Here’s what I plan to cover

• Doing sort of a survey of the relevant information so that you can find the appropriate resources when the time comes
• So if you want to dig deeper into any point – Feel free to ask questions as we go.
The first thing you should know about a funding mechanism is its purpose…

Expectations of NIH Research (R) and Career (K) grants

• R Grants
  *Have a sustained, powerful influence on the research field(s) involved*

• K Grants:
  *Enhance candidate’s potential for a productive, independent scientific career in a health-related field*
A few examples of what add up to quite a few mechanisms
• All have different goals, durations, requirements in writing
• Make sure you're clear on this – have seen lots of negative reviews of R21s because reviewers felt the fit was poor

R01 is best known – usually in support of a research program for a whole lab
• R01 (unlimited, up to 250K/yr), up to 5 years
R21 also common – harder to get
• (up to 275K, up to 200K/yr), up to 2 years
• Fewer are given out and LOTS of people apply
• Expectations are very high!
R03 (100K):
• Pilot or feasibility studies
• Secondary analysis of existing data
• Small, self-contained research projects
• Development of research methodology or new research technology
Examples of Career (K) Grant Types:

**K01: Mentored Research Scientist Career Development**
- For postdocs or early-career research scientists
  - committed to research
  - needing advanced research training and additional experience
- 12-page Career Goals plus Research Strategy

**K08: Mentored Clinical Scientist Research Career Development**
- Fill academic faculty gap in health sciences by supporting
  - clinician scientists, promising as independent investigators
  - faculty members
- 12-page Career Goals plus Research Strategy

**K99: Pathway to Independence**
- For postdocs seeking independent research positions
- Supports:
  - initial mentored research experience (K99)
  - subsequent independent research (R00)
- Must compete for independent R01 support (R00 phase)

- Even more subtypes than Rs
- Lots of variety regarding goals
  - For clinicians to learn science
  - For scientists needing additional experience
  - A springboard for junior scientists from K to R grants
  - again, CHOOSE ONE THAT’s A GOOD FIT
- Generally shorter than R01 as far as research component
How Research (R) and Career (K) grants are evaluated

• Overall impact score assesses:
  – R grants: *likelihood that project will have a sustained, powerful influence on the research field(s) involved*
  – K grants: *likelihood that the proposed career development will enhance candidate’s potential for a productive, independent scientific career in a health-related field*

• Core review criteria for impact score by application type:
  - **K Grants**
    - Candidate
    - Career Development Plan/Goals
    - Research Plan
    - Research Plan Mentors
    - Environment and Institutional Commitment
  - **R Grants**
    - Significance
    - Investigator(s)
    - Innovation
    - Approach
    - Environment

Grant review – Effectiveness is evaluated as “Overall Impact Score”
• How well the proposal supports the likelihood that…
• This score is derived from an evaluation of 5 criteria
• Criteria differ across grant types
• For Rs, likelihood that project will have a sustained and powerful influence is evaluated based on
  • (science is evaluated mainly on Significance and Approach in Research Plan)
• For Ks, likelihood that training will enhance candidate’s potential
  • (science is evaluated mainly in Research Plan)
Here is a comparison of the 5 scored review criteria for F, K and R and have highlighted:

- **where the science is evaluated** (as I’ve touched on already)
- Note differences from R grant to F grants –
  - R => Significance/Innovation/Approach all get own scores in evaluating the science.
  - K => Research Plan is evaluated as a unit (no separate scores for Significance/Innovation/Approach in evaluating the science)
  - F => Proposed Research is only half of one of the 5 criteria (no separate scores for Significance/Approach and shared with Training Plan)
### Questions about the Science:

- Are proposed research questions/design/methodology of significant scientific and technical merit?
- Is key support for project (prior research) rigorous?
- Plans to address weaknesses in rigor of prior research?
- Strategies to ensure robust and unbiased approach?
- Plans to address relevant biological variables?
- Is plan relevant to candidate's research career objectives?
- Is plan appropriate to stage of development and vehicle for developing research skills described in career development plan?
- Will any proposed clinical trial experience contribute to proposed research project?
### Scored Review Criteria by Grant Type

