

NCI Director's Update

Dr. John E. Niederhuber

Director, National Cancer Institute

Clinical Trials Advisory Committee

December 8, 2008



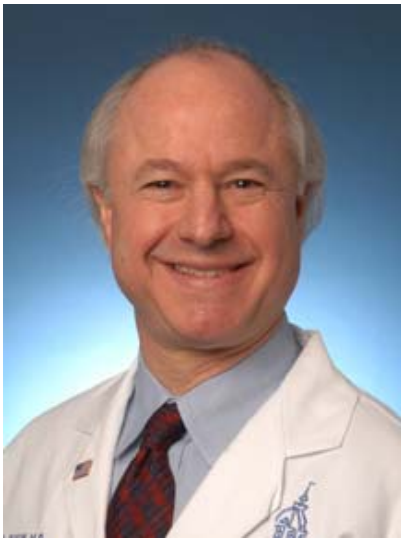
**Kenneth Cowan,
M.D., Ph.D.**



Everett Dodson



Nancy Roach



**Curt I. Civin,
M.D.**



Jeffrey Trent, Ph.D.



**Frank M. Torti,
M.D., M.P.H.**

NCI Director's Update

- **Managing the NCI budget: 2009 and 2010**
- **NCI Transition Team**
- **The NIH Clinical Center**
- **Facilitating patient-centered cancer research**



Closing Out FY 2008

- RPGs funded at the 14th percentile plus extensive exceptions (**20% success rate**)
- ***R01s** funded at the 19th percentile extended payline plus exceptions (**~234 awards**)
- NCI funded 1,284 competing RPGs in FY08 (including supplemental appropriation)
- NCI added **1 new Cancer Center**
 - Greenebaum Cancer Center, University of Maryland

Congratulations to NCI's budget office for closing the books on FY08 with a balance of **\$3,302.**



FY2008 – Supplemental

- Supplemental appropriation to NIH part of emergency appropriation
 - Possibly the way NIH will get incremental budget increases in the near future
- **NIH received \$150M; \$25.56M to NCI**
 - \$14M to fund additional 35 competing RPGs
 - \$1M for AIDS centers
 - \$0.5M for Clinical groups
 - \$4.8M for R&D contracts
 - \$5.2M for Drug Development Infrastructure

Non-Competing Policy Under CR

- NIH policy: **award T5s at 90% of commitment level** (training-careers/ fellowships are spared)
- NIH full year guidance: **1% inflation allowance** provided in FY 2009 (amounts to a reduction of the previously planned 3% COLA)

Non-Competing Comparison 2008 and 2009

	FY 2008 RPG Final Awards (Includes Cancer Control)	
	No.	Dollars
Noncompeting	3,879	\$1,502,608
Program Evaluation		\$68,382
Admin. Adjustments	266	\$24,665
Subtotal Noncompeting	3,879	\$1,595,655

	FY 2009 PB RPG (Includes Cancer Control)	
	No.	Dollars
	3,651	\$1,472,793
		\$68,382
	266	\$25,000
	3,651	\$1,566,175

(Dollars in thousands)

- \$30M decrease in non-competing commitments from FY08
- FY09 T5 estimates include anticipated savings
- Cancer Control: FY08 T5 = \$58.9M
FY09 est. T5 = \$40.1M

Competing RPG Paylines

Payline Comparison

	2008	CR 2009	Full PB 2009	
R01	14.0	12.0	13.0	percentile
P01	23	NA	27	no. of awards
R03	210	200	200	priority score
R21	14.0	12.0	13.0	percentile
R15	175	175	175	priority score

Competing Reduction Proposals

	2008 Actual	CR Proposed 2009	Full Year Proposed (PB) 2009
Smaller T1s	13%	20%	13%
Larger T-1s	17%	20%	17%
Smaller T-2s	5% over Current	90% of current	5% over Current
Larger T-2s	3% over Current	90% of current	3% over Current

Proposed cuts, PB

- Maintain policy reductions as 2008
- NIH has not provided CR guidance for competing grants
- One percent change in policy reduction will yield an additional \$4 million

Proposed cuts, CR

- Fund new grants (T1) at 80% of their requested level
- Fund competing renewals (T2) at 90% of current level

Competing Comparison, 2008 and 2009

FY 2008 RPG Final Awards			
* (Includes Cancer Control)			
	No.	Dollars	Payline
Non-exceptions			
R01	586	\$219,267	14.0
P01	23	\$42,929	n/a
Other	446	115,598	
Total w/in payline	1,055	\$377,794	

FY 2009 PB RPG			
* (Includes Cancer Control)			
	No.	Dollars	Payline
	631	\$238,150	13.0
	27	\$50,382	n/a
	492	117,047	
	1,150	\$405,579	

(Dollars in thousands)

Cancer Control: FY08 = 18 awards at \$1.3M
FY09 Est. = \$11M

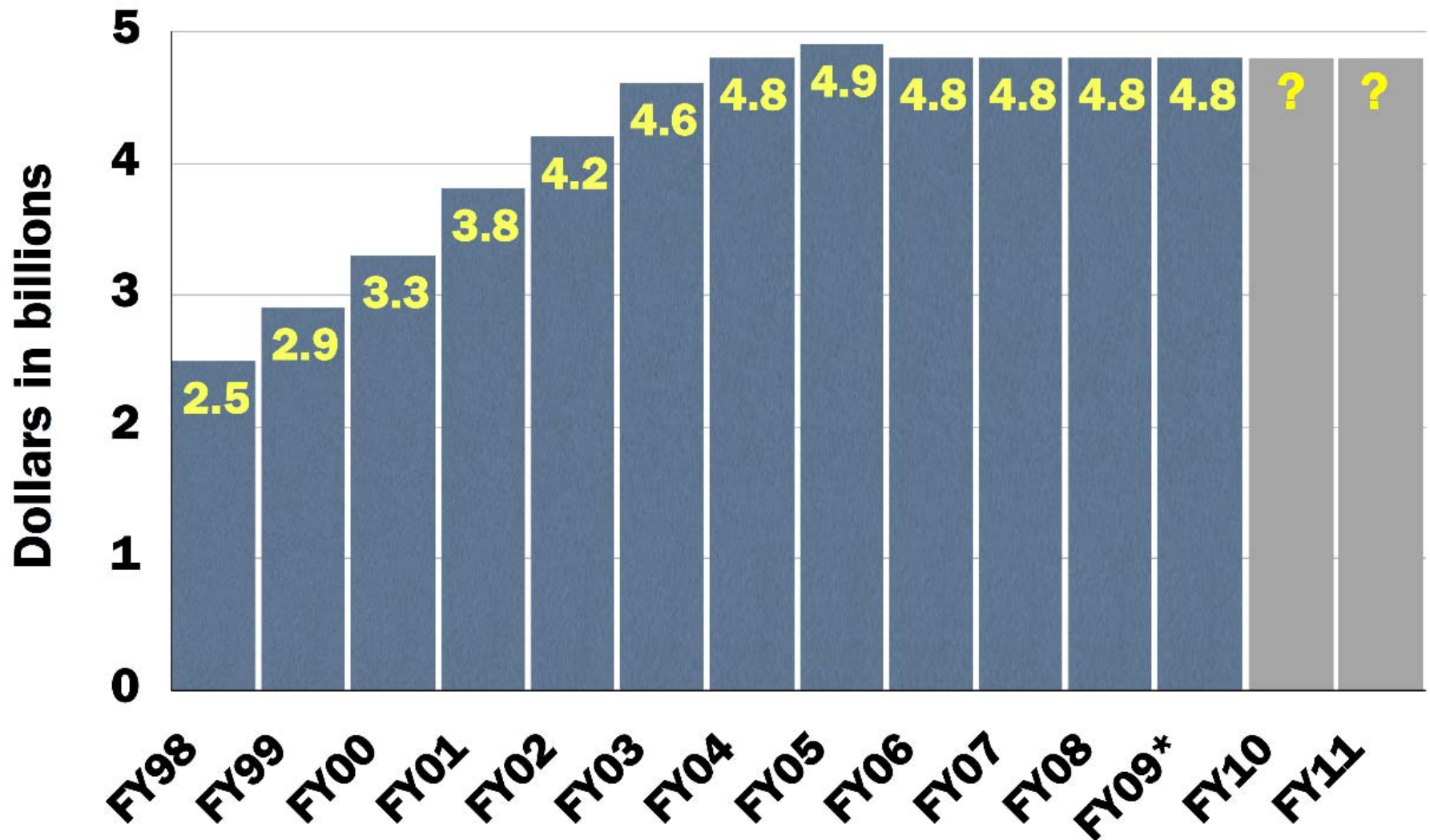


FY 2009 President's Budget

FY08 NCI base appropriation	\$4,805,088
FY 2009 PB for NCI	\$4,809,819
Difference '08 to '09	\$4,731
Percent change '08 to '09	+0.1%

