Mattel Children's Hospital UCLA

UCLA Children's Discovery and Innovation Institute

David Geffen School of Medicine

Human Lung Cancer Pathology and Cellular Biology

Mouse Lung Tumor Workshop

Jan 7th and 8th, 2014

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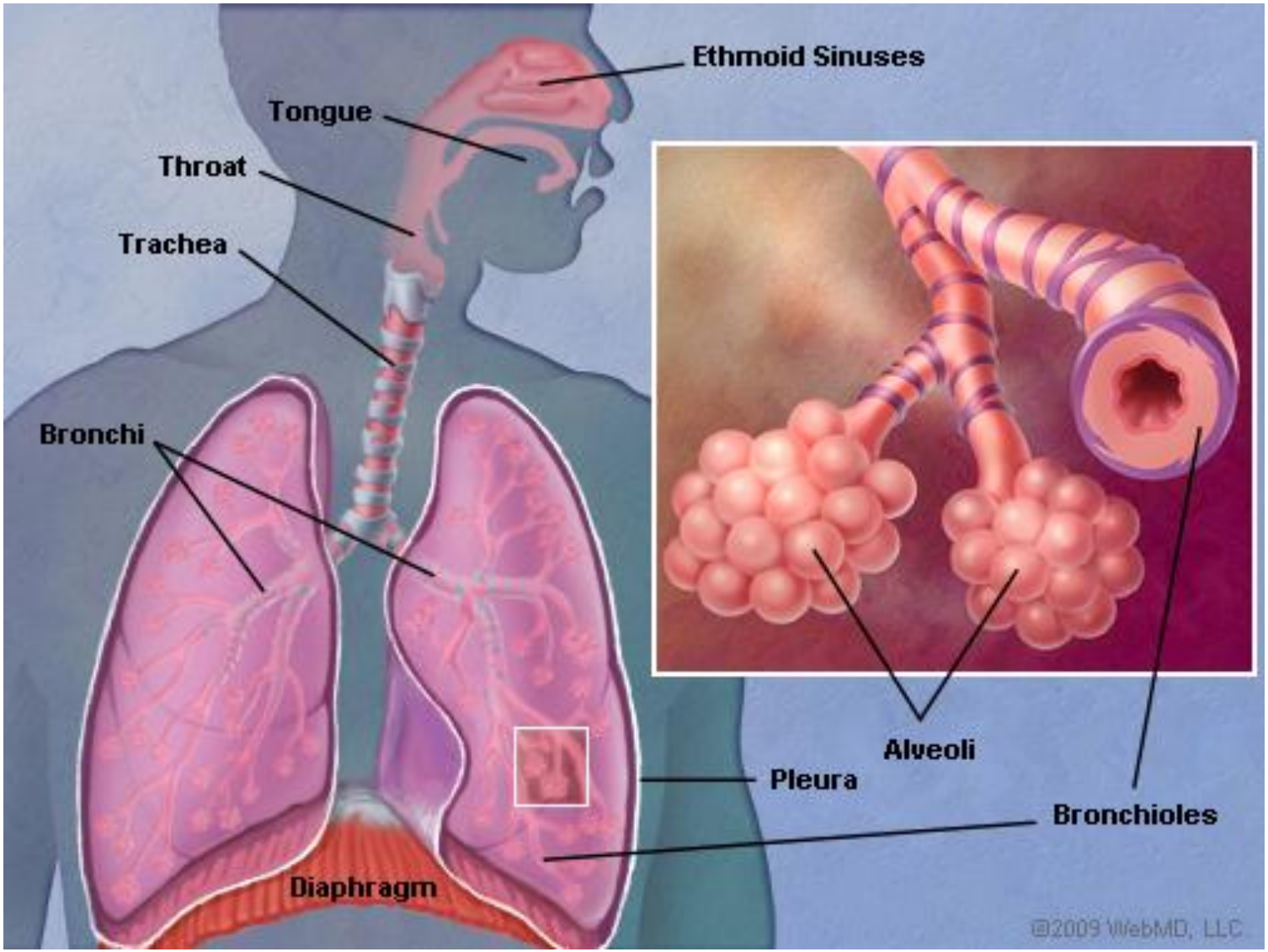
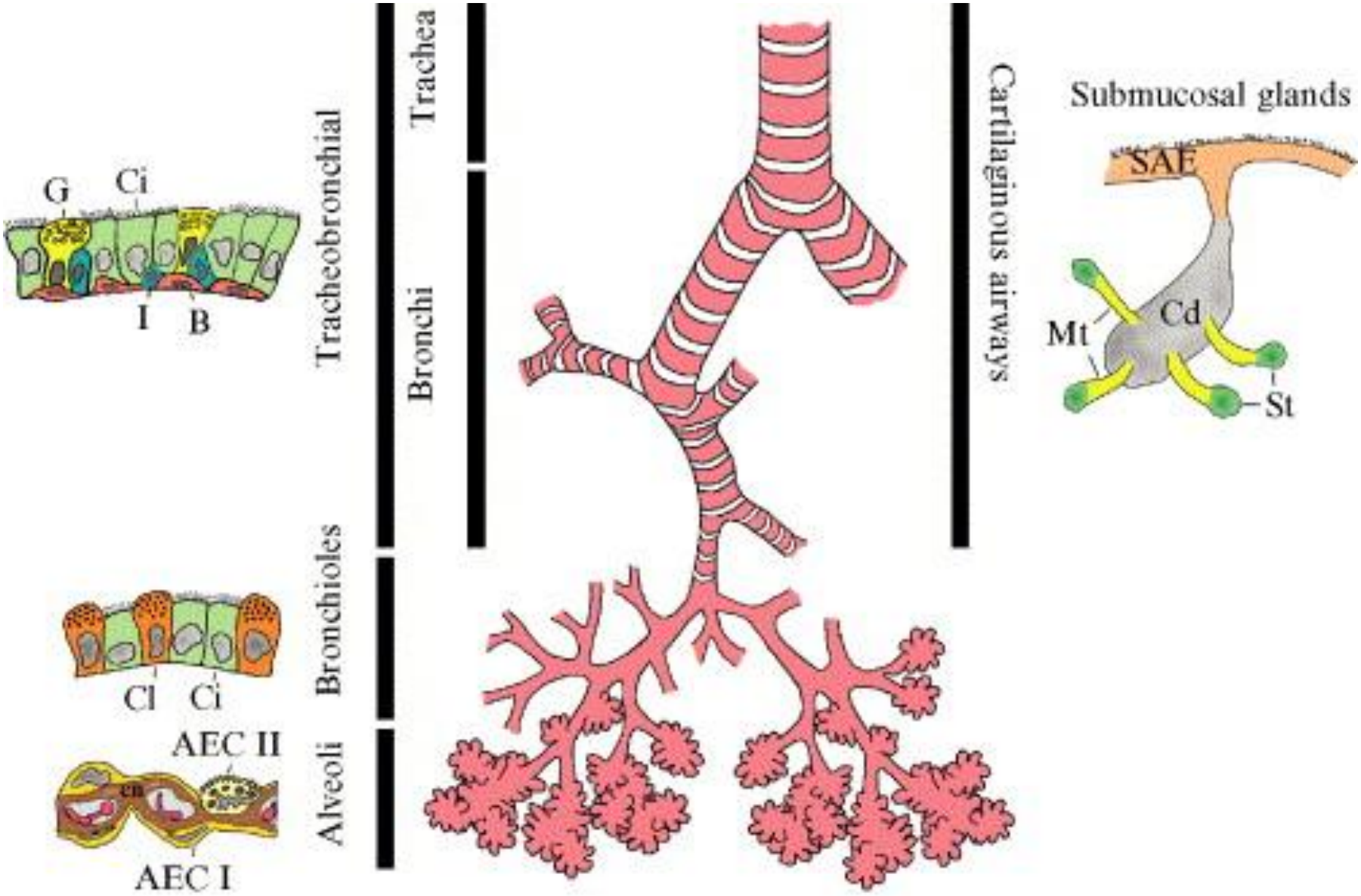
University of California, Los Angeles

