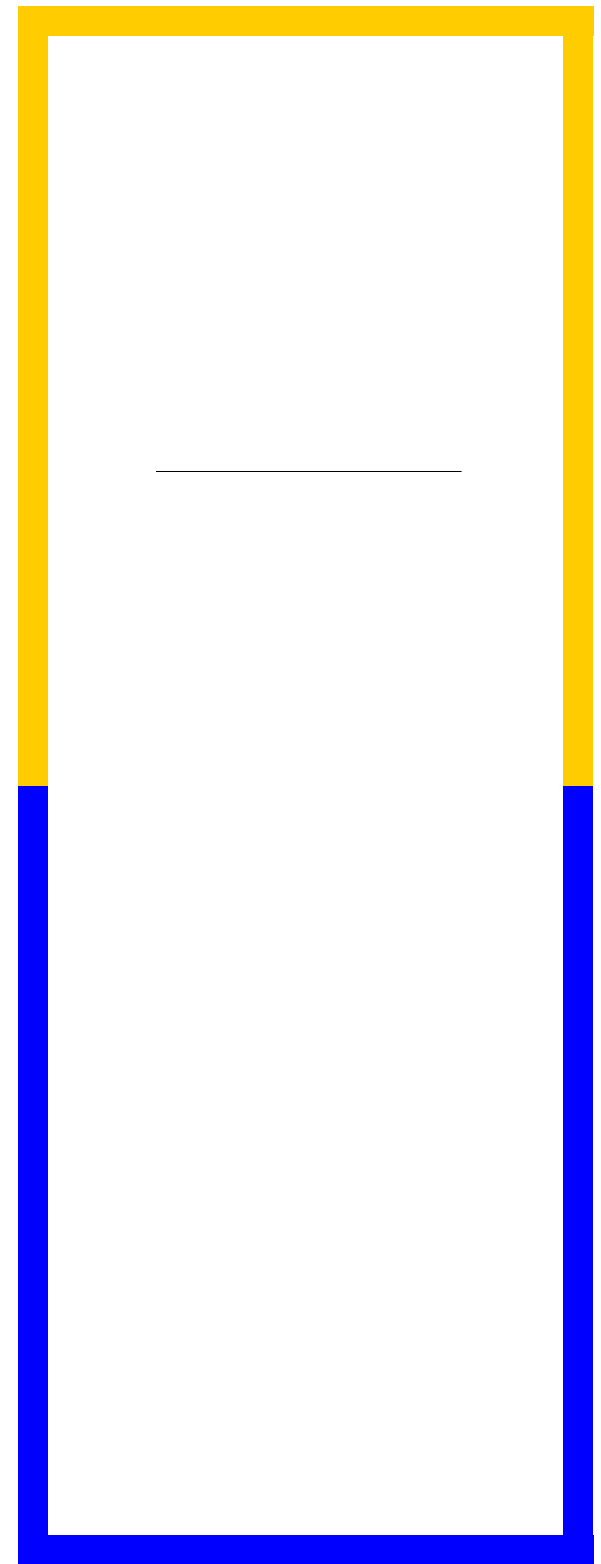


Sepsis is a process of severe immune dysregulation resulting from pathogenic disruption of immune homeostasis, leading to damage of multiple organ systems and high mortality. Case-fatality rates range from 10% to 60% or higher, with \$24 billion spent yearly on sepsis in the United States alone. In addition, organ damage and continued immune insufficiency require hospital readmission in nearly 50% of severe sepsis survivors within 6 months. Current symptomatic treatments, while effective to a certain degree even in cases of severe sepsis, do not address the mechanisms of sepsis or prevent complications in survivors. Immunosuppressive treatments also fail to address the dysregulation that causes sepsis, and may increase the rate of metabolic and cardiovascular issues after treatment is completed. Utilizing a novel drug-screening method, we have found that retinoic acid (RA) significantly upregulates the anti-inflammatory protein MAP kinase phosphatase 1 (MKP-1). Our experiments show that RA has significant beneficial effects on both sepsis and endotoxemia. RA, which is used to treat diverse diseases due to its ability to re-regulate the immune system, significantly reduces morbidity and mortality of early sepsis in two mouse models. RA, when administered in a true bacterial sepsis model, significantly reduces mortality by 75% in mice, and significantly reduces both visible lung damage and neutrophil infiltration into the lungs. Levels of pro-inflammatory cytokines are reduced in mouse organs and serum, indicating systemic pro-regulatory effects. In addition, RA significantly reduces pro-inflammatory cell signaling, downregulating the transcription, translation, and/or translocation into the nucleus of pro-inflammatory proteins in human and mouse cells. While the mechanisms of these ef-



AWARDS/ LEADERSHIP

- —College of Medicine and Life Sciences Representative, University of Toledo Graduate Student Association

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Dolin HH

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FUTURE PLANS