Recovery of Myocardial Infarction via Unique Modulation of the Cardiac Microenvironment

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Department of Cardiology, Cardiovascular Center
Chonnam National University Hospital

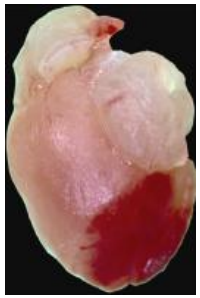
Main Events in Cardiac Injury

Cardiomyocytes Loss

Fibrosis

Delayed Angiogenesis

Uncontrolled Inflammation



Remodeling & Dysfunction

Current Strategies for Cardiac Repair

Well-Being Life Style

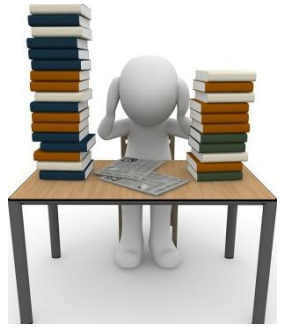
Medical Check-Up

Prevention

PCI Statins

Conventional Therapy (Attenuation)

ACEi β-Blockers



Reprogramming Cocktail

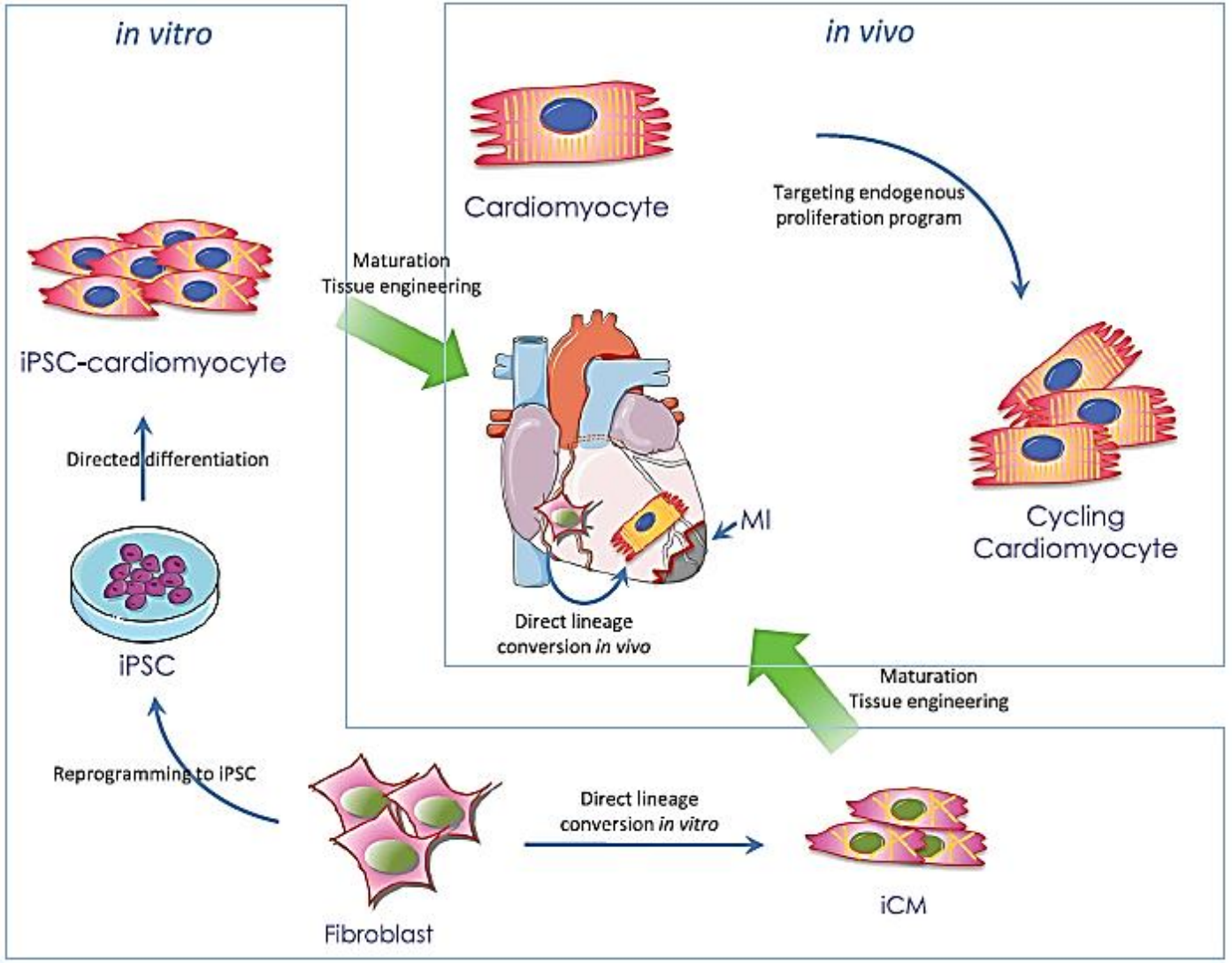
iPSC-CM Fb-CM

Regeneration

Primed MSC ESC-CM

MSC iPSC CSC

Cardiac Regeneration by New CM



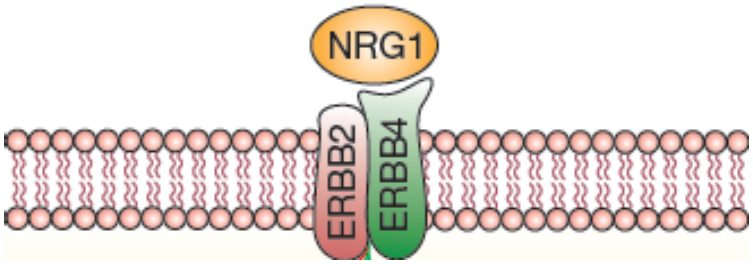
2016 Circ Res

Cardiac Regeneration by Nrg1

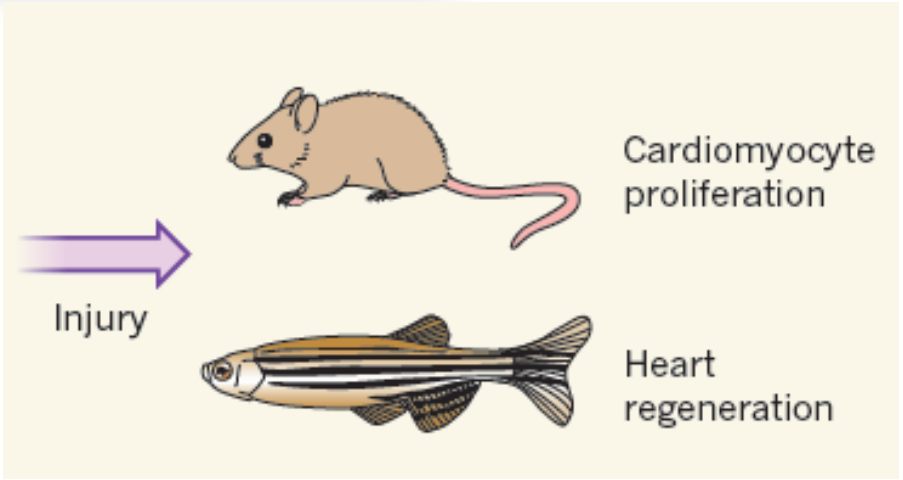
REGENERATIVE BIOLOGY

Neuregulin 1 makes heart muscle

Three studies reveal that augmentation of a signalling pathway involving the growth factor neuregulin 1 and its receptor protein ERBB2 can promote the generation of muscle cells in zebrafish, mice and infant heart tissue.

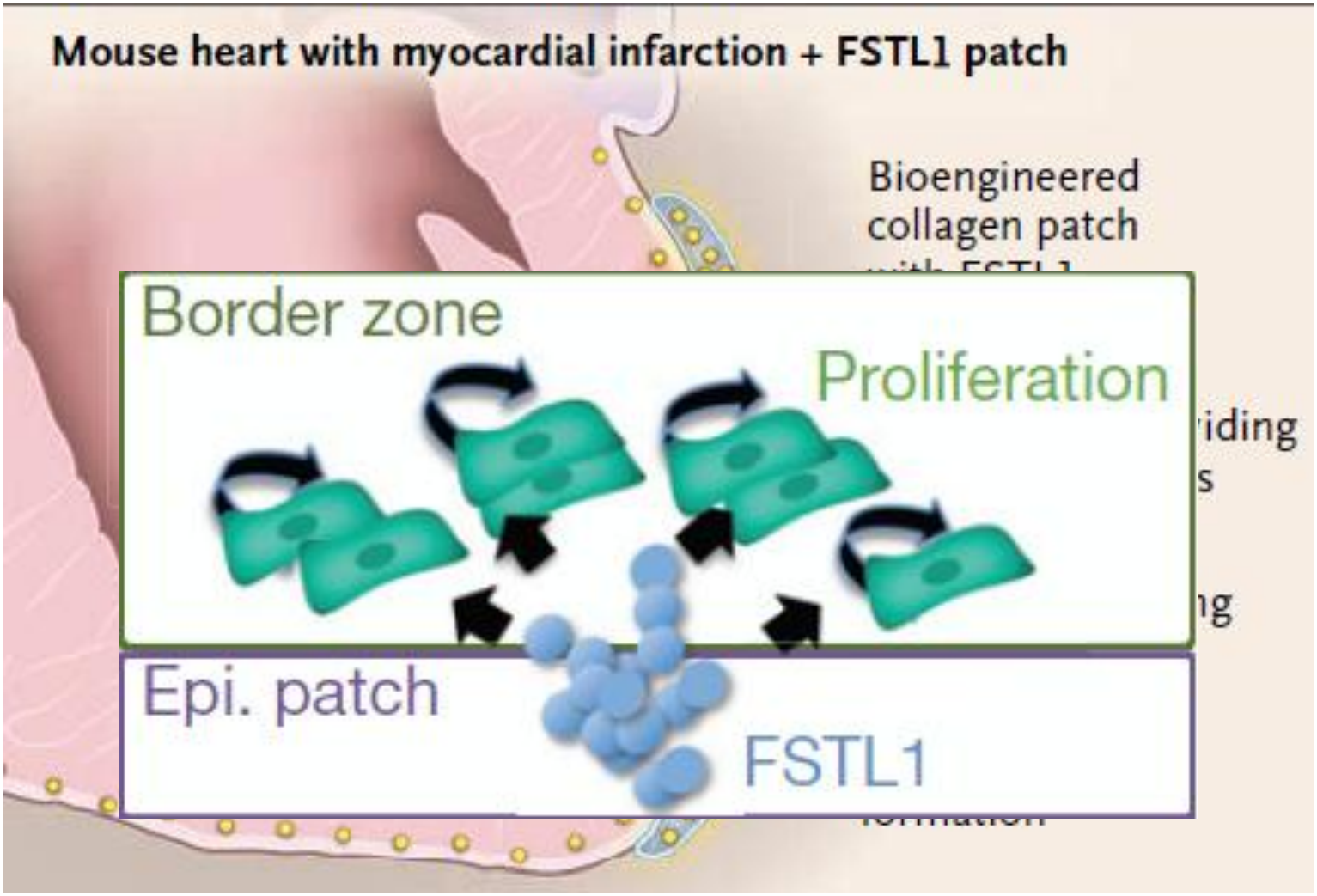


cardiomyocyte



2015 Nat Cell Biol, 2015 eLIFE, 2015 Sci Trans Med, 2015 Nature

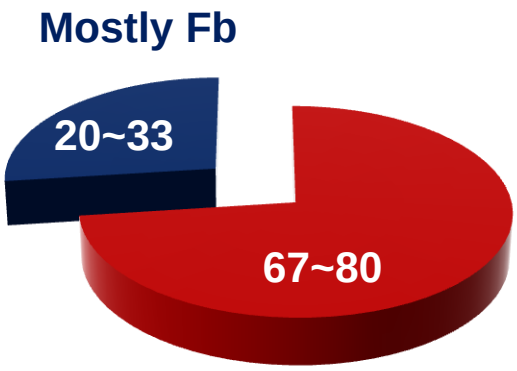
Cardiac Regeneration by FSTL1



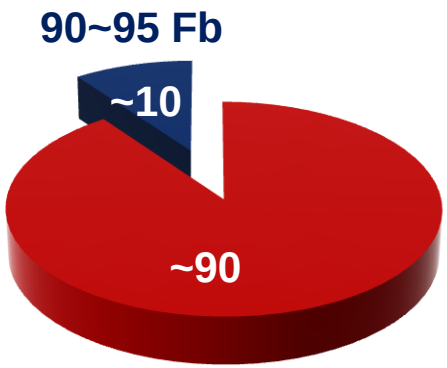
2015, Nature, 2016 NEJM

Myocytes and Nonmyocytes in the Myocardium

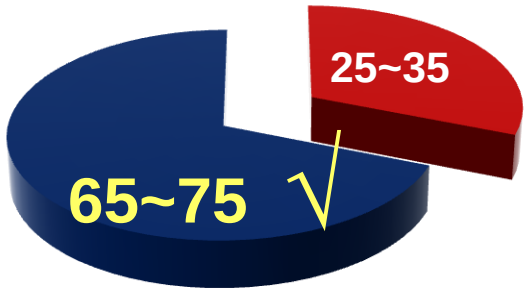
By Cell Vol.



