

# Nanomedicine for Acute Kidney Injury: Precision Delivery Strategies, Therapeutic Breakthroughs, Challenges, and Future Perspectives

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**Abstract:** Acute kidney injury (AKI) is a critical condition associated with high mortality rates, currently lacking effective early diagnostic methods and targeted therapeutics. Nanomaterials, due to their unique size effects and modifiability, offer breakthrough strategies for AKI management. This review systematically explores the advancements in the use of nanomaterials for the diagnosis and treatment of AKI: in the diagnostic realm, quantum dot biosensors and ultrasmall contrast agents significantly enhance the sensitivity of early biomarker detection (eg, KIM-1/NGAL); in the therapeutic domain, cerium oxide nanocatalysts (antioxidant), targeted liposomes (anti-inflammatory), and exosome-delivered miRNA (regenerative repair) demonstrate superior renal protection compared to traditional drugs by modulating oxidative stress, inflammation, and apoptosis pathways in animal models. The article emphasizes the design principles of nanomaterials (size <10 nm for renal clearance, cationic surfaces to enhance tubular uptake) and targeting mechanisms. Despite the promising outlook, the clinical translation of nanomaterials faces challenges related to biosafety (long-term retention toxicity) and large-scale production. This review critically evaluates key studies from recent years, providing a theoretical basis and technical roadmap for the development of next-generation nanomedicine platforms for AKI.

**Keywords:** acute kidney injury, oxidative stress, nanomedicine, nanoparticles, targeted therapy

## Introduction

Acute kidney injury (AKI) is a global healthcare crisis characterized by a rapid decline in renal function, affecting approximately 30–60% of critically ill patients and is associated with acute morbidity and mortality.<sup>1</sup> AKI arises from diverse etiologies, including sepsis, ischemia-reperfusion injury (IRI), nephrotoxic drugs (eg, cisplatin), and major surgeries. Despite advances in supportive care (eg, renal replacement therapy), no FDA-approved pharmacotherapy exists to halt AKI progression, primarily due to the complex pathophysiology involving oxidative stress, mitochondrial dysfunction, and maladaptive immune responses.<sup>2–4</sup> The clinical management of AKI faces two critical gaps: 1. Diagnostic limitations: Current biomarkers (serum creatinine, urea) lack sensitivity for early-stage AKI, often delaying intervention until irreversible damage occurs.<sup>5</sup> 2. Therapeutic inefficacy: Small-molecule drugs (eg, antioxidants, anti-inflammatories) suffer from poor renal bioavailability and off-target effects.<sup>6,7</sup> Nanotechnology offers transformative solutions to AKI's challenges by exploiting the unique physicochemical and biological properties of engineered materials (1–100 nm).<sup>8</sup> Nanoparticles (NPs) offer distinct advantages for renal therapy, including enhanced targeting, multi-functionality, and tunable clearance. Targeting is achieved both passively, through indirect effect in injured tissue, and actively, via ligand conjugation (eg, hyaluronic acid for CD44+).<sup>9–11</sup> Furthermore, NPs serve as multifunctional theranostic platforms that integrate diagnostic and therapeutic capabilities.<sup>12–14</sup> Finally, their pharmacokinetics can be tuned by size; small NPs (<10 nm) are rapidly cleared to reduce toxicity, while larger ones (>20 nm) are retained for

sustained drug release.<sup>15</sup> Despite promising preclinical advances—such as cerium oxide nanozymes mitigating oxidative stress in ischemia-reperjury injury and quantum dot biosensors enabling sensitive KIM-1 detection—significant barriers impede clinical translation.<sup>16,17</sup> These include unresolved biosafety concerns regarding long-term NP accumulation in off-target organs and major translational hurdles, such as the predominance of rodent studies and a scarcity of large-animal data and GMP-compliant manufacturing protocols.<sup>18–21</sup> This article provides a comprehensive evaluation of AKI-targeted nanomaterials, focusing on their design principles and structure–activity relationships. It highlights cutting-edge applications in diagnosis—including imaging and biosensing—and therapy, such as antioxidant, anti-inflammatory, and regenerative strategies. Key challenges in clinical translation and regulatory pathways are also critically examined. Ultimately, this review aims to bridge the gap between nanomaterial innovation and clinical practice, offering a roadmap for future research in AKI management.

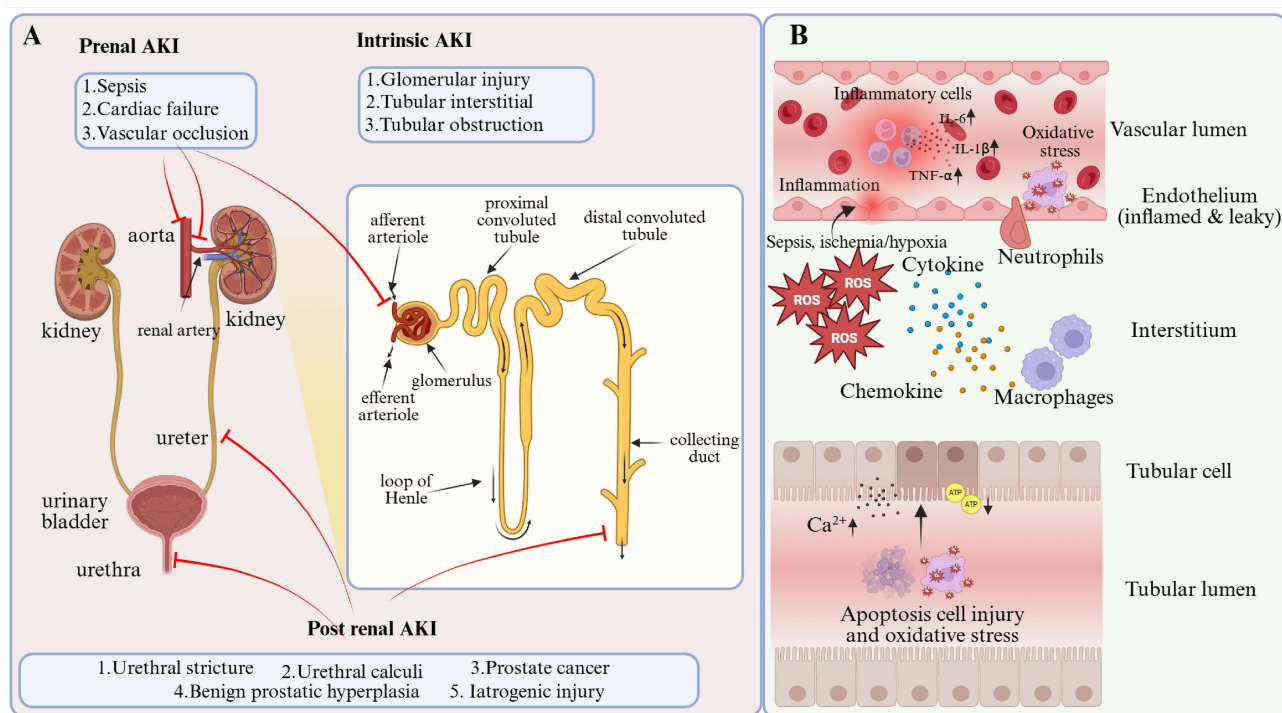
## Classification and Pathogenesis of Acute Kidney Injury

