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

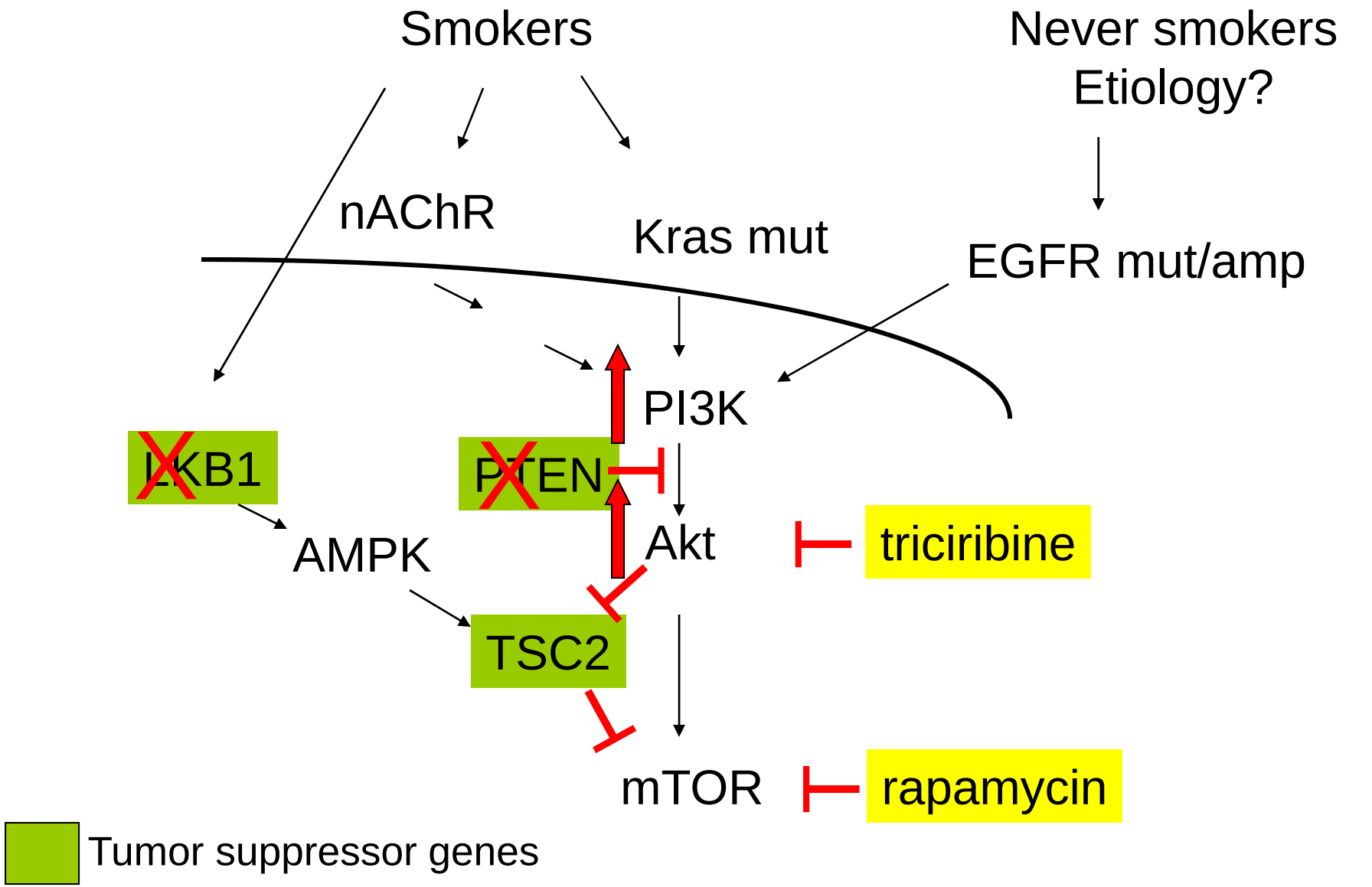
Relevance of models to human lung cancer subsets

- 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)

