Overall Impact Versus Significance Case Studies

DEFINITIONS AND KEY POINTS

Definitions of Overall Impact and Significance are available in the [Overall Impact versus Significance Reviewer Guidance document](#).

FREQUENTLY ASKED QUESTIONS

Frequently Asked Questions are available on the [Enhancing Peer Review FAQ web page](#).

CASE STUDIES

- The following case studies are intended to provide further clarity on the distinction between Significance and Overall Impact.
- They are not meant to be comprehensive or to be interpreted literally.
- Rather, they are intended to provide a conceptual framework for how to think about Significance and Overall Impact.

Case Study #1:

An investigator proposes using a novel method of viral vector-mediated siRNA delivery to knock-down the gene for a particular CNS receptor subtype in specific brain regions he/she hypothesizes to be involved in cognitive aspects of a rare mental illness. He/she proposes to use this method to examine disruption of this receptor subtype on cognitive performance in three animal models of the illness.

Scenario 1:

A. Reviewer 1 is an expert on research of the rare mental illness. He argues that the PI has previously confirmed the proposed hypothesis using pharmacological and genetic approaches. This reviewer felt that the successful accomplishment of the proposed aims would very minimally advance knowledge in the field of study devoted to the rare mental illness. Thus, Reviewer 1 feels the application is of low significance. Reviewer 1 notes that the proposed method is highly innovative, that the models used are appropriate, and that the investigator and environment are strong. Nevertheless, in light of the low Significance of the proposal, Reviewer 1 feels the Overall Impact would be modest and scores accordingly.

B. Reviewer 2 is an expert on viral vector-mediated siRNA delivery methods. He disagrees that the project's significance is low. He concedes that the proposed hypothesis has already been confirmed in the investigator's previous work. He argues, however, that the proposed technique is highly innovative and if successful, has the potential not only to transform the way scientists manipulate receptor function in the laboratory, but also has potential to provide the foundation for clinical application for many diseases. He suggests that the proposed replication of previous findings is actually a strength because it would confirm the successful implementation of the highly innovative methods. Thus, on the basis of the work's potential to transform technical capability and shape clinical practice in the future, Reviewer 2 argues that the application has high Significance. On the basis of high Significance and strengths in the other review criteria, Reviewer 2 believes the Overall Impact should be rated as high.

Scenario 2:
Both reviewers agree that the application addresses an important problem and that the hypothesis and methods are highly innovative. They believe that if the proposed aims were achieved, the project would significantly advance knowledge in the field and promote substantially new research directions in research on the rare mental illness as well as the broader field of mental health. Therefore, they rate Significance as high. They have strong reservations, however, about the application relative to other review criteria. The investigator and his/her colleagues do not appear to have the relevant training and expertise to successfully accomplish the work and there are some flaws in the approach that may reflect their inexperience with critical methods. Therefore, they rate the Overall Impact as moderate.

Case Study #2:

An application proposes to disrupt a well-known signal transduction pathway in mice and see if it results in an increased incidence of a particular type of breast cancer in mice.

Significance: Breast cancer is an important disease in women. However, that alone is not sufficient to say that this project has high significance. The reviewers should evaluate whether this proposed project addresses an important problem in breast cancer or a critical barrier to progress in breast cancer research. For example, will research on this signal transduction pathway in mice advance the concepts, methods, technologies, etc, related to studies of human breast cancer?
- Although breast cancer is a very important disease, the reviewers need to address whether the proposed signaling pathway and the work in mice will be important for understanding, treating, or preventing human breast cancer.
- If the signaling pathway under study is also important in another disease, such as colon cancer, the Significance might be higher, since the results of the project will be more broadly applicable.
- A project that addresses a slow growing type of breast cancer that responds well to existing therapies/treatments would be of lower significance because it is less likely to change clinical practice.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field?
- If the proposed work in mice will strongly predict what is happening in humans, the investigators are highly qualified, the environment is strong, the approach to disrupting the pathway is innovative, and the approach is flawless the project may be likely to have high Overall Impact.
- Even if the pathway and the mouse model are very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the approaches are sound, if the proposed work is not innovative or is confirmatory and duplicates many other published reports, the Overall Impact of the project on breast cancer research might be only moderate to low.
- Even if the topic is very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the project is innovative, the approach may be flawed, reducing the chance of generating useful data, which would reduce the likely Overall Impact on breast cancer research.
- Even if this project is very innovative, well conceived, and likely to have high overall impact, a subsequent project to clone and characterize receptor subtypes for this family of signal transduction molecules may be viewed as having less Overall Impact, since it might not be as innovative. Conversely, such a project might be viewed as

having a greater Overall Impact, since the work is essential to develop a new drug treatment for breast cancer.

Case Study # 3:

An application proposes to develop and test an antidote for a chemical agent in an animal model.

Significance: The potential use of chemical agents in wars or related to terrorist activities is of national security concern. However, the significance of the project depends on how the project will contribute to the development of effective therapeutic agents and/or change therapeutic approach.
- Although such agents may directly affect a very limited number of individuals and the therapeutic agent(s) may have no other uses, the project has the strong likelihood of yielding life saving therapeutic agents should an exposure occur; thus the significance is very high.
- However, if well established clinical practices and multiple effective antidotes are widely available, contribution to the field of development therapeutics for chemical agent exposure will be lower and significance diminished.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field?
- The project resolves an unmet need; there are no effective therapies for this chemical exposure with high mortality. The reviewers might note the highly qualified investigators, flawless methods, an excellent animal model, and therapeutic compounds that will work on various chemical agents - High Overall Impact
- While other therapeutic agents exist, the proposed compounds have numerous advantages in terms of side effect, ease of use and efficacy and will likely be the treatment of choice - High Overall Impact
- The project contributes to the enhancement of the therapeutic arsenal but will not result in major changes to current clinical/therapeutic practices - Medium Overall Impact
- While the idea is significant and sound, methodologies are flawed and investigators have very limited experience in the field. The probability of achieving the goals is low - Low Overall Impact

- Technically sound with good investigators but the animal model has no relevance to human condition - Low Overall Impact.