

# Nanomedicine-Based Therapeutics to Combat Acute Lung Injury

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Shuai Bian<sup>1</sup>  
Hongfei Cai<sup>1</sup>  
Youbin Cui<sup>1,\*</sup>  
Wanguo Liu<sup>2,\*</sup>  
Chunsheng Xiao<sup>3</sup>

<sup>1</sup>Department of Thoracic Surgery, The First Hospital of Jilin University, Changchun, 130021, People's Republic of China; <sup>2</sup>Department of Orthopedic Surgery, China-Japan Union Hospital of Jilin University, Changchun, 130033, People's Republic of China; <sup>3</sup>Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, People's Republic of China

\*These authors contributed equally to this work

**Abstract:** Acute lung injury (ALI) or its aggravated stage acute respiratory distress syndrome (ARDS) may lead to a life-threatening form of respiratory failure, resulting in high mortality of up to 30–40% in most studies. Although there have been decades of research since ALI was first described in 1967, the clinical therapeutic alternatives for ALI are still in a state of limited availability. Supportive treatment and mechanical ventilation still have priority. Despite some preclinical studies demonstrating the benefit of pharmacological interventions, none of these has been proved completely effective to date. Recent advances in nanotechnology may shed new light on the pharmacotherapy of ALI. Nanomedicine possesses targeting and synergistic therapeutic capability, thus boosting pharmaceutical efficacy and mitigating the side effects. Currently, a variety of nanomedicine with diverse frameworks and functional groups have been elaborately developed, in accordance with their lung targeting ability and the pathophysiology of ALI. The in-depth review of the current literature reveals that liposomes, polymers, inorganic materials, cell membranes, platelets, and other nanomedicine approaches have conferred attractive therapeutic benefits for ALI treatment. In this review, we explore the recent progress in the study of the nanomedicine-based therapy of ALI, presenting various nanomedical approaches, drug choices, therapeutic strategies, and outcomes, thereby providing insight into the trends.

**Keywords:** acute lung injury, acute respiratory distress syndrome, drug delivery, nanoparticle, nanomedicine

## Introduction

Acute lung injury (ALI) or its aggravated stage acute respiratory distress syndrome (ARDS) is a common cause of respiratory failure in severely ill patients. Despite substantial progress in intensive care therapy and organ supportive technology, the mortality of ALI remains high at 30%–40% in most studies.<sup>1,2</sup> The most common cause of ALI is a bacterial or viral infection. For example, patients who are infected with SARS-CoV-2 can present with pneumonia and hypoxemia, even progressing to ALI/ARDS.<sup>3</sup> Sepsis, aspiration of chemical agents and gastric contents, and shock are other common causes of ALI.<sup>4</sup> The pathogenesis and pathophysiology of ALI are characterized by the destruction of alveolar–capillary integrity and by increased permeability, resulting in fluid, proteins, inflammatory agents and red blood cells accumulating in the alveolar space,<sup>2</sup> and the clearance ability of the lung also being impaired.<sup>5</sup> Clinical treatment of ALI/ARDS focuses on early diagnosis, control of infections, supportive ventilation, careful fluid management, and general supportive measures.<sup>2</sup>

Until now, clinical short-term or long-term mortality has not been able to be reduced by pharmaceutical drugs,<sup>6</sup> but some pharmacologic agents have been

Correspondence: Youbin Cui  
Department of Thoracic Surgery, The First Hospital of Jilin University, Changchun, 130021, People's Republic of China  
Email cuiyb@jlu.edu.cn

Wanguo Liu  
Department of Orthopedic Surgery, China-Japan Union Hospital of Jilin University, Changchun, 130033, People's Republic of China  
Email liuwanguo6016@jlu.edu.cn

proved to be effective in ameliorating ALI/ARDS. Glucocorticoids, such as dexamethasone, when administered at an early stage, may decrease the duration of supportive ventilation, as well as the overall mortality,<sup>7</sup> but they are harmful at approximately 2 weeks after ARDS has been diagnosed.<sup>8</sup> Neutrophil elastase increases the permeability of the alveolar–capillary barrier and causes proteolytic lung tissue damage.<sup>2</sup> Neutrophil elastase inhibitors, such as sivelestat, could be optional for the treatment of ALI; however, a multi-national clinical trial proved that sivelestat therapy was unsuccessful.<sup>9</sup> Simvastatin has been reported to prevent organ dysfunction experimentally in ALI by decreasing vascular inflammation and leakage.<sup>10</sup> However, a clinical trial reported that, although its safety was guaranteed and its adverse effects were minimal, simvastatin did not show distinct clinical benefits.<sup>11</sup> Inhaled nitric oxide can improve oxygenation and lung function but may have side effects or even be harmful when applied improperly.<sup>12</sup> Gene silencing, via short-interfering RNA (siRNA) to protect the integrity of the epithelial–endothelial barrier and prevent lung cell death, is a promising therapeutic option, but its application has been hampered by delivery technology challenges and safeties.<sup>13</sup> Surfactant replacements, anticoagulation, and antioxidants have shown some effects in experiments but have failed in clinical trials<sup>14</sup> (Table 1).

The limited success of pharmacological therapies forces us to develop new agents to combat ALI. The rapid development of nanomedicine might shed new light on this issue. Nanomedicines that possess active or passive targeting abilities have shown therapeutic advantages in various diseases. For example, it is recommended that nano-formulating dexamethasone be used to improve the efficacy in treating COVID-19, due to its ability to target hyper-activated immune cells, as well as its anti-edema activity.<sup>15</sup> Therapeutic agents such as drugs, siRNA, and proteins can be conjugated or encapsulated inside nanomedicines.<sup>16,17</sup> In the presence of ALI, there arose enhanced permeability of blood vessels, along with alterations in oxidants, pH and enzymes in the microenvironment, as well as regulation of the expression of various cell surface receptors.<sup>18</sup> The above characteristics offer targets for site-specific delivery and the microenvironment for responsive drug release. To this end, the nanomedicine for ALI has broad alternative therapeutic strategies, including the delivery of anti-inflammatory agents to the disease site,<sup>19–34</sup> the direct scavenging of inflammatory factors,<sup>35–47</sup> the regulating of inflammatory cell activities,<sup>48–59</sup> or the modulating of inflammatory signaling

pathways.<sup>60–73</sup> Various nanomedicines act on different cells or pathophysiology processes to achieve therapeutic effects, many of which have demonstrated satisfying in vitro and in vivo effects.

In this review, we will focus on a systematic overview of the state-of-the-art and advances in therapeutic nanomedicines for ALI. Firstly, a brief profile of essential cellular targets of nanomedicine for enhanced therapeutic effects will be presented. Subsequently, the diverse nanomedicines will be categorized into four groups and their applications in the treatment of ALI will be shown in elaborate detail. Lastly, we will analyze both the ongoing chances and challenges of nanomedicine-based therapy for ALI, especially presenting some of the innovative technologies that will navigate the future direction of nanomedicine, such as nanorobotics, machine learning and artificial intelligence (Figure 1).

## Cellular Targets for Nanomedicine

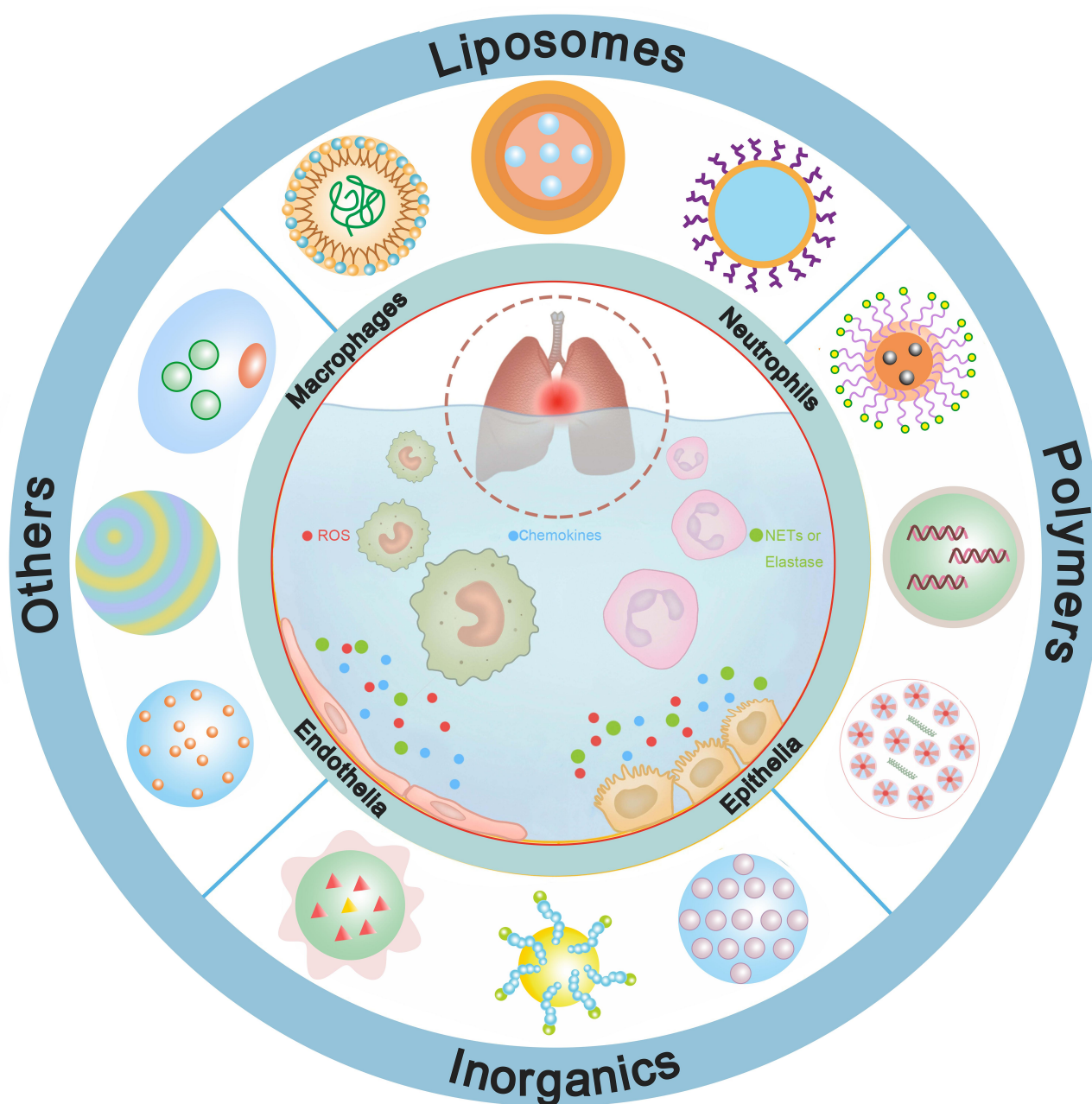
During ALI, the damage of the alveolar–capillary barrier increases vascular permeability and fluid accumulation.<sup>2,4</sup> This process is mediated by macrophages, neutrophils, and epithelial and endothelial cells through the innate immune response.<sup>74</sup>

