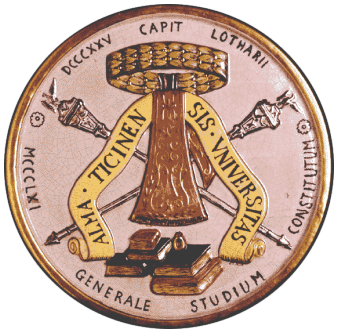
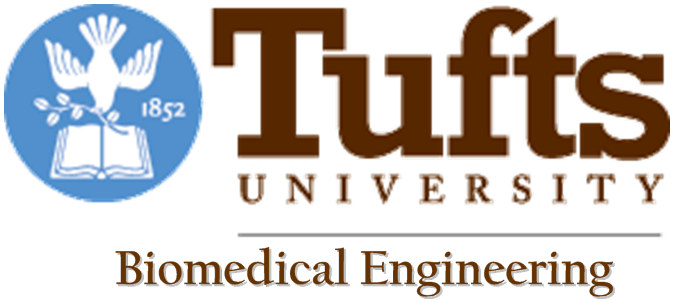




3D Bone marrow modeling for platelet production

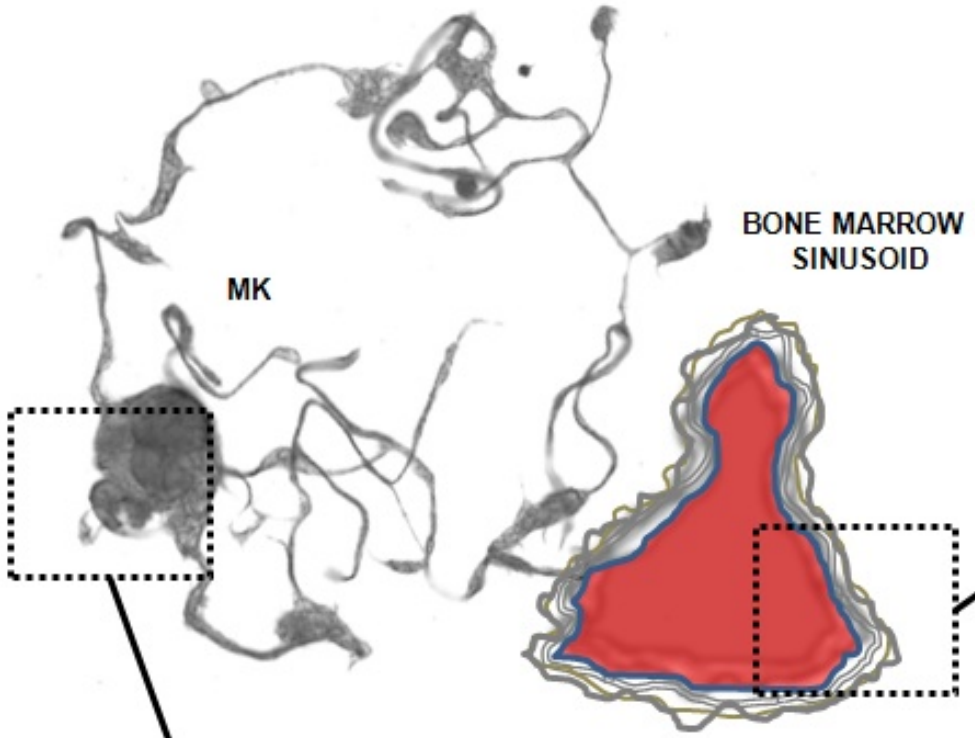
Alessandra Balduini, MD

University of Pavia, Pavia, Italy
Tufts University, Boston, MA, USA

Pavia 4 April 2012

About 13 millions platelet concentrates are collected annually in Europe at a cost of about 0.75 billion-euro. In Italy about 1 million of platelet concentrates are collected and about 0.7 million are transfused annually. They are needed by people who lack platelets or whose platelets function improperly, such as certain cancer chemotherapy, bone marrow transplant patients, trauma patients given massive blood transfusion and people with aplastic anemia. The short shelf life means that platelets cannot not easily be shipped from an area of surplus to one of scarcity, and hospitals occasionally experience shortages that require surgeries to be postponed.

BONE MARROW ENVIRONMENT



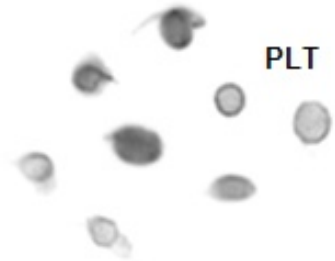
EXTRACELLULAR CONSTITUENTS

-EXTRACELLULAR MATRICES
- PHYSICAL PARAMETERS (i.e. OXYGEN TENSION)
- SOLUBLE FACTORS (CYTOKINES, CHEMOKINES)
- FLUIDS AND MATRICES MECHANICS AND STRUCTURE (i.e. FIBROSIS)

CELLULAR CONSTITUENTS

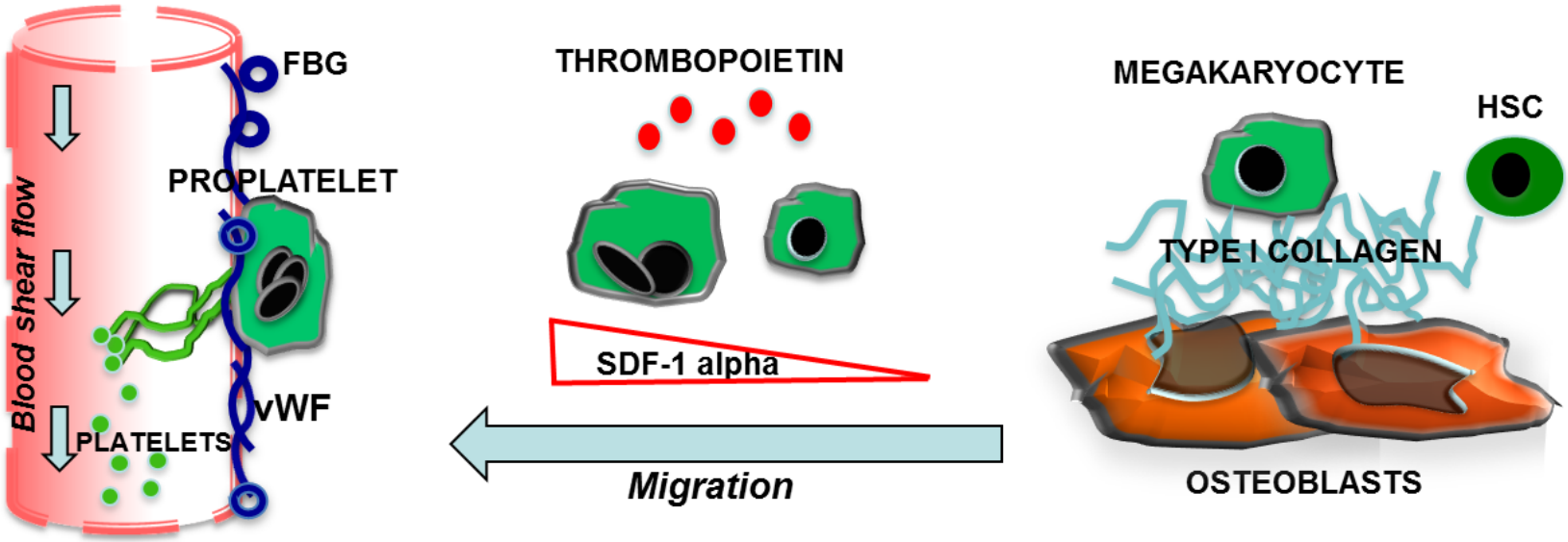
-MEMBRANE RECEPTORS (GPIb-IX-V, INTEGRINS)
-CYTOSKELETAL PROTEINS (MYOSIN IIA, TUBULIN, FILAMIN-A)

FUNCTIONAL AND NORMAL SIZED PLATELET

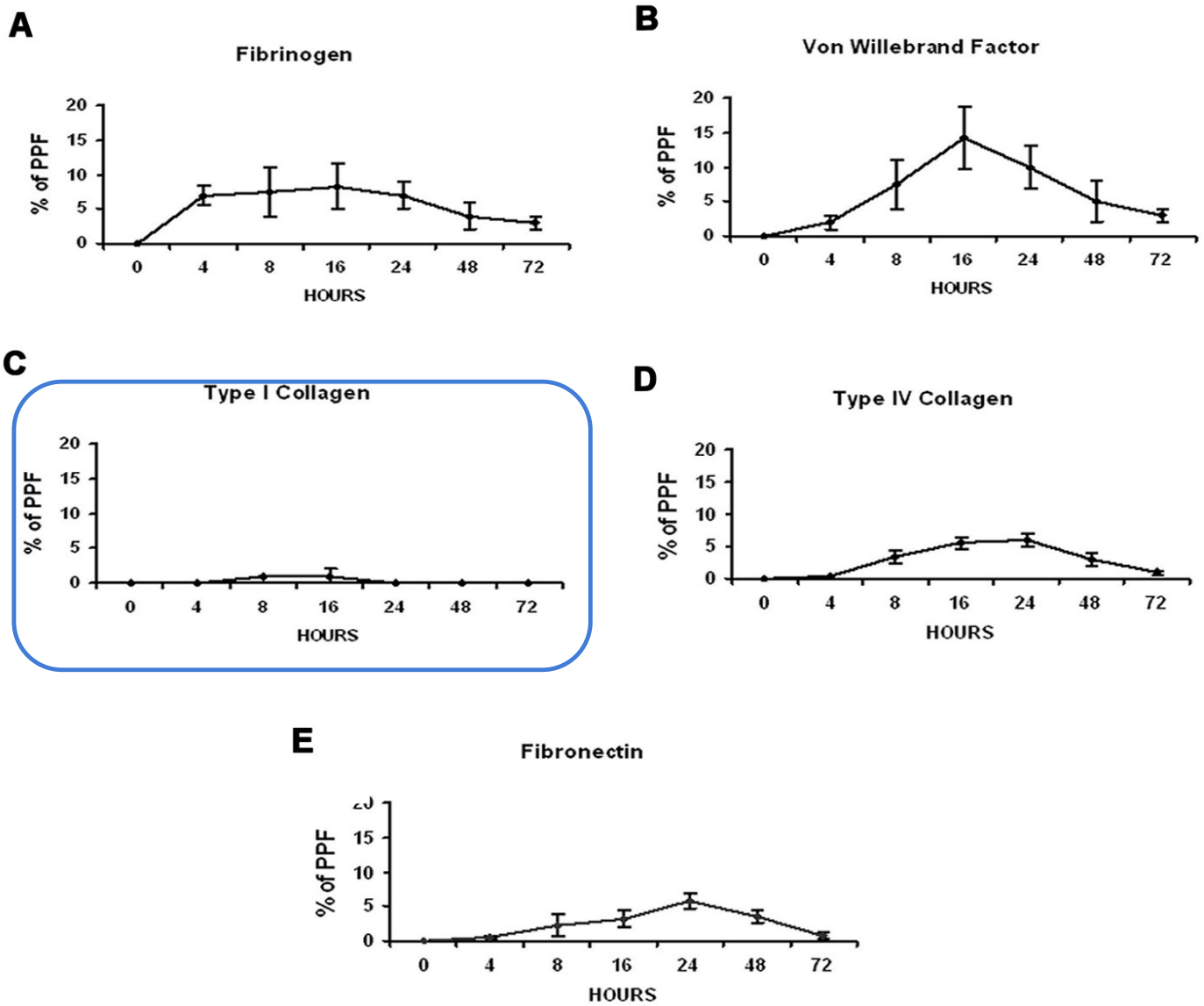


PERIPHERAL BLOOD

Bone marrow niches and MK function

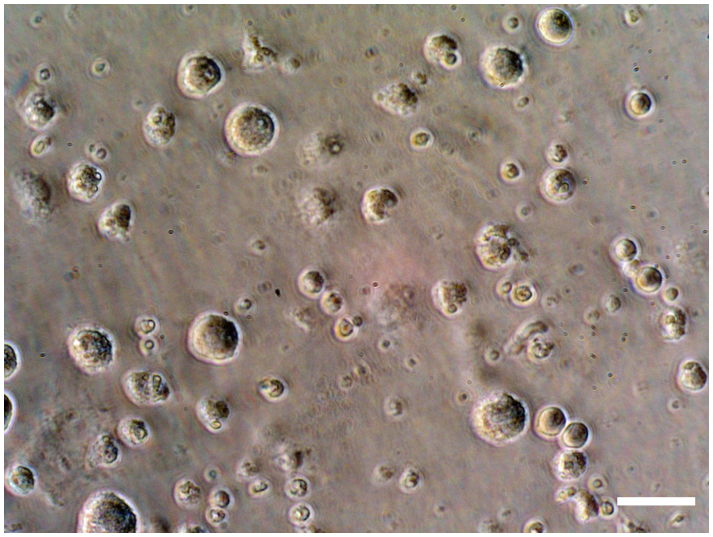


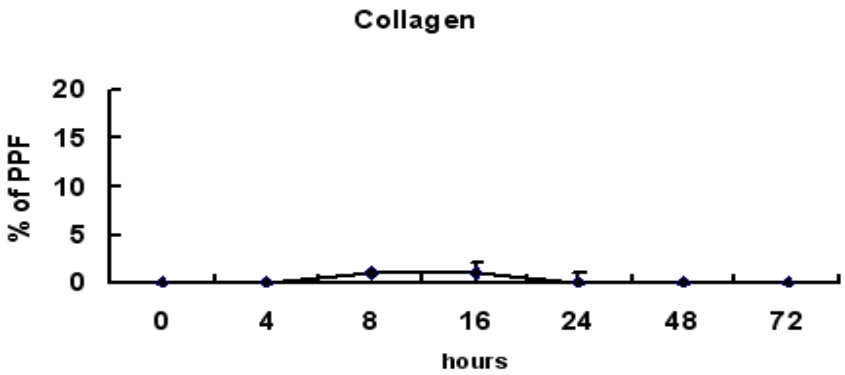
Mk adhesion to different adhesive proteins



