NIH R01 Grant Writing Strategies and New Policies for Review

SF VAMC Research Seminar Series
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Support of biomedical research at US universities

Source	% Total
NIH	72
NSF, DOD, DOA, DOE, NASA	12
HHMI, ACS, other private	11
Industry	5

Research is always something of an adventure. The more freedom it enjoys, the more likely it is to achieve important results.

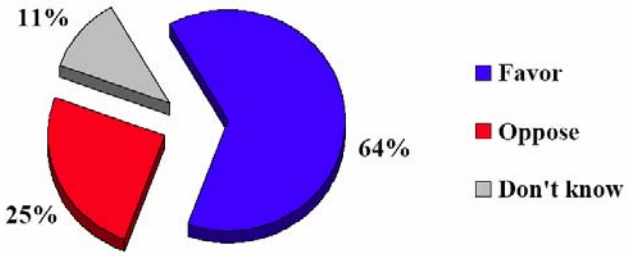
National Resources Committee,
Research -- A National Resource, 1935

The only possible source for adequate support of our medical schools and medical research is the taxing power of the Federal Government. …such a program must assure complete freedom for the institutions and the individual scientists in developing and conducting their research work.

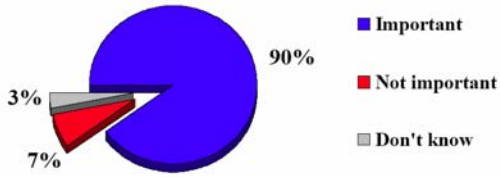
Surgeon General Thomas Parran
December 1945

US public supports government funding for research

There is a proposal to double our total national spending on government-sponsored science and engineering research over five years. In general, do you favor or oppose this idea?



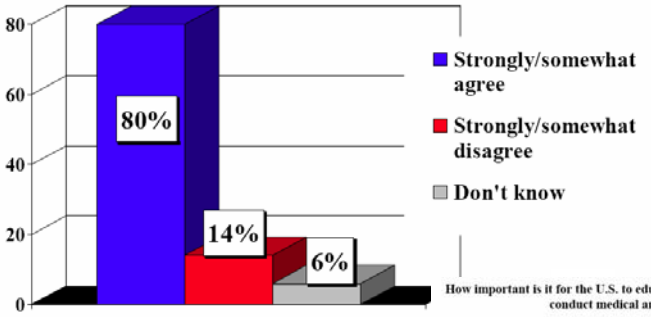
How important do you think medical and health research is to the U.S. economy?



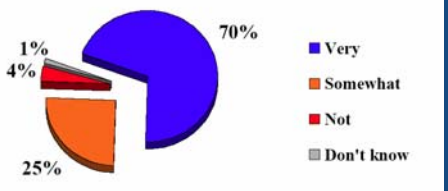
2004 Research!America Health Poll

US public supports government funding for research

Even if it brings no immediate benefits, basic science research which advances the frontiers of knowledge is necessary and should be supported by the federal government.



How important is it for the U.S. to educate and train individuals qualified to conduct medical and health research?



2004 Research!America Health Poll

Congressional Support for NIH Budget

Proposed doubling, FY 1999-2003 (~15%/year increase)

FY 1998 budget: $13.6 billion

FY 2003 budget (year 5):

OMB proposal, FY 2003: $26.5 billion (13.8% increase)
Specter-Harkin resolution: $27.2 billion (vote: 96-4)
FY 2003 budget, signed: $27.2 billion

FY 2004: 2.9% increase

FY 2005: 2.1% increase

FY 2006: 0.1% decrease

FY 2007: 0.0% increase

FY 2008: 1.3% increase

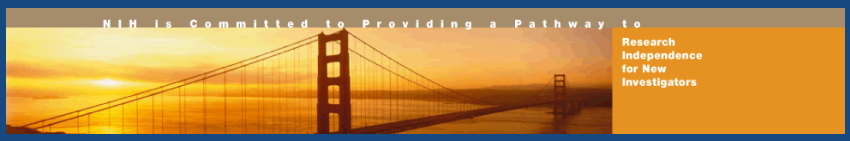
- *~1% of Federal budget; ~$95 per citizen*
- *83% of NIH budget supports extramural research, all allocated by peer review*

Be informed, get involved

Join the Congressional Liaison Committee

NIH Pathway to Independence Award: K99/R00

http://grants2.nih.gov/grants/new_investigators/pathway_independence.htm



Response to NAS Report: *Bridges to Independence: Fostering the Independence of New Investigators in Biomedical Research*
http://fermat.hap.edu/books/030909626X/html/

