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Surface-engineered smart nanocarrier-based inhalation formulations for targeted lung cancer chemotherapy: a review of current practices

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ABSTRACT

Lung cancer is the second most common and lethal cancer in the world. Chemotherapy is the preferred treatment modality for lung cancer and prolongs patient survival by effective controlling of tumor growth. However, owing to the nonspecific delivery of anticancer drugs, systemic chemotherapy has limited clinical efficacy and significant systemic adverse effects. Inhalation routes, on the other hand, allow for direct delivery of drugs to the lungs in high local concentrations, enhancing their antitumor activity with minimum side effects. Preliminary research studies have shown that inhaled chemotherapy may be tolerated with manageable adverse effects such as bronchospasm and cough. Enhancing the anticancer drugs deposition in tumor cells and limiting their distribution to other healthy cells will therefore increase their clinical efficacy and decrease their local and systemic toxicities. Because of the controlled release and localization of tumors, nanoparticle formulations are a viable option for the delivery of chemotherapeutics to lung cancers via inhalation. The respiratory tract physiology and lung clearance mechanisms are the key barriers to the effective deposition and preservation of inhaled nanoparticle formulations in the lungs. Designing and creating smart nanoformulations to optimize lung deposition, minimize pulmonary clearance, and improve cancerous tissue targeting have been the subject of recent research studies. This review focuses on recent examples of work in this area, along with the opportunities and challenges for the pulmonary delivery of smart nanoformulations to treat lung cancers.

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1. Introduction

Cancer has been one of the challenging health issues around the world. Global demographic statistics forecast rising incidences of cancer; new cases are expected to rise by almost 420 million per year by 2025 (Zugazagoitia et al., 2016). Similarly, in the USA, the number of new cases in 2017 was 1,688,780, and 600,920 deaths occurred due to cancer (Siegel et al., 2017). Global predictions show that 26 million new cases will occur, and 17 million people will die of lung cancer by 2030 (Bray et al., 2018). Lung cancer is the leading cause of death in both men and women all over the world (Barta et al., 2019). The American Cancer Society has so far predicted the diagnosis of about 228,820 new lung cancer cases in the USA in 2020, with 135,720 people expected to die from the disease (The American Cancer Society, 2021). Most forms of lung cancer (85%) are categorized as non-small cell lung cancer (NSCLC), while the rest are categorized as small cell lung cancer (SCLC) (Mangal et al., 2017).

Unfortunately, lung cancer is difficult to be identified in its early stages. At the time of diagnosis, most lung cancers are in advanced stages. The dominant cause of poor survival rates in patients with advanced-stage lung cancer is the metastatic spreading of cancer to surrounding tissues, with a 5-year survival rate of just 10% (Asamura et al., 2015; Kuribayashi et al., 2016; DeSantis et al., 2019; Arneth, 2020; Fares et al., 2020). For lung cancer, the most common metastatic sites include the liver, bone, adrenal glands, respiratory system, and nervous system (Riihimäki et al., 2014). The primary therapy for nonmetastatic lung cancers is surgical removal/resection. Therefore, this procedure can be performed only in 10–20% of NSCLC patients and is constrained by the location and number of lesions and the patient's respiratory and/or general conditions (Spiro & Porter, 2002; Rodríguez & Padellano, 2007). Chemotherapy is used to treat symptoms, prolong survival, and improve the life quality in lung cancer patients who are unable to undergo surgery (Board PATE, 2020; Chen et al., 2020; Katsurada et al., 2020; Takashima et al., 2020).

To achieve an effective concentration of drugs required for successful tumor killing, anticancer drugs must reach

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cancer tissues; however, suboptimal drug concentrations usuallyshow insufficient anti-tumor activity and cause additional drug resistance concerns (Al-Abd et al., 2020; He et al., 2020; Seynhaeve et al., 2020). Ultimately, intravenous administration allows a large proportion of chemotherapeutics to be uniformly dispersed in different tissues, resulting in substantially low concentrations of drugs at tumor sites. Therapeutically effective drug concentrations can be achieved at the diseased sites via administration of higher drug dosage. These high doses can have serious side effects, particularly at the locations of rapidly dividing cells which include skin, hair, liver, and spleen (Cheng et al., 2020). The compliance and efficacy of systemic chemotherapy against lung cancer are threatened by these toxicity problems (Schiller et al., 1996; Clegg et al., 2001; Mavroudis et al., 2002; Hosomi et al., 2011). Besides, subtypes of lung cancer can also be genetically complex, rendering treatment much more challenging. Many chemotherapeutic agents have low water solubility, which is another significant disadvantage for pulmonary delivery of anticancer drugs. Furthermore, the pulmonary epithelium's thinness results in short ingestion of the lung's inhaled substance and leads to systemic adverse effects (Kadam et al., 2014). Therefore, new therapeutic delivery modalities with improved safety and efficacy are highly needed.

Localized chemotherapy can directly deliver anticancer drugs to affected tumor tissues in high concentrations compared to other non-targeted sites. Effective chemotherapy via localized drug delivery has been documented for various types of cancer, including colorectal and ovarian cancers (Senapati et al., 2018; Liyanage et al., 2019; Pucci et al., 2019; Mazzotta et al., 2020; Yan et al., 2020). The administration of inhaled drugs enables the localization of delivered drugs directly in the lungs via the nasal or oral inhalation route. It has been shown that inhaled chemotherapy is effective for lung cancer (Patil & Sarasija, 2012; Cidem et al., 2020; Hickey, 2020; Jin et al., 2020; Mishra & Singh, 2020; Yıldız-Peköz & Ehrhardt, 2020). Relative to parenteral administration, inhalation can modify drugs' biodistribution and improve the accumulation of their significantly high fraction in the lungs (Hershey et al., 1999; Koshkina et al., 2001; Sharma et al., 2001; Labiris & Dolovich, 2003; Gagnadoux et al., 2008). Inhalation also restricts the systemic distribution and hence the associated toxicity of anticancer drugs (Zarogoulidis et al., 2010; Lemarie et al., 2011). Inhaled chemotherapy has also been particularly advantageous in those cancers that have metastasized to the lungs, typically located away from the central airways but receives blood from the pulmonary arteries and veins (Miller & Rosenbaum, 1967; Milne et al., 1969; Keith et al., 2000). Figure 1 illustrates the various steps of the inhalational approach for lung drug delivery.

While inhalational chemotherapy shows substantial pharmacokinetic benefits over oral and systemic delivery, drug deposition still remains a complex task in the resident tumor. The clinical efficacy of inhalation chemotherapy relies on different factors such as disease stage, patient condition, tumor size, penetration of drugs into the tumor, local adverse effects, and drugs' physicochemical properties (Mangal et al., 2017). The aerosols distribution and deposition patterns in the lungs can be affected by obstruction exerted by the respiratory tract because of lung cancer and various other obstructive conditions of the respiratory tract such as bronchiectasis and cystic fibrosis (Verbanck et al., 2020; Zuo et al., 2020; Chaurasiya & Zhao, 2021). Also, drug penetration into tumors is generally restricted by the drug's physico-chemical characteristics, such as solubility, molecular weight, and apoptotic activity (Zarogoulidis et al., 2012). Likewise, drug penetration into the tumor is also limited by tumor characteristics, such as tumor cellularity, size, and interstitial density (Mangal et al., 2017). Therefore, the failure to obtain a therapeutic concentration of drugs and a restricted penetration of tumors decrease the efficacy of inhaled chemotherapy.

