DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
National Institutes of
Health Bethesda, MD
20892

center for
scientific review

April 11, 2017

TO: Reviewers, Neural Basis of Psychopathology, Addictions and Sleep Disorders Study Section (NPAS)

FROM: Julius Cinque
SRO, NPAS Study Section

SUBJECT: NPAS Study Section Meeting, June 1-2, 2017

July 9-28 S 12

Thank you for agreeing to participate in the meeting of NPAS study section. This letter provides information about the meeting and about the new review policies, procedures, schedules, deadlines, and instructions for preparing your reviews.

PLEASE NOTE: SCORES AND CRITIQUES ARE DUE NOON, EST, Friday, May 26, 2017

HOTEL AND TRAVEL

MEETING INFORMATION:

MEETING TIME: Thursday, June 1, 2017, 8:30 am Eastern time – COB
HOTEL: The Mayflower Hotel, Autograph Collection
1127 Connecticut Avenue
Washington, DC 20036
(202) 347-3000

SRO Contact Information: Julius Cinque, SRO
301-435-1252
cinquej@csr.nih.gov

ESA Contact Information: Joel Kirkpatrick kirkpatj@csr.nih.gov
Pedro Chacon chaconj@csr.nih.gov

FOR YOUR IMMEDIATE ATTENTION: Please look at the current list of applications (Master List of Application) assigned to NPAS in the meeting folder on Commons, there is also an excel spreadsheet which has list of abstracts, key personnel, etc. and let me know if you have

any conflicts. My e-mail address is cinquej@csr.nih.gov. THERE WILL BE NO CD MAIL OUT. The zApp (formerly eCD) will be in the meeting material in era/Commons within two weeks.

HOTEL ARRANGEMENTS: **Please do not contact the hotel directly to reserve your room as this may lead to a double-booking.** A hotel reservation has already been made for you under a group block paid for by the NIH. We can email your hotel room confirmation number to you once it becomes available.

TRAVEL ARRANGEMENTS: **(If you are a federal reviewer or part-time federal reviewer – please contact Mr. Joel Kirkpatrick so he can process your travel and federal travel order)**

Please do not buy your own plane ticket. It is mandatory please that you use World Travel Services (WTS) to obtain your airline or train tickets, which NIH will purchase at NO COST to you. WTS is the authorized government contractor. If you buy your own ticket, the NIH may not reimburse you.

Even if your trip to our meeting is part of an extended, multi-leg road trip, WTS can still pay for the portion of travel that pertains to our meeting. Moreover, they can even arrange the entire trip and bill you just for the portions that are not NIH-related. In many cases, this can be more cost-effective and convenient.

Please contact WTS for guidance on how to arrange for the government to pay for your airfare, or contact Mr. Joel Kirkpatrick or Mr. Pedro Chacon with your itinerary and they will glady contact the WTS on your behalf.

1. You can book online. Go to: www.nihreviewers.com and click on the second link in the middle called "Submit Request Online". Under "Traveler Information for" please select: "CSR" and for group code select: "NPAS".

2. You can send e-mail to: nih@worldtravelservice.com Please include in your email all of your travel itinerary information (e.g., window seat, preferred airports, time of departure, etc.).
3. You can call WTS directly at 1-800-638-8500 and tell them your **group codes is: "NPAS".**

The meeting will start promptly at **8:30 AM Eastern time on Thursday, June 1, 2017.** Given the number of applications to be reviewed we anticipate this to be a two-day meeting, and plan on having a committee group dinner Thursday evening after the meeting.

Please, do not plan early departures from the meeting before 3pm on Friday, June 2rd. After the meeting, if you cannot reach your home town or the West Coast by 8:00 p.m. (your local time), the federal government allows you to stay the Friday night at the hotel paid by the NIH and leave for home the next day. Accordingly, should you need to stay at the hotel on Friday evening, June 2nd, please let Mr. Joel Kirkpatrick (kirkpatj@csr.nih.gov) or myself know so we arrange for extension of your stay by one more night at no cost to you. Please do not book the Friday

night on your own, as the hotel may charge you a higher room rate and this will lead to reimbursement problems.

TRAVEL EXCEPTIONS: If you expect your costs for ground transportation and incidentals to exceed the flat rate of $235.00/day, or IF YOU HAVE BEEN PRE-APPROVED by the CSR Travel Office for buying your own plane ticket, then you will need to request a "travel exception". By claiming the travel exception before the reimbursement occurs, you can have the extra amount included with your reimbursement. If you are claiming a travel exception, please contact my assistant, Mr. Joel Kirkpatrick, kirkpatj@csr.nih.gov If you are driving, please note your mileage and save all receipts for ground transportation, including parking, tolls, etc.

DECLARING NON-FEDERAL REGISTERED LOBBYIST STATUS: This is a new requirement. In addition to the confidentiality agreement, you are now required please to declare that you are NOT a "federal registered lobbyist". This does not include minor lobbying you may perform on health related issues. Please, check this carefully for if you accidently click on "yes", you will then be locked-out of the meeting until your account is reset, which may be a long and arduous process.

CONFIDENTIALITY AGREEMENT: You are required please to sign a separate Confidentiality Agreement BEFORE you can gain access to any of the materials related to the meeting. The Confidentiality Agreement is a blanket statement promising that no information about any application data for the meeting will be disclosed by the Reviewer. After reading the Confidentiality Agreement and agreeing to the terms, please select the "**I agree**" button to gain access to the meeting and your applications to review. All applications are confidential, privileged material, and under no circumstance should you discuss the application or any aspect of the review with the applicant, your colleagues, or NIH program personnel. Any questions you have regarding an application should be referred to this office.

CONFLICT OF INTEREST: Please review the electronic file of the Master List of Applications (all of the applications that will be reviewed) in Commons for any possible conflicts of interest. Reviewers who are in conflict with an application will be asked to leave the room while the application is being discussed. You are most familiar with your own situation and it is your responsibility to bring to my attention any conflict of interest that may exist, whether real or apparent. Definitions of a conflict of interest are explained in the Conflict form in Commons. The most common conflicts are when you have co-published with any person who is key personnel on the application within the last three years. Individuals who have been mentors/mentees for training are in conflict for ten (10) years after the end of the training experience. There is a list of all Principal investigators and all key personnel on the commons site under Meeting Materials. This list should facilitate your identification of applications with which you have a conflict.

CONFLICT OF INTEREST FORMS: Conflict of interest forms MUST be done electronically through Commons (eCOI). You should see a link on the List of Meetings Screen under the "Action" column. Both Pre and Post meeting conflict forms will be located there. Please review the enclosed master list of applications (The list of key personnel is listed in the Meeting Material for each application). If the listing of your conflicts is correct, sign the pre meeting form by clicking on the appropriate box and then scroll down and click on "I Certify" tab. If additional conflicts exist, notify Joel Kirkpatrick, kirkpatj@csr.nih.gov or me. We will add them

to your list and then you can "Certify after you check off the appropriate box" the Pre-Conflict form electronically. **NIH policy states that you must sign your pre-meeting conflict of interest form before any applications are discussed.**

REVIEW POLICY, CONFIDENTIALITY, AND ASSIGNMENTS: As the SRO and the official government representative for this review meeting, I am responsible for managing the review and for providing information on NIH and relevant institute review practices and policies. No unpublished information or ideas in the applications or information about the review proceedings themselves may be shared or discussed with anyone outside the membership of the review panel or involved government staff. You must not discuss the contents of the applications with any of the investigators or other participants involved in the application. You also should not communicate with any of the other reviewers about their reviews prior to the review meeting.

Your assignment list will be listed on the Commons soon. Every effort was made to appropriately assign applications based on your expertise and in order to retain continuity with the previous reviewed submissions. **Please take a few moments to review your applications for content and the appropriateness of the assignment.** If you lack the appropriate scientific expertise to review any assigned application, please contact me immediately. Otherwise, I will assume that you are not in conflict and appropriately qualified to review the assigned applications.

PROCEDURES FOR REVIEWER REIMBURSEMENT AND HONORARIUM:

- Your lodging cost will be paid directly by NIH so you need not contact the hotel. However, you will need to provide a credit card to the hotel at check-in to cover incidental expenses (room service, laundry, movies, wireless internet fees, etc.). NOTE please that wireless internet in your sleeping room is NOT reimbursed separately.
- Reviewers who participate in a review will receive an honorarium of $200 per meeting day.
- You will receive a flat rate reimbursement of $80 per day for each meeting day for meals and incidentals + $235 for ground transportation and incidentals (such as baggage fees).
- Your reimbursement will be deposited after the meeting into the bank account you designate on the Secure Payee System (SPRS) which is linked to the Commons. If you have not already signed up, please let us know so we can send the instructions.

ACCESSING THE APPLICATIONS FOR THIS MEETING: Your IAR account has been enabled in the Commons. Soon you will receive the link to this meeting and to your assignments on COMMONS. **Please examine those applications that you have been assigned to ensure that you:**

1. ARE NOT IN CONFLICT WITH THE PRINCIPAL INVESTIGATOR, CO-INVESTIGATORS OR INSTITUTION.
2. ARE AN APPROPRIATE REVIEWER FOR THE APPLICATION ASSIGNED TO YOU.

In addition, there will be a link for this meeting on the Commons and under Meeting Materials., will be a link to the zApp (formerly called the "electronic CD"). **The password is NPAS1234!** All applications are electronic and should be on the zApp on the Commons web site. You will not receive a hard copy.

SUPPLEMENTAL MATERIALS IN ERACOMMONS: While there are no longer supplemental materials allowed to be submitted, some corrections and citations for recently published papers can be submitted and will be placed in the applicant's grant folder.

WHAT TO BRING TO THE MEETING: Please bring an USB with your Critiques and/or at least **one paper copy of each of your critiques** with you to refer to at the review meeting just in case the wireless connection or your computer fails. Also please bring **your laptop computer** to view the application images on the eCD or on Commons, to edit your critiques to reflect your final opinions of the applications after the discussion, to enter final scores, and to "electronically sign" pre- and post-meeting conflict of interest forms.

REVIEW AND CRITIQUE GUIDELINES: The new Enhanced Peer Review process is described on links found at the Enhancing Peer Review at NIH web site: http://enhancing-peer-review.nih.gov/restructured_applications.html

Guidelines for critiques and templates for the critiques are available at: http://grants.nih.gov/grants/peer/reviewer_guidelines.htm. The critique templates and instructions will also be in Meeting Materials on the Commons site and on the eCD.

Please note that there are different review templates for RO1 applications and K applications. Be sure that use a new template for each applicant.

A reviewer will write a critique of each assigned application using a new template which permits a listing of bulleted strengths and weaknesses for the five criteria *significance, investigator, innovation, approach, and environment*. The assigned reviewer will assign a score (in whole numbers) 1 best to 9 worst for each of the criteria. These scores will be included in the summary statement. The reviewer will also assign a preliminary Overall Impact score (1-9) which is analogous to the Priority Score. The preliminary overall impact scores will be used to provide the initial ranking of applications for discussion. The aim of the new format is to focus reviews on the major factors influencing the scoring of applications. Each criterion section should be no more than ¼ page long. DO NOT copy or rephrase components of the application, such as specific aims. Keep it brief, with whole sentences as bullets, but not paragraphs!

