The role of TGF-β and the transcription factor KLF-10 in the function of Early Endothelial Progenitor Cells

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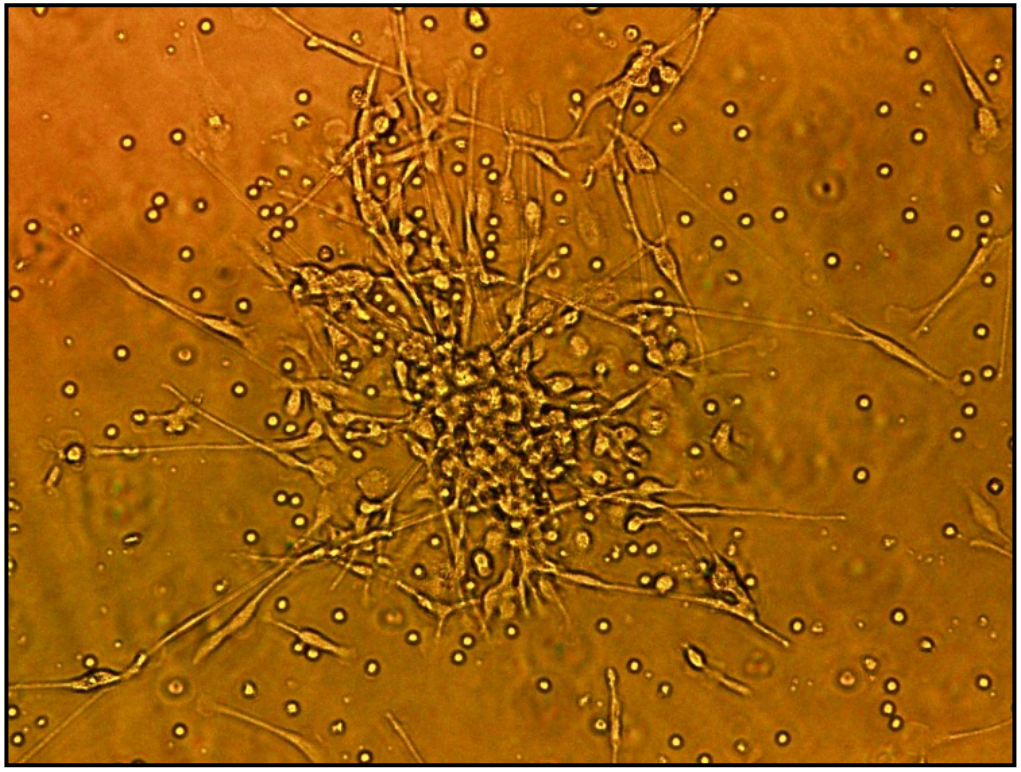
Disclosures

None!

Early proangiogenic cells (EPCs)



EPCs and cardiovascular Risk factors

Table I Factors affecting EPC mobilization

Stimulus	Response
Age[36–38]	↓ EPC cytopoiesis ↓ EPC mobilization (chronic e acute) ↓ EPC survival ↓ EPC functional activity
Oestrogens[35]	↑ EPC concentration
Exercise[31–34]	↑ EPC concentration
CV risk factors	
Number of CV risk factors[42]	↓ EPC number
Framingham CV total risk score[45]	↓ EPC number ↓ CD34/KDR+ number
Optimal flow-mediated dilation[45]	↑ EPC number ↑ CD34/KDR+ number
Smoking[44]	↓ EPC number
Hypertension[46]	↑ EPC proliferation ↓ EPC survival
Hypercholesterolaemia[47]	↓ EPC proliferation ↓ EPC migratory capacity ↓ EPC vasculogenetic property ↓ EPC survival
Diabetes mellitus[48]	↓ EPC number

EPCs and cardiovascular disorders

The level of circulating CD34+KDR+ endothelial progenitor cells predicts the occurrence of cardiovascular events and death from cardiovascular causes and may help to identify patients at increased cardiovascular risk

Werner N, Kosiol S, Schiegl T, Ahlers P, Walenta K, Link A, Böhm M, Nickenig G. **Circulating endothelial progenitor cells and cardiovascular outcomes ,**N Engl J Med, 2005 ;353(10):999-1007.