By Cell Mass

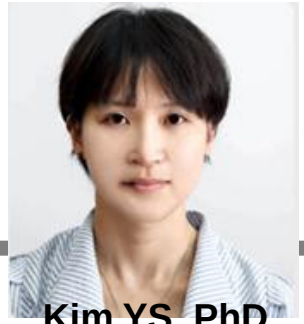


By Cell No.



Myocytes
Nonmyocytes

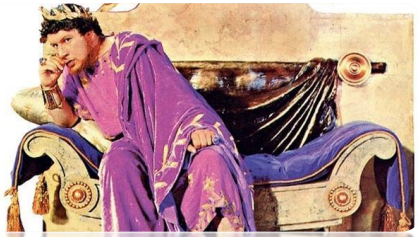
Introduction of BIO



Kim YS, PhD

Jeong HY, MS

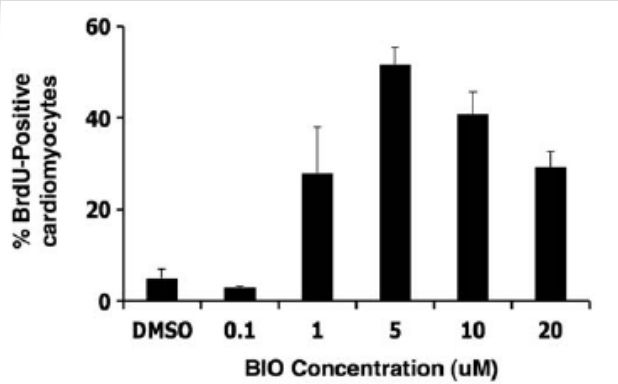
'Tyrian purple' dye

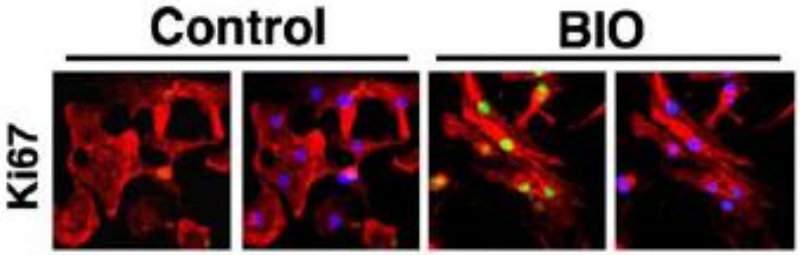


2'Z,3'E-6-Bromoindirubin-3'-oxime

Chemistry & Biology *13*, 957–963, September 2006 ©2006 Elsevier Ltd All rights reserved DOI 10.1016/j.chembiol.2006.08.004

The GSK-3 Inhibitor BIO Promotes Proliferation in Mammalian Cardiomyocytes

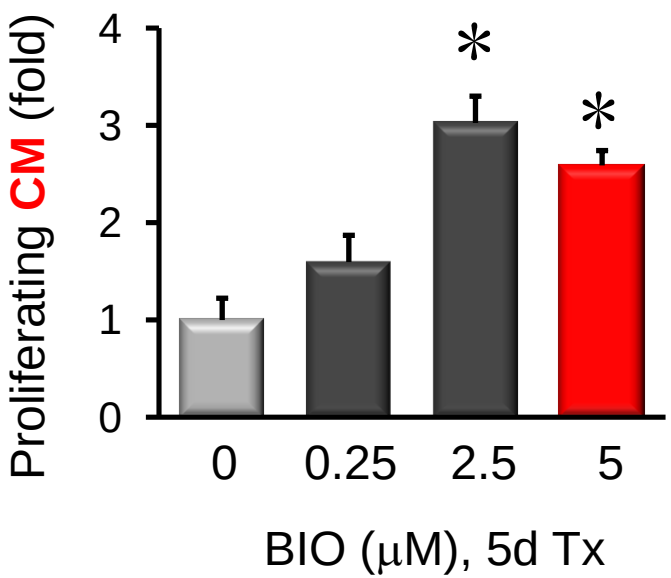


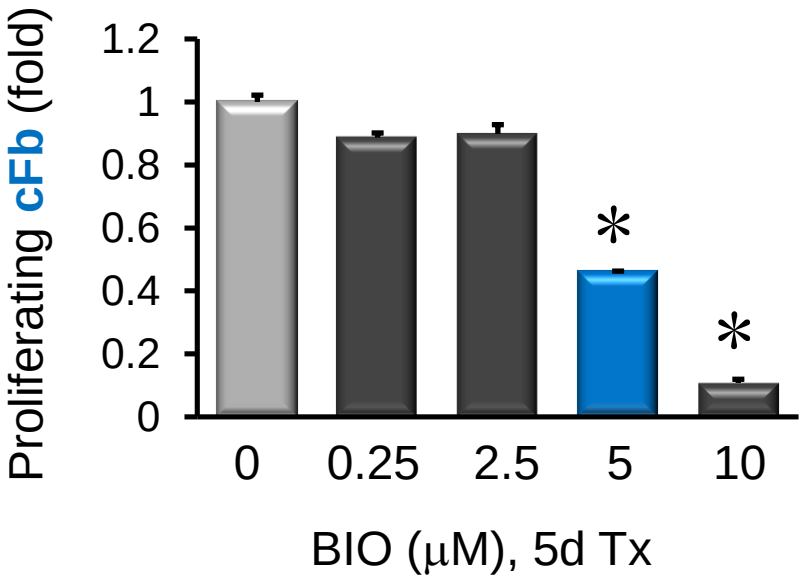


No Further Study…

2006 Chem Biol

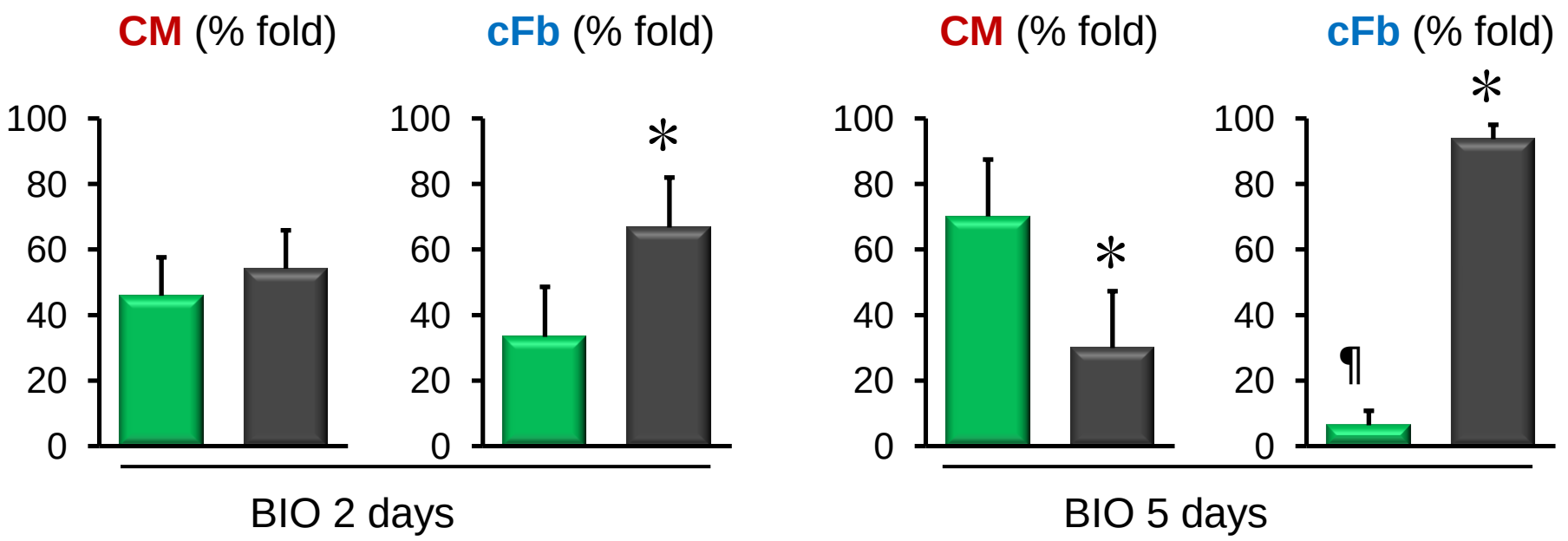
Effect of BIO on Proliferation of CM and cFb

