Chapter 17
Targeted Delivery of Surface-Modified Nanoparticles: Modulation of Inflammation for Acute Lung Injury

Hiep X. Nguyen

Abstract Nanocarriers have been widely employed in the diagnosis and treatment of various diseases. The drug release kinetics and pharmacodynamics could be adjusted by changing the materials, designs, and physicochemical properties of the carriers. Furthermore, the carrier surface could be modified to minimize the particle clearance, increase the circulation duration, escape the biological protective mechanisms, penetrate through physical barriers, and prolong the residence of the drug at the target site. Among lung diseases, acute lung injury has been considered life-threatening with approximately 190,000 cases and 74,500 deaths per year in the USA. Numerous researches have reported the efficacy of drug-encapsulated nanoparticles in the treatment of acute lung injury. The use of nanoparticles could help minimize the effect of airway defenses in the lung, thus provides a prolonged retention, sustained drug release, and targeted delivery to the lung tissues. Meanwhile, the toxicity of nanoparticles in the lungs needs to be investigated thoroughly to alleviate the safety concerns. In this chapter, we discuss the targeted pulmonary delivery of surface-modified nanocarriers to efficiently treat acute lung injury.

Keywords Nanocarriers · Acute lung injury · Surface-modified nanoparticles Pulmonary delivery · Toxicity

H. X. Nguyen (✉)
Department of Pharmaceutical Sciences, College of Pharmacy,
Mercer University, Atlanta, GA, USA
e-mail: Hiep.Xuan.Nguyen@live.mercer.edu

1 Nanoparticles

1.1 Introduction of Nanoparticles

Targeted nanoparticles especially nano-sized drug delivery systems were first introduced into the field of medicine in the nineteenth century. In the 1960s, nanoparticles were developed for vaccination delivery [1]. From then on, nanotechnology has been furthered in numerous clinical trials and several products available on the market, particularly in the diagnosis and treatment of cancer [2, 3]. Also, a wide range of nanocarrier types has been fabricated and optimized as advanced drug delivery systems.

Nanoparticles have been fabricated from various macromolecular materials with the size ranging from 1 to 200 nm to drive therapeutic agents into the body tissue [4]. A wide range of diseases has been targeted with nanoparticles such as cancer [5] or tuberculosis [6]. Despite a long history of research and development, the number of marketed products with nanoparticles remains limited. The first commercial product was Abraxane® (available in 2005), which was formulated as an injectable albumin nanoparticle suspension with paclitaxel to treat cancer [7] (Table 17.1).

1.2 Properties of Nanoparticles

Nanoparticles have been commonly used as drug carriers where the active therapeutical ingredients could be dissolved, entrapped, encapsulated, adsorbed, or attached to the particles using various fabrication methods including solvent evaporation, nanoprecipitation, or multiple emulsions [7–9]. The drugs can be retained in the particles with covalent, electrostatic interactions or the like [10]. These solid colloidal nano-sized particles are constructed with biocompatible and biodegradable materials that decompose at a certain rate in the body. The degradation process of these materials could be adjusted to alter the drug release and the physicochemical properties of the nanoparticles [11].

The circulation, absorption, and elimination of nanoparticles in the human body vary depending on the properties of the particles and the targeted tissues. Blood–brain barrier allows nanoparticles with size less than 1 nm to efficiently pass through while nanoparticle of 6 nm dimension could penetrate the continuous capillaries in muscles, lungs, and skin tissue. With the size range from 40 to 60 nm, nanoparticles could escape the fenestrated capillaries in kidney, intestine, and endocrine or exocrine glands [12]. There has been found agglomeration of large nanoparticles (size of more than 600 nm) in liver, spleen, and bone marrow [13]. The electrostatic properties of nanoparticles could be employed to facilitate or inhibit the particle endocytosis. Positively charged nanoparticles could be attached rapidly to cells with the negatively charged surface [12]. Nanoparticles have long been used as imaging agents and drug carriers due to their numerous advantages such as (1) large

Table 17.1 List of approved nanopharmaceuticals

Brand name	Active ingredient	Properties	Indication	Provider	Approval
Liposomes					
AmBisome®	Amphotericin B	Amphotericin B encapsulated in liposomes for injection	Systemic fungal infections (IV)	Sigma-Tau Pharmaceuticals, Inc.	FDA 1997
DaunoXome®	Daunorubicin	Daunorubicin citrate-encapsulated liposome for injection	HIV-related Kaposi's sarcoma (IV)	Galen US Inc.	FDA 1996
DepoCyt®	Cytarabine	Cytarabine-encapsulated in multivesicular liposomes for injection	Lymphomatous malignant meningitis (IV)	Sigma-Tau Pharmaceuticals, Inc	FDA 1999/2007
DepoDur®	Morphine Sulfate	Morphine sulfate-encapsulated in multivesicular extended-release liposomes for injection	For the treatment of pain following major surgery	Endo Pharmaceuticals Inc.	FDA 2004
Doxil®	Doxorubicin hydrochloride	Doxorubicin hydrochloride encapsulated in Stealth® liposomes	AIDS-related Kaposi's sarcoma, multiple myeloma, ovarian cancer (IV)	ALZA Corporation	FDA 1995
Inflexal® V	Influenza vaccine	Influenza virus antigens on liposomes	Influenza vaccine	Crucell (former Berna Biotech Ltd.)	Switzerland 1997
Marqibo®	Vincristine sulfate	Vincristine sulfate encapsulated in liposomes	Acute lymphoid leukemia, Philadelphia chromosome-negative, relapsed or progressed (IV)	Talon Therapeutics, Inc.	FDA 2012
Mepact™	Mifamurtide	Mifamurtide incorporated into large multilamellar liposomes	Nonmetastasizing resectable osteosarcoma (IV)	Takeda France SAS	Europe 2009
Myocet®	Doxorubicin hydrochloride	Doxorubicin encapsulated in oligolamellar liposomes	The first line treatment of metastatic breast cancer in adult women (IV)	Teva UK Limited	Europe 2000
Visudyne®	Verteporfin	Verteporfin in liposomes for injection	Photodynamic therapy of wet age-related macular degeneration, pathological myopia, ocular histoplasmosis syndrome (IV)	Novartis AG	FDA 2000

(continued)

Table 17.1 (continued)

Brand name	Active ingredient	Properties	Indication	Provider	Approval
Nonliposomal lipid-based formulations					
Abelcet®	Amphotericin B	Amphotericin B complexed with two phospholipids (1-α-dimyristoyl phosphatidyl choline and 1-α-dimyristoyl phosphatidyl glycerol)	The treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy	Exelead, Inc.	FDA 1995 and 1996
Amphotec®	Amphotericin B	Complex of amphotericin B and cholesteryl sulfate	The treatment of invasive aspergillosis	InterMune, Inc.	FDA 1996
PEGylated proteins, polypeptides, aptamers					
Adagen®	Pegademase bovine	PEGylated adenosine deaminase	Adenosine deaminase deficiency—severe combined immunodeficiency disease	Leadiant Biosciences, Inc.	FDA 1990
Cimzia®	Certolizumab pegol	PEGylated antibody	Crohn's disease, rheumatoid arthritis	UCB, Inc.	FDA 2008
Neulasta®	Pegfilgrastim	PEGylated filgrastim	Febrile neutropenia, In patients with nonmyeloid malignancies; prophylaxis (SC)	Amgen Inc	FDA 2002
Oncaspar®	Pegaspargase	PEGylated L-asparaginase	Acute lymphoblastic leukemia	Sigma-Tau Pharmaceuticals, Inc	FDA 1994
Pegasys®	Peginterferon Alfa-2a	PEGylated interferon alfa-2b	Hepatitis B and C	F. Hoffmann-La Roche AG	FDA 2002
PegIntron®	Peginterferon alfa-2b	PEGylated interferon alfa-2b	Hepatitis C	Schering-Plough Corporation	FDA 2001
Somavert®	Pegvisomant	PEGylated human growth hormone receptor antagonist	Acromegaly, second-line therapy	Pharmacia and Upjohn Company, LLC	FDA 2003
Macugen®	Pegaptanib Sodium	PEGylated anti-VEGF aptamer	Intravitreal Neovascular age-related macular degeneration	Valeant Pharmaceuticals International, Inc.	FDA 2004
Mircera®	Methoxy polyethylene glycol-epoetin beta	PEGylated epoetin beta	Anemia associated with chronic renal failure in adults	F. Hoffmann-La Roche AG	FDA 2007

