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REVIEW

Decoy Nanoparticles and Protein Corona Modulation: A Novel Frontier in Sepsis Treatment

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Abstract: Sepsis remains a major global health challenge due to its complex pathophysiology and limited therapeutic options. Nanomedicine offers innovative strategies to address these limitations by enabling diverse nanoparticle designs and mechanisms that modulate the septic response. This review examines the dynamic interactions between nanoparticles and the immune system, with a focus on how protein corona formation shapes nanoparticle behavior, biodistribution, and therapeutic efficacy. Disease-specific protein corona profiles can serve as pathology "fingerprints" for diagnosis and targeted delivery, and their controlled formation is now emerging as a therapeutic tool rather than only a diagnostic readout. While the protein corona is a spontaneous biomolecular layer, its composition can be rationally steered to support defined therapeutic goals. In this context, decoy nanoparticles are engineered to sequester pathogens or inflammatory mediators, such as cytokines, histones, and neutrophil extracellular traps, thereby mitigating inflammation and tissue damage. This review discusses how protein corona engineering can potentiate decoy strategies in sepsis diagnosis and therapy, highlighting key platforms including macrophage-like nanoparticles that neutralize endotoxins and cytokines, histone-binding hydrogels, and mesoporous silica nanoparticles that scavenge cell-free DNA and inhibit Toll-like receptor activation. We also address how Artificial Intelligence can improve prediction of protein corona dynamics and identification of disease-specific protein signatures, enabling more personalized nanodecoy design. Given the highly dynamic and heterogeneous nature of sepsis, characterized by evolving circulating mediators and protein profiles, integrating protein corona control with decoy mechanisms offers a multifaceted route to limit immune dysregulation, enhance drug delivery, and reduce organ damage, paving the way toward precision nanomedicine in sepsis.

Keywords: sepsis, nanoparticles, protein corona, inflammation, drug delivery, immune modulation, nanomedicine

Introduction

Between 2010 and 2023, global data on sepsis incidence and mortality revealed a concerning rise in cases worldwide, with a disproportionately higher burden observed in low- and middle-income countries compared to high-income regions.[1,2] Despite this trend, many regional areas have reported a relative decline in in-hospital crude mortality rates, attributed to advancements in sepsis recognition, therapeutic interventions, and improved patient outcomes.[3] Nevertheless, sepsis continues to pose a formidable global health challenge, accounting each year for millions of new

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cases and related deaths. The highest mortality rates remain concentrated in sub-Saharan Africa and some Asia regions, underscoring the persistent inequities in healthcare access and outcomes[4] (Figure 1). The most recent Russian government-related data confirm that sepsis and septic shock persist as major public health concerns in the country. Clinical guidelines updated in 2023 estimate that sepsis impacts approximately 9.3 per 1,000 hospitalized patients, with rates escalating to 56.5 per 1,000 among those in intensive care units. Mortality in these critical care settings remains exceedingly high, reaching up to 50%, with even higher figures reported during the COVID-19 pandemic,[5] underscoring the severe impact of sepsis in these environments. Sepsis is defined as an inflammatory syndrome characterized by organ dysfunction caused by a dysregulated immune response,[6] often involving resistant pathogens.[7]

Early detection of sepsis is critical for improving patient outcomes, as survival rates decline rapidly without timely and appropriate treatment.[6] Management primarily involves supportive care, often requiring prolonged hospitalization.[8] While sepsis is most commonly linked to bacterial infections and their toxins,[9] other pathogens, including viruses, can also trigger its onset, as observed during the COVID-19 pandemic.[10]

At the onset of sepsis, the immune system increases its activity, triggering a robust inflammatory reaction known as a "cytokine storm"[11] (Figure 2).

This response is driven by pathogen-associated molecular patterns (PAMPs) released by bacteria and their toxins, alongside danger-associated molecular patterns (DAMPs) from dying host cells.[12] Over time, this hyperinflammatory state shifts into a prolonged or severe low-inflammatory phase, resulting in immunosuppression. This weakened immune state is marked by significant T cell depletion, impaired function, exhaustion, and reduced antigen presentation. These events increase susceptibility to viral reactivation, secondary infections, and long-term mortality risks, which can persist for up to a year after the initial sepsis episode.[9]

This scenario is further complicated by pathological activity of matrix metalloproteinases (MMPs), such as MMP-3,[13] MMP-8, and MMP-9.[14,15] These enzymes become dysregulated and contribute to extracellular matrix degradation, disruption of the endothelial glycocalyx and barrier,[16] leukocyte infiltration and exhaustion,[15] and organ dysfunction. Although we were unable to identify nanomedicine studies that directly target MMPs in sepsis, several

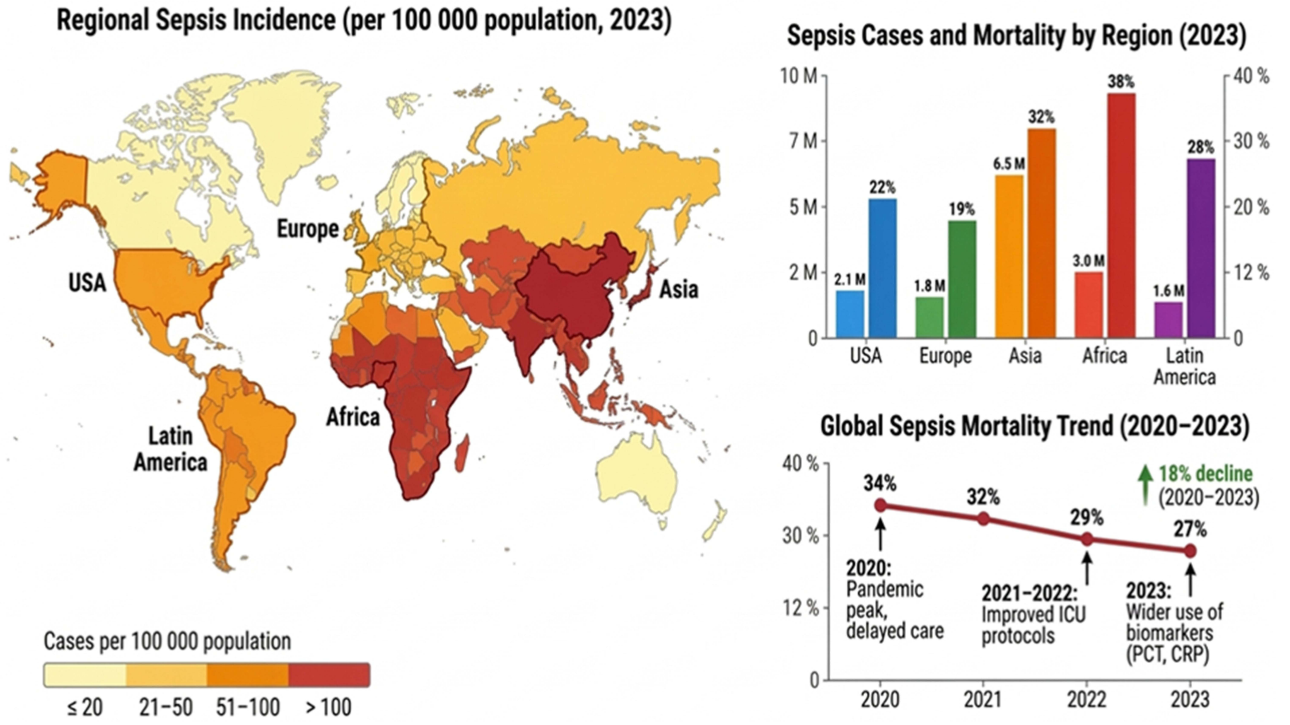

Figure 1 Global sepsis statistics (2020–2023). Data sources: WHO Sepsis Report 2023, Lancet Infection Diseases 2024, National Health Databases (2020–2023). This figure was created with Gemini.