Over the last decade, a significant increase has been observed in the production of nanocarrier-based drug delivery systems. Researchers have designed highly stable, viable, and effective nanocarrier systems for highly sensitive and selective imaging and improved therapeutic applications (Ahmad et al., 2015). Besides, nanocarriers provide potentials for surface functionalization with targeting ligands so that they can efficiently deliver their loaded therapeutic material to target tumors. This corresponds to a more selective accumulation of drugs, resulting in enhanced chemotherapeutic effects and fewer adverse off-target side effects (Senapati et al., 2018). Correspondingly, nanocarriers can be designed in such a way that they release their loaded materials in a controlled way, thus retaining the therapeutic level of drugs at the target sites for a more extended period. This, in turn, leads to the increased clinical effectiveness of drugs at low

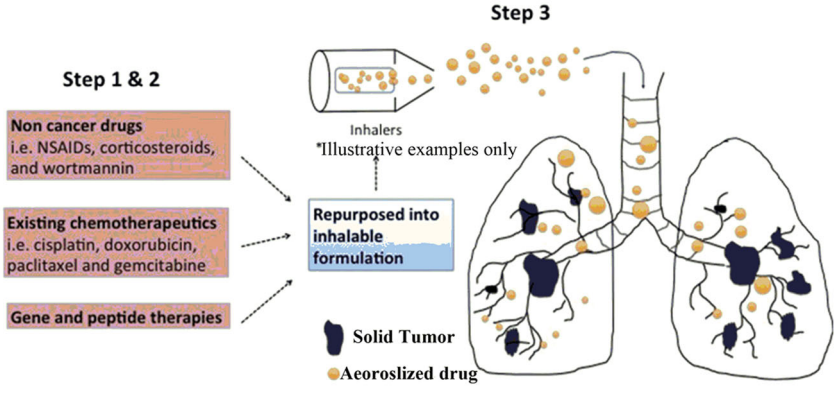

Figure 1. Illustrating the various inhalational approaches for lung cancer. Reproduced with permission from (Lee et al., 2018).

doses with greater patient compliance (Patra et al., 2018). The main objectives of this review include the recent advances in the field of surface-engineered smart nanocarrier inhalation formulations for targeted chemotherapy of lung cancer. First, we briefly explain the obstacles to inhalation formulations based on nanocarriers. This will be followed by a comprehensive literature review of recent trends used to improve lung cancer treatment by inhalation formulations based on surfaceengineered smart nanocarriers.

2. Barriers to conventional nanocarriers based inhalational formulations

Nanocarriers used to treat lung cancer have several issues, including biological barriers due to the lungs' physiology and anatomy and inappropriate physicochemical properties of the particles. In clinical practice, drug delivery systems based on nanocarriers establish tremendous obstacles such as higher circulation clearance, immune reaction, and lower targeting efficiency (Ahmad et al., 2015). Detailed understanding of nanocarriers' biological activity is therefore essential to achieve the most effective delivery of drugs. Like many other cancerous tissues, the poor lymphatic flow and appearance of delicate blood vasculature in the lungs promote the enhanced permeation and retention (EPR) effect, enhancing nanocarriers' entry into tumors. Nevertheless, NPs smaller than 50 nm are less likely to remain for a prolonged duration of time in tumor tissue (Maeda, 2001). Active targeting requires rearranging the nanocarrier's surface with particular ligands to promote the interaction with overexpressed receptors on tumor cells. Different approaches are used for size optimization of nanocarriers; although, they end up with a distorted explosion of encapsulated drugs. Hence, maintaining the size up to 200 nm in the production cycle is a challenge. Surface charge plays a crucial role in determining nanocarriers' fate *in vivo*; their particle interaction and agglomeration depend primarily on the zeta potential of the nanocomposites. Even then, it also triggers hemolytic action and raises the issue of safe delivery (Schreier et al., 1997). The stability of nanocarriers due to the accumulation of nanocarriers in the physiological environment is another issue. Once the aggregates are established, it is very difficult to isolate or redisperse the nanocarriers following forced application. It may also trigger drug leaching and reduce the loading and therapeutic efficacy of the drug. Furthermore, physical instabilities such as agglomeration and poor dispersibility have remained obstacles. Besides, chemical instability linked to drug and carrier material hydrolysis or decomposition is an additional and equally significant concern (Lee et al., 2015).

To have an effective anti-tumor effect with inhaled chemotherapy, medications must be deposited and stored in the lungs at therapeutically effective doses. However, the respiratory tract composition and the lungs' clearance processes make difficult the accumulation of inhaled nanoparticles in the lungs (Mangal et al., 2017). Therefore, understanding the challenges to inhaled nanoparticle deposition and preservation is critical to successfully addressing these problems. The current knowledge of inhaled nanoparticle deposition and clearance activities is primarily focused on research into the clearance of environmental nanoparticle contaminants, which can be extrapolated to a certain degree to medication nanoparticles (Zhang et al., 2011). However, the late-phase clinical trials of NPs are restricted because of the lack of standard protocol for characterization of nanocarriers and nanodrugs, toxicity, physicochemical, and biological instability, disease heterogeneity, and abnormal *in vivo* activity of NPs.

3. Surface modification strategies for deeper penetration to tumors

Due to the complexity of the components of tumors and their impermeable nature, they limit the treatment effect of nanotechnology-based medicines and impede their clinical translation. There are various methods for increasing the penetrability of nanomedicines, but they are much complex to be reliable, functional, or operational. Surface modification can be classified into two categories: tumor microenvironment (TME) destruction strategies and TME adaptation strategies (Li et al., 2020). These techniques can help to increase the penetration of nanomedicine. The TME destruction strategies include those requiring exogenous energy and those that do not require the capability to dissolve various essential components of the solid TME, and thus promote deep penetration, which is the most popular solution in schemes used for surface modification without energy consumption. Collagenase is the widely used enzyme for surface modification for deep penetration into tumor tissues (Wang et al., 2018). Though the application of exogenous enzymes for surface modification can open a channel for deep penetration they have obvious limitations too. They can be easily deactivated in the complex *in vivo* delivery process because they are biological macromolecules. In addition, the risk of inactivation is further increased upon direct contact of the delivery environment surface-modified nanomedicine. Thus, a perfect surface-modified exogenous enzyme system via the design of tumor microenvironmental-responsive nanocarriers is needed for the enzyme wrapping. However, these modifications result in more complex nanomaterials and thus do not conform to the purpose of achieving deep penetration through easy and simple strategies for surface modification. Alternatively, non-enzyme molecules-based functionalization of nanocarriers' surfaces has been reported which can also cause TME damage, leading to deeper nanomedicine penetration. Fluorinated chitosan was used by Li et al. for the construction of a nanosystem that enhanced deep penetration via the conjectural function of transiently opening tight junctions between cells (Li et al., 2020). Fortunately, virus-derived junction opener protein also can transiently open intercellular junctions in epithelial tumors by causing the cleavage in protein desmoglein-2, and can also be used in surface modification for tumor penetration (Wang et al., 2018).

Due to the infinite nature of exogenous energy, nanomaterials can be manipulated in such a way that it releases energy continuously until it penetrates deep enough into

the solid tumor. External energy sources for nanomedicine include light, ultrasound, and magnetic forces, all of which are widely used and have made significant progress. In photothermal and photodynamic strategies, exogenous light energy is used as an energy source for achieving deeper penetration. A rapid rise in temperature over a short period can effectively damage solid tumors via photothermal transformation of near-infrared (NIR) light, thus promote penetration in photothermal strategies. Various studies have been conducted on deep penetration using photothermal transformation strategies including a variety of photothermal agents being packaged within nanocarriers for delivery. The overall limitation of such strategies is a reduction in light intensity because of the external enclosure barrier occupying the loading space of other drugs such as chemotherapy and gene drugs, compared with the modification on the surface of nanomedicine. In addition, internal photothermal agents need to be designed for release at the solid tumor site, making the nanosystems complex and impractical (Li et al., 2020).

Another good option for deeper penetration to tumors is the generation of mechanical forces via modification of the nanocarrier surface with magnetic materials and providing energy through external magnetic fields. For instance, Gram-negative prokaryotes (i.e. magnetotactic bacteria) with an inherent chain of iron oxide nanocrystals can be used for surface modification. This strategy led to 55% penetration into hypoxic regions of colorectal xenografts (Felfoul et al., 2016). The use of alternating magnetic fields to increase the temperature of the magnetic material and damage the ECM is another magnetism-mediated deep penetration strategy having great potential in the surface modification field (Kolosnjaj-Tabi et al., 2017; Beola et al., 2018). However, the technique of exogenous magnetic forces for deep penetration has only been used as an auxiliary strategy for superficial tumors because the magnetic field weakens rapidly as the distance from the magnet increases thus its application is greatly reduced because of this limitation. Liu et al. constructed a system with two oppositely polarized magnets to address this challenge and this system achieved a fivefold increase in penetration in solid tumors compared to the EPR effect (Liu et al., 2020).