Brand name	Active ingredient	Properties	Indication	Provider	Approval
Nanocrystals					
Emend®	Aprepitant	Aprepitant as nanocrystal	Emesis, antiemetic	Merck	FDA 2003
Megace ES®	Megestrol acetate	Megestrol acetate as nanocrystal	Anorexia, cachexia	Endo Pharmaceuticals	FDA 2005
Rapamune®	Sirolimus	Rapamycin (sirolimus) as nanocrystals formulated in tablets	Immunosuppressant	PF Prism C.V.	FDA 2002
Tricor®	Fenofibrate	Fenofibrate as nanocrystals	Hypercholesterolemia, hypertriglyceridemia	AbbVie Inc.	FDA 2004
Triglide®	Fenofibrate	Fenofibrate as insoluble drug-delivery microparticles	Hypercholesterolemia, hypertriglyceridemia	Skye Pharma AG	FDA 2005
Polymer-based nanoformulations					
Copaxone®	Glatiramer acetate	Polypeptide consist of four amino acids	Multiple sclerosis (SC)	Teva Pharmaceuticals USA	FDA 1996/2014
Eligard®	Leuprorelin acetate	Leuprolide acetate incorporated in nanoparticles	Advanced prostate cancer (SC)	Tolmar Therapeutics	FDA 2002
Genexol®	Paclitaxel	Paclitaxel incorporated in micelles	Metastatic breast cancer, pancreatic cancer (IV)	Samyang Biopharma	South Korea 2001
Opaxio®	Paclitaxel poliglumex	Paclitaxel covalently linked to solid nanoparticles	Glioblastoma	Cell Therapeutics, Inc.	FDA 2012
Renagel®	Sevelamer hydrochloride	Cross-linked poly allylamine hydrochloride	Hyperphosphatemia	Sanofi Genzyme	FDA 2000
Protein–drug conjugates					
Abraxane®	Paclitaxel	Paclitaxe-encapsulated nanoparticles	Metastatic breast cancer, non-small-cell lung cancer (IV)	Abraxis BioScience	FDA 2005
Kadcyla®	Ado-Trastuzumab Emtansine	Immunoconjugate	Metastatic breast cancer	Genentech	FDA 2013

(continued)

Table 17.1 (continued)

Brand name	Active ingredient	Properties	Indication	Provider	Approval
Ontak®	Denileukin diftitox	Recombinant fusion protein of fragment A of diphtheria toxin and subunit binding to interleukin-2 receptor	Primary cutaneous T-cell lymphoma, CD25-positive, persistent or recurrent disease	Eisai Inc.	FDA 1994/2006
Surfactant-based nanoformulations					
Fungizone®	Amphotericin B	Lyophilized powder of amphotericin B with added sodium deoxycholate	Systemic fungal infections (IV)	Bristol-Myers Squibb	FDA 1966
Diprivan®	Propofol	Oil-in-water emulsion of propofol	Sedative–hypnotic agent for induction and maintenance of anesthesia (IV)	Fresenius Kabi USA	FDA 1989
Estrasorb™	Estradiol hemihydrate	Emulsion of estradiol	Hormone replacement therapy during menopause	Exeltis USA, Inc.	FDA 2003
Metal-based nanoformulations					
Feridex®	Ferumoxides	Dextran-coated superparamagnetic iron oxide nanoparticles	Liver/spleen lesion magnetic resonance imaging (IV)	AMAG Pharmaceuticals, Inc.	FDA 1996
Feraheme™ (Ferumoxytol)	Ferumoxytol	Dextran-coated superparamagnetic iron oxide nanoparticles	Treatment of iron deficiency anemia in adults with chronic kidney disease	AMAG Pharmaceuticals, Inc.	FDA 2009
NanoTherm®	Iron oxide	Aminosilane-coated superparamagnetic iron oxide nanoparticles	Local ablation in glioblastoma, prostate, and pancreatic cancer	MagForce AG	Europe 2013
Virosomes					
Gendicine®	Gene therapy	A recombinant adenovirus engineered to express wild-typep53	Treat patients with tumors which have mutated p53 genes. Head and neck squamous cell carcinoma	Shenzhen SiBiono GeneTech	People's Republic of China 2003
Rexin-G®	Gene therapy	Gene inserted into the retroviral core of viral genes	For all solid tumors	Epeius Biotechnologies	Philippines 2007

FDA US Food and Drug Administration, *IV* intravenous, *SC* subcutaneous

surface-volume ratio, (2) biological mobility, (3) enhanced tissue penetration, (4) drug protection against degradation or loss, (5) sustained and controlled drug release, (6) reduction of dose frequency, (7) improved patient compliance, and (8) increased drug level at the target site [7, 14, 15].

1.3   Surface-Modified Nanoparticles

These days, nanoparticle surface and dimensions have been modified to minimize the particle clearance, increase the circulation time, escape the biological protective mechanisms, penetrate through physical barriers, and prolong the residence of the drug at the target site [7]. Thus, various moieties have been utilized for modification and functionalization of the nanoparticle surface in accord with different stimuli [12].

Nanoparticles could be stimulated by endogenous or exogenous factors. The endogenous stimulus includes redox, enzyme, and pH while light, ultrasound, and magnetic fields have been employed as exogenous factors to manipulate the behavior of nanoparticles [16]. Surface modification and polymeric coating of nanocarriers could allow altering the half-life, biocompatibility, biodistribution, circulation duration, stimuli reactivity, and therapeutic application [10, 17]. Furthermore, the hydrophilicity of nanoparticles was found to primarily determine the rate of particle binding on blood components. Hydrophobic nanoparticles without surface functionalization have been indicated to be eliminated rapidly whereas the circulation was significantly enhanced as these particles were coated with hydrophilic polymers or surfactant to increase the hydrophilicity [18] (Fig. 17.1).

Controlled and sustained drug release from nanoparticles is critical to the therapeutic efficacy. The drug release can be triggered by stimuli or occur in sustained mode over a certain period of time [10]. The drugs could diffuse out of the particles or the particles might slowly and gradually degrade to release the drug load. The
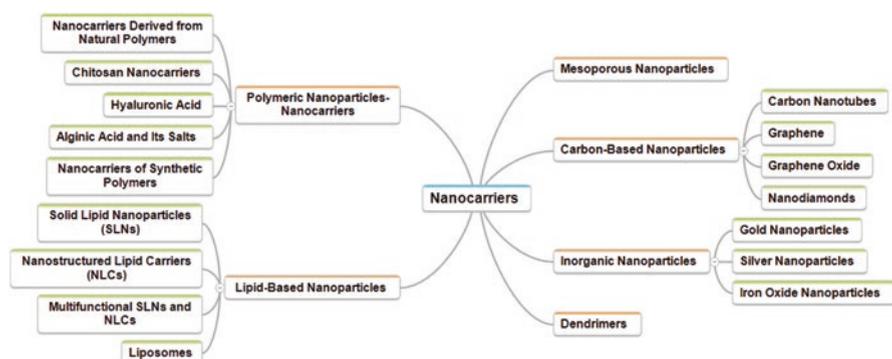

Fig. 17.1 Types of nanocarriers. *Source:* Author's representation

stimuli-responsive release of drug from nanoparticles may facilitate the drug accumulation in the targeted tissues. These stimuli could be generated by a modification in the biological environment including cell environment, pH alteration, and disease-related enzymes or external physical forces such as light, ultrasound, heat, electrical, and magnetic fields. Ultrasound-sensitive microbubbles have been employed to release therapeutic agent to the local targets [19]. Microbubbles fabricated from lung surfactants caused a significant enhancement in drug targeted deposition as compared to lipid-only microbubbles [20]. Interestingly, the application and control of magnetic fields could drive aerosol droplets encompassing superparamagnetic iron oxide to the targeted locations in the mice's lungs in vivo [21].