Concerns with the use of the Vertebrate Animals and Risks to Humans are also considered for the scoring of an application. There are some applications that are "Multiple PI" applications. These must have a leadership plan included in the application and it should be evaluated as part of the investigator criterion review. Your review should focus on the quality of science and the overall impact or significance of the research, rather than on details of technique and methodology. Your role is not to rewrite the application, redesign the experiments, or act as mentor to the principal investigator; it is to review the scientific merit of the application as written. It is as important that you identify why an application is outstanding as it is to identify what problems there are with an application. In the approach section, your critiques **should not copy** the Specific Aims or describe how the investigator proposes to carry out the research unless

you include appropriate evaluative statements. The "Overall Evaluation" section should consist of an evaluative list of the application's major strengths and weaknesses that is consistent with the priority score you assign and the general tone of your detailed comments under each criterion. Do not simply write a score or a statement like "This is an outstanding application." The critiques and criterion scores can be revised after the meeting, if you feel changes are needed to reflect your final evaluation of the application.
A guide for reviewers' comments is enclosed on the eCD and explains the evaluation criteria. Your comments will be provided to the investigator in the final summary statement. The summary statement then becomes the official document describing the application and justifying the Study Section's recommendation to the National Advisory Council. Please note that we have R21 (Exploratory/Development) applications, RO3 (Small grant applications), K applications as well as R01 applications for review. The guidelines for reviewing R21's, and K applications differ from those for R01s and can be found on the eCD. A major difference is that NO PRELIMINARY DATA are required for an R21 application.

Each application will have three reviewers, each writing a critique.

ELECTRONIC SUBMISSION OF YOUR CRITIQUE: You will need to submit your critique and score electronically via the NIH eRA Commons Internet Assisted Review (IAR) system. To have access to the IAR system you must first have your own IAR account. You will receive a computer generated email that invites you to create your own IAR account or that links you to our meeting using the same username and password that you have previously established in NIH Commons. The subject line will say "NIH Commons". **Please do not delete this email.** Please refer to the "Instructions and helpful tips for establishing your IAR account on the eCD. If you need assistance, please contact Joel Kirkpatrick. When you use this system, you will be able to access the other critiques prior to the meeting, after you submit your critique. After the meeting, there will be a period of time to modify/update your critique, if needed. It is essential that you meet the deadline for critique submission prior to the meeting so that other reviewers have an opportunity to read your comments prior to the study section meeting.

All reviews and scores should be posted on NIH eRA Commons IAR by Friday, May 26, 2017 at Noon, EST along with the electronic "signing" of your Pre-Conflict Form. More time is needed to prepare for the meeting in this new review process, so please post your reviews on time! Please post early, if possible.

Additional points to consider when preparing your critiques.

1. PRIOR SUMMARY STATEMENTS: For all resubmissions applications and renewals, the prior summary statement is on your eCD and in the grant folder on Commons. For amended applications (A1), please be sensitive to the following three issues regarding prior reviews:

- Avoid creating a moving target for the principal investigator as you consider the comments from previous summary statement.
- Consider the level of responsiveness, not the previous score, in determining the new score.
- All applications are to be scored relative to the applications being reviewed this round.
- **The new critique template has specific sections for comments about resubmissions and renewals.**

2. NEW INVESTIGATOR: For review purposes, this is someone who is applying for an R01 and has not been a Principal Investigator on a funded R01 application or similar independent investigator award. The expectations for these individuals is that they may have less preliminary data than an established investigator, but the expectations with respect to the quality of the proposed science are not different.

3. HUMAN SUBJECTS, GENDER, MINORITY, AND CHILD SUBJECTS: Congress requires that studies involving human participants include both genders, minorities and children (individuals less than 21 years of age) to reflect the population in general, unless there is scientific justification otherwise. Please review "Evaluating Research Involving Human Subjects..." on the eCD. In your review, comment on how the application addresses this requirement, whether the manner in which it is addressed is appropriate, and list the appropriate code for representation of gender, minority, and children **(G, M, and C)**. During the study section meeting, we will ask for your human subject codes. IRB approval is **not** needed at the time of application review and such approval does not replace our evaluation of the risks.

4. VERTEBRATE ANIMALS: Investigators using vertebrate animals must complete the Vertebrate Animal Section and address all requirements in their applications. Please provide specific comments if you are concerned that there is an inappropriate risk to the animals or an ethical consideration. The investigator does **not** need to provide IACUC approval at the time of the application review and such approval does not replace our evaluation of the risks.

5. MODEL ORGANISM SHARING PLAN: If the application is developing model organisms, then there must be a sharing plan. This needs to be addressed in your critique. Guidelines are included on the eCD.

6. BUDGET: Each critique should include a separate evaluation of the requested budget. Note that the level of support requested should not impact the priority score for an application.

7. GREEK LETTERS: In your critiques, please spell out Greek characters ('alpha' not 'α') to ensure proper conversion. Umlauts, accents and other similar modifiers should be avoided. If not converted properly, these turn into other marks that are hard to decipher.

PRIORITY SCORES/UNSCORING/ORDER OF REVIEW: It is Center for Scientific Review (CSR) policy to not discuss a portion of applications that are, based upon preliminary scoring, unlikely to be under consideration for funding (usually about the bottom 50%). Any application, regardless of funding mechanism, may not be discussed. Summary statements will be prepared for all applications, but those that the committee ranks in the bottom half of scores will probably not be discussed at the meeting. We will be reviewing New Investigator applications in a group. In addition, we will probably group R21s and K's for review. Applications will be discussed in order of best to worst average preliminary impact score. It is felt that this order of review will aid reviewers in comparing applications and help to spread the scores.

SCORE SPREADING: It is important to spread scores across the full range of 1 -9. It is your primary responsibility as a reviewer is to evaluate, in a fair, thorough, and consistent manner, the scientific and technical merit, **but not the funding chances** of these applications.

I will compile the proposed order of review based on your scores and **will post the draft on IAR Commons under Meeting Materials as soon as possible after the critique deadline.** The posted preliminary scores allow me to construct the Order of Review and serve to alert us to potential problems prior to the meeting (e.g., score compression on the part of the study section, major differences in opinion on a given application, etc.), so **please post preliminary scores on time by Noon EST, Friday, May 26, 2017.**

VERBAL PRESENTATION OF YOUR CRITIQUE AT THE MEETING: The review of each application will begin with the three assigned reviewers stating their preliminary score. Then, the primary reviewer will give a verbal critique. Your verbal presentation of your critique to the study section is not the same as your written review. **DO NOT READ your written critique.** The presentation should begin with a very brief description of the proposed research including a statement of the problem or question to be examined and the overall hypothesis that will be tested or the rationale for hypothesis-generating research. Then provide a SUMMARY of the application's major strengths and weaknesses and any other important issues you feel the committee should consider when assigning a priority score and an assessment of the potential significance of the proposed work. Second and third reviewers should not repeat what has already been presented. In fact, if you have nothing to add, it is entirely appropriate to indicate that you agree with what has already been stated and that you have no additional comments. After each assigned reviewer provides their input, the application will be opened to all reviewers for discussion. After discussion is complete, each assigned reviewer will be asked to provide a final score. All study section members will then vote. Votes should be within the stated scoring range of the assigned reviewers. If someone wishes to score outside of that range, they must voice their intent at the meeting to explain their decision.

If you have any questions or if anything appears to be missing from this mailing, please do not hesitate to contact me or my Support Assistants, Mr. Joel Kirkpatrick or Mr. Pedro Chacon.

Thank you, again, for your participation,

Jay

Julius J Cinque
Scientific Review Officer
NPAS Review Committee
Center for Scientific Review
6701 Rockledge Drive, Room 5198
Bethesda, Md. 20892
(301) 435-1252
cinquej@csr.nih.gov

Joel Kirkpatrick
301-318-5064
kirkpatj@csr.nih.gov

McCullumsmith, Robert (mccullrr)

From: McCullumsmith, Robert (mccullrr)
Sent: Thursday, April 27, 2017 11:13 AM
To: Cinque, Julius (NIH/CSR) [E]
Subject: RE: Tentative list of assignments for NPAS Review on June 1-2nd

No conflict and happy to review: Kalin, Petryshen, Zink, Irunga, Ishisuka (I really should review this one), Jain, Mackin, Mattay, Nielsen (I really should review this one),

No conflict but a little outside my area (but could still do if needed): Manelis, Meyer, Kristal, Zeitzer.

Looking at the whole list I don't see any COI on 1st pass.

Rob

From: Cinque, Julius (NIH/CSR) [E] [cinquej@csr.nih.gov]
Sent: Tuesday, April 25, 2017 4:19 PM
To: McCullumsmith, Robert (mccullrr)
Subject: Tentative list of assignments for NPAS Review on June 1-2nd

Hi Robert, I hope all is going well for you. In preparation for our upcoming NPAS meeting on June 1-2nd in Washington I have tentatively assigned you to the following applications: Kalin-1st; Petryshen-2nd; Zink-2nd; Irungu-2nd; Ishizuka-1st; Jain-1st; Mackin-2nd; Manelis-1st; Mattay-2nd; Meyer-1st; Nielson-3rd; Kristal-3rd; and Zeitzer-2nd. I realize that this is far too many for you to do but I will let you tell me which one you would like to pass on or if there are others that you would prefer instead. Also please send me your conflicts. As soon as I hear back from you we can finalize your assignments. Looking forward to hearing from you. Very Best, Jay

Julius J Cinque
Scientific Review Administrator
NPAS Review Committee
Center for Scientific Review
NIH
Room 5198
6701 Rockledge Drive
Bethesda, Md. 20892

SRF RPG/R01/R03/R21/R33/R34 Review

-template for working offline only

Application #:

Principal Investigator(s):

OVERALL IMPACT

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following scored review criteria and additional review criteria (as applicable for the proposed project). An application does not need to be strong in all categories to be judged likely to have major scientific impact.

Overall Impact *Write a clear, concise paragraph that explains the basis for your score. Identify and weigh the most important strengths and weaknesses of the application.*
Whan typos occur what happens? Whan typos occur what happens?

REVIEW CRITERIA

Reviewers will consider Factors 1, 2 and 3 in the determination of scientific merit, and in providing an overall impact score. In addition, Factors 1 and 2 will each receive a separate criterion score.

Factor 1. Importance of the Research (Significance and Innovation)
Major Score-Drivers **Strengths** • **Weaknesses** •

Factor 2. Rigor and Feasibility (Approach)
Major Score-Drivers **Strengths** • **Weaknesses** •

Inclusion Plans **Applicable Only for Human Subjects research and not Human Subjects Exemption #4**

As part of their evaluation, reviewers should consider the population characteristics of the disease, condition, behavior, and/or the scientific goals of the work proposed:

- Sex: Click Here to Select
- Race and Ethnicity: Click Here to Select
- For NIH-Defined Phase III trials, plans for valid design and analysis (applicable to sex and race and ethnicity): Click Here to Select
- Based on Age: Click Here to Select

If not previously addressed in Factor 2 Major Score-Drivers, briefly address specific concerns regarding inclusion or plans for valid design and analyses:

-

Factor 3. Expertise and Resources (Investigator(s) and Environment)

Click Here to Select

Address specific gaps in expertise or resources needed to carry out the project:

-

ADDITIONAL REVIEW CRITERIA

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

Click Here to Select

Briefly address specific concerns regarding human subject protections:

-

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Click Here to Select

- Briefly address specific concerns regarding the Data and Safety Monitoring Plan:

Vertebrate Animals

Click Here to Select

Briefly address specific concerns regarding vertebrate animal protections:

-

Biohazards
Click Here to Select Briefly address specific concerns regarding biohazards: •

Resubmissions
Comments (if applicable): •

Renewals
Comments (if applicable): •

Revisions
Comments (if applicable): •

ADDITIONAL REVIEW CONSIDERATIONS

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Authentication of Key Biological and/or Chemical Resources
Click Here to Select Briefly address specific concerns regarding the identification or validity of key biological and/or chemical resources: •

Budget and Period of Support
Click Here to Select Briefly address specific concerns regarding the proposed budget: •

Scientific Premise

What does "scientific premise" mean for a grant application?

