National Cancer Institute

NCI Director's Update

Dr. John E. Niederhuber

Director, National Cancer Institute

Board of Scientific Advisors

November 6, 2008

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

New BSA Members

Andrea Califano, Ph.D.
Professor,
Department of Biomedical Informatics and the Institute of Cancer Genetics at the Columbia University Medical Center

Robert Diasio, MD
Professor of Pharmacology,
Mayo Clinic College of Medicine and the Director of the Mayo Comprehensive Cancer Center

Louise Strong, MD
Professor,
Department of Cancer Genetics,
M.D. Anderson Cancer Center

NCI Director's Update

- Managing the NCI budget: 2009 and 2010
- NCI Transition Team
- Physical sciences meetings
- Facilitating patient-centered cancer research
- Economic returns from NCI funding

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

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)

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)		FY 2009 PB RPG (Includes Cancer Control)	
	No.	Dollars	No.	Dollars
Noncompeting	3,879	$1,502,608	3,651	$1,472,793
Program Evaluation		$68,382		$68,382
Admin. Adjustments	266	$24,665	266	$25,000
Subtotal Noncompeting	3,879	$1,595,655	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

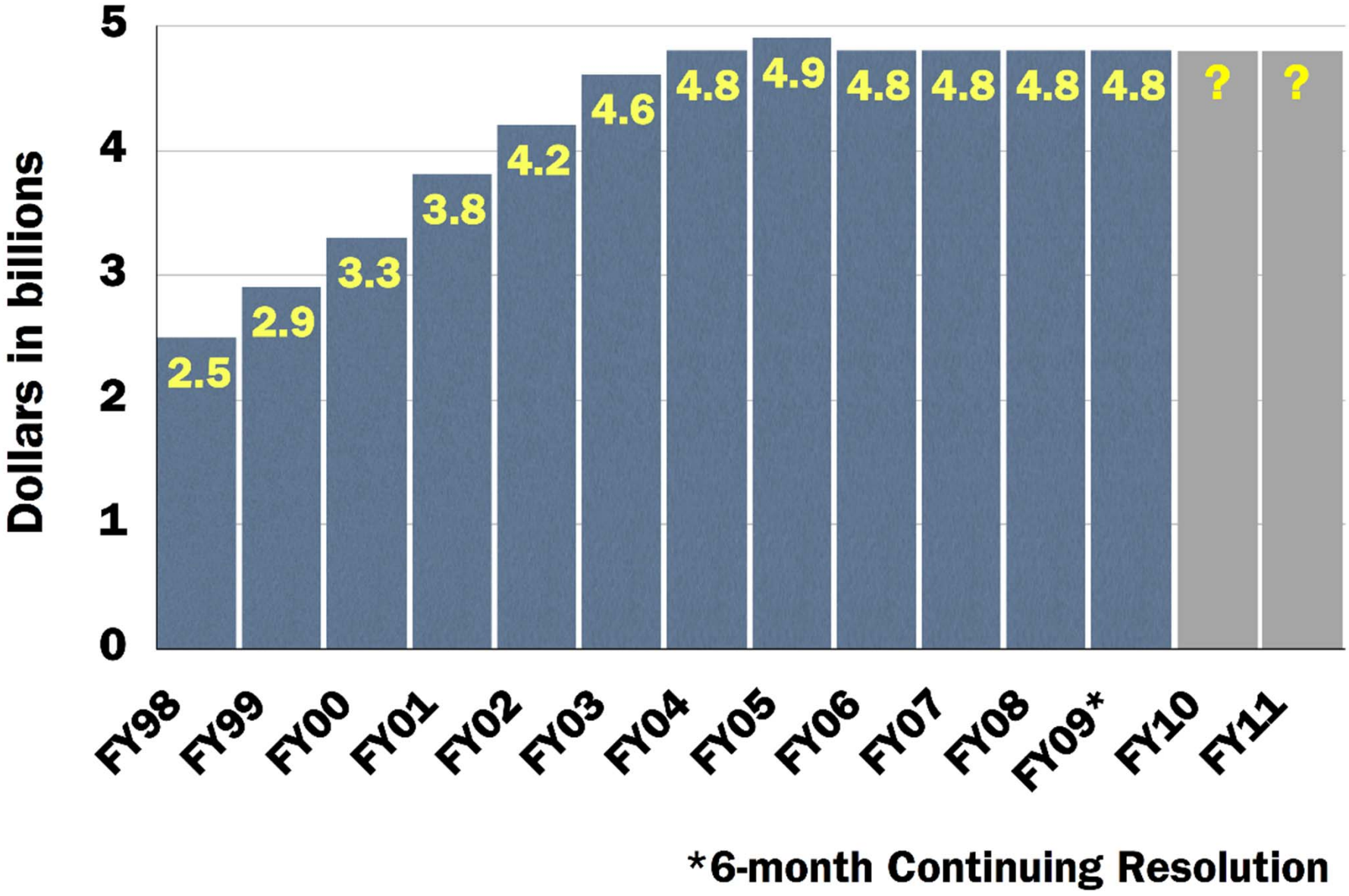
Competing Comparison, 2008 and 2009

	FY 2008 RPG Final Awards * (Includes Cancer Control)			FY 2009 PB RPG * (Includes Cancer Control)		
	No.	Dollars	Payline	No.	Dollars	Payline
Non-exceptions						
R01	586	$219,267	14.0	631	$238,150	13.0
P01	23	$42,929	n/a	27	$50,382	n/a
Other	446	115,598		492	117,047	
Total w/in payline	1,055	$377,794		1,150	$405,579	

(Dollars in thousands)

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

NCI's Congressional Appropriations



2008 EC Budget Retreat

Next budget retreat will be Jan 27-28, 2009

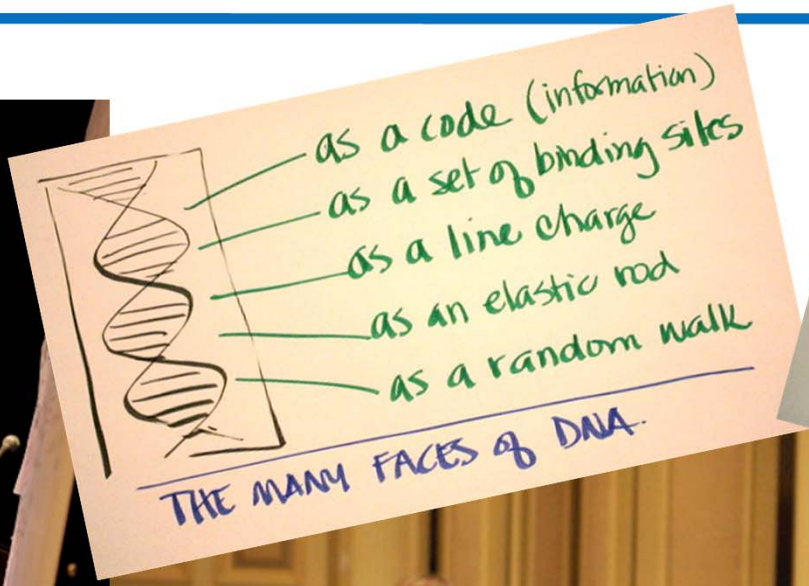
Transition Team

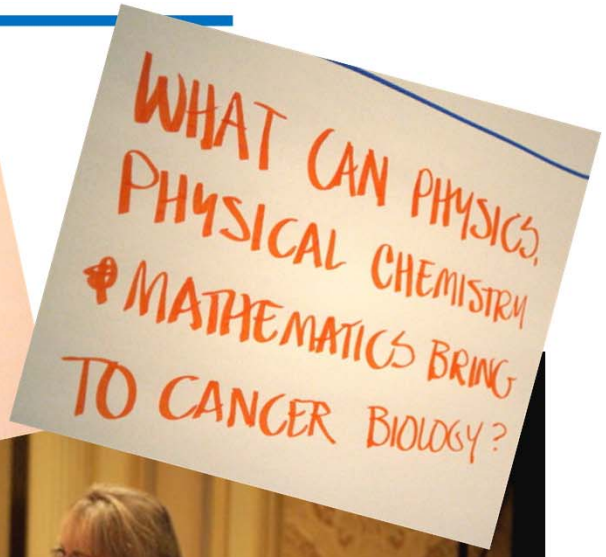
- Divisional leadership and senior staff in the Office of the Director (communications, legislation, planning, media)
- Identified topics of importance to the Institute and the National Cancer Program and working to develop content
  - Clinical research
  - Health IT
  - Pharmaceutical costs to society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

