1521-0103/389/3/289–300$35.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

dx.doi.org/10.1124/jpet.123.002095
J Pharmacol Exp Ther 389:289–300, June 2024

Minireview

The Prospect of Biomimetic Immune Cell Membrane-Coated Nanomedicines for Treatment of Serious Bacterial Infections and Sepsis

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Received December 24, 2023; accepted March 7, 2024

ABSTRACT

Invasive bacterial infections and sepsis are persistent global health concerns, complicated further by the escalating threat of antibiotic resistance. Over the past 40 years, collaborative endeavors to improve the diagnosis and critical care of septic patients have improved outcomes, yet grappling with the intricate immune dysfunction underlying the septic condition remains a formidable challenge. Anti-inflammatory interventions that exhibited promise in murine models failed to manifest consistent survival benefits in clinical studies through recent decades. Novel therapeutic approaches that target bacterial virulence factors, for example with monoclonal antibodies, aim to thwart pathogen-driven damage and restore an advantage to the immune system. A pioneering technology addressing this challenge is biomimetic nanoparticles—a therapeutic platform featuring nanoscale particles enveloped in natural cell membranes. Borne from the quest for a durable drug delivery system, the original red blood cell-coated nanoparticles showcased a broad capacity to absorb bacterial and environmental toxins from serum. Tailoring the membrane coating to immune cell sources imparts unique characteristics to the nanoparticles suitable for broader application in infectious disease. Their capacity to bind both inflammatory signals and virulence factors assembles the most promising sepsis therapies into a singular, pathogen-agnostic therapeutic. This review explores the ongoing work on immune cell-coated nanoparticle therapeutics for infection and sepsis.

SIGNIFICANCE STATEMENT

Invasive bacterial infections and sepsis are a major global health problem made worse by expanding antibiotic resistance, meaning better treatment options are urgently needed. Biomimetic cell-membrane–coated nanoparticles are an innovative therapeutic platform that deploys a multifaceted mechanism to action to neutralize microbial virulence factors, capture endotoxins, and bind excessive host proinflammatory cytokines, seeking to reduce host tissue injury, aid in microbial clearance, and improve patient outcomes.

Introduction

Accurately assessing the global burden of sepsis is challenging due to frequent changes in its definition (Bone et al., 1992; Levy et al., 2003; Singer et al., 2016). Nevertheless, a meta-analysis of studies from high-income countries estimates that there are over 50 million cases of sepsis worldwide each year (Fleischmann et al., 2016). Although sepsis manifests as a highly heterogeneous disease, it typically originates from an inciting infection. Findings from the Sepsis Occurrence in Acutely Ill Patients, Extended Prevalence of Infection in Intensive Care II, and Intensive Care Over Nations studies consistently indicate that a substantial number of these infections originate in the lung or abdomen (Vincent et al., 2006, 2009; Sakr et al., 2018). Furthermore, consensus across these studies highlights the prevalence of specific pathogens: *Staphylococcus aureus* emerges as the most common Gram-positive organism, whereas *Escherichia coli* and *Pseudomonas aeruginosa* stand out as the

This work was supported in part by grants from the National Institutes of Health National Institute of General Medical Sciences [Grant K12GM068524] (to A.H.); the National Institutes of Health [Grant R01AI176554] (to A.H.); the National Institute of Allergy and Infectious Diseases [Grant T32AI007469]; and the CARB-X Accelerator.

V.N. serves on the Scientific Advisory Board of Cellics Therapeutics, which is developing membrane-coated nanotherapeutics for medical applications; the company had no role in the content of this manuscript. A.H. declares no conflicts of interest.

dx.doi.org/10.1124/jpet.123.002095.

ABBREVIATIONS: ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; CD47, integrin associated protein; DIC, disseminated intravascular coagulation; IL, interleukin; LPS, lipopolysaccharide; MAb, monoclonal antibody; M-NP, macrophage membrane-coated nanoparticle; NET, neutrophil extracellular trap; N-NP, neutrophil membrane-coated nanoparticle; PEG, poly(ethylene glycol); PLGA, poly(lactic-co-glycolic acid); P-NP, platelet membrane-coated nanoparticle; RBC, red blood cell; RBC-NP, red blood cell membrane-coated nanoparticle; ROS, reactive oxygen species; T3SS, type III secretion system; TC-NP, T cell membrane-coated nanoparticle; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha.

most prevalent Gram-negative isolates. A seemingly straightforward infection can progress to sepsis when the host's immune response fails to control the infection, leading to a self-destructive hyperinflammatory state. Even with effective antibiotic administration, this hyperinflammatory state can culminate in organ failure and death in the most severe cases. The ongoing rise of antibiotic-resistant strains has only heightened the urgency to discover effective management strategies for these perilous medical conditions (Singer et al., 2016).

Despite advances in supportive care, the occurrence of organ failure continues to serve as a robust predictor of sepsis mortality (Metnitz et al., 2001; Blanco et al., 2008). In a recent multicenter study, respiratory and cardiovascular failure emerged as the most common types of organ failure, and their combination detrimentally impacts systemic oxygenation, playing a pivotal role in determining sepsis outcomes (Blanco et al., 2008). Severe sepsis poses a particularly life-threatening scenario for pediatric and geriatric populations, with predicted in-hospital mortality rates of 25% and 48%, respectively (Weiss et al., 2015; Martin-Loeches et al., 2019). Even among survivors, severe sepsis can lead to persistent cognitive and physical limitations that endure for years after hospital discharge (Iwashyna et al., 2010). Initiatives by organizations such as the World Health Organization and the Surviving Sepsis Campaign have significantly enhanced sepsis diagnosis and supportive care (Rhodes et al., 2015; World Health Organization, 2020; Evans et al., 2021). Current supportive therapies encompass fluid resuscitation, vasoactive medications, mechanical ventilation, as well as blood products and corticosteroids in specific situations (Evans et al., 2021). Beyond supportive therapy, sepsis treatment revolves around antimicrobial agents. The guidelines from the Surviving Sepsis Campaign underscore the critical importance of promptly administering antibiotics and removing any identifiable sources of infection, such as catheters (Evans et al., 2021). Specific sepsis therapies targeting the dysregulated immune response are currently lacking. Despite the impressive progress made in supportive therapies, sepsis mortality and disability rates remain high, underscoring the urgent need for innovative treatments. A shift toward therapeutic strategies addressing the dysregulated immune response could present promising avenues for improving outcomes in sepsis.

Septic Inflammation: A Double-Edged Sword. The initial definition of sepsis classified it as part of a broader condition known as systemic inflammatory response syndrome (Bone et al., 1992). Despite multiple updates to its definition, the close association between sepsis and systemic inflammation remains paramount. In patients with sepsis, elevated inflammatory cytokines are closely linked to organ dysfunction and mortality (Damas et al., 1989, 1992; Pinsky et al., 1993; Bozza et al., 2007). In mouse models, these cytokines have been implicated in acute kidney and lung injuries (Cunningham et al., 2002; Nechemia-Arbely et al., 2008; Ahuja et al., 2012; Bhargava et al., 2013; Xu et al., 2014). Notably, mice lacking inflammatory cytokines or certain inflammatory pathways exhibit resistance to endotoxemia models of sepsis (Pfeffer et al., 1993; Böhrer et al., 1997; Cunningham et al., 2002). However, when confronted with live bacterial or viral infections, mice deficient in the cytokines tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 (IL-6), two key inflammatory cytokines, show poorer control of the infection (Pfeffer et al., 1993; Kopf et al., 1994). This underscores the dual role of inflammatory cytokines in coordinating the immune response—they are crucial for infection control, but prolonged excessive inflammation has detrimental effects on organ function. Consequently, anti-inflammatory therapy in sepsis must strike a delicate balance to preserve an effective immune response while limiting organ damage.

The early conceptualization of sepsis as an inflammatory disease led to the emergence of a first wave of immunomodulatory sepsis therapies that aimed to mitigate inflammation by obstructing inflammatory cytokines. Despite encouraging preclinical outcomes, all of these therapies faced disappointment in clinical trials. Anti–TNF-α monoclonal antibodies (MAbs) (Fisher et al., 1993; Abraham et al., 1995, 1998; Dhainaut et al., 1995; Cohen and Carlet, 1996; Clark et al., 1998), antibody fragments (Reinhart et al., 1996, 2001), and soluble TNF-α receptors (Fisher et al., 1996) did not demonstrate improved survival in human studies. Similarly, IL-1 receptor antagonists, although initially displaying promise, proved ineffective in improving 28-day mortality in larger clinical trials (Fisher et al., 1994a,b; Opal et al., 1997). Furthermore, efforts targeting other specific sources of heightened inflammation, such as oxidative stress and eicosanoids, yielded no significant improvement in the survival of sepsis patients (Bernard et al., 1997; Patel et al., 2012; Sakr et al., 2014).

Anti-Toxin Therapy. Pathogenic bacteria exhibit a spectrum of virulence factors that empower them to evade or neutralize the host immune system (Johnson, 1991; Zecconi and Scali, 2013). When targeted against these virulence factors, MAb therapy holds the potential to augment the immune system's capacity to clear the infection while simultaneously mitigating damage to non-immune cells. Encouragingly, human trials involving MAbs against *Clostridioides difficile* toxins have already demonstrated a reduction in the recurrence of colitis caused by this pathogen (Lowy et al., 2010). This success has spurred ongoing endeavors to develop MAb anti-toxin therapies for other pathogens responsible for the majority of sepsis cases, including *S. aureus*, *E. coli*, and *P. aeruginosa*.

In *S. aureus* infection, α-toxin, also known as α-hemolysin, plays a significant role in inducing host cell death and immune dysfunction (Tkaczyk et al., 2013; Scherr et al., 2015). This potent virulence factor targets host cells by binding to a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) expressed on the host cell surface. Studies have revealed that mice deficient in ADAM10 are protected against lethal *S. aureus* infections, underscoring the importance of α-toxin's interaction with ADAM10 in the pathogenesis of the infection (Inoshima et al., 2011). Researchers have been exploring the use of MAbs targeting α-toxin as a potential therapeutic approach with promising results in preclinical models. In a pneumonia model, anti–α-toxin MAbs improved survival, and in a dermonecrosis model, these MAbs reduced the size of skin lesions (Ragle and Bubeck Wardenburg, 2009; Tkaczyk et al., 2012). Early human trials of two distinct monoclonal anti–α-toxin therapies have demonstrated good tolerability, paving the way for ongoing analysis in larger randomized controlled trials (François et al., 2018, 2021).

