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

<table>
<thead>
<tr>
<th>Source</th>
<th>% Total</th>
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<tbody>
<tr>
<td>NIH</td>
<td>72</td>
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<tr>
<td>NSF, DOD, DOA, DOE, NASA</td>
<td>12</td>
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<tr>
<td>HHMI, ACS, other private</td>
<td>11</td>
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<tr>
<td>Industry</td>
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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

- Favor: 64%
- Oppose: 11%
- Don't know: 25%

2004 Research!America Health Poll

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.

- Strongly/somewhat agree: 80%
- Strongly/somewhat disagree: 14%
- Don't know: 6%

2004 Research!America Health Poll

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

- Important: 90%
- Not important: 3%
- Don't know: 7%
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 and NSF Budgets in Jeopardy

It is more important now than ever for scientists to become involved. Join the Congressional Liaison Committee.

www.jscpp.org
Scientific Citizenship

Join the
Congressional Liaison Committee
NIH Pathway to Independence Award: K99/R00

NIH is committed to providing a pathway to research independence for new investigators.

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

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

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**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)

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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

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**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 Study Sections, which are clustered under 24 recently reorganized Integrated Review Groups (IRGs).

- AARR: AIDS and Related Research
- BRB: Behavioral and Biobehavioral Processes
- BCS: Biochemical Sciences
- BDA: Biology of Development and Aging
- BPC: Biophysical and Chemical Sciences
- BST: Bioengineering Sciences and Technologies
- BRDN: Brain Disorders and Clinical Neuroscience
- CSS: Cardiovascular Sciences
- CDF: Cell Development and Function
- DPL: Digestive Sciences
- ENR: Endocrinology, Metabolism, Nutrition and Reproductive Sciences
- GGG: Genes, Genomes and Genetics
- HEM: Hematology
- IMM: Immunology
- IDM: Infectious Diseases and Microbiology
- IFCN: Integrative, Functional, and Cognitive Neuroscience
- MDCN: Molecular, Cellular, and Developmental Neuroscience
- MDBS: Musculoskeletal, Oral and Skin Sciences
- ONS: 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

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**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, hyperglycemia, 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 identity 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, 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 vitro 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 allostery 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 microscopy analysis alterations of gene expression 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-DDB.

   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-DDB bound to different sequences, and NMR to study the dynamics of the bound receptor.

   a. Structure of GR-DDB bound to different GRBs

      **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 sites. To examine the initial step in these paths, we wish to compare the structure of GR-DDB on a set of distinct naïveoccurring GBSs.

      **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.

   b. Alternative approaches: Although positive GBSs have crystallized readily, the negative GREs, POMC and Osteo, 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 10bp-binding site. The very similar crystal packing may impose some bias on the model. We shall explore this in two ways. First, using the most readily crystallized GBSs, we shall attempt to produce crystals of the protein fragment, and 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 towards 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 the receptor, 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 govern it is a particular functional array. The actual potential for components within complexes to create multiple patterns of functional surfaces, the numbers 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 vivo, they are startlingly dynamic in vitro. Rates of transcription from GR-activated genes revert rapidly to basal upon hormone withdrawal (15), and a GRE in vivo releases one GR and is re-occupied by another with a t1/2 ~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 concentration 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-regulator interactions in vitro, and that they localize in vivo to genomic response elements in a hormone-dependent manner, disrupting receptor-mediated transcriptional activation in vitro and in vivo. In independent studies, Hager and coworkers suggested that the ATPase-containing subunit of the Srv/Snf chromatin remodeling complex appears to play a role in regulatory complex release from chromatin templates in vitro (16). How the disassembly activities of chaperones in regulatory complexes might be related is not known. More generally, the dynamic functions 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

  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

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**Celebrate!**