
2019台灣胸腔暨重症加護醫學會

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# Induced pluripotent stem cells through leukemia inhibitory factor to attenuate neutrophil transendothelial migration in sepsis-induced acute lung injury

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CHEST

Original Research

CRITICAL CARE

# IV Delivery of Induced Pluripotent Stem Cells Attenuates Endotoxin-Induced Acute Lung Injury in Mice

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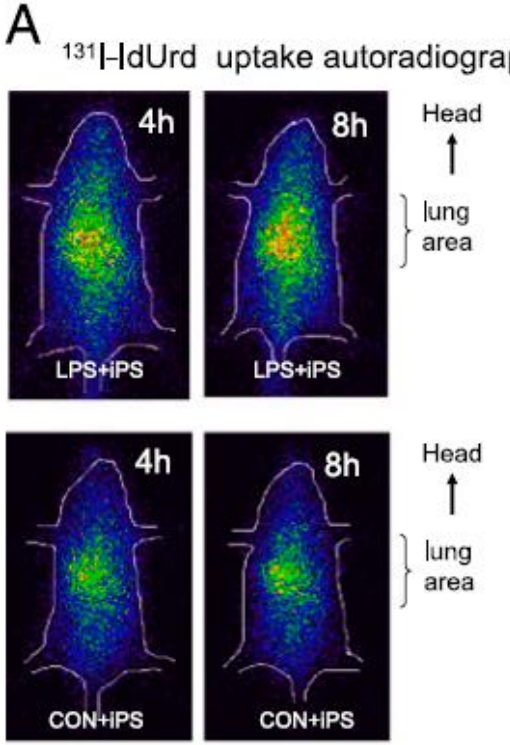
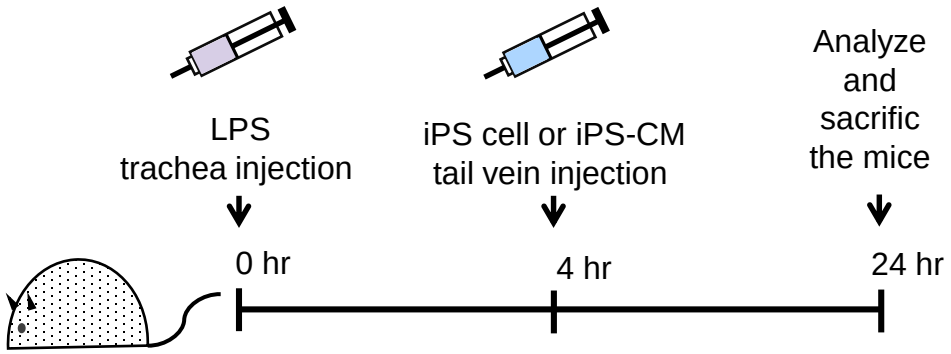
**CHEST 2011; 140(5):1243–1253**



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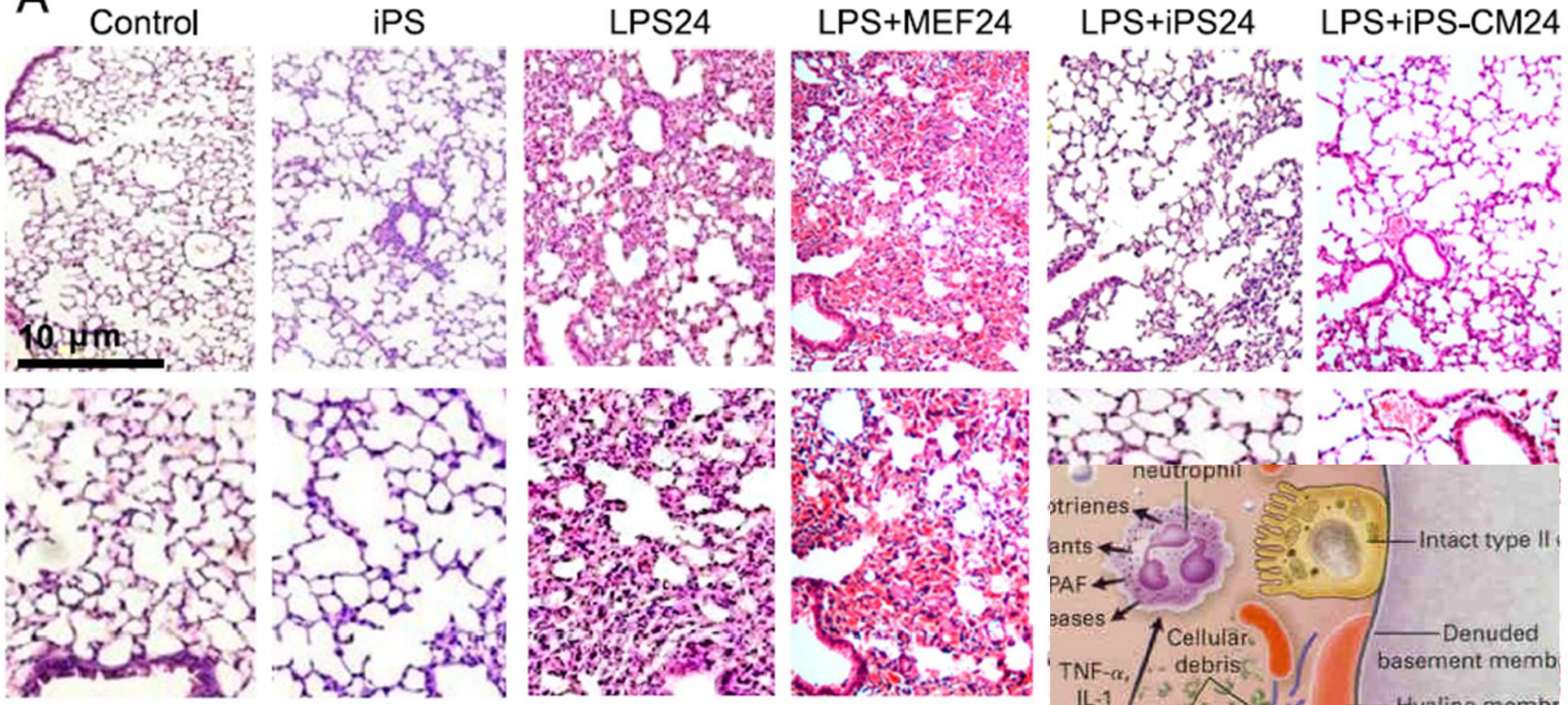