(dollars in thousands)

NCI's Congressional Appropriations



*6-month Continuing Resolution

2008 EC Budget Retreat



Next budget retreat will be Jan 27-28, 2009



Transition Team

- Divisional leadership and senior staff in the Office of the Director (communications, legislation, planning, media)
- Identified topics of importance to the Institute and the National Cancer Program and working to develop content
 - Clinical research
 - Health IT
 - Pharmaceutical costs to society
 - Cancer as a model
 - Quality of cancer care/outcomes research



Trans-NCI Programs and Initiatives

- **caBIG[®], BIGHealth**
- **NCI Community Cancer Centers Program**
- **NCI drug development platform**
- **NCI Alliance for Nanotechnology in Cancer**
- **TCGA: The Cancer Genome Atlas**
- **Proteomics initiative**
- **Biorepositories and biospecimens**
- **Clinical Trials Working Group/
Translational Research Working Group**

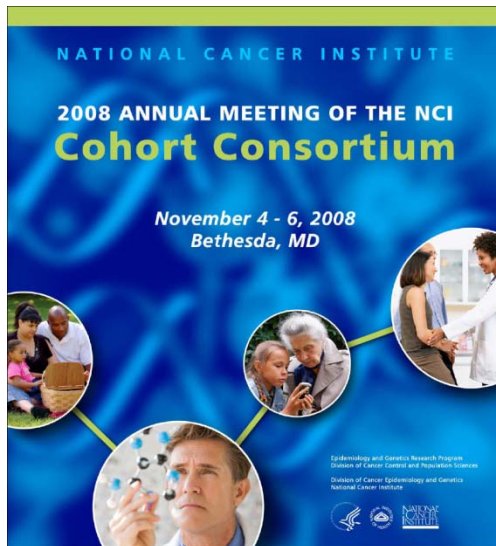
NIH Clinical Center

NIH Intramural Clinical Research Steering Committee (ICRSC)

- **Advisory committee consisting of a cross-section of IC leadership involved in clinical research**
- **Advise the NIH Deputy Director for Intramural Research**
- **Address ways to:**
 - **Harmonize policy and operations**
 - **Develop standards for IRBs**
 - **Insure protocols receive adequate, consistent scientific review**
 - **Review the level of support provided to investigators whose work includes development of human subjects research protocols**

NCI Cohort Consortium

Nurses' Health (1973)
CLUE (1974)
Physicians' Health (1982)
Cancer Prevention Study II (1992)
European (EPIC) (1992)
Prostate, Lung, Colorectal,
Ovarian (PLCO) (1992)
Multiethnic (1992)
Women's Health (1993)
Agricultural Health (1993)
Black Women (1994)
Southern Community (2001)
more...



- **Launched in 2000**
 - Multi-national, intramural and extramural partnership
 - 37 population cohorts
 - 3.5 million individuals

8q24 Region Possible Master Cancer Susceptibility Region

127.6 M

rs979200

rs1456310
rs6993569
rs6470494

rs13281615
rs16902124
rs16902126

rs6983267
rs10505476
rs7837328

rs1447295
rs7837688

MYC

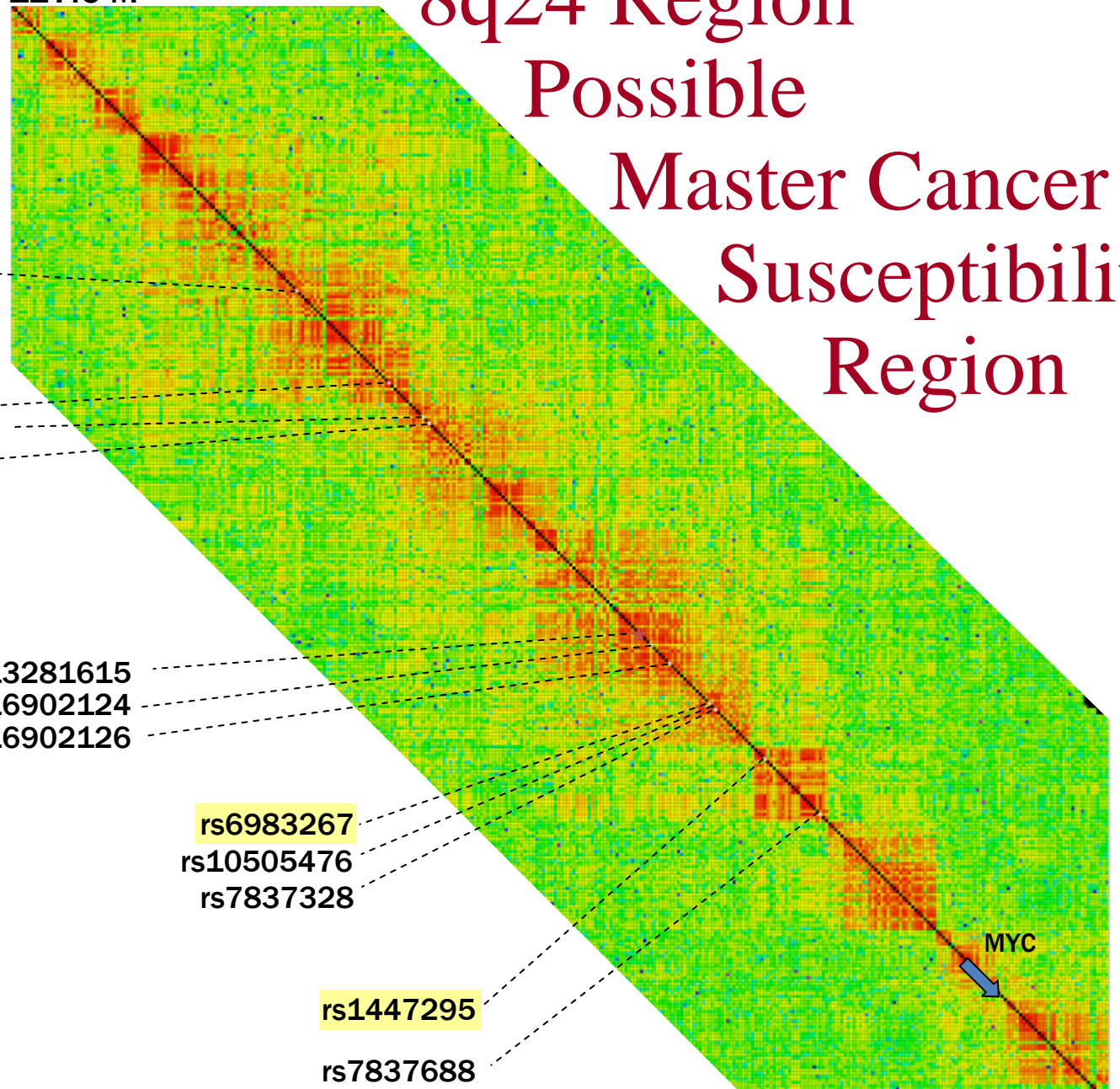
129.0 M

Region 2
Prostate
only

Breast only

Region 3
Prostate & Colon

Region 1
Prostate only



Replication Studies in CGEMS Prostate Cancer GWAS

			rs6983267			rs1447295		
Subjects			Predisposing allele frequency		P-value	Predisposing allele frequency		P-value
			Cases	Cont.		Cases	Cont.	
PLCO	1157	1172	0.55	0.49	2.4×10^{-05}	0.14	0.10	9.8×10^{-05}
ACS	1151	1150	0.55	0.50	3.2×10^{-03}	0.12	0.08	2.7×10^{-05}
ATBC	896	894	0.57	0.51	1.9×10^{-03}	0.21	0.17	2.9×10^{-02}
FPCC	459	455	0.56	0.51	1.2×10^{-01}	0.12	0.07	4.4×10^{-03}
HPFS	636	625	0.57	0.51	1.0×10^{-02}	0.13	0.09	2.7×10^{-03}
ALL	4299	4296	0.56	0.50	9.4×10^{-13}	0.15	0.11	1.5×10^{-14}