- 150-200 awards/yr
- 2 year Mentored Phase: $90k/yr
- 3 year Independent Phase: $249k/yr
- Noncitizens eligible
- Maintains new investigator status for subsequent R01 application

NIH Director's New Innovator Award

http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-08-014.html

Launched March 2007

- For new investigators who have not received R01 grant
- To support highly innovative projects with potential for exceptionally great impact on biomedical or behavioral science
- 5 years, $1.5M direct costs
- 31 awards announced September 2008 (2 at UCSF)

NIH Adaptive strategies for tough times

- No inflationary adjustments for noncompeting renewals
- Increase number of competing research project grants
- Strengthen support for at-risk scientists
  - new investigators
  - first grant renewals
  - established investigators with little or no current support
- Ongoing efforts to increase FY09 budget

Enhancing NIH Peer Review: the first full assessment

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

June 2007-Feb 2008: Collect information, develop recommendations
March-June 2008: Design implementation
Sept 2008: Begin implementation

Goals:

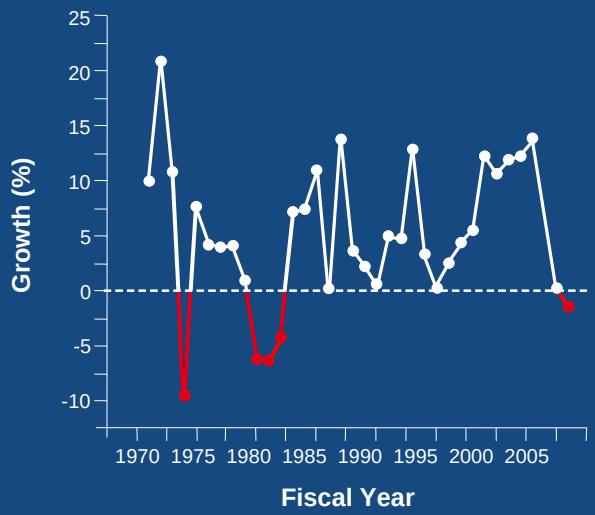
- Review process that motivates top scientists to serve
- Rating scheme that accurately reflects impact and excellence
- Evaluation/funding policies and mechanisms that serve multiple types of science and scientists
- Periodic review of peer review that maintains excellence and adapts to change

Enhancing NIH Peer Review: initial implementation

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

- Engage the best reviewers
  - -- Improve reviewer retention (Jan 2009)
  - -- Enhance reviewer training (May 2009)
  - -- Test virtual reviewing (pilots in 2009)
- Improve quality and transparency of review
  - -- Integer (1-7) scoring of five review criteria (May 2009)
  - -- Score streamlined applications (Jan 2009)
  - -- Shorten and restructure applications (12 pages, aligned w/ criteria, Jan 2010)
- Ensure balanced reviews across fields and career stages; reduce administrative burden
  - -- Consider separate percentiling of new and revised applications, w/ one revision limit
  - -- Review like applications together (establish Early Stage Investigator (ESI); consider clustering ESI reviews; consider clustering clinical reviews)

The long view: Annualized growth of the NIH budget



Source: Loscalzo , NEJM (2006)

...better times are ahead!

NIH Core Strategic Vision

- Transform medicine and health from a *curative* to a *preemptive* paradigm
- Support basic research to identify the earliest molecular stages of disease in complex biological systems
- Accelerate translation of findings from the bench to the bedside to the community

- Provide the evidence and knowledge base to allow for a rational transformation of our healthcare system

National Institutes of Health

A federation of **27 separate Institutes and Centers**; one of the agencies of the **Public Health Service**, which in turn is part of the **US Department of Health and Human Services**.

Nineteen Institutes fund biomedical research grants:

National Cancer Institute
National Eye Institute
National Heart, Lung, and Blood Institute
National Human Genome Research Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute on Drug Abuse
National Institute of Environmental Health Sciences
National Institute of General Medical Sciences National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research

Also:

- Center for Scientific Review (CSR)

Center for Information Technology
National Center for Complementary and Alternative Medicine
National Center for Research Resources
National Library of Medicine

The Center for Scientific Review (CSR)

CSR oversees referral for the ~80,000 NIH Grant Applications submitted per year, and reviews 70% of them in >120 newly reorganized and populated **Study Sections**, which are clustered under 24 recently reorganized **Integrated Review Groups (IRGs).**