Scientific premise concerns the **quality and strength of the research used to form the basis for the proposed research question**. NIH expects applicants to describe the general strengths and weaknesses of the prior research *being cited by the applicant as crucial to support the application*. The NIH expects this consideration of general strengths and weaknesses to include attention to the rigor of the previous experimental designs, as well as relevant biological variables and authentication of key resources. **All prior research cited by an investigator as crucial to support their application should be assessed for strengths and weaknesses, regardless of whether it is the investigator's own preliminary data (published or unpublished) or published data from others**. Any weaknesses or gaps in rigor, or reporting on rigor, should be acknowledged, along with a plan to address those gaps going forward

What is the difference between "scientific premise" and "significance"?

The scientific premise will be reviewed as part of the Significance criterion for research grant applications. Instructions for significance already include consideration of the importance of the problem, critical barriers to progress, how the proposed project will improve scientific knowledge, and how the field will change if the aims are achieved. Scientific premise includes a **retrospective consideration of the foundation for the application, rather than a prospective analysis should the aims be achieved.**

http://grants.nih.gov/reproducibility/faqs.htm#4827

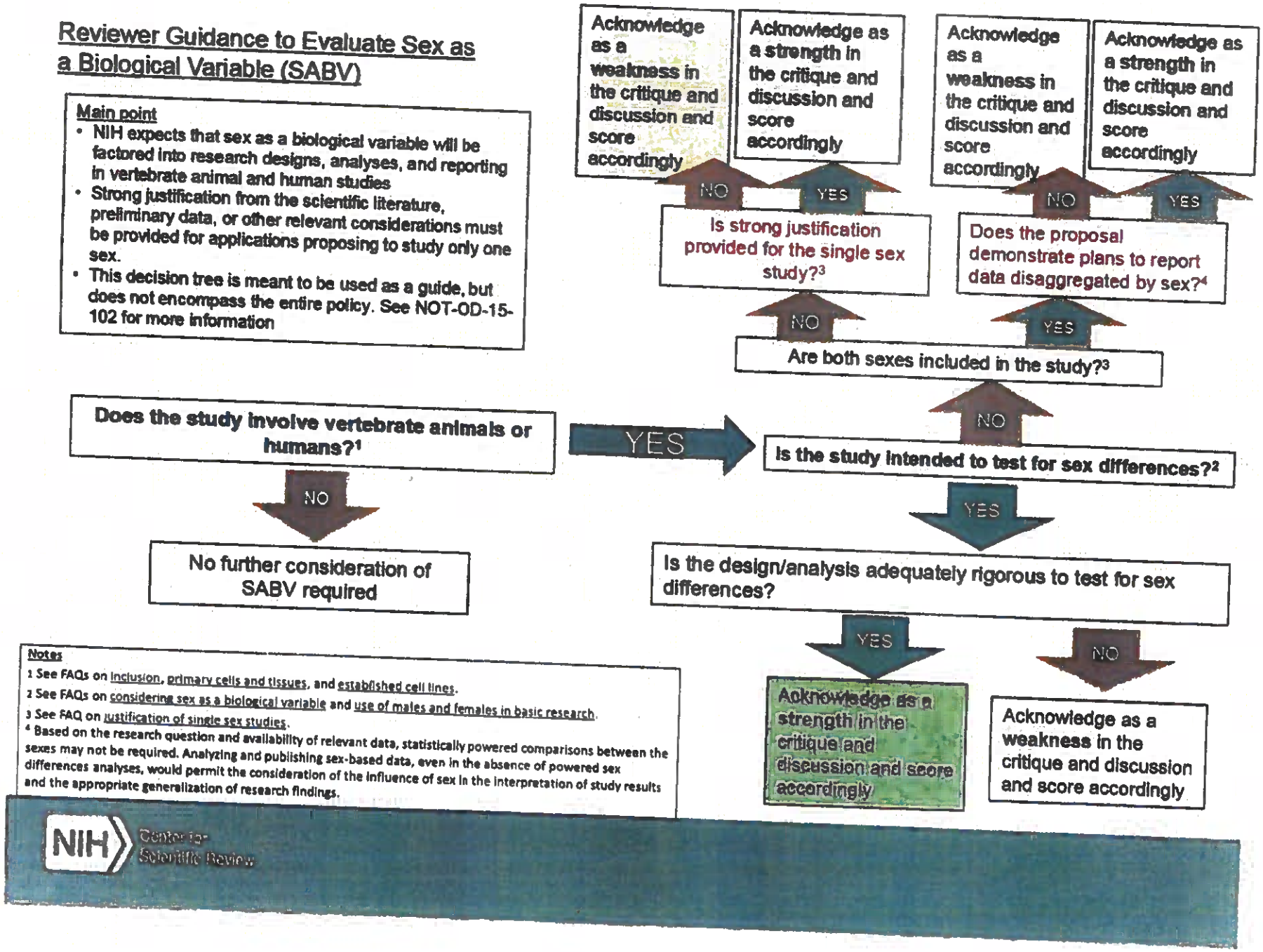
Reviewing Rigor and Transparency of Research: RPG Applications

	Applies to which applications?	Where will I find it in the application?	Where do I include it in my critique?	Addition to review criteria	Affect overall impact score?
Scientific Premise	All	Research Strategy (Significance)	Significance	Is there a strong scientific premise for the project?	Yes
Scientific Rigor	All	Research Strategy (Approach)	Approach	Are there strategies to ensure a robust and unbiased approach?	Yes
Consideration of Relevant Biological Variables, Such as Sex	Projects with vertebrate animals and/or human subjects	Research Strategy (Approach)	Approach	Are adequate plans to address relevant biological variables, such as sex, included for studies in vertebrate animals or human subjects?	Yes
Authentication of Key Biological and/or Chemical Resources	Project involving key biological and/or chemical resources	New Attachment	Additional review considerations	Comment on plans for identifying and ensuring validity of resources.	No

Reviewer Guidance to Evaluate Sex as a Biological Variable (SABV)

Main point

- NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies
- Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.
- This decision tree is meant to be used as a guide, but does not encompass the entire policy. See NOT-OD-15-102 for more information



Notes

1 See FAQs on inclusion, primary cells and tissues, and established cell lines.

2 See FAQs on considering sex as a biological variable and use of males and females in basic research.

3 See FAQ on justification of single sex studies.

4 Based on the research question and availability of relevant data, statistically powered comparisons between the sexes may not be required. Analyzing and publishing sex-based data, even in the absence of powered sex differences analyses, would permit the consideration of the influence of sex in the interpretation of study results and the appropriate generalization of research findings.

NIH Center for Scientific Review

Neuropsychopharmacology (2017) 42, 386–396

www.neuropsychopharmacology.org

Review

Sex as a Biological Variable: Who, What, When, Why, and How

Tracy L Bale[*,1,2,3] and C Neill Epperson[2,3,4]

[1]Department of Biomedical Sciences, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Penn PROMOTES Research on Sex and Gender in Health, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Obstetrics and Gynecology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

The inclusion of sex as a biological variable in research is absolutely essential for improving our understanding of disease mechanisms contributing to risk and resilience. Studies focusing on examining sex differences have demonstrated across many levels of analyses and stages of brain development and maturation that males and females can differ significantly. This review will discuss examples of animal models and clinical studies to provide guidance and reference for the inclusion of sex as an important biological variable relevant to a *Neuropsychopharmacology* audience.

Neuropsychopharmacology (2017) **42**, 386–396; doi:10.1038/npp.2016.215; published online 26 October 2016

INTRODUCTION

An appreciation for sex as a biological variable (SABV) in preclinical and clinical research is essential for our understanding of basic mechanisms contributing to disease risk and resilience, especially in cases where there are known sex differences in phenomenology, natural history, treatment, or severity. Studies focusing on examining sex differences have demonstrated across many levels of analyses and stages of brain development and maturation that males and females can differ significantly. From sex chromosomes that allow for disparities in gene dosage and regulatory mechanisms, to the important role of gonadal hormones across the life span, our appreciation for the unique and highly mechanistic insight that including SABV affords us has gained great attention. This review will provide general oversight as to animal models and clinical studies that have demonstrated novel outcomes because both sexes were examined across research areas and human health and disease relevant to a *Neuropsychopharmacology* audience. This is by no means a comprehensive review of all research in these areas, but rather a selection of appropriate and representative examples to provide guidance and reference for the inclusion of sex as an important biological variable. In addition, we have included several helpful out-takes as reference and citation for the 'benefits of' and the 'how to' complete studies in this area in preclinical and clinical research (Box 1; Figures 1 and 2). Finally, the role of developmental windows and changes across the life span to the contribution of sex differences in neuropsychiatric and cognitive disorders is highlighted where appropriate and in Figure 3.

*Correspondence: Dr TL Bale, Department of Biomedical Sciences, School of Veterinary Medicine, University of Pennsylvania, 410F Hill Pavilion, 380 South University, Philadelphia, PA 19104, USA, Tel: +1 215 898 1369, Fax: +1 215 573 5186, E-mail: tbale@vet.upenn.edu

Received 1 July 2016; revised 22 August 2016; accepted 16 September 2016; accepted article preview online 23 September 2016

Defining Sex and Gender

Although all cells have a sex, designated by the presence and dosage of X or Y chromosomes, which in most cases will be XX (female) or XY (male), gender is a designated societal determinant and therefore traditionally described only in humans (Bachmann and Mussman, 2015). Of particular importance for this discussion, rodents do not have a gender. Discussed below are the primary contributions of gonadal hormones and sex chromosomes in organizing the sexually dimorphic brain, a key foundation throughout life where the internal and external environments can provoke phenotypic sex differences.

Importantly, the sexually dimorphic brain, similar to most sex differences, does not fall into a hard binary readout—but rather is on a continuum or spectrum with each cell and each brain region comprised of varying degrees of 'male' and 'female' (Hines, 2005; Joel and McCarthy, 2016). This is because the influences from very early neurodevelopmental time points, and perhaps even earlier than fertilization, are complex and multifaceted and frequently depend on the sex chromosome compliment of the individual or the sex of the parent contributing a given gene. Finally, the combination of genetic sex and gonadal hormones alone can produce a plethora of points at which subtle differences promote dramatic trajectory changes in development.