Estimated Odds Ratios Overall

Heterozygotes

1.26

1.43

Homozygotes

1.58

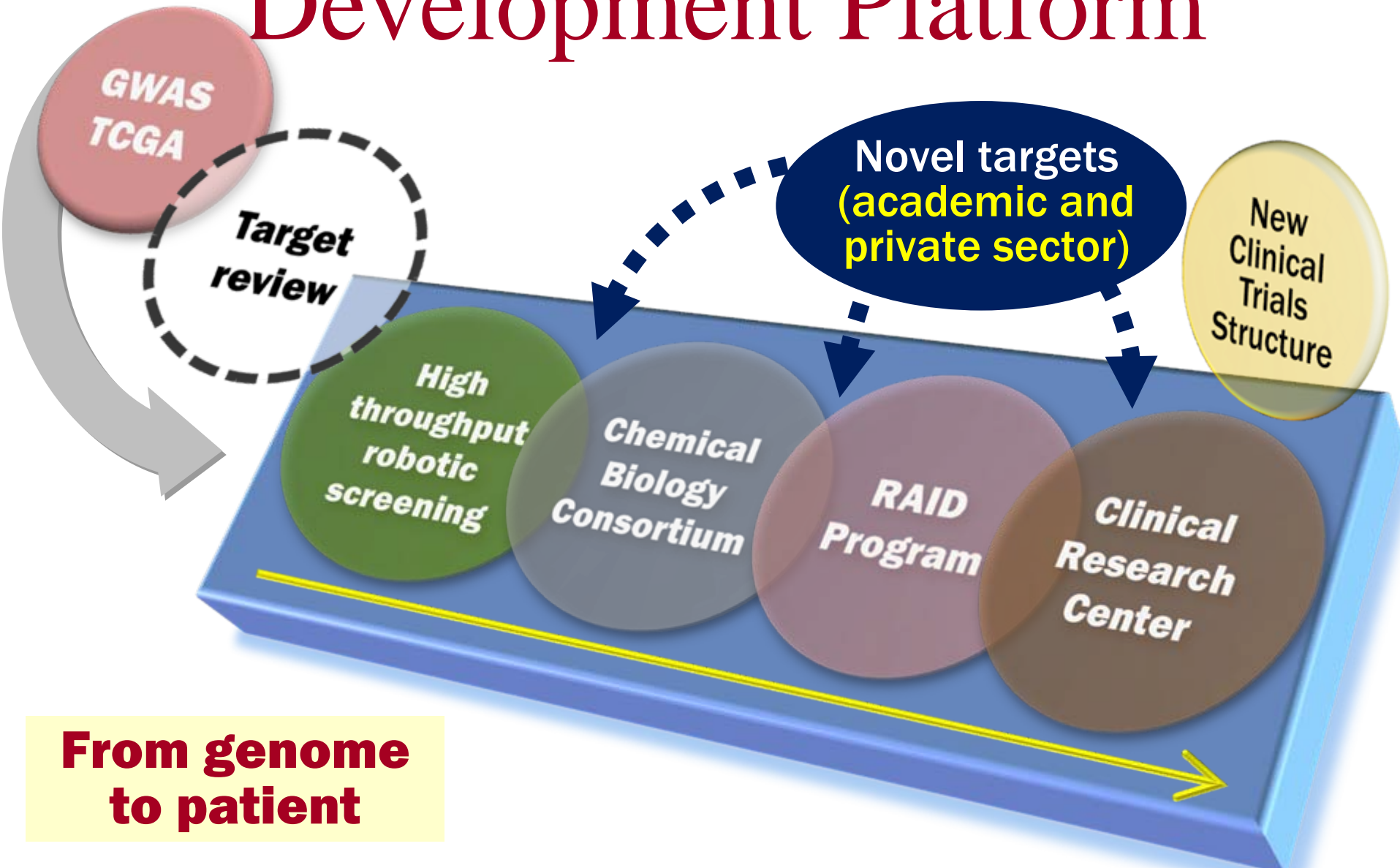
2.23


The Cancer Genome Atlas

- Pilot includes glioblastoma, ovarian and lung cancers
- **Glioblastoma** (all tissue must have 80% tumor and matched normal DNA)
 - >200 tissues analyzed; >100 sequenced
 - Identified NF1, Erbb2, and PIK3R1 as highly associated with GBM (EGFR, p53)
 - **At least 4 subtypes emerging**
- Beginning to analyze ovarian and lung
- Newer sequencing technology being applied



NCI Targeted Drug Development Platform





**New
Clinical
Trials
Structure**



**New
Clinical
Trials
Structure**

Translational Science: The Paradigm Shift

The 20th Century Paradigm:

Organ site-based, single agent based trials

- Reactive
- Based on gross differences
- Toxic (MTD/DLT)
- Emerging resistance
- Poor life quality

