Chapter 1

Introduction

1.1. Introduction

Cancer is characterized by uncontrolled multiplication of cells [1]. Lung cancer originates from within the lungs and if not treated can spread further to other vital organs such as brain via lymph nodes and vice-versa. Lung cancers broadly categorized as small cell and non-small cell lung cancers. These different kinds of lung tumors feature diverse growth patterns and need treatments accordingly. Non-small cell lung cancer (NSCLC) is most commonly occurring than small cell lung cancer (SCLC) [2]. The percent incidence of NSCLC is approximately from 80 to 85% among all lung cancer cases [3]. About 30% of these arise from the cells that line the cavities and surfaces of the human body. This usually starts in the lung's exterior region (adenocarcinomas). Another type constitutes 30% that involve the cells that line the ducts of the respiratory tract (squamous cell carcinoma). A rare subtype of adenocarcinoma involves the principle sites of gas exchange, i.e. the alveoli and is named as adenocarcinoma in situ (AIS). This AIS is not as aggressive and invasive as other types and therefore do not necessitate immediate intervention. Remaining subtypes of NSCLC include large-cell carcinoma and large-cell neuroendocrine tumors which are highly invasive [4, 5].

- **Squamous-cell carcinoma**

It constitutes about 25–30% of NSCLC. It starts from the epithelial cells of bronchi, particularly from premature squamous cells in the airways. Squamous cell carcinoma is highly linked to cigarette smoking [6].

- **Adenocarcinoma**

Adenocarcinoma accounts for 40% of all NSCLC cases. It usually originates from type II alveolar cells which are secretory in function. It is the most frequently occurring lung cancer in smokers as well as nonsmokers, in both sexes of all ages. It mainly occurs in the lung periphery and the possible explanation may be the provision of filters in

cigarettes which avoid large particles from entering into the deeper regions of lungs. Adenocarcinoma is not aggressive and more likely be diagnosed before its further spread to distant organs from lungs [7].

- **Large-cell carcinoma**.

It constitutes about 5–10% of all reported lung cancer cases. Although no sign of mutations in squamous or glandular tissue, only by exclusion of other causes, it is frequently diagnosed. From the central area of the lungs where it starts, it spreads to lymph nodes, then to the chest wall followed by distant organs too. These tumors are evidently linked to smoking [8].

Pleural malignancy cases, in addition to above types, are also reported every year. The 5-year survival rate however remains lower than 10% and as of now, no potential cure for such cases is available. The global incidence of plural malignancy is expected to increase, particularly in developing countries in the coming years [9-11].

Small-cell lung cancer (SCLC) accounts for 20% of total lung cancers. Unlike NSCLC, SCLC is quite aggressive in that it develops and spreads quickly. The same factor makes it highly responsive to medical intervention. Still, it's quite difficult to treat. Few cases were reported where the patient was diagnosed with both NSCLC and SCLC. Mesothelioma or plural malignancy is usually caused by exposure to asbestos dust. Carcinoid cancers originate within the neuroendocrine cells. Lung tumors may become quite larger by the time patient experience any symptoms. Due to the initial symptoms like common cold and other conditions, patients generally do not go for medical support immediately and this is the principle cause of under diagnosis of lung cancer at early stages [12].

1.2. Risk factors for lung cancer

- **Tobacco smoke**

Smoking is the most contributing risk factor for lung cancer. Smoking is the major reason for almost 80% of deaths related to lung cancer. The risk of incidence of lung cancer associated with smoking is many times higher than that of in non-smokers. The longer and the more packs a day one smokes, the greater the risk of lung cancer.

- **Second hand smoke**

Passive smoking, i.e. inhaling the smoke left by others may also increase the risk of lung cancer incidence. Second hand smoke or passive smoking is estimated to result in nearly 7,000 lung cancer associated deaths every year.

- **Exposure to radon**

Radon is a naturally occurring radioactive gas that results from the release of uranium from soil and rocks into the air. According to the US Environmental Protection Agency (EPA), radon is the second most contributing cause to lung cancer incidence and is the leading cause of lung cancer among non-smokers.