An example of this is from Catherine Dulac's group in which they investigated the genetics of sex differences in the brain by comparing parent-of-origin allelic gene expression and found that imprinted genes inherited from maternal or paternal origin were dependent on the offspring sex as

Power calculations: SA1.1: For experiment 1.1b, a peptide substrate from our preliminary LCMS data on the high end of the range for variance (STD: 0.443), with mean 7.04, alpha 0.05, 1-beta = 0.9, and *an effect size of 10%, we need n = 10 subjects/group*. SA1.2: for our distance measurement studies with mean 0.42 and STD 0.057 to detect *a 15% effect size* with alpha = 0.05 and 1-beta = 0.8, we need *n = 11 subjects per group*.

Power calculations: SA2.1: For experiment 2.1a, we used the mean (0.87) and STD (0.17) from our control sample for *an effect size of 15%*, alpha 0.05, 1-beta = 0.8, we would need *n = 16 subjects per group*. For experiment 2.2a, for our LDH assay, for an *effect size of 10% we would need 8 subjects per group*.

Rigor and reproducibility. All studies will be performed and analyzed blind to diagnosis or treatment group. We have sufficient numbers of subjects to reject the null hypothesis with effect sizes as low as 10-15% *within each brain bank cohort* (n = 40/diagnosis total, n = 20/diagnosis from each brain bank). It is notable that we have found *effects sizes larger than 10-15%* in the progress report and preliminary data sections, and that our power calculations are based on the minimal numbers of subjects needed to detect a significant effect for each technique. We measure coefficients of variability for all our assays (typically < 3% for enzyme activity, < 1% for LCM-QPCR) and *routinely revalidate our assays between experiments*. Our preliminary studies using diverse techniques and approaches markedly converge on our overarching hypothesis and we also routinely publish extensive supplemental methods sections [82], *suggesting that our findings will be reproducible*. Each of our proposed experiments is falsifiable, and we have sufficient numbers of subjects *to assess the effects of gender*, brain bank origin, and other variables relevant to postmortem work. Finally, within the laboratory we have brain tissues from 3 different brain collections *available for replication studies* of significant findings.

Authentication of Key Biological and/or chemical resources.

General: Persons performing experiments and analyzing experimental data will be blinded to diagnosis. We routinely publish extensive, detailed methods (typically in supplemental sections) in our publications to promote the reproducibility of our results. All of our data files are centrally stored on secure drive space that is routinely backed up and monitored by information technology officers at our university. All data related to postmortem brain specimens is de-identified by the brain bank it originates from and tracked by sample number.

Chemicals: All chemicals used in the laboratory are standard reagents commercially available.

Antibodies: We use commercial and custom made antibodies in our laboratory. We use LCMS and Western blot analyses to confirm the specificity of antibodies for our IP studies. For immunohistochemistry and immuno-electron microscopy studies we use KO mouse tissues (when available), blocking peptides, transfected cell lines, and gel shift assays (with deglycosylation) to confirm specificity. We routinely test new batches of antibodies to confirm specificity. Antibodies are aliquoted and stored per the manufacturers recommendation.

Brain tissue storage. We have five state-of-the-art -80 C freezers with CO2 backup and wireless telemetry/alarms. Temperatures are manually confirmed 5 days per week and every other day over holiday breaks.

Human brain specimens. We routinely perform RIN analyses, as well as enhanced silver staining of protein blots, to assess mRNA and protein integrity, respectfully, of all postmortem brain samples.

Drugs. Haloperidol and olanzapine are purchased from the manufacturer and are clinical grade pharmaceuticals suitable for use in humans. We have previously confirmed our dosing regimens by measuring blood levels, changes in animal mass (ie expected weight gain), and other behaviors including increased sedation and extrapyramidal signs (such as vacuous chewing movements).

ELSEVIER

Neurobiology of Disease

www.elsevier.com/locate/ynbdi
Neurobiology of Disease 26 (2007) 1–13

Review

Lost in translation: Treatment trials in the SOD1 mouse and in human ALS

Michael Benatar*

Department of Neurology, Emory University School of Medicine, Woodruff Memorial Building, 1639 Pierce Drive, Atlanta, GA 30322, USA

Received 20 October 2006; revised 12 December 2006; accepted 20 December 2006
Available online 3 January 2007

Therapeutic success in the superoxide dismutase (SOD1) mouse model of amyotrophic lateral sclerosis (ALS) has not translated into effective therapy for human ALS, calling into question the utility of such preclinical data for identifying therapeutic agents that are worthy of further study in humans. This random effects meta-analysis of treatment trials in the superoxide dismutase (SOD1) mouse was undertaken in order to explore possible reasons for this failure of translational research and to identify potential pharmacological interventions that might be used in either a preventative or therapeutic trial in familial ALS. Among studies in which treatment was initiated presymptomatically, the weighted mean differences (WMDs) comparing the active treatment to control treated animals were 12 days (onset), 13 days (survival) and 5 days (survival interval). Among studies in which treatment was initiated at the time of symptom onset, the WMDs were 15 days (survival) and 8 days (survival interval). Subgroup analysis suggests that drugs such as minocycline and Cox-2 inhibitors with an anti-inflammatory mechanism of action, and anti-oxidative agents such as creatine or the manganese porphyrin AEOL-10150, appear to be the most promising for preventative and therapeutic trials respectively in patients with familial ALS. These conclusions should be tempered by the methodological limitations of the relevant literature.

Keywords: SOD1 mouse; Meta-analysis; Familial ALS; G93A; Treatment trials; Systematic review; Amyotrophic lateral sclerosis; Motor neuron disease; Mouse model; Animal model

Contents

Introduction

The scientific and ethical justification for animal models of human disease is that they may provide an opportunity to investigate disease biology and to identify potential therapies that might be beneficial to humans. The most popular animal model of amyotrophic lateral sclerosis (ALS) is the mouse that has been genetically engineered to express a mutant form of the human superoxide dismutase (SOD1) gene. The most commonly used SOD1 mouse harbors the glycine to alanine mutation at amino acid 93 (G93A). Since the identification of mutations in the SOD1 gene as an important cause of familial ALS (Rosen et al., 1993) and the generation of the SOD1 mouse model of ALS several years later (Gurney et al., 1994), there have been dozens of studies of a panoply of therapeutic agents in SOD1 mice. The choice of therapeutic agents in many clinical trials of human ALS (Cudkowicz et al., 2006; Groeneveld et al., 2003; Shefner et al., 2004) has been predicated, at least in part, on the efficacy of these drugs when studied in the SOD1 mouse (Drachman et al., 2002; Klivenyi et al., 1999). Nevertheless, success in human clinical trials has been extremely limited, calling into question the utility of such preclinical data for identifying therapeutic agents that are worthy of further study in humans.

There are several possible explanations for the failure of successful animal studies to translate into effective therapies in humans. One possibility is that the SOD1 mouse really represents an animal model of familial ALS rather than sporadic ALS. It might even be argued that the SOD1 mouse only models familial ALS due

* Fax: +1 404 727 3157.
E-mail address: michael.benatar@emory.edu.
Available online on ScienceDirect (www.sciencedirect.com).

0969-9961/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.nbd.2006.12.015

1. Sex matters

http://www.nature.com/npp/journal/v42/n2/full/npp2016215a.html?foxtrotcallback=true

2. Lost in translation

http://www.sciencedirect.com/science/article/pii/S0969996106003287?via%3Dihub

3. SOD1 power study

https://www.ncbi.nlm.nih.gov/pubmed/18273714

Overall Impact:
The likelihood that a project will have a sustained and powerful influence on science (and/or clinical practice and/or technological developments?)

Overall Impact	High	Medium	Low
Score	1 2 3	4 5 6	7 8 9

e.g. Applications are addressing a problem of high importance in the field. May have some or no technical weaknesses.

e.g. Applications may be addressing a problem of high importance in the field, but weaknesses in the criteria bring down the overall impact to medium.

e.g. Applications may be addressing a problem of moderate importance in the field, with some or no technical weaknesses

e.g. Applications may be addressing a problem of moderate/high importance in the field, but weaknesses in the criteria bring down the overall impact to low.

e.g. Applications may be addressing a problem of low or no importance in the field, with some or no technical weaknesses.

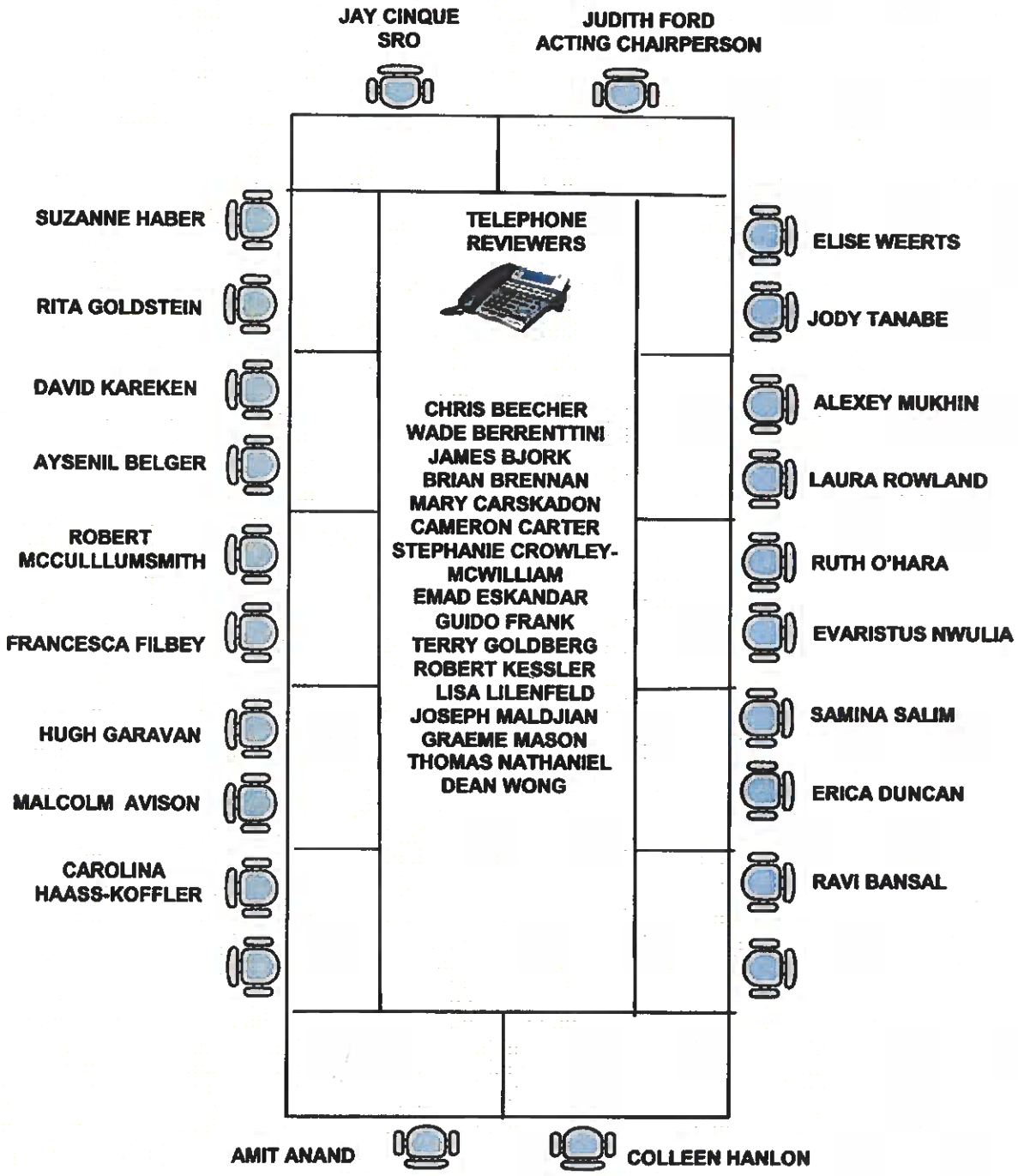
Evaluating Overall Impact:
Consider the 5 criteria: significance, investigator, innovation, approach, environment (weighted based on reviewer's judgment)

5 is a good medium-impact application, and the entire scale (1-9) should always be considered.