Radiotherapy is another most commonly used tumor therapy in clinical practice working on the principle of TME destruction principal for deeper penetration (Haume et al., 2016; Song et al., 2017). Nearly, half of all cancer patients receive radiotherapy alone or in combination with other treatments suggesting its effectiveness and irreplaceability (Wang & Tepper, 2014). The technique can be used to achieve deep penetration of nanomedicine due to the destructive effects of ionizing radiation on solid tumors and the deeper penetration of rays compared to NIR (Escobar-Chávez et al., 2012). Moreover, tumor-associated macrophages (TAMs) have been shown to accumulate near the tumor microvasculature after radiotherapy in large numbers, causing vascular bursts and further promote tumor site penetration of the nanomedicine (Miller et al., 2017). Combination techniques have also been used to combine the effects of two different strategies for spatio-temporally controlled cancer photothermal/immunotherapy. Zhang et al. prepared a delivery system composed of iron oxide magnetic nanoparticles (MPs) as core for loading indocyanine green (ICG) and polyethylene glycol polyphenols (DPA-PEG) as coating layer for loading immunostimulator R837 hydrochloride (R837). This system was formulated as R837 loaded polyphenols coating ICG loaded magnetic nanoparticles (MIRDs). The constructed system worked as magnetic resonance imaging (MRI) guides and resulted in long circulation and magnetic targeting after intravenous injection to mice. The synergism of the photothermal therapy (PTT) and immunotherapy inhibited tumor growth, metastasis, and recurrence, which resulted in potent anticancer therapeutic effects with few side effects (Zhang et al., 2020).

Tumor microenvironment adaptation strategies include non-bionic strategies in which physical and chemical properties of the nanomedicine's surface, i.e. shape, surface charge, hydrophobicity, and softness are controlled. By this strategy, nanomedicines are enabled to adapt to the complex microenvironment of a solid tumor, penetrate blood vessels and the tumor matrix, and promote tumor cell internalization and deeper penetration into solid tumors. Another TME adaptation strategy is the modification of nanocarriers surface via bionics. In nature, viruses, bacteria, or certain functional cells can penetrate deeper into tumors because of their inherent surface properties. Thus, the use of biomimetics is a clever and practical surface modification strategy for achieving deeper penetration of drugs to solid tumors. Surface bionics can either mimic only some substances on the surface of living entities to promote penetration (partial bionic strategy) or apply the whole outer layer of the living entities (such as virus shell and cell membrane) for nanomedicine surface modification (complete bionic strategy) (Li et al., 2020). Liang et al. prepared a biomimetic black phosphorus quantum dots (BPQDs) formulation for induction of breast cancer cell apoptosis *in situ* via NIR laser irradiation to mobilize the immune system and eliminate the residual and metastatic cancer cells. They used erythrocyte membranes (RMs) for coating the BPQDs, forming a BPQD-RM nanovesicle (BPQD-RMNV) biomimetic formulation that exhibited a long circulation time and tumor accumulation *in vivo*. The BPQD-RMNV-mediated PTT combined with immune checkpoint blockade antibody increased the infiltration and activity of CD8+ T cells in the tumor, which directly restrained basal-like breast tumor growth *in vivo* (Liang et al., 2019).

4. Surface-engineered smart nanocarriers and targeted inhalational lung cancer chemotherapy

Recently, the use of surface engineered smart nanocarriers-based inhalational formulations has been the subject of greater scientific interest for targeted chemotherapy of lung cancer. This strategy has the potential to overcome issues associated with inhalational chemotherapy based on conventional nanocarriers. Inhalational formulations based on surface engineered smart nanocarriers can achieve uniform drug distribution between the alveoli, improve drug

solubilization, and control drug release, thus reduce dosing frequency, improve patient compliance, reduce side effects, and enhance selective drug accumulation in tumors (Alipour et al., 2010). Therefore, surface engineered smart nanocarriers based inhalational formulations attract biomedical scientists in cancer research for highly effective and targeted lung cancer therapy. The following section describes various surface engineered smart nanocarriers based and inhalational formulations for targeted chemotherapy of lung cancer chemotherapy (Figure 2).

Anticancer drugs can be encapsulated in nanoparticles with biocompatible and biodegradable excipients, allowing for selective and/or controlled delivery (Müller et al., 2000; Moghimi et al., 2001; Panyam & Labhasetwar, 2003; Ghosh et al., 2008; Farokhzad & Langer, 2009). Drug nanocrystals with high drug loading and low excipients can also be used to formulate anticancer drugs (Zhang et al., 2011; Hollis et al., 2013, 2014). As a result, relative to free drugs, pulmonary administration of nanoparticles could reduce the systemic toxicity of chemotherapeutic agents. Roa et al., for example, observed that inhaled doxorubicin (Dox) nanoparticles had lower cardiac toxicity after intratracheal administration than the same dose of free Dox (Roa et al., 2011). In addition, mice tolerated paclitaxel–polyglutamic acid conjugate well after intratracheal administration, according to Zou et al. (Zou et al., 2004). Furthermore, nanoparticles' sustained-release properties may improve inhaled chemotherapy's efficacy by keeping drug concentrations at tumor sites for longer periods (Gill et al., 2011; Taratula et al., 2011; Jyoti et al., 2015). As medication is administered through systemic administration, nanoparticles naturally appear to penetrate and accumulate inside the leaky tumor vasculature due to their small size, which is known as the EPR impact.

To ensure effective and effective tumor destruction, nanoparticles must unleash a chemotherapeutic agent close to the tumor. Premature release of an encapsulated compound from nanoparticles, on the other hand, could cause nonspecific toxicity in the normal lung parenchyma. Nanoparticles with site-specific and induced release characteristics have been studied to address this constraint. The pH-sensitive fusogenic lipid nano-vesicles' design exploited the low extracellular and intracellular pH of tumor tissue/cells to allow triggered release. These nano-vesicles combine with the cell plasma membrane and lysosomal membrane at low pH, allowing anticancer drugs to be delivered to cancer cells on a site-specific and activated basis (Tseng et al., 2009; Zarogoulidis et al., 2012; Pérez-Herrero & Fernández-Medarde, 2015; Islam and Richard 2019; Okuda & Okamoto, 2020).

4.1. Long circulating inhalable surface-engineered smart nanocarriers

Though inhalational chemotherapy demonstrates a clear pharmacokinetic advantage over oral and systemic delivery, once it has been accumulated in the lung, the therapeutic agent's removal is instantly started. Inhaled drugs, whether in solution or as particles, are easily expelled from the lungs. Systemic absorption of solubilized and permeable drugs (i.e. lymphatic and/or blood circulation) and elimination mechanisms for non-solubilized drugs or particles (i.e. macrophage uptake in the upper and smaller airways and mucociliary clearance, respectively) are the main removal mechanisms (Ruge et al., 2013).

