Center for Scientific Review
Peer Review Advisory Committee Meeting
National Institutes of Health
U.S. Department of Health and Human Services

August 28, 2006

The third 2006 meeting of the Peer Review Advisory Committee (PRAC) convened at 8:30 a.m. on Monday, August 28, 2006, at the Hyatt Regency, Bethesda, Maryland. The entire meeting was held in open session. Dr. Antonio Scarpa and Dr. Jeremy Berg presided as Co-Chairs.

Members

Jeremy Berg, Ph.D., Co-Chair
Antonio Scarpa, M.D., Ph.D., Co-Chair
Dean E. Brenner, M.D.
Joe Martinez, Jr., Ph.D.
Craig McClain, M.D.
Daria Mochly-Rosen, Ph.D.
Louise Ramm, Ph.D.
Anne P. Sassaman, Ph.D.
Matt Winkler, Ph.D.

Ad Hoc Members

Faye Calhoun, Ph.D.
Leslie A. Leinwand, Ph.D.
R. Lorraine Collins, Ph.D.

Dr. Beverly Torok-Storb, Ph.D., attended via telephone. Dr. Edward Pugh, Jr., Ph.D., was not present. Dr. Norka Ruiz Bravo, Ph.D., attended as an Ex Officio member. Dr. Cheryl Kitt, Ph.D., was the Executive Secretary for the meeting.

Welcome, Approval of the May 2006 PRAC Minutes, and Upcoming Meetings

Dr. Berg welcomed participants and introduced Executive Secretary Dr. Cheryl Kitt. Dr. Kitt asked for approval of the minutes of the May 2006 meeting. The minutes were unanimously approved. She then confirmed PRAC's next three meeting dates: December 4, 2006, and April 19 and August 27, 2007. The dates were chosen to coordinate with Institute Council meetings.

Update on Electronic Submission of Grant Applications

Ms. Megan Columbus, Program Manager for Electronic Receipt of Grant Applications in the Office of Extramural Research, reported that the June 1, 2006, submission date for small grant applications was an important indicator of how electronic submission would fare with the R01s in 2007. She reported that things are working well so far.

Improvements in June 2006
About 12,000 unique NIH applications have been submitted through Grants.gov, more than 2,700 of them for the June 1 deadline. The number of applications per successful submission dropped from an average of 4+ for the small business applications in December 2005 to 1.7 in

June 2006. Ninety-four percent of the applications were available to the Division of Receipt and Referral in the Center for Scientific Review (CSR) within six days in June, compared to 34 percent in December. The help desk handled the call volume, and the number of calls to the desk decreased because of software improvements, outreach, and better preparedness.

Next Steps
To gear up for the R01s, systems are being monitored closely. The staff is also following up on Grants.gov's efforts to make the Pure Edge forms Mac-compatible; while the Citrix solution for Macs seems to work, it is not ideal. Spreading out receipt dates is under discussion so that, for example, R03s or R21s may be due later than R01s. This change would give newer investigators more time to prepare their applications and spread the workload both for the institutions and for NIH. The use of appendix materials is being evaluated. A Request for Information (RFI) about appendix materials is out, and comments are due in the fall 2006.

Continued outreach will help reduce call volume and stress in the applicant community. Hands-on training for the outside community and for NIH staff is scheduled, along with communications through listservs, Web sites, meetings, and other means.

Continuing challenges include the fact that the Grants.gov form model is not well suited to evolving business needs, such as NIH's three-year program announcements. A requirements analysis that focuses on NIH's complex mechanisms is ongoing to see what kinds of forms may be needed to capture information differently.

Discussion
Deadline dates: Dr. Louise Ramm asked whether spreading the receipt dates out was being considered because other agencies' receipt dates coincide with those of NIH. Ms. Columbus said that the 1st, 15th, and last day of a month are peak dates for Grants.gov, so a change is under consideration. Dr. Ramm also asked for status on electronic submission of complex mechanisms. Ms. Columbus said that efforts are under way to move this process forward. The Office of Management and Budget is pushing hard to reach 100-percent electronic submission by FY 2007. Even with the aggressive time line, NIH will not reach 100 percent by that deadline.

PI perspective: Dr. Joe Martinez said he wanted to share some observations as a Principal Investigator (PI). First, he sought clarification about eRA Commons accounts for PIs who submit grants from multiple institutions. Ms. Columbus clarified that individuals maintain a single Commons account which is used even if he or she changes institutions or submits applications from more than one institution. Second, he asked how tables in appendices, such as for the T-32, are handled. Ms. Columbus said that each mechanism has a working group looking at it, and that the T group is looking at how to handle tables. If tables are not in the appendix, it will be included in the body of the application itself. Other elements, such as publicly available brochures, can possibly be taken out of an electronically submitted application and linked to instead, which would shorten an application.

Dr. Berg said that he has been hearing comments from applicants about Mac compatibility, which he termed a credibility and responsiveness issue. The ability of NIH to make the system user-friendly for PIs is crucial. Ms. Columbus said they will continue to pursue the issue.

Formatting: Dr. Kitt asked about application formatting, which she said can appear messy in an electronic submission. Ms. Columbus said that there is no current way to manipulate appearance of the image, but that the issue remains "on the burner." If, however, the formatting results in an image being distorted or another substantive change, the signing official should reject the application and the eRA help desk should assist in correcting it. More broadly, the message to emphasize is that the PI should review the application after submission through Grants.gov to see the image of the application. Dr. Martinez asked how inappropriate information can be withdrawn. Ms. Columbus said a utility is being created to update a grants folder that a scientific review administrator (SRA) can use when corrected materials come in. A redact feature is also being developed, which should be completed in time for the R01s.