Alveolar macrophages (AMs) are resident cells in the alveoli that use a variety of mechanisms as a defense against the invasion of foreign particles and pathogens at the first line.<sup>75</sup> Upon stimulation, resting macrophages (M0) are activated through classical and alternative pathways that are polarized and mainly classified into pro-inflammatory phenotype (M1) and anti-inflammatory phenotype (M2).<sup>76</sup> The M1 macrophages can release various potent pro-inflammatory cytokines including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ .<sup>77</sup> Modulation of AMs has been found to mitigate lung injury by attenuating neutrophil accumulation and reducing pro-inflammatory cytokines.<sup>78</sup> The mannosylated nanomedicine can target to macrophages by mannose receptors,<sup>25,52,61</sup> and sialic acid bound to the E-selectin on the macrophages<sup>29,67</sup> can also be utilized for active targeting. Because nanoparticles can be easily phagocytosed by macrophages, they possess a superior ability to control the inflammatory responses mediated by macrophages.<sup>37,45–47,62,64,67,68,71,73,79</sup>

Among the leukocytes at the sites of inflammation, neutrophils are the first to be recruited in response to chemotactic factors.<sup>80</sup> They migrate across the endothelium and through the epithelium into the alveoli, then release histotoxic mediators to damage lung tissue, such as reactive oxygen species (ROS), neutrophil extracellular

**Table I** The Medication to Construct Nanomedicine for ALI/ARDS

Medication	Therapeutic Mechanisms	Drawbacks	Ref.
<b>Glucocorticoids</b>			
Dexamethasone, Methylprednisolone	Inhibit production of inflammatory cytokines, attenuate fluid accumulation and anti-fibrosis	Various side effects including hypertension, Cushing's syndrome, gastrointestinal bleeding, immunosuppression, bone necrosis and osteoporosis etc.	[15,136]
<b>Anti-inflammatory agents and antioxidants</b>			
Curcumin	Reduces inflammation by inhibiting NF- $\kappa$ B and activating protein-I, by down-regulating COX-2 and inducible nitric oxide synthase	Poor water solubility and fast degradation result in low bioavailability	[29,70]
Resveratrol	Anti-inflammation by targeting MAPK and NF- $\kappa$ B, anti-oxidation by increasing the activity of antioxidant enzymes	Low bioavailability and solubility, require to be consumed regularly at a high dose	[19,71]
$\alpha$ -bisabolol	Anti-inflammation and anti-oxidation, inhibits pro-inflammatory cytokines	Highly lipophilic and easily oxidizable, easily forming two bisabolol oxides	[23,137]
EUK-134	A synthetic salen-manganese complexes, small molecule SOD/catalase mimetic, scavenges ROS	Poor solubility and stability	[35,138]
Oleic acid	Inhibits upregulated superoxide anion and elastase in activated neutrophils, reduces ROS	Extremely high lipophilicity, infeasible to formulate into injectable aqueous formulation	[48,139]
<b>Inhibitors</b>			
TPCA-I	An I $\kappa$ B kinase-2 (IKK-2) inhibitor, blocks NF- $\kappa$ B nuclear translocation, reduces inflammatory cytokine production	Insoluble in water, lack of tissue targeting feature	[28,140]
Simvastatin	3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, reduces vascular inflammation and permeability, protects endothelium	Require high-dose and prolonged treatment, which increases the risk of liver toxicity and myopathy	[21,60,141]
Cilomilast, Rolipram	PDE4 inhibitors; repress neutrophil overactivation through regulating intracellular levels of cAMP	Emesis, nausea and headache caused by brain penetration; low therapeutic index	[50,51]
Sivelestat	Second-generation NE inhibitor; inhibit NE activity to preventing NETs formation	Hypersensitivity, hepatobiliary disorders, anemia, protein urine, protein total decreased; failed in clinical trial	[49,142]
Piceatannol	Spleen tyrosine kinase inhibitor, blocks "outside-in" $\beta$ 2 integrin signaling in leukocytes, reduced neutrophil adhesion and migration	Poor solubility, poor bioavailability and biological activity	[58,143]
PP2	Src tyrosine kinase inhibitor, blocks the recruitment and activation of various immune cells, reduces vascular permeability and tissue inflammation	Non-selective and inhibits many other kinases with similar affinities	[34,144]
Ruthenium red	Transient receptor potential vanilloid 4 (TRPV4) inhibitor, blocks force-sensitive TRPV4-mediated calcium signaling to reduce vascular permeability	Non-selective transient receptor potential (TRP) inhibitor and interacts with a number of non-TRP proteins	[30,145]



**Figure 1** Nanomedicines can be fabricated based on various nanomaterials, including liposomes, polymers, inorganics, cell membranes, platelets, etc. They interfere one or more pathophysiologic processes of ALI to present beneficial effects.

traps (NETs), and proteases,<sup>81</sup> as well as disrupting the endothelial–epithelial barrier.<sup>82</sup> Nanomedicine can suppress neutrophil function by inhibiting upregulated superoxide anions and elastase,<sup>48,49</sup> repressing activity of neutrophil overactivation by inhibiting phosphodiesterase 4 (PDE4) activity<sup>50,51</sup> and detaching neutrophil adherence by blocking integrin signaling,<sup>58</sup> or using neutrophils as vehicles<sup>54,56,57</sup> for targeted ALI therapy.

Restoring the integrity of the endothelial–epithelial barrier is critical in ALI therapy.<sup>83,84</sup> As the primary injured structure, the pulmonary epithelium is subject to dissociation of intercellular junctions<sup>85</sup> and cell death,<sup>31</sup> but is more resistant to injury than the endothelium.<sup>86</sup> The endothelial junctions' breakdown or the endothelial cells' death will increase the lung's vascular permeability, thus resulting in excessive fluid and protein leakage into the



alveoli.<sup>2</sup> To target the endothelium and epithelium, intercellular adhesion molecule-1 (ICAM-1),<sup>87</sup> platelet-endothelial cell adhesion molecule (PECAM-1)<sup>88</sup> and surfactant protein (SP)<sup>89</sup> can be bio-conjugated by corresponding antibodies for active targeting nanotherapy.<sup>20–22,24,28,35,56,60,63</sup> Nanomedicine can restore barrier integrity and prevent cell death by influencing inflammatory pathways<sup>20,21,44,60,63,65,70–72</sup> and alleviating oxidative stress.<sup>28,35,36,42,54,56</sup> The influence of nanomedicine on cellular architecture can be assessed by a pragmatic optimized air–liquid interface system, which showed comparable results as those in an *in vivo* study.<sup>90</sup>

## Different Nanomedicine Applications in Treating ALI

For ALI treatment, nanomedicines are mainly administered through the intrapulmonary or the intravenous route. For the intrapulmonary route, the agents should be sufficiently potent to penetrate the mucus layer and pass through the cell membrane; two major barriers that affect pulmonary delivery efficiency.<sup>91</sup> As the mucus layer is rich in negatively charged glycoproteins and phospholipid pulmonary surfactant that can trap cationic agents, it is reasonable to modify the nanomedicines to enhance penetration.<sup>62,92</sup> For the intravenous route, target delivery to the inflammatory site ensures satisfactory therapeutic efficacy. Targeting strategies include the passive targeting effect called ELVIS (extravasation through leaky vasculature and the subsequent inflammatory cell-mediated sequestration)<sup>18</sup> and the conjugating of active targeting moieties to the backbone of the nanomedicine. Next, some of the nanomedicine applications in treating ALI through different mechanisms and the therapeutic efficacy are introduced.

## Lipid-Based Nanomedicine

Liposomes are a well-established drug delivery system in the clinical context that are composed of single or multiple concentric lipid bilayers and aqueous compartments. The lipophilic agents are embedded within the phospholipid bilayer, while the aqueous core can encapsulate hydrophilic agents.<sup>93</sup> Nanostructured lipid carriers (NLCs) or oil-loaded solid lipid carriers are the second generation of lipid carriers. The oil core of NLCs offers a variety of fascinating properties, including increased loading capacity, excellent biocompatibility, controlled release compared to the rapid release of liposomes, and feasibility of

large-scale production.<sup>20,94</sup> Anti-inflammatory drugs,<sup>20–22,24–26,49,60,61</sup> anti-oxidant agents,<sup>27,35</sup> and neutrophil function inhibitors<sup>48,50,51</sup> were transformed into nanomedicines to improve their effectiveness and decrease their side effects (Table 2).

The lipophilic antioxidant ( $\alpha$ -tocopherol) and the hydrophilic anti-inflammatory agent (Glutathione, GSH or DEX) were encapsulated into liposomes, which showed an advantageous effect in ameliorating lung injury over the free drug.<sup>26,27</sup> PDE4 inhibitors, rolipram or cilomilast, can repress the activity of neutrophil overactivation,<sup>95</sup> however, the brain penetration side effects and narrow therapeutic index have restricted their application.<sup>50</sup> Employing phosphatidosomes to deliver PDE4 inhibitor showed enhance pulmonary surfactant affinity and reduced penetration into the brain; additionally, neutrophil activation was repressed by decreasing the  $O_2^{\cdot-}$ ,  $Ca^{2+}$  content and increasing the cyclic adenosine monophosphate (cAMP) production.<sup>50,51</sup> Oleic acid (OA) can also inhibit inflammation of activated neutrophils at a certain dose. The changing amount of mineral oil in OA-loaded nanocarriers enabled mean diameters to vary among 105, 153, and 225 nm. Smaller sizes exhibited greater neutrophil uptake to decrease the cell viability and the intracellular calcium level, while larger sizes exhibited greater lung targeting ability than the smaller ones<sup>48</sup> (Figure 2A). Overproduction of NETs promoted inflammatory pathologies,<sup>96</sup> and neutrophil elastase (NE) participated in the formation of NETs.<sup>97</sup> Sivelestat is an NE inhibitor that is clinically used in patients with ALI who develop a systemic inflammatory response. Interbilayer-crosslinked multilamellar vesicles (ICMVs) loading sivelestat (ICMV-sivelestat) were readily taken up by neutrophils and inhibited the formation of NETs effectively *in vitro*. ICMV-sivelestat alleviated lung injury by reducing NE and production of other pro-inflammatory cytokines.<sup>49</sup>