1.4 Potential Toxicity of Nanoparticles

A comprehensive understanding of biocompatibility, biodistribution, and degradation of nanoparticles is expected to properly utilize the particles [10]. The physical properties including geometry, dimensions, surface charge, and morphology have been found to alter the therapeutic effects of nanoparticles [22]. In particular, rod-shaped particles were more toxic than spherical particles [23]. Long fibers could less likely be captured by macrophages, thus minimize their elimination from the system and cause inflammation [24]. Surface functionalization of nanoparticles could change their biodistribution, effectiveness, and toxicity. Specifically, biopersistent carbon nanotubes could be modified and functionalized to enhance the hydrophilicity and rapid clearance via renal excretion [25]. A small change in the physicochemical properties of nanoparticles could be exaggerated into significant alteration in the biological response. Thus, the biological safety of nanoparticles needs to be evaluated and monitored with care [10].

1.5 Conclusion

Nano-sized carriers are a promising platform for controlled drug delivery due to their dimensions, permeability, and drug loading. Furthermore, surface functionalization could be used to enhance the targetability as well as to reduce the toxicity [12]. The nanomaterials could be coated or conjugated with various segments to prepare multifunctional and stimuli-responsive drug delivery system [12] which allows to modify drug release profile, specific targeting, compatibility, and several other advantages. More and more clinically effective nanocarriers are expected in the market in the future.

2 Acute Lung Injury

2.1 Pulmonary Drug Delivery

The lung offers several beneficial properties for rapid and efficient drug delivery due to the large alveolar surface area, a thin layer of the epithelial barrier, extensive blood circulation, avoidance of the first-pass hepatic metabolism, and low proteolytic activity in the alveolar space [26–29]. The metabolic activities in the lung are significantly lower than that in the gastrointestinal tract and the liver [10]. These properties not only enhance the systemic drug delivery but also improve the efficacy of treatment of lung diseases. Furthermore, drug administration via the lung has been preferred due to its noninvasiveness and the possibility for self-administration.

Despite the aforementioned advantages, there are only limited products on the market for lung delivery. The only inhalable product of therapeutic protein on the market is Pulmozyme® (dornase alfa, Genentech Inc., San Francisco, CA, USA). Exubera (Inhalable insulin, Pfizer, New York, NY, USA) was approved by US Food and Drug Administration in 2006, but later withdrawn from the US market in 2007 due to the deficiency of consumer demand.

The lung has an effective mechanism of clearing external agent, thus making it challenging to deposit drugs in a region in the lung. Inhalable particles could be eliminated from the lung by two mechanisms. Firstly, particles can be cleared by the moving patches of mucus layer in the conducting zone of the lung. The clearance would be more efficient in lung diseases with an increase in mucus production and thickness [10]. Secondly, in the deep lung, macrophages (on the air side of the alveolar cells) could engulf and digest to remove insoluble particles rapidly.

2.2 Introduction of Acute Lung Inflammation

An acute lung injury (ALI) is a disease in which the lungs could not sufficiently provide oxygen to the body, causing low levels of oxygen in the blood (hypoxemia). The leading causes of ALI have been found to be pneumonia, sepsis, lung trauma, burns, near drowning, and other condition related to inflammation or damage to the lungs. As first described in 1967, Acute lung injury (ALI) was diagnosed with acute respiratory distress, cyanosis refractory to oxygen therapy, decrease lung compliance, and diffuse infiltrates on chest radiography [30]. In 1988, this definition was expanded to encompass the level of positive end-expiratory pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, the static lung compliance, and the degree of infiltration evident on chest radiography [31]. Later, the lung injury score was included to evaluate the severity level of the disease in clinical trials [32]. American-European Consensus Conference Committee proposed a new definition that classifies the severity of lung injury and segregates the patients into two groups:acute lung injury (less severe hypoxemia) and acute respiratory distress syndrome (more severe hypoxemia) [33].

Recent surveys reveal that approximately 190,000 cases of ALI with 74,500 deaths per year in the US [34]. This life-threatening disease has been influencing millions of people every year over the world [35]. The in-hospital mortality rate of ALI was estimated to be 38.5% [34], which could be reduced to 31% using low-tidal volume ventilation [36, 37]. The primary cause of death was attributed to sepsis or multiple organ dysfunction syndromes.

2.3   *Mechanism and Properties of Acute Lung Injury*

ALI could occur due to either direct or indirect mechanical, toxic, infectious, or inflammatory challenges to the lung [38]. The most common cause of ALI was severe pulmonary sepsis, following by trauma, aspiration, multiple blood transfusion, acute pancreatitis, inhalation injury, and drug toxicity [39].

The interaction and communication between different cell types have been investigated to discover the pathology of ALI. Mechanism of ALI most likely relates to cell death in necrosis and apoptosis [35]. In lung injury, cell death could occur based on oncosis [40], cathepsin-dependent cell death, or autophagy. A wide range of cell types is associated with ALI such as alveolar epithelial and vascular endothelial cells (change in permeability to cause edema formation and alveolocapillary injury) and platelets and immune cells (inflammatory response) [41–44]. ALI is involved in a prothrombotic and antifibrinolytic shift that facilitate fibrin deposition, thus, advance the inflammation [45].

ALI and ARDS are represented by bilateral exudative chest infiltrate which could be diagnosed by roentgenograms [44, 46]. ALI can progress rapidly from an initial stage of a leaky edematous lung to a proliferative phase with deposition of fibrin and a reduction in respiratory compliance, and to a fibrotic phase with scarring lung. The hallmarks of ALI—protein extravasation and formation of lung edema—were caused by excessive inflammation, alteration in coagulation and fibrin deposition, and increase in permeability of the alveolocapillary barrier [38].

3   Nanoparticles to Treat Acute Lung Injury

3.1   *Advantages of Nanoparticles for Lung Delivery*

The large surface area of alveolar, a thin layer of epithelial barrier, and a dense network of blood vessels facilitate the delivery of various therapeutic agents [47]. The use of nanoparticles could help to minimize the effect of airway defenses in the lung. Once delivered to the lungs, nanoparticles could have a prolonged retention, sustained drug release, and targeted delivery to the lung tissues [10, 48]. Extensive studies have been conducted for the pulmonary delivery of polymeric nanoparticles for various compounds including asthmatic drugs [49, 50], antituberculosis drugs [51],