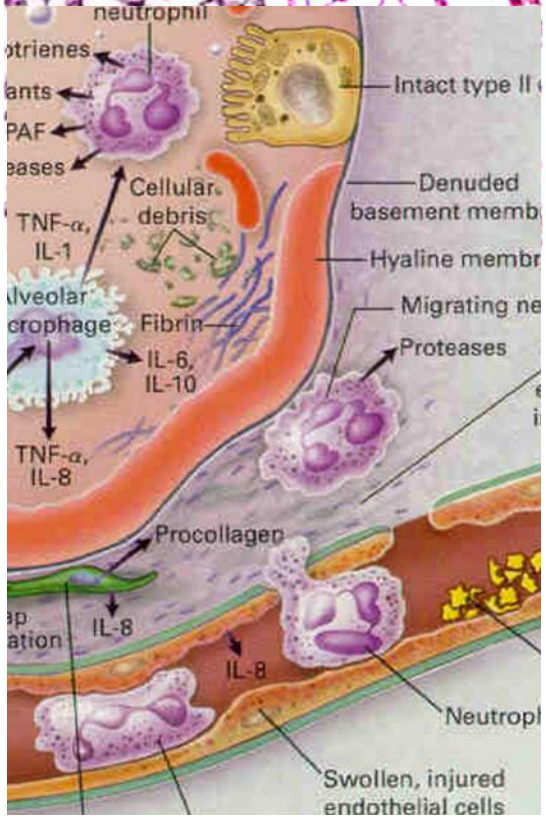


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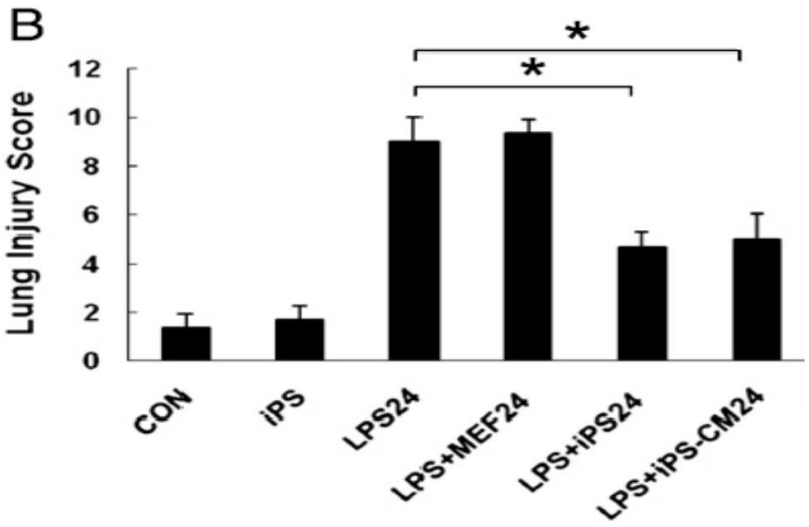
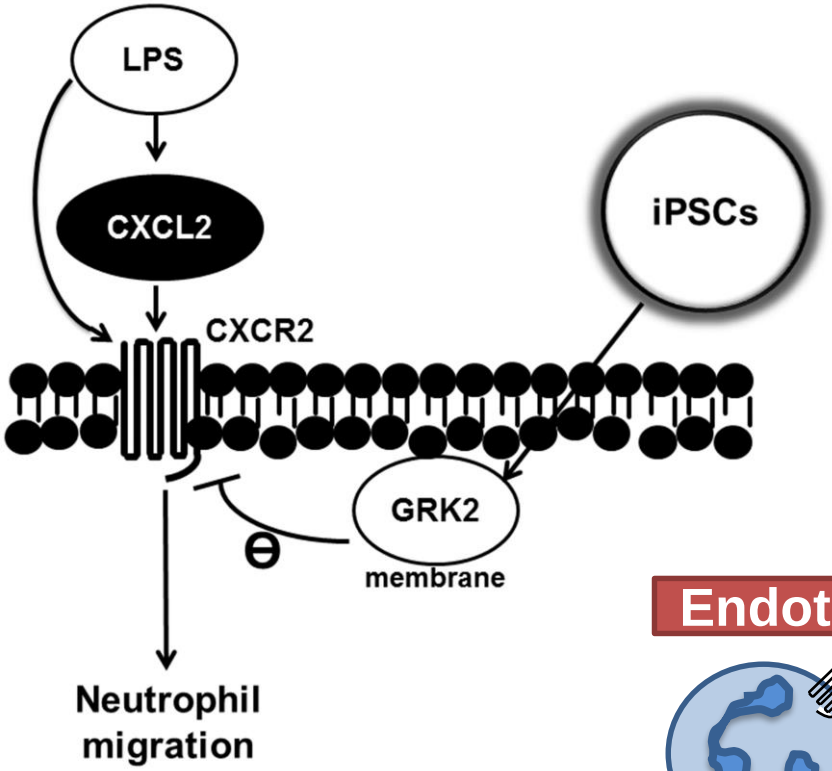
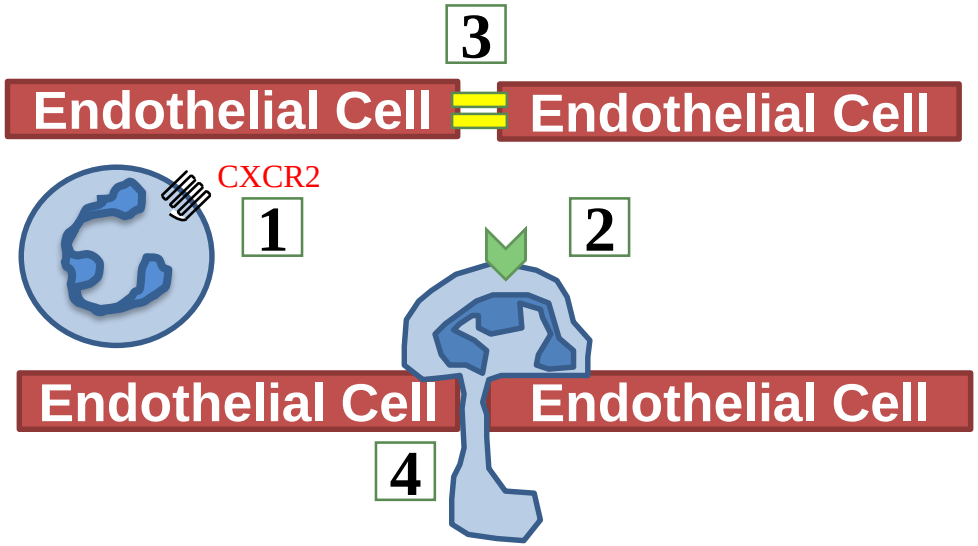



CHEST 2011; 140(5):1243–1253

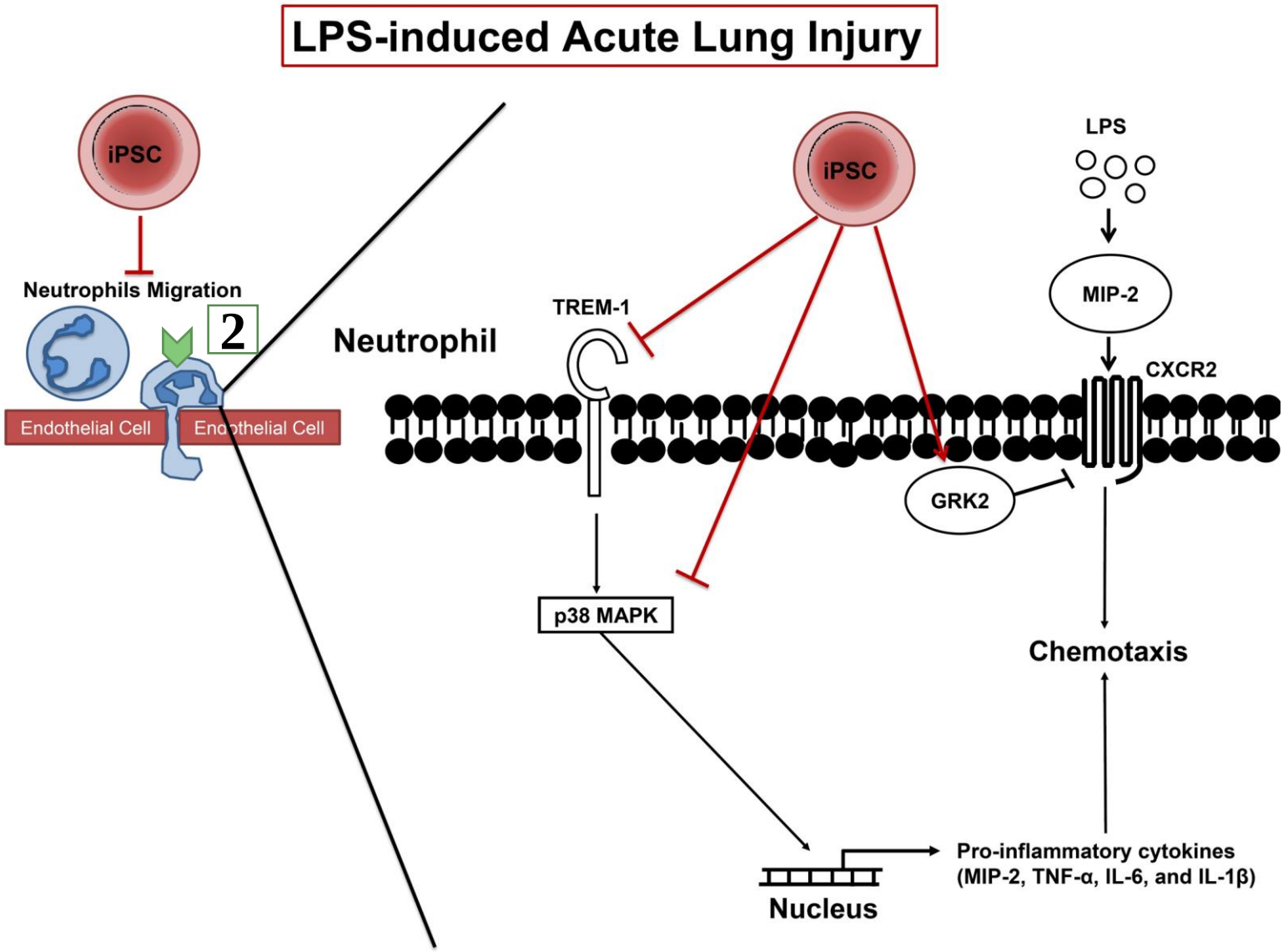
# iPSCs reduce neutrophil chemotaxis via activating GRK2 in endotoxin-induced acute lung injury



