Molecular Biology of Tobacco-Related Cancers

EMORY
WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

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National Cancer Policy Forum Workshop on
Reducing Tobacco-Related Cancer Incidence and Mortality
Washington DC, June 11-12 2012

Epidemiology of Tobacco-Related Cancers in the US, Estimated in 2012

Cancer type	# cases	# deaths
Lung	**226,160**	**160,340**
Head and neck*	**52,610**	**11,500**
Esophageal	**17,460**	**15,070**
Stomach	21,320	10,540
Pancreas	43,920	37,390
Kidney	64,770	13,570
Bladder	73,510	14,880
Uterus	47,130	8,010
Cervix	12,170	4,220
Colon/rectum	143,460	51,690
Ovary	22,280	15,500
AML	13,780	10,200

* larynx, oral cavity, nasopharynx, pharynx

NCI SEER

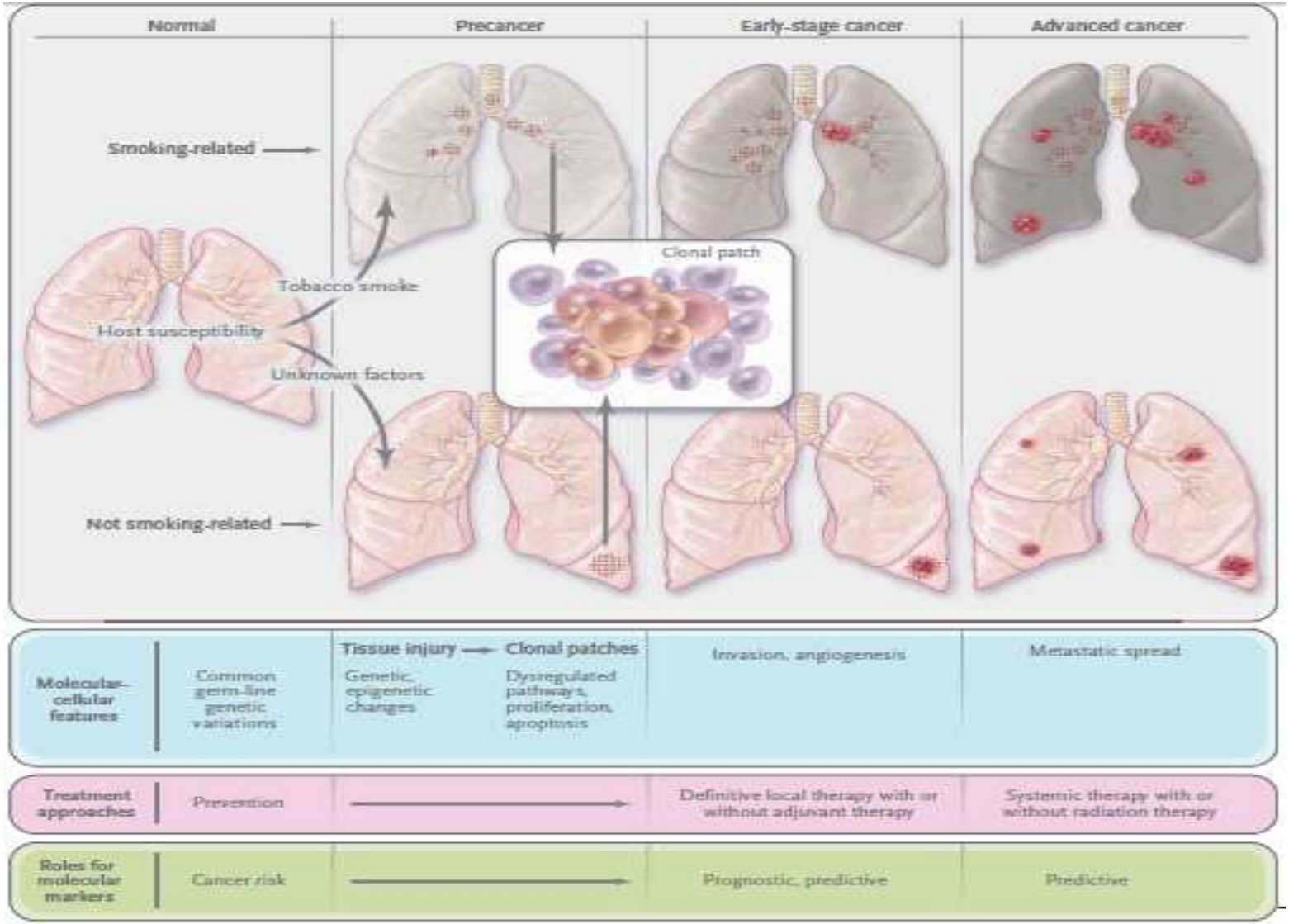
Epidemiology of Tobacco-Related Cancers Worldwide in 2008

Cancer type	# cases	# deaths
Lung	**1,606,911**	**1,375,919**
Head and neck*	**631,786**	**355,217**
Esophageal	**481,645**	**406,198**
Stomach	987,904	736,976
Pancreas	278,470	266,543
Kidney	264,146	110,824
Bladder	382,130	150,143
Uterus	288,265	73,818
Cervix	529,601	274,668
Colon/rectum	570,795	288,323
Ovary	222,613	139,472
AML		