Center for Scientific Review

NEURAL BASIS OF PSYCHOPATHOLOGY, ADDICTIONS AND SLEEP (NPAS) STUDY SECTION

June 1-2, 2017



MEETING ROSTER

Neural Basis of Psychopathology, Addictions and Sleep Disorders Study Section
Brain Disorders and Clinical Neuroscience Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
NPAS
Agenda Seq Num - 00320141
06/01/2017 - 06/02/2017

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 and NOT-OD-15-106, including removal of the application from immediate review.

ACTING CHAIR

FORD, JUDITH M, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
SAN FRANCISCO, CA 94121

MEMBERS

ANAND, AMIT, MD *
PROFESSOR
DEPARTMENT OF PSYCHIATRY AND PSYCHOLOGY
CLEVELAND CLINIC
CLEVELAND, OH 44195

AVISON, MALCOLM J, PHD *
PROFESSOR
DEPARTMENT OF RADIOLOGY AND RADIOLOGICAL SCIENCES
INSTITUTE OF IMAGING SCIENCE
VANDERBILT UNIVERSITY SCHOOL OF MEDICINE
NASHVILLE, TN 37232

BANSAL, RAVI, PHD *
PROFESSOR
DEPARTMENT OF RESARCH PEDIATRICS
KECK SCHOOL OF MEDICINE
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA 90033

BEECHER, CHRIS WW, PHD *
PROFESSOR
CENTER FOR TRANSLATIONAL PATHOLOGY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MI 48013

BELGER, AYSENIL, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL
CHAPEL HILL, NC 27599

BERRENTTINI, WADE H, PHD, MD *
PROFESSOR
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA 19104

BJORK, JAMES M, PHD *
ASSOCIATE PROFESSOR
DEPARTMENTS OF PSYCHIATRY, PHARMACOLOGY AND TOXICOLOGY
INSTITUTE FOR DRUG AND ALCOHOL STUDIES
VIRGINIA COMMONWEALTH UNIVERSITY
RICHMOND, VA 23060

BRENNAN, BRIAN P., MD *
ASSISTANT PROFESSOR
DEPARTMENT OF PSYCHIATRY
MCLEAN HOSPITAL
HARVARD MEDICAL SCHOOL
BELMONT, MA 02478

CARSKADON, MARY A, PHD
PROFESSOR AND DIRECTOR
DEPARTMENT OF PSYCHIATRY AND HUMAN BEHAVIOR
E P BRADLEY HOSPITAL SLEEP RESEARCH LABORATORY
BROWN UNIVERSITY SCHOOL OF MEDICINE
EAST PROVIDENCE, RI 02915

CARTER, CAMERON S., MD *
PROFESSOR
DEPARTMENT OF PSYCHIATRY AND PSYCHOLOGY
IMAGING RESEARCH CENTER
UNIVERSITY OF CALIFORNIA DAVIS MEDICAL CENTER
SACRAMENTO, CA 95817

CROWLEY MCWILLIAM, STEPHANIE, PHD *
ASSISTANT PROFESSOR
DEPARTMENT OF BEHAVIORAL SCIENCES
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, IL 60612

DUNCAN, ERICA J, MD *
DIRECTOR
DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES
EMORY UNIVERSITY SCHOOL OF MEDICINE
DIRECTOR
PSYCHOPHYSIOLOGY AND COGNITION LABORATORY
DECATUR, GA 30033

ESKANDAR, EMAD N, MD
PROFESSOR
DEPARTMENT OF NEUROSURGERY
MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MA 02114

MEETING ROSTER

Neural Basis of Psychopathology, Addictions and Sleep Disorders Study Section
Brain Disorders and Clinical Neuroscience Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
NPAS
Agenda Seq Num - 00320141
06/01/2017 - 06/02/2017

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 and NOT-OD-15-106, including removal of the application from immediate review.

FILBEY, FRANCESCA, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF NEUROGENETICS OF ADDICTIVE BEHAVIOR
CENTER FOR BRAIN HEALTH
SCHOOL OF BEHAVIORAL AND BRAIN SCIENCES
UNIVERSITY OF TEXAS, DALLAS
DALLAS, TX 75235

FRANK, GUIDO KW, MD *
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF COLORADO
AURORA, CO 80045

GARAVAN, HUGH P, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF VERMONT
BURLINGTON, VT 05401

GOLDBERG, TERRY, PHD *
PROFESSOR
MEDICAL PSYCHOLOGY IN
PSYCHIATRY AND ANESTHESIOLOGY
DIVISION OF GERIATRIC PSYCHIATRY
NEW YORK, NY 10032

GOLDSTEIN, RITA Z, PHD
PROFESSOR
DEPARTMENT OF NEUROSCIENCE
HESS CENTER FOR SCIENCE AND MEDICINE
ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI
NEW YORK, NY 10029

HAASS-KOFFLER, CAROLINA L, PHMD *
PROFESSOR
DEPARTMENT OF OF BEHAVIORAL AND SOCIAL SCIENCES
BROWN UNIVERSITY
NEWTON, MA 02459

HABER, SUZANNE N, PHD
PROFESSOR
DEPARTMENT OF PHARMACOLOGY AND PHYSIOLOGY
SCHOOL OF MEDICINE AND DENTISTRY
UNIVERSITY OF ROCHESTER MEDICAL CENTER
ROCHESTER, NY 14642

HANLON, COLLEEN A, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY
MEDICAL UNIVERSITY OF SOUTH CAROLINA
CHARLESTON, SC 29425

KAREKEN, DAVID A, PHD
PROFESSOR
DEPARTMENT OF NEUROLOGY
INDIANA UNIVERSITY SCHOOL OF MEDICINE
INDIANAPOLIS, IN 46202

KESSLER, ROBERT M, MD *
DIRECTOR
NEUROIMAGING CONSULTANTS
NASHVILLE, TN 37215

LILENFELD, LISA, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF CLINICAL PSYCHOLOGY
ACADEMY FOR EATING DISORDERS
CLINICAL PSYCHOLOGY PROGRAM
ARGOSY UNIVERSITY, WASHINGTON DC
ARLINGTON, VA 22209

MALDJIAN, JOSEPH A, MD *
PROFESSOR AND CHIEF OF NEURORADIOLOGY
DIRECTOR, ADVANCED NEUROSCIENCE
DEPARTMENT OF RADIOLOGY
UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER
DALLAS, TX 75390

MASON, GRAEME F, PHD *
PROFESSOR
DEPARTMENT OF DIAGNOSTIC RADIOLOGY
SCHOOL OF MEDICINE
YALE UNIVERSITY
NEW HAVEN, CT 06520

MCCARLEY, ROBERT W, MD
PROFESSOR
DEPARTMENT OF PSYCHIATRY
BROCKTON VA MEDICAL CENTER
BROCKTON, MA 02301

MEETING ROSTER

Neural Basis of Psychopathology, Addictions and Sleep Disorders Study Section
Brain Disorders and Clinical Neuroscience Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
NPAS
Agenda Seq Num - 00320141
06/01/2017 - 06/02/2017

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 and NOT-OD-15-106, including removal of the application from immediate review.

MCCULLUMSMITH, ROBERT E, MD, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY AND
BEHAVIORAL NEUROSCIENCE
UNIVERSITY OF CINCINNATI
CINCINNATI, OH 45267

MUKHIN, ALEXEY G, MD, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY AND
BEHAVORIAL SCIENCES
DUKE UNIVERSITY MEDICAL CENTER
DURHAM, NC 27701

NATHANIEL, THOMAS I, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF BIOMEDICAL SCIENCES
UNIVERSITY OF SOUTH CAROLINA SCHOOL OF MEDICINE
GREENVILLE, SC 29605

NWULIA, EVARISTUS A, MD
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY
HOWARD UNIVERSITY COLLEGE OF MEDICINE
WASHINGTON, DC 20060

O'HARA, RUTH M, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY AND
BEHAVIORAL SCIENCES
STANFORD UNIVERSITY SCHOOL OF MEDICINE
STANFORD, CA 94305

ROWLAND, LAURA M, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF MARYLAND, SCHOOL OF MEDICINE
BALTIMORE, MD 21228

SALIM, SAMINA, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF PHARMACOLOGICAL AND
PHARMACEUTICAL SCIENCES
COLLEGE OF PHARMACY
UNIVERSITY OF HOUSTON
HOUSTON, TX 77204

TANABE, JODY L, MD
PROFESSOR
DEPARTMENT OF RADIOLOGY
UNIVERSITY OF COLORADO, DENVER
AURORA, CO 80045

WEERTS, ELISE M, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY AND
BEHAVIORAL SCIENCE
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
BALTIMORE, MD 21224

WONG, DEAN F, MD, PHD
PROFESSOR AND VICE CHAIR, RADIOLOGY
DIRECTOR, SECTION OF HIGH RESOLUTION
PET IMAGING
JOHNS HOPKINS UNIVERSITY
BALTIMORE, MD 21287

SCIENTIFIC REVIEW OFFICER

CINQUE, JULIUS
SCIENTIFIC REVIEW OFFICER
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

EXTRAMURAL SUPPORT ASSISTANT

CHACON, PEDRO
EXTRAMURAL SUPPORT ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

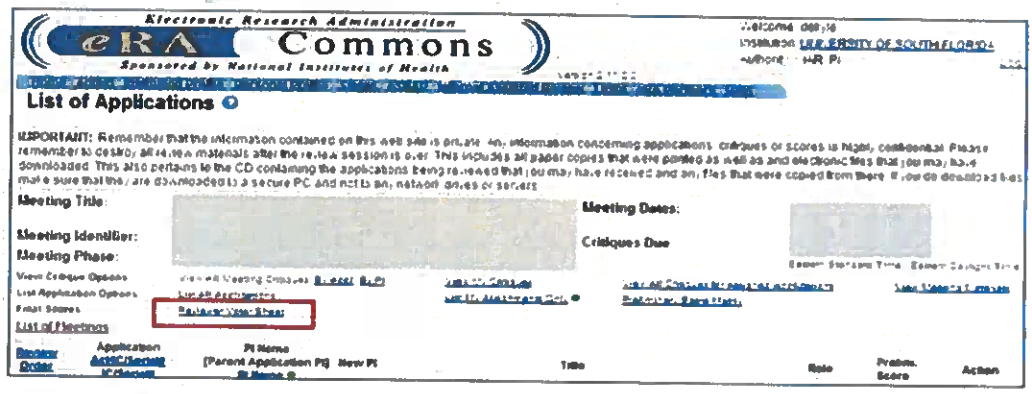
KIRKPATRICK, JOEL D
LEAD EXTRAMURAL SUPPORT ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

