Welcome

R01 Grant Writing Seminar
February 25, 2019
History and Mechanism of R01

Dr. William Duncan
Vice Provost for Research
Office of Research and Sponsored Programs
27 Institutes and Centers (IC)

Each with a different:

– mission & priorities
– budget
– funding strategy
Individual Research Grants

One project

Examples

$R = \text{NIH research grants}$

$R01 -$ Research Project Grant

$R15 -$ Research Project Grant (REAP)

$R03 -$ Small Grant

$R21 -$ Exploratory/Developmental Grant

$R41/R42 -$ Small Business Technology Transfer Research Grants

$R43/R44 -$ Small Business Innovation Research Grants
NIH Grant Mechanisms

• **R01** Traditional investigator-initiated grant
  
  < $500K/yr, 3-5 yrs. Need approval if more than $500K for any year of the grant

• **R03** Small Grant
  
  < $100K for 2 yrs

• **R21** Exploratory/Developmental Grant
  
  < $275K for 2 yrs

• **R34** Grant – pilot and feasibility studies
  
  < $450K for 3 yrs
NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed)

R01 Research Project Grant

- PA-19-056
- 24 Institutes and Centers participate in this Program Announcement
**Figure 2**

**NIH funding, FY 1950–2019**

In thousands of constant 2013 BRDPI adjusted dollars

Sources: NIH funding figures through FY 2014 are based on total budget authority. Projected NIH funding figures for FY 2015 through FY 2019 are based on data from the Congressional Budget Office.
Federal Budget Breakdown

Figure 3: Base Budget R&D by Agency, FY 2017
(budget authority in billions of dollars)

- DOD: $73.7
- HHS (NIH): $30.9
- NSF: $6.2
- DOE: $16.6
- NASA: $12.2
- USDA: $2.6
- COMMERCE: $1.9
- ALL OTHER: $6.0

TOTAL R&D = $150.1 BILLION

Source: OMB R&D data, agency budget justifications, and other agency documents and data. R&D includes conduct of R&D and R&D facilities. © 2016 AAAS
Total NIH Budget Authority: FY 2017 Final

- RPGs: $19.1B (57.16%)
- Centers: $2.5B (7.59%)
- Other Research: $2.2B (6.53%)
- Research Training: $827M (2.48%)
- R&D Contracts: $3.1B (9.19%)
- Intramural Research: $3.8B (11.32%)
- Research Mgmt & Support: $1.7B (5.23%)
- All Others: $166M (0.5%)
Applications (with First-time R01)

Source: NIH Data Book [http://report.nih.gov/nihdatabook/index.aspx](http://report.nih.gov/nihdatabook/index.aspx) and supplemental tables available in RePORT
Average Grant Size

Source: NIH Data Book [http://report.nih.gov/nihdatabook/index.aspx](http://report.nih.gov/nihdatabook/index.aspx) and supplemental tables available in RePORT
Success Rates for New (Type 1) Applications

Source: NIH Data Book [http://report.nih.gov/nihdbook/index.aspx](http://report.nih.gov/nihdbook/index.aspx) and supplemental tables available in RePORT
Total NIH Budget Authority: FY 2018 Operating Plan

- RPGs: $21B (57.58%)
- Research Centers: $2.6B (7.17%)
- Other Research Grants: $2.3B (6.33%)
- Research Training: $878M (2.41%)
- R&D Contracts: $3.5B (9.61%)
- Intramural Research: $4B (10.93%)
- Research Mgmt & Support: $1.8B (5.02%)
- All Other: $346M (0.95%)

Data for this report are available at NIH Data Book - https://report.nih.gov/nihdatabook/report/5
Research Project Grants: Success Rates of New (Type 1) Competing Applications for Targeted and Untargeted Research

Data for this report are available at NIH Data Book - https://report.nih.gov/nihdatabook/report/157
R01-Equivalent Investigators, New (Type 1): Funding Rates, by Career Stage of Investigator

Funding Rate (%)

Fiscal Year

Fiscal Year

Data for this report are available at NIH Data Book - https://report.nih.gov/nihdatabook/report/166
Number of Research Project Grants

![Graph showing the number of research project grants with data points for total number of grants from FY 2019 to FY 2019, with a note that FY 2018 estimate is not available pending release of NIH Operating Plan.]

Success Rates

Note: FY 2018 estimate not available pending release of NIH Operating Plan

Source: NIH Data Book [http://report.nih.gov/nihdatabook/index.aspx](http://report.nih.gov/nihdatabook/index.aspx) and supplemental tables available in RePORT
Early Stage and New Investigator

- A Program Director / Principal Investigator (PD/PI) who has completed their terminal research degree or end of post-graduate clinical training, whichever date is later, within the past 10 years and who has not previously competed successfully as PD/PI for a substantial NIH independent research award.

- An investigator who has not previously received substantial, independent funding from NIH.
Early Stage and New Investigator

- Early Stage and New Investigator applications with meritorious scores will be prioritized for funding.