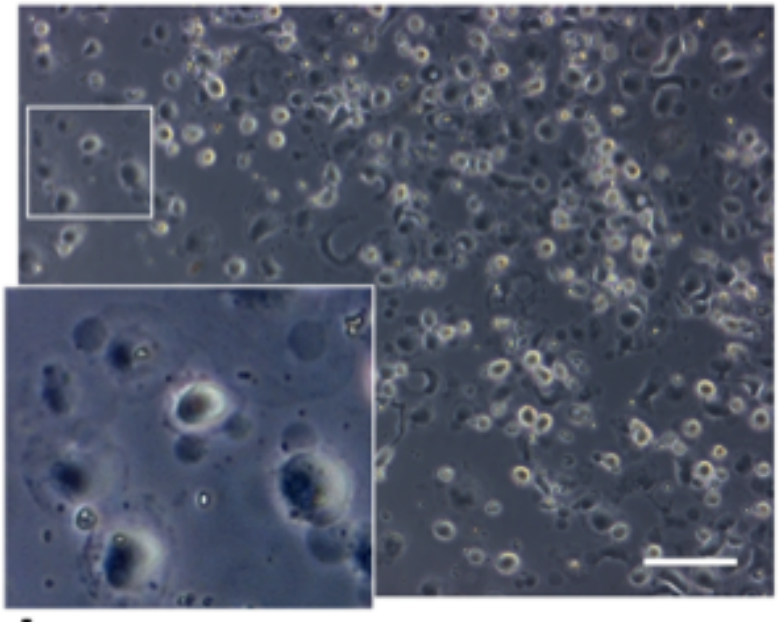
Balduini A et al. JTH 2008

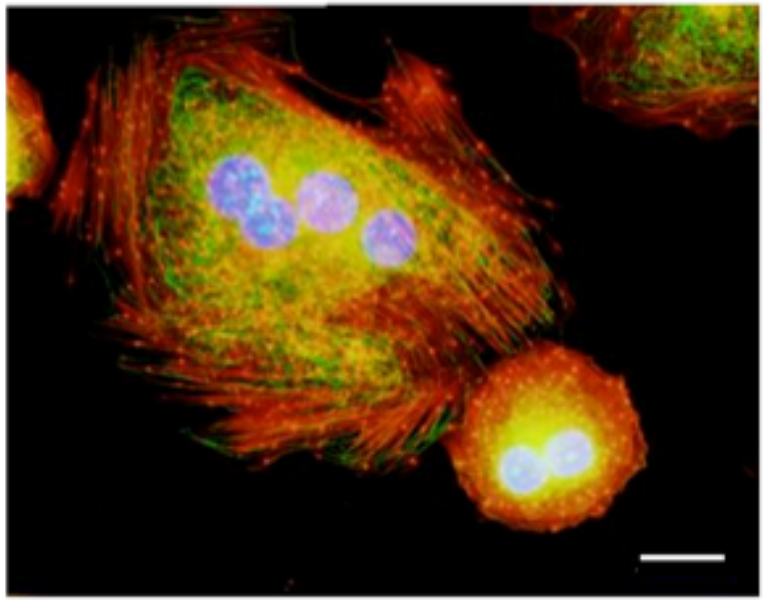
Mk behavior on type I Collagen





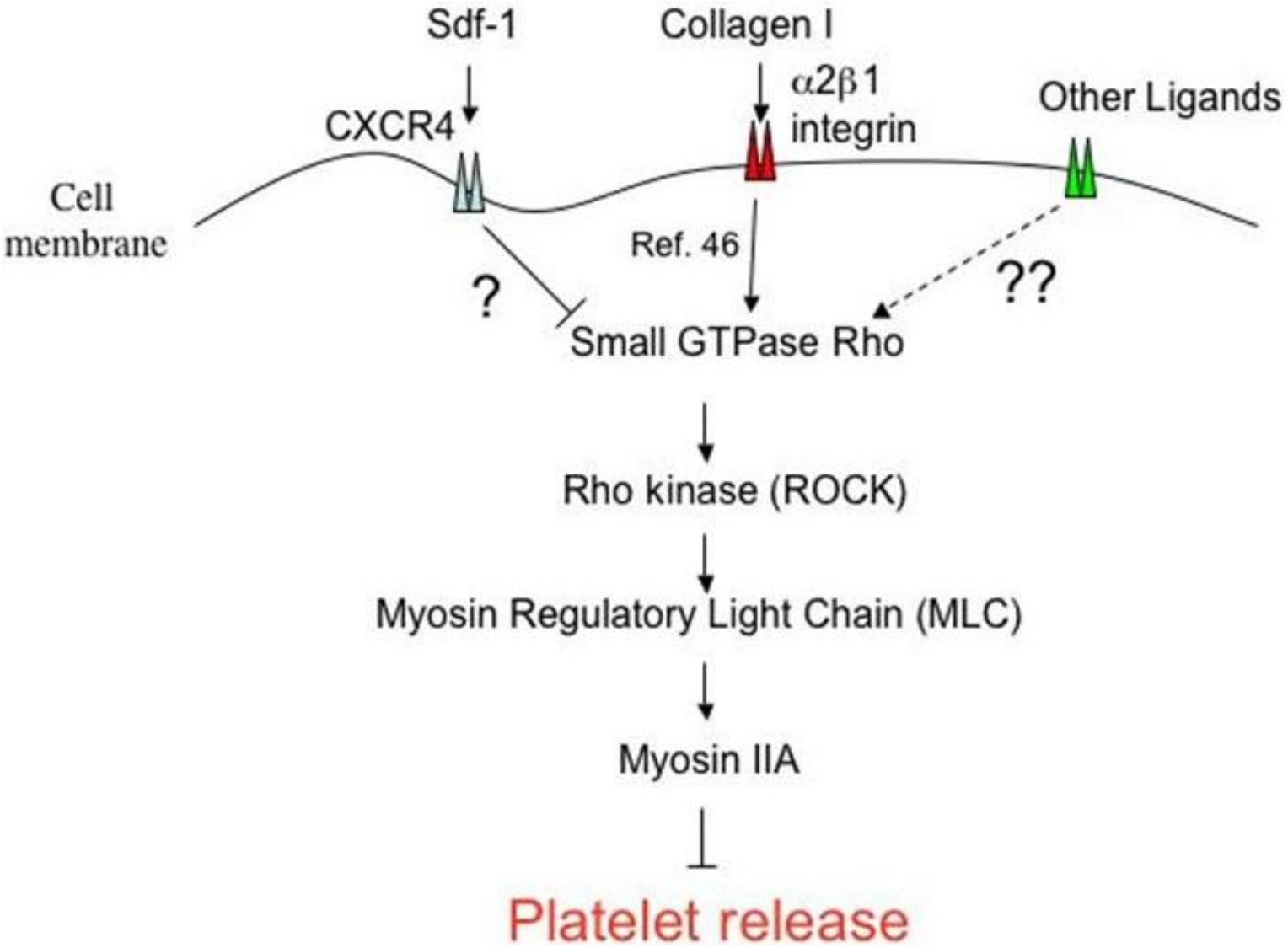
Balduini et al., JTH 2008





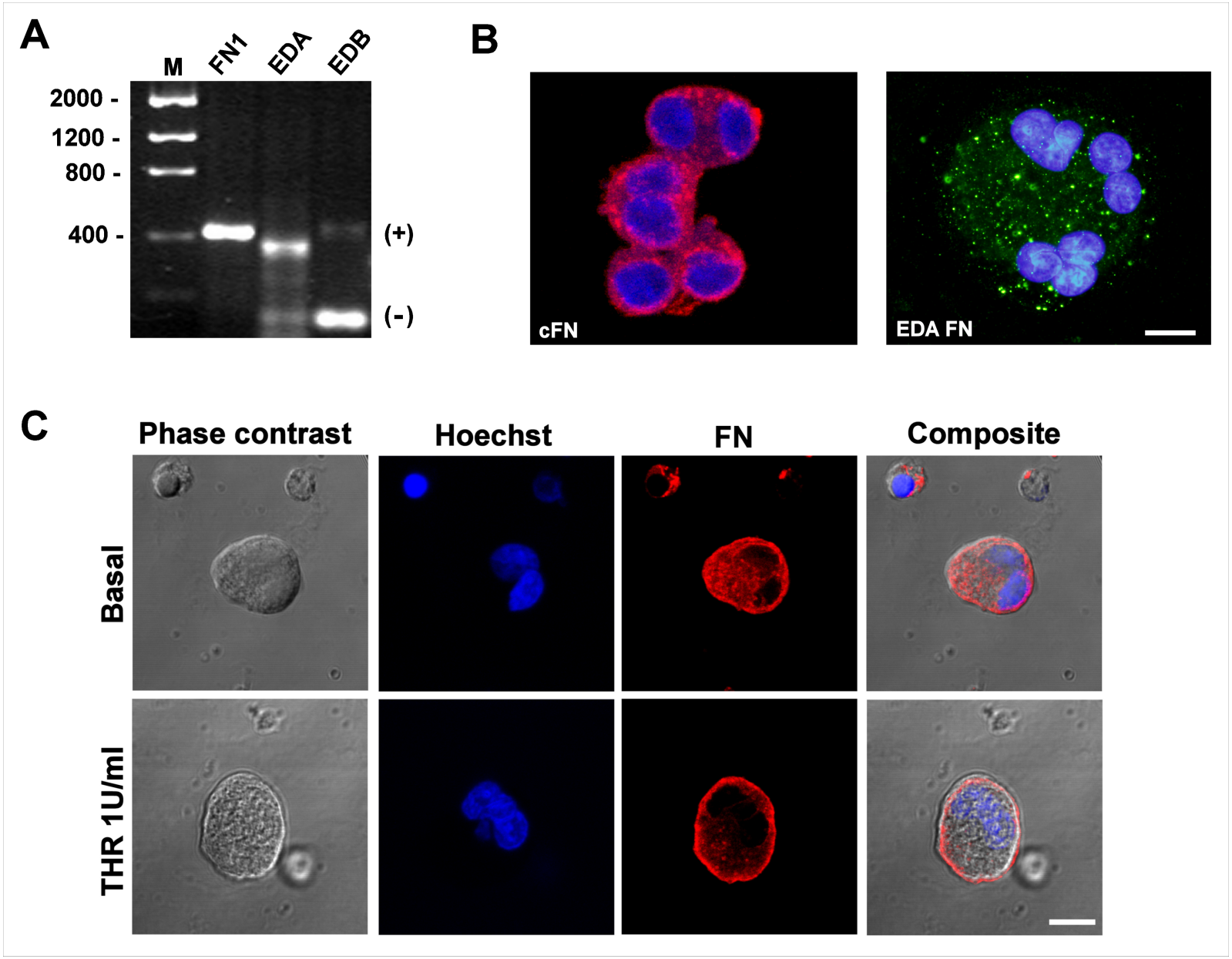
Malara et al., Blood 2010

Proplatelet regulation model



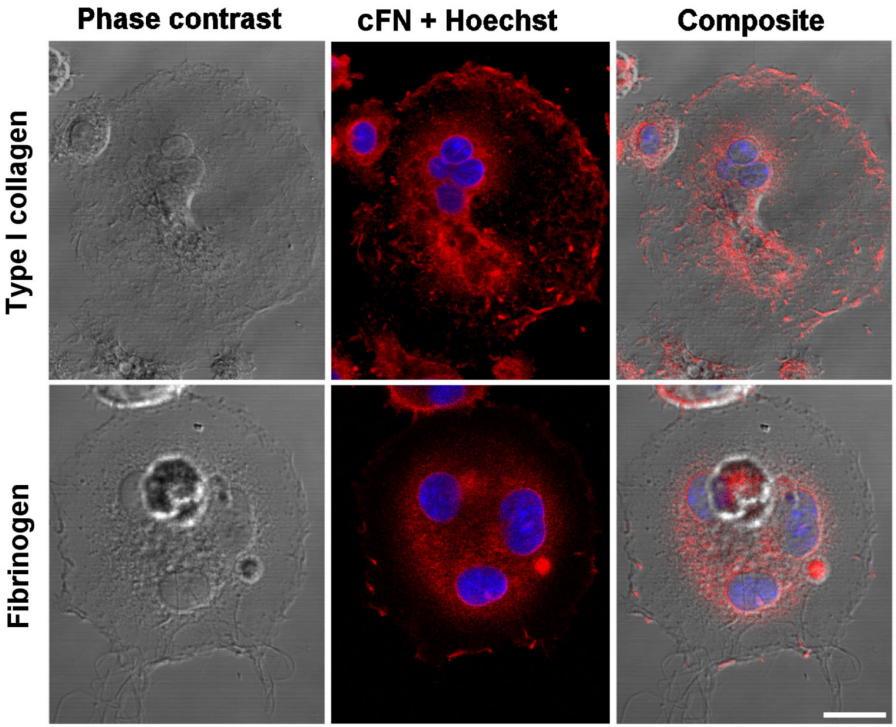
Chen et al., Blood 2007

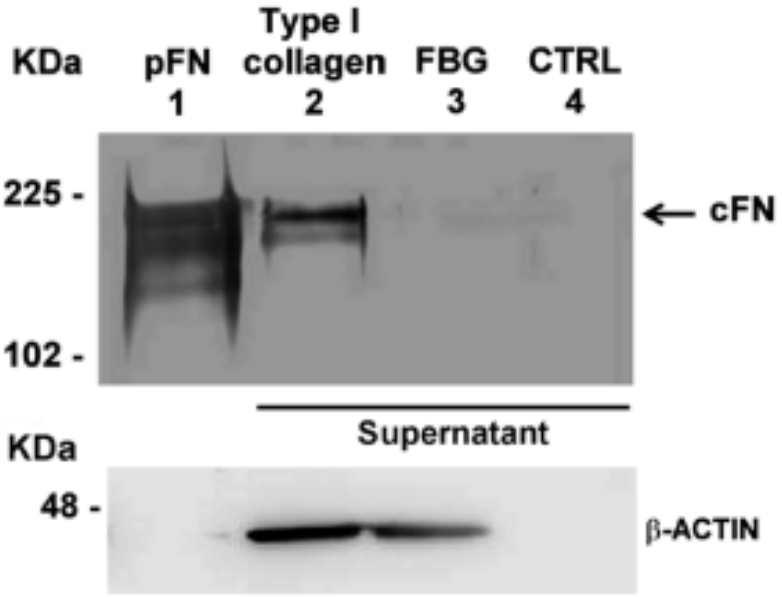
Mks express fibronectin