AKI refers to a rapid decline in kidney function over hours to days, characterized by elevated serum creatinine (Scr) levels and/or decreased urine output. According to clinical standards such as the KDIGO guidelines, AKI is classified into three stages: Staging of AKI-Stage 1: Scr increases by  $\geq 0.3$  mg/dL or to 1.5–1.9 times baseline, or urine output  $< 0.5$  mL/kg/h for 6–12 hours. Stage 2: Scr increases to 2.0–2.9 times baseline, or urine output  $< 0.5$  mL/kg/h for  $\geq 12$  hours. Stage 3: Scr increases to  $> 3$  times baseline, or  $\geq 4.0$  mg/dL, or requires renal replacement therapy (RRT), or urine output  $< 0.3$  mL/kg/h for  $\geq 24$  hours (or anuria for  $\geq 12$  hours).<sup>22,23</sup> Classification of AKI. Based on etiology and pathophysiology, AKI can be categorized into three main types: (1) Prerenal AKI. Etiology: Insufficient renal perfusion (eg, hemorrhage, heart failure, dehydration, shock). Mechanism: Decreased glomerular filtration rate (GFR) occurs without intrinsic damage to renal parenchyma. Prolonged ischemia may progress to acute tubular necrosis (ATN). (2) Intrinsic AKI. Primary Types: Acute tubular necrosis (ATN): Accounts for 85% of hospitalized AKI cases, caused by ischemia (eg, shock) or nephrotoxicity (eg, contrast agents, antibiotics, chemotherapy). Glomerular diseases: Such as acute glomerulonephritis (AGN) or vasculitis. Interstitial nephritis: Resulting from drug allergies (eg, NSAIDs, penicillin) or infections. Vascular pathologies: Such as thrombotic microangiopathy (TMA) or renal artery embolism. (3) Postrenal AKI. Etiology: Urinary tract obstruction (eg, stones, tumors, benign prostatic hyperplasia). Mechanism: Obstruction leads to increased renal pelvis pressure, resulting in decreased GFR. Prompt relief of obstruction can reverse renal function.<sup>24–26</sup> AKI pathogenesis involves multiple interconnected mechanisms. (1) Ischemia-Reperfusion Injury (IRI): Characterized by renal vasoconstriction due to endothelin upregulation and nitric oxide reduction,<sup>27</sup> oxidative stress from mitochondrial dysfunction and reactive oxygen species (ROS) generation,<sup>28</sup> and inflammation via NF- $\kappa$ B/NLRP3 activation and pro-inflammatory cytokine release (eg, IL-1 $\beta$ , TNF- $\alpha$ ).<sup>29,30</sup> (2) Tubular Epithelial Cell Injury: Includes ATP depletion-induced apoptosis or necrosis,<sup>31,32</sup> loss of cellular polarity and brush border leading to cast formation and obstruction,<sup>33</sup> and mitochondrial fragmentation impairing energy production.<sup>34</sup> (3) Microcirculatory Dysfunction: Features endothelial cell swelling, microthrombi formation, and increased vascular permeability exacerbating ischemia and inflammation.<sup>35</sup> (4) Dysregulated Immunity: Involves DAMP-mediated M1 macrophage polarization via TLR4/MyD88 signaling<sup>36</sup> and imbalanced T-cell responses (eg, Th17 pro-inflammatory vs Treg protective effects).<sup>37</sup> (5) Fibrotic Progression: Incomplete repair may lead to chronic kidney disease via persistent inflammation and fibroblast activation.<sup>38</sup> While prerenal and postrenal AKI often resolve with causal intervention, intrinsic AKI (eg, acute tubular necrosis) necessitates targeting oxidative stress, inflammation, and cellular repair.<sup>39,40</sup> Future directions emphasize early biomarker validation (eg, NGAL, KIM-1) and novel targeted therapies (eg, nanomedicine, stem cells) to improve outcomes<sup>41–43</sup> (Figure 1).

## Advantages and Disadvantages of Traditional Drugs and Nanomaterials in the Treatment of AKI

### Traditional Drug Treatment for AKI: Advantages and Disadvantages

Commonly used drugs and mechanisms. Antioxidants (eg, N-acetylcysteine, NAC): Scavenge reactive oxygen species (ROS) and reduce oxidative stress.<sup>44</sup> Anti-inflammatory drugs (eg, corticosteroids): Inhibit the NF- $\kappa$ B pathway and



**Figure 1** Classification and pathophysiology of AKI. (A) illustrates the three categories of AKI—pre-renal, intrinsic, and post-renal—along with their associated causes related to the site of injury (indicated by colored arrows). (B) describes the pathophysiology of AKI, highlighting that the initial insult leads to morphological and functional alterations in vascular endothelial cells and tubular epithelium. Black ↑ upgraded; ↓ downgraded.

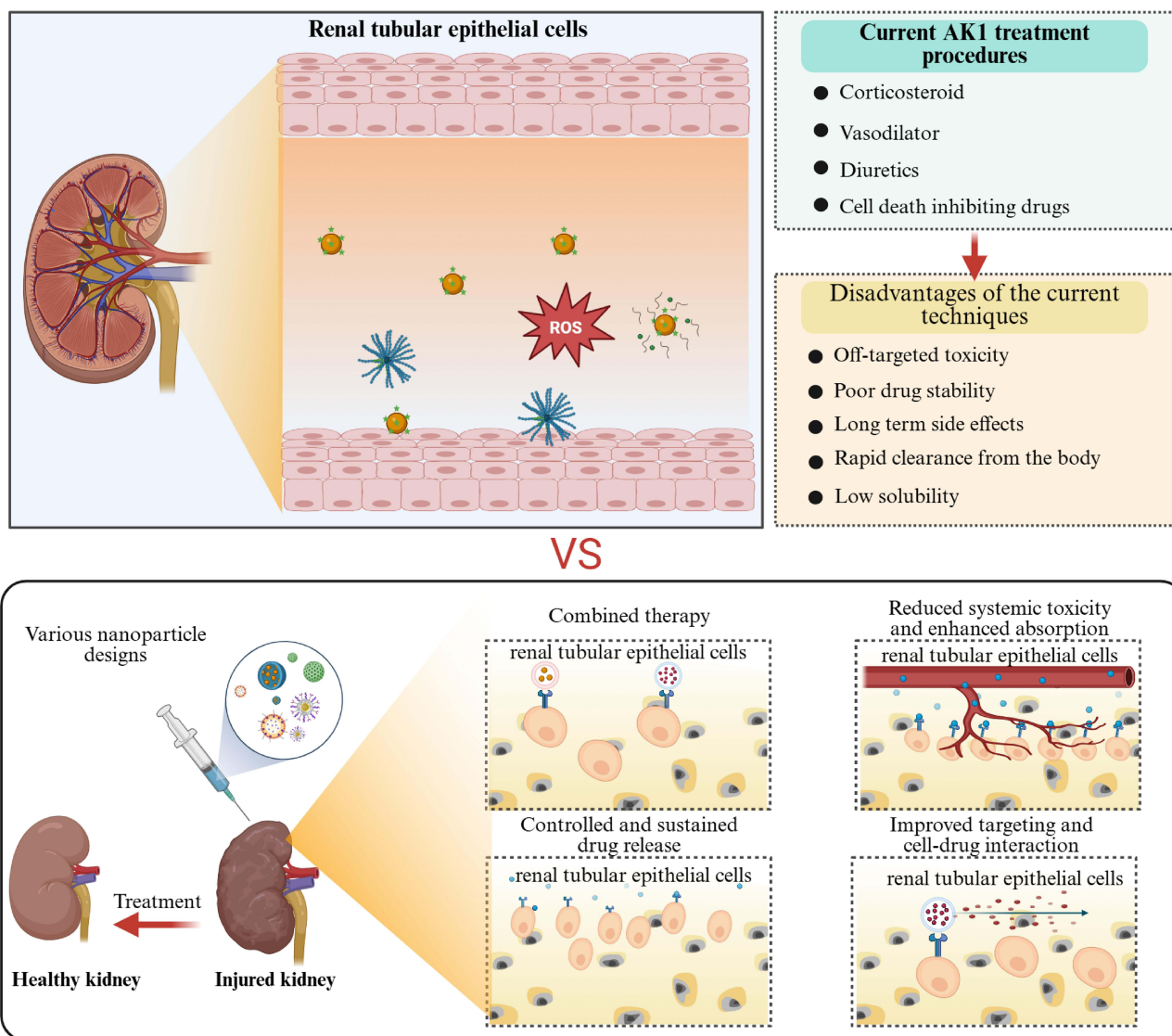
decrease the release of inflammatory factors.<sup>45</sup> Vasodilators (eg, dopamine): Improve renal blood flow, although their efficacy is widely debated.<sup>46</sup> Diuretics (eg, furosemide): Increase urine output but do not provide renal protection.<sup>47</sup> Conventional pharmacological agents for AKI offer advantages including established clinical availability and low cost (eg, NAC),<sup>48,49</sup> as well as straightforward administration via oral or intravenous routes without complex formulation requirements. However, they suffer from significant limitations: non-specific systemic distribution causing off-target effects (eg, steroid-induced immunosuppression), low bioavailability due to rapid metabolism (eg, NAC clearance in tubules), an inability to target key pathological pathways (eg, mitochondrial dysfunction), and a lack of integrated diagnostic capabilities.<sup>50–53</sup>