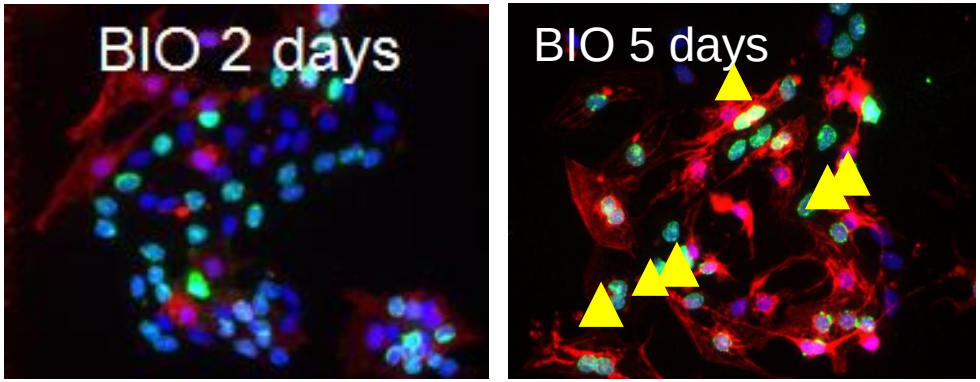




Effect of BIO on Proliferation of CM and cFb

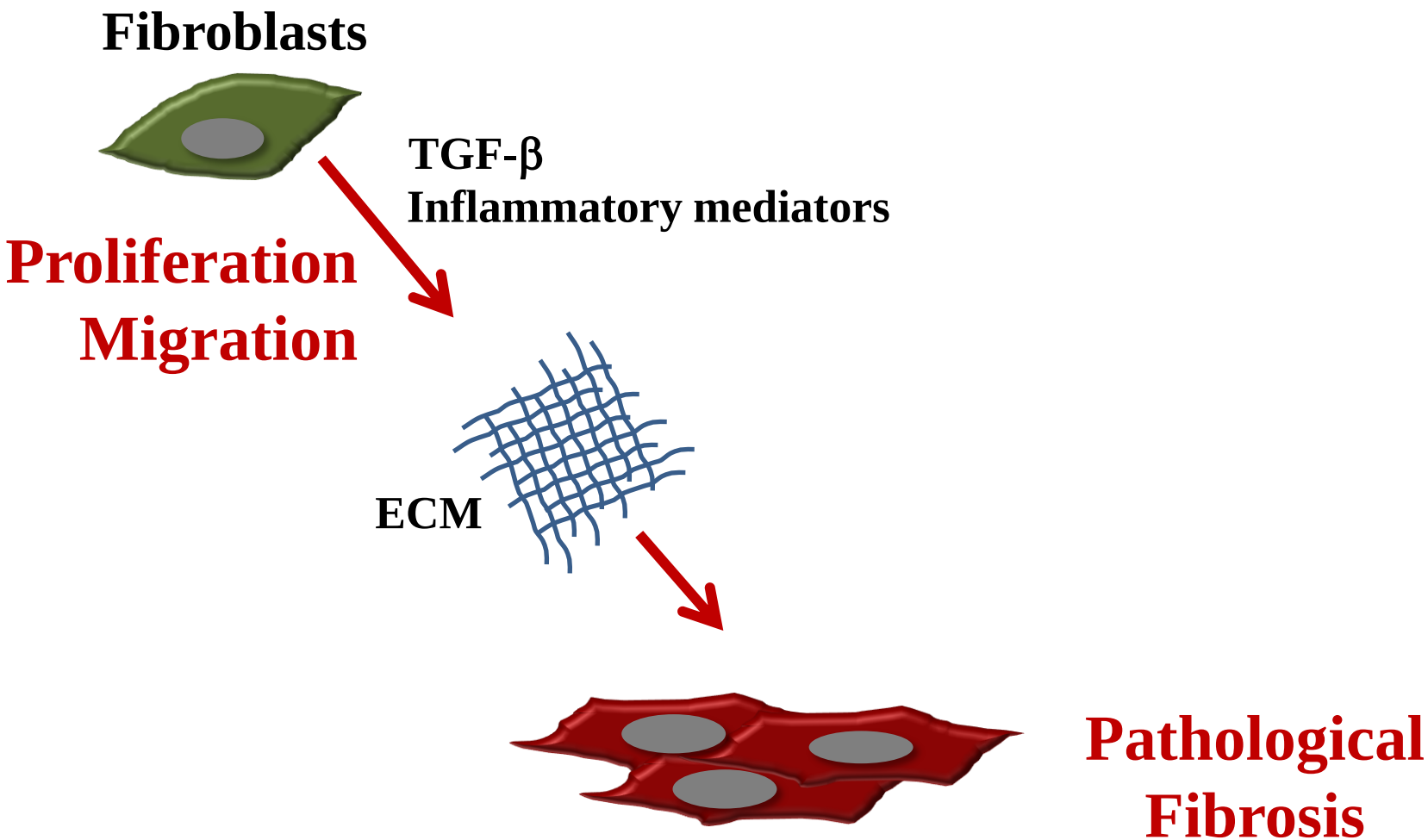
Proliferating cells
Non-proliferating cells



