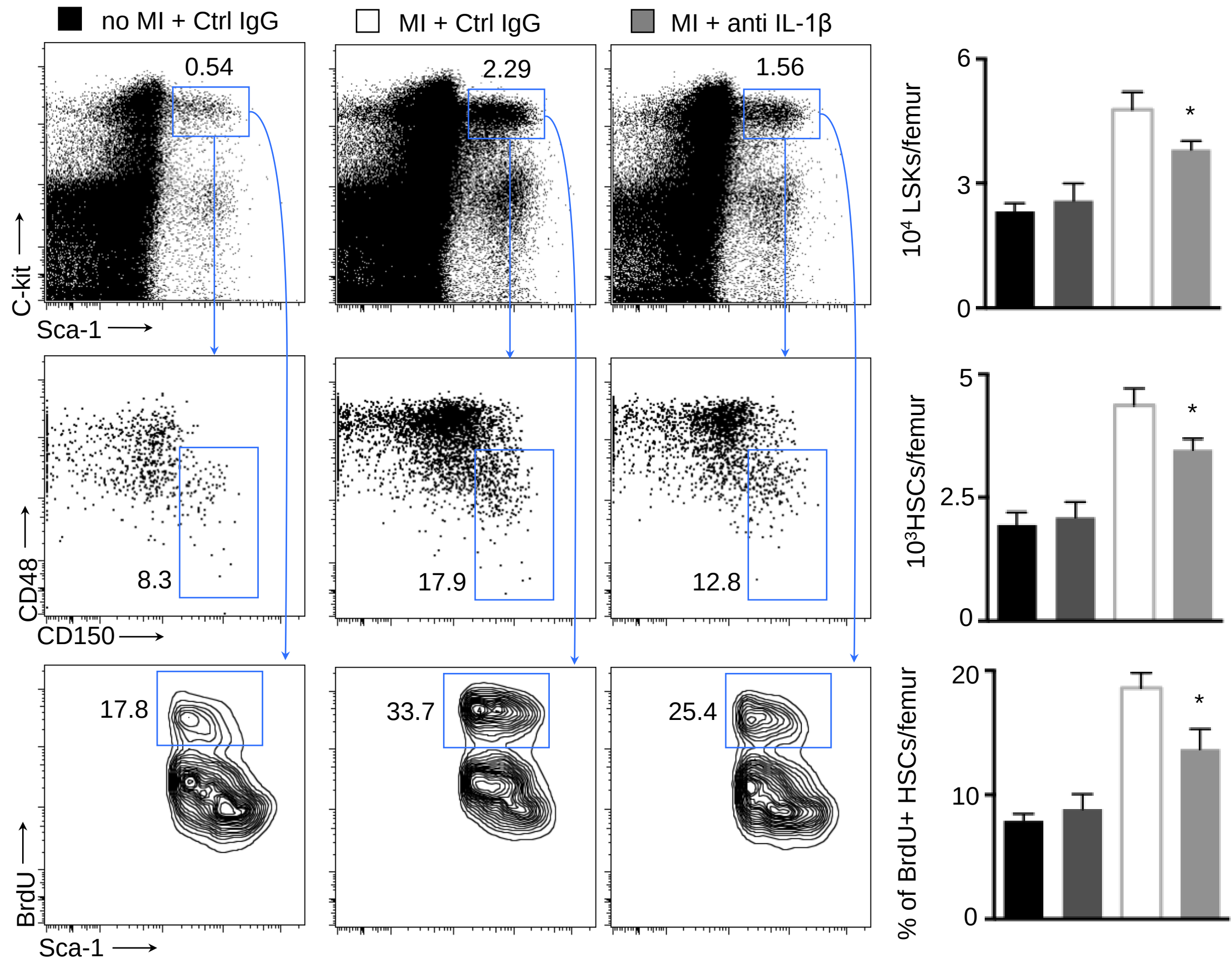
Blood



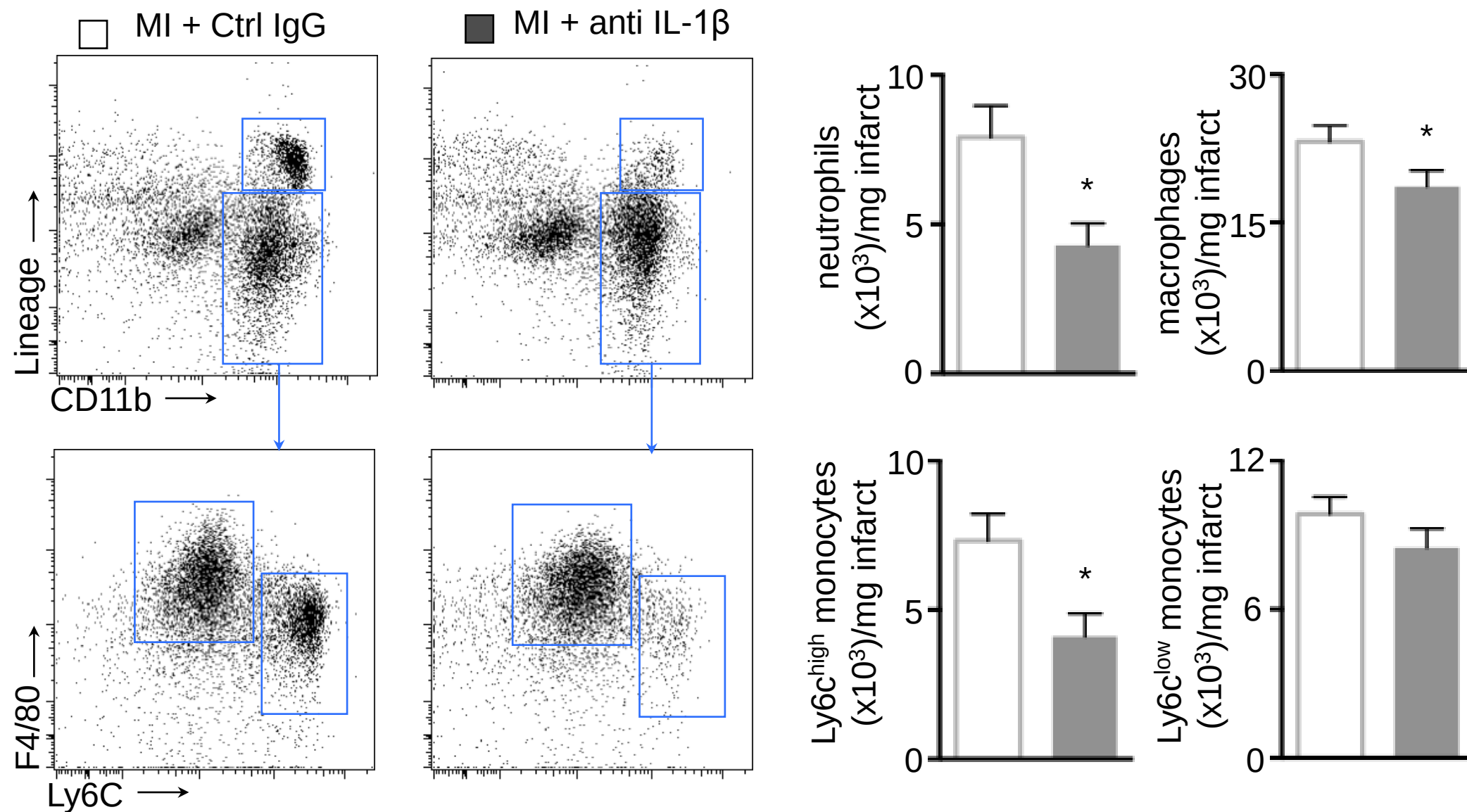
