SHORT PERSPECTIVE
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Targeting Reactive Oxygen Species-dominant Neutrophil Extracellular Trap Formation in Immunothrombosis: A Perspective on the Dual-functional Potential of Nanoceria

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ABSTRACT

Sepsis-induced immunothrombosis is driven in part by dysregulated neutrophil extracellular traps (NETs), yet existing therapies fail to adequately address the oxidative checkpoints that initiate this cascade.

This mechanistic Perspective proposes a paradigm shift toward dual-functional inorganic nanomedicine aimed at modulating both inflammation and coagulation. We discuss emerging evidence supporting a "prevention-plus-clearance" strategy employing PEGylated cerium oxide nanoparticles (nanoceria) surface-grafted with DNase I.

The inorganic core functions as a prolonged superoxide dismutase–like redox buffer through the regenerative Ce^{3+}/Ce^{4+} cycle, thereby attenuating reactive oxygen species (ROS)-dominant NETosis pathways rather than universally blocking NET formation. In parallel, the surface-immobilized DNase I facilitates enzymatic degradation of extracellular chromatin scaffolds. We hypothesize that this bio-inorganic combination may address the biphasic nature of sepsis pathogenesis by limiting NET initiation while promoting microvascular de-obstruction.

Finally, we outline a translational roadmap required to validate this "circuit-breaker" strategy in vivo, positioning the cerium–NETosis axis as a promising frontier in the management of sepsis-associated coagulopathy.

Keywords: Cerium oxide; DNase I; Immunothrombosis; Neutrophil; Reactive oxygen species

INTRODUCTION

Sepsis continues to be among the leading causes of hospital mortality worldwide despite substantial advances in critical care management; current estimates place the annual global burden at over 21 million fatalities.[1,2] This condition is triggered by a catastrophic dysregulation of the host response, in which the

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coagulation cascade and the innate immune system collaborate to contain intravascular infection rather than solely eliminate pathogen burden.[3] This physiological axis, termed immunothrombosis, evolved as a host defense strategy to spatially restrict infection (“walling off” pathogens); however, during systemic infection it becomes profoundly maladaptive, leading to microvascular occlusion and disseminated intravascular coagulation (DIC), ultimately depriving tissues of oxygen.[4]

Significantly, there is currently no targeted therapy for this hazardous immuno-coagulatory interface. Existing approaches remain blunt instruments: conventional anticoagulants such as heparin attenuate clot formation but carry a substantial bleeding risk and may fail due to “heparin resistance” arising from reduced antithrombin levels.[5] Unlike heparin, which relies on adequate circulating antithrombin to exert its anticoagulant effect—a factor often depleted in septic patients—the proposed inorganic nanomedicine operates via direct catalytic redox buffering and enzymatic cleavage, thereby functioning independently of the host’s antithrombin levels.[6] Conversely, broad-spectrum anti-inflammatory strategies have consistently failed to improve survival in clinical trials, in part because they disrupt essential host defense mechanisms.[7] Precision therapeutics capable of interrupting the thrombo-inflammatory cycle–particularly its immunological triggers–without compromising systemic hemostasis are therefore urgently needed. This narrative perspective synthesizes recent mechanistic findings to propose a dual-functional nanotherapeutic strategy. Literature was selected based on a targeted search of PubMed and Web of Science for studies intersecting “nanoceria,” “NETosis,” and “immunothrombosis” published between 2010 and 2025, with a focus on identifying the dominant structural and molecular drivers of immunothrombosis and potential inorganic interventions.