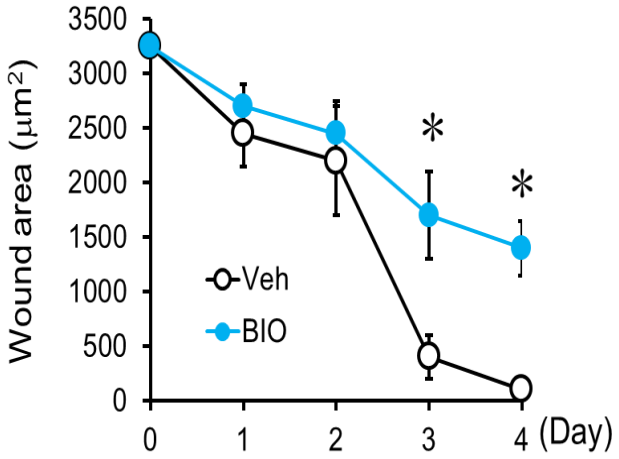


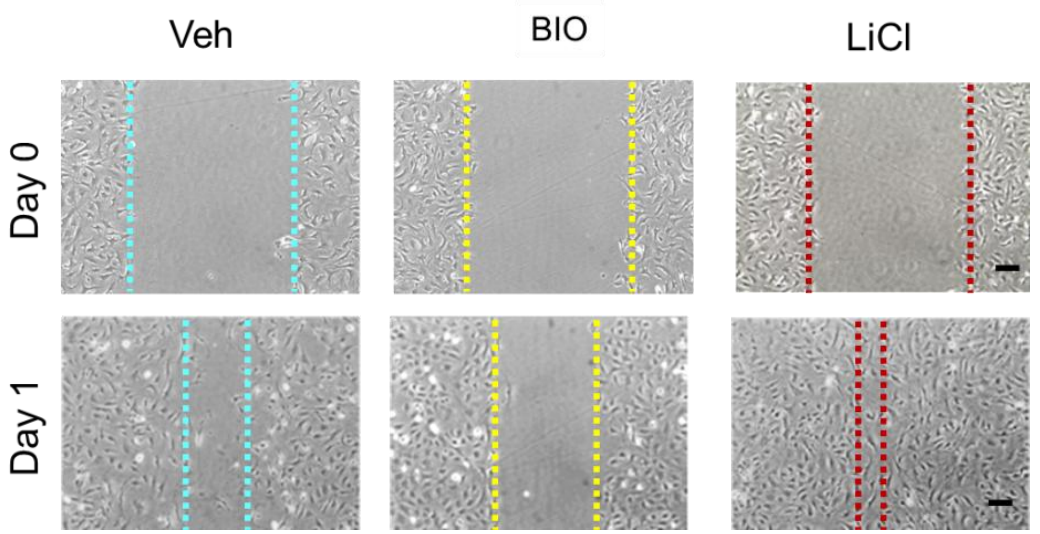
BrdU(+)cTnI(+)
Proliferating CM

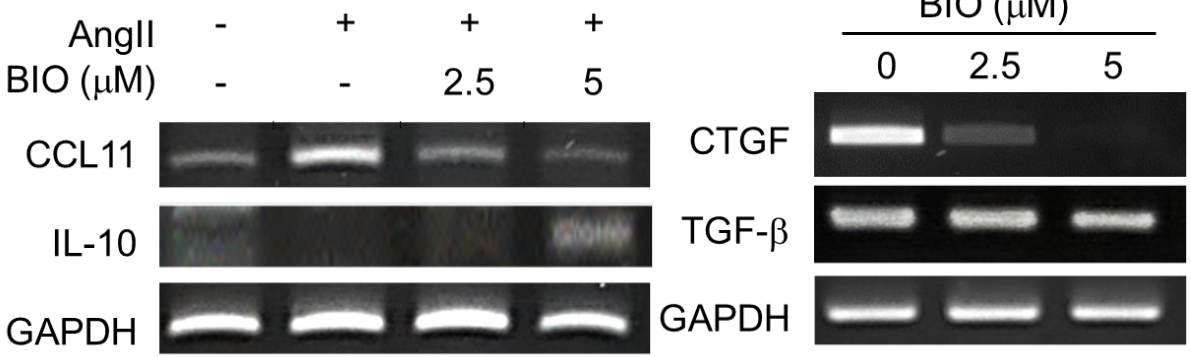
Cardiac Fibroblasts

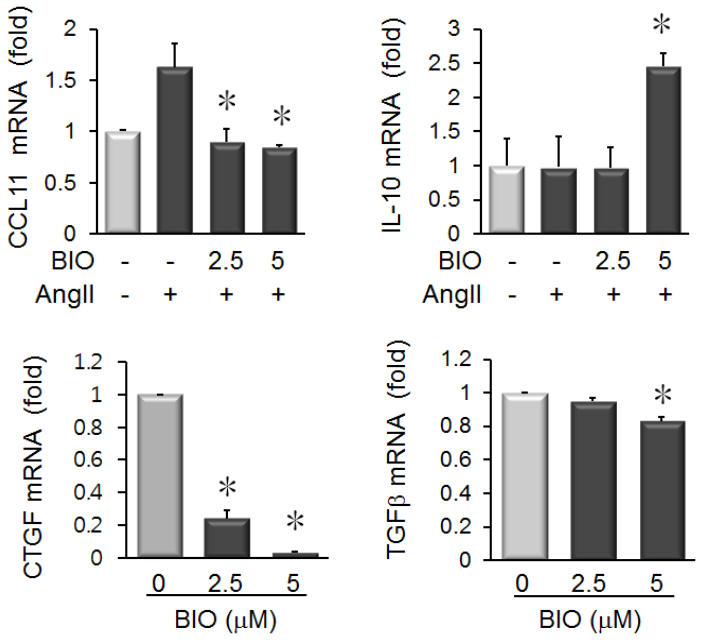


Effect of BIO on Pro-fibrotic cFb



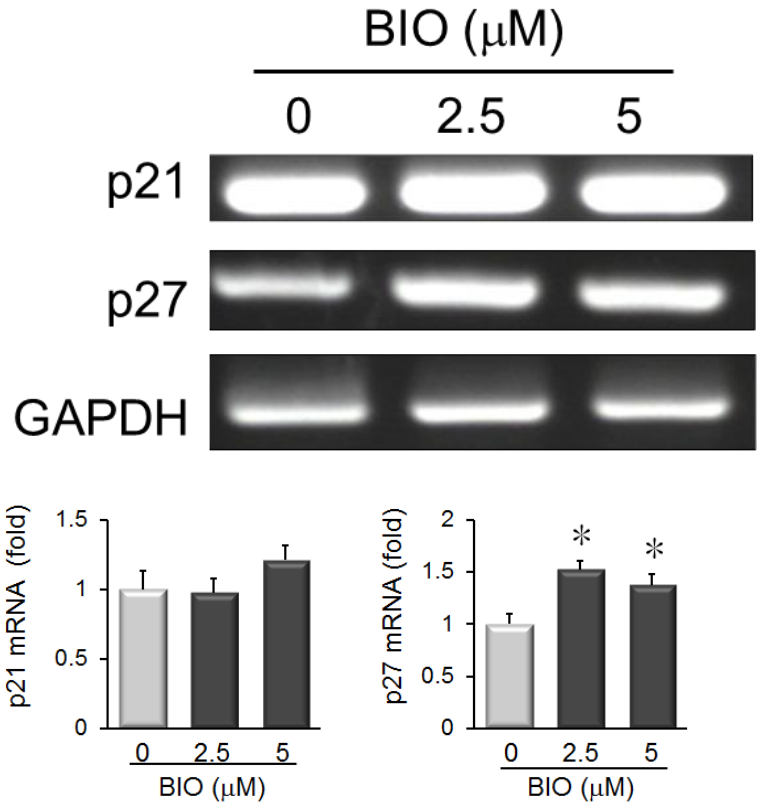


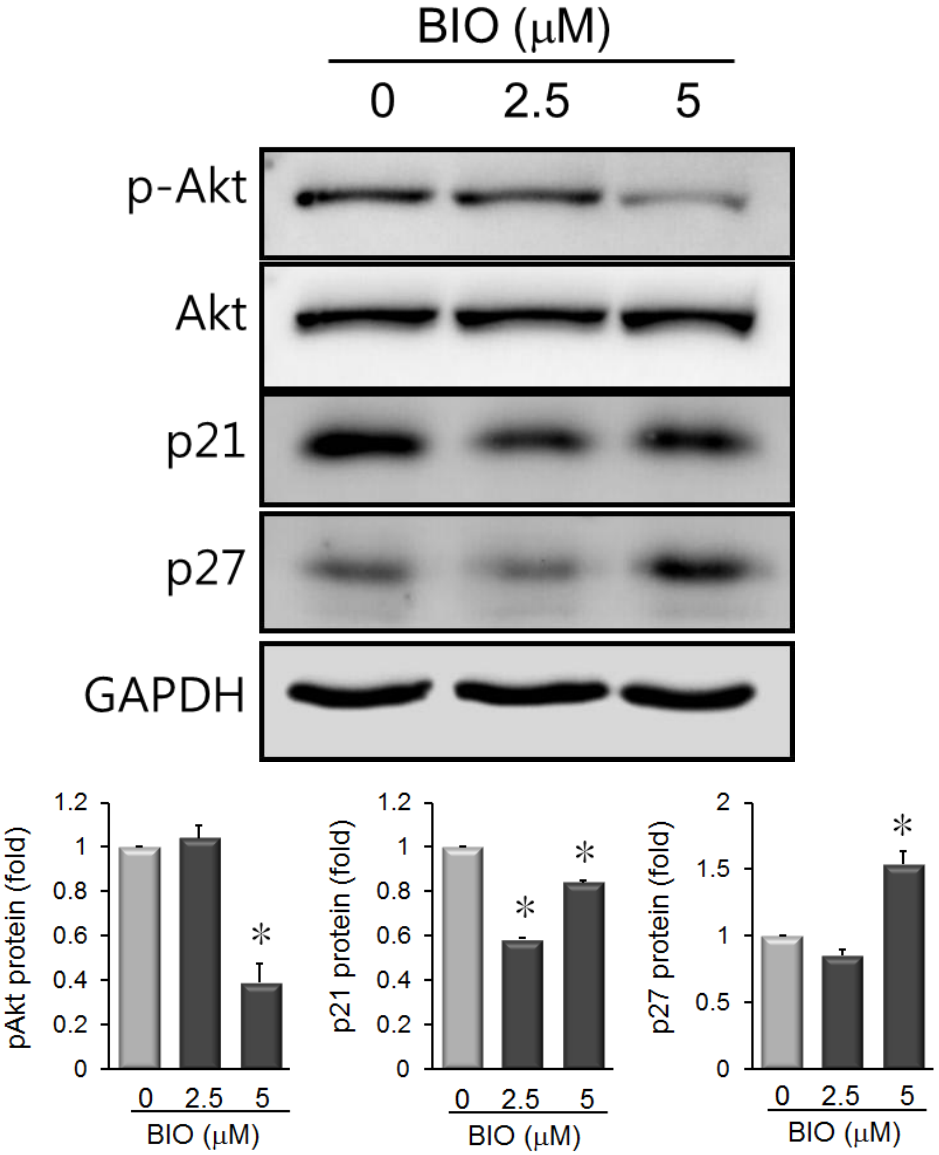




20 mM LiCl, BIO 3 days Tx

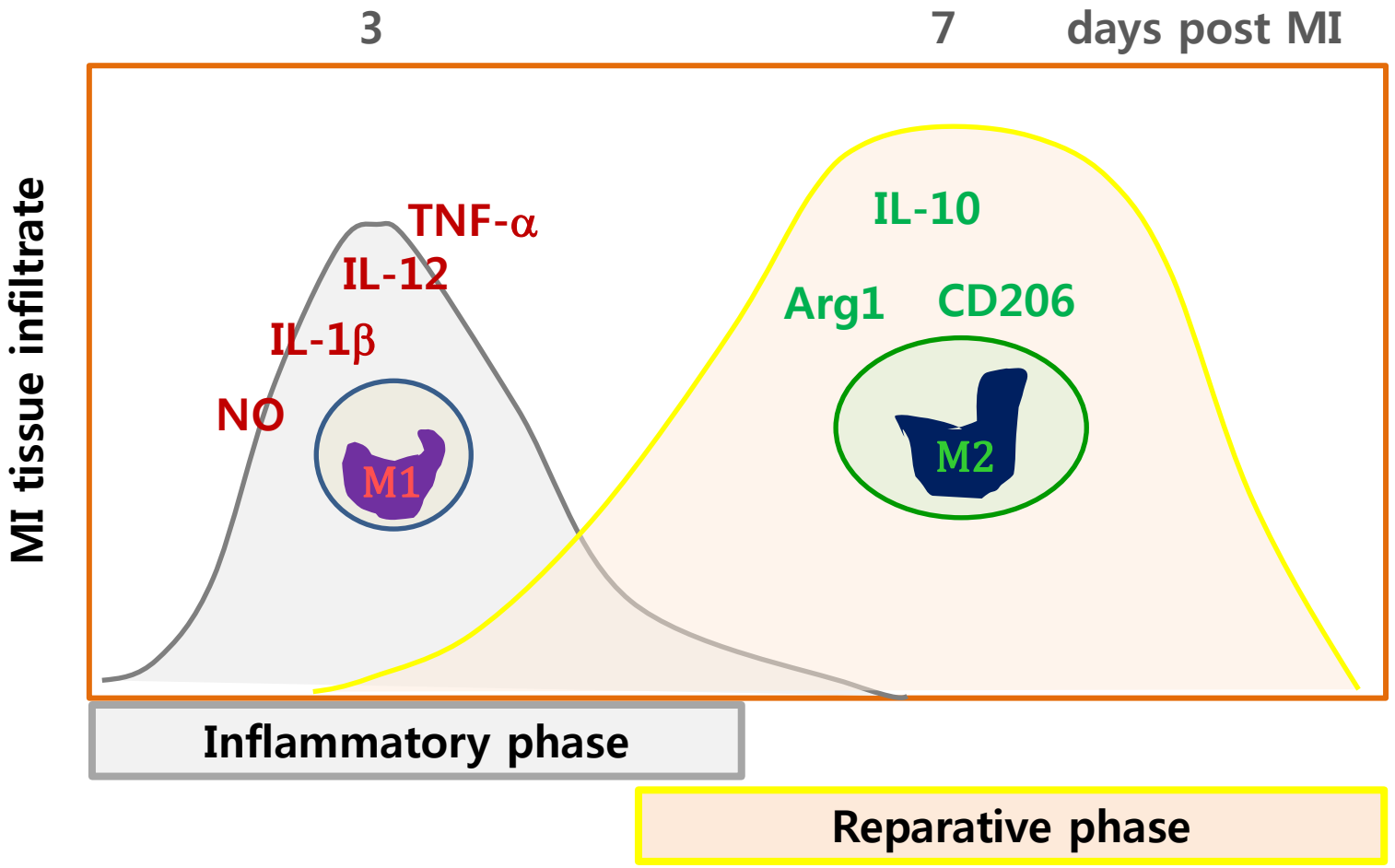
Effect of BIO on Akt and p27 in cFb



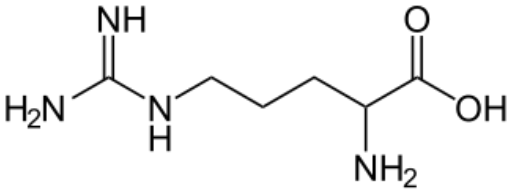


BIO 5 days Tx

Cardiac Macrophages



Arter Thromb Vasc Biol 2009, J Am Coll Cardiol 2012, Circ Res 2014



L-Arginine

iNOS

NOHA

NO + L-Citrulline

Cytotoxicity
Inflammation

Arginase-1

L-Ornithine + urea

OAT

ODC

P5C

Putrescine

L-Proline

Spermidine

Collagen

Spermine

Tissue Regeneration
Cell Proliferation
Anti-inflammation

Cardiac Recovery by Macrophage Modulation

Protective role of 5-azacytidine on myocardial infarction is associated with modulation of macrophag inhibition of fibrosis

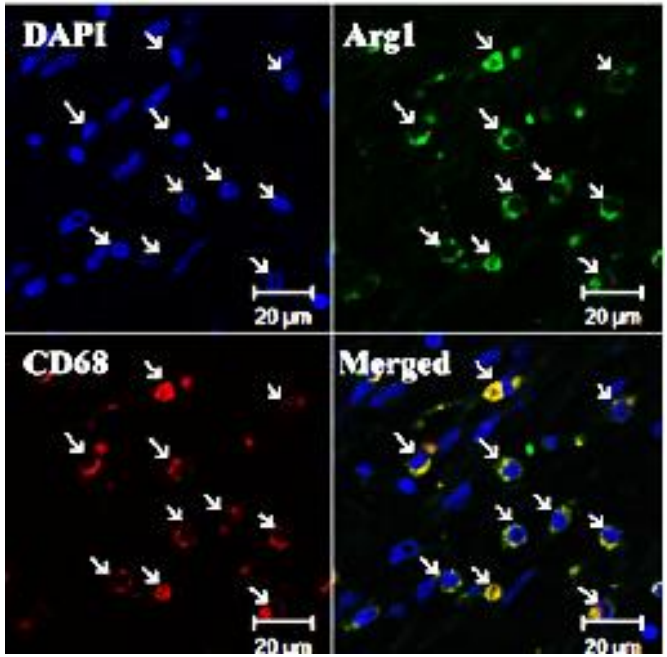
Yong Sook Kim [a], Wan Seok Kang [b, c], Jin Sook Kwon [a], Moon Hwa
Hae Chang Jeong [d], Myung Ho Jeong [a, d], Youngkeun

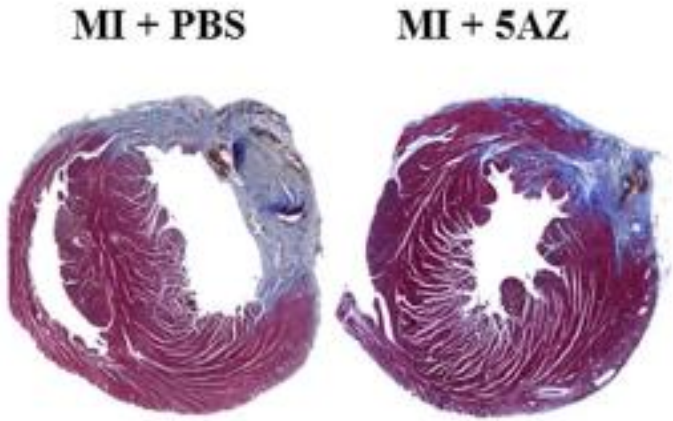
SCIENTIFIC REPORTS

OPEN

5-Azacytidine modulates interferon regulatory factor 1 in macrophages to exert a cardioprotective effect

