THE UNIVERSITY OF KANSAS
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Useful Insights to the NIH Review Process

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Disclaimer

The following slides are based on my own individual experiences as a frequent NIH grant/contract reviewer over the past 15 years.

The content is the sole responsibility of the presenter and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health.

Some Initial Thoughts

- Depending on Study Section, a permanent member will be assigned as a reviewer for between 7 – 10 grants
  - Lower initial workload for a Chair
- Permanent members must attend at least 2 of the 3 scheduled meetings per year.
- Most study sections are three days worth of travel
  - In night before, two review days, out after 5 pm on final day of panel
- Who reviews what is not always predictable
  - *Most reviewers are not always certified experts in the areas they review*
- ***The single best way to write better grants is to serve on a review panel***

Choice of Study Section for Review

- The Center for Scientific Review maintains a number of permanent study sections based on scientific area.
  - Based on need, CSR will populate “one-time” panels or special emphasis panels (SEPs)

- For a CNS medicinal chemist, there are a number of relevant study sections to select
  - *DDNS (Drug Discovery for the Nervous System)*
  - MNPS (Molecular Neuropharmacology and Signaling)
  - SBCB (Synthetic and Biological Chemistry B) (*peptides*)
  - SBCA (Synthetic and Biological Chemistry A) (*carbohydrates and nucleic acids*)

DDNS reviews pre-clinical applications with the ultimate goal of discovering new pharmacotherapeutic and immunotherapeutic agents for treating or preventing disorders of the nervous system, including drug abuse, that will eventually lead to clinical trials and approval by FDA.

Generic Scoring Chart

Score 5 is given to good, medium-impact applications

Overall Impact or Criterion Strength	Score	Descriptor
High	1	Exceptional
	2	Outstanding
	3	Excellent
Medium	4	Very Good
	5	Good
	6	Satisfactory
Low	7	Fair
	8	Marginal
	9	Poor
Other Designations for Final Outcome		
AB	Abstention	
CF	Conflict of Interest	
DF	Deferred	
ND	Not Discussed	
NP	Not Present	
NR	Not Recommended for Further Consideration	

The Review Process

- **Scored Review Criteria**
  - Significance
  - Investigator(s)
  - Innovation
  - Approach
  - Environment

- **Additional Review Criteria**
  - Protection for Human Subjects
  - Inclusion of Women, Minorities, and Children
  - Vertebrate Animals
  - Biohazards
  - Resubmissions
  - Renewals
  - Revisions

Rigor and Transparency in Research

To support the **highest quality science, public accountability, and social responsibility in the conduct of science**, NIH's Rigor and Transparency efforts are intended to clarify expectations and highlight attention to four areas that may need more explicit attention by applicants and reviewers:

- Scientific premise
- Scientific rigor
- Consideration of relevant biological variables, such as sex
- Authentication of key biological and/or chemical resources

- Much of this initiative codifies activities that have already been part of the review process for most fields

Reviewing Rigor and Transparency of Research

	Applies to ?	Where in the application?	Where in my critique?	Addition to review criteria	Affects score?
Scientific Premise	All	Research Strategy	Significance	Is there a strong scientific premise?	Yes
Scientific Rigor	All	Research Strategy	Approach	Are there strategies to ensure a robust and unbiased approach?	Yes
Consideration of Relevant Biological Variables, Such as Sex	Use of vertebrate animals/ human subjects	Research Strategy	Approach	Are adequate plans to address relevant biological variables, such as sex, included?	Yes
Authentication of Key Biological and/or Chemical Resources	Use of biological/ chemical resources	New Attachment	Additional review considerations	Comment on plans for identifying and ensuring validity of resources.	No

Plan for Resource Authentication

Ensure processes are in place to identify and regularly validate key resources used in their research and avoid unreliable research as a result of misidentified or contaminated resources.

- Additional Review Consideration (**not scorable**)
- Authentication of key biological and/or chemical resources to ensure that the resources are genuine.
- This refers to resources such as antibodies and cell lines, not to more common reagents such as buffers or solvents.
- Comment on the brief plan proposed for identifying and ensuring the validity of those resources.
- Rate as acceptable/unacceptable (provide brief explanation if unacceptable)

Study Section Chair's Discussion Cheat Sheet

Announce application
Identify conflicts
Ask reviewers to state current overall impact scores.

Reviewer 1: Ask to describe overall impact, significance, and major score-driving issues **(5-10 minutes)**
Reviewer 2: Anything to add, focusing on overall impact, differences **(3-5 minutes)**
Reviewer 3: Anything to add, focusing on overall impact, differences **(0-5 minutes)**

Additional Review Criteria. Appropriately addressed (as needed)?

