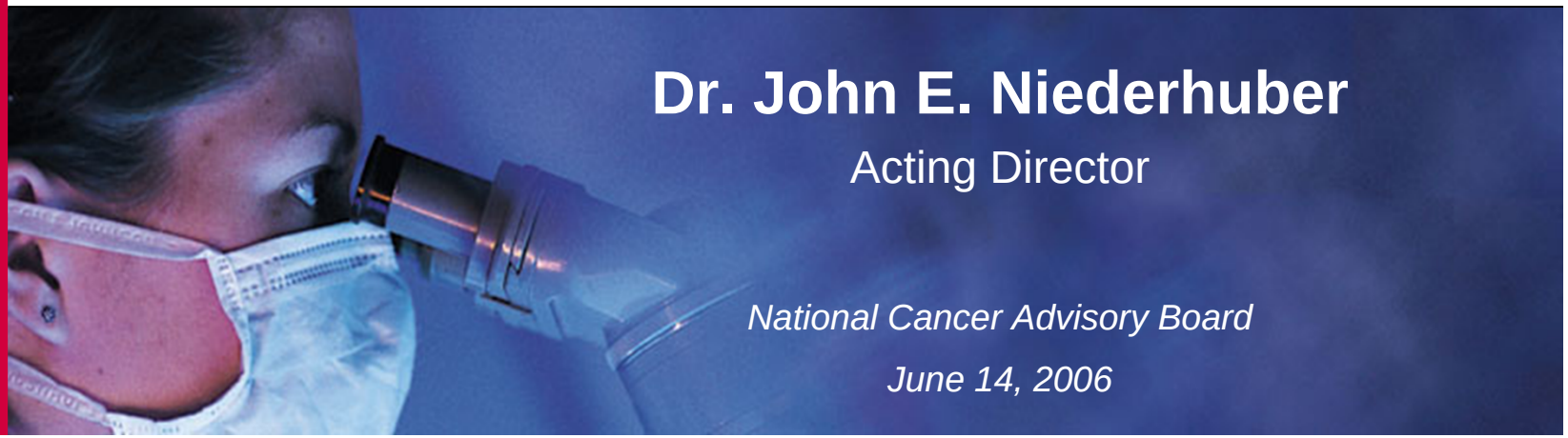
National Cancer Institute



Director's Update



Dr. John E. Niederhuber

Acting Director

National Cancer Advisory Board

June 14, 2006

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

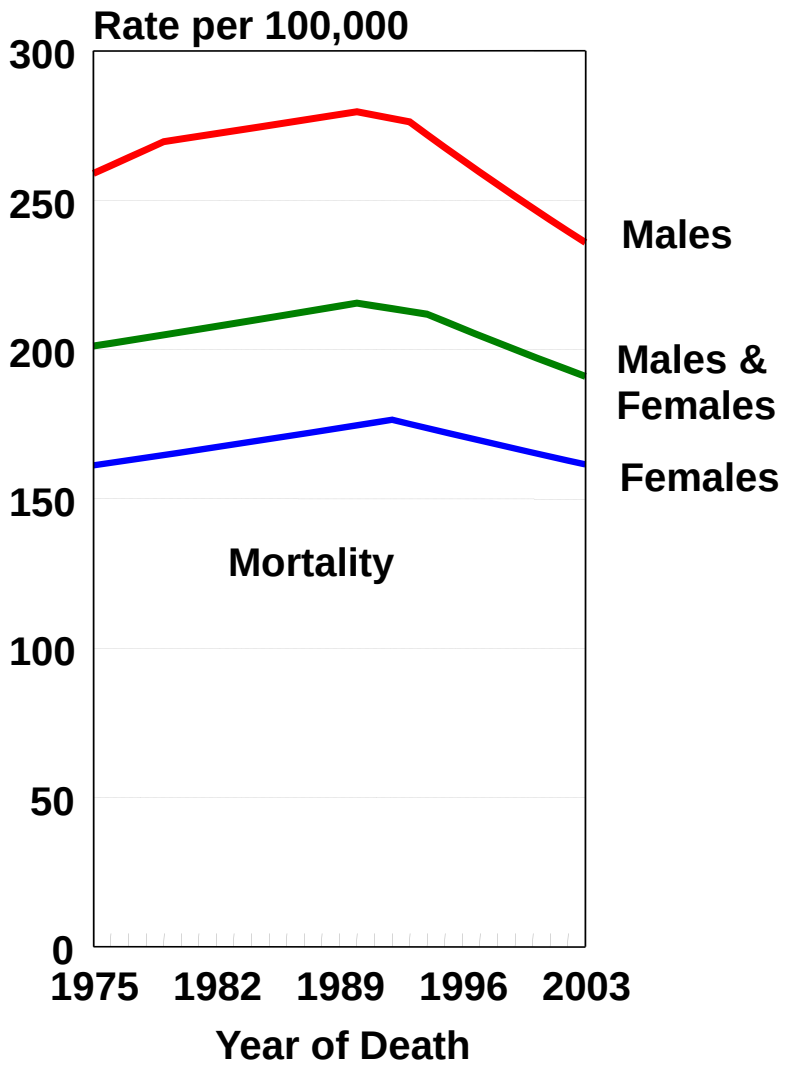
National Institutes of Health

NCAB – Director's Update

- **Awards to intramural scientists**
- **New appointments to NCI**
- **Applications, Awards and Success Rates**
- **Lung cancer program**
- **HPV vaccine**

U.S. Death Trends: Cancer of All Sites, 1975-2003

- **Decline of -1.1% since 1994**
- **Decline for men is -1.6% per year since 1993**
- **Decline for women is -0.8% per year since 1992**
- **Decline continues for Prostate, Breast (F), Colorectal, Lung (M), and many other sites**



2006 – Final Quarter

- **Have been hit with a mid-year increase in taps for direct utility costs to NIH of almost $4 million**
- **RPG payline running about 11th percentile; 15% of the competing pool in reserve for some exceptions**
- **Type 5s generally 2.35% below the commitment of record**
- **SPOREs are 2% below FY2005 and Centers are essentially flat with FY05**
- **Training is 1% above the FY05 level**

Honors

Medal of Honor, International Agency for Research on Cancer

Joseph Fraumeni, M.D.

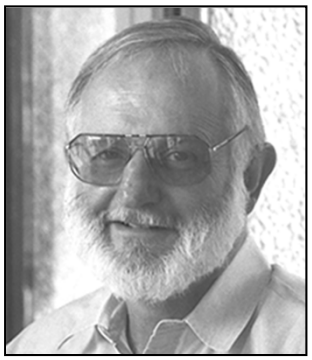
Director, DCEG

Marvin Zelen Leadership Award in Statistical Science

Mitchell Gail, M.D., Ph.D.

Chief of the Biostatistics Branch, DCEG

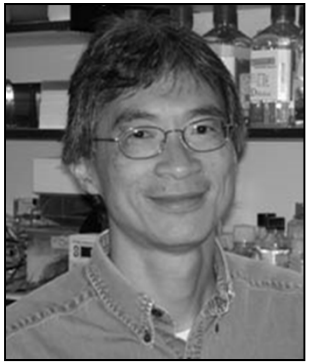
Honors



Outstanding Mentor Award

Dolph Hatfield, Ph.D.

Chief, Molecular Biology of Selenium Section, CCR



Elected to the National Academy of Sciences April 25

Carl Wu, Ph.D.

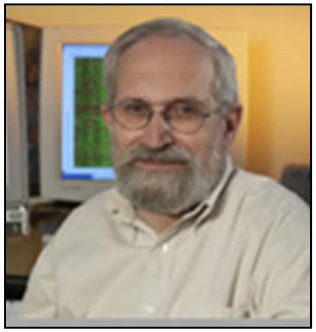
Chief, Laboratory of Molecular Cell Biology

Honors for caBIG

21st Century Achievement Award—Science

***Computerworld* magazine**

Appointments



Paul Meltzer, M.D., Ph.D.

Chief, Genetics Branch and Head, Clinical Molecular Profiling Core, CCR

Margaret Tucker, M.D.

Director, Human Genetics Program, DCEG

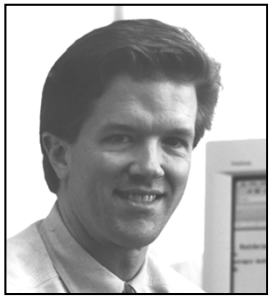
Dr. Mark Udey, M.D., Ph.D.

Deputy Director, CCR

Coordinating Center for Clinical Trials

- **Sheila Prindiville, M.D., M.P.H., Director**
- **Program Directors:**
  - **Deborah Jaffe, Ph.D.**
  - **LeeAnn Jensen, Ph.D.**
  - **Ray Petryshyn, Ph.D.**

Receiving Tenure at CCR



Philip Dennis, M.D., Ph.D.

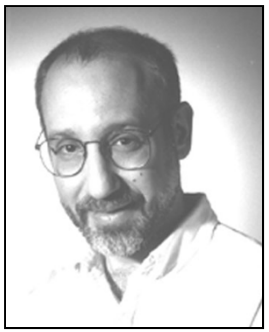
Medical Oncology Branch & Affiliates

Steven Libutti, M.D.

Surgery Branch

Steven Hou, Ph.D.

Mouse Cancer Genetics Program



Stanley Lipkowitz, M.D., Ph.D.

Laboratory of Cellular and Molecular Biology

Trans-NIH Programs

- **TARP: Trans-NIH Angiogenesis Research Program**
- **Planning for:**
  - **Embryogenesis and cancer development**
  - **Cancer stem cells and stem cell biology**

New Trans-NCI Programs

- **Lung Cancer Program**
- **Breast Cancer Stamp Premalignancy Research Program**
- **Planning for programs in:**
  - **Epidemiology and Prevention**
  - **Computational Biology and Biostatistics**

Cancer Center Directors' Retreat

- **Chair: Dr. John Mendelsohn**
  - **Subcommittees**
    - **Prevention; Dr. David Alberts, Chair**
    - **Early Detection; Dr. Stan Gerson, Chair**
    - **Treatment; Dr. Martin Abeloff, Chair**
    - **Survivorship; Dr. William Dalton, Chair**
    - **Coordination and Integration; Dr. Leland Hartwell, Chair**
    - **Dissemination; Dr. Ron Herberman, Chair**
    - **At-large members: Drs. Judy Gasson, John Kersey and Frank McCormick**

Director's Consumer Liaison Group

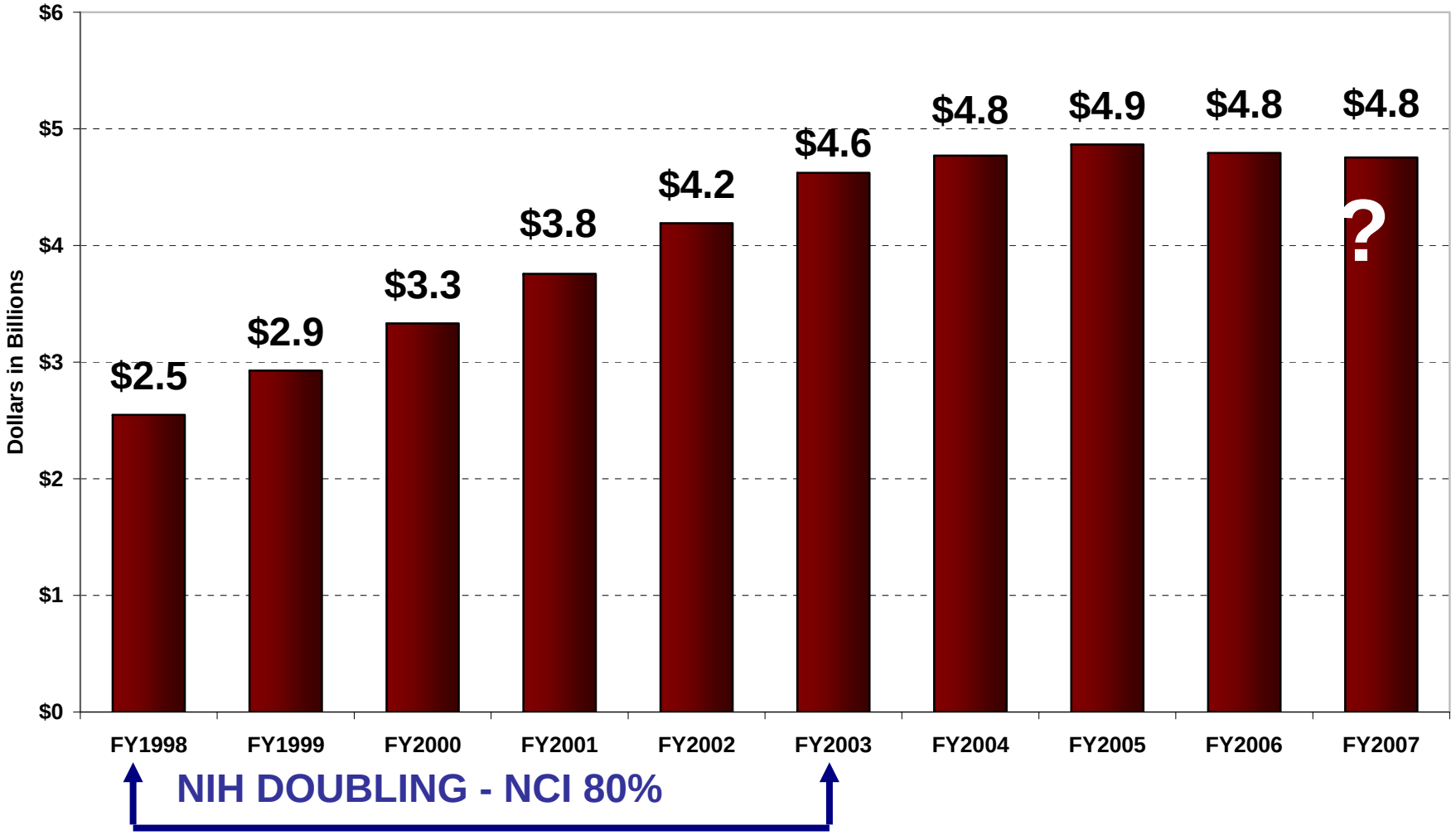
- **Listening and Learning Together: Building a Bridge of Trust**
  - **A summit for the cancer advocacy community**
  - **June 19-20, 2006; Natcher Conference Center**
  - **Dedicated to the work of Ms. Nancy Caliman (former DCLG Executive Secretary)**