- **Exposure to asbestos**

People working with or come in contact to asbestos (those working in mines, mills, textile industries, shipyards and places with thermal insulation) are at several times higher risk of death by lung cancer. Lung cancer risk is even more higher in workers who smoke and also exposed to asbestos fibers. However, it is unclear that what extent and duration of low-level exposure to asbestos actually pose the threat of lung cancer.

- **Exposure to other occupation related carcinogens**

The workplace-associated exposure to other carcinogens such as radioactive ores of uranium, chemicals and minerals like arsenic, silica, beryllium, nickel compounds,

cadmium, vinyl chloride, chromium and coal products, mustard gas, chloromethyl ethers and diesel exhaust.

- **Air pollution**

In highly populated cities, air pollution seems to increase the threat of lung cancer notably. But compared with that of smoking, the risk associated with air pollution is relatively low. According to some studies, approximately 5% of all lung cancer related deaths are estimated to be because of the outdoor air pollution.

- **Arsenic in drinking water**

Due to the high levels of arsenic in the drinking water in some regions of Southeast Asia and South America, the people living in those regions are found to be at greater risk of lung cancer. As reported by various researchers, the levels of arsenic in the water from these regions are considerably higher than those typically found in that of the United States. For most of the Americans who rely on public water systems for drinking, water is not a major source of arsenic [13].

1.3. Symptoms of lung cancer

Dyspnoea: Atelectasis, pleural effusion and rarely diaphragmatic paralysis due to spread of tumour to the phrenic nerve.

Oedema in the head and neck: When vena cava superior is affected with tumour infiltration, it leads to swelling in the areas of head and neck, which necessitates the patient to be admitted in hospital for critical care.

Cough: If the persons with no previous episodes of lung disease experience cough for more than six weeks and even if there is a change in the cough pattern in patients with previous history of bronchitis need immediate referral for chest x-ray for hoarseness.

Haemoptysis: Haemoptysis for the first time promptly requires a chest x-ray. Haemoptysis is quite often in individuals with chronic bronchitis but patients with lung cancer may also experience this. For the individuals in high risk zone for lung cancer such as smokers with age > 50 years, haemoptysis for longer than a week should opt for bronchoscopy even though the chest x-ray reveals no pathological lesions.

Thoracic pain: Thoracic pain is the result of tumour infiltration to the chest and if it becomes persistent, it warrants chest x-ray particularly in the individuals who are at higher risk of lung cancer. As the tumour progress to ribs and brachial plexus, patients usually experience pain in the upper region of the chest that is radiating to shoulder and arm (Pancoast tumour).

Bone pain: It is quite common in lung cancer as there are higher rates of bone metastases and therefore if there is bone pain without any reason, patient should be referred to chest x-ray [14-16].

1.4. Causative agent for lung cancer

90% of lung cancer cases arise due to the habit of smoking. Tobacco smoke contains more than 7,000 chemicals and out of which, at least 70 are confirmed as highly carcinogenic. Passive smoking (inhaling secondhand smoke) is a major contributing factor to lung cancers. From the moment cigarette smoke enters into the lungs, it immediately starts harming the lung tissue. The lungs can manage to repair the initial damage, but persistent insult makes it harder for the lungs to reverse the damage. At this stage, cells start to behave abnormally, leading to the development of lung cancer. SCLC is highly correlated with heavy smoking. When subjects quit to smoke, their risk of getting lung cancer is slowly lowered over time. Inhaling radon, a naturally occurring radioactive gas, is the second leading cause, according to the American Lung Association. Radon enters

buildings through small cracks in the foundation. Smokers who are also exposed to radon have a very high risk of lung cancer. Breathing in other hazardous substances, especially over a long period of time, can also cause lung cancer [17]. Substances that can cause lung cancer are: arsenic, cadmium, chromium, nickel, some petroleum products, uranium. Inherited genetic mutations may make subjects more prone to develop lung cancer, especially if subjects smoke or are exposed to other carcinogens. Sometimes, there's no obvious cause for lung cancer [18].

1.5. Stages of lung cancer

Cancer stages tell how far the cancer has spread and guide the treatment. The chance of successful or curative treatment is much higher when lung cancer is diagnosed and treated in the early stages, before it spreads [19].