CSR: Where We Are and Where We Would Like to Be

Dr. Scarpa marked his one-year anniversary as CSR Director over the summer. He focused his presentation on two areas: changes in CSR operations and future visions for peer review. He explained that the 60-year-old system must change to meet changing scientific needs and the increase in applications.

Changes in CSR Operations
Increased communication and transparency: Biweekly meetings with SRAs and other staff, as well as a comprehensive communications plan, have improved communications. CSR has also expanded communications with the community by expanding the *Peer Review Notes* newsletter, and proposed "open houses" with leaders from the scientific community will also advance communications and transparency.

Increased uniformity: Thanks to SRA efforts, all summary statements are posted within 30 days, with those of new investigators posted within 1 week. Investigators thus have more time to make decisions about revising applications. More complete and structured resumes are being produced, and unscoring is now consistently set at 50 percent. Dr. Kitt is chairing a committee to look at best practices for study sections, such as appropriate rosters and types of meetings.

Increased efficiency: Electronic submission increases efficiency once applications are received in CSR. A major pilot to use text fingerprinting and artificial intelligence software to directly assign applications will begin in October with full implementation expected by February 2007.

Vision for the Future
Dr. Scarpa and Dr. Kitt have attended many study sections and noticed much variability. People are guessing about pay lines, and also often focus too much on the approach and not enough on the significance of a proposed idea. Time is spent calibrating a competitive renewal application score; thus, Dr. Scarpa asked for PRAC input on whether an A1 score should be known when reviewing an A2.

Another concern stems from the realignment. Applicants, societies, and disease groups are expressing concern about the variance in the breadth of science in different study sections. CSR

regularly monitors the Integrated Review Groups (IRGs) and study sections and suggests changes as needed.

Dr. Scarpa asked for PRAC comment on the agenda of top priorities: shorten the review cycle, address the concern that clinical research is not properly evaluated, improve the assessment of high-risk/high-reward research, and do more to recruit and retain more high-quality reviewers. He reviewed progress on these priorities.

Shorten the review cycle: Besides posting summary statements sooner, the pilot on the shortened review cycle showed that 14 percent in the pilot resubmitted the very next cycle. He called this a good, conservative number. Program officers and department chairs provided good advice about whether investigators should apply immediately. An evaluation of the pilot is under way.

Evaluation of clinical and of innovative research: Dr. Scarpa referred to studies by Dr. Ted Kochen and Dr. Michael Martin on scoring of clinical research. Dr. Martin's analysis showed the difference in scores can be quantitatively accounted for because submission of competitive renewals is lower for human subject-positive than -negative applications. Dr. Scarpa said Dr. Keith Yamamoto would address the topic of innovative research later in the meeting.

Recruiting and retaining reviewers: More must be done to recruit and retain more high-quality reviewers. Five years ago, less than 6,000 reviewers were needed. This year, ~18,000 were used, in part because applications grew from 45,000 to nearly 80,000. Some investigators are in new areas for NIH, such as engineering and law. In addition to a larger number of investigators, the average investigator submits an average 1.4 applications per year and that number is probably rising. The number of R21 applications has grown from 1,000 to 9,000 in 5 years, with the mechanism used by Institutes and Centers (ICs) in many different ways. This variation makes it difficult for study sections to review R21s.

The reviewer load has decreased to an average of 6 applications per reviewer, down from 12. Reviewers are also, on average, getting younger, with more assistant professors serving. Meetings may involve 40 to 50 reviewers, many of whom participate by phone, which dilutes group chemistry. Ways to address these issues include the following: using electronic review modes to reduce travel, shortening review meetings, convening pre-meetings to streamline, using various review platforms, using hybrid review platforms, unscoring 40 percent of the F32 applications, and shortening the grant application. For 2007, CSR is working to expand the use of electronic reviews to 10 percent when doing so allows it to recruit the best reviewers.

A trans-NIH committee is looking at the size of the R01 application. A shorter R01 can increase the number that each reviewer is assigned, decrease the number of reviewers in a study section, and may also result in a format that is more consonant with review criteria and a focus on significance and innovation. The concept has strong support from the scientific community and many NIH Institute and Center advisory councils.

Dr. Scarpa ended his presentation with special thanks to Mr. Dave Witmer, CSR Executive Officer, who is leaving CSR, and to two PRAC members who are retiring—Dr. Faye Calhoun and Dr. Anne Sassaman.

Discussion

A1 scores: Dr. Leslie Leinwand asked about the effect of removing the A1 score from an A2 application. She asked if there is a difference in success rate if the same, versus different, reviewers review an A2. Dr. Scarpa said he did not think so and, in any event, it is almost impossible that all three reviewers would be the same both times.

Dr. Sassaman said, as much as possible, a revised application should go to the same reviewers because an amended application is often responsive to concerns the previous reviewers raised. Dr. Calhoun said when the question about keeping track of who reviews an application had come up at previous meetings, the response was that keeping a record is not allowed, although an SRA may simply remember. Dr. Scarpa said he would check on the legality and then what might be do-able in terms of an experiment.

Dr. Dean Brenner said retaining the A1 score is an important guide to get at significance. Splits occur in study sections over the importance of a proposed work. An A1 receiving the same or worse scores the second time implies a split in the study section about the relative importance of the work. Focusing more of a written review and the response to an applicant on how the study section sees significance is critical. Dr. Martinez agreed that reviewers want to see the response to the previous review, so removing the A1 score seems strange. Dr. Lorraine Collins said it is crucial as a reviewer and as an applicant to have the A1 score available. There is no guarantee that the A2 score will improve, but it is informative to know what previous reviewers thought.