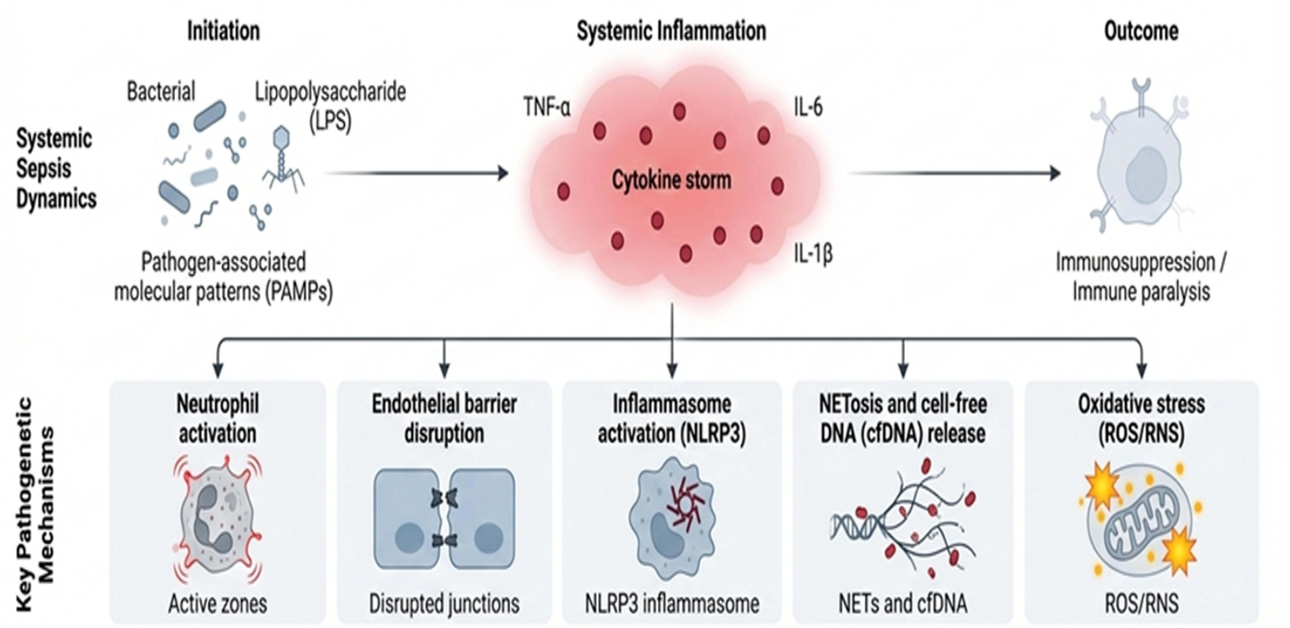

Figure 2 Pathophysiology of sepsis and nanomedicine potential intervention This figure was created with Gemini.

nanoparticle-based strategies have been developed in other inflammatory settings to modulate MMP expression or activity using siRNA[17] delivery or peptide/small-molecule inhibitors.[18]

Current treatments primarily rely on antibiotics to combat infection, alongside agents targeting inflammation and oxidative stress.[19] To improve outcomes, innovative drug delivery approaches are being explored, focusing on enhancing therapeutic targeting and bioavailability, particularly in the organs most affected by infection and inflammation.[20] These strategies also aim to expand the treatment landscape by incorporating biologics and localized therapies. Among these advancements, nanomedicine offers promising solutions through nanoscale carriers, enabling unique approaches to improve drug delivery, targeting precision, and overall treatment efficacy.[7]

The application of nanomedicine to sepsis offers unique advantages that partially overlap or completely differ from its traditional use in oncology, primarily due to the broader targeting scope, which shifts from specific cells and lesions to entire organs. Drug encapsulation within nanocarriers can significantly improve pharmacokinetic properties,[21] which are often disrupted during sepsis by inflammatory mediators, such as cytokines, that impair vascular function, permeability, and drug metabolism.[22] Additionally, physiological and pathological barriers, such as the extracellular matrix, are less prominent in sepsis compared to many solid tumors, partially simplifying drug delivery. Interestingly, biological barriers traditionally seen as challenges in nanomedicine can, in certain cases, enhance therapeutic performance or provide new avenues of treatment. One example is the formation of the protein corona (PC), which is typically associated with rapid clearance and reduced efficacy of nanocarriers.

In this scenario it is paramount to hallmark the heterogeneous nature of septic syndrome, that depends on infection source, age, comorbidities, and baseline immune status, which together shape distinct clinical and molecular profiles,[23,24] characterized by different patterns of circulating cytokines, damage-associated molecules, and immune cell activation states.[25] Such heterogeneity can influence the plasma proteome and, consequently, the composition and evolution of the PC that forms on nanoparticles during sepsis, as shown by studies where inflammatory status and disease stage altered corona signatures and enabled discrimination between sepsis and non-infectious systemic inflammation.[26,27] Because PC features govern nanoparticle opsonization, biodistribution, and cellular uptake, patient- and disease stage-specific differences are expected to modify organ targeting and clearance of nanocarriers.

Recent advancements have demonstrated the potential of rational particle design to harness the PC as a "decoy" system, improving therapeutic targeting and outcomes. This review highlights recent progress in nanomedicine for sepsis treatment and diagnosis, with a focus on leveraging PC formation to optimize carrier performance and therapeutic effects by exploiting decoy functions. The referenced papers were limited to those published within the last six years. Additionally, the language and some images were refined and generated using various Large Language Models, including ChatGPT, Monica, Peplexity, and Elicit.

Recent Nanodelivery Approaches to Combat Sepsis

While this specific topic has been extensively covered in previous literature,[28–30] this section aims to provide a comprehensive introduction of current nanodrug delivery systems applied to sepsis, highlighting potentialities and limitations. Pharmaceutical delivery represents a considerable but not exclusive portion of the research in the field, that is focusing also on anti-inflammatory materials, replacement therapy, and biological drug delivery.

Traditional Nanodelivery Approaches

Given the inflammatory nature of sepsis, targeting immune cells represents a highly investigated approach to mitigate systemic inflammation. The research teams led by Dr. Malik and Dr. Wang have harnessed the inherent affinity of albumin nanoparticles for neutrophils, which are pivotal in the sepsis cascade. These nanoparticles, synthesized through a process of albumin denaturation in ethanol followed by crosslinking with glutaraldehyde, exhibited enhanced internalization in activated neutrophils via Fcgamma receptor-mediated recognition. This platform effectively delivered the spleen tyrosine kinase inhibitor pinnaceatenol, decreasing neutrophil adhesion to inflammatory endothelium and reducing infiltration into the subendothelial space, a phenomenon observed across various tissues, including the lungs and genitalia[31] (Figure 3). Interesting the same platform was functional to define neutrophil heterogeneity and functional adaptations after inflammatory insult. In particular, two subsets of neutrophils were identified: ANPhigh neutrophils, which readily internalized the nanoparticles and exhibited pro-inflammatory properties, and ANPlow, which showed lower endocytosis and enhanced bacterial killing capabilities.[32] These cells were also well defined by differential surface biomarkers' expression and transcriptomic profile. By utilizing ANP, the study elucidated how these neutrophil subsets can be specifically targeted for therapeutic interventions, demonstrating that targeting ANPhigh neutrophils can effectively mitigates tissue inflammation while preserving the host-defense functions of ANPlow neutrophils. This approach not only advances the understanding of neutrophil biology in disease contexts but also highlights the potential of nanotechnology in developing precision therapies for inflammatory conditions. Recently, this platform has been