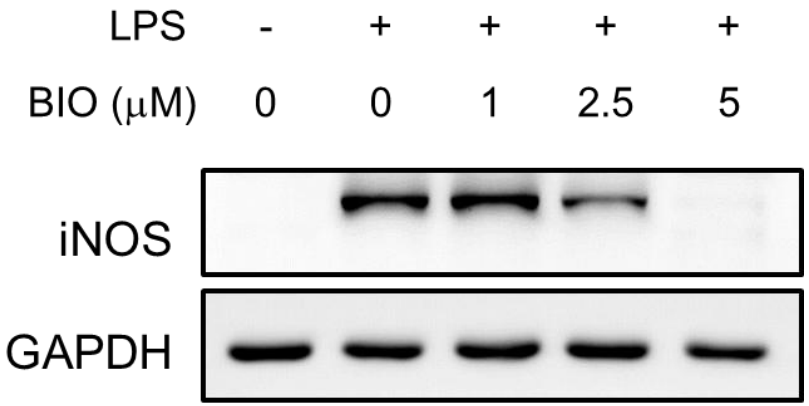
Received: 6 January 2015

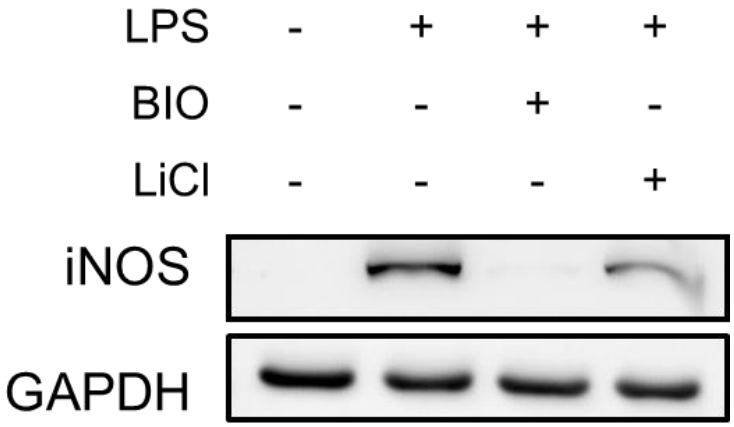




J Cell Mol Med 2014, Sci Rep 2015

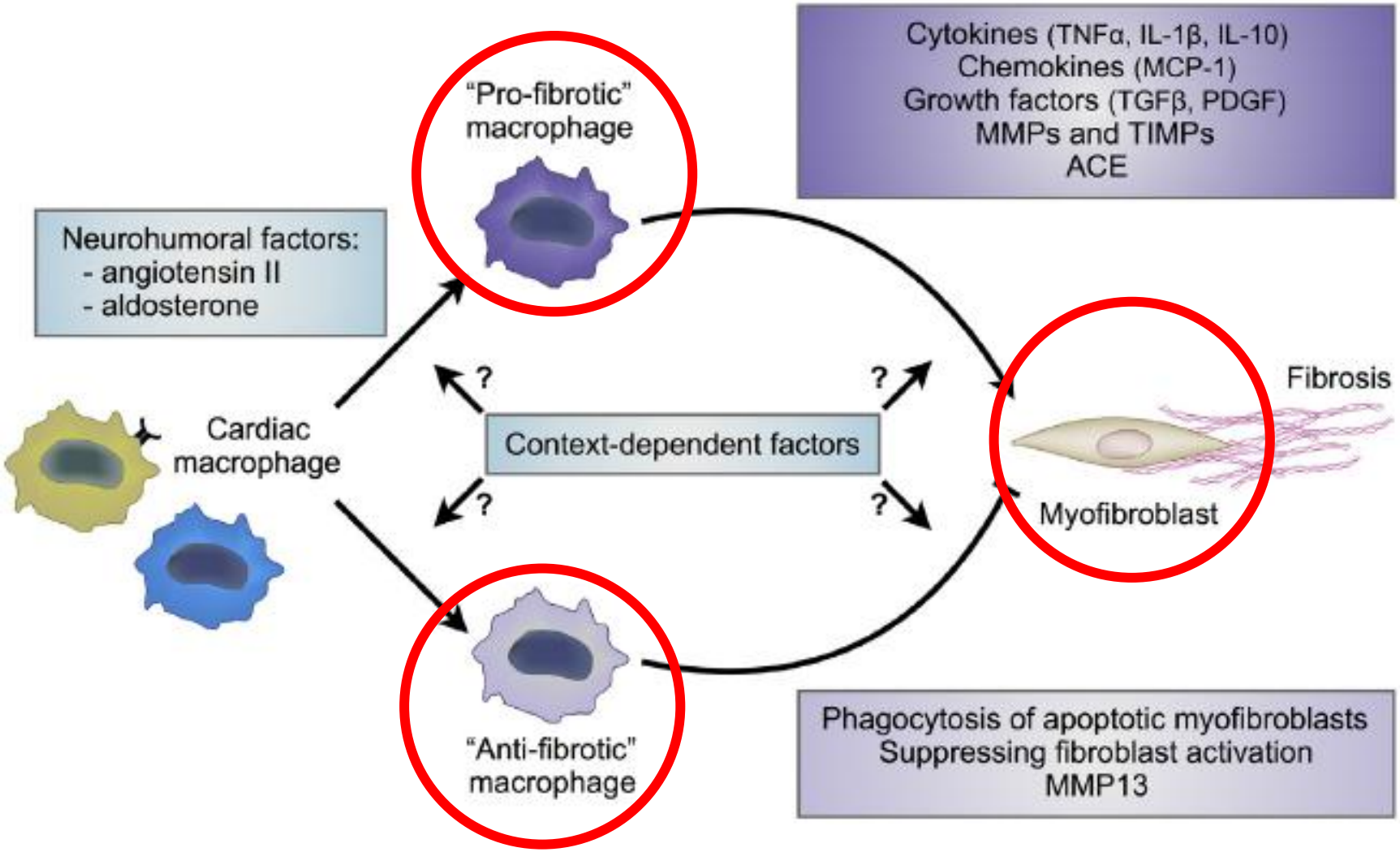
Anti-inflammatory Effect of BIO on RAW264.7 cells





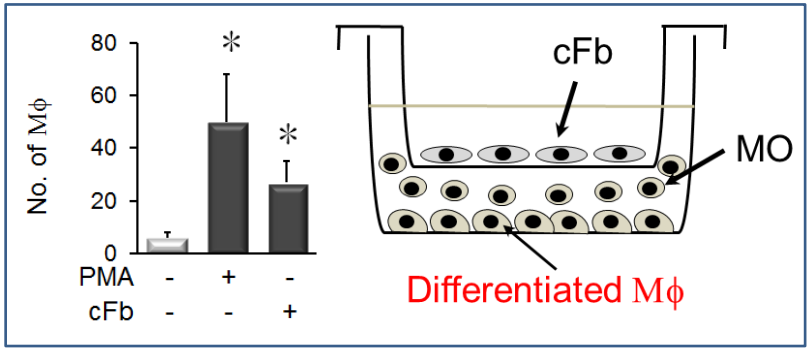
LPS (100 ng/mL) treatment for 24 hours
20 mM LiCl

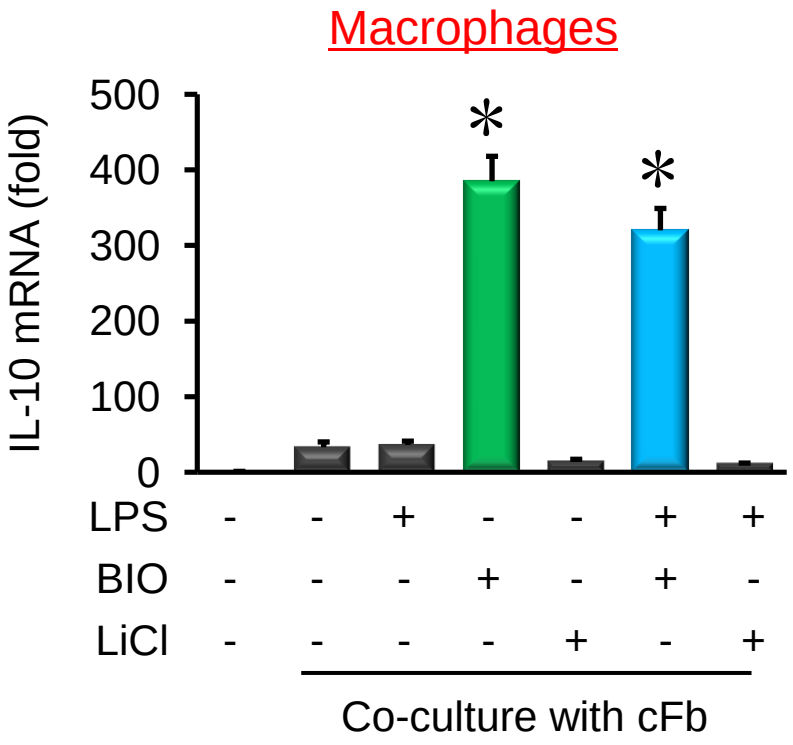
Fibroblasts and Macrophages

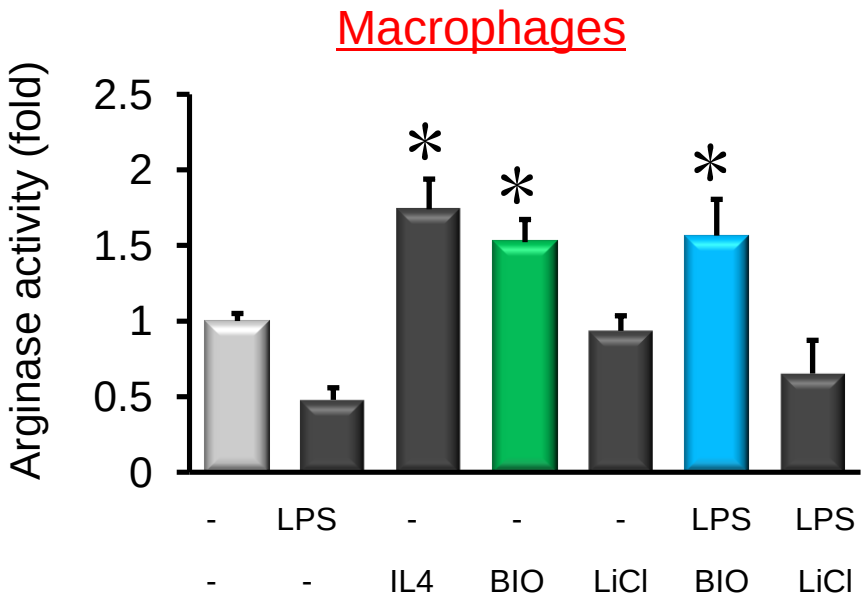


2013 J Mol Cell Cardiol

Effect of BIO on Crosstalk between cFb and Mϕ (1)

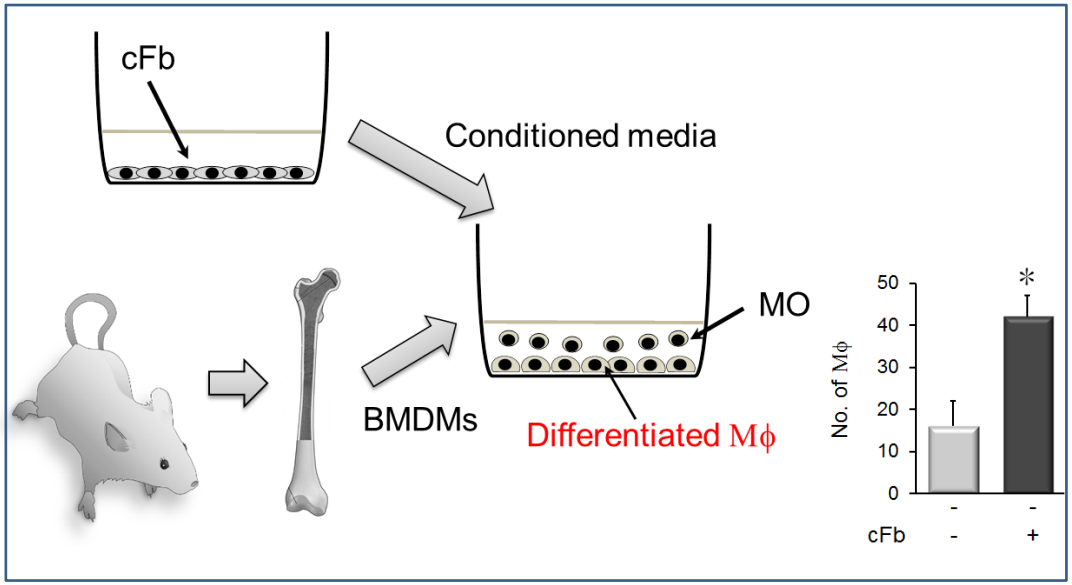


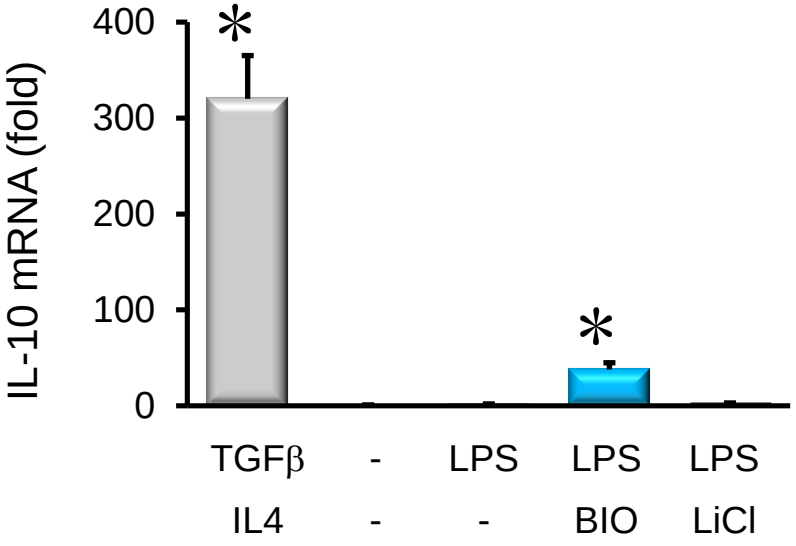


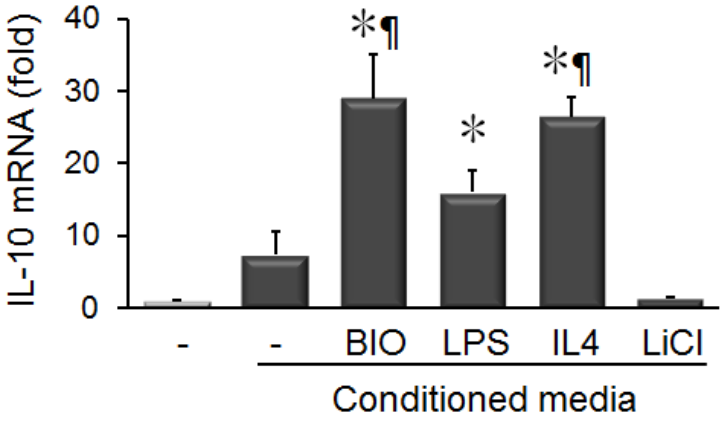


5 μM BIO or 10 ng/mL IL-4
20 mM LiCl
Co-culture of cFb with THP-1 MO for 72 h induced MΦ differentiation