* larynx, oral cavity, nasopharynx, pharynx

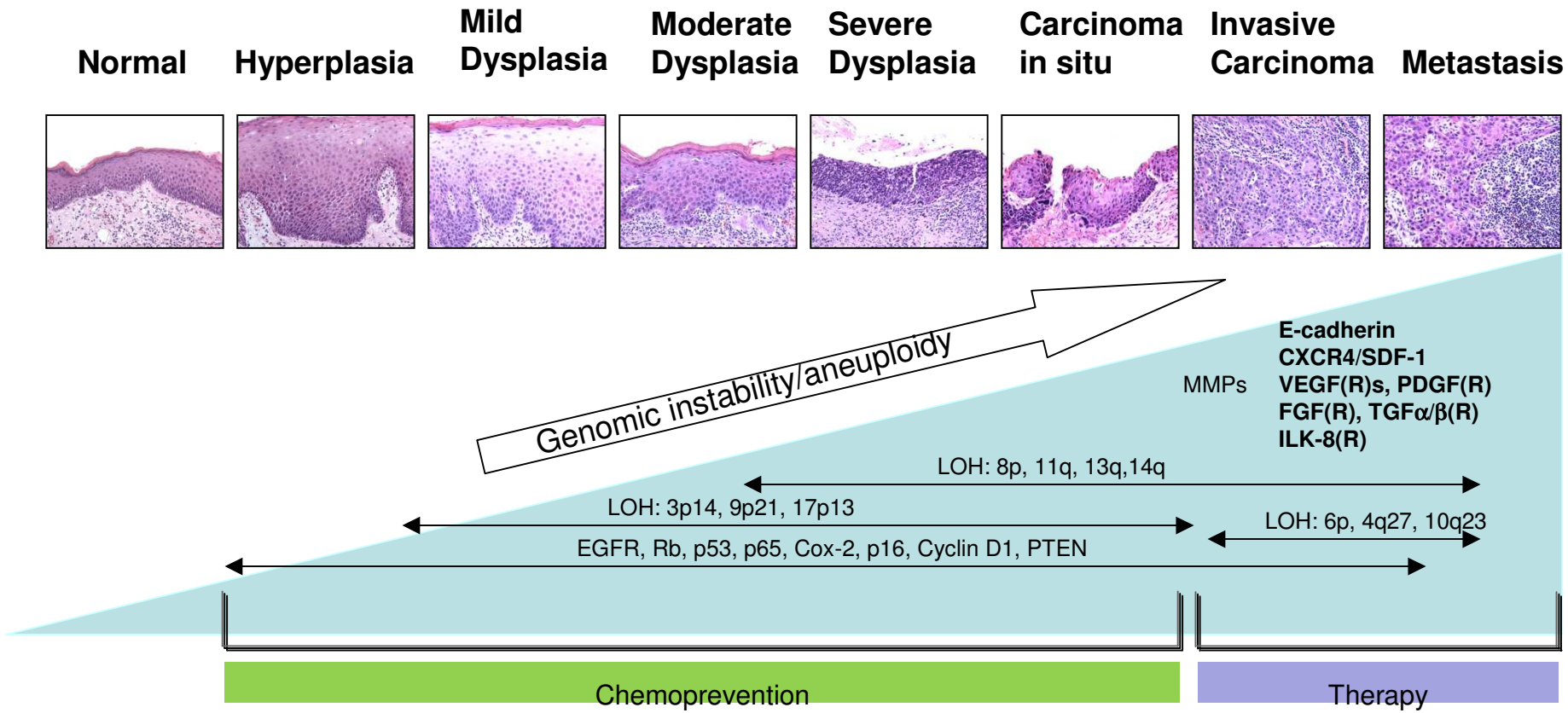
WHO GLOBOCAN 2008

Molecular Carcinogenesis of Lung Cancer



RS Herbst, et al, N Engl J Med 2008

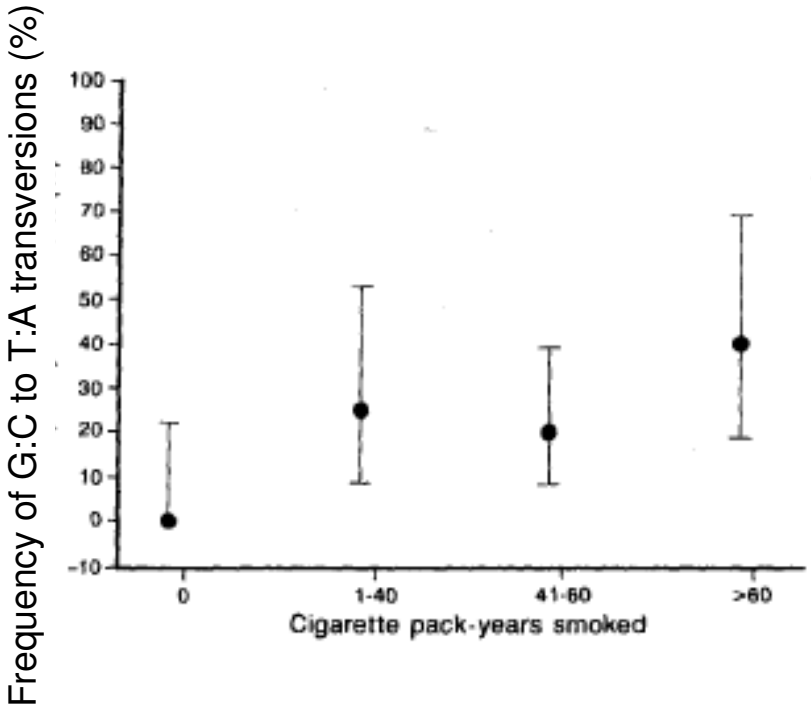
Molecular Carcinogenesis of Head and Neck Cancer



Haddad RI and Shin DM. NEJM 2008;359:1143-1154.

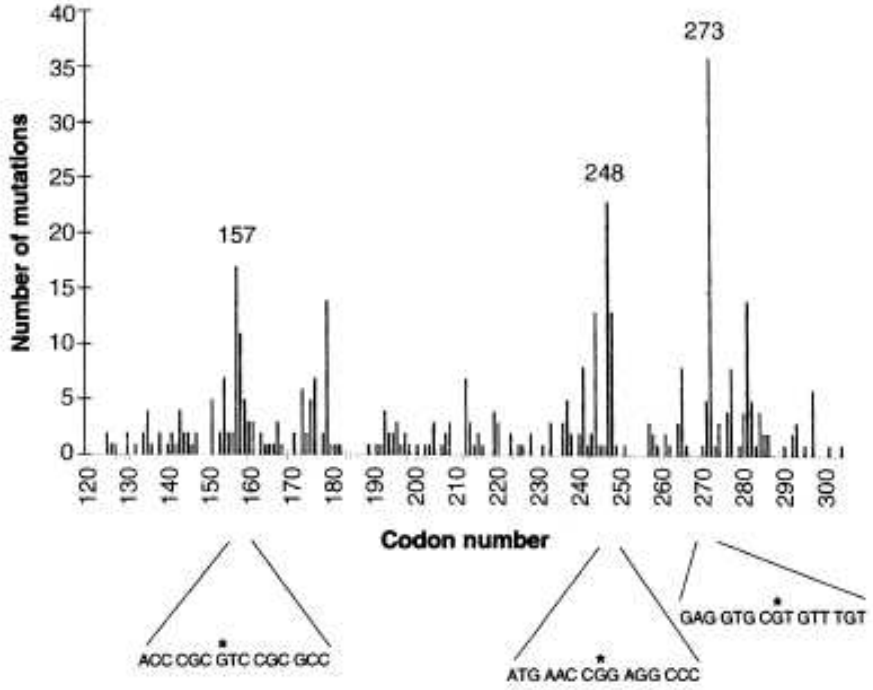
Cigarette Smoke Carcinogen Adducts at Lung Cancer Mutational Hotspots in P53

- Identification of p53 G:C to T:A mutations in lung cancer smokers



Takeshima et al. Lancet 1993; 342:1520-21

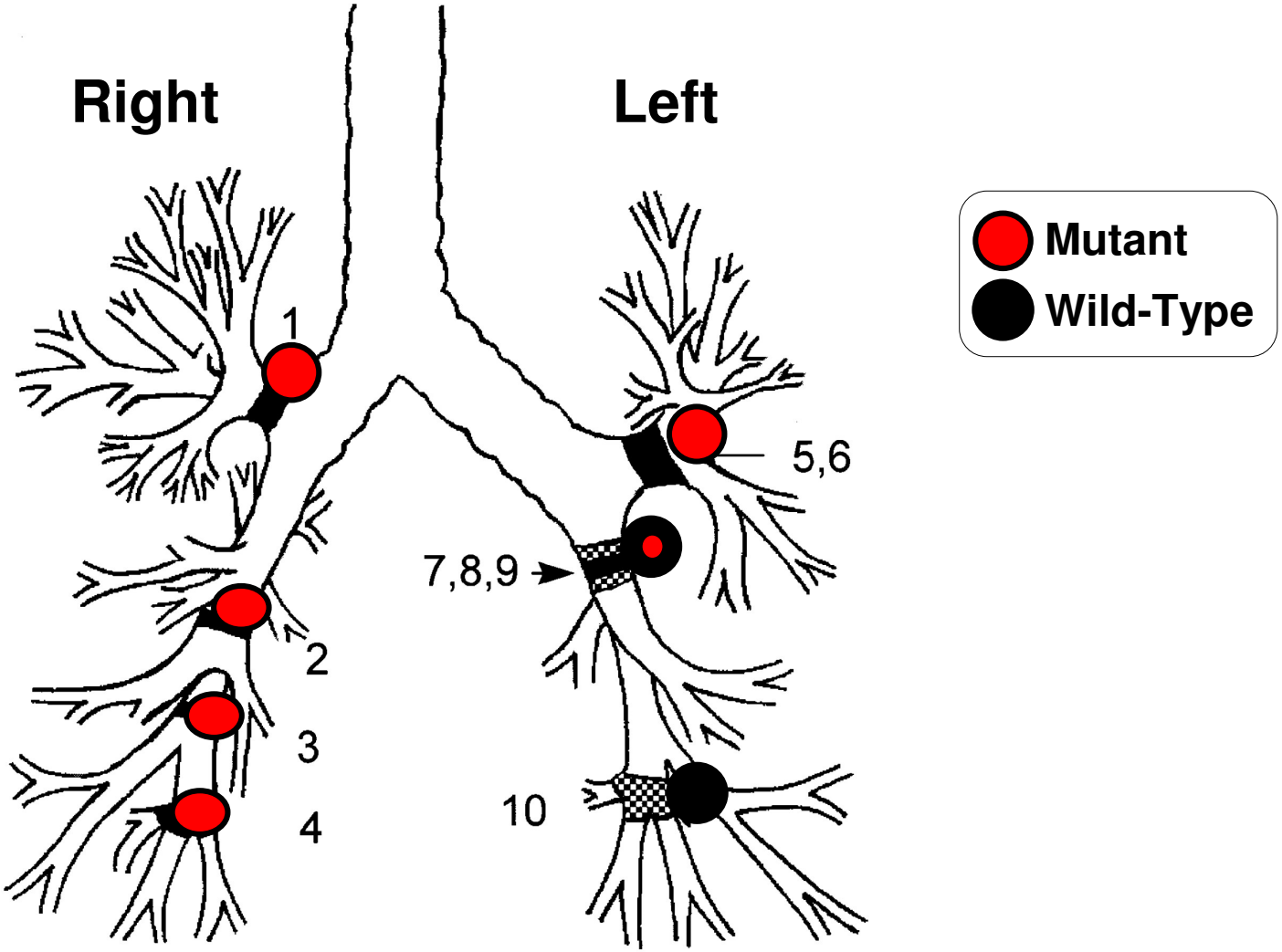
- Cigarette smoke carcinogen BPDE adducts in p53 mapped to guanines in codons 157, 248, and 273 - major mutational hotspots in human lung cancer



Dennisenko et al. Science 1996;274:430-432.