<table>
<thead>
<tr>
<th>Fellowship (F)</th>
<th>Career (K)</th>
<th>Research (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Applicant</td>
<td>• Candidate</td>
<td>• Significance</td>
</tr>
<tr>
<td>• Sponsors, Collaborators, Consultants</td>
<td>• Career Development Plan/Career Goals</td>
<td>• Investigator</td>
</tr>
<tr>
<td>• Research Training Plan</td>
<td>• Research Plan</td>
<td>• Innovation</td>
</tr>
<tr>
<td>• Proposed Research</td>
<td>• Mentor(s), Co-Mentor(s)…</td>
<td>• Approach</td>
</tr>
<tr>
<td>• Training plan</td>
<td>• Environment Commitment to the Candidate</td>
<td>• Environment</td>
</tr>
<tr>
<td>• Training Potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Environment &amp; Inst. Commitment to Training</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Here I’ve highlighted:

- **where the training that’s proposed is evaluated**

- BIG difference between these and R grants!
  - Not relevant in Rs
  - Two sections contribute in Ks
  - Three sections contribute in Fs

For more on review criteria and scoring system, see: [http://grants.nih.gov/grants/peer-review.htm](http://grants.nih.gov/grants/peer-review.htm)
Questions about Proposed Training:

• Likelihood that plan will contribute substantially to scientific development and lead to scientific independence?
• Are prior training and research experience appropriate for this award?
• Are content, scope, phasing, and duration appropriate relative to:
  — prior training/research experience and stated training
  — and research objectives for achieving research independence?
• Are plans for monitoring and evaluating the candidate's research and career development progress adequate?
• Will any proposed clinical trial experience contribute to applicant's research career development?

These questions are about both:

Proposed training...
Questions about Proposed Trainers:

- Is mentor qualified in the proposed area of research?
- Does mentor adequately address candidate's potential, strengths, and areas improvement?
- Is description of quality and extent of mentor's role adequate?
- Is mentor's description of activities, including formal course work, adequate?
- Evidence of experience fostering development of independent investigators?
- Evidence of current research productivity/peer-reviewed support?
- Adequate support for proposed research project (active/pending)?
- Adequate plans for monitoring/evaluating progress to independence?
- Is any clinical trial supported by mentor expertise/experience/ability?

...and proposed trainer
### Scored Review Criteria by Grant Type

<table>
<thead>
<tr>
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<td>• Training Potential</td>
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<td>Commitment to the Applicant</td>
</tr>
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For more on review criteria and scoring system, see: [http://grants.nih.gov/grants/peer-review.htm](http://grants.nih.gov/grants/peer-review.htm)

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The applicant is evaluated in all three types of grants
Questions about Applicant/Candidate:

- Are they likely to become an independent and productive researcher?
- Are their prior training and research experience appropriate?
- Are their academic, clinical (if relevant), and research records of high quality?
- Is there evidence of their commitment to becoming independent research investigator?
- Do letters of reference provide evidence of high potential for candidate to become an independent investigator?

My synopsis of the questions reviewers are asked

- i.e. what authors need to be sure to address explicitly
Finally, in all cases, the NIH wants to know if the applicant has sufficient support for the proposed project.
Questions about Environment/Institutional Commitment:

- Is commitment to reasonable %effort (direct) to described research adequate? Is remaining %effort balanced between research, teaching, administrative, and clinical responsibilities?
- Strong institutional commitment to career development?
- Adequate research facilities, resources, and training opportunities, including faculty capable of productive collaboration with candidate?
- High quality environment for scientific and professional development?
- Assurance that candidate will be integral part of institution’s research program as independent investigator?

Environment & Institutional Commitment to the Candidate:

Just want to highlight that for K grants,

It’s important to show that your department will give you sufficient protected time to do the research

especially if you are a clinician
For those of you writing K grants:

- These are some of the key sections you and your mentors will need to prepare
- Don't ignore the ones without arrows
- and here are the page limits

<table>
<thead>
<tr>
<th>Section of Application</th>
<th>Page Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Summary/Abstract</td>
<td>30 lines of text</td>
</tr>
<tr>
<td>Project Narrative</td>
<td>Three sentences</td>
</tr>
<tr>
<td>Introduction to Resubmission or Revision Application (when applicable)</td>
<td>1</td>
</tr>
<tr>
<td>Candidate Information and Goals for Career Development and Research Strategy</td>
<td>12 (for both attachments combined)</td>
</tr>
<tr>
<td>Specific Aims</td>
<td>1</td>
</tr>
<tr>
<td>Training in the Responsible Conduct of Research</td>
<td>1</td>
</tr>
<tr>
<td>Candidate’s Plan to Provide Mentoring (include only when required by the specific FOA, e.g., K24 and K65)</td>
<td>6</td>
</tr>
<tr>
<td>Plans and Statements of Mentor and Co-mentor(s)</td>
<td>6</td>
</tr>
<tr>
<td>Letters of Support from Collaborators, Contributors, and Consultants</td>
<td>6</td>
</tr>
<tr>
<td>Description of Institutional Environment</td>
<td>1</td>
</tr>
<tr>
<td>Institutional Commitment to Candidate’s Research Career Development</td>
<td>1</td>
</tr>
<tr>
<td>Biographical Sketch</td>
<td>5</td>
</tr>
</tbody>
</table>