Dr. Norka Ruiz Bravo asked whether any data show a problem with removing or not removing A1scores. Dr. Scarpa said observations show that much time is spent on A2 scores when a previous A1 score was higher. It is not a high issue on the CSR agenda, but he is asking PRAC for direction because of the time factor. He said he would explore possibilities of collecting data.

Significance: Dr. Collins cautioned about overemphasizing significance, since significance of research is sometimes not known until years later. Dr. Scarpa clarified the significance could be on advancing the field and not necessarily whether the research is significant to a disease.

Dr. Sassaman shared comments from the perspective of the program staff who interpret summary statements. The issue of significance is important to get across, and anything in the statements that make it clearer would help. The issue of A1 versus A2 scores, and the reviewers on each, is tricky for program staff to communicate to applicants. In addition, she asked about any way to differentiate between unscored applications in, for example, the 52nd versus the 99th percentile. Dr. Scarpa said an application is scored or not, although letters come in each week on this issue.

Dr. Berg raised an idea he said was discussed at the first PRAC meeting and also in relation to the Pioneer Awards: individual reviewers could provide an application's best possible score independent of approach. This practice could provide a sense of what individual reviewers thought about a proposal and some bundled sense of significance, as well as provide applicants with a sense of whether it is worth resubmitting an application. He offered to prepare a white paper on the concept. Dr. Scarpa suggested a format in which an applicant writes perhaps a half-page on significance that all the reviewers could read.

Reviews by telephone: Dr. Craig McClain said that telephone reviews are critical to bring in the best reviewers for complex grants. Also, a problem in reviewing R21s is the various criteria applied to it. He said from an investigator point of view, there is no better discussion than time spent on an application in for a second time if it is near the pay line. Dr. Scarpa agreed with the need for telephone participants but said if most participate by phone, scoring might come out of context if the phone participants only come in for brief periods of time.

Recruiting reviewers: Dr. Brenner said he becomes concerned at his institution when he hears about assistant professors serving on study sections because the burden may hinder their own development and chances for tenure. He also said comfort and location affect reviewers and noted that a study section with a good reputation serves as a recruiting tool. Dr. Scarpa said four cities have been selected as alternatives to Washington to hold meetings. Chicago, Los Angeles, San Francisco, and Seattle have lower costs than Washington and are easier for those in other parts of the country to travel to.

Dr. Collins asked about the background of assistant professors doing review. Dr. Kitt replied that they need to have had some past funding, but not necessarily NIH funding. Dr. Collins said using younger reviewers, who may be most productive and aware of the science, is not necessarily a problem. Concern about the "old boys' network" occurred when mostly senior people sat on study sections. Moving away from that model might make study sections more diverse.

Scoring: In response to a comment from Dr. Leinwand about reviewers who tend to love or hate all their assigned applications, Dr. Scarpa said study sections are supposed to take tendencies like that into account when the reviewers share their scores. Dr. Daria Mochly-Rosen said the increase in the number of R21s reflects the perception that R01s no longer reward for innovation and risk. She also asked about coordination of scores before a meeting. Dr. Scarpa responded after a reviewer posts a score, he or she can see the other two reviewers' critiques. Dr. Kitt said, as a former program director, her staff told investigators there was no guarantee that an amended application would go to the same reviewers and the risk existed of doing worse. In some cases, investigators figure out which reviewers look at their application, but anonymity protects reviewers and the unbias of the review.

Further discussion: Dr. Collins said there were many issues in the presentation without time to hash them out. She suggested a committee to address them or perhaps more time for general discussion. Dr. Kitt invited members to e-mail with immediate questions.

Peer Review Outcomes for the R03 and R21 Mechanisms

The next presentations on peer review and the R03 and R21 mechanisms were made at PRAC request to follow up on presentations at the May 2006 meeting.

R03 Outcomes
Dr. Valerie Durrant, SRA in the Health of the Population IRG, reviewed the conclusions presented at the May meeting: Review outcomes of R03s are similar to Type 1 R01s, with no systematic differences between R03s reviewed in different review venues. The questions that

arose in May centered on whether the averages hide variations among study sections and whether differential treatment occurs with streamlining. A recommendation was also made to track outcomes of an early-career R03 on later R01 success, but data are not available for this analysis.

Additional analysis: The additional analysis examined variation across study sections by focusing on the percentage streamlined within study sections that had considered at least 10 R03s over the last three rounds. The analysis also looked at the program announcements (PAs) and types of R03 applications, including new versus amended applications and new versus experienced PIs.

R03s represent only about 3 percent all CSR-reviewed applications or about 1,660 applications; almost 75 percent of them go to standing study sections and about 14 percent to special emphasis panels (SEPs). Looking at study sections and SEPs that reviewed 10 or more R03s over three rounds showed no systematic variation in streamlining between Type 1 new R03 versus R01 applications. No consistent pattern shows that R03s are being sacrificed to keep more R01s on the discussion table.

She next looked at whether any pockets of R03s are being streamlined more frequently, which might drive the perception that R03s and R21s are at a disadvantage. Most R03s come in response to PA 03-108 (recently replaced by PA 06-180), which, as a free-form process, limits the analysis. However, she did point to two unique characteristics of R03s compared to R01s: They are more likely to have a new investigator as PI, and less likely to be resubmitted. Score distribution of Type 1 R03s for new and A1 applications look similar to those of R01s. In addition, score distribution of Type 1 R03s from experienced and from new PIs are similar to Type 1 R01s. Experienced investigators tend to do better in both R03 and R01 applications.