FY 2007 President's Budget

FY 2006 Appropriation	$4,793,356
FY 2007 President's Budget	$4,753,609
Difference '06 to '07	- $39,747
Percent Change '06 to'07	- 0.8%

(dollars in thousands)

NCI's Congressional Appropriations, FY 1998 to FY 2007

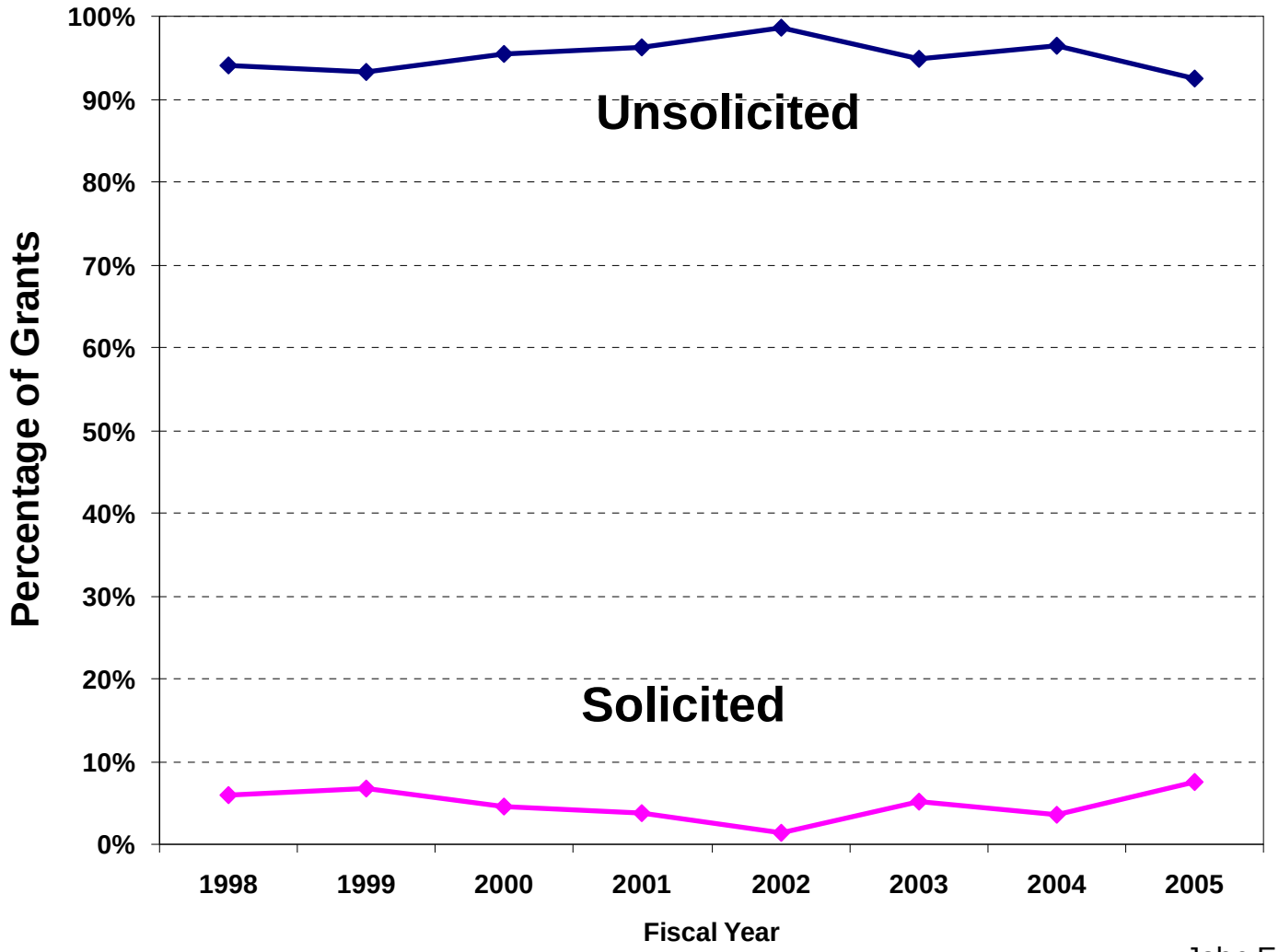


John E. Niederhuber, MD
June 2006

What is driving NCI's budget woes?

- **Federal deficit, Defense and Homeland Security priority requirements, Katrina, pandemic flu and domestic budget cuts (-2.7% for HHS)**
- **Sense in Congress that "Doubling Mission" was accomplished: show us how this has gotten us closer to the goal**
- **Overall support for NIH is still good. No cuts for NIH even though HHS total is down 2.7% and NCI down 0.8%**
- **Decreases compounded by biomedical research inflation (BRDPI), which is around 4%**

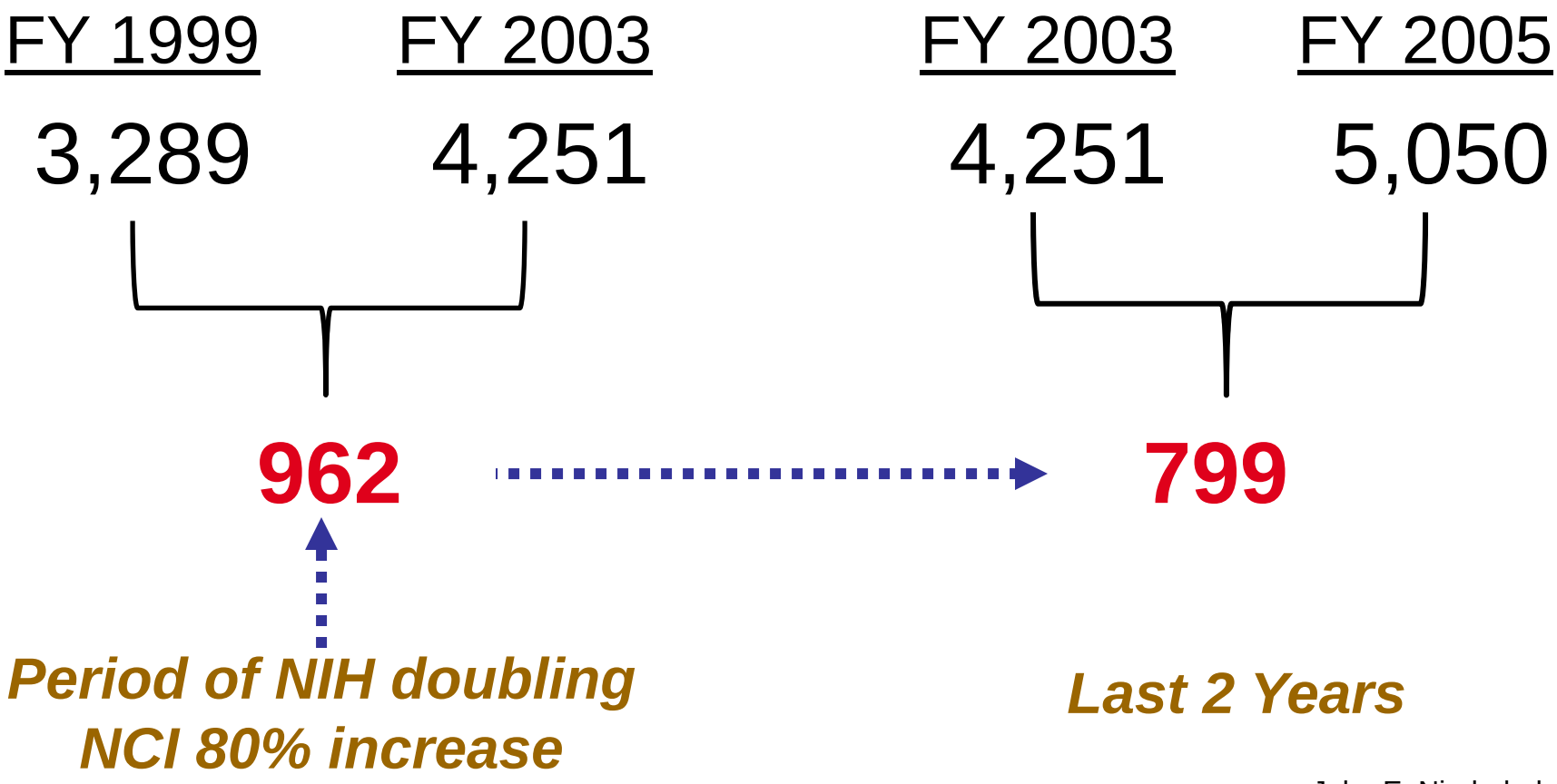
NCI's Unsolicited RPGs Far Outnumber Solicited



John E. Niederhuber, MD
June 2006

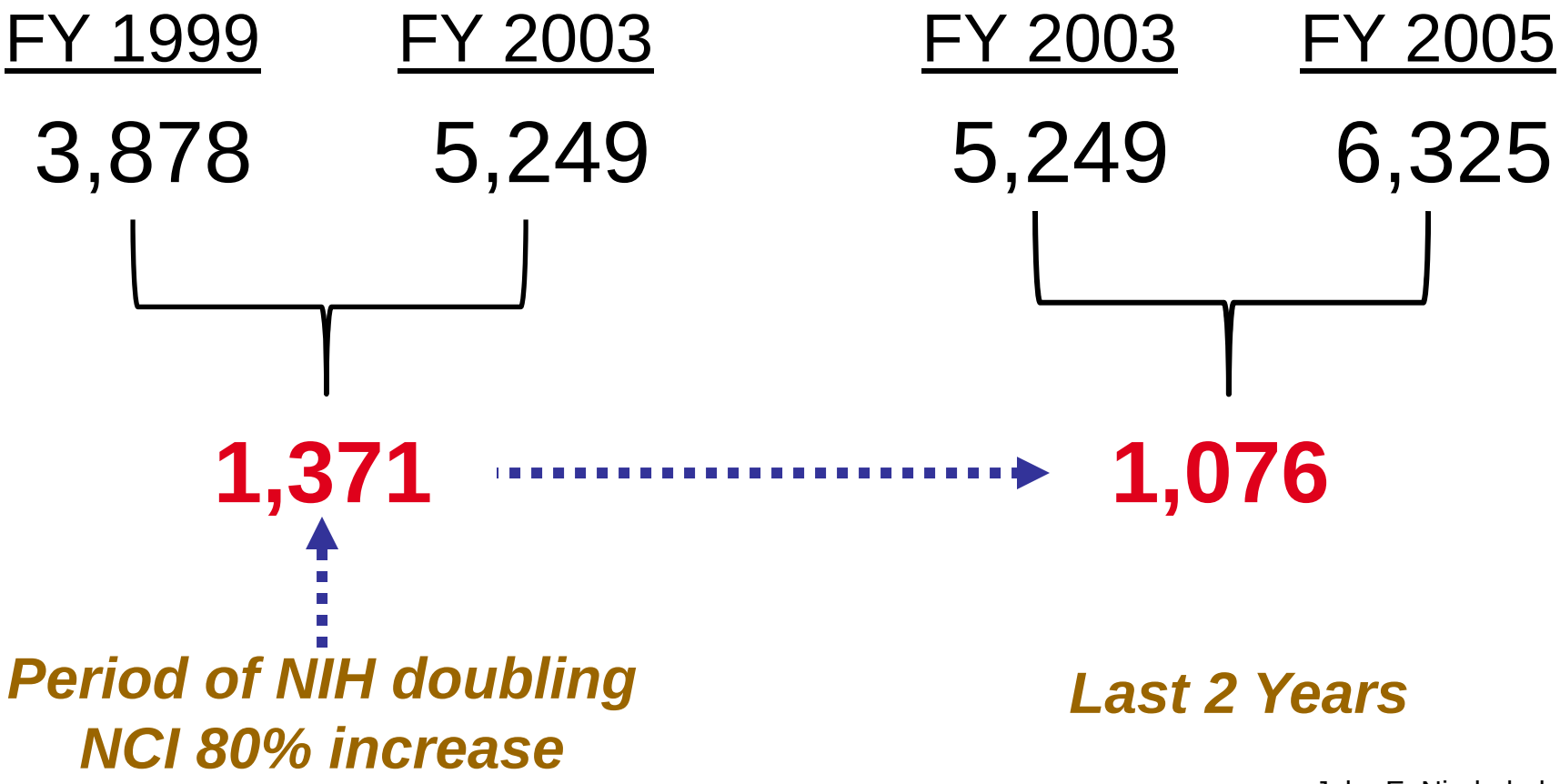

FEB 11 2005

Nearly as Many Competing Applicants in the Last 2 Years as During the NIH Doubling



John E. Niederhuber, MD
June 2006

Nearly as Many Competing Applications in the Last 2 Years as During the NIH Doubling



