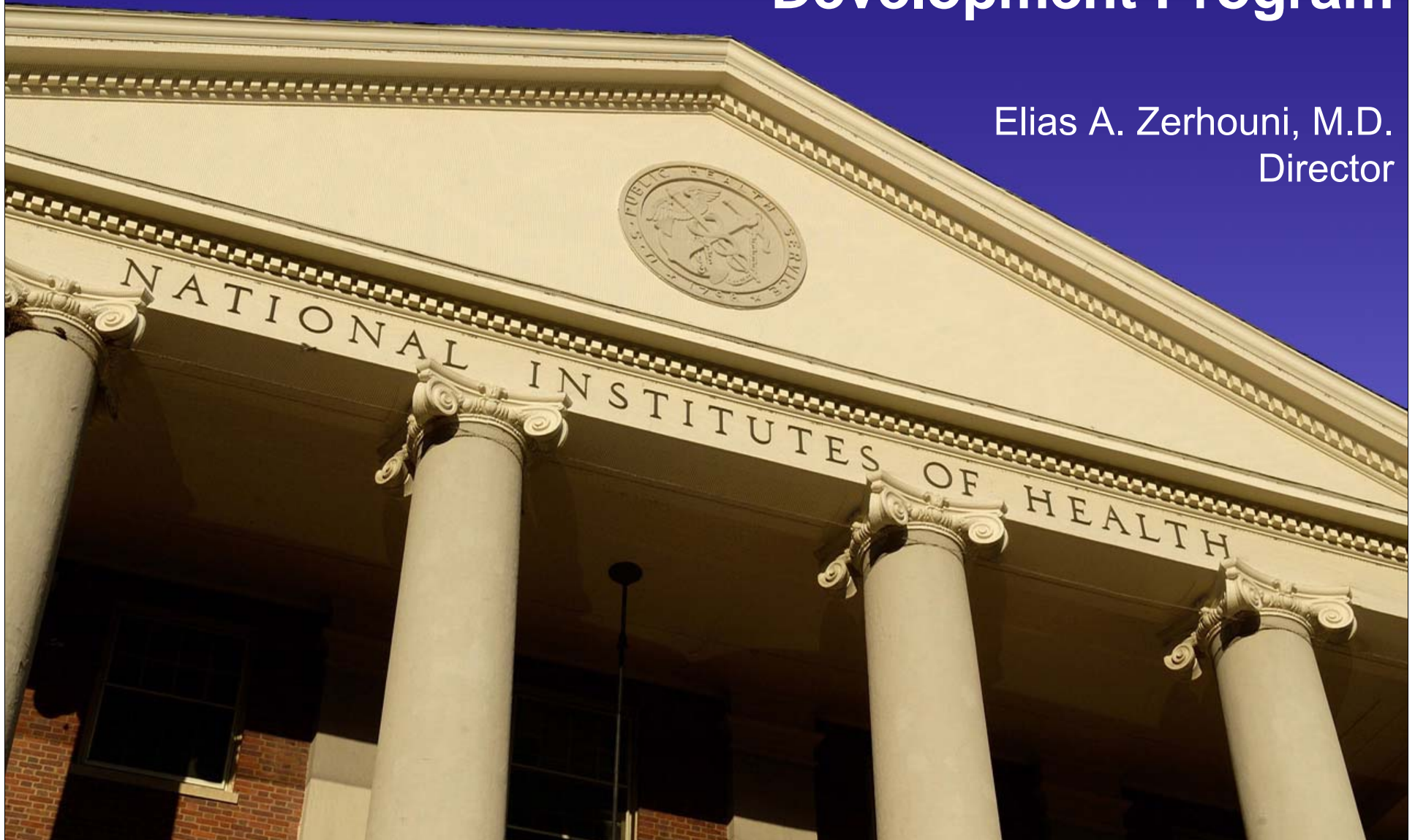




Annual Meeting of the Roadmap Multidisciplinary Clinical Research Career Development Program

Elias A. Zerhouni, M.D.
Director





NIH Roadmap

New Pathways to Discovery

**Research Teams
of the Future**



**Re-engineering the
Clinical Research
Enterprise**





How Did We Get Here?

- Difficulty recruiting and retaining clinical researchers
- Rising overhead costs and regulatory demands
- Limitations due to NIH funding mechanisms, review, and program structure
- Lack of a viable career pathway deters investigators from conducting clinical and translational research – impedes basic research results from entering into clinical practice



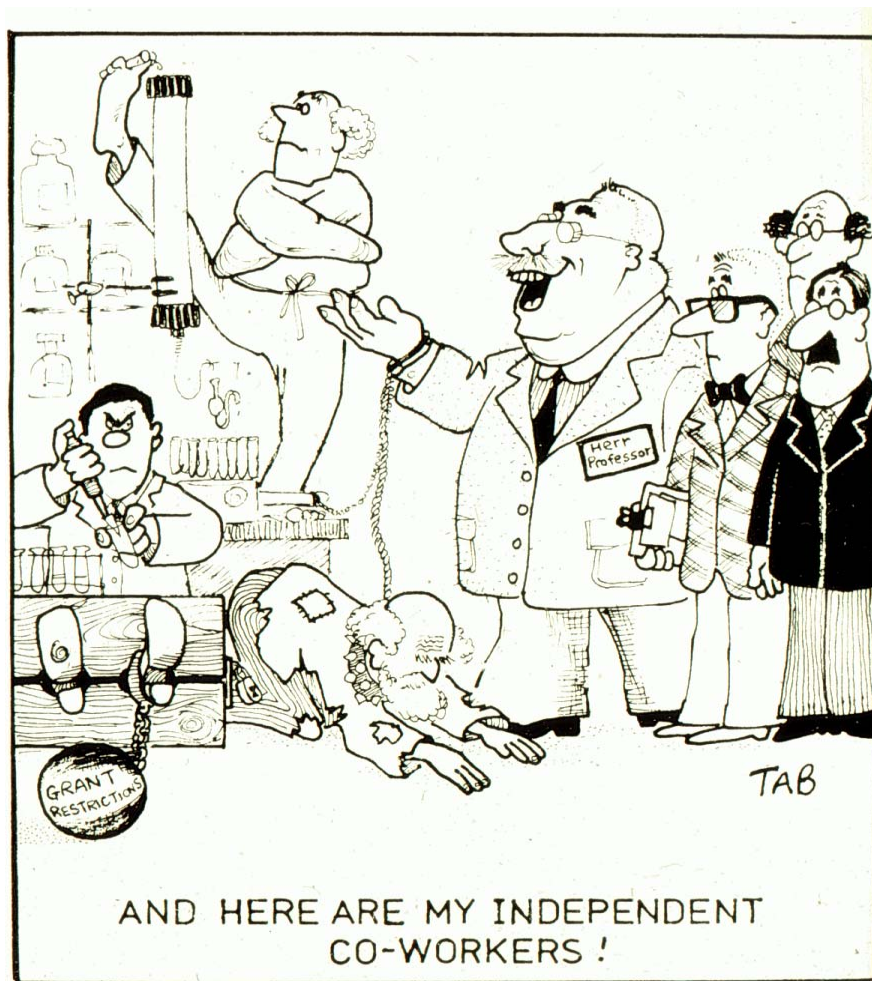


What Can We Do?

- **Create an integrated environment for the clinical and translational researcher that can provide:**
 - Academic home for clinical research (e.g., Center, Department, or Institute)
 - Support for protocol preparation, regulatory compliance and data management
 - Support for participant recruitment, human subject safety monitoring
 - Education leading to advanced degrees in clinical research
 - Specialized cores and services for translational research
 - A FOCUS FOR ORIGINAL RESEARCH ON THE SCIENCE OF TRANSLATION!



Challenges of Interdisciplinary Research



- The current system of academic advancement favors the independent investigator
- Most institutions house scientists in discrete departments
- Interdisciplinary science requires interdisciplinary peer-review
- Project management and oversight is currently performed by discrete ICs
- Interdisciplinary research teams take time to assemble and require unique resources

Everyone's a Critic . . .



