

## Guidelines for Overall Impact Statements in Critiques

The following information is provided as a guide to preparation of the Overall Impact statement. Samples are provided of Overall Impact paragraphs along with the corresponding preliminary overall impact score.

What should be included in the Overall Impact paragraph?

1. A statement that indicates the purpose of proposed research:

Example: The proposed studies will investigate the mechanisms by which the expression and regulation of activity of protein X occurs in normal individuals and how the alteration of that regulation contributes to development of disease Y.

2. A statement that indicates the likelihood that the project will exert a sustained, powerful influence on the research field involved, stating the actual impact (for example, high, medium or low):

Example: Successful completion of the specific aims will establish a mechanistic link between elevated X and tissue specific injury and will help to develop novel strategies for the prevention and treatment of disease Y. If correct, the principal investigator's hypothesis regarding the potential detrimental effects of some current treatment strategies would have a high impact on the understanding the pathogenesis of Y and alter current clinical practice.

3. Descriptions of the strengths and weaknesses for the application, specifically identifying those which are score driving:

- Strengths or weaknesses in significance or innovation may contribute to your evaluation of the extent to which progress in the field will be "sustained" and "powerful".
- Strengths or weaknesses in approach, investigator, or environment may contribute to your evaluation of whether progress is "likely".

Example of high impact: The preliminary data presented supporting this hypothesis and the studies designed to further test the hypothesis are a major strength of the application. These studies will provide a much clearer understanding of how misregulation of X contributes to disease. Minor weaknesses are evident in the experimental approach; however, the principal investigator acknowledges the problems most and others may be addressed without reducing the impact or feasibility of the project.

## Sample Overall Impact Paragraphs

### Sample 1 - High Impact, Overall Impact Score 2:

This is an application from an accomplished investigator that explores the cell biology of pathostuff; the hypothesis being that calcium positively affects cell cycling resulting in pathostuff. This application will have considerable impact in basic cell biology and in bacterial pathogenesis. Basic insight will be gained into glycoprotein sub-cellular localization. Moreover, the model for pathostuff-mediated enhancement of the Nelson Cycle is paradigm shifting and likely relevant to other pathogen-host interactions. The principal investigator was productive in the previous project period with high impact publications. In the current application, the principal investigator proposes innovative studies on pathostuff intracellular interactions in vitro and in an innovative murine model of pathostuff-mediated disease. The animal studies are not well developed but the investigative team has extensive experience in whole animal studies. Therefore, these experiments should prove successful and could change the current understanding of the involvement of pathostuff in

pathophysiology. Overall, this application will have high impact in basic cell biology and in bacterial pathogenesis.

**Sample 2 - High Impact, Overall Impact Score 1:**

This application will discover how the distinct subunits of the Widget complex regulate protein degradation in a substrate-specific manner. Overall, there is no doubt that the results of this project will have a major lasting impact on the protein degradation field since the mechanism by which the Widget complex mediates substrate specificity is a major gap in knowledge. The application reflects the principal investigator's extraordinary depth in attacking questions of fundamental importance and his preeminent role in shaping the field. This is also reflected by the world-class group of collaborators. The experiments are exceedingly clever, well supported by published findings, highly innovative both conceptually and experimentally, and fundamentally important both in their relevance to basic biology and clinical implications. The principal investigator has carefully addressed nearly all previous concerns by redirecting several aims and carefully addressing previously noted weaknesses.

**Sample 3 - High Impact, Overall Impact Score 2:**

This application seeks to understand the mechanism of compound X in vascular remodeling as it relates to hypertension. The principal investigator provides strong evidence that hypertension increases compound X levels and that decreasing these levels through treatment mitigates the side effects induced by hypertension. These studies are highly significant from mechanistic standpoint with regard to therapy of some forms of hypertension. The principal investigator is a well trained, promising investigator with an excellent record in this field. The senior scientists recruited by the principal investigator as collaborators have complementary expertise and are critical for the success of this project. The studies proposed investigate the mechanistic pathway by which treatment with drug Y decreases compound X, and in turn hypertension. These studies are a strength of the application and should provide insights that could explain the results of recent clinical trial. Overall, the studies are based on an innovative hypothesis, are supported by strong preliminary results, and are likely to provide new knowledge, which will have a significant impact on current understanding of vascular remodeling in hypertension, an important clinical problem.

**Sample 4 - Moderate Impact, Preliminary Overall Impact Score 5:**

The proposed studies are designed to use differentiated cardiac muscle and examine scaffold proteins involved in the regulation of both calcium-dependent and calcium-independent contraction and in the regulation of phenotype switching. Obtaining a clearer picture of the spatiotemporal regulation of signaling systems is a highly significant goal that can potentially move this complex field forward. The use of differentiated cardiac muscle cells to identify scaffolding has several important regulatory factors as they apply to the regulation of contraction is novel. The principal investigator has been very productive, is highly qualified to undertake this project, and the environment is excellent. The principal investigator proposes multiple techniques designed to provide definitive information about molecular interactions and regulation. The scope of the experiments was quite expansive and lacked cohesiveness (other than the theme of scaffold proteins), making evaluation of the proposed studies difficult. Overall, this application is likely to have moderate impact on current understanding of the regulation of calcium-dependent and -independent scaffold proteins and regulation of phenotype switching.