John E. Niederhuber, MD
June 2006

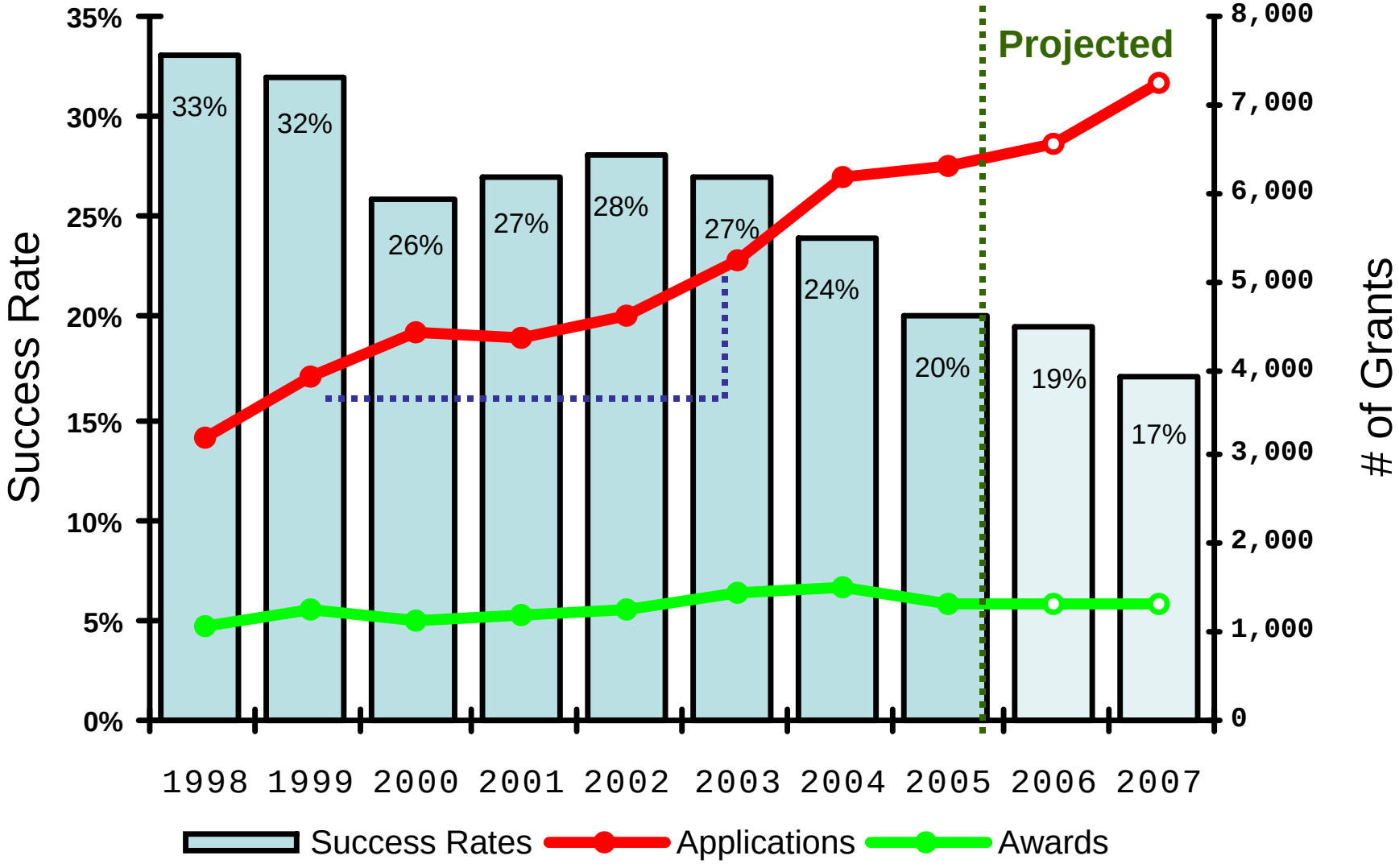
RPG Competing Applications and Applicants FY 1995 to 2005

	Data on Individuals						Data on Applications					
	All RPG			R01 Equivalent			All RPG			R01 Equivalent		
FY	Reviewed	Awarded	% Funded	Reviewed	Awarded	% Funded	Reviewed	Awarded	Success Rate	Reviewed	Awarded	Success Rate
1995	3,095	838	27.1%	2,773	665	24.0%	3,671	870	23.7%	3,190	685	21.5%
1996	2,888	916	31.7%	2,569	782	30.4%	3,380	976	28.9%	2,918	819	28.1%
1997	2,970	951	32.0%	2,645	802	30.3%	3,520	993	28.2%	3,048	826	27.1%
1998	2,773	983	35.4%	2,436	793	32.6%	3,195	1,047	32.8%	2,748	842	30.6%
1999	3,289	1,165	35.4%	2,722	888	32.6%	3,878	1,244	32.1%	3,093	932	30.1%
2000	3,635	1,086	29.9%	2,724	816	30.0%	4,382	1,151	26.3%	3,129	855	27.3%
2001	3,666	1,126	30.7%	2,836	827	29.2%	4,374	1,188	27.2%	3,254	856	26.3%
2002	3,794	1,181	31.1%	2,844	828	29.1%	4,588	1,264	27.6%	3,311	867	26.2%
2003	4,251	1,326	31.2%	3,172	943	29.7%	5,249	1,421	27.1%	3,745	996	26.6%
2004	4,870	1,393	28.6%	3,325	946	28.5%	6,148	1,487	24.2%	3,986	992	24.9%
2005	5,050	1,226	24.3%	3,480	812	23.3%	6,325	1,292	20.4%	4,147	844	20.4%

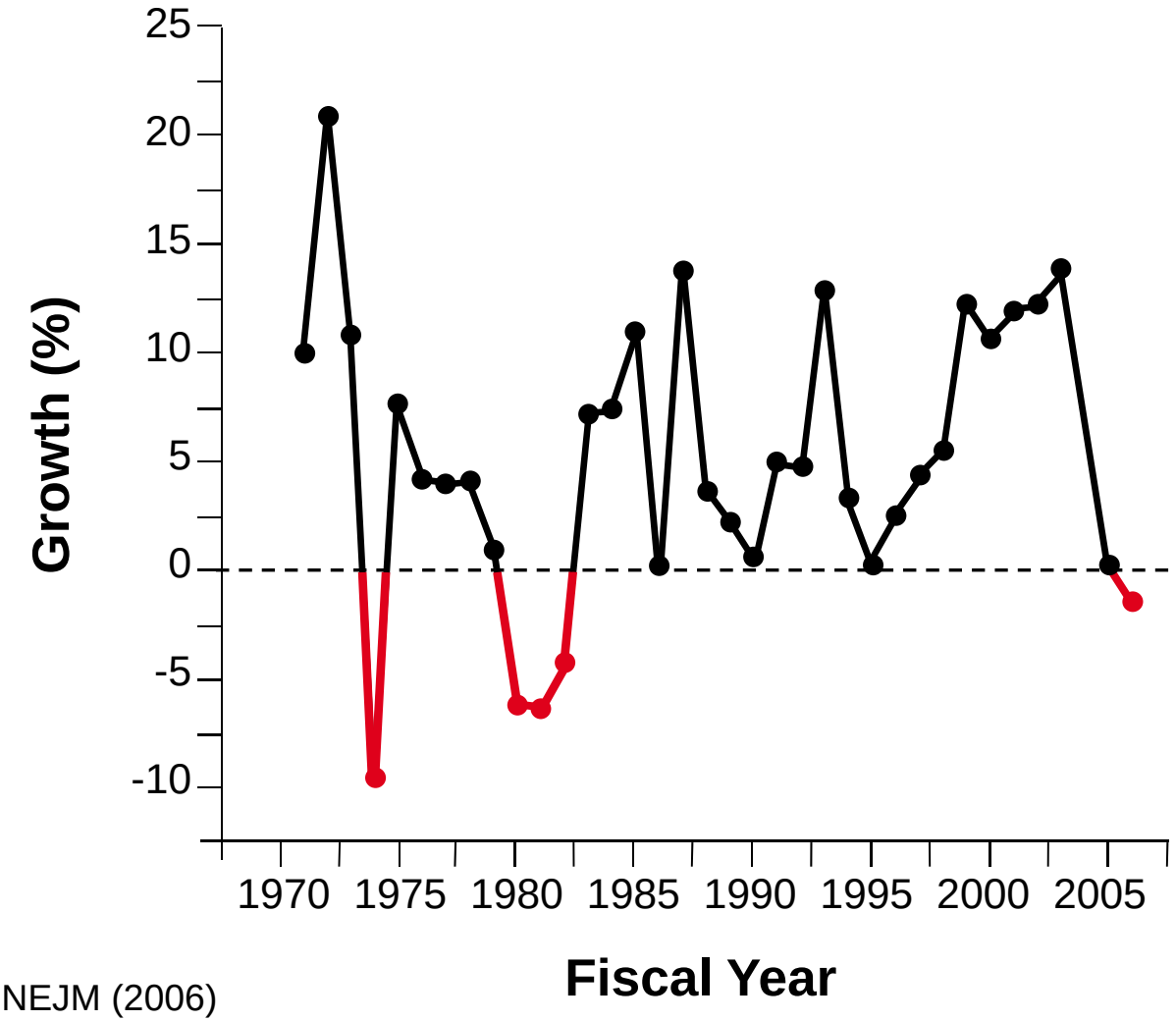
R01 Equivalent includes R01, R29 and R37

Success Rate Based on Applications or Individual Applicants

Applications, Awards & Success Rates: 1998 to 2007 Estimate Competing RPGs



Annualized Growth of the NIH Budget, 1971 to 2005



Source: Loscalzo, NEJM (2006)

Burden of Illness FY 2006 Estimates

Cancer Site	Deaths	Funding, in thousands	New Cases
Lung	162,460 (1)	$264, 806 (3)	174,470 (3)
Colon/Rectum	55,170 (2)	$251,874 (4)	148,610 (4)
Breast	41,430 (3)	$557,252 (1)	214,640 (2)
Pancreas	32,300 (4)	$ 66,671 (11)	33,730 (10)
Prostate	27,350 (5)	$312,043 (2)	234,460 (1)

(Blue numbers are ranks)

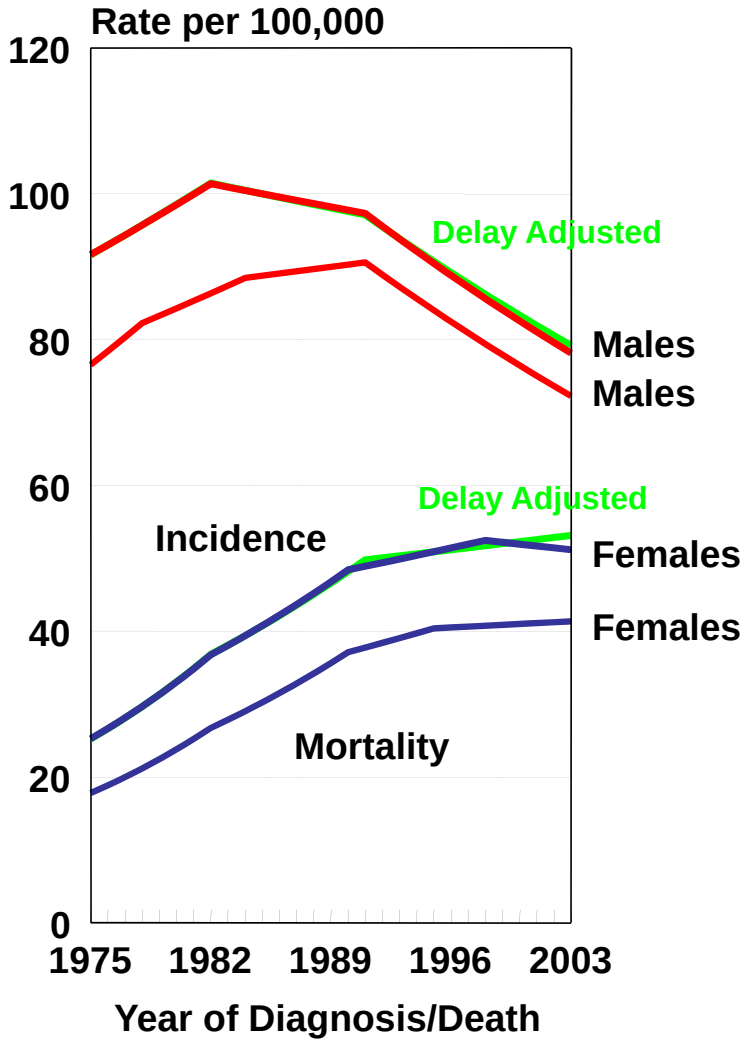
Lung Cancer, 1975-2003

Incidence

- Decline began in 1982 for men
- Long term increase for women appears to be starting to decline

Mortality

- Decline for men since 1991
- Increase for women is slower since 1995



Lung cancer SEER incidence and U.S. death rates, 1975-2003

Members of Lung I2

Margaret Spitz, Ph.D., Chair
M.D. Anderson Cancer Center

Christine Berg, M.D.
Division of Cancer Prevention

Neil Caporaso, M.D.
Division of Cancer Epidemiology and Genetics

Phil Dennis, M.D., Ph.D.
Center for Cancer Research

Scott Leischow, Ph.D
Division of Cancer Control and Population Sciences

Suresh Mohla, Ph.D.
Division of Cancer Biology

Cherie Nichols, M.B.A.
Office of Science Planning & Assessment

Jack Ruckdeschel, M.D.
Karmanos Cancer Institute

Samir Sauma, Ph.D.
Office of Science Planning & Assessment

Scott Saxman, M.D.
Division of Cancer Treatment and Diagnosis

Eva Szabo, M.D.
Division of Cancer Prevention

Peter Ujhazy, M.D., Ph.D.
Organ System Branch, ODDES

Gary Dorfman, M.D.
U. of Mass Med Center; Brown U.
IPA, Cancer Imaging Program

Lung Cancer I2 Team Recommendations

1. **Organizational structure and program leadership $600,000**
   - **an operational focus for lung cancer**
2. **Cancer Intervention & Surveillance Modeling Network (CISNET) $400,000**
3. **Tobacco control $2,900,000**
   - **smoking cessation/prevention**
   - **biology of addiction**
   - **therapy of addiction**
4. **Early detection $1,250,000**
5. **New drug development & response to therapy $3,200,000**
   - **lung cancer biology RFA**
   - **imaging response to therapy**
   - **workshops**