"I'm on the verge of a major breakthrough, but I'm also at that point where chemistry leaves off and physics begins, so I'll have to drop the whole thing."



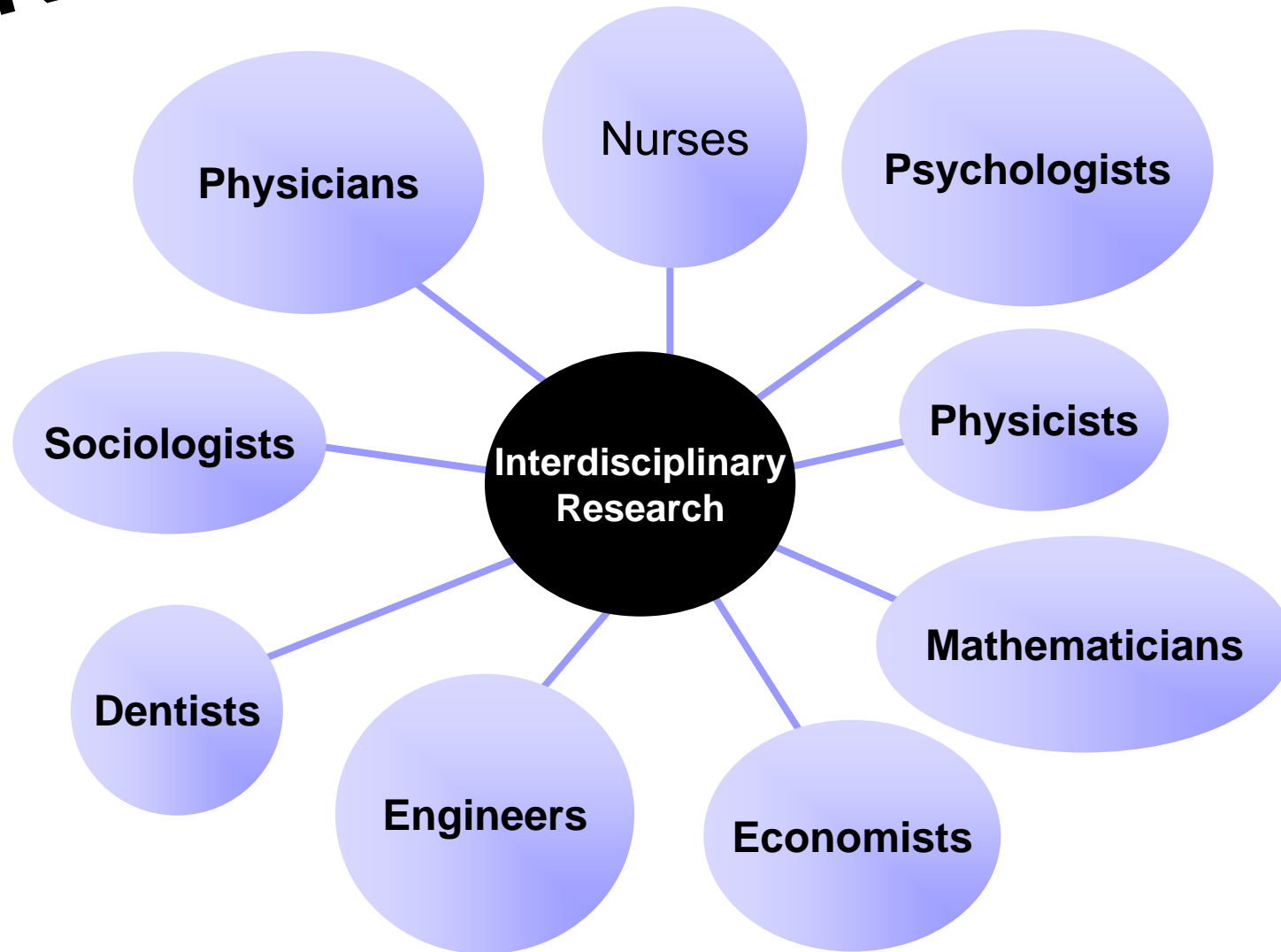
Research Teams of the Future

- **Exploratory Centers for Interdisciplinary Research**
- **Goals:**
 - *Encourage collaboration* among researchers from seemingly unrelated disciplines to address biomedical issues
 - *Provide solutions* to biomedical problems that have not been solved using traditional approaches
 - *Forge new disciplines* from existing ones to accelerate the pace of scientific discovery, ultimately to benefit public health
- **Funding:**
 - *More than \$36M will be awarded over three years to support the 21 Exploratory Centers for Interdisciplinary Research*



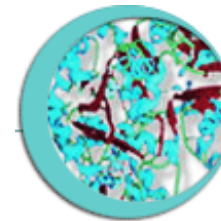


Research Teams of the Future



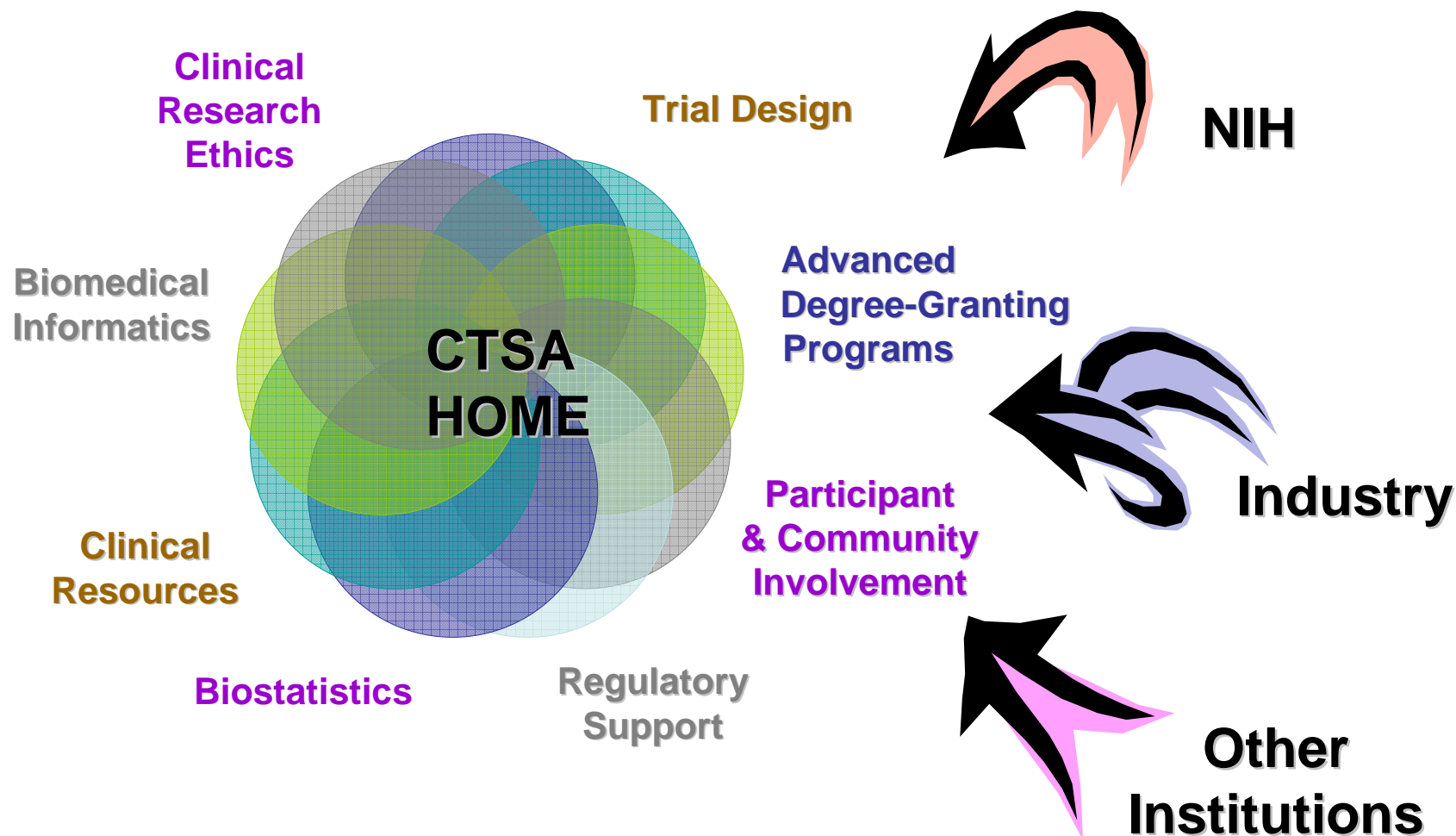
Clinical and Translational Science Awards (CTSAs)