A critical step toward such therapies is the identification of the dominant structural and molecular drivers of immunothrombosis. Brinkmann et al first described neutrophil extracellular traps (NETs) in 2004 as a distinct antimicrobial defense mechanism separate from phagocytosis.[8] NETs are expansive web-like structures composed of a decondensed chromatin (DNA) backbone decorated with cytotoxic granule proteins, including neutrophil elastase (NE), myeloperoxidase (MPO), and histones.[9] NET formation, termed NETosis, frequently proceeds via a “suicidal” pathway that is highly dependent on a respiratory burst: activation of NADPH oxidase (NOX2) generates intracellular reactive oxygen species (ROS), which promote the nuclear translocation and activation of peptidylarginine deiminase 4 (PAD4).[10] PAD4 catalyzes histone citrullination–particularly citrullinated histone H3 (CitH3), a widely used NET marker–driving chromatin decondensation and eventual rupture of the neutrophil membrane, releasing NETs into the extracellular milieu.[11] Although originally intended to immobilize and neutralize pathogens during sepsis, NETs function as a double-edged sword. Extracellular DNA provides a negatively charged scaffold capable of activating factor XII and recruiting platelets and erythrocytes, while associated histones and proteases amplify platelet aggregation and impair endogenous anticoagulant pathways.[12,13] Consequently, NETs may transition from localized antimicrobial traps into a systemic framework for microvascular thrombosis, mechanistically linking neutrophil oxidative stress to vascular occlusion and organ dysfunction.[14]

In response, the field has increasingly pursued more stable and effective therapeutic platforms to overcome the limitations of conventional DNase I, particularly its rapid inactivation by serum G-actin.[15] Emerging biological strategies include adeno-associated viral-mediated gene delivery to sustain circulating nuclease levels and DNase γ, which exhibits partial resistance to actin inhibition.[15] Complementing these biological approaches, inorganic nanotherapeutics–most notably cerium oxide nanoparticles (nanoceria)–have attracted attention. Owing to their auto-catalytic Ce^{3+}/Ce^{4+} redox cycle, nanoceria function upstream of NET degradation by acting as regenerative antioxidants. Rather than dismantling NETs after formation, they may attenuate ROS-dominant triggers of NETosis, potentially interrupting the cascade at its initiation stage.[16]

PERSPECTIVE

The Biological Requirement: ROS-dominant NETosis as a Therapeutic Checkpoint

To develop an efficient inhibitor, it is necessary to target a non-redundant and therapeutically actionable checkpoint within the NETosis pathway. While neutrophils can undergo multiple forms of cell death, the regulated release of extracellular traps is frequently and mechanistically linked to an oxidative burst. Upon stimulation by pathogens or inflammatory cytokines, neutrophils assemble the NOX2 complex at the plasma membrane, generating a rapid surge of superoxide anions ($O_2^{\cdot -}$) that are subsequently dismutated into hydrogen peroxide (H_2O_2).[10,17] It is important to note that neutrophils can also undergo "vital" NETosis, a rapid, ROS-independent pathway mediated by vesicular exocytosis that preserves cellular viability and function.[18] However, in the context of sepsis-induced immunothrombosis, the maladaptive, massive release of NETs is predominantly driven by the suicidal, ROS-dependent pathway described here, making oxidative stress the primary therapeutic target. These reactive species act as critical secondary messengers, promoting the dissociation of NE and MPO from azurophilic granules and their translocation to the nucleus.[19] There, these enzymes act in concert with PAD4 to modify histones and disrupt nuclear architecture, driving chromatin decondensation that precedes membrane rupture.

Patients with chronic granulomatous disease (CGD), who harbor genetic defects in the NOX2 complex, illustrate the central role of oxidative signaling in classical NETosis. In a landmark study, Fuchs et al (2007) demonstrated that neutrophils from CGD patients exhibit a profound impairment in NET formation, rendering them highly susceptible to certain infections while simultaneously conferring resistance to NET-mediated inflammatory pathology.[10,20] This biological dependency supports a context-specific therapeutic principle: sustained suppression of intracellular ROS can markedly attenuate ROS-dependent NETosis pathways. Under such conditions, the upstream signaling cascade is disrupted, substantially limiting the neutrophil’s capacity to externalize chromatin.

