

# Overview of Cell Therapy in Lung Biology and Disease

Carol J. Blaisdell M.D.

Medical Officer

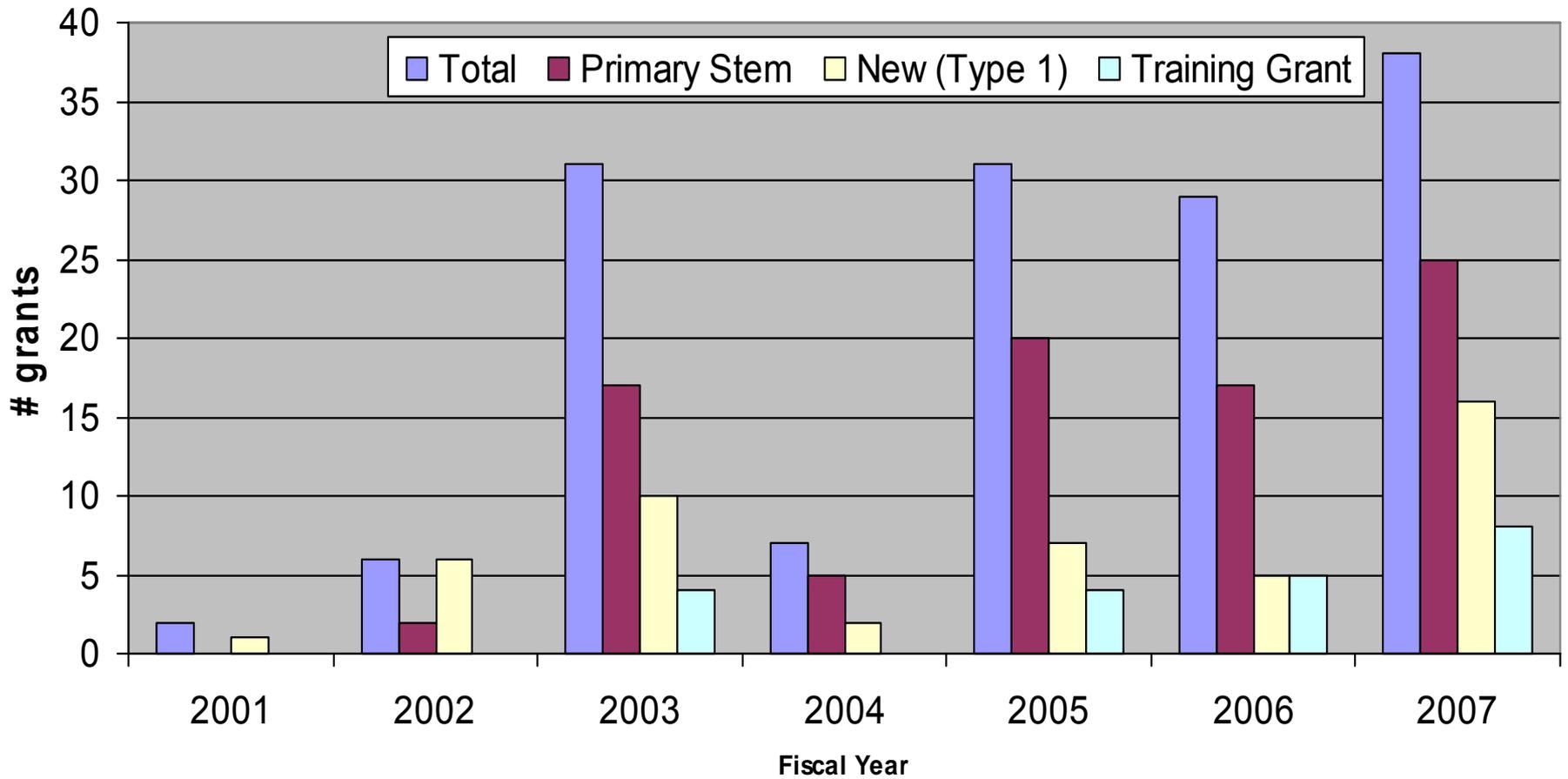
Developmental Biology and Pediatrics

Division of Lung Diseases, NHLBI

# FY08 DLD Program in Stem Cell Research

- Major areas of investigation
  - Identification of putative stem cell populations
  - Mechanisms of recruitment of stem cells to lung
  - Reparative mechanisms by stem cell populations
  - No studies in preclinical/clinical testing
  - Few using human models (3 non embryonic, 2 embryonic)

# DLD funded Stem Cell Grants



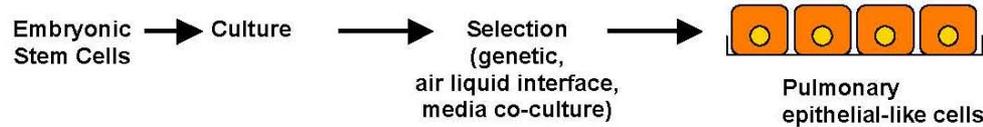
# **RFA“Collaborative Studies on Lung Stem Cell Biology and Cell Based Therapy” (R01) (HL-07-003)**