In contrast to the free release of α-toxin by *S. aureus*, the opportunistic pathogen *P. aeruginosa* employs a type III secretion system (T3SS) to directly inject toxins into host cells (Hauser, 2009). Strains of *P. aeruginosa* possessing the T3SS are more likely to infect humans and are associated with

poor clinical outcomes (Hauser et al., 2002; Ledizet et al., 2012). In mouse models, the attenuation of *P. aeruginosa* virulence has been observed on knocking out components of the T3SS (Shaver and Hauser, 2004). Despite the direct injection of effector proteins into host cells by the T3SS, targeting the structural proteins with MAbs has shown promising results. Preclinical studies indicate that MAbs against these structural proteins effectively reduce lung injury and edema caused by *P. aeruginosa* infections (Faure et al., 2003). A notable example is a bivalent MAb therapy targeting the T3SS structural proteins PcrV and Psl, which has demonstrated good tolerability in humans and shown potential for efficacy in patients with less systemic inflammation (Chastre et al., 2022). MAbs targeting bacterial virulence factors exhibit promise as adjunctive therapies for bacterial infections. However, their efficacy in sepsis is constrained by the time required for a positive culture to identify the pathogen. In the context of sepsis, where time is crucial, a faster and more versatile method of neutralizing bacterial toxins would be highly advantageous compared with a delayed and pathogen-specific approach.

As outlined above, sepsis is a multifaceted condition involving an invasive pathogen alongside a protracted heightened immune response. Although MAbs hold promise as therapies against the initiating infection, their scope does not extend to alleviating the overactive immune response. Conversely, although anti-inflammatory therapy may effectively curtail the immune response, it lacks the capacity to assist the immune system in managing the infection. In this review, we will scrutinize the existing literature on immune biomimetic nanoparticles in the context of infection and sepsis, exploring their potential to address both aspects of this intricate clinical scenario (Fig. 1).

Development of Biomimetic Nanoparticles

Nanoparticles in Medicine: Origins and Advantages. The most basic form of membranous nanoparticle is the liposome. Initially developed in the 1960s, liposomes were under investigation as delivery systems for therapies as early as 1971 (Bangham et al., 1965; Gregoriadis and Ryman, 1971). By 1995, a liposomal drug formulation of doxorubicin (Doxil) had gained approval in the United States (Barenholz, 2012). When drugs are enclosed within a liposome, their bioavailability is not immediate. Instead, they become locally available when liposomes accumulate in clearance organs, such as the liver, or in specific tissues through the enhanced permeability and retention effect (Gregoriadis and Ryman, 1971). This localized availability is particularly advantageous for chemotherapeutic drugs, enabling them to target tumors and diminish overall toxicity (Meunier et al., 1991; Gabizon, 1995). Additionally, liposomes offer the benefit of transporting usually insoluble drugs by manipulating the pH of the nanomedicine or incorporating the drugs into the liposomal bilayer (Mayer et al., 1986; Haran et al., 1993). The use of liposomal drug delivery systems extends the retention time of small molecule therapies in the bloodstream compared with their "free" counterparts (Gill et al., 1995). Nevertheless, the limited nanoparticle retention time in the blood is a continuing challenge.

Nanoparticle Retention: A Recurring Challenge. The loading of drugs into liposomes enhances their retention in the bloodstream compared with their "free" counterparts

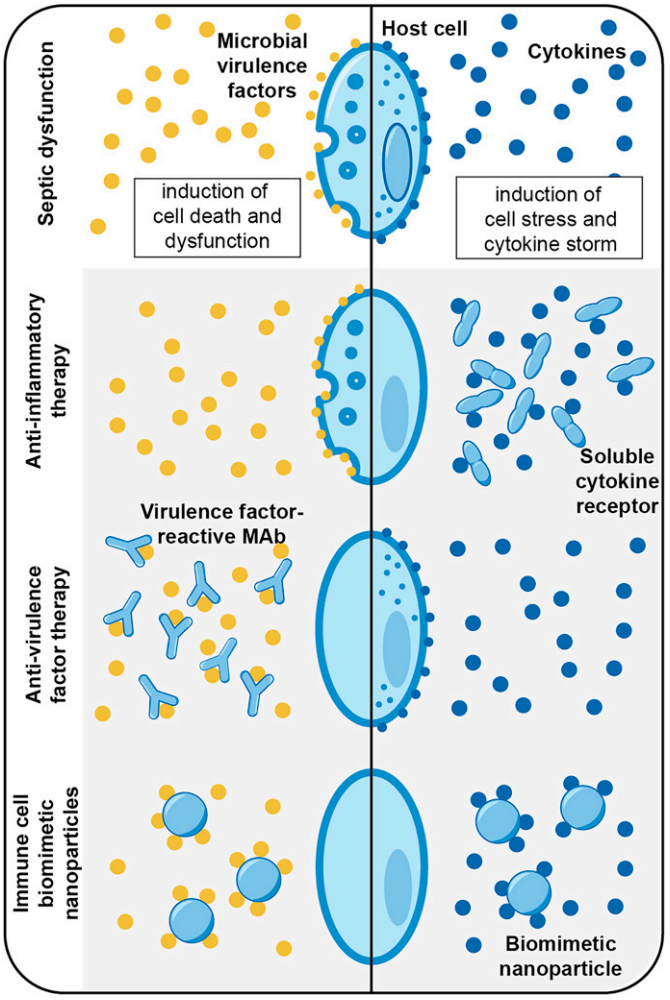

Fig. 1. Potential for multifactorial mechanism of action of biomimetic nanoparticles compared with targeted sepsis therapeutics. The pathophysiological disturbance to cell and organ system function in sepsis is precipitated and driven by both microbial and host factors. Microbial virulence factors, such as toxins, can directly induce host cell death or dysfunction, whereas an excessive proinflammatory "cytokine storm" can drive hypotension, ventilation-perfusion mismatch, coagulopathy, and multi-organ system failure. A number of investigational sepsis therapeutics, including monoclonal antibodies, has been targeted to inactivate specific microbial virulence factors, such as a pore-forming toxin. Others (e.g., soluble cytokine receptors) seek to neutralize a key individual pro-inflammatory host factor. Because a host immune cell membrane-coated nanoparticle mimics the natural surface of the cell from which it was derived, it has the potential to bind and sequester diverse bacterial and host cell factors in a pathogen-agnostic or toxin-agnostic manner, to reduce diverse harmful stimuli in the infected host experiencing sepsis.

(Gill et al., 1995). However, the mononuclear phagocyte system in the liver and spleen can still rapidly clear them from the body (Senior et al., 1985). This clearance is somewhat size-dependent, with smaller liposomes exhibiting longer retention times (Allen et al., 1995). To surmount this limitation and enhance retention while evading the mononuclear phagocyte system, researchers have devised strategies such as coating liposomes with negatively charged sugars to create Stealth liposomes (Allen and Hansen, 1991). A significant advancement in liposomal retention occurred with the introduction of poly (ethylene glycol) (PEG) liposomes, substantially reducing clearance (Klibanov et al., 1990; Allen et al., 1991). Nevertheless, the presence of naturally occurring anti-PEG antibodies in

some patients poses a potential challenge to the universal effectiveness of PEGylated liposomes (Knop et al., 2010). Furthermore, after an initial dose of PEGylated liposomes, subsequent doses of the same nanoparticles are cleared at an accelerated rate (Ishida et al., 2003), prompting concerns about the use of PEGylated liposomes for drugs requiring prolonged regimens.

Nanoparticle Retention: Biomimicry for Immune Evasion. In an innovative approach to enhance nanoparticle retention, researchers took inspiration from the natural characteristics of circulating red blood cells (RBCs). RBCs exhibit an impressive lifespan of approximately 120 days and present multiple signals that deter their opsonization or phagocytosis by the systems responsible for clearing nanoparticles. One such signal found on healthy RBCs is integrin-associated protein (CD47), serving as a "don't eat me" signal. CD47 on RBCs binds to signal regulatory protein α on macrophages, effectively inhibiting phagocytosis (Oldenborg et al., 2000). Additionally, RBCs express various complement inactivating proteins including C8 binding protein (Schönermark et al., 1986), homologous restriction protein (Zalman et al., 1986), decay-accelerating factor, complement receptor 1 (Kim et al., 2008), and membrane attack complex-inhibitory protein (Babiker et al., 2002). These proteins prevent the complement aggregation on the surface of RBCs, a process that could lead to the rapid clearance of liposomes (Szebeni et al., 2011). The objective of researchers was to integrate these "don't eat me" signals onto engineered nanoparticles, aiming to confer upon them some of the retention advantages observed in circulating RBCs.

Rather than opting for a single "don't eat me" signal, researchers repurposed intact RBC membranes containing the complete array of signals to craft RBC biomimetic nanoparticles (RBC-NP). These RBC-NP can be engineered either as liposomes or with solid biodegradable cores. Although the retention time of RBC-liposome hybrids is not explicitly reported, RBC-NP with poly(lactic-co-glycolic acid) (PLGA) cores exhibit prolonged retention in the bloodstream. At 24 hours, their retention increases from 11% to 29%, and at 48 hours, it rises from 2% to 11% compared with PEGylated PLGA cores (Hu et al., 2011). Similar to liposomes, the clearance time of RBC biomimetic nanoparticles is size-dependent, with larger nanoparticles (200 nm) being cleared more rapidly than smaller ones (80 nm) (Li et al., 2019). Importantly, subsequent doses of RBC biomimetic nanoparticles do not exhibit accelerated blood clearance, suggesting that these nanoparticles can circumvent the clearance issues observed with PEGylated nanoparticles (Rao et al., 2015). In summary, the utilization of RBC membranes to cloak nanoparticles allows them to elude endogenous clearance mechanisms, significantly enhancing retention times in the bloodstream.

Biomimetic Nanoparticles and Their Use in Infectious Disease

Biomimetic nanoparticles have potential beyond drug delivery. The suite of plasma membrane proteins on these nanoparticles enables them to function as effective decoys for endogenous cells, mimicking their receptor profile and serving as reservoirs for soluble mediators of infection and sepsis (Fig. 2). This decoy effect has the capacity to protect host cells from damage and reinforce the immune response, thereby enhancing the host's ability to combat infections.

