Functional Effects of TGF-beta1 on Mesenchymal Stem Cell Mobilization in Cockroach Allergen Induced Asthma

Pei-Song Gao, MD, PhD

Division of Allergy & Clinical Immunology

Johns Hopkins University School of Medicine

Cockroach Allergy and Asthma

- In the US, cockroach allergy is most prevalent in urban areas and inner cities (17-41%).
- 23-60% of asthmatics who live in urban areas are allergic to cockroaches (*Gruchalla et al. JACI 2005*).
- Cockroach sensitization and exposure is an important risk factor for developing asthma (*Rosenstreich et al NEJM 1997*).
- Cockroach-specific immunotherapy for asthma is being conducted under the NIAID-funded Inner-City Asthma Initiatives (ICACII, 2009-2013) (*Togias et al. JACI 2010*).
- Bla g1 DNA vaccine has been suggested to be effective in the treatment of allergic airway inflammation in mouse model (Zhou *et al.* Allergy 2012).

Neighborhood differences in exposure and sensitization to cockroach, mouse, dust mite, cat, and dog allergens in New York City

Omar Olmedo, BS,[a] Inge F. Goldstein, DrPH,[b] Luis Acosta, MD,[a] Adnan Divjan,[a] Andrew G. Rundle, DrPH,[b] Ginger L. Chew, ScD,[a] Robert B. Mellins, MD,[e] Lori Hoepner, MPH,[a,c] Howard Andrews, PhD,[c,d] Sara Lopez-Pintado, PhD,[d] James W. Quinn, MA,[g] Frederica P. Perera, DrPH,[a] Rachel L. Miller, MD,[a,e,f] Judith S. Jacobson, DrPH,[b] and Matthew S. Perzanowski, PhD[a] *New York, NY*

HYPOTHESIS

Household income ↓
Older apartment ↑

↓

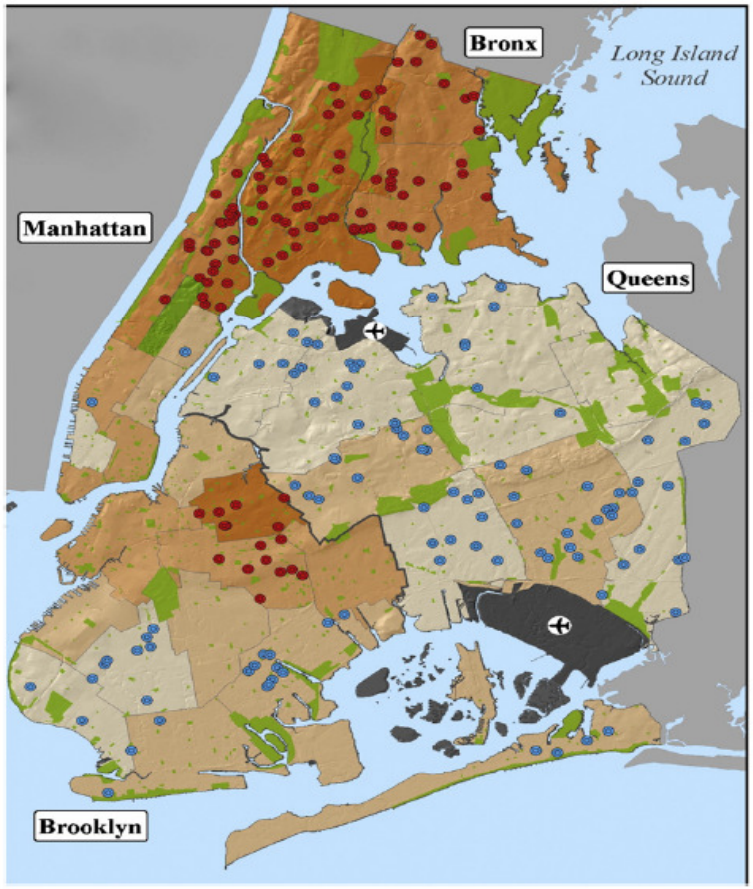
Allergen exposure
(cockroach, mouse, dust mite)

↓

Allergic sensitization

↓

Asthma ↑



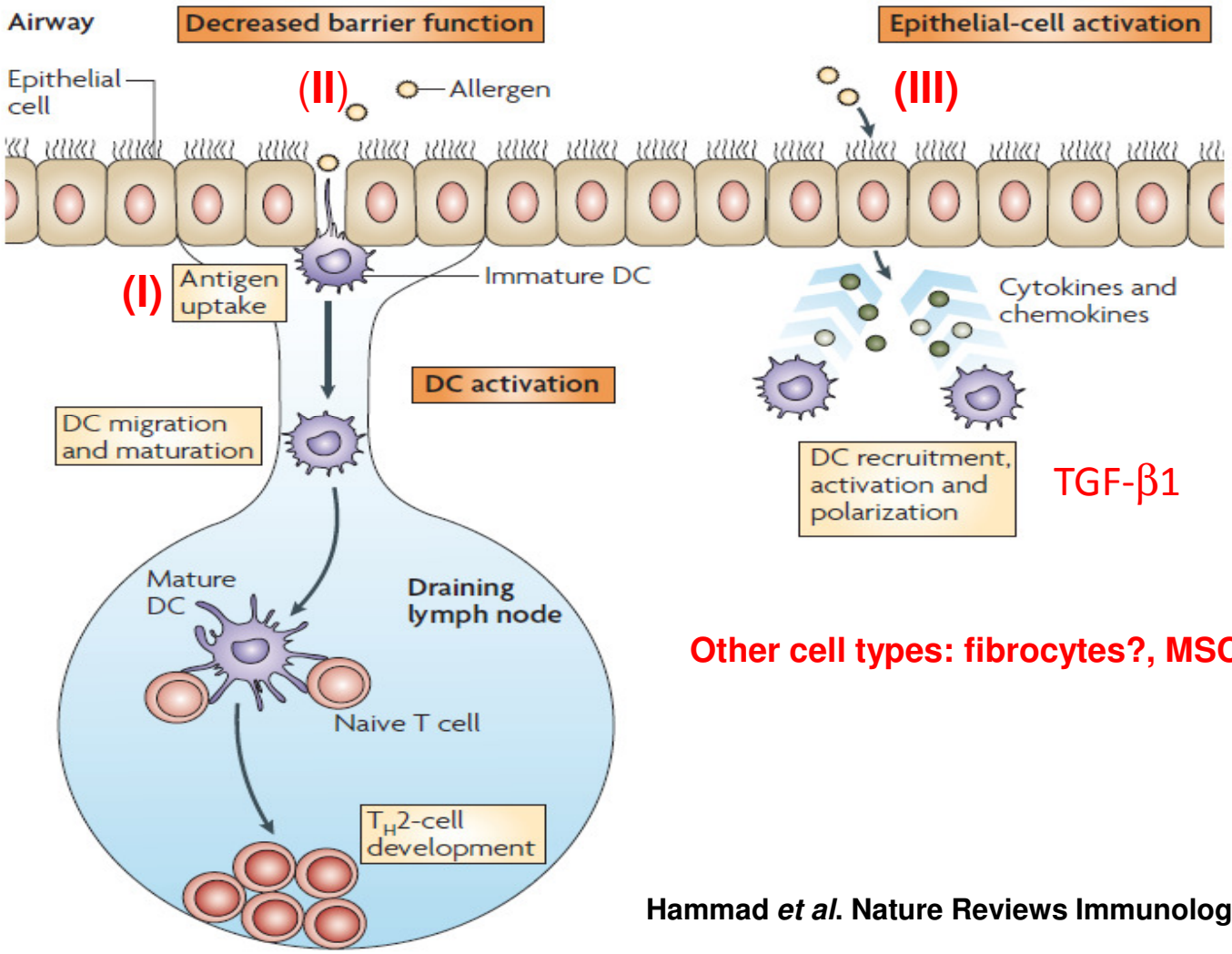
Among all tested allergens, sensitization to cockroach allergen was more common among children (cases and controls) living in the HAPNs than LAPNs (23.7% vs 10.8%).