**7 investigators funded 9/07 (32 applications), met 12/07**

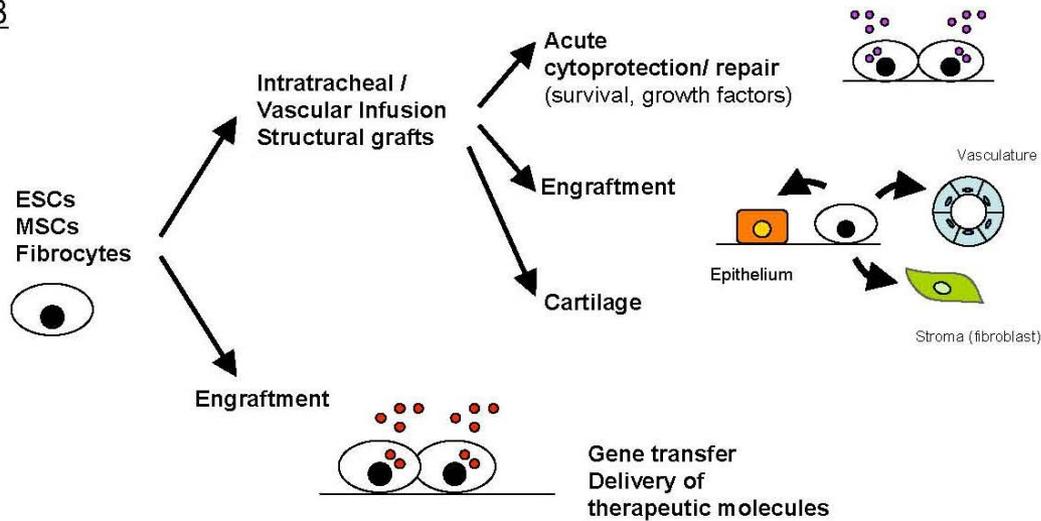
- Characterization and identification of endogenous lung stem cells**
- Role of bone marrow stromal cells in mediating lung repair**
- Innovative strategies in delivery of regenerative cells**
- Strategies to enhance epithelial reparative capacity**
- Use of support matrices to augment lung tissue repair**