- Example – NIAID 2019 paylines
  - R01 (non-new PI) 14 percentile
  - R01 (new PI) 18 percentile
## Summary of Trends in NIH Funding
### FY1995-FY2017

<table>
<thead>
<tr>
<th>Category</th>
<th>FY1995</th>
<th>FY2003</th>
<th>FY2017</th>
<th>% Change since 1995</th>
<th>% Change since 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Budget (in millions)</td>
<td>$11,300</td>
<td>$27,167</td>
<td>$34,229</td>
<td>202.9%</td>
<td>26.0%</td>
</tr>
<tr>
<td>NIH Budget (constant 1995 $ millions)</td>
<td>$11,300</td>
<td>$21,080</td>
<td>$17,629</td>
<td>56.0%</td>
<td>-16.4%</td>
</tr>
<tr>
<td>R01 Equivalent Funding ($ millions)</td>
<td>$4,718</td>
<td>$10,102</td>
<td>$11,960</td>
<td>153.5%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Total # R01 Equivalent Grants (Competing and Continuing)</td>
<td>21,680</td>
<td>29,626</td>
<td>24,793</td>
<td>14.4%</td>
<td>-16.3%</td>
</tr>
<tr>
<td>R01 Equivalent Applications</td>
<td>22,542</td>
<td>24,634</td>
<td>31,221</td>
<td>38.5%</td>
<td>26.7%</td>
</tr>
<tr>
<td># of R01 Equivalent Awards (New and Competing)</td>
<td>5,849</td>
<td>7,430</td>
<td>6,041</td>
<td>3.3%</td>
<td>-18.7%</td>
</tr>
<tr>
<td>R01 Equivalent Success Rates</td>
<td>25.9%</td>
<td>30.2%</td>
<td>19.3%</td>
<td>-25.5%</td>
<td>-36.1%</td>
</tr>
</tbody>
</table>
NIH Budget Mechanism Detail

Amount for 2017

Amount Trend Total

Fiscal Year

Data for this report are available at NIH Data Book - https://report.nih.gov/nihdatabook/report/226
NIH Institutes and Centers (ICs)

• 27 Institutes and Centers
  – Each with a specific research agenda
    • Focusing on different diseases, body systems, etc.

• 24 ICs fund extramural research
Get a sense of who and what NIH funds

- Award trends
- Which ICs fund research like yours
- Organizational funding information
- Potential collaborators
- NIH-funded workforce data
  - NIH staff contacts
  - NIH grantees in your area
- Success rates
Submitting a Sponsored Project
Constructing a R01 Budget

Cynthia Hardin
Associate Director of Sponsored Programs
Office of Research and Sponsored Programs
Online Submission Sites

• National Institutes of Health
  – eRA Commons:
  – https://era.nih.gov/
  – ASSIST:
  – https://public.era.nih.gov/assist/

• Grants.gov (Multiple grant opportunities)
  – http://www.grants.gov/
Submitting a Sponsored Project

• Route your Proposal with our *Internal Routing Form* (located on the ORSPA forms page)

• Need budget help? Use our spreadsheet (also on the ORSPA forms page)

• ORSPA Forms Page:
  – [https://www.etsu.edu/research/orspa/forms/](https://www.etsu.edu/research/orspa/forms/)

• Other questions regarding the grant process? Check the *iGuide*:
Preparing Your R01 Submission: Specific Aims, Significance, and Innovation

Dr. Jonathan Moorman
Professor, Infectious Disease Division Chief
Department of Internal Medicine
Vice Chair of Research and Scholarship
Co-Director, CIIDI
Specific Aims (1 page)

• The major reviewers will definitely read these
  – The rest of the study section might…
• Need to gain the reviewers’ trust/confidence
• Convince them that your work is important
• Convey that your team are the best people to complete the work you have proposed

https://www.niaid.nih.gov/grants-contracts/draft-specific-aims
Viruses are thought to be involved in 15% to 20% of human cancers worldwide, thus providing critical tools to reveal common mechanisms involved in human malignancies. As the etiologic agent of adult T cell leukemia/lymphoma (ATLL), human T cell leukemia virus type I (HTLV-1) is just such a virus. HTLV-1 encodes a potent oncoprotein, Tax, which regulates important cellular pathways including gene expression, proliferation, apoptosis, and polarity. Over the years, Tax has proven to be a valuable model system in which to interrogate cellular processes, revealing pathways and mechanisms that play important roles in cellular transformation. Although the Tax oncoprotein has been shown to transform cells in culture and to induce tumors in a variety of transgenic mouse models, the mechanism by which Tax transforms cells is not well understood. A large number of Tax mutants have been generated and their biological activities have been thoroughly characterized, primarily in cell culture systems. Currently, a major obstacle in the field is that the transforming activity of Tax mutants cannot be compared using available transgenic models due to random transgene integration sites, variable transgene copy number, and inconsistent transgene expression levels, making it difficult to link the biological activities of Tax mutants with their transforming potential.
Breaking down the Specific Aims