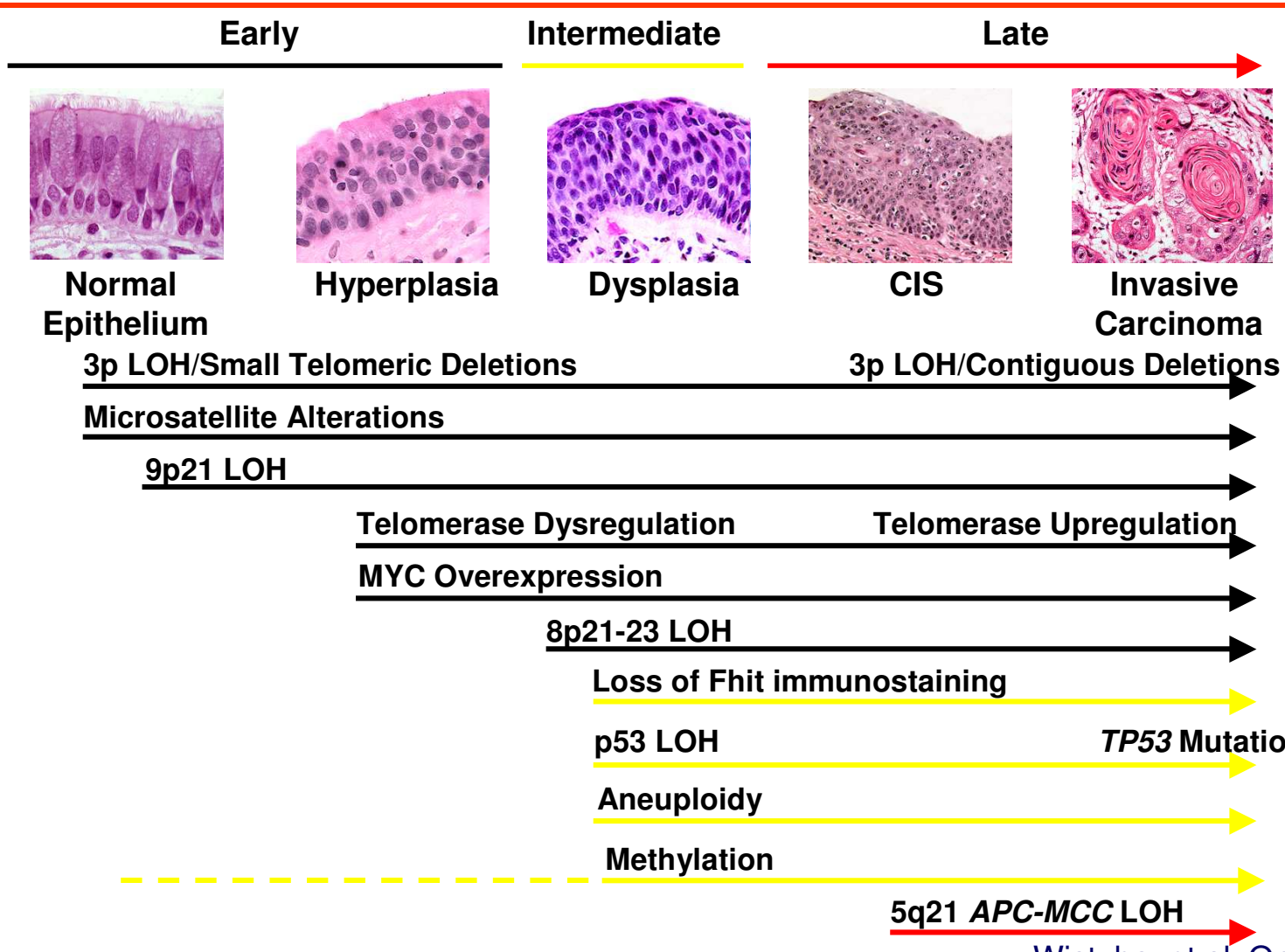
Widespread Dispersed p53 Mutation in Respiratory Epithelium of a Smoker

66-yr-old
Smoker – Male
TP53 Mutation
Codon 245
(G:C to T:A)



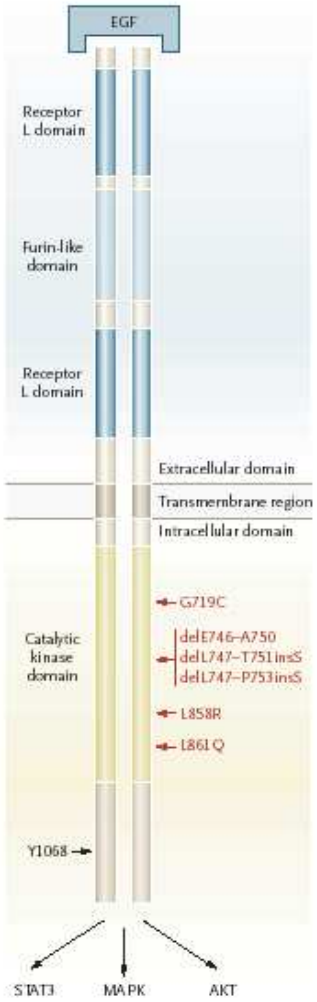
Franklin WA et al. J Clin Invest. 1997;100:2133-2137.

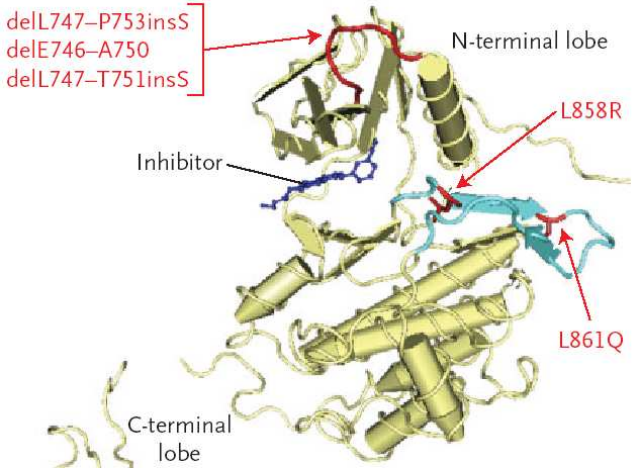
Complexity of Tobacco-Related Carcinogenesis



Wistuba, et al. Oncogene 2008

Therapeutic Opportunities: Targeting Oncogenic Growth Factors- EGFR



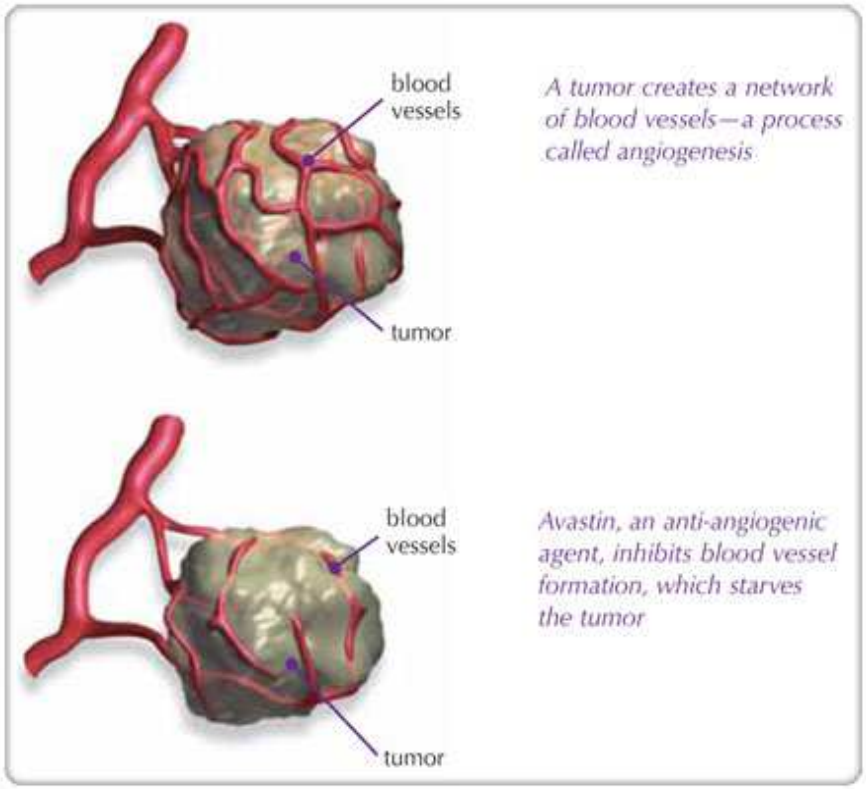


- ***EGFR*** **TK mutations**
  - **Adenocarcinoma**
  - **Never smokers**
  - **Asian ethnicity**
  - **Female**
- **Increased gene copy number**
- **Increased protein expression**

TJ Lynch et al, N Engl J Med. 2004

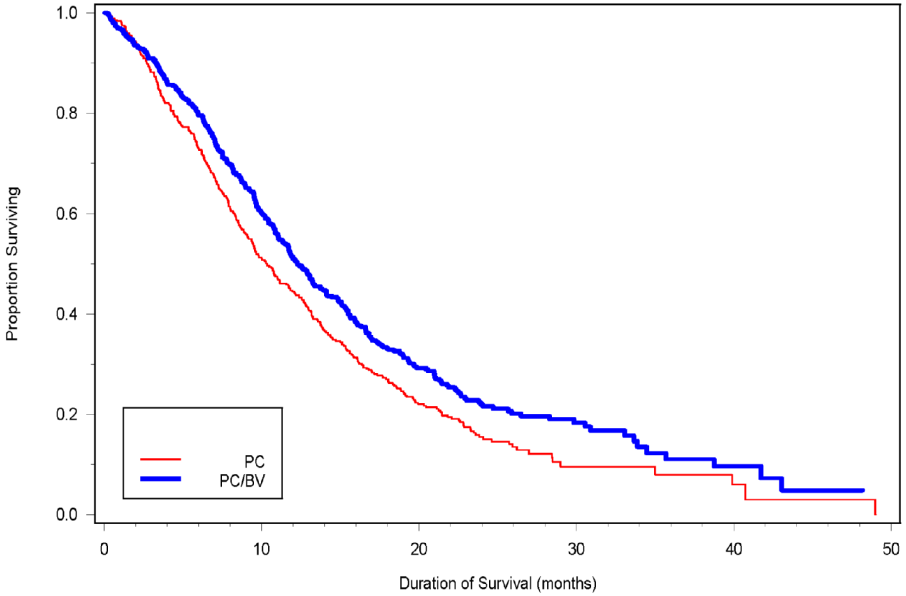
Therapeutic Opportunities: Targeting Angiogenesis