Marrow



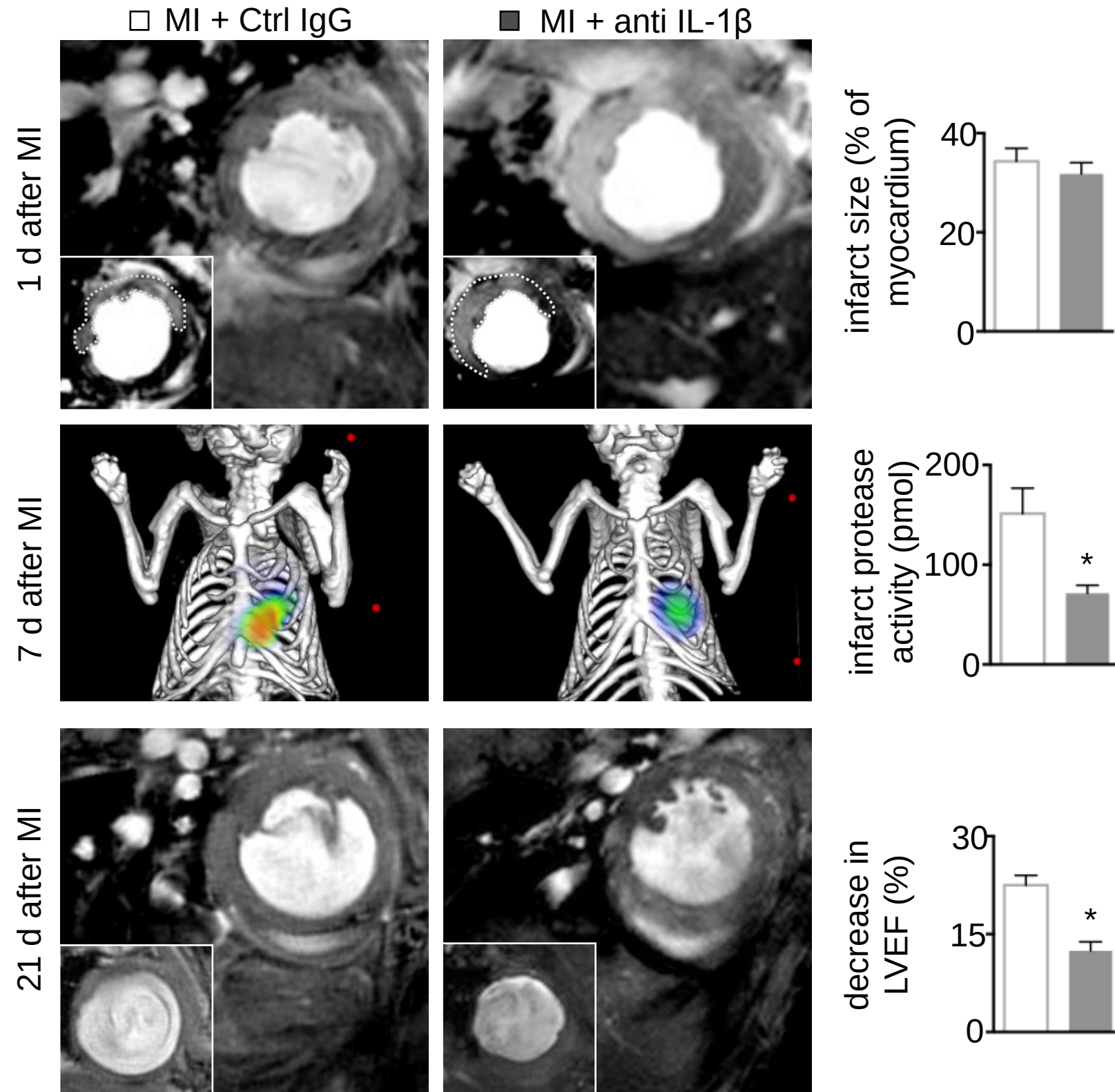
Anti IL-1 β therapy modulates hematopoiesis



