the free counterpart whose release occurred over a few hours [94]. Liposomes and niosomes with antiasthmatic drugs for inhalation therapy were also developed for SDR in the lungs with positive results [95, 96].

## 7. NANOBIOTECHNOLOGY SOLUTIONS AGAINST PULMONARY INFECTIONS AND CANCER

Infectious diseases and cancer are among the top 10 causes of death worldwide [97]. According to the WHO, of the 56.9 million deaths around the world in 2016, lower respiratory infections were the most deadly communicable diseases, with 3 million deaths, and lung cancer was the most deadly cancer with 1.7 million deaths and tuberculosis claimed 1.3 million deaths [97]. Among lung infections, pneumonia, tuberculosis, aspergillosis, influenza, and chronic obstructive CF-related bacterial diseases are increasingly hard to treat and can be life threatening. Noteworthy, for the effective treatment of intracellular infections, such as tuberculosis, histoplasmosis, and atypical pneumonia, the inhaled therapeutic formulation should be easily internalized by alveolar macrophages. For this purpose, active targeting of the nanocarriers at the mannose receptors present in the cell surface of macrophages can be achieved by anchoring mannose residues onto the carrier surface. Other ligands for macrophage targeting can include galactomannan, maleylated bovine serum albumin, *O*-steroyl amylopectin, *O*-palmitoylmannan, *p*-aminophenyl-mannopyranoside, *O*-palmitoylpullulan, the tetrapeptide tufsin, and the surfactant proteins SP-A and SP-D [98, 99]. A similar approach can be achieved for active targeting at cancer cells using nanocarriers decorated in their surface with proteins, antibodies, or other extracellular ligands able to interact with specific cell markers that, for example, are overexpressed in cancer. Thus, using nanotechnology, the performance of many drugs can be significantly improved to an extent not achievable by conventional formulations, as it was mentioned in Sections 2 and 4, and in addition to SDR, nano-based formulations can also be used to overcome or reduce the problems of drug resistance and biofilms in respiratory infectious diseases [100].

As stated earlier, the local pulmonary deposition and delivery of an inhaled drug facilitate a targeted treatment of other respiratory conditions other than asthma and COPD, such as the treatment of pulmonary aspergillosis with voriconazole, the delivery of mucolytics and antibiotics in CF patients, the delivery of rifampicin and capreomycin in the treatment of tuberculosis, or the delivery of antitumorals in patients with lung cancer or lung metastases, without the need for high dose exposures by other routes of administration, decreasing severe systemic side effects, and increasing the therapeutic responses. For example, nebulization of paclitaxel-loaded SLNPs in mice with lung metastases achieved a 20-fold decrease in $IC_{50}$ values when compared with the intravenous administration of paclitaxel [101].

To optimize the efficacy of inhaled drugs, many strategies were described in addition to SDR using nanotechnology, as it is the incorporation of protease inhibitors, mucolytics, or PEG with the (nano)formulation so as to overcome many of the mechanical and biochemical barriers present in the respiratory tract, which in turn lead to an enhanced lung deposition of the drug and a better inhaler device performance [102]. For example, in CF, there is an evidence that NP- or microparticle-based PDD for antibiotics and mucolytics can control many CF complications of inhaled therapy, including the adherent viscous mucus obstructing the airways and protecting bacterial biofilm sand the development of bacterial resistance. An interesting approach was the development of $CaCO_3$ microparticles loaded with the mucolytic DNase and the antibiotic levofloxacin to treat local infections in CF. [54] Inhalation of antipseudomonal antibiotics (tobramycin, colistin, and aztreonam) using lipid-based systems such as liposomes and SLNPs is most intensively investigated with liposomal amikacin (Arikayce), recently approved by the FDA. Advances in other NP- or microparticle-based PDD for other antibiotics, such as antistaphylococcal vancomycin, are still in early stages [103].

Among antifungal drugs for PDD, liposomal amphotericin B (AmB) was delivered with vibrating mesh nebulizers that maintain the liposome integrity. Chitosan-coated liposomes, prepared by an ethanol-based proliposome method, was demonstrated to be a promising carrier system for the delivery of AmB, preserving lung surfactants using an air-jet nebulizer [104]. AmB lipid nanoemulsion and itraconazole nanosuspension aerosols and PLGA-NPs containing voriconazole were also developed [105–107].

For tuberculosis, a dry powder consisting of PLGA-NPs containing three of the first-line antitubercular drugs (i.e., rifampicin, isoniazid, and pyrazinamide) was formulated and nebulized in *Mycobacterium tuberculosis*-infected guinea pigs and showed enhanced bioavailability and reduced dosing frequency when compared with oral or intravenous administration of the parent drugs [108]. Nanopolymersomes and hydrolyzed galactomannan-modified NPs and flower-like polymeric micelles for the active targeting of rifampicin at alveolar macrophages were developed [109, 110].

Regarding lung cancer, nonsmall cell lung cancer (NSCLC) is the most common type, and traditional chemotherapy using taxanes (paclitaxel and docetaxel) or