# Origin of Lung Reparative Cells

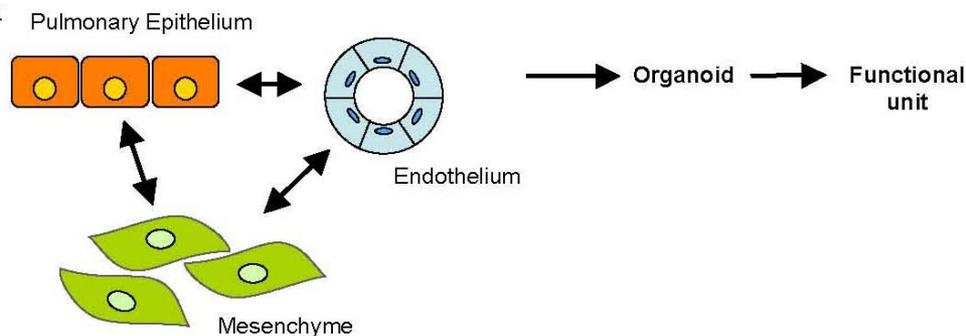
A



B



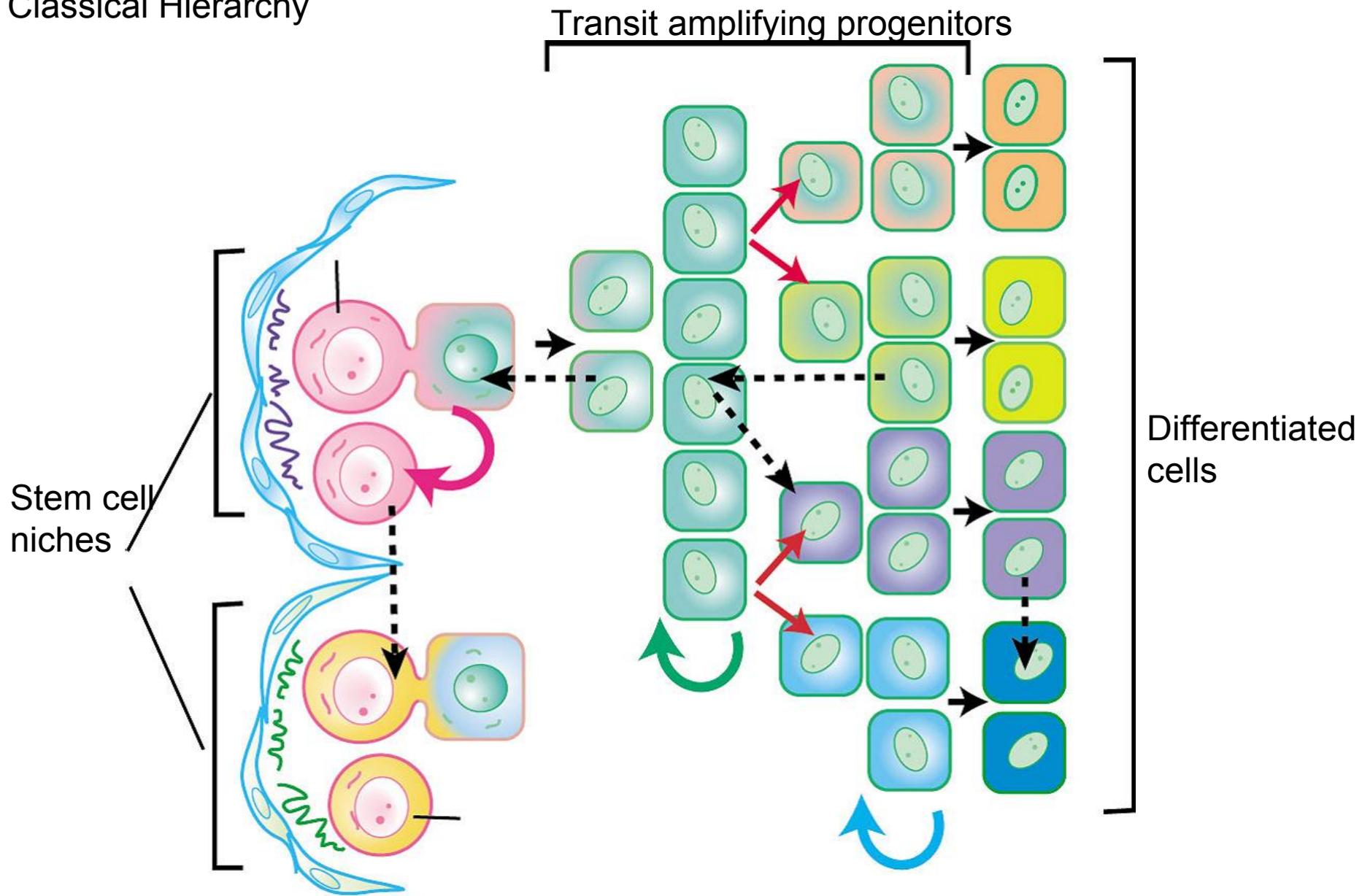
C



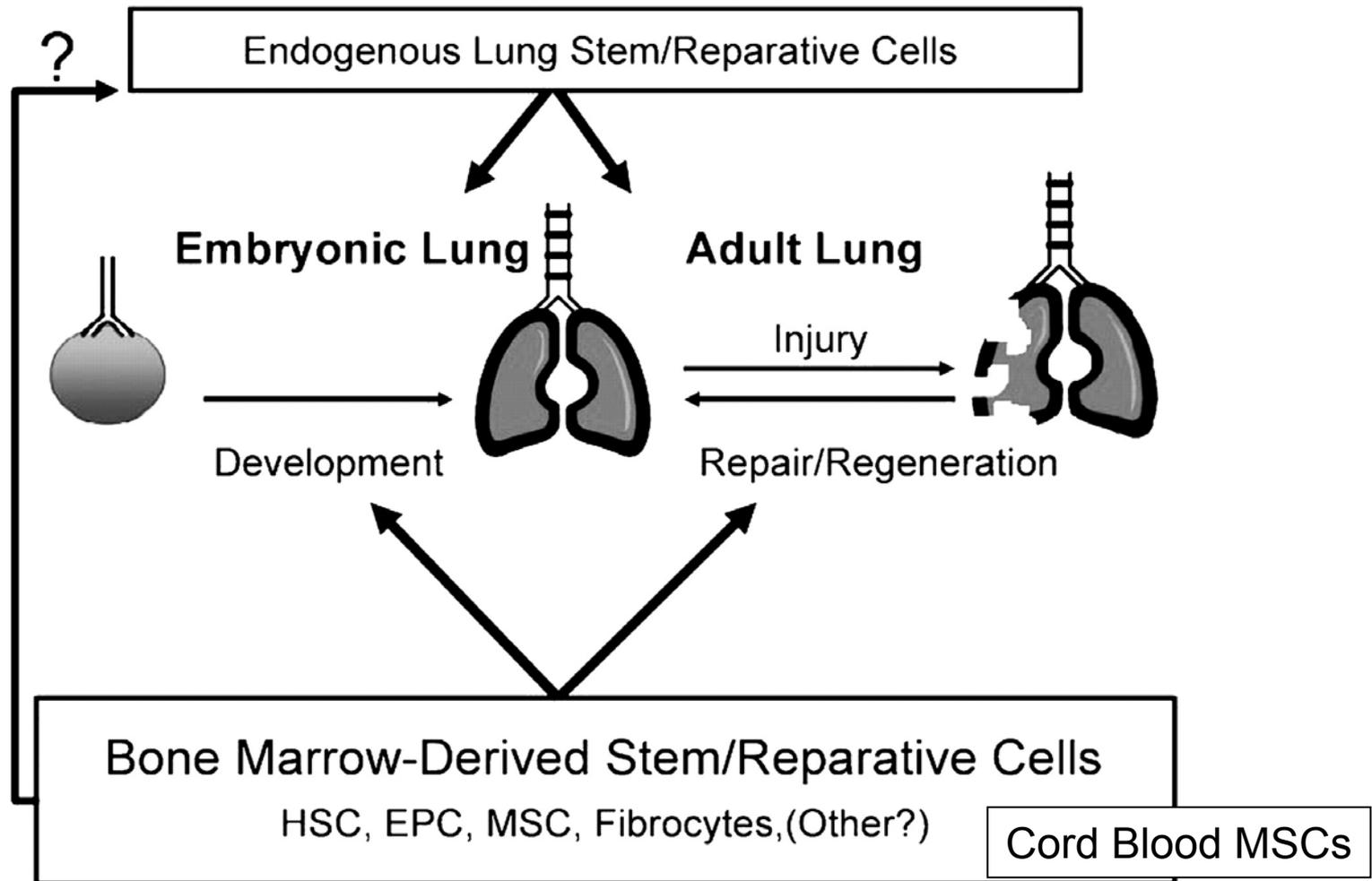
# Glossary of Terms

- **Dedicated stem cell** A relatively undifferentiated cell present in the adult organ, usually in localized niches. It normally divides infrequently; is capable of both long-term ('lifetime') self-renewal and of giving rise to daughter cells that differentiate into one or more specialized cell type; and it functions in both tissue homeostasis and repair.
- **Facultative stem cell** Differentiated cell that is normally quiescent but responds to injury by dividing and self-renewing, and giving rise to progeny that differentiate into one or more cell types.
- **Metaplasia** Strictly, the process by which a stem or progenitor cell of one tissue switches to become a progenitor of cells of another tissue type.
- **Post-mitotic differentiated cell** A cell that can no longer divide and must be replenished during normal turnover or injury.
- **Progenitor cell** Either a cell in the developing organ, usually multipotent, that is the source of an initial population of adult cells before turnover begins, or, more loosely, a cell that gives rise to another cell. Cell lineage relationships during development may not necessarily reflect those that occur during repair.
- **Self-renewing differentiated cell** Differentiated cell that divides and self-renews over the long term. Functions in both normal tissue homeostasis and in response to injury.
- **Transit amplifying (TA) cell** An intermediate between a dedicated stem cell and its final differentiated progeny. Can proliferate, self-renew over the short term and give rise to one or more differentiated cell type.