## Examples of Nanotherapy Strategies, Advantages, and Challenges

The translation of nanotechnology into therapeutic applications is exemplified by strategies such as antioxidant nanozymes (eg, CeO<sub>2</sub> nanoparticles<sup>16</sup>), targeted delivery systems (eg, HA-liposomes<sup>54</sup>), and theranostic platforms (eg, quantum dot-drug conjugates<sup>55</sup>), which offer advantages including precision targeting via active mechanisms, synergistic therapy with reduced toxicity,<sup>56,57</sup> multi-mechanism integration,<sup>58,59</sup> and combined imaging/therapy.<sup>60</sup> However, clinical adoption remains challenged by safety concerns (eg, fibrosis risks and immunogenicity), translational barriers (eg, physiological disparities and manufacturing reproducibility), and regulatory/economic hurdles in GMP production and clinical approval<sup>61–63</sup> (Figure 2).

## The Construction and Main Categories of Nanomaterials for AKI

AKI treatment faces challenges such as low drug delivery efficiency and poor targeting. Nanomaterials, due to their unique physicochemical properties, can significantly improve drug accumulation and efficacy in the kidneys.<sup>64</sup> The following sections systematically summarized three major strategies: optimizing renal targeting, designing stimuli-responsive materials, and selecting biocompatible materials, providing a theoretical basis for developing efficient and low-toxicity nanomedicines for AKI.



**Figure 2** Overall advantages and disadvantages of traditional drugs and nanomaterials in the treatment of AKI.

Renal targeting of nanomaterials is optimized through passive and active strategies. Passive targeting leverages renal physiological barriers: nanoparticles <6 nm undergo rapid glomerular filtration and clearance, while those 6–10 nm exhibit partial retention in glomerular or tubular structures. Larger nanoparticles (>10 nm) are predominantly sequestered by the mononuclear phagocyte system (MPS), though exceptions exist (eg, 5 nm mesoporous silica nanoparticles accumulating in ischemic reperfusion injury models).<sup>65</sup> Surface charge also modulates distribution; cationic surfaces enhance binding to anionic renal structures but may induce complement activation or thrombosis.<sup>66</sup> Active targeting employs ligand-functionalized nanoparticles for precision delivery: hyaluronic acid (HA) targets CD44 on injured tubules,<sup>67</sup> ICAM-1 antibodies bind to inflamed endothelium, and low molecular weight proteins (eg, lysozyme) facilitate proximal tubule reabsorption.<sup>68,69</sup>

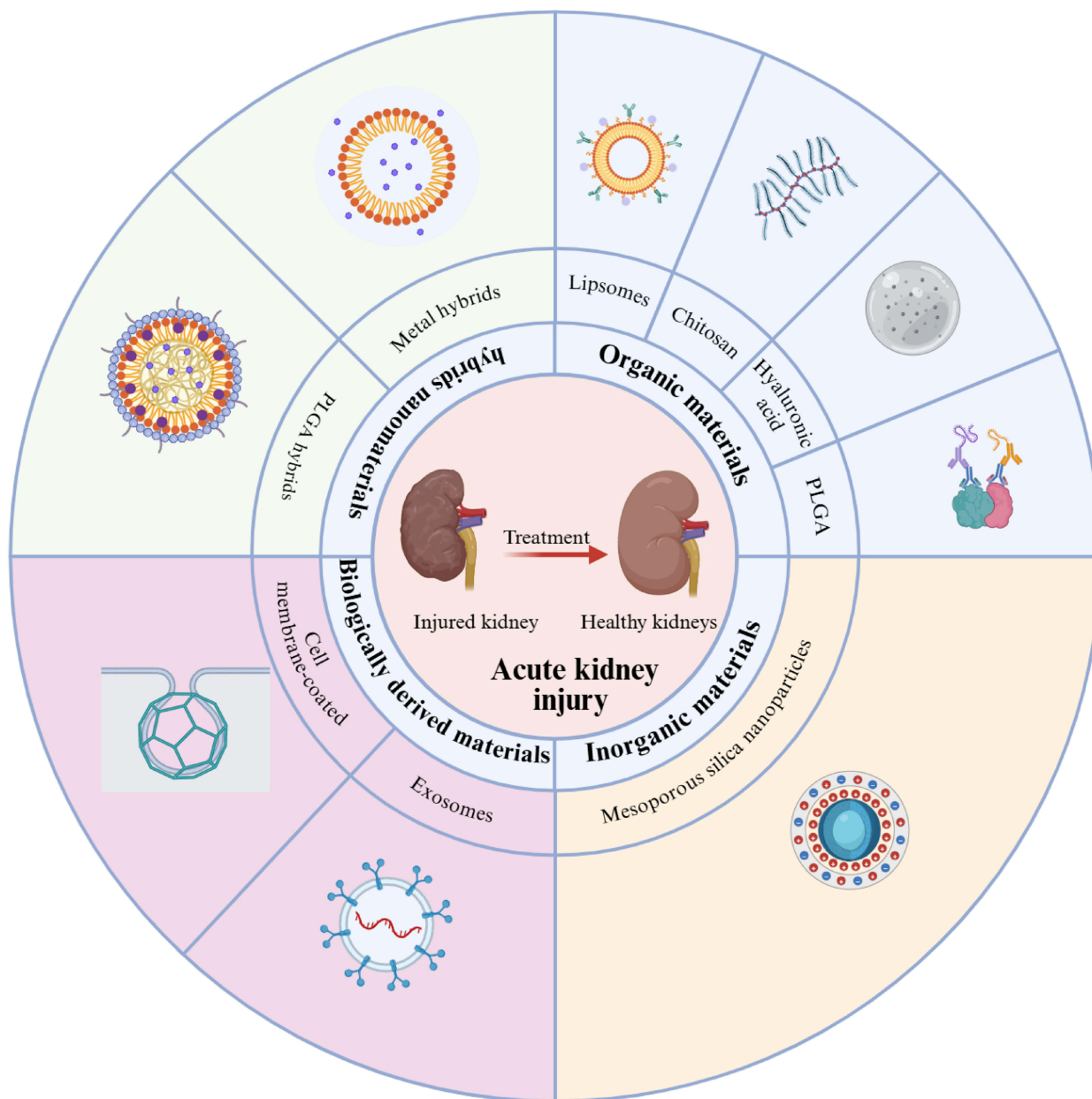
Stimuli-responsive nanomaterials enhance therapeutic precision in AKI by leveraging pathological cues or external triggers for controlled drug release. Endogenous stimuli include the acidic pH (6.5–7.0) of injured tissue, exploited by pH-sensitive polymers (eg, poly ( $\beta$ -amino ester)) for targeted NAC delivery,<sup>70</sup> elevated glutathione (GSH) levels triggering disulfide bond cleavage in carriers like PEG-SS-PLGA, and overexpression of enzymes (eg, MMP-2/9)