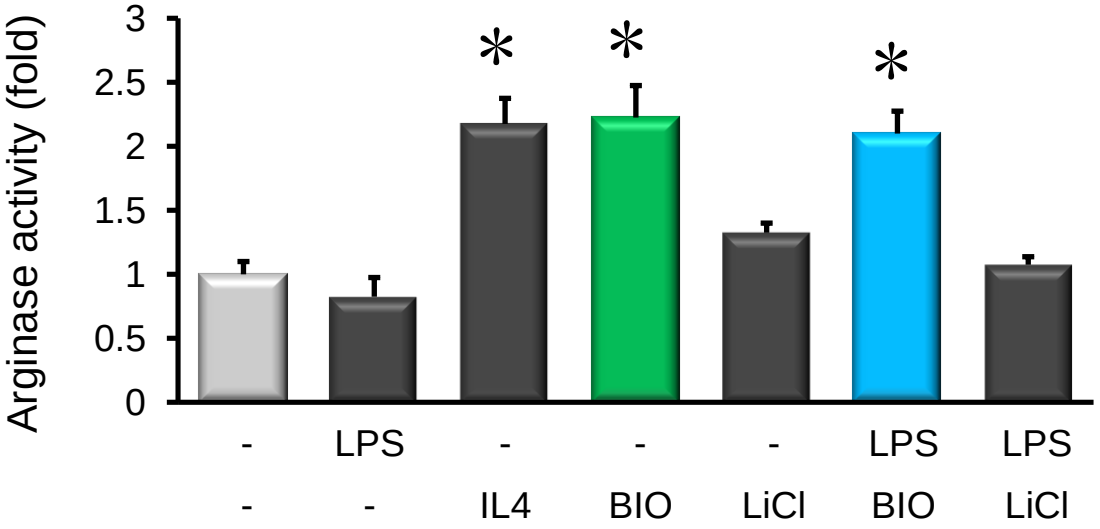
Effect of BIO on Crosstalk between cFb and Mϕ (2)



