The Translational Value of Rodent Models of Sepsis

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Sepsis remains a major cause of morbidity and mortality worldwide (1), but progress in identifying effective therapies has been slow (2), reflecting not only the variability of the clinical manifestations of sepsis (e.g., shock, renal failure, respiratory failure, coagulopathy) but also the patient-level biological heterogeneity and complexity of the pathogenic processes responsible for varied clinical manifestations. Although there is a widely accepted need for more research into the clinical heterogeneity of sepsis in both patients and animal models (https://www.nigms.nih.gov/News/Documents), the value of animal models to this research effort has been questioned by some investigators on the basis of differences in genomic responses between animals and humans (3), whereas others have stressed the importance of animal models and the need for further refinements (4, 5). This *Viewpoint* addresses the value of small animal models in both forward- and reverse-translational investigations of sepsis, with specific attention to their importance in advancing the understanding of disease pathogenesis and preclinical testing of new therapeutics, as well as efforts to improve the relevance of rodent models for the problem of human sepsis.

Many, but not all, biological responses to sepsis and severe infection are evolutionarily conserved in mice, rats, and humans. Although some genomic responses differ, there are similarities between proteomic, lipidomic, and glycomic signatures in mice and humans (3, 6, 7). Mice have been invaluable in dissecting human responses to infection, including the Nobel Prize–winning discovery of Toll-like receptors (8). Moreover, rodents with sepsis develop acute organ failures, such as respiratory failure and shock, and demonstrate heterogeneity in organ injury, as seen in humans.

Given these important similarities, rodent models of sepsis have contributed to the scientific foundations of (and justification for) human studies that have led to fundamental advances in therapy of critically ill patients. Rat and mouse models provided the critical preclinical evidence (9, 10) that led to the landmark clinical trial of lung-protective mechanical ventilation for acute respiratory distress syndrome, a common sequela of sepsis, which identified a 9% absolute decrease in mortality (40–31%) (11). Mouse models of sepsis demonstrated the potential value of glucocorticoids (12), providing preclinical evidence supporting a recent clinical trial that reported the major morbidity and mortality benefit of hydrocortisone in severe community-acquired pneumonia with sepsis in critically ill patients (13). Mouse studies have provided important evidence about the importance of cytokine-dependent pathways in sepsis and organ injury, including the importance of the IL-6 pathway, the blockade of which has proven to benefit severe coronavirus disease (COVID-19) pneumonia (14). Furthermore, mouse models were critical for developing vaccines and antiviral therapies necessary to respond to COVID-19 (15).

Like all models, rodent models of sepsis have limitations (4, 5). Rodent models do not typically incorporate the many clinical comorbidities seen in patients or the treatments used in clinical care, including mechanical ventilation, vasopressors, and nutrition. However, efforts are being made to model comorbidities in mouse experiments, including using mice of younger and older ages; mice of different genders; and mice with diabetes, obesity, or cigarette smoke exposure, to more closely mimic the heterogeneity of human sepsis (16). In addition, the clinical value of rodent models has improved with the ability to monitor oxygenation and include antibiotics and fluid therapy (17). Animal models are sometimes criticized for lack of individual heterogeneity, but the ability to modify a single aspect of human heterogeneity in mice is actually a strength of the models, making them ideal for reverse-translation. For example, recent work in pediatrics illustrates how clinically identified biomarkers in children with sepsis can be reverse-translated to mice with experimental sepsis, with the results subsequently translated back to humans. Mice identified as having a high risk for mortality using the clinical biomarkers had a greater bacterial burden and could be rescued with higher doses of antibiotics, providing biological support for the hypothesis that high-risk critically ill children with septic shock may benefit from higher antibiotic doses (18).

Just as there is no stereotyped natural history of human sepsis, there is not a perfect

(Received in original form August 26, 2023; accepted in final form December 11, 2023)

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Am J Respir Crit Care Med Vol 209, Iss 5, pp 488–490, Mar 1, 2024

Originally Published in Press as DOI: 10.1164/rccm.202308-1489VP on December 13, 2023
Internet address: www.atsjournals.org