Conclusions: There is no evidence of systematic bias in the streamlining or score distributions of R03s across study sections, and review outcomes of amended R03s and of R03s with new and experienced PIs are similar to those of R01s. However, because the perception of bias may exist, it is important to remind reviewers to review the R03 differently than the R01.

R21 Outcomes

Dr. Elaine Sierra-Rivera, SRA in the Oncological Sciences IRG, said her group began its analysis thinking that R21s and R03s are mistreated in study sections. They found this is not so.

Dr. Sierra-Rivera reviewed characteristics of the R21. As of June 1, 2006, all R21s are submitted electronically. CSR study sections reviewed 86 percent of the 3,474 R21 applications in the last round. Based on the check-off box on the face page, new PIs submitted about 48 percent of them.

Findings presented at the May 2006 PRAC meeting showed no difference in streamlining or scoring patterns between R21 and R01 applications when evaluated in the context of review environment. At that time, PRAC members asked whether R21s are streamlined at a higher rate than R01s, if discrepancies exist among study sections, and if the R21 mechanism is used for its intended purpose. After that meeting, instructions for reviewers were amended to clarify how to review these mechanisms, including the reminder that preliminary data are not required.

Additional analysis: Her analysis looked at the study sections that review the highest number of R21s and groups the applications by PA. It is limited to Type I applications from the October 2005 to May 2006 review cycles. Looking across chartered study sections, the unscoring pattern of R21s compared to R01s is about the same. The analysis then looked at applications that came under different PAs. Most came in under the Parent PA, which she termed a catch-all for PI-initiated research. A total of 2,132 R21 applications were analyzed, and Dr. Sierra-Rivera presented several graphs that showed how they fared in study sections.

Conclusions: R21s are not differently unscored compared to R01s, and the scores are comparable to Type 1 R01s. SRAs are attempting to properly orient reviewers to the R21 mechanism. She closed by acknowledging the team who worked on the analysis.

Discussion

Scoring perceptions: An audience member said the perception that the R03 or R21 applications were not doing well might be driven by which study sections are involved. The suggestion was made to look at the history of these mechanisms in a few of those study sections where they did not seem to fare well. Dr. Sierra-Rivera noted that the data all come from the parent PA, even applications that really should not be an R21. Dr. Durrant added that looking specifically at study sections that appeared to disproportionately streamline the R03s and R21s showed that it was not a pattern that occurred over time. She also noted that the perception may come from study sections that review just a few R03s per year and thus fall below the cut-off of 10 used in the analysis. Dr. Kitt noted not all ICs have their R03s reviewed at CSR.

Dr. Calhoun asked about analyzing whether certain areas of science are not doing well with these mechanisms. Dr. Kitt said the ICs have better data on what kinds of applications come in. Dr. Calhoun said it would be useful to look at applications across various categories of science to see how they are succeeding. The answer is critical to areas that NIH is trying to encourage. Dr. Ruiz Bravo suggested refining some questions, since PRAC is advisory to all of NIH, not just CSR. She agreed that Institute data would be interesting if specific questions to them could be defined.

Dr. Berg said the National Institute of General Medical Sciences abandoned the R21 because of a mismatch between the review scores and comments. Scores were good when there was a lot of preliminary data, which went against the intent of the mechanism.

Dr. Martinez asked for clarification on the R21 data, which he interpreted as perhaps showing a variance. Dr. Sierra-Rivera said the CSR analyst advised that variance was not the best measure for this type of analysis and another method was used. Dr. Ruiz Bravo noted different types of research are presented for the R21s, many from new investigators. Dr. Kitt said they would look into the topic, but the more global question about a bias toward the R21s or R03s shows no pattern. There is tremendous variance from round to round, partly because there are over 200 PAs. Reviewers have many variables to keep in mind.

Innovation and the R21: Dr. Mochly-Rosen said she wanted to return to the idea that investigators now view the R21 as an alternative to the R01. Many people tell her, as dean of research, they did not get an R21 funded because they had no preliminary data, which is a problem. Including the clarification in reviewer instructions is wonderful, but it will be

interesting to see whether reviewers heed the instructions. Dr. Kitt said the parent PA no longer says "high-risk innovation," although it states that no preliminary data are required. Dr. Ruiz Bravo said new investigators are using the R21, which is an additional complication to evaluating how they fare. Dr. Sierra-Bravo said not all R21s are intended for high-risk, innovative research, and use of the mechanism has expanded to meet other goals.

Outstanding New Environmental Scientist (ONES) Award

Dr. Sassaman, Director of the Division of Extramural Research and Training of the National Institute of Environmental Health Sciences (NIEHS), expressed appreciation for serving on PRAC and then turned to her presentation. NIEHS initiated the Outstanding New Environmental Scientist (ONES) Award to increase the number of new investigators in the environmental health sciences. Some of the elements of the program, she said, may be applicable to other ICs.

The NIEHS 2006–2011 Strategic Plan's overarching goals include recruiting and training the next generation of environmental health scientists. The ONES Award is designed to develop a selective group of researchers with less than 8 years of postdoctoral experience. Proposed research aligns with a specific human disease, dysfunction, or pathophysiologic condition or biological process, and use environmentally relevant toxicants.

Review challenges: Dr. Sassaman described the program and application process, including how NIEHS defines a commitment to environmental health research. They are now on the second iteration of the award. The award has been time-intensive for program staff, requiring hand-holding to help young investigators submit applications. Interpretation of eligibility criteria must be consistent, which involves internal discussion and getting the message out to applicants. The review process has been complicated because of the breadth of the science. Reviewers must be established, broad-thinking scientists who are involved in training and recruitment/hiring of junior faculty. They must be committed to understanding and buying into the goals of the NIEHS vision and possess appropriate scientific expertise to review applications. Selection of the chairperson is also very important. Extensive reviewer orientation took place before and at the review meetings and throughout the streamlining process.