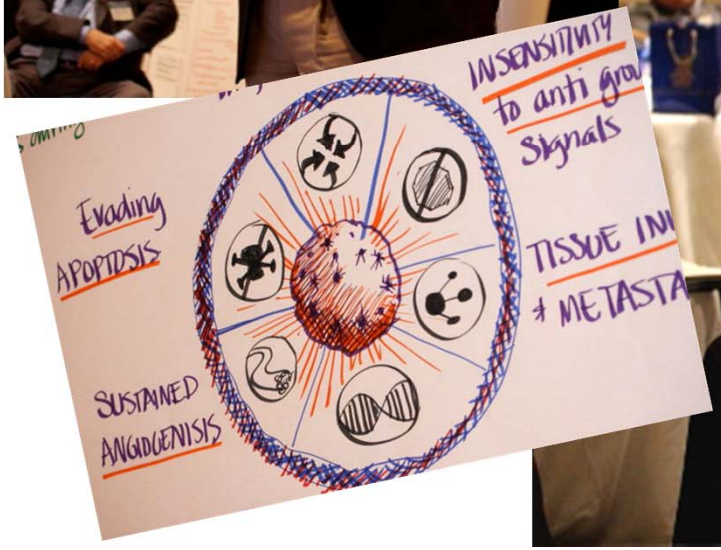
Trans-NCI Programs and Initiatives

- 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

Physical Sciences Meetings

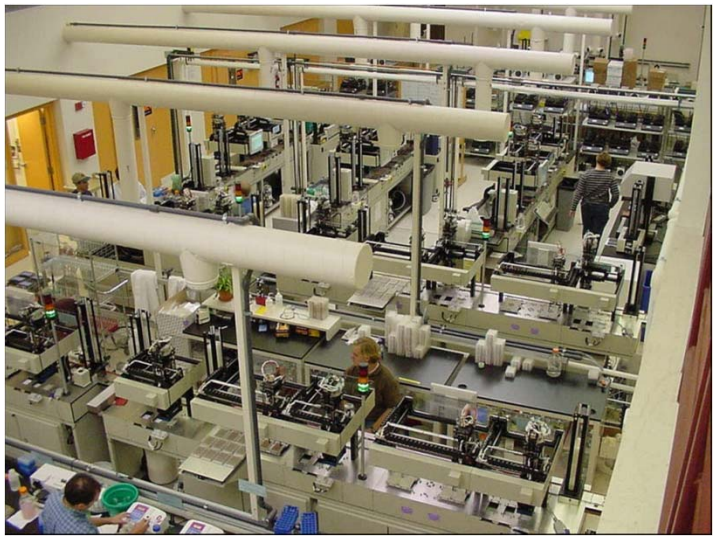






The Cancer Genome Atlas (TCGA)

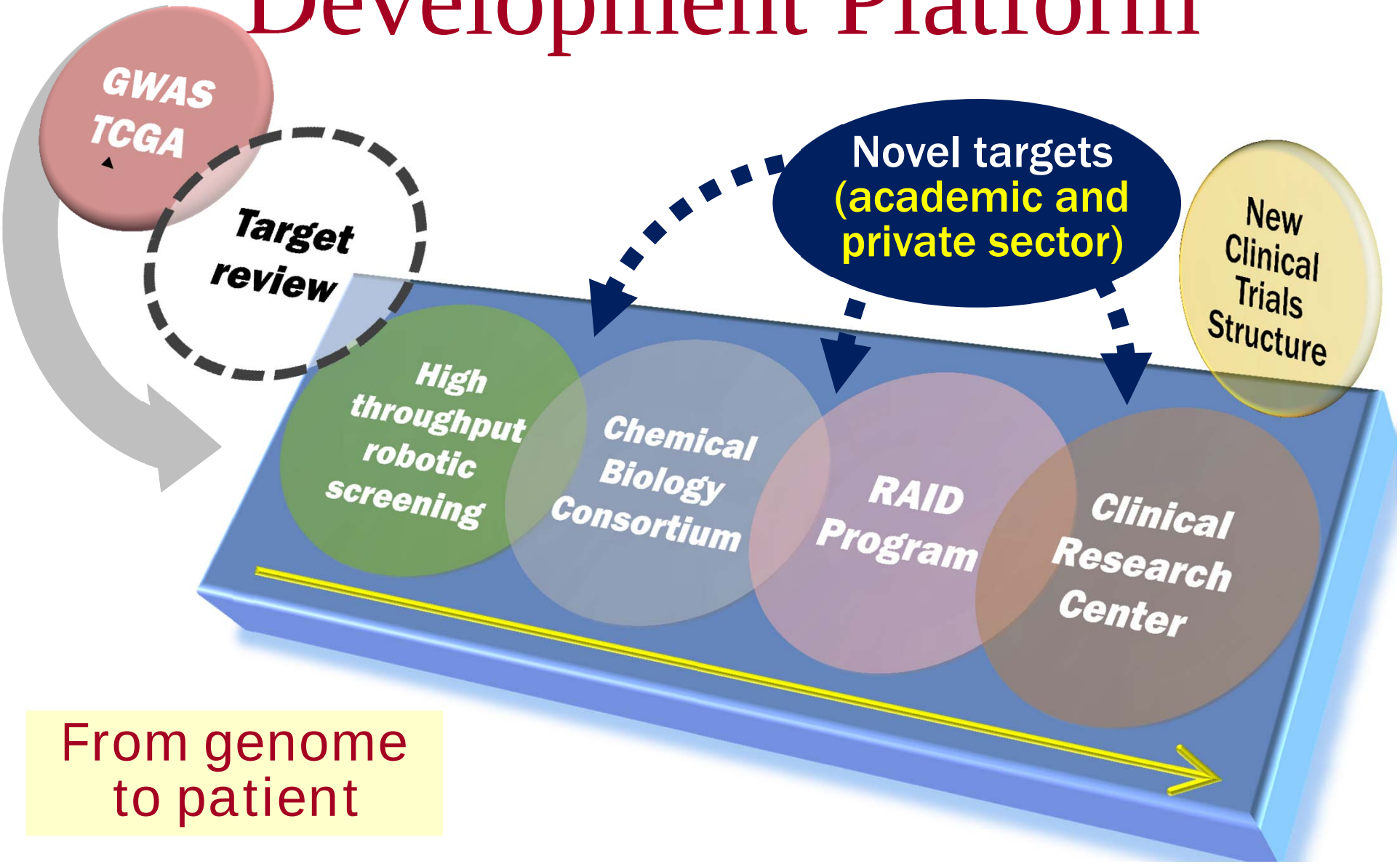
- To assess the value of large-scale multi-dimensional analysis of the molecular characteristics present in human cancer
- To provide integrative analysis (pathways) of:
  - nucleotide sequence
  - DNA copy number
  - gene expression
  - DNA methylation