• Second paragraph
  – *Long-Term Goal:* This is your overarching research goal. Because you are asking for support from a particular funding entity, it is important to ensure that your long-term goals align with the mission of your funding entity. Keep your wording general in this sentence—you are stating your long-term plans, and the reviewers understand that the specifics may be subject to change.
  – *Hypothesis and Proposal Objectives:* State your central hypothesis clearly, specifically, and with simple language. You want to demonstrate to the reviewers that you have a hypothesis-driven proposal that is testable. Describe how your project addresses the critical need, and clearly state the proposed solution. In general, avoid vague hypotheses because it will be unclear to the reviewers what you expect to determine with the proposed research.
  – *Rationale:* Explain how you arrived at your central hypothesis (for example, using past studies and published literature). Briefly, state what your project’s completion would make possible (e.g., new therapeutics), and tie it to the funding entity’s mission.
  – *Qualifications:* Briefly state why your experimental design and your team are the best to accomplish the research goals. You can mention factors such as your preliminary data, personnel qualifications, laboratory equipment, etc., but it is important to keep it concise.

To solve this problem we will develop an innovative mouse model system in which to study Tax tumorigenesis using targeting vectors containing wild-type or mutant Tax genes that are silenced by a preceding floxed stop cassette. These vectors will be knocked in to the Rosa26 locus of recipient mice by recombination. After crossing these mice with Lck-CRE mice, the stop cassette will be specifically excised in developing thymocytes where the Lck promoter is active, allowing conditional expression of wild-type or mutant Tax proteins in T cells, the natural target of HTLV-1 infection. The feasibility of our proposed mouse model is supported by the fact that Lck-Tax transgenic mice have been developed and produce a leukemia that closely resembles ATLL. Thus, targeting of Tax expression in cells in which the Lck promoter is active is expected to produce a similar disease in our model. In our improved model system, insertion into the Rosa26 locus will eliminate random integration sites and standardize gene copy number resulting in consistent levels of wild-type and mutant Tax protein expression.

Color Key: Long-term Goal Proposal Objective Rationale Hypothesis Pay-off
Breaking down the Specific Aims

The Aims

- **describe briefly each of the aims** you will use to test your hypothesis. Ideally, the aims should be related, but not dependent, upon each other. If you do this, the failure of one aim (or an unexpected result from one aim) does not negatively influence any other aim or prevent the completion of the other aims.

- Give your aim an active title that clearly states the objective in relationship to the hypothesis.

- Include a brief summary of the experimental approach and anticipated outcomes for each aim.

- If you have room, you may wish to include a sub-hypothesis (the small portion of the overall hypothesis) and a small description of the pay-off of each aim. Including these is helpful to creating the impression that each aim is valuable, testable, and independent of the others.

- To make it easier for the reviewers to clearly read and understand each aim, it is often helpful to use headings and/or bullets to delineate each specific aim.

**Aim 1** will establish an innovative mouse model for HTLV-1 Tax tumorigenesis. Targeting vectors containing silenced wild-type or mutant Tax genes will be knocked in to the Rosa26 locus of C57BL/6 mice. These mice will then be crossed with homozygous Lck-CRE mice, thereby excising the stop cassette and generating mice that express wild-type or mutant Tax proteins specifically in T cells.

**Aim 2** will examine the effect of mutations that disable specific biological functions of Tax on Tax-mediated tumorigenesis. Tax can bind to and regulate the activity of members of the SRF, CREB, NF-kB and PBM protein families, each of which has been implicated in oncogenesis. Mice established in Aim 1 will allow us to compare for the first time the tumorigenic potential of wild-type and mutant Tax proteins in an effort to identify pathways that are required for Tax tumorigenesis.
Breaking down the Specific Aims

• **The Final Summary Paragraph/Statement**
  - This final paragraph of the Specific Aims is often overlooked, but it is vital for the impact of your proposal. Think of your Specific Aims page as an hourglass, where the wide parts represent the general information and global significance, and the narrow parts are the fine details. If you end with the Aims Section (above) you will end on fine details and a narrow scope. An hourglass with a narrow base is unstable and will topple. Therefore, this final paragraph creates a firm, broad base to support your entire proposal.
  - The final paragraph should include the following important details:
    - **Innovation:** Plainly state what is innovative about your project. What would completion of this proposal bring to the field that is not present currently?
    - **Expected Outcomes:** Specifically state your expected outcomes for this project. Use plain language. What do you expect to see at the completion of each aim? Include this information only if you have not placed it in the Aims.
    - **Impact:** State how your project would help those who need it, (i.e. the development of a new treatment, vaccine, disease model or diagnostic tool) Include a broad impact statement about how your proposal will benefit the people or other subjects that you mentioned in the opening paragraph.