1.5.1. Non-small cell lung cancer has four main stages:

Stage 1: Cancer is found in the lung, but it has not spread outside the lung.

Stage 2: Cancer is found in the lung and nearby lymph nodes.

Stage 3: Cancer is in the lung and lymph nodes in the middle of the chest.

Stage 3A: Cancer is found in lymph nodes, but only on the same side of the chest where cancer first started growing.

Stage 3B: Cancer has spread to lymph nodes on the opposite side of the chest or to lymph nodes above the collarbone.

Stage 4: Cancer has spread to both lungs, into the area around the lungs, or to distant organs.

Small-cell lung cancer (SCLC) has two main stages. In the limited stage, cancer is found in only one lung or nearby lymph nodes on the same side of the chest [20-22].

1.6. Risk factors for lung cancer

The biggest risk factor for lung cancer is smoking. That includes cigarettes, cigars, and pipes. Tobacco products contain thousands of toxic substances. According to the Centers for Disease Control and Prevention (CDC)Trusted Source, cigarette smokers are 15 to 30 times more likely to get lung cancer than nonsmokers. The longer smoker, the greater the chance of developing lung cancer. Quitting smoking can lower that risk. Breathing in secondhand smoke is also a major risk factor. Every year in the United States, about 7,300 people who've never smoked die from lung cancer caused by secondhand smoke. Exposure to radon, a naturally occurring gas, increases their risk of lung cancer. Radon rises from the ground, entering buildings through small cracks. It's the leading cause of lung cancer in nonsmokers. A simple home test can tell them if the level of radon in their home is hazardous. Their risk of developing lung cancer is higher if they're exposed to toxic substances such as asbestos or diesel exhaust in the workplace [23-25].

1.7. Diagnosing lung cancer

After a physical examination and imaging tests: an abnormal mass can be seen on X-ray, MRI, CT, and PET scans. These scans produce more details and can find smaller lesions. Sputum cytology: if produce phlegm when patients cough, microscopic examination can determine if cancer cells are present [26,27].

A biopsy can determine if tumor cells are cancerous. A tissue sample can be obtained by:

Bronchoscopy: While under sedation, a lighted tube is passed down patient's throat and into lungs, allowing closer examination.

Mediastinoscopy: The doctor makes an incision at the base of the neck. A lighted instrument is inserted and surgical tools are used to take samples from lymph nodes. It's usually performed in a hospital under general anesthesia.

Needle: Using imaging tests as a guide, a needle is inserted through the chest wall and into the suspicious lung tissue. Needle biopsy can also be used to test lymph nodes.

Tissue samples are sent to a pathologist for analysis. If the result is positive for cancer, further testing, such as a bone scan, can help determine if cancer has spread and to help with staging. For this test, patients will be injected with a radioactive chemical. Abnormal areas of bone will then be highlighted on the images. MRI, CT, and PET scan are also used for staging [28-31].

1.8. Treatment for lung cancer

It's usually a good idea to seek a second opinion before beginning treatment. Treatment for non-small cell lung cancer (NSCLC) varies from person to person. Much depends on specific details of patient health.

Stage 1 NSCLC: Surgery to remove a portion of the lung may be all patients need. Chemotherapy may also be recommended, especially if they're at high risk of recurrence.

Stage 2 NSCLC: may need surgery to remove part or all of their lung. Chemotherapy is usually recommended.

Stage 3 NSCLC: may require a combination of chemotherapy, surgery, and radiation treatment.

Stage 4 NSCLC is particularly hard to cure. Options include surgery, radiation, chemotherapy, targeted therapy, and immunotherapy.

Options for small cell-lung cancer (NSCLC) also include surgery, chemotherapy, and radiation therapy. In most cases, the cancer will be too advanced for surgery. Clinical trials provide access to promising new treatments. Some people with advanced lung cancer choose not to continue with treatment [32,33].