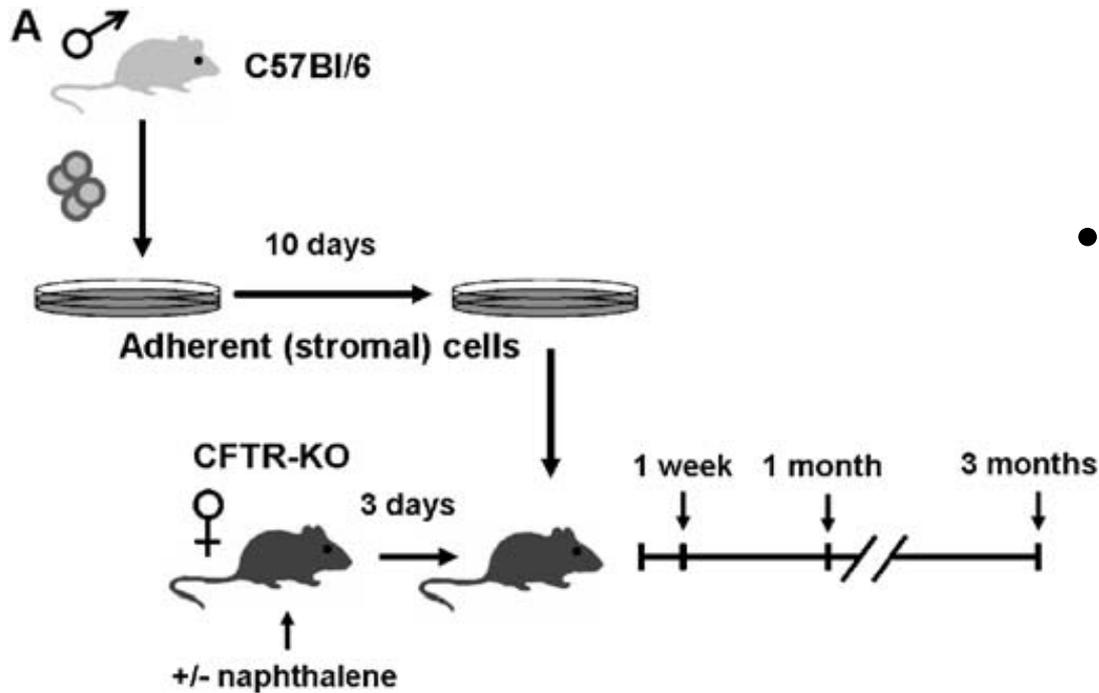
# Classical Hierarchy



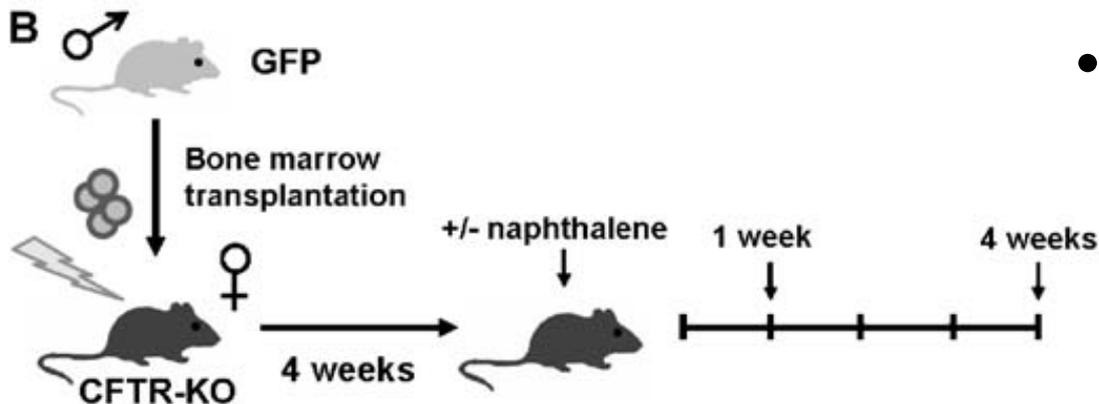
# Origin of Lung Reparative Cells



# Marrow Stem Cells for Cystic Fibrosis

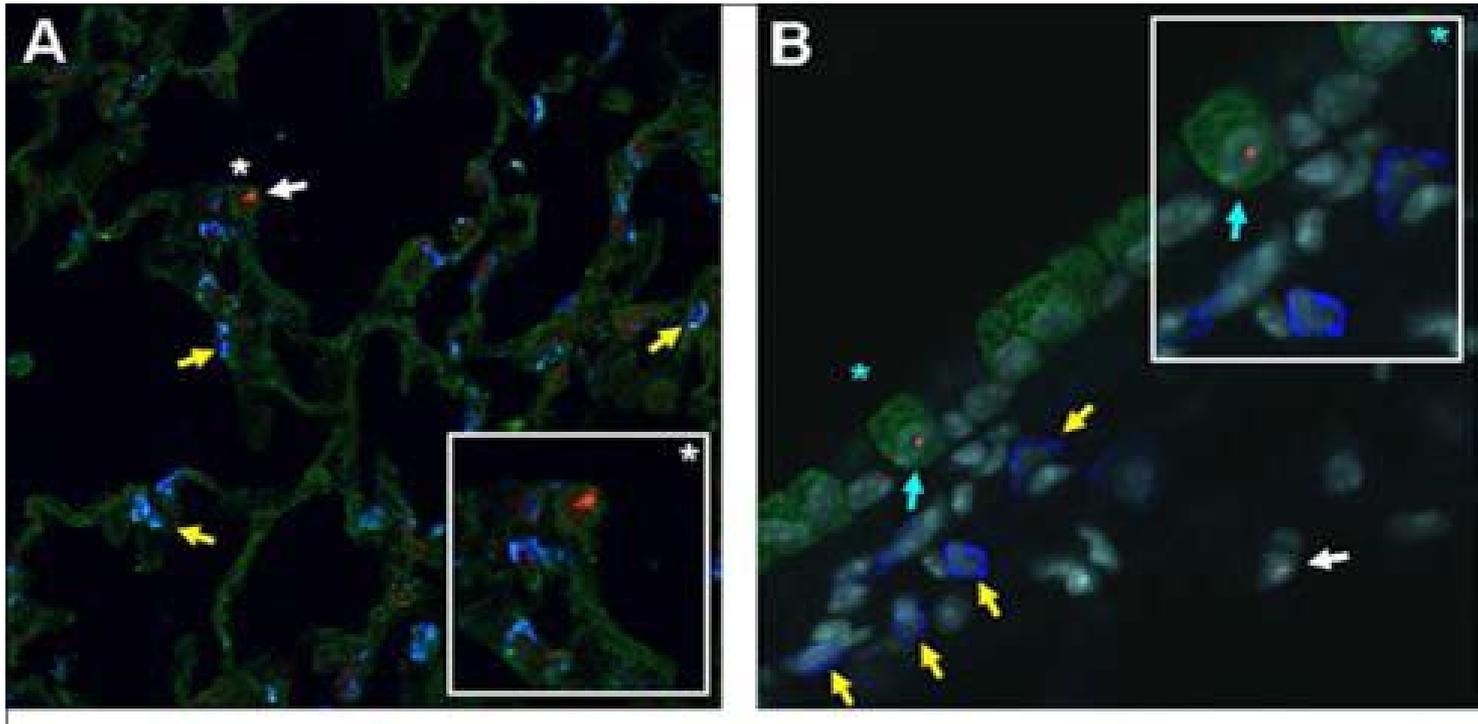


- Administration of stromal marrow cells to CFTR knock out mice with intact bone marrow