Lung Structure and Function



Airway Epithelial Cell Types



X. Liu *et al* Methods Enzymol. 2006;419:285-321

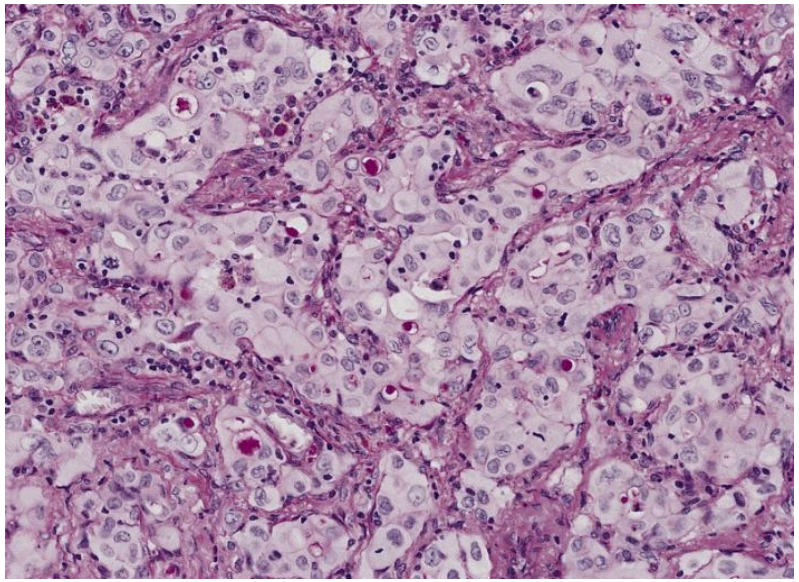
Key Differences Between Mouse and Human Lungs

- Submucosal gland ducts extend throughout cartilaginous airways in humans
- Goblet cells are present in the airway epithelium in humans
- Mouse stem cell turnover is very slow in uninjured/unexposed mice (7 days for basal cell, 365 days for type II cell)
- Humans do not develop lung adenomas that progress to adenocarcinoma

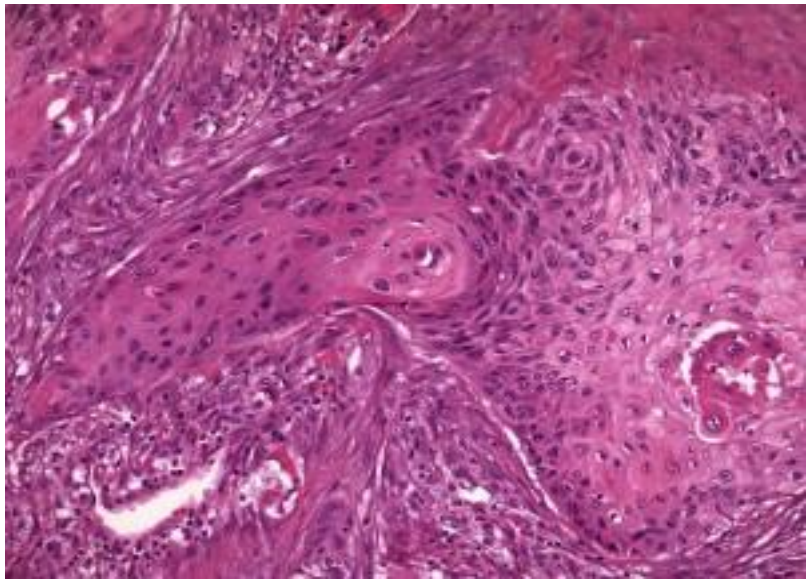
Lung Cancer Histopathology – WHO Classification

CLASS	*PREVALENCE (%)*
Small cell carcinoma	20
Non small cell carcinoma	
Adenocarcinoma	40
Squamous cell carcinoma	25
Large cell carcinoma	10
Adenosquamous carcinoma	< 5
Carcinoid	< 5

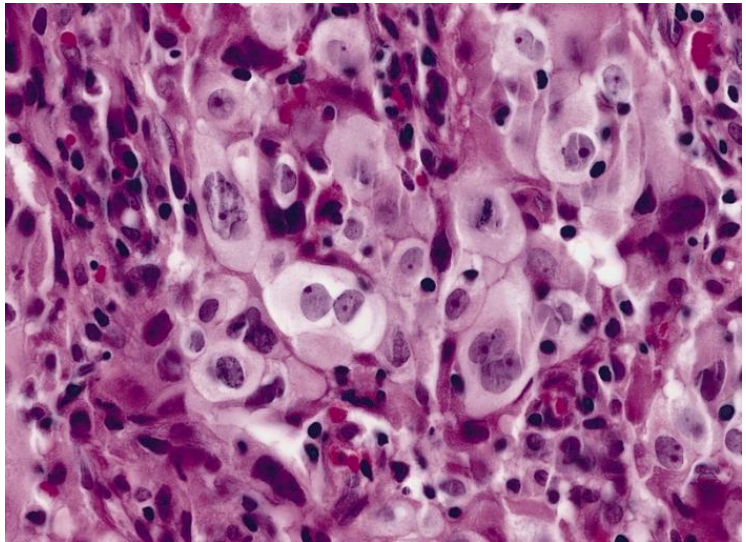
Histopathology of Non Small Cell Lung Cancer