- Lower barriers between disciplines
- Encourage creative, innovative approaches in solving complex medical problems
- Catalyze change: break silos, break barriers, and break conventions





NIH CTSA Awards: A Home for Clinical and Translational Science





CTSA Objectives: Speed Discoveries to Improve Patient Care

- Develop a distinct discipline for clinical and translational science at institutions across the country
- Provide opportunities and resources for original research on novel methods
- Develop translational technologies and a knowledge base for the full spectrum of clinical and translational science
- Synergize partnerships with industry, foundations, and community physicians
- Train the interdisciplinary teams who will conduct the clinical and translational research of the future





Multidisciplinary Clinical Research Career Development Program

- Roadmap K12 Program is designed to increase the national pool of clinician-scientists from many disciplines
- The program differs in its goal by supporting career development of the clinical research team
- The clinical research team includes: nurses, sociologists, pharmacologists, biostatisticians, and epidemiologists, in addition to physicians, dentists, and scientists.
- Funding for up to 5 years includes didactic and practical training in design, conduct, and analysis of clinical research
- Each clinical research scholar may be recruited from within a grantee institution or externally and has two mentors





RM K-12 Scholars Scientific Highlights

- Creating Technology for Stroke Rehabilitation
- Developing Prevention Strategies for Chronic Diseases
- Testing HIV Therapies
- Examining Novel Markers of Obesity
- Reducing Health Disparities in Minority Populations





NIH Budget Facing a “Perfect Storm”



- Federal Deficit, Defense and Homeland Security priority requirements, Katrina, Pandemic flu and domestic budget cuts (-2.7% for HHS)
- Congressional support for Physical Sciences for competitiveness
- Overall support for NIH is still strong
- Biomedical research inflation is around 4%





Why Are Success Rates So Low?

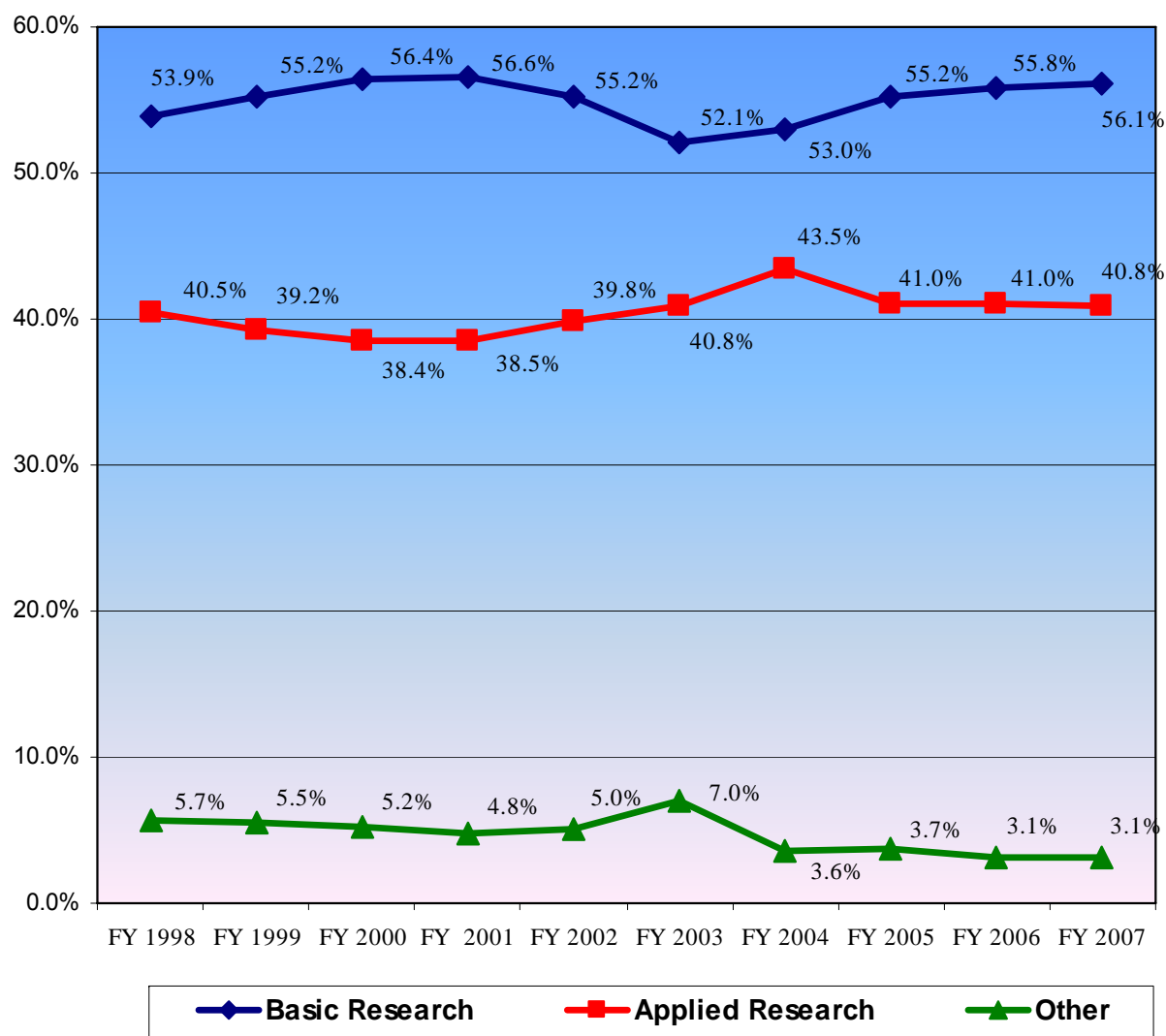
- Too much emphasis on translational science away from basic science!
- It must be that big projects and initiatives (RFAs, PAs) are taking money away from unsolicited grant applications
- It must be the Roadmap!