1.8.1. Nanomedicine and nanotheranostics for lung cancer therapy

Nanotechnology offers new solutions for the development of cancer therapeutics that display improved efficacy and safety. Although several nanotherapeutics have received clinical approval, the most promising nanotechnology applications for patients still lie ahead [34]. Nanoparticles display unique transport, biological, optical, magnetic, electronic, and thermal properties that are not apparent on the molecular or macroscale, and can be utilized for therapeutic purposes. These characteristics arise because nanoparticles are in the same size range as the wavelength of light and display large surface area to volume ratios [35]. The large size of nanoparticles compared to conventional chemotherapeutic agents or biological macromolecule drugs also enables incorporation of several supportive components in addition to active pharmaceutical ingredients. These components can facilitate solubilization, protection from degradation, sustained release, immunoevasion, tissue penetration, imaging, targeting, and triggered activation. Nanoparticles are also processed differently in the body compared to conventional drugs. Specifically, nanoparticles display unique hemodynamic properties and biodistribution profiles. Notably, the interactions that occur at the bio-nano interface can be exploited for improved drug delivery [36].

The word “nanotheranostic” refers to the simultaneous integration of diagnosis and therapy, which can be very useful to optimize efficacy and safety of therapeutic agents. The word “nanotheranostic nanomedicine” can be explained as, colloidal nanoparticles ranging in sizes from 10 to 1000 nm (<1 μm). Theranostic nanomaterials have shown potential for targeted drug delivery, image-guided surgery and minimally invasive interventions [37]. Various nanomedicine platforms can be used as highly efficient carriers for therapeutic and theranostic purpose after the attachment of various drugs, ligands and macromolecules to its surface for the targeting of lung cancer treatment. This

nanomedicine can then specifically bind to receptors that are overexpressed on the membrane of the cells to be targeted as advanced nanomedicine. The theranostic nanomedicine can be circulated for prolonged periods in the lungs, lymph, blood, evading host defenses, and release drug and diagnostic agent together in the diseased cells and simultaneously facilitate *in-vivo* imaging and therapy [38,39].

1.8.1.1. Liposomes based nanotheranostics for lung cancer

Liposomes are artificially generated vesicles with a bilayer structure, spontaneously formed when natural or synthetic amphipathic lipids get dispersed in water. Ever since their inception, they have largely been explored as drug delivery vehicles because of their biocompatibility and beneficial safety profile. The bilayer structure of liposomes comprises of phosphatidylcholine, cholesterol, etc. and they are known to carry an array of small molecule and large molecule therapeutics of hydrophobic and hydrophilic origin. Their surface can be modified by grafting polyethylene glycol (PEG), which prolongs their half-life in circulation [40,41]. Doxil and Myocet, two leading Doxorubicin liposomes, received FDA approval in 1995 and 1999, respectively, followed by many of the category [42,43]. Despite availability of around sixteen liposomal drugs in the market as of now, very few formulations are designated as the treatment modality for NSCLC.

In 2014, Cheng et al. [44] exploited EGFR binding affinity of a novel peptide GE11 in doxorubicin-loaded liposomes and characterized them in terms of size distribution, zeta potential, drug entrapment efficiency, and morphology. It turned out that optimal GE11 density was 10% in A549 cytotoxicity. Major involvement of clathrin-mediated endocytosis pathway was also determined by cellular uptake experiments. Using a near infrared (NIR) fluorescence imaging system, they found that the accumulation and

retention of the GE-11 modified liposomes was 2.2-fold higher compared to unmodified liposomes [45].