- Study E4599: Overall survival with chemotherapy +/- bevacizumab



RS Herbst, et al, J Clin Oncol 2007

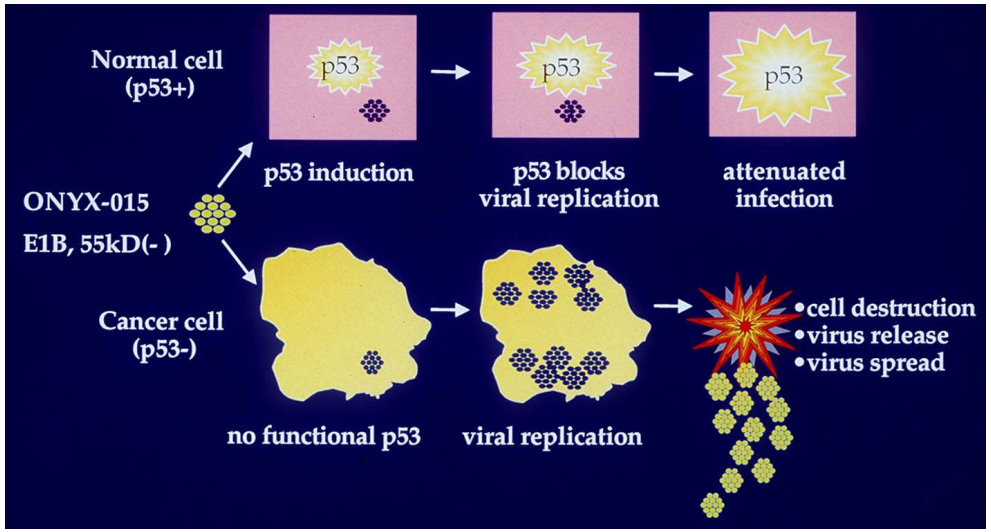
	BCP (N = 434)	CP (N=444)
Median Survival (months)	**12.3**	**10.3**
1-year Survival (%)	**51.0**	**44.4**
2-year Survival (%)	**22.0**	**15.4**

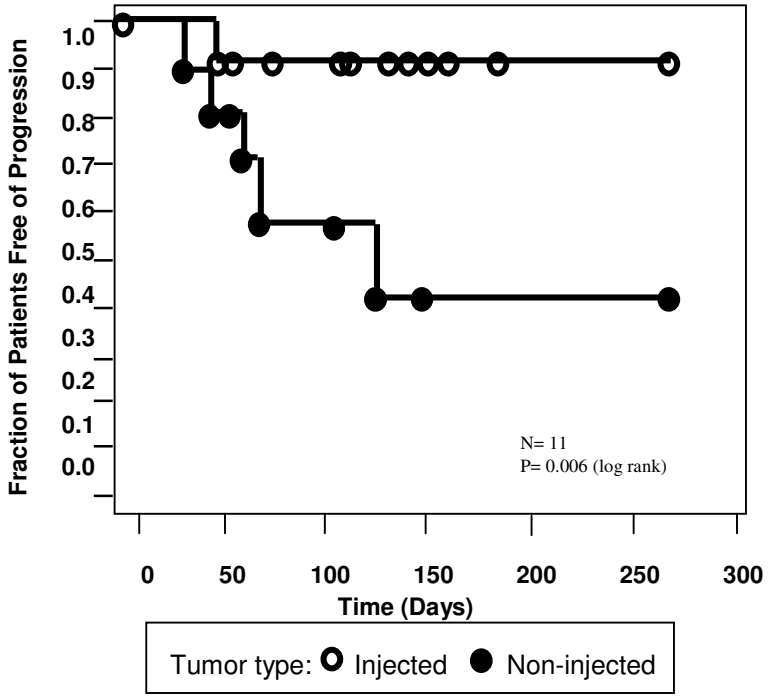


A Sandler et al, N Engl J Med. 2006

Therapeutic Opportunities: Targeting Tumor Suppressor Genes

- Gene therapy, siRNA, oncolytic viruses (eg ONYX-15)
- Phase III trial of Onyx-015 plus chemotherapy in nasopharynx cancer using in China showed a dramatic advantage in ORR

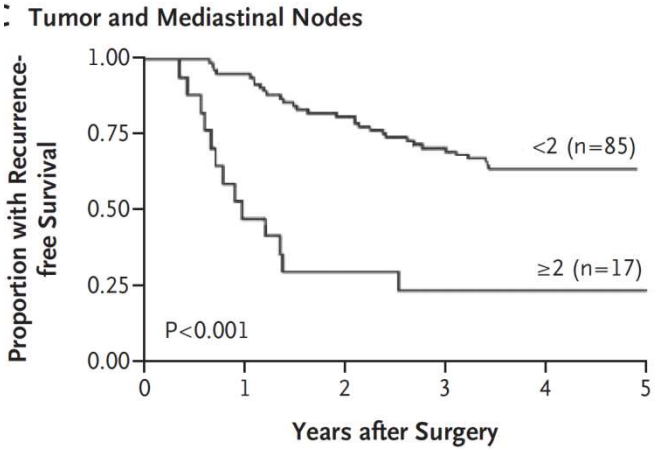


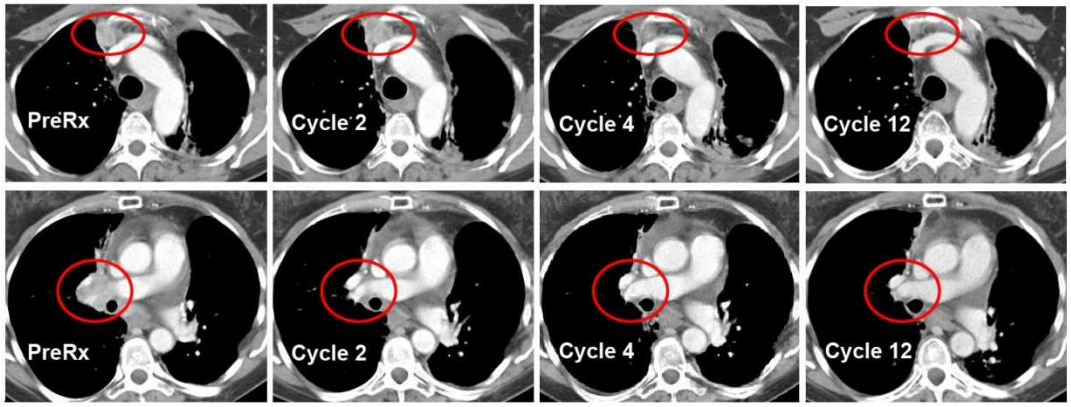


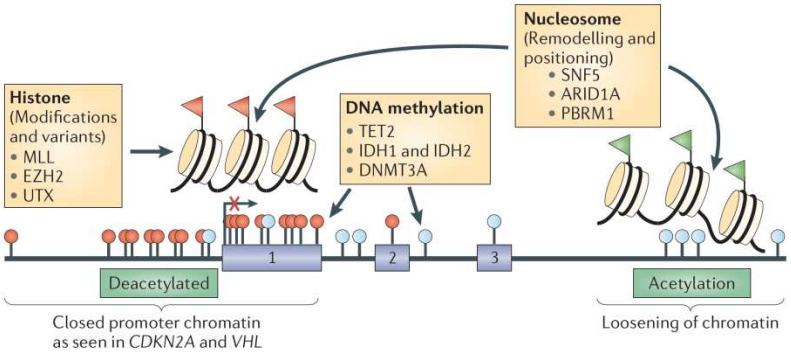
Khuri et al. Nature Med 2000;6:879-885.

