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Nanomedicine for the management of lung and blood diseases

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Abstract

Nanotechnology provides a broad range of opportunities to develop new solutions for clinical problems. For the pulmonary field, nanotechnology promises better delivery of drugs and nucleic acid-based therapeutics to disease sites. Administration of therapeutics via inhalation provides the opportunity for direct delivery to the lung epithelium, the lining of the respiratory tract. By appropriate selection of particle size, deep lung delivery can be obtained with control of phagocytic uptake, the removal of particles by resident macrophages. Nanotechnology can also help in pulmonary therapies administered by intravenous and oral routes through targeting specific cell types and controlling bioavailability and release kinetics. In the hematology field, nanotechnology can counter multiple drug resistance in leukemia by blocking drug efflux from cancer cells, and provide effective delivery of siRNA into lymphocytes to block apoptosis in sepsis. Controlling the surface properties of materials on devices such as valves and stents promises improved biocompatibility by inhibition of thrombosis, the formation of blood clots, and regulating cell adhesion and activation. Nanoparticle-based thrombolytic agents have the potential to improve the effectiveness of clot removal. Treatment of both lung and blood diseases is also likely to benefit from nano-scaffold-based methods for controlling the differentiation and proliferation of stem and progenitor cells.

Keywords

drug delivery; gene therapy; hematopoietic; nanoparticle; pulmonary; thrombosis

The application of nanotechnology to solve clinical problems is still in its infancy. Pulmonary disease exerts a huge toll on the global population in terms of morbidity and mortality, as well as economically. Blood diseases also offer unique opportunities for the application of nanotechnology. This review focuses on some of the emerging nanotechnology solutions being pursued for the treatment of pulmonary and blood diseases.

Pulmonary diseases

Therapeutic delivery to the lung

Therapy can be delivered to the lungs by inhalation, intravenous and oral routes, and nanotechnology is being employed to help in all three approaches. The lung has a

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considerable absorptive surface area (140 m^2 [1]), reflecting the large number of alveolae, the hollow air sacs that terminate the respiratory tree. This large surface area makes inhalation therapy an attractive therapeutic route for treatment of both pulmonary and systemic diseases [1]. Inhalation delivery of nanoscale particles has been comprehensively reviewed recently [2–6], and so only a few main points will be summarized here. The principal mechanisms of particle deposition in the respiratory tract depend on particle size; for larger particles, impaction and sedimentation are important, but for nanoparticles less than 160 nm in diameter, diffusion represents the principal mechanism [2]. Following deposition in lung fluid, mucus within the airways or surfactant in the alveolae, relatively insoluble material is removed, while material more soluble in body fluids will enter the blood circulation [2,5]. In the airways, clearance of insoluble material is carried out by cilia, hair-like structures on the epithelial cells, which move the particles towards the mouth, while in the alveolae, macrophages, the cells responsible for defending the lung from microorganisms, take up the particles. Phagocytic clearance is dependent on particle size, with 1–3 μm particles being cleared most rapidly and smaller particles more slowly. Delivery platforms include; nebulizers, which can dispense both solid residues and suspension formulations; pressurized metered-dose inhalers, which can be used for a range of nanoparticle solutions and emulsions; and dry particle inhalers, which are generally used to deliver nanoparticles as part of larger microscale particles such as ‘trojan particles’ or ‘strawberry particles’ [3]. Because of their size, nanoparticles have low inertia and tend to be lost from the lung during exhalation; incorporation of nanoparticles into larger and heavier particles can reduce this nanoparticle loss [7].

Drug delivery to the lung

Chronic lung infections can be difficult to treat owing to difficulties in getting therapeutic quantities of antibiotic to the site of infection [8]. To address this problem, inhalational delivery of a variety of antimicrobial agents is being explored. The antibiotic ciprofloxacin has been formulated into nanoparticles and encapsulated into poly(D,L-lactic-co-glycolic acid) (PLGA) microparticles ranging in size from 5 to 27 μm to facilitate inhalational delivery into the deep lung and avoid macrophage clearance [8]. *In vitro* experiments show steady release of drug over 2–4 weeks depending on microparticle size and structure. Further development of this technology to provide sustained release of ciprofloxacin in the deep lung may prove beneficial in treating a range of pulmonary bacterial infections [8].