HAPN: high asthma prevalence neighborhood

LAPN: low asthma prevalence neighborhood

JACI 2011;128(2):284-92 e7

Unifying Concept for Understanding TH2-cell Sensitization

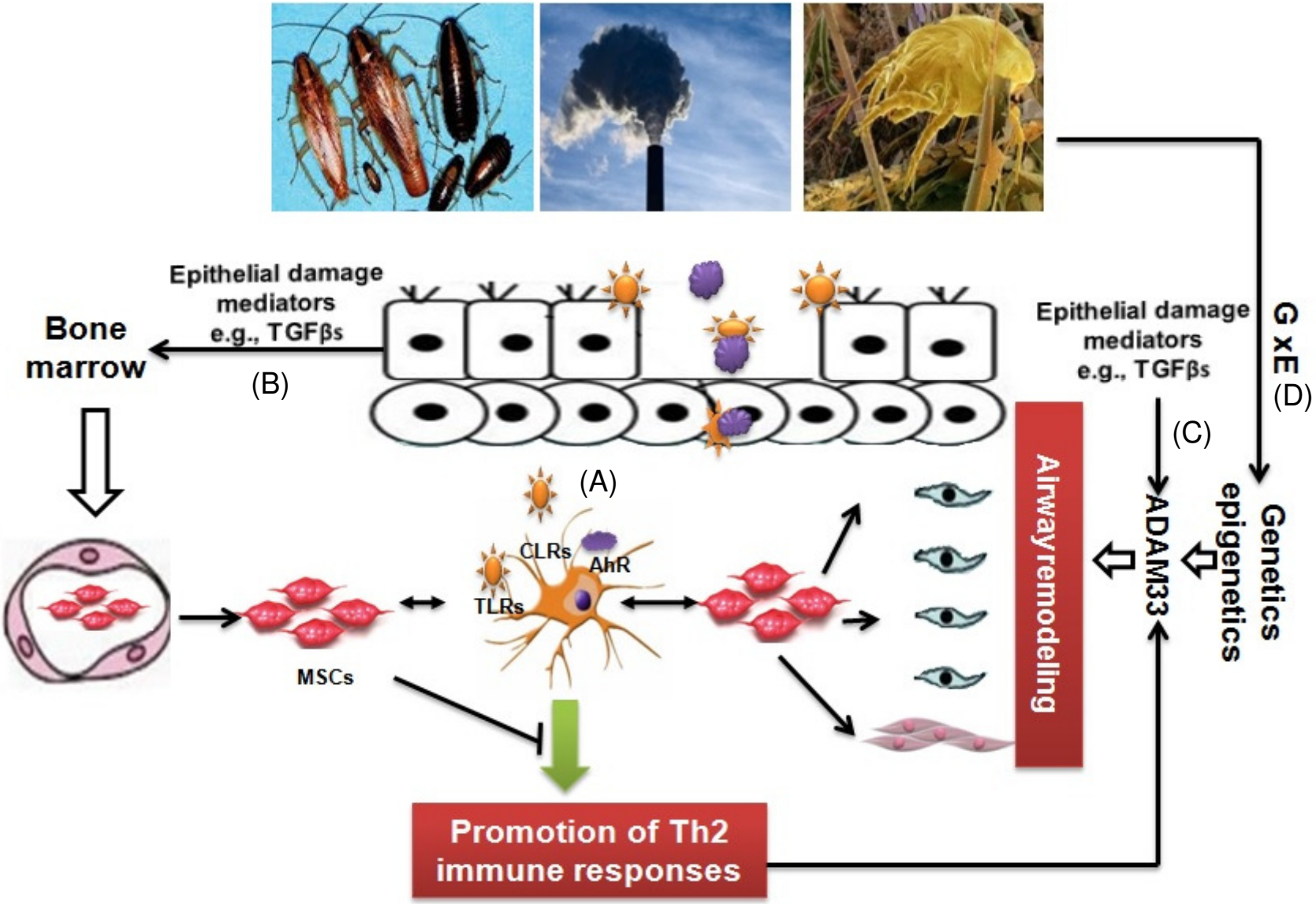


Other cell types: fibrocytes?, MSCs?

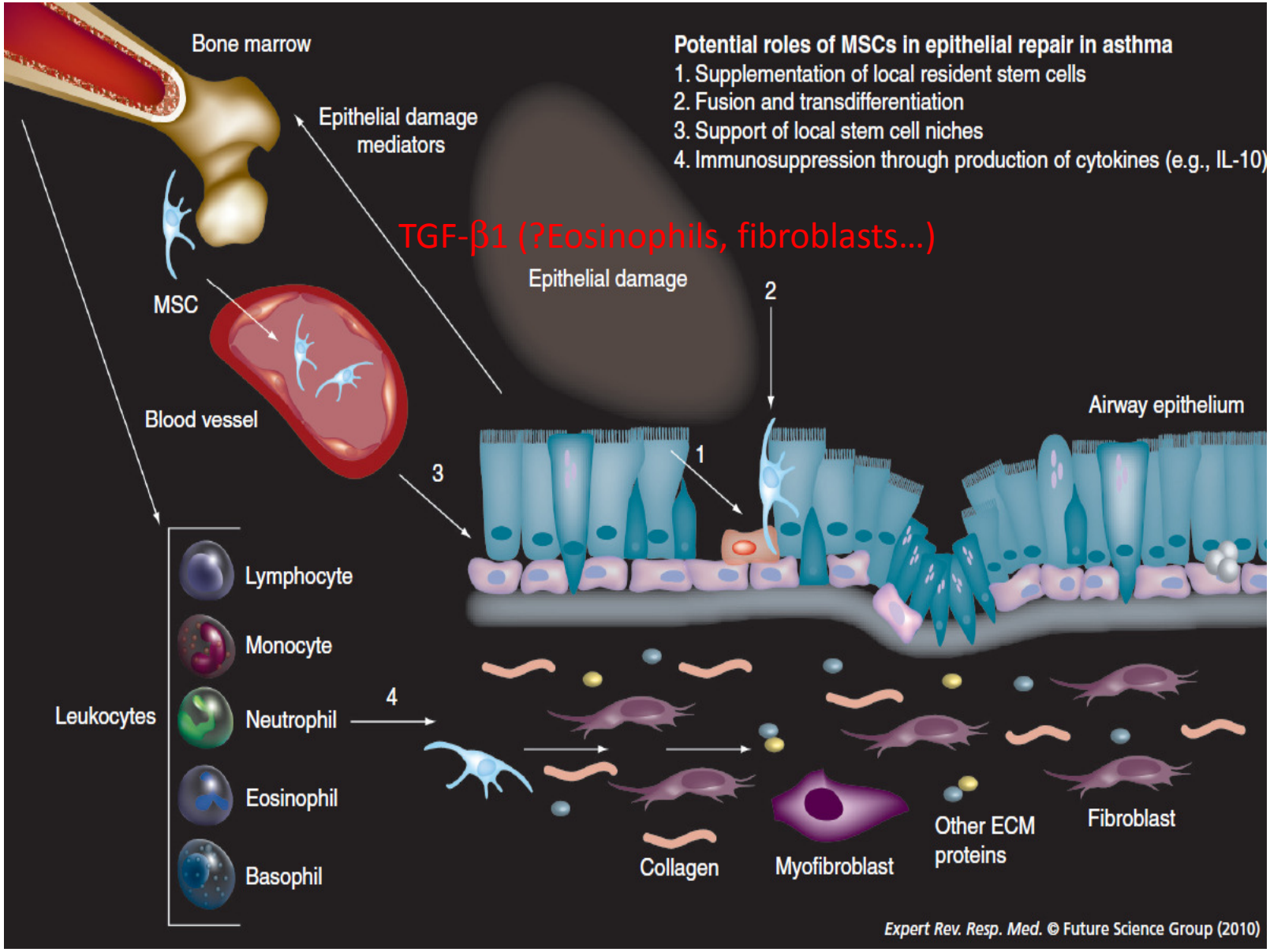
Hammad *et al*. Nature Reviews Immunology 2008

Hypothesis

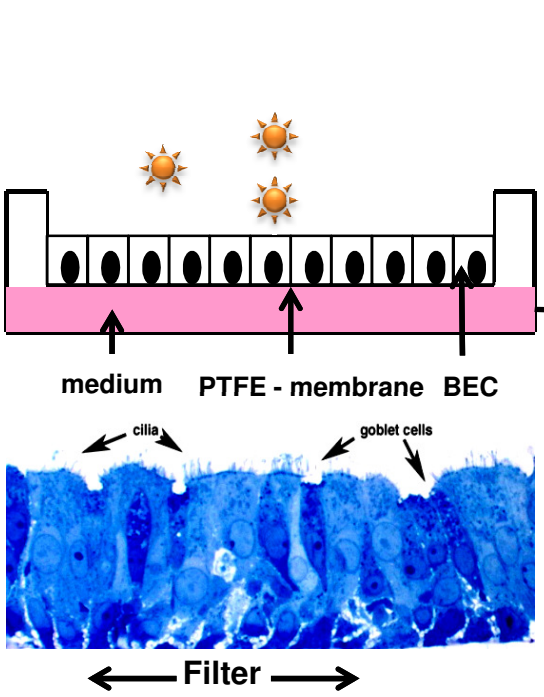
Cockroach Allergen Exposure, Together with Environmental Chemicals, Contributes to the development of Asthma



