New NIH grant application guidelines "Enhancing Peer Review":

Writing a 12 page proposal

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Previous Research Plan

1. Introduction (Resubmissions only)
2. Specific Aims
3. Background and Significance
4. Preliminary Studies/Progress Report
5. Research Design and Methods

Restructured Research Plan

1. Introduction (Resubmissions only)
2. Specific Aims = 1 page
3. Research Strategy
    a. Significance
    b. Innovation
    c. Approach

} 12 pages

- Preliminary Studies (New Applications)
- Progress Report (Renewal/Revision)

Scoring criteria

- Overall Impact/Priority Score (Scale 1 to 9)

1) Significance
2) Investigator(s)
3) Innovation
4) Approach
5) Environment

Research Strategy
Significance, Innovation and Approach

- Depending on whether your application is new or a renewal/revision, “Preliminary Studies for New Applications” or “Progress Report for Renewal/Revision Applications”, will also be included in the Research Strategy.

-Importantly, the list of publications, patents or other printed materials should be included in the “Progress Report Publication List” and NOT part of the Progress Report within the Research Strategy.

- This will save you space in the Research Strategy section

Where to place Preliminary Studies within the Research Strategy?

- It is up to you!
- Place it where it makes the most sense to your application
- The Guide Notice suggests to place it in the Approach Section
- But you can also place it in the other two sections: Significance or Innovation

- If the data is pertinent to a particular Aim only, you might include it when you discuss this Aim.

- If the data is pertinent to multiple aims, you might have a section for this data at the beginning of the approach, before you get into the individual aims

Organizing the Research Strategy Section:

- You should again use your discretion in organizing the information to best convey the desired information to the reviewers.

- Either of the following choices would be acceptable, and the decision is up to you.

1. Significance: Specific Aim 1, Specific Aim 2
   Innovation: Specific Aim 1, Specific Aim 2
   Approach: Specific Aim 1, Specific Aim 2

   OR:

2. Specific Aim 1: Significance, Innovation, Approach
   Specific Aim 2: Significance, Innovation, Approach

Don’t try to use other sections to talk about your research strategy

- For example, don’t put any important information in Appendices.

Resources

The Facilities and Other Resources section requires a description of how the scientific environment will contribute to the probability of success of the project, unique features of the environment, and for Early Stage Investigators, the institutional investment in the success of the investigator.

Resources

- How will the environment help you perform the study?

- Especially for new PIs – what has the department done/provided to support the research efforts of the PI?
  - no or limited teaching to allow the lab to be set up
  - start-up package
  - resources, classes (This Workshop!)

Biosketch (4 pages limit)

A Personal Statement is now incorporated as Part A, changing the parts formerly called A, B, and C to Parts B, C, and D.

Applicants should limit the list of selected peer-reviewed publications to no more than 15. These 15 publications should be chosen on the basis of recency, importance to the field, and relevance to the proposed research.

Biosketch (4 pages limit)

- Use the personal statement in the biosketch to give the reviewers more background on why you are very appropriate to do the study – otherwise you are losing an opportunity.

- You are limited to 15 publications in the Biosketch – but you can briefly explain why some of the publications you included is more evidence that you are extremely appropriate to lead this study.

Example of Reference List in NIH Biosketch

C. Selected Peer-Reviewed Publications (selected from XX publications)

Most relevant to the current application

1. Breton S, Smith PJ, Lui B, Brown D. Acidification of the male reproductive tract by a proton pumping (H+)-ATPase. **Nat Med** 1996; 2: 470-472.

This paper was the first to show that the proton pumping H^+-ATPase (also known as the V-ATPase), expressed in the apical membrane of clear cells, is a key player in luminal acidification in the epididymis and vas deferens. We proposed that this acidification mechanism might be a potential target for novel strategies aimed at regulating male fertility. This article was the subject of a News and Views article that was published in the same issue of Nat. Med. (Malcolm Potts, p. 470). The role of the V-ATPase in male fertility was further confirmed in a subsequent paper (see ref 13).

2. Miller RL, Zhang P, Smith M, Beaulieu V, Paunescu TG, Brown D, Breton S, Nelson RD. V-ATPase B1 subunit promoter drives expression of EGFP in intercalated cells of kidney, clear cells of epididymis and airway cells of lung in transgenic mice. **Am J Physiol Cell Physiol** 2005; 288: C1134-C1144.

In collaboration with Raoul Nelson we generated transgenic mice in which EGFP is expressed exclusively in epididymal clear cells. We are using these mice extensively in the present application.

3. Shum WW, Da Silva N, McKee M, Smith PJS, Brown D, Breton S. Transepithelial projections from basal cells are luminal sensors in pseudostratified epithelia. **Cell** 2008; 135: 1108-1117.

This paper was highlighted by the editors of Science (Cough NR Vol 323, Number 5911, 09 January 2009) and Science Signaling (Cough NR, Vol. 1, Issue 50, p. ec428, 2008). We made the paradigm-shifting discovery that basal cells extend narrow body projections that cross the tight junction barrier of the epididymis to monitor the luminal environment. Luminal angiotensin II triggers the production of NO in basal cells, via activation of the ANGII type II receptor. NO then diffuses out to reach clear cells, where it activates the cGMP pathway to increase V-ATPase-dependent proton secretion. "Apical-reaching" basal cells were found in all pseudostratified epithelia examined, including the prostate, seminal vesicles and trachea. Thus, this novel sensor and transmitter property of basal cells can be applicable to other systems.