The Material Capability: Cerium as a Redox Machine

To meet the biological requirement for sustained suppression of oxidative signaling, a therapeutic agent must function catalytically rather than as a consumable reactant. Conventional antioxidants, such as vitamin C or N-acetylcysteine, are stoichiometrically exhausted upon neutralizing reactive species. In contrast, nanoceria possess a distinctive fluorite lattice enriched with oxygen vacancies, enabling reversible redox cycling and prolonged antioxidant activity. The dynamic interconversion between trivalent (Ce^{3+}) and tetravalent (Ce^{4+}) oxidation states at the nanoparticle surface underlies this behavior, allowing nanoceria to functionally mimic key redox activities of endogenous antioxidant enzymes rather than act as a one-time radical scavenger.[21]

Mechanistically, nanoceria exhibits broad-spectrum ROS-buffering capacity through two well-characterized surface-mediated pathways. Sites enriched in Ce^{3+} display superoxide dismutase (SOD)–like activity, interacting with superoxide anions ($O_2^{\bullet -}$)—a proximal trigger of ROS-dependent NETosis—and facilitating their conversion into hydrogen peroxide (H_2O_2), concomitant with oxidation of cerium to the Ce^{4+} state.[22] Subsequently, Ce^{4+}-rich sites exhibit catalase–like activity, promoting the decomposition of hydrogen peroxide into water and molecular oxygen, thereby regenerating Ce^{3+} at the surface.[23] Through this auto-regenerative Ce^{3+}/Ce^{4+} redox cycle, nanoceria functions as a persistent ROS buffer, with the potential to attenuate excessive oxidative bursts over extended periods, contingent on dose, surface chemistry, and biological context.[24]

The Convergence: Proof of Concept

The theoretical requirement to quench the oxidative burst has been translated into experimental validation by Dich et al (2025), who provided compelling proof-of-concept evidence supporting the proposed “cerium–NETosis” axis.[25] To this end, the investigators engineered a dual-functional nanoplatform consisting of a cerium oxide core functionalized with phosphonic acid–terminated PEG copolymers and surface-grafted DNase I.[25] This rigorous functionalization strategy is chemically essential not only for preserving catalytic activity, but also for ensuring biocompatibility.[25] In line with a comparative study by Baryshev et al (2024), which demonstrated that bare or high-dose exposure to inorganic nanoparticles can paradoxically promote neutrophil degranulation and MPO release, appropriate surface shielding is critical.[26] Accordingly, the PEG corona employed by Dich et al likely enables the nanoplatform to function as a biological stabilizer rather than an inflammatory irritant.

Upon internalization by human neutrophils, these engineered nanoparticles exhibited a pronounced capacity to modulate key immunothrombotic signaling events.[25] Specifically, treatment significantly reduced ROS generation in phorbol 12-myristate 13-acetate (PMA)–stimulated cells, flattening the oxidative response relative to untreated controls and arresting neutrophils in a chromatin-decondensed yet membrane-intact state.[25] These findings suggest that the Ce^{3+}/Ce^{4+} redox cycle can functionally interrupt the oxidative threshold required for NET release, rather than inducing terminal cell rupture. Supporting this interpretation, Ernst and Puntes (2022) demonstrated that nanoceria modulates immunometabolism through redox buffering, reducing intracellular ROS levels necessary to sustain the glycolytic, pro-inflammatory state that underpins respiratory burst activation in myeloid cells.[27]

Importantly, in the context of pre-existing NETs—a frequent clinical scenario—the surface-conjugated DNase I retained substantial nucleolytic activity, degrading fibrillar extracellular DNA in a dose-dependent manner.[25] While nanoceria exhibit catalytic antioxidant behavior, including SOD- and catalase-like activity, they lack intrinsic capacity to enzymatically cleave complex extracellular biomolecular structures.[28,29] Accordingly, the incorporation of DNase I is a necessary design element for physical NET dismantling. By integrating redox modulation with enzymatic clearance, the dual-functional nanoplatform addresses key limitations inherent to antioxidant-only approaches.[25] Collectively, these findings support the concept that dual-functional nanoceria can simultaneously attenuate ROS-dominant NET formation and facilitate clearance of established extracellular traps, offering a mechanistically integrated—though context-dependent—strategy for mitigating immunothrombosis.