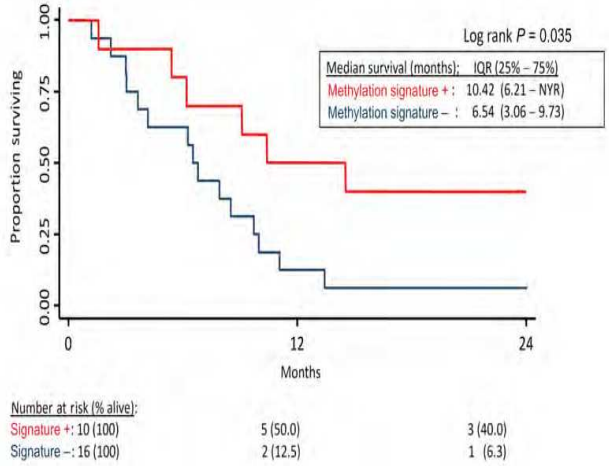
Therapeutic Opportunities: Targeting Epigenetics

- Phase I/II trial of low dose azacitidine with entinostat (HDAC inhibitor)







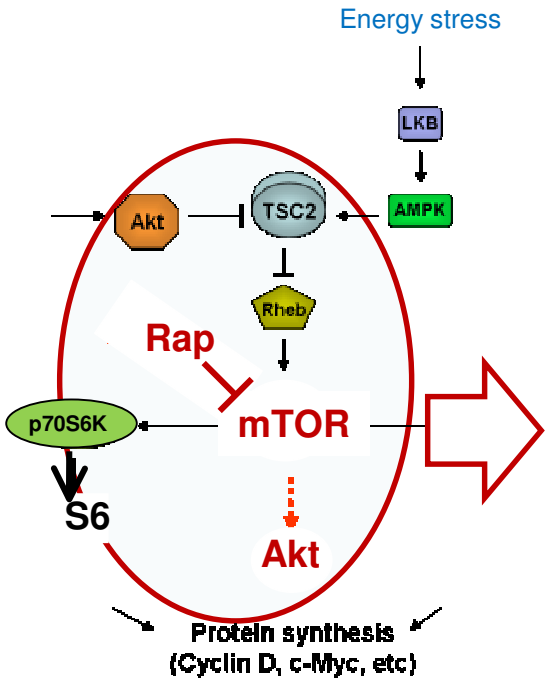


Brock et al. *N Engl J Med*, 2008.

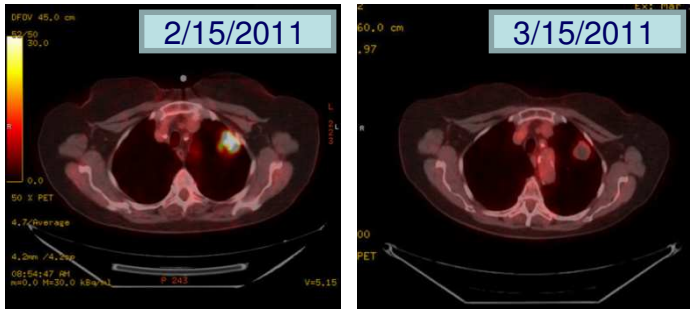
Juergens et al. Cancer Discovery 2011;1:598-607.

Therapeutic Opportunities: Targeting Survival Pathways

Linking basic findings to clinical trials with molecular imaging



Sun et al. Cancer Res 2005



Everolimus Ph1 clinical trial PET scan
Phase I: N = 29 (RAD001)
Phase I/II: N= 52 (RAD001+docetaxel)

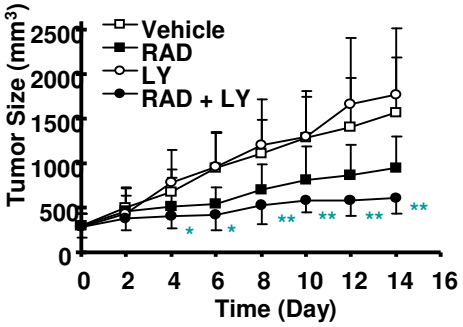
p-AKT in all 21 RAD001 patients

pS6 **only inhibited in 1/12 patients at 5mg of RAD001, in 7/9 patients at 10 mg of RAD001**

Limited clinical activity of RAD001: Limited target effect

Owonikoko et al. WCLC, Amsterdam, 2011;
Ramalingam et al. Cancer, 2010; Khuri et al. NCI Translates, 2011.

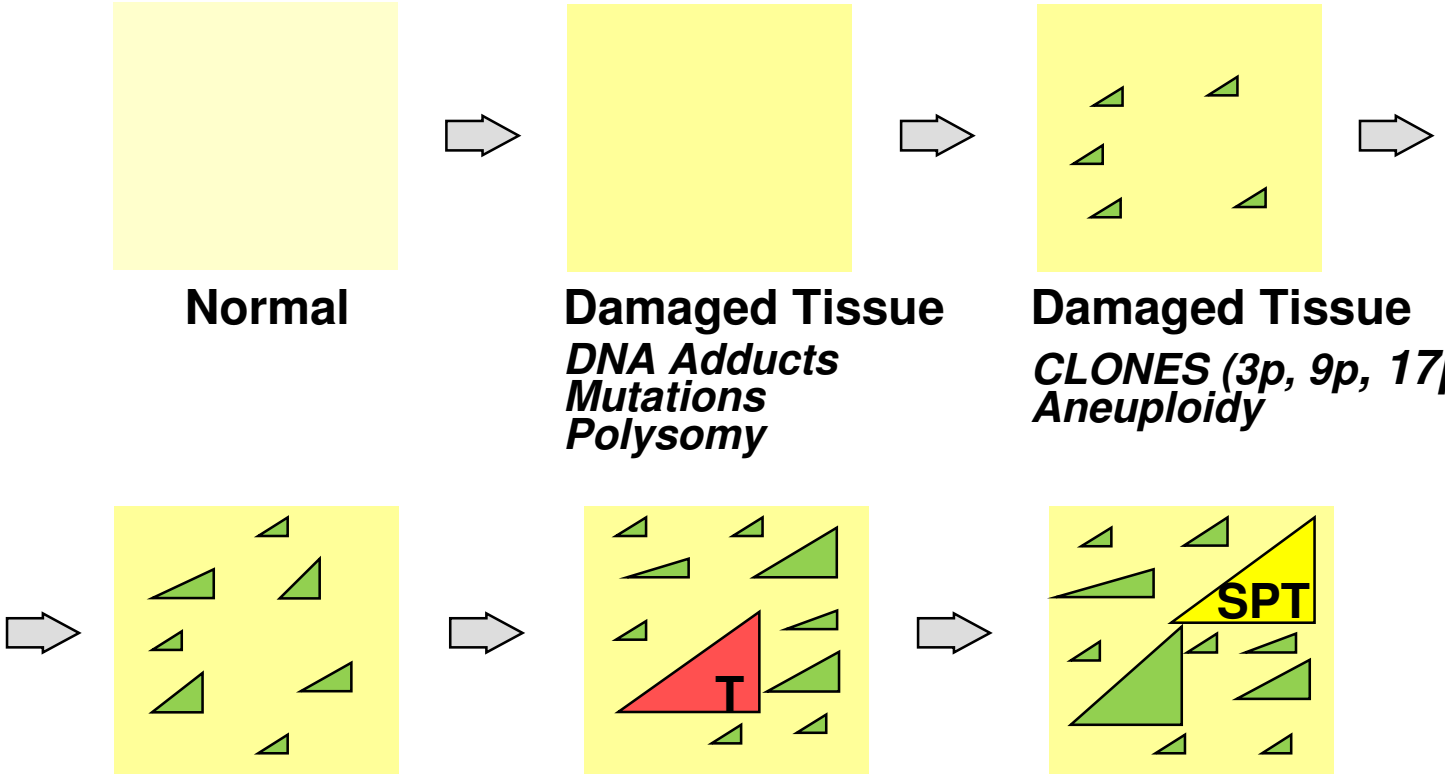
Inhibitors of PI3K + mTOR Synergistically inhibit tumor growth in xenograft



Phase I trial:
BKM120 + RAD001
to achieve complete
target blockade
(Proj 1, P01)

Khuri et al. NCI Translates 2011.

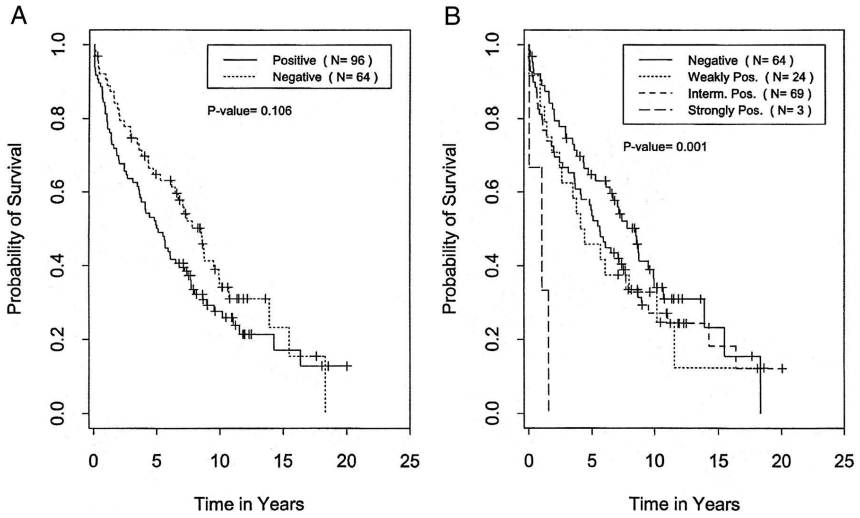
Field Carcinogenesis: The rationale for Cancer Chemoprevention