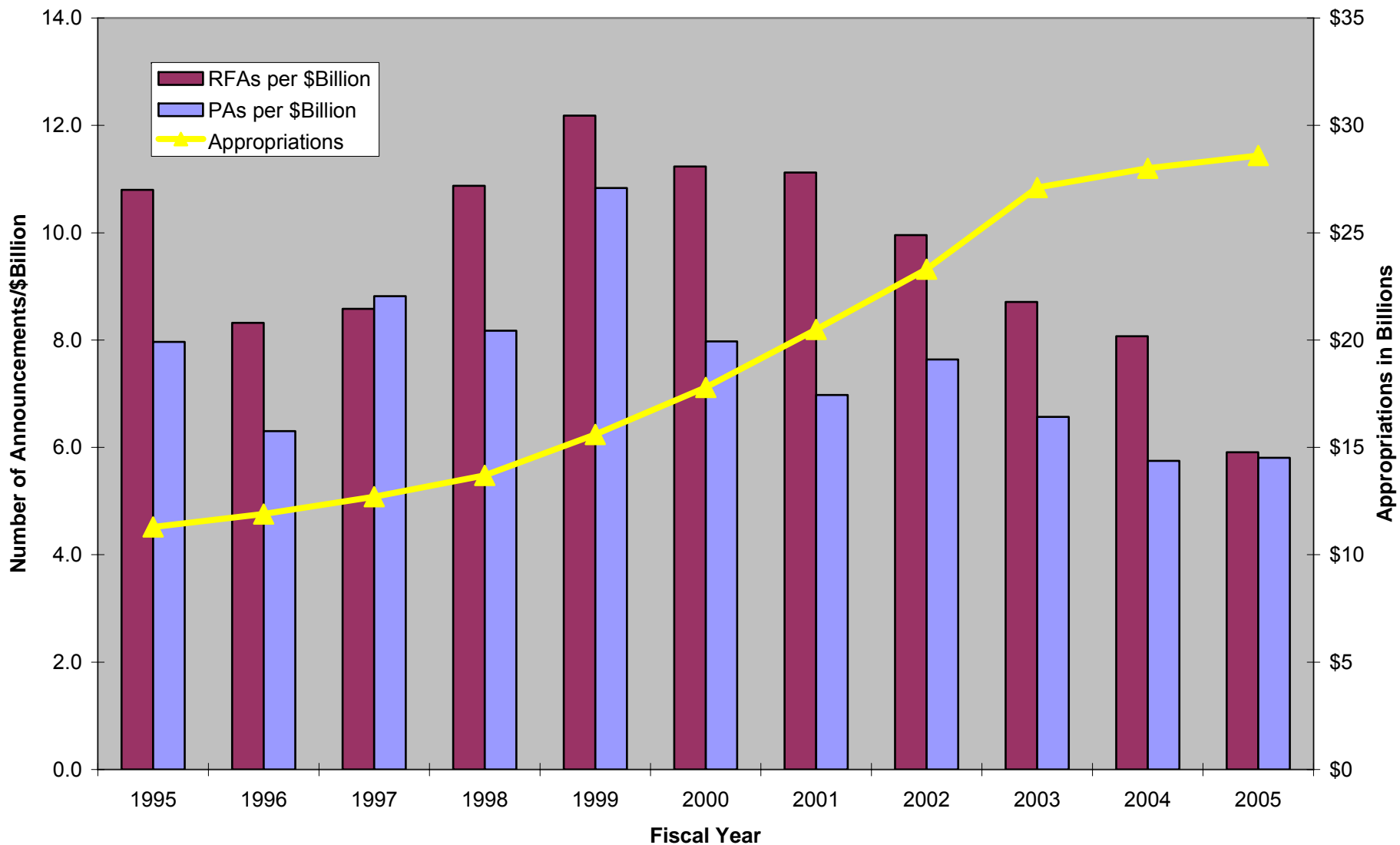
Basic and Applied Research

Budget Authority
(\$ in millions)



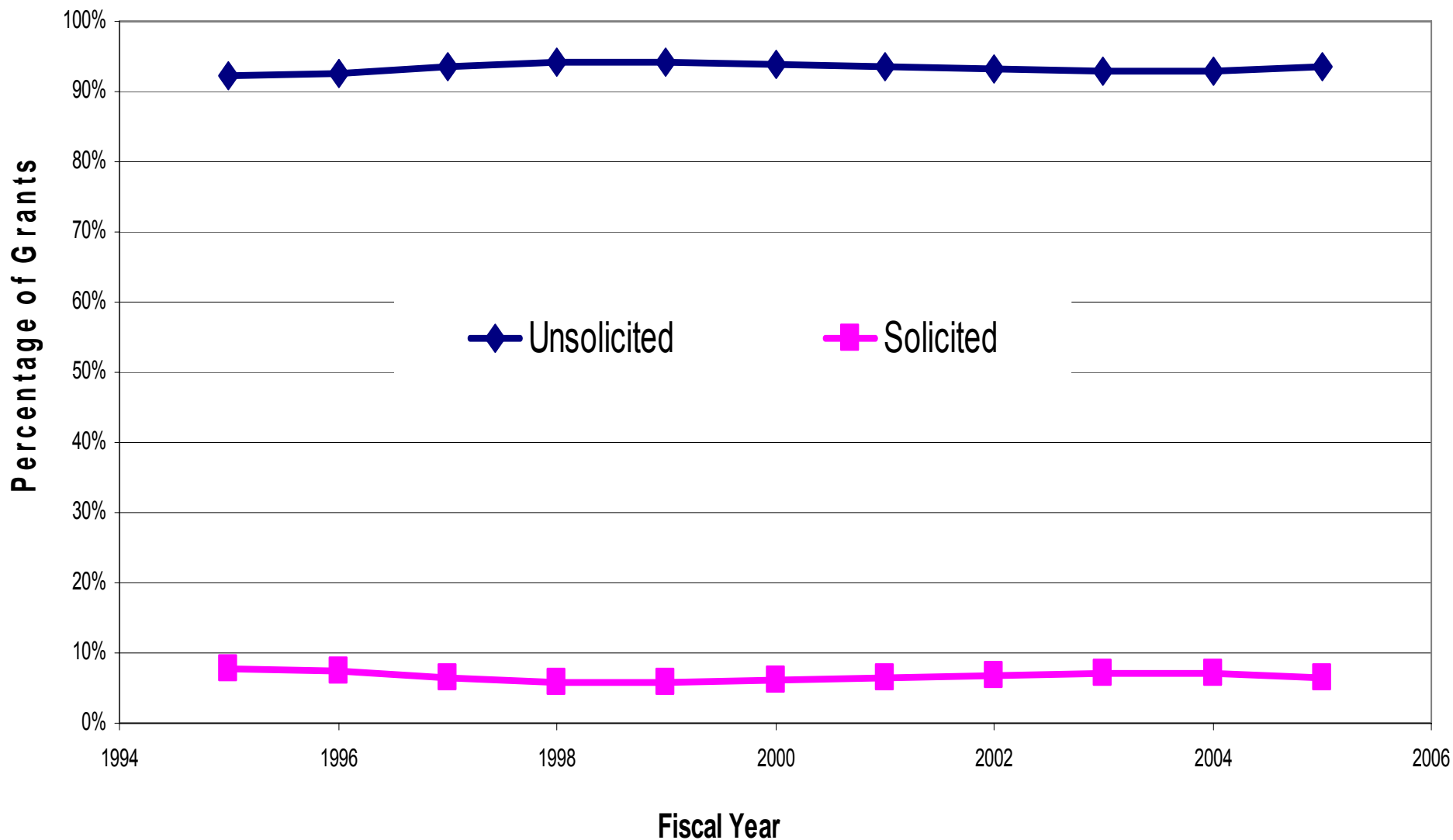


4B. Number of NIH Guide Announcements Compared to Annual NIH Appropriations Fiscal Years 1995 - 2005