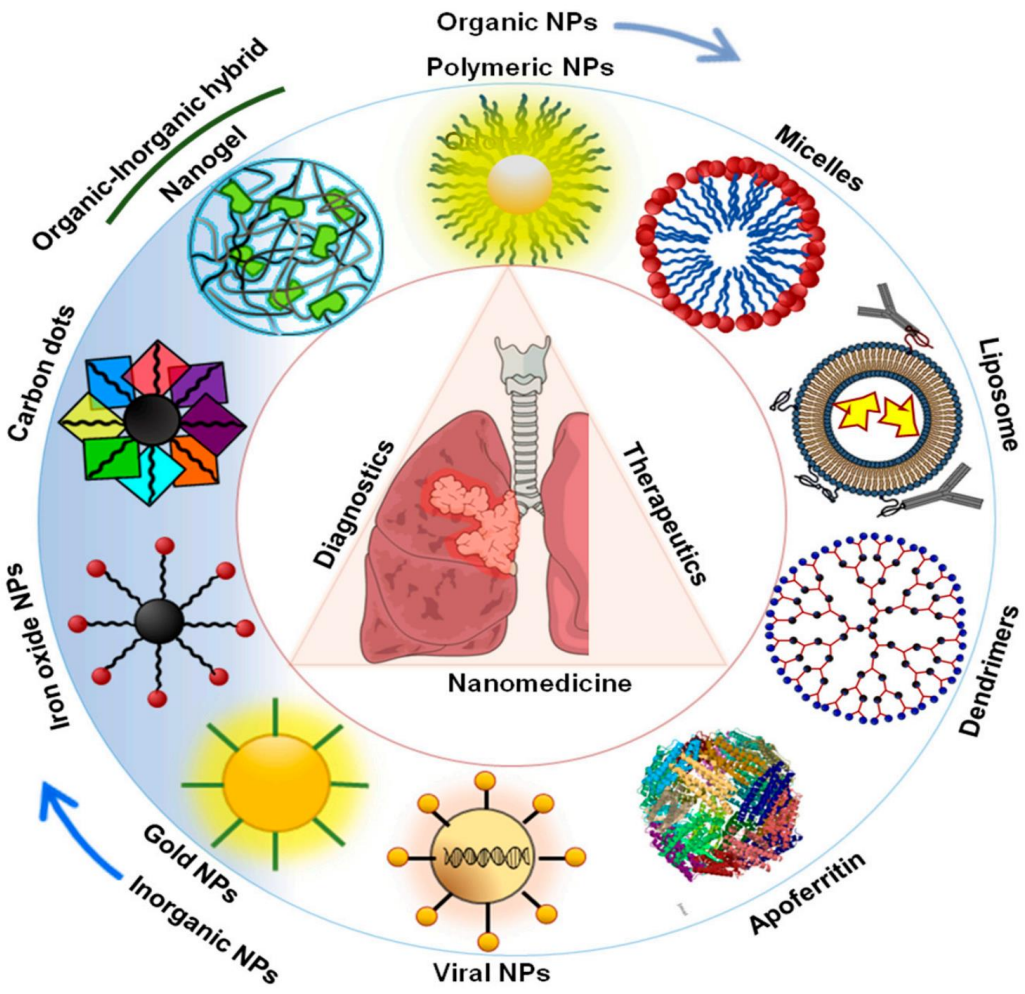

Figure 1.1. Schematic representation of different nanomedicine approaches in lung cancer therapy.

For effective delivery of triptolide (TPL) to NSCLC by pulmonary administration, a dual ligand (anti-carbonic anhydrase IX (anti-CA IX) antibody and CPP33) modified triptolide-loaded liposomes (dl-TPL-lip) was designed, synthesized, and characterized by Lin et al. [46] in 2018. The cell killing ability was evaluated by an apoptosis assay. Importantly, superior tumor penetration and tumor growth inhibition efficacy of the liposomes were further demonstrated using 3D tumor spheroids. Pharmacokinetics

studies in rats after endotracheal administration of the liposomal formulations exhibited a lower concentration of TPL in circulation [47].

1.8.1.2. Polymeric nanoparticles based nanotheranostics for lung cancer

Polymeric NPs can be prepared either by nanoprecipitation or a double emulsion method via self-assembly of biodegradable amphiphilic block-copolymers with varying hydrophobicity's between blocks and are suitable for systemic administration. The core-shell structure of polymeric NPs facilitates encapsulation of hydrophobic drugs, extension of circulation time, and sustained drug release. Their surfaces can also be decorated for targeted drug delivery [48,49]. For instance, Genexol-PM is a formulation of paclitaxel and poly (D,L-lactide)-b-polyethylene glycol-methoxy (PLGA-mPEG), which is already marketed for metastatic breast cancer therapy in Korea and other European countries [50,51].