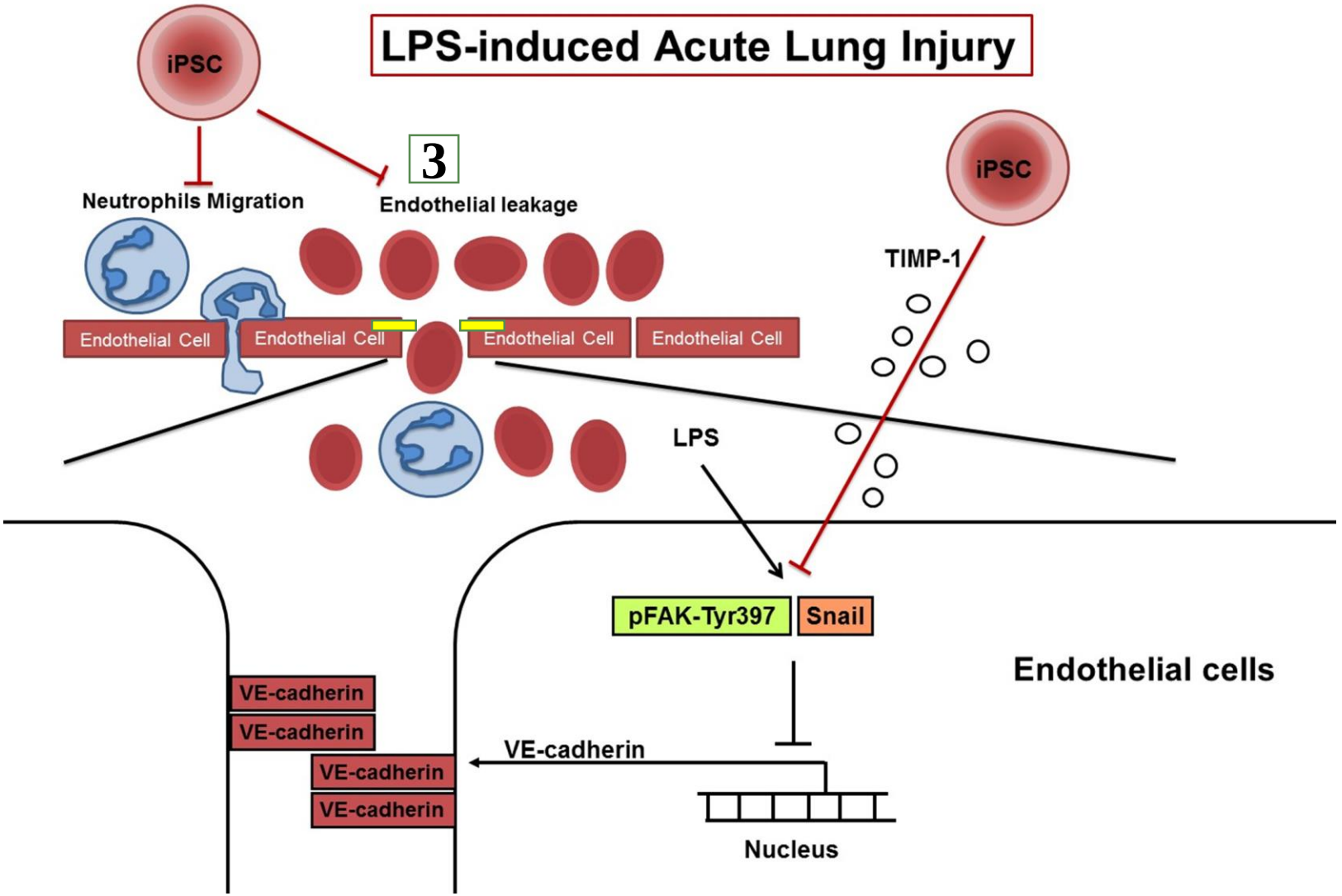

*Respirology* 2017;22(6):1156-1164

# iPSCs regulate TREM-1 expression and the p38 MAPK pathway in endotoxin-induced acute lung injury




Stem Cells 2019; 37:631-639

# iPSCs attenuate endothelial leakage in acute lung injury via TIMP-1 to reduce FAK activity




Stem Cells 2019 Oct 6. Epub.

# Mechanism of Neutrophil Transendothelial Migration

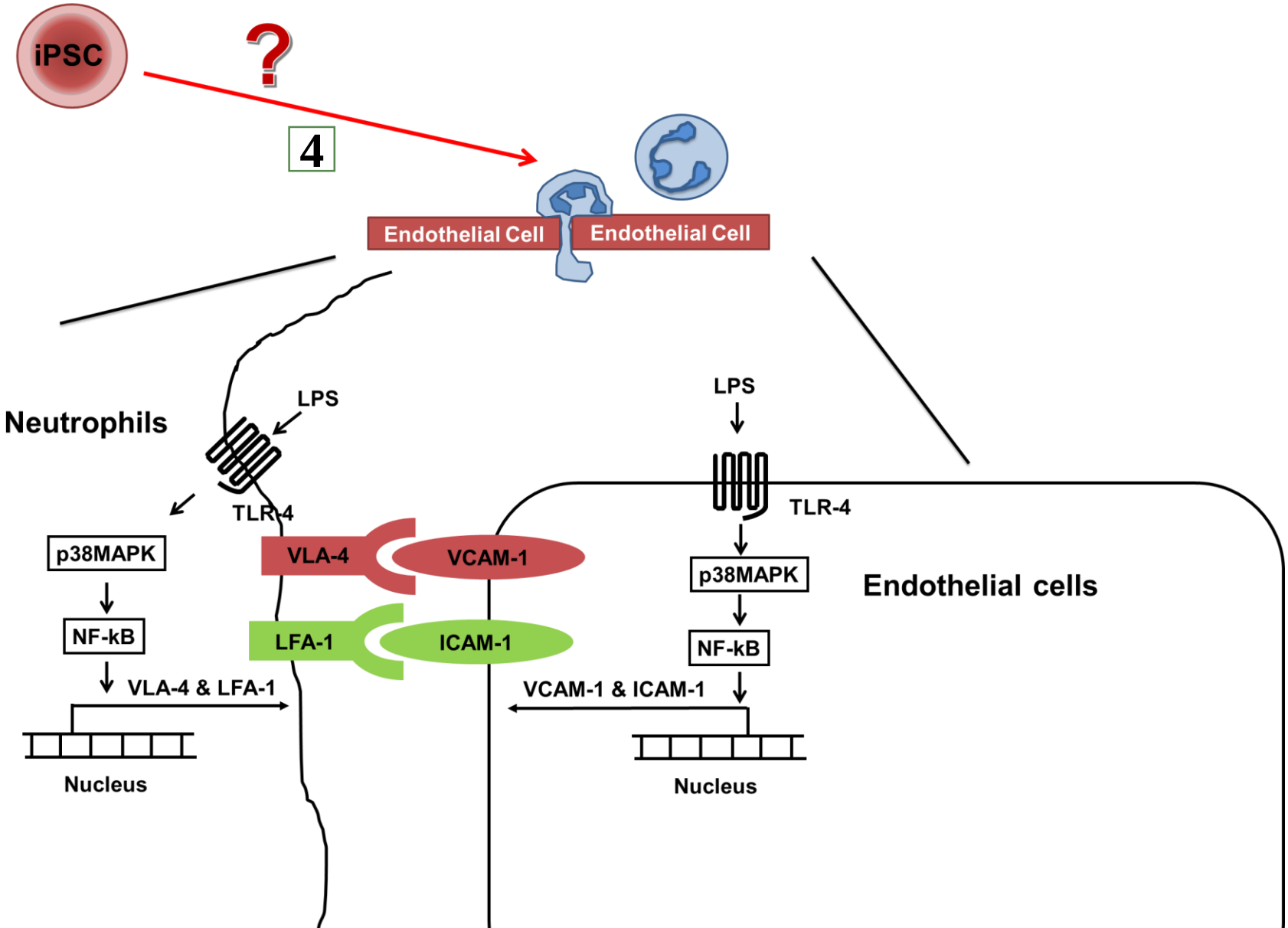
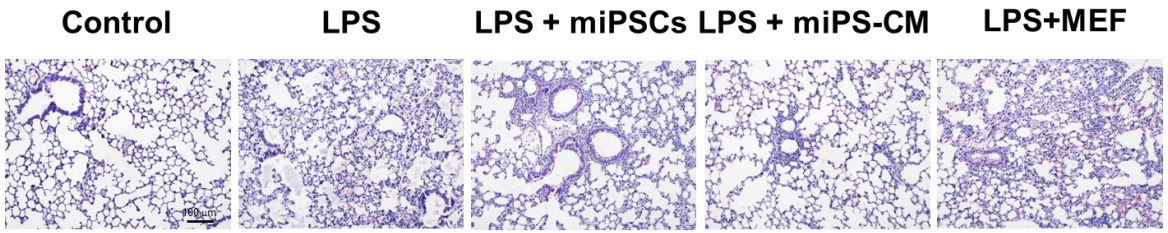