https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/page-limits.htm#car
Here are the ones I’ll focus on through the rest of the talk

- Note that where R grants have a 12-page Research Strategy
- K grants have the Research Strategy combined with Candidate Info/Goals – in the same amount of space
This is a breakdown:

- Although there is no formal recommendation for how to split this in a K,
- we recommend starting with the idea of 6+6
Here are some insights we’ve gained during previous discussions with panelists who have served on study sections evaluating training grants (F30/F31).

• Also relevant to K grants
What happens during review at NIH?

- 2–3 reviewers among ~ 20 panel members will read in entirety
- these reviewers will present and discuss it at meeting and give it a preliminary impact score
- they may revise opinions based on discussion
- non-presenting reviewers will get main overview from Specific Aims page
- all reviewers contribute to final overall impact score

Ultimately, even reviewers who read little more than your Specific Aims page have a major influence on your score!

Start out by talking about what happens in study sections…
- As you may know, NIH study sections are large
- go for a couple of days
- Disrupt the reviewers’ schedule (preparation and meeting time
- What a non-presenting reviewer relies on is:
  - Discussion
  - Aims page (or Abstract) – use as "roadmap" during discussion
Topics

Grants:
Mechanisms and Review at NIH

Grantsmanship:
Structuring the Specific Aims Page
Considerations for the Innovation Section

Grantsmanship and Rigor/Reproducibility:
The Significance Section
The Approach Section

Resources
Something to remember about the Specific Aims page

- It's hard to write because you’re expected to fit a lot of information into a single page (think of this as a roadmap)
- It would be a lot easier if you had a few pages – but that would defeat the purpose
- Remember – *tell a story*!
Just want to very briefly get your thoughts about the three examples you were asked to read before class...

• Which was most inviting?
• Which proposal was most informative?
• What strategies (in any example) were effective?
• What aspects (of any example) need improvement?
Specific Aim

Understanding the bases of an immune response that controls infection or enables selective immunity, remains a critical and the most fundamental issue in the development of new antiviral therapies to combat HIV/AIDS. Because of the tremendous heterogeneity of the virus, we are still struggling to understand how the immune system can be manipulated to control HIV. We hypothesize that variations in ADCC activity of sera are dictated by the characteristics of Abs that mediate ADCC that are likely important goals in the design of HIV vaccines or immunotherapies.

Hypothesis: Antibody-dependent cell-mediated phagocytosis (ADCC) is a major goal in the search for effective vaccines or immunotherapies for HIV. Antibodies (Abs) induced by vaccine trials. However, this approach has not been successful in containing viral replication in vaccinees that have become HIV-infected.

1. Could be improved
   - Lots of detail at the expense of the big picture
   - Some information is redundant
   - Aims sound more descriptive than they probably are
   - Unclear what the expected outcomes will be and how this particular information will move the field forward.

2. Effective
   - Logic breaks down in paragraph 1.
   - Problem sounds interesting to NIH
   - Great first sentence – and focus is on biology without needing to invoke the number of affected patients.

3. Could be improved
   - Logic breaks down in paragraph 1.
   - Problem sounds interesting to NIH
   - Great first sentence – and focus is on biology without needing to invoke the number of affected patients.

4. Effective
   - Problem sounds interesting to NIH
   - Great first sentence – and focus is on biology without needing to invoke the number of affected patients.
Example 2

Specific Aims

Rationale: Serotype 11E is a novel pneumococcal serotype, previously unidentified due to its serological similarity to the epidemiologically prevalent 11A, a significant serotype in both asymptomatic carriage and disease-causing strains. Genetic findings indicate that each 11E strain emerged independently in separate hosts, which suggests that 11E emerged independently of 11A. We hypothesize that disruption of the wcjE capsule synthesis gene, which encodes a Phosphoglycerol transferase, allows a strain initially expressing 11A capsule to evade a host humoral response by changing the capsule structure, setting the stage for future studies addressing the persistence and control of disease caused by serotype 11A.