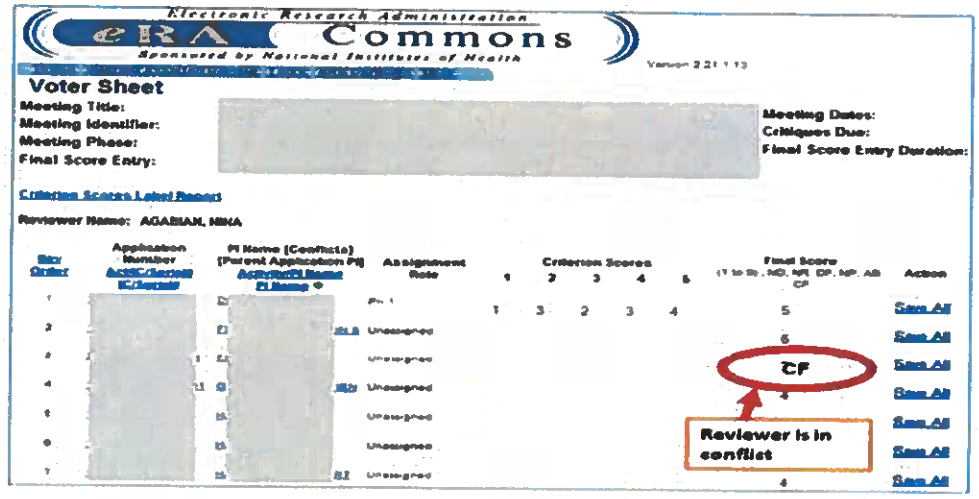
Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

IAR FINAL SCORING INSTRUCTIONS FOR REVIEWERS

- A link to the Reviewer Voter Sheet will only appear on the IAR "List of Applications" page when the meeting begins (see below).



- IAR final scoring voter sheets will allow valid scores 1 – 9, ND (not discussed), NR (not recommended for further consideration), DF (deferred), NP (not present), AB (abstain), and CF (conflict). If you are in conflict with an application, CF should automatically appear in the space for entering scores (see below).



- You can enter or modify final scores from the start of the meeting to the end. You should save after each score entry or modification using the **SAVE button at the bottom of the voter sheet list**.
- The voter sheet can be sorted by Review Order, Application Number, or PI Name. Sorting by Review Order is usually preferred. If it does not return to the Review Order after you save, resort to Review Order.
- Do not enter Criterion Scores if you are not an assigned reviewer.
- Preliminary overall scores submitted before the start of the meeting do not appear on the voter sheet.
- Record your scores on paper in parallel to entering them in IAR as a back-up for any problems with internet connections, the IAR website, etc.

FOR CHANGING AIRLINE OR TRAIN RESERVATIONS
YOU MUST PLEASE CONTACT THE WORLD TRAVEL SERVICE (WTS):

Please call the World Travel Service (WTS) to make any changes to your meeting travel. **Please note that if you make changes on your own by directly contacting the airline, you will NOT BE REIMBURSED.**

Please contact WTS by one of the following methods and **indicate our meeting code which is: " NPAS "**

1.) Call WTS directly at 1-800-638-8500 number M-F 8:00am – 7:00pm EST (calling WTS is preferred over email)
2.) After hours number for when WTS is closed 1- 877 853-3648 (516) 730-2648 if outside the USA
3.) Please send an e-mail (AS EARY AS POSSIBLE) to: NIH@worldtravelservice.com with your flight change request
4). If any special approval is required through the CSR Travel Office, please let us know as soon as possible, so we can assist if necessary with getting approval.

PLEASE note that these are restricted air fares and that ONLY ONE change is allowed per your trip (within reason) and that there is a "TWO- HOUR RULE". WTS is only permitted to make a change if the change is greater than two hours. For example you have a 5:30pm return flight, they could not change you to a 4:30p since less than two hours, but you could book a 3:30pm since that is two hours.

Finally, please also understand that if you already made a change to your incoming flight, that you will not be allowed to change for your return flight for free - unless you obtain CSR Travel Office approval - you would then be responsible for the second change.

Thank you.

SUMMARY STATEMENT

PROGRAM CONTACT:
Dr. Douglas Meinecke
(301) 443-6767
dmeineck@mail.nih.gov

(Privileged Communication)

Release Date: **08/18/2025**
Revised Date:

Application Number: **2R01MH107487-07A1**
Formerly: **2R01MH107487-07**

Principal Investigators (Listed Alphabetically):

MCCULLUMSMITH, ROBERT E (Contact)
WALSS-BASS, CONSUELO

Applicant Organization: UNIVERSITY OF TOLEDO HEALTH SCI CAMPUS

Review Group: **ZRG1 BN-F (90)**
Center for Scientific Review Special Emphasis Panel
Molecular and Cellular Topics in Basic Neuroscience

Meeting Date: **08/05/2025**
Council: **OCT 2025**
Requested Start: **12/01/2025**

Opportunity Number: **PA-25-301**
PCC: **A3-NSM**

Project Title: **Protein kinase networks underlying insulin signaling pathway dysregulation in schizophrenia**
SRG Action: **++**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**

Project Year	Direct Costs Requested
7	499,355
8	499,995
9	499,985
10	498,564
11	499,861
TOTAL	2,497,760

++NOTE TO APPLICANT: Members of the Scientific Review Group (SRG) were asked to identify those applications with the highest scientific merit, generally the top half. Written comments, criterion scores, and preliminary impact scores were submitted by the assigned reviewers prior to the SRG meeting. At the meeting, the more meritorious applications were discussed and given final impact scores; by concurrence of the full SRG, the remaining applications, including this application, were not discussed or scored. The reviewers' comments (largely unedited by NIH staff) and criterion scores for this application are provided below. Because applications deemed by the SRG to have the highest scientific merit generally are considered for funding first, it is highly unlikely that an application with an ND recommendation will be funded. Each applicant should read the written critiques carefully and, if there are questions about the review or future options for the project, discuss them with the Program Contact listed above.

2R01MH107487-07A1 MCCULLUMSMITH, ROBERT

ADMINISTRATIVE NOTE

DESCRIPTION (provided by applicant): This is a resubmission of a competitive renewal of a grant line with the overarching goal of examining perturbations of signaling networks in disorders of cognition. While we made considerable progress during the first period of this project, we have one carryover objective which we combine with two new specific aims, all focused on examining perturbations of canonical insulin signaling pathways (CISP) in schizophrenia. Notably, patients with schizophrenia exhibit dysfunction of CISPs, with onset of insulin resistance premorbid and in antipsychotic naïve first episode patients. Remarkably, the insulin hypothesis of SCZ is almost as old as the diagnostic formulation of SCZ itself. Appel and Farr wrote in 1929 [1], "It is conceivable that endocrine relations might be disturbed in psychoses, so that blood sugar reactions to insulin would consistently give different reactions than in normal persons." While there is a large body of compelling old and new data supporting the hypothesis that CISPs are perturbed in schizophrenia, the paucity of GWAS, CNV and rare mutations connecting genetic risk with this biological process has lessened enthusiasm for this concept. However, we posit that perturbations of CISPs represent an intermediate pathophysiological phenotype, indirectly connecting genetic and environmental risk for schizophrenia with manifestation of the illness. To this end, we propose to investigate an understudied signaling node in CISPs, Serum and Glucocorticoid-regulated Kinase 1 (SGK1). SGK1 mediates CISPs and may be driving increased neurite formation during development, leading to over pruning and/or activation of synapse elimination processes during brain maturation. Our project's specific aims are as follows: SA1, continuing from the previous period, will rigorously examine cell-subtype specific signaling networks in postmortem neurons from schizophrenia and control subjects, utilizing RNAseq and kinome array activity assays. Through the use of multi-omics integration and network modeling, we aim to undertake both targeted (SGK1) and unbiased analyses. In SA2, our focus is on exploring signaling networks in iPSC-derived cortical glutamatergic neurons. The techniques we'll employ include RNAseq, LCMS, and kinome array assays, with Western blots, QPCR, immunostaining, and enzyme activity assays being used for biochemical validation of findings. In SA3, we will modulate SGK1 expression in iPSC-derived cortical glutamatergic neurons and analyze the effects on CISPs, as well as bioenergetic measures and neuronal morphology. These concerted efforts will yield a comprehensive understanding of the role of SGK1 and other key kinase nodes within CISPs in schizophrenia. We expect to generate cell-subtype and subcellular compartment specific data informing protein kinase signaling networks, with SGK1 being the central focus. Our findings will elucidate potential targets for the development of new treatment strategies for the cognitive and negative symptoms of schizophrenia, currently a significant gap in existing pharmacological interventions. At the completion of this project, we will deliver a robust, richly detailed dataset that may serve as a stepping-stone for future research and drug development efforts.

PUBLIC HEALTH RELEVANCE: This project will identify the critical elements of brain function that contribute to the pathophysiology of schizophrenia. Identification of the molecular elements underlying schizophrenia will provide new targets for the development of strategies to improve cognition in this illness.

CRITIQUE 1

Factor 1. Importance of the Research (Significance and Innovation): 3
Factor 2. Rigor and Feasibility (Approach): 5
Factor 3. Expertise and Resources (Investigator(s) and Environment): Additional expertise and/or resources needed

Overall Impact: This is a resubmitted competitive renewal continuing the investigation of perturbations of signaling network in schizophrenia (SCZ), focusing on the Serum and Glucocorticoid-regulated Kinase 1 (SGK1) in mediating the disruption of canonical insulin signaling pathways (CISP) in SCZ neurons. The insulin hypothesis in SCZ was postulated decades ago based on insulin resistance in the periphery. More recent discoveries support perturbations of insulin signaling in SCZ postmortem brains and iPSC-derived neurons. This topic is underappreciated partly due to the lack of GWAS identified genetic risk and the downstream molecular mechanisms connecting CISP to SCZ pathophysiology remains vastly elusive. The overarching hypothesis of this application postulates that SGK1 drives an intermediate pathophysiological phenotype in SCZ, based on its known function in CISP and neurite formation. However, because SGK expression is not altered in SCZ postmortem brains, the sole support and premise for focusing on SGK1 has to rely on preliminary data to demonstrate altered SGK activity consistent with perturbation of CISP. The cited literature indicates that insulin signaling activates SGK1, thus insulin resistance and perturbation of CISP in SCZ is expected to reduce SGK1 activity. However, some preliminary data suggests increased SGK1 activity, without explaining this potential conflict. The proposed studies will apply multi-omics analysis established by the PI's team to identify pathophysiological kinase network/hubs centered on the SGK1 as the "node kinase" in microdissected neuronal layers in the SCZ postmortem brains (Aim 1) and iPSC-derived neurons (Aim 2) that provide complementary advantages. If successful, these studies will provide important insights regarding novel kinase networks affected in SCZ neurons, a breakthrough as compared to previous studies that mostly build on a single kinase. In addition, Aim 3 will test whether modulating SGK1 expression in SCZ iPSCs will normalize CISP defects and neurite/synapse morphology in IPSC-derived neurons. However, the premise for the model that connects CISP disturbance to the biphasic neurite/synapse defects in SCZ is not strong. There is a lack of sufficient description of the proposed experiments to judge the feasibility and success of synaptic analysis. It is also unclear that the MPI or listed key personnel have sufficient expertise for synaptic formation. Overall, the proposal is strong on the exciting kinase network studies. However, the weaknesses in the premise for focusing on SGK1 to mediate sophisticated CISP that involve other key signaling events, the somewhat superficial model and proposed experiments on SGK1 to correct SCZ neuronal/synapse phenotypes, together with concerns of expertise on synaptic studies dampened the enthusiasm.