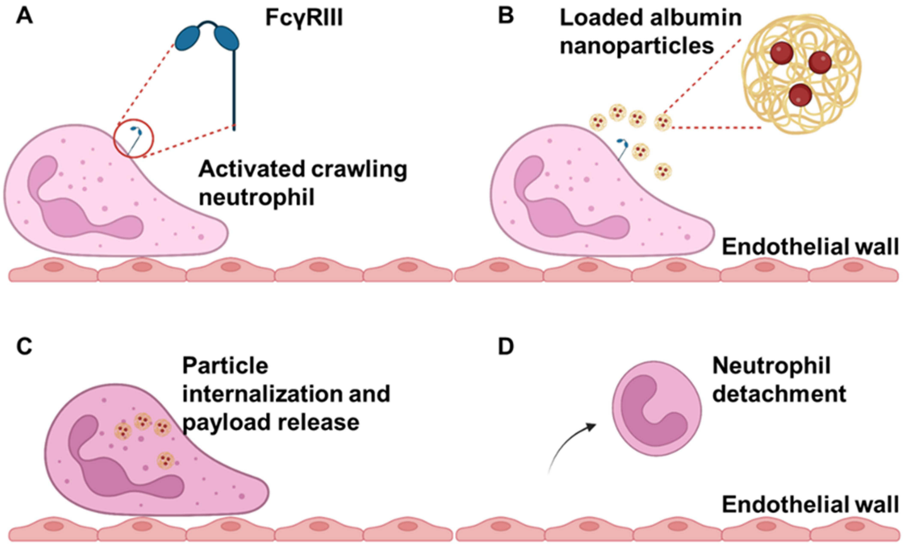

Figure 3 Ability of albumin nanoparticles to deliver a payload to activated neutrophils: (**A**) Activated Neutrophils infiltrating inflamed tissue expressing FCγ receptors; (**B**) Albumin nanoparticles binds the receptors and are internalized in the cells, (**C**) internalized particles release the therapeutic payload (ie. pinnaceatenol); (**D**) The payload determines neutrophil detachment decreasing the inflammatory process. This figure was created with Biorender.

conjugated with doxorubicin through a pH-sensitive linker, allowing for the controlled release of the therapeutic agent within the endosomal compartment post-internalization.[33] This mechanism leaded to neutrophil apoptosis, thereby regulating the immune response. The efficacy of this technology has been demonstrated in both LPS-induced sepsis models and ischemia-reperfusion scenarios, wherein neutrophils play a critical role in orchestrating the inflammatory response. Even though neutrophils represent major player in the development of this conditions, more factors and immune cells can be targeted to mirror the complexity of sepsis development.

To tackle the multifactorial nature of sepsis, current carriers' design is conceived to deliver multiple therapeutic agents concurrently. In this effort, nanocarriers are enabled to encapsulate various pharmaceuticals, such as anti-inflammatory drugs and antibiotics, within a single system that is usually modified with targeting molecules. This design allows the carriers to specifically accumulate in inflamed tissues, enhancing the efficacy of the treatment. For example, polymeric particles co-loaded with the antibiotic ciprofloxacin and the anti-inflammatory drug TPCA-1[8] have been shown to target inflamed endothelium through surface modification with anti-ICAM1 antibodies. The polymeric assembly was sensitive to the acidic pH and enzymatic content (such as lipase) characteristic of the infection micro-environment, allowing for disassembly and substantial payload burst release exclusively in diseased tissues. This approach aligns with recent trends in flash release and localized delivery to enhance therapeutic efficacy avoiding the use of long-circulating carriers.[34,35] This delivery platform demonstrated a strong ability to bind pathogens at acidic pH, likely due to electrostatic interactions between the protonated amines on the particles and the bacteria. In vitro studies confirmed their high targeting properties, and in vivo experiments showed significant efficacy against Pseudomonas aeruginosa infections. Another strategy for co-delivering anti-inflammatory and antibiotic drugs has been based on a core/shell design following modern concepts of biomimicry.[36,37] This platform comprised a core of silver metal-organic framework (AgMOF), known for its high drug-loading capacity and antimicrobial properties.[38] The AgMOF was loaded with the broad-spectrum antibiotic meropenem and the RAGE inhibitor FPS-ZM1 to block the HMGB1/RAGE axis and mitigate inflammatory responses. The shell derived from the cell membrane of lipopolysaccharide (LPS)-treated bone marrow stem cells (BMSC), which retained immune-regulating molecules like ICAM-1, VCAM-1, and PD-1 for targeting inflamed tissues. This formulation, FZ/MER-AgMOF@Bm, demonstrated a dual effect: on one hand it reduced inflammatory cytokines and promoted macrophage M2 polarization, while on the other hand it released silver ions and meropenem for antibacterial action. The membrane coating enhanced lung targeting and ensured safe clearance in the liver. In an in vivo Cecal Ligation and Puncture (CLP) sepsis model, FZ/MER-AgMOF@Bm showed superior therapeutic effects, significantly reducing pro-inflammatory cytokines, stabilizing body temperature, and achieving a 60% survival rate at six days. Histological analysis revealed reduced lung and liver injury, along with decreased bacterial counts in blood and peritoneal fluid. These findings underscore the potential of BMSC membrane-coated nanoparticles as a promising treatment for sepsis. On the other hand, it has to be highlight that increasing the complexity of the carriers very often results in a significant increase in regulations approval and consequent clinical translation.[37]

In this scenario, it is important to highlight the ongoing efforts to influence the inflammasome process, which plays a central role in the pathogenesis of sepsis.[39,40] Given its significance, optimizing the design of carriers is essential. One such strategy involved liposomes co-encapsulating MCC-950, an NLRP3 inflammasome inhibitor, and disulfiram, a gasdermin D inhibitor.[41] The formulation with DOPC and DSPE-PEG ensured enhanced drug solubility, bioavailability, and sustained release. The mechanism of action involved MCC-950 preventing NLRP3 oligomerization, thereby inhibiting inflammasome activation, while disulfiram blocked gasdermin D-mediated pore formation, reducing IL-1β cytokine release. The dual-drug nanoparticles demonstrated superior efficacy compared to individual drug nanoparticles or free-drug combinations, showing significant inhibition of IL-1β and active caspase-1 expression in vitro. They also provided complete protection in an LPS-induced sepsis mouse model. The innovation of this work lay in the synergistic therapeutic approach, which reduced required drug dosages, minimized toxicity, and ensured sustained action. This work represents a significant advancement in overcoming limitations of existing inflammasome inhibitors for sepsis therapy, though—like many promising approaches in the field—it requires expanded studies in humanized models and diverse in vivo sepsis models.

Nontraditional Nanodelivery Approaches

Nanomedicine can enhance the therapeutic options available for sepsis, particularly through biologics offering targeted immune modulation. Unlike conventional treatments, which often fail to control hyperinflammation, biologics like RNA-based therapies can precisely regulate gene expression and inhibit pro-inflammatory mediators.[42] Vitamin-derived lipid nanoparticles (VLNPs)[43] were designed to facilitate adoptive macrophage transfer for the treatment of multidrug-resistant (MDR) bacterial sepsis. These systems delivered mRNA that encoded an antimicrobial peptide (AMP-IB367), which was linked to cathepsin B through a cleavable linker. The synthesis of lipid vitamins for the final particle formulation ensured the presence of tertiary amines, which were crucial for the efficient loading of mRNA. Notably, the formulation based on vitamin C demonstrated the highest transfection efficiency. Incorporating cathepsin B into the construct favored AMP-IB367 trafficking to lysosomes, significantly enhancing bacterial clearance. VLNPs not only protected the mRNA but also ensured its efficient delivery and promoted lysosomal activation, effectively targeting MDR bacteria such as Staphylococcus aureus and Escherichia coli. This innovative approach presented a groundbreaking alternative to traditional antibiotics, addressing the pressing challenge of antimicrobial resistance. The characteristics of the material used to generate the carriers can be exploited to mitigate the damage induced by sepsis. Wang et al,[44] for example, investigated the protective effects of zero-valent iron nanoparticles (nanoFe) against sepsis and septic heart failure, which are significant concerns in critical care due to high mortality rates. Their research revealed that nanoFe provided cardioprotective benefits through several mechanisms. It reduced inflammation by lowering levels of pro-inflammatory cytokines, minimizing neutrophil accumulation, and decreasing oxidative stress in myocardial tissues. Additionally, nanoFe enhanced the expression of antioxidant mediators such as Nrf2, NQO1, and HO-1, and improved mitochondrial function by upregulating proteins involved in mitochondrial biogenesis, including SIRT1 and PGC-1α. The nanoparticles also positively influenced endoplasmic reticulum stress by regulating UPR-related proteins like GRP78 and activating ATF6, thereby preventing cell apoptosis. Finally, the activation of the AMPK pathway by nanoFe enhanced cellular energy metabolism, leading to improved cardiac function under septic conditions (Figure 4).