Aim 1. Examine nasopharyngeal (NP) isolates for the presence of 11E strains

(1A) Develop a FACS-based assay for efficient detection and distinction of 11A and 11E strains.
(1B) Identify additional 11E clinical strains, focusing on NP isolates originally typed as serotype 11A.
(1C) Examine newly identified 11E isolates for heterogeneity of wcjE disruption.

Aim 2. Determine whether a human humoral immune response can be selective for 11A and not 11E in vivo

(2A) Generate isogenic 11A and 11E strains for comparative studies.
(2B) Determine antibody specificity for 11A or 11E polysaccharide (PS) in sera from individuals vaccinated with the pneumococcal vaccine PPV-23 (PPV-23 sera) by using ELISA.
(2D) Determine competitive advantage of 11E by immunological escape in PPV-23 sera by using Multiplex Opsonophagocytic Killing Assay (MOPKA).
(2E) Verify the role of anti-capsular PS antibodies in 11A and 11E opsonization.

Aim 3. Determine that 11E has a selective advantage in an immune response against 11A in vivo and whether 11E bacteria emerge from initial infection with 11A

(3A) Develop an 11A and 11E mouse infection model.
(3B) Detect total and functional anti-11A and anti-11E antibodies in murine sera following 11A and 11E infection.
(3C) Determine in vivo survival of 11A and 11E in mice actively immunized against 11A and 11E PS.

Example

Confidential

Effective

1. Topic likely of interest to NIH
2. Studies are both in vivo and in vitro.

Could be improved

1. Unclear exactly what the key gap in knowledge is and how the study will move the field forward.
2. Aims are list-like and lack of linkage and detail makes it hard to understand how they fit together.
3. “Examine”, “Determine whether”, “Determine that” in aims titles are problematic.
4. Unclear what the expected outcomes will be.
Example 3

Aims

1. Pursue the following two specific aims:
   
   a. Evaluate the influence that inbred CECs have on CCT. We will evaluate the influence that inbred CECs have on CCT. We will evaluate the influence that inbred CECs have on CCT.

   b. Evaluate the influence that inbred CECs have on CCT. We will evaluate the influence that inbred CECs have on CCT. We will evaluate the influence that inbred CECs have on CCT.

Effects

1. Walks reader through key points in first two paragraphs; progression is logical

2. Spells out general problem and specifically what gap will be addressed.

3. Supports hypothesis by describing data on which it is based.

4. Highlights key concepts, making it easy for reviewers to find information.

Could be improved

1. Aim 2 depends on Aim 1.

2. Details of experiments to be done are unclear, making aims vague.

3. Final paragraph could use clearer logic.

4. Aims not written in parallel (passive/active voice is distracting).

This one is the best attempt to tell a story
Now I'll go through a summary based on grant-writing workbook (reference is at the end of this talk)

- Order of presentation designed to get the reader interested in the big-picture/problem before inundating them with details
- Writers often forget the need for this in their own work – but not typically when they read that of others!
- Continues with What they are setting out to do
- How they plan to do it
- And how the funding agency will be rewarded for its investment
• Keep in mind:
  • The purpose of each paragraph
  • Key elements and how the order pulls a logical thread through
Do this as a bullet outline first

This is one of our Specific Aims page templates
• Opening sentence: immediately establish relevance of the proposal to agency mission
• Current knowledge: enough background for the reader to follow why the gap is important = why your study will be significant.
  • Do not go off on a tangent that will distract the reader
• Gap in knowledge – key to logic of whole page
  • everything downstream must be consistent with it
  • Should not go on tangents that stray from addressing this gap
• The significance of this gap – vertical vs lateral change
  Vertical change — e.g. how something works
  Lateral change — how a known process works in another cell line, incremental
Reviewers should

• understand why your research area is relevant to agency’s mission

• be up to speed with state of knowledge in the field

• understand the gap in the knowledge base, and that it is an important problem

Formula for a 1-page Specific Aims section

Background/Significance paragraph

Significance & Background Paragraph

Why?

What?

How?

How?

How?