Surface engineered nanocarriers have displayed a reduction in the clearance of drugs from the lungs. This phenomenon has been linked to the ability of certain polymers to promote muco-penetration and decrease the absorption of alveolar macrophages. Some polymers' potential to promote muco-penetration and decrease alveolar macrophage absorption has been related to this phenomenon (Mangal et al., 2017). Surface engineering of nanocarriers with polymers

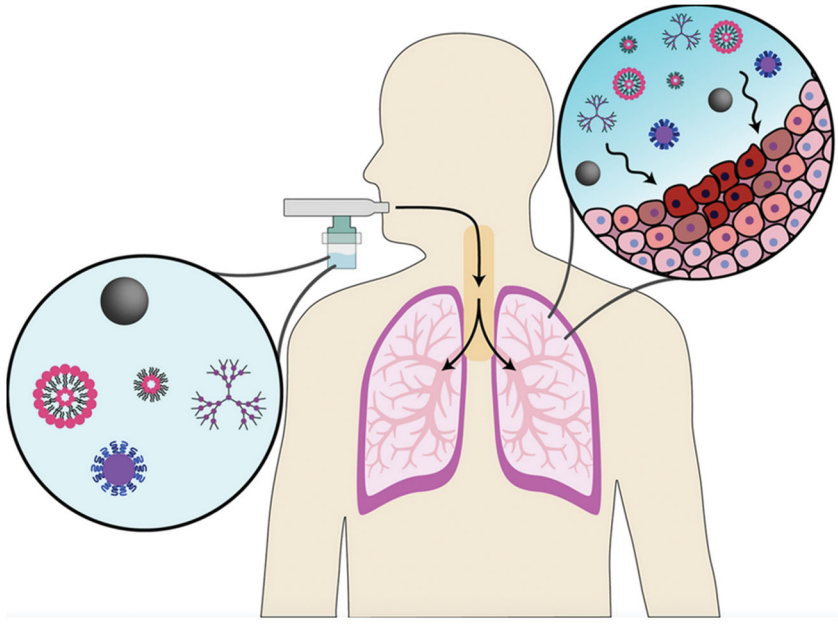

Figure 2. Illustrating the surface-engineered smart nanocarriers and targeted inhalational lung cancer chemotherapy (Anderson et al., 2020).

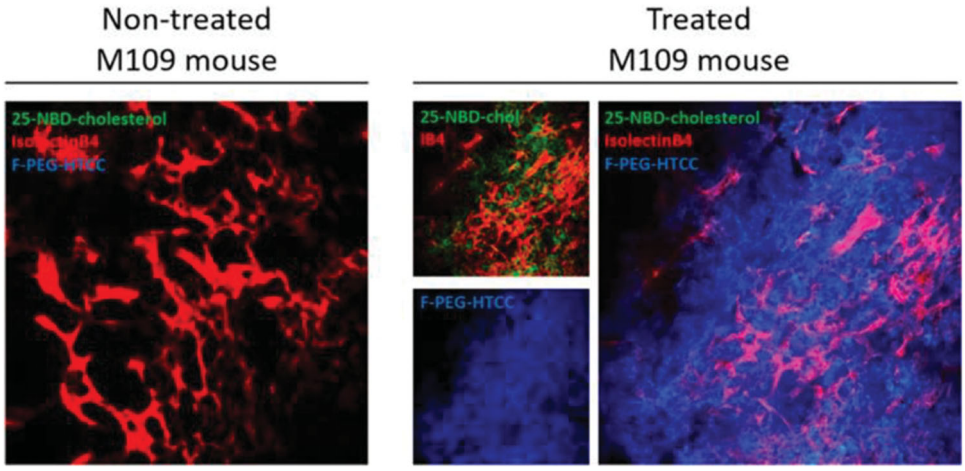

Figure 3. *In vivo* tumor distribution in the M109 model after inhalation of coated fluorescent folate-grafted copolymer nanocarriers. Confocal images of control untreated M109 mouse lung and coated fluorescent folate-grafted copolymer nanocarriers-treated mouse lung. Green: 25-NBD-cholesterol labeling SLN; red: vessels labeled with isolectinB4; blue: Alexa Fluor 405 labeling the coating. Reproduced with permission from (Rosiere et al., 2018). Copyright (2018) American Chemical Society.

including polyethylene glycol and chitosan gives them 'stealth' properties, which prevents clearance and phagocytic uptake. This in turn makes the nanocarriers long circulating in the systemic circulation system with ultimately better therapeutic efficacy of their loaded drugs (Chen et al., 2018). Furthermore, stealth nanocarriers have been considered to enhance anti-cancer agents' biodistribution, resulting in superior tumor accumulation through an EPR effect (Li et al., 2013). Similarly, stealth nanocarriers can release their loaded therapeutic agents in a controlled manner, thus, improved therapeutic efficacy is achieved over an extended period (Anderson et al., 2020).

PEGylated polylysine dendrimers conjugated to Dox have been reported for a significant anticancer activity of the drug after intratracheal instillation. The long-circulating dendrimer resulted in a reduction of >95% in the lung tumor burden in mice after 2 weeks compared to IV or intratracheal Dox solution administration at the same dose. Similarly, Dox delivered in these PEGylated polylysine dendrimers remained in the lungs for a longer time. In contrast to the bolus accumulation of free Dox on lung tissues that induced the intolerability of treatment and animals' deaths, these findings may be due to the depot release of dendrimers that subjected the lungs to low levels of Dox for an extended period (Kaminskas et al., 2014).

In a recent study, nanocarriers loaded with paclitaxel for inhalation were designed by Rosiere et al. (Rosiere et al., 2018). A folate-grafted copolymer (polyethylene glycol and chitosan) was provided on their surface to extend respiratory retention via bioadhesive properties and target the folate receptor-alpha overexpressed on lung tumor cells. In healthy mice, release profile was retained with prolonged retention of paclitaxel of around 7 h inside the lungs. The most imperative finding of the study includes the penetration of nanocarriers *in vivo* murine M109 lung tumors, as shown in Figure 3.

In another study, paclitaxel-loaded PEGylated micelles produced from PEG_{5000}–DSPE were noted for the persistent release of drugs accompanying pulmonary delivery. Intratracheally administered PEGylated micelles demonstrated a 45-fold higher paclitaxel accumulation in the lungs than the intravenous formulation and a threefold higher taxol accumulation than the intratracheally administered formulation. Likewise, paclitaxel concentrations in plasma and other non-targeted tissues were substantially lower relative to other groups when PEGylated micelles were administered intratracheally. Also, intratracheally delivered PEGylated micelles maintained the highest amount of paclitaxel in the lungs for extended periods (Gill et al., 2011). Taratula et al. developed a multifunctional nanocarrier system (Taratula et al., 2013), which comprised several components for enhancing the therapeutic response of the drug as shown in Figure 4. Doxorubicin or paclitaxel was embedded in a positively charged lipid nanocarrier (DOTAP) coated with siRNA (silencing MRP1 and BCL2, both involved in pump and non-pump resistance), poly (ethylene glycol) chains (DSPE-PEG) that confer 'stealth' and targeting moiety (luteinizing hormone-releasing hormone (LHRH) analog) to target lung cancer cells. *In vivo* targeting was illustrated in an orthotopic lung tumor mice model (human A549 adenocarcinoma tumors) with (i) slight nanocarrier distribution in untargeted organs (compared to iv) and (ii) preferential delivery in cells of lung cancer, keeping healthy lung tissues unchanged. Relative with iv, antitumor activity was also increased, with a ~40-fold reduction in tumor volume and permitting complete regression in 50% of mice.