- Human Subject Protections
- Inclusion of Women, Minorities, and Children
- Vertebrate Animal Protections
- Biohazards
- Resubmission/Renewal

This is for an R01, same but shorter for R21

Open discussion (0-10 minutes)

Summarize key issues (should be brief and focus on main points)

- The panel's opinion(s) regarding the importance of proposal's goal
- Key score driving issues
- Major differences in opinion

Final scores

Budget and Other Nonscorable Issues

NIH Center for Scientific Review

Suggestions for a Strong Application

- **Scored Review Criteria**
  - *Significance*
  - ***Investigator(s)***
  - *Innovation*
  - ***Approach***
  - *Environment*

Major driver of score

Will help improve score

Will drop score if not addressed

- **Additional Review Criteria**
  - Protection for Human Subjects
  - Inclusion of Women, Minorities, and Children
  - ***Vertebrate Animals***
  - Biohazards
  - Resubmissions
  - ***Renewals***
  - ***Revisions***

All sections do not drive score equally

Suggestions for a Strong Application

- There is a ***huge*** difference between a drug discovery campaign and a probe development campaign

Drug = *a[potency] + b[efficacy] + c[selectivity]*+d[toxicity] + e[absorption] + f[distribution] + g[metabolism] + h[excretion] + i[protein binding] + j{acute toxicity] + k[chronic toxicity] + l[mutagenicity] + m[stability] + n[accessibility] + o[cost] + p[patentability] + q[clinical efficacy] + r[solubility] + s[taste] + t[formulability] + u[idiosyncratic problem]

Probe =
cellular potency < 1 μM
biochemical potency < 100 nM
selectivity > 100-fold
aqueous solubility
active or passive transport
reversible or covalent mechanism

Suggestions for a Strong Application

- The most successful grant applications ***combine strong chemistry and strong pharmacology***
  - One can be successful with great chemistry and average pharmacology
  - One can be successful with great pharmacology and average chemistry

- There is an increased emphasis on innovation
  - Generally novel targets or hypotheses are preferred over well established one

- One should focus on using contemporary techniques
  - If an X-Ray crystal structure of the target is available, one should be incorporating it into any ligand design (exceptions are possible but one should be explicit)

- One should explicitly state why the molecules being proposed for synthesis are the right ones to make
  - Most organic chemicals are worthless medicinally

Suggestions for a Strong Application

- If proposing to develop a drug or probe, one should explicitly state the goals for the campaign
  - What is desired potency, solubility, and/or selectivity?
  - What is new/interesting about your research?

- Potential off-target effects are important and need to be considered
  - Off-target testing should be included in any development campaign

- Pharmacokinetic properties are important and need to be considered
  - PK testing should be included in any development campaign

Suggestions for a Strong Application

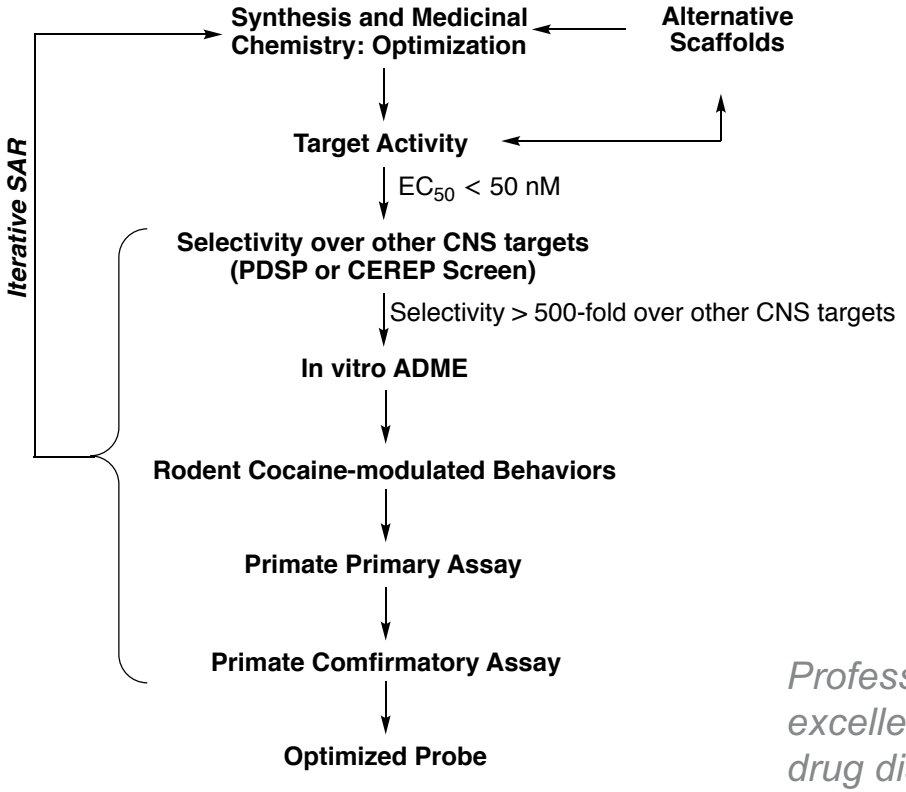
- The specific aims page is the most important page of the entire proposal
  - *This page should be written in a way that someone unfamiliar with you, your mentor, or previous successes can quickly understand what you are proposing to research.*