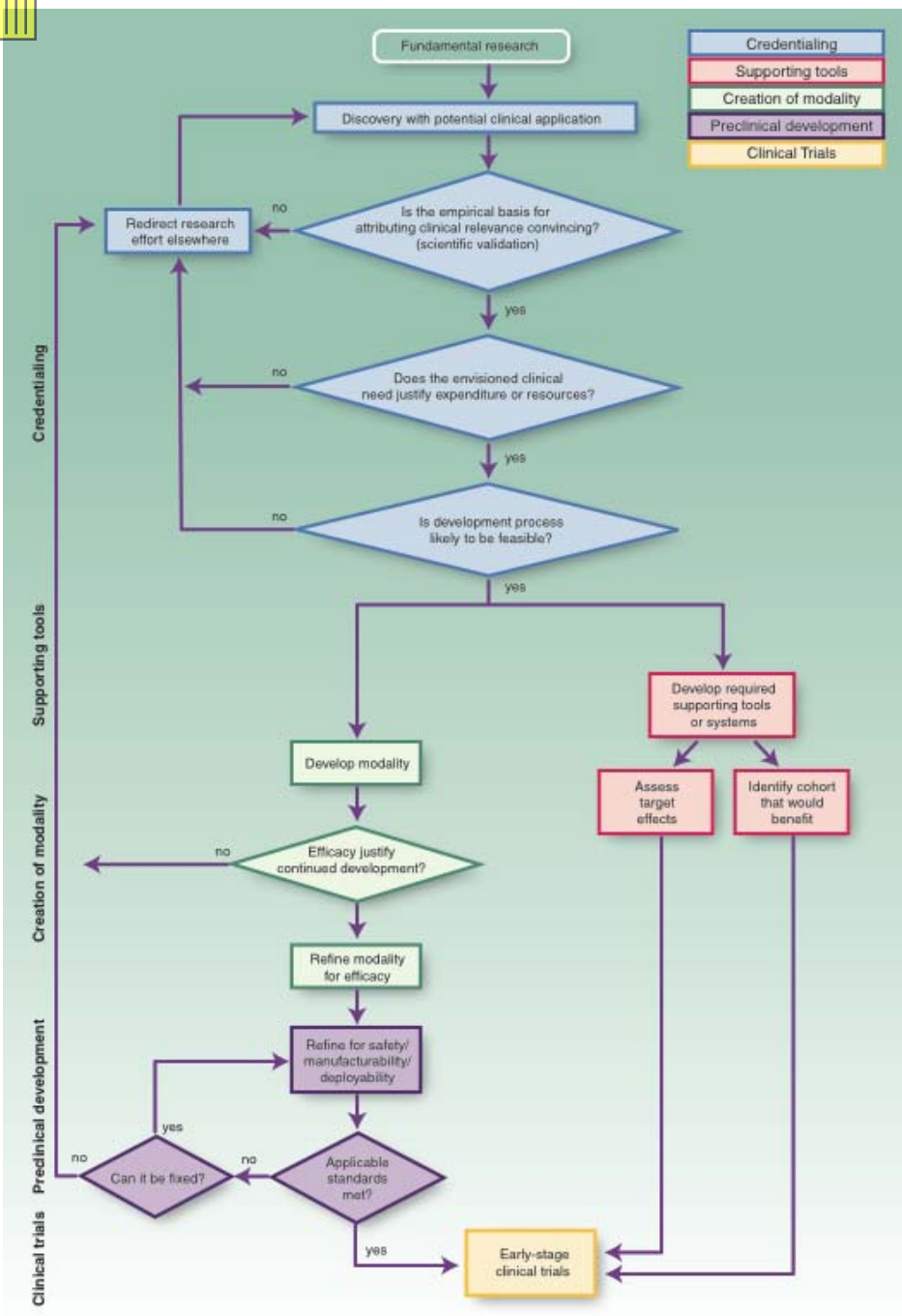
Research

- Human genome
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational design

The New Paradigm:

Multiple, highly targeted agents matched to molecularly selected patients

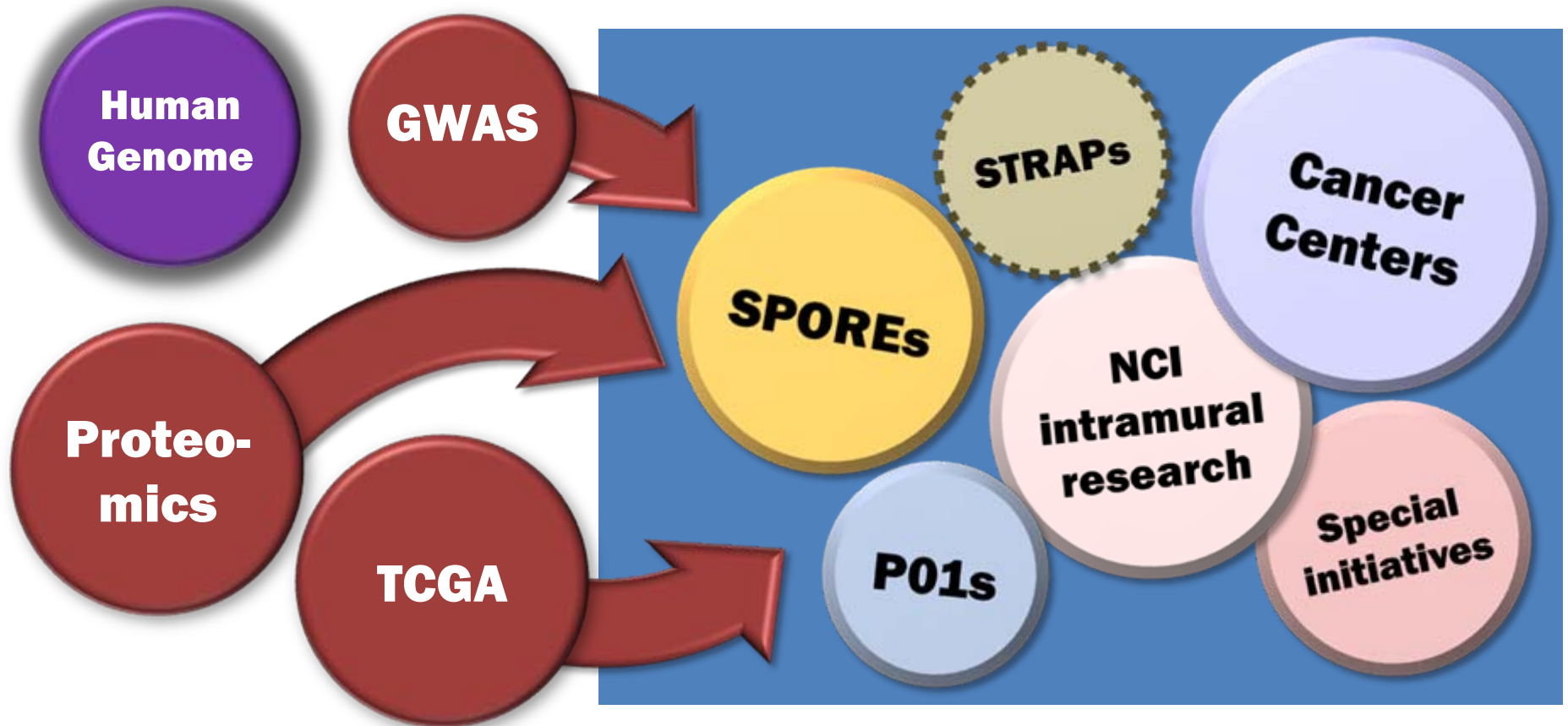
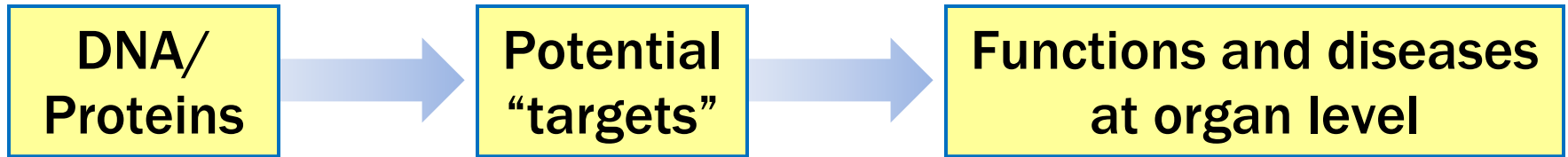
- Proactive
- Rational/targeted
- Less toxicity
- Biomarker endpoints (subcellular target imaging)
- Significant savings of cost and time



“Set priorities through a systematic and **transparent process** involving all stakeholders.”