Total: $8,350,000

NCI Lung Cancer Program

- **April 2006: Dr. Niederhuber convened a meeting at AACR to discuss the NCI Lung Cancer Program**
  - **Goals: to organize a structure for the allocation of NCI's resources towards lung cancer research on the basis of the Lung I2 team recommendations**
- **May 2006: Follow-up teleconference to discuss interim progress including:**
  - **Discussions with FDA on joint clinical trial**
  - **Meeting with Division of Cancer Biology**
  - **Trans-NCI lung investigator meeting**

Lung Cancer Initiatives

Lung Cancer I2 Team

Governance

- **Recruit Program Director**
- **CISNET supplements**

Lung Cancer Program

Governance

- **Recruit senior clinician to oversee lung cancer program, coalesce and expand expertise at NCI**
- **CISNET supplements**

Lung Cancer Initiatives

Lung Cancer I2 Team

Governance

- Recruit Program Director
- CISNET supplements

Early detection

- **NLST biorepository, processing, archive and database**

Lung Cancer Program

Governance

- Recruit senior clinician to oversee lung cancer program, coalesce and expand expertise at NCI
- CISNET supplements

Early detection

- **Support NLST biorepository**

Lung Cancer Initiatives

Lung Cancer I2 Team

Drug Development

- **Lung cancer biology RFA**
- **Workshop for drug delivery strategies; anti-angiogenesis**

Lung Cancer Program

Drug Development

- **Lung cancer biology RFA**
- **Biomarkers trial in NSCLC with FDA and CMS**
- **Early phase epigenetic trial**

Lung Cancer Initiatives

Lung Cancer I2 Team

Drug Development

- Lung cancer biology RFA
- Workshop for drug delivery strategies; anti-angiogenesis

Imaging

- **Response to therapy**

Lung Cancer Program

Drug Development

- Lung cancer biology RFA
- Biomarkers trial in NSCLC with FDA and CMS
- Early phase epigenetic trial

Imaging

- **Novel imaging probes to monitor tumor uptake in early phase epigenetic trial**

Lung Cancer Initiatives

Lung Cancer I2 Team

Tobacco Control

- Genetics of nicotine dependency
- Tobacco informatics grid
- Workshops

Lung Cancer Program

Tobacco Control

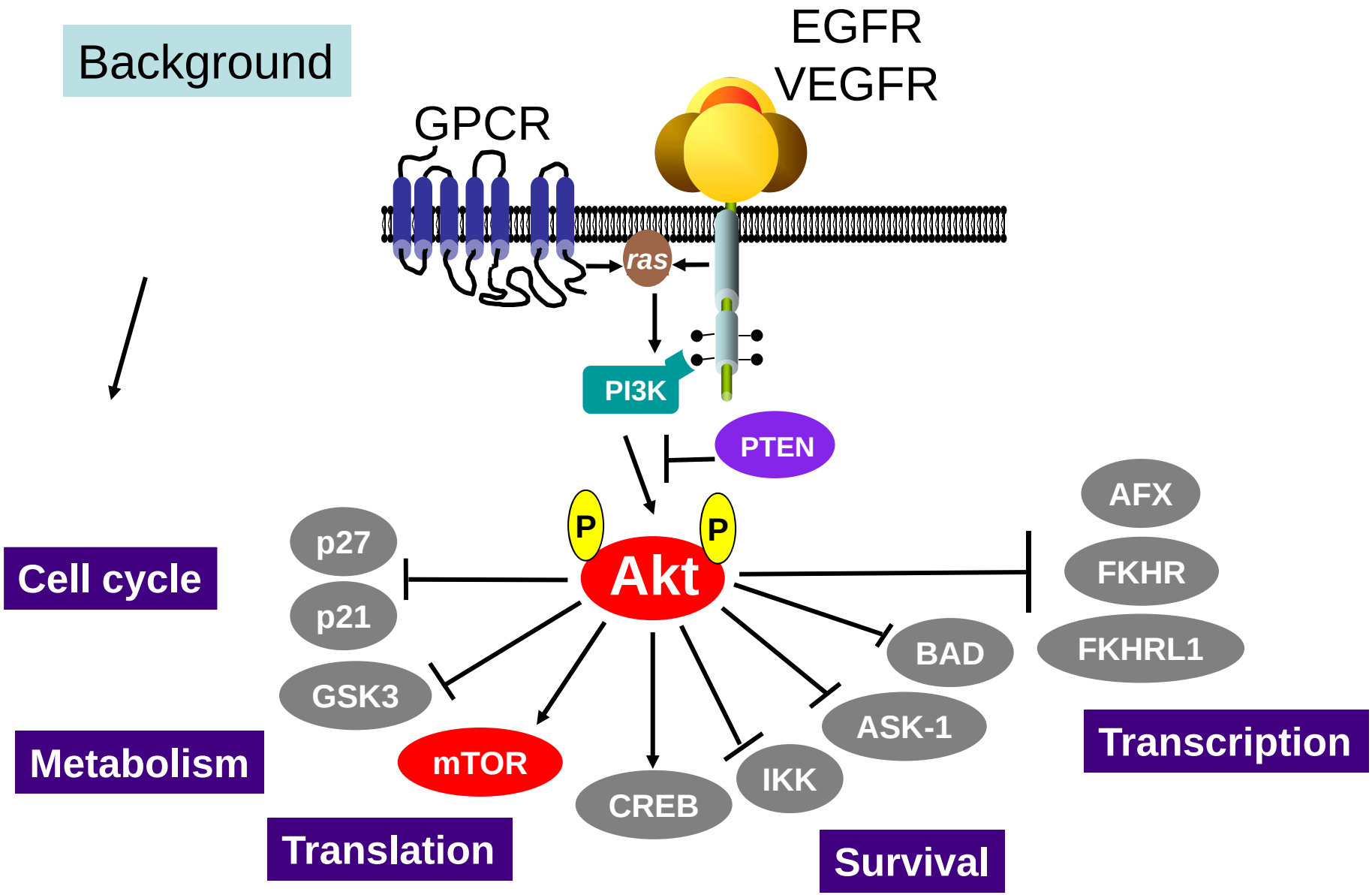
- Leverage outside resources
- 187 funded projects= ~$137M
  - tobacco control
  - mechanisms of nicotine addiction

Genetic Susceptibility to Lung Cancer

- **Strong evidence of linkage under heterogeneity in 6q region**
  - **LOH, CGH studies support this as a lung cancer susceptibility region**
- **Additional suggestive evidence of linkage under heterogeneity in several other regions**
- **Suggests that there are major loci for lung cancer susceptibility**
- **Sequencing ongoing in over 100 candidate loci in 6q23**
- **Fine-mapping planned in the strongest linkage regions**
- **Family data collection is continuing**

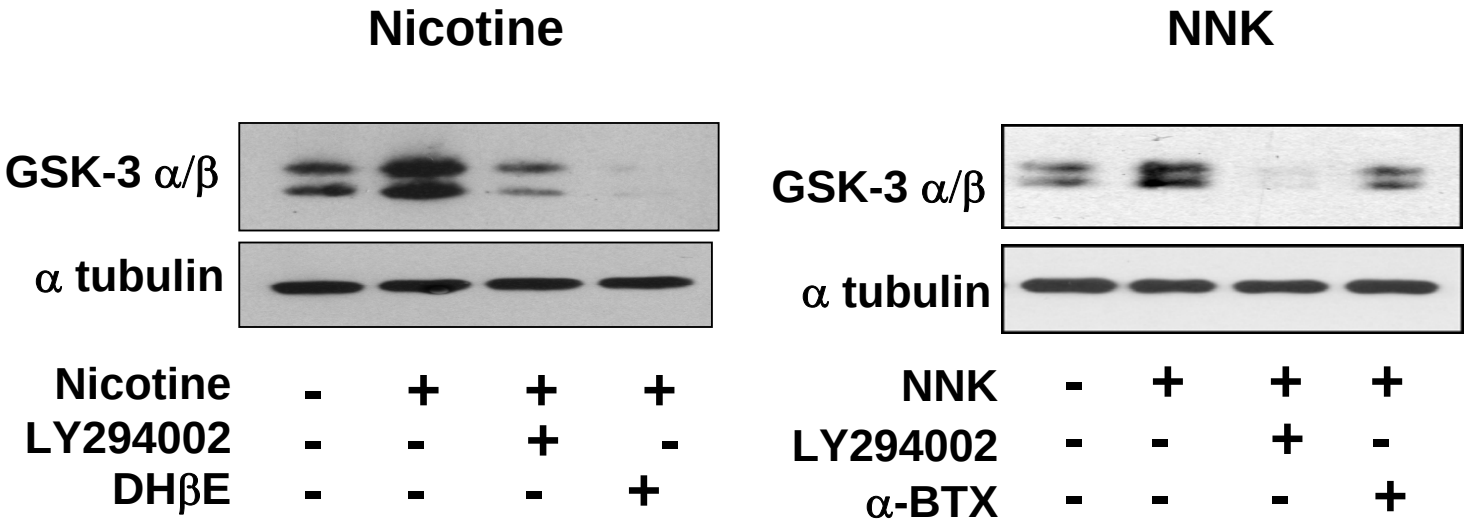
Lung Cancer Drug Development: The Akt/mTOR Pathway