Selection: Seventy applications were received, with 61 responsive and 28 scored. Two-day, face-to-face interviews were held with the top 10 applicants, and impressions from the interviews were consistent with study section reviews. The May Council concurred and awards to eight of the top 10 are planned for September 1. The award recipients are scheduled to come to NIEHS in October to meet with staff and participate in seminars and presentations as a way to nurture this cohort of researchers. She summarized the research proposed in the top 10 applications.

Applicability: Dr. Sassaman discussed the applicability of the ONES Award as a trans-NIH mechanism perhaps to complement the K99 ROO awards. It meets the objective of targeting young investigators at an important point in their careers. It helps create a special relationship with the Institute that should increase the probability of the investigators staying in the environmental health field and in developing competitive renewals. She characterized the ONES Award as an R01 award with special features attached. How to conduct reviews remains a challenge and would have to be considered if the mechanism were more widely used. Yet, the

challenges can be met. NIEHS intends to evaluate and continue the program over the next several years and will have more information to bring to the greater NIH community.

Discussion
Dr. Ramm thanked Dr. Sassaman for the presentation but noted the workload implications if other ICs went about the program in the same way. In response to Dr. Ramm's question about evaluation, Dr. Sassaman said NIEHS will track the funding success of the investigators, as well as whether they keep their research focused on the environmental health sciences.

Program goals: Dr. Brenner praised the program, but it covers only 10 new investigators when 15,000 new investigators came "on line" in the past few years. He asked about the program's ability to meet their needs or whether it selects the very few individuals who would succeed in any event. Dr. Sassaman said the award does not represent a small start for NIEHS. Other ICs might consider a similar mechanism to focus on a new direction or recruit in a particular field.

External advisory board: Dr. Winkler agreed on the importance of nurturing researchers at the critical period up to tenure. He said the external advisory committee, which he compared to a board of directors that can provide accountability and feedback, was particularly intriguing. Dr. Martinez said perhaps the board could improve the chances of the investigators competing successfully for future funding. However, he remembered that R29 recipients from the past did not compete very well later on. He asked about successful transitioning if so much program staff time was required. Dr. Sassaman clarified that staff time was needed to understand and comply with the ONES criteria and objectives. Dr. Ruiz Bravo agreed the external advisory committee is particularly innovative and perhaps generalizable for new investigators for R01s.

MD experience: Dr. McClain asked about the maximum postdoctoral experience for MDs, who may be just getting out of their fellowships after 8 years. Dr. Sassaman said the criteria accommodated their training and expressed hope that more MDs would apply in the next round.

Targeting research areas: Dr. Calhoun said the mechanism might be helpful for specific areas that NIH needs to nurture as expressed in the NIH Roadmap, such as certain types of translational research. Dr. Mochly-Rosen said, while she usually agreed with Dr. Calhoun, she disagreed with the trend to influence what researchers do by awarding grants in particular areas or particular fields. Excellence, no matter the field, should be rewarded.

ONES versus K Award: Dr. Brenner asked how the ONES Award differs from a K award. Dr. Sassaman said the ONES Award emphasizes the research project, as in an R01. She said that the cachet of an R01-type award drove the argument to focus on the research and the research plan.

X02: New Mechanism for the Review of Complex Applications

Dr. Greg Farber, Program Officer for the Center for Computational Biology at the National Center for Research Resources (NCRR), said the X mechanisms are a result of the NIH Roadmap initiative. They are basically permission mechanisms. The X01 allows assays to be submitted in a Roadmap Program. The X02, the subject of this presentation, is a preapplication,

in that it gives applicants permission to submit a full application when doing so would be a tremendous burden on both the applicant and review communities.

Dr. Farber reminded PRAC the NIH Roadmap supports interdisciplinary research. In 2004, the interdisciplinary group released seven PAs, including a P20 for exploratory centers. NCRR agreed to be the principal Institute in charge of the program. In the first year, 21 awards were made to bring groups of investigators together who do not normally speak a common language. There were 150 applications, with many more potential applicants expressing interest.

The follow-on to the P20 is the Interdisciplinary Consortia Program. These consortia will be large--$3 million in direct costs per year for a total of 5 years. The awards will be made in September 2007. Site visits to the 21 currently funded centers gave him a sense of the type of mechanisms necessary for these consortia. A key issue is to give credit to all members of a team. The community expressed the desire for a large set of mechanisms, as well as a central award for program management. The consortia will be complex and ultimately involve independent awards from various ICs, although all with Roadmap funds.

The problem, said Dr. Farber, is size. The $3 million in direct costs can fund about 10 components per consortium. If 150 full applications for consortium funding were received, this could be the equivalent of about 1,500 R01-sized components to review, and the load would be even greater if the number rose above 150. With funds for only eight consortia, it did not make sense to ask everyone to prepare a full application. Three possible solutions were to restrict the applications only to current P20 awardees, require potential applicants to submit an R03 or other "placeholder" award, or, as was ultimately decided on, invent a preapplication mechanism that can be peer reviewed but does not require an award. Dr. Farber acknowledged the assistance of Dr. Ruiz Bravo's staff, as well as staff in CSR and NCRR, to develop the X02.

Dr. Farber said the Roadmap has created new mechanisms that support nontraditional programs. Review of X02 applications was managed by a small group of NCRR SRAs, using Internet Assisted Review (IAR). Scores were released in August. Applicants have two weeks to communicate concerns to program staff. In mid-September, a project team of IC representatives will meet to construct the first draft of an invitation list to submit a full application. The list will go to the Roadmap Implementation Group and the NCRR Council, with the plan to make invitations known on September 27. Applications, which will be due December 19, must contain the same elements as the X02 preapplication. An NCRR-convened SEP will conduct the review.