Pulmonary aspergillosis, an opportunistic fungal infection of the lungs, is a leading cause of mortality in patients undergoing hematopoietic stem cell transplantation or with hematologic malignancies, and therapy is often limited by toxicity to the kidneys and lungs, and by drug interactions [9]. In a mouse model of pulmonary aspergillosis, Alvarez *et al.* compared nanostructured itraconazole, prepared by spray freezing into liquid and delivered by nebulizer, with oral delivery of liquid itraconazole as a prophylaxis against invasive pulmonary aspergillosis [9]. Aerosol delivery improved survival and limited invasive disease of small airways [9], meriting further investigation to optimize dosing strategies.

Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (CFTR), affects multiple organs, but pulmonary disease manifestations are the most

common cause of death. Imbalanced water and ion movements across the airway epithelium lead to thickened mucus, chronic bacterial infection and inflammation, resulting in progressive loss of pulmonary function [10]. Infections with *Pseudomonas aeruginosa* are common and can be particularly challenging because they grow in biofilms [11]. When the antibiotic amikacin was encapsulated in a nanoscale liposomal formulation of dipalmitoyl phosphatidylcholine and cholesterol, the liposomes were shown to penetrate readily into *P. aeruginosa* biofilms and infected mucus, while micron-sized beads did not [11]. Amikacin was actively released from the liposomes by rhamnolipids, biosurfactants produced by the *P. aeruginosa* biofilm. In rat lungs, inhaled liposomal amikacin was released in a slow, sustained manner, and was orders of magnitude more effective than free amikacin in a rat model of *P. aeruginosa* lung infection [11]. Transave Inc. have completed a Phase II clinical trial of nebulized liposomal amikacin (Arikace™) in Europe [101], and are currently recruiting for a Phase lb/IIa safety and tolerability study of Arikace in the USA [102]. A similar trial is also being carried out in non-CF patients with bronchiectasis, a chronic disorder of the major bronchi and bronchioles characterized by permanent dilation, microbial infection and persistent inflammatory response, with the release of immune mediators and microbial toxins leading to airway destruction [103].

Inhalational delivery of chemotherapy for lung cancer offers the opportunity for direct delivery of drugs to the cancer cells, achieving higher pulmonary concentrations with a lower dose. In a mouse model, Tseng *et al.* tested targeting of gelatin nanoparticles decorated with EGF to a human adenocarcinoma that overexpresses the EGF receptor [12]. The nebulized nanoparticles formed 0.5–5 μm aggregates suitable for delivery into the lower airway. EGF-targeted nanoparticles were shown to accumulate preferentially in tumor-carrying lungs relative to normal lungs, and colocalized histologically with the EGF receptor (FIGURE 1). These proof-of-principle studies support the potential of targeted chemotherapy delivery via aerosol delivery for treatment of lung cancers [12].

Nanotechnology is also being applied to improve intravenous and oral drug delivery to the lung, including packaging the antimitotic drug paclitaxel for the treatment of lung cancer and other solid tumors [13]. Paclitaxel is poorly soluble, and so is dissolved in Cremophor, a castor oil derivative, and marketed as Taxol® by Bristol-Myers Squibb. However, Cremophor causes hypersensitivity, requiring pretreatment with steroids or antihistamines and slow intravenous infusion of the drug. Packaging paclitaxel into 130-nm albumin nanoparticles avoids the hypersensitivity issue and other Cremophor-related complications, and allows faster infusion. This formulation is marketed by Abraxis Bioscience under the trade name Abraxane®. Albumin-bound paclitaxel has been shown to have superior antitumor activity, possibly reflecting increased uptake of albumin in tumors through the extracellular matrix glycoprotein SPARC, and is also better tolerated, allowing higher dosing [13]. A recent Phase I/II clinical trial in patients with stage IV non-small-cell lung cancer using Abraxane as initial chemotherapy showed the formulation to be well tolerated with encouraging single-agent activity [14]. A number of additional early-phase clinical trials using Abraxane in combination with other chemotherapeutics are now underway.