Background



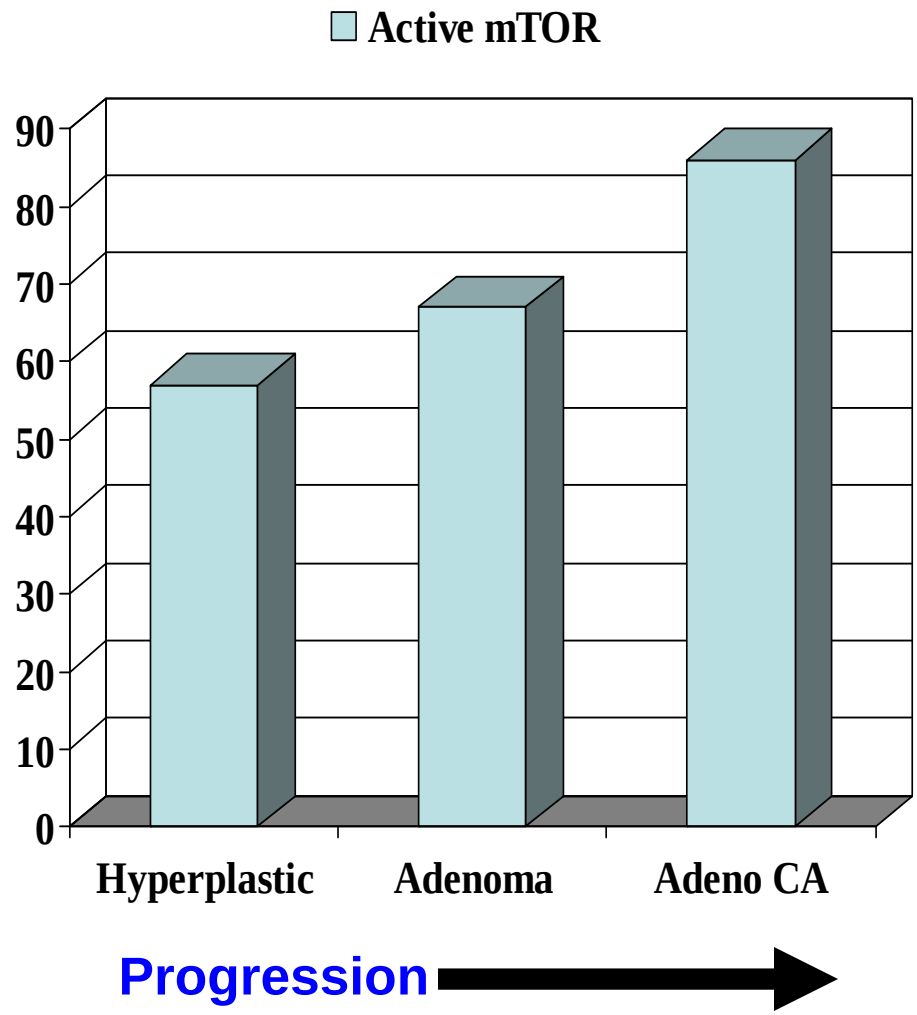
Prevention

Tobacco components activate the pathway in normal human airway cells



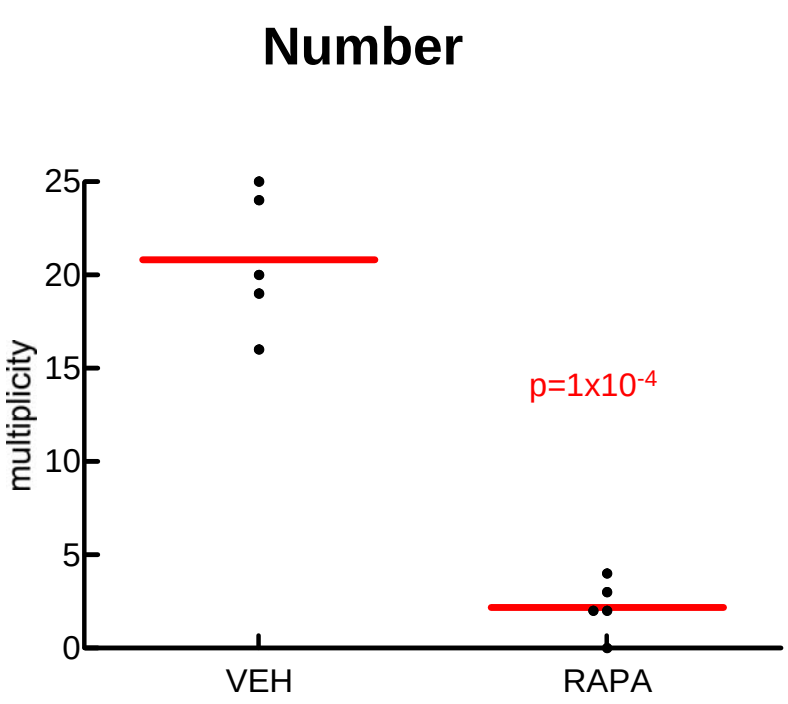
Prevention

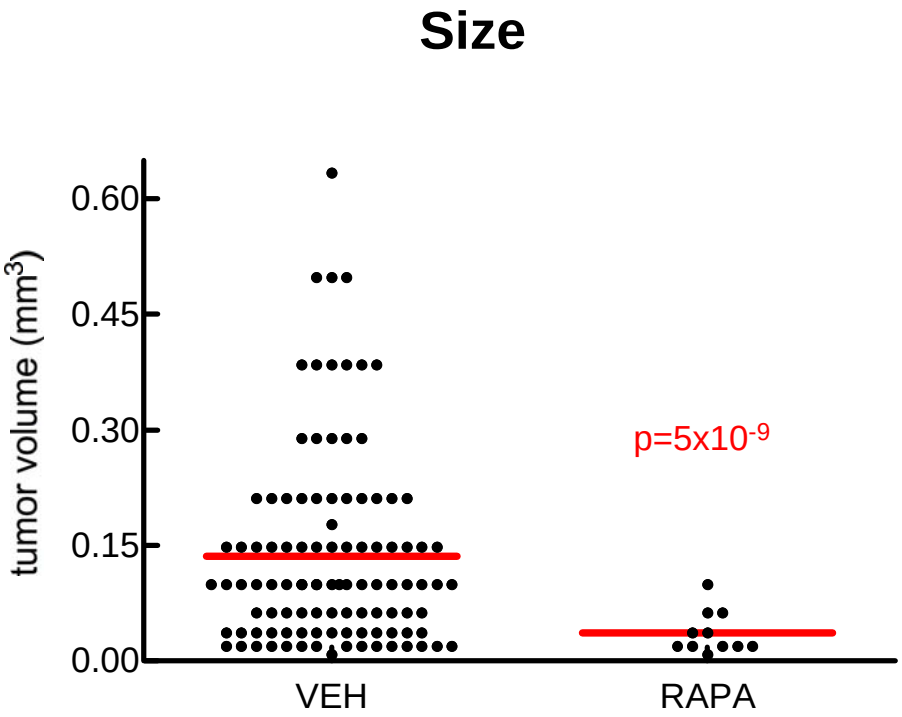
Pathway activation correlates with progression of tobacco carcinogen-induced lung lesions



Prevention

An FDA-approved mTOR inhibitor, rapamycin, decreases number and size of tobacco carcinogen-induced lung lesions





Prevention

Impact:

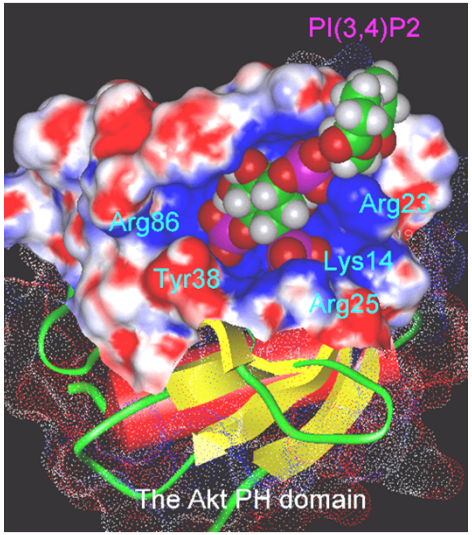
- **Conceptual shift in tobacco-related carcinogenesis**
- **Pathway activation as biomarker in prevention trials**
- **Provides strong rationale to test mTOR inhibitors for lung cancer prevention**

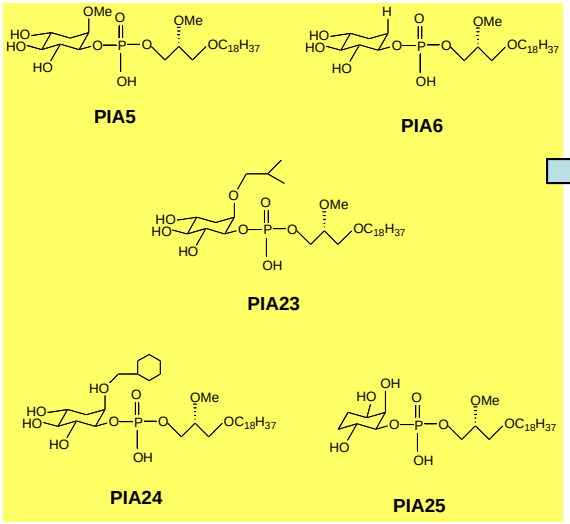
Treatment

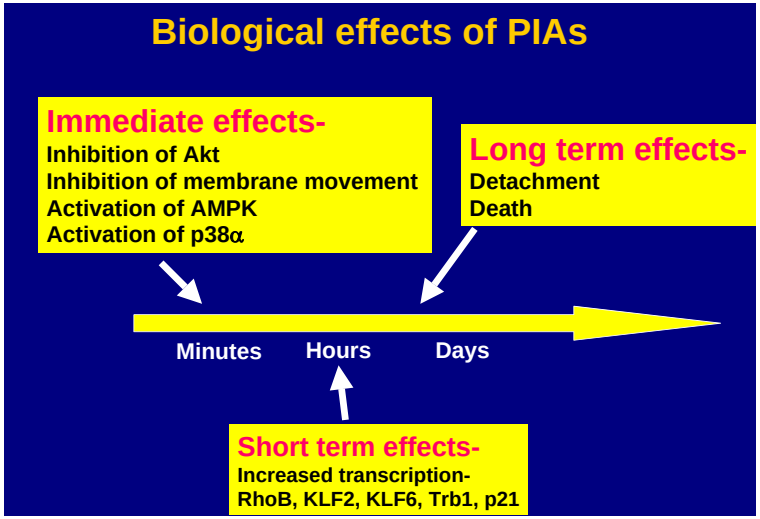
Development of Akt inhibitors

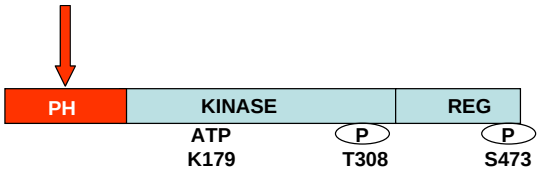
Preclinical

Phosphatidylinositol ether lipid analogues (PIAs)









Clinical

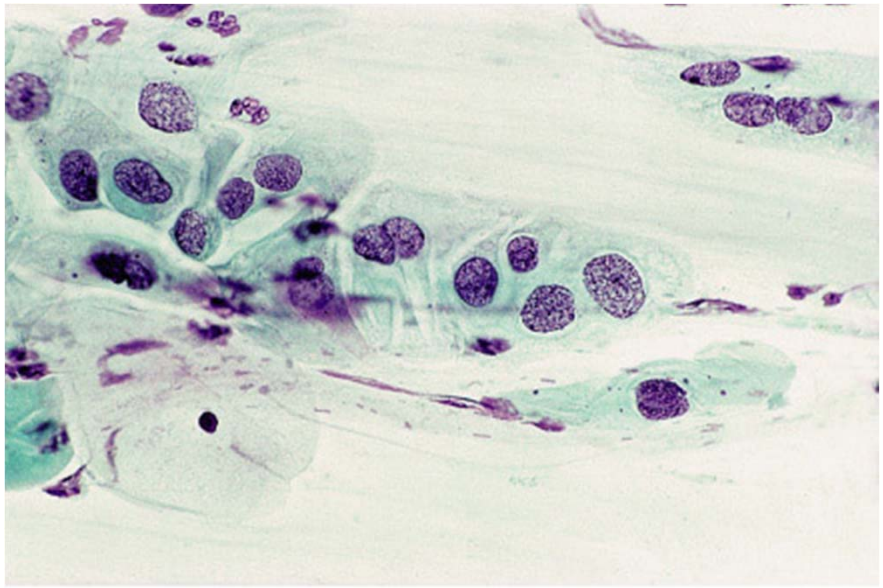
Early phase clinical protocols

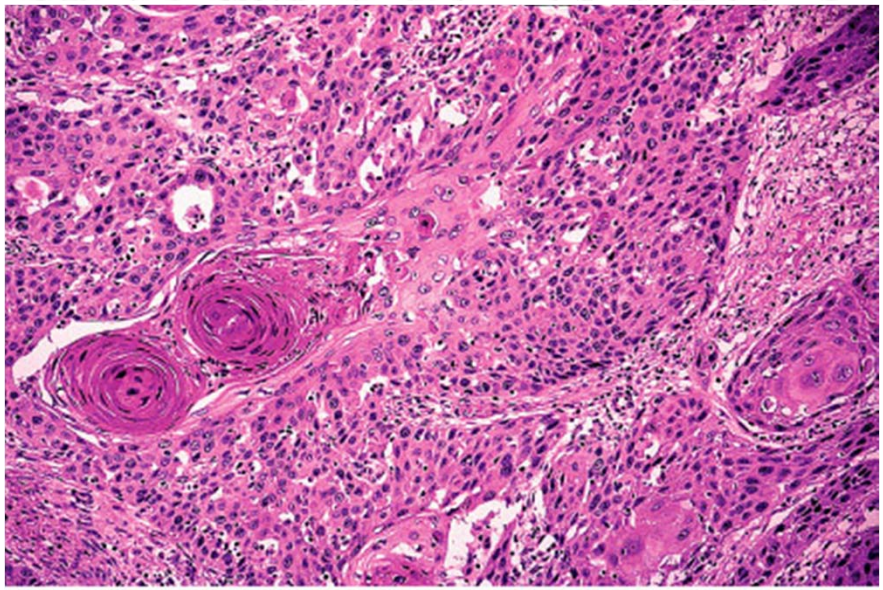
- Phase 0 trials- PIAs
- Phase I, II trials - rapamycin + chemotherapy, “off the shelf” pathway inhibitors

Current Efforts

- **Determine steps in tobacco-mediated activation of Akt**
- **Develop new models of lung cancer that incorporate genetic modifications of the Akt/mTOR pathway**
- **Identify new PH domain-targeted Akt inhibitors using bioinformatics and *in silico* screening**
- **Refine clinical trials in lung cancer to individualize therapies based on expression of specific molecular targets**
- **Develop consortium with Johns Hopkins FAMRI Center of Excellence to expedite drug development for lung cancer patients.**

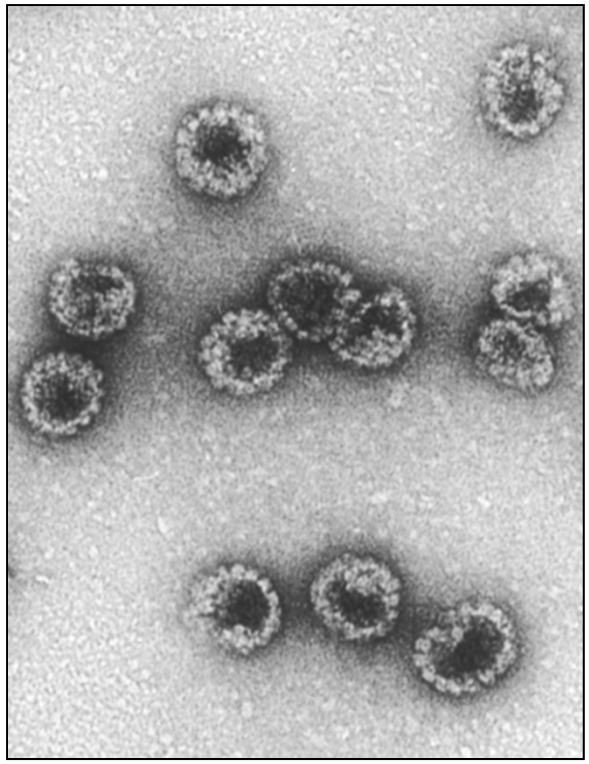
Burden of Cervical Cancer





- **Incidence**
  - **9,710 cases estimated in U.S. in 2006**
  - **470,000 cases per year worldwide**
- **Deaths**
  - **3,700 estimated deaths in U.S. in 2006**
  - **233,000 deaths per year worldwide**

Current Prophylactic Vaccines are Based on Purified Papillomavirus-Like Particles (VLPs)



- **Empty shells composed of only the L1 major virion protein***
- **Induce high titers of virion-neutralizing serum antibodies after IM injection***
- **Non-infectious and non-oncogenic**
- **Vaccination with VLPs of animal PVs induces type-specific protection from experimental infection with high dose virus**
- **Protection passively transferred in serum**
- **No regression of established lesions**
- **No sexual transmission model**

Kirnbauer et al. PNAS 89:12180-4, 1992

HPV VLP Vaccines in Phase III Trials

GlaxoSmithKline: HPV16, HPV18 } 70% of Cervical Ca

ASO4 Adjuvant (MPL + Alum)

Made in insect cells

Merck:

HPV16, HPV18 } 70% of Cervical Ca

HPV6, HPV11 } 90% of Genital Warts

Alum Adjuvant

Made in yeast

IM Injections at 0, 1 or 2, and 6 months

Merck Phase 3 Tetravalent Vaccine: Interim Analysis (Unpublished)