In 2015, Jiang [52] developed a nano-carrier encapsulating Crizotinib (approved for EML4-ALK fusion positive lung cancer) within polylactide tocopheryl polyethylene glycol 1000 succinate (PLA-TPGS), which showed a sustained release, induced remarkable cytotoxicity in NCIH3122 lung cancer cells, and noticeable early and late apoptosis. The polymeric nanoparticle followed an endocytosis-mediated cellular uptake. Interestingly, in 2017, Hu et al. [53] reported on the efficiency of paclitaxel (PTX) loaded Polycaprolactone/ Poly (ethylene glycol)/Polycaprolactone (PCEC) nanoparticles combined with chronomodulated chemotherapy for use in lung cancer. The authors set out to map the suitable time of the day for administering drug loaded nano-carriers by making out the crucial role of circadian rhythms in cancer propagation. The combination therapy demonstrated remarkable tumor growth inhibition *in-vivo*, while it turned out that 15HALO is optimal for chemotherapy. Very recently, to circumvent the low targeting

capacity of nanoparticles, Wang et al. used mesenchymal stem cells (MSC) as a carrier for drug delivery loaded with nanoparticles with docetaxel (DTX). MSC proved its superiority over fibroblasts in drug loading. Both cellular and animal experiments justified the intercellular translocation of nanoparticles from MSC to cancer cell. It also inhibited primary tumor growth *in-vivo* [54]. Much to our intrigue, Ganesh et al. explored HA-PEI/PEG nano-carriers for CD44-targeted siRNA delivery to lung cancer cells. They undertook a detailed structure-activity study for optimal siRNA encapsulation efficiency. Importantly, the targeted HA-PEI/PEG nanosystems encapsulating SSB/PLK1 siRNA showed higher cellular uptake and sequence specific gene knockdown *in-vivo* both in sensitive and resistant A549 primary and metastatic [55].

1.8.1.3. Micelles nanomedicine for lung cancer therapy

Polymeric micelles have gained interest as novel drug delivery systems for the treatment and diagnosis of cancer, as they offer several advantages over conventional drug therapies. This includes drug targeting to tumor tissue, *in-vivo* biocompatibility and biodegradability, prolonged circulation time, enhanced accumulation, retention of the drug loaded micelle in the tumor and decreased side effects [56].

Cancer chemotherapy effect has been largely limited by cell autophagy and little drug accumulation at the action sites. He *et al*, designed an intelligent strategy involving paclitaxel (PTX) polymer micelles in response to biological functions of ambroxol. The amphiphilic polymers polyethyleneglycol-polylactic acid (PEG-PLA) and Pluronic P105 were selected as nanocarriers to encapsulate PTX to form into lung affinity PEG-PLA/P105/PTX micelles. Ambroxol which can up-regulate the secretion of pulmonary surfactant (PS) and inhibit autophagy was hired to change the microenvironment of the lung, thereby promoting the lung accumulation and increasing cell-killing sensitivity of

the micelles. The physical and chemical properties of the micelles were characterized including size, morphology, critical micellar concentration (CMC) and *in-vitro* drug release behavior. The therapeutic effects of the combination regimen were characterized both *in-vitro* and *in-vivo* including study on ambroxol in promoting the secretion of pulmonary surfactant, *in-vitro* cytotoxicity, cellular uptake, Western blotting, *in-vivo* biodistribution, *in-vivo* pharmacokinetics and *in-vivo* antitumor efficacy. The PEG-PLA/P105/PTX micelles showed a particle size of 16.7 ± 0.5 nm, a nearly round shape, small CMC and sustained drug release property. Moreover, the *in-vitro* results indicated that Ax could increase PS and LC3 protein secretion and enhance the cytotoxicity of PEG-PLA/P105/PTX micelles toward A549 cells. The *in-vivo* results indicated that the combination therapeutic regimen could promote the micelles to distribute in lung and enhance the therapeutic effect on lung cancer. This multifunctional approach of modulating the tumor microenvironment to enhance drug transportation and cell-killing sensitivity in the action sites might offer a new avenue for effective lung cancer treatment [57].

1.8.1.4. Mesoporous Silica as nanocarriers for lung cancer therapy

Since mesoporous silica-based nanomaterials were first employed as drug delivery vehicles in 2001, mesoporous silica nanoparticles (MSNs) have attracted much attention in the field of drug delivery. MSNs present a number of excellent material properties, such as good *in-vitro* and *in-vivo* biocompatibility, chemical and mechanical stability, and easy functionalization ability [58]. In fact, the favorable structural features of MSNs, such as intrinsic tunable pore size, high pore volume, and high surface area, could guarantee an extraordinary drug loading capacity and high encapsulation efficiency of a wide variety of cargo molecules. Additionally, their surfaces can be functionalized with “gate

keepers," some of which are highly sensitive to a variety of exogenous and endogenous stimuli, such as light, pH, temperature, and remote magnetic actuation, enabling controlled and on-command release of the cargo [59].