From Information to Function

Translational Research Program



Solutions for the Individual



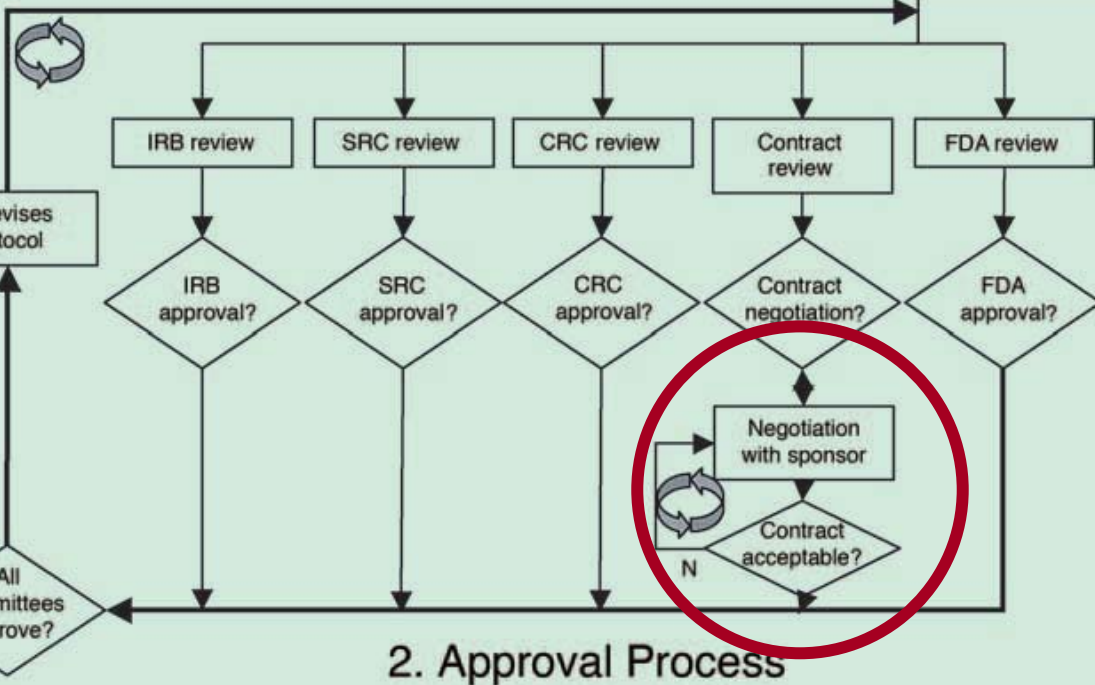
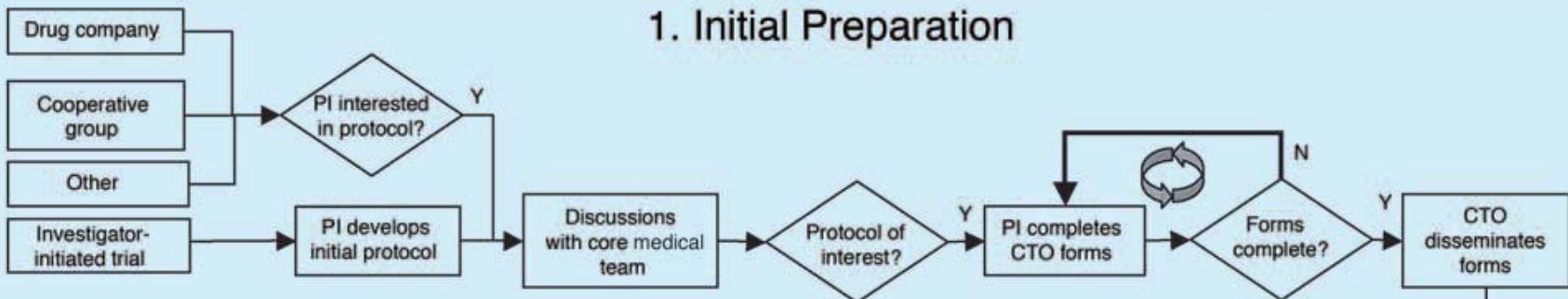
Science and
technology



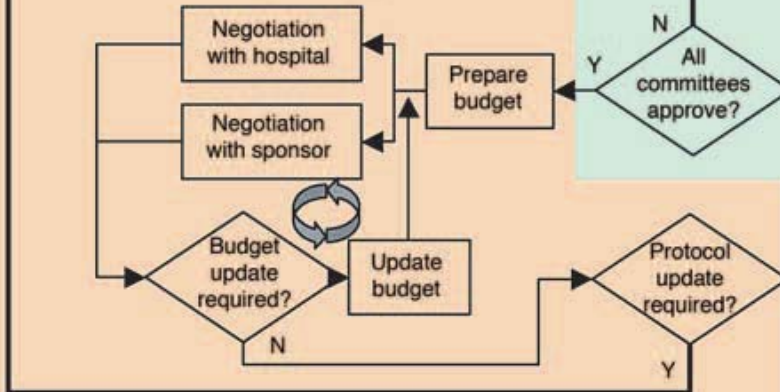
Phase 0/1

- ✓ IND30452
- ✓ Approved Drug A
- ✓ Approved Drug B
- ✓ Approved Drug C

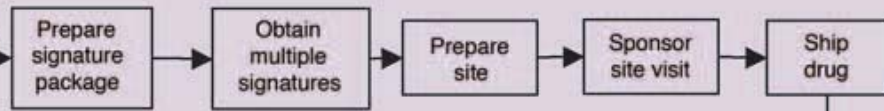
1. Initial Preparation



3. Budgeting



2. Approval Process



Open clinical trial

Life Sciences Consortium

Common language

IP

Antitrust

CEO Roundtable on Cancer

- Founded in 2001 by Pres. George H.W. Bush
 - **“Do something bold and venturesome about cancer”**
 - 28 members; 20 honorary members
 - Life Sciences Consortium
 - 11 companies
 - Chair: Dr. Gregory Curt of AstraZeneca



CEO ROUNDTABLE
ON CANCER

Project Structure

- **Involved legal and business representatives from participants**
 - 17 reps. from LSC companies
 - 26 reps. from NCI-Designated Cancer Centers
- **Obtained copies of 78 clinical trial agreements from participating organizations**
 - 49 redacted copies of final negotiated agreements
 - 29 agreement templates
 - Approximately equal numbers of agreements from LSC companies and Cancer Centers
 - Agreements included company-sponsored and investigator-initiated trials

Agreement Analysis

- **Identified 45 key concepts** in the 7 clause categories
- **Captured exact language** that embodied these concepts for all 78 agreements
- **Organized agreement language** into categories representing embodied concept
- **Analyzed results** for similarities and differences in key concepts across final negotiated agreements
- **Analyzed template agreements** for key differences with negotiated agreements

Key Clauses

- Through discussions with legal and business representatives, identified:
 - **Intellectual property**
 - Study data
 - Subject injury
 - Indemnification
 - Confidentiality
 - Publication rights
 - Biological samples

Life Sciences Consortium



“The Department of Justice announced today that it will not oppose a proposal by the CEO Roundtable on Cancer to develop and publicize model contract language for clinical trials of potential new cancer treatments.”

Department of Justice press release
Wednesday Sept. 17, 2008

Economic Stimulus Package

Two types of government investment

- Most common is project directed to create new jobs
- **Need is for “true investment”**
 - research, research capacity/infrastructure
 - creation of new knowledge
 - capacity to produce “goods and services” through a virtual cycling of discovery

New Business Activity

- NCI research grant and contract expenditures generated **~\$7.864 billion in state economic output**, or about **\$2.57** of increased economic activity for every dollar of NCI research funding
- Business activity generated per dollar of NCI research funding was highest in Texas, lowest in South Dakota

New Jobs and Wages

- NCI research grants and contracts created and supported **over 54,000 jobs** in the United States in FY 2007
- These jobs generated more than \$2.84 billion in wages and salaries
- The average wage associated with these jobs was more than \$52,000 per year
 - Average wage nationally is \$42,000

What I Worry About!

- More years with less-than-inflation budgets
- Providing leadership/resources to both academia and industry
- **Attracting the best and brightest**
- Building the translation programs of the future
 - Efficient model for trial design to first patient
 - Building leadership in molecular prevention
- What does knowledge management mean at NIH?
- Finding new ways to think about cancer
- The transition to a new administration