AARR	AIDS and Related Research
BBBP	Behavioral and Biobehavioral Processes
BCS	Biochemical Sciences
BDA	Biology of Development and Aging
BPC	Biophysical and Chemical Sciences
BST	Bioengineering Sciences and Technologies
BDCN	Brain Disorders and Clinical Neuroscience
CVS	Cardiovascular Sciences
CDF	Cell Development and Function
DIG	Digestive Sciences
EMNR	Endocrinology, Metabolism, Nutrition and Reproductive Sciences
GGG	Genes, Genomes and Genetics
HEME	Hematology
IMM	Immunology
IDM	Infectious Diseases and Microbiology
IFCN	Integrative, Functional, and Cognitive Neuroscience
MDCN	Molecular, Cellular, and Developmental Neuroscience
MOSS	Musculoskeletal, Oral and Skin Sciences
ONC	Oncological Sciences
RES	Respiratory Sciences
RPHB	Risk, Prevention and Health Behavior
RUS	Renal and Urological Sciences
HOP	Health of the Population
SBIB	Surgical Sciences, Biomedical Imaging, and Bioengineering

NIH R01 Grants: Investigator-Initiated

Two levels of review:

1. ***Study Section*** ***(committee of expert scientists)***

   —> Knowledge
   Assess scientific merit
   Your contact: Scientific Review Officer (SRO)

2. ***Institute Council*** ***(scientists and nonscientists)***

   —> Money
   Assess relevance to institute, program portfolio
   Your contact: Program Director

How do Study Sections work?

- Application is assigned to Institute, and to IRG, then to a Study Section
- SROs (and Chair) scan abstracts (~75); assess needed expertise
- SRO (and Chair) invite ad hoc members (~30% of total)
- SRO (and Chair) assign applications to members for primary or secondary review (avg. 11) or for reading (avg. 4)
- Applications are distributed to members for reading and preparation of review, identification of potentially 'streamlined' applications
- At Study Section meeting, SRO summarizes procedures, conflict of interest sanctions; identification of 'streamlined' applications
- Each remaining applications is reviewed, discussed and scored; Institute representative is present; members in conflict are not
- Written and oral reviews must comment on each of *five standardized review criteria*; single final score (1.0 – 5.0; 1.0 is top) is assigned *subjectively*
- Scores for each application are multiplied by 100 and averaged
- SRO prepares summary statement ('pink sheet') for applicant and Institute Council

CRITERIA FOR RATING OF NIH GRANT APPLICATIONS

Each review must address and score (1-7 integer scale) each of the following:

Significance [impact]

- **address an important problem?**
- **will scientific knowledge be advanced?**
- **effect on concepts or methods in this field?**

Approach

- **experimental design and methods appropriate to aims?**
- **acknowledge problem areas and consider alternative tactics?**

Innovation

- **employ novel concepts, approaches or methods?**
- **challenge existing paradigms or develop new methodologies?**

Investigator

- **appropriately trained to carry out work?**
- **appropriate work for experience of P.I. and collaborators?**

Environment

- **contribute to the probability of success?**
- **evidence of institutional support?**

Components of the NIH grant application

Research Plan

- Abstract
- Specific Aims
- Background/Significance
- Progress Report/Preliminary Results
- Research Design and Methods

Other important stuff

- Budget/Budget Justification
- Consultants/Collaborators

Sections of NIH grant applications, and how to use them to your advantage

2 Abstract
determines Study Section and Institute assignments; state health/disease relevance here

1 Specific Aims
start here; 3-5 aims

4 Background/Significance
set the stage, frame *your* questions; state *impact* clearly

3a Progress Report/Preliminary Results
emphasize your expertise, note coworkers

3b Research Design and Methods
organize around Specific Aims; address caveats; highlight innovations

Budget/Budget Justification
breakdown costs (supply $/researcher/week); justify everything

Consultants/Collaborators
support/noncompetition from mentors; certify sources of materials, expertise

>> Be sure to address the five rating criteria!

A strategy for Abstracts (and Specific Aims):

The *long term objectives* of this project are to define mechanisms of transcriptional regulation in metazoans, to understand how a regulatory factor specifies programs of gene expression as a function of developmental, cellular or physiological cues, and to determine operating principles for gene regulatory networks.

The *general strategy* is to identify in cell lines and whole organisms target genes that are directly regulated by members of the intracellular receptor (IR) superfamily, which includes receptors for steroids and other small lipophilic ligands. By comparing the regulatory machinery at subsets of those target genes, determinants of selective assembly and disassembly of regulatory complexes will be defined; in turn, the complexes will be probed to elucidate signaling and regulatory mechanisms, and to describe the syntax of gene regulatory circuits and networks.