Factor 1. Importance of the Research (Significance and Innovation):

Major Score-Drivers

Strengths

- Integration of findings from microdissected DLPFC regions and iPSC-derived cortical neurons from control and SCZ subjects will unveil kinase networks/hubs/notes affected in SCZ, which is highly significant and impactful, if successful.
- The resubmission strengthened the premise of the etiopathogenesis roles of disturbed canonical insulin signaling pathways (CISP) in SCZ as a pathophysiological intermediate, and the argument for kinase activity changes without altered expression or genetic risks.

Weaknesses

- Because the literature does not provide strong connection of SGK1 with schizophrenia, the alteration of SGK1 activity, as argued in the proposal, is crucial for the proposed studies to demonstrate strong evidence the foundation of the project. Insulin is known to activate SGK1 thus insulin resistance in SCZ is expected to reduce SGK1 activity. However, preliminary data indicating increased SGK1 activity in SCZ samples, without mentioning of this potential conflict. This raises substantial concerns.

- The postulated increase of neurite/synapse formation due to SGK1 hyperactivity in SCZ during development that triggers immune activation and excess synapse elimination are somewhat superficial, not based on literature or morphological data in preliminary studies.

Factor 2. Rigor and Feasibility (Approach):

Major Score-Drivers

Strengths

- Laser microdissected superficial and deep pyramidal neurons (Aim 1) and iPSC-derived cortical neurons of control and SCZ subjects (Aim2) provide complementary assessments of kinase network/hub by the centered on the "node" kinase SGK1 by a multi-omics approach based on kinome array, RNAseq and phospho-LCMS analysis. The integration across these multi-omics data sets, including the neuronal age and subcellular fractions, will generate a comprehensive database and unveil novel kinase networks and signaling notes, which will have valuable outcomes for understanding the pathophysiology of SCZ.
- Utilization of SCZ and control postmortem DLPFC tissue and iPSCs-derived cortical neurons is well rationalized and collected on hand. Well-powered statistical analyses to determine the numbers of male and female subjects for the postmortem study, in which SGK1 is likely affected in a sex-differential manner.
- The causative roles and functional consequences of SGK1 overproduction/deficiency and stress responses will be directly addressed in SCZ and control iPSC-derived neurons.

Weaknesses

- The entire project is contingent on alterations of SGK1 activity in SCZ neurons in the correct direction with disturbed CISP. Based on the stated insulin-PI3K-GSK1 signaling (Page 83), consistent with the reported reduction of PI3K signaling in SCZ (Law, 2012), disrupted CISP and insulin insensitivity are expected to lower SGK1 activity. However, the preliminary data suggests paradoxically increased SGK1 activity in SCZ, without explanation of this conflict.
- There are several weaknesses in preliminary data key for the hypothesis and proposed studies: a) The direct assessment of p-SGK1 in SCZ brain/iPSC-derived neurons and upon induced stress is normalized to the unjustified loading reference VCP instead of total SGK1; b) evidence suggesting SGK1 to promote neurite formation is NOT based on morphology; c) the inhibitor of SGK1 is used to assess SGK1 specificity, but the concentration is much beyond the IC_{50} and likely also affects other kinases.
- The pilot kinome array indicates feasibility to detect phosphorylation of reporter peptides by microdissected neurons. However, whether a reporter peptide phosphorylated by recombinant SGK1 can also be phosphorylated by multiple kinases in tissue lysates is not demonstrated.
- No experiment is listed under Aim 3 to examine neurite, axon or dendrites, and synapse formation, but this is mentioned in hypothesized results. In the methodology section, the description for quantifying synapse formation is very brief and superficial, without citation. No rigorous description is provided for quantification of synaptic density on what part of the neuron. No consideration was given to synaptic pruning, although that is part of the hypothesis.
- The expectation of little to no impact of SGK1 KD on neurons from control subjects is based on SGK1 KO mice, which may not recapitulate human neurons.
- Experiment 3.4 will explore rat neuron stress responses and use the result to guide studies on human iPSC-derived neuron, which may not be helpful.

Inclusion Plans

- Sex or Gender: Not Applicable
- Race and Ethnicity: Not Applicable
- For NIH-Defined Phase III trials, plans for valid design and analysis (applicable to sex or gender and race and ethnicity): Not Applicable
- Based on Age: Not Applicable

Factor 3. Expertise and Resources (Investigator(s) and Environment):

Additional expertise and/or resources needed

- Neither MPIs nor listed key personnel had experience for synaptic formation in iPSC-derived neurons. This is reflected by the over-simplified experimental description that do not test the hypothesized biphasic neurite/synapse defects in SCZ.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmissions:

- The resubmission is responsive to previous critiques, especially regarding the unnecessary genetic risk for SGK1 to be involved in SCZ pathophysiology. However, concerns still remain for the premise to focus on SGK1.
- Sample size of DLPFC is increased and justified by power analysis.
- There are concerns raised in last round of submission but still remain: e.g. premise for SGK1 as the mediator for perturbation of CISP; feasibility for proposed experiments, such as phosphor-LCMS, quantitative SGK1 knockdown and overexpression, and quantitative analysis of SCZ neuronal morphology.

Renewals:

- Great productivity for the last award period, with 48 publications cited.
- Aim1 continues from the previous award and expands to SGK1.

Authentication of Key Biological and/or Chemical Resources:

Appropriate

Budget and Period of Support:

Appropriate to support the proposed research

CRITIQUE 2

Factor 1. Importance of the Research (Significance and Innovation): 3
Factor 2. Rigor and Feasibility (Approach): 3
Factor 3. Expertise and Resources (Investigator(s) and Environment): Appropriate

Overall Impact: In this renewal application, Dr. McCullumsmith and team, continue to pursue the overarching hypothesis of perturbations in the Canonical Insulin Signaling Pathway (CISP) impacting schizophrenia (SCZ). CISP has been proposed to do so through influencing brain metabolism, synaptic plasticity, neuronal survival, and cognitive function, with disruptions in CISP being observed in antipsychotic-naïve, first-episode SCZ patients, indicating it is not merely a side effect of treatment, but potentially a core pathophysiological feature. The CISP pathway consists of multiple protein kinases that form a kinase signaling network that have been shown to mediate cellular responses to external stimuli. SGK1 is one such kinase and a less studied kinase, Serum and Glucocorticoid-regulated Kinase 1 (SGK1). The renewal application builds on the work of the first period by continuing one aim (Aim 1) and proposing two new aims (Aims 2 and 3). There is multiple score driving factors of this application.

Strengths

- The team of investigators has been quite productive with six to eight publications from the first phase.
- Increased samples sizes for postmortem (N = 48) and iPSCs (N = 15) studies compared to the prior submission.
- The investigation of treatments and mechanisms that would enable better management of individuals suffering from the negative and cognitive symptoms of this illness is equally important as that of managing the primary symptoms.
- The employment of a dual approach, involving both postmortem brains and iPSCs is valuable and complementary.
- A sound data integration approach, both within and across specific aims.

Weaknesses

- The main weakness here is the sole focus on SGK1. Yes, the investigators have provided multiple lines of evidence suggesting why SGK1 should be studied and the insights that will be gained. However, given that premise here is one of "...intermediate pathophysiological phenotype that follows developing a brain with genetic risk for SCZ along with environmental stressors", how actionable will the findings be.
- The CVCR cohort used for hIPSCs is less admixed of a population. How generalizable and/or translatable will the findings from this cohort be, to the cohort of Hispanic (H), black (B), white (W), Hispanic white (HW) being analyzed in Aim 1 be?
- Given that the investigator intend of performing network analyses, stronger candidates genes/kinases might emerge that are first degree neighbors of SGK1. There has been no mention of what and how that information will be used.

Factor 1. Importance of the Research (Significance and Innovation):

Major Score-Drivers

Strengths

- The proposal investigates the role of CISP in SCZ, thereby enabling new insights and possible treatment opportunities for individuals suffering from the negative and cognitive symptoms of SCZ.
- The use of both postmortem brains and iPSCs along with a multiomic approach (transcriptome, kinome and metabalome) is valuable and will generate a rich data resource for the research community along with deeper insights into the role of the insulin pathway in SCZ.
- From the perspective of innovation:
- The methods that will be developed for assessing protein kinase signaling networks in laser microdissected (LMD) pyramidal neurons using kinase activity arrays will be innovative and of value to the broader research community.
- As with the first phase of the R01, this renewal application will result in innovative multi-omics integration and modeling packages.

Weaknesses

- The primary weakness as stated above is the role of SGK1 in SCZ. As the investigators state, SGK1 is not a smoking gun as it relates to GWAS etc. This is totally understandable (not every actionable candidate needs to be a GWAS finding), however, even within CISP, there are other stronger genes and proteins. There is limited discussion around this.

Factor 2. Rigor and Feasibility (Approach):

Major Score-Drivers

Strengths

- Several new computational tools to analyze both the multiomic data, specifically kinomes have been developed by the investigators and will be applied to the current project.
- Good experimental designs, with sufficient detail is provided. Though in some places details are limited (e.g. LINCS)
- The analytical methods and frameworks using open-source environments and will support rigor and reproducibility of both methods and findings.
- The investigators were responsive to prior reviews indicating the need to increased sample sizes. The sample sizes provided here should enable for well powered studies and thereby reproducible and robust findings.

Weaknesses

- The cohort used for hIPSCs (CVCR) are less admixed, while this will help with the genomic stability and QC of the cell lines, the question that comes to mind is how the differences in population structure between the cohorts in Aim 1 would and 2, result in generalizability and robustness of findings.
- The network analysis as proposed falls short of the potential of gaining the most insights. The investigators do not necessarily discuss or interpret the value of 1st, 2nd degree neighbors, that could result in stronger findings towards implicating SGK1 and CISP in SCZ.
- One of the key outcomes here would be actionable drug target. To that end, the description of how LINCS would be leverages falls short.

- The investigators state that the cohort in Table 1 will be "All subjects (Table 1) will be genotyped for GWAS, CNV, and rare mutations associated with SCZ." However, there are no methods associated for these analyses.
- There is no mention of why the FDR less than 0.30 statistic was removed. This was something R2 (prior submission) had raised.

Inclusion Plans

- Sex or Gender: Not Applicable
- Race and Ethnicity: Not Applicable
- For NIH-Defined Phase III trials, plans for valid design and analysis (applicable to sex or gender and race and ethnicity): Not Applicable
- Based on Age: Not Applicable

Factor 3. Expertise and Resources (Investigator(s) and Environment):

Appropriate

Protections for Human Subjects:

Appropriate

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Appropriate

Resubmissions:

- In this resubmission, the investigators have mostly addressed the prior reviewers concerns and feedback.