Grants: Unsolicited Far Outnumber Solicited



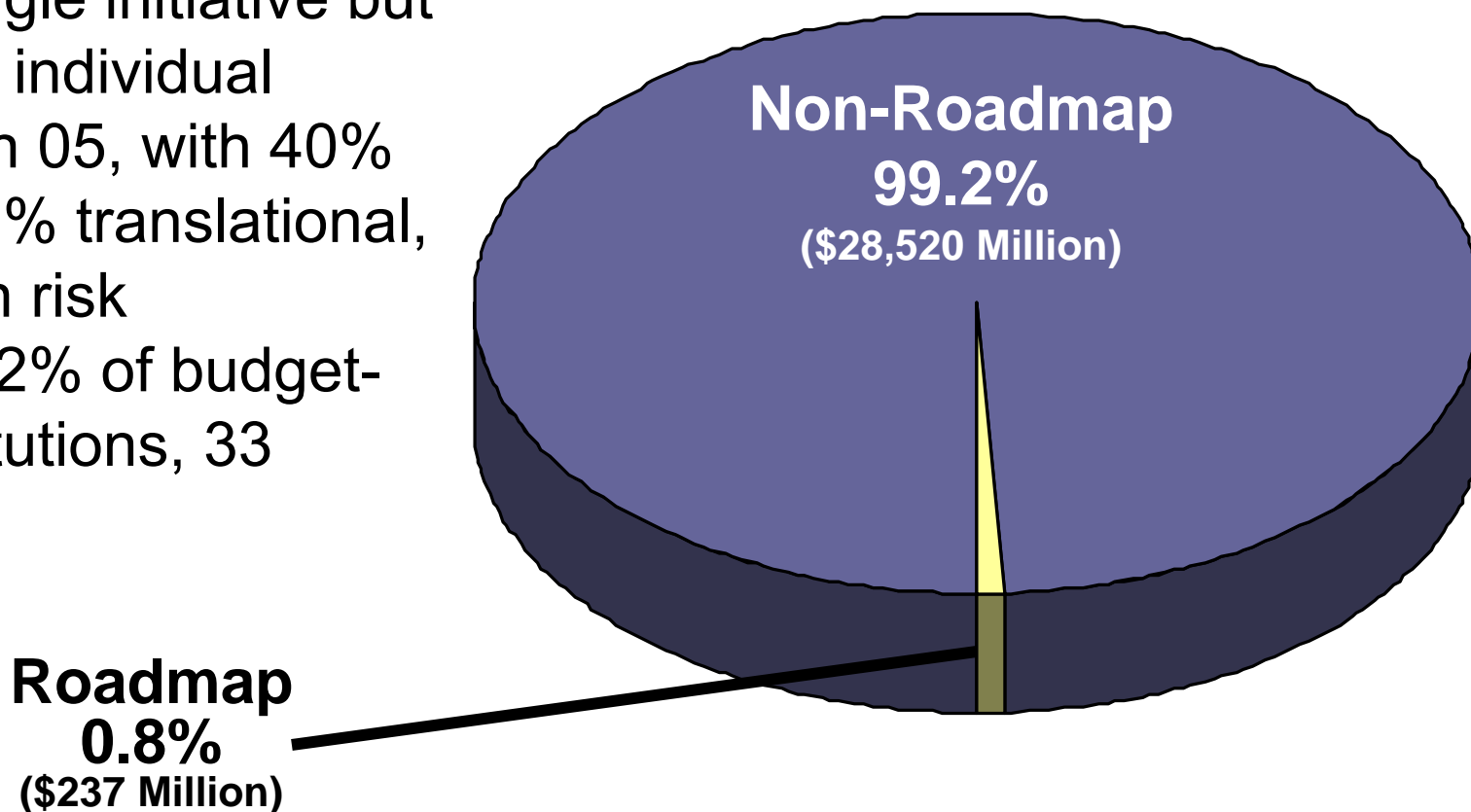


FY2005: Roadmap = 0.8% of Total Budget

NIH Roadmap:

- Not a single initiative but over 352 individual awards in 05, with 40% basic, 40% translational, 20% high risk
- FY 06 1.2% of budget- 133 institutions, 33 states

FY2005 Request = \$28,757M





Past, Current and Prospective Roadmap Funding Dollars (\$M)

	FY04	FY05	FY06	FY07	FY08	FY09	TOTAL
Pathways to Discovery	65	136	167	181	207	187	943
Research Teams	28	43	44	81	86	82	364
Clinical Research	39	61	118	181	222	234	855
TOTAL	132	240	329	443	515	503	2,162

Roadmap Initiative ~ 1% of NIH Budget





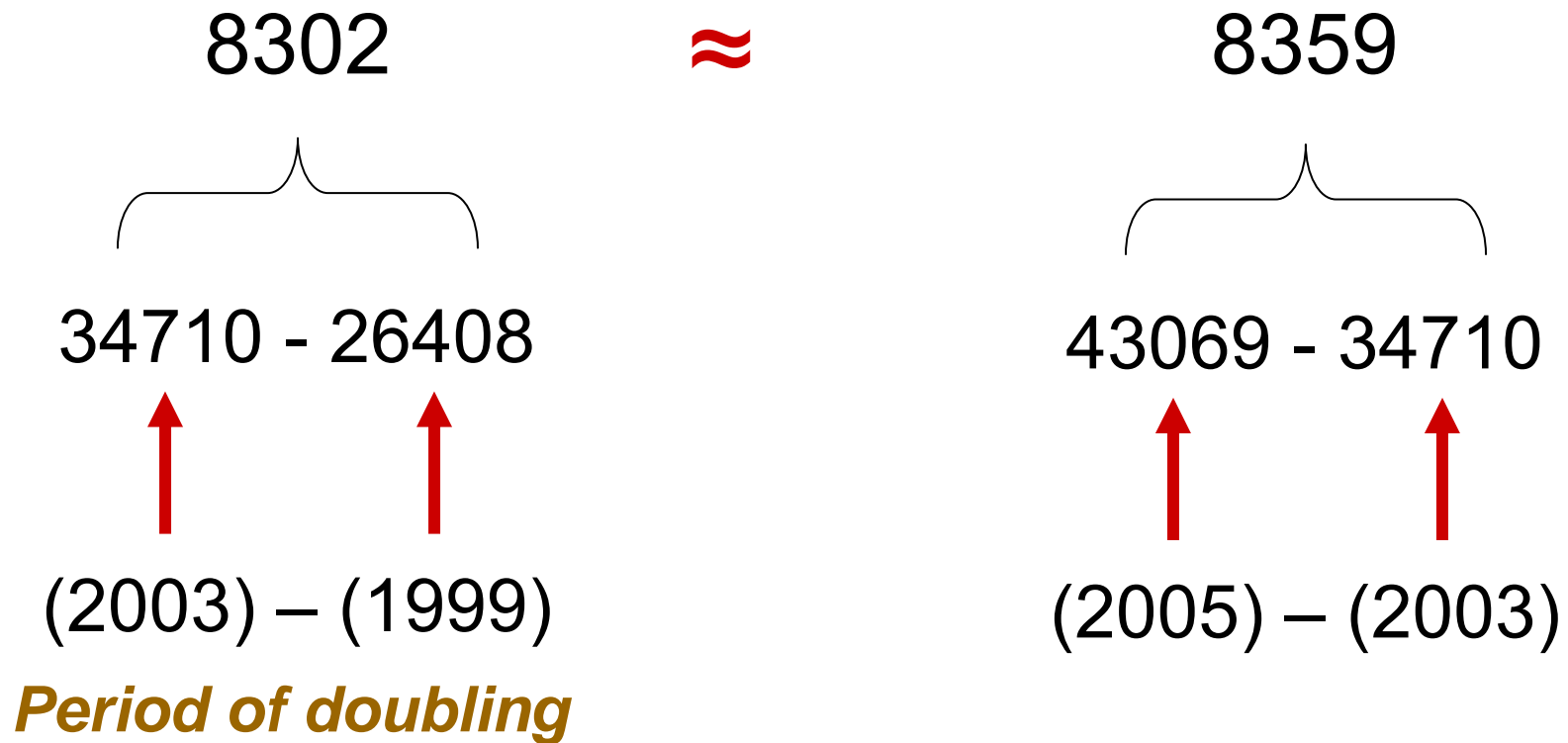
What Is Really Happening?