and anticancer drugs [52, 53]. Also, liposomal nanoformulations have been investigated and evaluated to be a promising platform for drug delivery. Currently, multiple liposomal formulations are FDA-approval products available on the market while several others are studied in clinical trials [54]. Liposome has a major advantage of being fabricated from compounds compatible and endogenous to the lung (such as lung surfactants), thus becoming a preferred pulmonary drug delivery system. Some marketed liposomal products for the treatment of acute respiratory distress syndrome are Exosurf® (Colfosceril Palmitate, GlaxoSmithKline, Brentford, UK) and Alveofact® (Bovactant, Lyomark Pharma, Oberhaching, Germany) [55]. Budesonide-encapsulated liposomes have been developed to deliver the drug at a controlled release rate to maintain the therapeutic concentrations in rat lungs in vivo. This liposomal formulation also helped to reduce the systemic exposure and toxicity [56]. Interestingly, multiple drugs could be combined and delivered to the lung simultaneously using nanocarrier systems. Nanoparticles offer several benefits as they could penetrate the lung more deeply and enter the alveolar areas [10]. Furthermore, nanoparticle-based systems evade macrophage clearance effectively and permeate the lung epithelium. Also, the surface of nanoparticles could be modified and functionalized to enhance the drug bioavailability, to improve the penetration into the mucus layer, and aid targeted delivery [10]. The deposition of nanocarriers could be prolonged by using mucoadhesive materials, for instance, biodegradable polysaccharide chitosan [7]. Yamamoto and colleagues fabricated peptide elcatonin-encapsulated PLGA nanoparticles whose surface was modified with chitosan. Once delivered to the lungs of guinea pigs, the particles caused a significant decrease in blood calcium levels as compared to the initial concentrations. Furthermore, this effect was prolonged and sustained up to 24 h (due to the slow elimination of chitosan-modified particles), which was markedly longer than unmodified particles [57].

3.2   Surface-Modified Nanoparticles for Lung Delivery

The use of surface-modified nanoparticles is beneficial for lung delivery. Brush-shaped nanoparticles have been formed with low molecular weight poly(ethylene glycol) chains (PEG) for a reduction of phagocytosis [58]. Furthermore, PEGylated nanocarriers were found to easily and readily penetrate the mucus layer in chronic obstructive lung diseases [59]. In contrary, chitosan could be used to modify the particle surface to enhance the mucoadhesion and circulation. Thus, chitosan-modified nanoparticles could reside for a longer period at the targeted site to improve the drug uptake, bioavailability, and therapeutic efficacy. This property is particularly desirable for the treatment of nonobstructive lung diseases including allergy and lung cancer [10]. Interestingly, biological fluids could modify the surface of particles to form protein corona whose properties are enhanced as compared to the original particles [60]. Lung surfactant phospholipids have been used to coat nanoparticles to alleviate toxicity as well as to improve cellular uptake [61]. Furthermore, the agglomeration of the particles helps create large agglomerates to be digested by macrophages [62] (Table 17.2).

Table 17.2 Surface-modified nanoparticles for acute lung injury

Nanoparticles	Effect	Mechanism	Study model	References
Polydopamine nanoparticles (similar to melanin)	Anti-inflammation therapeutic effect on acute inflammation-induced injury	Polydopamine with enriched phenol groups functioned as a radical scavenger to eliminate reactive oxygen species	Murine models	[63]
Lung-targeting functionalized nano-sterically stabilized unilamellar liposomes loaded with glucocorticoids methylprednisolone	Good particle size distribution, morphology, encapsulation efficiency, and high specificity to the lung.	Reduce the levels of TNF-α, IL-8, and TGF-β1 in rat bronchoalveolar lavage fluid and the expression of NK-κB in the lung tissues, thus alleviate lung injuries and enhance rat survival	Rat	[64]
Generation IV polyamidoamine dendrimers	The treatment of ischemia-reperfusion-induced acute lung injury	Dendrimers were taken up in epithelial cells and macrophages.	Ex vivo rabbit model	[65]
Dry powder formulations of inhalable apigenin-loaded bovine serum albumin nanoparticles	Good aerodynamic properties of the particles and antioxidant activity of encapsulated apigenin	Novel delivery system against lung injury with potential antioxidant activity		[66]
Two-component co-spray dried DMF:D-Man DPIs with high load of dimethyl fumarate	Capability to reach lower airways to treat inflammation in pulmonary diseases	Exhibit excellent aerosol dispersion performance with a human DPI device	In vitro predictive lung deposition modeling	[67]
Human amniotic fluid stem cells labeled with dual-polymer-coated UCNP-PEG-PEI nanoparticles	Display remarkable positive effects on ALI-damaged lung tissue repair.	Recover the integrity of the alveolar-capillary membrane, attenuate transepithelial leukocyte and neutrophil migration, and down-regulate proinflammatory cytokine and chemokine expression	A murine model of acute lung injury	[68]

Table 17.2 (continued)

Nanoparticles	Effect	Mechanism	Study model	References
Poly-lactic-co-glycolic acid nanoparticles-facilitated cDNA delivery	Upregulate pulmonary EpoR expression and downstream signal transduction in rats for 21 days, Attenuate hyperoxia-induced damage in lung tissue based on apoptosis, oxidative damage of DNA, protein and lipid, tissue edema, and alveolar morphology	Targeted pulmonary EpoR upregulation mitigates acute oxidative lung damage	Rat lungs	[69]
Nanoparticles based on polyethyleneimine and DNA	When β2-Adrenergic Receptor (β2AR) was applied as the therapeutic gene, PEI/β2AR treatment significantly attenuated the severity of ALI. PEI/DNA nanoparticles could be an efficient agent in ALI treatment.	Attenuate alveolar fluid clearance, lung water content, histopathology, bronchioalveolar lavage cellularity, protein concentration, and inflammatory cytokines in mice with preexisting ALI	Mouse model of ALI induced by lipopolysaccharide	[70]
Shell cross-linked knedel-like polymer nanoparticles	The $K(d)$ values of the nanoparticle-attached PNAs were about an order of magnitude greater than the free PNAs	Recognize and selectively inhibit of mRNA sequences for inducible nitric oxide synthase (iNOS), which are overexpressed at sites of inflammation		[71]

3.3 Factors Affecting Nanoparticles Delivery to the Lung

The deposition and distribution of nanoparticles in the lungs vary depending on several factors such as breathing rate, lung volume, air flow, and particle size [10]. Multiple studies have suggested that particle size plays the most important role in manipulating the distribution and deposition of the particles in the lung. Small particles (size range from 1 to 5 μm) are deposited in the deep regions while inhaled particles (whose size is larger than 10 μm) are found primarily in the oropharyngeal region [72, 73]. A requirement for lung delivery is the proper design of the carrier systems [74]. Pulmonary delivery of inhaled particles is dominated by various factors such as particle size, particle density, and the mass median aerodynamic diameter in which the particle size could guarantee a maximum distribution and deposition of the particle in the deep lung [75]. The rate of clearance is primarily affected by the particle size in the alveolar region. Several studies have been performed to investigate the interaction between nanoparticles and macrophages. Large particle (aerodynamic diameter more than 6 μm) are exhaled without being phagocytosed [76], microparticles (aerodynamic diameter 1–5 μm) are effectively taken up by macrophages, while nanoparticles (aerodynamic diameter less than 200 nm) could penetrate the cellular barrier and the particle phagocytosis by alveolar macrophages can be reduced [48, 77, 78]. These indicate that nanoscale particles could avoid macrophage clearance while being deposited in the deep lung, especially the alveolar regions [10]. However, small particles require a high level of energy for fabrication and disaggregation. Inhaled particles could be deposited in the lung by inertial impaction, sedimentation, and diffusion. The particle deposition is analogous to the settling of spherical particles under gravity force through the air. Nanoparticles, which is not deposited in the lungs, is exhaled to result in a major loss of the delivered dose [79].