To improve the targeting ability of liposomes, mannosylated,<sup>25,61</sup> and antibody-modified<sup>20–22,24,35,60</sup> liposomes were developed. Mannosylated (Man) liposomes can target AMs, inhaled liposomes encapsulating dexamethasone palmitate, and Man-cationic liposome/NF $\kappa$ B decoy reduced pro-inflammatory cytokines, and suppress neutrophil infiltration.<sup>25,61</sup> Surfactant protein A (SP-A) is a type of pulmonary SP that is mostly expressed in type II alveolar epithelial cells but is rarely expressed in extrapulmonary tissues and organs.<sup>24</sup> SP-A nanobody-conjugated immune-liposomes delivering glucocorticoids showed good lung-targeting specificity and decreased the

**Table 2** Lipid-Based Nanomedicine

Material (Moiety)	Drug/Gene	Size (nm)	Dose (Route)	Animal Model (Route)	In vivo Therapeutic Outcomes	Ref.
DPPE	Dexamethasone	231 ± 32	800 µg/kg (i.t. 1 h pre)	Male SD rats LPS (i.v.)	Wet lung weight↓; ACE & AKP↑; MPO, elastase and chloramine↓; phospholipase A2, leukotriene B4 & thromboxane B2↓	[26]
DPPE	α-Tocopherol, GSH	370 ± 58	2 mg α-tocopherol, 10 µmol GSH (i.t. 30 min pre)	Male SD rats Paraquat (i.p.)	ACE & AKP↑; GSH↑; wet lung weight-	[27]
Span 60, cholesterol, soybean PC, DSPE-PEG, Soyaethyl morphonium ethosulfate	Cilomilast	120.67 ± 0.27; 100.29 ± 0.32	2.5 mg/kg (i.v. 30 min pre)	Male C57BL/6 mice LPS (i.t.)	H&E, Ly6G antibody and MPO antibody staining↑; MPO, IL-1β, IL-6 and THF-α↓	[50]
Span 60, cholesterol, soybean PC, DSPE-PEG	Rolipram	154	NG (i.v. 1 h pre)	Male C57BL/6 mice LPS (i.t.)	Lung W/D ratio-, MPO-, H&E-	[51]
DOPC, MPB, DID, or DiR	Sivelestat	266 ± 12	50 mg/kg (i.p. 1 h post)	Female BALB/c mice LPS (i.p.)	Clinical score↓; survival↑; NETs formation↓; H&E↑; neutrophil elastase, IL-6 and KC↓	[49]
SPC, mineral oil	OA	105, 153, and 225	NG (i.v. 30 min pre)	Male C57BL/6 mice LPS (i.t.)	H&E, Ly6G antibody and MPO antibody staining↑; MPO, TNF-α, IL-1β, IL-6 and CXCL-2↓	[48]
DSPC/Chol/Man-C4-Chol	Dexamethasone	110 ± 6.9	5 mg/kg (i.t. 1 h pre)	Male Wistar rats LPS (i.t.)	TNF-α, IL-1β, CINC-1, BALF neutrophil, MPO↓; H&E↑; NF-κB activation, and p38MAPK phosphorylation↓	[25]
Man-, Fuc- and galactosyl-C4-Chol /DOTMA/Chol	NF-κB decoy	~100	50 µg (i.t. 30 min pre)	Male Wistar rats LPS (i.t.)	TNF-α, neutrophil count, IL-1β, CINC-1, MPO↓; H&E↑; NF-κB↓	[61]
DSPE-PEG3400-iodoacetate (Surfactant protein-A antibody)	Methylprednisolone	106	0.5/1 mg/kg (i.v. 0 h)	Male SD rats Bleomycin (i.t.)	H&E↑; IL-8, TGF-β, TNF-α, NF-κB↓	[22]
Soy lecithin, cholesterol, DSPE-PEG2000 (Surfactant protein-A antibody)	Dexamethasone	136 ± 38	0.5/1.0 mg/kg (i.v. 0 h)	Male SD rats Bleomycin (i.t.)	H&E↑ and score↓; TNF-α, TGF-β↓; survival rate↑	[24]
DPPE, PC, PG, cholesterol, DSPE-PEG (2000)-biotin or DSPE-PEG(2000)-maleimide (PECAM-I antibody)	EUK-134	197.8 ± 4.5	NG (i.v. 15 min pre)	Male C57BL/6 mice LPS (i.t.)	Lung protection↑	[35]

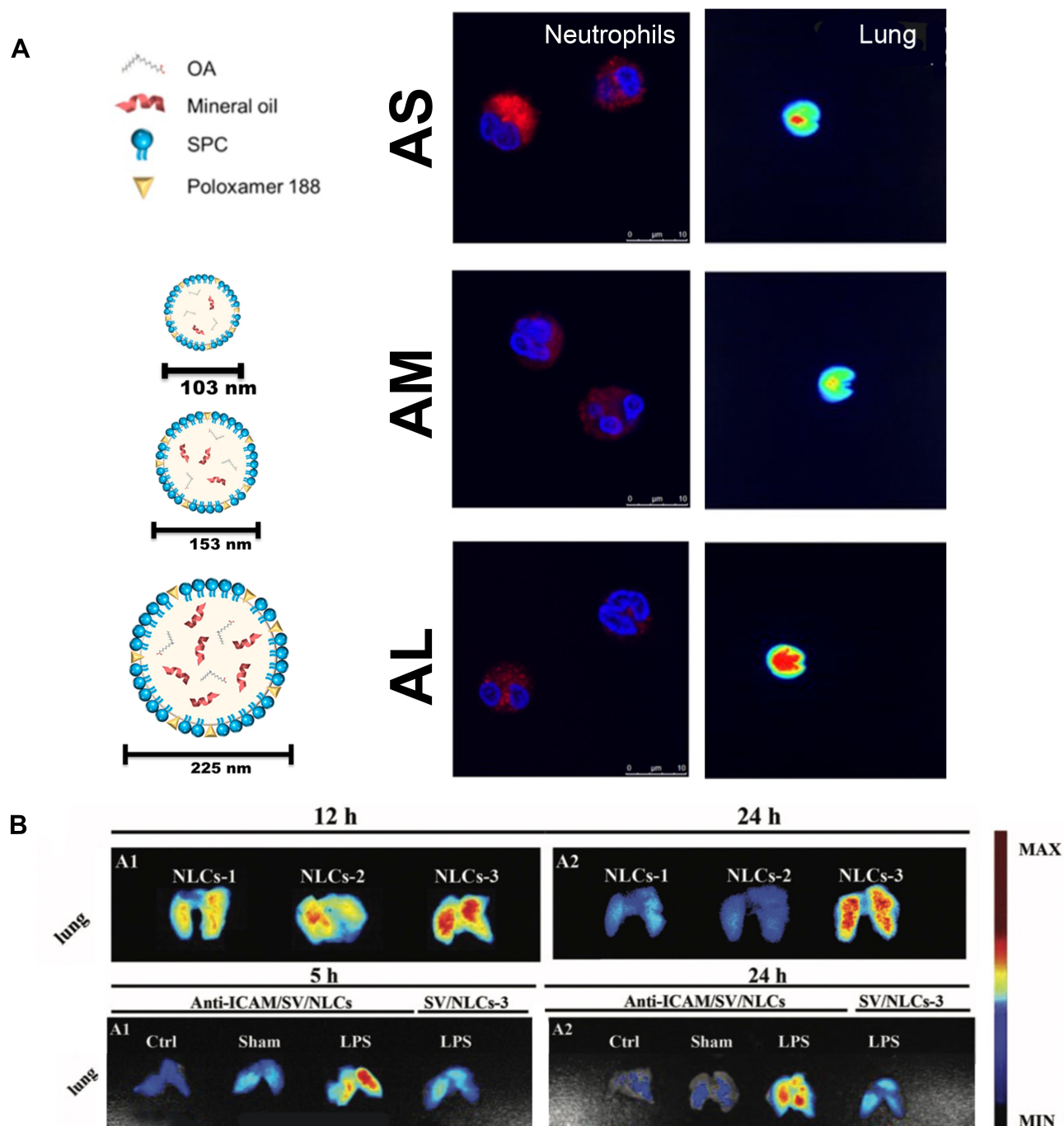
Monostearin, MCT, NH-PEG 2000-SA, PEG 2000-SA (ICAM-1 antibody)	Dexamethasone	227.9–249.9	1.2 mg/kg (i.v. NG)	Male BALB/c mice LPS (i.t.)	TNF- $\alpha$ , IL-6, total cell counts, neutrophil counts; H&E $\uparrow$	[20]
Monostearin, PEG 2000-SA, MCT (ICAM-1 antibody)	Simvastatin	354.7 $\pm$ 18.2	2 mg/kg (i.v. 6 h pre)	Male BALB/c mice LPS (i.t.)	TNF- $\alpha$ , IL-6, total cell counts, neutrophil counts; H&E $\uparrow$	[21]
NLCs (ICAM-1 antibody)	Simvastatin, protamine, angiopoietin-1 gene	258.0 $\pm$ 12.5–351.7 $\pm$ 13.1	NG (i.v. 6 h)	Male BALB/c mice LPS	TNF- $\alpha$ , IL-6, total cell counts, neutrophil counts; H&E $\uparrow$	[60]

cytokine level in bronchoalveolar lavage fluid (BALF).<sup>22,24</sup> NLCs can be incorporated into lung endothelial cells via caveolar vesicles, and thus possess endothelial-protective effects.<sup>98</sup> Conjugating ICAM-1 antibody to NLCs endowed its active targeting ability to lung endothelium, and the size and zeta potential of the liposomes were correlated with the therapeutic effects.<sup>20,21,60</sup> The larger NLCs (337.8 nm) loading simvastatin exhibited ideal lung-targeting characteristics<sup>21</sup> (Figure 2B). Other lung-targeted ternary NLCs loaded with simvastatin, protamine (Pro), and the angiopoietin-1 (Ang-1) gene with a larger size (357.1 nm) also showed better improvements.<sup>60</sup> The anionic NLCs exhibited higher cellular uptake and stronger pulmonary distribution, showing significant anti-inflammatory efficacy.<sup>20</sup> PECAM-1 binds to the endothelium and is internalized via the noncanonical cell adhesion molecule (CAM)-mediated endocytic pathway<sup>99</sup> and can be adopted to endow lung-targeting ability. PEGylated liposomes conjugated with anti-PECAM-1 loaded with EUK-134 accumulated in the lungs after i.v. administration, inhibited cytokine-induced inflammatory activation, and provided >60% protection against lung edema in the endotoxin-stimulated mouse model.<sup>35</sup> Recently, a soft nanobot composed of double micellar microemulsions has been developed, which possess the capability of active nanodrug delivery to strictures of air–liquid interface, and this could become a promising technology for therapeutic carriers and targeted delivery to ALI/ARDS.<sup>100</sup>

## Polymeric Nanomedicine

Polymeric nanomedicines can be engineered from natural or synthetic polymers,<sup>101</sup> most of which are biodegradable and biocompatible. Synthetic polymers are usually coated with polyethylene glycol (PEG) to reduce their toxicity and increase their solubility. Their high drug-loading capacity makes them favorable carriers for in vivo therapies;<sup>102</sup> they deliver drugs<sup>19,23,28–30,34,70–72</sup> and genes<sup>31,33,53,62–65,68–73</sup> to the targeted site or act as therapeutic agents by themselves<sup>52,67</sup> for ALI treatment (Table 3).