- Large increase in number of applicants and applications due to large capacity building throughout US research institutions
- Large increase in number of tenure track faculty
- Increased number of applications per applicant
- Confusion about Payline, success rates (per application) and “what are my chances of being funded?”
- Budget cycling phenomenon



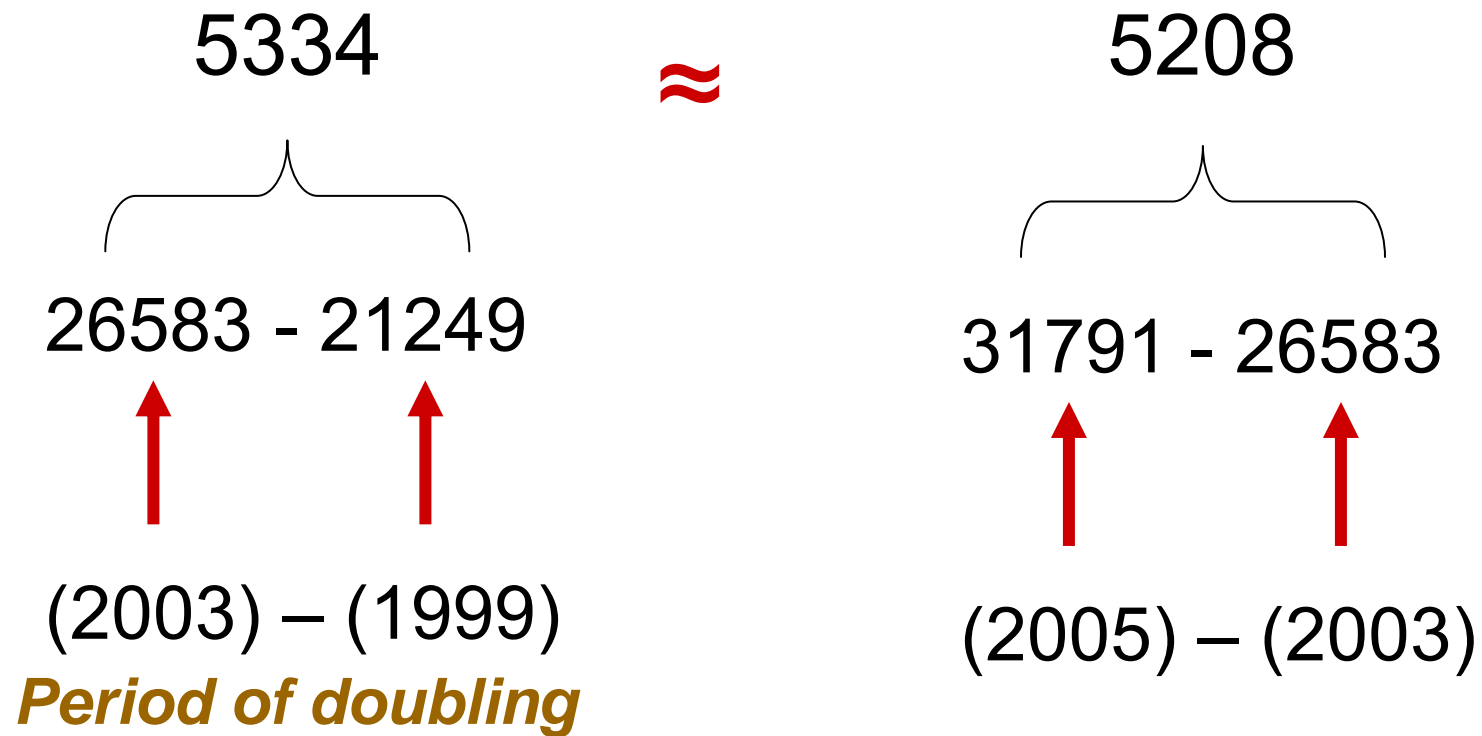


As Many **New Applications** in the Last 2 years as During the Doubling





As Many New **Applicants** in the Last 2 years as During the Doubling





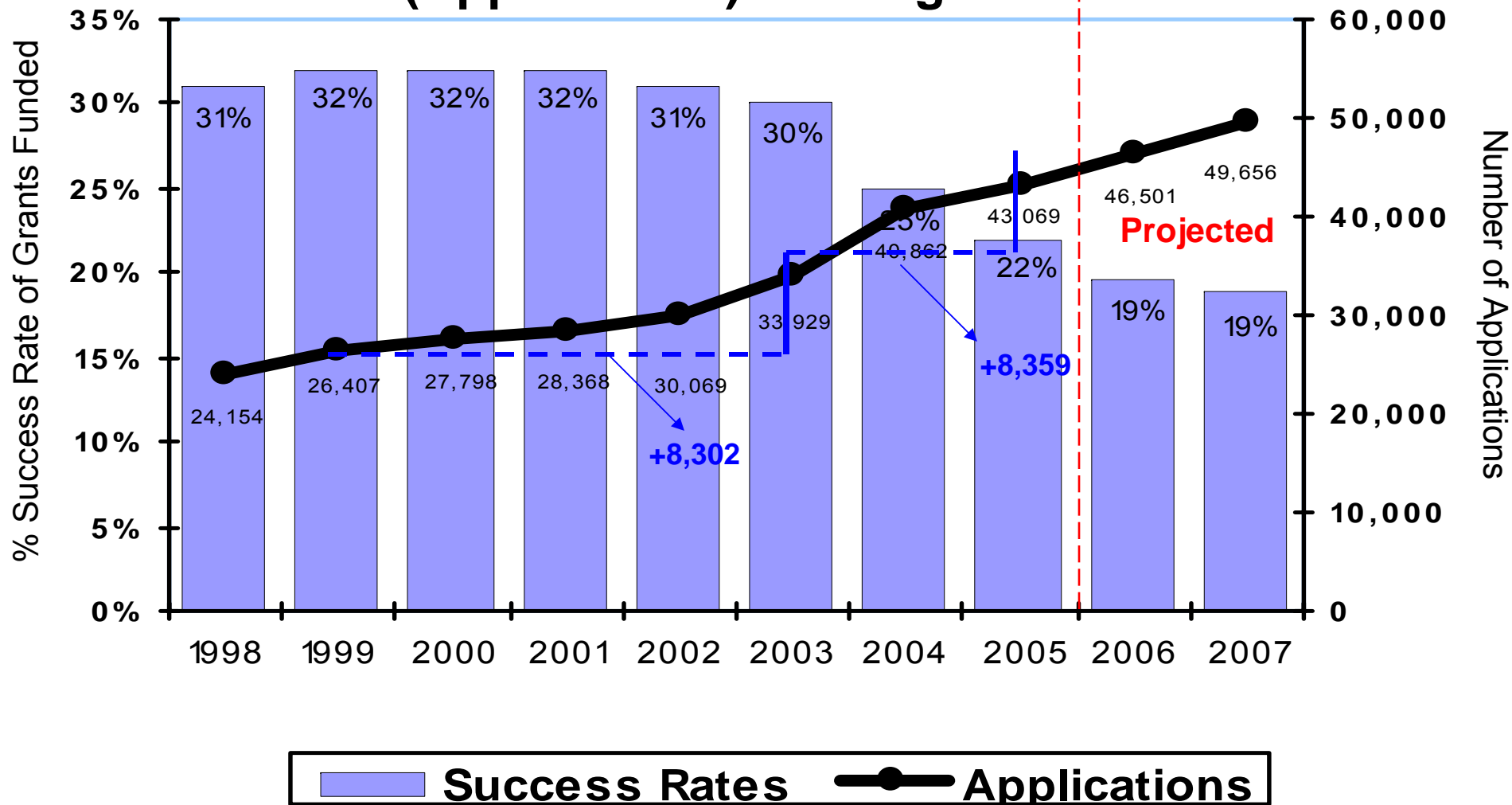
Elias A. Zerhouni, MD, Director, NIH

May 4, 2006





How Does the % of Grant Applications Funded (or “Success Rate”) Compare with the Number of New Ideas (Applications) Coming In?