3.4 Pulmonary Delivery of Nanoparticles Using Dry Powder Carriers

Proper dry powder formulations and carrier systems have been developed and optimized to deposit nanoparticles to the alveolar regions to enhance the efficacy of their pulmonary delivery [80]. Kawashima and coworkers employed hydroxypropylmethyl cellulose phthalate (HPMCP) nanospheres (hydrophilic nanoparticles) to facilitate the inhalation properties of dry powder pranlukast hydrate [81]. The authors mixed the surface nanospheres and drug powder with lactose. Thus, in the in vitro inhalation test, the emission and dispersibility of surface-modified drug powder increased significantly and the powder was effectively delivered to the deep lung. Kawashima et al. fabricated insulin-loaded PLGA nanospheres. Then, an

ultrasonically assisted nebulizer was utilized to deliver the nanospheres to the trachea of guinea pigs. The authors reported a significant decrease in the blood glucose and a sustained hypoglycemic effect for 48 h. The results were attributed to the controlled release of insulin from the nanospheres and their deposition in multiple regions of the lung [82]. Tsapis and coworkers employed a spray drying method to manufacture large porous particles. Using 1,2-dipalmitoyl-sn-glycero-3-phosphocholine and 1,2-dimyristoyl-sn-glycero-3-phophoethanolamine (surfactants), and lactose, the authors could tailor the physicochemical properties of the spray-dried powder for pulmonary delivery [78]. Interestingly, nanoparticles could be loaded in a carrier matrix. Sham and colleagues dissolved lactose in nanoparticle suspension before spray drying to obtain nanoparticles-incorporated carrier powder. The authors observed a marked change in the particle size and reported the possibility of manipulating the delivery and release of nanoparticles [80]. In another study, Grenha et al. used lactose and mannitol together with a spray drying method to prepare microspheres, which contain insulin-incorporated nanoparticles for pulmonary drug delivery. The drug release from nanoparticles was found to be unaffected by the microencapsulation. Furthermore, this system allows to effectively deliver macromolecules via pulmonary administration [47]. The spray drying technique was also employed by Ely and colleagues to prepare effervescent carrier particles which incorporate ciprofloxacin-loaded nanoparticles. The authors could manage to alter the particle size to maximize the particle deposition in the deep lung. The use of effervescent carrier particles resulted in a marked enhancement in the drug release. Also, they observed an insignificant change in the nanoparticles dimension upon being released from the effervescent carrier particles [74]. Pulmonary administration is a promising platform to deliver nanoparticles carried in dry powders. The nebulization parameters of the matrix should be optimized to minimize particle aggregation and to facilitate the drug delivery into the deep lungs [83].

3.5   Pulmonary Delivery of Nanoparticle Suspensions Using Nebulization

Nanoparticles could be delivered by spraying or nebulizing the nanoparticle suspension. Dailey and coworkers formulated a surfactant-free nanoparticle suspension for pulmonary drug delivery. This system could provide a high encapsulation efficiency due to the electrostatic interactions between the drug molecules and the particles. The authors reported that the use of anionic diethylaminopropyl amine-poly(vinyl alcohol)-grafted-poly(lactide-co-glycolide)-contained formulation and an increase in the amount of carboxy methyl cellulose helped to minimize the particle aggregation [84]. Also, Yamamoto et al. prepared and modified the surface of PLGA nanospheres using chitosan to enhance the delivery efficacy of calcitonin to the lung. After the administration of chitosan-modified PLGA nanoparticles to the trachea of

guinea pigs, the blood calcium was reported to decrease by 80%. Furthermore, the therapeutic level of the drug was sustained for 24 h, which was markedly longer than the unmodified particles. This result could be explained by the mucoadhesion of the nanoparticles to the bronchial mucous and local tissue in the lung as well as the prolonged drug release from the particles. Moreover, chitosan could enhance the drug permeability by loosening the intercellular tight junctions [57]. In another study, itraconazole-loaded nanoparticles were fabricated, dispersed in aqueous media, and nebulized to the murine lung in vivo. This local delivery system led to a high drug concentration in the lung, and a decreased possibility of adverse effects [85]. Thus, nebulizing nanoparticle suspensions is a promising technique to deliver therapeutical agents to the lung. The physicochemical stability of the suspension needs to be maintained for clinical efficacy.

3.6   *Local Delivery of Nanoparticles to the Lung*

The local delivery of nanoparticles allows to enhance, sustain, and control the drug level at the target site to treat respiratory diseases [7]. Also, this targeted delivery could reduce the required dose, avoid the drug degradation in the gastrointestinal tract (oral administration), and minimize the systemic toxicity. Vaughn and colleagues delivered itraconazole-loaded nanoparticles to treat fungal infections of *Aspergillus fumigatus*. The pulmonary delivery of itraconazole nanoparticles to mice in vivo showed a significantly high and sustained drug concentration in the lung tissues while the drug level in serum was controlled to maximize the treatment efficacy as well as to reduce the possible systemic toxicity [86]. In addition to sustained drug concentrations in the lung, target delivery to certain cells or tissues has been found beneficial. For example, various therapeutic compounds including rifampicin, isoniazid, and pyrazinamide were formulated to target the drug delivery to alveolar macrophages to optimize the treatment of pulmonary tuberculosis [6]. Several studies fabricated and characterized drug-encapsulated nanoparticles for in vivo tests on guinea pigs. PLGA nanoparticles could be delivered to the lungs to maintain the therapeutic levels of the drugs in the plasma as well as in the lungs for a prolonged period of time [87]. Also, this approach allowed to decrease the overall dose and reduce the systemic exposure. Furthermore, the surface of PLGA nanoparticles has been functionalized and modified with wheat germ agglutinin whose bioadhesive properties facilitate its interaction with lectin receptors embedded in the alveolar epithelium to maintain the drug concentration in the lung tissues [88]. This system could result in a sustained drug level in the plasma for 14 days and in the lung for 15 days. Similarly, PLGA nanoparticles which were formulated with sodium alginate and chitosan provided a sustained drug delivery to the lungs of guinea pigs in vivo to eradicate tubercle bacilli from *M. tuberculosis*-infected guinea pigs [51].

3.7 Technical Issues of Nanoparticles to the Lung

Nanoparticles are usually formulated in colloidal solutions for nebulization [7]. However, the storage in an aqueous medium could induce polymer hydrolysis and degradation of drugs. Furthermore, the small dimensions and interactions between particles result in the agglomeration and settling of nanoparticles, thus, cause a reduced functionality of the nebulizer. To overcome these challenges, lyophilization has been employed to dry nanoparticles to obtain a stable storage form which can be later dispersed in an aqueous solution for administration [89, 90]. Stabilizers such as cryoprotectant sugars and surfactants are used to enhance the stability, maintain the characteristics of nanoparticles during lyophilization, and to facilitate resuspension of the dry particles. These stabilizers dissolve in the resuspended solution and are delivered together with the particles.

3.8 Toxicity of Nanoparticles to the Lung

Despite multiple advantages offered by nanoparticles, they still possess some safety concerns. Li et al. reported that polyamidoamine which is a promising material for nanocarriers could cause autophagic cell death in human lung carcinoma cell line (A549 cells) and acute lung injury in mice in vivo, especially the administration of polyamidoamine might lead to mortality [91]. Card and coworkers reviewed the applications of nanoparticles for imaging, diagnostic, and therapeutic use in the lung [92] and stated that several nanomaterials could cause inflammation and fibrosis in the lung. Toxicity of nanoparticles in the lungs has been evaluated in the environmental health field, especially "ultrafine" particles with the aerodynamic diameter less than 100 nm [7]. The nanoscale dimension of ultrafine particles, on the one hand, provide the therapeutic application, on the other hand, might result in toxicity and undesirable health effects. Ultrafine particles could penetrate epithelial and endothelial cells, be taken up efficiently by cells, and distributed in bone marrow, lymph nodes, spleen, liver, heart, the central nervous system, and ganglia [93–95]. The biological activity of nanoparticles could lead to inflammatory and oxidative stress reactions. Several authors have reviewed the effects of physicochemical properties of nanoparticles such as dimensions, surface charge, geometry, and lipophilicity on their efficacy in vivo [96–99]. The toxicity of nonbiodegradable nanoparticles could be markedly different from those biodegradables. There is an insignificant interaction between biodegradable materials and biological systems. Moreover, the speed of degradation of biodegradable nanoparticles leads to a certain variation in the toxic responses. In particular, biodegradable PLGA nanoparticles resulted in markedly lower inflammatory response than nonbiodegradable polystyrene nanoparticles [100]. Nanoparticles could translocate from the lung to other organs to cause adverse reactions in those organs. The toxicological potential of nanoparticles is negatively correlated with the particle size. Certain levels of

toxicity have been observed with inhalable single-wall carbon nanotubes (SWCNT) [85]. Warheit and colleagues investigated the toxicity of SWCNT on rats in vivo and reported that a high-dose pulmonary exposure led to mortality after 24 h. Pulmonary delivery of SWCNT caused multifocal granulomas, which indicated the nonuniform distribution and translocation of SWCNT-induced toxicity in rats [101]. Similarly, Shvedova et al. reported inflammatory responses in the lungs of mice after exposure to SWCNTs. The toxicity could progress to a reduction of pulmonary function as well as increased vulnerability to infection [102].