Poly-lactic-co-glycolic acid (PLGA) is the most commonly used polymer with good biodegradability and biocompatibility.<sup>103</sup> The PLGA nanoparticle-containing ruthenium red was used in the ventilator-induced lung injury (VILI) model via inhalation. This nanomedicine reacted through the alveolar macrophages and the capillary endothelial cells, blocked calcium signaling, and inhibited vascular permeability in ex vivo ventilation–perfusion



**Figure 2** Lipid-based nanomedicine. **(A)** Various diameters of OA-loaded nanocarriers showed different characteristics. Smaller sizes (AS) exhibited greater neutrophil uptake, while larger sizes (AL) exhibited greater lung targeting ability. Note: Reproduced with the permission from Yu HP, Liu FC, Umoro A et al. Oleic acid-based nanosystems for mitigating acute respiratory distress syndrome in mice through neutrophil suppression: how the particulate size affects therapeutic efficiency. *JNanobiotechnology*. 2020;18(1):25. Copyright (2020) Journal of Nanobiotechnology under Creative Commons Attribution 4.0 International License.<sup>48</sup> **(B)** The larger NLCs-3 (337.8 nm) exhibited greater lung retention ability. Conjugating ICAM-I antibody to NLC endowed it active targeting ability to lung endothelium, and showed better lung distribution. Note: Reproduced with the permission from Li SJ, Wang XJ, Hu JB et al. Targeting delivery of simvastatin using ICAM-I antibody-conjugated nanostructured lipid carriers for acute lung injury therapy. *Drug Deliv*. 2017;24(1):402–413. Copyright (2017) Drug Delivery under Creative Commons Attribution 4.0 International License.<sup>21</sup>

experiments.<sup>30</sup> Murine sialic acid-binding immunoglobulin-like lectin-E (Siglec-E) is an immunomodulatory receptor that negatively regulates acute inflammatory responses. PLGA nanoparticles decorated with di(a2→8)

N-acetylneuraminic acid (a2,8 NANA-NP), a natural Siglec ligand, could induce enhanced oligomerization of Siglec-E receptors on macrophages, blocking the production of inflammatory cytokines in a Siglec-E-dependent

Table 3 Polymeric Nanomedicine

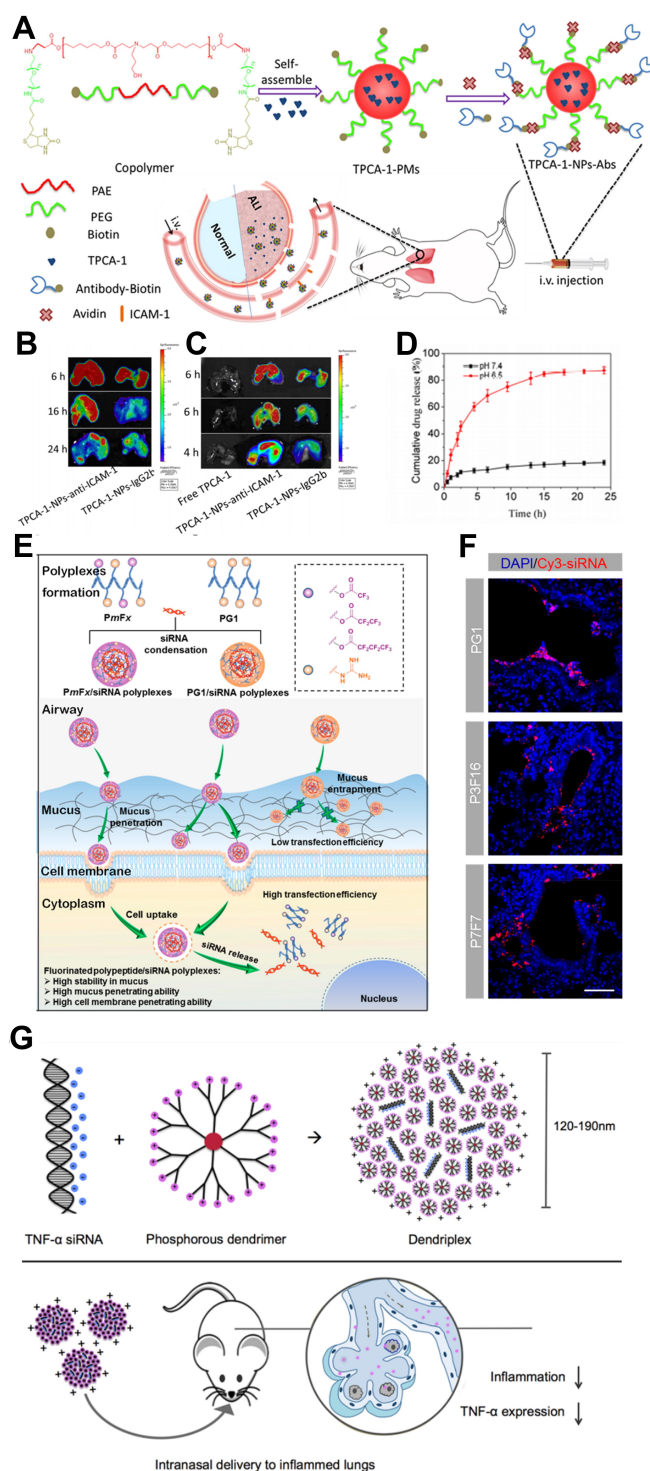
Material (Moiety)	Drug/Gene	Size (nm)	Dose (Route)	Animal Model (Route)	In vivo Therapeutic Outcomes	Ref.
PLGA	Ruthenium red	300	1 mM (inh.)	Male C57BL/6 mice (VILI)	Wet lung weight/body weight ratio↓; wet/dry lung weight ratio↓; H&E↑; lung edema↓	[30]
PLGA di(a2→8) N-acetylneuraminic acid		150	2 mg (i.p. 2 h post) for LPS; 20 µg (i.t. 6 h/8 h post) for CLP	C57BL/6 mice LPS (i.t.) and CLP	Total, macrophage and neutrophil counts↓; IL-10↑; clinical score↓; survival rate↑	[67]
PLGA (sialic acid)	Cur-TPP	852 ± 30.70	2.4 mg/kg (i.v. 4 h post)	Male ICR mice LPS (i.t.)	Lung wet/dry ratio↓; total protein↓; TNF-α, IL-6, total cell and neutrophil counts↓; MDA↓; SOD↑; ROS↓; H&E↑	[29]
Poly (ε-caprolactone), capric/caprylic triglyceride, sorbitan monostearate	RSV	241 ± 7	2.5, 5, or 10 mg/kg (p.o. 1, 4, 6 or 12 h pre)	Male A/J mice LPS (i.n.)	Total leukocyte, neutrophil counts↓; MPO↓; H&E↑, score↓; IL-6, KC, MIP-1α, MIP-2, MCP-1, RANTES↓; elastase↓; MDA, SOD↓	[19]
Poly (ε-caprolactone), capric/caprylic triglyceride, sorbitan monostearate	α-bisabolol	160 ± 10	30, 50, or 100 mg/kg (p.o. 4 h pre)	Male A/J mice LPS (i.n.)	Elastase↓; neutrophil counts↓; MPO↓; KC, MIP-2↓; H&E↑, score↓	[23]
Poly(β-amino esters) (ICAM-1 antibody)	TPCA-1	100	2 mg/kg (i.v. 4 h post)	Adult CD-1 mice LPS (i.t.)	Neutrophil counts, IL-6, TNF-α, protein↓; H&E↑	[28]
PLGA	EpoR cDNA	196 ± 36	2 mg (inh.)	S-D rats (Hyperoxia)	H&E↑; Wet/dry and sodium (Na)/dry weight ratios↓; Caspase-8 activity and oxidative DNA damage↓; Protein and lipid oxidation↓	[65]
PEI2k-Dexamethasone	plasmid DNA	~100	10 µg (i.t. 2 h post)	Male BALB/c mice LPS (i.t.)	TNF-α, IL-6↓; total protein, IgM↓; H&E↑	[33]
PEI/DNA	β2-adrenergic receptor gene	~60	NG (i.v. 24 h post)	Blow:CD1 (ICR) mice LPS (i.t.)	Alveolar fluid clearance, lung W/D ratio↓; H&E↑, score↓; cell number, protein, TNF-α, IL-6↓; survival rate↑	[31]
Proteolipid dex-HEMA-co-TMAEMA nanogels (Surfactant protein B)	TNF-α siRNA	~200	100 mg nanogel loaded with 1 pmol siTNF-α (i.t. 24 h pre)	Female BALB/c mice LPS (i.t.)	TNF-α expression↓	[63]
HMGB1A/heparin complex	HMGB1A	113	NG (i.t. 2 h post)	Male BALB/c mice LPS (i.t.)	TNF-α, IL-6, IL-1β↓; IL-4↑; IgM↓; H&E↑	[64]
Perfluorocarbon emulsion polyplexes containing a fluorinated polymeric CXCR4 antagonist (F-PAMD@PFC)	PAI-1 siRNA	~140	0.55 mg/kg siRNA (i.t. 45 min post)	Male Balb/C mice LPS (i.t.)	Lung W/D ratio, HYP, MPO, total cell counts↓; H&E↑	[53]

(Continued)



Table 3 (Continued).