RBCs. Experimental evidence indicates that RBC-NPs serve as highly effective decoys for blood borne toxins that typically target host RBCs and innate immune cells. In vitro studies demonstrate that RBC-NPs can effectively mitigate

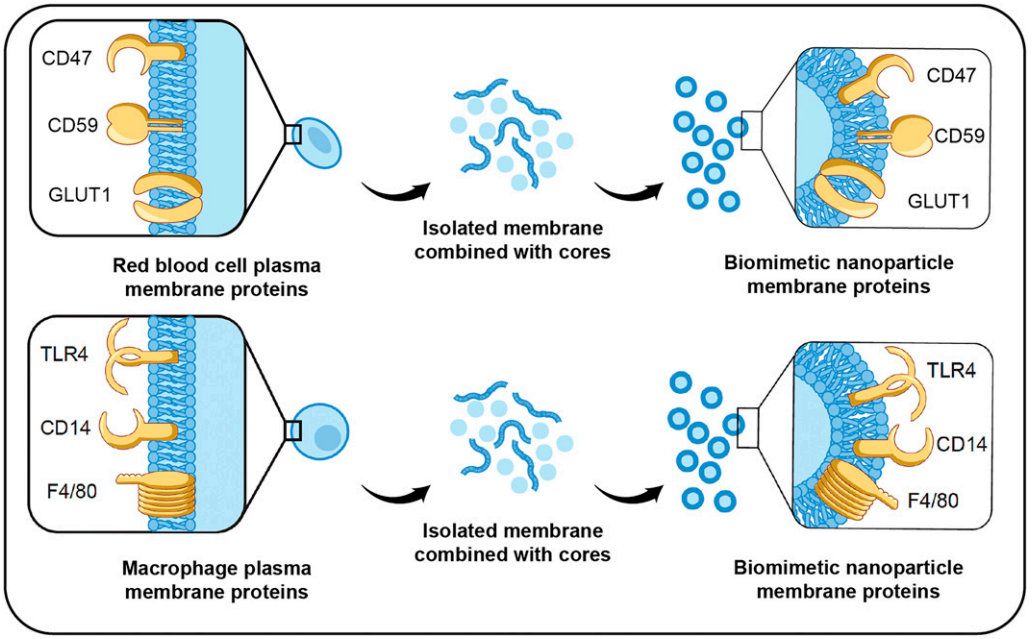

Fig. 2. Biomimetic membrane-coated nanoparticles retain the surface architecture of the cell from which they were derived. Following self-assembly on a precision engineered nanocore of a specified size, for ~100 nM, and chosen composition, such as the biodegradable polymer poly(lactic-co-glycolic acid), host cell membranes retain their native, properly oriented lipid bilayer architecture. Surface expressed structures including proteins and glycoconjugates reflect the parent cell of origin, such as CD47 present on RBC membranes, which serves as a "don't eat me signal" to prolong circulating half-life of the nanoparticle, or TLR4 present on macrophage membranes, which can capture and neutralize bacterial LPS.

hemolysis induced by *S. aureus* α-toxin (Hu et al., 2013; Zhang et al., 2017; He et al., 2019). These protective effects extend beyond specific pathogens, with RBC-NPs exhibiting similar efficacy against streptolysin O from Streptococcus pyogenes, listeriolysin O from *Listeria monocytogenes*, and the bee venom component melittin (Escajadillo et al., 2017; Chen et al., 2018). In addition to RBCs, bacterial toxins also target immune cells to compromise their function or lead to their lysis. In this context, the RBC-NPs decoy function protects the integrity of immune cells, preventing streptolysin O-induced macrophage death and enhancing neutrophil killing of *S. pyogenes* (Escajadillo et al., 2017). In a more complex system involving *S. aureus* supernatant, wherein additional secreted leukocidins beyond α-toxin are present, administration of RBC-NPs demonstrated a significant reduction in toxicity and cell death (Chen et al., 2019). In vivo studies highlight the capacity of RBC-NPs to enhance survival in mouse models of intravenous toxemia caused by a broad range of toxins, surpassing the efficacy of both free RBC membranes and PEGylated PLGA cores (Hu et al., 2013; Chen et al., 2018, 2019; He et al., 2019). Additionally, RBC biomimetic nanoparticles exhibit a noteworthy scavenging of human-made chemical pollutants. Specifically, they effectively bind to free dichlorvos, a common pesticide ingredient that impairs acetylcholinesterase, preserving systemic acetylcholinesterase activity. Administration of RBC-NPs to mice challenged with intravenous and oral dichlorvos showed significant improvement in survival in both models (Pang et al., 2015). These cumulative findings underscore the role of biomimetic nanoparticles as efficient scavengers for a diverse array of naturally occurring and manufactured toxins.

Platelets. Although not traditionally classified as immune cells, circulating platelets play a crucial role in host defense against bacterial pathogens. Their rapid adherence to the vascular endothelium and aggregation with one another enable effective collaboration with the innate immune system, forming bacteria-immobilizing immuno-thrombi (Wong et al., 2013; Prasad et al., 2015; McDonald et al., 2017). On activation, platelets release stored platelet microbicidal proteins that exhibit dual microbicidal and chemokine properties (Nicolai et al., 2019). In bacterial infections and sepsis, platelet dysfunction and pathology are common. Notably, platelets are targeted by well-known virulence factors such as *S. aureus* αtoxin and clumping factor A (Bhakdi et al., 1988; Siboo et al., 2001). The widespread thrombosis induced by these factors can lead to disseminated intravascular coagulation (DIC) and severe organ damage while concurrently depleting the body of platelets necessary to maintain vascular integrity (Levi et al., 1999). Consequently, low platelet counts, referred to as thrombocytopenia, are prevalent in human sepsis, and this condition is associated with kidney injury and prolonged stays in intensive care units (Venkata et al., 2013).

Platelet membrane-coated nanoparticles (P-NPs) inherit functional properties from platelets, including the capacity to bind to areas of damaged or inflamed vasculature. On intravenous injection of fluorescent P-NPs, they selectively localize to aortic atherosclerotic lesions (Hu et al., 2015; Dehaini et al., 2017). In contrast, RBC-NPs do not exhibit such localization, and blended nanoparticles containing both platelet and RBC membranes show reduced degrees of localization, suggesting localization to the lesion is contingent on the NP membrane's identity (Dehaini et al., 2017). Furthermore, P-NPs can directly bind to bacteria, such as *P. aeruginosa* and *S. aureus*, through various cell membrane receptors (Hu et al., 2015; Peng et al., 2021). This bacterial binding is also influenced by the membrane identity, with P-NPs demonstrating significantly increased binding to *S. aureus* compared with RBC-NPs (Hu et al., 2015).

Although bacterial adhesion in isolation has limited therapeutic value, when coupled with a functionalized core, it can enhance microbicidal activity. P-NPs loaded with vancomycin demonstrate improved killing of *S. aureus* compared with vancomycin-loaded RBC-NPs (Hu et al., 2015). Similarly, when a copper silicate microsphere with inherent antimicrobial action under near-infrared light is coated with a platelet membrane, it exhibits enhanced killing of *P. aeruginosa* (Peng et al., 2021). In mouse models, coating these functionalized cores with platelet membrane led to a reduction in bacterial burden compared with antibiotics alone, cores alone, and RBC membrane-coated controls (Hu et al., 2015; Peng et al., 2021).

Beyond their adhesive properties, platelets are targeted by bacterial virulence factors. P-NPs can function as decoys for these products, effectively shielding host platelets and other immune targets from damage or activation, promoting a more effective host response. Notably, P-NPs demonstrate a dose-responsive adsorption of lipopolysaccharide (LPS), preventing macrophage activation and inflammation (Peng et al., 2021). This decoy function also reduces the cytotoxicity of *S. aureus* supernatant against platelets and macrophages (Kim et al., 2021). Even without the addition of a functionalized core, P-NPs exhibit potent effects in vivo. In a mouse model of systemic *S. aureus* infection, P-NPs improve survival, reduce bacterial burden, and decrease serum IL-6 levels, underscoring their therapeutic potential in combating bacterial infections and mitigating the associated inflammatory response (Kim et al., 2021).

Immune Cell Biomimetic Nanoparticles in Infection and Sepsis

The studies mentioned above demonstrate the effectiveness of RBC-NPs as decoys for blood borne toxins, highlighting the advantage of inhibiting these toxins to enhance the immune system's response during an infection. However, bacterial toxins represent only one facet of sepsis. Cytokines produced by the host immune system play a significant role in causing damage and organ dysfunction during sepsis. Intercepting both pathogen-derived toxins and host-derived cytokines necessitates a nanoparticle coated with the membrane of a cell that has evolved to detect and respond to pathogens, cellular damage, and inflammation. In the following discussion, we will explore recent advancements in the development of biomimetic nanoparticles derived from innate and adaptive immune cells.

Neutrophils. Neutrophils, as a critical component of the immune response, play a vital role in combating infections during sepsis. They represent the first and most abundant immune cells to arrive at the site of infection, enabling them to initiate an immediate microbicidal response (Page and Good, 1958). Neutrophils accomplish this through the production of antimicrobial peptides, reactive oxygen species, and neutrophil extracellular traps (NETs), contributing to the containment and neutralization of invading pathogens (Kolaczkowska and Kubes, 2013). Additionally, neutrophils contribute to the activation and recruitment of professional antigen-presenting

cells, engaging the entire immune system in the defense against the infection (Chertov et al., 1997; Bennouna et al., 2003). During sepsis, neutrophils can display dysfunctional behaviors, including impaired apoptosis and migration, as well as deleterious overproduction of NETs, which may contribute to tissue damage (Shen et al., 2017). In clinical settings, markers associated with neutrophil activity, such as Fc receptor expression and serum IL-8, a neutrophil chemokine, have been linked to the severity of sepsis and the development of organ failure (Livaditi et al., 2006). Additionally, ratios of mature neutrophils to immature granulocytes or leukocytes have been identified as potential predictors of sepsis mortality (Ahn et al., 2018; Ni et al., 2019).

The potential of N-NPs in infectious disease models is relatively unexplored, yet they encompass several valuable functions that could be advantageous for managing infections and sepsis. One of their key abilities is to sequester soluble mediators of sepsis. In models of inflammatory arthritis and spinal cord injury, N-NPs have demonstrated the capability to adsorb inflammatory cytokines like IL-1β and TNF-α in a dose-dependent manner, effectively reducing the inflammatory activation of macrophages (Zhang et al., 2018; Bi et al., 2021). Moreover, in the inflammatory arthritis model, N-NPs exhibited significant efficacy in reducing serum inflammatory cytokines and preserving cartilage content (Zhang et al., 2018).

N-NPs also inherit the ability to accumulate at sites of injury and inflammation from neutrophils. In various disease models, N-NPs have demonstrated superior penetration into specific tissues compared with control nanoparticles, such as RBC-NPs. For instance, in a model of inflammatory arthritis, N-NPs exhibited greater accumulation in cartilage, showcasing their ability to target and deliver therapeutic agents effectively to affected areas (Zhang et al., 2018). In acute pancreatitis models, N-NPs displayed a dramatic ability to accumulate in the pancreas, making them a promising candidate for targeted drug delivery to this specific organ during inflammatory conditions (Zhou et al., 2019; Hassanzadeh et al., 2021). Additionally, N-NPs have shown temporary accumulation in injured spinal and brain tissue, indicating their potential application in delivering therapies to these sensitive regions (Dong et al., 2019; Bi et al., 2021). When N-NPs are combined with anti-inflammatory cores, they can significantly enhance the anti-inflammatory activity of these cores, effectively reducing local inflammation and tissue damage (Dong et al., 2019; Zhou et al., 2019; Bi et al., 2021; Hassanzadeh et al., 2021). Importantly, it is not yet determined how much of this anti-inflammatory effect is due to the adsorption of cytokines, extended nanoparticle clearance time, or improved proximity to the inflamed tissue.