Dr. Farber said the X02 might have other uses throughout NIH in situations in which a large number of complex applications are expected.

Discussion

Dr. Brenner asked how many X02s came in and what the review process was like. Dr. Farber said about 100 were received and that electronic review worked well. Applications that were really extensions of multidisciplinary efforts, rather than interdisciplinary, often did not fare well in review. About 70 to 80 reviewers were associated with the process.

Dr. Winkler said he liked the idea of a preapplication process when funding is very tight. He suggested informing applicants of the example of people from different departments who have co-published in the past as a good way to illustrate interdisciplinary work in contrast to a consortium that is artificially assembled as a way to receive funding.

Dr. Sassaman asked about wider use of the X02. Dr. Ruiz Bravo said its use elsewhere would depend on the circumstance and should be looked at on a case-by-case basis.

Challenges, Models, and Mechanisms for High-Risk and Innovative Research Proposals in Peer Review

Dr. Keith Yamamoto, Executive Vice Dean of the University of California, San Francisco, was invited to speak to PRAC on grant formats and review mechanisms for innovative and transformative research. He began with what he termed one of his favorite quotes, by Surgeon General Thomas Parran in 1945, that underscores the importance of the federal government's involvement in biomedical research and need for complete freedom for scientists. Yet, he said three aspects of grant and review processes impede, rather than support, discovery and innovation: (1) study sections, because by nature they reach compromises and because they tend to be populated by creators of the prevailing paradigms; (2) the focus on projects rather than people, which emphasizes data and not promises of future success; and (3) numerical scoring, which tends to make the system failure-averse and hard to propose something outside of the mainstream.

The challenge for NIH, said Dr. Yamamoto, is to devise a grant format and a review mechanism that foster and nurture research to not only achieve continuous progress and breakthroughs, but also create occasional revolutions. The system needs to invite the really brilliant ideas that can change or make a field, or undo a field and make something different. He differentiated between innovative research, which is evolutionary and advances or shifts paradigms, and transformative research, as defined by a National Science Foundation panel on which he serves, which does not so much as extend paradigms as crush them and make new ones. NIH needs to support both innovative and transformative research.

Two-Track System
Dr. Yamamoto proposed a two-track system in which the investigator chooses whether to apply to the Innovative or to the transformative research track. He described what might be required for each track.

The Innovative Research Award would be large in size, like an R01, and project-focused. He suggested a 7-page application: 1 page on the issue to be approached, including just enough background to understand why the question is being asked; 1 page on specific aims; ½ page on impact to show the difference the experiment will make to the field; 4 pages on approaches, including the progress report and any preliminary data; and ½ page on the innovation of the concept or approach. This format would closely align to the review criteria. The biosketch would be restructured to place more focus on the investigator than seen in the current R01 applications: the investigator would list a maximum of five publications in each of three areas (most relevant to this proposal, most recent, and most significant in career) and explain why he/she is

particularly well suited to carry out the proposed work. A shorter, more closely aligned application would lighten the review load. Also, reviewers would rank, not score, the proposals.

The Transformative Research Award would be a small, investigator-focused, and highly prestigious program, like the Pioneer Awards. It would not have a fixed monetary amount but instead provide funds based on the needs of the proposed work. It might require a three- to five-page essay focusing on truly revolutionary concepts and approaches. It could offer 10 years of support, with few reporting requirements to allow bold things to occur over the course of the grant. He said a controversial, but important part of his proposal is to move away from panels of experts in a specific field to a review by a highly selective set of generalists using an electronic review process and personal interviews. The number of applicants would probably be self-limiting over time, as has happened with the Pioneer Awards.

Assessment
Dr. Yamamoto said that should these programs be adopted in some form, they should be assessed, but not by comparing the Innovative versus Transformative programs, but rather by examining the success of NIH research carried out under the Innovative program in the presence versus the absence of the Transformative program. He suggested several ways to carry out assessments of the Transformative program, stressing that the evaluation criteria should not be limited to conventional metrics or even to the applicants' original essay topic, but to the "revolutionary" impact of whatever contributions ensued.

He summarized that he is suggesting two formats and review mechanisms for R01 research: an R01(I) for innovative research and an R01(T) for transformative research. Both emphasize impact, and the applicant could choose under which track to apply. The vast majority, he said, would probably come under the R01(I) track. But even perhaps 40 paradigm-busting ideas that work would represent a huge difference to science and would also show that NIH supports this kind of research.

Discussion
Shorter application: Dr. Mochly-Rosen praised the ideas and focused on the suggested seven-page application. From reviewing grants from other countries, she said shorter grants can show the worth of an idea. Dr. Yamamoto said an important part of the effort would be to align the application with the criteria more explicitly.

Dr. Scarpa thanked Dr. Yamamoto for his presentation. He asked how the 10-year time frame would fit with current institutional structures for promotion and advancement. Dr. Yamamoto said people who receive the transformative awards would probably be well known as great thinkers. Also, his concept is that the award would not require 50 percent or more effort, so that individuals could continue with ongoing research that is continually productive.

Dr. Martinez asked how to select recipients when often the great findings in science are serendipitous. Dr. Yamamoto said judgments about quality have to be made in any event, and that the Transformative program is particularly focused on the investigator, not on the proposed project. Dr. Collins said she hoped some or all of Dr. Yamamoto's ideas are implemented, although the challenges of a psychosocial researcher to present a research approach in four pages

may be greater than for a biomedical researcher. In terms of reviewer loads, an application with fewer pages requires as much or more time to evaluate as a longer one. Dr. Yamamoto said one-size-fits-all will not work and the entire scientific community would have to scrutinize his ideas. He hoped cutting down an application would force an investigator to be very explicit and highly focused, and would make applications more transparent.