4. Belleannee C, Da Silva N, Shum WW, Brown D, and Breton S. Role of purinergic signaling pathways in V-ATPase recruitment to the apical membrane of acidifying epididymal clear cells. **Am J Physiol Cell Physiol** 2010; 298: C817-830.

This paper is at the core of the present application. We showed here that luminal ATP and adenosine induce the apical membrane accumulation of the V-ATPase in clear cells. Several ecto ATPases and purinergic P1 and P2 receptors were detected in the apical membrane of epithelial cells. These results are in agreement with our hypothesis that ATP, secreted by principal cells, might be a mediator in the crosstalk between principal cells and clear cells for the regulation of V-ATPase-dependent luminal acidification.

5. Da Silva N, Pisitkun T, Miller RL, Nelson RD, Knepper MA, Brown D, and Breton S. Proteomic analysis of proton-transporting epididymal clear cells and renal intercalated cells. **Am J Physiol Cell Physiol** 2010; 298: C1326-C1342.

We provide here a comprehensive catalog of the proteins that are expressed in epididymal clear cells and renal intercalated cells after their isolation by enzymatic digestion and fluorescence-activated cell sorting (FACS) from our transgenic B1-EGFP mice. Generating the clear cell database was one of the specific aims of the original application. These proteomic results provide a framework for comprehensive future analysis of the common and distinct functions of V-ATPase-B1-expressing cells in the kidney and epididymis.

Additional recent publications of importance to the field and to this application

10 more publications…

Significance *versus* Overall Impact

- Remember that the reviewers will be looking hard at significance and impact of the project

  - Significance and Impact are different

    - Overall Impact/Priority Score (Scale 1 to 9)

      1) Significance (Scale of 1 to 9)
      2) Investigator(s) (Scale of 1 to 9)
      3) Innovation (Scale of 1 to 9)
      4) Approach (Scale of 1 to 9)
      5) Environment (Scale of 1 to 9)

Overall Impact

- is not a sixth review criterion, but a synthesis of all the (scored and not scored) review criteria (Significance, Investigator(s), Innovation, Approach, Environment)

- is not necessarily the arithmetic mean of the scores for the scored review criteria.

- is th*e likelihood* that the project will exert a *sustained, powerful influence* on the research field(s) involved .

Significance

- Does the project address an important problem or critical barrier to progress in the field?
  - Significance is evaluated and scored independently of the evaluation and scoring of Investigator(s), Innovation, Approach and Environment.
  - The evaluation of significance assumes that the Aims of the project are achieved and/or will be successfully completed.

Significance *versus* Overall Impact

- An application can have high impact but moderate significance and *vice versa*:

High impact, moderate significance

A talented investigator in a very strong environment proposes a highly innovative and very sound approach to address a generally important problem (*e.g.*, breast cancer). However, the proposed project will be relevant to only a narrow area within the larger field of breast cancer research, thus reducing its Significance. Nevertheless, the Overall Impact score could still be strong since the strengths of the project in the other core review criteria give this work the potential to have a sustained, powerful influence on that part of this important field.

Significance *versus* Overall Impact

- An application can have high impact but moderate significance and *vice versa*:

Moderate impact, high significance

The Overall Impact score synthesizes all five core review criteria as well as all applicable additional review criteria. Thus, while the significance of the project is very strong, the investigator might lack key credentials, the innovation might be minimal, the approach might be problematic, and the environment might not offer adequate support for the project.

Significance *versus* Overall Impact

- With a shorter 12 page application, it is anticipated that specific experimental details will be eliminated so that significance and impact can be focused on.
  - » You might want to discuss the 'milestones' of the project.

SUMMARY:
Going from 25 to 12 pages

- More emphasis on Significance and Impact
- Less emphasis on experimental details
- Biosketch and environment are additional opportunities for you to tell the reviewers that you and your institution are well-qualified to perform the goals of the proposed study
- http://enhancing-peer-review.nih.gov/

Revised application

- Your grant received a non-fundable score and you have to resubmit. In the introduction page,where you will answer the reviewers comments:

- Be professional and rational.
- Start by stating the positive aspects of the previous review. (e.g. "We would like to thank the reviewers for their positive and constructive evaluation of our initial proposal. We are pleased that "*the panel considers the project to be strong with the potential to impact the field*", and that only "*a few minor weaknesses are present"*.)
- Do not give the impression that you think the reviewers "didn't get it" and provided stupid comments. Acknowledge their concerns and respond to them in a positive manner. (e.g. Aim 1B was perceived by this reviewer as not being hypothesis-driven. While we have modified this Aim to take this concern into account, we believe that the utilization of a synergistic approach combining MS, biochemistry, and molecular and cell biology, will allow us to identify for the first time important apical ATP and bicarbonate transporters (which could be potential drug targets) that are involved in principal-clear cell crosstalk. In response to the criticism that "*the proposal is open ended*", we have modified this Aim…)
- You can even tell them that you now feel that the current proposal is stronger, thanks to their contribution. (e.g. We feel that the current application is better focused on our overall goal to examine the intercellular communication networks that control luminal acidification in the epididymis.)


Good luck with your grant application!