Payoff
Long-term goal is most important for:
• Faculty, especially ESI's applying for R grants
• Faculty and post-docs applying for K awards
• Must reflect an area of research pursued by your laboratory
• NIH likes projects with the potential for RENEWAL

Objectives of the proposed research: (clear goal that addresses gap)
• Define purpose of proposed project (filling gap/unmet need)
• Must be achievable in allotted time
• If you have a long-term goal, this must be a logical next step toward achieving it (linkage must be obvious)
• Must have a defined endpoint (not simply "to study process x")
  o otherwise, when would you be done?
  o overemphasizes process, rather than product, of research

Central hypothesis – provide focus for your grant application
• Must link to objective
• Must give direction to project => the best bet for accomplishing objective
• Must be objectively testable (no predetermined conclusion)
• Should have components that are individually testable (by aims)
• If application addresses a need, provide best bet as to how to meet the need

What hypothesis is based on – PD? Literature?

Rationale – why you want to undertake this research, e.g., what will become possible that is not now
• Must link back to gap identified in first paragraph – whose resolution will allow you to take the important next step
• An opportunity to excite the reviewers!
• The challenge: to deliver this exciting message without repeating of the "gap as a problem" verbatim
Headlines (aims titles):

- **Purpose**: attract a reviewer’s attention/capture their interest
  - Must link back to some part of your central hypothesis
    - (If unmet-need based application, describe what will be done.)
  - Should not be descriptive* (focused on what is being done)
    - *do not use characterize/correlate/describe” if you have a hypothesis
  - Should be broad and open-ended
• What’s the problem if you use this as a title?
Working hypothesis:

- **Purpose**: to focus / provide direction for the aim
- If you only have space for the working hypothesis, be sure to write it so that it's clear what kind of approach you'll use.
- Ideally, you would add another sentence or two to spell this out, do so.
- Like the central hypothesis, this is ideally based on preliminary data (to justify focus on this vs. all other possibilities*)
- * **IF space allows**, briefly indicate a general approach after the working hypothesis
- **OVERALL**, the aim should be consistent with the objective(s) of the proposed research
• Each Aims title should reflect a component of the objective of the proposed research.
• Each working hypothesis should reflect a component of the central hypothesis.
Reviewers should understand

- What specific goals you plan to achieve
- How aims relate to overall objective and hypothesis

```
Aim 1
Aim 2
[Aim 3]
```

Why?

What?

How?

Payoff
Formula for a 1-page Specific Aims section

**Impact paragraph**

**Significance & Background Paragraph**
- Why?
  - Long-term goal
  - Objectives of research
  - Central hypothesis
  - Rationale

**Purpose Paragraph**
- What?
  - Broad problem, hook
  - Background knowledge
  - Gap in knowledge
  - Significance of gap

**Significance/general context Broader Impact**
- How?
  - What you will do
  - Why you will do it

**Aim 1**
- How?

**Aim 2**
- How?

**[Aim 3]**
- How?

**Payoff**
- Expected outcomes of aims
- Positive/broad impact of work
- Expected contributions to advancement of your career
Reviewers should:
- know what return they can expect if they recommend funding of your application
- will hopefully be inspired to advocate your project

Formula for a 1-page Specific Aims section
Impact paragraph

Why?
What?
How?
How?
How?
Payoff
Significance/general context
Broader Impact
Here’s a summary – showing the general principles of going from broad to narrow – culminating in what you will do

Any questions so far?

https://medicine.uiowa.edu/sercc/resources/writing-grants
Moving beyond the bullet points

Start with an outline of bullet points (based on template)

- Take a break before starting to expand the outline into sentences and paragraphs
- Seek constructive criticism from colleagues
  - Does each component serve its purpose?
  - Does each component link to the others in the right way?
  - Is the progression of the logic linear?
- Try to represent Specific Aims in a figure
  - Should be simple
  - Should illustrate relationships among aims
  - Even if it isn’t used on the Specific Aims page it can solidify your thinking and convey concepts

Example from Mengxi Jiang. NIH R01 funded in 2015, posted on Open Grants
https://grants.nih.gov/reproducibility/index.htm
Final thoughts on Specific Aims page:

• Leave nothing to interpretation of reviewers (spell out meaning)

• *Italicize* or *italicize and underline* key words
  — don’t overdo (frequency, style)

• Minimize number of citations in this section
  (maximally linchpin references)

• Talking about outcomes:
  — Do not overstate (we will discover/prove)
  — Do not understate (may lay the foundation for; may be relevant to)
  — Make it conditional (has the potential to; is expected to identify)

Highlighting must be meaningful and not overly complicated!
• Significance Section
• Innovation Section
• Approach

Before moving on to Rigor in RS, will just talk briefly about Innovation section
Innovation Section...