Comparative Nanotoxicology: Why Cerium Oxide Represents a Favorable Design Profile

To fully appreciate the distinctive positioning of nanoceria, they must be considered within the broader framework of nanotoxicology, where several otherwise promising nanomaterials have failed due to immunological incompatibility. The innate immune system—particularly neutrophils— sensitively discriminates based on physicochemical properties, with particle shape, aspect ratio, and surface charge critically influencing the propensity for immune overactivation and pathological NET formation.

High–aspect ratio carbon nanotubes (CNTs) exemplify shape-driven nanotoxicity. Their rigid, fiber-like geometry can impede complete phagocytic uptake, resulting in frustrated phagocytosis, mechanical stress, and sustained immune activation. In vivo studies have demonstrated that CNTs can activate platelets, increasing P-selectin expression, promoting platelet–leukocyte aggregate formation, and accelerating thrombus development,[30,31] although CNTs do not consistently induce NETosis directly, platelet activation and neutrophil engagement may converge to amplify thrombo-inflammatory responses. In parallel, NETs serve as pro-thrombotic scaffolds that recruit platelets and promote fibrin deposition,[32] illustrating how high–aspect ratio nanomaterials may indirectly potentiate immunothrombosis.

Surface charge represents a second major determinant of nanomaterial–immune interactions. Positively charged nanoparticles, including cationic liposomes, exhibit charge-mediated toxicity driven by strong electrostatic interactions with negatively charged neutrophil membranes. This interaction can induce membrane destabilization, calcium influx, oxidative burst activation, and rapid NET release.[33,34] While cationic surfaces may enhance binding to extracellular NET structures,[35] they also risk amplifying neutrophil activation in inflammatory environments such as sepsis, contributing to tissue injury—a phenomenon commonly described as charge toxicity.

Against this backdrop, nanoceria exhibit a comparatively favorable immunological profile when appropriately engineered. Nanoceria are typically spherical, reducing the likelihood of frustrated phagocytosis observed with high–aspect ratio materials. Moreover, their surface chemistry does not rely on strong cationic charge, minimizing charge-driven membrane disruption and calcium influx characteristic of cationic formulations. Importantly, nanoceria possess intrinsic redox-buffering capacity, enabling scavenging of reactive oxygen species and attenuation of pro-inflammatory signaling in macrophages and endothelial cells.[36,37] In vitro studies have demonstrated reduced oxidative injury and diminished inflammatory mediator expression in models of wound healing and tissue stress, supporting a higher degree of biocompatibility relative to more reactive nanomaterial classes.[38]

Collectively, these comparisons underscore the importance of rational nanomaterial design—particularly geometry and surface charge—in mitigating immune toxicity. While nanoceria are not inherently inert and remain subject to dose-, coating-, and context-dependent effects, their physicochemical properties and redox-modulating behavior position them as a promising and comparatively well-tolerated platform for applications where excessive immune activation and NETosis are pathologically relevant. However, while nanoceria exhibit a favorable profile, the "more is better" paradigm does not apply to redox modulation. Given the catalytic, self-regenerative nature of nanoceria, defining the optimal "therapeutic window" is critical. Excessive antioxidant activity could theoretically dampen the oxidative burst required for essential bacterial killing within phagosomes. Therefore, the translational goal is not the total abrogation of ROS, but the attenuation of the "spillover" oxidative stress that triggers systemic NETosis, without compromising the localized anti-microbial capacity.