Cheng *et al.*, developed a nanocarrier system of TPGS functionalized polydopamine-coated mesoporous silica nanoparticles (NPs) is developed for sustainable and pH-responsive delivery of doxorubicin (DOX) as a model drug for the treatment of drug-resistant non-small cell lung cancer. Such nanoparticles are of desired particle size, drug loading, and drug release profile. The surface morphology, surface charge, and surface chemical properties are also successfully characterized by a series of techniques such as transmission electron microscopy (TEM), X-ray photoelectron spectroscopy (XPS), Brunauer-Emmett-Teller (BET) method, thermal gravimetric analysis (TGA), dynamic light scattering (DLS), and Fourier transform infrared spectroscopy (FTIR). The normal A549 cells and drug resistant A549 cells are employed to access the cytotoxicity and cellular uptake of the NPs. The therapeutic effects of TPGS-conjugated nanoparticles are evaluated *in-vitro* and *in-vivo.* Compared with free DOX and DOX-loaded NPs without TPGS ligand modification, MSNs-DOX@PDA-TPGS exhibits outstanding capacity to overcome multidrug resistance and shows better *in-vivo* therapeutic efficacy. This splendid drug delivery platform can also be sued to deliver other hydrophilic and hydrophobic drugs [60].

1.9. Lung cancer and life expectancy

Once cancer enters the lymph nodes and bloodstream, it can spread anywhere in the body. The outlook is better when treatment begins before cancer spreads outside the lungs. Other factors include age, overall health, and how well subjects respond to treatment.

Because early symptoms can be easily overlooked, lung cancer is usually diagnosed in later stages. Survival rates and other statistics provide a broad picture of what to expect. There are significant individual differences, though. Current survival statistics don't tell the whole story. In recent years, new treatments have been approved for stage 4 non-small cell lung cancer (NSCLC). Some people are surviving much longer than previously seen with traditional treatments [61,62].