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



From genome to patient


New
Clinical
Trials
Structure


New
Clinical
Trials
Structure

Facilitating Patient-Centered Cancer Research

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

It is a necessity.

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

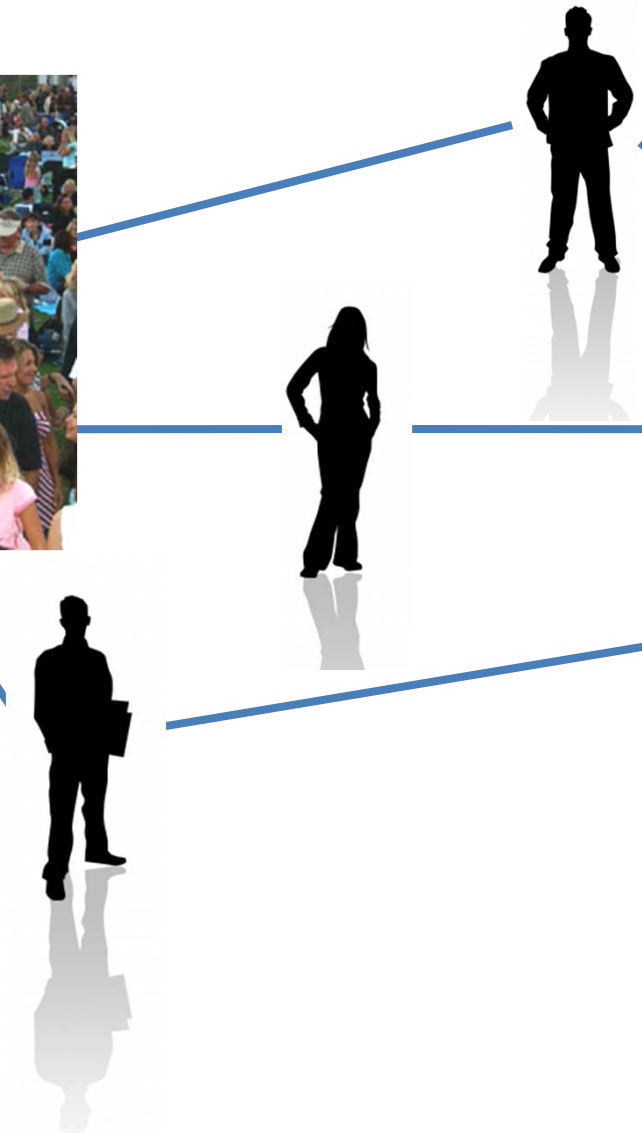
Research
- Human genome
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational design