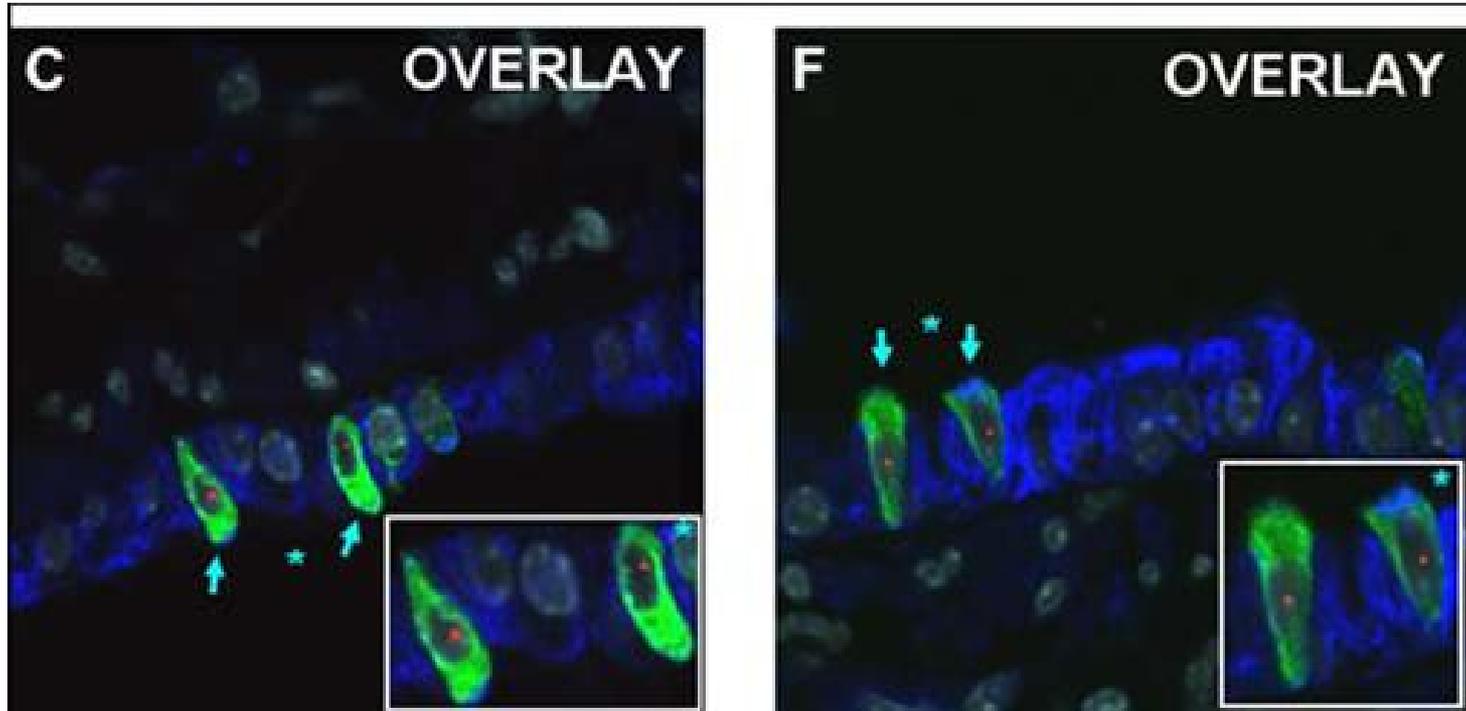
- Generation of chimeric CFTR-KO mice

# Localization of MSC in Transplanted CFTR ko mouse lung



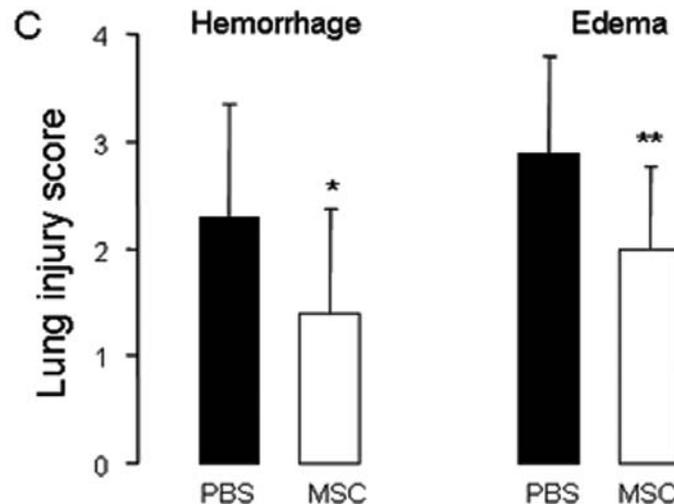
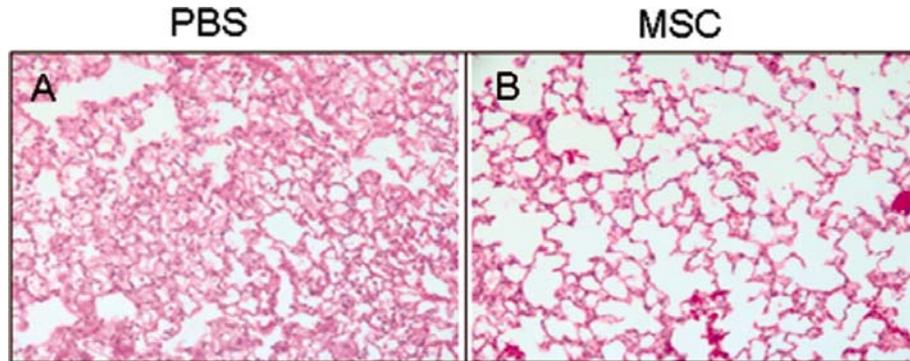
- Donor derived stromal marrow cells detected by FISH for the Y-chromosome (red) in female CF recipient (one month post transplant)
  - A—alveolar wall
  - B— airway wall (clara cell secretory protein positive cells in green)
  - Blue are immunostained leukocytes (CD45 positive)

# Detection of CFTR expression



- Detection of CFTR expression in female CFTR KO mouse lungs after transplantation with male GFP stromal marrow cells.
- (donor cells-red; CFTR pos-green; cytokeratin pos-blue)

