Director’s Update

Dr. John E. Niederhuber
Acting Director

National Cancer Advisory Board
June 14, 2006
NCAB – Director’s Update

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

- 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 Hou, Ph.D.
Mouse Cancer Genetics Program

Steven Libutti, M.D.
Surgery Branch

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

<table>
<thead>
<tr>
<th>FY 2006 Appropriation</th>
<th>$4,793,356</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY 2007 President’s Budget</td>
<td>$4,753,609</td>
</tr>
<tr>
<td>Difference ’06 to ’07</td>
<td>-$39,747</td>
</tr>
<tr>
<td>Percent Change ’06 to’07</td>
<td>-0.8%</td>
</tr>
</tbody>
</table>

(dollars in thousands)
NCI’s Congressional Appropriations, FY 1998 to FY 2007

Dollars in Billions

NIH DOUBLING - NCI 80%

FY1998 $2.5
FY1999 $2.9
FY2000 $3.3
FY2001 $3.8
FY2002 $4.2
FY2003 $4.6
FY2004 $4.8
FY2005 $4.9
FY2006 $4.8
FY2007 $4.8

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

Percentage of Grants

Fiscal Year

Unsolicited

Solicited

John E. Niederhuber, MD
June 2006
Nearly as Many Competing Applicants in the Last 2 Years as During the NIH Doubling

<table>
<thead>
<tr>
<th>Year</th>
<th>FY 1999</th>
<th>FY 2003</th>
<th>FY 2003</th>
<th>FY 2005</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3,289</td>
<td>4,251</td>
<td>4,251</td>
<td>5,050</td>
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</table>

Period of NIH doubling
NCI 80% increase

Last 2 Years

John E. Niederhuber, MD
June 2006
Nearly as Many Competing Applications in the Last 2 Years as During the NIH Doubling

<table>
<thead>
<tr>
<th>Period</th>
<th>FY 1999</th>
<th>FY 2003</th>
<th>FY 2003</th>
<th>FY 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI 80% increase</td>
<td>3,878</td>
<td>5,249</td>
<td>5,249</td>
<td>6,325</td>
</tr>
<tr>
<td>Last 2 Years</td>
<td>1,371</td>
<td></td>
<td>1,076</td>
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</table>

Period of NIH doubling

John E. Niederhuber, MD
June 2006
## RPG Competing Applications and Applicants FY 1995 to 2005

<table>
<thead>
<tr>
<th>FY</th>
<th>All RPG Reviewed</th>
<th>All RPG Awarded</th>
<th>% Funded</th>
<th>R01 Equivalent Reviewed</th>
<th>R01 Equivalent Awarded</th>
<th>% Funded</th>
<th>All RPG Success Rate</th>
<th>R01 Equivalent Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>3,095</td>
<td>838</td>
<td>27.1%</td>
<td>2,773</td>
<td>665</td>
<td>24.0%</td>
<td>3,671</td>
<td>685</td>
</tr>
<tr>
<td>1996</td>
<td>2,888</td>
<td>916</td>
<td>31.7%</td>
<td>2,569</td>
<td>782</td>
<td>30.4%</td>
<td>3,380</td>
<td>976</td>
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<tr>
<td>1997</td>
<td>2,970</td>
<td>951</td>
<td>32.0%</td>
<td>2,645</td>
<td>802</td>
<td>30.3%</td>
<td>3,520</td>
<td>993</td>
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<tr>
<td>1998</td>
<td>2,773</td>
<td>983</td>
<td>35.4%</td>
<td>2,436</td>
<td>793</td>
<td>32.6%</td>
<td>3,195</td>
<td>1,047</td>
</tr>
<tr>
<td>1999</td>
<td>3,289</td>
<td>1,165</td>
<td>35.4%</td>
<td>2,722</td>
<td>888</td>
<td>32.6%</td>
<td>3,878</td>
<td>1,244</td>
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<tr>
<td>2000</td>
<td>3,635</td>
<td>1,086</td>
<td>29.9%</td>
<td>2,724</td>
<td>816</td>
<td>30.0%</td>
<td>4,382</td>
<td>1,151</td>
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<tr>
<td>2001</td>
<td>3,666</td>
<td>1,126</td>
<td>30.7%</td>
<td>2,836</td>
<td>827</td>
<td>29.2%</td>
<td>4,374</td>
<td>1,188</td>
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<tr>
<td>2002</td>
<td>3,794</td>
<td>1,181</td>
<td>31.1%</td>
<td>2,844</td>
<td>828</td>
<td>29.1%</td>
<td>4,588</td>
<td>1,264</td>
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<tr>
<td>2003</td>
<td>4,251</td>
<td>1,326</td>
<td>31.2%</td>
<td>3,172</td>
<td>943</td>
<td>29.7%</td>
<td>5,249</td>
<td>1,421</td>
</tr>
<tr>
<td>2004</td>
<td>4,870</td>
<td>1,393</td>
<td>28.6%</td>
<td>3,325</td>
<td>946</td>
<td>28.5%</td>
<td>6,148</td>
<td>1,487</td>
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<tr>
<td>2005</td>
<td>5,050</td>
<td>1,226</td>
<td>24.3%</td>
<td>3,480</td>
<td>812</td>
<td>23.3%</td>
<td>6,325</td>
<td>1,292</td>
</tr>
</tbody>
</table>

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

Fiscal Year

Growth (%)