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

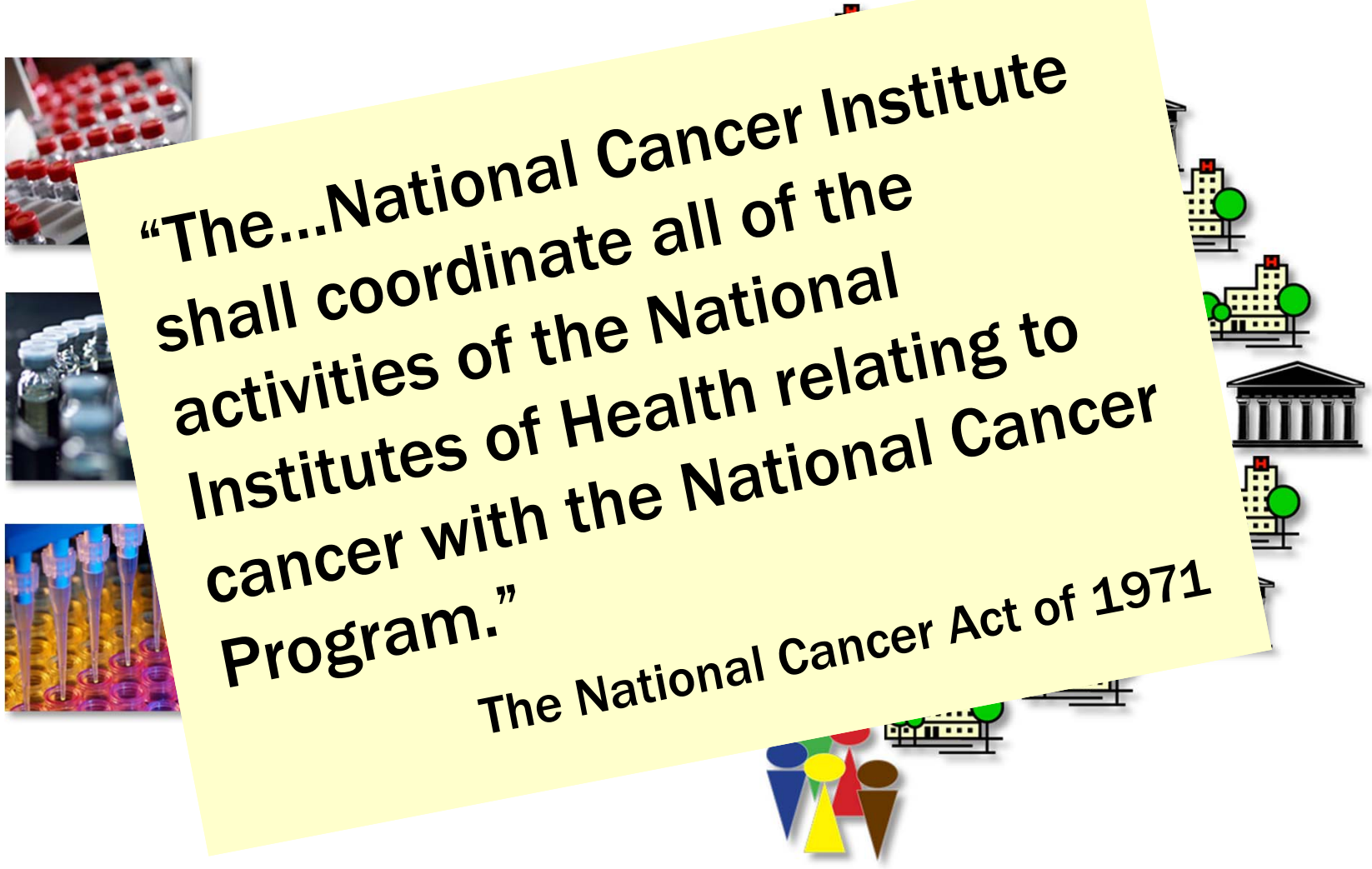
Solutions for the Individual

Science and technology



Phase 0/1

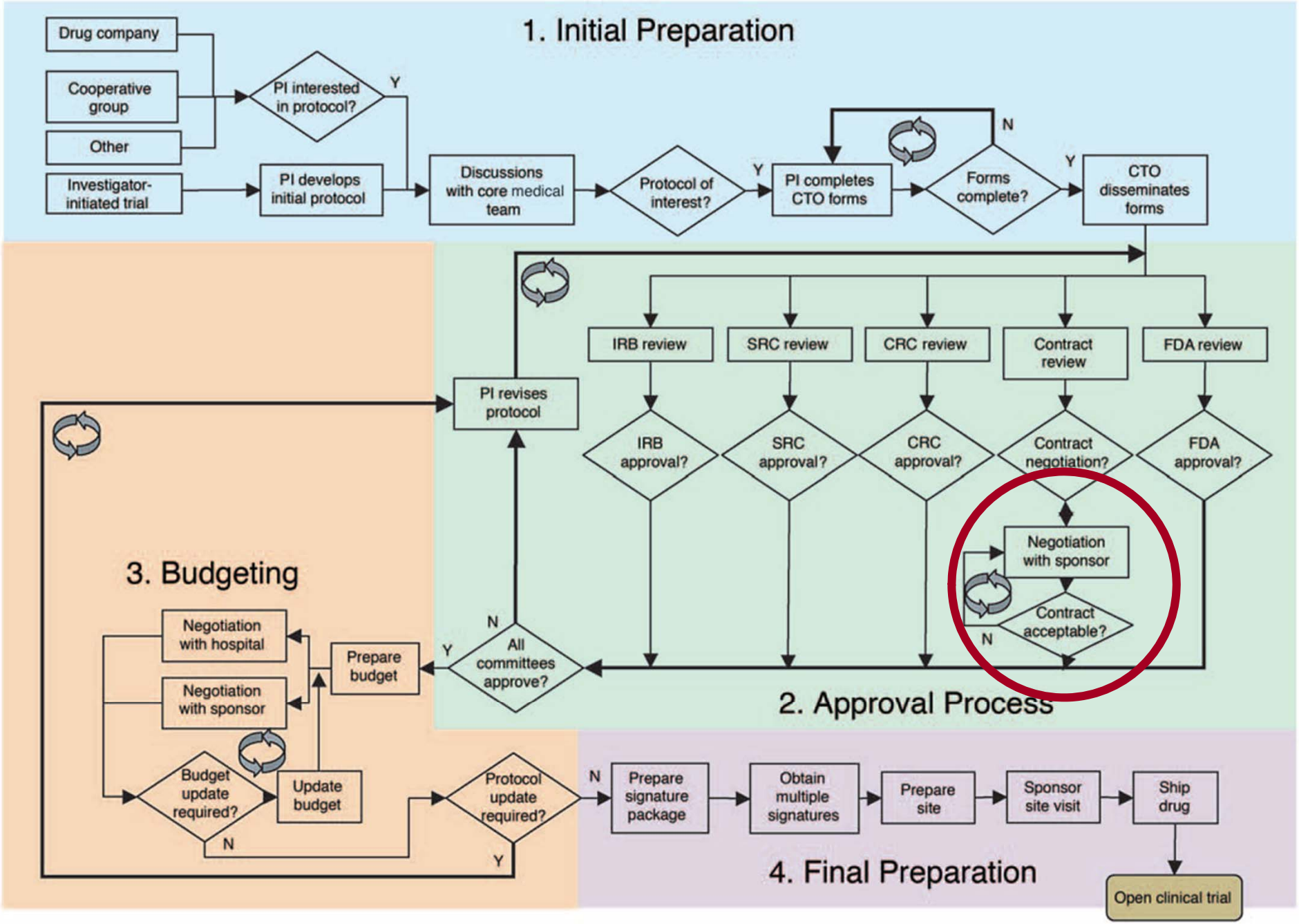
- ✓ IND30452
- ✓ Approved Drug A
- ✓ Approved Drug B
- ✓ Approved Drug C



- 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


1. Initial Preparation
Drug company
Cooperative group
Other
Investigator-initiated trial
PI interested in protocol?
Y
PI develops initial protocol
Discussions with core medical team
Protocol of interest?
Y
PI completes CTO forms
N
Forms complete?
Y
CTO disseminates forms
IRB review
SRC review
CRC review
Contract review
FDA review
PI revises protocol
IRB approval?
SRC approval?
CRC approval?
Contract negotiation?
FDA approval?
Negotiation with sponsor
Contract acceptable?
N
2. Approval Process
N
All committees approve?
Y
3. Budgeting
Negotiation with hospital
Negotiation with sponsor
Prepare budget
Budget update required?
Update budget
N
Protocol update required?
Y
N
Prepare signature package
Obtain multiple signatures
Prepare site
Sponsor site visit
Ship drug
4. Final Preparation
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

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

"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

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."