Material (Moiety)	Drug/Gene	Size (nm)	Dose (Route)	Animal Model (Route)	In vivo Therapeutic Outcomes	Ref.
$\gamma$ -(4-Propargyloxybenzyl)-L-glutamic acid (Guanidinated & fluorinated)	TNF- $\alpha$ siRNA	~150	200 $\mu$ g/kg siRNA (i.t. 2 h post)	Male BALB/c mice LPS (i.t.)	TNF- $\alpha$ , IL-6, MPO, lung W/D ratio $\downarrow$ ; blood gas $\uparrow$ ; H&E $\uparrow$	[62]
Poly(phosphorhydrazone) dendrimers (Mannose unit)			1 mg/kg (p.o. 15 d pre)	Female BALB/c and C57BL/6 mice LPS (inh.)	Neutrophil counts, TNF- $\alpha$ $\downarrow$ ; IL-10, CXCL-1, CXCL-2-	[52]
Polyamidoamine (Dexamethasone)	APN gene	57.05 $\pm$ 1.02	10 $\mu$ g pDNA (i.t. 0 h)	Male BALB/c mice LPS (i.t.)	TNF- $\alpha$ , IL-1 $\beta$ $\downarrow$ ; H&E $\uparrow$	[72]
Polyamidoamine (Dexamethasone)	APN gene and RAP	81.9	5 $\mu$ g pDNA (i.t. 2 h post)	Male BALB/c mice LPS (i.t.)	TNF- $\alpha$ , IL-6, IL-1 $\beta$ $\downarrow$ ; H&E $\uparrow$	[69]
Polyamidoamine (Cholesterol)	RSV & HO-1 gene	120.4 $\pm$ 20.6	5 $\mu$ g pDNA (i.t. 2 h post)	Male BALB/c mice LPS (i.t.)	NF- $\kappa$ B $\downarrow$ ; IL-1 $\beta$ , TNF- $\alpha$ , IL-6 $\downarrow$	[71]
Polyamidoamine (cholesterol)	Cur & HO-1 gene	~120	5 $\mu$ g pDNA (i.t. 2 h post)	Male BALB/c mice LPS (i.t.)	IL-1 $\beta$ , TNF- $\alpha$ , IL-6 $\downarrow$ ; H&E $\uparrow$	[70]
Phosphorus dendrimers (Pyrrolidinium)	Anti-TNF- $\alpha$ siRNA	120–190	2.0 mg/kg siRNA (i.n. 24 h pre)	Female CD-1 mice LPS (i.n.)	TNF- $\alpha$ , IFN- $\gamma$ $\downarrow$ ; IL-6, IL-10 $\uparrow$	[73]
Self-assembling peptides (EAK16-II) and amino acids	PP2	~700	0.2 mg/kg (i.t. 1 h pre)	Male BALB/c mice LPS (i.t.)	Survival rate $\uparrow$ ; total cells count, neutrophils/macrophages ratio, total protein, TNF- $\alpha$ $\downarrow$ ; IL-10 $\uparrow$	[34]
R3V6 (3 arginines and 6 valines) peptide	siIPlyase and HMGB1A	~50	300 pmol siRNA (i.t. 2 h post)	Male BALB/c mice LPS (i.t.)	IL-6, TNF- $\alpha$ $\downarrow$ ; H&E $\uparrow$	[68]



**Figure 3** Polymeric nanomedicine. **(A)** Anti-ICAM-1 antibody decorated poly(β-amino esters) targeted to mouse lungs. **(B and C)** The fluorescence of FITC-labeled nanoparticles and Cy5-labeled TPCA-1 was measured using in vivo imaging systems (IVIS). **(D)** The cumulative release of TPCA-1 at different pH. Note: Reprinted with permission from Zhang CY, Lin W, Gao J et al. pH-Responsive Nanoparticles Targeted to Lungs for Improved Therapy of Acute Lung Inflammation/Injury. *ACS Appl Mater Interfaces*. 2019;11(18):16380–16390. Copyright (2019) American Chemical Society.<sup>28</sup> **(E)** Fluorinated and guanidinated bifunctional helical polypeptides enhanced the mucus and cell membrane penetration. **(F)** Distribution of polyplexes in lung epithelial tissues. Note: Reprinted with the permission from Ge C, Yang J, Duan S, Liu Y, Meng F, Yin L. Fluorinated alpha-Helical Polypeptides Synchronize Mucus Permeation and Cell Penetration toward Highly Efficient Pulmonary siRNA Delivery against Acute Lung Injury. *Nano Lett*. 2020;20(3):1738–1746. Copyright (2020) American Chemical Society.<sup>62</sup> **(G)** Cationic phosphorus dendrimer nanocomplexes delivering anti-TNF-α siRNA to inhibited TNF-α with high efficiency. Note: Reprinted with the permission from Bohr A, Tsapis N, Andreana I et al. Anti-Inflammatory Effect of Anti-TNF-alpha SiRNA Cationic Phosphorus Dendrimer Nanocomplexes Administered Intranasally in a Murine Acute Lung Injury Model. *Biomacromolecules*. 2017;18(8):2379–2388. Copyright (2017) American Chemical Society.<sup>73</sup>

manner.<sup>67</sup> Oxidative stress plays an important role in ALI<sup>104</sup> and mitochondria are the main source of ROS production. Sialic acid (SA)-functionalized PEG-PLGA microspheres loaded with triphenylphosphonium (TPP) cation-modified curcumin (Cur) were utilized as mitochondria-targeting ALI therapy. The microsphere's size was larger than 800nm, thus enabling good lung distribution, and the SA modification exhibited an ideal lung-targeted characteristic.<sup>29</sup> Using poly( $\epsilon$ -caprolactone) to construct lipid-core nano-capsules (LNCs) and encapsulated  $\alpha$ -bisabolol ( $\alpha$ -bis) or resveratrol (RSV) into LNCs can minimize drug oxidation, improving internal absorption and showing satisfactory therapeutic effects.<sup>19,23</sup> The inflammatory microenvironment of ALI has the feature of a low pH; poly( $\beta$ -amino esters) have a sharp acid-sensitive segment; bio-conjugating anti-ICAM-1 antibodies enable satisfying lung targeting and extended circulation. The pH-responsive nanoparticles can load anti-inflammatory agent TPCA-1 at a high content (24%, w/w). The accumulative release of TPCA-1 increases from less than 20% 24 h at pH 7.4 to approximately 90% 15 h at pH 6.5<sup>28</sup> (Figure 3A–D).

Polymeric nanoparticles are also attractive gene carriers for ALI therapy.<sup>91</sup> Nebulized PLGA bearing erythropoietin receptor (EpoR) complementary DNA (cDNA) nanoparticles upregulated pulmonary EpoR expression and downstream signal transduction to counteract the inflammation in hyperoxia-induced lung injury in rats.<sup>65</sup> Modifying low molecular weight polyethyleneimine (PEI) with dexamethasone improves its translocation into the nucleus and its gene transfection efficiency.<sup>33</sup> PEI carries  $\beta$ 2-adrenergic receptor ( $\beta$ 2AR) gene, which regulates alveolar ion and fluid transport,<sup>105</sup> dramatically improving alveolar clearance and decreasing lung fluid content without major adverse effects.<sup>31</sup> Merckx et al used Curosurf<sup>®</sup>, a clinically used pulmonary surfactant (PS), as the shell and siRNA-loaded nanosized dextran nanogels as the core to form hybrid nanoparticles for inhalation therapy. The PS shell improved the particle stability, and the intracellular siRNA delivery was enhanced by inserting SP-B into the phospholipid shell.<sup>63</sup> High mobility group box-1 box A (HMGB1A) may be captured in the mucus layer due to its positive charges when administered intratracheally; heparin has negative charges and an anti-inflammatory effect. The HMGB1A/heparin complex was obtained using electrostatic interactions, and reduced pro-inflammatory cytokines synergically.<sup>64</sup> Fluoropolymers in the form of perfluorocarbon (PFC) nano-emulsions could

improve cellular siRNA delivery.<sup>106</sup> Wang et al reported a PFC emulsion polyplex as a gene carrier, containing fluorinated polymeric CX-C chemokine receptor type 4 (CXCR4) antagonist and delivered plasminogen activator inhibitor-1 (PAI-1) siRNA to inhibit CXCR4 and PAI-1 for combined therapy.<sup>53</sup> Another way to enhance mucus-penetrating ability is to develop bifunctional guanidine- and fluorine-decorated helical polypeptides. The fluorinated polypeptides dramatically enhanced mucus permeation capability by approximately 240-fold, while the guanidine domain and the  $\alpha$ -helix structure facilitated trans-membrane siRNA delivery. Using the top-performing polypeptide, P7F7, to administer TNF- $\alpha$  siRNA intratracheally produced highly efficient (~96%) gene knockdown<sup>62</sup> (Figure 3E and F).

Dendrimers are regularly branched macromolecules that are usually developed as forming dendrimer-drug conjugates or as gene carriers.<sup>101</sup> Inspired by *Mycobacterium tuberculosis*, Blattes et al designed manno-dendrimers that mimicked the bioactive supramolecular structure of mannose-capped lipoarabinomannan. The manno-dendrimers could target the C-type lectin receptor DC-specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN), thus inhibiting neutrophil recruitment significantly.<sup>52</sup> Adiponectin (APN) is an anti-inflammatory and cytoprotective adipokine.<sup>107</sup> Delivery of APN using dexamethasone conjugated poly-amidoamine (PAM-D) upregulated APN expression.<sup>72</sup> In a subsequent study, the RAGE-antagonist peptide (RAP) increased the gene delivery efficiency of PAM-D, and the RAP inhibited the RAGE-signal to show anti-inflammatory effects.<sup>69</sup> Cholesterol-conjugated polyamidoamine micelles could deliver pHO-1 (heme-oxygenase -1 plasmid) along with RSV or Cur, in which pHO-1 induced HO-1 expression to decrease pro-inflammatory cytokines, and RSV or Cur inhibited the inflammatory reactions synergically.<sup>70,71</sup> The phosphorus dendrimers have been shown to have more efficiency in the cellular delivery of siRNA<sup>108</sup> and exhibited anti-inflammatory properties simultaneously.<sup>109</sup> Compared with morpholinium-containing dendriplexes, pyrrolidinium-decorating dendriplexes demonstrated a stronger siRNA complexation, and the higher cellular uptake enabled an enhanced silencing efficiency of TNF- $\alpha$ <sup>73</sup> (Figure 3G).