# Bone-marrow Derived Stem Cells Reduce Lung Injury



Endotoxin model of ALI

Intrapulmonary administration  
Of MSCs

Increased survival at 48 h  
80 vs 42%

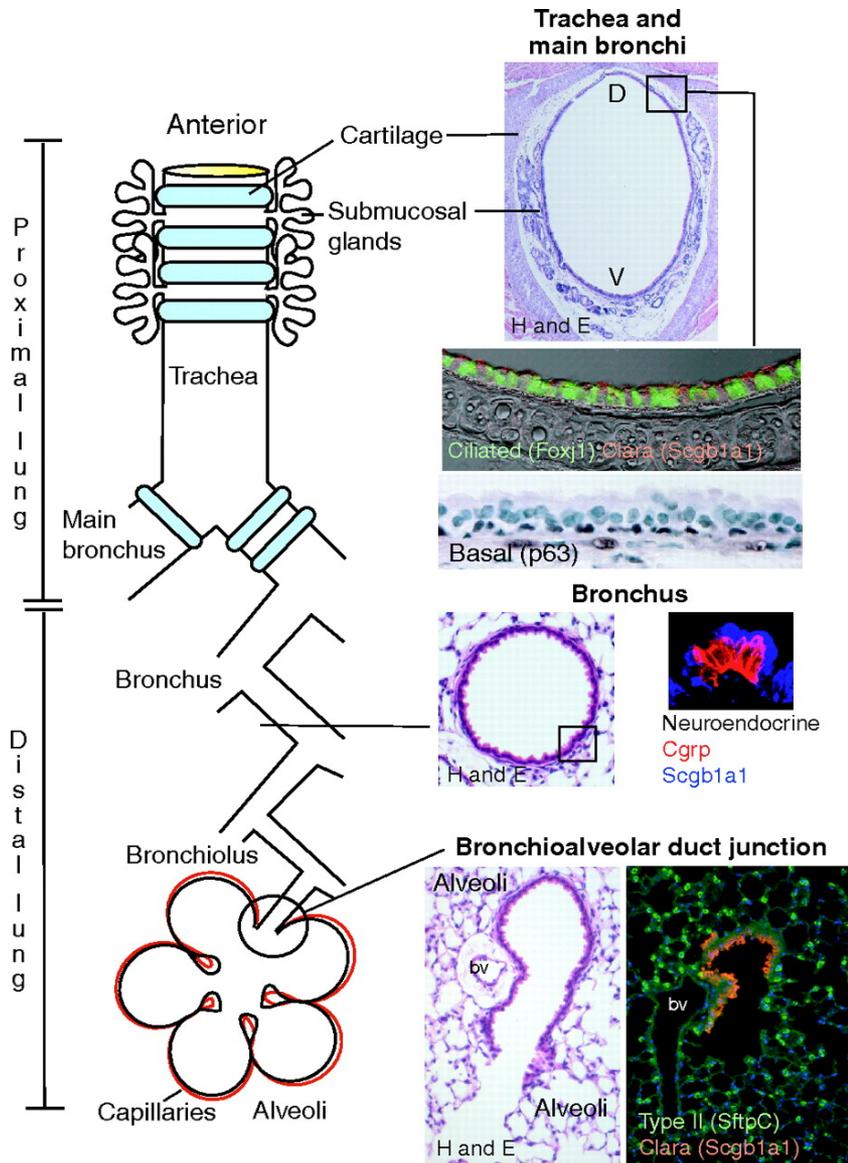
Decrease in pulmonary edema

Decreased permeability

Beneficial effect of MSC  
independent of engraftment

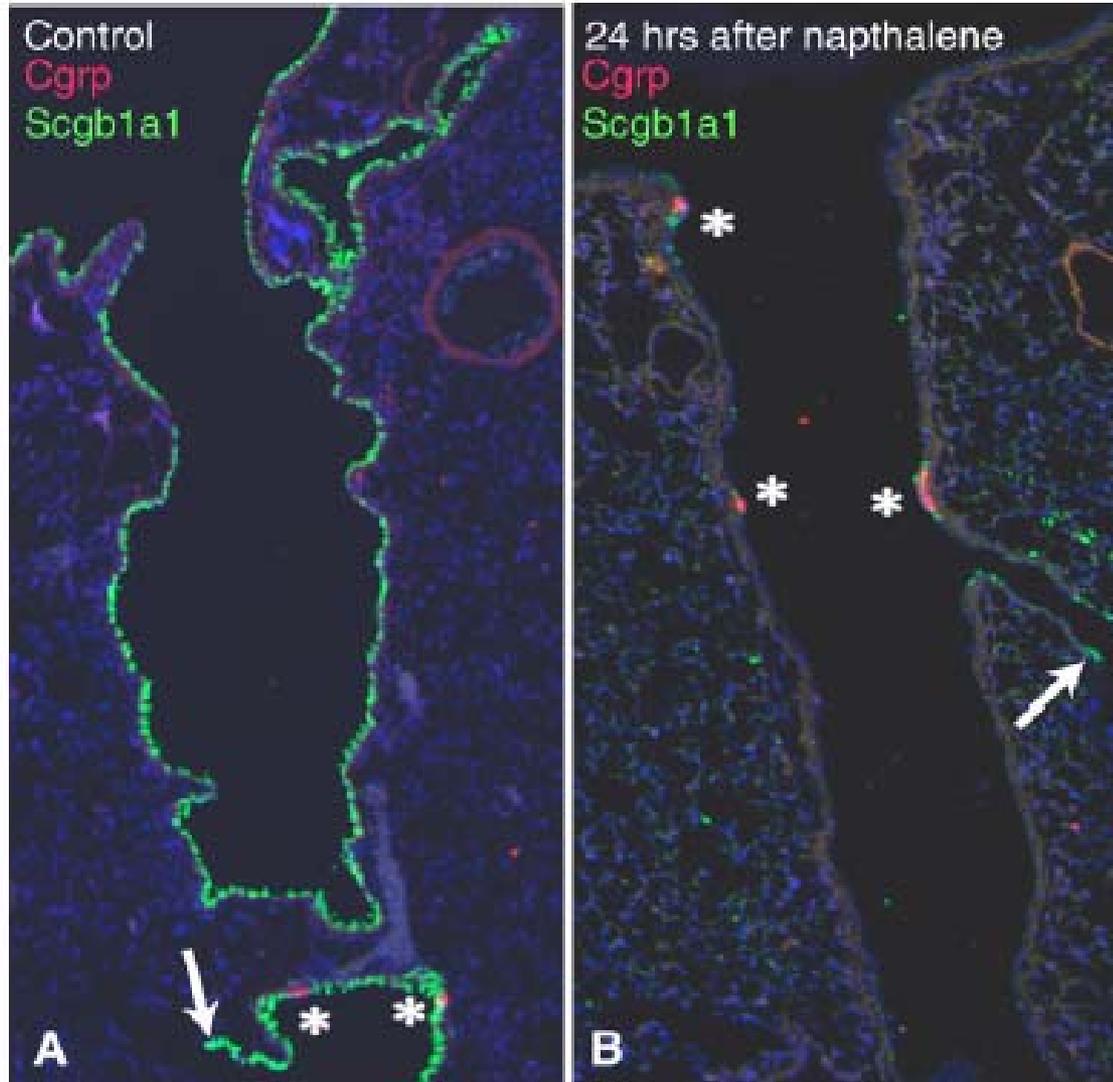
Antiinflammatory effect was  
paracrine and not cell contact  
dependent

# Potential Endogenous Progenitor Cells



- Multiple cell types in the lung with varying functions
- Progenitor cells will likely differ in proximal vs. distal compartments
- Signals that direct lung development likely play a role in regeneration/repair