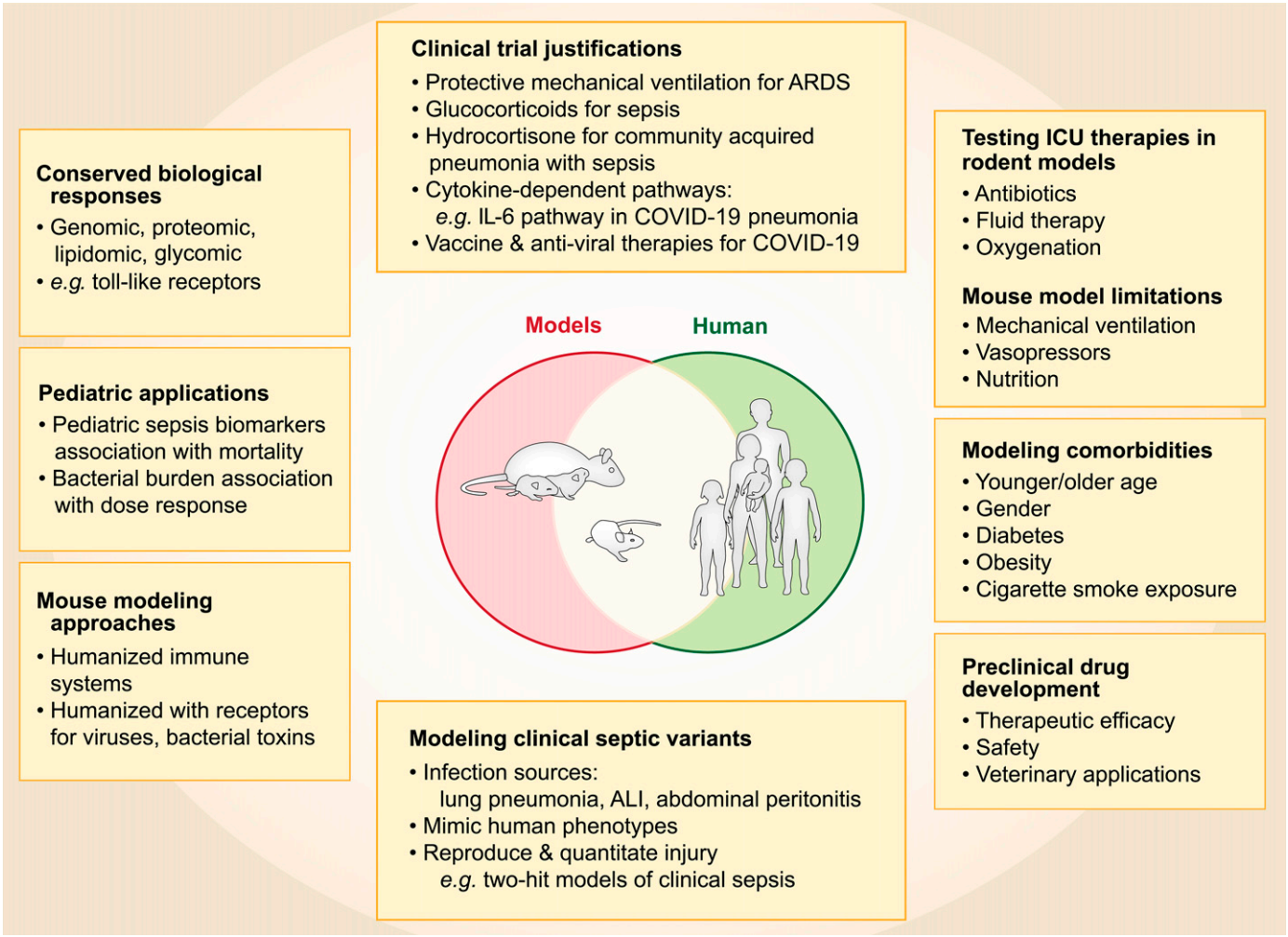

Figure 1. The translational value of rodent models for human sepsis. ALI = acute lung injury; ARDS = acute respiratory distress syndrome.

animal model of human sepsis (3–5). Indeed, research in sepsis benefits from the complementary use of different animal models, varying the source of infection (lungs as in pneumonia and acute lung injury, the abdomen as in peritonitis) to reflect the different clinical disorders that cause human sepsis. Thus, rodent models can be selected to mimic the specific human sepsis phenotype being investigated and should include key quantitative and reproducible measures of injury (19).

"Humanized" mice that are genetically modified with a humanized immune system or human receptors for viruses and/or bacterial toxins augment relevance to human sepsis and syndromes such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections (20). Although there is a high degree of similarity between mouse and human genomes, the specific gene clusters in mice that best simulate the response to sepsis in humans are still uncertain, providing a rationale for this experimental approach.

In therapeutic drug development, rodent models provide valuable preclinical testing of new therapies and help to identify candidates for clinical testing in humans. Rodent models enable early critical evaluation of the safety and potential efficacy of new therapeutics for sepsis and other diseases, although predicting efficacy in humans with sepsis has been difficult. Nevertheless, without these preclinical models, direct human testing would be necessary for the initial development of novel therapeutics, which would increase the risk of toxicity in early-phase human studies that could have been prevented with the use of appropriate animal models. Additionally, veterinarians taking a "One Health" approach have translated data collected from rodent models of sepsis to the clinical management of severe infections and sepsis in cats, dogs, horses, and other animals (21). Thus, rodent models of sepsis have direct benefit to domestic animal species, in addition to humans.

Animal welfare in research is stringently protected by local and national animal research committees to minimize the distress and suffering of rodents and other animals used in research. Investigators must include a specific plan for vertebrate animal protection as part of the rigorous peer-review process for NIH and other federal grant applications. Once a research program is approved and funded, investigators must comply with three levels of oversight. The first is that of the local institutional animal care and use committee,

which oversees and approves all animal research at an institution. The second is the NIH Office of Animal Welfare, which helps local institutional animal care and use committees interpret and enforce NIH Public Health Service policy, including the Guide for the Care and Use of Animals. The third is the international oversight provided by the Association for Assessment and Accreditation of Laboratory Animal Care International, which provides accreditation and oversight of animal research programs at most NIH-funded institutions.

In summary, rodent models have made important contributions to the understanding and treatment of sepsis and acute lung injury. In addition, improved rodent models using rapidly evolving genetic and molecular technologies, clinically relevant comorbidities, and appropriate safeguards for animal care will continue to be very important for future research in sepsis and other critical illnesses (Figure 1). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Diana Lim for the preparation of Figure 1.

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