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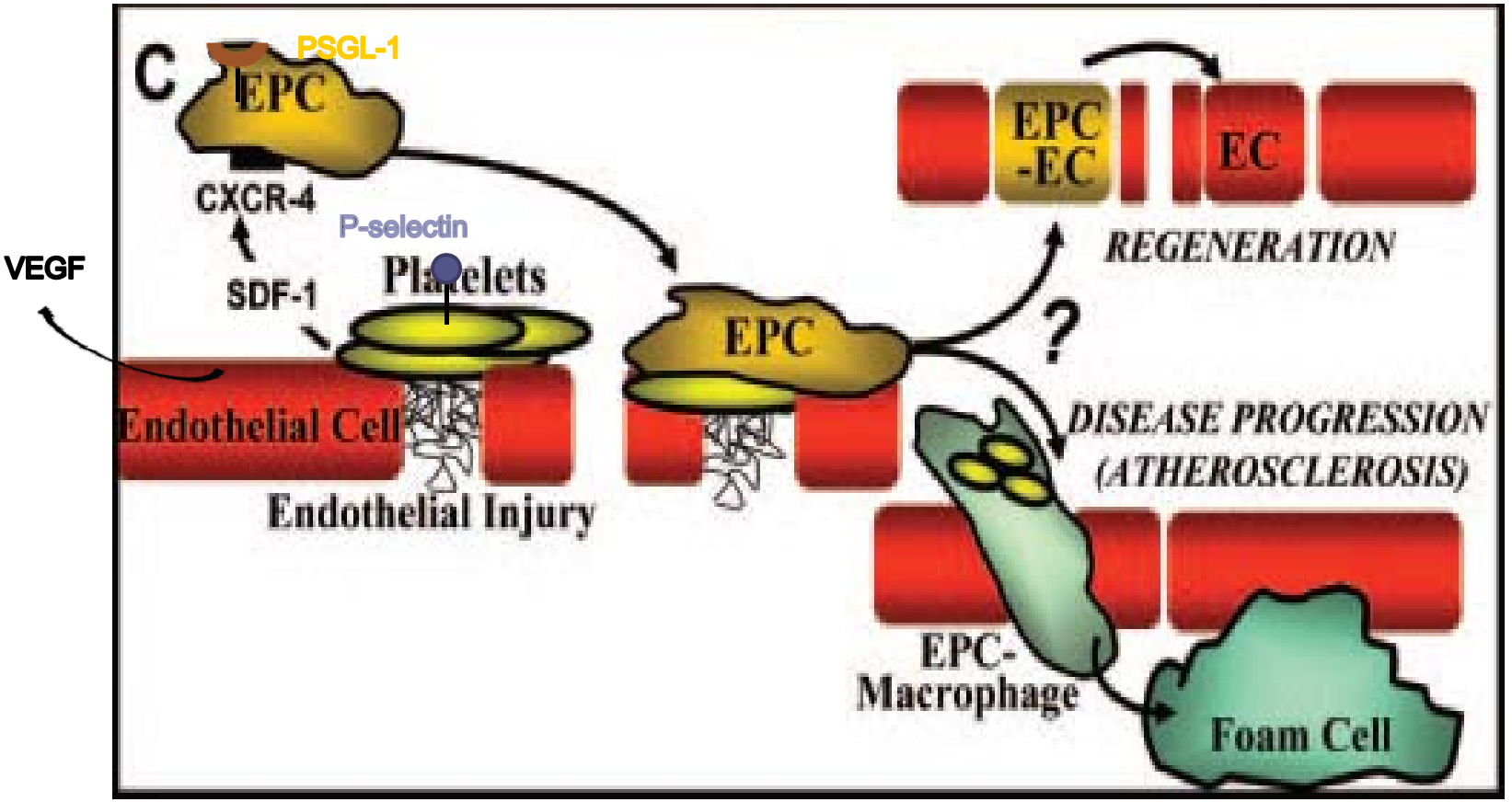
Platelets and EPCs



Andreas E, Platelets: Inflammatory Firebugs of Vascular Walls, Arterioscler Thromb Vasc Biol 2008.

Platelets And EPCs

Recent studies have shown that in the presence of direct interaction with platelets, EPCs improve their functional properties.

In vitro exposure to platelets in culture conditions enhances the capacity of EPCs to form colonies, to proliferate and migrate.

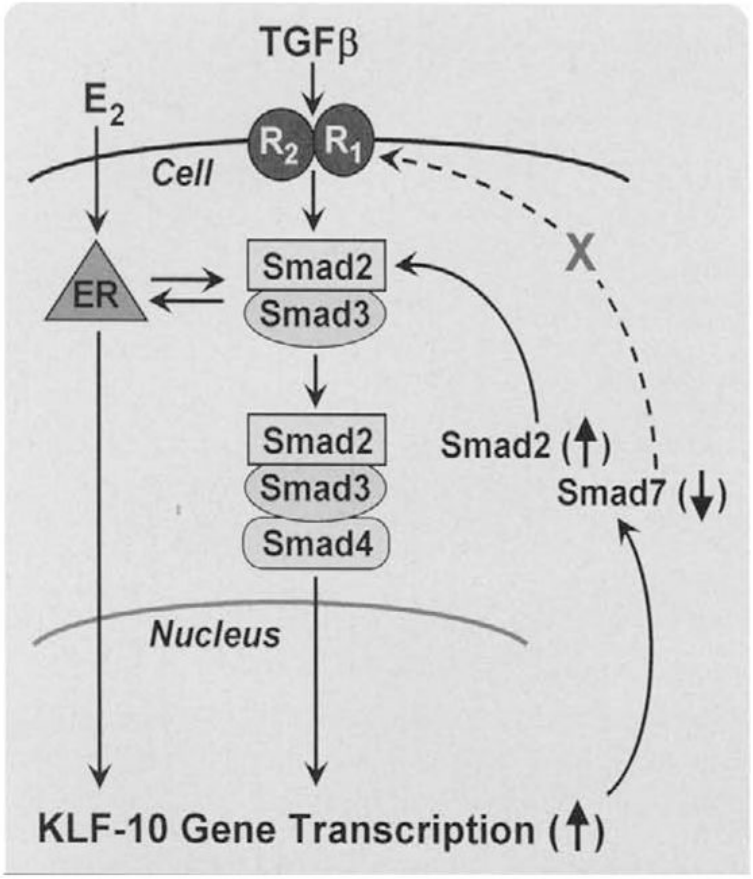
Dernbach et al Basic Res Cardiol Nov 2008, Leshem-Lev et al J. Thromb Thrombolysis Nov 2010

KLF-10

- a subclass of the zinc-finger family of transcription factors, participate in various aspects of cellular growth, development, and differentiation.