As an example of packaging for oral administration, TB and other mycobacterial infections represent an attractive target for nanotechnology-based therapy; treatment of TB typically

requires months of daily drug combination treatments, resulting in poor compliance and, frequently, treatment failure [15]. Encapsulation of drugs into nanoparticles offers the potential for controlled and sustained delivery of drugs, which in turn may reduce the frequency of dosing required. Johnson *et al.* compared the efficacy of a three-drug cocktail (rifampin, isoniazid and pyrazinamide) loaded into poly(D,L-lactic-co-glycolide) (PLG) nanoparticles with nonen-capsulated drugs [15]. In a guinea pig model of TB, they found that oral administration of the three-drug PLG nanoparticles every 10 days reduced bacterial count and lung histopathology to a similar extent as daily dosing of the nonen-capsulated drugs, supporting the feasibility of intermittent dosing with nanoparticle formulations of TB drugs. Similarly, in a mouse model of TB, following a single oral dose of drug-loaded PLG nanoparticles, therapeutic concentrations of econazole and moxiflozacin were found in the lung, liver and spleen 6 days later [16]. Weekly administration of encapsulated moxiflozacin or econazole was as effective as daily administration of moxiflozacin or twice-daily administration of econazole in reducing bacterial loads in the lung, liver and spleen after 8 weeks. Similarly, the increased effectiveness of combination therapy with the two nonencapsulated drugs on the same dosing schedules was matched by weekly administration of the two drugs encapsulated in nanoparticles. Finally, the addition of encapsulated rifampicin every 2 weeks to the encapsulated two-drug regimen resulted in total bacterial clearance after 8 weeks, comparable to a standard nonencapsulated four-drug regimen given daily [16].

Nucleic acid delivery to the lung

A broad range of nanoparticle formulations are being tested for delivery of vectors and siRNA to modulate pulmonary disease processes. These include biodegradable polyester nanoparticles [17], modified chitosan nanocomplexes [18] and cationic liposomes [10]. While CP has been an attractive target for gene therapy, clinical trials have shown first-generation vectors to be ineffective [19]. In order to treat CF, there is a need for synthetic vectors that can transfect airway epithelial cells specifically, rather than alveolar airway cells or macrophages. Nonimmunogenicity is another requirement, permitting repeated delivery without eliciting immune responses [10]. Tagalakis *et al.* have developed a second-generation vector containing cationic liposomes and a cationic peptide, K16GACSERSMNFCG, which targets ICAM-1 [10]. The vector preferentially targets airway epithelial cells in mice *in vivo*, was effective on repeat dosing and is effectively delivered with a nebulizer. Delivery of nanoparticles containing a human CFTR plasmid to mouse lung resulted in expression of human CFTR in the lungs [10], supporting the potential of this approach for CF gene therapy.

siRNA is being pursued as a therapeutic agent for a broad range of diseases because of its high specificity, high efficiency and low toxicity. However, efficient delivery of siRNA to the target can be challenging. The lung is a common site of tumor metastasis, and despite aggressive surgical resection the relapse rate is high and response to chemotherapy poor. To address the need for new therapies, Li *et al.* developed nanoparticles self-assembled from siRNA, a DNA carrier, poly-cationic peptide and cationic liposome [20]. The nanoparticles were targeted to the sigma receptor of B16F10 metastatic tumor by modification with the targeting ligand, anisamide, conjugated to pegylated lipid [20]. Feasibility studies in a

mouse lung metastasis model showed that intravenous injection of a low dose of antiluciferase siRNA could silence 70–80% of luciferase activity in metastatic tumors stably transfected with the luciferase gene [20]. In the same model, a mixture of siRNAs targeted to the oncogenes *mdm2* and *c-myc* and to the VEGF gene *vegf* effectively reduced expression of the three target proteins when delivered in targeted nanoparticles, while nontargeted nanoparticles and free siRNA were ineffective [21]. This was reflected in a 70–80% reduction in metastasis after two intravenous injections of targeted nanoparticles, and a 30% increase in survival time compared with untreated controls [21].

A Phase I clinical trial testing safety, efficacy and maximum tolerated dose of an intravenous nanoparticle-based siRNA treatment for lung and other solid tumors is now recruiting patients [104]. The siRNA used inhibits expression of the M2 subunit of ribonucleotide reductase, an enzyme essential for DNA replication and hence cell proliferation. The nanoparticles are formulated using the three-part RONDEL technology developed by Calando Inc., which combines a cyclodextrin polymer, an adamantine-modified stabilizer, and an adamantine-modified ligand targeted to the transferrin receptor on cancer cells [22]. Multiple systemic doses of these targeted nanoparticles were tested in nonhuman primates and shown to be safe [22].