Operationalization: Dr. Ruiz Bravo said the presentation presented wonderful challenges, as well as posed a series of questions about operationalization. It is opportune to bring forward this idea as NIH is in the midst of thinking about another roadmap. Although Dr. Yamamoto's idea has roots in peer review, it is really a programmatic issue for the attention of the Advisory Committee and NIH Director. Dr. Yamamoto stressed very high standards would be needed in which only truly transformative ideas get funding. Dr. Leinwand said having Dr. Yamamoto's name attached to the idea would help keep standards high.

Dr. Berg drew on his involvement with the Pioneer Award to discuss challenges in assessing impact. It is hard to assess ideas, rather than technology or solutions to specific problems. Reviewers tend to be conservative, but applicants tend to be more conservative than they need to be. Sometimes innovative ideas do score very well.

Dr. Winkler said implicit in the discussion is that the awards should drive the entire research community to be more innovative in their approaches and planning. Dr. Yamamoto said young people are taught to write conventional grants to get funding. The system must be de-encrypted. If NIH said it is inviting the best ideas and they will be rewarded, that would be a huge change.

Dr. Calhoun asked what it would take to implement the system. One option is to implement the transformative award and gradually move toward adjusting the regular R01, for example first by reducing application size. Dr. Yamamoto agreed there are many ways to act incrementally. The only immediate change needed, he said, is the standards used to judge transformative awards.

Shortening the Research Application

Dr. Robert Finkelstein, Director of Extramural Research at the National Institute of Neurological Disorders and Stroke (NINDS), and Dr. Don Schneider, Director of the CSR Division of Molecular and Cellular Mechanisms, discussed the Trans-NIH Committee to Shorten the Application, which they co-chair. The committee has been charged with looking at the possibilities of shortening the research plan section of the standard NIH grant application.

Charge to the Committee
Dr. Finkelstein stressed the presentation was to get PRAC input and no decisions have been made. The charge to the committee came from the Extramural Activities Working Group (EAWG). The committee's goal, besides looking at page limits, is to consider aligning the application sections more closely with review criteria, focusing on the R01 and then other mechanisms as appropriate. He briefly reviewed application lengths of other organizations in the United States, United Kingdom, and Canada, all of which are shorter than NIH's 25-page limit.

Dr. Finkelstein identified four issues influencing the committee's charge: (1) many applicants and reviewers say the NIH application process is excessively time-consuming; (2) reviewer workloads have declined; (3) the number of reviewers has increased per study section and overall; and (4) last year, CSR used nearly 20,000 reviewers.

The committee began work a few months ago. It will get input from external and internal stakeholders and then recommend an application length and format, which would be widely vetted. He stressed the committee has no preconceived idea of what, if anything, should be changed. Anecdotally, most applicants and reviewers support shortening the application. The committee has presented to several internal groups, including the Extramural Program Management Committee (EPMC), which urged broad communication with stakeholders and coordination with those undertaking other changes, such as electronic submission.

Request for Information
Dr. Schneider discussed the draft Request for Information (RFI) to solicit feedback from a wide array of communities. He described sample questions for applicants and reviewers and explained plans for distribution of the RFI. Dr. Cheryl Oros, Director of CSR Planning, Analysis and Evaluation, has offered to analyze the feedback. Adequate information gathering and education of the community make implementation before fall 2007 impractical.

Discussion
Coordinating changes: Dr. Sassaman said this effort is going on at the same time as many other potential changes. She suggested presenting these potential changes as a whole, rather than individually. It is important to coordinate efforts so that the information coming back from the RFI is as helpful as possible. Dr. Finkelstein said the committee is coordinating with the Appendix Committee. Dr. Schneider added the RFI about appendices is still out and no decision has been made, although, on an interim basis, the Appendix Committee recommended eliminating appendices in a standard R01 application. Dr. Kitt clarified a decision has not been made. The committee is determining what kinds of exceptions would be needed. Dr. Ruiz Bravo said many changes are simultaneously under consideration: electronic receipt, multiple PIs on an application, the appendices, shortening the cycle of the review, and shortening the application. Dr. Finkelstein said people involved in these other efforts are adjunct members of the application committee to enable coordination.

Dr. Martinez supported the idea of aligning the application format with review criteria but said he would probably still be unwilling to review 12 applications. In thinking about why not, he said individual workloads have increased. He also said some grants, such as clinical and training grants, may get bigger since what was in the appendix would be included in the application.

Clinical applications: Dr. Brenner said the tools are different between cell and human research, but there are also similarities in developing and asking research questions. It is extremely difficult to write a good quality short application for either type of research. Clinical research would be better off with a shorter application, as long as there is a place to show that the researcher knows how to work with humans and can deal with the protocols. It is important to ensure that innovative research involving humans gets to the floor. Getting at significance in

innovation is important to incorporate into the process, as Dr. Yamamoto discussed in his presentation.

RFI content: Dr. Collins said consideration of the application format is timely, given Dr. Yamamoto's presentation. His model application format could be used in the RFI to ask for input, rather than asking open-ended questions that may be hard to analyze. In terms of including clinical protocols in an application, she said some page limit should be established. Dr. Finkelstein said the RFI would try to strike a balance between presenting a particular model and asking open-ended questions. It will present preliminary proposals, one of which is a 15-page research plan. The open-ended part could capture other ideas but not to the point where an amalgam of useless information results. Dr. McClain said going from 25 to 15 pages would help immensely, and urged presenting formats used by others as examples in the RFI. He strongly opposes putting the design of a clinical trial in the human subject section of an application, because it moves scientific merit into the human subjects section. Dr. Finkelstein said the clinical issue was a subset of unintended consequences that need discussion.