Pan et al[45] directed their research towards modulating macrophage responses to achieve a more effective antibiotic effect. Their study presents a novel delivery system utilizing β-glucan-coupled superparamagnetic iron oxide nanoparticles (BSNPs), designed to induce trained immunity. This strategy enhanced, nonspecific immune response in monocytes and macrophages resulting from epigenetic reprogramming following exposure to specific pathological and inflammatory stimuli. These nanoparticles capitalize on the biocompatibility of superparamagnetic iron oxide (SPIO) and the immune-stimulating properties of β-glucan, effectively reprogramming macrophages to enhance their phagocytic activity and inflammatory cytokine production. The mechanism of action is primarily mediated through the activation of the mTOR signaling pathway, which amplifies cellular responses to bacterial infections and stimulates the production of crucial pro-inflammatory markers such as TNF-α, IL-1β, and IL-6. The efficacy of BSNPs has been validated in mouse models of sepsis induced by Escherichia coli and CLP, demonstrating significant reductions in bacterial burden, improved survival rates, and alleviated organ injuries compared to individual or combined treatments of SPIO and β-glucan. This approach underscores the potential of nanotechnology in reprogramming immune cells, providing broad-spectrum protection against infections and secondary complications, thus addressing the urgent need for effective sepsis therapies. The significance of BSNPs lies in their capacity to enhance immune resilience while overcoming the limitations of traditional treatments, presenting a promising strategy to combat the high mortality and morbidity associated with sepsis. Great consideration is currently given also to systems capable of targeting secondary elements of the inflammatory process, such as reactive oxygen species (ROS) and proteases, which biology is often interconnected.[46] In this effort, Yim et al[47] synthesized three types of two-dimensional (2D) transition metal dichalcogenide nanosheets. Experiments evaluating their ROS and reactive nitrogen species (RNS) scavenging capabilities showed that they effectively eliminated mitochondrial and cytosolic ROS and RNS in inflammatory cells. Tungsten diselenide nanosheets (WS_2), in particular, demonstrated superior efficacy in reducing excessive inflammatory cytokine secretion while scavenging ROS and RNS, leading to a significantly improved survival rate in severe sepsis mouse models (up to 90%). Furthermore, pharmacokinetic analysis revealed that WS_2 nanosheets were completely excreted from mice within three days following intravenous administration. Another approach to mitigating the inflammatory properties of sepsis through nanomedicine relied on the ability of particles to promote the degradation of inflammatory molecules. In this scenario, long-acting

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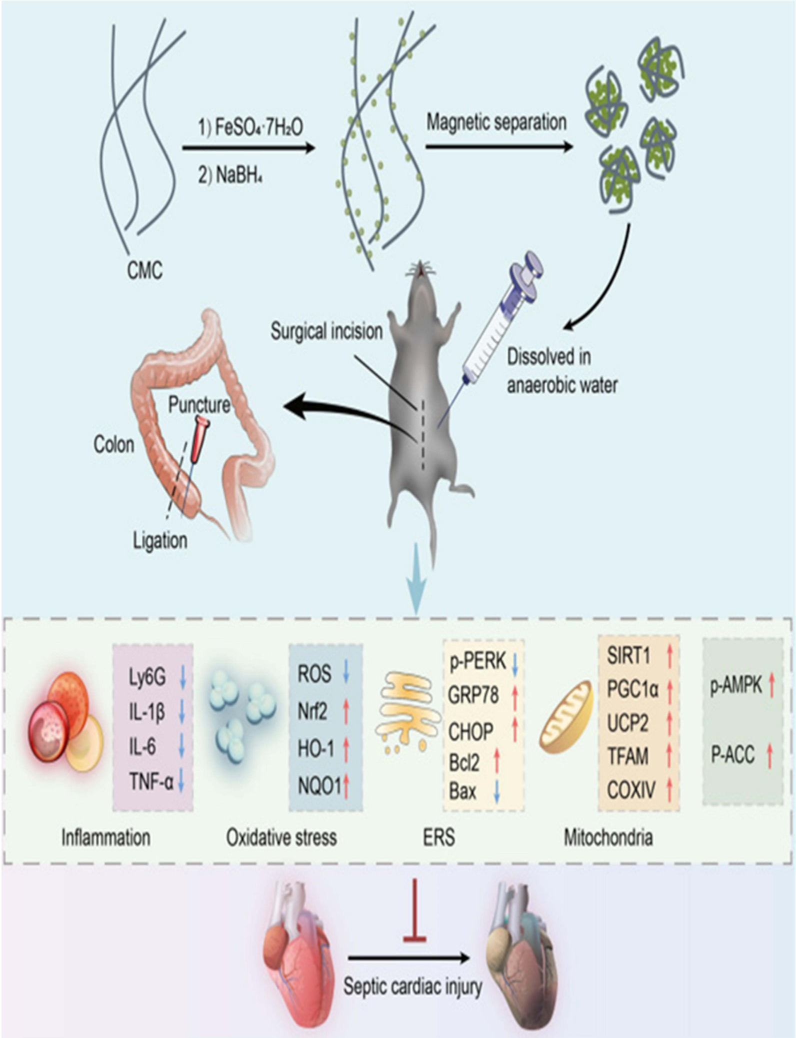

Figure 4 Synthesis and effects of zero-valent iron nanoparticles (nanoFe) against sepsis and septic heart failure (from Wang et al[33]): nanoFe demonstrated cardioprotective benefits via several mechanisms including lowering the levels of pro-inflammatory cytokines, minimizing neutrophil accumulation, decreasing oxidative stress in myocardial tissues, improving Mitochondrial Function, regulating Endoplasmic Reticulum Stress and activating.

nanoparticulate DNase-1 was developed as a therapeutic strategy for mitigating SARS-CoV-2-induced sepsis, focusing on its ability to reduce neutrophil extracellular trap (NET) formation and cytokine storms.[48] The carrier structure consisted of polydopamine-coated poly(lactic-co-glycolic acid) (PLGA) nanoparticles functionalized with polyethylene glycol (PEG) and immobilized DNase-1. This design enhanced the enzyme's stability and activity by extending its half-life in vivo and protecting it from rapid degradation. The DNase-1 coating enabled the nanoparticles to degrade cell-free DNA (cfDNA), a key component of NETs, thereby reducing inflammation, neutrophil activity, and related cytokine production. By targeting NETosis and suppressing excessive immune responses, the nanoparticulate DNase-1 formulation showed promise in alleviating sepsis-related complications and improving survival outcomes in preclinical models.