The use of siRNA for prophylaxis against respiratory syncytial virus (RSV) is also being explored [18]. RSV is a major cause of lower respiratory tract infections in infants and in immunodeficient or elderly adults. In addition to the short-term morbidity and mortality associated with RSV infections, infant RSV infection is a predisposing factor for the development of asthma later in life. However, there is no commercially available vaccine against RSV. Kong *et al.* employed siRNA to the *RSV-NS1* gene, which is critical for *in vivo* replication of RSV, as a prophylactic treatment in rats. The siRNA was complexed to modified chitosan nanoparticles and administered intranasally. They found that the siRNA was effective in reducing viral titer in the lung, and prevented the inflammation and airway hyper-responsiveness associated with the infection (Figure 2), factors associated with subsequent development of asthma [18].

Magnetofection

In a novel use of nanotechnology to improve targeting to specific lung regions, Dames *et al.* used a targeted magnetic field to direct an aerosol of superparamagnetic iron oxide nanoparticles preferentially to one lung lobe in a murine model [23]. They were able to achieve as much as an eightfold increase in particle delivery to the target lung relative to the nontarget lung. The aerosol technology is very flexible, allowing ready adjustment of drug dose, and delivery of multiple drugs with different formulations simultaneously. While scaling-up to the human lung poses significant technical challenges, this technology has the potential for providing localized therapy to a small lung area.

Blood diseases

Leukemia

The treatment of hematological cancers such as leukemia has improved dramatically in recent years, but problems such as metastasis and development of multidrug resistance (MDR) can decrease treatment efficacy. To address the issue of MDR, Sharma *et al.* have developed a formulation of doxorubicin in polymeric nanomicelles containing the block polymer Pluronic P85 [24]. P85 inhibits the P-glycoprotein drug efflux system, responsible for the energy-dependent transport of drugs out of cancer cells. The investigators demonstrated that the nanoformulation of doxorubicin with P85 was effective in preventing the development of MDR in leukemia cells *in vitro* and *in vivo* in mice, and that the formulation prevented drug-dependent alterations in a number of genes associated with MDR [24].

The formulation of gemcitabine into nanoparticles by conjugation to squalene and self-assembly in water has also shown promise in improving drug efficacy against leukemia in mice [25,26]. In this case, the mechanisms are believed to be the protection of the drug against deamination, and also improved intracellular pharmacokinetics and retention [27]. The squalene–gemcitabine formulation was shown to be much more potent than free gemcitabine at equitoxic doses in leukemia-bearing rats, and also more effective than cytarabine [27].

Sepsis

Sepsis, an overwhelming infection of the blood-stream by toxin-producing bacteria, remains the leading cause of death in intensive care units; the majority of deaths occur late in the course of sepsis and frequently reflect failure to clear the primary infection or the development of hospital-acquired infections [28]. Large numbers of lymphocytes and dendritic cells, key components of the immune response, are lost through activation of multiple apoptotic (or programmed cell death) pathways in sepsis, hampering immune responses. The use of siRNA to reduce expression of proteins in these apoptotic pathways has the potential to reduce immune cell apoptosis and preserve immune responses, but effective delivery of siRNA to lymphocytes is challenging. Schwulst *et al.* have used the Calando RONDEL technology described earlier for targeting lung cancer with siRNA, but in this case the siRNA is directed towards Bim, a key cell death protein upregulated in sepsis [28]. In a mouse model of sepsis, they showed that treatment with Bim siRNA effectively reduced Bim expression in B and T lymphocytes, blocked lymphocyte apoptosis in spleen and thymus, and improved survival.

Thrombosis & thrombolysis

Thrombosis and thrombolysis, the formation and lysis of blood clots, represent two inter-related areas where nanotechnology is expected to play a role. Thrombosis remains a significant problem for implanted blood-contacting medical devices such as mechanical valves [29] and ventricular assist devices [30]. One approach to making mechanical valves less thrombogenic is to use nanocrystalline thin film surface coatings with materials such as titanium dioxide, which are expected to have superior thrombogenic properties compared

with the pyrolytic carbon typically used in mechanical heart valves [31]. Nanocomposite materials, such as the polymer polyhedral oligomeric silsesquioxane poly(carbonate-urea)urethane, are also being studied as materials for heart valves, bringing a combination of good surface properties and mechanical strength [29]. A third option for avoiding the thrombogenicity of current mechanical heart valves is the use of biopros-thetic valves from pig or human sources, but these suffer from limited durability [32]. Tissue-engineered valves may be able to offer better durability as well as low thrombogenicity [32], and nanotechnology provides new opportunities for scaffold materials with desired physical properties that can also be modified to supply growth factors and cytokines.