The proposed studies will establish a new mouse model that will overcome current limitations and provide greater insight into the mechanism of HTLV-1 Tax tumorigenesis, knowledge that is currently lacking and that promises to yield novel insights into viral and cellular biology. The new and improved mouse model for Tax tumorigenesis will provide a valuable resource for the wider scientific community to pursue a multitude of studies that have not previously been possible due to limitations of existing mouse models of Tax.
Significance

• **It is about the problem**
  – why are they important?
  – whom do they impact?
  – why is a solution currently missing?
  – what have people tried? (be brief with this, don’t do a literature review)
  – why is a solution needed *now*?
  – what has happened that makes you think you and your team have a solution? (in broad terms – leave the specifics for later)
  – in which aim will you solve which problem?
  – why is your team qualified to solve the problem(s)?

• Goal is to engage the reader and give a compelling reason to pay attention

• **Do not assume the reviewer already understands the problems/challenges of your field**
Significance is a key score-driving review criterion that evaluates the potential effect on the field if the aims are SUCCESSFULLY completed.

You will be evaluated on whether the project:
• Addresses an important problem or critical barrier to progress in the field
• Is based on a strong premise
• Extends and improves scientific knowledge/technical capability/clinical practice (if successful)
• Changes concepts, methods, technologies, treatments, services, preventative interventions in the field

Make it EASY for the reviewer to find why your proposal is significant.
An application need not have a direct link to health nor be hypothesis-driven to have significance

Examples of projects with potential high significance and high overall impact:

- studies of fundamental properties of basic biological processes without any translational aim
- projects that study rare diseases
- projects that use in silico, in vitro, or in vivo models (cell lines, invertebrate or vertebrate animal models, or human subjects)
- non-hypothesis driven, exploratory studies
  - technological, methods development, models creation, data analytic and analytic methods development efforts
  - data collecting, cataloguing, cohort building or other resource development projects
Innovation

It is about the solution:
– what advance has happened to make your solution potentially likely to work?
– what new enabling ideas or technologies does it use?
– what new approaches do you use?
– how are you combining existing approaches in a new way?
– what unique resources have you developed or have access to?

You will be evaluated as to whether the application:
• Employs novel theoretical concepts, approaches, methodologies, instrumentation or interventions to shift research or clinical practice
• Proposes refinement, improvement or new application of theoretical concepts, approaches, methodologies, instrumentation or interventions

Make it EASY for the reviewer to find why your proposal is innovative.
Conclusions

• There is a defined structure to your proposal that the reviewers want to see
• Specific aims should answer many of the questions a reviewer should have as to what your project is about
• Significance and Innovation are score-driving sections that are often poorly developed
  – Reviewers are required to focus on specific elements of your proposal
  – The easier you can make it for them to find those elements, the more appreciated your grant will be
• The earlier you start, the better your proposal will be
Resources

• https://www.niaid.nih.gov/sites/default/files/1-R01-AI121500-01A1_Gordon_Application_0.pdf

Supporting Documents

Dr. David L. Williams
Professor, Carroll H. Long Chair of Excellence for Surgical Research
Department of Surgery
Co-Director, CIIDI

EAST TENNESSEE STATE UNIVERSITY
Supporting documents are required elements of an RO1 grant application!

- Abstract
- Narrative
- Biosketch
- Facilities and Other resources
- Key personnel
- Budget justification
- Multiple PI/PD Leadership plan
- Vertebrate animals
- Human subjects
- Biohazards
- Authentication of key biological and/or chemical resources
- Resource sharing plan
- **Letters of support** and Assignment request (optional)
NIH Biosketch

• The biosketch is used to highlight each individual's qualifications for a specific role in a proposed project.

• The personal statement and contributions to science can be big factors in how you rate on the Investigator review criterion.

• Carefully select the publications you list in the biosketch.
  
  – Make sure they support your experience/expertise and, more importantly, are relevant to the application.

• Use the 1st person, show enthusiasm and be an advocate for your strengths and accomplishments.
A. Personal Statement

My background and expertise are uniquely suited to the research described in this application. Indeed, my two primary areas of research expertise are the focus of this proposal, i.e. sepsis and immunity. I have more than twenty-five years of experience studying sepsis and septic sequelae with specific emphasis on the role of innate immunity, inflammation, pattern recognition receptors and intracellular signaling pathways. I also have extensive leadership and administrative experience in research. This application is submitted under the multiple PI initiative (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-118.html). Dr. Chuanfu Li and I will be the co-Principal investigators for the application. Dr. Li and I have collaborated for many years. We have been co-PIs on this grant since its inception. Our collaboration has resulted in numerous peer-reviewed publications. Our combined expertise addresses every aspect of the research described in this application. We have assembled a highly skilled group of co-investigators, collaborators and consultants whose combined expertise addresses all aspects of the work proposed. My specific role in this project will be as a co-Principal Investigator at East Tennessee State University. My specific contributions in the scientific areas most relevant to this proposal and to the larger scientific community are described below.
Example of how to write the Contributions to Science section