Fig. 1a H&E stain



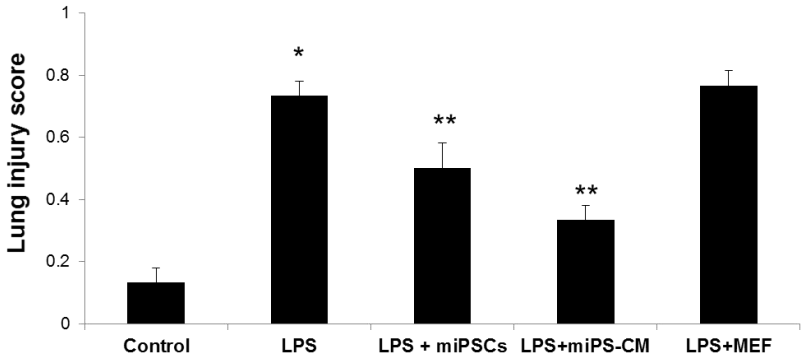
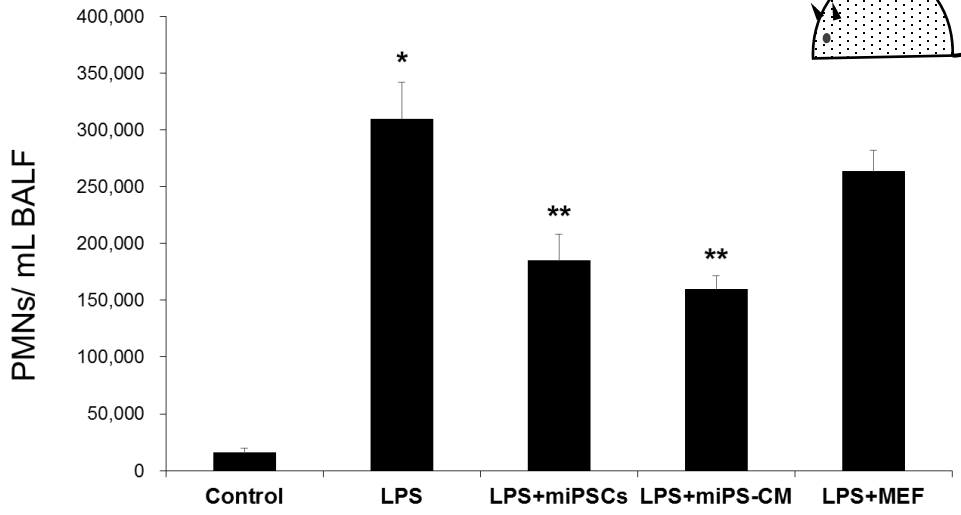