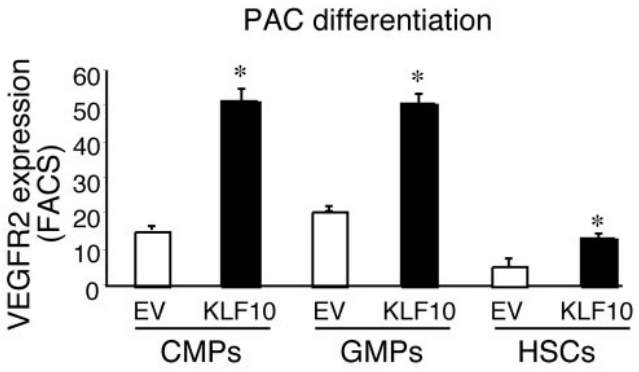
- KLF-10 targets CACCC element or GC BOX which are present in a large number of growth regulatory gene sequence including TGF-β, PDGF and FGF.

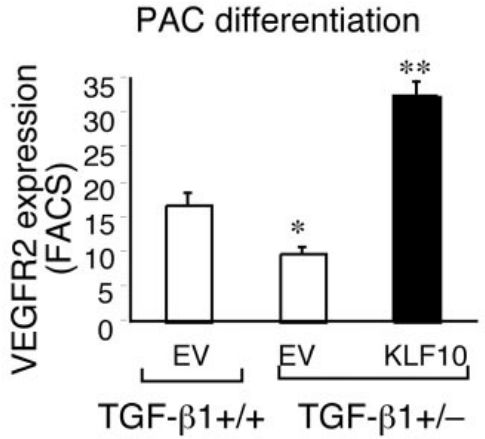
TGF-β and KLF-10 Signal Transduction

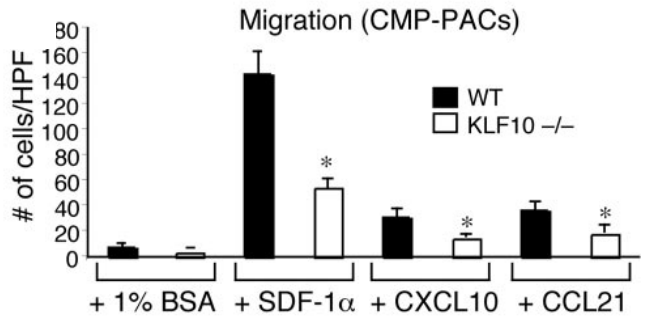


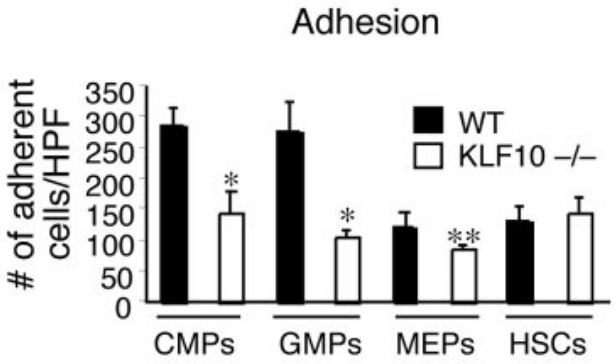
Functional role of KLF10 in multiple disease processes. Malayannan Subramaniam1,*, John R. Hawse1, Nalini M. Rajamannan2, James N. Ingle3 and Thomas C. Spelsberg. Biofactors. 2010 ; 36(1): 8–18.

In response to TGFß-1, KLF10 plays an important role in controlling EPC differentiation and function in vitro and in vivo



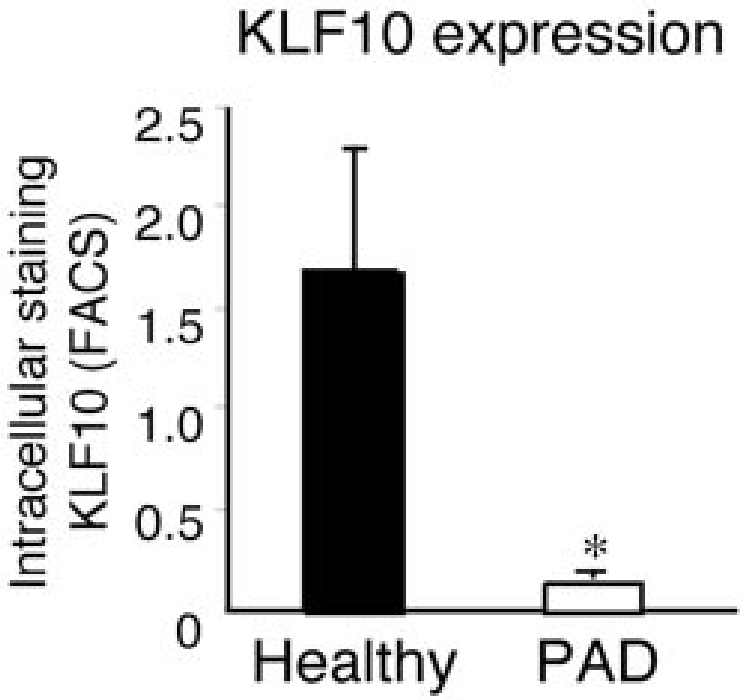






Wara AK, Foo S, Croce K, Sun X, Icli B, Tesmenitsky Y, Esen F, Lee JS, Subramaniam M, Spelsberg TC, Lev EI, Leshem-Lev D, Pande RL, Creager MA, Rosenzweig A, Feinberg MW. **TGF-β1 signaling and Krüppel-like factor 10 regulate bone marrow-derived proangiogenic cell differentiation, function, and neovascularization**. Blood. 2011 Dec 8;118(24):6450-60

KLF10 expression was found to be reduced in EPCs from patients with Peripheral Artery Disease.