C. Contributions to Science

1. I have worked in the area of sepsis, infectious disease and immunity since I was a graduate student at Tulane University School of Medicine. For the past twenty-one years my NIH funded research has focused on sepsis and septic sequelae with an emphasis on the role of innate immunity, pattern recognition receptors and intracellular signaling. My research group was among the first to investigate the role of NFκB and NF-IL6 intracellular signaling and transcription factor pathways in polymicrobial sepsis. We demonstrated that modulation of key signaling and transcription factor pathways alters morbidity and mortality in a clinically relevant model of sepsis. We were the first research group to identify the class A scavenger receptor (CD204) as a critical mediator of the pro-inflammatory phenotype as well as lethality in sepsis. Of specific interest to this application, we were also among the first groups to elucidate the cellular and molecular mechanisms of septic cardiomyopathy. When considered together my research group has extensive knowledge and experience in the field of sepsis, which is vital to the success of this research.
Facilities and Other resources

• The information provided in this section of a grant proposal allows the applicant to expound upon factors and features available to ensure the success of the project.

• The Facilities and Other resources document should be specific to the proposal, not simply a generic recitation of current facilities.

• Describe how the scientific environment in which the research will be done contributes to the probability of success (e.g., institutional support, physical resources, equipment, core facilities and technical support, etc).
Example of Facilities and Other resources

**Laboratories.** The research program will be conducted in laboratory facilities in the Division of Surgical Research, Dept. of Surgery (Building 119), James H. Quillen College of Medicine, East Tennessee State University. The co-PIs have four dedicated, fully equipped, newly renovated laboratories, three of which are 750 sq. ft. and the other is 350 sq. ft. The laboratories are within the Division of Surgical Research and they are outfitted with all of the equipment (fixed and movable) required for general laboratory work in infectious disease, immunology and intracellular signaling research. The Division of Surgical Research has an additional 2,880 sq. ft. of newly renovated laboratory space on the same floor of Building 119. This includes multiple laboratories, a dedicated tissue culture facility, a cold room and a departmental equipment room. All of the facilities within the Division of Surgical Research will be available to the PIs, the postdoctoral fellows and the co-investigators.

**Laboratory Animal Resources.** The division of Laboratory Animal Resources (DLAR) is located in the same building as the PIs laboratories on the 4th floor. The DLAR is a fully AAALAC accredited USDA registered facility. The DLAR is managed by a full-time veterinarian (Greg Hanley, DVM, PhD) who is also the facility director along with a full-time support staff.

**Core facilities available to the PIs.** The Flow cytometry facility in Bldg. 119 houses a new BD LSRFortessa flow cytometer (2017) and a new Amnis ImageStreamX Mark II (2017). A new BD FACSAria cell sorter (2017) is located in Bldg. 5. The Confocal Microscope Facility (Leica SP8) is located in Bldg. 119. The Molecular Biology Core Facility provides a variety of cellular and molecular services and equipment. The Molecular Biology Core Facility is located in the same building (Bldg. 119) as the PI’s laboratories. Of specific interest to this study the MBCF has a Bio-Rad MagPix instrument for multiplexed analysis of cytokines, chemokines and intracellular signaling. The core facility also has a ProteinSimple Wes system for automated Western blot analysis.
Human subjects

• Start early, especially if you haven’t previously incorporated human subjects into your grants.

• Carefully read the requirements for research involving human subjects as described in the NIH instructions.

• Check the Clinical Terms of Award for your institute to see if there are institute-specific requirements you need to fulfill.

• Ask for help from grantees who have been successful doing translational and/or clinical research.

• Translational/clinical research usually requires the participation of a clinician and/or a clinical coordinator.

• Start the IRB process early….because it may take longer than you think.
Letters of support

• The importance of letters of support cannot be overstated!

• There is no limit on the number of letters you can include with the application, but it is prudent to only include letters that are essential.

• Letters of support document that you will have:
  – All of the expertise necessary to complete the specific objectives of the grant
  – Have access to essential resources, *i.e.* animal models, reagents, equipment, techniques, etc.

• The letters should be specific to the application.
  – If necessary provide the author with specifics points that should be incorporated into the letter

• Whenever possible, letters of support should provide enthusiastic support for the proposal.
Required letters of Support

- Subcontract PI
- Other Significant Contributors
- Paid Consultants
  - Include the rate/charge
Assignment request

- You can include an “assignment request” letter with your application.
- The assignment letter is a request for your application to be assigned to a specific study section assignment and even institute.
- CSR does not have to grant the request, but they frequently do take it into consideration.
- This should only be done if you know for certain which study section is best suited for your grant application.
Conclusions

• Supporting documents are essential elements of a grant proposal, but their importance is often under appreciated.

• Supporting documents should be specific to the application.