Macrophages. Macrophages play a crucial role in the recognition and clearance of infections, contributing to both the early innate response and the activation of adaptive immune cells (Unanue, 1984; Gordon and Plüddemann, 2017). During infections, they secrete inflammatory cytokines such as IL-1β, IL-6, and TNF-α in response to bacterial components and host-derived cytokines (Sagy et al., 2013). In sepsis, macrophages do not undergo apoptosis during the immunosuppressive phase; however, their response to bacterial stimuli becomes blunted (Munoz et al., 1991). Researchers have explored strategies to reprogram macrophages into an anti-inflammatory phenotype, utilizing signals like prostaglandin-E2, which has demonstrated improved survival in mouse models of sepsis (Németh et al., 2009). Additionally, supplementing endogenous macrophages with reprogrammed macrophages has also shown potential benefits (Anderson et al., 2013). Another innovative approach to modulating macrophage behavior is through the use of macrophage membrane-coated nanoparticles (M-NPs). By harnessing the repertoire of plasma membrane proteins from macrophages, these nanoparticles have the ability to intercept both pathogen-derived and host-derived inflammatory signals (Fig. 3).

Of all the immune nanoparticles discussed in this review, M-NPs have the greatest diversity in their fabrication. In their simplest form, M-NPs are created by isolating macrophage membranes and incorporating them into either empty liposomes or onto a PLGA core (Thamphiwatana et al., 2017; Ou et al., 2020; Zhang et al., 2020b). Hybrid M-NPs can be formed by blending macrophage membranes with PEGylated lipids, resulting in M-NP/PEGylated liposomes. This combination leverages the benefits of both components, potentially enhancing the retention time of the nanoparticles in the bloodstream and improving their stability (Jiang et al., 2019). Alternatively, investigators can isolate macrophage plasma membrane proteins and insert them into a synthetic membrane, creating a pseudo-macrophage liposome. This approach allows for more precise control over the nanoparticle composition and properties (Molinaro et al., 2019). Whole cell methods can also introduce polyethylene glycol diacrylate into the live cells, followed by the application of UV light to form a stable gel in the cytosolic compartment with an intact and stable plasma membrane (Gao et al., 2023). More complex M-NPs incorporate antibiotic cores to enhance bacterial killing. By loading antibiotics within the nanoparticle, these M-NPs can directly target pathogens and improve the efficiency of antimicrobial treatment. In some cases, researchers have explored the use of near-infrared–responsive or microwave-responsive cores for M-NPs (Wang et al., 2018; Fu et al., 2021). When activated, these cores produce hyper-localized heat or reactive oxygen species (ROS), further enhancing the therapeutic effects of the nanoparticles in targeted regions. Differences in M-NP preparation methods can significantly impact their effectiveness in killing bacteria. For instance, in a comparison between the widely used co-extrusion method and the gentler electroporation method, electroporated M-NPs exhibited significantly greater bactericidal activity than coextruded M-NPs (Shi et al., 2021). This suggests that the coextrusion process may deform or inactivate the membrane proteins responsible for bacterial attachment, leading to less effective killing of bacteria.

The capability of M-NPs to bind LPS underscores their potential as potent immune regulators. Numerous studies have shown that M-NPs can effectively sequester LPS, preventing its activation of macrophages and the subsequent propagation of inflammatory responses (Thamphiwatana et al., 2017; Jiang et al., 2019; Molinaro et al., 2019; Shen et al., 2019; Ou et al., 2020; Shi et al., 2021). The binding of LPS by M-NPs is facilitated by specific cell surface proteins rather than nonspecific interactions. This specificity is evident from the fact that coincubation with either anti–toll-like receptor 4 (TLR4) or anti-CD14 antibodies significantly hampers the sequestration of LPS by M-NPs (Thamphiwatana et al., 2017). Furthermore, in a hybrid M-NP/liposome composed of a combination of macrophage membrane and PEGylated lipids, the capacity for LPS binding increased proportionally with the higher percentage of macrophage membrane incorporated into the liposome (Jiang et al., 2019). LPS binding capacity was further enhanced when the source macrophages were genetically modified to

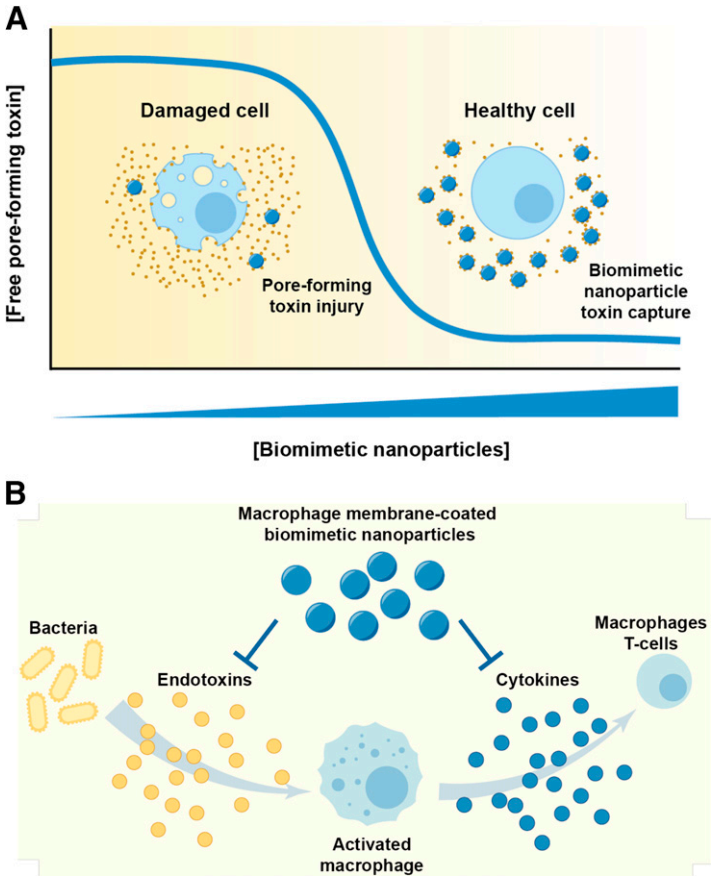

Fig. 3. Shared and unique properties of immune cell membrane-coated biomimetic nanoparticles. (A) By presenting an intact host cell-derived lipid bilayer on their nanoscale surface, both RBC-derived and immune cell-derived nanoparticles can absorb and neutralize harmful bacterial pore-forming toxins, thus serving as a "nanosponge" to limit cell death and toxicity. (B) Immune cell membrane-derived nanoparticles (e.g., macrophage membrane biomimetic nanoparticles), by virtue of their specific array of surface receptors, provide additional immunomodulatory mechanisms of action beyond toxin neutralization, because they can bind and inactivate bacterial endotoxins (e.g., LPS) and pro-inflammatory cytokines to mitigate the initiation and propagation of cytokine storm.

overexpress TLR4 (Ou et al., 2020). This demonstrates the active involvement of specific cell surface proteins in the effective binding of LPS by M-NPs. In mouse endotoxemia models, M-NPs demonstrated a significant improvement in survival when administered either before, during, or 30 minutes after LPS injection (Jiang et al., 2019; Molinaro et al., 2019; Shen et al., 2019). These beneficial effects were specific to M-NPs and were not observed with RBC-NPs when compared side-by-side (Thamphiwatana et al., 2017).

In addition to intercepting bacterial products, the array of cytokine receptors on macrophages enables M-NPs to intercept host inflammatory signals as well. In experiments involving purified cytokines, M-NPs specifically sequestered IL-6, TNF-α, and interferon γ in a dose-dependent manner (Thamphiwatana et al., 2017; Fu et al., 2021). In various in vivo mouse models of *E. coli* peritonitis, osteomyelitis, endotoxemia, and acute pancreatitis, M-NP treatment resulted in decreased levels of inflammatory cytokines in the serum (Thamphiwatana et al., 2017; Shen et al., 2019; Fu et al., 2021; Zhang et al., 2021a). However, it is essential to acknowledge that determining whether this decrease is solely due to cytokine sequestration is challenging. Nevertheless, these findings underscore the potential of M-NPs as promising candidates for the treatment of sepsis and inflammatory conditions.

Macrophages display a remarkable ability to adapt and alter their plasma membrane protein composition in response to external stimuli. When exposed to bacterial stimuli, macrophages shift toward a pathogen-killing phenotype (Ma et al., 2003). Studies have demonstrated that by exposing live macrophages to either *E. coli*or *S. aureus* before isolating their membranes, the resulting M-NPs exhibit an enhanced ability to trap the specific bacteria to which they were previously exposed (Wang et al., 2018; Shen et al., 2019; Gao et al., 2023). Importantly, these studies did not directly compare the LPS- or cytokine-binding capacity of unactivated M-NPs. In contrast, another group conducted experiments using a transgenic RAW cell line with constitutive TLR4 overexpression. They found that M-NPs derived from these cells exhibited a higher efficiency in binding LPS compared with M-NPs derived from wild-type RAW macrophages (Ou et al., 2020). In gelated macrophages, pre-activation against any bacteria improved survival and bacterial clearance in both *E. coli* and *S. aureus* infections (Gao et al., 2023). This suggests that the level of receptor expression on the macrophage membrane at the time of isolation directly corresponds to the amount of that receptor's ligand that the resulting M-NP can bind. Therefore, there is potential for fine-tuning the binding capacity of M-NPs through pre-activation, which could open up new possibilities for targeted therapeutic interventions in the future.

M-NPs exhibit enhanced efficacy in combating infections when paired with functionalized cores. Cores containing titanium dioxide generate bactericidal ROS in response to UV light (Shi et al., 2021). Fe_3O_4/Au nanoparticles can produce ROS and heat in response to microwaves (Fu et al., 2021), whereas gold nanorods or gold/silver nanocages can generate bactericidal heat in response to near infrared light (Wang et al., 2018; Li et al., 2021). Furthermore, drugs can be loaded into the core of the M-NP or directly into the macrophage membranes, capitalizing on the membranes' ability to evade

immune cell clearance and adhere to pathogenic bacteria (Li et al., 2020; Zhang et al., 2021a). In laboratory studies, the bactericidal effects of the functionalized cores and/or drugs were consistently beneficial. However, the advantages of membrane coating over the naked core were not always straightforward. Membrane coating appeared to be particularly advantageous when macrophages were first exposed to specific bacteria before harvesting their membranes. For instance, mixing the nanogel containing gold rods with membranes from macrophages exposed to *S. aureus*resulted in significantly greater *S. aureus* killing. Similarly, mixing *E. coli*-exposed macrophage membranes with the same nanogel increased the killing of *E. coli*. Interestingly, this effect seemed to be species-specific, as the nanogel containing *S. aureus* membrane had poorer performance against *E. coli*and vice versa (Li et al., 2021). In animal models of *S. aureus*skin infection, osteomyelitis, and peritonitis, macrophage membrane-coated nanoparticles demonstrated a significant decrease in bacterial loads compared with core-only controls (Wang et al., 2018; Li et al., 2020; Shi et al., 2021). Additionally, these models exhibited improved healing outcomes, as indicated by reduced lesion size or increased bone deposition (Wang et al., 2018; Shi et al., 2021). Like N-NPs, M-NPs and gelated macrophages can accumulate at sites of inflammation including infection, atherosclerotic lesions, and tumors (Wang et al., 2021; Yue et al., 2021; Gao et al., 2023, 2024). This allows them to deliver an anti-inflammatory or antibiotic payload efficiently. Although some of these effects may be attributed to the increased retention time of the M-NPs in vivo, comparisons between pre-activated and unactivated membrane-coated nanoparticles suggest that the membrane identity also contributes to these improvements (Wang et al., 2018). Taken together, the preparation method and the in vivo context both play essential roles in determining the effectiveness of M-NPs in combating infections.