enabling peptide-cleavable drug release.<sup>71</sup> Exogenous stimuli allow spatiotemporal control: near-infrared (NIR) light activates photothermal/photodynamic agents (eg, black phosphorus quantum dots, gold nanorods) for ROS generation or hyperthermia, while ultrasound-responsive systems (eg, perfluorohexane emulsions) enable non-invasive deep tissue penetration.<sup>72,73</sup>

Selection of biocompatible materials. (1) Inorganic nanomaterials. Mesoporous silica nanoparticles (MSNs): High drug loading capacity (>500 mg/g) and easily functionalizable surfaces. It can be excreted in urine when particle size is <100 nm. Quantum Dots (QDs): CdSe/ZnS core-shell structures used for real-time imaging, but cadmium toxicity needs to be addressed.<sup>65,74</sup> (2) Organic nanomaterials. Zhang et al<sup>75</sup> explored the therapeutic potential of PM for facilitating tissue repair, suggesting it as a promising strategy for treating AKI and preventing its progression to CKD. Yin et al found that long-term administration of chitosan oligosaccharides (COS) reduces myofibroblast proliferation and extracellular matrix deposition, thereby inhibiting the transition from AKI to CKD through metabolic and redox processes.<sup>76</sup> Additionally, nHA/PLBR enhances the biodistribution and delivery efficiency of bilirubin, indicating potential for improved AKI treatment in the future.<sup>77</sup> Poly (lactic-co-glycolic acid) (PLGA): FDA-approved biodegradable material suitable for sustained release (eg, anti-inflammatory nanoparticles loaded with TPCA-1).<sup>78</sup> Dendritic Polymers (PAMAM): Precise control of molecular weight (G3–G5 generations are optimal), but higher generations may cause hemolysis.<sup>79</sup> Cell membrane-mimetic nanoparticles: Such as macrophage membrane-coated nanoparticles, which can evade immune clearance and target inflammatory sites.<sup>80</sup> Li et al identified strategies to modify FRC-derived exosomes as a promising approach for developing therapeutics against kidney injury.<sup>81</sup> Research on hybrid nanomaterials indicated that acetamide (NA-2) and NA2-conjugated gold nanoparticles (NA2-AuNPs) mitigate cisplatin-induced AKI in mouse models through anti-inflammatory and antioxidant mechanisms.<sup>82</sup> Additionally, chito oligosaccharide PLGA-protopanaxadiol nanoparticles demonstrated efficacy in ameliorating lipopolysaccharide-induced acute kidney injury in rats by inhibiting the NF- $\kappa$ B signaling pathway, supporting their potential for treating such conditions.<sup>83</sup> Metal-phenolic networks (MPNs)—supramolecular amorphous structures formed through the coordination of polyphenols with metal ions—are garnering increasing interest in nanomedicine.<sup>84,85</sup> Huang et al developed copper (II)–curcumin metal-phenolic networks (Cur–Cu MPNs) that integrate the reactive oxygen species (ROS)-scavenging properties of both components. The resulting Cur–Cu nanoparticles (NPs) exhibited potent antioxidative enzyme-like activities. PEG-modified particles (Cur–Cu@PEG) mitigated ROS-induced oxidative damage in HK-2 cells and demonstrated good biocompatibility in vivo. In murine models of cisplatin- and rhabdomyolysis-induced AKI (CP-AKI and RM-AKI), Cur–Cu@PEG facilitated kidney-targeted delivery, reduced ROS production, and suppressed caspase-3-mediated apoptotic and pyroptotic cell death.<sup>86</sup> Self-assembling peptides represent an emerging class of biomaterials with growing applications in biomedicine and materials science owing to their biocompatibility and controlled-release capabilities. These peptides spontaneously organize into diverse nanostructures through molecular interactions, enabling versatile functionalization. Upon assembly, they can mimic native biological processes and facilitate the combinatorial delivery of therapeutic agents, including cytokines and pharmaceuticals.<sup>87</sup> Xin et al engineered a novel self-assembling peptide nanoparticle by conjugating the cell-penetrating TAT sequence to MKK3b, a functional p38 domain, enabling its self-assembly into TAT-MKK3b nanoparticles (TMNPs) via tyrosinase oxidation. The multifunctional TMNPs demonstrated renal targeting, ROS scavenging, and ferroptosis inhibition, positioning them as a promising therapeutic to treat AKI and impede its progression to CKD.<sup>88</sup> Wang et al developed a nucleic acid delivery platform by hybridizing synthetic p53 siRNA with autologous plasma and incubating the complex with platelets. These engineered platelets selectively delivered siRNA to injured renal tubular cells via extracellular vesicle (EV)-mediated release, achieving targeted p53 suppression and attenuating AKI progression. This platelet-based strategy exploits endogenous trafficking mechanisms for precise therapeutic delivery to injury sites, demonstrating significant potential for advancing AKI therapeutics<sup>89</sup> (Figure 3).

## Advances in the Application of Nanomaterials for Treating AKI

AKI involves a complex pathophysiological process characterized by oxidative stress, inflammatory responses, apoptosis, and fibrosis. Traditional drug therapies have limited efficacy due to poor targeting and low bioavailability. Nanodelivery systems, through strategies such as precise delivery, multi-mechanistic synergy, and integrated diagnosis and therapy,



**Figure 3** Main nano-based materials used as nano drug delivery systems against AKI in this review.

provide groundbreaking solutions for AKI treatment.<sup>90,91</sup> This following sections systematically reviewed the latest advancements in nanomaterials for addressing oxidative stress, modulating inflammatory immune responses, regulating cell fate, and facilitating multimodal synergistic therapy.