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AIMs

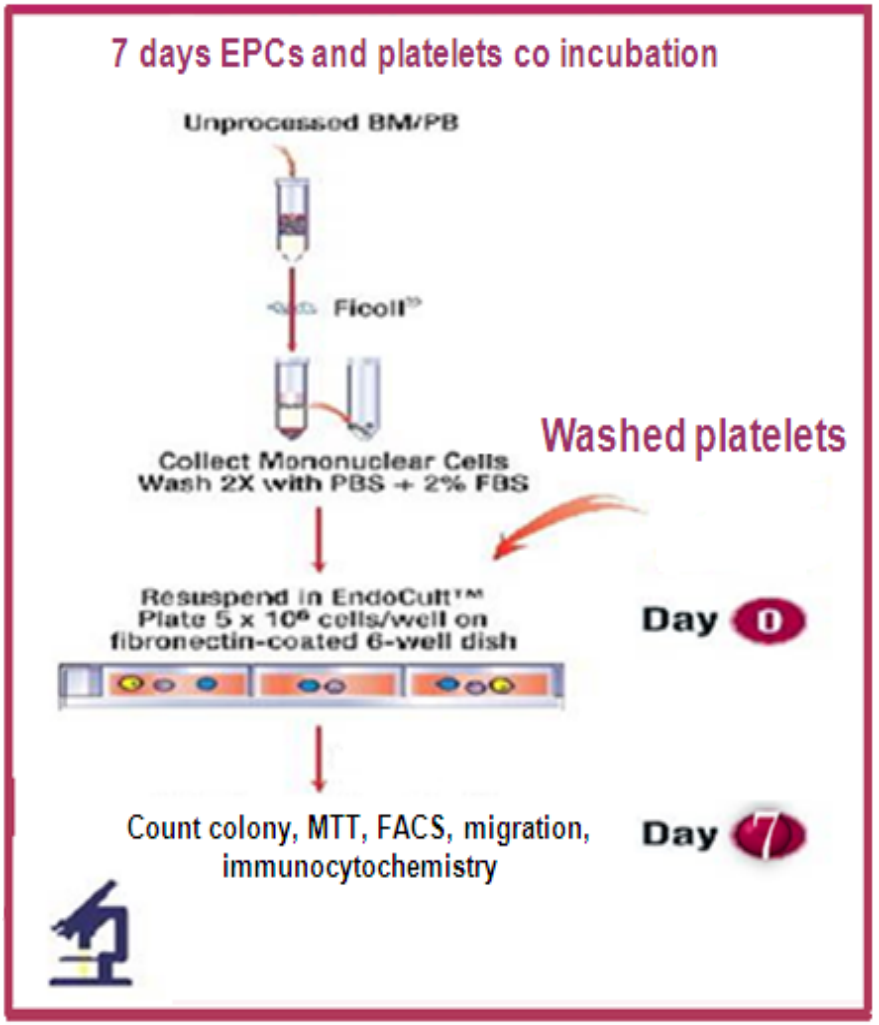
- **General aim-** to explore the mechanism of enhancement of EPCs function by platelets.
- **Specific aims-**

to examine the role of TGF-β and its transcription factor KLF-10 in the enhancement of EPCs function by platelets.

Experimental Design

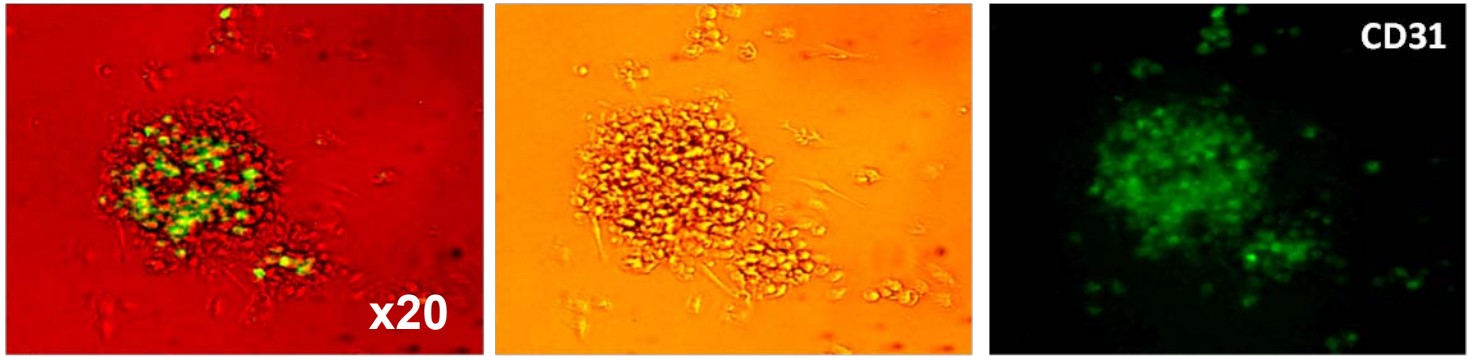
Human EPCs were isolated from donated buffy coats and cultured for 7 days on a traditional fibronectin matrix in one of the following conditions:

