Chapter-1

Introduction
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Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms. Cancer arises from one single cell. The transformation from a normal cell into a tumour cell is a multistage process, typically a progression from a pre-cancerous lesion to malignant tumours. These changes are the result of the interaction between a person's genetic factors and three categories of external agents, including:

- physical carcinogens, such as ultraviolet and ionizing radiation;
- chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin (a food contaminant) and arsenic (a drinking water contaminant); and
- biological carcinogens, such as infections from certain viruses, bacteria or parasites.

One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and, which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as metastasizing. Metastases are the major cause of death from cancer.

Cancer is the leading cause of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 (Stewart and Wild, 2014). The number of new cases is expected to rise by about 70% over the next 2 decades (WHO, 2016). Among men, the 5 most common sites of cancer diagnosed in 2012 were lung, prostate, colorectum, stomach, and liver. Among women, the 5 most common sites diagnosed were breast, colorectum, lung, cervix, and stomach.

Traditional chemotherapy is an indispensable approach for cancer treatment. However, its therapeutic efficacy is usually limited by two major challenges. (1) The occurrence of multidrug resistance (MDR) phenotypes leads to chemotherapeutic failure. P-glycoprotein (P-gp) encoded by MDR1 gene in cancer cells has been regarded as the major mechanism of MDR (Gao et al., 2011; Takahashi et al., 2006). (2) Cancer chemotherapeutic agents can unselectively enter into both normal tissues and tumor tissues, resulting in undesirable side effects and even death of the patients (Fan et al., 2010). Therefore, significant efforts have been made to develop alternative therapies that improve the therapeutic indices of anticancer drugs both by increasing efficiency and
decreasing toxicity. Newly developed nano technological techniques are bringing hope to the world of oncologic research. Currently, nano techniques are being tested and used for the improvement of current technologies and for the development of new ones, in cancer detection, prevention, and treatment. It is the innate qualities of nanoparticles that make them advantageous for use in cancer management. Nanoscale particles have a maximum surface to volume ratio making them perfect for surface functionalization and conjugation with therapeutic agents. Furthermore, due to their size and malleable surface properties, nanoparticles can be synthesized to use passive or active targeting systems with superior tumour specificity than current drug methods (Mousa and Bharali, 2011).

In recent years, the design, synthesis and application of nanosized biocompatible composites have opened up new perspectives for biological and biomedical applications. Among them, the polymeric nanoparticulate drug delivery system has emerged recently as a promising carrier for targeting poorly water-soluble or amphiphilic drugs as well as genes to tumor tissues (Wang et al., 2008). The vasculature in tumors is leaky to macromolecules, and the tumor lymphatic system is usually deficient, so nanoparticles (NPs) can be preferentially delivered into the tumor through the enhanced permeation and retention (EPR) effect via its blood vessels (Matsumura and Maeda, 1986). Still, it was found that polymeric NPs could reduce the multi-drug resistance by a mechanism of internalization of the drug and reducing its efflux from cells mediated by the P-glycoprotein (Li et al., 2010; Patil et al., 2009). However, it is of critical importance to develop a more specific and active system that could target to the tumor and enhance intracellular uptake of drug to the tumor site. A rational approach to achieve these goals is to exploit specific interactions between receptors on the cancer cell surface and targeting moieties conjugated to the polymer back bone (Allen, 2002). Some ligands, such as folate and transferrin, can substantially increase site-specific targeting (Zhang et al., 2010; Zheng et al., 2010).

The major challenge in the active targeting using the nano carriers is the development of drug/gene loaded nano formulation containing a conjugated ligand or antibody. The complexity of the formulation development, stability of the formulation and difficulty in scaling up are the reasons for very little marketed products of this kind (Venditto and Szoka, 2013). Hence there is an urgent need of intense research in this area for developing simple and new techniques for tumour targeted delivery of anticancer drugs.