Antioxidative stress nanotherapy represents a promising avenue for managing cisplatin-induced acute kidney injury (CI-AKI), a serious complication of chemotherapy with no currently approved pharmacological treatment. Williams et al demonstrated that edaravone-loaded magnetic nanoparticles (MNPs) significantly improved renal function by reducing tubular epithelial cell damage and death, underscoring the potential of renal-targeted antioxidant delivery.<sup>92</sup> Similarly, Pan et al developed an acid-resistant epigallocatechin gallate (EGCG)-based nanoplatform (Cur@EGA) that, via oral or

intravenous administration, attenuated acute kidney injury and colitis with superior anti-inflammatory efficacy compared to free curcumin.<sup>93</sup> Further supporting this approach, Yao et al highlighted the utility of a mitochondria-targeted antioxidant, elamipretide (SS31), delivered via a nanocarrier, which reduced oxidative stress, inflammation, and apoptosis while protecting against mitochondrial dysfunction. This theroistic strategy exemplifies a targeted method for AKI prevention and treatment.<sup>73</sup>

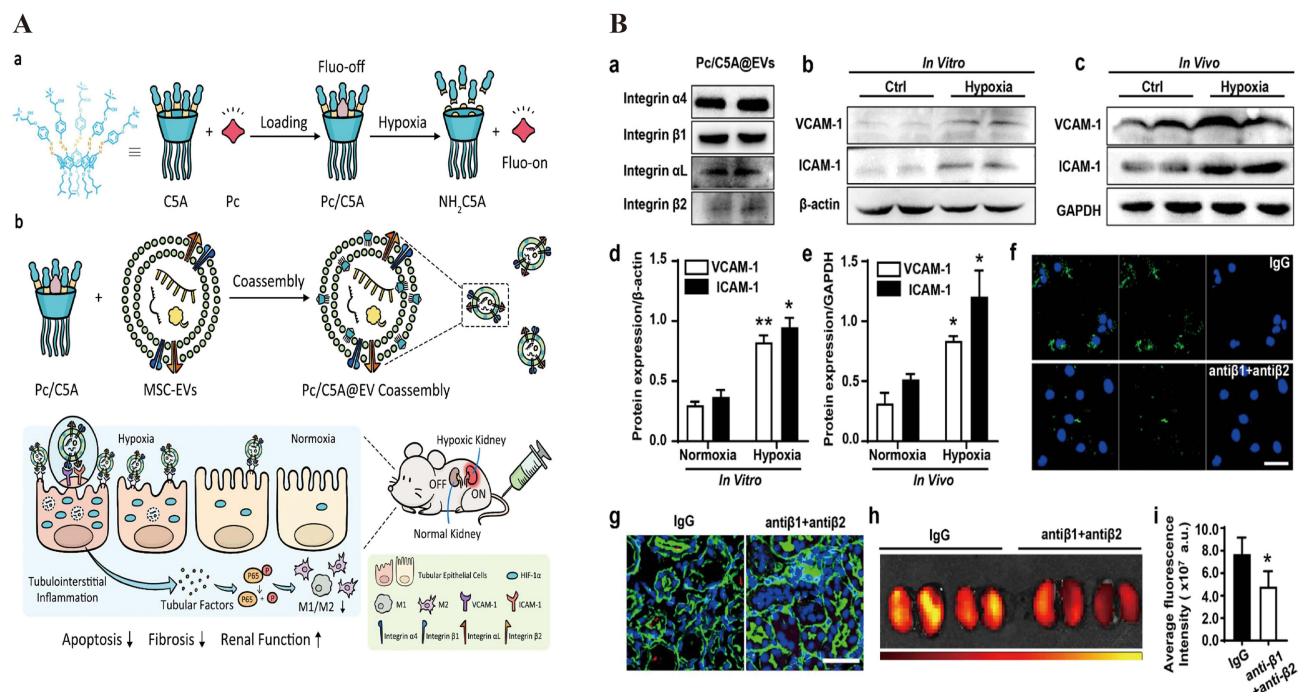
Nanotherapeutic strategies for anti-inflammation and immune modulation in AKI continue to advance. Van et al reported that liposomal prednisolone polarized macrophages toward an anti-inflammatory phenotype (ED2-positive) and suppressed monocyte chemoattractant protein-1 (MCP-1) expression, attenuating renal inflammation.<sup>94</sup> Deng et al designed a biomimetic nanosystem (MM-PtNCs) comprising ROS-responsive platinum nanozyme clusters coated with macrophage membranes, which mitigated oxidative stress and inflammation, restored renal function, and impeded AKI-to-CKD progression.<sup>80</sup> Further supporting immunomodulatory nanotherapy, Lin et al demonstrated that resveratrol nanoparticles (Res NPs) inhibited NLRP3 inflammasome activation and IL-1 $\beta$  secretion while inducing autophagy, significantly reducing creatinine levels and tubulointerstitial injury in a murine CKD model.<sup>95</sup>

Nanotherapies targeting cellular fate regulation in AKI employ diverse mechanisms to mitigate injury and promote repair. Yin et al demonstrated that dihydromyricetin nanoparticles attenuated lipopolysaccharide-induced AKI by suppressing inflammation and apoptosis via TLR4/NF- $\kappa$ B pathway inhibition.<sup>96</sup> Cao et al developed a ROS-responsive nanosystem (M2FPPF@Cur) that accumulated selectively in injured kidneys, scavenged reactive oxygen and nitrogen species (RONS), inhibited GPX4-mediated ferroptosis, and repolarized macrophages toward the M2 phenotype, thereby exerting multifunctional renoprotective effects.<sup>97</sup> Similarly, Li et al reported that Zt-SeCDs enhanced renal function and tissue regeneration by alleviating oxidative stress and inflammation through activation of the AMPK/FoxO1 pathway, highlighting a potent nanotherapeutic strategy for AKI prevention and treatment.<sup>98</sup>

Multimodal nanotherapies demonstrate synergistic efficacy in AKI by concurrently addressing oxidative stress, inflammation, and cellular dysfunction. Kadir et al showed that NA-2 and NA2-AuNPs attenuated cisplatin-induced AKI by downregulating pro-inflammatory markers (NF- $\kappa$ B p50, iNOS, IL-6) and upregulating antioxidant HO-1 expression.<sup>82</sup> Cheng et al developed a Pc/C5A coassembly that induced M1-to-M2 macrophage polarization via HIF-1 $\alpha$  inhibition in hypoxic tubules, suppressing NF- $\kappa$ B signaling and enabling simultaneous renal hypoxia imaging and treatment<sup>72</sup> (Figure 4). Further reinforcing this approach, Saleh et al reported that PEG-AuNPs reduced biochemical markers (BUN, creatinine), ameliorated histopathological damage, and mitigated oxidative stress (via MDA reduction) and inflammation (TNF- $\alpha$ , IL-1 $\beta$  downregulation) by activating the AMPK-Nrf2 and PI3K/AKT pathways, highlighting their potential for diabetic ischemia-reperfusion injury<sup>99</sup> (Table 1).