1. Alone (control)
2. Co-incubated with platelets
3. Co-incubated with platelets and TGFβRII inhibitor.



EPCs identification

.A



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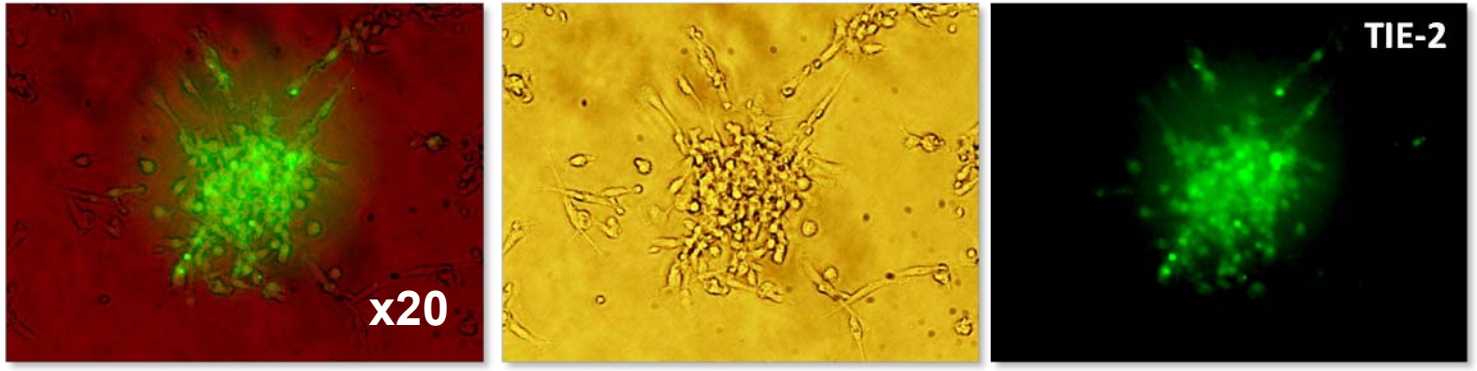

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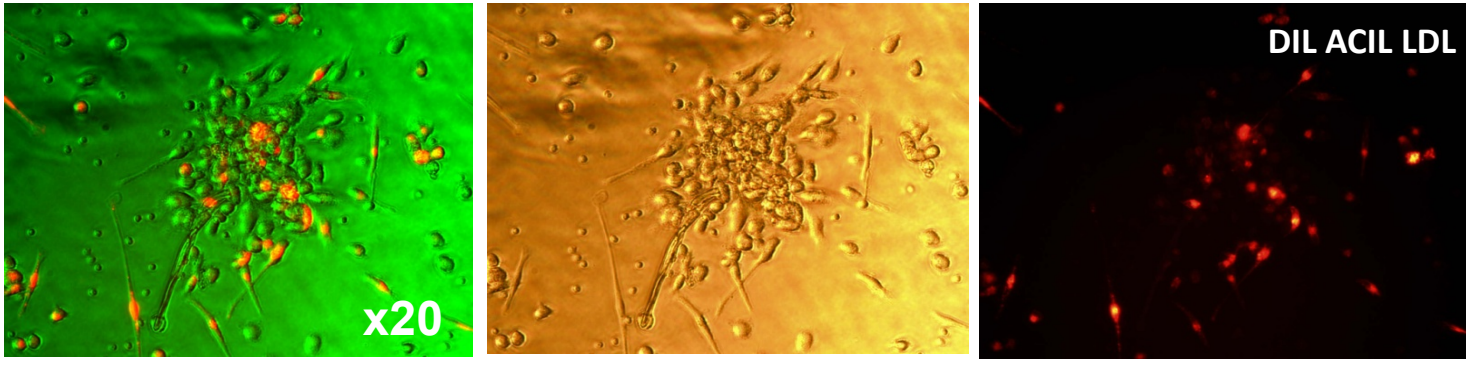
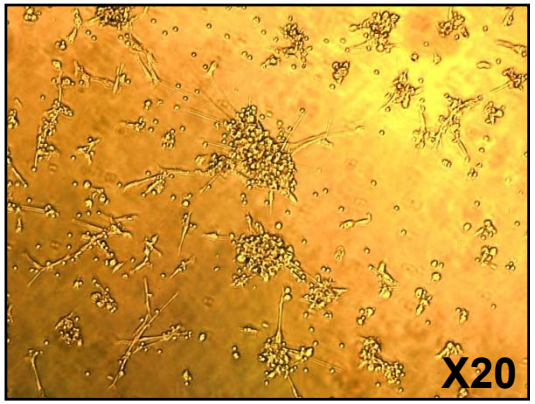
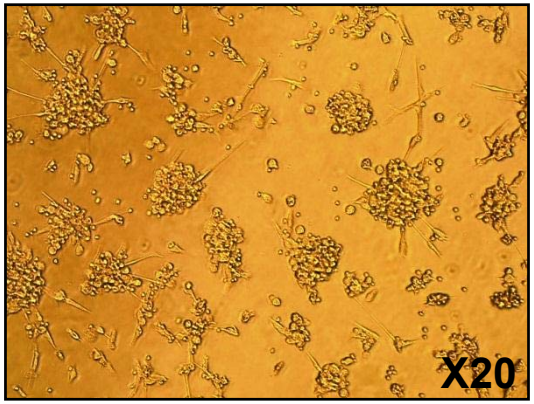