• They should be structured so that they strongly support the applicant(s) and the application!

• Save your supporting documents as “boiler plates” that can be modified/updated as needed for each new or revised grant application you submit.
Elements that should be included in a letter of support

• Letters can be formal or they can be more personal, *i.e.* the first person.

• I welcome the opportunity to serve as a consultant/co-investigator for your NIH RO1 grant application entitled……..

• You have identified an important problem which focuses on…..

• My research group has expertise/experience in…..

• **I understand that my role in the project will be to…advise and assist you….provide you with…**

• I acknowledge that we have discussed the budget and timeline. I am confident that we can complete this phase of the research in a timely manner.
Nota Bene!

• Start early!

• Be objective and realistic!

• Make sure you have everything you need to make the application successful!

• Prepare the best and strongest application package possible!

• Get advice and/or help from experienced investigators!

• Think about the people you are trying to convince, *i.e.* the reviewers!
Approach and Research Plan

Dr. Zhi Q. Yao
Professor, Department of Internal Medicine
Director, HIV Center of Excellence
Director, Mountain Home VA Medical Center Hepatitis Program
Five Review Criteria (to be scored) for Research Plan

1. Significance (Dr. Moorman)
2. Investigators (Dr. Williams)
3. Innovation (Dr. Moorman)
4. Approach (Dr. Yao)
5. Environment (Dr. Williams)
Approach
– the main body of your application

(Three reviewers will read this part in details. They will evaluate the potential impact of your application on the field and the feasibility the aims to be completed successfully)

They will evaluate if the project:
• Has a well-reasoned approach, methodology, analyses to address the scientific problems and accomplish the proposed specific aims
• explain how the preliminary data and/or published literature support the hypothesis and specific aims (Scientific Premise)
• Has a sound and rigorous experimental strategy that can eventually be reproducible (Scientific Rigor and Transparency)
• Has addressed potential problems, alternative strategies and benchmarks (Expected Results, Pitfalls and Alternatives)
• Has adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects
How to Write a Successful Research Strategy

When writing your Research Strategy, your goal is to present a well-organized, visually appealing, and readable description of your proposed project.

That means your writing should be streamlined and organized so your reviewers can readily get the information in your proposal.

Use simple, short sentences to describe complex scientific stories. Start each section with an appropriate heading or conclusive point (do not assume that reviewers will make the conclusion or link your data to your experiment for you).

Don't stop at the Significance section to emphasize the project's importance, and look beyond your biosketches to highlight your team's expertise.
The Big Three when you draft the Approach

As you write, put the big picture in your sights. When reviewers read your application, they'll look for the answers to the following three basic questions:

1. Can your research move the field forward?

2. Is the field important, or if the proposed work is successfully completed, will it make a difference to human health?

3. If the impact is deemed significant, can your team carry out the proposed work?
Anticipate Reviewers’ Questions

As an applicant, you write not only with the reviewers in mind, you also anticipate their potential questions. There are some basic questions (in addition to the "big three" listed above) that will surely be on your reviewers' minds:

- Will the investigators be able to get the work done within the proposed period, or is the proposed work too ambitious? (hypothesis-driven, focused proposal)
- Did the PI describe potential pitfalls and possible alternatives?
- Will the experiments generate meaningful data?
- Could the resulting data prove the hypothesis?
- Are others already doing the work, or, has it been already completed?

Address these questions; then spend time thinking about more potential issues specific to your proposal - and address those too.
Format and Structure of the Approach - It’s Up-to-You

- Preliminary Studies
- Experimental Design and Methods

---------------------------------------------

Overall Approach
Overall Statistics
Scientific Rigor and transparency

---------------------------------------------

Aim 1
1.1 Rationale
1.2 Experimental Design
1.3 Anticipated results and alternative approaches

Aim 2
2.1 Rationale
2.2 Experimental Design
2.3 Anticipated results and alternative approaches

Aim 3
Preliminary Studies

Preliminary Studies (for new applications) or a Progress Report (for competing renewal applications) are critical to build the scientific premise to convince your reviewers.

– You can either include this information as a subsection of the Approach or integrate it into the three main sections of your proposal.
– If you do the latter, be sure to mark the information clearly, for example, with a bold subhead.

Explain how the preliminary data support your hypothesis and specific aims.

Link each piece of data with a specific aim to avoid criticisms such as lack of data to support Aim 2, or, the feasibility of aim 3 is not supported by preliminary studies…
How to Describe the Preliminary Studies

- Your preliminary studies show that you can handle the methods and interpret the results. Here's where you build reviewer confidence that you are headed in the right direction by pursuing research that builds on your accomplishments.

- Reviewers use your preliminary studies together with the biosketches to assess the PI and Co-Investigators, which reflects the competence of the research team.

- Give alternative interpretations to your data to show reviewers you've thought through problems in-depth and are prepared to meet future challenges. If you don't do this, the reviewers will!