4.2. Inhalable surface-engineered smart nanocarriers for lung cancer targeted chemotherapy

Two primary methods may be employed for targeting lung cancer cells: active and passive targeting. The passive tumor targeting process is carried out during systemic drug delivery via EPR effect (Abdelaziz et al., 2018). However, the active targeting mechanism is more sensitive to cancer tissues than that of the EPR effect via receptor-mediated endocytosis,

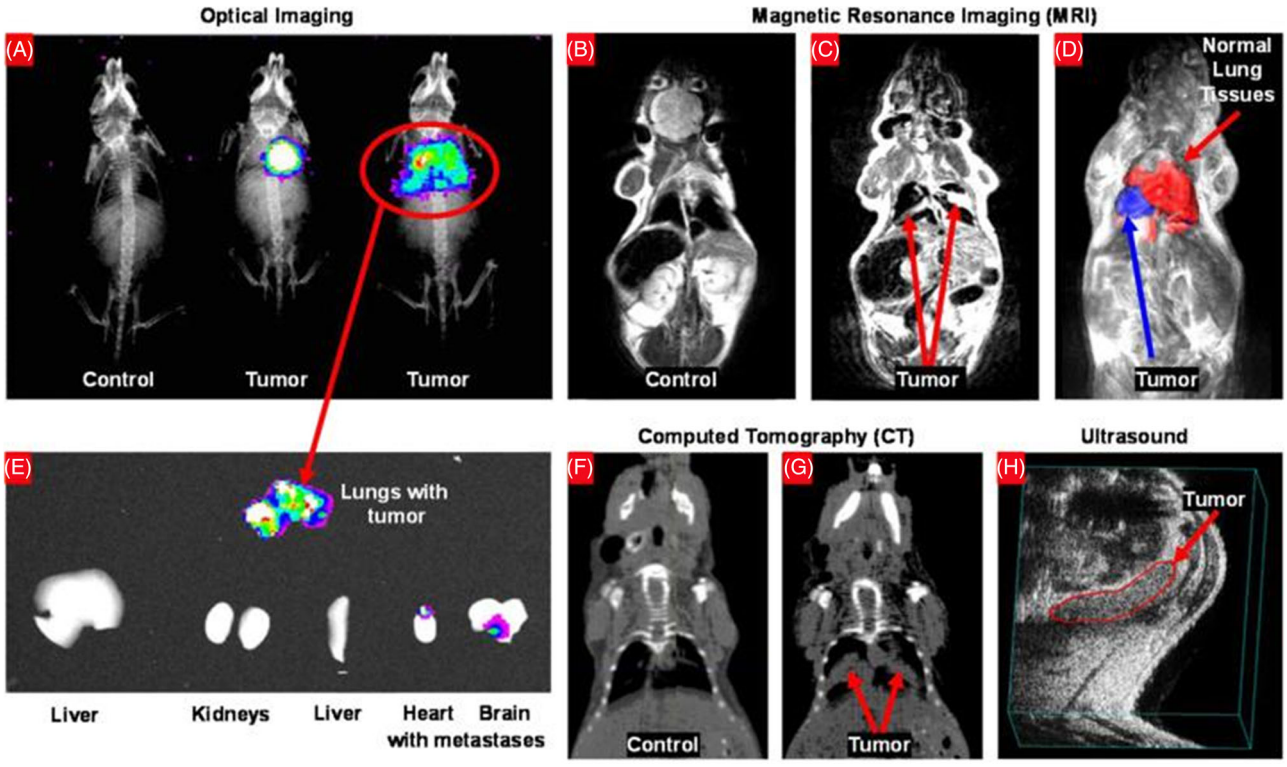

Figure 4. Imaging evaluation of the orthotopic lung cancer model. (A) Bioluminescence optical imaging of control mouse and lung tumor mice of various sizes. (B–D) Magnetic resonance imaging of the control mouse (B) and lung tumor mice of various sizes (C, D). Healthy lung tissues (red) and lung tumors (blue) are displayed (D). (E) Optical imaging of excised organs. (F, G) Computed tomography images of a control mouse (F) and mouse with lung tumors (G). (H) Visualization of lung tumor by the ultrasound imaging system. Reproduced with permission from (Taratula et al., 2013).

which ensures additional targeting of tumor sites. Active targeting may be accomplished by either vascular endothelium tumor-targeting or cancer cells (Danhier, 2016). This section highlights the studies reported for actively targeted chemotherapy of inhalable surface engineered smart nanocarriers for lung cancer.

In 40–80% of NSCLC cells, the epidermal growth factor receptor (EGFR) gets overexpressed. (Hirsch et al., 2009). In a study, cisplatin was loaded with biotinylated epidermal growth factor (EGF) engineered on gelatin nanocarriers' surface. Cisplatin delivered through inhalable gelatin nanocarriers surface engineered with biotinylated-EGF specifically localized in lung carcinoma in mice in higher doses while showing reduced toxicity to kidneys (Tseng et al., 2009). Luteinizing hormone-releasing hormone receptors get overexpressed lung cancer cells relative to normal cells. This phenomenon encourages active tumor site targeting without impacting healthy cells (Kuzmov & Minko, 2015). In a study, the efficacy of mesoporous silica nanocarriers targeting LHRH in delivering anticancer payloads inside lung cancer cells was revealed. The nanocarriers' surface was functionalized with LHRH peptide and loaded with Dox, cisplatin, and siRNA. Due to LHRH-targeted mesoporous silica nanocarriers loaded with both MRP1 and BCL2 siRNA, the surface engineered nanocarriers enhanced the antitumor efficacy of both Dox and cisplatin upon inhalation. The enhanced cytotoxicity of mesoporous silica nanocarriers loaded with LHRH-PEGylated Dox or cisplatin was due to their accumulation within lung cancer cells (Taratula et al., 2011).

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) has been identified to interact especially with death receptors, i.e. DR4/TRAIL-R1, that overexpressed on cancer cells but not in healthy cells. The surface of porous PLGA carriers was functionalized with Apo2L/TRAIL for Dox targeted delivery to metastatic lung cancer cells (Kim et al., 2013). Co-treatment of H226 cells with TRAIL and Dox showed significant apoptosis, suggesting the synergistic cytotoxicity. PLGA carriers surface-functionalized with Apo2L/TRAIL upon pulmonary administration led to effective deposition in the mouse lung and persisted for a week. These Dox-loaded carriers in mice carrying H226 metastatic lung cells substantially minimized the size and number of lesions. Likewise, the use of the tumor-homing peptide iRGD (CRGDKGPDC) as a binder to αv integrins helps resolve tumor penetration limitations. Acetylated dextran nanocarrier surfaces engineered with iRGD and loaded with paclitaxel have been used for targeted lung cancer in the form of inhalable dry powder nanocomposites. Due to the simple Ac-Dex biodegradability, the drug can be rapidly released in tumor tissues under acidic environments (Torrico-Guzman & Meenach, 2015). Various successful clinical studies have been conducted for evaluating the efficacy of inhalational therapy to treat lung disorders (Table 1).

4.3. Inhalable smart nanoparticles for lung cancer targeting

A large number of inhalable nanocarriers have been suggested for use in lung cancer treatment.

Table 1. Representative preclinical and clinical studies showing the safety and efficacy of inhalational smart nanocarriers in various lung cancers.