## Clinical Translation Challenges of Nano-Delivery Drugs for AKI

Despite demonstrating significant therapeutic potential in preclinical studies, the clinical translation of nanodelivery systems for AKI faces multiple challenges, primarily including safety concerns, barriers to large-scale production, and discrepancies between animal models and clinical settings. These factors directly impact the reproducibility, efficacy assessment, and likelihood of regulatory approval for nanomedicines. Wang et al comprehensively reviewed nanomedicines for AKI diagnosis and highlighted the potential of nanotechnology-based drug delivery systems to improve the therapeutic index. However, their work lacks a systematic discussion of future application challenges.<sup>8</sup> This section systematically examines key translational bottlenecks in renal nanomedicine across three domains. Safety considerations include long-term toxicity from metal ion leakage (eg, Ce<sup>3+</sup> from inorganic NPs) or acidic polymer degradation products, addressed via core-shell structures (eg, ZnS-coated QDs<sup>100–102</sup>) or tuned biodegradability (eg, PLGA LA/GA ratio<sup>103,104</sup>), alongside immunogenicity risks such as complement activation (mitigated by PEGylation<sup>105</sup> or zwitterionic coatings<sup>106</sup>) and anti-PEG antibody induction.<sup>107</sup> Large-scale production barriers involve batch inconsistency (eg, PDI > 0.2, drug loading variations) and low yields (eg, exosome purification <1 mg/L<sup>108</sup>), compounded by regulatory gaps for complex nanomaterials (eg, MOFs, combination products<sup>109,110</sup>) requiring extensive characterization and dual-species toxicology. Animal-to-human translation challenges arise from physiological disparities (eg, murine AKI models lacking human comorbidities and biodistribution differences (eg, filtration thresholds), necessitating humanized models (eg, renal



**Figure 4** The co-assembly of hypoxia-sensitive macrocyclic amphiphiles with extracellular vesicles presents an innovative approach for accurate diagnosis of kidney hypoxia and effective treatment of kidney injury. **(A)** (a) Schematic illustration of Pc/CSA@EV preparation. (b) Simultaneous hypoxia-sensitive imaging and therapy in the injured kidneys. **(B)** The coassembly targeted to the hypoxic kidneys via integrin receptor  $\alpha 4\beta 1$  and  $\alpha L\beta 2$ . (a) Western blot of the integrin  $\alpha 4$ ,  $\alpha L$ ,  $\beta 1$  and  $\beta 2$  expression in Pc/CSA@EVs. (b–e) Western blot of the VCAM-1 (b, d) and ICAM-1 (c, e) expression in TECs or renal tissues under hypoxia. ( $n = 5$ ;  $*P < 0.05$  compared with normoxia group;  $**P < 0.01$  compared with normoxia group) (f, g) Representative CLSM images of the cellular uptake of Pc/CSA@EVs after blocking of integrin  $\beta 1$  and  $\beta 2$  in hypoxic TECs or renal tissues. Scale bars = 50  $\mu\text{m}$ . (h, i) Fluorescence imaging and quantitative analysis of IgG- or blocking antibody-treated Pc/CSA@EVs in bilateral hypoxic renal injury mice. ( $n = 5$ ;  $*P < 0.05$  compared with the IgG group). Figure 4 is reprinted from Cheng YQ, Yue YX, Cao HM, Geng WC, Wang LX, Hu XY, Li HB, Bian Q, Kong XL, Liu JF, Kong DL, Guo DS, Wang YB. Coassembly of hypoxia-sensitive macrocyclic amphiphiles and extracellular vesicles for targeted kidney injury imaging and therapy. *J Nanobiotechnology*. 2021 Dec 27;19(1):451<sup>72</sup> (Open access). Black  $\uparrow$ , upgraded;  $\downarrow$ , downgraded.

organoids, PBMC-NSG mice<sup>111,112</sup>), large-animal studies (eg, porcine models), and PBPK modeling to predict human pharmacokinetics<sup>113,114</sup> (Table 2).

## Future Directions for Breakthroughs

Future advancements in renal nanomedicine require focused efforts on safety optimization, production scalability, and translational rigor. Safety can be enhanced through biodegradable alternatives like manganese single-atom catalysts (Mn-N-C), which degrade into endogenous  $\text{Mn}^{2+}$ ,<sup>78,115,116</sup> and immuno-stealth strategies such as CD47-overexpressing exosomes to evade phagocytic clearance.<sup>117</sup> Production processes necessitate continuous flow systems (eg, microfluidics) for kilogram-scale nanoparticle synthesis and proactive regulatory collaboration to update FDA/EMA guidelines for novel nanotherapeutics.<sup>118</sup> Translational research must prioritize non-human primate (NHP) models for dose validation and implement microdosing clinical trials with PET tracking to preliminarily assess human biodistribution.<sup>119,120</sup> While Geo et al reviewed the use of nanosized drug carriers (NDCs) for delivering reno-protective agents and improving renal targeting in AKI, their discussion was limited and lacked an in-depth exploration of future directions and breakthroughs.<sup>121</sup> The clinical translation of nano-based therapeutics for AKI hinges on addressing three fundamental challenges: comprehensive safety validation, robust production standardization, and interspecies physiological disparities. Through interdisciplinary collaboration—spanning materials science, toxicology, and clinical medicine—coupled with regulatory innovation, the first AKI nanomedicines are anticipated to achieve clinical adoption within the next 5–10 years.