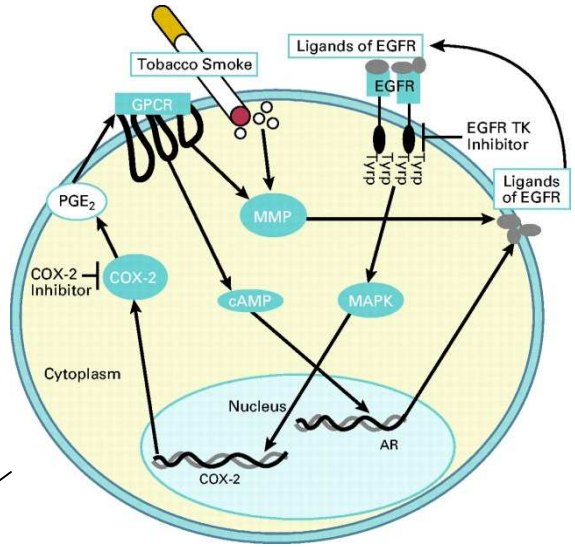
W Hittelman, MDACC

Tobacco as a Potent Molecular Probe:

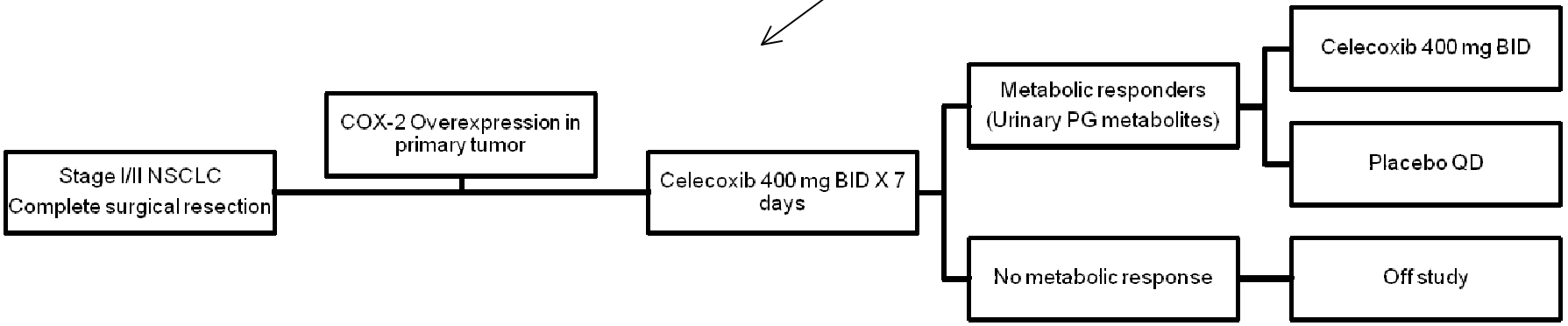
Tobacco Smoke-mediated Induction of Cyclooxygenase-2 (COX-2) is Dependent on Activation of EGFR



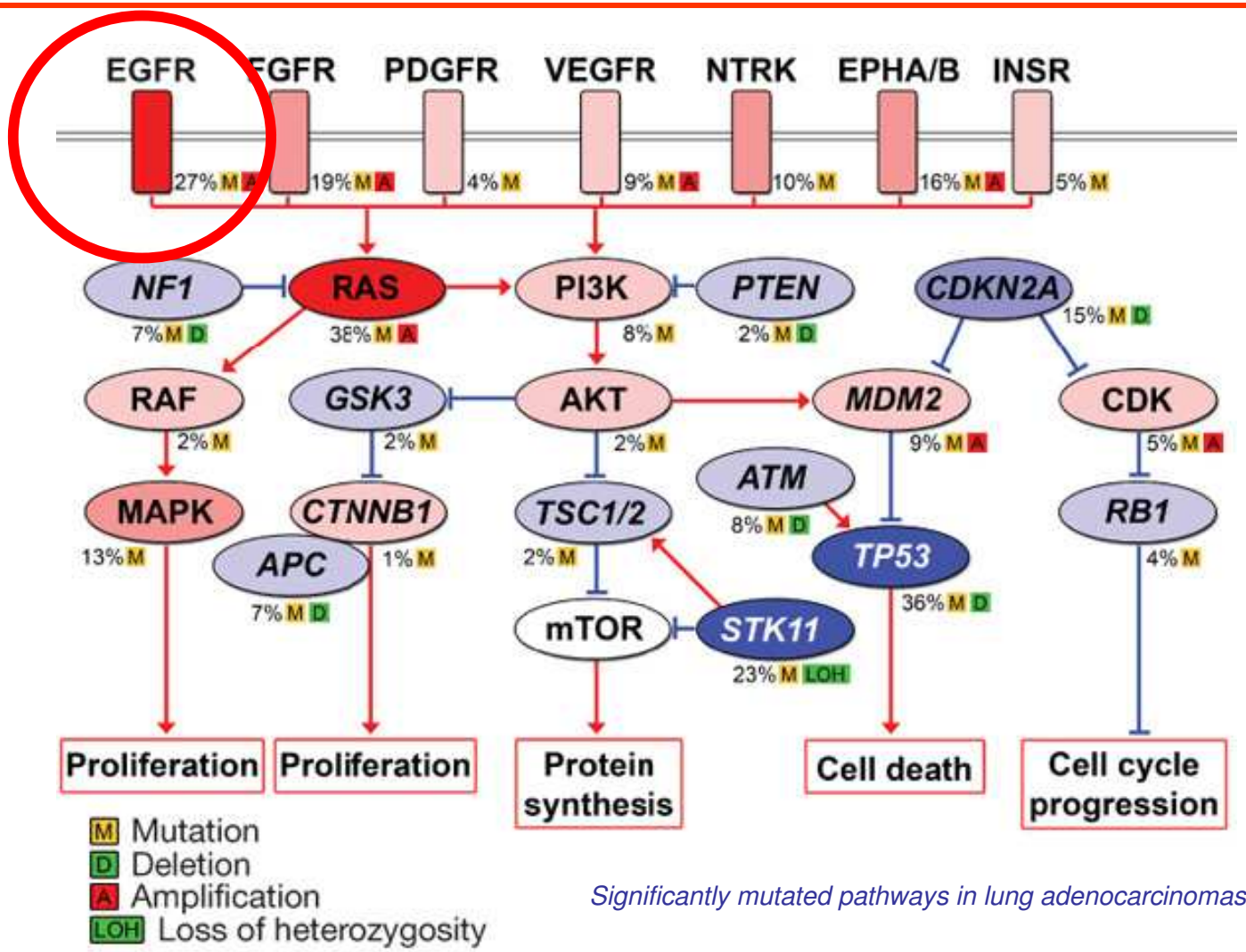
Khuri et al. CCR 2001;7:861-867.



Dannenberg et al. JCO 2005;23:254-266.



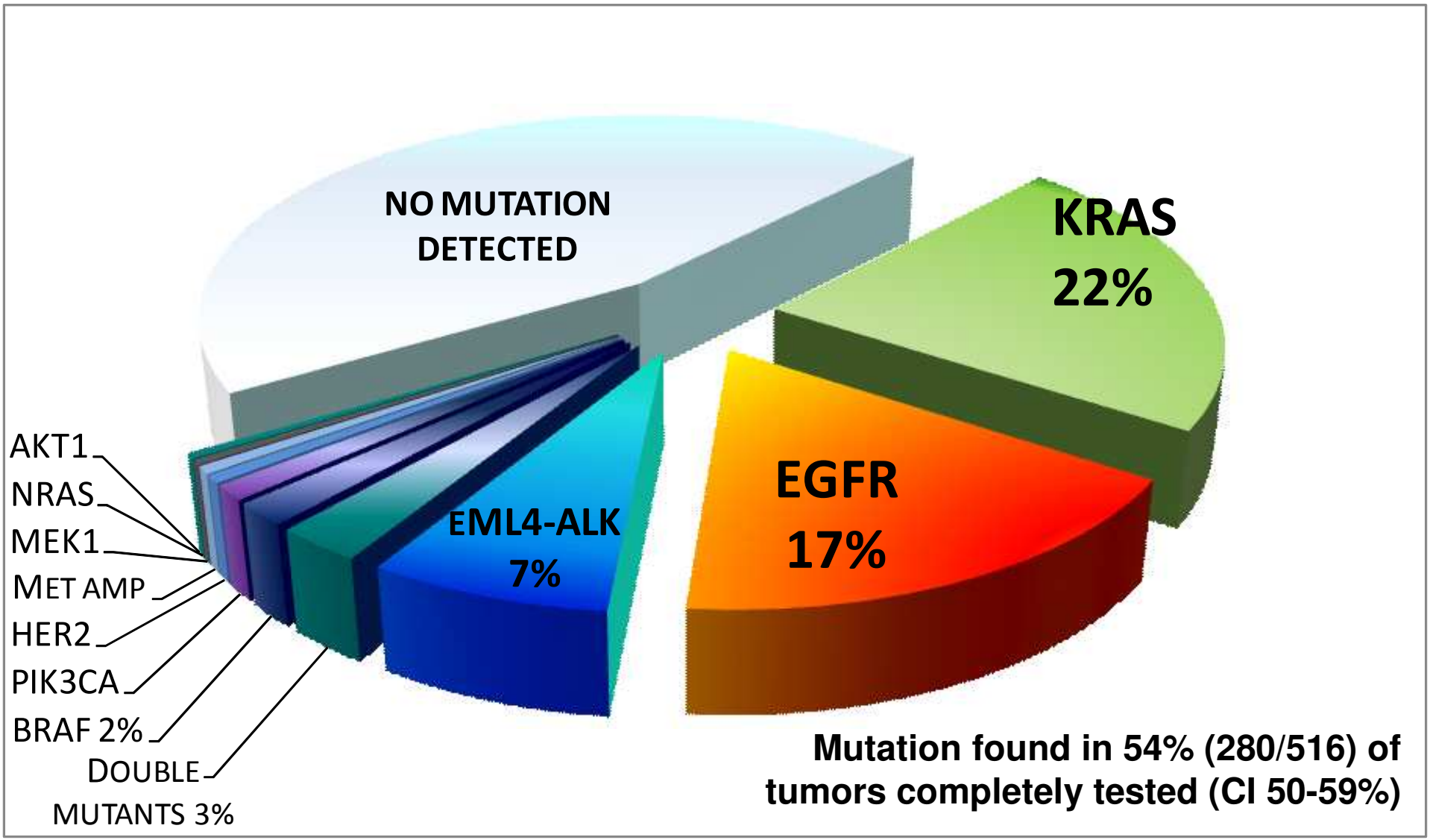
Opportunities: Most Common Alterations Driving Lung Cancer