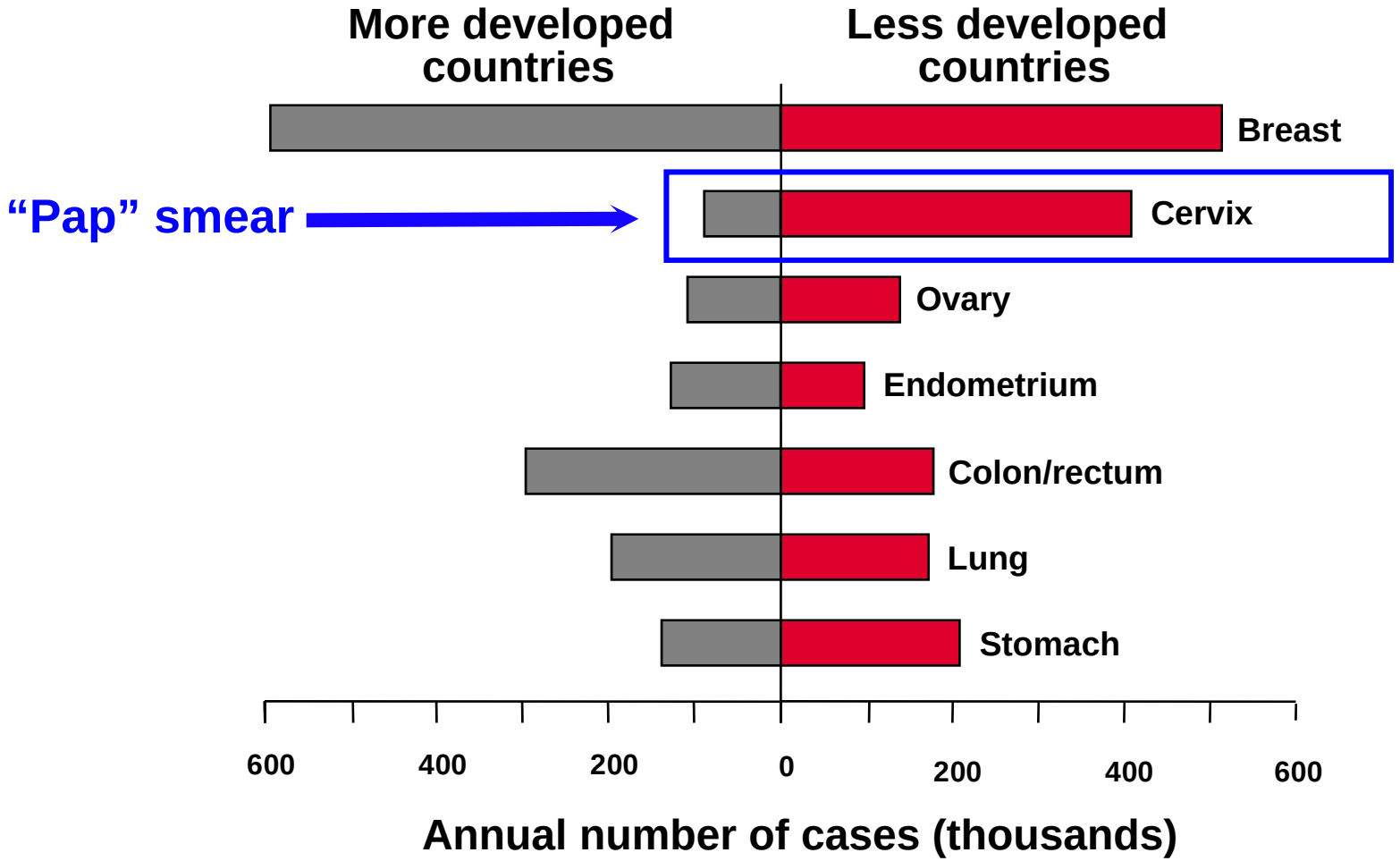
ATP analysis. HPV6,11,16, 18 Associated Disease Only

	Vaccine (N = 2717)		Placebo (N = 2725)				
	n	Cases	n	Cases	Efficacy (%)	CI	P Value
CIN or worse	2240	0	2258	37	100	(87–100)	<0.001
Genital warts, vulvar/vaginal neoplasia	2261	0	2279	40	100	(88–100)	<0.001

ATP = received 3 doses of vaccine; HPV sero(-) at day 1 and HPV DNA(-) from day 1 to month 7; cases counted starting after month 7.

Average Duration of Follow-up: 1.5 Years After the Last Vaccination

Will the HPV Vaccine Reach the Women Who Need it Most?



Adapted from Parkin et al, Eur J Cancer 37:S4, 2001

Vaccine Policy, United States

- **Greatest benefit if given to 10-13 year old girls or older girls/women who have not become sexually active**
- **Make available to poorer women**
- **Vaccinated women must continue to follow standard guidelines for cervical cancer screening**
- **Vaccination before becoming sexually active and screening after becoming sexually active could reduce cervical cancer by more than 90%**

Vaccine Policy, Developing World

- **80% of cervical cancer cases occur in the developing world**
- **Currently lacks high-quality screening programs**
- **Screening is useful for current generation**
- **Vaccination, because it should be given to adolescents, is useful for the next generation**
- **Reduction in cost of vaccine or organized distribution program will be needed**

Summary of HPV VLP Vaccine Efficacy Data in Women

- **Vaccine well tolerated; no vaccine-related SAEs**
- **>99% seroconversion**
- **95-100% protection from persistent infection by the types in the vaccine**
- **100% protection from cervical pre-cancer by the types in the vaccine (up to 4 yrs post vaccination)**
- **100% protection against external genital warts**
- **Limited or no protection against types not in the vaccine**
- **No evidence for inducing regression of preexisting lesions**

In Memoriam: Dr. Anita Roberts

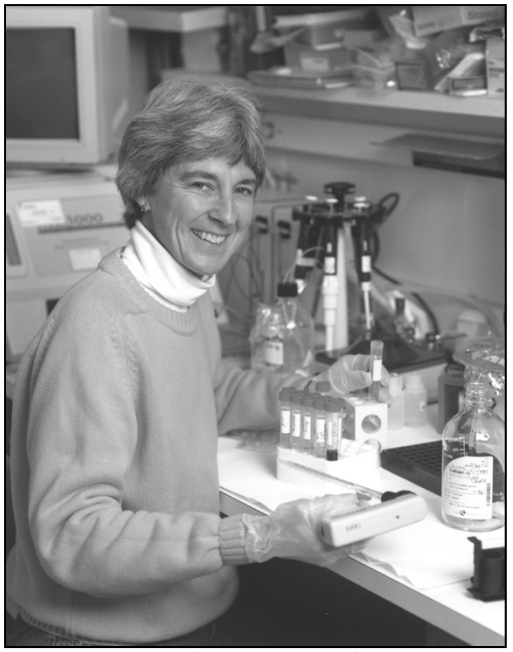
“I’m quickly approaching the end of my journey… I’ve been rapidly losing ground to this disease and I’ve now come home to end my life’s journey in peace.”

Excerpted from the final entry of Anita Roberts’ online journal, Wednesday, May 10, 2006

May 26, 2006

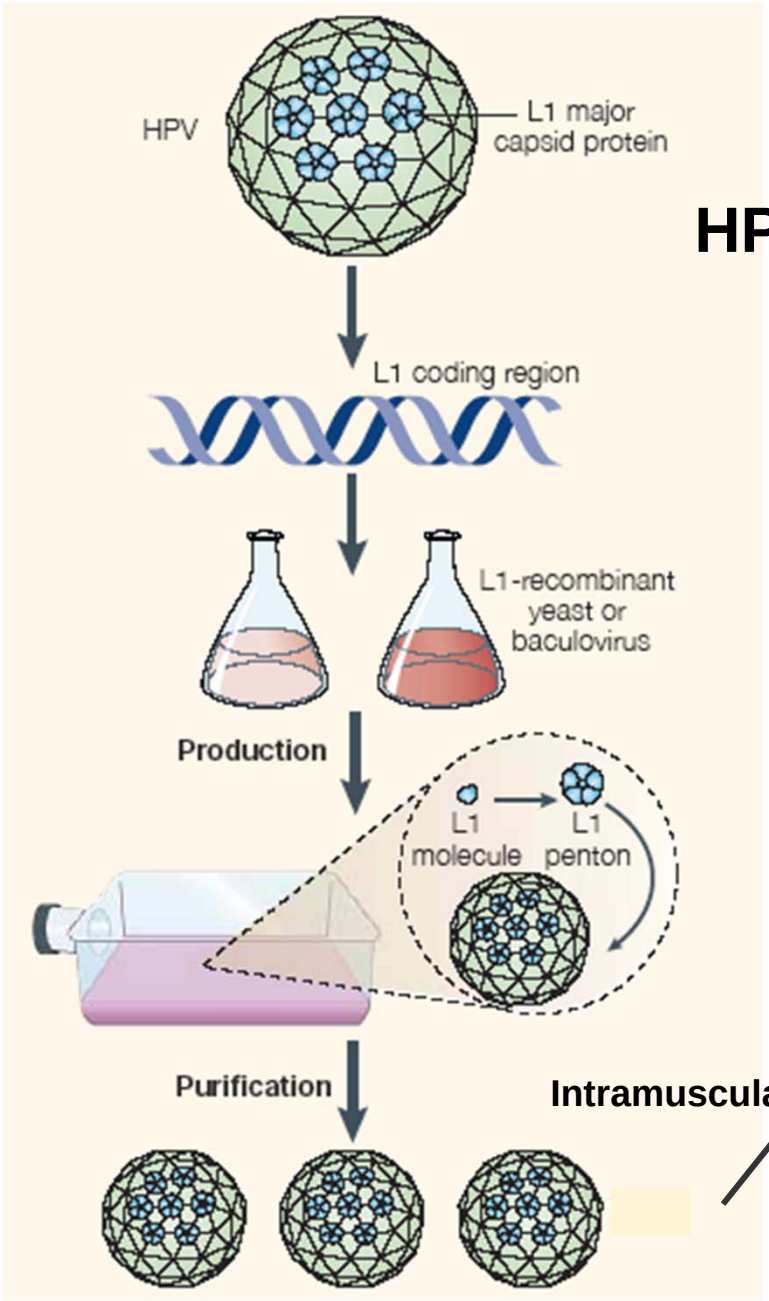
A Lifetime of Accomplishments

- Ph.D. from University of Wisconsin
- Postdoctoral Research at Harvard
- Chief, Laboratory of Cell Regulation and Carcinogenesis in CCR
- Second-most-cited female scientist in the world
- In collaboration with Michael Sporn conducted seminal research into the role of TGFß
- FASEB Award for Excellence in Science
- Susan G. Komen Foundation's Brinker Award for Scientific Distinction