**Table 1** Representative Mechanisms of Nano-Delivery Materials in the Treatment of AKI

Treatment Strategy	Loaded Drugs/ Active Ingredients	Type of Nanomaterials	Targeting Mechanism	Model/Effects (eGFR Improvement/ Survival Rate)	References (Examples)
<b>Antioxidants</b>	Edaravone	PLGA-PEG nanoparticles	A decrease in tubular epithelial cell damage and death	Renal-selective edaravone delivery holds potential for the prevention of acute kidney injury among patients undergoing cisplatin-based chemotherapy	[92]
	Curcumin	Epigallocatechin gallate	Effectively scavenging reactive oxygen species and reducing intracellular oxidative stress	It is a novel acid-resistant nanopatform based on EGCG for the treatment of acute inflammation	[93]
	Indocyanine green/elamipretide	Platelet membrane-coated bio-nanoparticles	Acts as a mitochondria-targeted antioxidant that protects against mitochondrial damage and reduces oxidative stress, inflammation, and apoptosis	The in vivo distribution of PISP can be observed for NIR diagnosis of AKI	[73]
<b>Anti-inflammation and immune modulation</b>	Prednisolone	PEGylated liposomes	Regulation of PER1 messenger RNA (mRNA),	It reduced monocyte chemoattractant protein-1 (MCP-1) mRNA production, indicating a reduced pro-inflammatory profile in the kidney.	[94]
	Macrophage membrane	MM-PtNCs	Scavenge ROS and regulate the oxidative stress situations both in injured cells and tissues	MM-PtNCs effectively prevented the progression of AKI to chronic kidney disease	[80]
	Resveratrol	Kim-1 antibody-conjugated PLGA nanoparticles	Res NPs inhibited the NLRP3 inflammasome and IL-1 $\beta$ secretion	Res NPs through NLRP3 inflammasome attenuation and autophagy induction may be as a strategy to prevent CKD	[95]
<b>Inhibiting cell death</b>	Dihydropyridin	Nanoparticles	TLR4/NF- $\kappa$ B Pathway	Decreasing inflammation and cell apoptosis	[96]
	Curcumin	Biomimetic reactive oxygen/nitrogen noscavengers	Ferroptosis and immune system	Preventing the progression of AKI.	[97]
<b>Multimodal therapy</b>	Selenium	Selenium-doped carbon dots	Alleviate oxidative stress and ferroptosis	Reversal of acute kidney injury	[98]
	N-(2-Hydroxyphenyl) acetamide	NA-2-conjugated gold nanoparticles (NA2-AuNPs)	Inducible nitric oxide synthase (iNOS); hemeoxygenase-1 (HO-1); and interleukin-6 (IL-6)	It is concluded that NA-2 and NA2-AuNPs attenuates CP-induced AKI in mice models through anti-inflammatory and anti-oxidant mechanisms	[82]
	Polyethylene glycol	Polyethylene glycol capped gold nanoparticles	PEG-AuNPs increased the recovering of damaged renal cells, suppressed significantly levels of malondialdehyde (MDA), downregulated significantly the level of inflammatory cytokines (TNF- $\alpha$ and IL-1 $\beta$ ), and upregulated the AMPK-Nrf2 pathway.	PEG-AuNPs exhibited a promising alternative therapeutic target for diabetic renal I/R-induced AKI	[99]
	Macrocyclic amphiphiles	Pc/C5A@EVs	Surface integrin receptor $\alpha$ 4 $\beta$ 1 and $\alpha$ L $\beta$ 2	This synergetic nanoscale coassembly with great translational potential provides a novel strategy for precise kidney hypoxia diagnosis and efficient kidney injury treatment.	[72]

**Table 2** Challenges and Strategies for Clinical Translation of Nano-Delivery Materials in the Treatment of AKI

Challenge Category	Specific Issues	Existing Solutions	Limitations/Unresolved Issues	Reference
Safety	Long-term renal accumulation toxicity of nanomaterials	Biodegradable materials (eg, PLGA, liposomes)	Degradation products may induce chronic inflammation	[78,115]
	Immunogenicity (complement activation, cytokine storm)	PEGylation modification, biomimetic membrane coatings (red blood cell membranes)	PEG antibodies can lead to accelerated clearance (ABC phenomenon)	[80,116]
Scalability	Batch-to-batch consistency (particle size/drug loading)	Microfluidic technology for standardized production	Complex materials (eg, hybrid nanoparticles) remain difficult to standardize	[75,82]
	Sterilization processes affecting material stability	Aseptic filtration as an alternative to $\gamma$ -irradiation	Large-sized materials like virus-like particles cannot be filtered	[117,118]
Pharmacodynamic differences	Differences in animal models versus human AKI pathology	Organoid chips simulating the human renal tubular microenvironment	Inability to fully replicate the immune microenvironment	[112,119]
	Species-dependent renal targeting efficiency	Humanized mouse models for validation	High costs of non-human primate experiments	[113,114]
Regulatory pathways	Lack of AKI-specific evaluation guidelines	Referencing FDA guidelines for nanomedicines in oncology	Absence of kidney-specific biodistribution standards	[120,121]
	Correlation between biomarkers and clinical endpoints	Combining traditional biomarkers (Scr) with novel biomarkers (NGAL)	Nanomaterials may interfere with detection	[122,123]

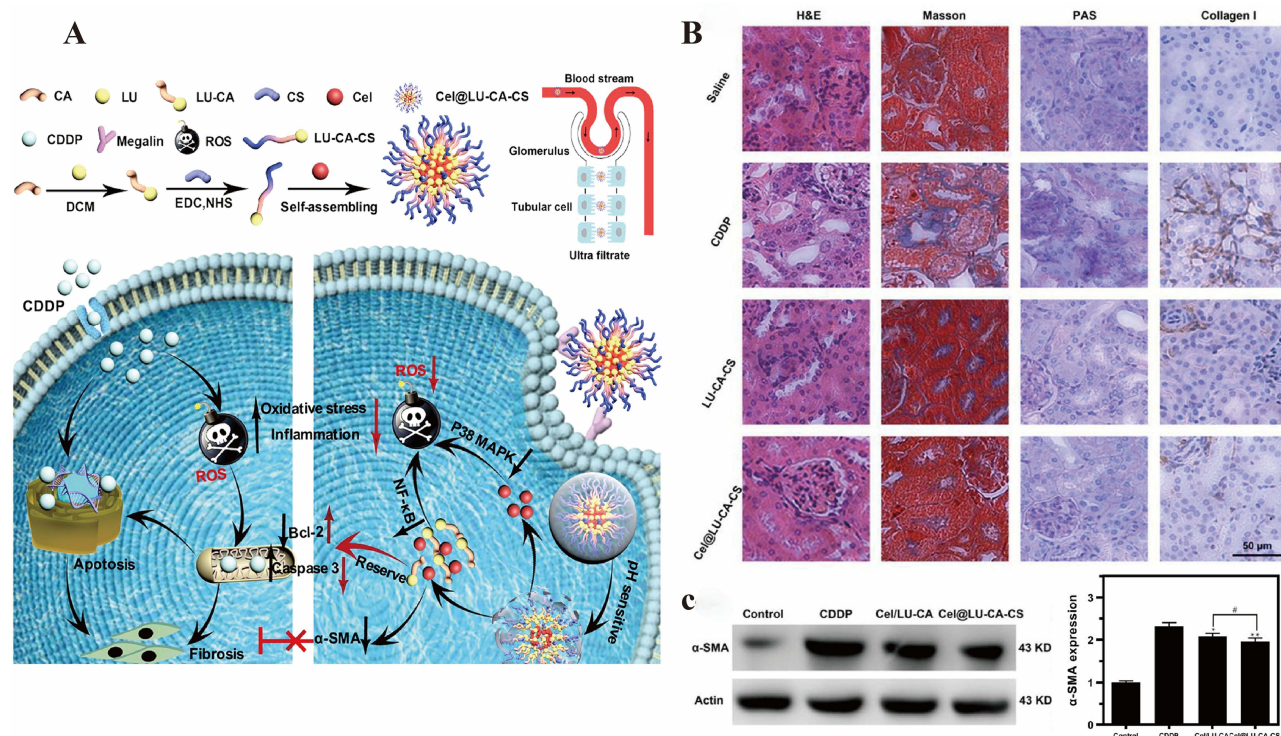
## Future Perspectives on Nanodelivery Systems for Treating AKI

With the deep integration of nanotechnology and medicine, nanodelivery systems are advancing from fundamental research to clinical translation in the field of AKI treatment. Over the next 5–10 years, developments in this area will focus on smart material design, efficient validation platforms, accelerated clinical translation, and expansion into preventive medicine, ultimately achieving precise, efficient, and accessible nanomedicine solutions for AKI.