Lung Adenocarcinoma



Squamous Lung Cancer



Large Cell Lung Cancer

2011 IASLC/ATS/ERS Classification of Adenocarcinoma

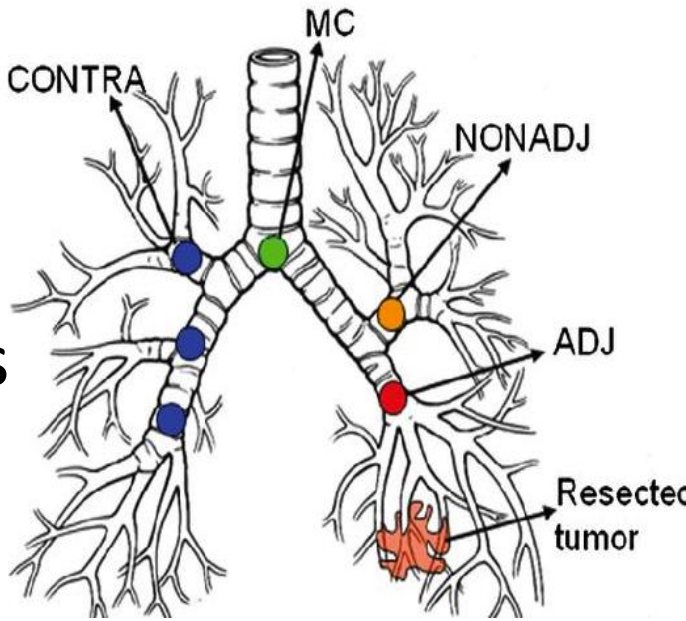
- Histology of preneoplastic lesions (adenocarcinoma in situ and minimally invasive lung adenocarcinoma) (complete resection – near 100% survival)
- Refines the classification for application to lung cancer diagnosis in small biopsies and cytology specimens
- Stresses importance of distinguishing between adenocarcinoma and squamous cell carcinoma for prognosis and treatment

Biology of Lung Carcinogenesis

- Injury (from e.g. toxins in the environment) leads to aberrant repair by stem/progenitor cells, which undergo self-renewal to form a group of indefinitely self-renewing daughter cells.
- Additional genetic and epigenetic alterations prevent normal differentiation of these cells but instead result in proliferation of these cells
- This “field cancerization” expands gradually displacing the normal epithelium.

Evidence for “Field Cancerization”

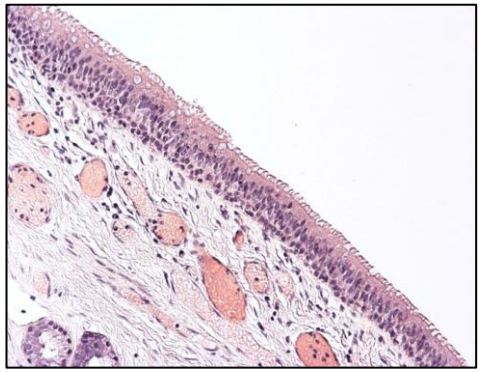
- Definition - Histologically normal adjacent airway epithelium has molecular changes, some of which are found in the cancer
- Avi Spira- airway gene expression signature that accurately distinguishes smokers with and without lung cancer
- MicroRNAs in the field – Huang et al 2012
- Ignacio Wistuba – temperospatial changes in the field



Kadara et al 2013

Stepwise Progression to Lung Cancer

- Premalignancy in Squamous Lung Cancer



Histologically normal airway epithelium

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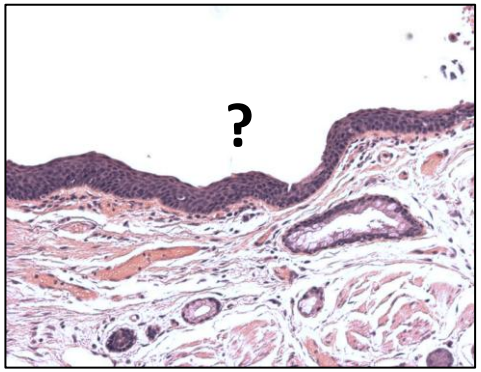
Early stage



Premalignant lesion (squamous metaplasia and dysplasia)

