CHAPTER

6 Nanocarrier-based targeted pulmonary delivery: novel approaches for effective lung cancer treatment

6.1 Introduction

Cancer is among the scariest diseases and leading causes of death worldwide. It is often whispered about as incurable and its victims die a very painful death. No doubt, it is a serious disease taking millions of lives every year (Bandyopadhyay et al., 2015). According to the World Health Organization (WHO), around 8.8 million deaths occurred due to cancer around the world in 2015 (http://www.who.int/news-room/fact-sheets/detail/cancer). The Cancer Research UK reported 14.1 million new cancer cases, 8.2 million deaths from cancer, and nearly 32.6 million people living with cancer around the world in year 2012 (Stewart and Wild, 2014). In 2018 609,640 cancer deaths and 1,735,350 new cancer cases are expected to occur in the United States (Siegel et al., 2017). Lung, bowel, female breast, and prostate cancers are the most common cancers around the globe. Collectively, these four cancers accounts for nearly 4/10 of all cancers diagnosed worldwide (Siegel et al., 2011). Among these, lung cancer is the most frequently occurring cancer in men worldwide. Roughly 1 in 10 of all cancers diagnosed in men turn out to be lung cancer.

Lung cancer is the most common cancer, accounting for nearly 1,378,400 mortalities per year worldwide (Didkowska et al., 2016; Torre et al., 2016) with a 15% overall 5-year survival rate (Mittal et al., 2016). Histologically, lung cancer is mainly divided into two types: small-cell lung carcinoma (SCLC), which constitutes about 13% of total lung cancer cases, and non-SCLC (NSCLC). Small-cell lung cancer is significantly more aggressive than NSCLC, as it is far less sensitive to chemotherapy. About 80%–85% of NSCLC patients show metastasis characterized by distant and local propagation of the disease into lymph nodes and other organs (Zarogoulidis et al., 2012). Subtypes of NSCLC include large-cell lung cancer, epidermoid or squamous-cell carcinoma, bronchoalveolar carcinoma, and adenocarcinoma (Abdelaziz et al., 2017). The overall 5-year survival rate of NSCLC patients in all stages remains below 20% due to lack of effective therapeutic methods and has not been appreciably improved over the

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phophatidylglycerols, phosphatidylcholines, cholesterol, and several other anionic lipids (Goerke, 1998). The remaining 10% by weight of pulmonary surfactant is composed of four proteins: the hydrophilic SP-C and SP-A and the liphophilic SP-B and SP-D (Johansson et al., 1994). Lipids, enzymes, and other detergents can destroy this surfactant. NPs or drugs first come in contact with surfactant layer in the lungs upon their inhalation and the interactions between them can critically affect the fate and lifetime of the inhaled substance in the airways (Hidalgo et al., 2015). Because it is basically made out of lipids, the pulmonary surfactant system offers an excellent lipophilic environment for solubilization of various less water-soluble drugs (Haitsma et al., 2001). However, pulmonary surfactant is not a good medium for retaining water-soluble drugs due to its major lipid component DPPC (Vermehren et al., 2006). Therefore it is necessary to consider the pulmonary surfactant system when formulating a pulmonary drug-delivery system.

6.10.2 The epithelial surface fluid

The mucus blanket is a thin fluid layer about 5 μm thick that covers the walls of the respiratory tract. This mucus blanket barrier works to trap any foreign substance for subsequent removal and protects the lungs' surface epithelium from dehydration when unsaturated air is inspired. Before entering the blood circulation, the drug or carrier must cross this thin layer of fluid. This layer tends to collect at the corners of the alveoli and is covered by an attenuated layer of surfactant (Shah et al., 2012). Cholinergic drugs or α-adrenergic antagonists act directly on the submucosal glands' secreting cells, resulting in the hypersecretion of mucus. Mucus is stored in peripheral granules that works as a mucus reservoir and secretes it when exposed to an irritating stimulus. Disease state can also modify the composition of the fluids and distribution of the cell goblets in the respiratory tract. This is therefore also a key component to be considered when developing a pulmonary drug-delivery system.

6.10.3 The epithelium

The transepithelial transport of molecules is characterized by large quantitative differences along the respiratory tract epithelium, from the upper airways with nasopharynx, trachea, and large bronchi to the lower respiratory tract with small bronchioles and alveoli. Due to lower regional blood flow and smaller surface area in the upper airways, the transport of molecules is limited. In addition to this, the upper respiratory tract displays a high filtering capacity and clears nearly 70%–90% of pressurized particles. However, more than 95% of the lungs' total surface area is formed by the smaller airways and alveolar spaces in the respiratory zone. This part of lung is also directly connected to the systemic blood circulation through the pulmonary circulation (Weibel et al., 1963).