Fig. 1b PMNs in BALF




In vivo Mice study

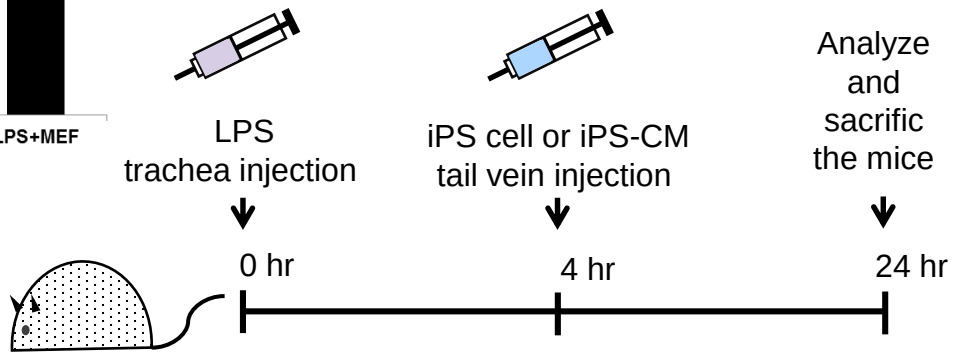


Fig. 1c Lung IHC analysis for VCAM-1

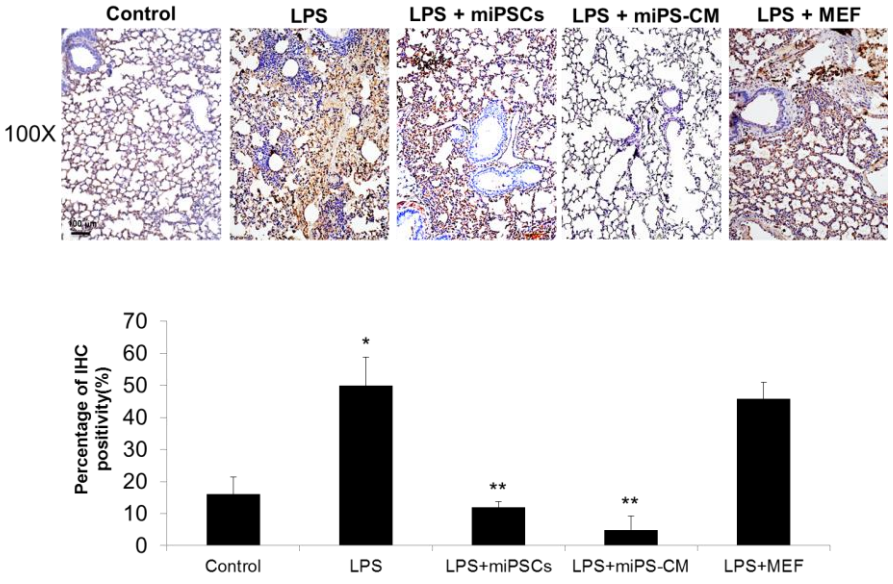



Fig. 1d Lung IHC analysis for ICAM-1

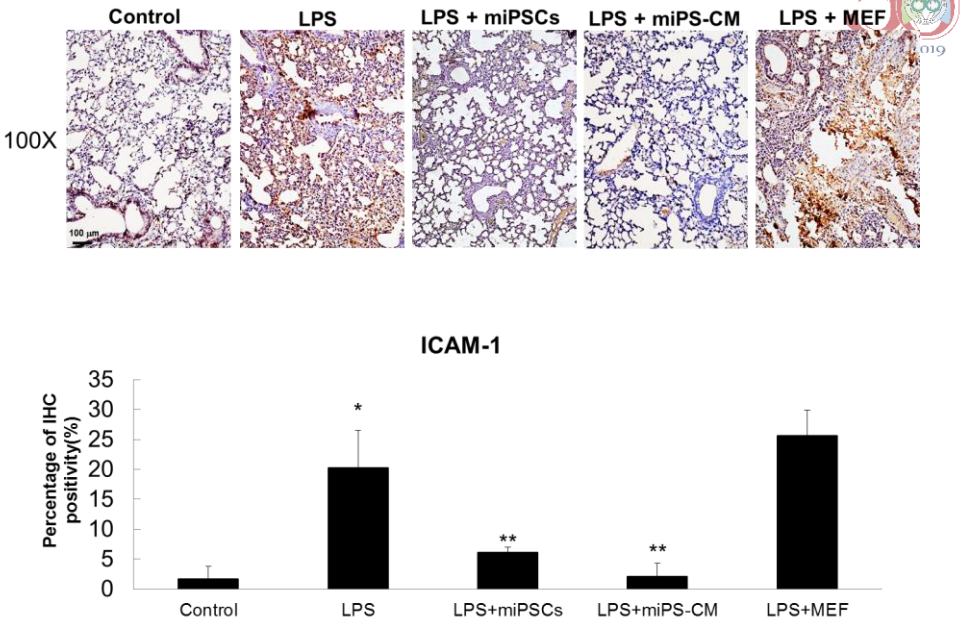



Fig. 1e Lung IHC analysis for VLA-4

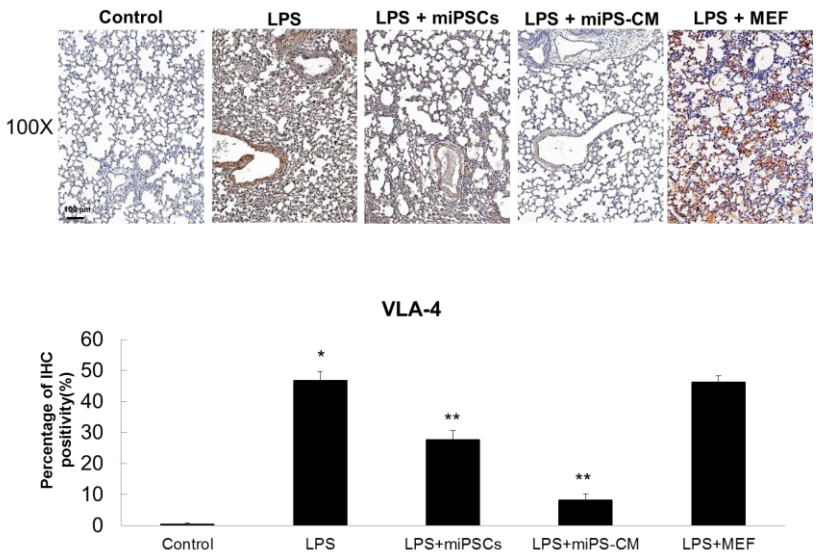
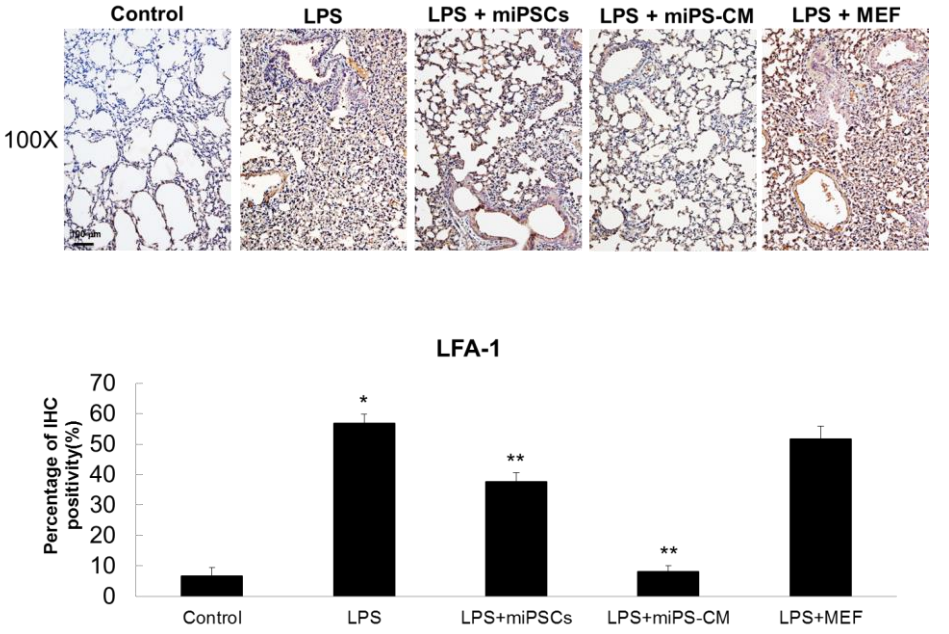
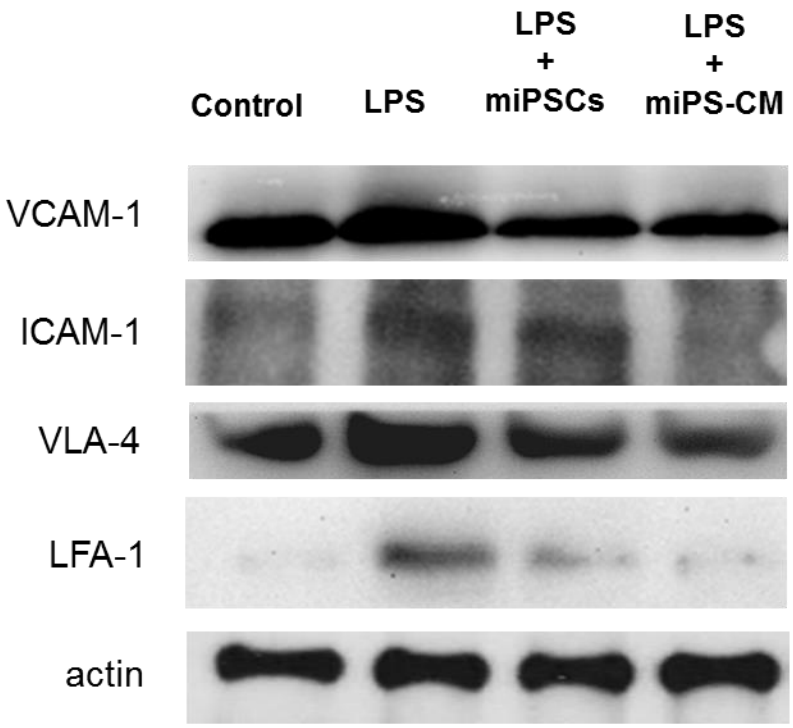
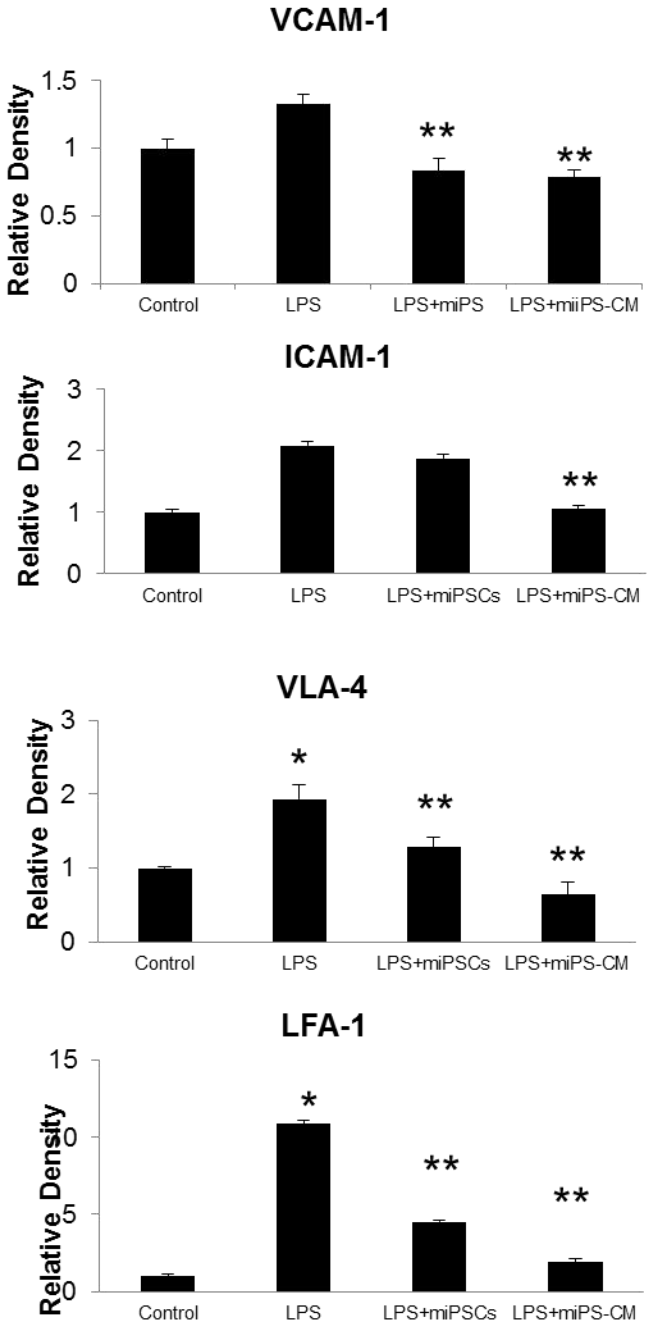