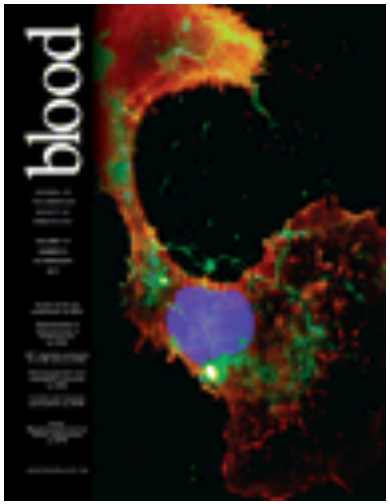
Malara et al., Blood 2010

Fibronectin modulates Mk adhesion

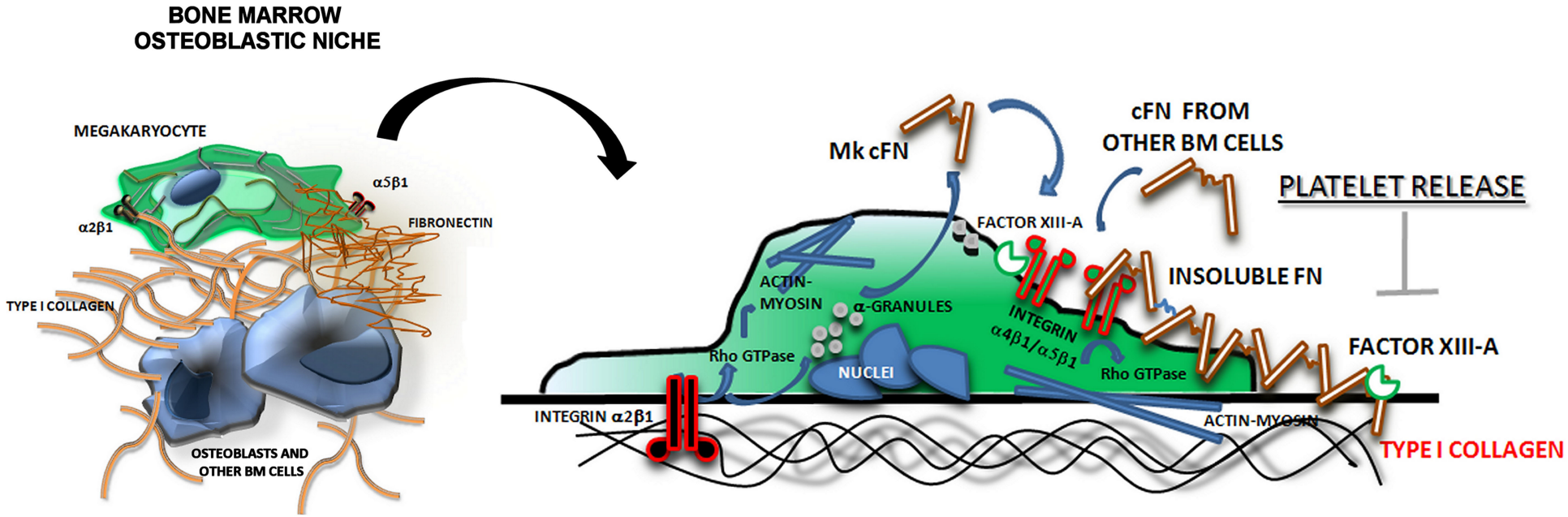




Malara et al., Blood 2010

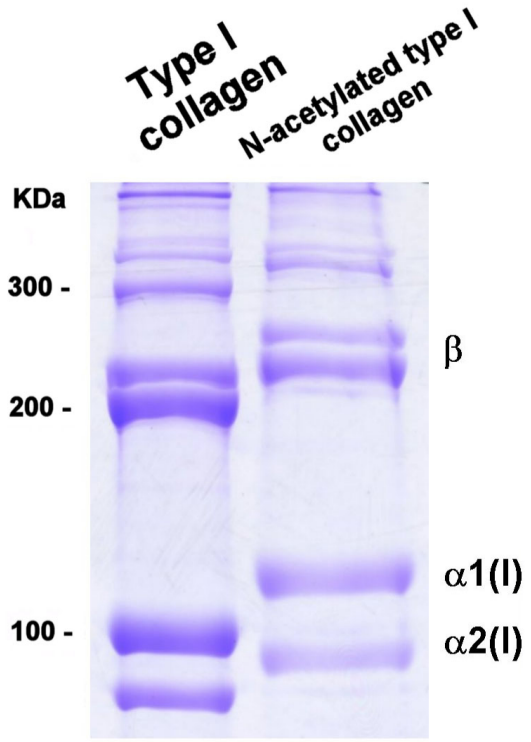


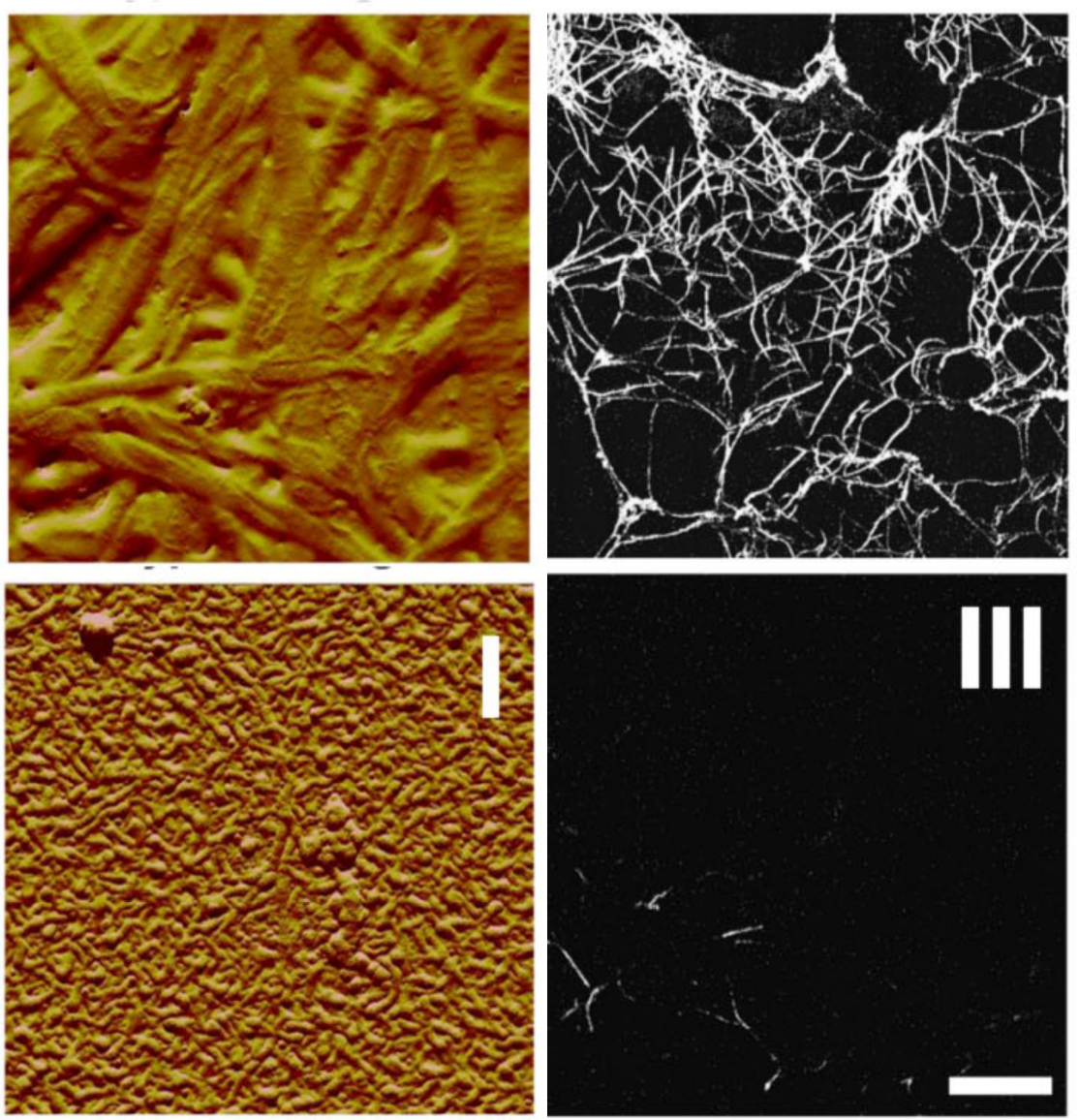
Model of Mk interaction within bone marrow environment



Malara et al., Blood 2010

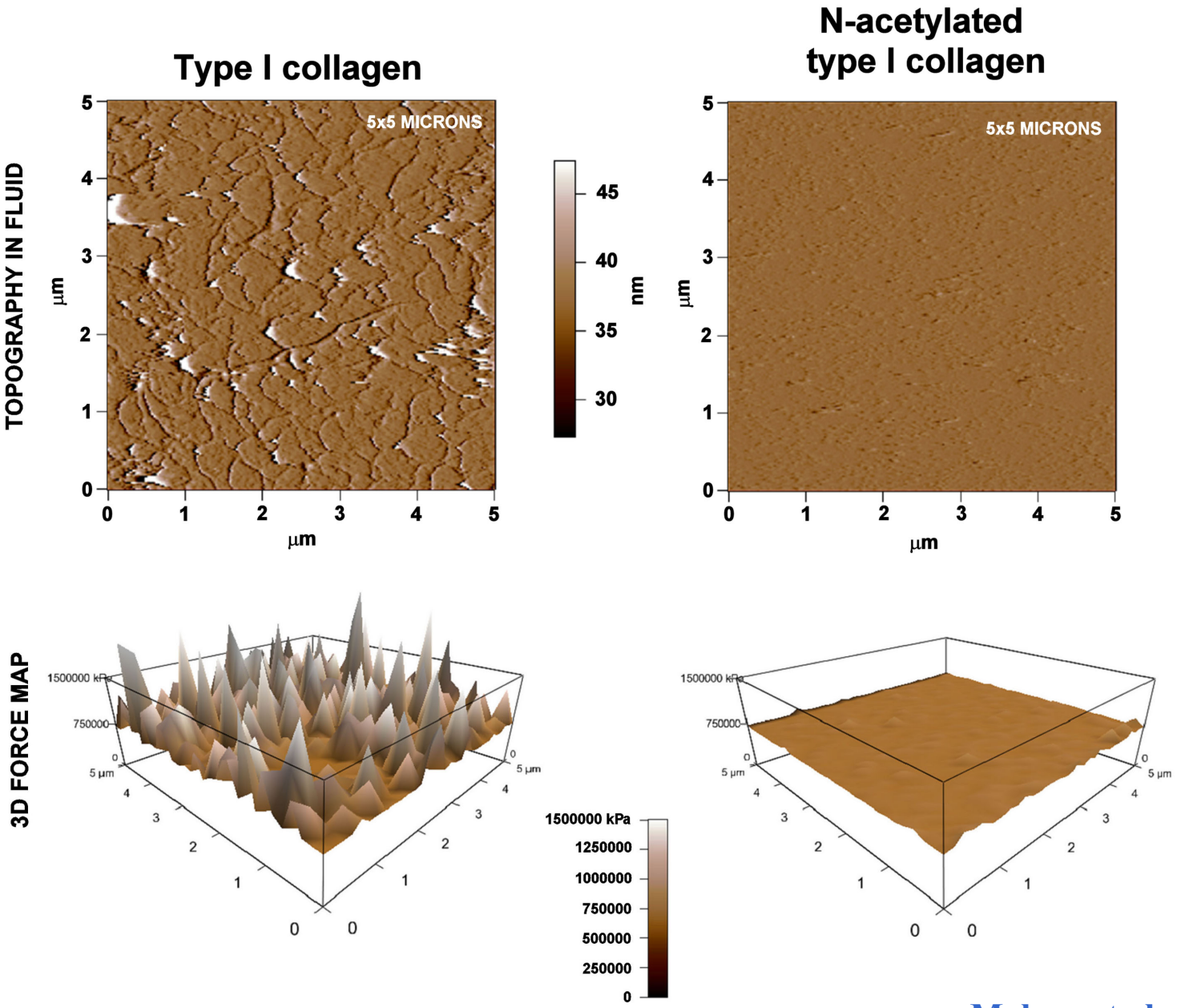
Chemical and Structural characterization