- Explain what makes your proposed approach a new and substantially different way of addressing an important problem
- For every aspect of innovation you discuss (ideally, limit to 1–3)
  - Current strategies and their limitations.
  - What makes the proposed research innovative: new approach? use of unconventional technology?
  - Advances that are only possible because of this new approach.

https://medicine.uiowa.edu/sercc/resources/writing-grants
Topics

Grants:
Mechanisms and Review at NIH

Grantsmanship:
Structuring the Specific Aims Page
Considerations for the Innovation Section

Grantsmanship and Rigor/Reproducibility:
The Significance Section
The Approach Section

Resources
In 2018, the NIH made serious efforts to address the problem that some researchers were building proposals on poor previous research and poor experimental design.

- What does "Scientific Rigor" mean to the NIH? What do they want you to pay attention to?
  - Studies on which ideas are based are sound experimentally.
  - Study design is sound
  - Results proposed will be interpretable
  - Will account for potential differences in outcomes due to factors like sex, weight, age...
  - Samples used will actually be what the authors think they are
Current NIH instructions related to Rigor and Reproducibility

- Here is what they want you to pay attention to in ALL grant types
Where does this go?
Here this is mapped to another NIH resource (this is going to get messy…)

- We ask ourselves – is the required information in the right places
  \textit{(many times – no)}
- Staff of the Division of Sponsored Program DSP ask too, especially for ancillary documents

Significance section
- Weaknesses in rigor of prior research

Approach section
- How weaknesses in rigor of prior research will be addressed
- How rigor of proposed research will be ensured
- Consideration of biological variables, including sex, in the proposed research

Ancillary Document
- Resource authentication

\url{https://grants.nih.gov/policy/reproducibility/guidance.htm}

Updated November 26, 2018
Addressed in grant writing templates…

- Our writing templates address these requirements in both the Significance and Approach sections
Reviewer questions for Significance section

1) Does the project address an important problem or a critical barrier to progress in the field?

2) Is the prior research that serves as the key support for the proposed project rigorous?

3) If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

4) How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Going back to the review questions for standard R, K, and F grants FOA (turn into bullet list)

• Have turned scoring criteria into headings
• These are all pretty much included for R, K, and F grants.
• Again, summarized in the template
• Avoid making this too long
  • At most, provide the data for 1 or 2 experiments that are the linchpins of the scientific premise.
  • Other supporting data for premise and for feasibility should be presented under Approach.
What does “rigor of prior research” apply to?

Importance of the problem and/or critical barriers to progress

Scientific premise* and rigor of the prior research

Significance of the expected research contribution

• Impact of the project on scientific knowledge / technical capability / clinical practice
• Impact of the project on the field

* The relevant literature: Strengths and weaknesses
  • Rigor of study design (e.g. statistical power, blinded analysis)
  • Incorporation of relevant biological variables (e.g. detail regarding sex)

Your preliminary data that contribute to scientific foundation of proposal.

What does rigor apply to?

• The literature
• Your preliminary data
How this might be worded

1) Importance of the problem and/or critical barriers to progress

2) Scientific premise and rigor of the prior research (organize overall or by aim)*
   - Numerous studies have…
   - However, studies X and Y have important limitations…
   - In addition, the rigor of study Z was not sufficient in that…
   - To overcome these gaps in rigor, we will… [keep this general here]
   - Thus, our proposed studies will circumvent the limitations of… by …

3) Significance of the expected research contribution
   - Impact of the project on scientific knowledge / technical capability / clinical practice
   - Impact of the project on the field

   Specifically mention limitations … good lead-in for innovation

   If there was a lack of rigor and it’s possible to discuss diplomatically…

- Thoughts on what to include and how to say it!
- Trick is to do this well without alienating potential reviewers
An example of this layout (but with just SP) – still works well
Topics

Grants:
Mechanisms and Review at NIH

Grantsmanship:
Structuring the Specific Aims Page
Considerations for the Innovation Section

Grantsmanship and Rigor/Reproducibility:
The Significance Section
The Approach Section

Resources
Reviewer questions for Approach section

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? (2016)
- Have the investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project? (2018)
- Are potential problems, alternative strategies, and benchmarks for success presented?
- If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
- Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects? (2016)
- If the project involves human subjects and/or NIH-defined clinical research, are the plans for: protections for human subjects, and inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, …?