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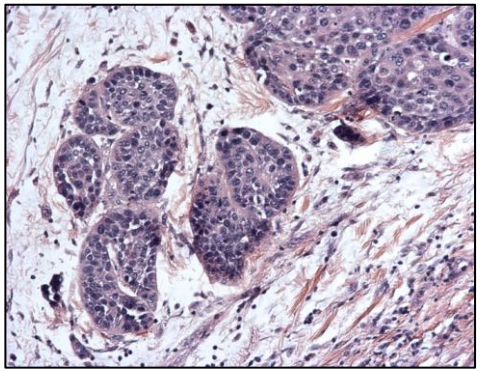
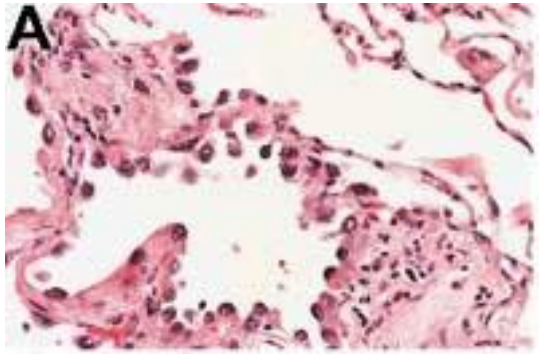
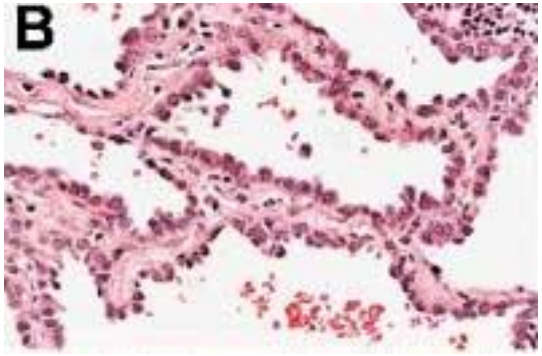
Late stage