1. Next-generation smart materials: AI-driven nano-design. The development of traditional nanomaterials has relied on trial-and-error methods, which are time-consuming and costly. The introduction of artificial intelligence (AI) will revolutionize this approach: AI-assisted material screening. Application: Machine learning models (eg, graph neural networks, GNN) can predict the renal targeting efficiency of nanomaterials. For instance, by analyzing parameters such as particle size (5–50 nm), surface charge (–30 mV to +20 mV), and hydrophobicity (LogP values), AI can optimize the design of nanoparticles for enhanced kidney accumulation.<sup>124–126</sup> Intelligent upgrading of responsive materials. Dynamic response: AI can simulate various AKI microenvironments (eg, pH 6.5–7.2, GSH levels 5–10 mM) to design multi-stimuli responsive materials. For example, pH/ROS dual-sensitive polymers can release SOD in early AKI and anti-inflammatory drugs in later stages<sup>96,125</sup> (Figure 5).

2. Organ-on-a-chip technology to accelerate preclinical validation. The limitations of animal models have led to the emergence of kidney-on-a-chip technologies as a new standard for validating nanomedicines. Humanized models: Microfluidic chips integrate human glomerular endothelial cells and proximal tubular epithelial cells to simulate AKI pathologies (eg, hypoxia, inflammation).<sup>127–129</sup> High-throughput screening: Single experiments can test hundreds of nanocompositions, significantly shortening development timelines. Proximal tubule chips have been employed to evaluate the cellular uptake and toxicity of CeO<sub>2</sub> nanocatalysts.<sup>130,131</sup>

3. Current status and breakthrough directions in clinical trials. Currently, only a limited number of AKI nanomedicines have entered clinical stages.<sup>132</sup> Qin et al summarized active clinical trials using nanoparticles for kidney diseases; however, their focus was predominantly on CKD and renal cancers, and they did not address strategies for optimizing clinical trial design to facilitate translational success.<sup>133</sup> Future clinical trial design will emphasize precision enrollment through biomarker-guided selection, such as urinary exosomal KIM-1 positivity,<sup>134</sup> and explore combination strategies integrating nanomedicines with regenerative approaches like MSC exosomes.<sup>135–137</sup> Nanomedicine also holds significant potential for AKI prevention in high-risk cohorts. Prophylactic interventions may include glutathione-responsive nanoparticles for NAC release prior to cisplatin chemotherapy,<sup>44,138</sup> or preoperative administration of antioxidant nano-



**Figure 5** Co-delivery of celastrol and lutein using pH-sensitive nanomicelles offers a highly effective and low-toxicity treatment for AKI while also inhibiting renal fibrosis. **(A)** The synthesis and mechanism of the Cel@LU-CA-CS nanodelivery system. **(B)** Anti-fibrosis effect of different formulations. Kidney tissues were stained by H&E, Masson, PAS, and collagen I, respectively. **(C)** Western blot analysis and related semi-quantitative results of  $\alpha$ -SMA protein in renal tissues ( $n = 3$ , #  $P < 0.05$ , Cel@LU-CA-CS group vs Cel/LU-CA group). \* $P < 0.05$ , \*\* $P < 0.01$ . Figure 5 is reprinted by Pang M, Duan S, Zhao M, Jiao Q, Bai Y, Yu L, Du B, Cheng G. Co-delivery of celastrol and lutein with pH sensitive nano micelles for treating acute kidney injury. Toxicol Appl Pharmacol. 2022 Sep 1;450:116,155.<sup>125</sup> With the permission from Elsevier Inc.6098780578547. Both red and black  $\uparrow$ , upgraded; red and black  $\downarrow$ , downgraded.

catalysts (eg, Pt NPs) to mitigate ischemia-reperfusion injury in cardiac surgery.<sup>139</sup> Further innovation may involve integrated health monitoring systems coupling wearable nano-sensors for real-time NGAL detection with triggered therapeutic release<sup>140,141</sup> (Table 3).

**Table 3** Future Directions and Breakthroughs in Nano-Delivery Systems for the Treatment of AKI

Research Direction	Key Technologies/Strategies	Potential Clinical Value	Challenges	Reference
Smart Responsive Nanomaterials	AI-driven material design (high-throughput screening of optimal ligands/carriers)	Dynamic adaptation to the AKI microenvironment (pH/ROS/enzyme-triggered drug release)	Complex synthesis processes, inter-batch stability issues	[124,125]
Organ-on-a-chip and Organoid Models	Humanized renal tubular chips to validate nanodelivery efficiency	Reduction of animal testing, acceleration of preclinical predictive research	Incomplete simulation of vascularization and immune microenvironments	[142,143]
CRISPR-Cas9 Gene Editing	Nanocarriers for delivering gene editing tools (targeting pro-fibrotic genes)	Reversal of AKI-CKD transition	Off-target effects and unknown long-term safety	[144,145]
Engineered Exosomes	Engineered exosomes loaded with miRNA or anti-inflammatory factors	Low immunogenicity, natural renal tropism	Difficulties in large-scale production, low drug-loading efficiency	[135,136]
Integrated Multimodal Diagnosis and Therapy	Nanoparticles combining imaging agents (MRI/ultrasound) with therapeutic functions	Real-time monitoring of treatment efficacy and adjustment of therapeutic protocols	Balancing imaging sensitivity and therapeutic payload	[12,146]
Advancement of Clinical Translation	Industry-academic collaboration	Promotion of 1–2 nanodrugs into Phase II clinical trials for AKI		[147,148]

## Conclusions

The treatment of AKI has been limited by diagnostic delays, ineffective drug targeting, and suboptimal therapeutic outcomes. Nanotechnology is transforming this landscape by enabling precise drug delivery, synergistic mechanisms, and integrated diagnosis and therapy, shifting AKI management from “passive support” to “active repair.” The unique characteristics of nanomaterials, including size-dependent renal accumulation and stimuli-responsive release, allow targeted intervention in AKI’s core pathological processes: oxidative stress, inflammation, immune function, apoptosis, ferroptosis. Additionally, multifunctional nanoplatforms that combine diagnostic and therapeutic functions offer a comprehensive approach for early AKI intervention. Future advancements in this field will depend on interdisciplinary collaboration across materials science (designing biodegradable, low-toxicity nanocarriers), nephrology (identifying molecular targets and clinical needs), and engineering (developing microfluidic production and organ-on-a-chip validation technologies). With AI-driven material design and expedited clinical trials, nanotechnology is expected to revolutionize AKI treatment within the next 5–10 years, significantly reducing global incidence and mortality rates. Achieving this progress will require close cooperation among researchers, clinical doctors, industry, and regulatory bodies to address translational challenges and improve patient outcomes.

## Abbreviations

Acute kidney injury, AKI; Ischemia-reperfusion injury, IRI; Nanoparticles, NPs; Reactive oxygen species, ROS; Chronic kidney disease, CKD; Extracellular vesicle, EV; Metal-phenolic networks, MPNs; Nanosized drug carriers, NDCs; Artificial intelligence, AI.

## Data Sharing Statement

All data analyzed was included in this study, further request could be consulted and obtained from corresponding author Pro. Zhaoyang Xiao.

## Ethics Approval and Consent to Participate

This is a review study, then ethic approval is waived.

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## Disclosure

The authors report no conflicts of interest in this work.

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