Nanocarrier	Drug	Results
Human serum albumin (HSA) nanoparticles adsorbed with apoptotic TRAIL protein (TRAIL/Dox HSA-NP).	Doxorubicin	TRAIL/Dox HSA-NP nanoparticles were distributed effectively throughout the lungs upon inhalation and provided sustained release of the drug. The inhaled TRAIL/Dox HSA-NP also showed more pronounced anti-cancer activity and minimal side effects than TRAIL or Dox HSA-NP alone (Choi et al., 2015).
56-kDa PEGylated-polylysine dendrimer.	Doxorubicin	The dendrimer formulation showed improved anti-cancer activity following intratracheal administration compared with the intravenously administered drug solution. The drug–dendrimer complex was better tolerated than the free drug by the lungs after intratracheal administration (Kaminskas et al., 2014).
Polyethylene $glycol_{5000}$–distearoyl phosphatidyl ethanolamine (PEG_{5000}–DSPE) micelles.	Paclitaxel	In comparison with the intravenous route, the lung targeting efficiency via the pulmonary route was 132-fold higher. The distribution of paclitaxel in non-targeted tissues was reduced in micelles when compared with free paclitaxel following intratracheal administration. Moreover, drug-loaded micelles showed no sign of inflammation in lung tissues, highlighting the delivery vehicle's safety and suitability for inhaled delivery (Gill et al., 2011).
Polystyrene nanoparticles	Losartan and Telmisartan	Losartan and Telmisartan polystyrene nanoparticles showed substantial anticancer activity *in vivo* against metastatic and orthotopic lung cancers. The drugs were well tolerated by normal lung tissues. Animals receiving inhaled losartan and Telmisartan survived longer than untreated animals (Godugu et al., 2013).
Solid lipid nanoparticles	Epirubicin	Upon inhalation, the epirubicin concentration in the lungs was higher than in plasma. The drug concentration in the lungs was higher with inhaled epirubicin nanoparticles compared with inhaled epirubicin solution (Hu & Jia, 2010).
Nanostructured lipid particles (NLPs)	9-Bromo-noscapine	The half-life of 9-Br-Nos-NLPs increased in the lungs compared with free drug powder after inhalation (Jyoti et al., 2015).
Lung surfactant mimetic and pH-responsive lipid nanovesicles	Paclitaxel	Fusogenicity of the nanoparticles enabled cytosolic delivery of paclitaxel to cancer cells but was nontoxic to normal cells. Inhaled delivery of drug-loaded nanoparticles led to lower drug concentrations in non-targeted sites (liver, spleen, and plasma) compared with intravenous paclitaxel solution. Drug-loaded nanoparticles showed no lung toxicity (Joshi et al., 2014).
Sustained-release lipid inhalation targeting (SLIT)	Cisplatin	Inhaled cisplatin liposomes were well tolerated with no signs of systemic toxicity (nephrotoxicity, ototoxicity, or neurotoxicity) in lung cancer patients, which was attributed to a low systemic drug concentration. Side effects, including nausea, vomiting, dyspnea, fatigue, and hoarseness, were observed (Wittgen et al., 2007).
Liposomes	9-Nitrocamptothecin	Inhaled 9-nitrocamptothecin liposomes were safe and enabled disease stabilization in some lung cancer patients. The drug was also systemically absorbed following inhalation at high doses, leading to systemic side effects, including anemia, neutropenia, and anorexia. Partial remission of liver metastasis was also observed in a patient with endometrial cancer, indicating the systemic potential of inhaled administration (Verschraegen et al., 2004).
Luteinizing hormone-releasing hormone receptor-targeted mesoporous silica nanoparticles	Doxorubicin and cisplatin, two types of siRNA targeted to MRP1 and BCL2 mRNAs	Inhalation led to greater concentrations of drugs and siRNA to be retained in the lungs than the same formulation's intravenous administration. Inhaled delivery also restricted the systemic uptake and accumulation of nanoparticles in other organs (Taratula et al., 2011).

Pontes and Grenha have explicitly explained the use of multifunctional nanocarriers for lung delivery of active biologicals and pharmaceuticals (Pontes & Grenha, 2020). The majority of research predicted a therapeutic impact, but some of the studies focused on diagnosis. Even though this is important for cancer, particularly in its early stages, these approaches are not discussed in more detail because as they are outside the scope of this review. Mottaghitalab et al. and Silva et al. provided two detailed reports on possible methods for diagnosis for further reading about this topic (Mottaghitalab et al., 2019; Silva et al., 2019). Only research on nanocarriers that predict therapeutic approaches would therefore be summarized here. The general observation of the research shows that nanocarriers' proposal for a cancer therapy application implies functionalization in most cases; carriers with some form of alteration of the surface benefit from contact with the environment of the tumor. One of the techniques widely discussed in this context is the application of a matrix to molecules possibly identified by cell receptors that are more prevalent in cancer cells than in healthy cells. Such a strategy, attributed to mannose-mediated cell-targeting carriers has been addressed briefly in the preceding section.

Lactoferrin–chondroitin sulfate nanocomplexes (~190 nm) were designed as a co-delivering system for Dox and ellagic acid in lung cancer. Initially, because of the hydrophobicity, the former was converted into water-soluble nanocrystals. The electrostatic interaction between chondroitin sulfate and lactoferrin and the two integrated drugs leads to the formation of nanocomplexes during this procedure. As the cell surface of lung cancer showed overexpression of lactoferrin and CD44 receptors, these nanocomplexes have been observed to favor cell recognition, facilitated by lactoferrin and chondroitin sulfate, respectively. The researchers also speculated that nanocomplex internalization may have been assisted by clathrin-mediated endocytosis because their size was within the clathrin receptor's pore range (up to 200 nm) (Rejman et al., 2004). Consequently, their size and composition provide the functionality of these carriers, which ensures precise targeting capacity. After that, in a mannitol matrix, the nanocomplexes were microencapsulated to provide appropriate aerodynamics for the lung delivery, reaching almost 90% FPF and 2.56-m MMAD. Tumor growth biomarkers were found to be lower after administering microencapsulated nanocomplexes in tumor-bearing mice when the inhalable formulation was used compared to free drug inhalation or intravenous administration (Abd Elwakil et al., 2018).

In studies involving gold nanoparticles, strategies for cell recognition have also been addressed. In cancer therapy, these carriers have been of keen interest as they are used in radiotherapy, PTT, and as drug carriers. These carriers, upon inhalation, accumulate in the lungs, which can be effective to treat lung cancer (Gadoue & Toomeh, 2019). On the topic, there is a recent review article available (Sztandera et al., 2019). Thiolated PEG-coated gold nanoparticles (2 nm) demonstrated invisibility to the immune system (Kumar et al., 2013) and allows the other attached moieties to provide precise targeting as well. The nanocarrier's surface was thus altered with the ligand RGD, a large and uniquely overexpressed peptide in tumor neovasculature (Di Pietro et al., 2016; Ganipineni et al., 2019). In a single-nodule lung adenocarcinoma mouse model, the nanocarriers were tested to see which administration route, intravenous or inhalation, would be more effective to target adenocarcinoma (Herter-Sprie et al., 2014). According to the biodistribution data, higher carrier content was achieved by inhalation (Figure 5) (Ngwa et al., 2017). In another study, temozolomide loaded gold nanoparticles (40 nm), which is an alkylating agent that is already being used to treat other cancers. The administration of gold nanoparticles to healthy mice demonstrated their safety by quantifying tumor markers which include carcinoembryonic antigen, lactate dehydrogenase, and alpha-fetoprotein. Appropriate carriers have been identified to cause oxidative damage and to inhibit cell cycle and cell proliferation of G1-phase, whereas drug-laden carriers delivered to lung cancer-bearing mice demonstrated a synergistic effect of loaded drug and carriers (Hamzawy et al., 2017; Pontes & Grenha, 2020).

Optimization of the interaction between nanocarriers and cancer cells has also been documented via solid lipid nanoparticles (SLN) (Pontes & Grenha, 2020). A complex SLN-based nano-delivery system consisting of multi-compartmental lipid nanocomposites (190–225 nm) was presented. Initially, rapamycin and berberine were encapsulated in SLN with a synergic anticancer activity. Multicompartment systems were established for the optimization of the delivery rate of both drugs. Berberine was incorporated into the core of SLN as a hydrophobic ion pair with sodium dodecyl sulfate, which helped to preserve its release, while pre-formulated rapamycin was served as a phospholipid complex, which helped to increase its release and solubility. Layer-by-layer assembly of anionic hyaluronic acid and cationic lactoferrin targeting overly expressed CD44 and lactoferrin receptors present on lung cancer cells, which in turn increased the tumor-targeting ability. A mixture of mannitol/leucine/maltodextrin (MMAD of 3.3 m, FPF of 56%) achieved sufficient aerodynamics after spray-drying. An assay revealed that inhaled nanocomposites reduced lung weight compared to free drug inhalation, as well as tumor size and angiogenic marker levels in mice with lung tumors (Kabary et al., 2018). Another study suggested the SLN surface modification with a chitosan derivative initially introduced to folate moieties (Rosiere et al., 2018). Both the chitosan derivative and folate engraft, the researchers hypothesized, would increase nanoparticle retention inside the lungs with activation of folate receptors, thus enhancing the delivered drug content to cancerous cells after coating. The nanocarriers (~250 nm; +32 mV) provided a slower release of paclitaxel (58% in three days) and binding affinity to cell lines expressing the folate receptor. When tested *in vivo*, inhaled chitosan-coated SLN had a higher pulmonary paclitaxel concentration than intravenous drug administration. Besides, the drug concentration was higher for the coated formulation at 1 and 6 h of post-administration relative to paclitaxel inhaled and intravenously administered. The SLN was found to be distributed among solid lung tumors, with low vessel interaction with