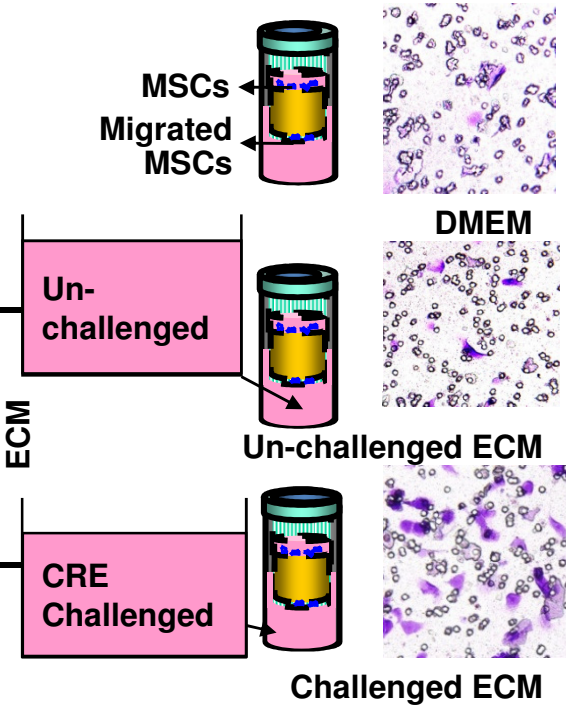
MSCs in Epithelial Repair in Asthma



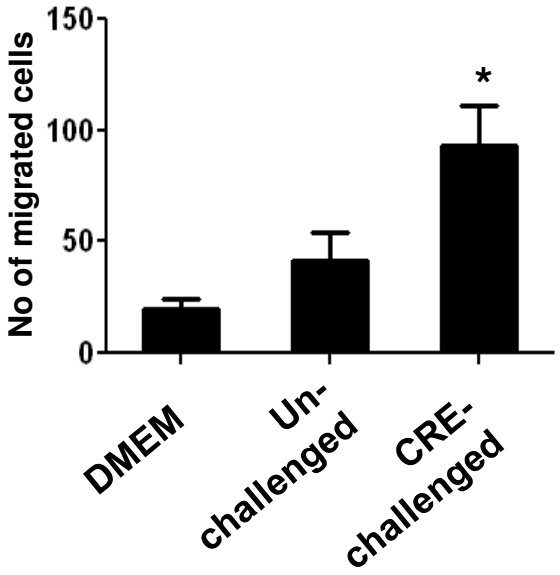
Epithelium-Conditioned Medium (ECM) Prepared by Cockroach Extract (CRE) Challenged Epithelium Induces MSC Migration



