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Judith H. Greenberg, Ph.D.
National Institute of General Medical Sciences (NIGMS)
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Re: Request for Information: Strategies for Advancing Sepsis Research Supported by NIGMS (NOT-GM-18-039)

Dear Dr. Greenberg:

The Association of American Medical Colleges (AAMC) appreciates the opportunity to offer comments related to strategies for advancing sepsis research supported by NIGMS. Founded in 1876 and based in Washington, D.C., the AAMC is a not-for-profit association dedicated to transforming health care through innovative medical education, cutting-edge patient care, and groundbreaking medical research. Its members are all 151 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems, including 51 Department of Veterans Affairs medical centers; and more than 80 academic societies. Through these institutions and organizations, the AAMC serves the leaders of America's medical schools and teaching hospitals and their more than 173,000 full-time faculty members, 89,000 medical students, 129,000 resident physicians, and more than 60,000 graduate students and postdoctoral researchers in the biomedical sciences.

The AAMC recognizes the importance of advancing sepsis research. Sepsis is a tremendous public health problem, with more than 1.5 million cases per year and on the order of 250,000 deaths (https://www.cdc.gov/sepsis/datareports/index.html), reflecting in part the increasing number of immunocompromised patients, the complexity of the pathogenic process, and the fact that sepsis can be triggered by a wide range of microbial organisms, including some like *Serratia* that were long felt to have little intrinsic potential for virulence. Although advances in critical care have improved treatment of sepsis, several pharmacologic treatments in clinical development have been unsuccessful, despite promising early stage research results. If there has been a flaw in the approach to sepsis research, it may be from the erroneous belief that there is a single linchpin that can be addressed therapeutically, rather than an acceptance that multiple systems are going awry at the same time. This complexity is why animal models must be one of the primary avenues of exploration.

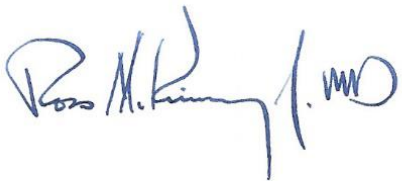
There has been a broad and sustained interest across the spectrum of research in understanding the relationship of infection and injury to sepsis. Understanding sepsis requires study of the interactions of the immune system and the host organism it is trying to protect, since studies of these interactional elements are more important than the nature of the pathogens themselves. Sepsis can be triggered by exotoxin producing organisms like *Staphylococcus aureus*, or more classically by the endotoxin containing gram negative rods. A critical issue in the broad design of an approach to understanding sepsis and designing more effective treatments is the complexity of the disease process. Although we simplify the description of the disease state by giving it a single word name, "sepsis," the clinical condition is a classic example of a complicated multi-organ, multi-system condition, with multiple pathways all leading to the same end result.

Sepsis research requires a mix of fundamental and clinical research, and recognition that fundamental research alone cannot provide researchers with the complex, systems-based nature of the condition. *In vitro* research that explores one element at a time may be useful, but does not provide researchers with a complete picture of the confounding factors that complicate attempts to develop effective treatments for sepsis. *In silico* research makes assumptions about the nature of predicted interactions that may or may not be true – we lack a sufficient understanding so that computer models will be anything more than very primitive. Human investigation is very important, but almost any human sepsis research is confounded by the nature of who gets sepsis, the wide range of pre-existing conditions that make individuals susceptible. In addition, the timing of sepsis is not sufficiently predictable to know when someone will develop the condition, missing the opportunity to see the earliest, critical stages of the disease process. We are, therefore, left dependent on animal models. The challenge in animal modeling is that research organisms are not perfect mimics for humans, particularly when it comes to studies of interventions, and most particularly with murine models (Seok, et al, Proc. Natl. Acad. Sci. USA. 110, 3507–3512). Nevertheless, animal research is necessary to study of the early stages of the disease process, and it is in the early stages, before the full storm of the inflammatory cascade erupts, that intervention is most likely to succeed.

Sepsis is one of the complicated conditions where animal models hold the most promise for advancing our knowledge of the disease and its management. While we do not specify which animal model is most useful, it is our belief that the issues of timing and complexity make animal models more likely to be productive for the long-term end of understanding and treatment of sepsis. A commitment to ensuring the availability of funding and support for animal model in the study of sepsis is key and does not detract from opportunities also to learn important lessons by studying pathogenic microbes, elements of the immune system, vascular endothelial function, platelet and leukocyte function, and other elements in the pathogenesis of sepsis. Advancing the understanding of sepsis by studying the human immune response is also important, as are clinical trials that attempt to modify the disease process.

The AAMC is appreciative of the NIGMS's commitment to engaging the relevant stakeholders to advance sepsis research and would be happy to engage with our member institutions and work with the agency as it moves forward. Please feel free to contact me or my colleague, Heather Pierce, Senior Director for Science Policy and Regulatory Counsel at hpierce@aamc.org or (202) 478-9926 with any questions about these comments.

Sincerely,



Ross E. McKinney, Jr., MD
Chief Scientific Officer