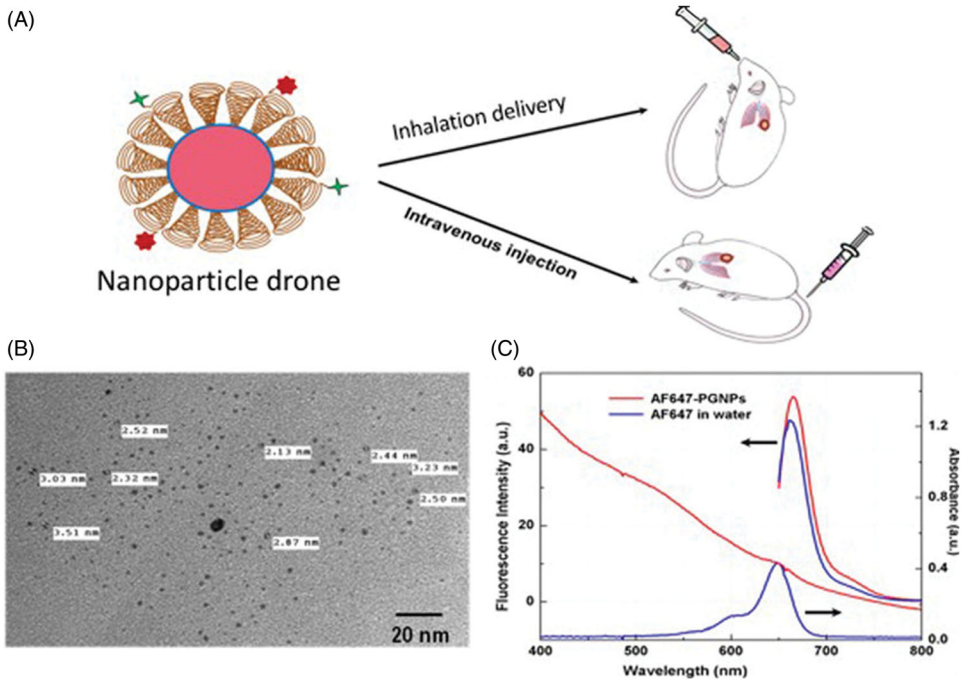

Figure 5. Illustration showing both intravenous and inhalation (INH) delivery of nanoparticle drones; (B) TEM image of lung tumor-targeted with drones; and (C) absorption spectra of drone technology uniquely customized for INH delivery to lung tumors (Ngwa et al., 2017).

anticancer agents' systemic delivery. Paclitaxel was also loaded into PEG-polylactic acid (PLA) nanoparticles, which were then conjugated with the epithelial cell adhesion molecule (EpCAM, CD326), which was overexpressed in lung cancer. Drug toxicity was reduced in c-Raf transgenic lung cancer mice after intratracheal delivery of nanoparticles, and animal survival increased from 20% to 70% (Karra et al., 2013). Another strategy suggested lipid polymeric nanoparticles (phospholipid layer and an outer layer of EGF, hydrophobic polymeric core, PEG, and distearoylphosphoethanolamine) for targeting the EGFR (Nan, 2019), overly expressed in lung carcinoma (Pancewicz-Wojtkiewicz, 2016; Yuan et al., 2019). The related drugs were cisplatin and Dox. The EGF presence in the outer part of the nanoparticle made it possible to interact with EGFR, which resulted in drugs being released at the site of cancer. An *in vivo* assay showed a tumor inhibition ratio of ~75% (Pontes & Grenha, 2020).

Inhalable self-assembled nanoparticles consisting of human serum albumin (HSA), TNF-related apoptosis-inducing ligand (TRAIL), and Dox were proposed as a solution to a resistant type of cancer (Choi et al., 2015). The latter was linked to HSA and nanoparticles were formed and then coated with TRAIL (342 nm). Initial experiments in NSCLC-representing H226 cells showed that Dox and TRAIL's presence simultaneously allowed increased cytotoxicity as cell viability decreased from approximately 60% after three days of exposure when 20–30% presence of only one of the molecules in HSA nanoparticles after double association (Pontes & Grenha, 2020).

Nanoparticles were delivered in the form of liquid droplets of micron size to lung tumor-bearing mice in an *in vivo* assay. Mice tumors treated with HSA nanoparticles that combined Dox and TRAIL were significantly lighter and smaller compared to treated with TRAIL nanoparticles or Dox nanoparticles that only contained one molecule. Haloperidol was also used as a ligand to increase albumin-based nanoparticles' targeting potential (218 nm). The nanoparticles, prior to haloperidol conjugation and Dox loading, were prepared through bovine serum albumin desolvation. Nano-in-microparticles of 4.6 m of an aerodynamic diameter and 66% of an FPF were produced by spray drying with leucine, mannitol, and trehalose (Varshosaz et al., 2015).

Some studies have also identified therapeutic methods focused on the carrier matrix's ability to react to different stimuli (Lakkadwala et al., 2015; Liu et al., 2017). Changes in pH and temperature are common stimuli (Hoffman, 2013) and these provide the framework for the development of so-called smart polymers or systems. The reason for their utilization includes that if any stimulus (temperature or pH) is reached, it would activate the phase transition in the matrix of the carrier, resulting in the drug release at a specific location. In the current context, we developed a methoxy poly(-ethylene glycol)–poly(ethylenimine)–poly(L-glutamate)-based copolymer and prepared the nanoparticles (<75 nm) via and chelate effect and electrostatic interaction for simultaneous encapsulation of cisplatin and Dox (Xu et al., 2019). *In vitro* assays revealed the enhanced release of Dox at acidic pH, indicating that the drug could be released in a cancer environment. A microsprayer aerosolizer was used to deliver the nanocarriers to metastatic lung cancer mice via pulmonary administration, corresponding to enhanced carrier accumulation within the lungs compared to tissues, particularly in the area surrounding tumor lesions. The smaller size carrier has been reported to assist the penetration into the cancer mass, while the systemic dissemination is prevented by an insufficient vessel structure. The results also show that tumor

masses have shrunk, implying that nanoformulation efficacy has improved. In a related pH stimulation strategy, poly(amidoamine) dendrimers have also been used. We combined the Dox with polymer and spray dried the dendrimers in mannitol to offer good aerodynamic features (FPF was 40–60%). Dendrimers emitted instantly from aqueous medium microparticles and drug release was only observed in response to a drop in intracellular pH (Zhong, 2018). Similar dendrimers have demonstrated substantial toxicity (time-dependent) in Calu-3 cells, a respiratory epithelium model attributed to sustained drug release. The results suggested that conjugating PEG molecules to dendrimers increased their concentration-dependent permeation across the cell layer (Pontes & Grenha, 2020).

In this case, we formulated the dendrimers in a pressurized metered-dose inhaler, resulting in aerosols with 82% FPF and 1.3 μm MMAD (Zhong et al., 2017). A lung metastasized breast cancer syngeneic rat model was given PEGylated polylysine dendrimers that were also conjugated with Dox. After two weeks, the lung tumors decreased over 95% relative to IV Dox solution administration, resulting in a decrease of 30–50% (Kaminskas et al., 2014; Pontes & Grenha, 2020).

A combination of the above-mentioned strategies has been proposed in some cases, as reported in a work about folic acid conjugated stimuli-responsive core-shell nanoparticles. This formulation aimed to create a network of poly(N-isopropylacrylamide) copolymer and carboxymethyl chitosan, which include pH and temperature-sensitive nanosystem shells. The core, in turn, included PLGA and an image contrast agent (superparamagnetic iron oxide, SPIO). The PLGA allowed encapsulated molecules to be released in a controlled manner, in this case, gemcitabine, through an alternating magnetic field applied externally, SPIO served as both a contrasting agent and a temperature change inductor. SPIO-induced changes in temperature contributed to the polymeric shell's conformational transition, enabling drug release. Besides, the system shell was pH-sensitive, supplying drug release at the cancer environment's typical acidic pH. Furthermore, due to folic acid surface conjugation, the transmission was even more targeted, taking advantage of cancer cells' overexpression of the folate receptor (Menon et al., 2017). The increased cellular uptake of the nanocarriers (289 nm, −36 mV) was observed under the influence of magnets as a result of the SPIO inclusion in the formulation. Compared to the controls, reduced tumor volume was observed in mice with lung tumors (*in vivo*). Magnetic resonance imaging confirmed the pulmonary retention of nanoparticles and, when combined with radiotherapy, the growth of tumors was suppressed via synergic effect.