Air-liquid interface

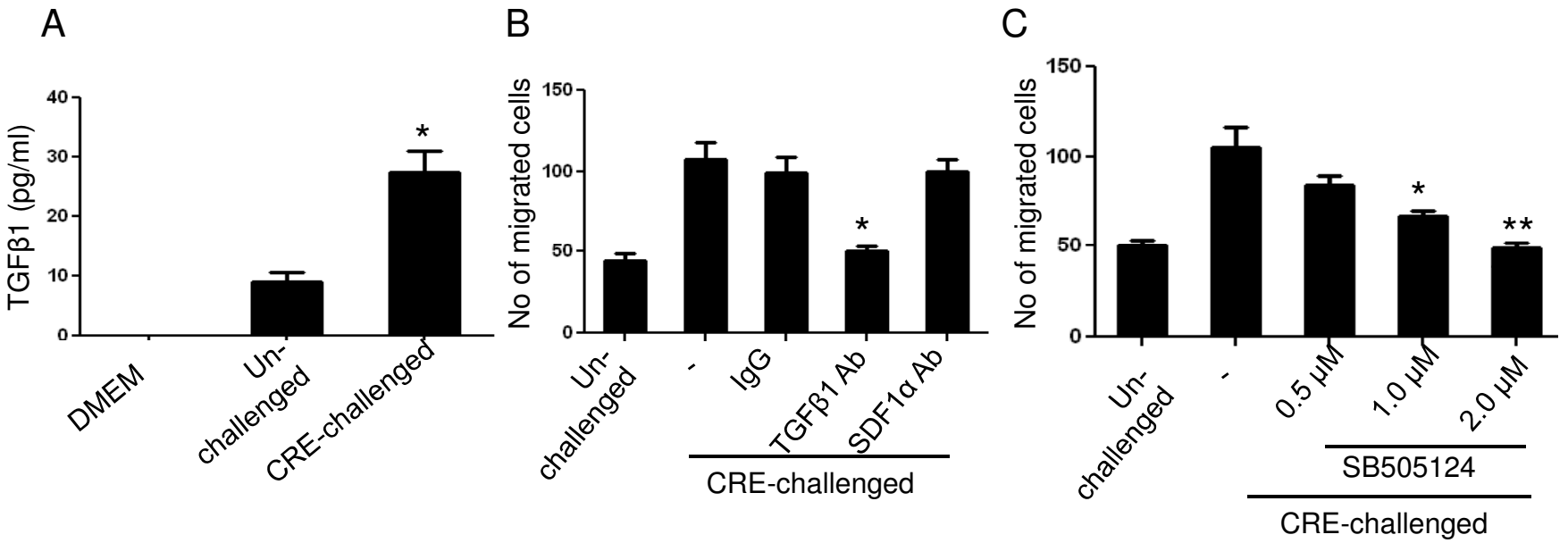


Transwell assays

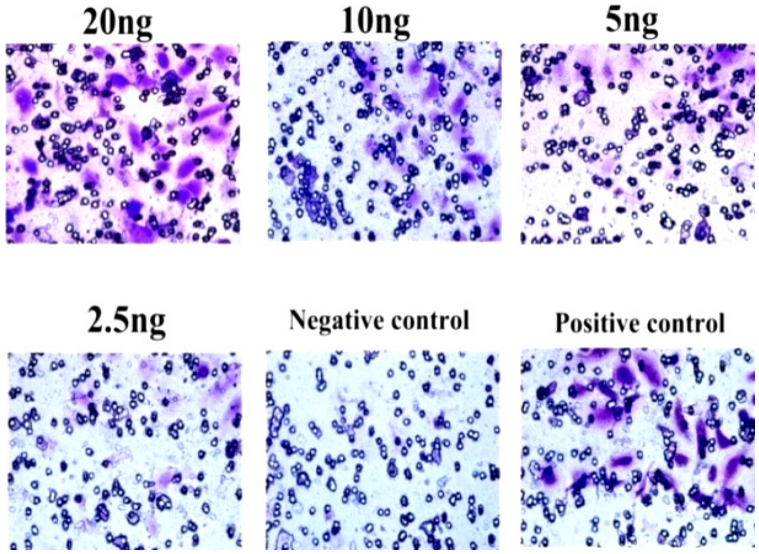


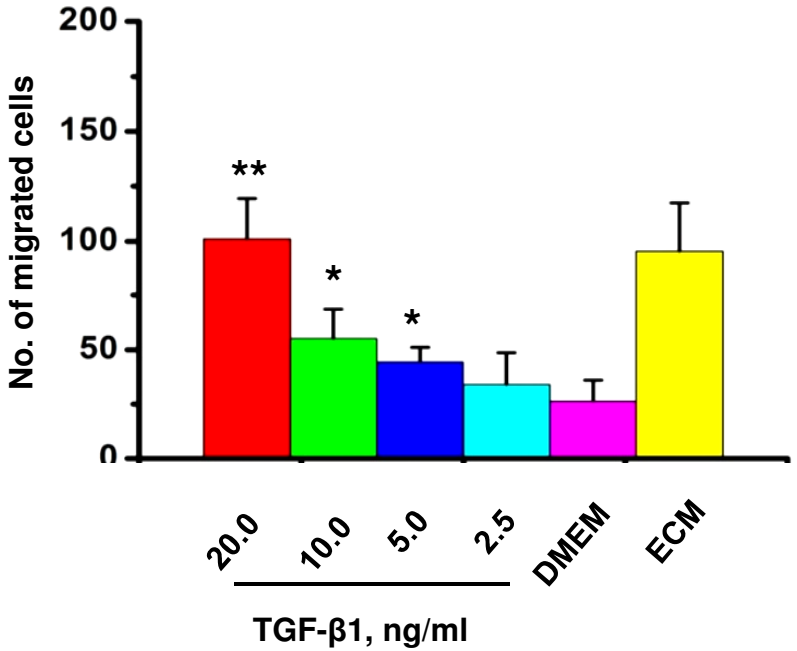
Migration

TGF-β1 Signaling in ECM-Induced MSC Migration

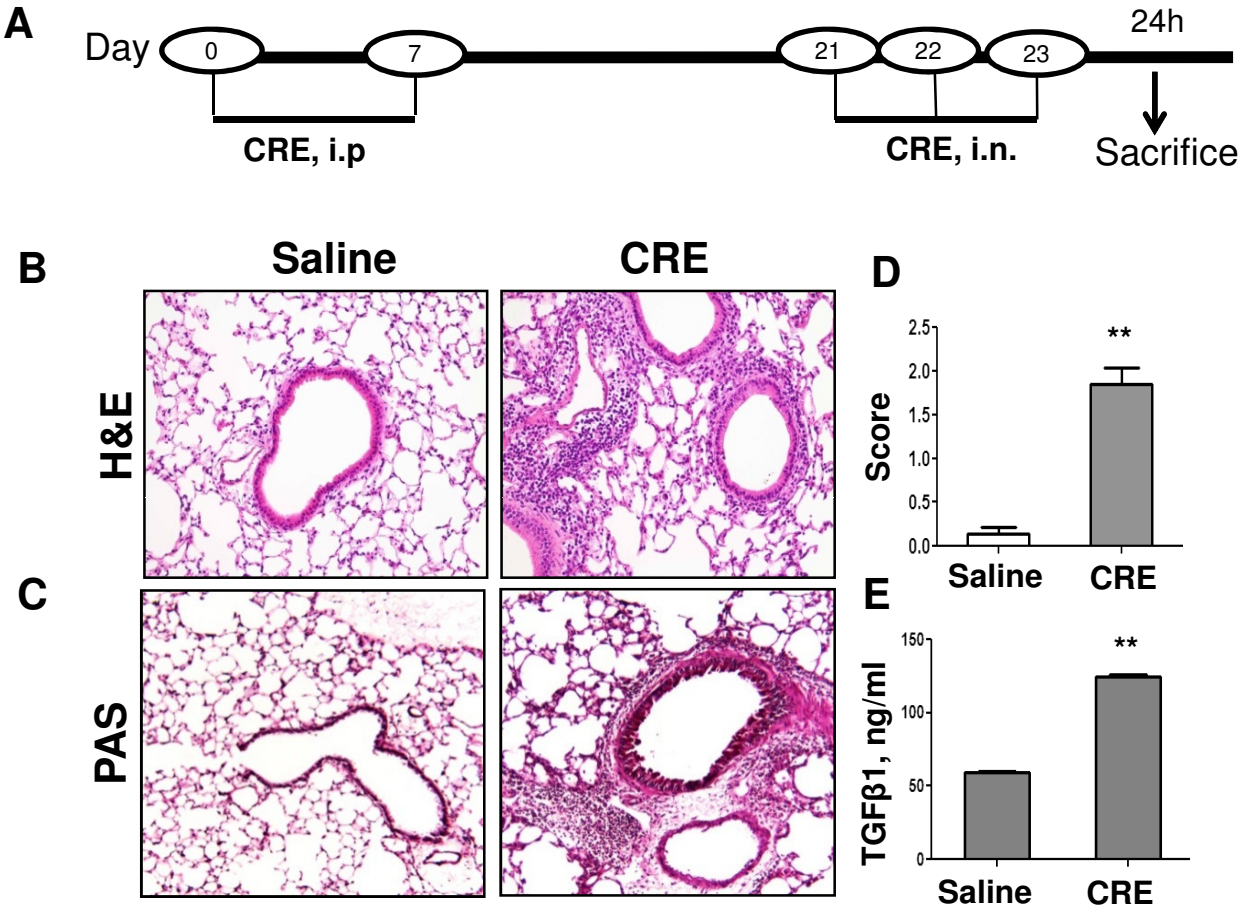


TGF-β1 Induced MSC Migration in a Dose-Dependent Manner



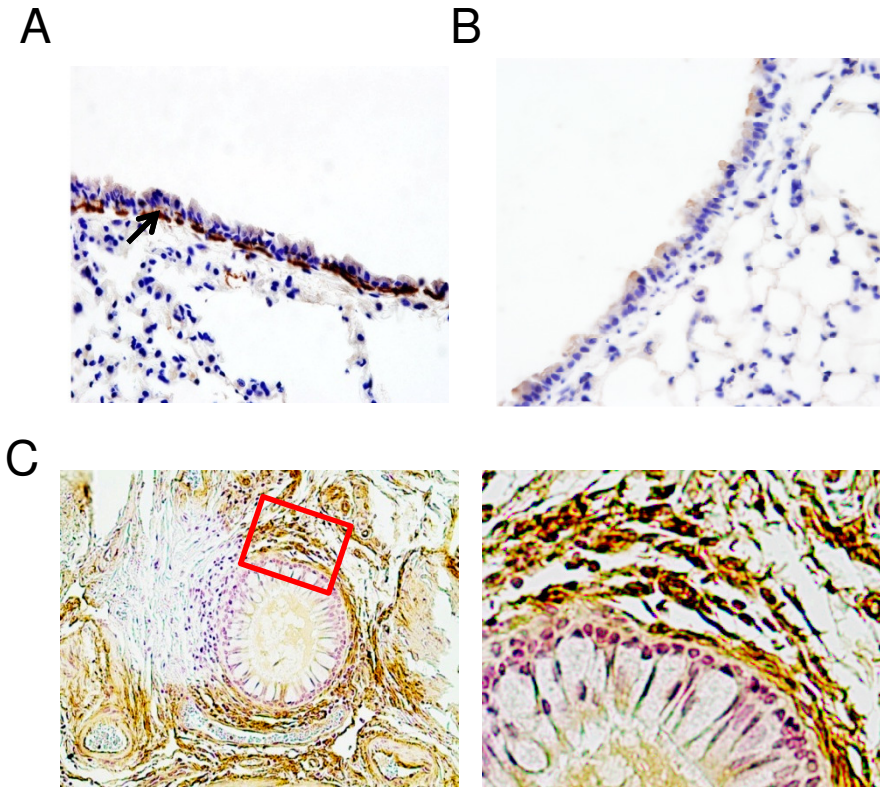


Establishment of a Cockroach Allergen-Induced Asthma Mouse Model:



A: Protocol for mouse models of asthma
B:H&E stained sections
C: PAS stained sections
D: Dense peribronchial infiltrates scored by the number of infilitrates.
E: Serum levels of active TGFβ1. ***P*<0.01.

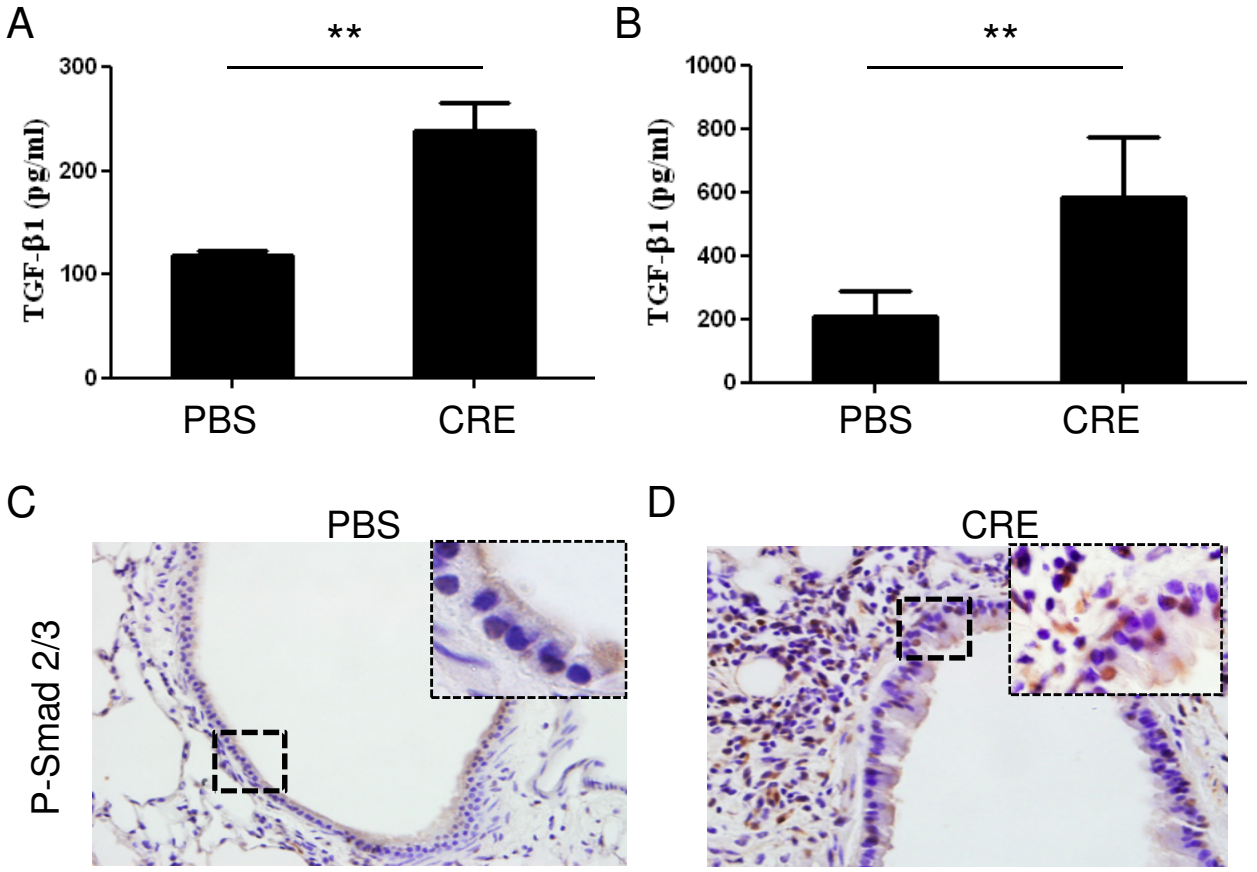
MSCs in Lungs of Cockroach Extract (CRE)-Challenged Mice