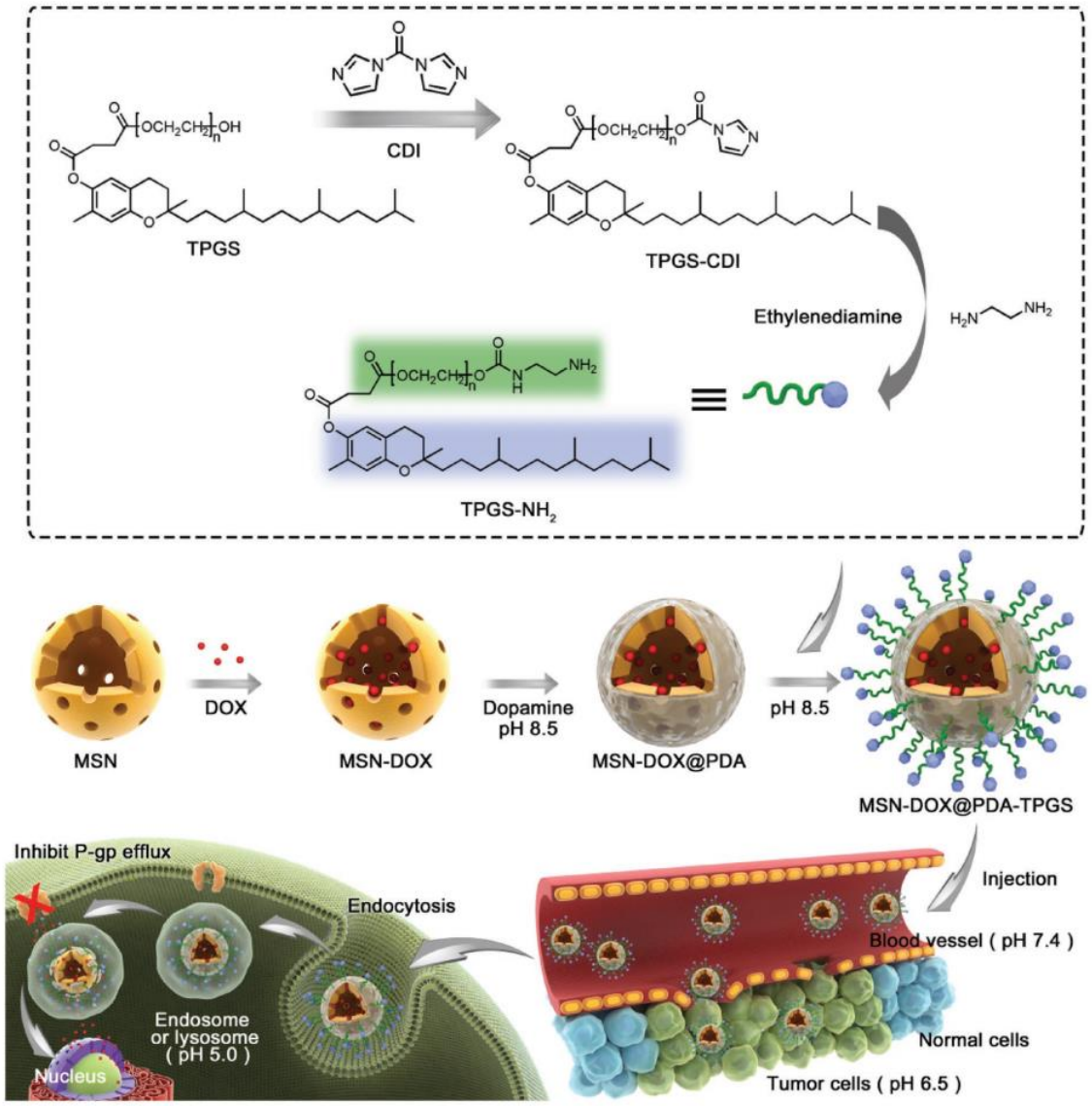

Figure 1.2. Schematic illustration of doxorubicin-loaded MSNs-DOX@PDA-TPGS [60]

***1.9.1. The following are the estimated five-year survival rates for NSCLC by SEER stage*:**

Localized: 60 percent

Regional: 33 percent

Distant: 6 percent

Small-cell lung cancer (SCLC) is very aggressive. For limited stage SCLC, the five-year survival rate is 14 percent. Median survival is 16 to 24 months. Median survival for extensive stage SCLC is six to 12 months. Long-term disease-free survival is rare. Without treatment, median survival from diagnosis of SCLC is only two to four months. The relative five-year survival rate for mesothelioma, a type of cancer caused by asbestos exposure, is 5 to 10 percent [63,64].

1.10. Facts and statistics about lung cancer

Lung cancer is the most common cancer in the world. According to the American Lung Association, there were 2.1 million new cases in 2018, as well as 1.8 million deaths from lung cancer. The most common type is non-small cell lung cancer (NSCLC), accounting for 80 to 85 percent of all cases, according to the Lung Cancer Alliance. Small-cell lung cancer (SCLC) represents about 15 to 20 percent of lung cancers. At the time of diagnosis, 2 out of 3 people with SCLC are already in the extensive stage. Anyone can get lung cancer, but smoking or exposure to secondhand smoke is linked to about 90 percent of lung cancer cases. According to the Centers for Disease Control and Prevention (CDC)Trusted Source, cigarette smokers are 15 to 30 times more likely to get lung cancer than nonsmokers. In the United States, each year about 7,300 people who never smoked die from lung cancer caused by secondhand smoke. Former smokers are still at risk of developing lung cancer, but quitting can significantly lower that risk. Within 10 years of

quitting, the risk of dying from lung cancer drops by half. Tobacco products contain more than 7,000 chemicals. At least 70 are known carcinogens. According to the US Environmental Protection Agency (EPA), radon is responsible for about 21,000 lung cancer deaths every year in the United States. About 2,900 of these deaths occur among people who have never smoked. Black people are at higher risk of developing and dying from lung cancer than other racial and ethnic groups [65-67].