Source: Loscalzo, NEJM (2006)
## Burden of Illness FY 2006 Estimates

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

(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

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
<table>
<thead>
<tr>
<th>Lung Cancer Initiatives</th>
<th>Lung Cancer I2 Team</th>
<th>Lung Cancer Program</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Governance</strong></td>
<td>• Recruit Program Director</td>
<td>• Recruit senior clinician to oversee lung cancer program, coalesce and expand expertise at NCI</td>
</tr>
<tr>
<td></td>
<td>• CISNET supplements</td>
<td>• CISNET supplements</td>
</tr>
<tr>
<td><strong>Early detection</strong></td>
<td>• NLST biorepository, processing, archive and database</td>
<td>• Support NLST biorepository</td>
</tr>
</tbody>
</table>
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

EGFR
VEGFR

GPCR

ras

PI3K

PTEN

Akt

P

Cell cycle

p27
p21
GSK3

mTOR

CREB
IKK

Translation

mTOR

Survival

p27
p21
GSK3

FKHR
FKHRL1

Transcription

AFX

Metabolism
**Prevention**

*Tobacco components activate the pathway in normal human airway cells*

<table>
<thead>
<tr>
<th></th>
<th>Nicotine</th>
<th>NNK</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK-3 α/β</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>α tubulin</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Nicotine</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>LY294002</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>DHβE</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>NNK</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>LY294002</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>α-BTX</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

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

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

Active mTOR

Progression

Hyperplastic  Adenoma  Adeno CA
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
Development of Akt inhibitors

Preclinical
Phosphatidylinositol ether lipid analogues (PIAs)

Biological effects of PIAs
- **Immediate effects-**
  - Inhibition of Akt
  - Inhibition of membrane movement
  - Activation of AMPK
  - Activation of p38α

- **Short term effects-**
  - Increased transcription-
    - RhoB, KLF2, KLF6, Trb1, p21

- **Long term effects-**
  - Detachment
  - Death

Treatment

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
  \[ \text{70\% of Cervical Ca} \]
- ASO4 Adjuvant (MPL + Alum)
- Made in insect cells

**Merck:**
- HPV16
- HPV18
  \[ \text{70\% of Cervical Ca} \]
- HPV6
- HPV11
  \[ \text{90\% of Genital Warts} \]
- 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

<table>
<thead>
<tr>
<th></th>
<th>Vaccine (N = 2717)</th>
<th>Placebo (N = 2725)</th>
<th>Efficacy (%)</th>
<th>CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN or worse</td>
<td>n 2240, Cases 0</td>
<td>n 2258, Cases 37</td>
<td>100</td>
<td>(87–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genital warts, vulvar/vaginal neoplasia</td>
<td>n 2261, Cases 0</td>
<td>n 2279, Cases 40</td>
<td>100</td>
<td>(88–100)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**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?

More developed countries

Less developed countries

Breast

Cervix

Ovary

Endometrium

Colon/rectum

Lung

Stomach

"Pap" smear

Annual number of cases (thousands)

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 TGFβ
• FASEB Award for Excellence in Science
• Susan G. Komen Foundation’s Brinker Award for Scientific Distinction
HPV Virus-Like Particle Vaccine

- HPV major capsid protein
- L1 coding region
- L1 recombinant yeast or baculovirus
- Production
- Purification
- Intramuscular Vaccination
- VLPs

Localization:
- Endocervix
- Neutralizing Antibodies
- Transformation Zone
- Cervical Mucus
- Ectocervix
HPV and Cervical Cancer

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

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Infections</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16</td>
<td>465</td>
<td>49.9</td>
</tr>
<tr>
<td>HPV 18</td>
<td>128</td>
<td>13.7</td>
</tr>
<tr>
<td>HPV 45</td>
<td>78</td>
<td>8.4</td>
</tr>
<tr>
<td>HPV 31</td>
<td>49</td>
<td>5.3</td>
</tr>
<tr>
<td>HPV 33</td>
<td>26</td>
<td>2.8</td>
</tr>
<tr>
<td>Other HPV</td>
<td>156</td>
<td>16.7</td>
</tr>
<tr>
<td>HPV neg</td>
<td>66</td>
<td>7.1</td>
</tr>
</tbody>
</table>

• 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

- **1982**: First VLPs produced
- **1990**: HP16 and HP18 discovered
- **1995**: HPV proposed as a necessary cause of cervical cancer
- **1999**: VLP clinical trials begin
- **2001**: Initial report of efficacy
- **2006?**: Vaccine licensure

HPV: human papillomavirus; VLP: virus-like particle
Mutations and other changes: RAS, NYC, p53, p16, RB, FHIT & other critical genes

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       NNK

GSK-3 α/β
α tubulin

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

GGSK-3 α/β
α tubulin

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

Fig. 1. Scheme linking nicotine addiction and lung cancer via tobacco smoke carcinogens. PAH = polycyclic aromatic hydrocarbons; N-nitrosamines; NNK = 2-[(N-nitroso-n-propyl)amino]-3-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; DNA adducts = DNA adducts due to tobacco smoke carcinogens.
Prevention

A biochemical gatekeeper for tobacco-related cancers?
Akt activation

A biochemical gatekeeper for tobacco-related cancers

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

<table>
<thead>
<tr>
<th></th>
<th>Nicotine</th>
<th>NNK</th>
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</table>

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

![Graph showing progression](image)

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

![Graph showing number and size](image)

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
NCI’s Allocation of 2007 Request
$4.8 Billion

Research Project Grants 46%
R&D Contracts 7%
Cancer Control 11%
SPOREs 3%
Intramural 15%
- Research 9%
- Support 6%
Coop Groups 3%
Training 4%
Other 5%
Cancer Centers 6%
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

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

(dollars in thousands)
STAR Trial: Study of Tamoxifen and Raloxifene

- Comparison of reduced risk of breast cancer in postmenopausal women at increased 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

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  - Full detailed review with written critiques
  - Value of critique for A1, A2 resubmissions

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- 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