The *specific aims* are to define key aspects of the structure, mechanisms, dynamics and combinatorial selectivities of IR regulatory complexes, and how they serve as nexus for integration of signaling pathways in regulatory networks. Five goals are envisioned: (1) define determinants of composition and architecture for assembly of IR regulatory complexes; (2) determine molecular mechanisms by which IR regulatory complexes modulate transcription; (3) determine how small molecule ligands specify functional surfaces of IRs; (4) determine mechanisms of disassembly of IR regulatory complexes; (5) describe organizational and operating principles for IR-specific regulatory networks.

IRs have been implicated in a wide range of diseases and developmental disorders, including cancer, hyperlipidemia, hypertension and inflammation, and IR ligands are the most heavily prescribed therapeutics. Thus, understanding the principles and mechanisms of IR action has important implications for health, and for detecting, treating and curing disease.

A strategy for Specific Aims (and Research Design and Methods)

Our long term objectives are to define mechanisms of transcriptional regulation in metazoans, to understand how a regulatory factor specifies programs of gene expression as a function of developmental, cellular or physiological cues, and to determine operating principles of gene regulatory networks.

Our general strategy is to identify in cell lines and whole organisms genes that are directly regulated by members of the intracellular receptor (IR) superfamily, which includes receptors for steroids and other small lipophilic ligands. By comparing the regulatory machinery at subsets of those target genes, we shall define determinants of selective assembly and disassembly of regulatory complexes, and in turn use that information to elucidate signaling and regulatory mechanisms, and to describe gene regulatory circuits and networks.

Our specific aims are to define key aspects of the structure, mechanisms, dynamics and combinatorial selectivities of IR regulatory complexes, and how they serve as nexus for integration of signaling pathways in regulatory networks. Five goals are envisioned:

1. Define determinants of composition and architecture for assembly of IR regulatory complexes.

We shall develop and refine novel principles and methodologies for comparative analyses of transcriptional regulatory complexes; specifically, we shall employ cell-based approaches to identify components and surfaces within complexes that lead to distinguishable functions and mechanisms.

2. Determine molecular mechanisms by which IR regulatory complexes modulate transcription.

We shall use molecular and cellular approaches *in vivo* and biochemical approaches *in vitro* to dissect and define multiple IR regulatory mechanisms at the molecular level, and to infer how crosstalk pathways modulate those mechanisms.

3. Determine how small molecule ligands specify functional surfaces of IRs.

We shall use molecular genetic, chemical, biochemical and biophysical approaches to identify novel IR ligands, to characterize allosteric effects of ligand-receptor interactions, and to determine the consequences of specific ligand binding on the localization and activities of regulatory complexes.

4. Determine mechanisms of disassembly of IR regulatory complexes.

We shall assess the role of IR regulatory complex dynamics in maintaining signal responsiveness, and develop genetic and biochemical approaches to the identification and mechanistic analysis of factors that effect disassembly.

5. Describe organizational and operating principles for IR-specific regulatory networks.

We shall determine by microarray analysis alterations of gene expression *C. elegans* in response to defects in IRs DAF-12 and NHR-49; we shall develop cellular assays to define regulatory mechanisms, and define circuit elements and network motifs using genetic and proteomic approaches.

An organizational approach for Research Design and Methods

1. Determine the effects of different core GR binding sequences on the conformation and/or dynamics of the GR-DBD.

Protein allostery involves two types of structural alteration-- conformational and dynamic [30,43,44]. In the conformational component, changes in shape either create or occlude functional surfaces, which may harbor enzymatic activities, sites for modification, or interaction surfaces for coregulatory factors.…Thus, we shall use x-ray crystallography and NMR to study the conformation of the GR-DBD bound to different sequences, and NMR to study the dynamics of the bound receptor.

a. X-ray crystallography of GR-DBD bound to different GBSs

Rationale: We know that GR binding sequences (GBSs) that differ by as little as a single base pair can produce differences in GR function (Section 7.C.2), implying the GBSs engage different allosteric paths. To examine the initial step in these paths, we wish to compare the structure of GR DBD on a set of distinct nativeoccurring GBSs…..

Goal: To determine how different GBSs change the structure of GR-DBD

Methods: Our overall goal is to understand how changes in DNA sequences that direct both GR binding and regulatory activity impact the structure of the GR-DBD. In our initial screen we shall use the highest affinity site identified to ensure complex formation, Gha; three *bona fide* activating sequences that test the effect of variations….