Moving on to Approach:
- These are the current review criteria
- We’ve built our recommendations for this on the old Grant Writers’ model for this section
Here is our favorite suggestion

- Can work in strategies for ensuring rigor and SABV into aims if that’s a better fit for your story (e.g., different aims require very different approaches)
- Make it part of Research Design
- For Justification and Feasibility
  - Remind reader of any PD in Significance, provide any additional support here
  - Tell reader about feasibility data
- Expected outcomes and alternative strategies – recommend doing by aim rather than sub aims
- Timeline and Future directions are their own major headers = to Aims
  - Don’t make them look like they’re part of Aim 2 or 3 (final aim)
Note that we’ve moved beyond this – be sure to include the power analysis information
• even if you don’t have it now, explain why not and how you’ll do it.
Examples of Strategies to Ensure Rigor (posted by NIH)

• Excerpts from awarded applications reviewed under a pilot FOA for rigorous experimental design … this is only one part of updated instruction and review language.
• Selected based on high overall impact scores and positive reviewer comments specific to rigor.
• Provided to show how elements of rigor and transparency have been succinctly provided in applications; they may not represent all of the aspects/may still have room for improvement.
• May be updated as applications are reviewed and awarded under the revised rigor and transparency review.

Example 1:

**Aim 3:** Male and female mice will be randomly allocated to experimental groups at age 3 months. At this age the accumulation of CUG repeat RNA, sequestration of MBNL1, splicing defects, and myotonia are fully developed. The compound will be administered at 3 doses (25%, 50%, and 100% of the MTD) for 4 weeks, compared to vehicle-treated controls. IP administration will be used unless biodistribution studies indicate a clear preference for the IV route. A group size of n = 10 (5 males, 5 females) will provide 90% power to detect a 22% reduction of the CUG repeat RNA in quadriceps muscle by qRT-PCR (ANOVA, α set at 0.05). The treatment assignment will be blinded to investigators who participate in drug administration and endpoint analyses. This laboratory has previous experience with randomized allocation and blinded analysis using this mouse model [refs]. Their results showed good reproducibility when replicated by investigators in the pharmaceutical industry [ref].

**Key points:**
• Number of groups, allocation random, age, why that age.
• Dosage, number of doses administered
• Route of administration, contingency
• Group size, power
• Blinding, of whom
• Experience

Rigor and Reproducibility
https://grants.nih.gov/reproducibility/index.htm
Example 2:

Aim 1: Primary screen: In this high throughput screening assay, we combined the SMN promoter with exons 1-6 and an exon 7 splicing cassette in a single construct that should respond to compounds that increase SMN transcription, exon 7 inclusion, or potentially stabilize the SMN RNA or protein [refs]. The details of the assay and the SMN2-luciferase reporter HEK393 cell line have been extensively validated [refs]. Each point is run in triplicate, the compounds are tested on three separate occasions, and the results are averaged to give an EC50 with standard deviation. Secondary screen: ... We analyze SMN protein levels by dose response in quantitative immunoblots with statistical analysis by one-way ANOVA with post-hoc analysis using Dunnett or Bonferroni, as appropriate.

Aim 2: Each set of compounds will include a blinded negative control compound that has been determined to be inactive and that is solubilized in the same manner as test compounds. Mice will be randomly assigned within a litter, and data will be collected and submitted to the PI. For compounds that demonstrate extended survival, the PI will be sure to have these tested in (the collaborators') labs, and data will be merged and evaluated. To calculate the number of the experimental mice, we will perform an SSD sample size power analysis to ensure that the appropriately minimal number of mice is used in each experimental context. Typically for each compound in life span studies, we will need ~20 SMA animals in the treated group; ~20 SMA animals in the vehicle treated group; ~20 SMA animals in the untreated group. If we can administer the compound in aqueous solution without expedient, the vehicle and untreated groups might be combined, as these should have identical survival. Therefore, no more than 80 SMA animals will be needed per compound.