T Cells. T cells play a pivotal role in the immune response, and during sepsis, they undergo extensive apoptosis and transition toward an anti-inflammatory regulatory T-cell phenotype. This shift contributes to a secondary immunosuppressive phase, making patients susceptible to opportunistic pathogens (Monneret et al., 2003; Wesche et al., 2005). Despite their crucial role in sepsis and post-septic immunosuppression, the application of T cell membrane-coated nanoparticles (TC-NPs) in infectious diseases has been limited to viral infection models. TC-NPs have shown promising results in neutralizing multiple strains of the human immunodeficiency virus. The specific suite of membrane proteins on T cells allows TC-NPs to effectively target and neutralize the virus (Wei et al., 2018; Zhang et al., 2020a; Campbell et al., 2021). Furthermore, when loaded with apoptosis-inducing drugs, TC-NPs have exhibited a preferential ability to induce apoptotic cell death in human immunodeficiency virus-infected T cells and macrophages, while sparing uninfected cells (Campbell et al., 2021). This targeted approach underscores the potential of TC-NPs as a specific and effective therapeutic strategy in combating viral infections. The exploration of TC-NPs in bacterial sepsis and other infectious diseases represents an area that requires further investigation.

Manufacturing Challenges and Improvements. Immune biomimetic nanoparticles can protect the host from pathogenic insult and detrimental endogenous inflammation during sepsis. However, the novel nature of biomimetic nanoparticle therapy presents novel challenges in their production. First, biomimetic nanoparticle fabrication is a complex multistep process and can suffer from batch-to-batch variation. To detect and limit this variation, advances in computer modeling can predict nanoparticle-cell interactions based on standard measurements such as shape, size, and ζ potential (Singh et al., 2021; Zhang et al., 2021b). By applying these machine-learning based quality control steps, functional batch-to-batch

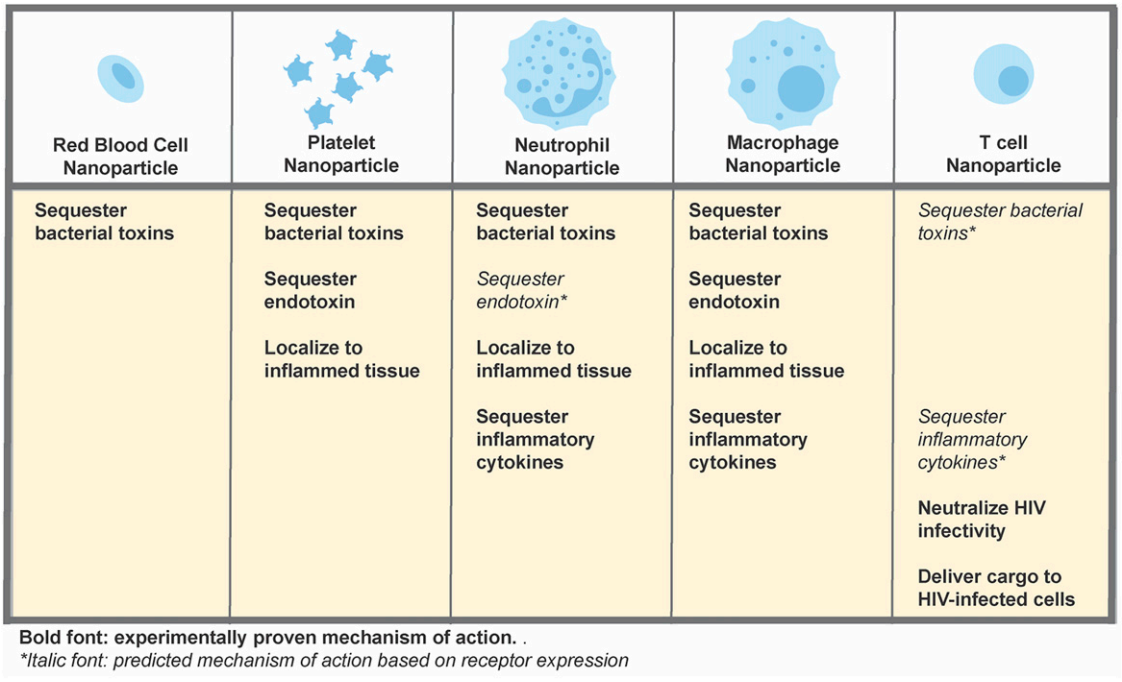

Fig. 4. Mechanisms of action of biomimetic cell membrane-coated nanoparticles. Potential therapeutic benefits in the setting of severe infection and sepsis reflect the particular surface properties and receptors of the parent cell from which the membranes were derived.

variation may be minimized. The second major manufacturing challenge is in parent-cell production. Acquisition of large numbers of RBCs or platelets only requires access to donated human blood; however, immune cells are much more time- and labor-intensive to collect. Rather than collecting directly from donors, the M-NPs and TC-NPs discussed in this review almost exclusively use immortalized cell lines. Sterile mass production of these cells is expensive, but achievable with bioreactors (Wang et al., 2005). Finally, the extraction of the membrane from the parent cell is labor and time intensive (Chugh et al., 2021). Recently, intracellular gelation has been used to separate intracellular contents from their plasma membrane for rapid membrane isolation (Lin et al., 2021, 2024). By understanding and overcoming the unique technical and practical challenges of biomimetic nanoparticle production, the future hope is that they can be safely translated into life-saving therapies for infection and sepsis.

Conclusion

Cell membrane-coated nanoparticles present a promising strategy for tackling bacterial infections and sepsis. By mimicking the functions of immune cells, these nanoparticles can adeptly intercept soluble virulence factors and host-derived inflammatory signals, potentially mitigating the detrimental effects of sepsis (Fig. 4). Additionally, their capacity to adhere to damaged tissues or microbes enables precise and targeted antibiotic delivery, thereby enhancing the effectiveness of infection treatment.

The complex nature of immune biomimetic nanoparticles positions them well to address the complexity of sepsis. By incorporating multiple functionalities into a single therapeutic system, these nanoparticles offer a novel and innovative approach to combat infectious diseases and sepsis, providing optimism for enhanced patient outcomes and the potential to revolutionize immunomodulatory therapies. Further research is essential to fully unlock their potential across various infectious scenarios and optimize their properties for successful translation into human clinical medicine.

Data Availability

This article contains no datasets generated or analyzed during the current study.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Hoffman, Nizet.

References

Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R, Dal Nogare A, Nasraway S, Berman S, Cooney R, et al.; NORASEPT II Study Group (1998) Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. *Lancet* **351**:929–933.

Abraham E, Wunderink R, Silverman H, Perl TM, Nasraway S, Levy H, Bone R, Wenzel RP, Balk R, Allred R, et al. (1995) Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. *JAMA* **273**:934–941.

Ahn C, Kim W, Lim TH, Cho Y, Choi K-S, and Jang B-H (2018) The delta neutrophil index (DNI) as a prognostic marker for mortality in adults with sepsis: a systematic review and meta-analysis. *Sci Rep* **8**:6621.

Ahuja N, Andres-Hernando A, Altmann C, Bhargava R, Bacalja J, Webb RG, He Z, Edelstein CL, and Faubel S (2012) Circulating IL-6 mediates lung injury via CXCL1 production after acute kidney injury in mice. *Am J Physiol Renal Physiol* **303**:F864–F872.

Allen TM and Hansen C (1991) Pharmacokinetics of stealth versus conventional liposomes: effect of dose. *Biochim Biophys Acta* **1068**:133–141.

Allen TM, Hansen CB, and de Menezes DEL (1995) Pharmacokinetics of long-circulating liposomes. *Adv Drug Deliv Rev* **16**:267–284.

Allen TM, Hansen C, Martin F, Redemann C, and Yau-Young A (1991) Liposomes containing synthetic lipid derivatives of poly(ethylene glycol) show prolonged circulation half-lives in vivo. *Biochim Biophys Acta* **1066**:29–36.

Anderson P, Souza-Moreira L, Morell M, Caro M, O'Valle F, Gonzalez-Rey E, and Delgado M (2013) Adipose-derived mesenchymal stromal cells induce immunomodulatory macrophages which protect from experimental colitis and sepsis. *Gut* **62**:1131–1141.

Babiker AA, Ronquist G, Nilsson UR, and Nilsson B (2002) Transfer of prostasomal CD59 to CD59-deficient red blood cells results in protection against complement-mediated hemolysis. *Am J Reprod Immunol* **47**:183–192.

Bangham AD, Standish MM, and Watkins JC (1965) Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Mol Biol* **13**:238–252.

Barenholz Y (2012) Doxil–the first FDA-approved nano-drug: lessons learned. *J Control Release* **160**:117–134.

Bennouna S, Bliss SK, Curiel TJ, and Denkers EY (2003) Cross-talk in the innate immune system: neutrophils instruct recruitment and activation of dendritic cells during microbial infection. *J Immunol* **171**:6052–6058.

Bernard GR, Wheeler AP, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson WJ, Wright PE, Christman BW, Dupont WD, et al.; The Ibuprofen in Sepsis Study Group (1997) The effects of ibuprofen on the physiology and survival of patients with sepsis. *N Engl J Med* **336**:912–918.

Bhakdi S, Muhly M, Mannhardt U, Hugo F, Klapettek K, Mueller-Eckhardt C, and Roka L (1988) Staphylococcal α toxin promotes blood coagulation via attack on human platelets. *J Exp Med* **168**:527–542.

Bhargava R, Altmann CJ, Andres-Hernando A, Webb RG, Okamura K, Yang Y, Falk S, Schmidt EP, and Faubel S (2013) Acute lung injury and acute kidney injury are established by four hours in experimental sepsis and are improved with pre, but not post, sepsis administration of TNF-α antibodies. *PLoS One* **8**:e79037.

Bi Y, Duan W, Chen J, You T, Li S, Jiang W, Li M, Wang G, Pan X, Wu J et al. (2021) Neutrophil decoys with anti-inflammatory and anti-oxidative properties reduce secondary spinal cord injury and improve neurological functional recovery. *Adv Funct Mater* **31**:2102912.