Significantly mutated pathways in lung adenocarcinomas

Modified based on Ding et al. Nature 2008;455;1069-1075.

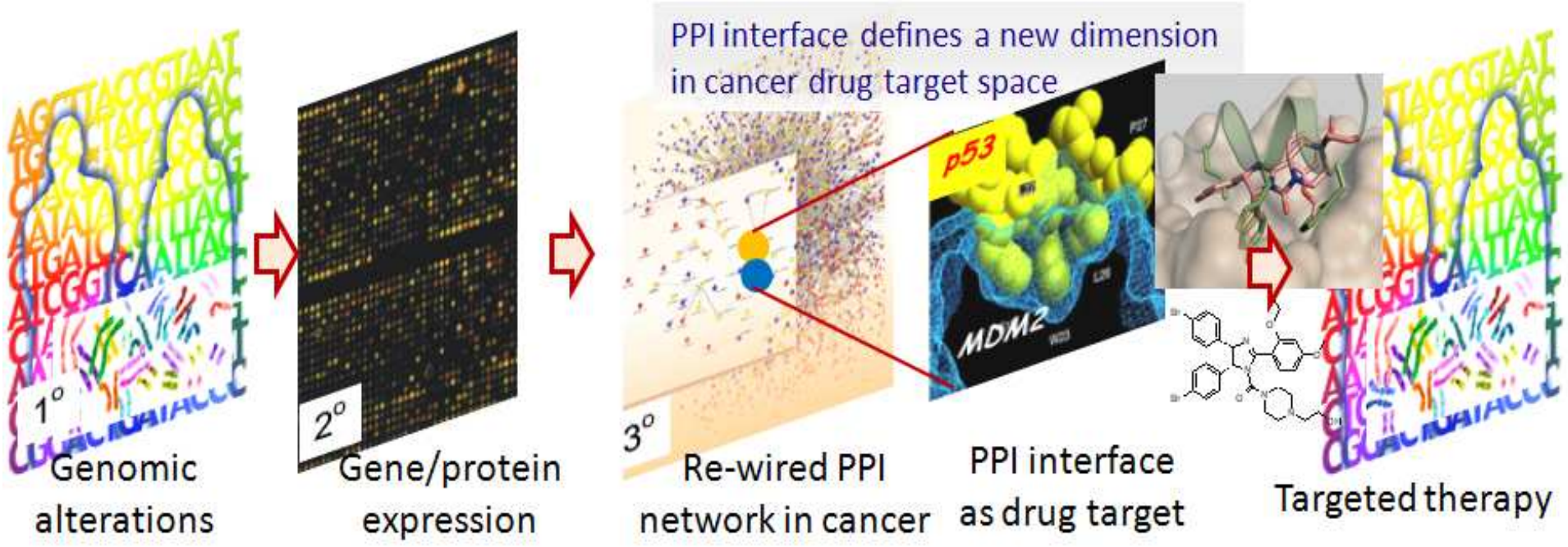
Lung Cancer Mutation Consortium: Incidence of Single Driver Mutations



Lung Cancer Mutation Consortium:
Squamous Cell Cancers also have driver mutations

Emory Molecular Interaction Center for Functional Genomics (MicFG): PPI Network Mapping