A: Nestin^{+} cells in airway epithelial cells from mice after CRE challenge.
B: Nestin^{+} cells in airway epithelial cells from saline treated mice.
C: Nestin^{+} cells were also observed in the airway sub-epithelial region of human patients with allergic asthma**.**

MSCs are increased in airway after allergen sensitization and challenge

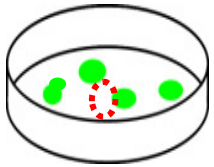
Increased Activation of TGFβ1 Signaling in Lung Tissue of Allergic Asthma

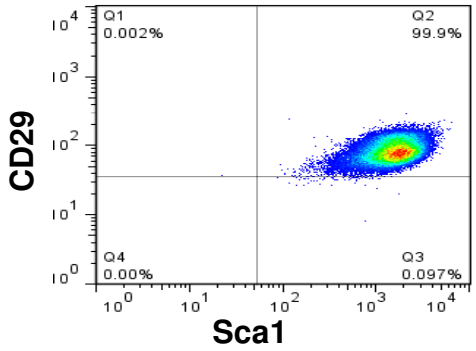


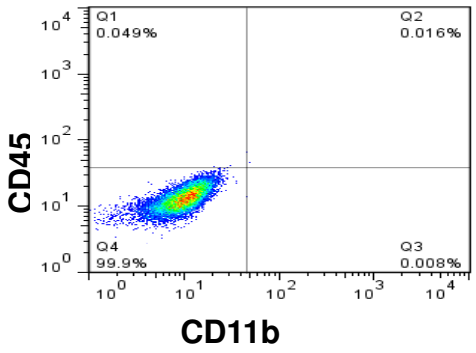
Characterization of Mouse GFP+ MSCs

A

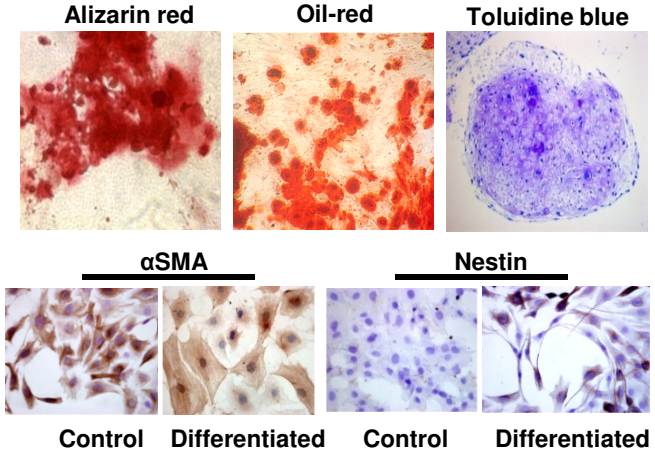
GFP+ Sca-1+CD29+
CD45− CD11b−



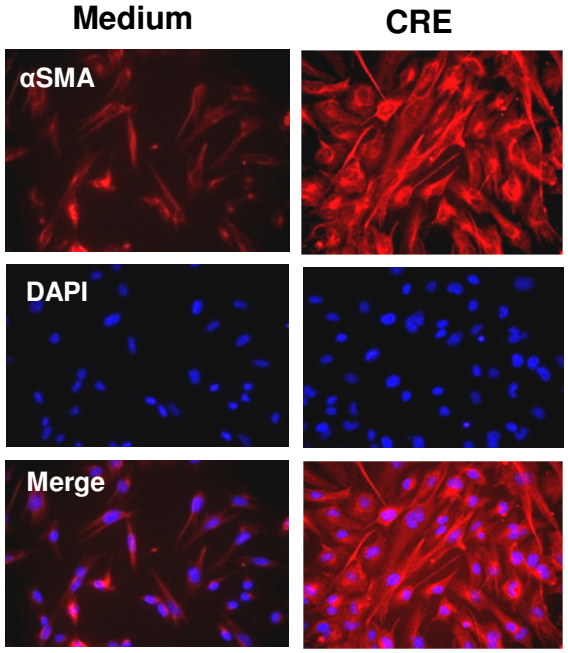




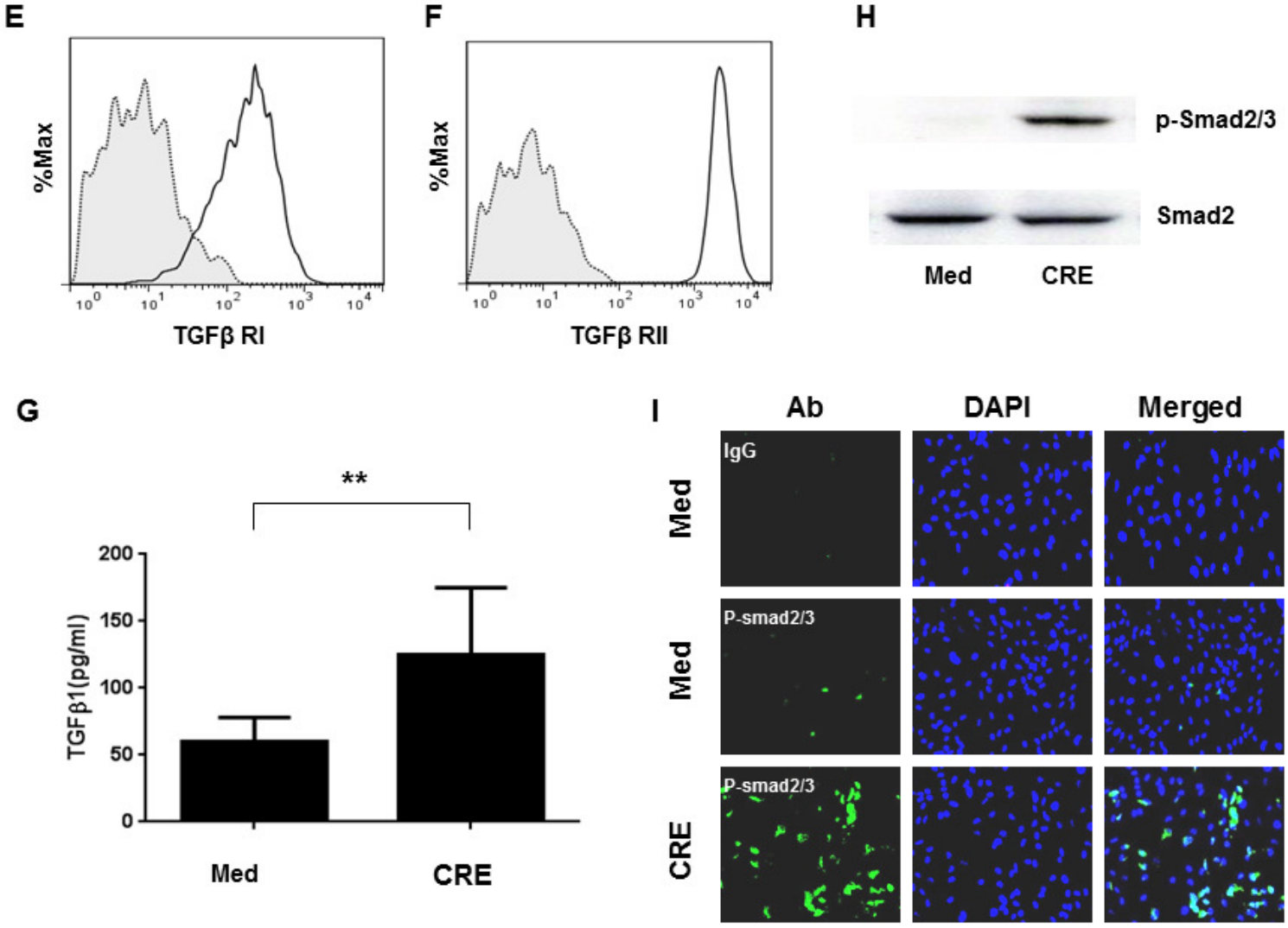
B



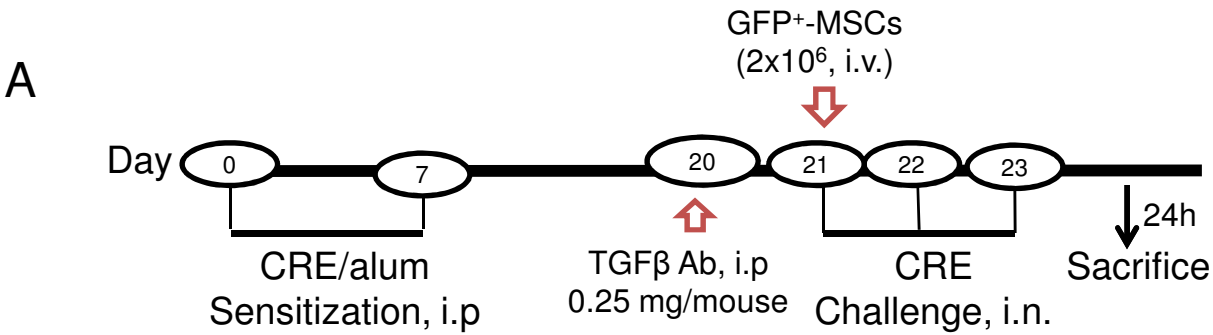
C

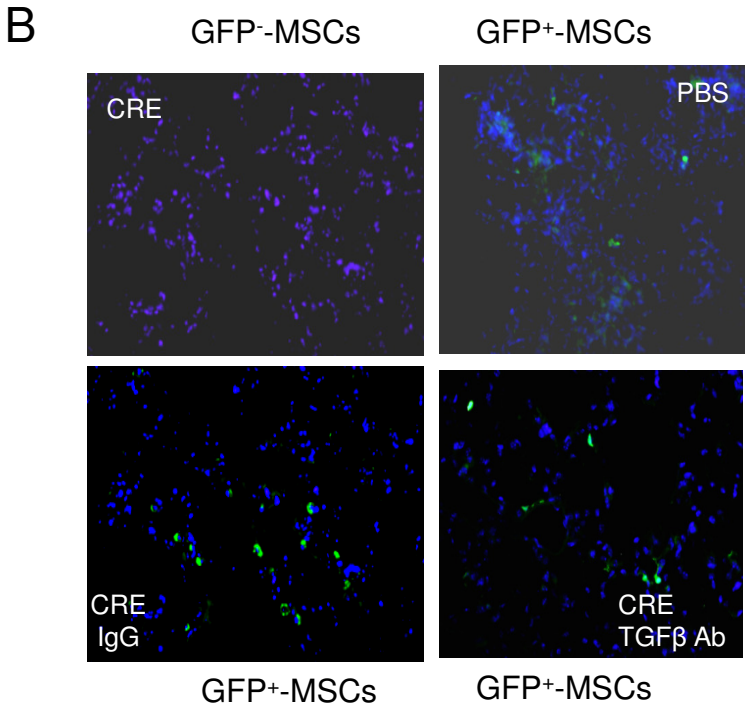


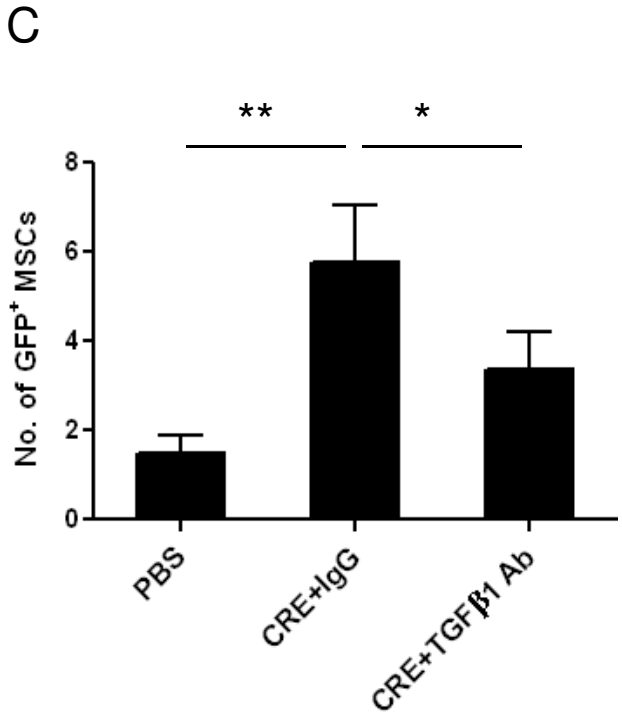
Increased Activation of TGFβ1 Signaling in CRE-treated MSCs



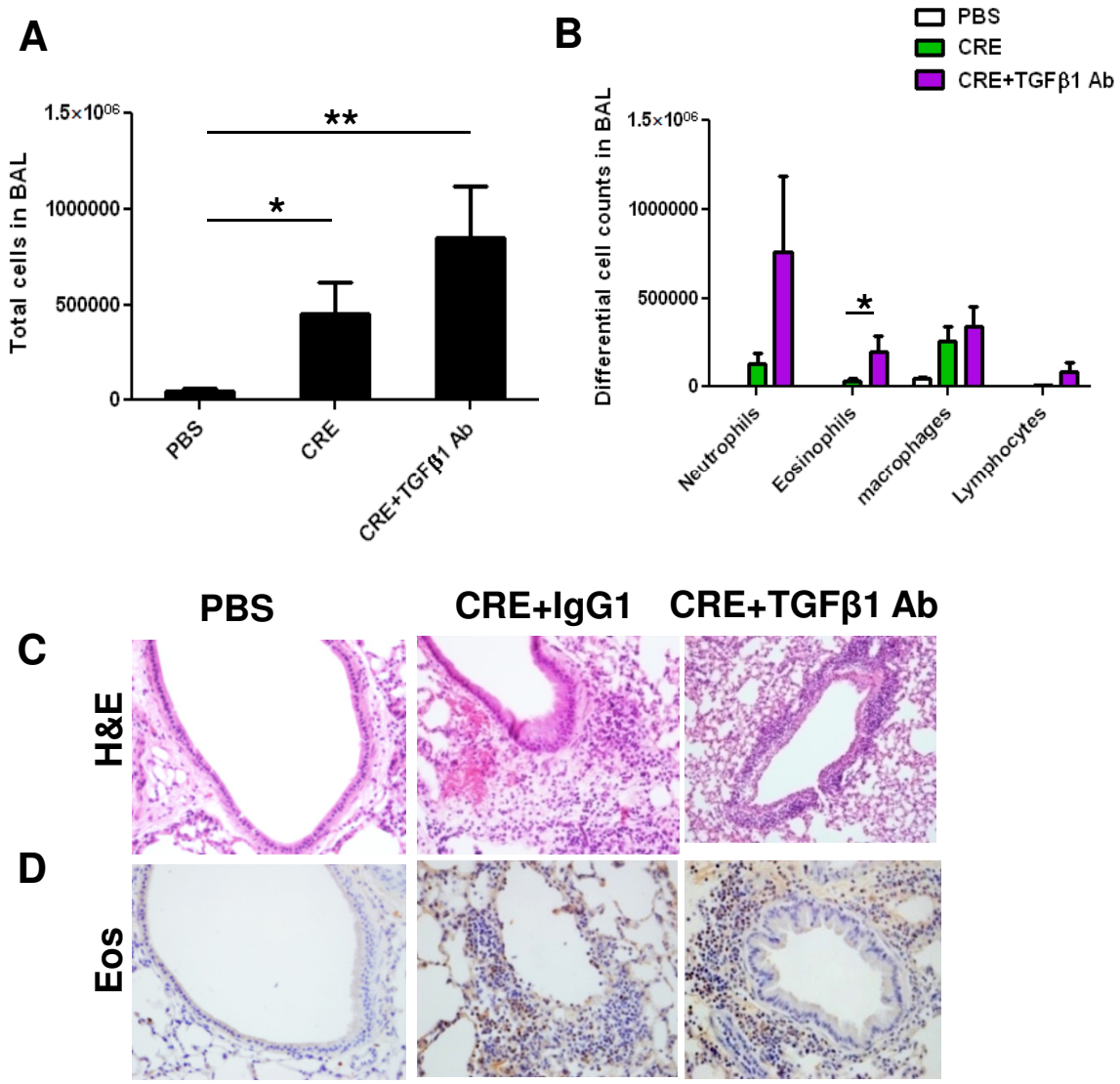
MSCs Mobilize to the Lungs from Peripheral Blood through TGFβ1