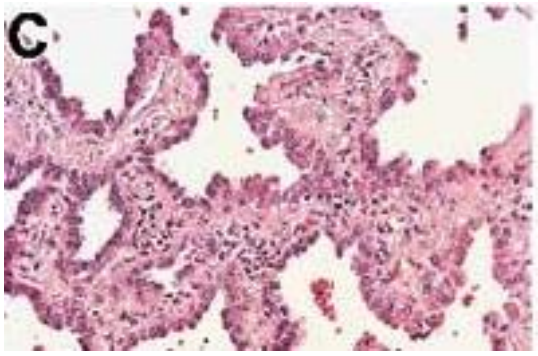


Squamous cell carcinoma

- Premalignancy in Adenocarcinoma

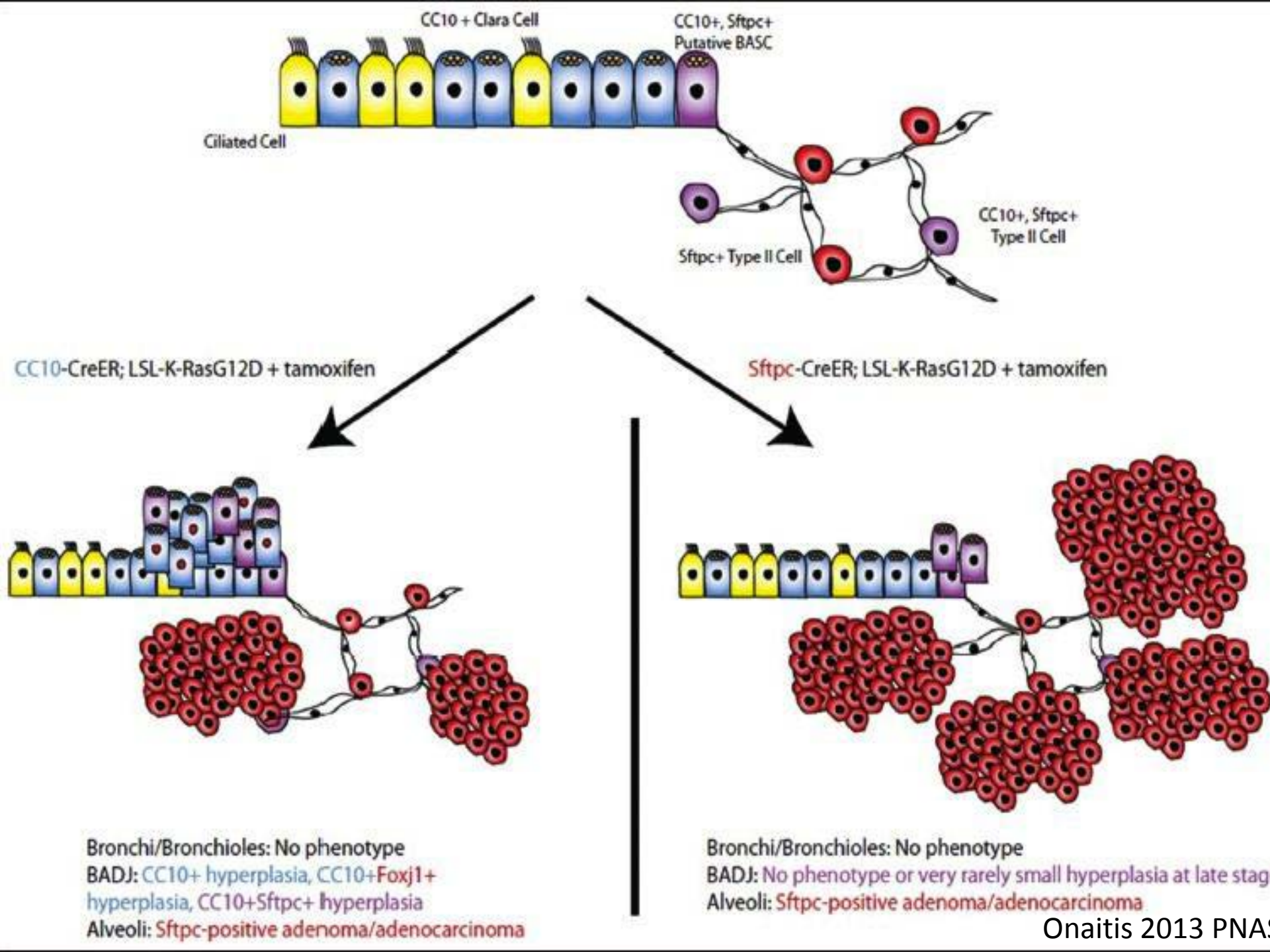






Tumor Initiating Cells in Lung Cancer

- Stem cells that develop uncontrolled self-renewal and block in differentiation that ultimately leads to tumor formation. Identified in other malignancies e.g. AML, breast cancer
- First suggested - Carla Kim – Cell 2005 – BASCs in the KrasG12D mouse model
- Carla Kim – Cell Stem Cell – 2010 – genotype alters tumor initiating potential
- Mark Onaitis – PNAS – 2012 – BASC controversy