# Endogenous Progenitor Cells



- Clara Cell protein positive cells in green immediately after naphthalene exposure (left) and 24 h later (right)

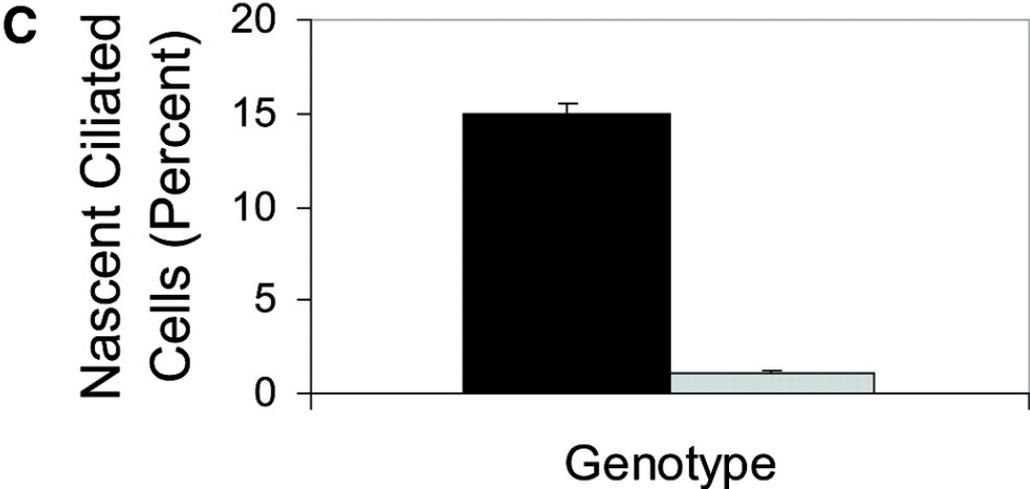
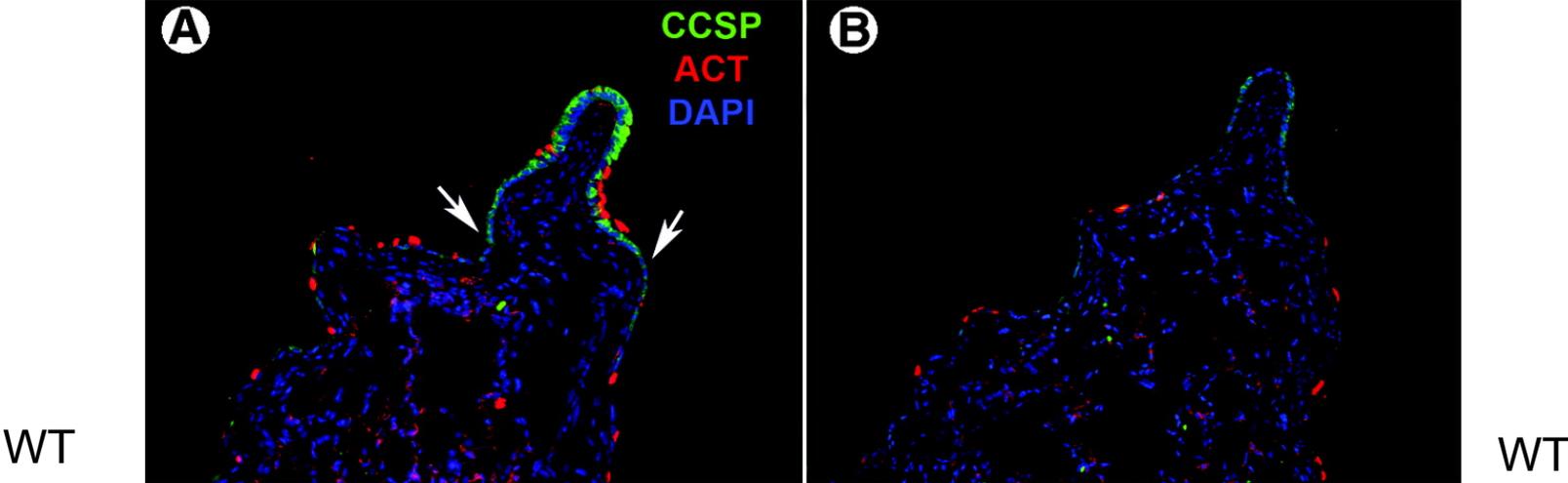
- Detection of potential endogenous progenitor cells, resistant to naphthalene

- Bronchoalveolar Stem Cells (BASCs)—C. Kim

# Ciliated cell regeneration after naphthalene injury

$\beta$ -catenin signaling functions as a negative regulator of bronchiolar cell differentiation

ACT, acetylated tubulin; CCSP, Clara cell secretory protein



# Unresolved Questions

- **What is the normal biology of lung stem cells and how are they regulated?**
- **Because engraftment of lung cells is rare in current models:**
  - **Can engraftment be enhanced with new models?**
  - **Can embryonic stem cells be directed to differentiate?**
- **What are the underlying mechanisms of repair by stem cells after lung injury in animal models, and can these results be safely and effectively translated to modulation of human lung inflammation, injury, and repair?**

# Lung Resources Needed

- Gene expression profiling of stem/progenitor cell populations.
- Monoclonal Ab libraries – screening, production.
- Human tissue/cells CORE for preparation and distribution of human lung tissue for in situ investigations of progenitor cell populations and for primary cell preparation.
- **PACT could be expanded for preclinical cell based therapy studies**
  - Bone marrow or cord blood MSCs
  - Lung biopsy expanded progenitor cells