Blanco J, Muriel-Bombín A, Sagredo V, Taboada F, Gandía F, Tamayo L, Collado J, García-Labattut A, Carriedo D, Valledor M, et al.; Grupo de Estudios y Análisis en Cuidados Intensivos (2008) Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. *Crit Care* **12**:R158.

Böhrer H, Qiu F, Zimmermann T, Zhang Y, Jllmer T, Männel D, Böttiger BW, Stern DM, Waldherr R, Saeger HD, et al. (1997) Role of NFkappaB in the mortality of sepsis. *J Clin Invest* **100**:972–985.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RMH, and Sibbald WJ; The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* **101**: 1644–1655.

Bozza FA, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, Bozza MT, Castro-Faria-Neto HC, and Bozza PT (2007) Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. *Crit Care* **11**:R49.

Campbell GR, Zhuang J, Zhang G, Landa I, Kubiatowicz LJ, Dehaini D, Fang RH, Zhang L, and Spector SA (2021) CD4+ T cell-mimicking nanoparticles encapsulating DIABLO/SMAC mimetics broadly neutralize HIV-1 and selectively kill HIV-1-infected cells. *Theranostics* **11**:9009–9021.

Chastre J, François B, Bourgeois M, Komnos A, Ferrer R, Rahav G, De Schryver N, Lepape A, Koksal I, Luyt C-E, et al.; COMBACTE-MAGNET EVADE Study Group (2022) Safety, efficacy, and pharmacokinetics of gremubamab (MEDI3902), an anti-*Pseudomonas aeruginosa* bispecific human monoclonal antibody, in *P. aeruginosa*-colonised, mechanically ventilated intensive care unit patients: a randomised controlled trial. *Crit Care* **26**:355.

Chen Y, Chen M, Zhang Y, Lee JH, Escajadillo T, Gong H, Fang RH, Gao W, Nizet V, and Zhang L (2018) Broad-Spectrum Neutralization of Pore-Forming Toxins with Human Erythrocyte Membrane-Coated Nanosponges. *Adv Healthc Mater* **7**: e1701366.

Chen Y, Zhang Y, Chen M, Zhuang J, Fang RH, Gao W, and Zhang L (2019) Biomimetic nanosponges suppress in vivo lethality induced by the whole secreted proteins of pathogenic bacteria. *Small* **15**:e1804994.

Chertov O, Ueda H, Xu LL, Tani K, Murphy WJ, Wang JM, Howard OM, Sayers TJ, and Oppenheim JJ (1997) Identification of human neutrophil-derived cathepsin G and azurocidin/CAP37 as chemoattractants for mononuclear cells and neutrophils. *J Exp Med* **186**:739–747.

Chugh V, Vijaya Krishna K, and Pandit A (2021) Cell membrane-coated mimics: A methodological approach for fabrication, characterization for therapeutic applications, and challenges for clinical translation. *ACS Nano* **15**:17080–17123.

Clark MA, Plank LD, Connolly AB, Streat SJ, Hill AA, Gupta R, Monk DN, Shenkin A, and Hill GL (1998) Effect of a chimeric antibody to tumor necrosis factor-alpha on cytokine and physiologic responses in patients with severe sepsis–a randomized, clinical trial. *Crit Care Med* **26**:1650–1659.

Cohen J and Carlet J; International Sepsis Trial Study Group (1996) INTERSEPT: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. *Crit Care Med* **24**: 1431–1440.

Cunningham PN, Dyanov HM, Park P, Wang J, Newell KA, and Quigg RJ (2002) Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. *J Immunol* **168**:5817–5823.

Damas P, Ledoux D, Nys M, Vrindts Y, De Groote D, Franchimont P, and Lamy M (1992) Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Ann Surg* **215**:356–362.

Damas P, Reuter A, Gysen P, Demonty J, Lamy M, and Franchimont P (1989) Tumor necrosis factor and interleukin-1 serum levels during severe sepsis in humans. *Crit Care Med* **17**:975–978.

Dehaini D, Wei X, Fang RH, Masson S, Angsantikul P, Luk BT, Zhang Y, Ying M, Jiang Y, Kroll AV, et al. (2017) Erythrocyte-platelet hybrid membrane coating for enhanced nanoparticle functionalization. *Adv Mater* **29**:10.1002/adma.201606209.

Dhainaut JF, Vincent JL, Richard C, Lejeune P, Martin C, Fierobe L, Stephens S, Ney UM, and Sopwith M (1995) CDP571, a humanized antibody to human tumor necrosis factor-alpha: safety, pharmacokinetics, immune response, and influence of the antibody on cytokine concentrations in patients with septic shock. CPD571 Sepsis Study Group. *Crit Care Med* **23**:1461–1469.

Dong X, Gao J, Zhang CY, Hayworth C, Frank M, and Wang Z (2019) Neutrophil membrane-derived nanovesicles alleviate inflammation to protect mouse brain injury from ischemic stroke. *ACS Nano* **13**:1272–1283.

Escajadillo T, Olson J, Luk BT, Zhang L, and Nizet V (2017) A red blood cell membrane-camouflaged nanoparticle counteracts streptolysin O-mediated virulence phenotypes of invasive group A *Streptococcus*. *Front Pharmacol* **8**:477.

Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, et al. (2021) Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med* **49**:e1063–e1143.

Faure K, Fujimoto J, Shimabukuro DW, Ajayi T, Shime N, Moriyama K, Spack EG, Wiener-Kronish JP, and Sawa T (2003) Effects of monoclonal anti-PcrV antibody on Pseudomonas aeruginosa-induced acute lung injury in a rat model. *J Immune Based Ther Vaccines* **1**:2.

Fisher Jr CJ, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, Abraham E, Schein RM, and Benjamin E; The Soluble TNF Receptor Sepsis Study Group (1996) Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. *N Engl J Med* **334**:1697–1702.

Fisher Jr CJ, Dhainaut JF, Opal SM, Pribble JP, Balk RA, Slotman GJ, Iberti TJ, Rackow EC, Shapiro MJ, Greenman RL, et al. (1994a) Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA* **271**:1836–1843.

Fisher Jr CJ, Opal SM, Dhainaut J-F, Stephens S, Zimmerman JL, Nightingale P, Harris SJ, Schein RMH, Panacek EA, Vincent J-L, et al. (1993) Influence of an anti-tumor necrosis factor monoclonal antibody on cytokine levels in patients with sepsis. The CB0006 Sepsis Syndrome Study Group. *Crit Care Med* **21**: 318–327.

Fisher Jr CJ, Slotman GJ, Opal SM, Pribble JP, Bone RC, Emmanuel G, Ng D, Bloedow DC, and Catalano MA; IL-1RA Sepsis Syndrome Study Group (1994b) Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med* **22**:12–21.

Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, and Reinhart K; International Forum of Acute Care Trialists (2016) Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* **193**:259–272.

François B, Jafri HS, Chastre J, Sánchez-García M, Eggimann P, Dequin P-F, Huberlant V, Viña Soria L, Boulain T, Bretonnière C, et al.; COMBACTE Consortium and the SAATELLITE Study Group (2021) Efficacy and safety of suvratoxumab for prevention of *Staphylococcus aureus* ventilator-associated pneumonia (SAATELLITE): a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2 pilot trial. *Lancet Infect Dis* **21**:1313–1323.

François B, Mercier E, Gonzalez C, Asehnoune K, Nseir S, Fiancette M, Desachy A, Plantefève G, Meziani F, de Lame P-A, et al.; MASTER 1 study group (2018) Safety and tolerability of a single administration of AR-301, a human monoclo*nal antibody, in ICU patients with severe pneumonia caused by* Staphylococcus aureus: first-in-human trial. *Intensive Care Med* **44**:1787–1796.

Fu J, Li Y, Zhang Y, Liang Y, Zheng Y, Li Z, Zhu S, Li C, Cui Z, and Wu S (2021) An engineered pseudo-macrophage for rapid treatment of bacteria-infected osteomyelitis via microwave-excited anti-infection and immunoregulation. *Adv Mater* **33**:e2102926.

Gabizon AA (1995) Liposome circulation time and tumor targeting: implications for cancer chemotherapy. *Adv Drug Deliv Rev* **16**:285–294.

Gao C, Kwong CHT, Tang M, Liu J, Kam H, Li S, Lee SMY, Fan C, Yu H-Z, and Wang R (2023) A bacterially engineered macrophage sponge as a neutralization decoy to treat bacterial infection. *Matter* **6**:3889–3911.

Gao C, Wang Q, Ding Y, Kwong CHT, Liu J, Xie B, Wei J, Lee SMY, Mok GSP, and Wang R (2024) Targeted therapies of inflammatory diseases with intracellularly gelated macrophages in mice and rats. *Nat Commun* **15**:328.

Gill PS, Espina BM, Muggia F, Cabriales S, Tulpule A, Esplin JA, Liebman HA, Forssen E, Ross ME, and Levine AM (1995) Phase I/II clinical and pharmacokinetic evaluation of liposomal daunorubicin. *J Clin Oncol* **13**:996–1003.

Gordon S and Plüddemann A (2017) Tissue macrophages: heterogeneity and functions. *BMC Biol* **15**:53.

Gregoriadis G and Ryman BE (1971) Liposomes as carriers of enzymes or drugs: a new approach to the treatment of storage diseases. *Biochem J* **124**:58P.

Haran G, Cohen R, Bar LK, and Barenholz Y (1993) Transmembrane ammonium sulfate gradients in liposomes produce efficient and stable entrapment of amphipathic weak bases. *Biochim Biophys Acta* **1151**:201–215.

Hassanzadeh P, Arbabi E, and Rostami F (2021) Coating of ferulic acid-loaded silk fibroin nanoparticles with neutrophil membranes: A promising strategy against the acute pancreatitis. *Life Sci* **270**:119128.

Hauser AR (2009) The type III secretion system of *Pseudomonas aeruginosa*: infection by injection. *Nat Rev Microbiol* **7**:654–665.

Hauser AR, Cobb E, Bodi M, Mariscal D, Vallés J, Engel JN, and Rello J (2002) Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. *Crit Care Med* **30**:521–528.

He Y, Li R, Li H, Zhang S, Dai W, Wu Q, Jiang L, Zheng Z, Shen S, Chen X, et al. (2019) Erythroliposomes: integrated hybrid nanovesicles composed of erythrocyte membranes and artificial lipid membranes for pore-forming toxin clearance. *ACS Nano* **13**:4148–4159.

Hu C-MJ, Fang RH, Copp J, Luk BT, and Zhang L (2013) A biomimetic nanosponge that absorbs pore-forming toxins. *Nat Nanotechnol* **8**:336–340.

Hu C-MJ, Fang RH, Wang K-C, Luk BT, Thamphiwatana S, Dehaini D, Nguyen P, Angsantikul P, Wen CH, Kroll AV, et al. (2015) Nanoparticle biointerfacing by platelet membrane cloaking. *Nature* **526**:118–121.