At a more basic level, the nanotexture of surfaces affects key determinates of coagulation, platelet adhesion and activation [33], and complement activation [34]. Using nanoporous alumina membranes with 20 or 200 nm diameters, Ferraz *et al.* showed that the smaller pore size led to platelet activation and spreading, but no platelet microparticle generation. By contrast, the results obtained with the larger pore size were consistent with only transient nonadherent platelet contact, resulting in abundant microparticle generation. The larger pore size also resulted in significantly more complement activation and binding of immunoglobulins and complement components to the surface [34]. These studies thus show that the nanoscale topography of blood-contacting surfaces can have significant impact on platelet reactivity and inflammatory responses.

The advent of thrombolytic therapy has had a major impact on the treatment of patients with acute myocardial infarction and ischemic stroke. However, in many cases reperfusion is ineffective, and most ischemic stroke patients do not receive thrombolytic therapy because of the danger of cerebral hemorrhage. Marsh *et al.* have developed nanoparticles targeted to fibrin to increase the effective dose of the plasminogen activator streptokinase at the blood clot and reduce systemic effects [35]. *In vitro* experiments with human plasma clots showed the targeted nanoparticles to be orders of magnitude more effective than the free drug in clot lysis [35].

Blood products: expansion & purification

The expansion of specific populations of hematopoietic stem or progenitor cells represents another area being explored. Chua *et al.* demonstrated that electrospun polymer nanofiber scaffolds functionalized with amine groups enhanced cell-substrate adhesion and *ex vivo* expansion of hematopoietic stem cells (Figure 3) [36,37]. Substrates promoting cell adhesion also enhanced the preservation of the $CD34^{+}CD45^{+}$ phenotype and the primitive characteristics of cord blood $CD34^{+}$ hematopoietic stem cells [37]. Advances in this area are also likely to impact the pulmonary field; the lung is formed from a complex mixture of progenitor cells [38], and nanosurface-based approaches may facilitate expansion of specific lung progenitor cell populations for regenerative therapies.

The removal of viruses from plasma and plasma products is essential to ensure their safety, but technologies such as pasteurization or dry-heat treatment may also lead to reduced biological activity of the desired product, or formation of neoantigens; denaturation of the product can expose antigens that are normally buried within the protein, leading to the generation of neutralizing antibodies that inhibit the blood product activity. Nanofilters with

pore sizes in the 15–20 nm range manufactured from cuprammonium-regenerated cellulose, modified polyvinylidene fluoride and nanostructured ceramics have proved effective in removing viruses from plasma products including factor VIII [39], factor IX [40] and immunoglobulin [41]. Products can be recovered with yields as high as 96% [40] and without significant loss of biological activity.

Nanoparticle toxicity

The potential for nanoparticles to cause pulmonary and systemic toxicity is well recognized [42,43]. The data available demonstrating toxicity largely represent materials that are not designed for *in vivo* use, such as carbon black, silica, metals and metal oxides, and carbon nanotubes [42,43], and so are of more immediate relevance to environmental and occupational exposures. For example, Poland *et al*. demonstrated that multiwalled carbon nanotubes injected into the abdominal cavity of mice resulted in pathlogical changes similar to those found in response to asbestos [44]. Engineered nanoparticles have also been shown to aggravate platelet aggregation *in vitro* and blood clotting in rats *in vivo*; mixed carbon nanoparticles and single-walled nanotubes had the greatest effect, followed by multiwalled carbon nanotubes, while fullerenes had no effect [45]. Li *et al*. have recently reviewed the effects of ambient particulate matter in causing pulmonary oxidative stress, and discuss the potential for engineered nanoparticles to cause human disease through proinflammatory mechanisms, but again the focus is primarily on environmental and occupational exposures [46].