Among compounds that may reduce sepsis-associated damage, NAD+ is crucial for restoring cellular energy, regulating inflammation, and preventing cell death. However, it cannot be freely administered due to its short half-life in serum and inability to cross cell membranes. To address this, NAD(H)-loaded nanoparticles (NPs) were developed to enhance the therapeutic potential of nicotinamide adenine dinucleotide (NAD+) and its reduced form (NADH) in treating sepsis.[49] The carrier structures included lipid-coated calcium phosphate (NAD+-LP-CaP) and lipid-coated metal-organic framework (NADH-LP-MOF) nanoparticles, designed to improve cellular uptake of free NAD(H). These nanoparticles facilitated direct cytosolic delivery by utilizing pH-sensitive cores that dissolve in acidic endosomal environments, triggering osmotic swelling for endosomal escape. This mechanism prevented premature drug release and protected NAD(H) from degradation. Once inside the cells, the NPs replenish the intracellular NAD(H) pool, restoring the NAD+/NADH ratio, enhancing energy supply, and preventing inflammation-induced energy depletion. The NAD(H)-loaded NPs also exhibited strong anti-inflammatory effects by reducing pro-inflammatory cytokines (eg., TNF-α and IL-6) and inhibiting inflammasome activation, pyroptosis, and apoptosis in immune and endothelial cells. They further prevented vascular endothelial damage by stabilizing tight junction proteins like VE-cadherin. In vivo studies demonstrated significant therapeutic benefits of NAD(H)-loaded NPs in mouse models of endotoxemia, polymicrobial sepsis, and secondary infections, leading to reduced mortality, cytokine storms, and organ damage. This work highlights the potential of NAD(H)-loaded NPs as a novel immunomodulatory and energy-restoring treatment for sepsis and related inflammation-related diseases. The design of structures with inherent anti-septic and anti-inflammatory or able of biological activity definitely provide several advantages compared to traditional carriers. However, more investigation should be dedicated to the long-terms effect of these technologies since they are often based on inorganic elements or they can affect delicate homeostatic balances in our body.

Protein Corona Occurrence During Sepsis

PC refers to the layer of proteins that adsorb onto the surface of nanoparticles when they are dispersed in biological fluids. Understanding PC is crucial as it significantly influences the behavior, therapeutic efficacy, toxicological potential, and overall fate of nanoparticles in the body.[50,51] Although various molecules can adsorb to nanoparticle surfaces, research has primarily focused on proteins due to their prevalence in biological fluids and their diverse functional properties.[52] Extensive studies—over 2000 published manuscripts[53]—have explored this phenomenon. The PC affects nanoparticle processing, biodistribution, toxicity, and clearance, which are vital for the development of safe and effective nanomedicine products.[51,53] While PC can obstruct therapeutic efficiency by masking surface antigens and effectors, it may also unpredictably enhance immune responses.[54] Ultimately, the PC defines the biological identity of nanocarriers, influencing interactions with target and immune system cells both in vitro and in vivo. Additionally, analyzing the PC can yield insights into disease proteomes, aiding in the identification of potential diagnostic and therapeutic targets.[51] PC formation is affected by nanoparticle properties, including surface charge, hydrophobicity, and shape.[55] For instance, rod-shaped nanoparticles adsorb more proteins than spherical ones, with differences in immunoglobulin and albumin adsorption.[55] On the other hand, also the biological fluid in which the carriers are dispersed has significant impact on the composition of the absorbed proteins. While the generation of protein corona is a relatively simple phenomenon (usually it consists of one step incubation), many variables can affect the quality of the PC including plasma protein concentration/nanoparticle ratio, time of incubation and sample pH.[56] The concept of personalized protein corona has emerged in the last 2 decades, suggesting that variations in plasma protein composition (ie., presence of a disease) due to different physiological conditions can be detected using ad hoc selected arrays of nanoparticles.[57] In this scenario, recent evidence indicates that investigating the PC can lead to significant advances in understanding disease progression. For example, in cancer research, PC profiles can serve as unique "fingerprints" for identifying and discriminating between different cancer types, including breast and prostate cancers.[58] In the context of sepsis, numerous studies have focused on this critical angle. We believe that the first work to be cited is the recent paper by Shaw et al,[26] which demonstrated the dynamic nature of PC during inflammation. This study demonstrated that during acute systemic inflammation, particularly after LPS treatment in a murine model (often used as experimental sterile model of sepsis), the composition of the biomolecular corona changes significantly over time. The findings revealed that NPs coated with plasma collected three hours post-LPS exhibit enhanced binding to macrophages compared to those from healthy mice, indicating increased recognition in inflammatory conditions. The 3-hour coronas triggered a strong pro-inflammatory response in macrophages, elevating cytokines such as TNFα, IL-6, and CXCL1, while coronas generated eight hours post-LPS challenge leaded to the adsorption of less inflammatory markers, reflecting the potential acquired inflammatory power of the particles. The study showed that NPs could differentially engage with immune-modulating molecules on macrophages, with the 3-hour coronas promoting co-stimulatory signals and the 8-hour coronas favoring co-inhibitory signals (Figure 5).

Using pharmacological and genetic methods, the research confirmed that these immune responses occurred through the TLR4/MyD88/NF-κB signaling pathway. The concept of a "personalized biomolecular corona" is emphasized, highlighting how individual patient conditions can affect NP behavior and outcomes in clinical trials. Overall, this research advocates for a tailored approach to nanomedicine, stressing the need to consider patient-specific factors in the design and application of therapeutic nanoparticles. These data align with our recent work[59] showing that the biodistribution of albumin nanoparticles and in particular lung accumulation and clearance in liver and spleen depends on the time in which particle are administered after LPS insult. In particular, the highest pulmonary accumulation was observed at 6 hours after a non-lethal dose of LPS intraperitoneally administered. At this time point it was also registered the lower level of pulmonary clearance, confirming the occurrence of complex dynamics during the inflammation-resolution process. In some cases, protein corona has been exploited to enhance therapeutic properties of materials like silver, which possess inherent antimicrobial properties. In particular it was recently shown that coating silver nanoparticles (AgNPs) with serum proteins can improve their antibacterial effectiveness.[60] The PC generated ex-vivo facilitated better interaction with the immune system and enhanced the stability and bioavailability of AgNPs in vivo. In experiments with mice infected with a multidrug-resistant strain of E. coli, the modified silver nanoparticles (MS-AgNPs) demonstrated significant efficacy, reducing bacterial load in the bloodstream and organs compared to uncoated nanoparticles. The presence of serum proteins lessened the inflammatory response typically seen in bacterial infections, as indicated by lower levels of pro-inflammatory cytokines like IL-6 and TNF-α. The study found that MS-AgNPs resulted in improved survival rates among treated mice, highlighting their potential as a therapeutic option for severe infections. By demonstrating that the protein coating enhanced the antibacterial properties of silver nanoparticles, this research presents a promising approach to combat antimicrobial resistance and supports further development of nanoparticle-based therapies in clinical settings.

New Artificial Intelligence Tools to Investigate Protein Corona

As aforementioned, there are many papers describing PC occurring during sepsis treatment, with detailed OMICS techniques used for this purpose.[61–63] In this review, we want instead to focused on recent advantages that mathematical models[64] including machine learning (ML) and artificial intelligence (AI) are providing to the field. In the scenario of generating decoy systems in sepsis treatments, in silico approached can provide significant advantages in terms of prediction of adsorption dynamics.