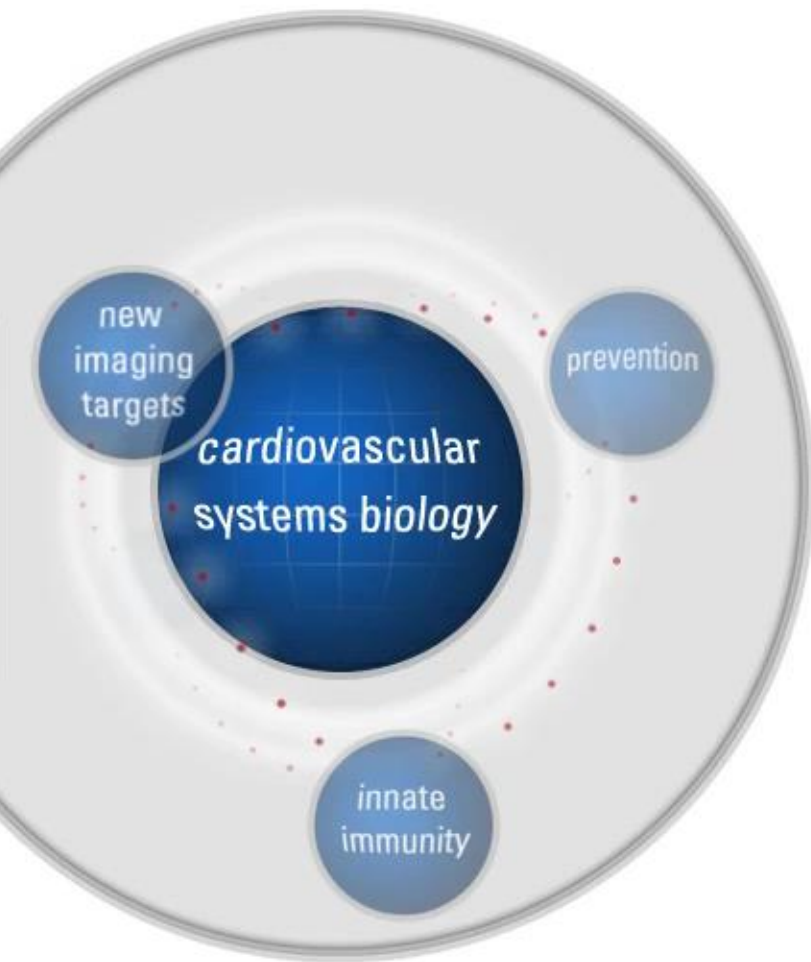
Anti IL-1 β therapy mutes inflammatory leukocytes during myocardial infarction



Anti IL-1 β therapy improves LV function post MI



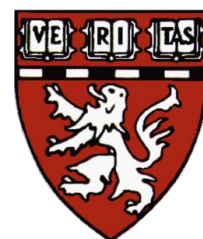
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R01HL117829



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