- Though you may include other people's publications, focus on the preliminary data from your lab and the labs of your team members as much as you can.

- As we noted above, you can put your preliminary data anywhere in the Research Strategy that you feel is appropriate, but make sure reviewers can distinguish it. (I usually put preliminary data in a separate section to build my hypothesis, and then insert additional data to support the feasibility of the approach in each aim).
Checkpoints for Preliminary Studies

After finishing the first draft, check and ask:

- Do I interpret my preliminary data accurately?

- Is there enough information to show I know what I’m talking about?

- If my project is very complex, do I give enough preliminary studies to support my hypothesis and aims?

- Do I show how my previous experience prepared me for this project.

- Is it clear which data are mine and which are not?
Experimental Design and Methods

• Under each aim, clearly describe the rationale, hypothesis and first set of experiments.

• Outline the branching of next steps:
  – If you get result X, you will follow pathway X;
    If you get result Y, you will follow pathway Y.
  – Consider illustrating this with a flowchart.

• If you are a new investigator or at early phase of your career, you need enough detail to convince reviewers that you understand what you are claiming and can handle the methods proposed.

• Cite a publication that shows you can handle the method where you can, but give more details if you and your team don't have a proven record using the method - and state why you think you will succeed.
Organize the Approach section around your Specific Aims. When you draft the Approach section considering the personnel and skills you'll need for each step, make sure you have relevant data, resources, and/or supporting letters.

- Don't take a chance your reviewer will gloss over that one critical sentence buried somewhere in your Research Strategy. Write yourself an insurance policy: if it's a key point, repeat it again elsewhere.

- Use an outline or numbering system - or both - be consistently throughout. Be sure to follow the rules for font, page limits (12 + 1), and more (x weblink).

- As you develop and finalize your experiments, go back and check other parts of the application to make sure everything is in sync and look again at the scope of your plans.
Experimental Design and Methods

• If space is short, you can also focus on experiments that highlight your expertise or are especially interesting.

• Trim the fat - omit all information not needed to make your case. If you try to wow reviewers with your knowledge, they'll find flaws and penalize you heavily. Don't give them ammunition by including anything you don't need.

• Be sure to lay out a plan for alternative experiments and approaches in case you get negative or unexpected results. Show reviewers you have a plan for spending the 4-5 years no matter where the experiments lead.

Look at NIH Sample Applications to see some different strategies successful PIs use to create an outstanding Research Plan.
Additional Nuts & Bolts in Approach that may affect score

**Scientific Premise:** is the scientific foundation of the project, including the quality and strength of prior research (score-driving).

- As defined by NIH, premise is distinct from a hypothesis or justification;
- It is a retrospective consideration of the foundation for the application.

NIH will ask reviewers to assess **Scientific Premise** by evaluating the strength of the scientific foundations of the application, but it is not the hypotheses or significance of the application.
Scientific Rigor and Reproducibility

- **Rationale:** To support the highest quality of research, public accountability, and social responsibility in the conduct of science, scientific community makes a special effort to advance rigor in designing and performing research and the ability to reproduce biomedical research findings. NIH’s Rigor and Reproducibility policy clarifies expectations and highlights **four areas** that need more attention by applicants and reviewers.
Scientific Rigor is the strict application of the scientific method that supports robust and unbiased approach in experimental design, analysis, interpretation, and reporting of results (score-driving).

- Sufficient information should be provided for the study to be assessed and reproduced.
- Animal numbers and other statistics should be included in the Research Plan.

NIH will ask reviewers to assess Scientific Rigor and Consideration of Relevant Biological Variables such as sex in Approach section.
Example of Scientific Rigor

- **Scientific Rigor and transparency**: The experiments will be rigorously designed to yield robust and unbiased results, including appropriate negative controls (irrelevant proteins, isotype antibodies, uninfected cells) and positive controls. Gain- or Loss-of-function approaches will serve as an important comparison for data quality. Positive signals in quantitative assays such as real-time RT-PCR or gene array analysis will be defined as at least 2x increase/decrease relative to background signal. All experiments will incorporate the use of independent technical and biological replicates. The studies will be powered to see expected differences, and the prospective sample size estimation is performed in consultation with a biostatistician. The relevant biological variables, such as patient sample heterogeneity including age-, race-, and sex-based differences will be well-considered to be matched within the groups.
Strategies from our successful PIs
- What Success Looks Like

Your Research Plan is the map that shows your reviewers how you plan to test your hypothesis. It not only lays out your experiments and expected outcomes, but must also convince your reviewers of your likely success by resolving any doubts that may cross their minds that you will be able to conduct the research.

Here are some success points to learn:

- While describing a method in the Approach section, they state their or collaborators' experience with it.

- They point out that they have access to a necessary piece of equipment.

- When explaining their field and the status of current research, they weave in their own work and their preliminary data.