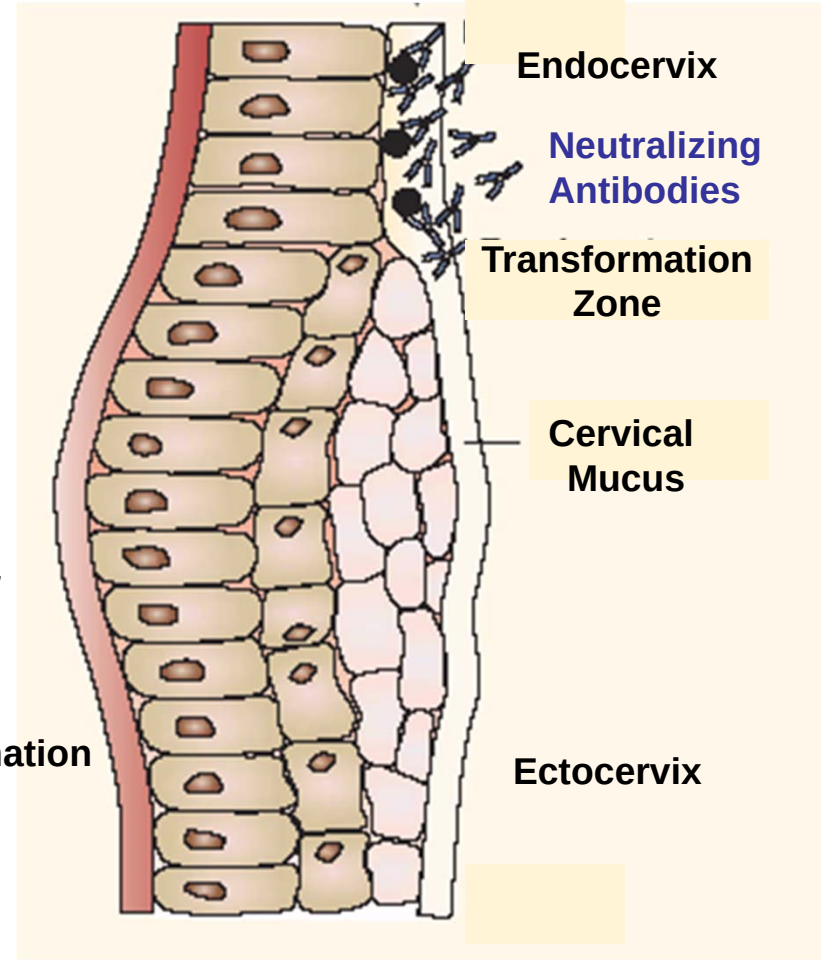



Patients & Families

HPV Virus-Like Particle Vaccine



Intramuscular Vaccination



HPV and Cervical Cancer

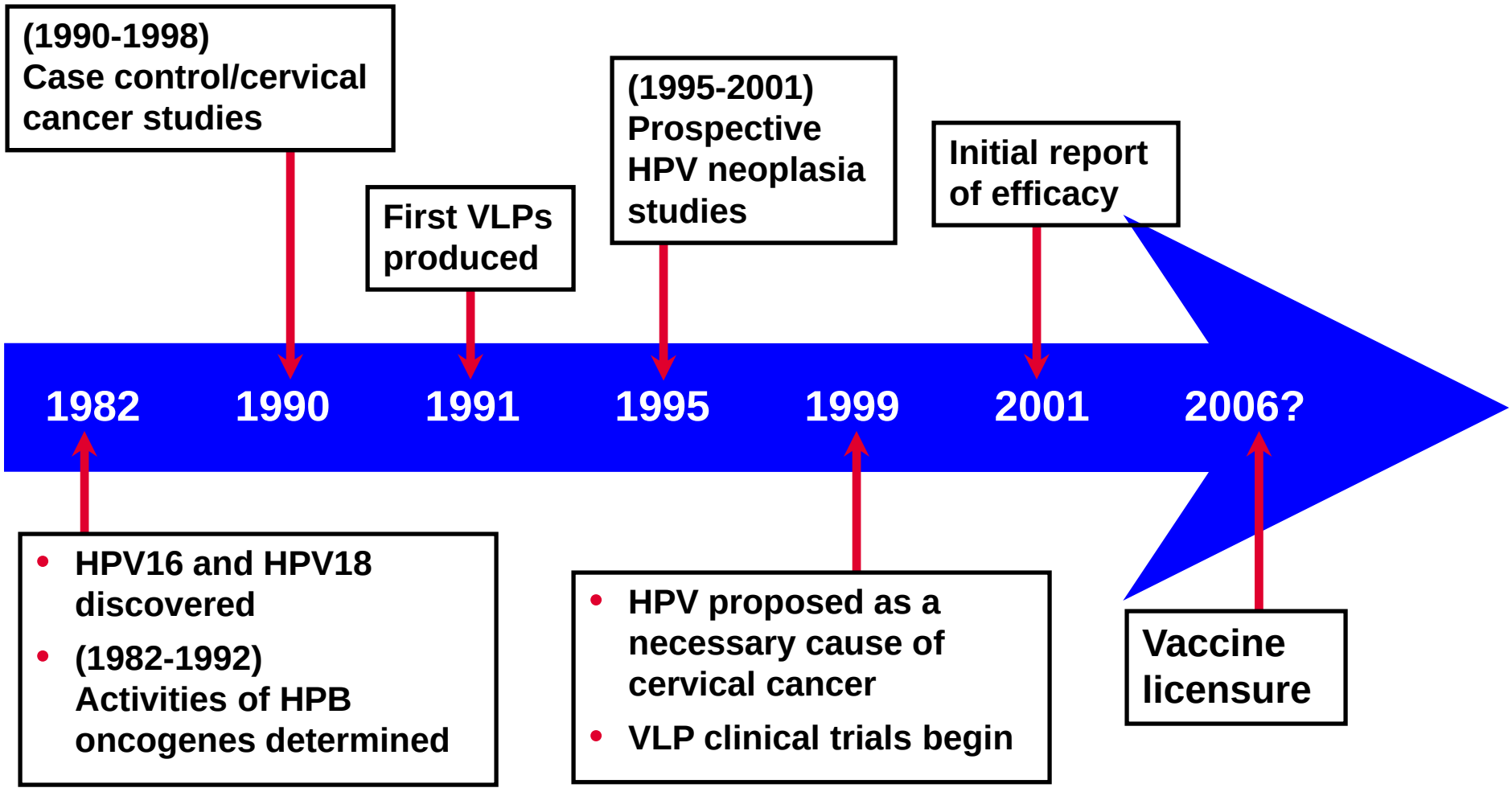
- 92.9% of 932 cases of invasive cervical cancer worldwide tested positive for HPV DNA in 1995 IARC study

HPV Type	Infections	Percent
HPV 16	465	49.9
HPV 18	128	13.7
HPV 45	78	8.4
HPV 31	49	5.3
HPV 33	26	2.8
Other HPV	156	16.7
HPV neg	66	7.1

- Of the 66 HPV neg cases, the 34 histologically adequate samples were later reanalyzed with more sensitive techniques. Only 2 were in fact HPV negative.
- Combined results yield 99.7% of ICC cases were HPV positive

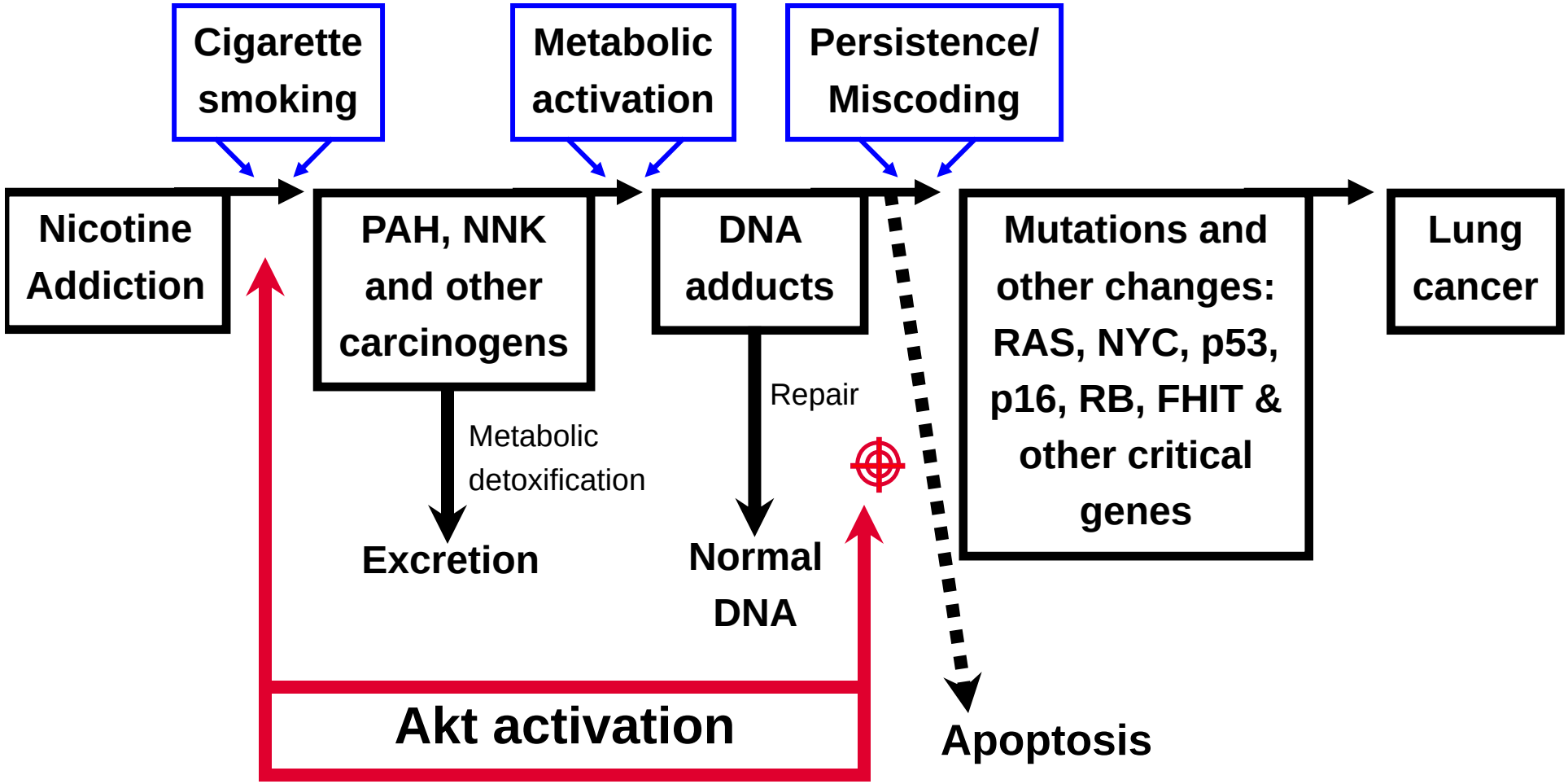
Walboomers et al Journal of Pathology 189: 12 – 19 1999

Timeline: HPV Vaccine Development



HPV: human papillomavirus; VLP: virus-like particle

Prevention



A biochemical gatekeeper for tobacco-related cancers?

Early Detection: Evidence for Genetic Risk in Lung Cancer

- **The majority of lung cancer cases are attributable to cigarette smoking and other behavioral and environmental risk factors.**
- **Several lines of evidence show that genes play a role in lung cancer, and that individuals may differ in their susceptibility to the pertinent environmental insults.**
- **Are there genes that have LARGE effects on risk of lung cancer similar to BRCA1, BRCA2, etc.?**

New Investigators

- All applicants at Assistant Professor rank will not have their applications triaged
  - Full detailed review with written critiques
  - Value of critique for A1, A2 resubmissions
- New grant application section designed to assure institution review and support
  - Faculty oversight committee for monitoring progress of the Assistant Professor
  - Written section will summarize work of the committee
- NCI's workshop for first-time grantees
- Metrics should be established to evaluate the value of the change

This is what I hear from the extramural community!

- **“Too much emphasis on translational science away from basic science!”**
- **“NCI is funding too many big projects and initiatives.”**
- **“RFAs, PAs are taking money away from unsolicited grant applications.”**
- **“It’s the Roadmap!”**

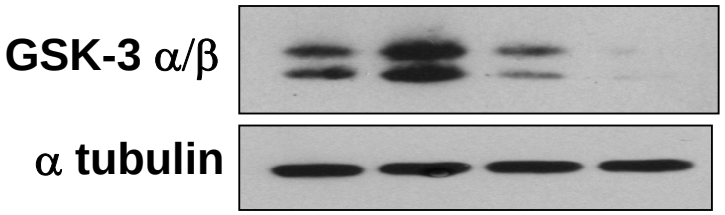
CGEMS: Cancer Genetic Markers of Susceptibility

- **Capitalizing on advances in human genetic research**
- **Three-year, $14M initiative**
- **Identify genetic alteration of susceptibility to prostate and breast cancer**
- **Using DNA from five large studies for each cancer**
- **“Scan” genome for variations between patients and control subjects**

Prevention

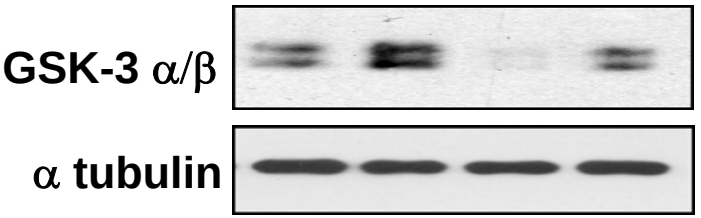
Tobacco components activate the pathway in normal human airway cells

Nicotine



Nicotine	-	+	+	+
LY294002	-	-	+	-
DHβE	-	-	-	+

NNK



NNK	-	+	+	+
LY294002	-	-	+	-
α-BTX	-	-	-	+

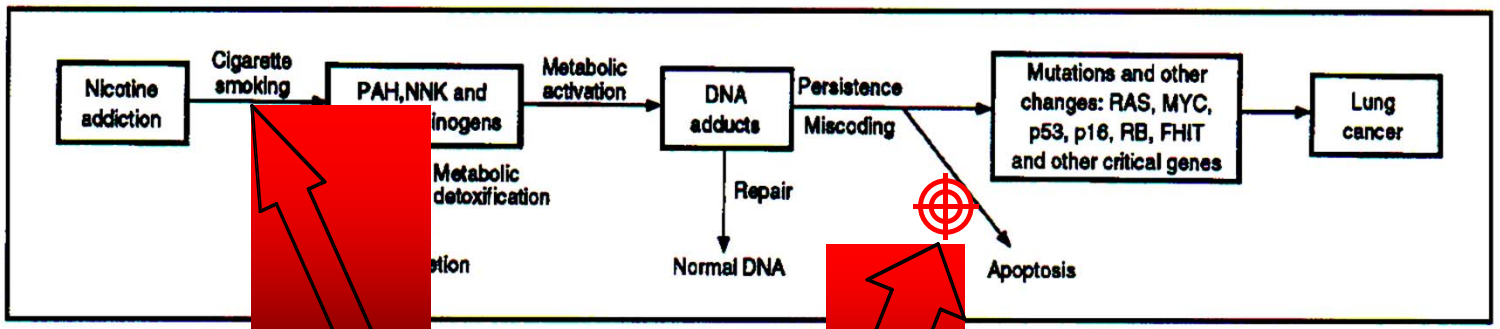
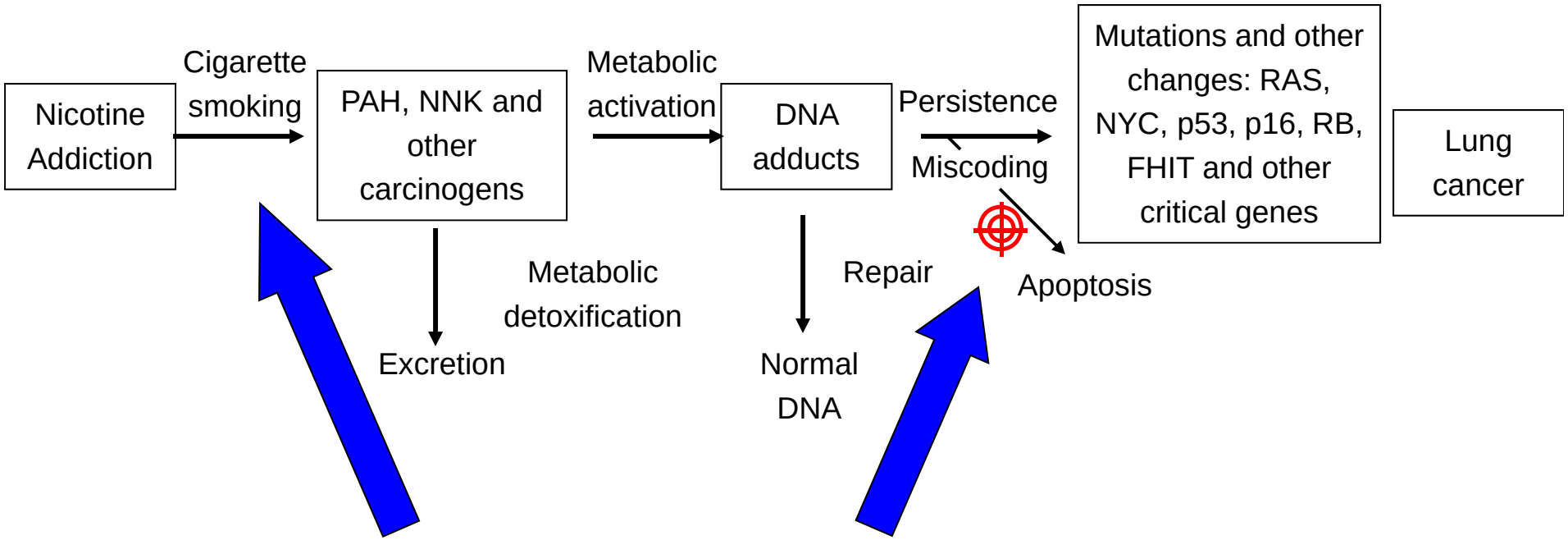