The implementation of standardized protocols in protein corona methodologies offers the capacity to generate extensive multi-omics datasets, which could serve as a robust foundation for training machine learning (ML) models.[65,66] These AI driven approaches are particularly valuable considering that characterizing relative protein

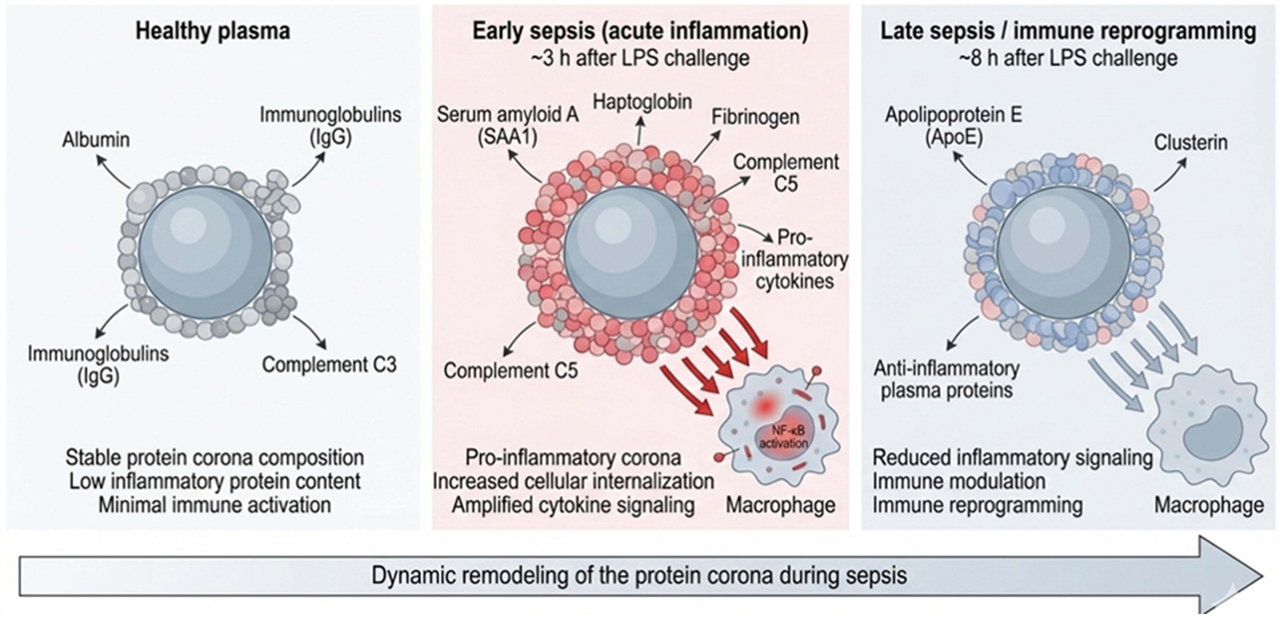

Figure 5 Dynamic formation and remodeling of the PC during sepsis. This figure was created with Gemini.

abundance (RPA) – a critical parameter for describing corona composition – via traditional liquid chromatography-tandem mass spectrometry (LC-MS/MS) is frequently laborious, expensive, and prone to variability,[65,66] while the expertise necessary for fine OMICS elaboration is not always available in every institute.

By managing high-dimensional data, ML algorithms can extract crucial information from complex variables – ranging from nanoparticle physicochemical properties (eg., size, surface charge, hydrophobicity) to specific incubation and isolation conditions – to accurately predict adsorption profiles and dynamic competition.[66–68] Beyond mere compositional prediction, these models provide critical insights into biological-material interactions that are difficult to observe experimentally, allowing researchers to correlate specific protein signatures with downstream outcomes including immunogenicity, biodistribution, and toxicity.[67,69] Ultimately, the application of ML establishes a cost- and time-efficient framework for rational nanomedicine design that circumvents the limitations of wet-lab experimentation while significantly reducing the number of animals required for efficacy testing[65,69] (Figure 6).

In practice, foundational studies successfully demonstrated the feasibility of AI in predicting protein-nanoparticle interactions, evolving from binary classification to complex quantitative modeling. Findlay et al[70] established early predictive frameworks using Random Forest (RF) classifiers to correlate protein biophysicochemical properties, basic nanoparticle characteristics, and solution conditions with protein adsorption on silver nanoparticles. Expanding the scope to quantitative predictions, RF regression can be used to estimate the specific RPA and functional composition (eg., apolipoproteins, immune proteins) across a heterogeneous library of nanoparticles, achieving high predictive accuracy.[71] Ouassil et al[72] refined these classification strategies specifically for single-walled carbon nanotubes by developing a model that predicts adsorption affinity based solely on protein sequence data, thereby eliminating the reliance on protein structural information. Recent advances in this methodology were performed by conducting a comprehensive comparative analysis of six distinct machine learning algorithms – Extremely Randomized Trees (ERT), RF, Gradient Boosted Decision Trees (GBDT), eXtreme Gradient Boosting (XGBoost), Light Gradient Boosting Machine (LightGBM), and Neural Networks (NN) – to predict RPA. Fu et al[30] proposed as a novel two-step predictive hierarchy: a binary classification task using all six algorithms to determine adsorption probability, followed by a regression task utilizing the top three performers (ERT, RF, and GBDT) to quantify specific abundance. Their analysis revealed that ERT consistently outperformed other architectures in classification metrics. In the regression task, ERT performed best according to the root mean square error (RMSE) metric, while RF performed best according to the R^2 metric. To

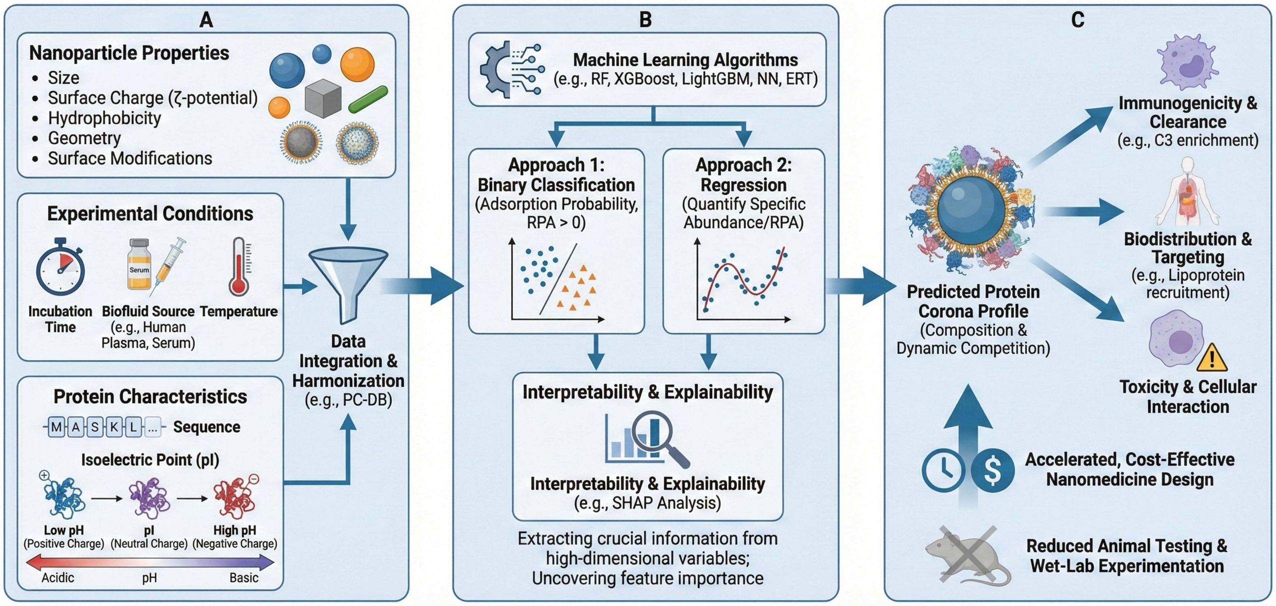

Figure 6 ML-driven workflow for predicting protein Corona formation and biological fate: (**A**) Multi-source data inputs and standardization; (**B**) ML-driven predictive modeling frameworks; (**C**) Predicted biological outcomes and design acceleration. This figure was created with Gemini.

provide transparency into feature contributions, the study successfully integrated Shapley Additive Explanations analysis for both classification and regression tasks.

Extending aforementioned predictive capabilities beyond traditional nanoparticles, Huzar et al[73] expanded the application of AI into programmable biomaterials, solving a complex classification task to characterize the protein corona of DNA nanostructures. By utilizing XGBoost to analyze a library of varied geometries, they achieved a high predictive accuracy, demonstrating that non-DNA surface modifications – such as cholesterol functionalization and cationic polymer coatings – exert a significantly more profound influence on corona composition than the nanostructure's structural properties. Furthermore, their methodology refined the predictive scope by distinguishing between proteins that are merely "present" versus those that are specifically "enriched" (statistically higher abundance than in bulk serum). While this "enrichment" classifier is designed to be robust against background serum noise and potentially generalizable to other biological fluids, the authors note that this generalizability requires further experimental verification.