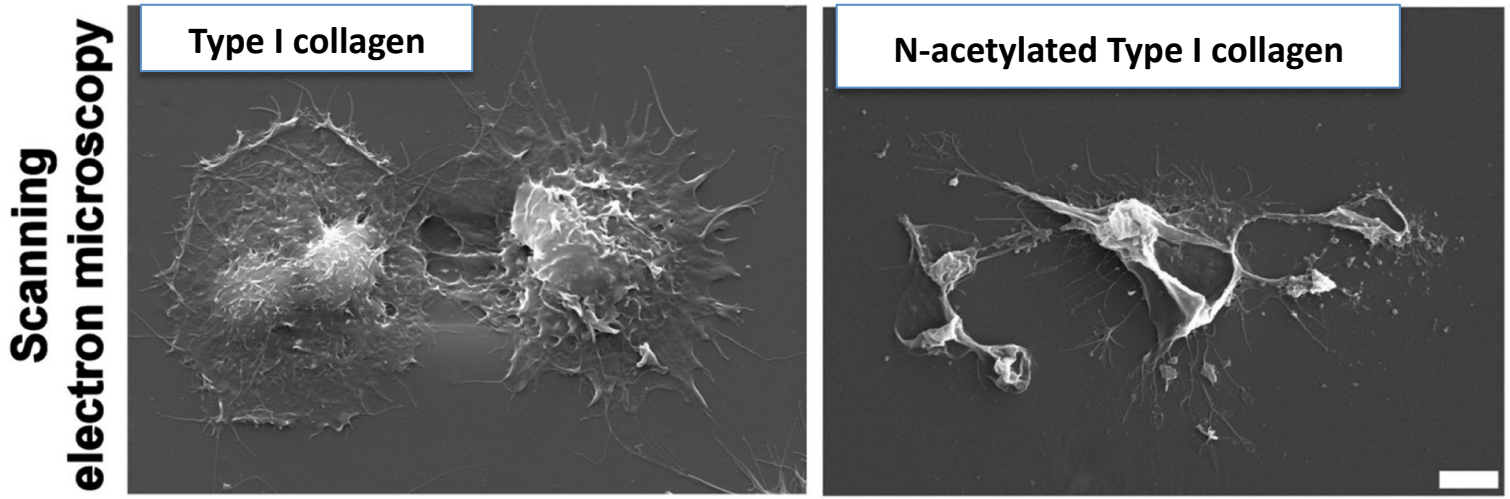
Malara et al., Blood 2011

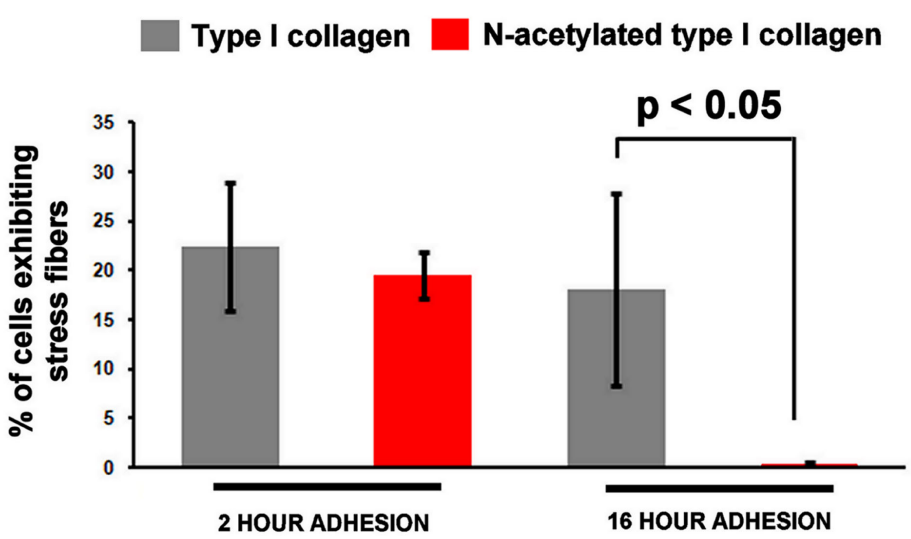
Nano-mechanical properties

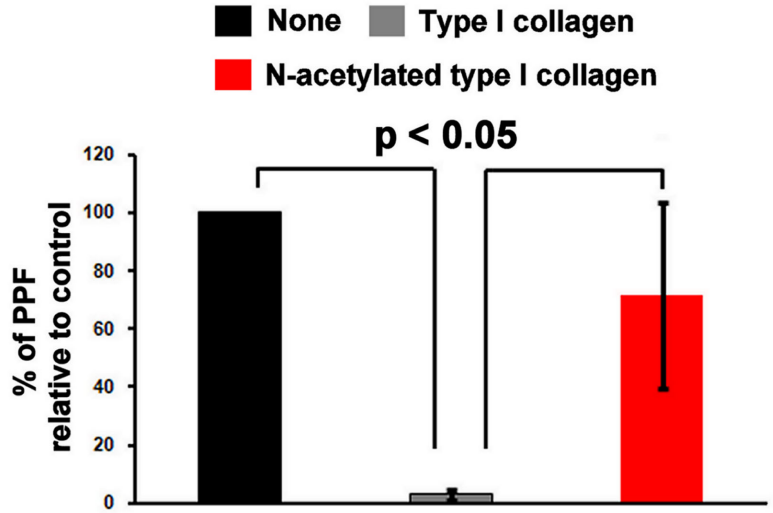


Malara et al., Blood 2011

Mk function



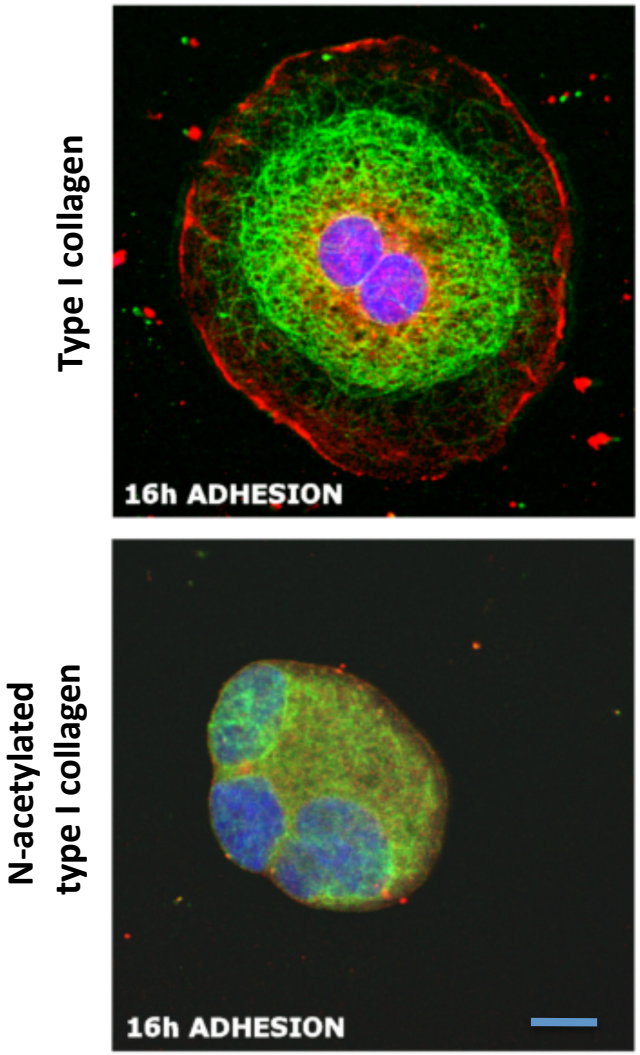




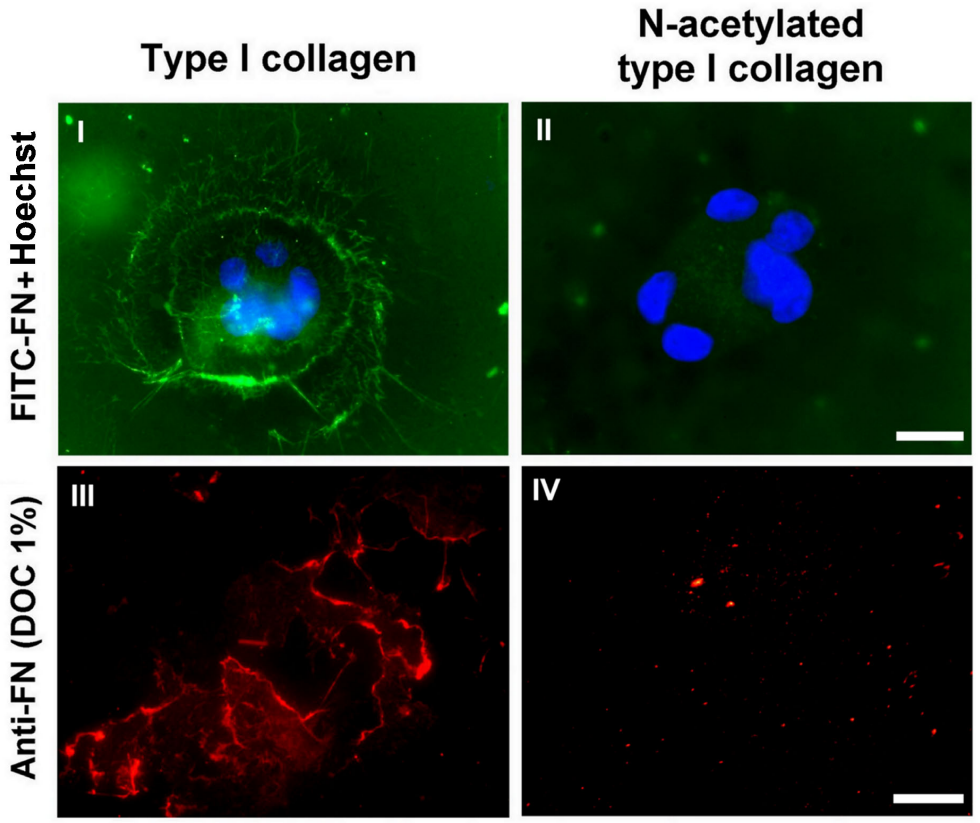
Malara et al., Blood 2011

Fibronectin assembly

Cellular Fibronectin

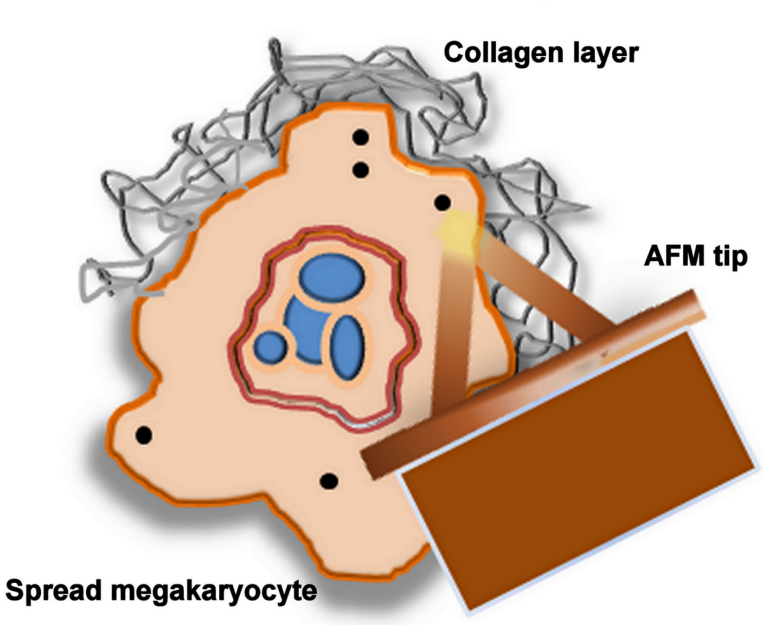


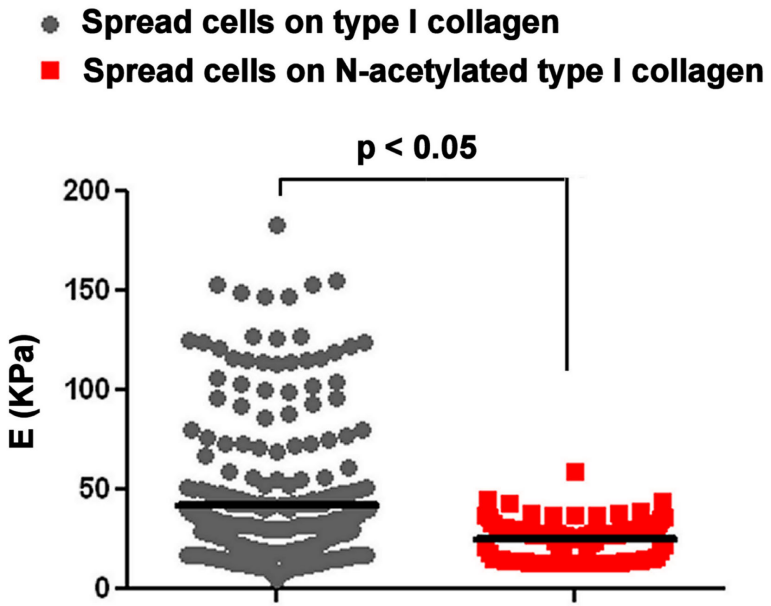
Plasma Fibronectin



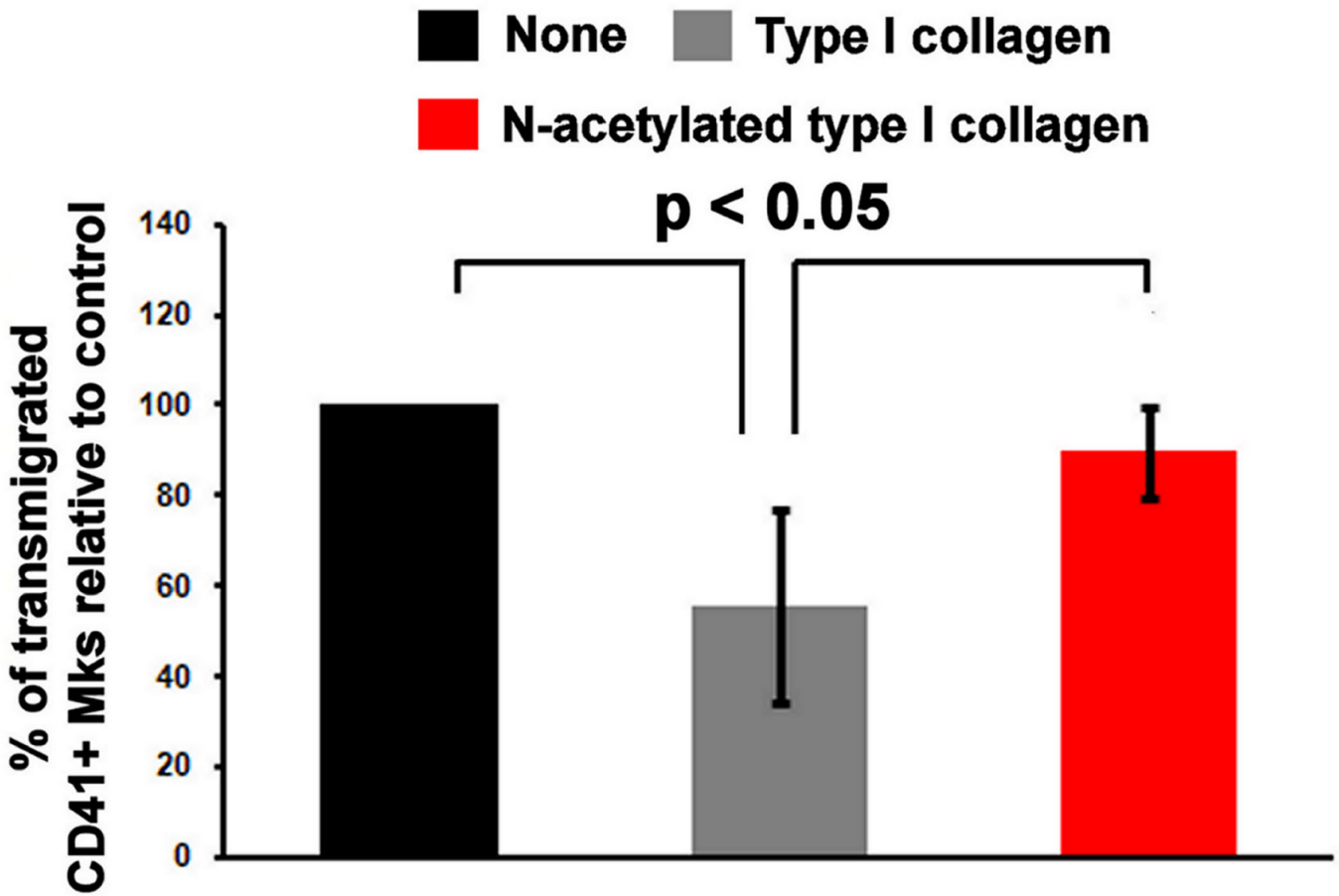