The biocompatibility, biodegradability, and the lack of immune response properties of self-assembling peptides make them ideal drug carriers and regenerative medicines.<sup>110</sup> Self-assembling R3V6 peptides with

**Table 4** Inorganic Nanomedicine

Material (Moiety)	Size (nm)	Dose (Route)	Animal Model (Route)	In vivo Therapeutic Outcomes	Ref.
GNPs (CLPFFD)	17.5 ± 0.6	50 pmol (i.t. 2 h pre)	Male C57BL/6 mice LPS (i.t.)	H&E↑, score↓; total cell, neutrophil, macrophage, lymphocyte↓; regulatory T cells	[41]
GNPs (CLPFFD) and (CSE)	23.9 ± 0.3	500 nM (i.t. 1 h pre)	Male C57BL/6 mice LPS (i.n.)	Total cell, neutrophil, protein↓; TNF-α, KC, IL-6, CCL-2↓; H&E↑, score↓	[40]
GNPs (CLPFFD)	26.9 ± 0.8	500 nM (i.t. 1 h pre)	Male C57BL/6 mice LPS (i.n.)	Total cell, neutrophil↓; KC, CCL-2↓; lung W/D ratio, lung protein↓; H&E↑, score↓	[39]
GNPs (CLPFFD)	18.8 ± 0.1	500 nM (i.t. 2 h pre)	Male C57BL/6 mice LPS (i.t.)	IL-12, IFN-γ↓; IL-10↑; total cell, neutrophil, macrophage, lymphocyte↓; M1↑, M2↓	[37]
CeO <sub>2</sub> @SiO <sub>2</sub>	220 ± 5	0.6 mg/kg (p.o. 0, 1, 3, 24 h post)	Male Wistar rats LPS (i.p.)	H&E↑; ROS↓; TNF-α, IL-6, CXCL-2↓; V'O <sub>2</sub> , V <sub>T</sub> , V'E↑	[43]
Se@SiO <sub>2</sub> PVP coated	~55	1 mg/kg (i.p. every 24 h)	Male S-D rats Paraquat (i.g.)	MDA↓, GSH↑, SOD↑; lung W/D ratio↓; H&E↑; IL-1β, TNF-α↓; NF-κB↓	[42]
Se@SiO <sub>2</sub> PVP coated	~55	100 μg/kg (i.n. 1 h pre)	Male C57BL/6 mice LPS (i.n.)	Total cell↓, neutrophil↓, macrophage↑; IL-1β, CCL-2, IL-6↓; total protein, lung W/D ratio↓; H&E↑, score↓	[36]

a positive charge and membrane-penetrating properties were suitable for gene delivery. The siS1PLyase/HMGB1A/R3V6 delivering a siRNA ternary complex, in which siS1PLyase down-regulates the S1PLyase (sphingosine-1-phosphate lyase) and S1P on alveolar macrophages to block the NF-κB signaling pathway, demonstrated synergistic anti-inflammatory effects.<sup>68</sup> Self-assembling peptide EAK16-II carrying Src tyrosine kinase inhibitor (PP2) demonstrated a lower toxicity, and a satisfactory anti-inflammatory effect against the lung ischemia–reperfusion (IR) model in rats.<sup>34</sup> Recently, a self-assemble DNA origami nanorobotic delivery platform is available with nanoscale precision sensing, movement and manipulation properties, which may provide a new strategy for nanomedicine-based gene therapy.<sup>111,112</sup>

## Inorganic Nanomedicine

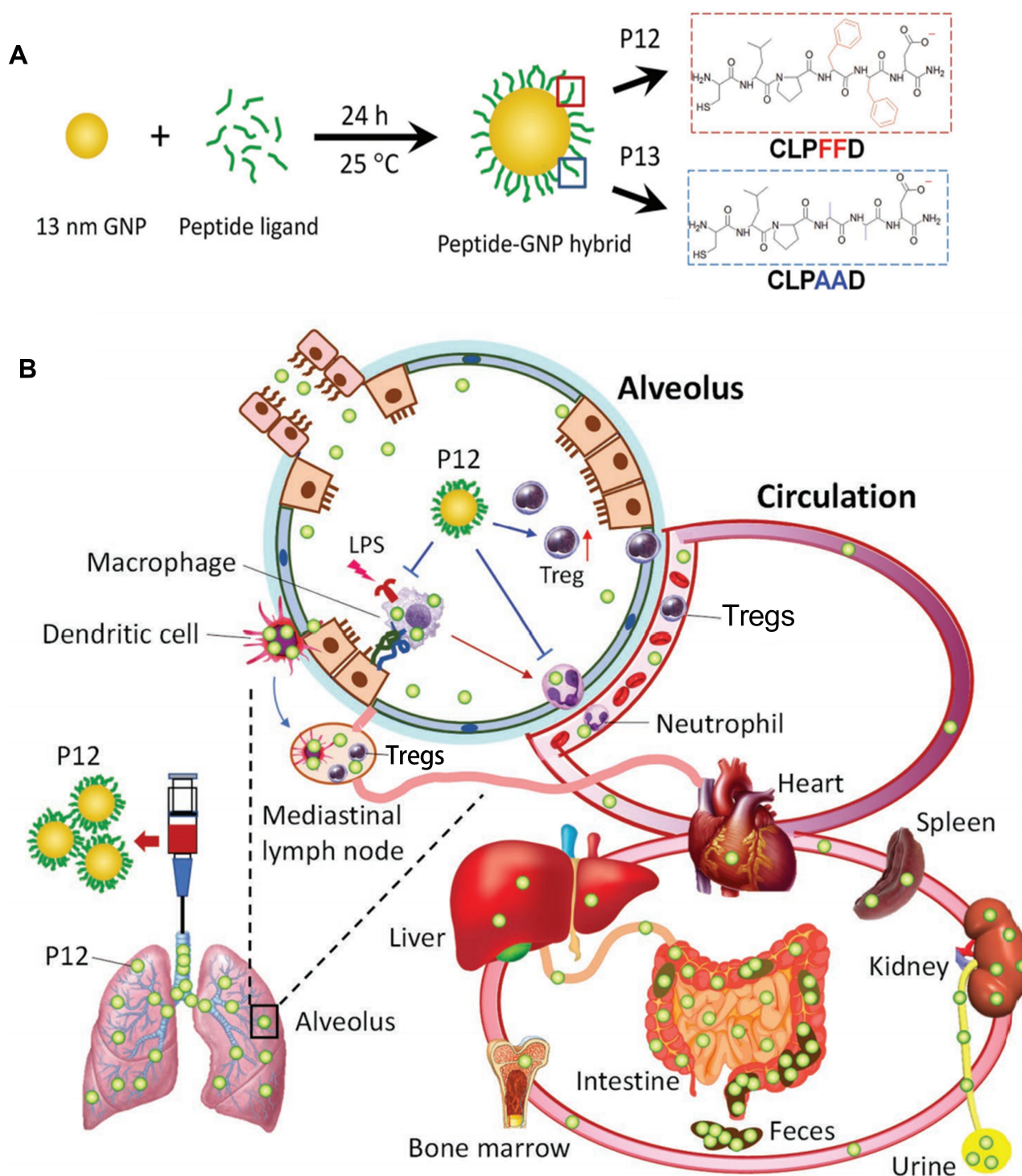
Inorganic nanomedicines are generally composed of inert and biocompatible metals, which endow them with stable characteristics and smaller diameters. Most inorganic nanomedicines are highly efficient and exhibit multiple effects during biological applications. Gold, cerium dioxide (CeO<sub>2</sub>) and selenium (Se) have been used to treat ALI. The biggest challenge that limits their application is their elimination from the body, as repeated administration can result in toxicity by accumulation effects.<sup>101</sup> The strategies

to tackle this problem include biogenic route of synthesis, conjugating peptides on metallic nanoparticles or immobilizing inorganic nanoparticles on silica nanoparticles. The main mechanisms of inorganic nanomedicine to treat ALI include inhibiting the inflammatory signal<sup>37–41,44</sup> and scavenging oxidants<sup>36,42,43</sup> (Table 4).

Gold nanoparticles (GNPs) could reduce the acute inflammatory response and excessive ROS production, protecting lung tissue from LPS-induced morphological changes.<sup>38</sup> However, they tend to be trapped in the liver and spleen and are nonbiodegradable; so, the biosafety concerns still exist. The biogenic route of GNPs synthesis offers an efficient way to tackle the biosafety problems, which can fabricate spherical,<sup>113</sup> anisotropic, and high aspect ratio gold nanomaterials.<sup>114</sup> The molecular dynamic simulation, supported with experimental photothermal therapy, has shown the excellent application of these GNPs in nanomedicine for clearing biofilm and promoting the growth of fibroblast.<sup>115,116</sup> These biomineralized nanomaterials proved excellent imaging agents<sup>117</sup> and are drug carriers with enhanced bioavailability in vitro<sup>118</sup> and in vivo.<sup>119</sup>

Modifying the GNPs with peptides is another way to enhance efficiency and safety. Peptide-modified GNPs could modulate the process of endosomal acidification and inhibit multiple Toll-like receptor (TLR)





