Preclinical lung cancer studies in the intramural program

Phillip Dennis, M.D., Ph.D.
Senior Investigator, Medical Oncology Branch
Value of preclinical lung cancer studies

- Evaluation of new drugs, new combinations in relevant model systems
- Elucidation of mechanisms of lung carcinogenesis
- Validation of genes or patterns of gene expression as predictive or prognostic factors for patients with lung cancer
Tools

• Cell lines
  – Primary human bronchial/alveolar epithelial cells
  – Human immortalized bronchial epithelial cells
    • BEAS-2B et al., HBEC et al.
  – Human lung cancer cell lines
    • SCLC, NSCLC
  – Syngeneic murine lung adenocarcinoma cell lines from tobacco carcinogen-driven model

• Mouse models
  – Xenograft
  – Tobacco carcinogen-driven
  – Genetically engineered

• Rat model
  – Radon +/- smoking
Advantages of carcinogen-driven and genetically engineered mouse models of lung cancer

- Prevention and treatment studies possible
- Physiologic analysis of tumor microenvironment (immunocompetent models)
- Preclinical PK, PD, toxicology- compare to human
- Imaging- longitudinal assessment of lung tumor growth/regression
Relevance of models to human lung cancer subsets

• Current/former smokers
  – Tobacco carcinogen-driven
    • NNK (mutant Kras-dependent)
    • urethane
  – GEM
    • Mutant K-Ras
    • Mutant LKB1
    • nAchR subunits

• Never smokers
  – EGFR-driven (L858R/T790M)
  – XPC (DNA damage)
Bench to bedside examples

- **Current/former smokers**
  - Rapamycin to prevent tobacco carcinogen-induced lung tumors

- **Never smokers**
  - Triciribine (Akt inhibitor) to overcome resistance to EGFR TKIs.
A common pathway for different lung cancer subsets

Smokers

EGFR mut/amp

π3K
Akt
mTOR

Kras mut

nAChR

LKB1
PTEN
TSC2

AMPK

Tumor suppressor genes

Never smokers

Etiology?

EGFR mut/amp

triciribine

rapamycin
Bench to bedside example- A lung cancer prevention model for current or former smokers (K-Ras driven)

Study Schema

I. Tx of established tumors
   - NNK or saline
   - 50% ↓ tumor size
   - rapamycin
   - 90% ↓ tumor size, multiplicity
II. Short term treatment
   - Ø size, multiplicity
III. Continuous treatment
   - 90% ↓ tumor size, multiplicity

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A working model for prevention of tobacco carcinogen-induced lung tumors by rapamycin

Exposure to tobacco carcinogens

Kras G12D

Permissive environment

→ cytotoxic T cell response

Foxp3

↑ genetic/epigenetic changes

↑ proliferation

Rapamycin

Anti-CD25 ab
Genetic ablation

Foxp3

Kras G12D

Rapamycin

Bench to bedside example- A model for never smokers whose lung cancers become resistant to an EGFR TKI

Hypothesis- Akt inhibition will resensitize cells to an EGFR TKI

In vitro model
H1975 cells (resistant to EGFR TKI) (L858R/T790M mutation)
Triciribine (Akt inhibitor)
Gefitinib/erlotinib (EGFR TKI)
Bench to bedside example- A model for never smokers whose lung cancers become resistant to an EGFR TKI

H1975 xenografts
Bench to bedside example- A model for never smokers whose lung cancers become resistant to an EGFR TKI-
An inducible L858R/T790M transgenic model of lung cancer

Specific induction of L858R/T790M mutations in Clara cells after 12 wk of doxycycline

Before triciribine

Day 9 triciribine
Conclusions

- Preclinical lung cancer expertise within the intramural program is extensive.
- Mouse models with relevance to many molecular subsets of human lung cancer improve our understanding of lung cancer and aid targeted drug development.
- The barriers between preclinical and clinical lung cancer research are minimized in the intramural program.
  - A lung cancer prevention trial with rapamycin and a lung cancer treatment trial combining triciribine with erlotinib (Tarceva) are in the approval process.
  - The development of new mouse models based on results from human lung cancer GWAS is ongoing.