References

1. Kreuter, J. (2007). Nanoparticles—A historical perspective. *International Journal of Pharmaceutics, 331*(1), 1–10.
2. Estanqueiro, M., Amaral, M. H., Conceição, J., et al. (2015). Nanotechnological carriers for cancer chemotherapy: The state of the art. *Colloids and Surfaces. B, Biointerfaces, 126*, 631–648.
3. Poon, W., Zhang, X., & Nadeau, J. (2014). Nanoparticle drug formulations for cancer diagnosis and treatment. *Critical Reviews in Oncogenesis, 19*(3–4), 223–245.
4. Kreuter, J. (1991). Nanoparticle-based dmg delivery systems. *Journal of Controlled Release, 16*(1–2), 169–176.
5. Bannon-Peppas, L., & Blanchette, J. O. (2004). Nanoparticle and targeted system for cancer therapy. *Advanced Drug Delivery Reviews, 56*, 1649–1659.
6. Pandey, R., & Khuller, G. K. (2005). Antitubercular inhaled therapy: Opportunities, progress and challenges. *The Journal of Antimicrobial Chemotherapy, 55*(4), 430–435.
7. Sung, J. C., Pulliam, B. L., & Edwards, D. A. (2007). Nanoparticles for drug delivery to the lungs. *Trends in Biotechnology, 25*(12), 563–570.
8. Astete, C. E., & Sabliov, C. M. (2006). Synthesis and characterization of PLGA nanoparticles. *Journal of Biomaterials Science. Polymer Edition, 17*(3), 247–289.
9. Birnbaum, D. T., Kosmala, J. D., & Brannon-Peppas, L. (2000). Optimization of preparation techniques for poly (lactic acid-co-glycolic acid) nanoparticles. *Journal of Nanoparticle Research, 2*(2), 173–181.
10. van Rijt, S. H., Bein, T., & Meiners, S. (2014). Medical nanoparticles for next generation drug delivery to the lungs. *The European Respiratory Journal, 44*(3), 765–774.
11. Panyam, J., Dali, M. M., Sahoo, S. K., et al. (2003). Polymer degradation and in vitro release of a model protein from poly (D,L-lactide-co-glycolide) nano-and microparticles. *Journal of Controlled Release, 92*(1), 173–187.
12. Siafaka, P. I., Üstündağ Okur, N., Karavas, E., et al. (2016). Surface modified multifunctional and stimuli responsive nanoparticles for drug targeting: current status and uses. *International Journal of Molecular Sciences, 17*(9), 1440.
13. Arruebo, M., Fernández-Pacheco, R., Ibarra, M. R., et al. (2007). Magnetic nanoparticles for drug delivery. *Nano Today, 2*(3), 22–32.
14. Schütz, C. A., Juillerat-Jeanneret, L., Mueller, H., et al. (2013). Therapeutic nanoparticles in clinics and under clinical evaluation. *Nanomedicine, 8*(3), 449–467.
15. Siafaka, P., Betsiou, M., Tsolou, A., et al. (2015). Synthesis of folate-pegylated polyester nanoparticles encapsulating ixabepilone for targeting folate receptor overexpressing breast cancer cells. *Journal of Materials Science. Materials in Medicine, 26*(12), 275.
16. Karimi, M., Mirshekari, H., Aliakbari, M., et al. (2016). Smart mesoporous silica nanoparticles for controlled-release drug delivery. *Nanotechnology Reviews, 5*(2), 195–207.

17. Filippousi, M., Siafaka, P. I., Amanatiadou, E. P., et al. (2015). Modified chitosan coated mesoporous strontium hydroxyapatite nanorods as drug carriers. *Journal of Materials Chemistry B, 3*(29), 5991–6000.

18. Yoo, J.-W., Doshi, N., & Mitragotri, S. (2011). Adaptive micro and nanoparticles: temporal control over carrier properties to facilitate drug delivery. *Advanced Drug Delivery Reviews, 63*(14–15), 1247–1256.

19. Geers, B., Dewitte, H., De Smedt, S. C., et al. (2012). Crucial factors and emerging concepts in ultrasound-triggered drug delivery. *Journal of Controlled Release, 164*(3), 248–255.

20. Sirsi, S. R., Fung, C., Garg, S., et al. (2013). Lung surfactant microbubbles increase lipophilic drug payload for ultrasound-targeted delivery. *Theranostics, 3*(6), 409.

21. Hasenpusch, G., Geiger, J., Wagner, K., et al. (2012). Magnetized aerosols comprising superparamagnetic iron oxide nanoparticles improve targeted drug and gene delivery to the lung. *Pharmaceutical Research, 29*(5), 1308–1318.

22. Thorley, A. J., & Tetley, T. D. (2013). New perspectives in nanomedicine. *Pharmacology & Therapeutics, 140*(2), 176–185.

23. Sharifi, S., Behzadi, S., Laurent, S., et al. (2012). Toxicity of nanomaterials. *Chemical Society Reviews, 41*(6), 2323–2343.

24. Madani, S. Y., Mandel, A., & Seifalian, A. M. (2013). A concise review of carbon nanotube's toxicology. *Nano Reviews, 4*(1), 21521.

25. Singh, R., Pantarotto, D., Lacerda, L., et al. (2006). Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers. *Proceedings of the National Academy of Sciences, 103*(9), 3357–3362.

26. Clark, A. (2002). Formulation of proteins and peptides for inhalation. *Drug Delivery System Sciences, 2*, 73–77.

27. Courrier, H. M., Butz, N., & Vandamme, T. F. (2002). Pulmonary drug delivery systems: Recent developments and prospects. *Critical Reviews in Therapeutic Drug Carrier Systems, 19*(4–5), 425–498.

28. Gill, S., Löbenberg, R., Ku, T., et al. (2007). Nanoparticles: Characteristics, mechanisms of action, and toxicity in pulmonary drug delivery—A review. *Journal of Biomedical Nanotechnology, 3*(2), 107–119.

29. Patton, J. S., & Platz, R. M. (1992). (D) Routes of delivery: Case studies: (2) Pulmonary delivery of peptides and proteins for systemic action. *Advanced Drug Delivery Reviews, 8*(2–3), 179–196.

30. Ashbaugh, D., Bigelow, D. B., Petty, T., et al. (1967). Acute respiratory distress in adults. *The Lancet, 290*(7511), 319–323.

31. Murray, J. F., Matthay, M. A., Luce, J. M., et al. (1988). An expanded definition of the adult respiratory distress syndrome. *The American Review of Respiratory Disease, 138*(3), 720–723.

32. Bernard, G. R., Artigas, A., Brigham, K. L., et al. (1994). The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *American Journal of Respiratory and Critical Care Medicine, 149*(3), 818–824.