Rigorous testing of any nanoparticle designed for clinical use will be essential, but comprehensive *in vivo* testing of all nanoparticles being developed is impractical. Shaw *et al*. recently described a high-throughput *in vitro* screening approach that may prove useful in testing nano-materials inexpensively early in the design process and eliminating structures that are likely to be problematic [47]. The screening employs multiple cell types and multiple assays reflecting different aspects of cellular physiology to provide a multidimensional characterization. The approach yielded robust and detailed structure-function relationships, and testing of a subset of nanomaterials in mice demonstrated that nanoparticles with similar profiles had similar effects on monocyte numbers [47]. Multidimensional *in vitro* screening methods may thus be beneficial in the initial design of nanoparticles, allowing materials with a high risk of toxicity to be identified early in the development process.

Future perspective

Several of the technologies described in this short review are already being applied clinically, and this number is likely to expand rapidly in coming years. For example, nanopore filters are already being used commercially to purify plasma proteins. A number of early-phase clinical trials are underway using nanotechnology to enhance drug delivery for lung cancer chemotherapy, and the use of siRNA as a treatment for lung cancer is also being tested in humans. Inhalational therapy using nanoparticles to treat chronic pulmonary infections in CF patients represents another area being tested clinically. Other pulmonary infections such as TB and fungal infections are likely to be pursued in future clinical studies.

Inflammatory diseases such as asthma and chronic obstructive pulmonary disease are also attractive targets for nanoparticle-based therapies. Table 1 summarizes representative clinical trials using nanoparticle-based therapy for the treatment of pulmonary diseases. Nanoparticle-based therapeutics also show promise in animal models of leukemia and sepsis. A rapid expansion of human studies for nanoparticle-based therapeutics can be expected in the next few years.

Nanoscale modification of surfaces to prevent thrombosis on stents and other devices represents a significant potential use of nanotechnology that is still in its infancy. Functionalized nano-scaf-folds show promise for the control of differentiation and proliferation of hematopoietic stem cells *in vitro,* and are also likely to be applied to the generation of specific lung progenitor cells for regenerative therapies. The potential of functionalized nano-scaffolds for *in vivo* lung regeneration has yet to be explored indepth, but the principal has been demonstrated for nerve [48] and myocardial regeneration [49] using peptides that self-assemble into nanofibers. The next 10 years are thus poised to see a rapid expansion of nanomedicine in the pulmonary and hematologic fields.

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Executive summary

Pulmonary therapeutic delivery

- Inhalation of nanoparticle-based therapeutics can provide direct access to all parts of the lung, with the potential to achieve better drug availability to the site of action. Delivery of both drugs and nucleic acid-based therapeutics is feasible.
- Nanotechnology can also improve lung drug availability for intravenous and oral administration by a variety of mechanisms including controlled release and targeted delivery.

Hematopoietic therapeutics

- Packaging leukemia chemotherapeutics into nanoparticles can improve efficacy by inhibiting drug efflux or protecting drugs from chemical modification.
- Nanoparticles can act as effective delivery vehicles to transport siRNA into lymphocytes to inhibit lymphocyte apoptosis in sepsis.

Nanoscale surfaces

- Surface modification at the nanoscale level can modify adhesion and activation of blood components, changing thrombogenicity of the surface.
- Functionalized nano-scaffolds show promise for controlling *in vitro* differentiation and proliferation of hematopoietic cells, and may have a similar role for lung progenitor cells.