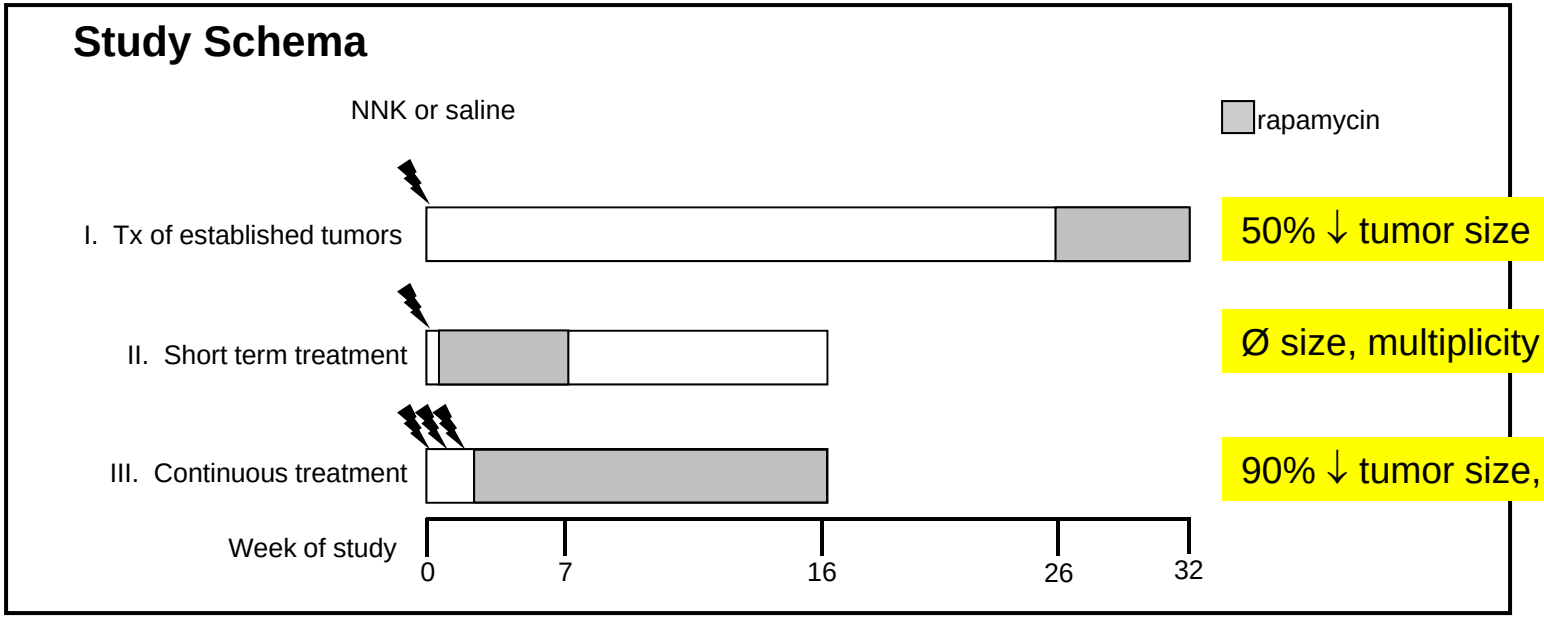
Bench to bedside examples

- 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