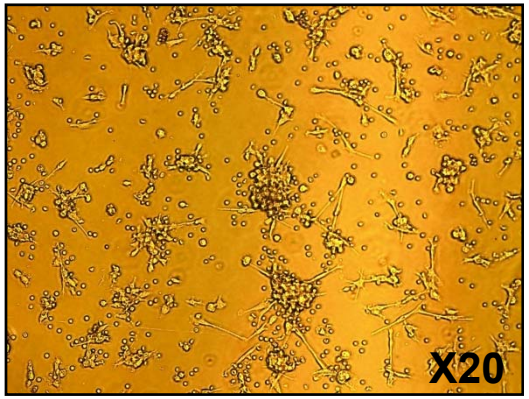
COLONY FORMING UNITS ASSAY (CFU)



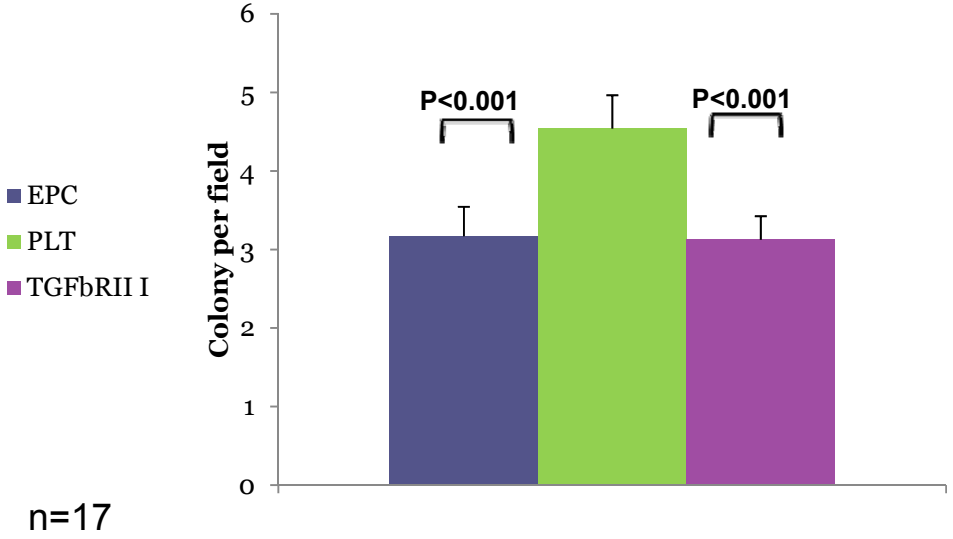
EPC



PLT



TGF-βRII inhibitor



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