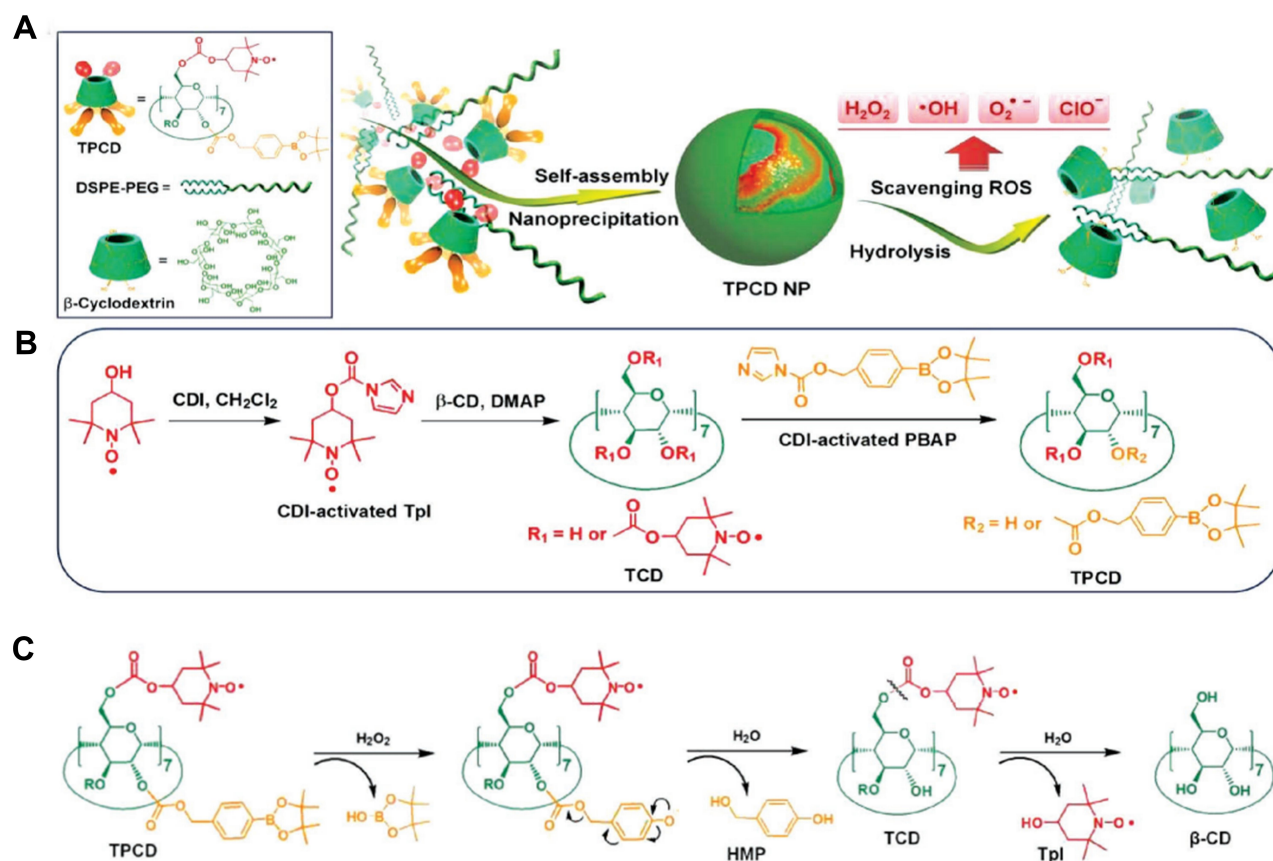
**Figure 4** Inorganic nanomedicine. (A) Peptide-gold nanoparticle hybrids. (B) The nanoparticles effectively reduced lung injury and were effectively excreted at 26 h post-administration.

**Notes:** Reproduced with the permission from Xiong Y, Gao W, Xia F et al. Peptide-Gold Nanoparticle Hybrids as Promising Anti-Inflammatory Nanotherapeutics for Acute Lung Injury: In Vivo Efficacy, Biodistribution, and Clearance. *Adv Healthc Mater.* 2018;7(19):e1800510. © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.<sup>41</sup>

signaling pathways in macrophages.<sup>120</sup> A unique class of hybrid GNPs (P12) was designed, which was made of a 13 nm GNP core and a hexapeptide (CLPFFD)

surface coating. P12 showed therapeutic effects by targeting the macrophages and increasing the regulatory T cells (Tregs). When administrated





**Figure 5** A superoxidase dismutase/catalase mimetic material based on functionalized β-cyclodextrin (β-CD) eliminated a broad spectrum of ROS. **(A)** Schematic illustration of material and nanoparticle. **(B)** The synthetic route of β-CD conjugated with Tempol (Tpi) and PBAP units (TPCD). **(C)** The mechanism for the  $H_2O_2$ -mediated hydrolysis of TPCD.

**Notes:** Reproduced with the permission from Li L, Guo J, Wang Y et al. A Broad-Spectrum ROS-Eliminating Material for Prevention of Inflammation and Drug-Induced Organ Toxicity. *Adv Sci (Weinh)*. 2018;5(10):1800781. © 2018 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim under Creative Commons Attribution 4.0 International License.<sup>47</sup>

intratracheally, only approximately  $8.49\% \pm 0.7\%$  of the injected dose remained in all the tested organs/tissues. At both 6 and 26 h post-intratracheal injection, a significant amount of P12 was detected in the feces and the amount in the intestine was much higher than that in the liver, suggesting that P12 was cleared through a hepatobiliary route<sup>41</sup> (Figure 4). Furthermore, the 20-nm hybrid P12 (G20) was more potent than the 13-nm hybrid P12 (G13) and 5-nm hybrid P12 (G5) in inhibiting TLR4 activation and its downstream cytokine production. The P12 (G20) exhibited a higher cellular uptake and a stronger endosomal pH buffering capacity, endowing it with enhanced inhibitory effects.<sup>39</sup> Cigarette smoke extract (CSE, 1%) was able to be adsorbed onto the GNP hybrids and largely increased their cellular uptake. CSE-P12 inhibited TLR4 activation through endosomal

acidification and contributed to autophagy induction and subsequent antioxidant protein expression.<sup>40</sup> P12 could also increase the alveolar anti-inflammatory M2 phenotype macrophages by polarization in the BALF and lung tissues, and decrease M1 macrophages in the alveolar and interstitial spaces.<sup>37</sup>

$CeO_2$  is a promising oxidant-scavenging nanoparticle, but its slow elimination induces concern for its toxic effect. By immobilizing it on the surface of silica, the toxicity of the cerium nanoparticles was reduced. The  $CeO_2$  nanoparticles showed anti-inflammatory and antioxidant effects, as well as stimulating oxygen consumption in healthy rats and those with pneumonia.<sup>43</sup> The same strategy was adopted to fabricate porous  $Se@SiO_2$  PVP coated nano-spheres. In a paraquat-induced rat model, the nano-spheres could attenuate oxidative stress, eliminate ROS, and reduce inflammatory cytokines.<sup>42</sup> The nano-

**Table 5** Other Nanomedicine

Material (Moiety)	Drug/ Gene	Size (nm)	Dose (Route)	Animal Model (Route)	In vivo Therapeutic Outcomes	Ref.
Polydopamine		~80	10 mg/kg (i.n. 30min post)	Female BALB/c mice LPS (i.n.)	IL-6, TNF- $\alpha$ , CXCL-2, MPO, protein, leukocyte, neutrophil $\downarrow$ ; H&E $\uparrow$	[46]
$\beta$ -cyclodextrin (Tempol & PBAP)		109 $\pm$ 2	0.1 or 1.0 mg/kg (i.v. 1 h post)	Male BALB/c mice LPS (i.t.)	Lung W/D ratio, TNF- $\alpha$ , IL-1 $\beta$ , H <sub>2</sub> O <sub>2</sub> , MPO, neutrophil $\downarrow$ ; H&E $\uparrow$	[47]
$\beta$ -cyclodextrin (Luminol)		238 $\pm$ 26	100 mg/kg (i.v. 1 h post)	Male BALB/c mice LPS (i.t.)	TNF- $\alpha$ , IL-1 $\beta$ , lung W/D ratio, lung permeability $\downarrow$ ; H&E $\uparrow$	[45]
Bovine serum albumin	Piceatannol	100 $\pm$ 10	4.3 mg/kg (i.v. 2 h post)	Male CD1 mice LPS (i.p.)	MPO, neutrophil, leukocyte $\downarrow$	[58]
Bovine serum albumin	TPCA-I	~140	8 mg/kg (i.v. 4 h post)	Adult CD1 mic LPS (i.t.)	Leukocyte & neutrophil, IL-6, TNF- $\alpha$ , protein $\downarrow$	[57]
Extracellular nanovesicles (ICAM-1 antibody)	TPCA-I	200	0.33 or 1 mg/kg (i.v. 3 h post)	Adult CD1 mice LPS (i.t.)	Neutrophil, protein, TNF- $\alpha$ , IL-6 $\downarrow$	[56]
Extracellular nanovesicles	Piceatannol	~260	2 mg/kg (i.v. 2 h post)	Adult CD1 mice LPS (i.t.)	Neutrophil, leukocyte, TNF- $\alpha$ , IL-6, protein $\downarrow$	[54]
PEVs	TPCA-I	100–150	1 mg/kg (i.v. 4 h post)	Female BALB/c mice LPS (i.t.)	TNF- $\alpha$ , IL-6, IL-1 $\beta$ , macrophages, T cells, ROS $\downarrow$ ; MPO, MDA, wet/dry ration $\downarrow$ ; H&E	[79]

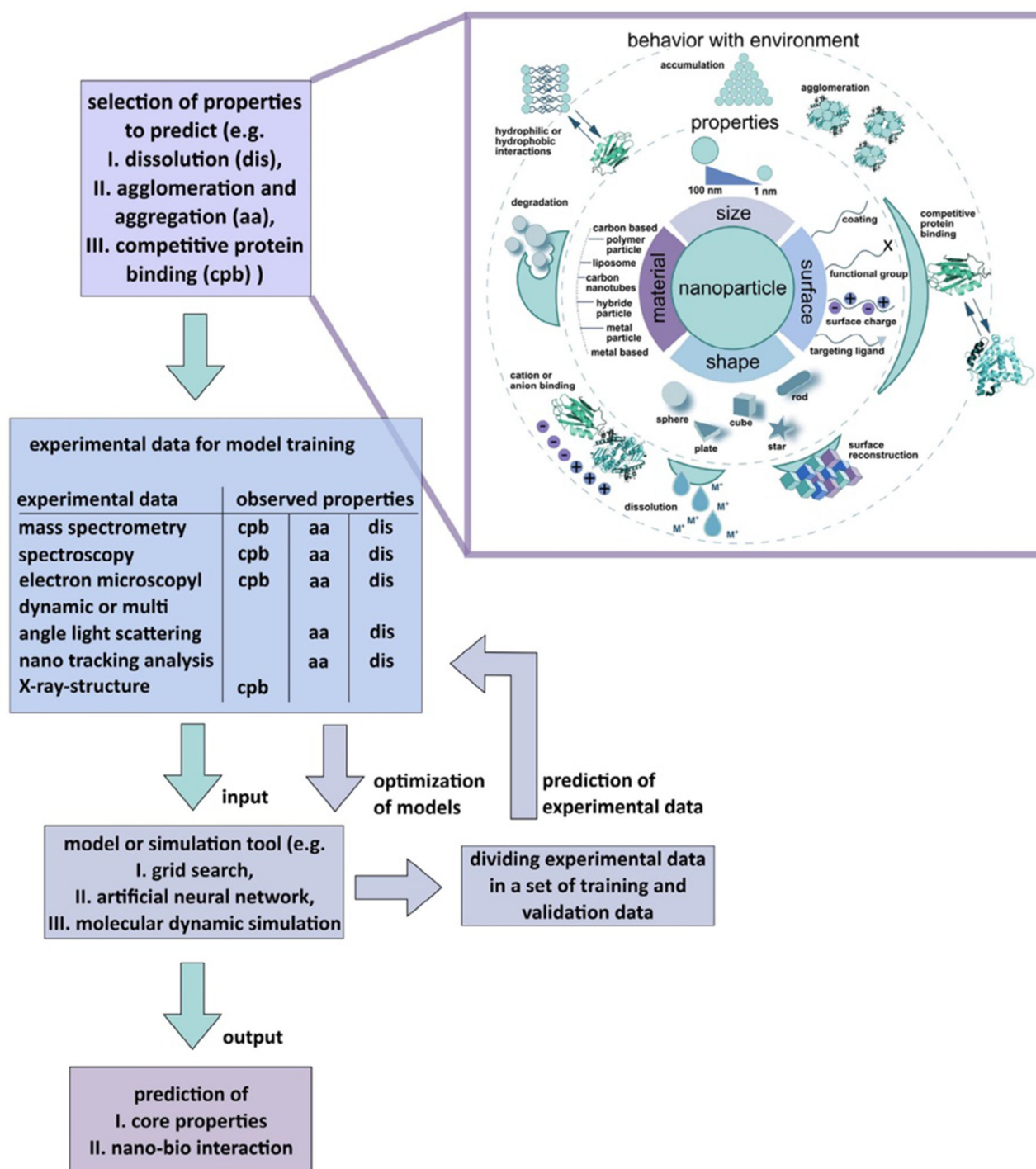
spheres could also modulate mitochondrial function, activity, and dynamics, significantly increasing the epithelial cells' resistance to oxidative injury.<sup>36</sup>