Recognizing that the success of such predictive frameworks is intrinsically linked to the quality and volume of the training data, Canchola et al[74] addressed the systemic challenge of fragmented datasets by establishing the Protein Corona Database (PC-DB), a centralized repository integrating quantitative profiles for 2497 proteins across 817 nanoparticle formulations from 25 years of literature. Leveraging this expansive dataset, they deployed advanced gradient boosting models (LightGBM and XGBoost) to confirm that nanoparticle size and ζ-potential are the dominant predictors of protein adsorption. Crucially, their work mapped these physicochemical properties to specific biological fates: silica, polystyrene, and lipid-based nanoparticles (<100 nm) were found to preferentially recruit lipoproteins (APOE, APOB-100) associated with receptor-mediated tissue targeting, whereas metal and metal-oxide nanoparticles frequently enriched complement component C3, signaling a higher propensity for immune recognition and rapid clearance.

The integration of AI and ML into nanomedicine represents a transformative shift from trial-and-error experimentation to rational, data-driven design.[67,68] These computational tools offer significant advantages, including the ability to model non-linear relationships between nanoparticle properties and biological outcomes, the acceleration of formulation screening, and the reduction of costs associated with in vivo validation.[67] However, significant challenges remain. The primary limitation is the scarcity of high-quality, standardized datasets; models trained on in vitro data often fail to generalize to the complex in vivo environment due to the lack of physiological parameters in training sets.[67,68] Furthermore, the lack of interpretability in complex algorithms complicates the understanding of the underlying decision-making process, potentially hindering regulatory acceptance.[67,68] To overcome these hurdles, there is a pressing need for interdisciplinary collaboration between computational scientists and biologists to develop standardized reporting protocols, such as FAIR (Findable, Accessible, Interoperable, Reusable) principles, and iterative refinement cycles.[65,67,68]

Within the specialized context of sepsis therapy, a critical gap remains: the absence of predictive frameworks specifically for nanoparticles designed to treat this condition. It is imperative that future computational strategies focus on training models with sepsis-specific proteomic libraries. Closing this gap is a prerequisite for achieving the precision required to effectively treat immune dysregulation through personalized nanomedicine.

Decoy Strategies: Utilizing Nanoparticles to Combat Sepsis-Driven Inflammation

While PC formation is a spontaneous process largely driven by stochastic protein adsorption, and decoy nanoparticles are rationally engineered to favor interactions with specific harmful molecules, both ultimately act through selective adsorption of circulating biomolecules onto the nanoparticle surface. This shared mechanistic basis justifies the core structure of this work, in which PC and decoy systems are discussed within a unified framework. Many technologies have been developed as decoys for inflammatory molecules released during sepsis.[6] A recent example of this approach involved the design of hydrogel nanoparticles that absorbed and neutralized histones released into the bloodstream by neutrophils during the immune response, which are significant inflammatory mediators of this condition.[75] The mechanism of action for these particles relied on their unique design, enabling them to bind effectively to histones—positively charged macromolecules—through a combination of hydrophobic interactions and electrostatic forces. By capturing histones in the bloodstream, the nanoparticles prevented these proteins from causing cell membrane damage and promoting complications such as coagulation and further inflammation. This selective binding was crucial in mitigating the toxic effects of histones on endothelial cells, thereby protecting vascular integrity and function. To maximize their therapeutic effects, the hydrogel nanoparticles were engineered for extended circulation time within the bloodstream, enhancing their ability to continuously neutralize histones over a prolonged period. This feature was particularly important in preclinical settings, as it allowed for sustained therapeutic action, improving outcomes in animal models of sepsis. Prolonged circulation was achieved through extensive optimization of PEG length and density, resulting in a coating that provided both extended circulation time and high affinity for histones. This technology demonstrated the ability to neutralize histones even after these proteins had adhered to cell surfaces, further reducing their harmful effects and preventing the activation of inflammatory pathways. While effective tools to tackle sepsis-related damage, these nanoparticles might be used for understanding of the underlying mechanisms of sepsis, potentially guiding future innovations in critical care therapies. Sung et al[76] tested maca-derived lipid nanoparticles (MDNPs) from Lepidium meyenii Walp as a simple, plant-based strategy to reduce sepsis-driven inflammation. These lipid-rich particles, approximately 175 nm in size, were well tolerated and efficiently internalized by macrophages. They mitigated activation markers and directly bound pro-inflammatory cytokines, such as IL-6 and TNF-α, thereby lowering NF-κB signaling. In mouse models of endotoxemia and polymicrobial sepsis, MDNPs significantly reduced circulating cytokines, minimized tissue injury, and improved survival rates. Notably, proteomic profiling revealed that in inflamed plasma, the nanoparticles acquired a disease-specific "multimodal" protein corona enriched not only with cytokines but also with acute phase proteins, such as haptoglobin, serum amyloid A1, and SerpinA3N. Pathway analysis indicated that these proteins were linked to acute phase response networks driven by IL-6, TNF, and IL-1β. Importantly, MDNPs with this PC did not activate macrophages, suggesting that the adsorption of these proteins coincided with functional neutralization of inflammatory signals. Overall, MDNPs functioned as broad-spectrum nanosponges that sequestered various inflammatory mediators through a context-dependent corona, providing a practical approach to mitigate hyperinflammation in sepsis.

Given the high-precision of current methods in determining PC, relatively old technologies should be revisited and re-evaluated under this new standpoint. This is the case of a recent effort that turned the nanotherapeutic AmBisome in a diagnostic tool. AmBisome is an approved liposomal formulation[77] of amphotericin B, composed of stable, unilamellar vesicles (<100 nm) comprising hydrogenated phosphatidylcholine, cholesterol, and DSPG. This design significantly improved pharmacokinetics by increasing plasma exposure and decreasing clearance compared to conventional lipid complexes and other formulations. Additionally, it reduced toxicity, particularly in terms of infusion reactions and nephrotoxicity. Clinically, AmBisome has been approved for empiric fungal therapy in febrile neutropenia, cryptococcal meningitis in HIV, refractory Aspergillus/Candida/Cryptococcus (or when deoxycholate is contraindicated), and visceral leishmaniasis. Papafilippou et al[27] exploited Ambisome as "nano-scavengers" to enrich diagnostic signals from human plasma and distinguish sepsis from non-infectious systemic inflammation (SIRS). By incubating these liposomes ex vivo with patient plasma and profiling the resulting PC by LC-MS/MS, the authors found quantitative and qualitative corona shifts in disease, identifying 67 differentially abundant proteins that separated sepsis from SIRS, whereas C-Reactive Protein levels did not discriminate the groups. Notably, the sepsis coronas were enriched for complement components, acute phase and host-defense factors, and proteins linked to bacterial infection pathways (eg., LBP, FCN2, APCS, VTN, ANXA2), further supporting the concept that the corona reflects pathophysiologic states. The approach effectively filtered out highly abundant background proteins, amplified low-abundance markers, and yields a multianalyte signature that outperformed single markers for this clinically challenging differential diagnosis. Following current trends in nanomimicry,[78] macrophage-like nanoparticles (MΦ-NPs) comprising PLGA nanocarriers coated with macrophage membranes have been designed to manage sepsis by dual detoxification processes: neutralizing endotoxin (LPS) and sequestering inflammatory cytokines.[79] The membrane coating preserved key pattern-recognition and cytokine receptors (eg., CD14, TLR4, IL-6 and TNF receptors), enabling the particles to act as decoys via enhanced expression of LPS binding proteins reduced downstream cell activation, nitric oxide production, endothelial E-selectin expression, and systemic cytokine surges. In mouse endotoxemia and E. coli bacteremia, MΦ-NPs lowered plasma IL-6/TNF, limited bacterial dissemination in blood and spleen, and improved survival. While the study focuses on receptor-mediated binding rather than an emergent PC, it underscores how a biologically authentic nanoparticle surface dictates selective adsorption/neutralization of soluble mediators, effectively interrupting the LPS–TLR4 axis and cytokine amplification to blunt the sepsis cascade. Scavenging LPS broadens the concept of the PC to include other inflammatory molecules of non-proteinaceous nature. Another example is represented by targeting cell-free DNA (cfDNA), which triggers Toll-like receptor 9 (TLR9)-mediated inflammatory pathways. A recent study introduced polyethylenimine-functionalized mesoporous silica nanoparticles (MSN-PEI) as cfDNA scavengers, designed with varying charge densities to optimize binding and therapeutic effects.[80] These nanoparticles effectively accumulated in inflamed tissues, had prolonged retention, and exhibited reduced systemic toxicity compared to soluble nucleic acid-binding polymers (NABPs). In murine models of severe sepsis induced by CLP and systemic inflammatory response syndrome (SIRS) triggered by CpG injection, MSN-PEI nanoparticles were administered intraperitoneally. They successfully scavenged cfDNA, inhibited TLR9 activation, and reduced pro-inflammatory cytokines such as TNF-α and IL-6, while reversing M1 macrophage polarization. Higher charge density MSN-PEI nanoparticles demonstrated superior efficacy compared to lower charge density variants. Histopathological analysis confirmed reduced inflammatory cell infiltration and tissue injury, indicating improved organ function. Overall, this innovative use of biodegradable, charge-tunable nanoparticles presents a promising therapeutic strategy for severe sepsis by effectively neutralizing inflammatory mediators and addressing immune dysregulation.