- They describe the key points to make sure reviewers will grasp the importance of their proposal and understand their field and how their work fits into it.
Review and Finalize Your Research Plan

- After drafting, look over what you have written with a critical eye of a reviewer to identify potential holes or weak spots.

- Ask others to do so too—they can look at your application with a fresh eye. Include people who are not familiar with your research to make sure you can get your point across to someone outside your field.

- As you finalize the details of your Research Strategy, you will also need to return to your Specific Aims to see if you must revise.
Maximizing Study Section Feedback

Dr. Chuanfu Li
Professor, Division of Surgical Research
Department of Surgery

EAST TENNESSEE STATE UNIVERSITY
RESUME AND SUMMARY OF DISCUSSION: This outstanding application from a well-established physician scientist is aimed at testing the hypothesis that histone methyltransferase EZH2, through epigenetic modification of Foxp3, plays a critical role in the homeostasis of Treg cells and that disruption of EZH2 function contributes to inflammatory bowel disease. During the previous period of funding, the principal investigator has been highly productive with important findings on EZH2-mediated transcriptional repression in Tregs. During a focused discussion, the reviewers noted numerous strengths of the application including the highly significant topic of research with clinical relevance and potential high impact on broad areas of autoimmune disease, the highly regarded and productive investigator, the innovative concepts regarding the epigenetic modifications of FoxP3 and cell autonomous mechanism of IL-6 in disrupting Treg function, the strong supportive preliminary data, the logically designed experiments with clear outcomes, as well as the exceptional research environment. Only minor concerns were noted and this application was viewed with high uniform enthusiasm.
Overall Impact of Research Applications

**Overall impact:** The likelihood for a project to exert a sustained, powerful influence on research field(s) involved

<table>
<thead>
<tr>
<th>Overall Impact</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>1 2 3</td>
<td>4 5 6</td>
<td>7 8 9</td>
</tr>
</tbody>
</table>

**Evaluating overall impact:**
Consider the 5 criteria: significance, investigator, innovation, approach, environment (weighted based on reviewers’ judgment) and other score influences, e.g. human subjects, animal welfare, inclusion plans and biohazards.

- e.g. Applications are addressing a problem of high importance /interest in the field. May there some or no weaknesses.
- e.g. Applications may be addressing a problem of high importance in the field, but weaknesses in criteria bring down the overall impact to medium.
- e.g. Applications may be addressing a problem of moderate/high importance in the field, with some or no weaknesses.
- e.g. Applications may be addressing a problem of moderate importance in the field, with some or no weaknesses.
- e.g. Applications may be addressing a problem of low or no importance in the field, with some or no weakness.
Study Section Panel Meeting to Discuss the Applications
Meeting Activities

• The SRO will begin the meeting by reviewing policies and describing meeting procedures.

• Applications will be grouped (young/new investigators, established, or training/high risk applications).

• Applications (50%) will be discussed based on the preliminary overall impact score (beginning with the best scores).
Presentation and Discussion

• Applications will be introduced by the Chair of the panel meeting.

• Assigned reviewers will share their initial overall impact score and explain the significance and the overall impact the research.

• Open discussion follows assigned reviewer presentations.

• Discussion of scientific merit may result in disparate levels of enthusiasm.

• Human subject protections, vertebrate animals or biohazards that can affect scientific merit are discussed before final scoring.
Final Score and Voting

• Based on the presentation and discussion, all reviewers give a final score to each discussed application.

• Both standing and temporary members vote on each application.

• Applications that are discussed at the meeting will receive a final impact score, and a summary statement with individually assigned reviewer criterion scores, reviewer critiques, and a résumé and summary of the discussion.

• Applications that are not discussed will receive summary statements containing written critiques and individual criterion scores from assigned reviewers.
RESUME AND SUMMARY OF DISCUSSION: The applicants propose to identify methods to prevent immune system clearance of hepatocytes transduced with adeno-associated virus (AAV) vectors by examining the role of empty capsids in the immune response, modifying AAV capsid antigen presentation and identifying new AAV vectors capable of avoiding the capsid-specific cytotoxic T lymphocyte (CTL) response through a directed evolution approach. The research was thought to be highly significant because of the importance of overcoming the immune response to AAV gene therapy for successful treatment of diseases such as hemophilia. The innovative concepts of exploring the CTL response and the role of empty capsids in the AAV immune response, thorough experimental plan and outstanding investigative team that includes a world leader in AAV gene therapy are among the other strengths of the application discussed by the panel. Questions were raised about the suitability of mouse models for identifying immune responses that will be relevant to humans. Reviewers disagreed about the necessity for testing multiple capsid mutants. Overall, reviewers agreed that the strengths outweigh the weaknesses and rated the application likely to have high impact on the field of AAV gene therapy.
Panel Discussion

Please feel free to ask questions.
Many thanks to all the presenters for sharing their expertise, and thank you for attending!

Please contact Joy Bohannon with questions, to request handouts, or to access the recorded seminar.

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