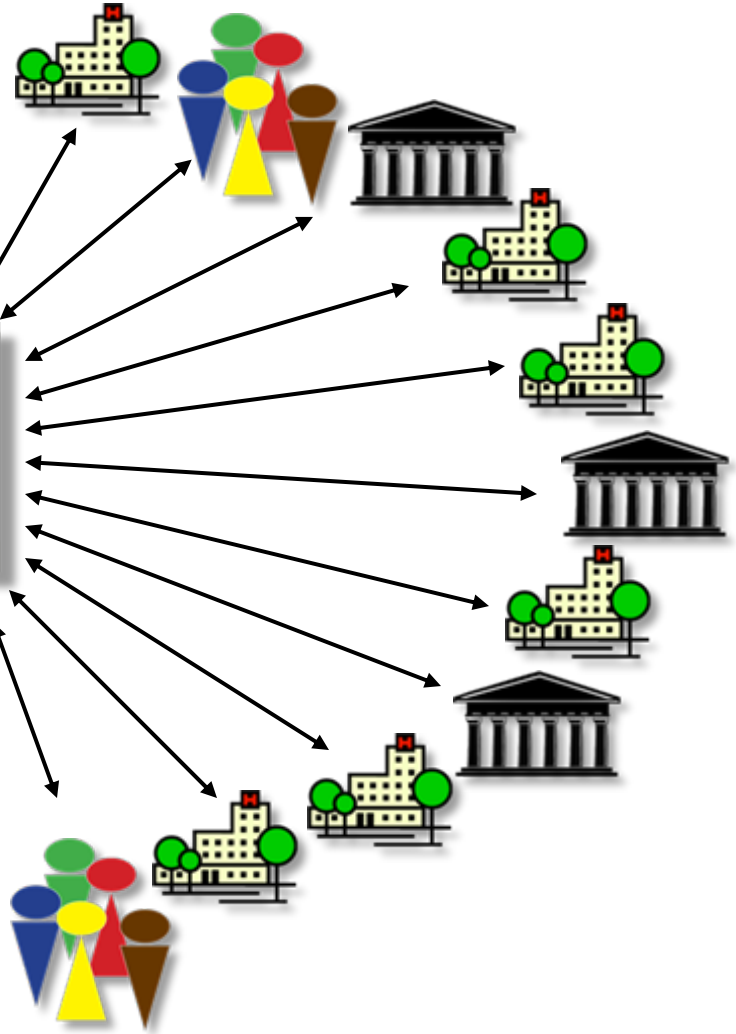
Patients & Families



www.cancer.gov



**NATIONAL
CANCER
INSTITUTE**



- Industry
- Pharma
- Biotechnology

- Advocacy Organizations
- Professional Societies
- Philanthropy/Foundations

- Universities
- NCI Cancer Centers
- NCI NCCCP
- NCI CCOPs

NCI Clinical Trials System: Current Status

- System is inefficient, time consuming, and under-funded
- In an era of targeted therapy, the system is geared toward the testing of non-specific regimens
 - Lacks the capacity to highly characterize each patient and carefully **match that patient profile to targeted therapeutic combinations**

Intellectual Property

- **Company-Sponsored Trials**

- Inventions owned by company
- Research institution retains right to use inventions for non-commercial research and education

- **Investigator-Initiated Trials**

- Inventions owned by research institution
- Research institution grants company a royalty-free, non-exclusive license and an option to obtain a royalty-bearing exclusive license



SELECT Trial

- **Selenium and Vitamin E Cancer Prevention Trial**
- **Launched in 2001; recruited 35,000 men age 50 and over**
- **8,000 men per group, randomly assigned to take:**
 - **Selenium and vitamin E**
 - **Selenium and a vitamin E placebo**
 - **Vitamin E and a selenium placebo**
 - **Placebos of both supplements**
- **Coordinated by the Southwest Oncology Group (SWOG) at more than 400 clinical sites in the United States, Puerto Rico, and Canada**



SELECT Trial (cont'd)

- Selenium and vitamin E supplements, taken either alone or together, did not prevent prostate cancer
- Data showed two concerning trends:
 - A small but not statistically significant increase in the **number of prostate cancer cases** among men in the trial taking only vitamin E
 - A small, but not statistically significant increase in the **number of cases of adult onset diabetes** in men taking only selenium
 - Neither finding proves increased risk from the supplements; **both may be due to chance**

Federal Dollars Invested in Communities

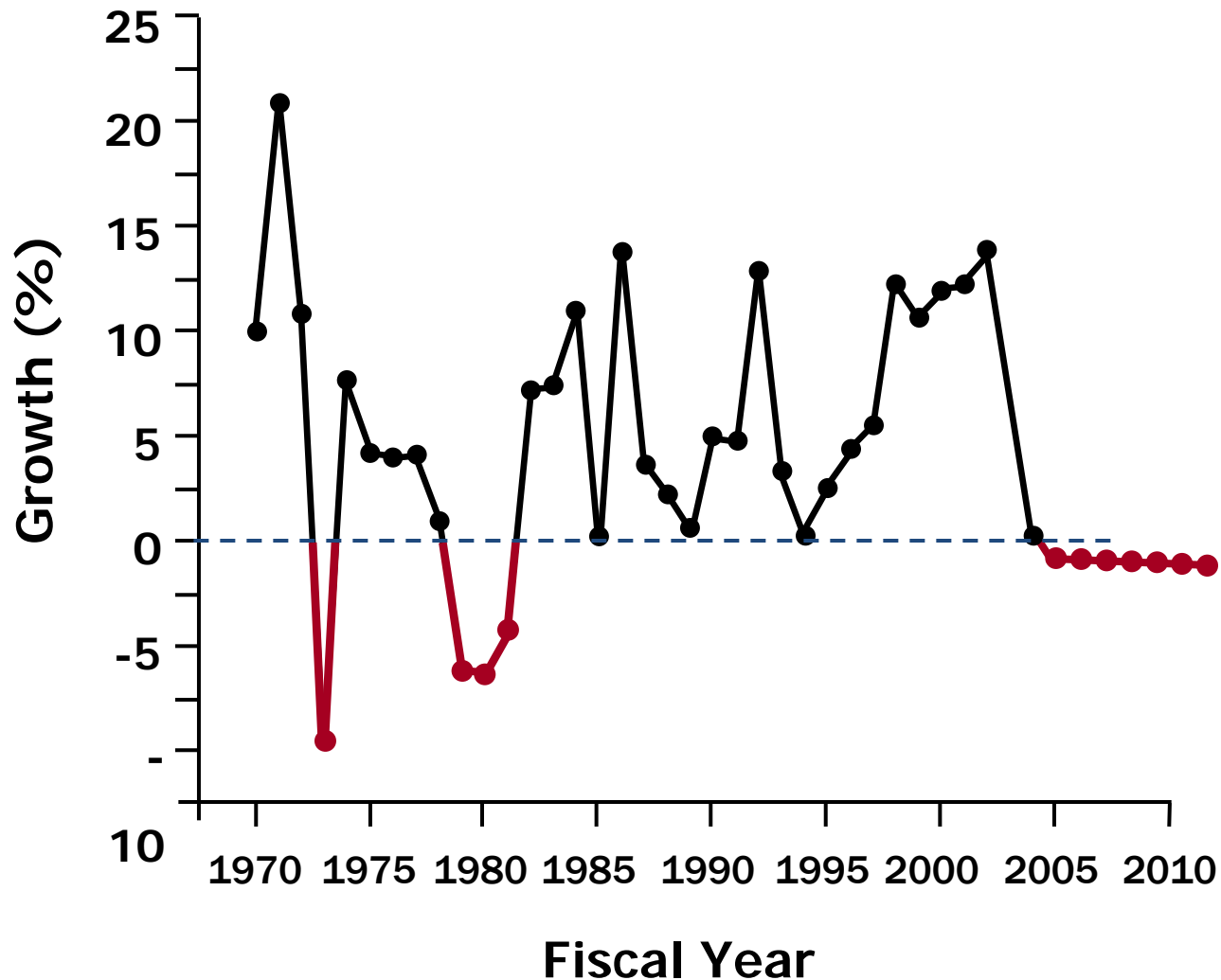
- In 2007, the NIH awarded almost \$23 billion in research grants and contracts, which:
 - Created more than **350,000 new jobs** nationwide
 - Generated more than **\$18 billion in wages** from those new jobs
 - Spurred more than **\$50 billion in business activity** in the states

“If NIH awards to the states were to increase by 6.6 percent, the national economic benefit would add up to \$3.1 billion worth of new business activity, 9,185 additional jobs, and \$1.1 billion in new wages.”