**Sample 5 - Moderate Impact, Overall Preliminary Impact Score 5**

The project would address the challenge of detecting and quantifying low levels of cancer biomolecule X in urine samples by a noninvasive assay that utilizes a novel, synthetic probe with phosphorescence detection. Such an assay would have the potential to impact the diagnosis of cancer if successfully completed. Though the team of investigators is expert in their areas, and the principal investigator is well qualified to lead the project, they could benefit from the addition of clinical expertise. The approach, though promising, has some weaknesses. While preliminary data is not required, a simple model of the proposed probe and its tagging mechanism based on known literature would have been helpful. Missing from the proposal is any discussion on the scale-up of the assay and how this relates to the feasibility and cost of the diagnostic assay. Additionally, the discussion is weak on how the presence of interferents in urine will affect the measurement, that is, non-specific adsorption of proteins could give false positives. These issues moderately detract from the overall impact of this high-risk yet high reward project.

**Sample 6 - Moderate Impact, Overall Preliminary Impact Score 5**

This application describes further advancements in technology X for studies of membrane proteins. The availability of methods to characterize structure-function relationships is extremely important for basic biochemical studies of cell function. Significant advances in the analytical methodology were achieved in the previous funding period. The proposed work could potentially impact many fields, including structural biology, drug screening/discovery, and protein engineering. Additional strengths of the proposal include the investigator and the approach. Significant weaknesses are the moderately low innovation (technology X is not new), lack of quantitative goals and analytical figures of merit, and it is not clear where this program will lead in the long-run, i.e. what is the deliverable. These lessened the anticipated impact of the proposed project.

**Sample 7 - Low Impact, Overall Impact Score 7:**

This prospective study will collect clinical data regarding the progression of Elder's disease in an aging cohort. Elder's disease is an important cause of organ failure in the elderly and there is a need for prospective data collection in this disease. However, the proposed study design will yield mostly incremental information. Therefore there will be limited impact on either the field of the physiology of aging or on geriatric clinical practice. This project draws upon Dr. Orange's basic physiology background and Dr. Indigo's clinical research experience. There is concern, however, that the study might not be sufficiently powered. Confounding variables such as medication use are not considered. The research strategy does not directly address the hypotheses and will yield limited new information.

**Sample 8 - Impact Low, Preliminary Overall Impact Score 7:**

The project addresses the potential value of combined versus independent intervention strategies in the treatment of asthma in children of different ethnicity. This is an important area of research given the high prevalence and sub-optimal management of asthma in children of some ethnic groups. The principal investigator is well suited for the project given her prior training, and prior work in this area. The team has an impressive record of collaborating with stakeholders and working within the community to successfully implement and modify evidence-based interventions. However, the record of original research publications is modest. Several weaknesses with the approach tempered enthusiasm for the proposed work. While the investigators refer to their preliminary work as evidence of their ability to recruit and intervene in the community, there were no clinical outcomes from the prior studies presented as preliminary data. In addition, given the proven efficacy of the two-component interventions, the additional benefit and innovation of this new project is likely to be modest. Other concerns include difficulty in interpreting data

from the quasi-experimental design to compare arms across the two studies, the potentially unreliable one-year recall of health expenses by participants and the lack of description for how the ABC data will be used if the data are not patient linked. Despite the need to develop new effective intervention strategies for this patient population, the weaknesses in the experimental design and data interpretation limit the potential impact of the proposed work on developing strategies for treatment of asthma in children of various ethnic backgrounds.

**Sample 9 - Low Impact, Overall Preliminary Impact Score 8**

Dr. XXX has previously characterized the role of Protein Y (pY) in endoplasmic reticulum (ER)-associated degradation and demonstrated that prolonged ER stress induces pY expression. The principal investigator now hypothesizes that pY promotes autophagy of irreversibly aggregated proteins that accumulate in the ER in response to prolonged ER stress. If this hypothesis is correct the proposed studies would be highly significant and the investigative team is uniquely positioned to conduct the studies since they have the requisite combination of expertise. However, it is unlikely that new mechanistic insight into pY function will be unveiled and that the proposed studies will lead to ground-breaking discoveries in the ERAD or autophagy fields due to major weaknesses in the experimental approach. The methodology primarily relies on light microscopy to evaluate protein co-localization, an approach that lacks adequate resolution to generate meaningful data. The planned electron microscopy will not identify the abundance of ER, making the needed morphometry analysis impossible to do. There is no plan to explain how the data will be interpreted. Further, the studies rely primarily on pY overexpression, which is non-physiological. There is also concern whether the proposed knockdowns will, themselves, activate ER stress pathways. Overall, the studies as currently designed are not likely to have a significant impact on understanding of ER stress pathways.

May 9, 2011