Fig. 1. Scheme linking ni l lung cancer via tobacco smoke carcinoge duction of multiple mutations in critical genes. PAH = polycyclic aromatic hydroc (methylnitrosamino)-1-(3-pyridyl)-1-butanc

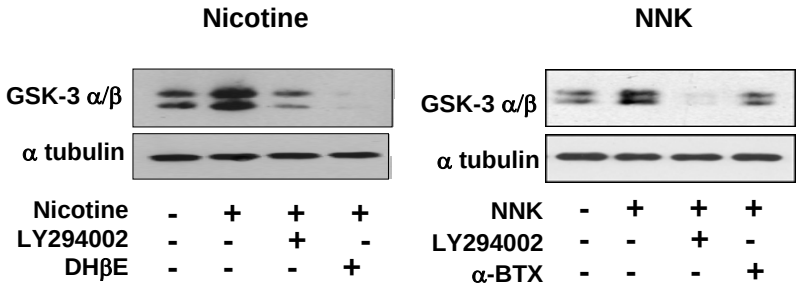
Prevention



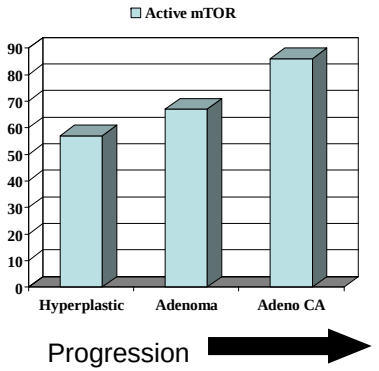
A biochemical gatekeeper for tobacco-related cancers?

Prevention

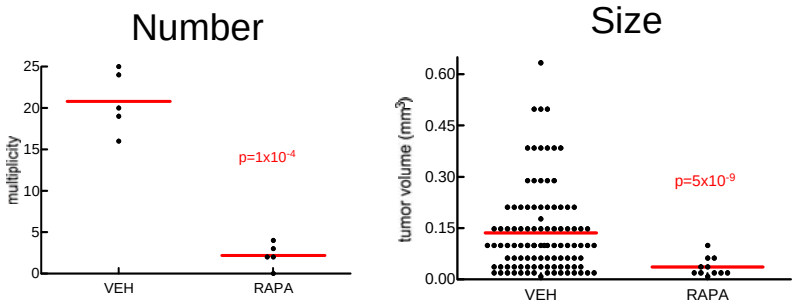
1. Tobacco components activate the pathway in normal human airway cells



2. Pathway activation correlates with progression of tobacco carcinogen-induced lung lesions



3. An FDA-approved mTOR inhibitor, rapamycin, decreases number and size of tobacco carcinogen-induced lung lesions



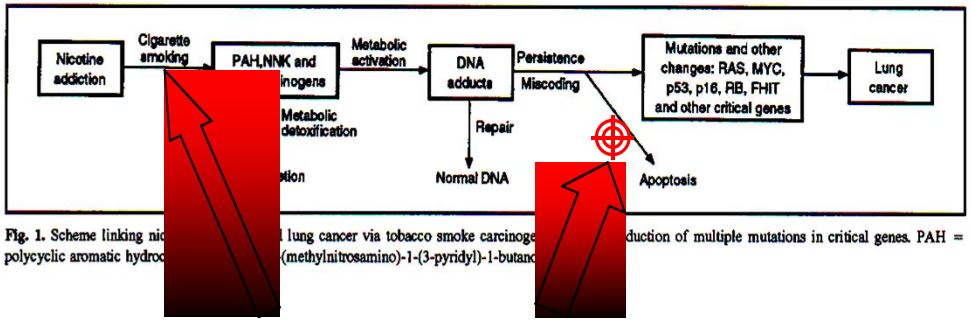


Fig. 1. Scheme linking nic ... lung cancer via tobacco smoke carcinoge ... duction of multiple mutations in critical genes. PAH = polycyclic aromatic hydroc ... (methylnitrosamino)-1-(3-pyridyl)-1-butanc

Akt activation

A biochemical gatekeeper for tobacco-related cancers

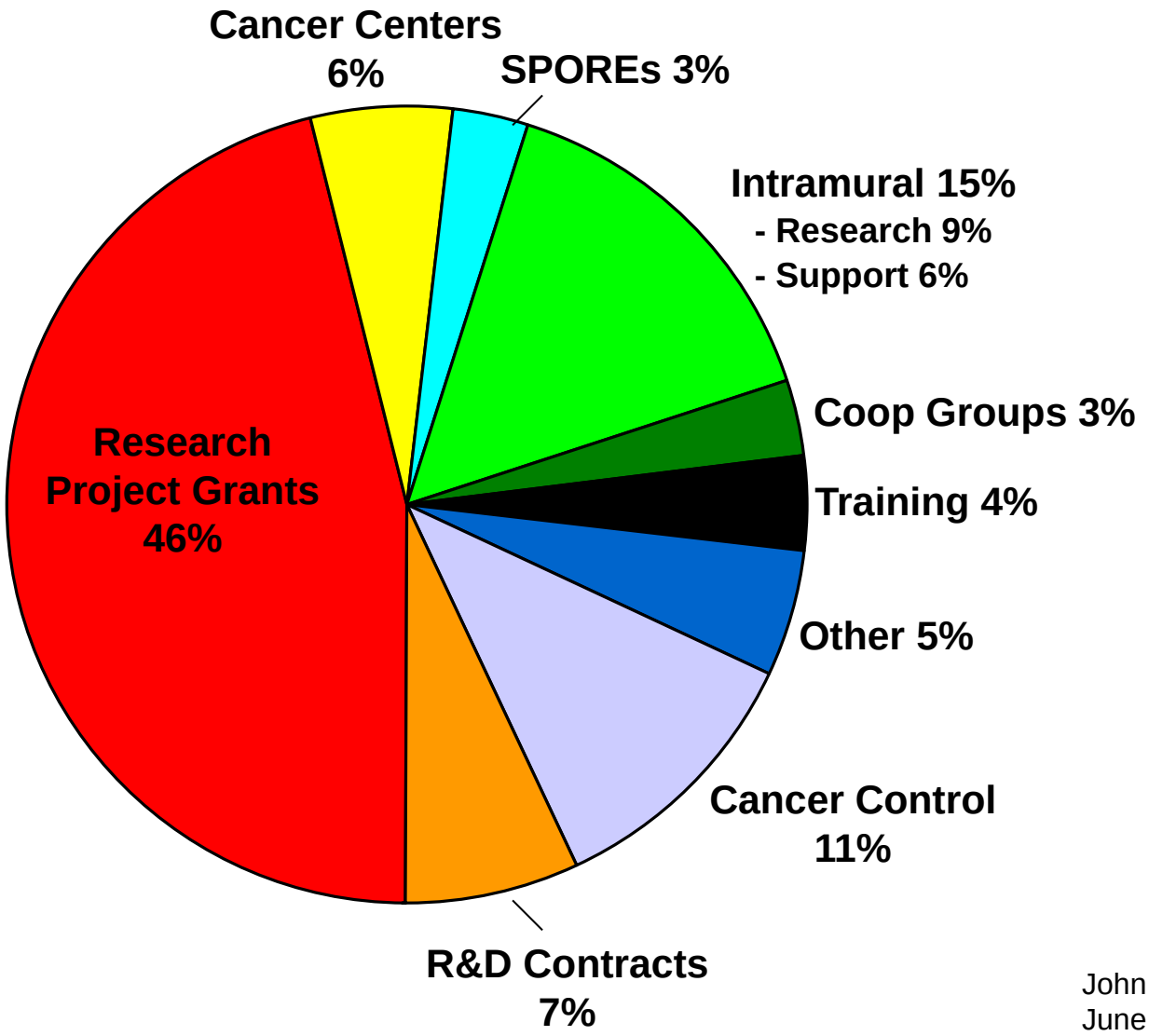
<u>Impact</u>

*Conceptual shift in tobacco-related carcinogenesis

*Pathway activation as biomarker in prevention trials

*Provides strong rationale to test mTOR inhibitors for lung cancer prevention

NCI's Allocation of 2007 Request
$4.8 Billion



John E. Niederhuber, MD
June 2006

Appropriations Hearings

- **Accompanied Dr. Zerhouni to House Hearings April 6**
- **Senate Hearings May 19, provided supplemental testimony:**
  - **Funding needed to carry The Cancer Genome Atlas forward**
  - **Funding needed to win the war on cancer overall**

Overall NCI Budget

	FY 2006 Appropriation	FY 2007 PB	Change
Total Res. Grants	$2,947,764	$2,894,978	-1.8%
NRSA	66,619	66,279	-0.5%
R&D Contracts	326,560	330,441	1.2%
Intramural Research	699,763	696,263	-0.5%
Rsch. Mgt. & Support	182,246	183,246	0.5%
Cancer Prev. & Control	519,650	517,100	-0.5%
Repair & Improvement	7,920	7,920	0.0%
Total, NCI	4,750,522	4,696,227	-1.1%
NIH Roadmap	42,834	57,382	34.0%
Total NCI w/ Roadmap	4,793,356	4,753,609	-0.8%

(dollars in thousands)

STAR Trial: Study of Tamoxifen and Raloxifene

- **Comparison of reduced risk of breast cancer in postmenopausal women at increase risk**
- **STAR enrolled 19,747 women**
- **Results show raloxifene as effective as tamoxifen in reducing risk; ~ 50%**
- **Raloxifene had fewer serious side effects, including fewer uterine cancers, blood clots and cataracts**

New Investigators

- **All applicants at Assistant Professor rank will not have their applications triaged**
  - **Full detailed review with written critiques**
  - **Value of critique for A1, A2 resubmissions**
- **New grant application section designed to assure institution review and support**
  - **Faculty oversight committee for monitoring progress of the Assistant Professor**
  - **Written section will summarize work of the committee**
- **Metrics should be established to evaluate the value of the change**

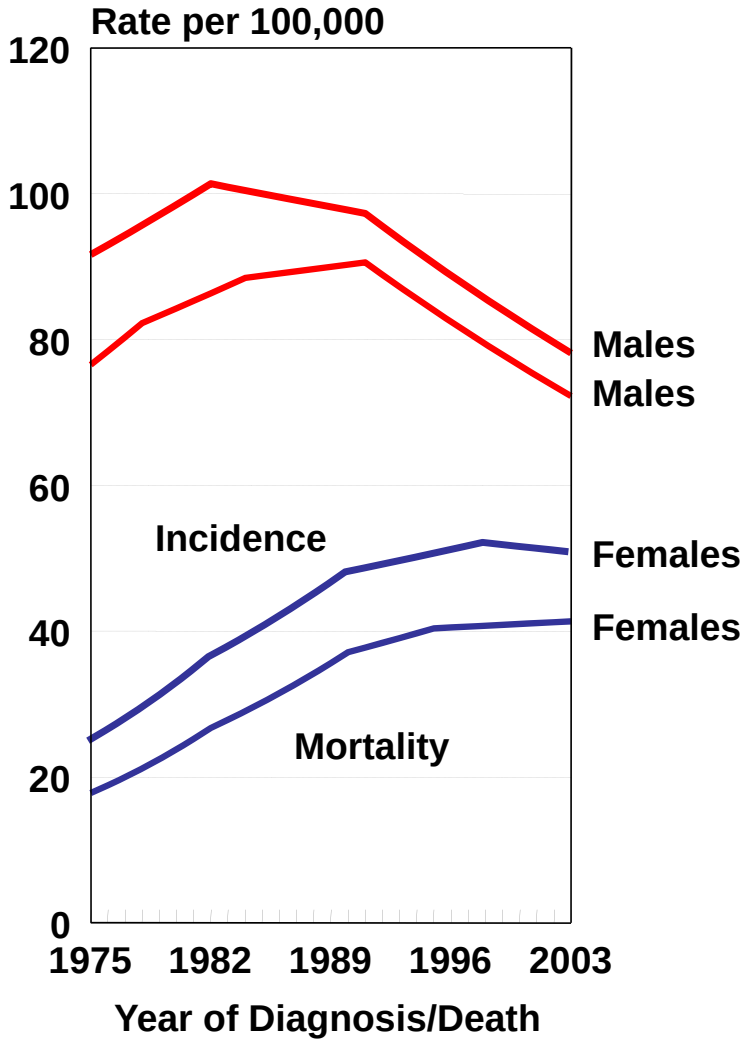
Lung Cancer, 1975-2003

Incidence

- Decline began in 1982 for men
- Long term increase for women appears to be starting to decline

Mortality

- Decline for men since 1991
- Increase for women is slower since 1995



Lung cancer SEER incidence and U.S. death rates, 1975-2003