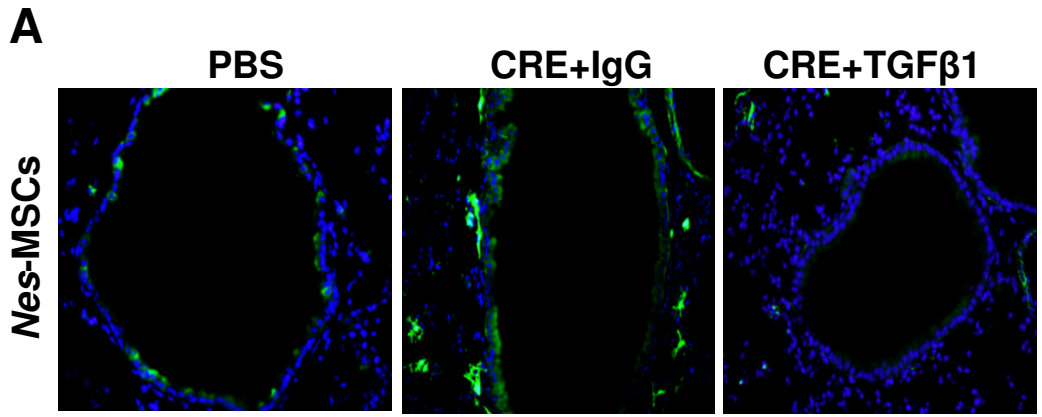


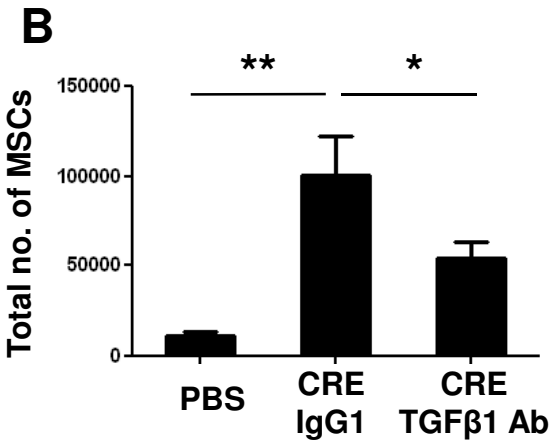


TGFβ1 Neutralizing Antibody Inhibits Airway Inflammation

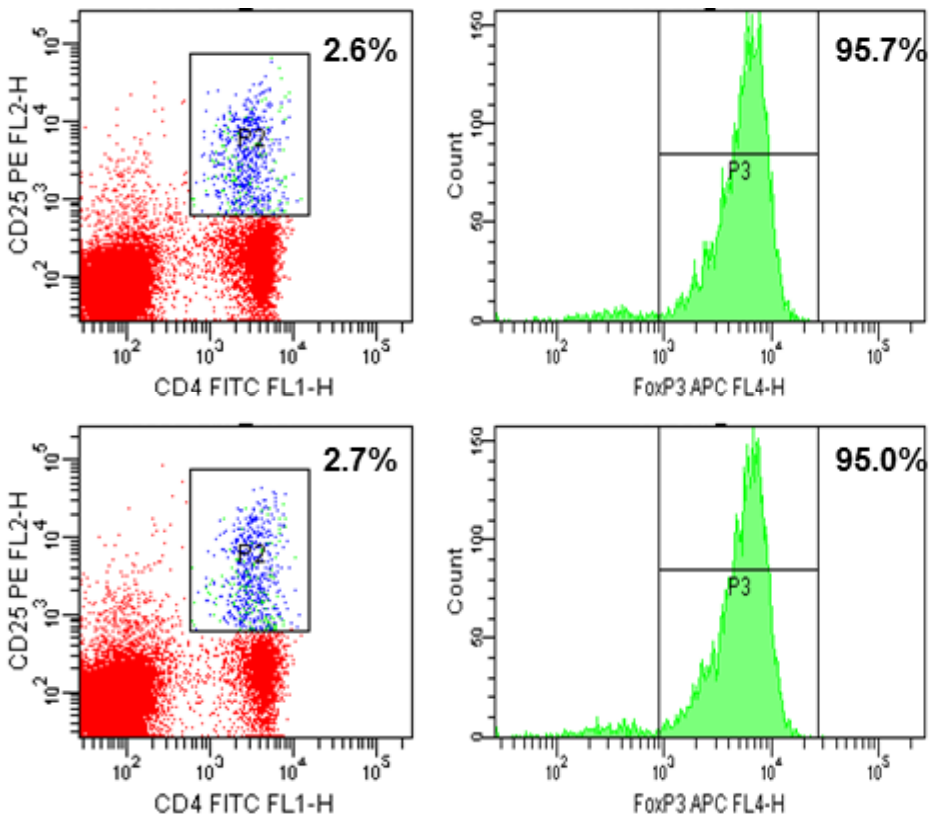


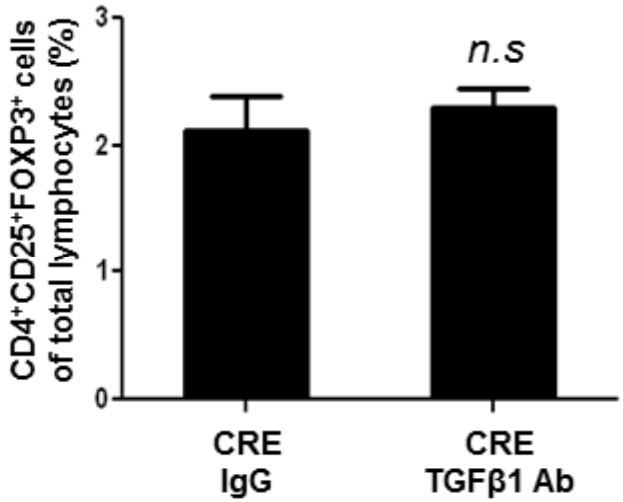
GFP+ cells and Cytokines in the Airways of CRE-Challenged or Saline-Treated *Nes*-GFP mice