Malara et al., Blood 2011

MK nano-mechanics

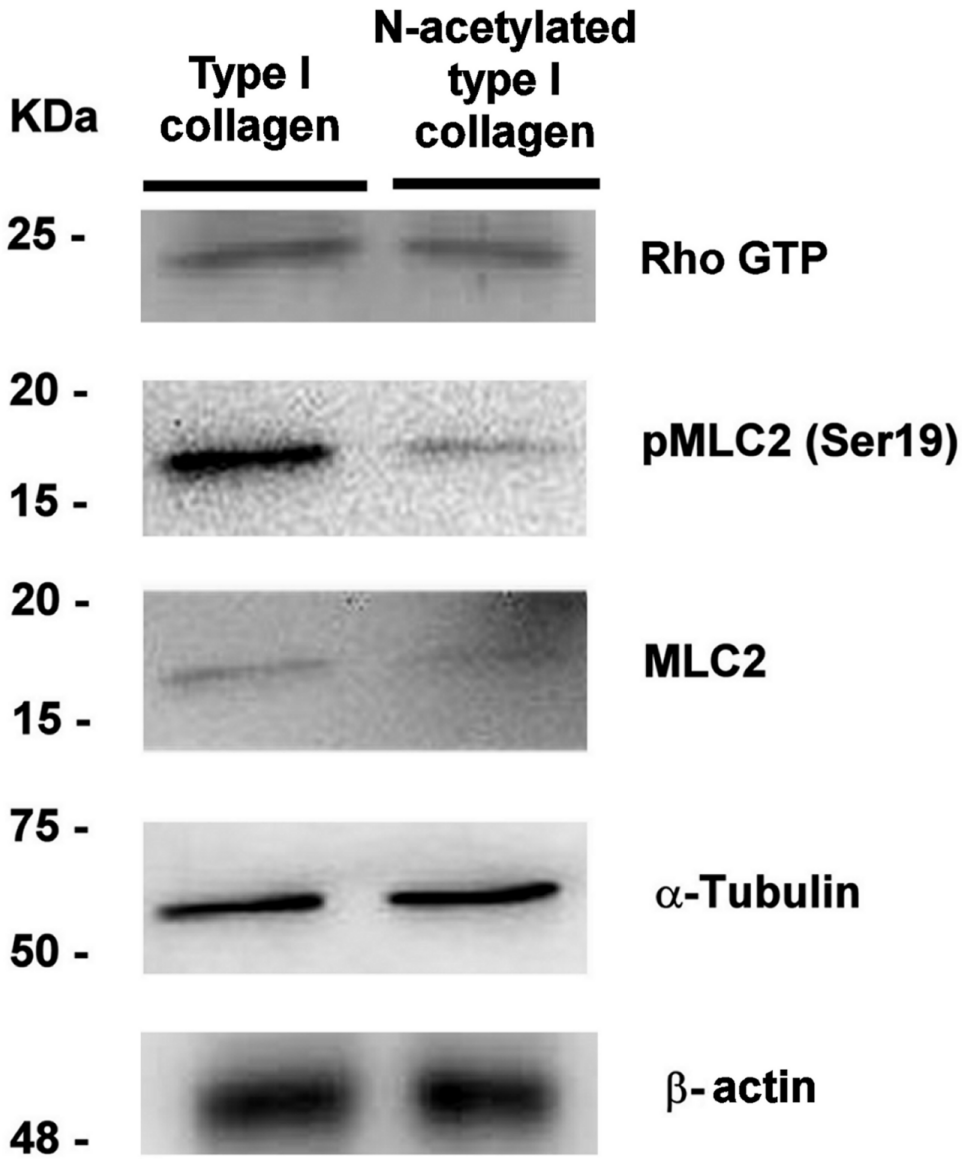




MK migration



Impact of collagen nano-mechanics on pMLC2

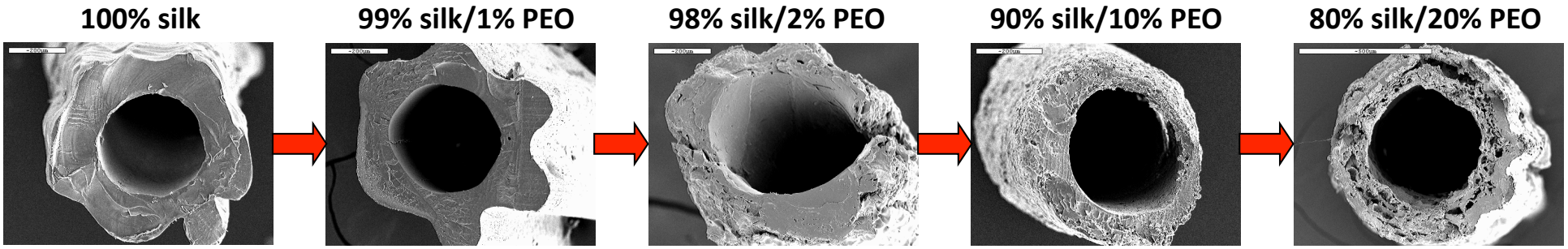


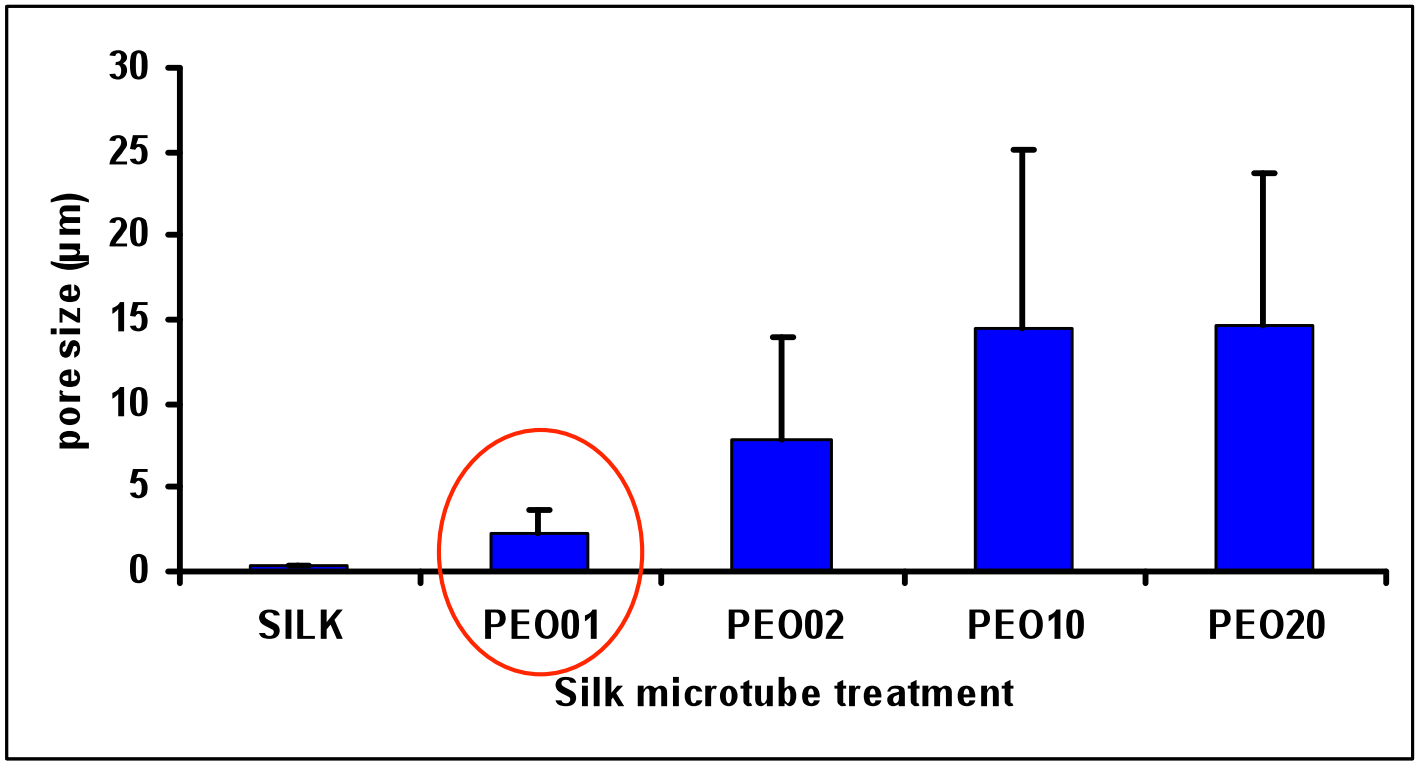
Malara et al., Blood 2011

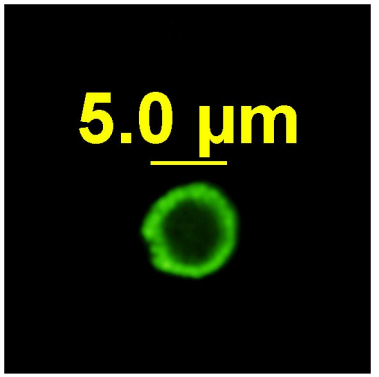
Silk

Omenetto and Kaplan, Science 2010

CONTROLLING PORE SIZE

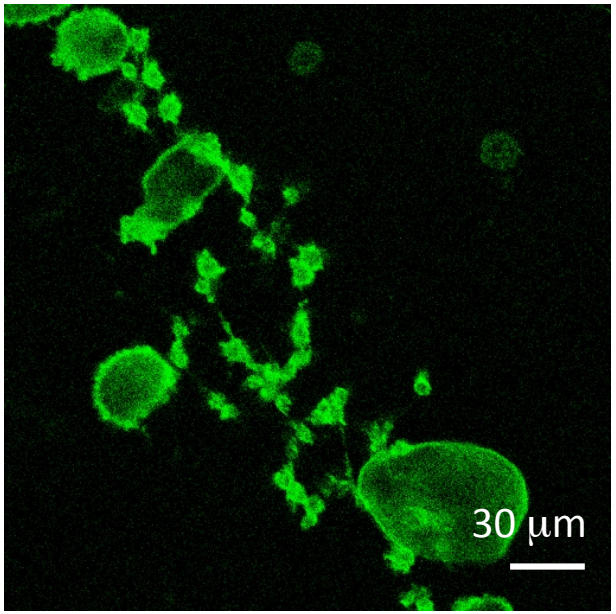


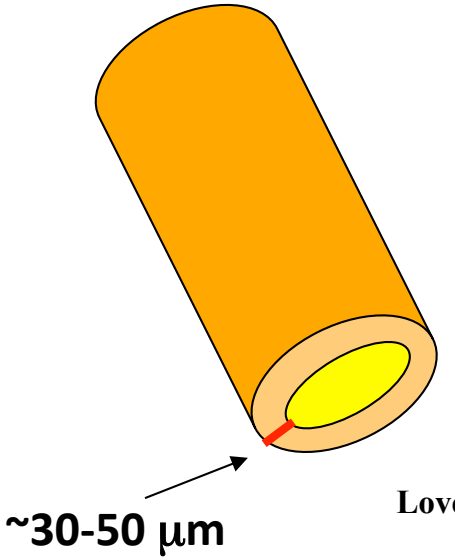




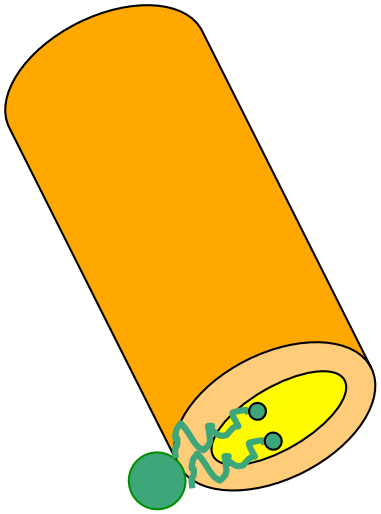
Lovett M. et al, *Biomaterials*. 2007;28:5271-9.