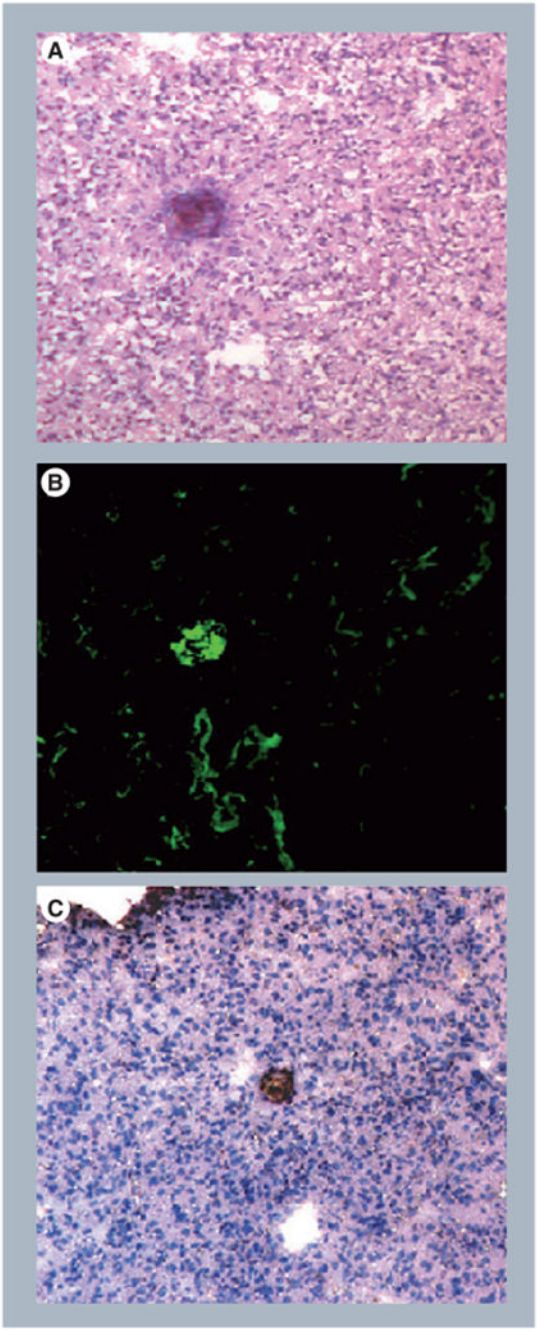

Figure 1. Targeting of nanoparticles to tumor EGF receptor.

(A) Hematoxylin and eosin staining shows a small nodule; (B) fluorescence staining of dye-conjugated nanoparticles (green) confirms localization to the nodule; (C) staining with anti-EGF receptor (EGFR; brown) demonstrates overexpression of EGFR in the same region. Reproduced from [12] with permission from Elsevier © (2008).

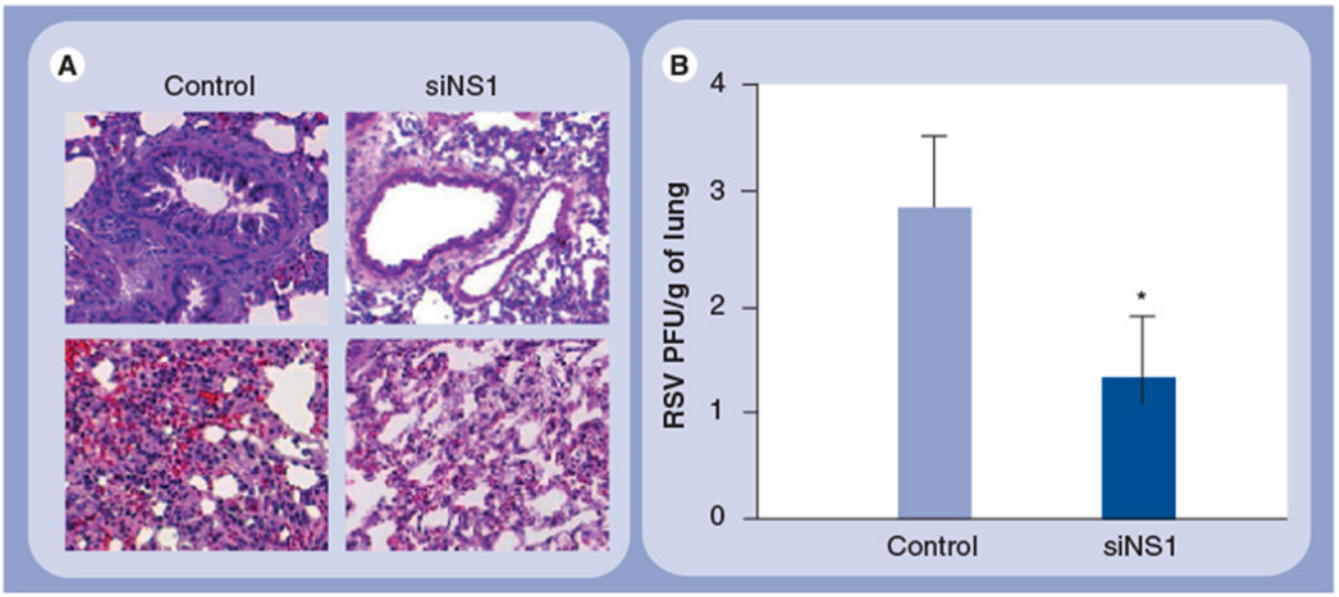

Figure 2. siNS1 prevents respiratory syncytial virus-induced lung pathology and reduces virus titer in the lung.