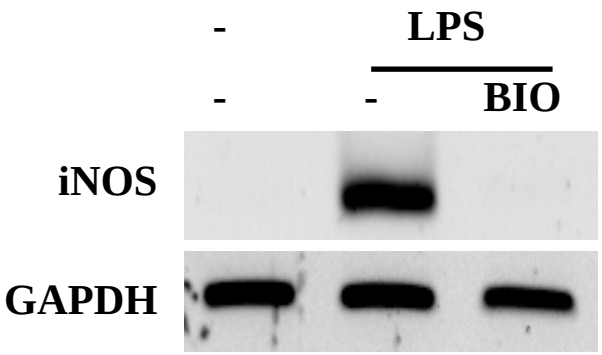


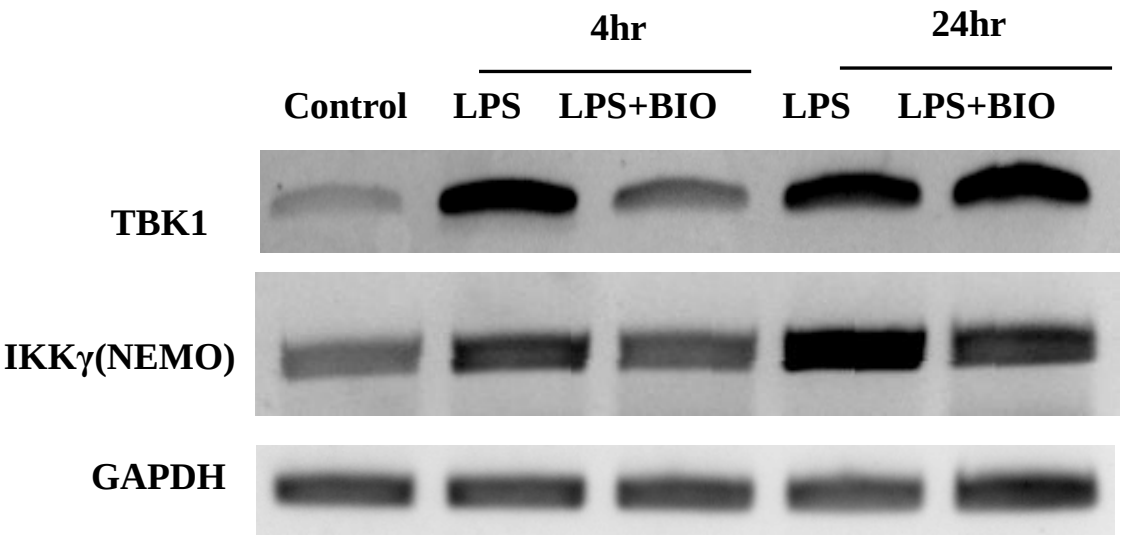


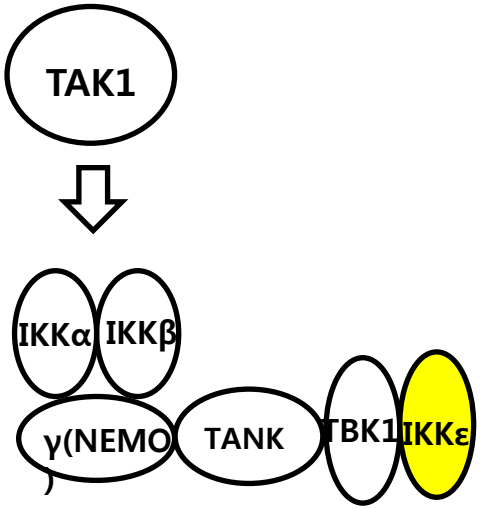
50 ng/mL TGF-β



Effect of BIO on Activated Macrophages

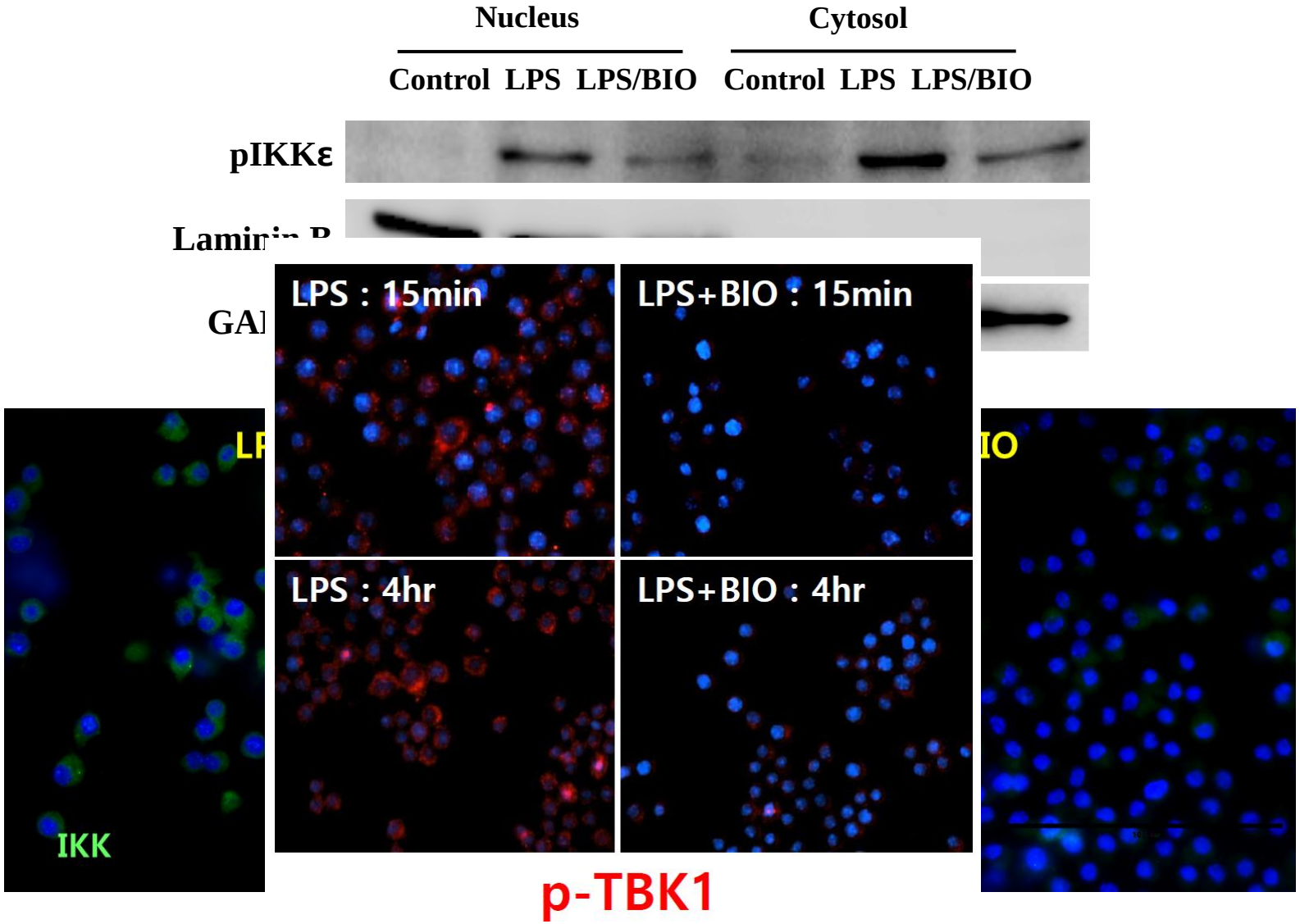




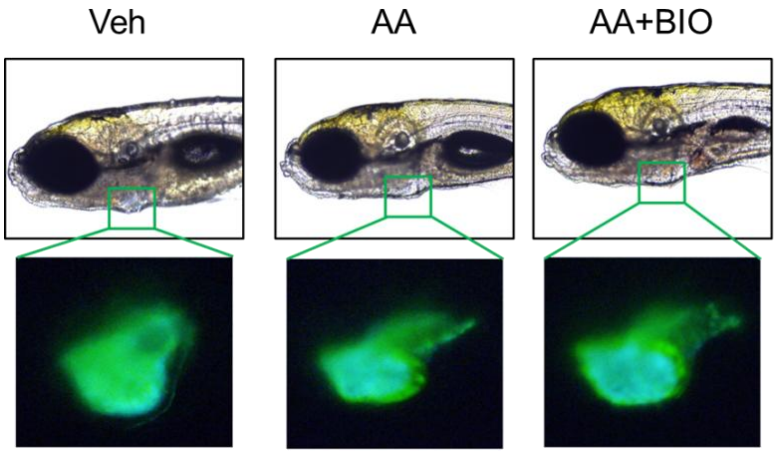


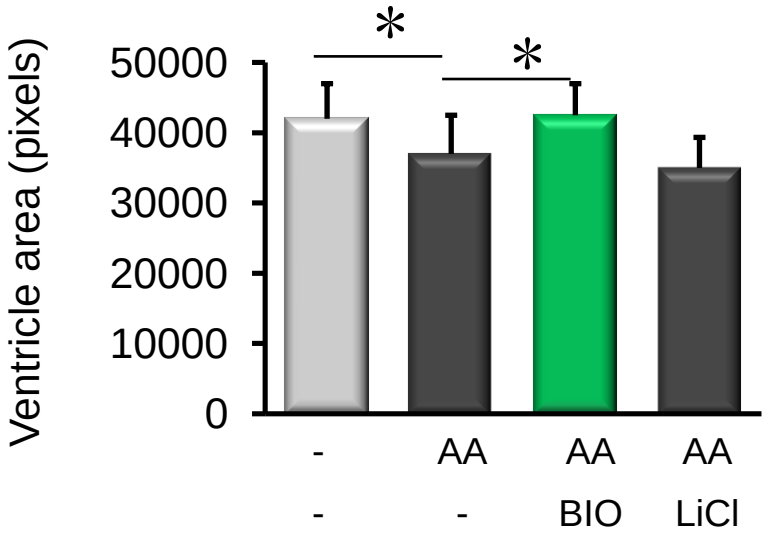
Raw cell 264.7, BIO 5μM

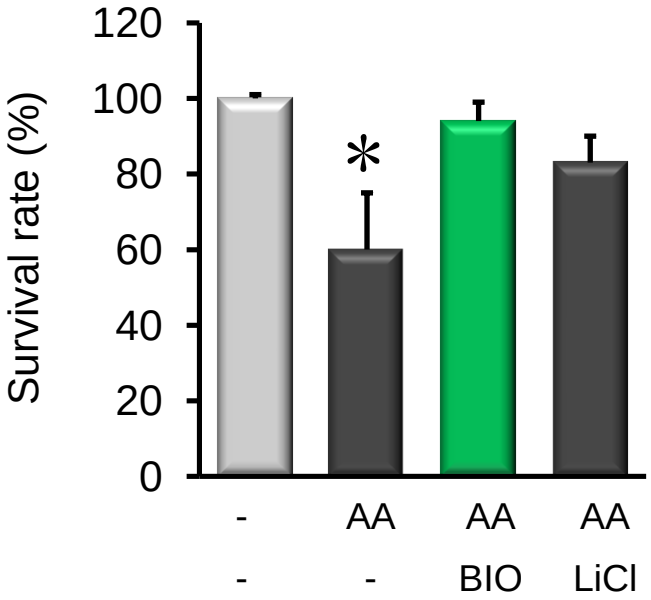
Effect of BIO on IKK in Macrophages

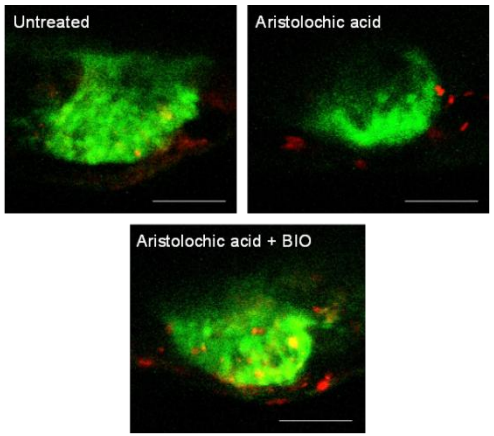


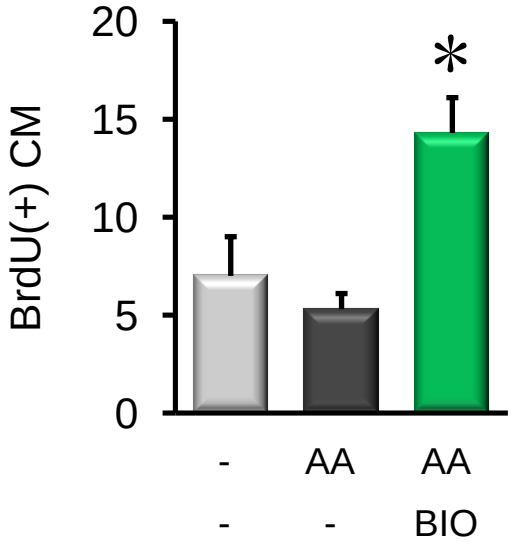
Cardiac Regeneration in Zebra Fish HF Model





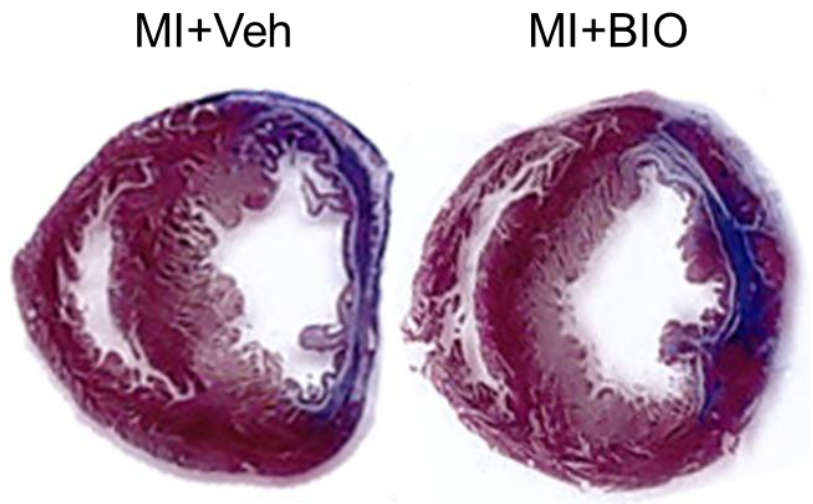


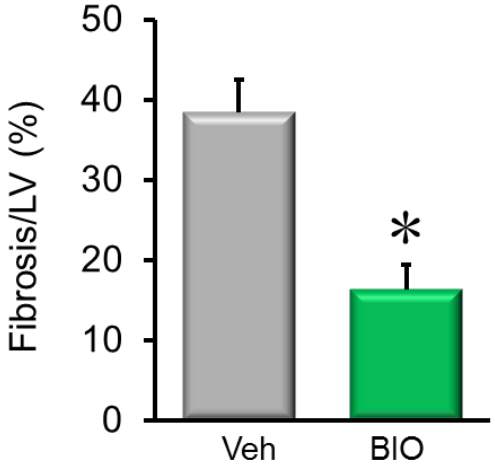




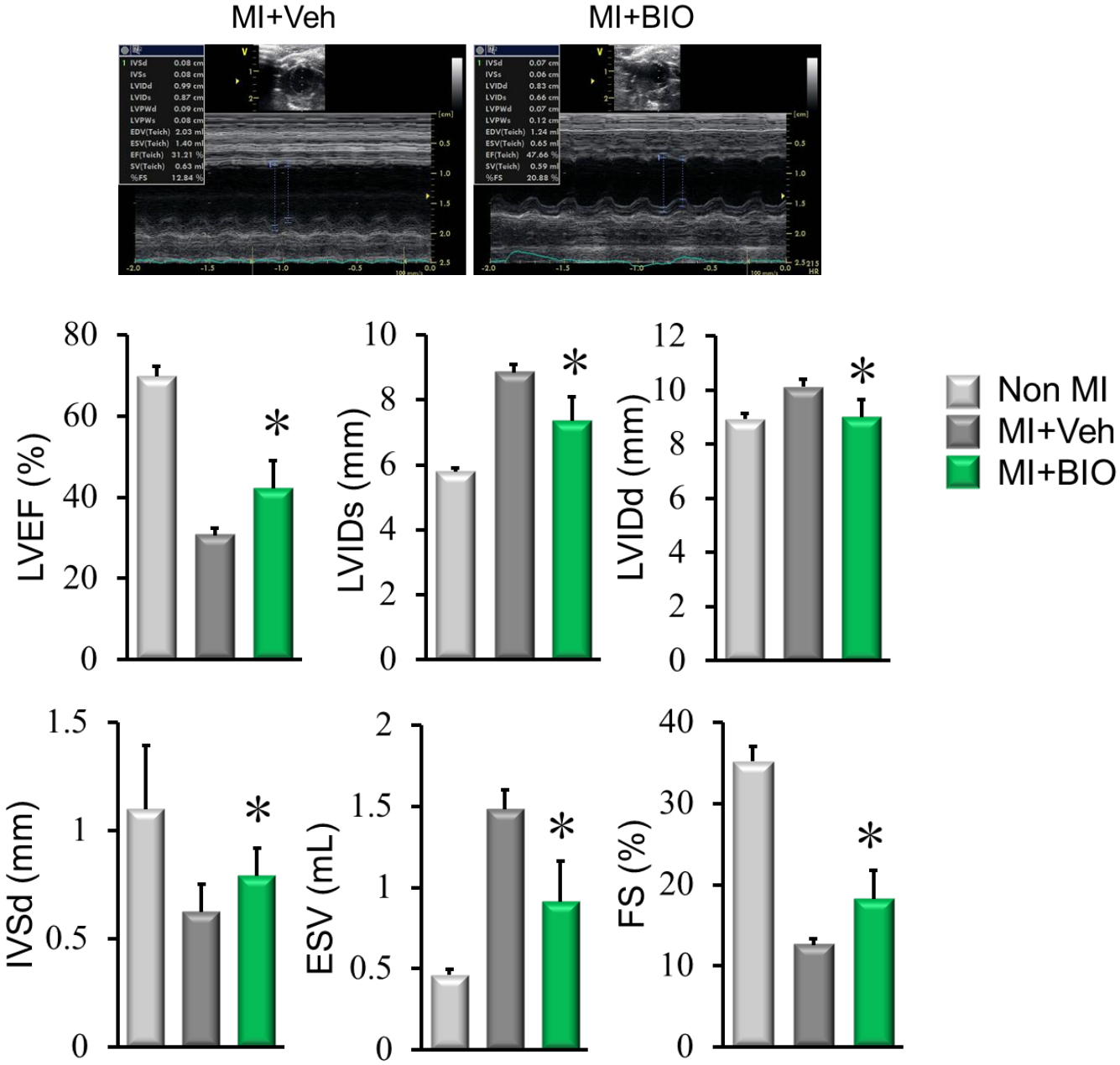
72 hpf *Tg(cmlc2:GFP)* transgenic zebrafish larvae, 2.5 μM aristolochic acid for 3 h