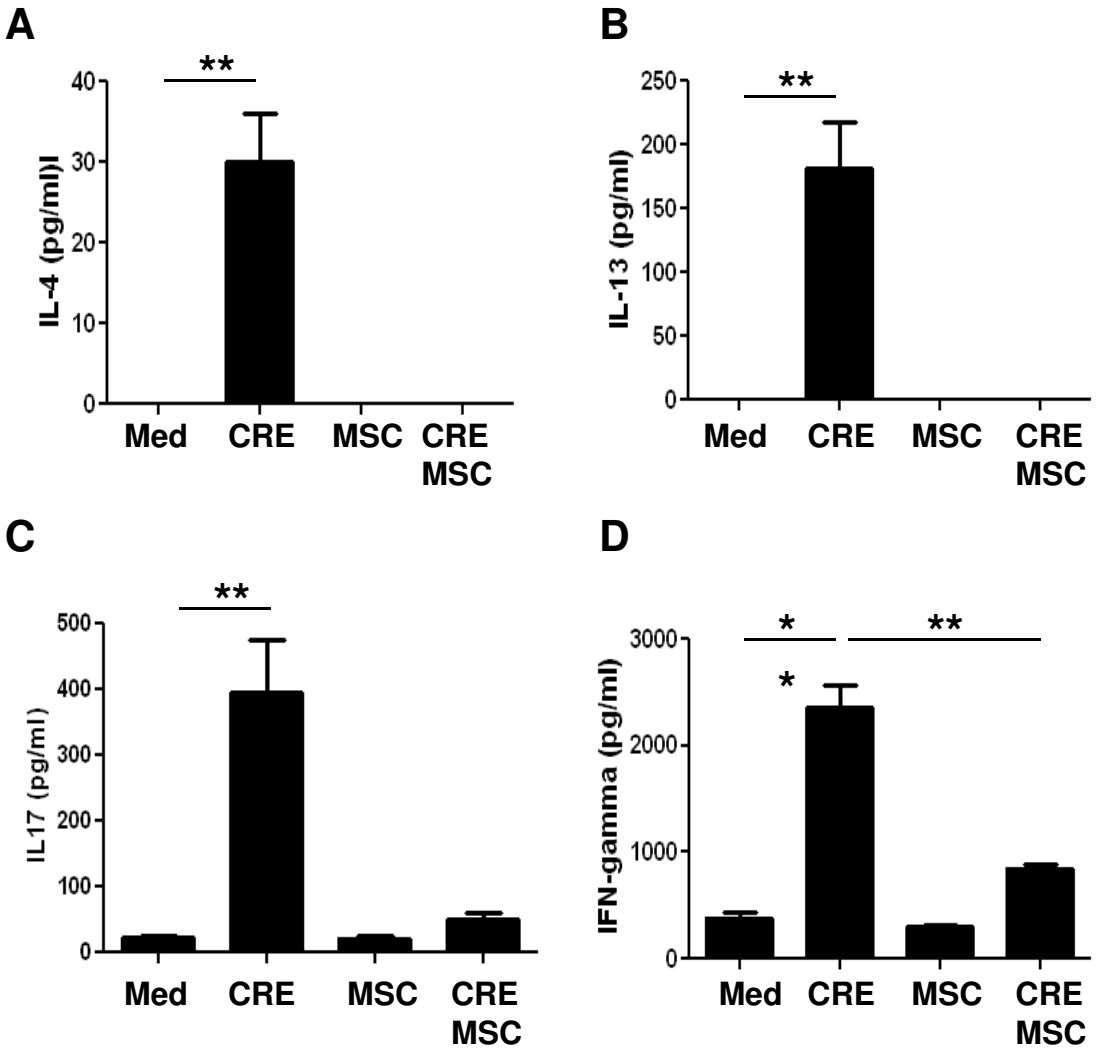


$CD4^+CD25^+Foxp3^+$ Cells from CRE-Challenged Mice Treated with TGFβ1 Antibody





Modulatory effects of MSCs on CRE-induced T responses *in vitro*



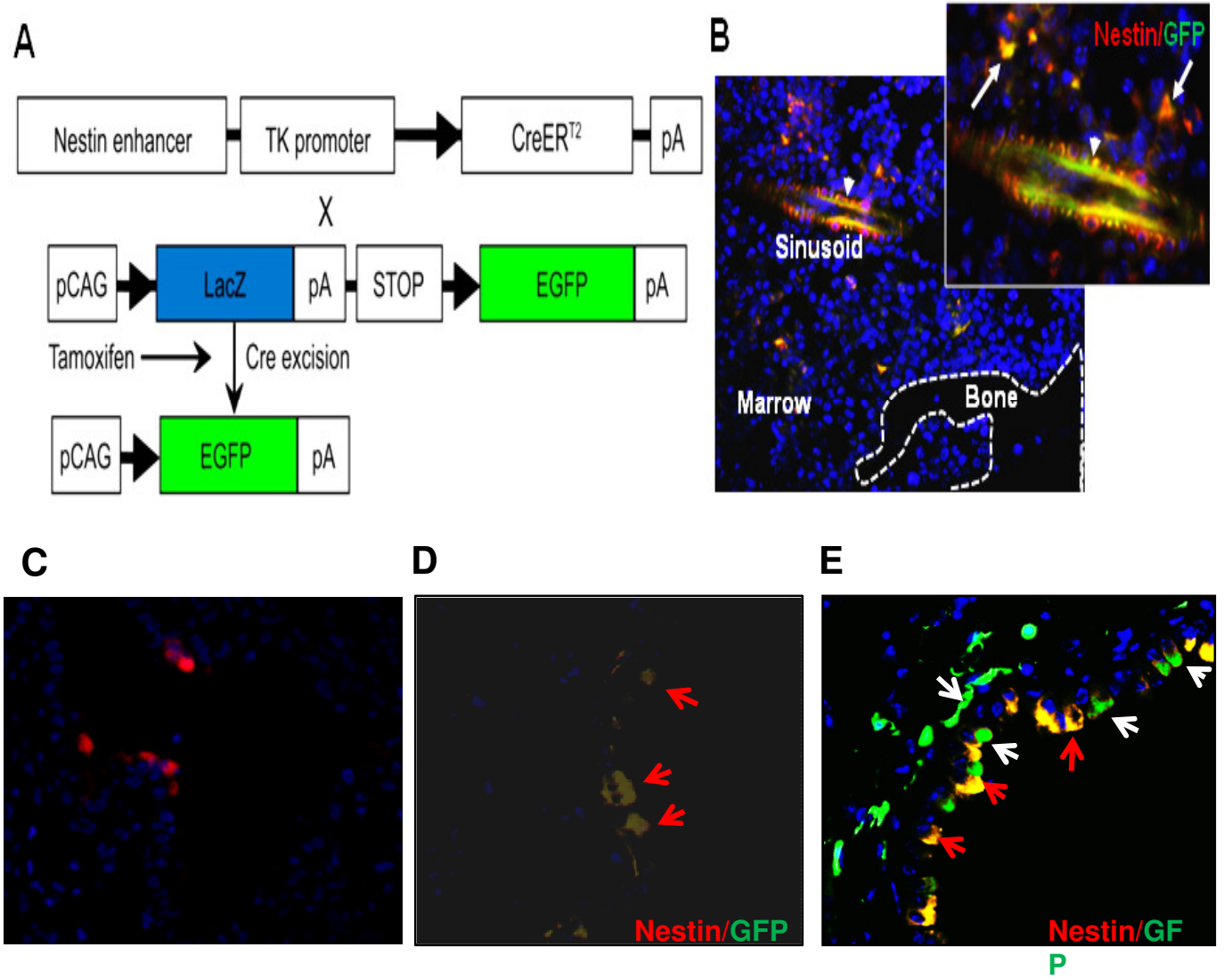
Summary

- MSCs are accumulated in lung tissue of CRE-challenged mice and asthmatic patients.
- TGFβ1 signaling is activated in lung tissue of allergic asthma.
- TGFβ1 mediates MSCs migration induced by human epithelium conditioned medium.
- TGFβ1 mediates the recruitment of MSCs to the lungs in asthma.
- TGFβ1 limits the allergic inflammation in mouse models of asthma.
- MSCs modulate T responses to CRE in vitro.

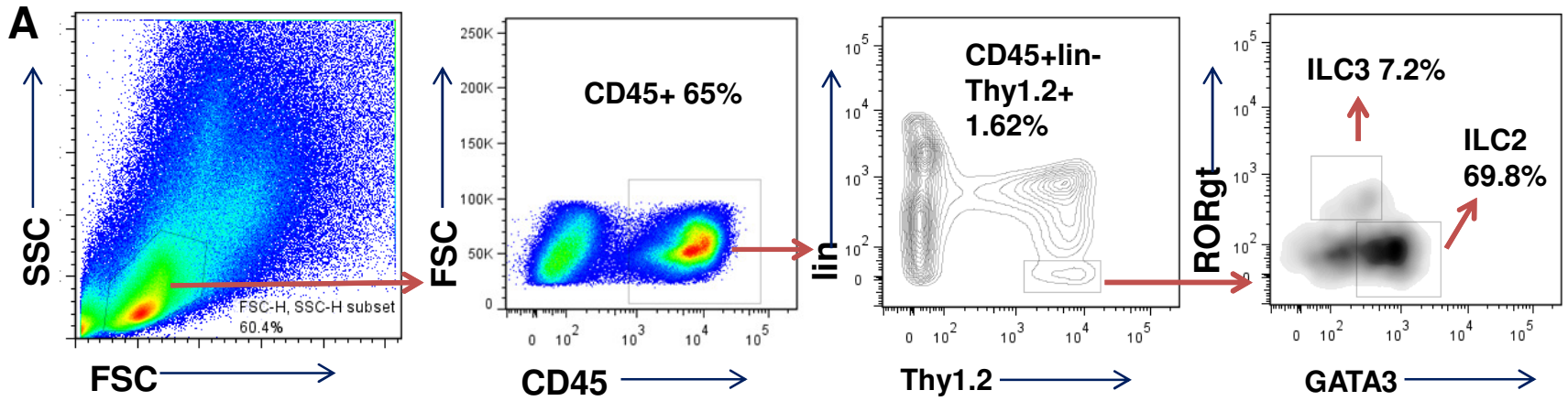
Ongoing Research Studies

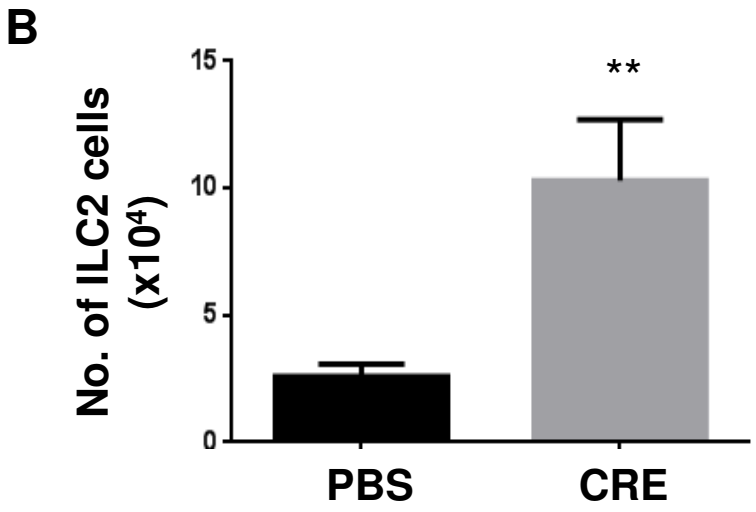
- Determine the role of active TGFβ1 in the recruitment of MSCs to the lung in asthma.
- Track the lineage commitment/differentiation of recruited MSCs in lungs
- Investigate the role of MSCs in CRE-induced allergic inflammation (CRE-MSCs-ILCs)

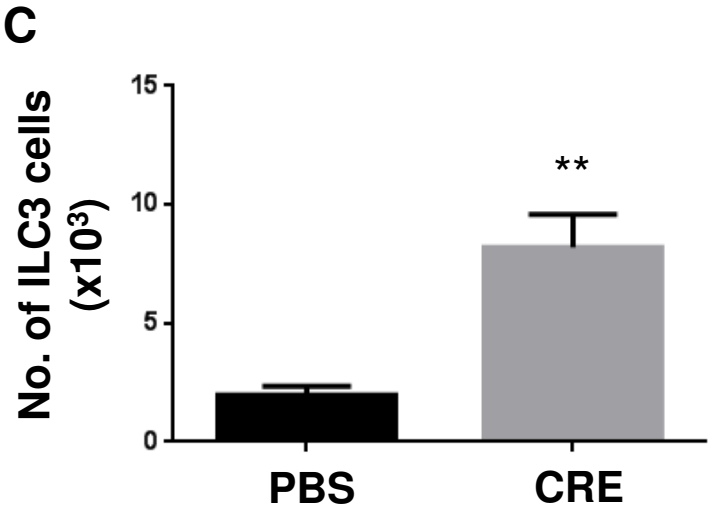
Genetic Marking Strategy for *in vivo* Analysis of Individual Nestin^{+} Cells



Increased Innate Lymphoid Cells (ILCs)-2 and 3 in CRE Induced Mouse Model







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