Hu C-MJ, Zhang L, Aryal S, Cheung C, Fang RH, and Zhang L (2011) Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proc Natl Acad Sci USA* **108**:10980–10985.

Inoshima I, Inoshima N, Wilke GA, Powers ME, Frank KM, Wang Y, and Bubeck Wardenburg J (2011) A *Staphylococcus aureus* pore-forming toxin subverts the activity of ADAM10 to cause lethal infection in mice. *Nat Med* **17**:1310–1314.

Ishida T, Maeda R, Ichihara M, Irimura K, and Kiwada H (2003) Accelerated clearance of PEGylated liposomes in rats after repeated injections. *J Control Release* **88**:35–42.

Iwashyna TJ, Ely EW, Smith DM, and Langa KM (2010) Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* **304**: 1787–1794.

Jiang L, Li R, Xu J, Luan P, Cui Q, Pang Z, Wang J, Lin G, and Zhang J (2019) Endotoxin-adsorbing macrophage-mimetic hybrid liposome for sepsis treatment. *Chem Eng J* **371**:15–25.

Johnson JR (1991) Virulence factors in *Escherichia coli* urinary tract infection. *Clin Microbiol Rev* **4**:80–128.

Kim DD, Miwa T, Kimura Y, Schwendener RA, van Lookeren Campagne M, and Song W-C (2008) Deficiency of decay-accelerating factor and complement receptor 1-related gene/protein y on murine platelets leads to complement-dependent clearance by the macrophage phagocytic receptor CRIg. *Blood* **112**:1109–1119.

Kim J-K, Uchiyama S, Gong H, Stream A, Zhang L, and Nizet V (2021) Engineered biomimetic platelet membrane-coated nanoparticles block *Staphylococcus aureus* cytotoxicity and protect against lethal systemic infection. *Engineering* **7**:1149–1156.

Klibanov AL, Maruyama K, Torchilin VP, and Huang L (1990) Amphipathic polyethyleneglycols effectively prolong the circulation time of liposomes. *FEBS Lett* **268**: 235–237.

Knop K, Hoogenboom R, Fischer D, and Schubert US (2010) Poly(ethylene glycol) in drug delivery: pros and cons as well as potential alternatives. *Angew Chem Int Ed Engl* **49**:6288–6308.

Kolaczkowska E and Kubes P (2013) Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol* **13**:159–175.

Kopf M, Baumann H, Freer G, Freudenberg M, Lamers M, Kishimoto T, Zinkernagel R, Bluethmann H, and Köhler G (1994) Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature* **368**:339–342.

Ledizet M, Murray TS, Puttagunta S, Slade MD, Quagliarello VJ, and Kazmierczak BI (2012) The ability of virulence factor expression by *Pseudomonas aeruginosa* to predict clinical disease in hospitalized patients. *PLoS One* **7**:e49578.

Levi M, de Jonge E, van der Poll T, and ten Cate H (1999) Disseminated intravascular coagulation. *Thromb Haemost* **82**:695–705.

Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent J-L, Ramsay G; International Sepsis Definitions Conference (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* **29**:530–538.

Li H, Jin K, Luo M, Wang X, Zhu X, Liu X, Jiang T, Zhang Q, Wang S, and Pang Z (2019) Size dependency of circulation and biodistribution of biomimetic nanoparticles: red blood cell membrane-coated nanoparticles. *Cells* **8**:881.

Li J, Wang Y, Yang J, and Liu W (2021) Bacteria activated-macrophage membrane-coated tough nanocomposite hydrogel with targeted photothermal antibacterial ability for infected wound healing. *Chem Eng J* **420**:127638.

Li Y, Liu Y, Ren Y, Su L, Li A, An Y, Rotello V, Zhang Z, Wang Y, Liu Y, et al. (2020) Coating of a novel antimicrobial nanoparticle with a macrophage membrane for the selective entry into infected macrophages and killing of intracellular staphylococci. *Adv Funct Mater* **30**:2004942 Wiley.

Lin C-L, Fang Z-S, Hsu C-Y, Liu Y-H, Lin J-C, Yao B-Y, Li F-A, Yen SB, Chang Y-C, and Hu CJ (2024) Rapid plasma membrane isolation via intracellular polymerization-mediated biomolecular confinement. *Acta Biomater* **173**:325–335.

Lin J-C, Hsu C-Y, Chen J-Y, Fang Z-S, Chen H-W, Yao B-Y, Shiau GHM, Tsai J-S, Gu M, Jung M, et al. (2021) Facile transformation of murine and human primary dendritic cells into robust and modular artificial antigen-presenting systems by intracellular hydrogelation. *Adv Mater* **33**:e2101190.

Livaditi O, Kotanidou A, Psarra A, Dimopoulou I, Sotiropoulou C, Augustatou K, Papasteriades C, Armaganidis A, Roussos C, Orfanos SE, et al. (2006) Neutrophil CD64 expression and serum IL-8: sensitive early markers of severity and outcome in sepsis. *Cytokine* **36**:283–290.

Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas Jr WD, Leney M, Sloan S, et al. (2010) Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *N Engl J Med* **362**:197–205.

Ma J, Chen T, Mandelin J, Ceponis A, Miller NE, Hukkanen M, Ma GF, and Konttinen YT (2003) Regulation of macrophage activation. *Cell Mol Life Sci* **60**:2334–2346.

Martin-Loeches I, Guia MC, Vallecoccia MS, Suarez D, Ibarz M, Irazabal M, Ferrer R, and Artigas A (2019) Risk factors for mortality in elderly and very elderly critically ill patients with sepsis: a prospective, observational, multicenter cohort study. *Ann Intensive Care* **9**:26.

Mayer LD, Bally MB, and Cullis PR (1986) Uptake of adriamycin into large unilamellar vesicles in response to a pH gradient. *Biochim Biophys Acta* **857**:123–126 Elsevier.

McDonald B, Davis RP, Kim S-J, Tse M, Esmon CT, Kolaczkowska E, and Jenne CN (2017) Platelets and neutrophil extracellular traps collaborate to promote intravascular coagulation during sepsis in mice. *Blood* **129**:1357–1367.

Metnitz PG, Lang T, Valentin A, Steltzer H, Krenn CG, and Le Gall JR (2001) Evaluation of the logistic organ dysfunction system for the assessment of organ dysfunction and mortality in critically ill patients. *Intensive Care Med* **27**:992–998.

Meunier F, Prentice HG, and Ringdén O (1991) Liposomal amphotericin B (AmBisome): safety data from a phase II/III clinical trial. *J Antimicrob Chemother* **28** (Suppl B): 83–91.

Molinaro R, Pastò A, Corbo C, Taraballi F, Giordano F, Martinez JO, Zhao P, Wang X, Zinger A, Boada C, et al. (2019) Macrophage-derived nanovesicles exert intrinsic anti-inflammatory properties and prolong survival in sepsis through a direct interaction with macrophages. *Nanoscale* **11**:13576–13586.

Monneret G, Debard A-L, Venet F, Bohe J, Hequet O, Bienvenu J, and Lepape A (2003) Marked elevation of human circulating CD4+CD25+ regulatory T cells in sepsis-induced immunoparalysis. *Crit Care Med* **31**:2068–2071.

Munoz C, Carlet J, Fitting C, Misset B, Blériot JP, and Cavaillon JM (1991) Dysregulation of in vitro cytokine production by monocytes during sepsis. *J Clin Invest* **88**:1747–1754.

Nechemia-Arbely Y, Barkan D, Pizov G, Shriki A, Rose-John S, Galun E, and Axelrod JH (2008) IL-6/IL-6R axis plays a critical role in acute kidney injury. *J Am Soc Nephrol* **19**:1106–1115.

Németh K, Leelahavanichkul A, Yuen PST, Mayer B, Parmelee A, Doi K, Robey PG, Leelahavanichkul K, Koller BH, Brown JM, et al. (2009) Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med* **15**:42–49.

Nicolai L, Gaertner F, and Massberg S (2019) Platelets in host defense: experimental and clinical insights. *Trends Immunol* **40**:922–938.

Ni J, Wang H, Li Y, Shu Y, and Liu Y (2019) Neutrophil to lymphocyte ratio (NLR) as a prognostic marker for in-hospital mortality of patients with sepsis: A secondary analysis based on a single-center, retrospective, cohort study. *Medicine (Baltimore)* **98**:e18029.

Oldenborg PA, Zheleznyak A, Fang YF, Lagenaur CF, Gresham HD, and Lindberg FP (2000) Role of CD47 as a marker of self on red blood cells. *Science* **288**: 2051–2054.

Opal SM, Fisher Jr CJ, Dhainaut JF, Vincent JL, Brase R, Lowry SF, Sadoff JC, Slotman GJ, Levy H, Balk RA, et al. (1997) Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* **25**:1115–1124.

Ou Z, Zhong H, Zhang L, Deng M, Zhang W, Wang J, Feng H, Gong J, Miao C, and Yi Z (2020) macrophage membrane-coated nanoparticles alleviate hepatic ischemia-reperfusion injury caused by orthotopic liver transplantation by neutralizing endotoxin. *Int J Nanomedicine* **15**:4125–4138.

Page AR and Good RA (1958) A clinical and experimental study of the function of neutrophils in the inflammatory response. *Am J Pathol* **34**:645–669.

Pang Z, Hu C-MJ, Fang RH, Luk BT, Gao W, Wang F, Chuluun E, Angsantikul P, Thamphiwatana S, Lu W, et al. (2015) Detoxification of organophosphate poisoning using nanoparticle bioscavengers. *ACS Nano* **9**:6450–6458.

Patel JM, Snaith C, Thickett DR, Linhartova L, Melody T, Hawkey P, Barnett AH, Jones A, Hong T, Cooke MW, et al. (2012) Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). *Crit Care* **16**:R231.

Peng Z, Zhang X, Yuan L, Li T, Chen Y, Tian H, Ma D, Deng J, Qi X, and Yin X (2021) Integrated endotoxin-adsorption and antibacterial properties of platelet-membrane-coated copper silicate hollow microspheres for wound healing. *J Nanobiotechnology* **19**:383.

Pfeffer K, Matsuyama T, Kündig TM, Wakeham A, Kishihara K, Shahinian A, Wiegmann K, Ohashi PS, Krönke M, and Mak TW (1993) Mice deficient for the 55 kd tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to *L. monocytogenes* infection. *Cell* **73**:457–467.

Pinsky MR, Vincent JL, Deviere J, Alegre M, Kahn RJ, and Dupont E (1993) Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality. *Chest* **103**:565–575.

Prasad JM, Gorkun OV, Raghu H, Thornton S, Mullins ES, Palumbo JS, Ko Y-P, Höök M, David T, Coughlin SR, et al. (2015) Mice expressing a mutant form of fibrinogen that cannot support fibrin formation exhibit compromised antimicrobial host defense. *Blood* **126**:2047–2058.