Therapeutic Effect of BIO on MI Model



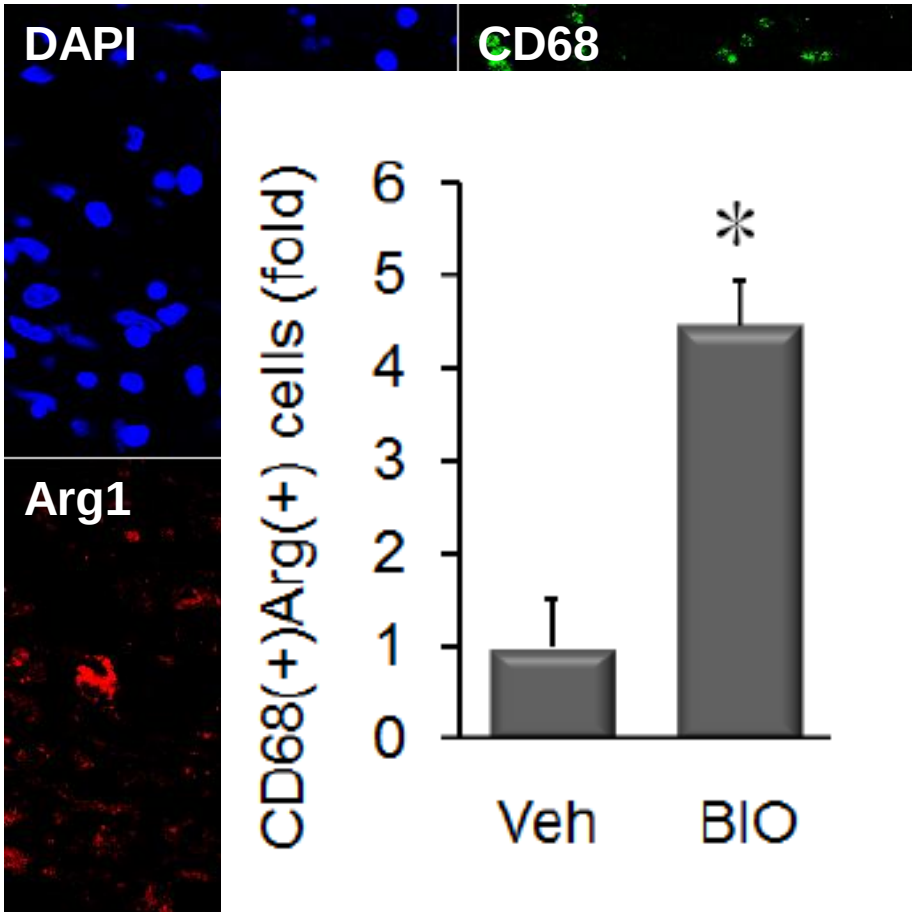


0.2 mg/kg BIO treatment

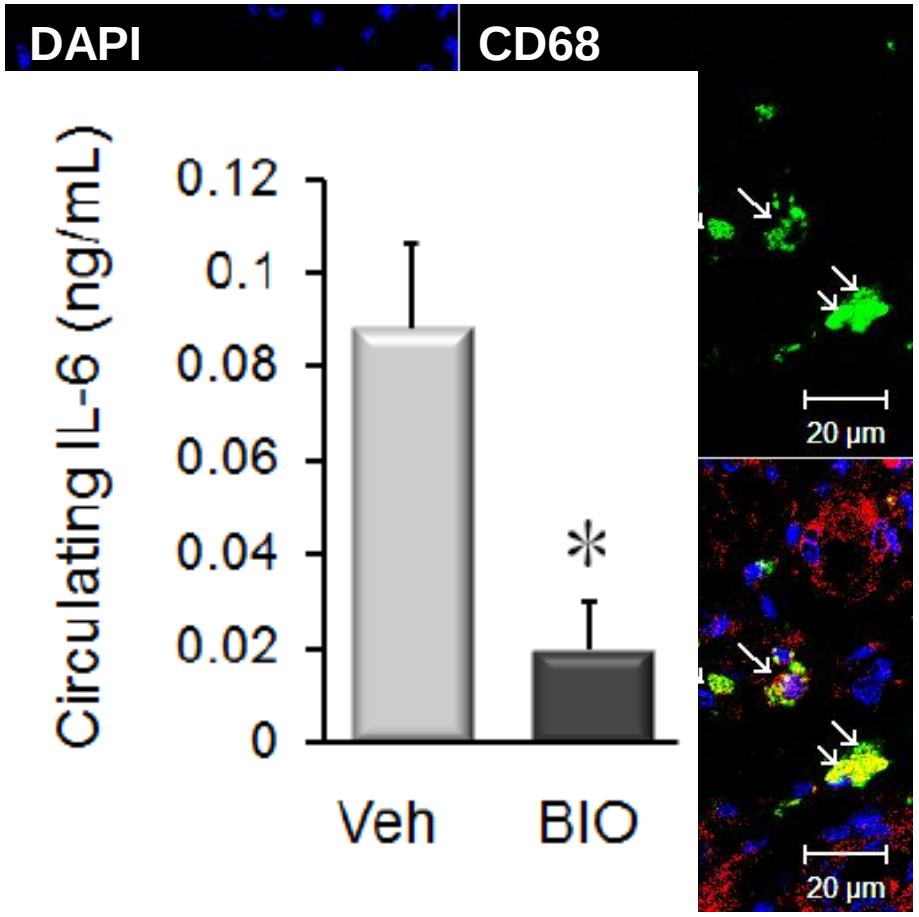

MI+Veh
MI+BIO
LVEF (%)
LVIDs (mm)
LVIDd (mm)
IVSd (mm)
ESV (mL)
FS (%)
*
Non MI
MI+Veh
MI+BIO

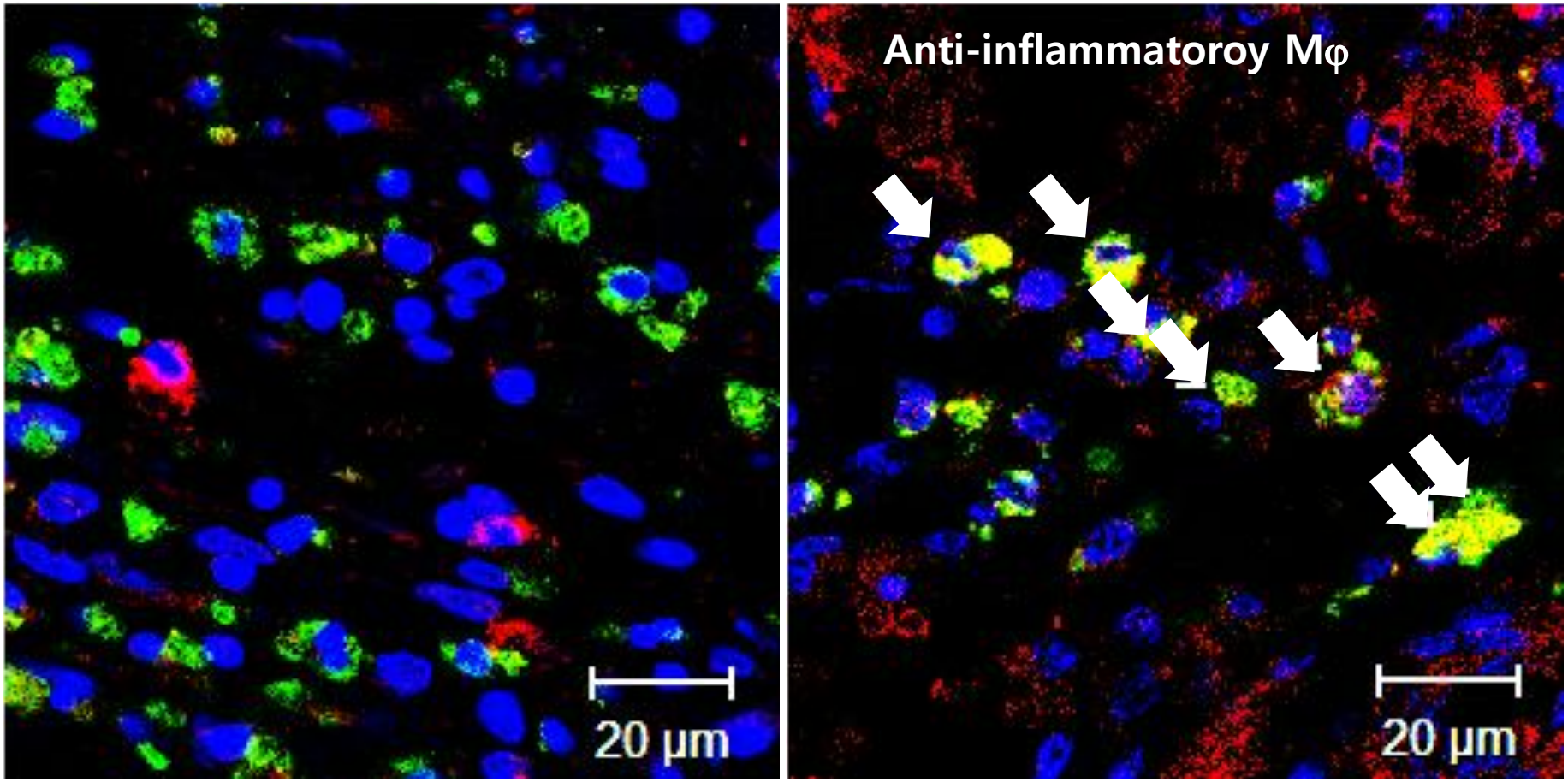
Anti-inflammatory Mϕ in BIO/MI Group

MI+Veh: CD68(+)Arg1(+)

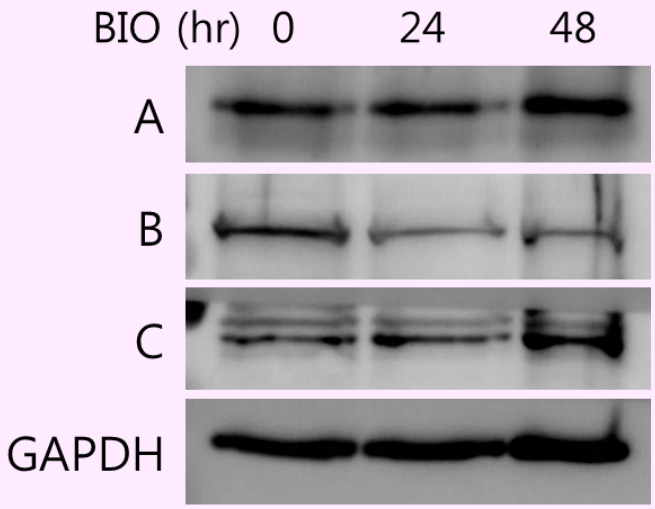


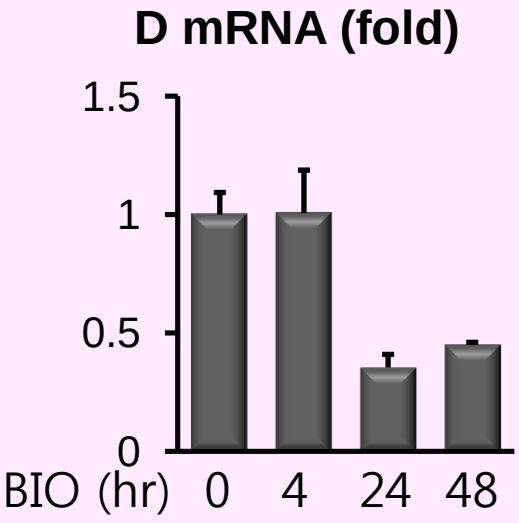
MI+BIO: CD68(+)Arg1(+)

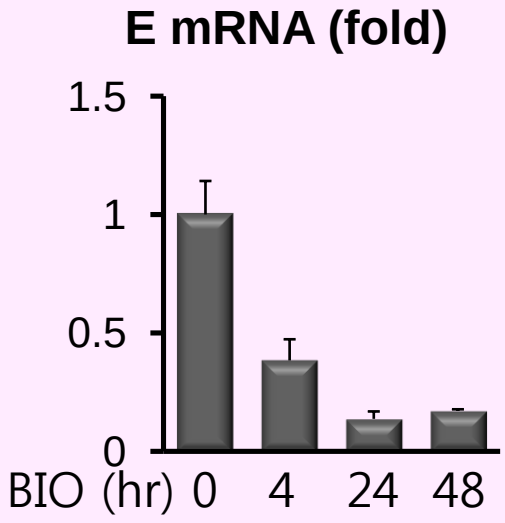



Anti-inflammatoroy Mφ
20 μm
20 μm

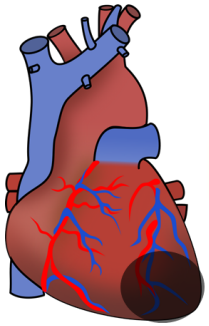
Microarray Analysis of BIO-treated CM







Summary: Pleiotropic Effects on Cardiac Environment Cells



Cardiomyocytes

Cardiac Fibroblasts

Macrophages

cross talk

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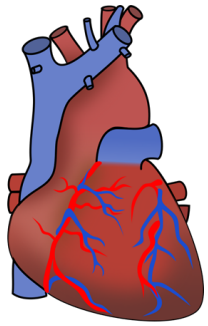

- **BIO enhan feration of Fb.**
- **BIO produ**
- **BIO promo ory Mϕ.**
- **These beneficial effects of BIO can be observed in a zebrafish HF model and a rat MI model.**
- **This study supports the further development of BIO as a drug to target**

F/E of BIO derivatives

2016
The 5th Gwangju-Boston Joint Cardiology Symposium

20-21st May, 2016, Myung-Hak Hall
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