Renewals:

- The investigators have been very productive over the last funding period. They have published at least six papers, along with releasing analytical packages for data analysis.

Authentication of Key Biological and/or Chemical Resources:

Appropriate

Budget and Period of Support:

Appropriate to support the proposed research

CRITIQUE 3

Factor 1. Importance of the Research (Significance and Innovation): 6
Factor 2. Rigor and Feasibility (Approach): 9
Factor 3. Expertise and Resources (Investigator(s) and Environment): Appropriate

Overall Impact: This is a renewal proposal to investigate the possible role of canonical insulin signaling pathway components in schizophrenia. Presentation made it difficult to assess any progress made during the prior funding period. The hypothesis that genetic and environmental stresses may dysregulate CISP components is supported by some observations in patients, but not supported by genetics. The data in some places did not fully support the assertions made. The lack of clear explanations and details about data analysis and interpretation and integration raised significant concerns about potential outcomes.

Factor 1. Importance of the Research (Significance and Innovation):

Major Score-Drivers

Strengths

- This application is for a continuation of project to interrogate signaling networks and identify new targets for drug development among canonical insulin signaling pathway (CISP) components for treatment of schizophrenia (SCZ).
- The team hypothesizes that genetic vulnerability in schizophrenia leads to alterations in CISPs.
- The possible involvement of CISPs in SCZ is supported by findings of lower insulin sensitivity in first episode psychosis and that polygenic risk scores for insulin resistance were higher in antipsychotic naive SCZ patients.

Weaknesses

- The lack of association of CISP genes with genetic risk for SCZ or clinical data showing that medications that act on CISPs alters SCZ risk or course raises questions about relevance of CISPs to SCZ.

Factor 2. Rigor and Feasibility (Approach):

Major Score-Drivers

Strengths

- The driving hypothesis is that genetic and environmental stressors activate SGK1 to trigger pathology in SCZ.
- Proof of principle strongly suggests that laser captured pyramidal neurons have kinome signals similar to fresh human or mouse brain.
- Hydrocortisone does appear to increase pSGK1 levels.

Weaknesses

- The progress report was not organized in a manner that facilitated a full understanding or appreciation of the significance or context of prior findings. While region specific changes in

AKT were found in the anterior cingulate cortex, the proposal did not indicate the direction of changes.

- Similarly, while there was extensive discussion of the protein kinase signaling arrays to measure kinase activity, there was no discussion of the results.
- It was challenging to interpret the rigor and significance of the network model. It appears to have been applied to the DISC1 gene proband (which is not a consensus SCZ risk gene). Fair
- How the kinome data are interpreted and integrated was not clear. Similarly, how other data are integrated across platforms was not clear.
- It is not entirely clear that the increase in b3 tubulin signal in iPSC-derived cells indicates that they are bona fide markers of neurites (or neurons). Hence, it is not clear what the SGK1 inhibitor is doing to these cells, nor is the specificity of the inhibitor addressed. Thus, the data presented do not establish that path to generating iPSC-derived neurons is robust. Four
- (Minor) Total protein staining is a better control for protein loading in western, unless the team has rigorously shown that VCP is not changed by the experimental conditions.
- It was not clear in Aim 1 what tissues would be used to verify changes observed in kinome profiling.
- There were no proof of principle data presented on phospho-LCMS. It was also not clear how any data would be integrated, interpreted, and acted on. Four
- Proof of principle is lacking for lentiviral mediated gene knockdown and rescue. Four

Inclusion Plans

- Sex or Gender: Not Applicable
- Race and Ethnicity: Not Applicable
- For NIH-Defined Phase III trials, plans for valid design and analysis (applicable to sex or gender and race and ethnicity): Not Applicable
- Based on Age: Not Applicable

Factor 3. Expertise and Resources (Investigator(s) and Environment):

Appropriate

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmissions:

- The introduction was disorganized and hard to understand.

Renewals:

- The progress report was not organized in a manner that facilitated a full understanding or appreciation of the significance or context of prior findings.
- One Aim is carried over from the previous funding period.

Authentication of Key Biological and/or Chemical Resources:

Appropriate

Budget and Period of Support:

Appropriate to support the proposed research

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

UNALLOWED HYPERTEXT ADMINISTRATIVE NOTE: During the review of this application, unallowed hypertext was noted in the application as only doi (digital object identifier) and .gov sites are allowed. Hypertext, hyperlinks, and URLs are only allowed when specifically noted in funding opportunities or application instructions. NIH is tracking this warning and has the authority to withdraw future noncompliant applications (NOT-OD-20-174).

Footnotes for 2R01MH107487-07A1; PI Name: McCullumsmith, Robert E

NIH has modified its policy regarding the receipt of resubmissions (amended applications).See Guide Notice NOT-OD-18-197 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-197.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
Molecular and Cellular Topics in Basic Neuroscience
ZRG1 BN-F (90)
08/05/2025 - 08/06/2025

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-22-044 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-044.html, including removal of the application from immediate review.

CHAIRPERSON(S)

GUPTON, STEPHANIE, PHD
PROFESSOR
DEPARTMENT OF CELL BIOLOGY
AND PHYSIOLOGY
SCHOOL OF MEDICINE
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC 27599

MEMBERS

ADAMS, KATRINA L, PHD
GALLAGHER ASSISTANT PROFESSOR
DEPARTMENT OF BIOLOGICAL SCIENCES
COLLEGE OF SCIENCE
UNIVERSITY OF NOTRE DAME
NOTRE DAME, IN 46556

ALFORD, SIMON T, PHD
PROFESSOR AND HEAD
DEPARTMENT OF ANATOMY
AND CELL BIOLOGY
COLLEGE OF MEDICINE
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, IL 60612

DAHMANE, NADIA, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF NEUROLOGICAL SURGERY
WEILL CORNELL MEDICAL COLLEGE
NEW YORK, NY 10065

FEANY, MEL B, MD, PHD
PROFESSOR
DEPARTMENT OF PATHOLOGY
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL
BOSTON, MA 02115

FENG, YUE, PHD, MD
PROFESSOR
DEPARTMENT OF PHARMACOLOGY
SCHOOL OF MEDICINE
EMORY UNIVERSITY
ATLANTA, GA 30322

GOMEZ, TIMOTHY M, PHD
PROFESSOR
DEPARTMENT OF NEUROSCIENCE
UNIVERSITY OF WISCONSIN-MADISON
MADISON, WI 53706

GREER, PAUL LIEBERMAN, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MOLECULAR MEDICINE
SCHOOL OF MEDICINE
UMASS CHAN MEDICAL SCHOOL
WORCESTER, MA 01655

GRILLO, ANTHONY STEVEN, PHD
ASSISTANT PROFESSOR
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CINCINNATI
CINCINNATI, OH 45221

HAMILTON, PETER JAMES, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF ANATOMY
AND NEUROBIOLOGY
VIRGINIA COMMONWEALTH UNIVERSITY
RICHMOND, VA 23298

HONG, JENNIFER, MD
ASSOCIATE PROFESSOR
DEPARTMENT OF NEUROSURGERY
DARTMOUTH HITCHCOCK MEDICAL CENTER
LEBANON, NH 03765

JADIYA, POOJA, PHD
ASSISTANT PROFESSOR
DEPARTMENT OF INTERNAL MEDICINE
SCHOOL OF MEDICINE
WAKE FOREST UNIVERSITY
WISTON-SALEM, NC 27157

KAMPMANN, MARTIN, PHD
PROFESSOR
DEPARTMENT OF BIOCHEMISTRY AND BIOPHYSICS
INSTITUTE FOR NEURODEGENERATIVE DISEASES
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
SAN FRANCISCO, CA 94143

KIM, HONGKYUN, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF CELL BIOLOGY
AND ANATOMY
ROSALIND FRANKLIN UNIVERSITY
NORTH CHICAGO, IL 60064

KOLESKE, ANTHONY J, PHD
PROFESSOR
DEPARTMENT OF MOLECULAR BIOPHYSICS
AND BIOCHEMISTRY
YALE UNIVERSITY
NEW HAVEN, CT 06520

LEVY, EFRAT, PHD
PROFESSOR
DEPARTMENTS OF PSYCHIATRY, BIOCHEMISTRY
AND MOLECULAR PHARMACOLOGY
NATHAN S KLINE INSTITUTE
NEW YORK UNIVERSITY LANGONE HEALTH
ORANGEBURG, NY 10962

LI, YUQING, PHD
PROFESSOR
DEPARTMENT OF NEUROLOGY
CENTER FOR MOVEMENT DISORDERS
AND NEURORESTORATION
UNIVERSITY OF FLORIDA
GAINESVILLE, FL 32610

PARK, YUNGKI, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF BIOCHEMISTRY
JACOBS SCHOOL OF MEDICINE
AND BIOMEDICAL SCIENCES
UNIVERSITY AT BUFFALO
BUFFALO, NY 14203

PHILIP, VIVEK, PHD
DIRECTOR
DEPARTMENT OF COMPUTATIONAL SCIENCES
THE JACKSON LABORATORY
BAR HARBOR, ME 04609

REN, DEJIAN, PHD
PROFESSOR
DEPARTMENT OF BIOLOGY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA 19104

RODGERS, KRISTA, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF CELLULAR BIOLOGY
AND ANATOMY
LOUISIANA STATE UNIVERSITY HEALTH SHREVEPORT
SHREVEPORT, LA 71103

SAMAL, JUHI, PHD
ASSISTANT PROFESSOR
DEPARTMENT OF BIOMEDICAL ENGINEERING
SCHOOL OF ENGINEERING
UNIVERSITY OF ALABAMA AT BIRMINGHAM
BIRMINGHAM, AL 35233

STOILOV, PETER, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF BIOCHEMISTRY
AND MOLECULAR MEDICINE
SCHOOL OF MEDICINE
WEST VIRGINIA UNIVERSITY
MORGANTOWN, WV 26506

SULZER, DAVID, PHD
PROFESSOR
DEPARTMENTS OF NEUROLOGY,
PSYCHIATRY AND PHARMACOLOGY
COLUMBIA UNIVERSITY
NEW YORK, NY 10032

WONG, YVETTE, PHD
ASSISTANT PROFESSOR
DEPARTMENT OF NEUROLOGY
FEINBERG SCHOOL OF MEDICINE
NORTHWESTERN UNIVERSITY
CHICAGO, IL 60611

YU, XINZHU, PHD
ASSISTANT PROFESSOR
DEPARTMENT OF MOLECULAR
AND INTEGRATIVE PHYSIOLOGY
COLLEGE OF LIBERAL ARTS & SCIENCES
UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN
CHAMPAIGN, IL 61822

ZHANG, HUAYE, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF NEUROSCIENCE AND CELL BIOLOGY
RUTGERS ROBERT WOOD JOHNSON MEDICAL SCHOOL
PISCATAWAY, NJ 08854

SCIENTIFIC REVIEW OFFICER

RAMADAN, IPOLIA R, PHD
SCIENTIFIC REVIEW OFFICER
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

EXTRAMURAL SUPPORT ASSISTANT

SCOTT, SHIN'YA M.
EXTRAMURAL SUPPORT ASSISTANT
CENTER FOR SCIENTIFIC REIVEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.