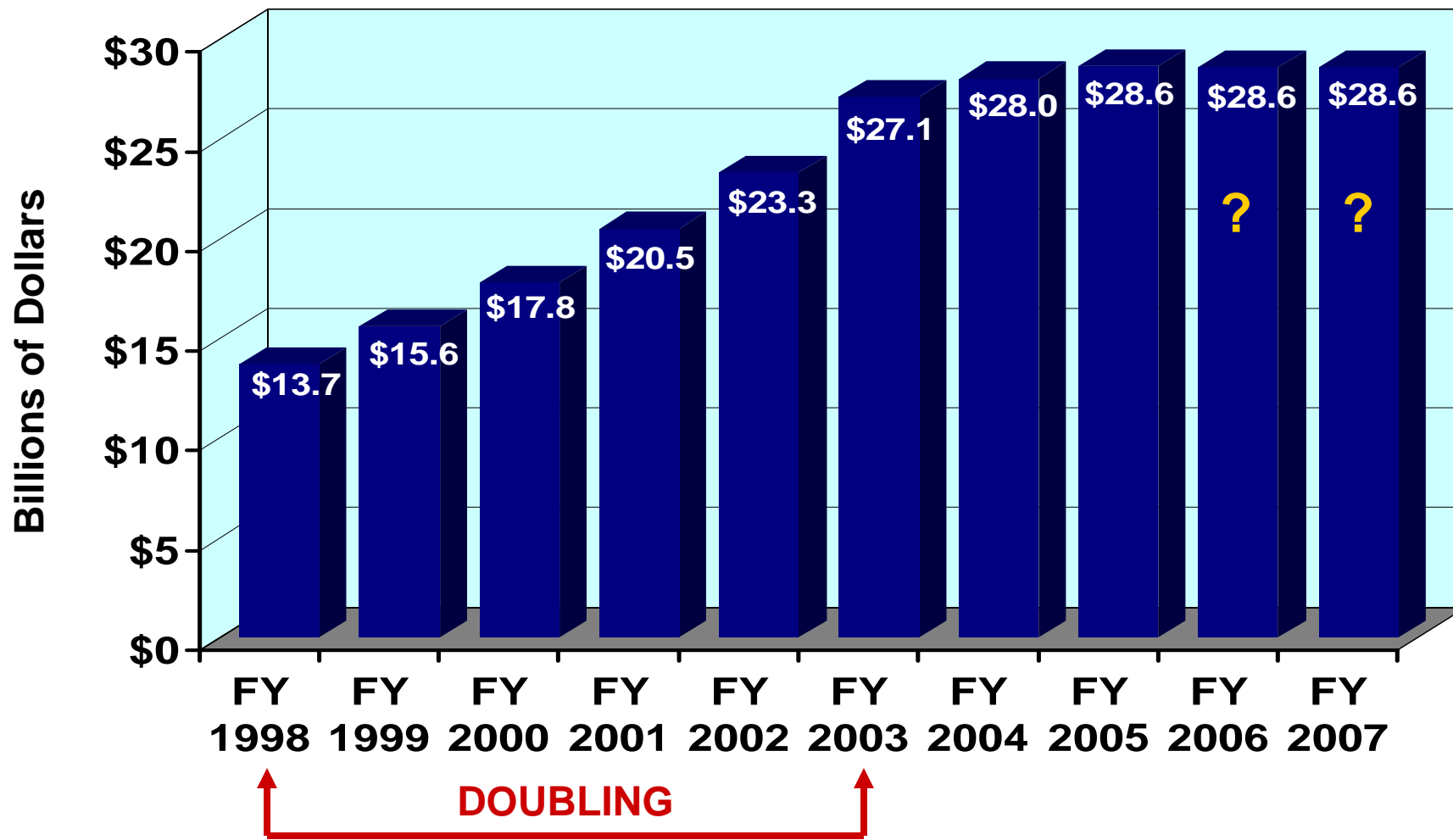
What Are My Chances of Being Funded?

- Because number of applications per applicant has increased from 1.2 to 1.5, success rate understate funding rates
- FY 05- 22.3% success rate for applications but 27.6% for individual applicants
- Fy06- 19.8% for applications but ~25% for individual applicants
- Payline is not the funding cut off line!





NIH Congressional Appropriations





Among the Priorities in the FY 2007 Budget :



Enhanced Support for New Investigators- PATHWAY TO INDEPENDENCE AWARD

- Five years of support consisting of two phases
- Phase I provides 1-2 years of mentored support for advanced fellows
- Total cost of \$90,000 per award including 8% F&A
- Phase II provides up to 3 years of independent research support contingent upon securing an independent research position and administrative review.
- Total cost of \$249,000 per award including full F&A





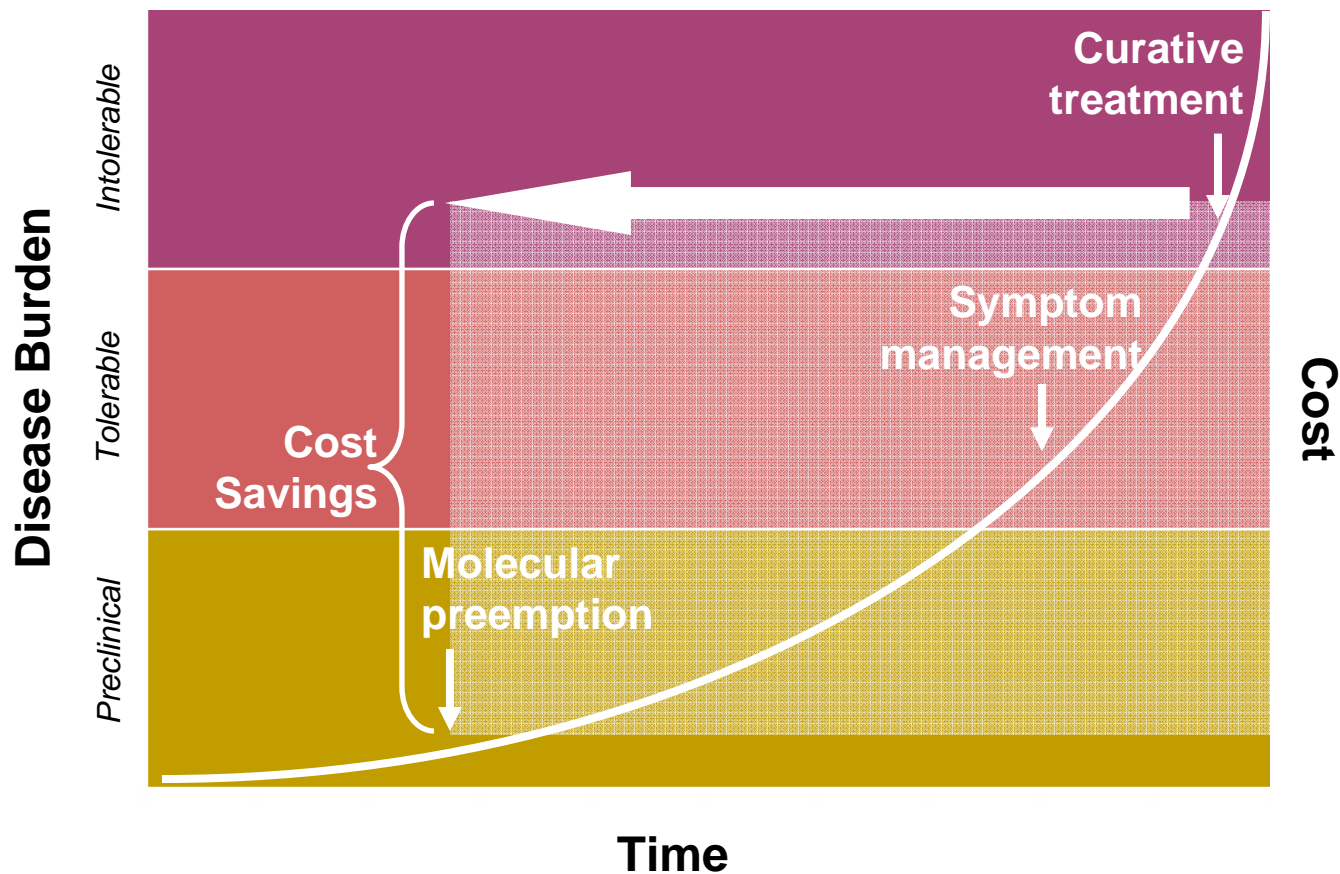
NIH Director's Pioneer Award Program



- Signal that NIH values innovation; business NOT as usual by:
 - Investing in people
 - Implementing new mechanisms
 - Allocating dollars
 - Shortening time to awards
- Support individuals with untested, potentially groundbreaking ideas in areas including: neuroscience, genetics, epidemiology, chemistry, stem cell biology, behavioral science, infectious diseases, and technology development
- Highly competitive -- 9 awards in the first year and 13 awards in the second year