Key points:

Aim 1
- Brief summary of overall approach
- Number of replicates, same/different dates, reporting of average with standard deviation
- Types of statistical analysis

Aim 2
- Blinding, solubilization of test and control compounds
- Random assignments
- Who will analyze
- Power analysis; number of animals per group
- Number of animals, contingency

Rigor and Reproducibility https://grants.nih.gov/reproducibility/index.htm
• Flow chart from NIH to figure out whether you need to consider sex as a biological variable in your study.
  • Does the study involve vertebrate animals? humans?
  • Y: Is the study intended to test of sex differences?
    • Y: Is the design/analysis adequately rigorous to test for them?
      • Y: STRENGTH
      • N: Weakness
    • N: Are both sexes included in the study?
      • Y: Will data be reported disaggregated by sex? ...
    • N: Is strong justification provided for not including both? ...
  • ADDRESS this even if it seems obvious that only one sex is needed!
Example of Consideration of SABV

"Recent" (2016) example including SABV – New subsection (before Aim 1)

Methods to achieve robust and unbiased results:

... and WT littermate controls were generated as described in Fig. 1. These lines were genotyped and cataloged across 10 backcrosses into the C57BL/6J strain. Only animals that are of the same genetic background and handled in the same way will be compared. Congenic Xxxx KO mice (B6.129P2-Xxxx/J; stock #xxxx) were obtained from Jackson Laboratories. These mice had been backcrossed with C57BL/6J animals >30 generations. For cultures of dissociated PFC cells obtained from neonates, there is no reason to think that gender differences exist; hence male and female pups will be randomly allocated to experimental groups at P1. For the experiments involving [brain] slices from P30 animals, samples will be prepared from equal numbers of age-matched male and female animals and results will be tracked by gender. Each experiment will be performed in triplicate and repeated at least three times. Dose-response and time-course analyses will be conducted for each compound to ensure that the responses are maximal. We have extensive experience with blinded analysis, treatment paradigms, and group analyses.44,45 The Co-Investigator has extensive experience in establishing LTP and LTP-D paradigms in both rats and mice. Experimental designs are rigorously vetted including, at a minimum, testing of only a priori hypotheses and blinding for subjective ratings. Except as noted, biological and chemical resources will be obtained from standard commercial suppliers; effects of novel agents are documented in the literature. Data will be analyzed using ANOVA followed by posthoc testing with Student’s t-test.

Great example of project that we had:

- some data for which sex was **not** going to be a concern
- and some data for which sex was a concern and how they would deal with it

- Key points:
  - Dealt with both (did not ignore the one where sex is not relevant)
  - It’s not good enough just to gather data from both sexes
  - Must also track and analyze by sex, at least in a first round

**Key: Explain your thinking**
This table illustrates that the aims are not dependent on one another!
Topics

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Resources
For grant writing…

Updates available at: https://medicine.uiowa.edu/sercc/resources/writing-grants
Our templates for R and K grants are
• Based in part on these resources

NOTE: CLARITY of BIG-PICTURE matters a lot.
For writing generally:

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<th>Title</th>
<th>Edition</th>
<th>Publisher</th>
<th>Publication Date</th>
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<tr>
<td>Joseph M. Williams</td>
<td>Style: Toward Clarity &amp; Grace</td>
<td>(Chicago Guides to Writing, Editing, and Publishing)</td>
<td>The University of Chicago Press</td>
<td>1995</td>
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<td>Lynne Truss</td>
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<td>Gotham Books</td>
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<td>George Gopen &amp; Judith Swan</td>
<td>The Science of Scientific Writing</td>
<td></td>
<td>American Scientist</td>
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Writing tips by Gary Westbrook & Linda Cooper

Society for Neuroscience and The Journal of Neuroscience websites

Subscribe to our online newsletter!
Planning for Submission

Advantages of filling out pre-submission form:

• it is helpful if people fill these out so we have advanced notice of projects that might come in, especially given how busy we are at times

• We can try to get your project done faster if you’re already in line! (must give a reasonable window for this to work)

• We get all the information we need right away (e.g. title, MFK) and won’t have to follow up

https://medicine.uiowa.edu/serrc/editing-other-services/pre-submission-forms
### Scientific Editing and Research Communication Core

#### Pricing

The following charges will be assessed based on author affiliation:
- University of Iowa Carver College of Medicine (UIC) - 50% off
- University of Iowa, College Other Than the COB - 50% off
- Outside the University of Iowa - full price

The service fee is fully embedded in these invoicings and programs.

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**Time spent is based on factors such as desired level of feedback, available time, and ease of project completion vs critical submission.

**Note:** Initial requests, proposal, and projects on the other.

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https://medicine.uiowa.edu/sercc/pricing-1
How to make your grant stand out

- Follow instructions
- Make all necessary information easy to find
- Make the text inviting
- Tell a story
- Make sure your meaning is clear – to others

Questions?