Many studies have investigated the use of Fe_3O_4 paramagnetic cores (Smulders et al., 2016) or gadolinium-based particles (Bianchi et al., 2014; Dufort et al., 2015) in the diagnosis of lung cancer, which further enables radiosensitizing effects. However, therapeutic systems were also formulated. Spray drying of Iron oxide (Fe_3O_4; 56 nm, −49 mV) nanoparticles with Dox and lactose, leads to 3.27 m of MMAD. *In vitro* studies have shown that microencapsulated nanoparticles have produced more than twice particle accumulation and retention in areas controlled by a high magnetic gradient compared to a liquid suspension (McBride et al., 2013).

Overall, numerous methods have been identified that result in positive outcomes in the treatment of lung cancer. However, cancer research still has a lot to consider, and related therapeutics are expanding rapidly at the same rate as new molecular cascades and receptors are discovered. With these results, nanotechnology is advancing with improved treatment methods for cancer. They are dominated by carrier surface optimization, whether through the engineering of specific ligands, the careful selection of matrix components, or the combination of all of the effects to provide intimate contact with cancer cells and more targeted drug delivery, resulting in better therapy (Pontes & Grenha, 2020).

5. Limitations and future challenges of surface-engineered nanocarriers-based inhalational formulations

Chemotherapy delivered through the lungs is thought to produce a significantly higher concentration of drug in the lungs thereby lowering systemic toxicity. For the treatment of lung cancer, this technology could be a viable alternative to oral and parenteral chemotherapies. Nonetheless, the impact of elevated doses of inhaled anticancer drugs on local toxicity in the lung centers is generally unclear. Furthermore, the most inhaled free anti-cancer medications do not have tumor-specific distributions in the lungs. Inhaled chemotherapeutics delivery against lung cancer could be feasible with nanoparticle formulations. Toxic drugs may be encapsulated in nanoparticles and released in a more targeted and regulated manner. Nanoparticles may also hold a variety of medications, RNAs, DNAs as well as imaging agents.

Although having very positive prospects, inhaled surface engineered inhalational-based nanocarriers have some significant limitations, such as poor drug payload, typically within the range of 1–10% (w/w). Therefore, it may be impractical to provide the patients with adequate anticancer drug doses via these nanocarriers (Rosière et al., 2019). The method of generating nanocarriers is another persistent challenge for these therapies. To produce large batches, the methods mentioned are often too complicated, as they comprise several steps. Indeed, while these techniques are essential for production at laboratory scales, only a few are easy to scale up reasonable clinical batches. An effective method will result in nanocarriers with highly reproducible characteristics (i.e. shape, size, drug payload, drug release, stability, etc.). Likewise, another major problem is toxicities associated with the excipients nanocarriers. Nanocarriers are consisting of excipients for which there is no toxicity/tolerance data available after inhalation delivery. Therefore, potential toxicity research should be more consistent in evaluating such new therapies based on nanocarriers (Kumar et al., 2014).

6. Conclusions and future perspectives

Nanotechnology progress is dependent on the emergence of new knowledge in more basic sciences, such as molecular disease mechanisms, which are critical measures of the techniques to be used in the development of novel therapies. Besides, it should not be ignored that many of the described carriers and materials have not yet been accepted for use by regulatory authorities for lung delivery. This in itself presents a tremendous difficulty. It is unavoidably necessary to resolve the toxicity of inhaled therapeutic nanocarriers. For several years, it has been clear that nanomaterials' biocompatibility differs from that of raw materials, and that nanomaterials research must go well beyond the evaluation of individual components. Rather, within the sense of a particular delivery route, the nanomaterial must be deemed a new attribute (Gaspar & Duncan, 2009). Therefore, in the context of the lung path, generating data on the protection of the nanocarriers and new materials known as possible adjuvants is widely recognized as an immediate need to potentiate the delivery of lung drug applications. This should include toxicity testing examining all potential pathways of toxicity, both *in vitro* and *in vivo*, thus guaranteeing that the strategy of 3Rs is implemented to minimize, refine and substitute the use of animals in research. Cytotoxicity and genotoxicity should be discussed in the initial *in vitro* test, and possible epigenetic toxicity should also be assessed (Dusinska et al., 2017). After delivery, the fate of the appropriate carriers is frequently neglected. Despite various deposition patterns, the latest review comparing liposomal clearance kinetics and SLN after IT delivery of rat suspensions showed similar clearance rates (Haque et al., 2018). Therefore, research in this area is crucial to provide data on protecting the materials and the beginning of their clinical uses.

To improve effectiveness and control side effects, recent research studies have focused to improve the lung tumor deposition of inhaled drug delivery systems with minimum clearance. Nanoparticles face several difficulties when it comes to pulmonary distribution, owing to their relatively low mass and cohesive form. Just a small portion of the compound released from nanoparticles has anti-cancer properties. It is difficult to measure the fraction of liberated drug from nanoparticles rather than the overall bound and unbound fraction of drug due to analytical limits, rendering it challenging to determine nanoparticles' true potential for enhancing drug penetration/uptake. Moreover, the drug is usually measured in the entire lung rather than the lung tumor, which could contribute to the confusion regarding nanoparticles' true targeting ability and, as a result, their anti-tumor effectiveness. Furthermore, doctors favor systemic routes over inhaled routes because they are more predictable and reliable (drug deposition may vary due to the patients' different lung functions). As a result, further advancements in aerosolization technologies are needed to increase dose regulation, purity, and predictability of the inhaled drug fraction.

This becomes essential to emphasize that nanocarriers' IT delivery was the preferred evaluation method when *in vivo* assays were listed, which existed in a significant number of the works described suggesting a high threat when forming potential relationships with human delivery. It is also critical that nanocarriers themselves do not show adequate inhalation aerodynamics, as this often implies an additional step, usually proposed to involve the spray-drying of nanocarriers to generate nano-in-microcarriers that can be deposited in the lung. In many subjects, the region still needs to develop before inhalable nanocarriers reach clinical trials. It is not only the problem of more practical in essential *in vivo* assays, but the toxicological evaluation often plays a deciding role. Helpful innovations have emerged, such as 3D printing, which has been used to print artificial airways, enabling particle flowability and dose assessment to be studied. This application was identified by Lim et al. in the neonate, demonstrating a useful tool for improving the ethics associated with formulation testing and providing solutions for children born with respiratory complications (Lim et al., 2018).

Overall, this research highlights an integrative process that considers the advances made at the basic science level, clarifying the pathophysiological implications of clinical conditions, and developing methods and techniques for achieving pharmacological goals. Several works with inhalable nanocarriers that have shown potential have been identified, even with the current shortcomings. Even then, all concerns lead to a common purpose of achieving expertise to permit nanocarriers to be designed to facilitate improved lung therapy.

Nano-aggregates, massive porous crystals, and other formulation methods may be used to ensure stable and highly effective distribution of nanoparticles to the lungs using particle engineering. Both physical targeting with MPs and successful targeting with ligand anchoring have been shown to improve inhaled anticancer drug targeting and efficacy. It has also been reported that nanoparticles facilitate the delivery of anticancer drugs in combination with antisense oligonucleotides, making them a promising candidate for treating drug-resistant lung cancers. The use of enlargement of particle size and surface modulation (e.g. with PEG and surfactants) to reduce the phagocytic clearance of nanoparticle formulations has been proposed. Finally, inhaled nanoparticulate chemotherapy has much promise for lung cancer care. More research into the safety and effectiveness of this technology in clinical settings is needed.

Disclosure statement

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