33. Abraham, E., Matthay, M. A., Dinarello, C. A., et al. (2000). Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: Time for a reevaluation. *Critical Care Medicine, 28*(1), 232–235.

34. Rubenfeld, G. D., Caldwell, E., Peabody, E., et al. (2005). Incidence and outcomes of acute lung injury. *The New England Journal of Medicine, 353*(16), 1685–1693.

35. Liu, M., Zhang, H., & Slutsky, A. S. (2009). Acute lung injury: A yellow card for engineered nanoparticles? *Journal of Molecular Cell Biology, 1*(1), 6–7.

36. Abel, S. J. C., Finney, S. J., Brett, S. J., et al. (1998). Reduced mortality in association with the acute respiratory distress syndrome (ARDS). *Thorax, 53*(4), 292–294.

37. Milberg, J. A., & Steinberg, M. D. (1995). Respiratory Distress Syndrome (ARDS): 1983–1993. *Journal of the American Medical Association, 273*, 306–309.

38. McVey, M., Tabuchi, A., & Kuebler, W. M. (2012). Microparticles and acute lung injury. *American Journal of Physiology. Lung Cellular and Molecular Physiology, 303*(5), L364–L381.

39. Tsushima, K., King, L. S., Aggarwal, N. R., et al. (2009). Acute lung injury review. *Internal Medicine, 48*(9), 621–630.

40. Mura, M., Andrade, C. F., Han, B., et al. (2007). Intestinal ischemia-reperfusion-induced acute lung injury and oncotic cell death in multiple organs. *Shock, 28*(2), 227–238.

41. Maniatis, N. A., Kotanidou, A., Catravas, J. D., et al. (2008). Endothelial pathomechanisms in acute lung injury. *Vascular Pharmacology, 49*(4–6), 119–133.

42. Matthay, M. A., & Zimmerman, G. A. (2005). Acute lung injury and the acute respiratory distress syndrome: Four decades of inquiry into pathogenesis and rational management. *American Journal of Respiratory Cell and Molecular Biology, 33*(4), 319–327.

43. Ware, L. B. (2006). Pathophysiology of acute lung injury and the acute respiratory distress syndrome. *Seminars in Respiratory and Critical Care Medicine, 27*(4), 337–349.

44. Ware, L. B., & Matthay, M. A. (2000). The acute respiratory distress syndrome. *The New England Journal of Medicine, 342*(18), 1334–1349.

45. Bastarache, J. A., Ware, L. B., & Bernard, G. R. (2006). The role of the coagulation cascade in the continuum of sepsis and acute lung injury and acute respiratory distress syndrome. *Seminars in Respiratory and Critical Care Medicine, 27*(4), 365–376.

46. Schwarz, M. I., & Albert, R. K. (2004). "Imitators" of the ARDS*: Implications for diagnosis and treatment. *Chest, 125*(4), 1530.

47. Grenha, A., Seijo, B., & Remunán-López, C. (2005). Microencapsulated chitosan nanoparticles for lung protein delivery. *European Journal of Pharmaceutical Sciences, 25*(4–5), 427–437.

48. Edwards, D. A., Hanes, J., Caponetti, G., et al. (1997). Large porous particles for pulmonary drug delivery. *Science, 276*(5320), 1868–1872.

49. Oh, Y. J., Lee, J., Seo, J. Y., et al. (2011). Preparation of budesonide-loaded porous PLGA microparticles and their therapeutic efficacy in a murine asthma model. *Journal of Controlled Release, 150*(1), 56–62.

50. Wernig, K., Griesbacher, M., Andreae, F., et al. (2008). Depot formulation of vasoactive intestinal peptide by protamine-based biodegradable nanoparticles. *Journal of Controlled Release, 130*(2), 192–198.

51. Zahoor, A., Sharma, S., & Khuller, G. K. (2005). Inhalable alginate nanoparticles as antitubercular drug carriers against experimental tuberculosis. *International Journal of Antimicrobial Agents, 26*(4), 298–303.

52. Azarmi, S., Tao, X., Chen, H., et al. (2006). Formulation and cytotoxicity of doxorubicin nanoparticles carried by dry powder aerosol particles. *International Journal of Pharmaceutics, 319*(1–2), 155–161.

53. Karra, N., Nassar, T., Ripin, A. N., et al. (2013). Antibody conjugated PLGA nanoparticles for targeted delivery of paclitaxel palmitate: Efficacy and biofate in a lung cancer mouse model. *Small, 9*(24), 4221–4236.

54. Zhang, L., Gu, F. X., Chan, J. M., et al. (2008). Nanoparticles in medicine: Therapeutic applications and developments. *Clinical Pharmacology and Therapeutics, 83*(5), 761–769.

55. Müller, R. H., MaÈder, K., & Gohla, S. (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery—A review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics, 50*(1), 161–177.

56. Joshi, M., & Misra, A. (2001). Pulmonary disposition of budesonide from liposomal dry powder inhaler. *Methods and Findings in Experimental and Clinical Pharmacology, 23*(10), 531–536.

57. Yamamoto, H., Kuno, Y., Sugimoto, S., et al. (2005). Surface-modified PLGA nanosphere with chitosan improved pulmonary delivery of calcitonin by mucoadhesion and opening of the intercellular tight junctions. *Journal of Controlled Release, 102*(2), 373–381.

58. Amoozgar, Z., & Yeo, Y. (2012). Recent advances in stealth coating of nanoparticle drug delivery systems. *Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology, 4*(2), 219–233.

59. Yuan, H., Chen, C.-Y., Chai, G., et al. (2013). Improved transport and absorption through gastrointestinal tract by PEGylated solid lipid nanoparticles. *Molecular Pharmaceutics, 10*(5), 1865–1873.

60. Monopoli MP, \AAberg C, Salvati A, et al. 2012. Biomolecular coronas provide the biological identity of nanosized materials. Nature Nanotechnology 7(12):779

61. Schleh, C., & Hohlfeld, J. M. (2009). Interaction of nanoparticles with the pulmonary surfactant system. *Inhalation Toxicology, 21*(sup1), 97–103.

62. Kendall, M., Ding, P., Mackay, R.-M., et al. (2013). Surfactant protein D (SP-D) alters cellular uptake of particles and nanoparticles. *Nanotoxicology, 7*(5), 963–973.

63. Zhao, H., Zeng, Z., Liu, L., et al. (2018). Polydopamine nanoparticles for the treatment of acute inflammation-induced injury. *Nanoscale, 10*(15), 6981–6991.

64. Li, N., Weng, D., Wang, S.-M., et al. (2017). Surfactant protein-A nanobody-conjugated liposomes loaded with methylprednisolone increase lung-targeting specificity and therapeutic effect for acute lung injury. *Drug Delivery, 24*(1), 1770–1781.

65. Grimm, J. C., Zhang, F., Magruder, J. T., et al. (2017). Accumulation and cellular localization of nanoparticles in an ex vivo model of acute lung injury. *The Journal of Surgical Research, 210*, 78–85.

66. Pápay, Z. E., Kósa, A., Böddi, B., et al. (2017). Study on the pulmonary delivery system of apigenin-loaded albumin nanocarriers with antioxidant activity. *Journal of Aerosol Medicine and Pulmonary Drug Delivery, 30*(4), 274–288.

67. Muralidharan, P., Hayes, D., Black, S. M., et al. (2016). Microparticulate/nanoparticulate powders of a novel Nrf2 activator and an aerosol performance enhancer for pulmonary delivery targeting the lung Nrf2/Keap-1 pathway. *Molecular Systems Design and Engineering, 1*(1), 48–65.

68. Xu, Y., Xiang, J., Zhao, H., et al. (2016). Human amniotic fluid stem cells labeled with upconversion nanoparticles for imaging-monitored repairing of acute lung injury. *Biomaterials, 100*, 91–100.