NCI Research Grants and Contracts to States

- In FY 2007, NCI awarded **~\$3.06 billion** in research project grants and research contracts
- NCI funding represented **13.3% of total NIH research grants and contracts** funding in FY07
- 5 states receiving the most research funding were California, Maryland, Massachusetts, New York, and Pennsylvania
- Alaska received the least funding; Idaho and Wyoming, received no NCI funding

Annualized Growth of the NIH Budget, 1971 to 2008



Source: Based on Loscalzo, NEJM (2006)

Challenges

- Although welcome, late-year appropriations make planning difficult
- **Uncertainty about the future year impacts of supplemental funds** (will the FY09 base be increased by \$25M?)
- Providing a healthy funding level for competing grants – without too much cutting
- **Uncertainty about the number of applications being submitted by investigators**
 - In 2008, the total number submitted was down
 - For 2009, it appears to be rising again

Background

ENHANCING PEER REVIEW

<http://enhancing-peer-review.nih.gov>

Year-long Deliberative Effort Gathering Feedback & Input:

- Request for Information
- NIH Staff survey
- IC White Papers
- Internal Town Hall Meetings
- External Consultation Meetings
- Data Analysis
- Internal and External Working Groups

Peer Review Oversight Committee (PROC) Established Working Groups:

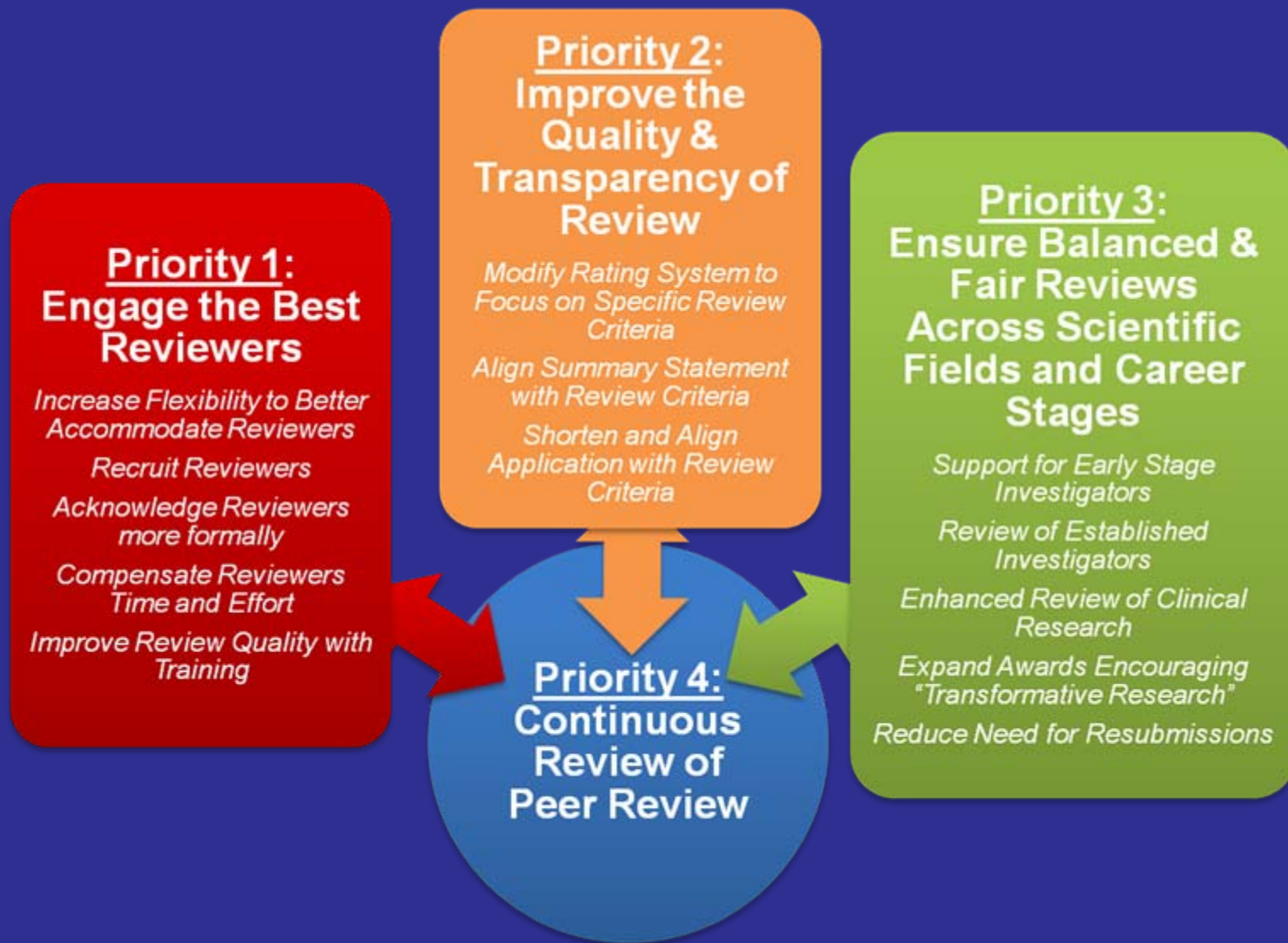
- 1.Engage the Best Reviewers
- 2.Improve the Quality and Transparency of Review
- 3.Ensure Balanced and Fair Reviews Across Scientific Fields and Career Stages
- 4.Continuous Review of Peer Review



**Identified Key
Recommendations**

"...fund the best science, by the best scientists, with the least amount of administrative burden."





"...fund the best science, by the best scientists, with the least amount of administrative burden."



Implementation Overview

Priority Area 1 – Engage the Best Reviewers

- **Improve Reviewer Retention.** In 2009, new reviewers will be given additional flexibility regarding their tour of duty and other efforts will be undertaken to improve retention of standing review members.
- **Recruit the Best Reviewers.** A toolkit, incorporating best practices for recruiting reviewers, will be made available to all NIH Institutes and Centers (ICs) in 2009.
- **Enhance Reviewer Training.** In spring 2009, training will be available to reviewers and Scientific Review Officers (SROs) related to the changes in peer review.
- **Allow Flexibility through Virtual Reviews.** Pilots will be conducted in 2009 on the feasibility of using high-bandwidth support for review meetings to provide reviewers greater flexibility and alternatives for in-person meetings.

“...fund the best science, by the best scientists, with the least amount of administrative burden.”



Implementation Overview

Priority Area 2 – Improve the Quality and Transparency of Review

- **Improve Scoring Transparency and Scale.** Review criteria-based scoring commences in May 2009. Reviewers will provide feedback through scores and critiques for each criterion in a structured summary statement.
- **Provide Scores for Streamlined Applications.** Currently, applications that are not considered to be in the top half are “streamlined.” Streamlined applications are not discussed by the full review committee and have no scoring information but the applicants do receive the reviewers’ critiques. In 2009, streamlined applications will receive scores on each criterion in addition to the reviewers’ critiques to help applicants assess whether or not they should resubmit an amended application.
- **Shorten and Restructure Applications.** Shorter (12 page research plan) R01 applications (with other activity codes scaled appropriately) will be restructured to align with review criteria for January 2010 receipt dates.

“...fund the best science, by the best scientists, with the least amount of administrative burden.”



Implementation Overview

Priority Area 3 – Ensure Balanced and Fair Reviews across Scientific Fields and Career Stages, and Reduce Administrative Burden

- **New NIH Policy to Fund Meritorious Science Earlier.** To ensure that the largest number of high quality and meritorious applications receive funding earlier and to improve system efficiency, NIH will enhance success rates of new and resubmitted applications by decreasing the number of allowed grant application resubmissions (amendments) from two to one. See the enhancing peer review web site (<http://enhancing-peer-review.nih.gov>) for the guide notice (NOT-OD-09-003), supporting data and press release.
- **Review Like Applications Together.** In September, 2008, NIH modified the NIH New Investigator Policy to identify Early Stage Investigators (NOT-OD-08-121). In 2009, where possible, NIH will cluster new investigator applications (including ESIs) for review. The same approach will be considered for clinical research applications.

“...fund the best science, by the best scientists, with the least amount of administrative burden.”