- Preliminary results are very important and should illustrate the feasibility of your proposed approach
  - Potential pitfalls should addressed and ideally solved
  - If proposing SAR, it should be suggestive of likely success (*i.e. potency has been improved*)
  - If your lead is flagged as a PAINS compound, *it must be derisked*.

- Keep in mind that sometimes you cannot improve a lead compound through an optimization campaign.
  - One should make sure you potential alternative scaffolds

Suggestions for a Strong Application

Consider using a flowchart to illustrate compound progression



Professor Dwoskin had an excellent slide illustrating her drug discovery pathway

Suggestions for a Strong Application

Timeline for Proposed Studies					
Aims/Tasks	***Year 1***	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Specific Aim 1					
Study 1.2.1					
Study 1.2.2					
Study 1.2.3					
Specific Aim 2					
Specific Aim 3					

It generally a good idea to include a timeline for the proposed research.
This is especially important for junior investigators.

Common Mistakes to Avoid

- Rationale for proposed research is underdeveloped
  - Why is the project necessary?
  - Why is your proposed approach the best strategy?

- Not giving enough information to describe what potential problems are likely to occur

- Not giving enough information to describe how potential pitfalls will be overcome

- “Solution in search of a problem”
  - Research proposed addresses a perceived problem but not really address the major scientific issues associated with the field.
  - *For example, a new synthesis of morphine is not essential for opioid research*

Common Mistakes to Avoid

- Insufficient and/or incorrect details on proposed experiments
  - Chemical routes contain errors
  - Rationale for the testing paradigms selected are missing
  - Description of how compounds will be progressed is missing or underdeveloped

- Required sections are not included
  - Description of environment section is missing

- Lack of appropriate consultants/collaborators
  - Insufficient pharmacological expertise based on biosketch
  - Insufficient chemical expertise based on training

NIH Grant Applications
Do's, Don't's and Musts

Nurulain T. Zaveri, PhD

Astraea Therapeutics

Do's

- Put a hypothesis statement and the Overall goal or point out Key significance concisely in the Specific Aims page

- Address relevant and current literature in the Background, especially if there is contrarian literature. Ignoring other lines of thought in the field, if they don't agree with your hypothesis, is not a good idea.

- If there are unestablished methods or experiments without feasibility data, then be sure to mention potential problems and how you may address them.

Do's

- Always a good idea to give a timeline for the project. Many applications do not!!

- Significance is arguably the most important section of the grant which can sway reviewers. *Significance of the project, NOT the disease area being addressed.*

- Pay attention to how you write the Significance. Just stating literature can be boring, if you don't point out how your work fits into it and how your work can address gaps.

Do's

- For R21/R33 Phased applications, pay attention to R21 Milestones.
- Milestones ≠ Specific Aims
- Milestones are 'events /results that should occur that indicate success of a Specific aim'.
- Milestones should be somewhat quantifiable or defined, such that a Go/No-Go decision can be made.
- Many applicants just re-state the R21 Specific Aims as milestones!

Dont's

- Don't undercut the page limits by putting information that should be in the Approach, but is in places where it shouldn't be (e.g. in Budget Justification, or in the Vert. Animal section)

- Don't forget to put in full citations, including titles, in the Bibliography.

- In a Revised application, address ALL major comments from previous reviewers.

- It is very likely that your application will end up with the same reviewers. If you ignore what they wrote and still have those weaknesses, it will only worsen the outcome of the next review.

Musts

- Have to address ‘scientific premise’ in the Significance section

- Rigor in Approach
  - Controls, Statistical analysis, concise but complete description of non-standard methodology.

- Animal studies need to include both sexes, unless scientifically justified for using only one gender.

- Authentication of Resources is now a must.