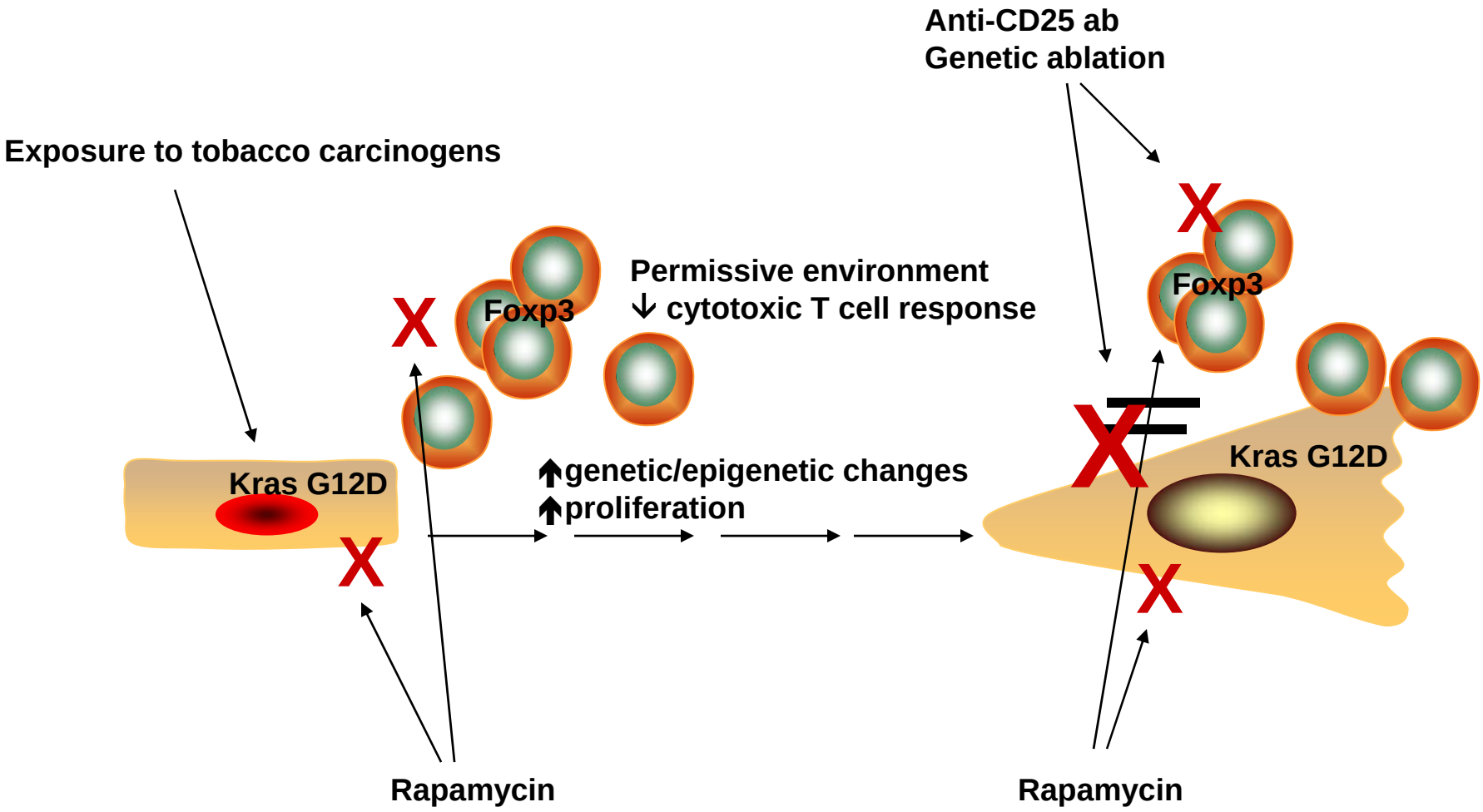


Bench to bedside example- A lung cancer prevention model for current or former smokers (K-Ras driven)