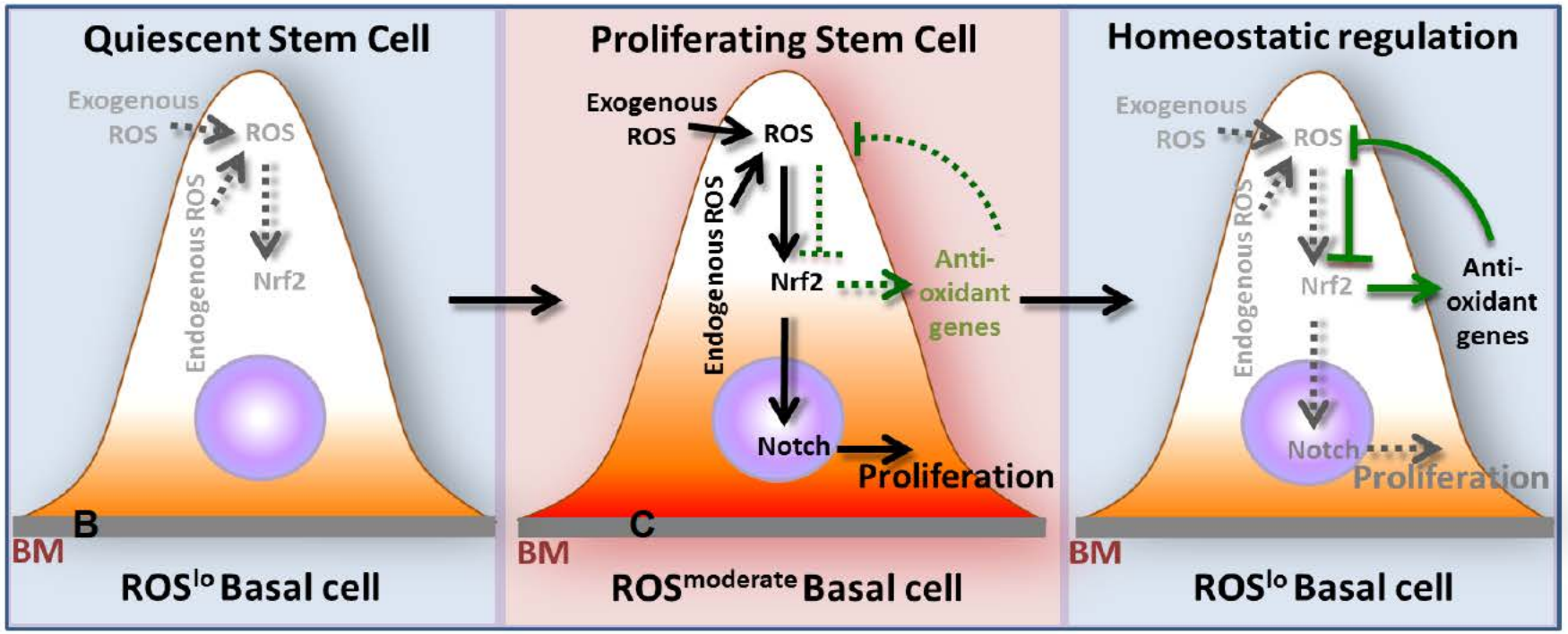


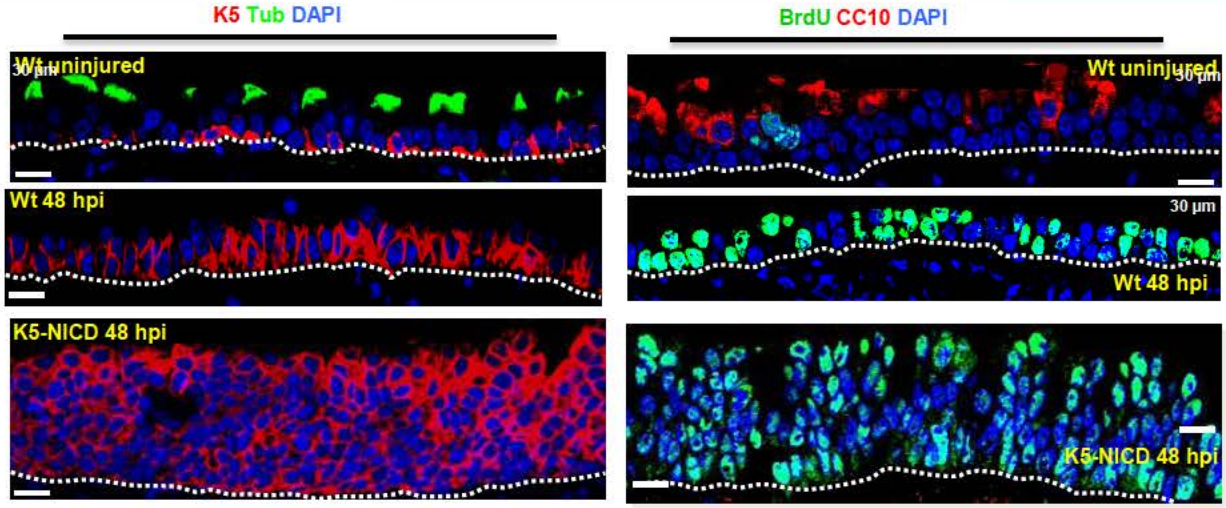
Onaitis 2013 PNAS

Inflammation and Lung Cancer

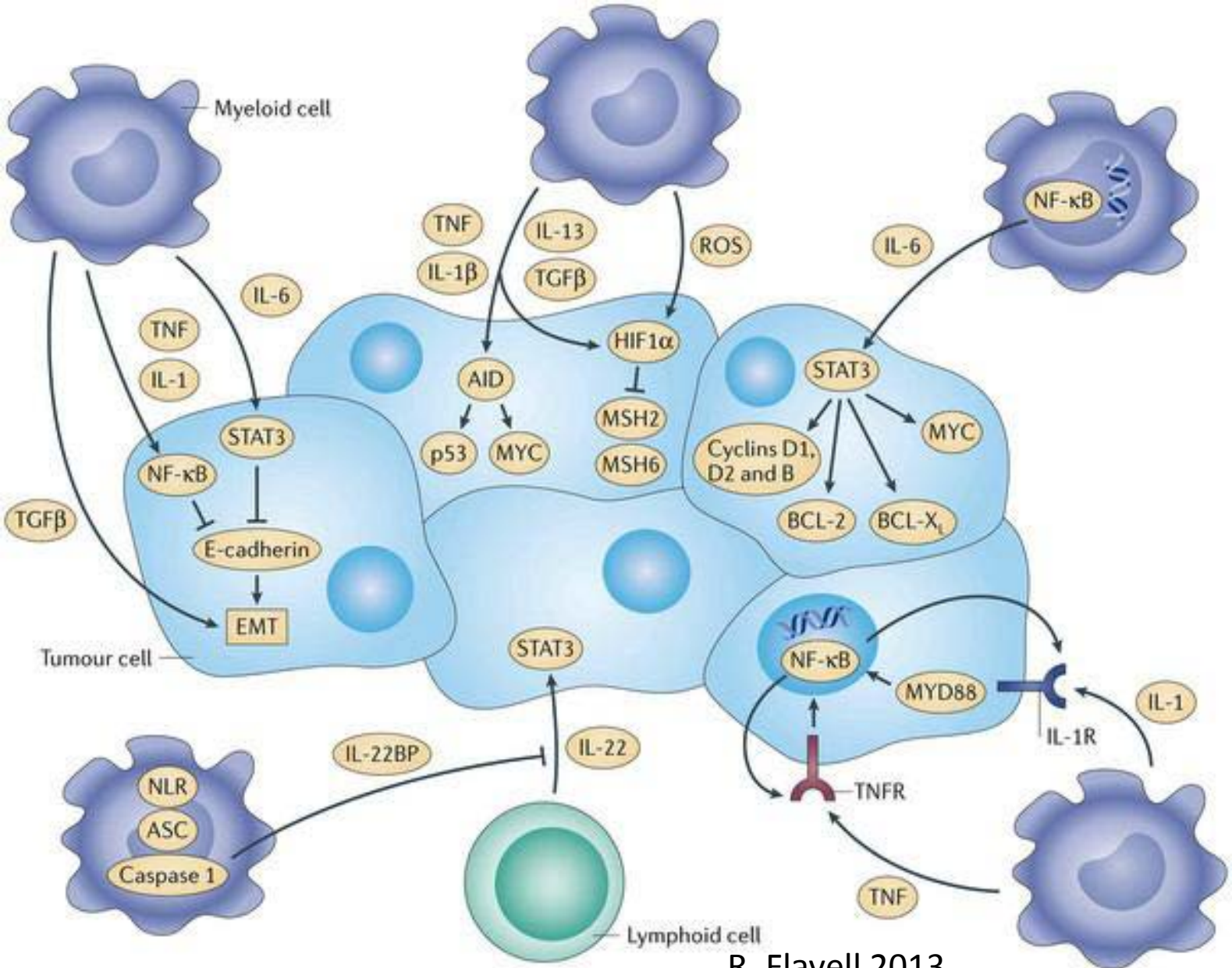
- Pro-tumor vs anti-tumor effect ?
  - PD1/PDL1 as new therapeutic targets
- Promote proliferation and cell survival
- Genomic instability – ROS, cytokines, epigenetics
- Inflammatory cells:
  - tumor-associated macrophages (TAM), mast cells, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils and lymphocytes
- Cytotoxic mediators:
  - ROS, proteases, MMPs, tumor necrosis factor α (TNFα), interleukins (IL-1, IL-6, IL-8), interferons (IFNs) and enzymes, as cyclooxygenase-2 (COX-2), lipooxygenase-5 (LOX-5) and phospholipase A2 (PLA2)

ROS in Lung Carcinogenesis





Inflammation and Cell Proliferation and Survival Signaling



R. Flavell 2013

Molecular Biology of Lung Cancer

- Activation of growth promoting proteins e.g., v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), epidermal growth factor receptor (EGFR), BRAF, MEK-1, HER2 (mutations), MET (amplification), ALK and rearranged during transfection (RET)(structural rearrangements)
- inactivation of tumor suppressor genes e.g., *P53,* phosphatase with tensin homology (*PTEN*)*, LKB-1 (STK11)*

Molecular Changes in Lung Adenocarcinoma

- **EGFR**: activating mutations lead to activation of PI3K/AKT/mTOR, RAS/RAF//MAPK and JAK/STAT signaling pathways. More common in females, non-smokers, younger age, 10-15% Western, 30-40% Asian
- **RAS**: activating mutations lead to activation of RAS/RAF/MEK/MAPK signaling pathways. Western populations, male, smokers
- **ALK**: rearrangements of receptor tyrosine kinase, most commonly EML4-ALK fusion, leads to RAS/RAF/MAPK1, PI3K/AKT and JAK3-STAT3 signaling pathway activation. Younger patients, never/light smokers

Are the Chemicals of Interest Involved in Lung Carcinogenesis?

- Naphthalene – toxic to Clara Cells – could this result in injury with aberrant repair?
- Styrene, Ethylbenzene - reactive metabolites – could this result in DNA damage, inflammation, ROS?
- Are there underlying genetic/epigenetic susceptibilities that promote lung carcinogenesis with these exposures?