Dr. Mochly-Rosen said the location of a specific example in an RFI influences the responses. She suggested including specific options at the end of the RFI so that people first understand the overall frame and make overall judgments. She also said questions about respondents' experience in reviewing shorter grants would be useful. Those who have reviewed shorter applications do not find it harder than judging longer applications.

Dr. Ramm agreed on the difficulty of writing a short application, but shorter applications really hone in on ideas. She also suggested the RFI apply to all Research Project Grants, not just the R01. Dr. Kitt said NIH reviewers are already familiar with how to review shorter applications. She related anecdotally that some study sections are acculturated into thinking that a longer application is better than a shorter one. Dr. Scarpa said he has received queries from applicants about submitting a 15-page plan, but he said they do so at their own risk for this reason. Dr. Brenner said dealing with regulations makes clinical applications hard to shorten. But the concept, significance, and overall rationale could be dealt with in seven pages.

Community input to the decision: Dr. Yamamoto said it is very important to get community input to make the community aware that the debate is going on within NIH on the issue and to get their views. The details of how questions are structured can have a big influence on results. People resist change, even though they do not like writing or reading 25-page applications. He agreed with Dr. Collins that providing an example of a model would be helpful.

Dr. Yamamoto asked what would happen with the results. Dr. Finkelstein said the committee's recommendations would be responsive to the input. He noted one researcher who supports a short application warned against too dramatic a change to avoid a backlash. Dr. Ruiz Bravo said the decision would be made through NIH governance. She agreed about the benefit of providing models in the RFI, such as lengths and structure of various sections. Dr. Scarpa concluded by observing that PRAC members are enthusiastic about a 7- or 10-page application.

Restructuring of Study Sections Handling Basic Grant Applications in Computational/Structural Biology and in Signaling Biology/Biochemistry

Dr. Schneider remained at the podium to discuss changes to several study sections. Three principles underlie any changes: core values guide the decisions, study sections are monitored continuously, and changes to study sections reflect changes in the science.

In 2004, the biochemistry, physical biochemistry, and physiological chemistry panels closed. Meanwhile, there has been an increase in applications in computational and structural biology. Members of some professional societies in these areas have expressed concern that the degree of clustering is low in areas important to their societies.

Computational Area
To deal with applications in the computational and enzymatic area, a Special Emphasis Panel (SEP) has been operating and dealing with about 45 applications per cycle. The SEP has developed a community and a following, yet has not been vetted by PRAC. In addition, three study sections that focus on macromolecular structure and function, known as MSF-A, -B, and -C, have been reviewing about 300 applications per cycle.

Over the summer, a working group was convened with broad representation from structural and computational biologists. The consensus was the SEP should become a regular study section in the MSF series with a slightly different charge. The group recommended five study sections. The current three would remain the same. A fourth would cluster computational applications like the current SEP does, but emphasize experimental application and validation. A fifth would cluster mechanistic enzymology. He presented possible guidelines for these two new study sections.

Signaling
Currently, the Cellular Signaling and Dynamics (CSD) study section handles about 80 applications per cycle. But across CSR, about 800 signaling applications are handled per cycle, with modest clustering outside of CSD. A working group of scientists in this area was convened and presented with options about how to handle signaling applications. The group suggested creating a new study section and restructuring the CSD study section. They proposed seeding the new section with their members, which, he said, showed their belief in what they proposed.

Dr. Schneider presented proposed guidelines for what would be called the Cellular Signaling and Regulatory Systems study section, reorganized from CSD. A new study section would be called Molecular and Integrative Signal Transduction and would focus on research at the protein and molecular level. He reviewed possible guidelines for this study section.

Next Steps
Dr. Schneider requested PRAC approval to move forward. If granted, the next steps would be to constitute the rosters and launch the new study sections for winter receipt dates and the October 2007 council rounds.

Discussion
Dr. Ramm thanked Dr. Schneider for outlining the thoughtful vetting process that takes place in CSR. Bringing in external scientists is very important. She supported the suggestions. Dr. Leinwand suggested presenting the model of working group members' willingness to seed the rosters to others. Dr. Ruiz Bravo said this process responds to what the community needs. She asked how these changes affect this and other divisions within CSR. Dr. Schneider said internal discussions are taking place. In the fall, three neuroscience IRGs will be reviewed in sequence, which will provide experience in looking at the bigger picture.

Dr. Scarpa said the monthly reviews of IRGs are very informative and are done continuously. As these reviews proceed, they have become more useful. Some study sections are very broad and need to be fixed immediately. Others are very narrow and something needs to be done with them as well.

Dr. Leinwand moved to establish the four new study sections, and the motion passed unanimously.

Conclusion

Dr. Kitt asked for other questions or comments. None were received, so she moved to adjourn the meeting. PRAC adjourned the meeting at 2:42 p.m.

We do hereby certify that, to the best of our knowledge, the foregoing minutes of the August 2006 meeting of PRAC are accurate and complete. The minutes will be considered at the December 2006 meeting of the Advisory Committee, and any corrections or comments will be made at that meeting.

Cheryl Kitt, Ph.D.
Executive Secretary
Peer Review Advisory Committee

Antonio Scarpa, M.D., Ph.D.
Co-Chair
Peer Review Advisory Committee

Jeremy Berg, Ph.D.
Co-Chair
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