Expected results: As described in Section 7.C.3, we have obtained crystals and have derived well-refined models for five of the six positively acting GBSs tested. We expect to be able to distinguish distinct changes by comparing the other Site D variants as well; of particular interest will be mutations that affect regulatory efficacy….

Potential problems/alternative approaches: Although positive GBSs have crystallized readily, the negative GREs, POMC and Oste, have not….Another concern is that structures obtained thus far have all come from very similar crystals (all C2 space group with very similar cell dimensions) that employ a minimal 16bp-binding site. The very similar crystal packing may impose some bias on the models. We shall explore this in two ways. First, using the most readily crystallized site, Sgk, we shall …. Should a crystal packing artifact be identified that cannot be overcome by changing the protein fragment or the DNA length, we shall pursue high-resolution structural determination using NMR….

A strategy for Background

• Not a review article; frame and rationalize the issues that you will approach in your study; emphasize impact.
• Include underlined statements of gaps in our current knowledge, which are addressed in your proposal.

B. BACKGROUND AND SIGNIFICANCE

[Underlined sentences describe gaps in existing knowledge that are approached in this proposal.]

Different IR-containing regulatory complexes confer distinct regulatory mechanisms. IRs can integrate signals from response elements and small molecules, giving rise to distinct functional consequences; moreover, IRs are also covalently modified (12), increasing the combinatorial scope of integration. The result is likely the differential assembly of IRs into distinct regulatory complexes. Like the IRs themselves, these complexes may be conceptualized as structural mosaics, displaying patterns of functional surfaces that produce a regulatory action (Section D.1.b). The presumed functional surfaces could correspond to one or more of three types of activities: an interacting surface for a target molecule, an enzymatic activity directed toward a target molecule, or a site for covalent modification (*e.g.,* phosphorylation, acetylation, methylation, sumoylation, etc.) that affects the function of a linked interaction surface or enzymatic activity directed to a target. Finally, there are three general classes of molecular targets for regulatory complexes: components of the transcription complex (including factors that mediate coupled processes such as splicing), components of chromatin, or other regulatory factors or complexes. It is these targets, then, that serve as the effectors of the regulatory mechanisms. Although this combinatorial hierarchy is likely conceptually correct, the "rules" that give rise to a particular functional surface, the actual potential for components within complexes to create multiple patterns of functional surfaces, the number and variety of such patterns that may be created, and the relationship between functional patterns and molecular mechanisms of regulation have yet to be investigated.

Continuous disassembly of regulatory complexes is essential for signaling. Although regulatory complexes assemble spontaneously and are quite stable *in vitro,* they are startlingly dynamic *in vivo.* Rates of transcription from GR-activated genes revert rapidly to basal upon hormone withdrawal (13), and a GRE *in vivo* releases one GR and is re-occupied by another with a $t_{1/2}$ ~4 sec (14). This implies that regulatory complexes may be actively disassembled, consistent with the physiologic requirement that modulatory regulators must detect and respond to fluctuations in signal strength (15); that is, if regulatory complexes containing hormone-bound IRs were *stably* assembled at response elements, a decline in circulating ligand concentrations would go undetected. Indeed, it appears that molecular chaperones may drive the process of regulatory complex disassembly. That work, summarized in Section C.1.d, showed that two components of a major molecular chaperone complex, can disassemble IR:DNA and IR:coregulator interactions *in vitro,* and that they localize *in vivo* to genomic response elements in a hormone-dependent manner, disrupting receptor-mediated transcriptional activation *in vivo* and *in vitro.* In independent studies, Hager and coworkers suggested that the ATPase-containing subunit of the Swi/Snf chromatin remodeling complex appears to play a role in regulatory complex release from chromatin templates *in vitro* (16). How the disassembly activities of chaperone and chromatin remodeling complexes might be related is not known. More generally, the nature and composition of the factors responsible for disassembly, and the biochemical mechanisms that mediate disassembly, remain to be elucidated.

Feed Forward: a general scheme for writing grant applications

-5. Choose three senior colleagues as your "grant committee"

-4. Read Criteria for Rating of NIH Grant Applications

-3. *'Feed forward 1'*: Discuss (1.5 hr) goals, aims, ideas with committee

-2. Draft one page, 3-5 Specific Aims

-1. '*Feed forward 2'*: Discuss (1.5 hr) with committee

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1. Finalize Aims; draft Abstract and Research Design and Methods

2. Draft Background and Significance

3. Re-read Criteria for Rating of NIH Grant Applications

4. Seek feedback from committee