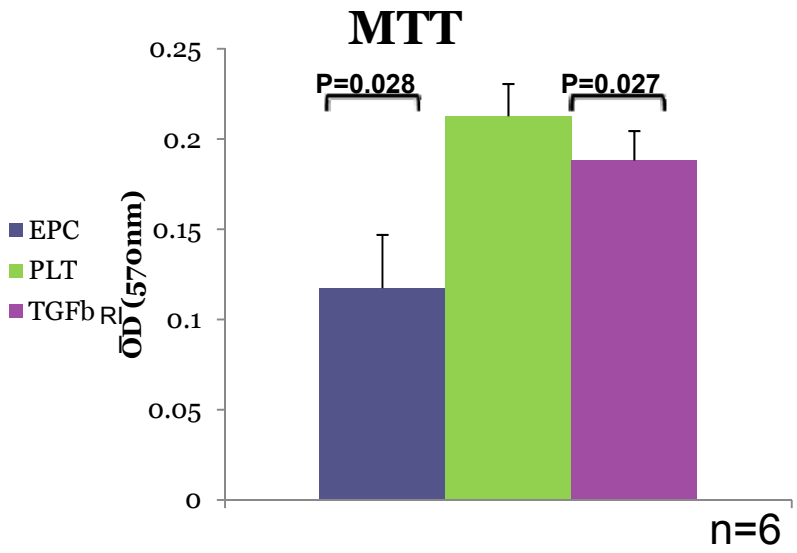
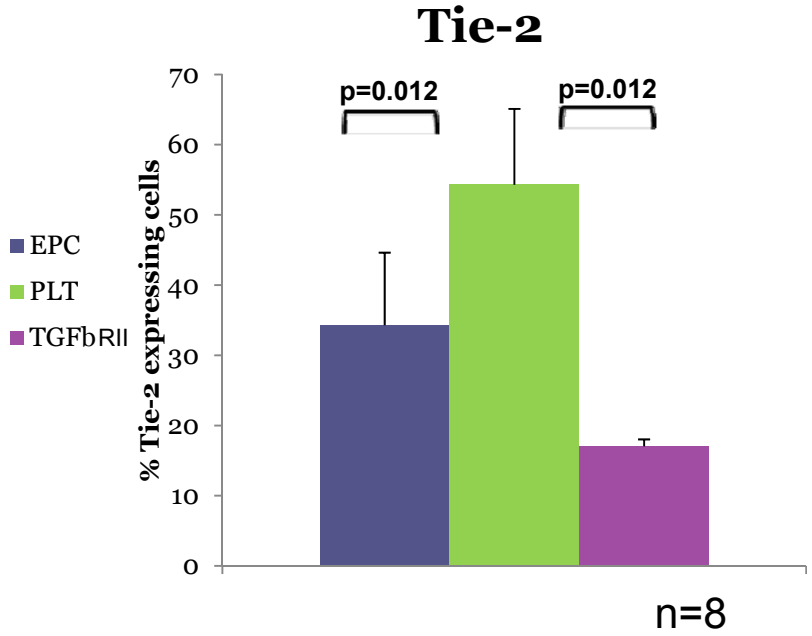
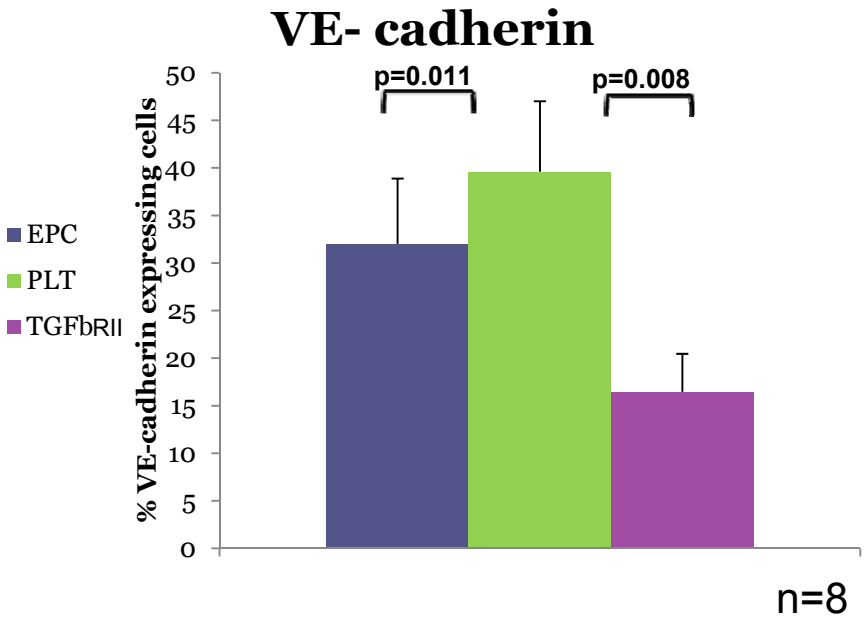
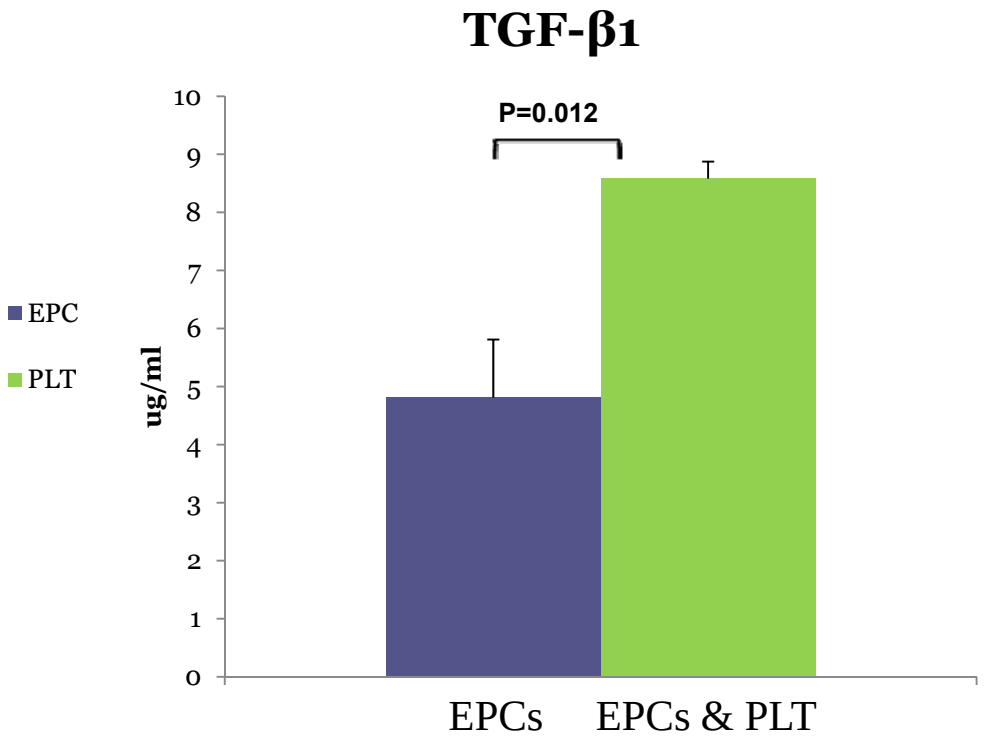
Viability and Endothelial Markers