WALL THICKNESS

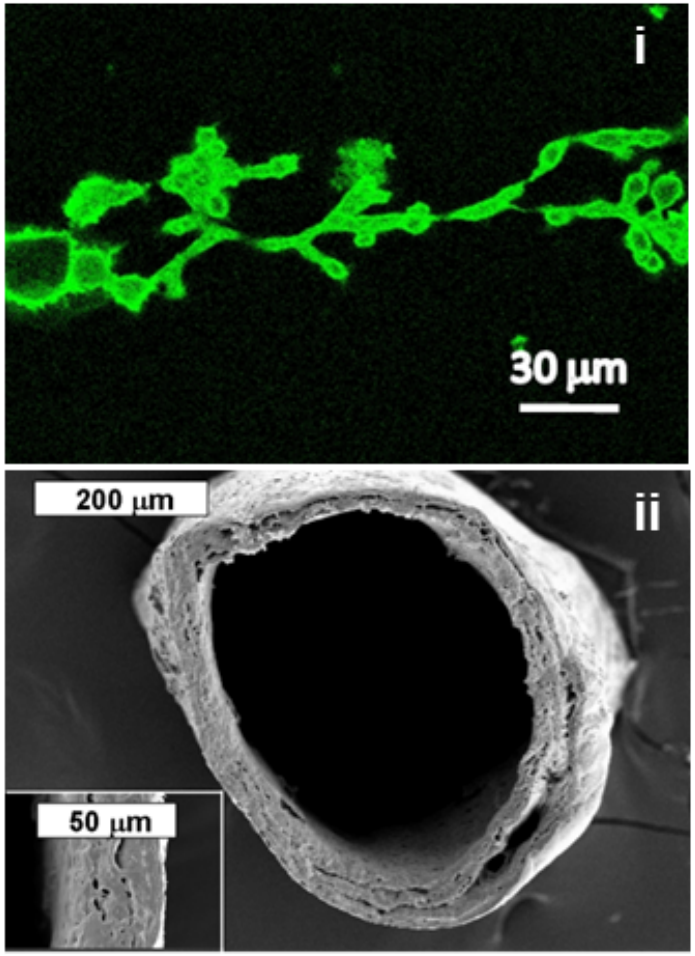


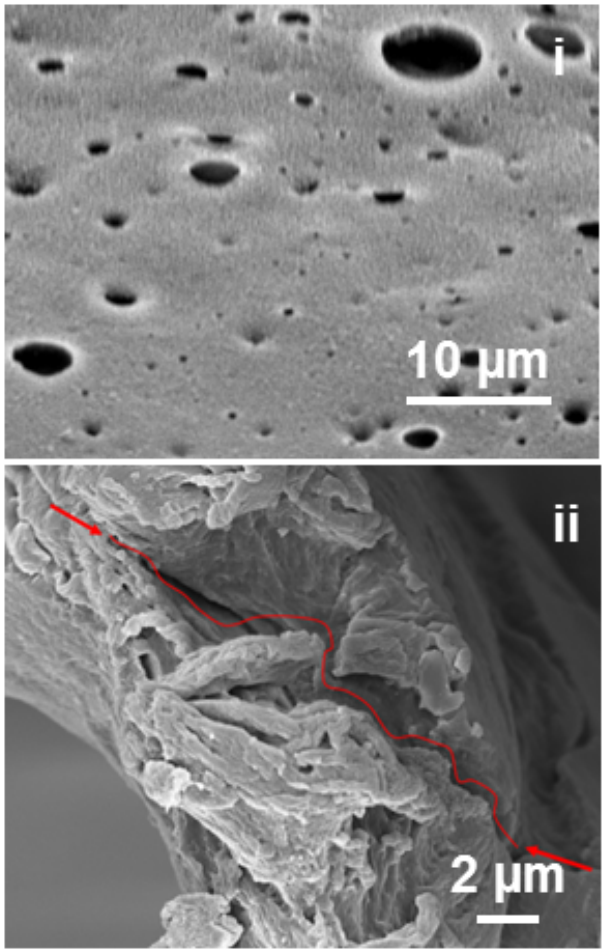


Lovett M. et al, *Biomaterials*. 2007;28:5271-9.



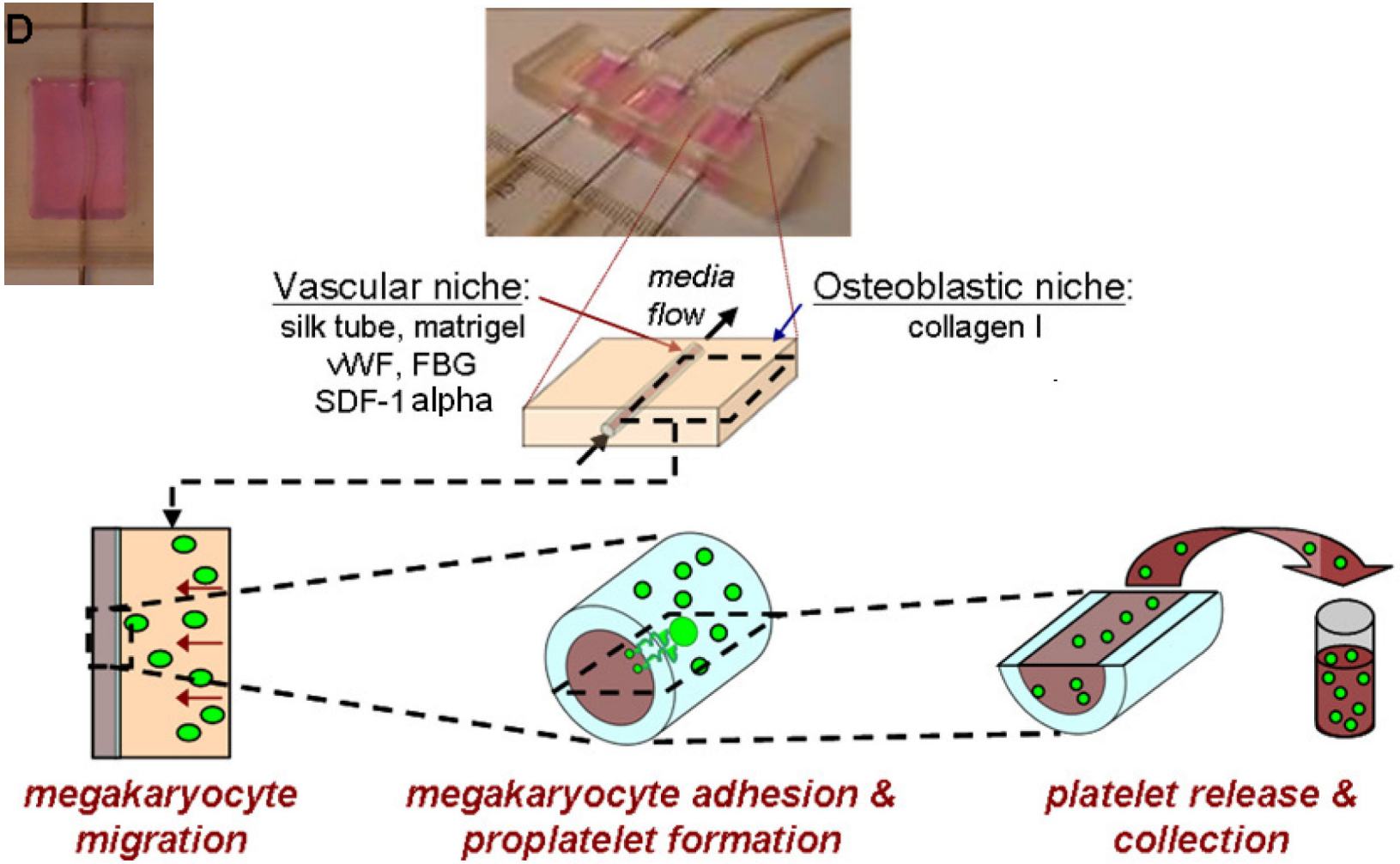
Silk vascular tubes





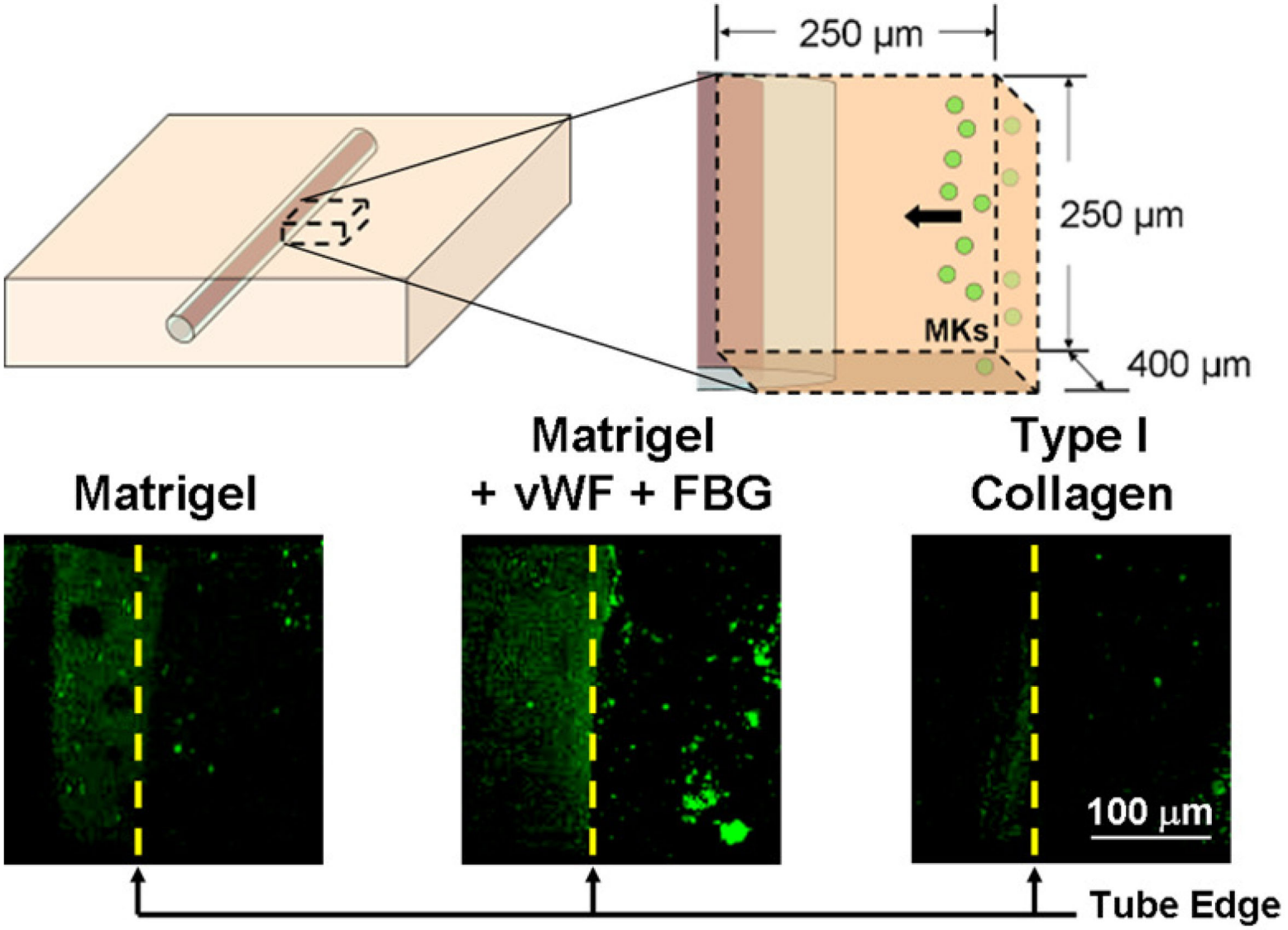
Pallotta et al., Tissue Engineering 2011

3D bone marrow model using silk based vascular tubes



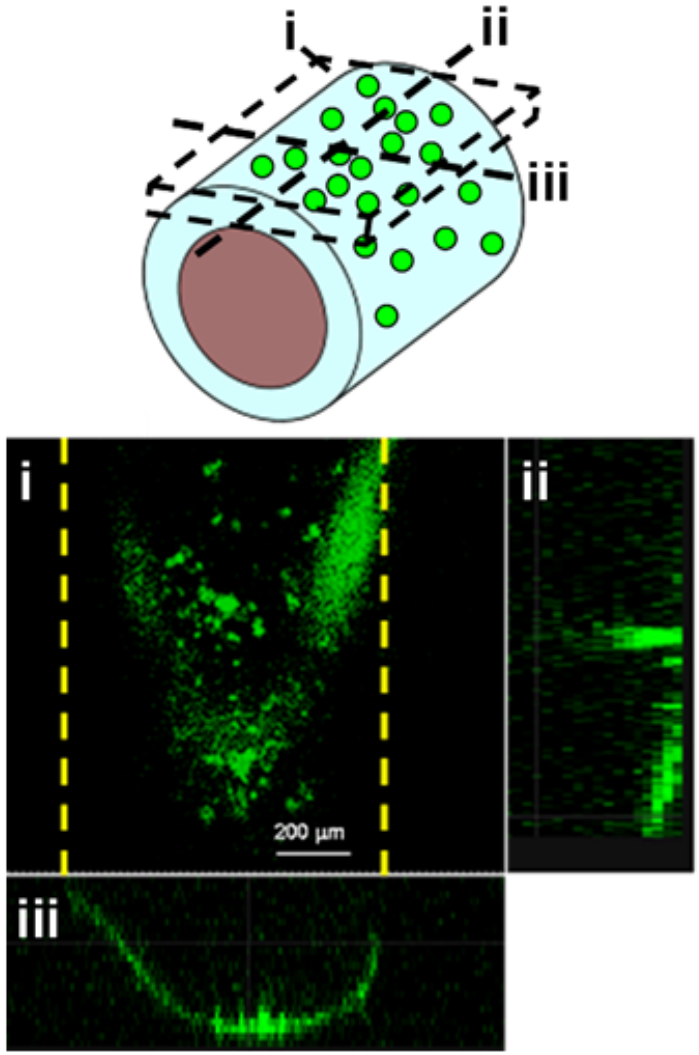
Pallotta et al., Tissue Engineering 2011