The Future Paradigm: Preempt Disease





Need to Transform Medical Research in the 21st Century

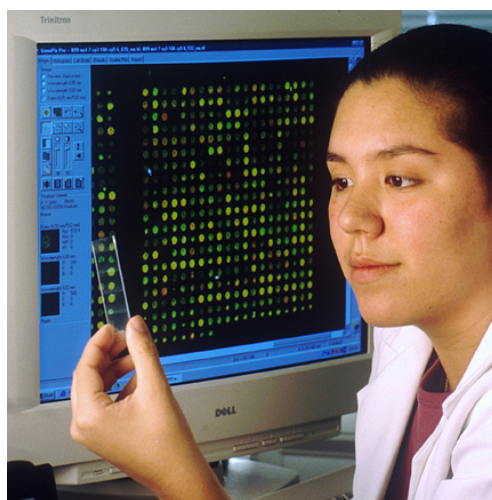
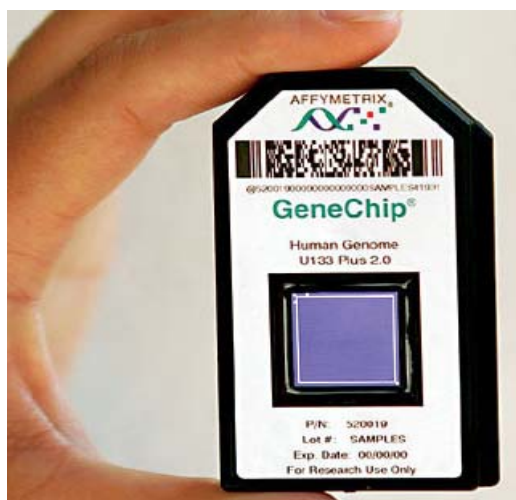
20th Century	21st Century
Treat disease when symptoms appear and normal function is lost	Intervene before symptoms appear and preserve normal function for as long as possible
Did not understand the molecular and cellular events that lead to disease	Understanding preclinical molecular events and ability to detect patients at risk
Expensive in financial and disability costs	Orders of magnitude more effective





Our Best Hope:

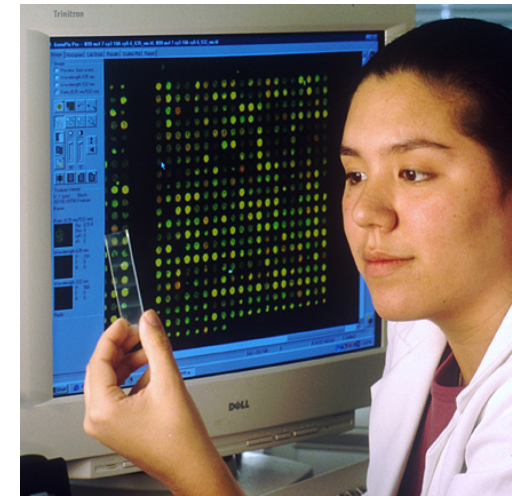
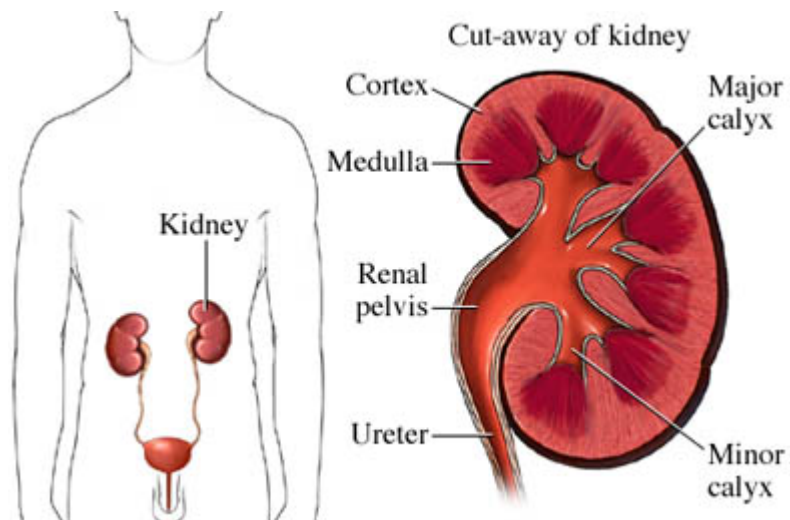
Transform Medicine Through Discovery



Predictive \longleftrightarrow Personalized \longleftrightarrow Preemptive



Predictive: End Stage Renal Disease



End-stage Renal Disease Statistics (NIDDK):

\$22.8 billion (2001) in public and private spending in the US

More than 85,000 new cases per year (incidence is 31% among African-Americans)

Apolipoprotein E (APOE) variation predicts kidney disease progression, independent of diabetes, race, lipid and non-lipid risk factors. Cellular mechanisms of kidney remodeling have been implicated. *Hsu, C. et al. (2005) JAMA 293:2892*

Personalized: Pharmacogenomics

Identified 16 informative genes



Test tumor samples for mutations in these genes



Technique:

Use mutation analysis to identify which women will benefit from chemotherapy vs. hormone therapy

Impact:

- 100,000 women *each year* can make a more informed choice
- 70,000 women do not have to undergo chemotherapy
- Reduces routine cost of treating these patients
 - For each patient year of life gained, we save ~\$8,000

Preemptive: HPV Vaccine

How the 'Cancer Shot' Works

Over 99 percent of cervical cancer cases are the product of long-term infection with human papillomavirus, or HPV. How it happens — and how the vaccine prevents it:

THE HPV INVASION

Papillomavirus

Layers of Epithelial cells

Papillomavirus

Layers of Epithelial cells

The Virus, passed by skin-to-skin contact, needs to penetrate deeply into the lining of the cervix to establish a chronic infection. Sex, which abrades the lining, or a sore can provide a breach.

Once inside the cervical lining, the viruses attach to the epithelial cells. Mistaking them for nutrients or other molecules that are normally in the environment, the cells take them in.

Nucleus

Virus "uncoats"

Epithelial cell interior

Mucus

Healthy cells

Cancerous epithelial cells

The HPV, which is housed in a protective shell made up of a viral protein called L1, "uncoats" and releases its genetic information into the host cell to infect it.

Viral Genes E6 and E7 then disable the cell's tumor-suppressors, allowing for abnormal cell division. It takes 12-15 years on average for the lesions to become cancerous.

THE BATTLEFIELD

Cervical Area: The HPV travels through the vagina to the cervix, which sits at the base of the uterus.

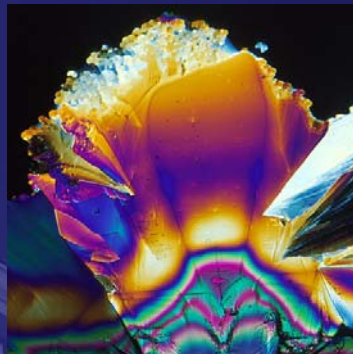
ANTIBODIES IN ACTION

The HPV Vaccine, essentially an empty shell made of the L1 protein, works by triggering the production of antibodies that neutralize the virus. If actual HPV appears in the body later, the antibodies cling to it, interfering with both its ability to bind to the cell and to release its genetic material.

Papillomavirus

Antibodies

- HPV infection is a **necessary** cause of cervical cancer
- Prevent sexually transmitted HPV infection = prevent cervical cancer
- Anti-Viral Vaccines are among the most cost effective public health interventions (e.g., smallpox, polio, & measles)



NIH *Transforming medicine through discovery*