Ragle BE and Bubeck Wardenburg J (2009) Anti-alpha-hemolysin monoclonal antibodies mediate protection against *Staphylococcus aureus* pneumonia. *Infect Immun* **77**:2712–2718.

Rao L, Bu L-L, Xu J-H, Cai B, Yu G-T, Yu X, He Z, Huang Q, Li A, Guo S-S et al. (2015) Red blood cell membrane as a biomimetic nanocoating for prolonged circulation time and reduced accelerated blood clearance. *Small* **11**:6225–6236.

Reinhart K, Menges T, Gardlund B, Harm Zwaveling J, Smithes M, Vincent JL, Tellado JM, Salgado-Remigio A, Zimlichman R, Withington S, et al. (2001) Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: the RAMSES study. *Crit Care Med* **29**:765–769.

Reinhart K, Wiegand-Löhnert C, Grimminger F, Kaul M, Withington S, Treacher D, Eckart J, Willatts S, Bouza C, Krausch D, et al. (1996) Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody-fragment, MAK 195F, in patients with sepsis and septic shock: a multicenter, randomized, placebo-controlled, dose-ranging study. *Crit Care Med* **24**:733–742.

Rhodes A, Phillips G, Beale R, Cecconi M, Chiche JD, De Backer D, Divatia J, Du B, Evans L, Ferrer R, et al. (2015) The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). *Intensive Care Med* **41**:1620–1628.

Sagy M, Al-Qaqaa Y, and Kim P (2013) Definitions and pathophysiology of sepsis. *Curr Probl Pediatr Adolesc Health Care* **43**:260–263.

Sakr Y, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA, Martin-Loeches I, Leone M, Lupu M-N, and Vincent J-L; ICON Investigators (2018) Sepsis in intensive care unit patients: worldwide data from the Intensive Care over Nations audit. *Open Forum Infect Dis* **5**:ofy313.

Sakr Y, Maia VPL, Santos C, Stracke J, Zeidan M, Bayer O, and Reinhart K (2014) Adjuvant selenium supplementation in the form of sodium selenite in postoperative critically ill patients with severe sepsis. *Crit Care* **18**:R68.

Scherr TD, Hanke ML, Huang O, James DBA, Horswill AR, Bayles KW, Fey PD, Torres VJ, and Kielian T (2015) *Staphylococcus aureus* biofilms induce macrophage dysfunction through leukocidin AB and alpha-toxin. *MBio* **6**:e01021-15.

Schönermark S, Rauterberg EW, Shin ML, Löke S, Roelcke D, and Hänsch GM (1986) Homologous species restriction in lysis of human erythrocytes: a membrane-derived protein with C8-binding capacity functions as an inhibitor. *J Immunol* **136**:1772–1776.

Senior J, Crawley JC, and Gregoriadis G (1985) Tissue distribution of liposomes exhibiting long half-lives in the circulation after intravenous injection. *Biochim Biophys Acta* **839**:1–8.

Shaver CM and Hauser AR (2004) Relative contributions of Pseudomonas aeruginosa ExoU, ExoS, and ExoT to virulence in the lung. *Infect Immun* **72**:6969–6977.

Shen S, Han F, Yuan A, Wu L, Cao J, Qian J, Qi X, Yan Y, and Ge Y (2019) Engineered nanoparticles disguised as macrophages for trapping lipopolysaccharide and preventing endotoxemia. *Biomaterials* **189**:60–68.

Shen X-F, Cao K, Jiang J-P, Guan W-X, and Du J-F (2017) Neutrophil dysregulation during sepsis: an overview and update. *J Cell Mol Med* **21**:1687–1697.

Shi M, Shen K, Yang B, Zhang P, Lv K, Qi H, Wang Y, Li M, Yuan Q, and Zhang Y (2021) An electroporation strategy to synthesize the membrane-coated nanoparticles for enhanced anti-inflammation therapy in bone infection. *Theranostics* **11**:2349–2363.

Siboo IR, Cheung AL, Bayer AS, and Sullam PM (2001) Clumping factor A mediates binding of Staphylococcus aureus to human platelets. *Infect Immun* **69**: 3120–3127.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, et al. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **315**: 801–810.

Singh AV, Maharjan R-S, Kanase A, Siewert K, Rosenkranz D, Singh R, Laux P, and Luch A (2021) Machine-learning-based approach to decode the influence of nanomaterial properties on their interaction with cells. *ACS Appl Mater Interfaces* **13**: 1943–1955.

Szebeni J, Muggia F, Gabizon A, and Barenholz Y (2011) Activation of complement by therapeutic liposomes and other lipid excipient-based therapeutic products: prediction and prevention. *Adv Drug Deliv Rev* **63**:1020–1030.

Thamphiwatana S, Angsantikul P, Escajadillo T, Zhang Q, Olson J, Luk BT, Zhang S, Fang RH, Gao W, Nizet V, et al. (2017) Macrophage-like nanoparticles concurrently absorbing endotoxins and proinflammatory cytokines for sepsis management. *Proc Natl Acad Sci USA* **114**:11488–11493.

Tkaczyk C, Hamilton MM, Datta V, Yang XP, Hilliard JJ, Stephens GL, Sadowska A, Hua L, O'Day T, Suzich J, et al. (2013) Staphylococcus aureus alpha toxin suppresses effective innate and adaptive immune responses in a murine dermonecrosis model. *PLoS One* **8**:e75103.

Tkaczyk C, Hua L, Varkey R, Shi Y, Dettinger L, Woods R, Barnes A, MacGill RS, Wilson S, Chowdhury P, et al. (2012) Identification of anti-alpha toxin monoclonal antibodies that reduce the severity of Staphylococcus aureus dermonecrosis and exhibit a correlation between affinity and potency. *Clin Vaccine Immunol* **19**: 377–385.

Unanue ER (1984) Antigen-presenting function of the macrophage. *Annu Rev Immunol* **2**:395–428.

Venkata C, Kashyap R, Farmer JC, and Afessa B (2013) Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. *J Intensive Care* **1**:9.

Vincent J-L, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, et al.; EPIC II Group of Investigators (2009) International study of the prevalence and outcomes of infection in intensive care units. *JAMA* **302**:2323–2329.

Vincent J-L, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall J-R, and Payen D; Sepsis Occurrence in Acutely Ill Patients Investigators (2006) Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* **34**:344–353.

Wang C, Wang Y, Zhang L, Miron RJ, Liang J, Shi M, Mo W, Zheng S, Zhao Y, and Zhang Y (2018) Pretreated macrophage-membrane-coated gold nanocages for precise drug delivery for treatment of bacterial infections. *Adv Mater* **30**:e1804023.

Wang D, Liu W, Han B, and Xu R (2005) The bioreactor: a powerful tool for large-scale culture of animal cells. *Curr Pharm Biotechnol* **6**:397–403.

Wang Y, Zhang K, Li T, Maruf A, Qin X, Luo L, Zhong Y, Qiu J, McGinty S, Pontrelli G, et al. (2021) Macrophage membrane functionalized biomimetic nanoparticles for targeted anti-atherosclerosis applications. *Theranostics* **11**:164–180.

Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, Singhi SC, Erickson S, Roy JA, Bush JL, et al.; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (2015) Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med* **191**:1147–1157.

Wei X, Zhang G, Ran D, Krishnan N, Fang RH, Gao W, Spector SA, and Zhang L (2018) T-cell-mimicking nanoparticles can neutralize HIV infectivity. *Adv Mater* **30**:e1802233.

Wesche DE, Lomas-Neira JL, Perl M, Chung C-S, and Ayala A (2005) Leukocyte apoptosis and its significance in sepsis and shock. *J Leukoc Biol* **78**:325–337.

Wong CHY, Jenne CN, Petri B, Chrobok NL, and Kubes P (2013) Nucleation of platelets with blood-borne pathogens on Kupffer cells precedes other innate immunity and contributes to bacterial clearance. *Nat Immunol* **14**:785–792.

World Health Organization (2020) Global report on the epidemiology and burden of sepsis. Current evidence, identifying gaps and future directions. World Health Organization.

Xu C, Chang A, Hack BK, Eadon MT, Alper SL, and Cunningham PN (2014) TNF-mediated damage to glomerular endothelium is an important determinant of acute kidney injury in sepsis. *Kidney Int* **85**:72–81.

Yue Y, Li F, Li Y, Wang Y, Guo X, Cheng Z, Li N, Ma X, Nie G, and Zhao X (2021) Biomimetic nanoparticles carrying a repolarization agent of tumor-associated macrophages for remodeling of the inflammatory microenvironment following photothermal therapy. *ACS Nano* **15**:15166–15179.

Zalman LS, Wood LM, and Müller-Eberhard HJ (1986) Isolation of a human erythrocyte membrane protein capable of inhibiting expression of homologous complement transmembrane channels. *Proc Natl Acad Sci USA* **83**:6975–6979.

Zecconi A and Scali F (2013) *Staphylococcus aureus* virulence factors in evasion from innate immune defenses in human and animal diseases. *Immunol Lett* **150**: 12–22 Elsevier.

Zhang G, Campbell GR, Zhang Q, Maule E, Hanna J, Gao W, Zhang L, and Spector SA (2020a) CD4+ T Cell-mimicking nanoparticles broadly neutralize HIV-1 and suppress viral replication through autophagy. *MBio* **11**:e00903-20.

Zhang Q, Dehaini D, Zhang Y, Zhou J, Chen X, Zhang L, Fang RH, Gao W, and Zhang L (2018) Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. *Nat Nanotechnol* **13**:1182–1190.

Zhang Q, Honko A, Zhou J, Gong H, Downs SN, Vasquez JH, Fang RH, Gao W, Griffiths A, and Zhang L (2020b) Cellular nanosponges inhibit SARS-CoV-2 infectivity. *Nano Lett* **20**:5570–5574.

Zhang Q, Zhou J, Zhou J, Fang RH, Gao W, and Zhang L (2021a) Lure-and-kill macrophage nanoparticles alleviate the severity of experimental acute pancreatitis. *Nat Commun* **12**:4136.

Zhang X, Ma G, and Wei W (2021b) Simulation of nanoparticles interacting with a cell membrane: probing the structural basis and potential biomedical application. *NPG Asia Mater* **13**:52.

Zhang Y, Zhang J, Chen W, Angsantikul P, Spiekermann KA, Fang RH, Gao W, and Zhang L (2017) Erythrocyte membrane-coated nanogel for combinatorial antivirulence and responsive antimicrobial delivery against Staphylococcus aureus infection. *J Control Release* **263**:185–191.

Zhou X, Cao X, Tu H, Zhang Z-R, and Deng L (2019) Inflammation-targeted delivery of celastrol via neutrophil membrane-coated nanoparticles in the management of acute pancreatitis. *Mol Pharm* **16**:1397–1405.

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