TGF-β LEVELS



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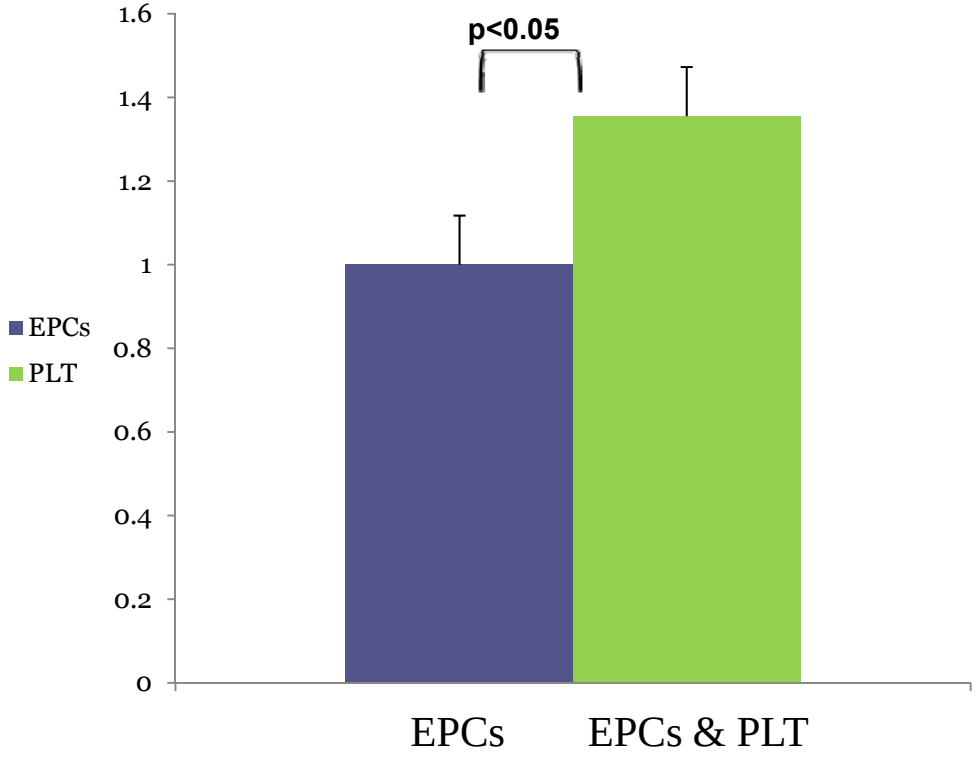
TGF beta mRNA levels in EPCs



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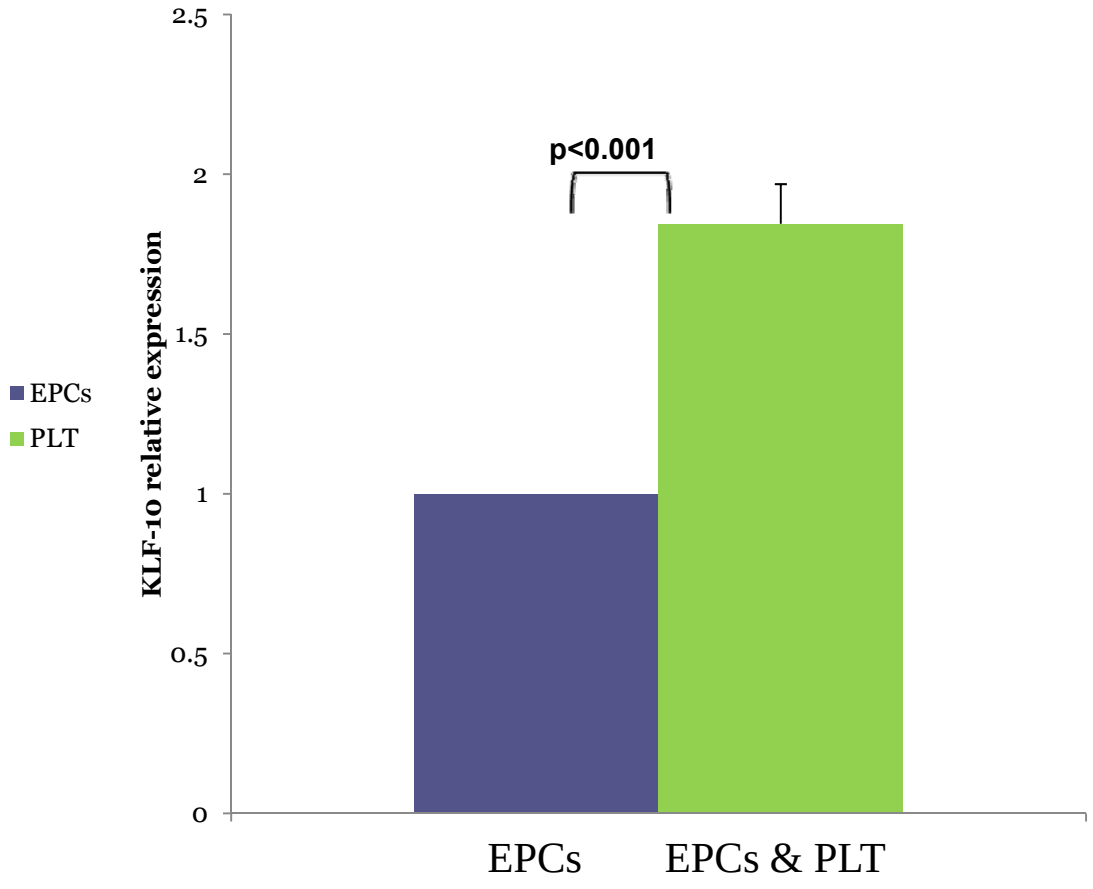
KLF-10 mRNA levels in EPCs



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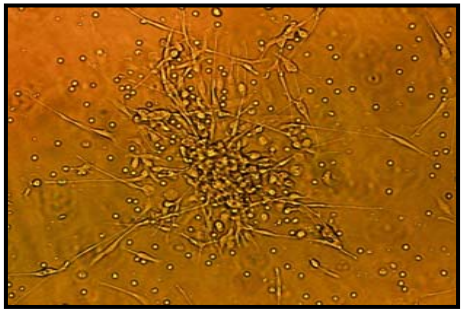

Improved functional properties

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TGFβ

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KLF10

EPCs

TGFβ

Growth Factors, cytokines and chemokines

PLT

CONCLUSIONS

- TGF-β has a central role in the effect of platelets on EPCs.
- This effect might be modulated by KLF-10.
- Further study is required in order to examine the role of KLF-10 in the enhancement of EPCs function by platelets and to explore its mechanisms of action.

THANKs

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THANK YOU FOR LISTENING!!