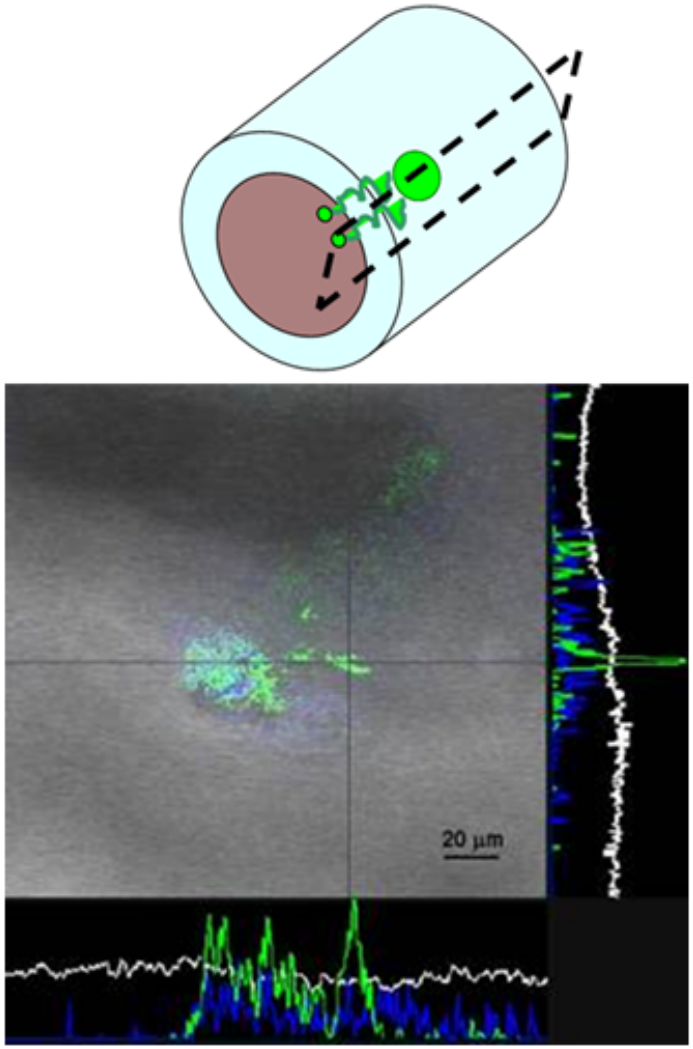
3D migration



Pallotta et al., Tissue Engineering 2011

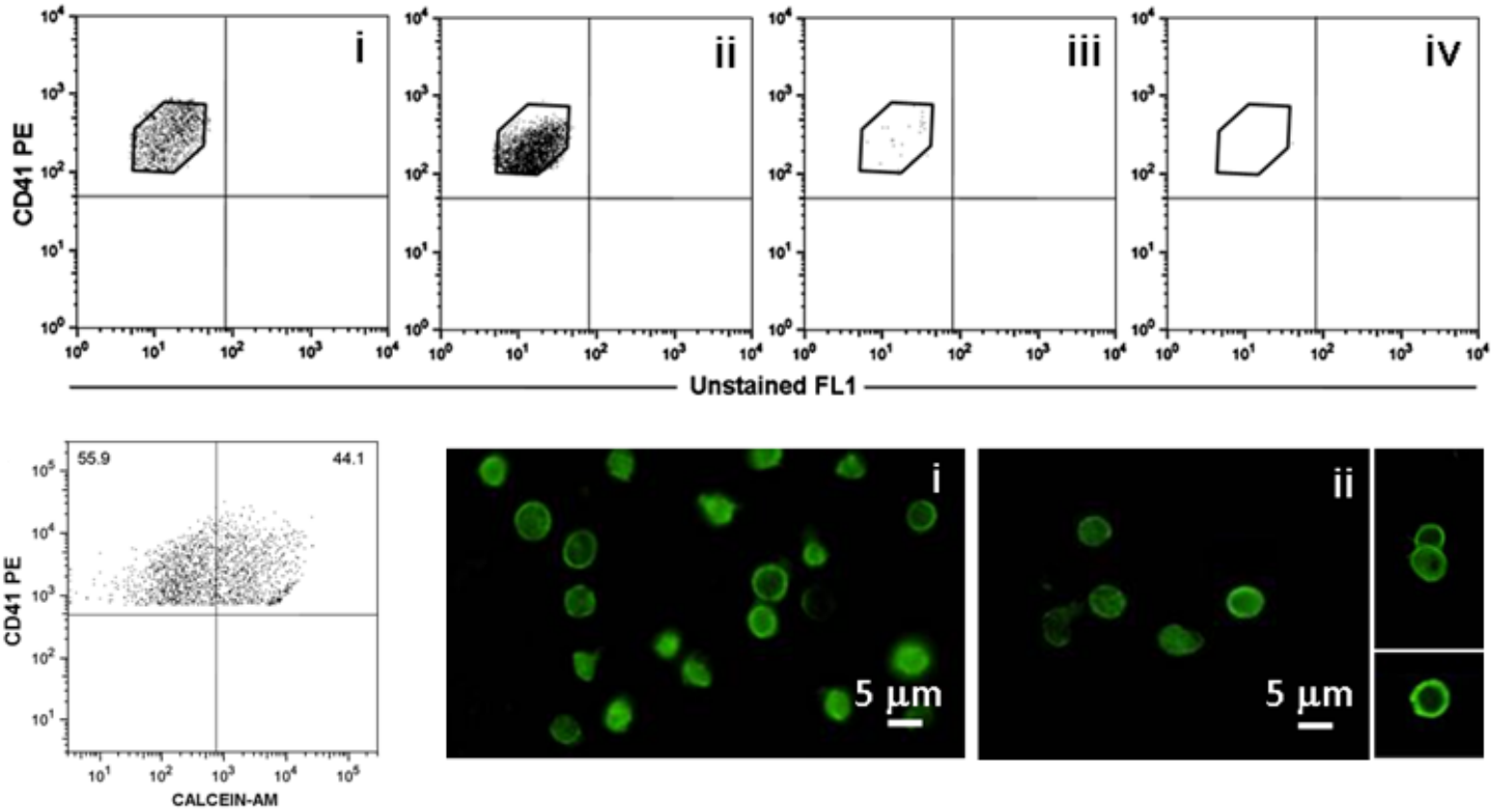
Mk adhesion and proplateet extension





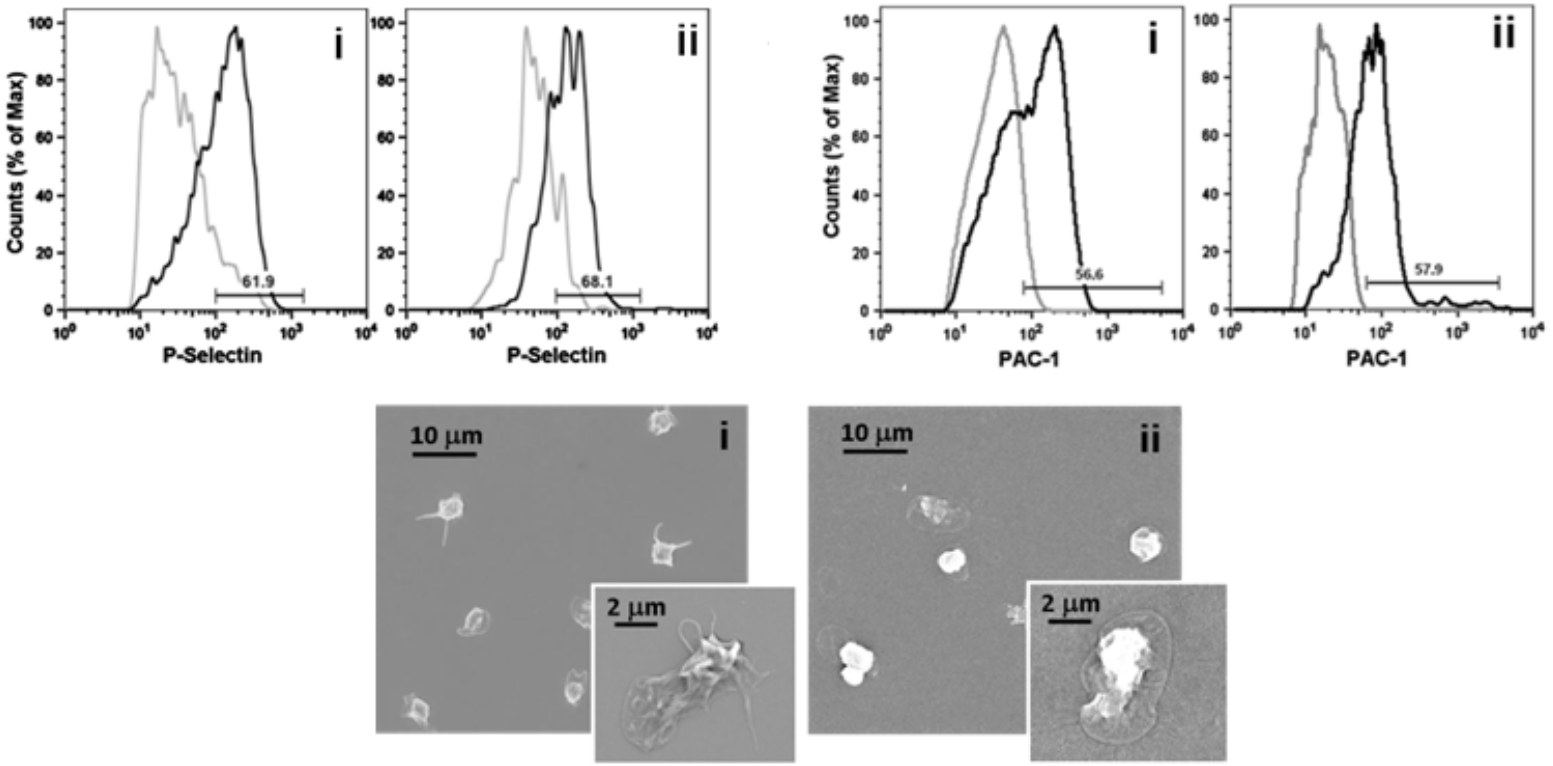
Pallotta et al., Tissue Engineering 2011

Released platelets in 3D model



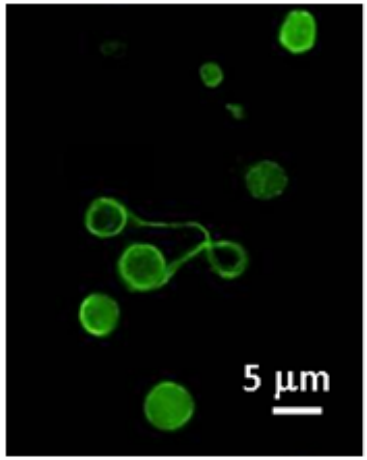
Pallotta et al., Tissue Engineering 2011

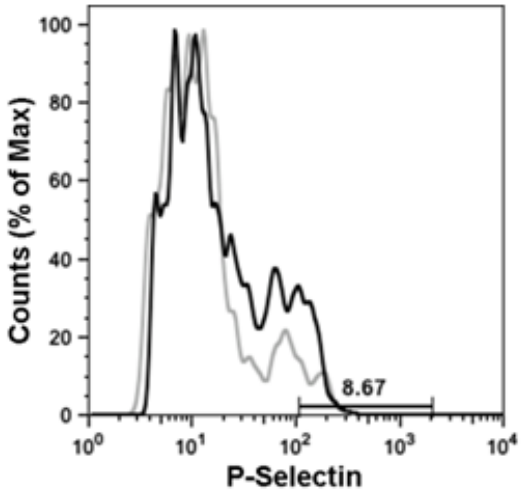
Released platelets in 3D model

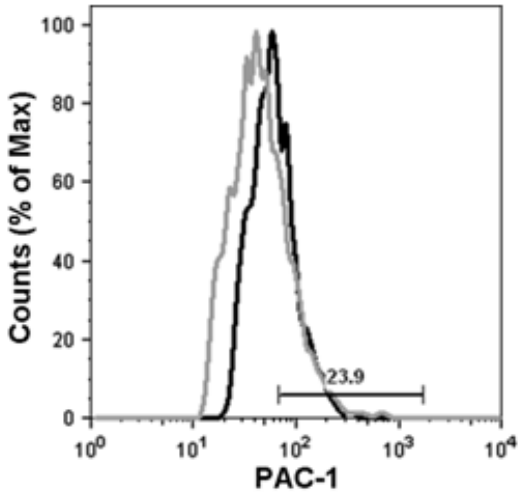


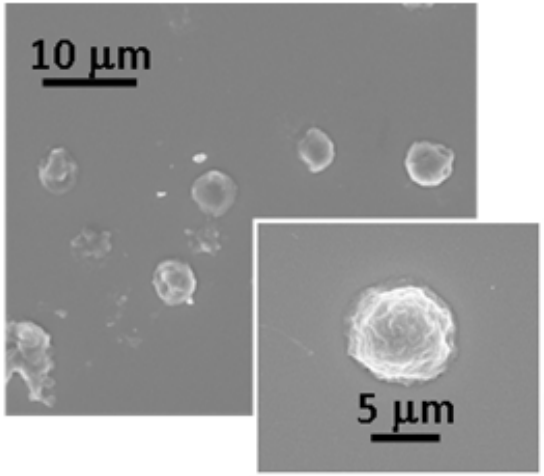
Pallotta et al., Tissue Engineering 2011