69. Ravikumar, P., Menon, J. U., Punnakitikashem, P., et al. (2016). Nanoparticle facilitated inhalational delivery of erythropoietin receptor cDNA protects against hyperoxic lung injury. *Nanomedicine: Nanotechnology, Biology and Medicine, 12*(3), 811–821.

70. Lin, E.-H., Chang, H.-Y., Yeh, S.-D., et al. (2013). Polyethyleneimine and DNA nanoparticles-based gene therapy for acute lung injury. *Nanomedicine: Nanotechnology, Biology and Medicine, 9*(8), 1293–1303.

71. Shrestha, R., Shen, Y., Pollack, K. A., et al. (2012). Dual peptide nucleic acid-and peptide-functionalized shell cross-linked nanoparticles designed to target mRNA toward the diagnosis and treatment of acute lung injury. *Bioconjugate Chemistry, 23*(3), 574–585.

72. Chow, A. H., Tong, H. H., Chattopadhyay, P., et al. (2007). Particle engineering for pulmonary drug delivery. *Pharmaceutical Research, 24*(3), 411–437.

73. Malcolmson, R. J., & Embleton, J. K. (1998). Dry powder formulations for pulmonary delivery. *Pharmaceutical Science & Technology Today, 1*(9), 394–398.

74. Ely, L., Roa, W., Finlay, W. H., et al. (2007). Effervescent dry powder for respiratory drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics, 65*(3), 346–353.

75. Bosquillon, C., Lombry, C., Preat, V., et al. (2001). Influence of formulation excipients and physical characteristics of inhalation dry powders on their aerosolization performance. *Journal of Controlled Release, 70*(3), 329–339.

76. Carvalho, T. C., Peters, J. I., & Williams, R. O., III. (2011). Influence of particle size on regional lung deposition—What evidence is there? *International Journal of Pharmaceutics, 406*(1–2), 1–10.

77. Niven, R. W. (1995). Delivery of biotherapeutics by inhalation aerosol. *Critical Reviews in Therapeutic Drug Carrier Systems, 12*(2–3), 151–231.

78. Tsapis, N., Bennett, D., Jackson, B., et al. (2002). Trojan particles: Large porous carriers of nanoparticles for drug delivery. *Proceedings of the National Academy of Sciences, 99*(19), 12001–12005.

79. Heyder, J., Gebhart, J., Rudolf, G., et al. (1986). Deposition of particles in the human respiratory tract in the size range 0.005–15 μm. *Journal of Aerosol Science, 17*(5), 811–825.

80. Sham, J. O.-H., Zhang, Y., Finlay, W. H., et al. (2004). Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung. *International Journal of Pharmaceutics, 269*(2), 457–467.

81. Kawashima, Y., Serigano, T., Hino, T., et al. (1998). A new powder design method to improve inhalation efficiency of pranlukast hydrate dry powder aerosols by surface modification with hydroxypropylmethylcellulose phthalate nanospheres. *Pharmaceutical Research, 15*(11), 1748–1752.

82. Kawashima, Y., Yamamoto, H., Takeuchi, H., et al. (1999). Pulmonary delivery of insulin with nebulized DL-lactide/glycolide copolymer (PLGA) nanospheres to prolong hypoglycemic effect. *Journal of Controlled Release, 62*(1–2), 279–287.

83. Azarmi, S., Roa, W. H., & Löbenberg, R. (2008). Targeted delivery of nanoparticles for the treatment of lung diseases. *Advanced Drug Delivery Reviews, 60*(8), 863–875.

84. Dailey, L. A., Kleemann, E., Wittmar, M., et al. (2003). Surfactant-free, biodegradable nanoparticles for aerosol therapy based on the branched polyesters, DEAPA-PVAL-g-PLGA. *Pharmaceutical Research, 20*(12), 2011–2020.

85. McConville, J. T., Overhoff, K. A., Sinswat, P., et al. (2006). Targeted high lung concentrations of itraconazole using nebulized dispersions in a murine model. *Pharmaceutical Research, 23*(5), 901–911.

86. Vaughn, J. M., McConville, J. T., Burgess, D., et al. (2006). Single dose and multiple dose studies of itraconazole nanoparticles. *European Journal of Pharmaceutics and Biopharmaceutics, 63*(2), 95–102.

87. Pandey, R., Sharma, A., Zahoor, A., et al. (2003). Poly (DL-lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. *The Journal of Antimicrobial Chemotherapy, 52*(6), 981–986.

88. Sharma, A., Sharma, S., & Khuller, G. K. (2004). Lectin-functionalized poly (lactide-co-glycolide) nanoparticles as oral/aerosolized antitubercular drug carriers for treatment of tuberculosis. *The Journal of Antimicrobial Chemotherapy, 54*(4), 761–766.

89. Saez, A., Guzman, M., Molpeceres, J., et al. (2000). Freeze-drying of polycaprolactone and poly (D,L-lactic-glycolic) nanoparticles induce minor particle size changes affecting the oral pharmacokinetics of loaded drugs. *European Journal of Pharmaceutics and Biopharmaceutics, 50*(3), 379–387.

90. Wendorf, J., Singh, M., Chesko, J., et al. (2006). A practical approach to the use of nanoparticles for vaccine delivery. *Journal of Pharmaceutical Sciences, 95*(12), 2738–2750.

91. Li, C., Liu, H., Sun, Y., et al. (2009). PAMAM nanoparticles promote acute lung injury by inducing autophagic cell death through the Akt-TSC2-mTOR signaling pathway. *Journal of Molecular Cell Biology, 1*(1), 37–45.

92. Card, J. W., Zeldin, D. C., Bonner, J. C., et al. (2008). Pulmonary applications and toxicity of engineered nanoparticles. *American Journal of Physiology. Lung Cellular and Molecular Physiology, 295*(3), L400–L411.

93. Elder, A., Gelein, R., Silva, V., et al. (2006). Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environmental Health Perspectives, 114*(8), 1172.

94. Kreyling, W. G., Semmler, M., Erbe, F., et al. (2002). Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low. *Journal of Toxicology and Environmental Health. Part A, 65*(20), 1513–1530.

95. Oberdörster, G., Sharp, Z., Atudorei, V., et al. (2002). Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. *Journal of Toxicology and Environmental Health. Part A, 65*(20), 1531–1543.

96. Borm, P. J., & Kreyling, W. (2004). Toxicological hazards of inhaled nanoparticles—Potential implications for drug delivery. *Journal of Nanoscience and Nanotechnology, 4*(5), 521–531.

97. Hoet, P. H., Brüske-Hohlfeld, I., & Salata, O. V. (2004). Nanoparticles – Known and unknown health risks. *Journal of Nanobiotechnology, 2*(1), 12.

98. Oberdörster, G., Oberdörster, E., & Oberdörster, J. (2005). Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. *Environmental Health Perspectives, 113*(7), 823.
99. Warheit, D. B., Webb, T. R., Reed, K. L., et al. (2007). Pulmonary toxicity study in rats with three forms of ultrafine-TiO$_2$ particles: Differential responses related to surface properties. *Toxicology, 230*(1), 90–104.
100. Dailey, L. A., Jekel, N., Fink, L., et al. (2006). Investigation of the proinflammatory potential of biodegradable nanoparticle drug delivery systems in the lung. *Toxicology and Applied Pharmacology, 215*(1), 100–108.
101. Warheit, D. B., Laurence, B. R., Reed, K. L., et al. (2004). Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats. *Toxicological Sciences, 77*(1), 117–125.
102. Shvedova, A. A., Murray, A. R., Kisin, E. R., et al. (2003). Exposure to carbon nanotube material: Evidence of exposure-induced oxidant stress in human keratinocyte and bronchial epithelial cells.