## Other Nanomedicine

Polydopamine is a natural biopolymer that can self-assemble or be a film coating. Enriched phenol groups enable it to act as a nano-enzyme to scavenge H<sub>2</sub>O<sub>2</sub> directly or to catalyze the decomposition of H<sub>2</sub>O<sub>2</sub>. Polydopamine alleviated lung tissue damage by diminishing ROS generation.<sup>46</sup>  $\beta$ -cyclodextrin ( $\beta$ -CD) is a cyclic oligosaccharide that mimics enzyme conformation with a hydrophilic rim and a hydrophobic cavity. Two ROS eliminating agents, Tempol and PBAP, were simultaneously conjugated to  $\beta$ -CD to construct a superoxidase dismutase/catalase mimetic material (TPCD). TPCD nanoparticles eliminated a broad spectrum of ROS, protected macrophages from apoptosis, attenuated inflammatory responses and oxidative stress<sup>47</sup> (Figure 5). In another study, luminol-conjugating  $\beta$ -CD (LCD) nanoparticles could act on both neutrophils and macrophages, effectively inhibiting the inflammatory response, oxidative stress and

cell migration, demonstrating desirable efficacy in treating ALI with biosafety<sup>45</sup> (Table 5).

Inflamed vasculature targeting ability was achieved by conjugating anti-ICAM-1 antibody or peptides to nanoparticles.<sup>121</sup> However, this strategy might impair their specificity and affinity, especially when administrated in vivo.<sup>122</sup> During inflammation, neutrophils abundantly express integrin  $\beta$ 2; this integrin interacts with the ICAM-1 molecules on the endothelial cells.<sup>123</sup> This interaction could be blocked to inhibit the accumulation of neutrophils, or use this interaction for targeting drug delivery. Piceatannol blocks the “outside-in” integrin signaling in neutrophils. Albumin nanoparticles loading piceatannol were taken up by neutrophils, detaching neutrophils' adherence and eliciting their release into the circulation.<sup>58</sup> Inspired by the study above, it is promising to design nanoparticles that hitchhike activated neutrophils in situ; then, neutrophils could deliver nanoparticles to the inflammatory site by adhering and migrating across the blood vessel endothelium into the inflammatory tissues. Using bovine serum albumin to deliver TPCA-1, this nanoparticle dramatically ameliorated inflammation and decreased permeability in the lung.<sup>57</sup> Nitrogen cavitation



**Figure 6** AI toolbox for understanding bio-physicochemical identity at the nano-bio interface.

**Notes:** Reproduced with the permission from Singh AV, Rosenkranz D, Ansari MHD et al. Artificial Intelligence and Machine Learning Empower Advanced Biomedical Material Design to Toxicity Prediction. *Advanced Intelligent Systems*. 2020;2(12). © 2020 The Authors. Published by Wiley-VCH GmbH under Creative Commons Attribution 4.0 International License.<sup>125</sup>

was initially employed to isolate neutrophil plasma membrane as sealed vesicles, which minimizes lysosomal and nuclear rupture. Neutrophils were placed in the cell disruption bomb with optimum pressure and duration of

equilibration, then the pressure was quickly released to disrupt cells, and the vesicles were obtained followed by a series of centrifuge.<sup>124</sup> The cell membrane nanovesicles, which are made from activated neutrophils using nitrogen

cavitation, possess intact targeting molecules of integrin  $\beta 2$ , and can selectively bind to inflamed vasculature. Human neutrophils are abundant in the blood; thus, this strategy could be utilized to develop personalized nanomedicines.<sup>56</sup> In another study, piceatannol was remotely loaded in nitrogen cavitation nanovesicles via a pH gradient. The piceatannol-loading nanovesicles dramatically alleviated ALI and sepsis induced by LPS.<sup>54</sup>

Platelet-derived extracellular vesicles (PEVs) are another cell-based drug-delivery system. The platelets intrinsically have inflammation-site affinity and are suitable for targeting ALI treatment. When loaded with TPCA-1, they significantly inhibited pulmonary inflammatory cell infiltration and calmed regional cytokine storm syndromes. This system is also suitable for the treatment of chronic atherosclerotic plaque, rheumatoid arthritis, and wounds associated with the skin.<sup>79</sup>

## Conclusion and Perspective

To date, no pharmacological therapy has been proved to be completely effective in treating ALI. Although many therapies have been proved to be effective in experiments, clinical translation is small. The advent of nanomedicine could open new avenues to address current limitations in the field of traditional pharmacological therapies, but challenges still remain to improve their clinical translatability.

The toxicity and safety concerns are great challenges for nanomedicine clinical translation. Recent advances in machine learning and artificial intelligence immensely decoded and empowered the cell-nanomaterial interaction, which gifted the computational tool for the prediction process<sup>125,126</sup> and in-silico methods<sup>127,128</sup> to potentially decipher the quantitative nanostructure activity-relationship (Nano-QSAR) for nanotoxicology and nanotherapeutics (Figure 6).

Similar to the enhanced permeability and retention (EPR) effect in a solid tumor, the inflammation-specific retention is called ELVIS.<sup>18</sup> The role of EPR in the cancer barrier is somewhat oversold considering that less than 5% of nanomedicine formulations accumulate at the site of tumor,<sup>129</sup> and the heterogeneous outcomes of clinical trials of nanomedicine can be explained by the inter- and intra-individual heterogeneity in EPR-mediated targeting. Biological nanomedicine which employs bacterial,<sup>100,130,131</sup> human cells and tissue<sup>59,132</sup> and

DNAs<sup>111</sup> as carriers seems promising ways to improve and individualize nanomedicine treatments.

A future direction to improve nanomedicine clinical translatability is about to integrate nanomedicines and/or nanorobots with biological cells, which do not need sophisticated instruments, space, chemicals, acoustic and magnetic setup to deliver agents inside the body.<sup>130–133</sup> Bacteria-driven microparticle swimmers possess actuation and sensing capabilities, which make them promising active carriers with high efficiency of tissue cells.<sup>100,130,131</sup> Sperm cell-driven microrobots are biocompatible microrobots, which are fast microswimmers in stagnant fluids without the need for toxic media or fuel, might have an impact on the development of assisted reproductive technologies.<sup>132</sup> These emerging strategies are a promising way to realize personalized pharmacological therapy.

The increasing use of nanodiagnostics and nanomedicine for personalized and targeting therapy raises potential social and ethical conundrums. Nanomedicine commercialization requires a large investment,<sup>134</sup> and the cost-effective benefit is an inevitable issue.<sup>135</sup> Extreme profitability concept leads to concerns that global equality in access to health care might be even further compromised. Continuous efforts to cultivate cost-effective nanomedicine with more security are mandatory to make better use of nanotechnologies for global welfare.

## Abbreviations

Symbols: “↑”, increase or improve; “↓”, decrease or deteriorate; “-”, no significant difference; NG, not given; pre, before stimulation; post, after stimulation; Administrations: i.g, intra gastric; i.n, intranasal; inh, inhalation; i.p, intraperitoneal; i.t, intratracheal; i.v, intravenous; p.o, per os; Others: ACE, angiotensin-converting enzyme; AKP, alkaline phosphatase; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CAT, catalase; Chol, cholesterol; CINC-1, cytokine induced neutrophil chemoattractant; CoV, coronavirus; COVID-19, coronavirus disease 2019; DCFH, 2,2-dichloro dihydro-fluorescein diacetate; DiD, 1,1'-Diiodododecyl-3,3',3'-Tetramethylindodicarbocyanine, 4-Chlorobenzenesulfonate Salt; DiR, 1,1'-diiodododecyl-3,3',3'-tetramethylindodicarbocyanine iodide; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; DOTMA, N [1-(2,3-dioleoyloxy) propyl]-N,N,N-trimethylammonium chloride; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine;



DSPE-PEG, distearylphosphatidylethanolamine–polyethylene glycol; EUK-134, chloro[[2,2'-(1,2-ethanediylbis[(nitrilo-κN)methylidene]] bis[6-methoxyphenolato-κO]]]-manganese; Fuc, fucosylated; GSH, glutathione; HEMA, hydroxyethyl methacrylate; HMGB1A, high mobility group box 1 antibody; HYP, hydroxyproline; KC, keratinocyte-derived chemokine; LPS, lipopolysaccharide; Man, mannosylated; MCT, medium-chain triglycerides; MDA, malondialdehyde; MIP, macrophage inflammatory protein; MPB, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine-N-[4-(p-maleimidophenyl)butyramide] sodium salt; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; PBAP, phenylboronic acid pinacol ester; PC, phosphatidylcholine; PEG, polyethylene glycol; PG, L-α-phosphatidylglycerol; PVP, polyvinylpyrrolidone; RAGE, advanced glycation end products; SARS, severe acute respiratory syndrome; siRNA, small interfering RNA; SOD, superoxide dismutase; SPC, soy phosphatidylcholine; SPION, superparamagnetic iron oxide nanoparticles; TMAEMA, [2-(methacryloyloxy)-ethyl] trimethylammonium chloride; TPCA-1, 2-[(Aminocarbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide; W/D ratio, wet-to-dry ratio; V'E, calculated minute ventilation; V'O<sub>2</sub>, rate of oxygen uptake per minute; VT, tidal volume.

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## Disclosure

The authors report no conflicts of interest in this work.

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