Clin Cancer Res. 2007 Apr 1;13(7):2281-9

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

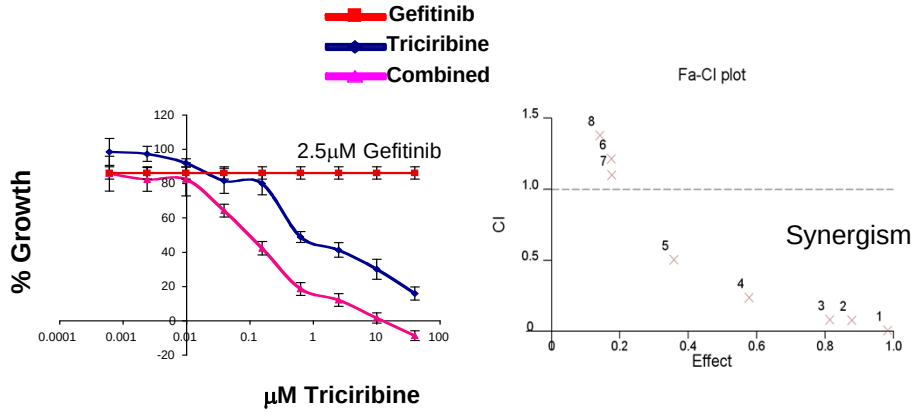


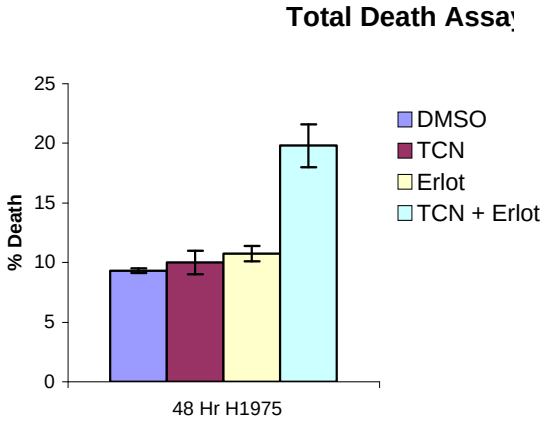
PLoS ONE. 2009;4(3):e5061

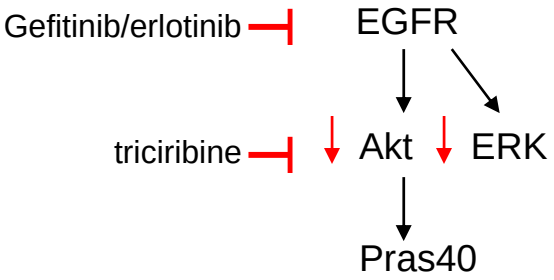
Bench to bedside example- A model for never smokers whose lung cancers become resistant to an EGFR TKI

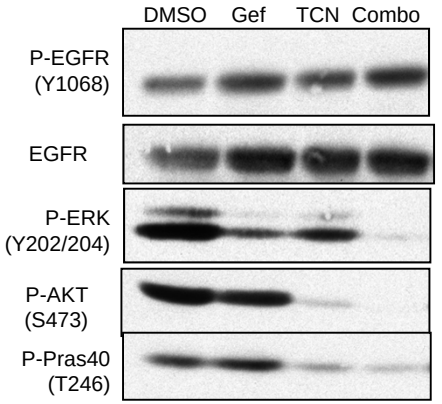
Hypothesis- Akt inhibition will resensitize cells to an EGFR TKI

In vitro model
H1975 cells (resistant to EGFR TKI) (L858R/T790M mutation)
Triciribine (Akt inhibitor)
Gefitinib/erlotinib (EGFR TKI)



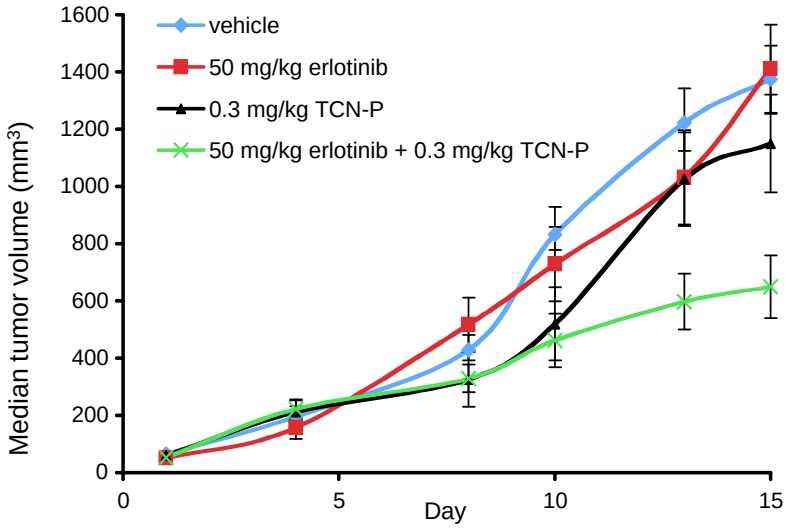






Bench to bedside example- A model for never smokers whose lung cancers become resistant to an EGFR TKI

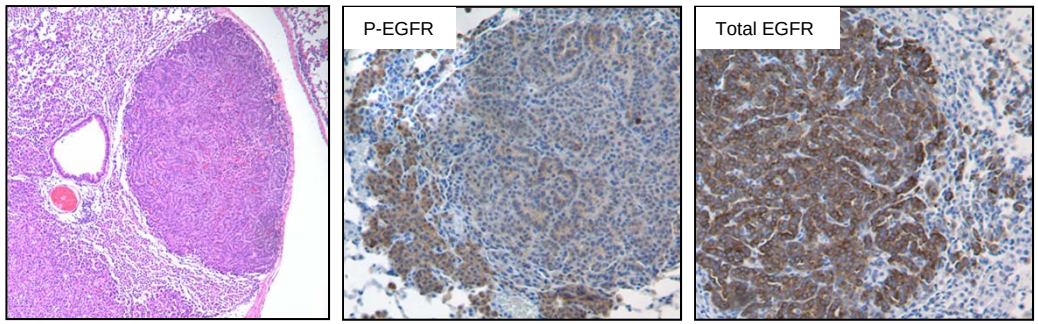
H1975 xenografts



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

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Motion JPEG OpenDML decompressor
are needed to see this picture.

QuickTime™ and a
Motion JPEG OpenDML decompressor
are needed to see this picture.

Day 9 triciribine

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Motion JPEG OpenDML decompressor
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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.