Fig. 1f Lung IHC analysis for LFA-1

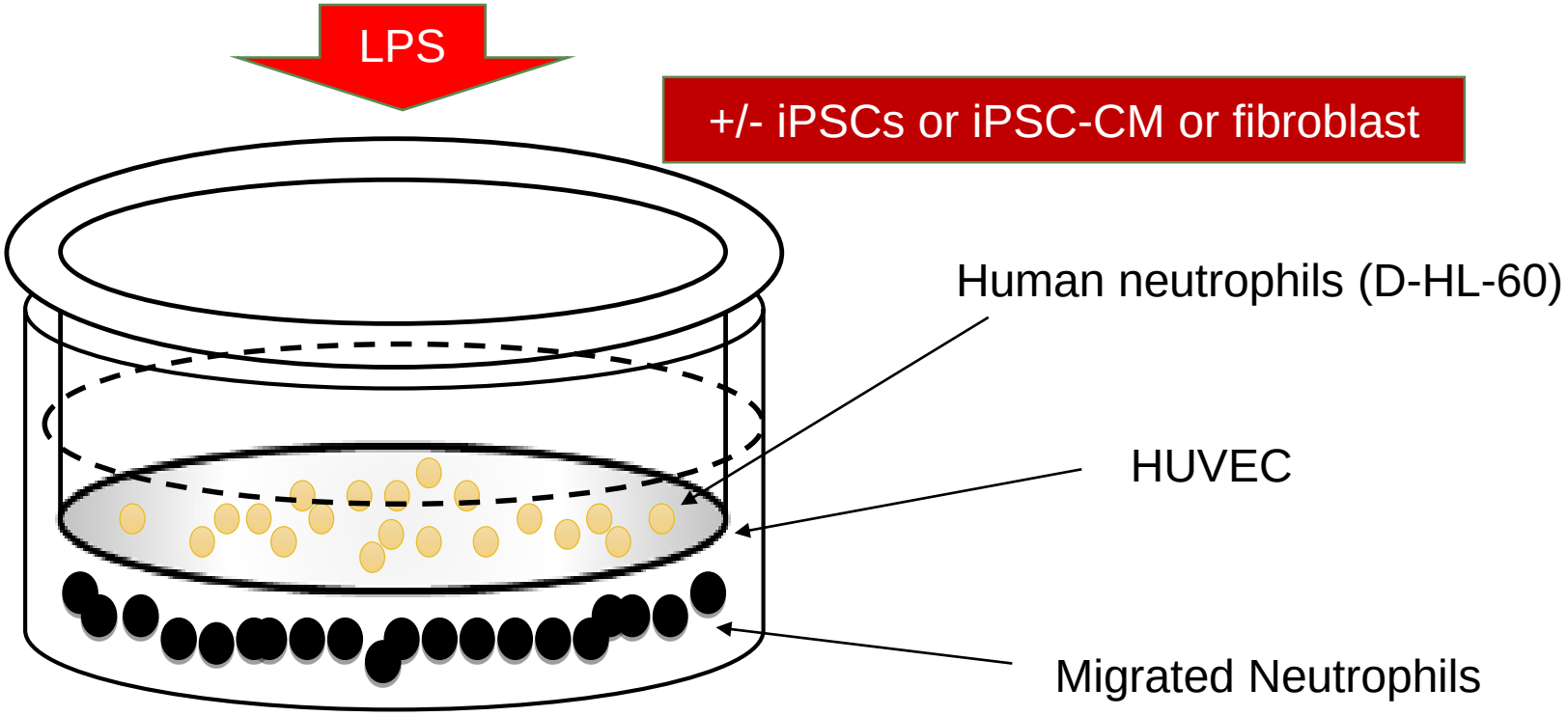


# Fig. 2 Whole lung lysate Lung



# Human neutrophils transendothelial migration model



# In vitro human neutrophils and endothelial cell line study

Fig. 3a D-HL-60 cells/HUVEC adhesion

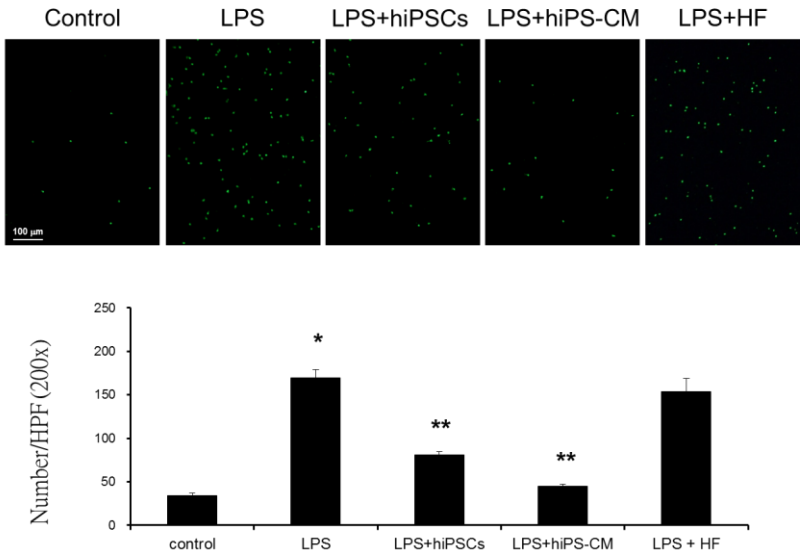
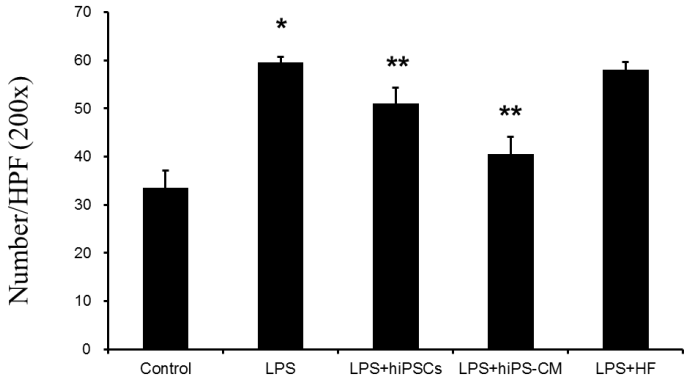



Fig. 3b D-HL-60 cells/HUVEC transmigration




DMSO-treated, neutrophil-like HL-60 cells (D-HL-60 cells)

Fig. 3c HUVECs adhesion factor (WB)

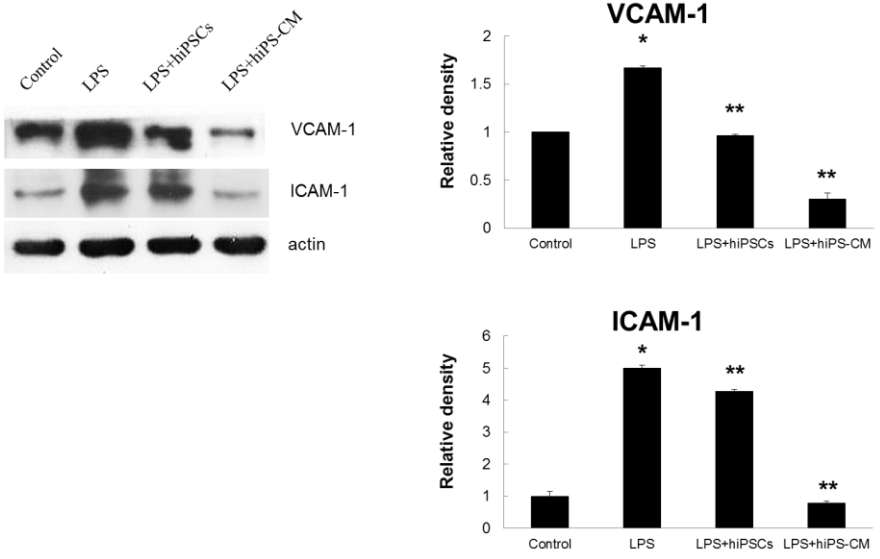
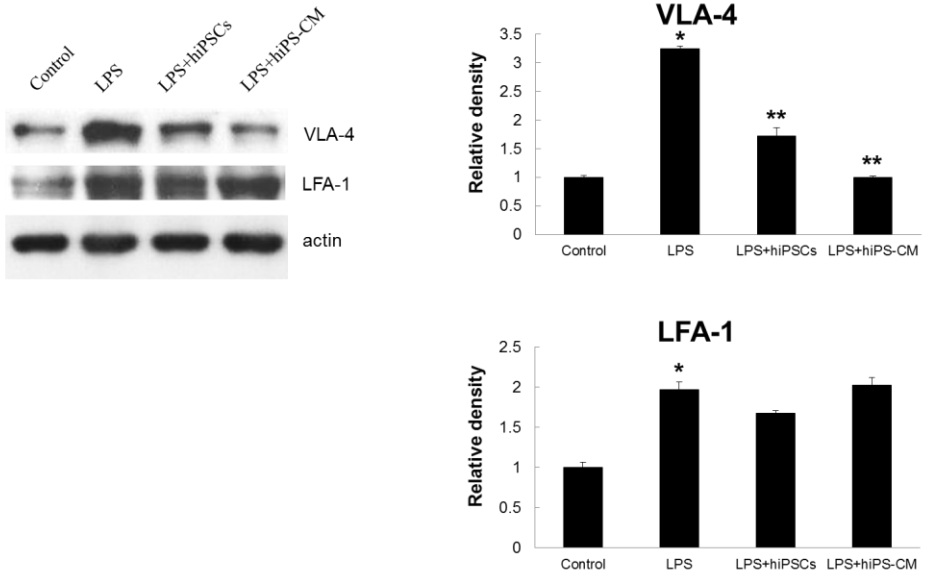