(A) siNS1 -treated rats show decreased bronchiolar goblet cell hyperplasia (top) and fewer infiltrating inflammatory cells (bottom). **(B)** RSV titer was reduced in lung homogenates. PFU: Plaque forming unit; RSV: Respiratory syncytial virus; siNS1: siRNA to the *RSV-NS1* gene.

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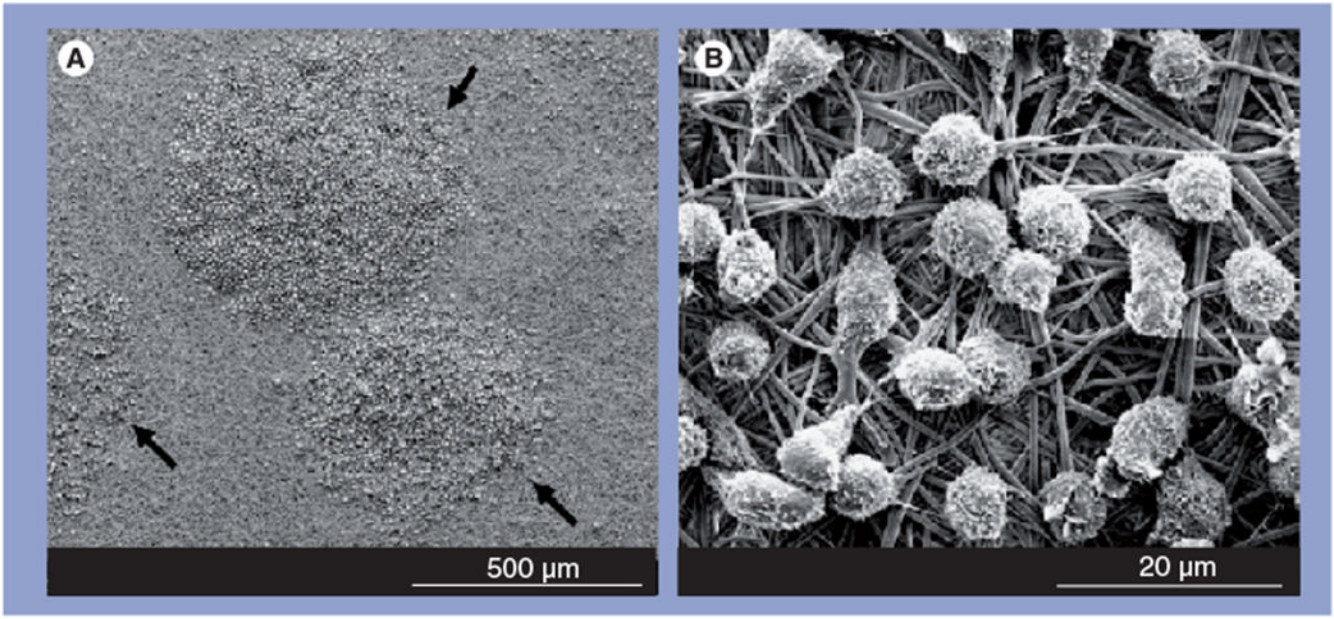

Figure 3. Scanning-electron microscope images of hematopoietic stem/progenitor cells after 8-day cultures on polyethersulfone 1,4-butanediamine nanofiber mesh.

(A) Cells proliferated to form circular colonies (black arrows) on the nanofiber surface, and **(B)** exhibited numerous filopodia, which were interacting with the aminated nanofibers. Reproduced from [37] with permission from Elsevier © (2007).

Table 1.

Nanoparticle therapeutics for pulmonary disease.

Disease	Therapeutic agent	Formulation	Administration	Ref.
Cystic fibrosis	Amicacin (antibiotic)	Liposomal	Inhalation	[102]
Bronchiectasis	Amicacin (antibiotic)	Liposomal	Inhalation	[103]
Non-small-cell lung cancer	Paclitaxel (chemotherapeutic)	Albumin nanoparticle	Intravenous	[14]
Lung and other solid tumor	siRNA (antiproliferative)	Cyclodextrin polymer/adamantine	Intravenous	[104]