To define the 3rd dimension of the cancer genome



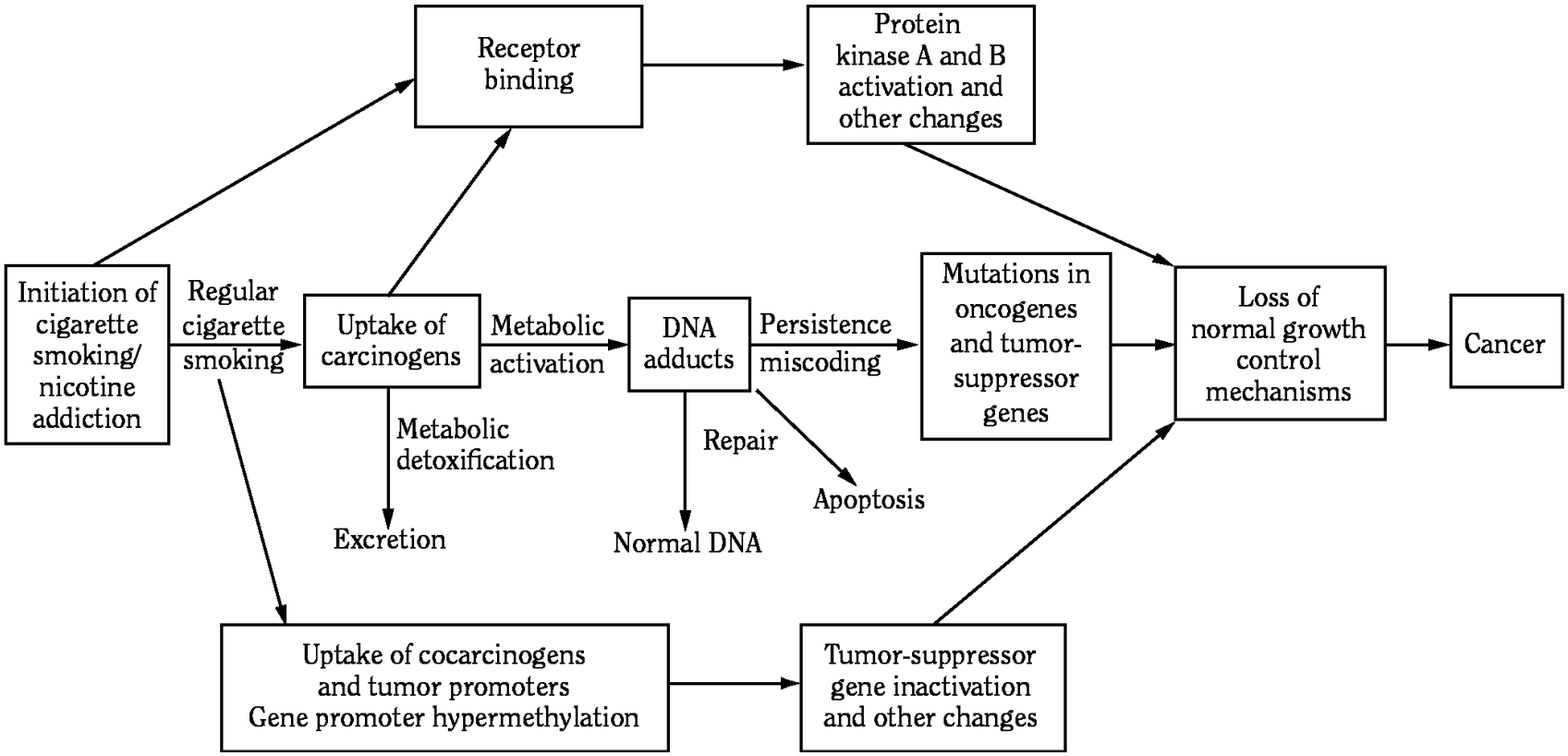
Drug targets

Drug targets

Drug targets

2010 Surgeon General's Report:

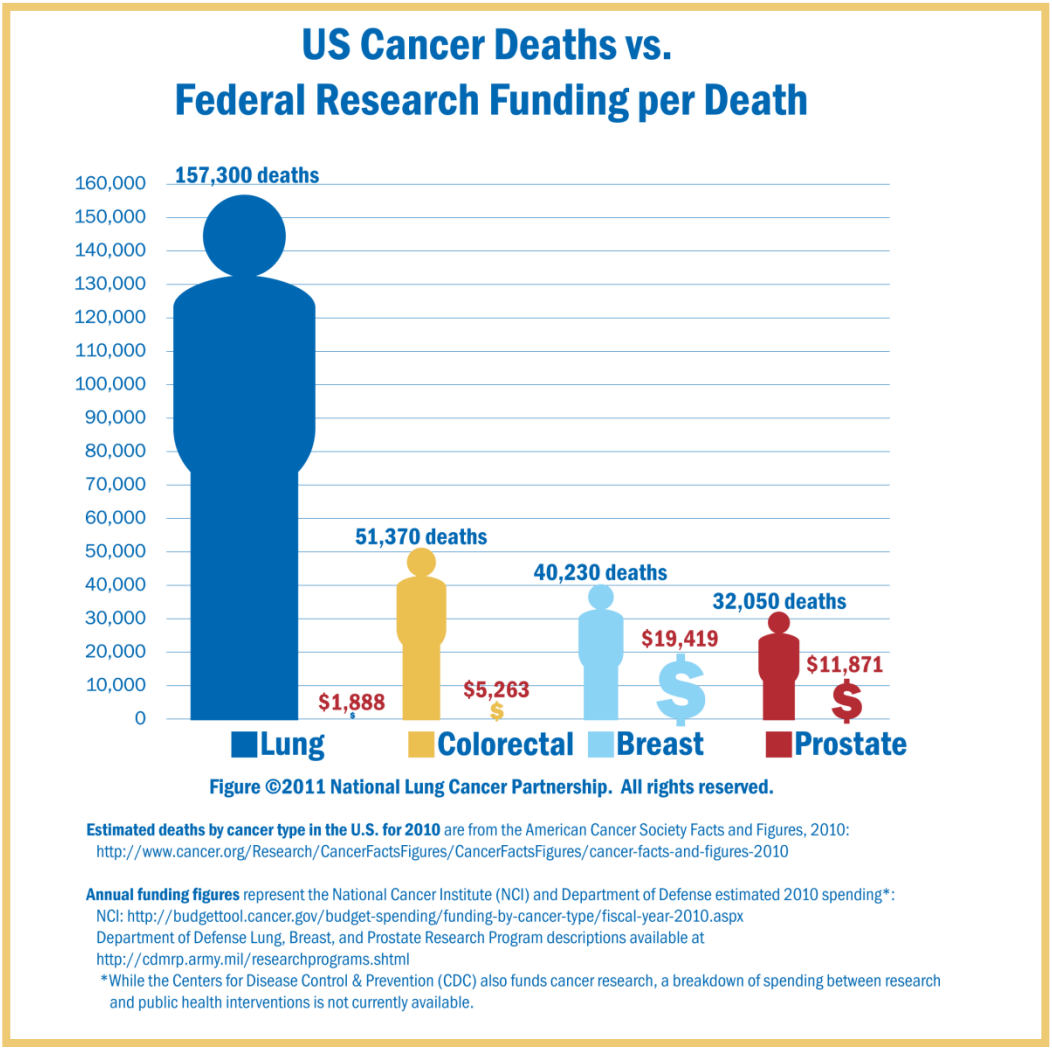
Link between Cigarette Smoking and Cancer through Carcinogens in Tobacco Smoke



2010 Surgeon General's Report:
Biology and Behavioral Basis for Smoking-Attributable Cancer

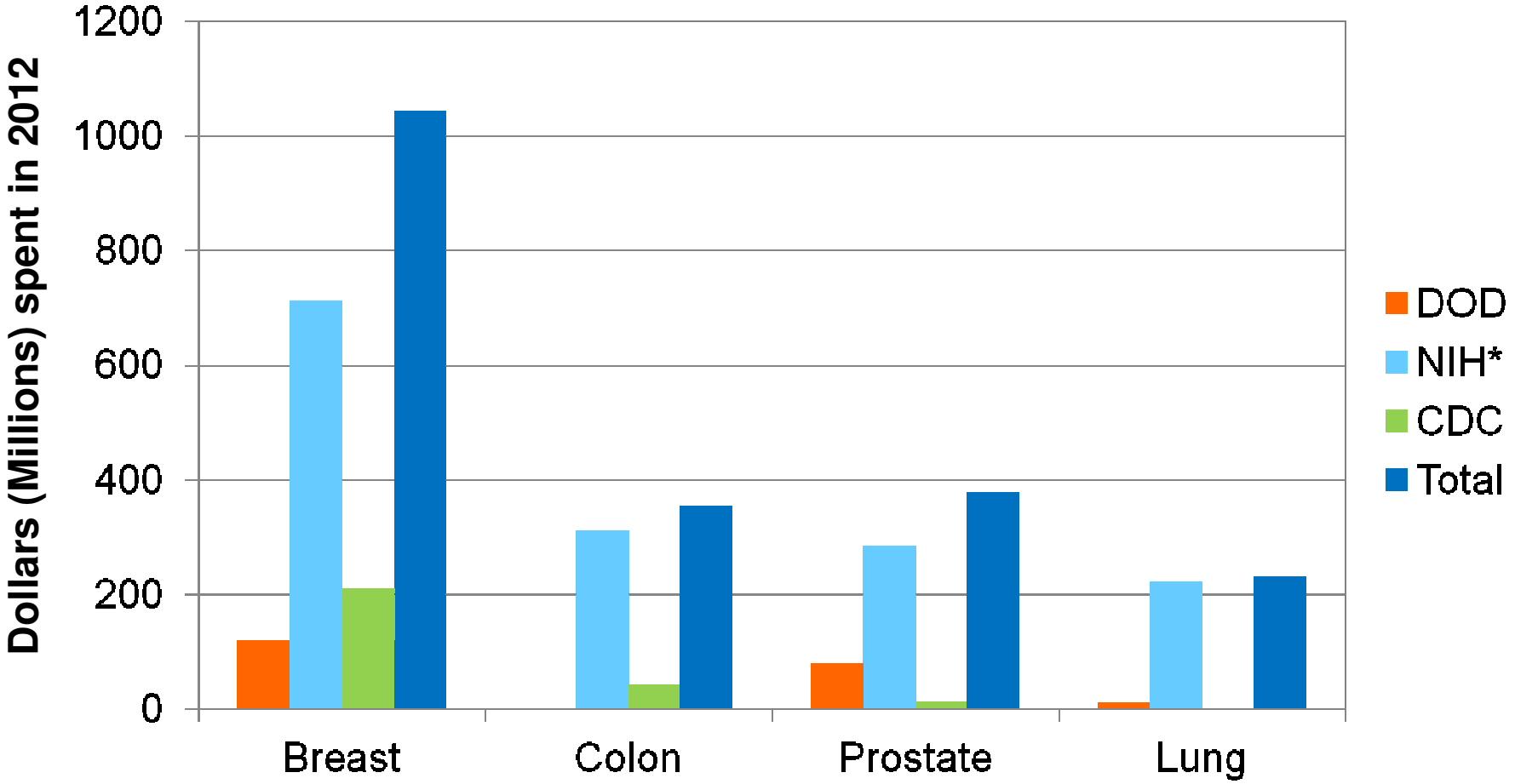
1. The doses of cigarette smoke carcinogens resulting from inhalation of tobacco smoke are reflected in levels of these carcinogens or their metabolites in the urine of smokers.
2. The metabolic activation of cigarette smoke carcinogens by cytochrome P-450 enzymes has a direct effect on the formation of DNA adducts.
3. Consistent evidence that a combination of polymorphisms in the *CYP1A1 and GSTM1 genes leads to higher DNA adduct levels in smokers and higher relative risks for lung cancer than in those smokers without this genetic profile.*
4. Carcinogen exposure and resulting DNA damage observed in smokers results directly in the numerous cytogenetic changes present in lung cancer.
5. Smoking increases the frequency of DNA adducts of cigarette smoke carcinogens such as benzo[*a]pyrene and tobacco-specific nitrosamines in the lung and other organs.*
6. Exposure to cigarette smoke carcinogens leads to DNA damage and subsequent mutations in *TP53 and KRAS in lung cancer.*
7. Consistent evidence that smoking leads to the presence of promoter methylation of key tumor suppressor genes such as *P16 in lung cancer and other smoking-caused cancers.*
8. Consistent evidence that smoke constituents such as nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone can activate signal transduction pathways directly through receptor-mediated events, allowing the survival of damaged epithelial cells that would normally die.
9. Consistent evidence for an inherited susceptibility of lung cancer with some less common genotypes unrelated to a familial clustering of smoking behaviors.
10. Smoking cessation remains the only proven strategy for reducing the pathogenic processes leading to cancer in that the specific contribution of many tobacco carcinogens, alone or in combination, to the development of cancer has not been identified.

Lung Cancer Funding



Source: National Lung Cancer Partnership

Federal Research Spending
Fiscal Year 2012 in Millions



*Includes FY10 stimulus funding

Source: National Lung Cancer Alliance

Molecular Carcinogenesis of Tobacco-related cancers: Conclusions

- Tobacco related carcinogenesis has been increasingly well characterized at the cellular and genomic level.
- Several mechanisms are in place for team and individual science in tobacco-related cancers (15 SPOREs, 3 P01's, more than 90 R01's, increased DOD funding) and foundation support, but all are currently under threat.
- We need to protect, enhance (not decrease!)and leverage state, federal, foundation (ACS and others) to enhance both therapeutic and prevention strategies for tobacco-related cancers, at a time when our biologic and genomic understanding of these diseases continues to grow exponentially.