"In Your Own Backyard," Families USA, July 2008

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

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.go

Advanced Technology Research Facility

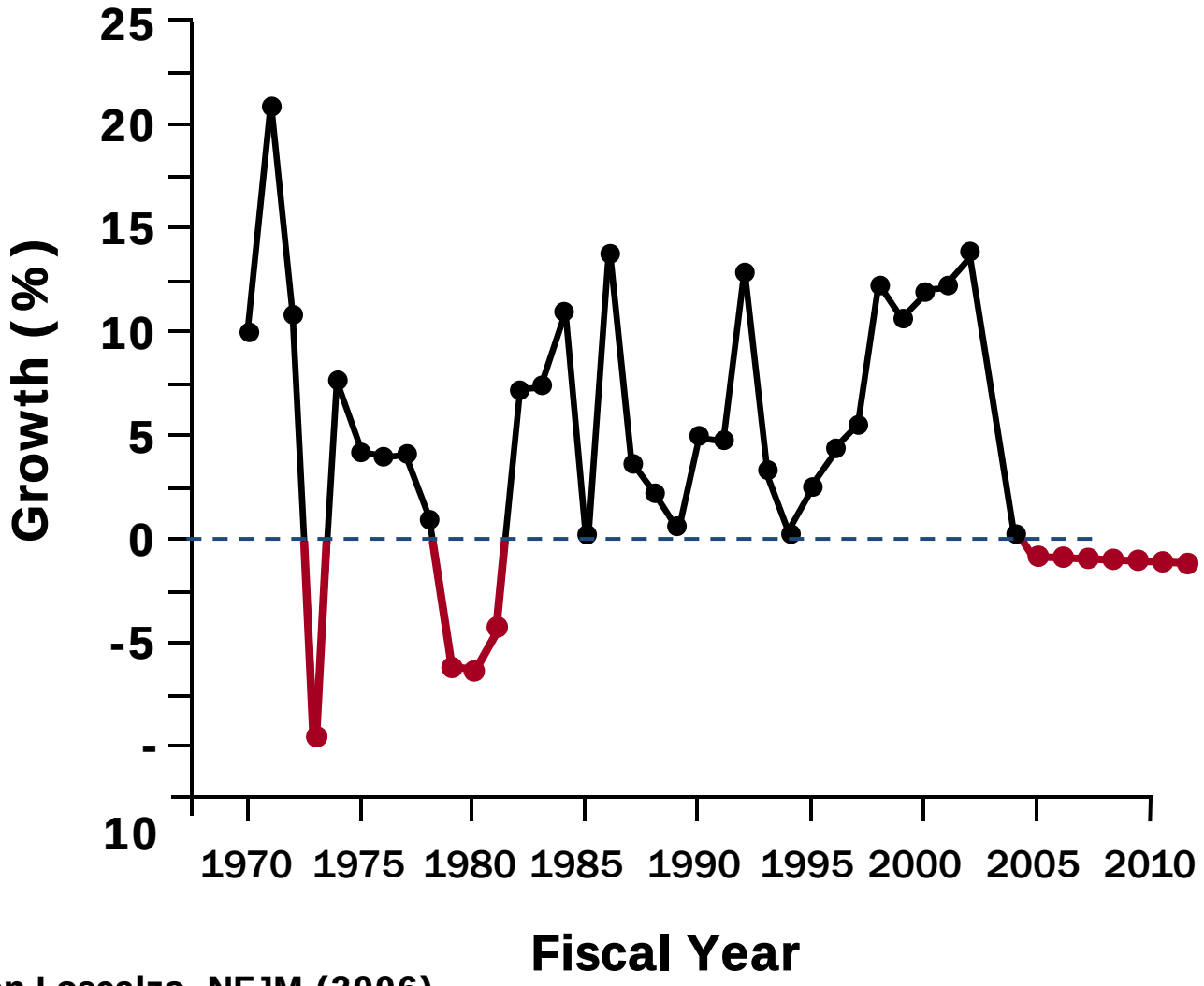
SELECT Trial

- 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

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

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

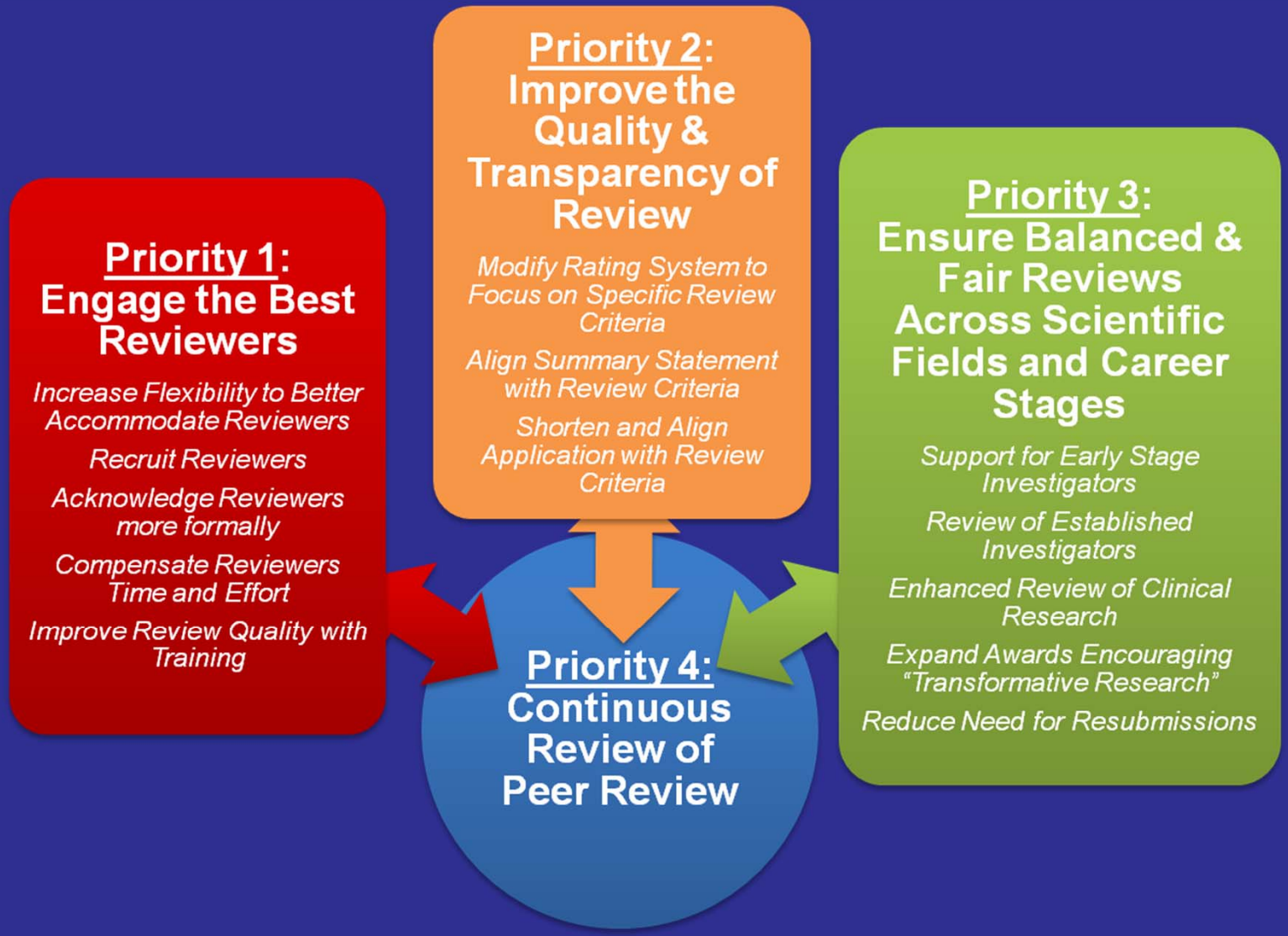
Diagnostic	Design Implementation Plan	Begin Phased Implementation of Selected Actions
June 2007 – Feb. 2008	March 2008 – June 2008	September 2008

Identified Key Recommendations

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

Summary of Recommendations

ENHANCING PEER REVIEW
http://enhancing-peer-review.nih.gov



"...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."

Programs the BSA Will Review Today

- Physical Sciences-Oncology Center
- Special Libraries to Enable Cancer Proteomics
- Stress Regulation of Tumor Biology
- Integrative Cancer Biology Program
- NCI Alliance for Nanotechnology in Cancer
- The Cancer Genome Atlas network

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?**

TCGA in the News

"Scientists have mapped the cascade of genetic changes that turn normal cells in the brain and pancreas into two of the most lethal cancers. The result points to a new approach for fighting tumors and maybe even catching them sooner."

Associated Press, Sept. 4, 2008

TCGA in the News

"'Even though it sounds complex, it's actually allowing us to simplify the complex into pathways that will allow us, I think, to truly understand cancer for the first time and take a much more rational approach to treatment,' said Dr. Anna Barker... who co-directs the cancer atlas project. 'I'm more optimistic.'"

Associated Press, Sept. 4, 2008

Full Year Exception Allocation

	FY 2008 RPG Final Awards (Includes Cancer Control)			FY 2009 PB RPG (Includes Cancer Control)		
	No.	Dollars	Payline	No.	Dollars	Payline
Star (*) R01	83	$26,737	19.0	45	$15,094	18.0
EC Exceptions	22	$15,803		19	$16,906	
Div Exceptions	125	36,702		55	14,000	
Total Exceptions	230	$79,242		119	$46,000	

(Dollars in thousands)

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