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SUMMARY
The proposed research study will facilitate the improvement of the education and career goals of the principal investigator (PI). Moreover, the PI will investigate the mechanisms that underlie reduced cardiac fatty acid oxidation during sepsis. The PI has set up an educative plan for the first two years (K99 phase) of the proposed study. This plan includes courses about bioinformatics tools, grant writing and responsible conduct of research. In addition, the PI will be trained in research techniques by his mentor and other experts, who are members of his advisory committee. The PI will perform experiments to investigate mechanisms that can increase cardiac fatty acid oxidation and will suggest therapeutic approaches for the treatment of cardiac septic shock. Upon conclusion of the mentored phase the PI will have established a pool of data, knowledge and new skills that will enhance his credentials for successful transition to independence.

During the K99 phase the PI has planned to attend one course on Biomedical Informatics, one on grant writing and another in the responsible conduct of research. In addition, he has set up a training plan with his mentor and his advisors/collaborators that will provide him with technical knowledge on how to perform echocardiography, induction of heart failure in animal models, chromatin immunoprecipitation and high throughput analysis tools and methods. These techniques represent useful tools that he will be able to transfer to his own lab. Besides the new techniques that he will acquire, the proposed project requires knowledge in areas that he has only recently been associated with, such as inflammation and Krüppel-like factor biology. Therefore, he has included in his advisory board a number of scientists with outstanding careers in these particular fields that will provide guidance of the highest possible level. All his advisors are employed by topnotch academic departments. They have agreed to invite the PI to present his work within their institutes, so that he receives input by a broad scientific audience and expands his scientific network. This will promote his transition to an independent research position and provide him a robust scientific foundation from which to apply for R01-level funding.

The proposal core questions are: (1) Can stimulation of energy production prevent LPS-mediated cardiac dysfunction? (2) How does LPS lead to changes in cardiac energetics? (3) How can the reduction in FAO be prevented in LPS treated animals? To address these questions the PI has designed an experimental plan with two branches. The first falls into the K99 phase and is based on preliminary data of the current submission. This set of experiments aims to identify the mechanism that makes PPARγ a more potent activator of fatty acid oxidation when PPARα is downregulated, like it happens in sepsis. Also, the PI will investigate the role of the JNK signaling pathway, which is activated by sepsis, in the reduction of the expression of PPARα, a protein that has been strongly associated with fatty acid oxidation. Furthermore, a new animal model with cardiomyocyte specific deletion of KLF5 will be generated and tested for resistance to cardiac dysfunction during sepsis. Besides, this novel animal model will be characterized with high throughput analysis methods and new targets may come up. The second branch of his plan falls into the R00 phase. Certain interventions that have been used successfully in the preliminary results and prevent sepsis will be explored for their therapeutic potential in heart failure. The elucidation of the mechanisms that will be investigated in the K99 phase will also identify new targets and may suggest novel approaches for the treatment of sepsis. Application

of these successful interventions, as well as targeting of new factors that the high throughput analysis is going to indicate will be used to prevent sepsis-mediated cardiac dysfunction, as well as to treat other conditions of cardiac dysfunction with impaired fatty acid oxidation, such as pressure overload heart failure. Therefore, after his training in new technologies and generation of heart failure models, his transition to independent position will be facilitated due to his increased capacity to apply methods that prevent sepsis-associated cardiac dysfunction and pressure overload heart failure, aiming to provide novel treatments for these diseases.

Overall, the current proposal will equip the PI with novel knowledge and useful tools to continue for independent career in molecular cardiology and stress signaling. His training plan has been designed to facilitate flawless production of data in the prominent environment of the Department of Medicine of the Columbia University, as well as the PI's acquaintance with modern tools of biomedical research that he will transfer to his independent laboratory. Approval of his application for the K99R00 award will result in the precise definition of novel mechanisms, which affect cardiac fatty acid oxidation and will thereby provide potential new therapeutics for the treatment of septic shock and heart failure.