Fig. 3d D-HL-60 cells integrin (WB)



# Fig. 4a Human *Angiogenesis Array* for neutrophil/HUVEC interaction

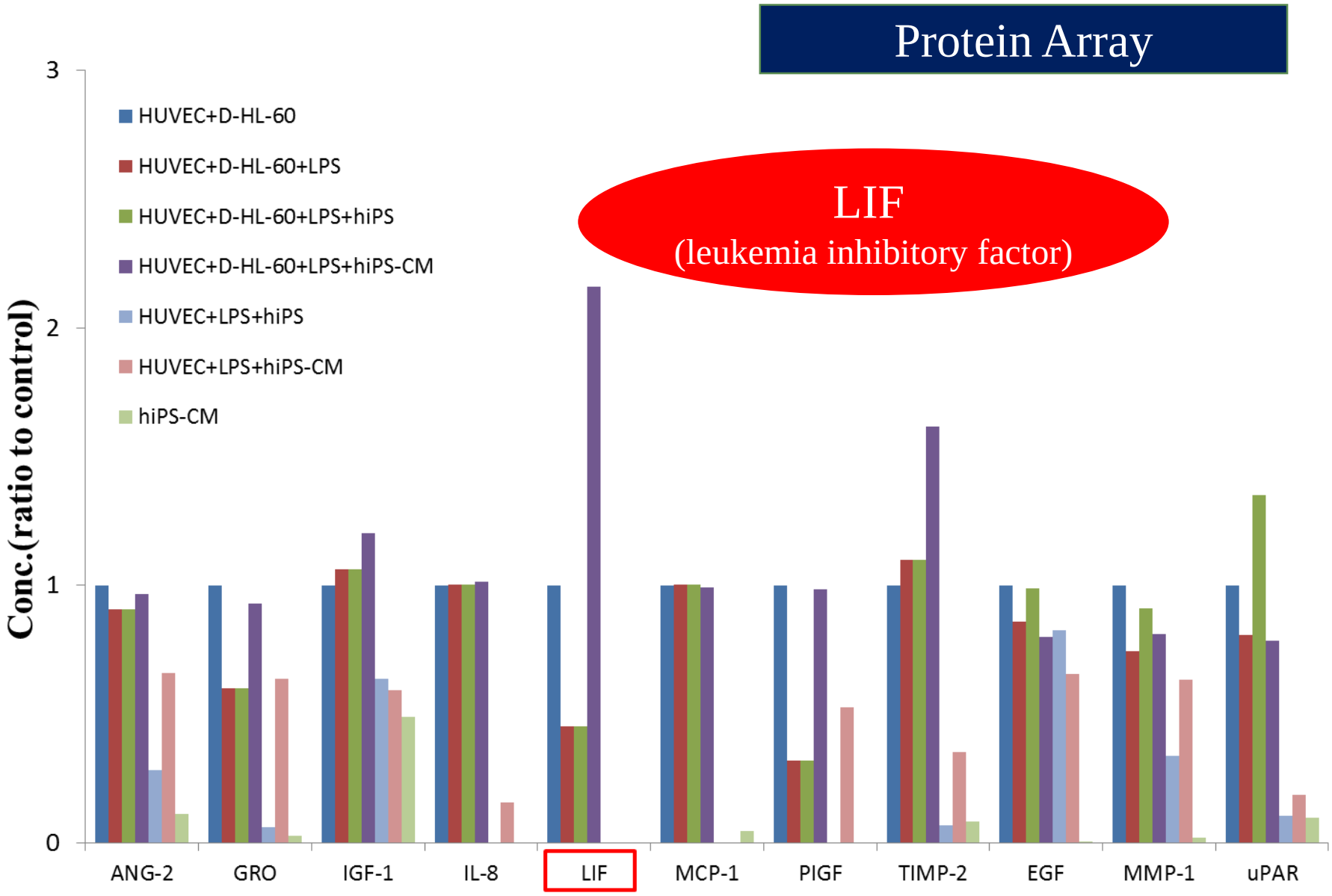


Fig. 4b D-HL-60 cells/HUVEC transmigration

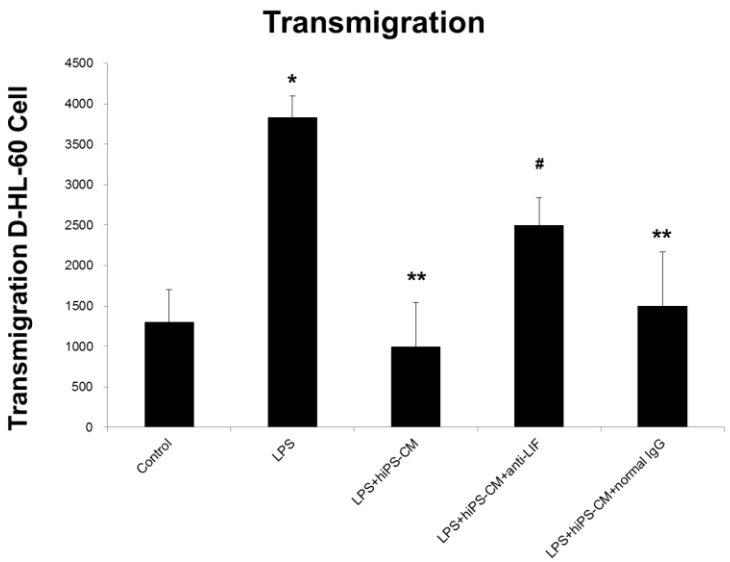



Fig. 5a HE stain for anti-LIF whole lung

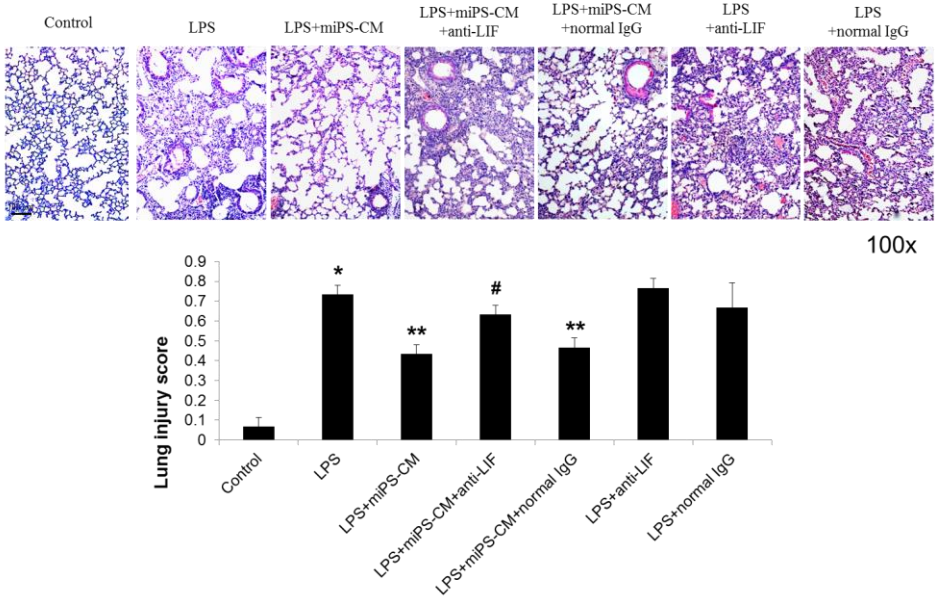



Fig. 5b Lung immunohistochemical analysis for VLA-4

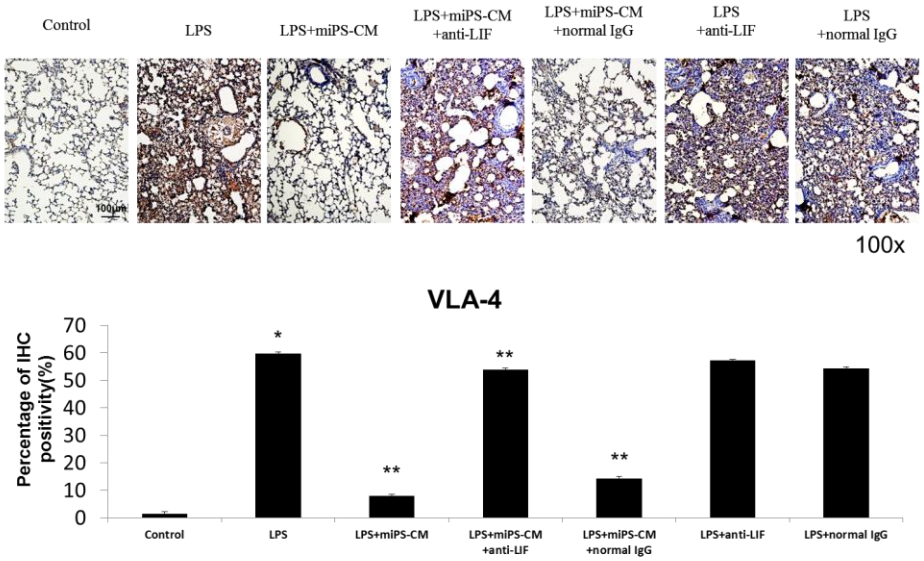
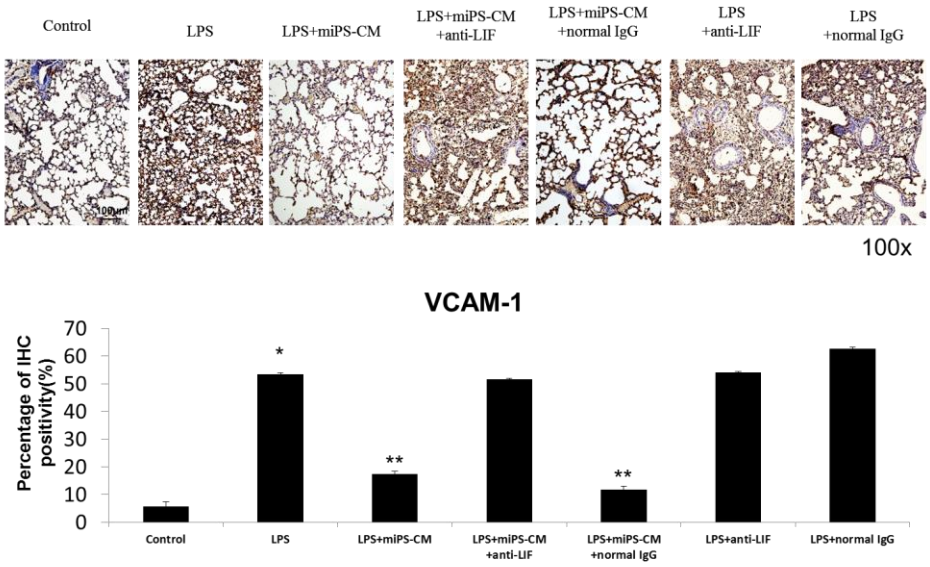
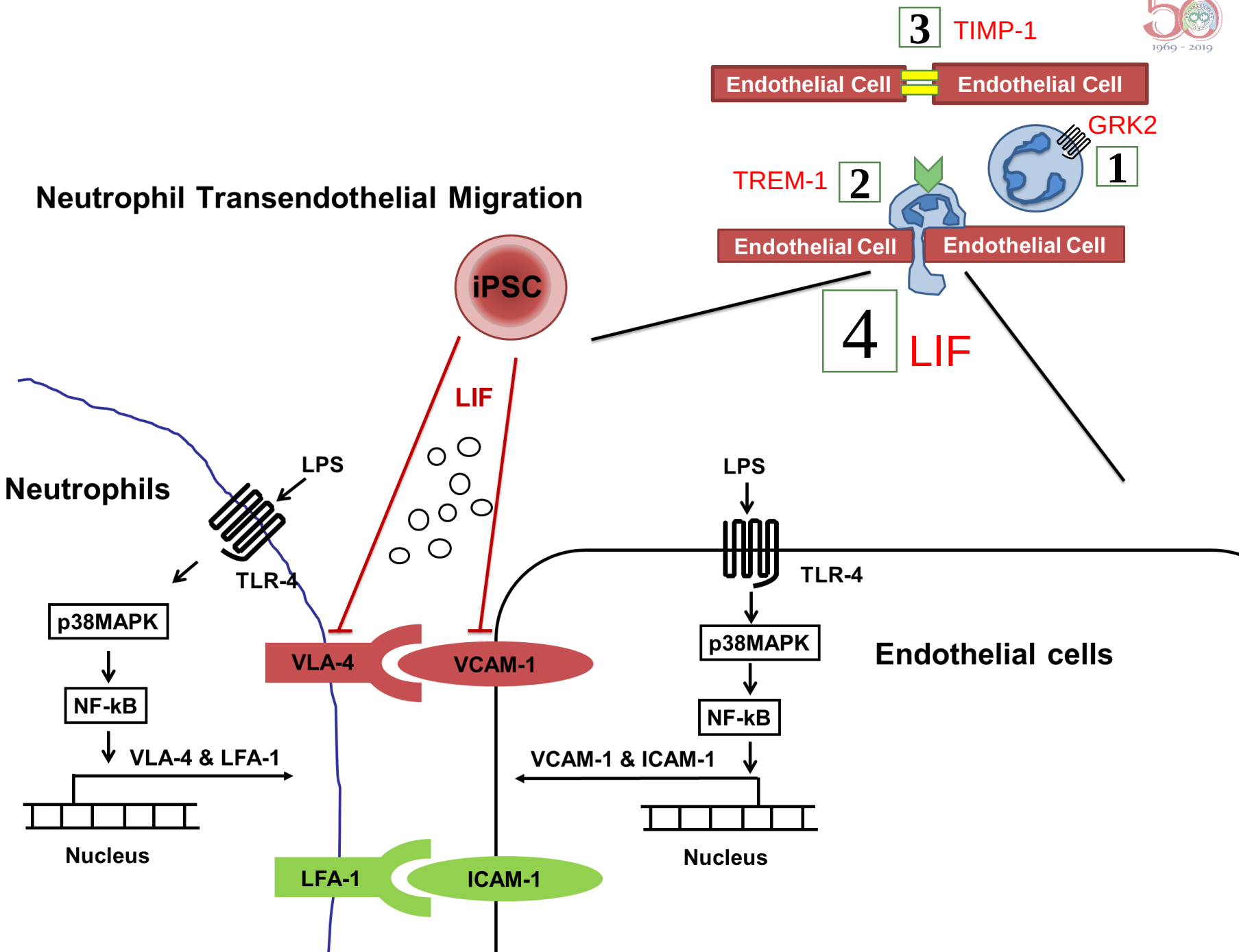



Fig. 5c Lung immunohistochemical analysis for VCAM-1




3
TIMP-1
Endothelial Cell
Endothelial Cell
GRK2
1
TREM-1
2
Endothelial Cell
Endothelial Cell
Neutrophil Transendothelial Migration
iPSC
4
LIF
LIF
Neutrophils
LPS
TLR-4
LPS
TLR-4
p38MAPK
NF-kB
VLA-4 & LFA-1
Nucleus
VLA-4
VCAM-1
p38MAPK
NF-kB
VCAM-1 & ICAM-1
Nucleus
Endothelial cells
LFA-1
ICAM-1

# Summary

- *In vivo* miPSCs therapy attenuated the expression of adhesion molecule of endothelium (VCAM-1) and neutrophils (VLA-4) in ALI mouse lungs.
- *In vitro* human cell-line model further confirmed that hiPSCs reduced the expression of VCAM-1 in HUVEC and VLA-4 in D-HL-60 to decrease neutrophils transendothelial migration (TEM).
- Angiogenesis protein assay demonstrated high level of leukemia inhibitory factor (LIF) in iPSC-CM, and anti-LIF antibody reversed the effect of hiPSC-CM on human neutrophils TEM.
- Anti-LIF antibody reduced the effect of miPSC-CM on the expression of VCAM-1 and VLA-4 in ALI mouse lungs and the severity of ALI.