Released platelets in 2D model



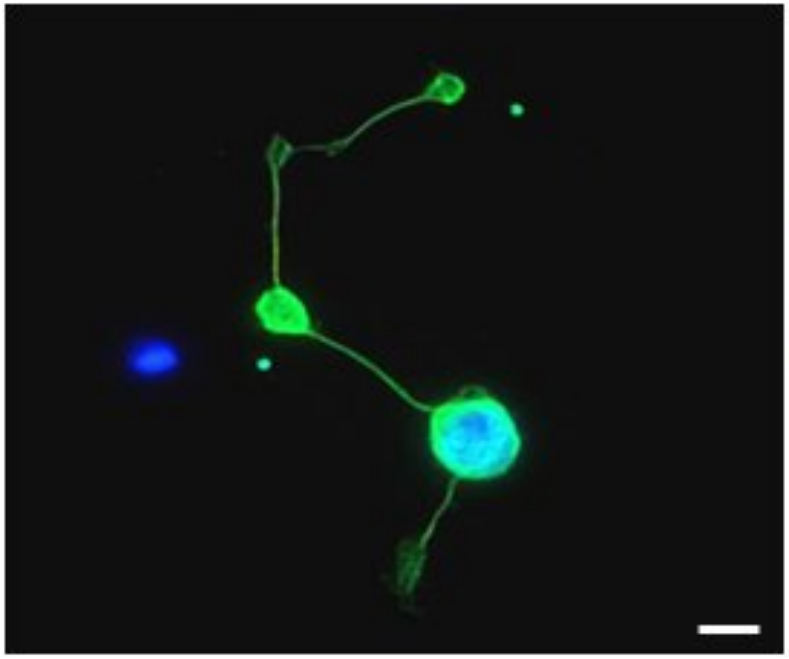




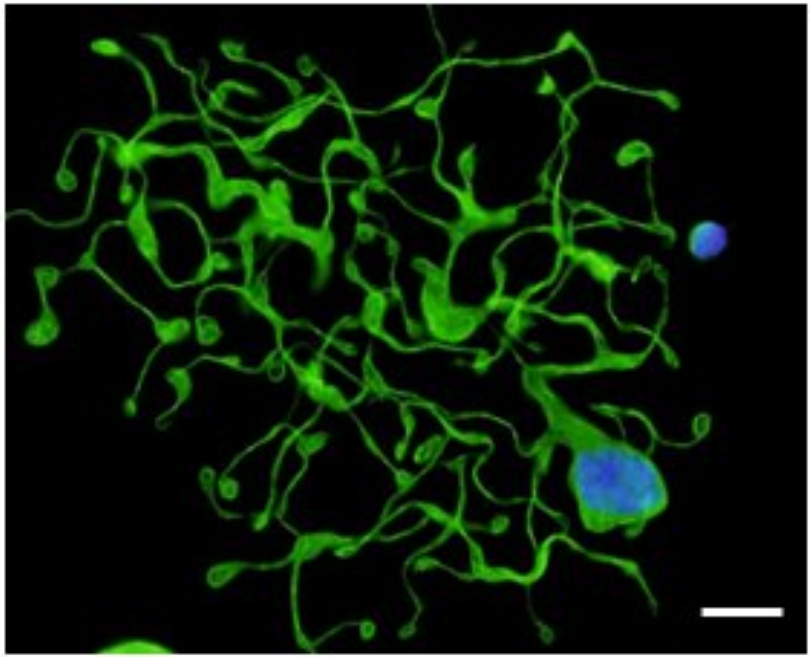


Pallotta et al., Tissue Engineering 2011

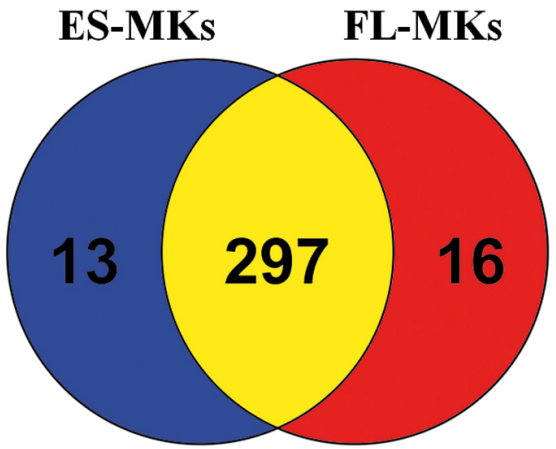
***MYH9*-RD**



MPNs



A)



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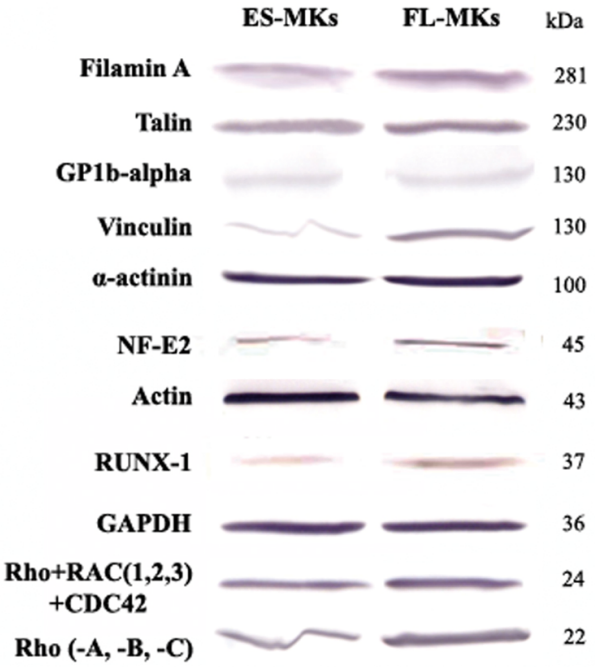
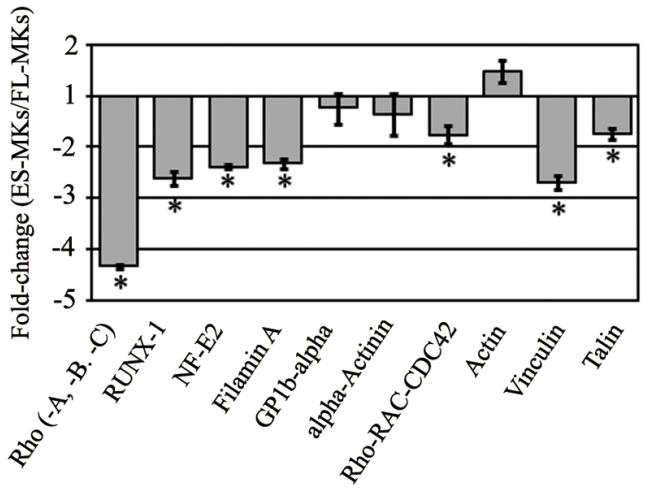
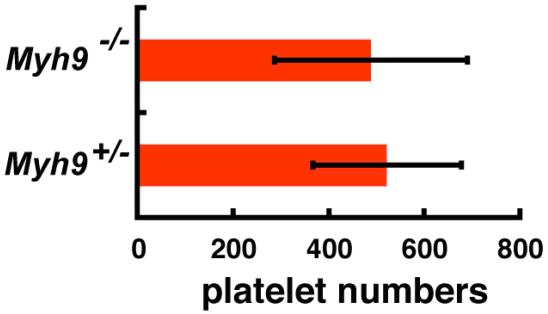


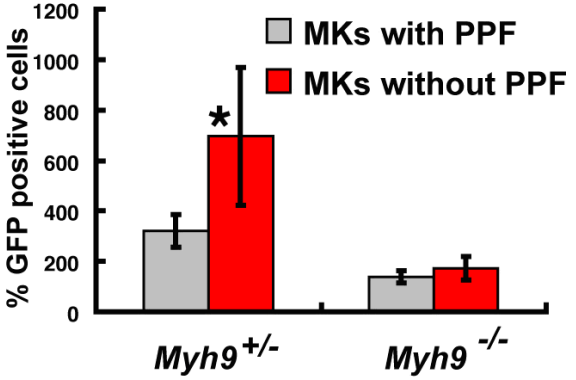
C)



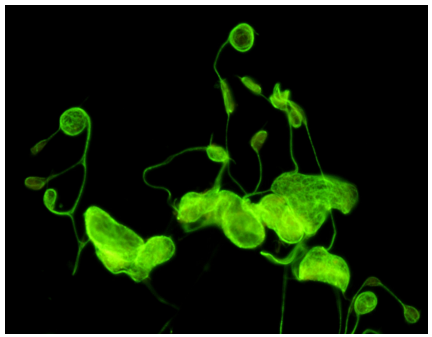
Merico et al., JTH 2012

MYH9 -/- ESC derived MKs extend proplatelets

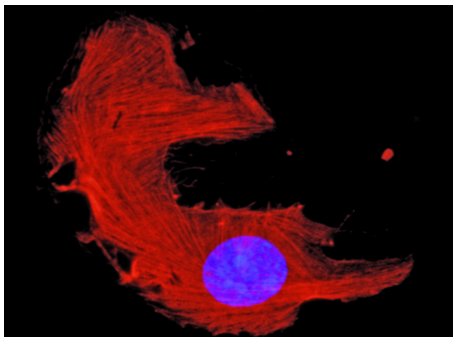




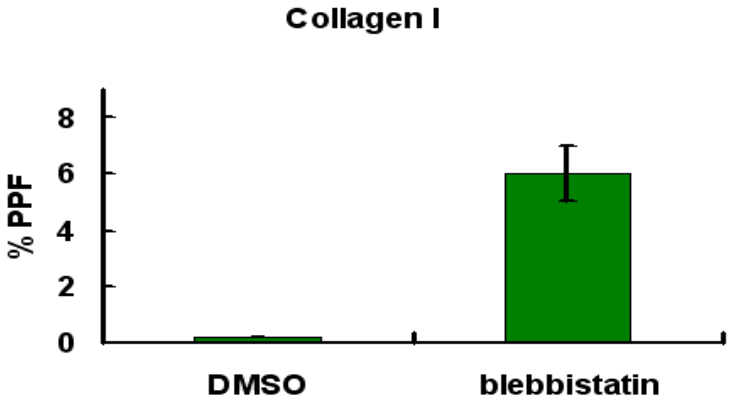
Chen et al., Blood 2007



blebbistatin

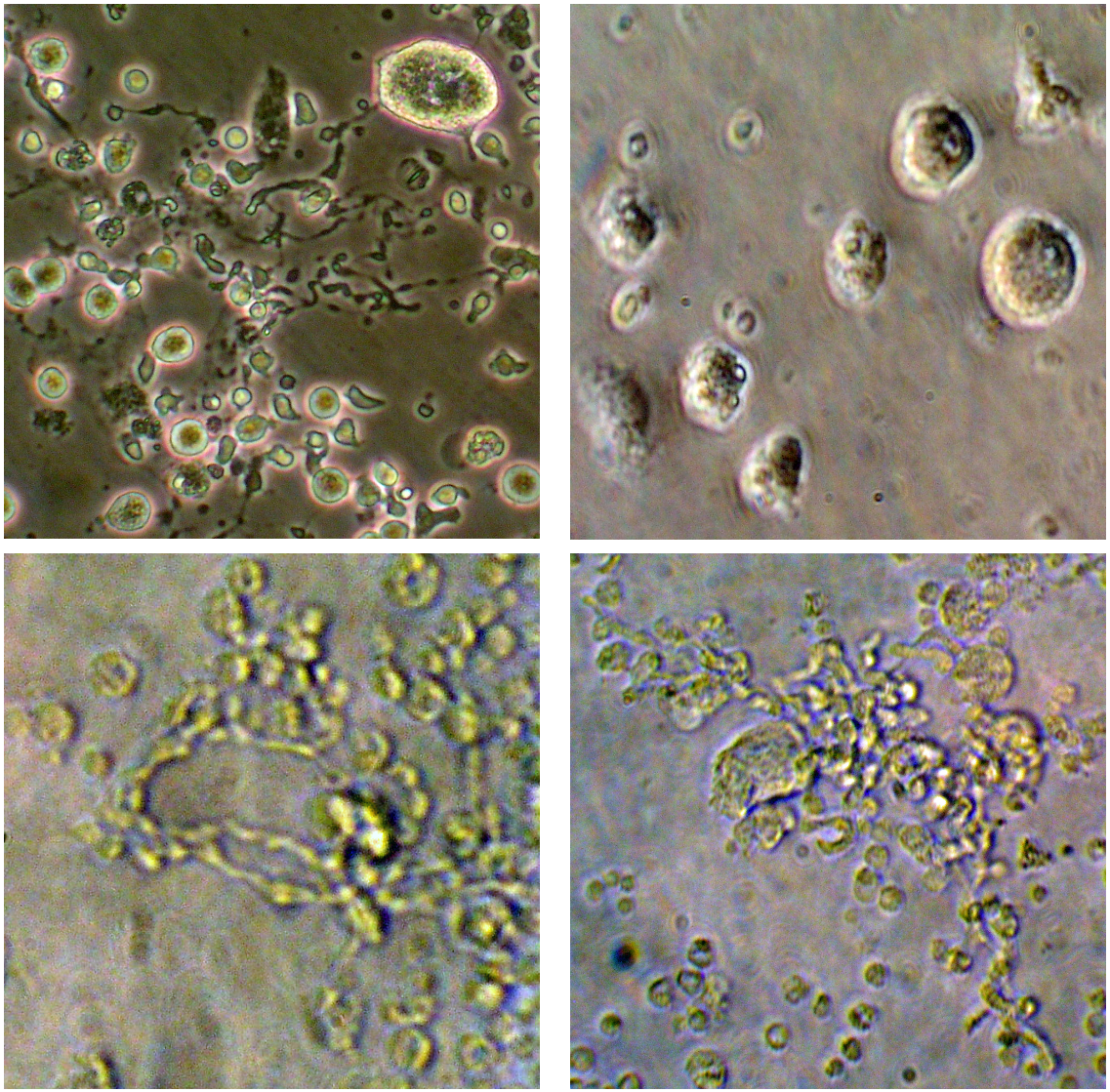


DMSO



Balduini et al., JTH 2008

Proplatelets on type I Collagen



Pecci et al., JTH 2009

Summary

- Type I collagen inhibits proplatelet formation

- Mk spreading on type I collagen is maintained by fibronectin assembly promoted by factor XIII

- Structure and nano-mechanics of type I collagen determine Mk behavior and signaling activation

- Mk actively regulate their fate depending on matrix Adhesion

- Disease state depend on both Mk and environment activity