Future Roadmap: From Bench to Bedside

The emerging evidence supporting a proposed “cerium–NETosis” axis provides a compelling proof of concept; however, translation of this nanotherapeutic strategy from controlled in vitro systems to clinical application requires careful navigation of a complex and dynamic biological landscape.

Bridging the gap between static experimental models and the hemodynamic, immunological, and coagulopathic complexity of sepsis remains a central challenge. While Dich et al demonstrated effective modulation of NET formation in isolated human neutrophils, the inflammatory milieu of a septic host—characterized by disturbed blood flow, endothelial dysfunction, and dysregulated coagulation—presents a substantially different context. Future studies must therefore prioritize in vivo validation in relevant sepsis and immunothrombosis models. Furthermore, designing clinical trials for this strategy will require distinct endpoints compared to standard anticoagulants. Rather than solely monitoring bleeding times (e.g., PTT), efficacy monitoring should include biomarkers of immunothrombosis such as circulating CitH3-DNA complexes and D-dimer levels to assess the specific "de-coupling" of inflammation and coagulation.

The protein corona challenge is another critical barrier lies at the bio–nano interface. Upon exposure to biological fluids, nanoparticles rapidly acquire a protein corona that can profoundly influence their surface chemistry, cellular interactions, and functional performance.[39] In the context of sepsis, where plasma proteomes are markedly altered, high-abundance proteins such as fibrinogen or albumin may sterically occlude Ce^{3+}/Ce^{4+} redox sites or impair the activity of surface-conjugated DNase I. Although PEGylation was employed by Dich et al to mitigate nonspecific protein adsorption, the inflammatory and proteolytic environment of sepsis may compromise this shielding. Furthermore, the stability of the PEG corona itself is of concern; recent studies indicate that anti-PEG antibodies or high-affinity plasma proteins can displace or degrade surface polymers, potentially leading to 'stealth' failure and accelerated clearance by the mononuclear phagocyte system.[40] Future designs must therefore validate the integrity of the PEG layer specifically within the protease-rich environment of septic plasma.

Despite the favorable immunological profile of nanoceria, their inorganic nature presents a challenge regarding biopersistence. Unlike organic platforms that undergo enzymatic hydrolysis, metal oxides are not readily biodegradable and may be sequestered by the reticuloendothelial system (RES), leading to potential accumulation in the liver and spleen. Consequently, while optimizing pharmacokinetics is critical for therapeutic efficacy, defining the long-term clearance pathways is equally vital to ensure that the management of acute sepsis does not compromise chronic organ health through heavy metal retention. This risk is amplified in sepsis treatment, which may require repeat dosing to match the kinetics of a sustained systemic infection. Translational efforts must therefore rigorously evaluate the implications of hepatic and splenic accumulation, particularly in vulnerable populations with pre-existing organ dysfunction.

CONCLUSION

In summary, the use of functionalized nanoceria represents a conceptual shift from reactive intervention toward upstream modulation of immunothrombotic triggers. By integrating redox buffering with enzymatic NET clearance, this bio-inorganic strategy offers a mechanistically coherent framework for addressing key drivers of sepsis-associated coagulopathy. If future studies can validate nanoparticle stability in human blood, preserve function in complex inflammatory milieus, and demonstrate efficacy in live immunothrombosis models, dual-functional nanoceria may emerge as a valuable adjunctive approach for mitigating thrombo-inflammatory complications in sepsis.

STATEMENT OF ETHICS

Ethical approval was not required for this study as it is a perspective article based on the analysis of previously published literature and does not involve the collection of primary human or animal data.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

As this is a perspective article, no primary data were generated or analyzed. Therefore, data sharing is not applicable.

AI ASSISTANCE DISCLOSURE

The content of this manuscript was authored and edited exclusively by the human contributors. No artificial intelligence (AI) tools, large language models, or automated generation software were used in the development, writing, or refinement of this work. All ideas, data interpretation, and conclusions presented are the original intellectual product of the authors.

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