In line with this approach, Liu et al[81] developed multifunctional tannic acid-Zn^{2+}-gentamicin nanoparticles (TA-Zn-Gen NPs) to target multiple sepsis mediators, including cfDNA. These particles also inhibited macrophage recruitment, scavenged ROS, and reduced nitric oxide production induced by bacterial LPS, while exhibiting potent antibacterial activity. In vivo tests in a CLP-induced sepsis model revealed that TA-Zn-Gen NPs significantly lowered cfDNA levels, inhibited TLR9 activation, decreased macrophage polarization and ROS levels, and reduced pro-inflammatory cytokines (TNF-α and IL-6). The treatment also led to superior bacterial clearance and less organ damage compared to untreated controls. The different characteristics of these technologies are shown in Table 1.

Current Limitations and Future Prospects of Decoy Strategies in Sepsis Condition

Despite the promise of nanodecoy designs, several limitations may hinder their ability to meet clinical standards. One major challenge lies in pharmacokinetics and biodistribution: it is difficult to achieve both prolonged circulation and robust accumulation in inflamed tissues, especially in sepsis, where heightened immune activity promotes rapid clearance by the mononuclear phagocytic system.[64] Additionally, many nanodecoys behave as broad-spectrum "sponges," particularly when designed to generate multimodal protein coronas enriched in cytokines and acute-phase proteins. Such non-selective adsorption can perturb immune homeostasis, causing off-target effects or unintended sequestration of beneficial factors and thereby dampening harmful inflammation at the cost of depleting protective components.

Table 1 Nanoparticle-based decoy and scavenger technologies targeting inflammatory mediators in sepsis

Technology	Description	Mechanism	Challenges
Hydrogel Nanoparticles (NPs)[75]	Designed to absorb and neutralize histones released during the immune response.	Binds effectively to positively charged histones via hydrophobic interactions and electrostatic forces.	Achieving prolonged circulation and targeted accumulation in inflamed tissues; rapid clearance.
Maca-Derived Lipid NPs (MDNPs)[76]	Plant-based nanoparticles that sequester pro-inflammatory cytokines like IL-6 and TNF-α.	Functions as broad-spectrum nanosponges, binding various inflammatory mediators.	Non-selective adsorption can disrupt immune homeostasis and deplete protective factors.
Macrophage Membrane-Coated NPs (MΦ-NPs)[78]	Nanoparticles designed to neutralize endotoxins and sequester inflammatory cytokines.	Preserves pattern-recognition receptors to enhance binding and reduce downstream cell activation.	Production complexity and cost; potential residual immunogenicity and long-term accumulation concerns.
Polyethylenimine-Functionalized Mesoporous Silica NPs (MSN-PEI)[80]	Scavengers for cell-free DNA (cfDNA) that trigger inflammatory pathways.	Accumulates in inflamed tissues, inhibits TLR9 activation, and reduces pro-inflammatory cytokines.	Scalability issues; preclinical success may not predict human outcomes due to sepsis heterogeneity.
Tannic Acid-Zn^{2+}-Gentamicin NPs (TA-Zn-Gen NPs)[81]	Multifunctional nanoparticles targeting multiple sepsis mediators, including cfDNA.	Inhibits macrophage recruitment, scavenges reactive oxygen species (ROS), and exhibits antibacterial activity.	Complex design and production challenges; potential toxicity concerns.

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Scalability, safety, and translational feasibility further complicate the development of complex designs, especially biomimetic systems, which are costly, technically demanding, and challenging to standardize for large-scale clinical use. Concerns about toxicity, including residual immunogenicity and long-term accumulation, also remain. While adsorption or affinity binding onto nanodecoys can mitigate the toxicity of inflammatory mediators, the same mechanisms are increasingly exploited to build multifunctional, biomimetic carriers, making rigorous short- and long-term safety evaluation indispensable for every new platform.[37] Finally, preclinical success in murine models such as CLP or endotoxemia does not necessarily translate to humans, owing to sepsis heterogeneity, limited patient-scale data, and stringent regulatory requirements for novel nanotherapeutics.[82,83] Addressing these gaps will require integrating computational and AI tools to predict protein corona formation and nanoparticle behavior in diverse patient contexts, coupled with explicit incorporation of sepsis endotypes and host factors—age, comorbidities, and immune competence—into corona-sensitive nanodecoy design. In parallel, surface-engineering strategies should broaden their portfolio of targets, including key inflammatory effectors such as matrix metalloproteinases, which are still largely overlooked in current decoy concepts.

Conclusions

PC engineering and decoy nanoparticle strategies represent a paradigm shift in the treatment and diagnosis of sepsis, addressing its multifactorial nature through innovative nanomedicine approaches. The PC, formed through nanoparticle interactions with biological fluids, has been shown to significantly influence therapeutic outcomes by modulating nanoparticle biodistribution, immune recognition, and targeting capabilities. Harnessing this dynamic layer has enabled the development of tailored nanoparticles that adapt to disease-specific environments, facilitating targeted delivery and enhanced therapeutic effects. Decoy nanoparticles, mimicking immune cells or adsorbing inflammatory mediators, provide a unique mechanism to neutralize key drivers of sepsis, including cytokines, histones, and NETs, reducing systemic inflammation and organ damage.

Advancements such as macrophage-like nanoparticles, hydrogel-based histone scavengers, and cfDNA-targeting mesoporous silica nanoparticles have demonstrated superior efficacy in preclinical models, improving survival rates and mitigating inflammatory cascades. These strategies not only address the immediate challenges of sepsis but also offer insights into its underlying pathophysiology, enabling the design of more precise and effective therapies. However, challenges remain in translating these findings into clinical practice, including the need for robust characterization of PC dynamics, optimization of nanoparticle formulations, and development of personalized approaches that account for patient-specific variability.

Consent for Publication

All authors have given their consent for the publication of this manuscript.

Author Contributions

E.R.D: Literature research, Writing original draft. D.S.V; V.V.S and S.A.K: Data curation, Visualization. A.S.K, A.V.G and N.Y: Description of AI and computational approaches applied to protein Corona. E.V.P, D.K, and C.C.: Writing and Editing. M.L: Supervision (cell biology), review & editing. A. A.Z Jr, V.S.P, and M.G.H –; Supervision (biochemistry) & review & editing. A.P.: Funding acquisition& review & editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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