The Challenge of Early Translation

How can we best assure that:

- **The most promising concepts enter the developmental pathways?**
- **Concepts that enter advance to the clinic or to productive failure?**
- **Progress is as rapid, efficient, and effective as possible?**

Full Year Exception Allocation

	FY 2008 RPG Final Awards (Includes Cancer Control)		
	No.	Dollars	Payline
Star (*) R01	83	\$26,737	19.0
EC Exceptions	22	\$15,803	
Div Exceptions	125	36,702	
Total Exceptions	230	\$79,242	

	FY 2009 PB RPG (Includes Cancer Control)		
	No.	Dollars	Payline
	45	\$15,094	18.0
	19	\$16,906	
	55	14,000	
	119	\$46,000	

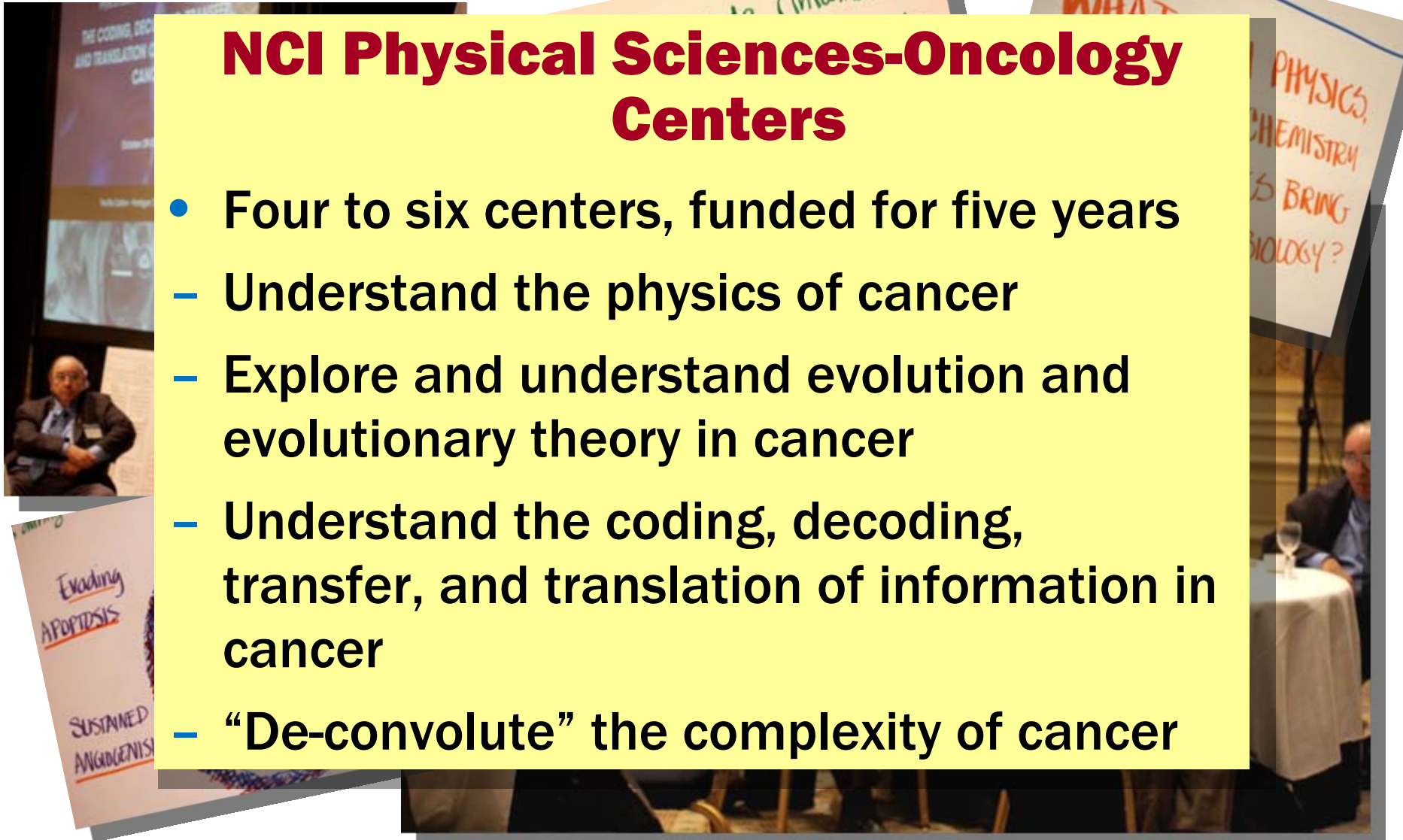
(Dollars in thousands)

FY09 exception allocation comparable to FY08 prior to supplemental appropriation exceptions.

Physical Sciences Meetings

NCI Physical Sciences-Oncology Centers

- Four to six centers, funded for five years
 - Understand the physics of cancer
 - Explore and understand evolution and evolutionary theory in cancer
 - Understand the coding, decoding, transfer, and translation of information in cancer
 - “De-convolute” the complexity of cancer



Advanced Technology Research Facility

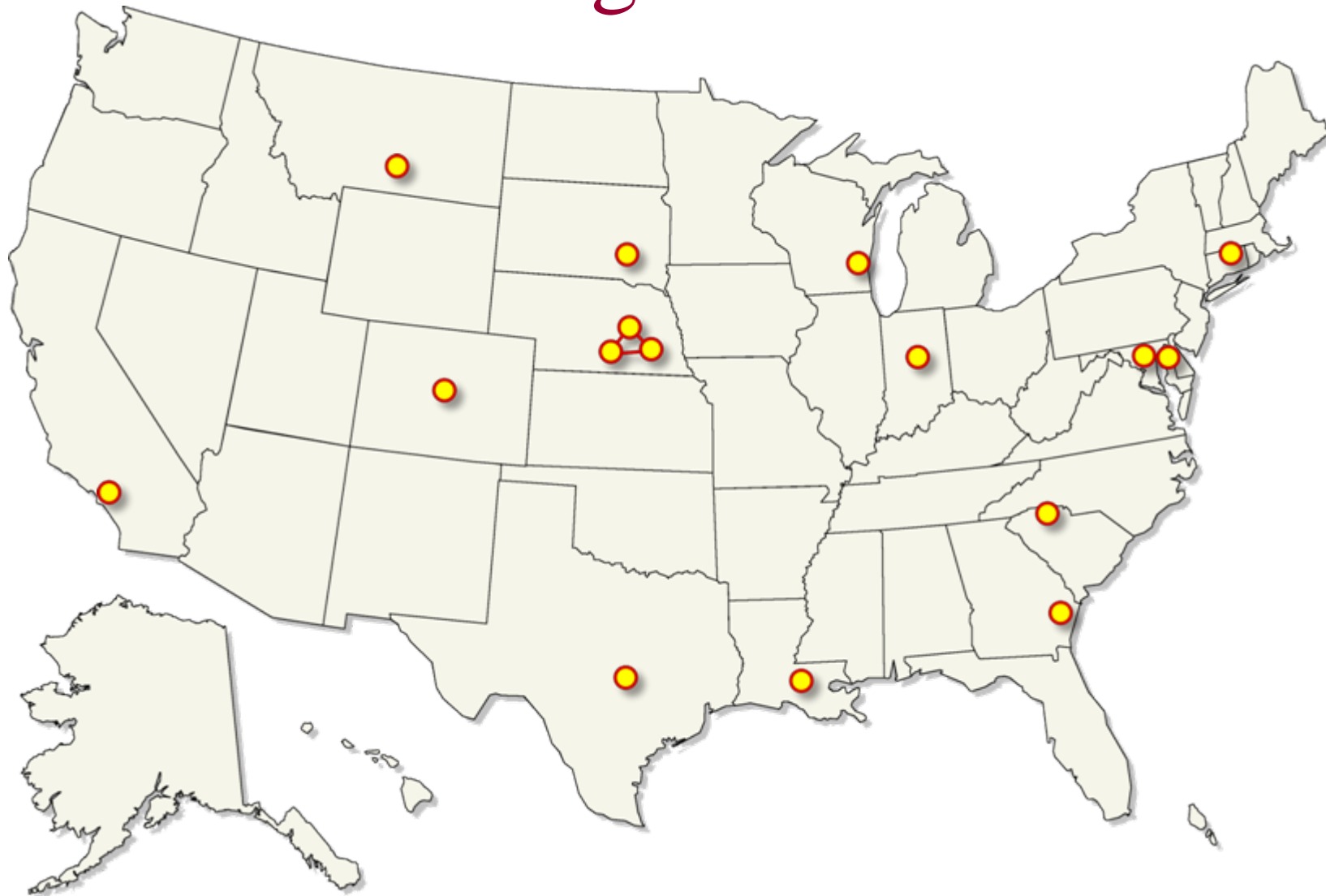


Advanced Technology Research Facility





NCI Community Cancer Centers Program Pilot Sites



Facilitating Patient-Centered Cancer Research

Changing how we get the
latest therapies to cancer
patients is not a goal.

It is a necessity.