Chapter 4

Current Developments and Innovative Approaches in Nanoparticle-Mediated Cancer Therapies

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Abstract

Recently, cancer is one of the significant reasons for deaths including all diseases. Although there are many different treatment options, the deaths majorly occurred due to high toxicity or drug resistance related to the cancer chemotherapeutics. There are many studies that can reduce toxicity and drug resistance using with nanotechnology approaches in drug delivery of cancer treatments. Targetable nanotechnological molecules are designed to support protect healthy tissues from high-level cytotoxic of chemotherapeutic agents by allowing the drug to penetrate inside to the tumor cell efficiently. In addition, due to these features, they prevent drug resistance by binding to specific targets in the tumor. This will help to select cancer cells more than the healthy cells preferably. In this section, a review is made about the innovative usage of nanotechnology in cancer and future perspectives. Various material types and nanoparticulation approaches will be discussed.

1. Nanotechnology in Cancer Treatment

Cancer is defined by the uncontrolled and excessive proliferation of cells, which is followed by their dissemination throughout the body, ultimately leading to mortality (Jin et al., 2020). Cancer ranks as the second deadliest disease globally, responsible for over 10 million deaths annually. Traditional cancer therapies, including radiotherapy and chemotherapy damage to

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healthy tissues and the possibility of insufficient tumour reduction during surgery. In addition, the emergence of multidrug resistance in patients during treatment presents another burden. The complex character of the tumour microenvironment underlines the need to develop renewed treatment options (Bray *et al.*, 2018; Baghban *et al.*, 2020; Sun *et al.*, 2023).

Nanotechnology has occurred as a significant tool in the field of oncology, particularly for its potential in early cancer diagnosis, treatment, and overcoming therapeutic resistance. By exploiting materials at the nanoscale, researchers have designed various diagnostic instruments that allow for the detection of tumours at much earlier stages than traditional methods (Hu *et al.*, 2016). Nanotechnology encompasses subfields including drug delivery, gene therapy, diagnostics, biomarker mapping, targeted therapy, and molecular imaging (Jin *et al.*, 2020). One of the most important advantages of nanotechnology is the increase in drug side effect profiles. Many cancer drugs can also affect the healthy tissues so lead to toxicity and numerous side effects. However, nanotechnological drugs present the possible to target medication more precisely, provided that their effects are limited to tumour tissues (Hu *et al.*, 2018; Ye *et al.*, 2018).

Nano-oncology is a multidisciplinary field that integrates various disciplines, including biology, chemistry, engineering, and medicine. The goal of cancer treatment is to deliver drugs to target cells in a controlled manner. However, the process of redesigning and introducing a new active substance can be quite lengthy. Nanotechnology accelerates this process, making it faster and easier to modify existing drugs that are already effective in treatment. Additionally, nanotechnology enhances the efficacy of these drugs at lower concentrations, resulting in reduced toxicity (Alrushaid *et al.*, 2023). The most important advantage of cancer treatment using nanotechnological drugs is the ability to selectively target malignant cells. Identifying markers that are present in cancer cells but are uncommon or absent in healthy tissues simplifies the application of nanotechnology. Specific targets, such as folate receptors, transferrin, antibodies are commonly found in a variety of cancers, including breast, ovarian, brain, and lung cancers (Figure 1) (Al-Thani *et al.*, 2024).

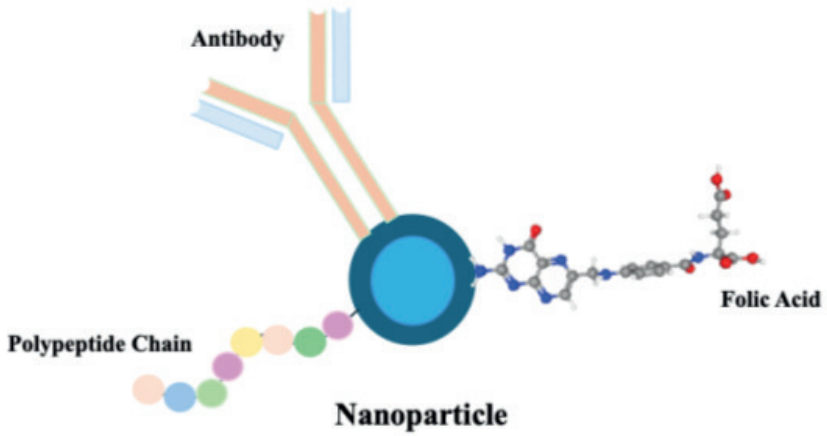

Figure 1. Demonstration of Surface Functionalization of Nanoparticles.

1.1. Nanoparticles

Nanoparticles are nano-objects that can be spherical, cylindrical, hollow, and have dimensions between 1-100 nm. They can generally consist of a single layer or several different layers. These layers can be metal ions such as gold or silver, or polymers (Machado *et al.*, 2015). Nanoparticles are basically divided into 3 classes: organic, inorganic and carbon-based. Liposomes, micelles and dendrimers are organic nanoparticles. The most prominent features of these nanoparticles are that they contain organic substances such as lipids, carbohydrates, polymers or proteins in their structures. For this reason, this group of nanoparticles is non-toxic and can be eliminated by breaking down from the body. Today, this group of nanoparticles is used for biomedical purposes such as cancer treatment (Gujrati *et al.*, 2014; Ng and Zheng, 2015; Pan and Zhong, 2016). Inorganic nanoparticles are composed of metal or ceramic. Metal nanoparticles are examined under three subheadings as monometallic, bimetallic and polymetallic. Metal nanoparticles have optical and electrical properties due to their surface plasmon properties. These properties increase their surface functionalizing. They also increase their potential for use in biomedical applications (Toshima and Yonezawa, 1998; Nascimento *et al.*, 2018). Carbon-based nanoparticles consist solely of carbon atoms and are highly biocompatible, making them used in drug delivery and tissue engineering applications (Long, Nascarella and Valberg, 2013; Ahlawat *et al.*, 2021).

1.2. Nanodiamonds

These carbon-based agents are distinguished from other nanoparticles by their very high biocompatibility (Figure 2). The nanodiamonds developed by (Chan *et al.*, 2017) have loaded with doxorubicin. They used this agent not only to target the cancer cell but also to ensure that it can enter the mitochondria of the cell directly. These nanodiamonds, which can be targeted not only to the cell but also to the mitochondria of the cell, were able to overcome resistance in resistant breast cancer cells.

Figure 2. Demonstration of nanodiamonds with different structures.

1.3. Liposomes

Liposomes, which have amphipathic properties, are vesicles consisting of a double layer and can be of different sizes. The sizes of those used for cancer usually vary between 10-200 nm. In addition to encapsulating and transporting drug molecules, their surfaces can also be coated with antibodies, aptamers or receptors (Figure 3). Recent studies on liposomes currently in use are exciting. Liposomal doxorubicin, which was developed to prevent metastasis, is promising for breast cancer patients.

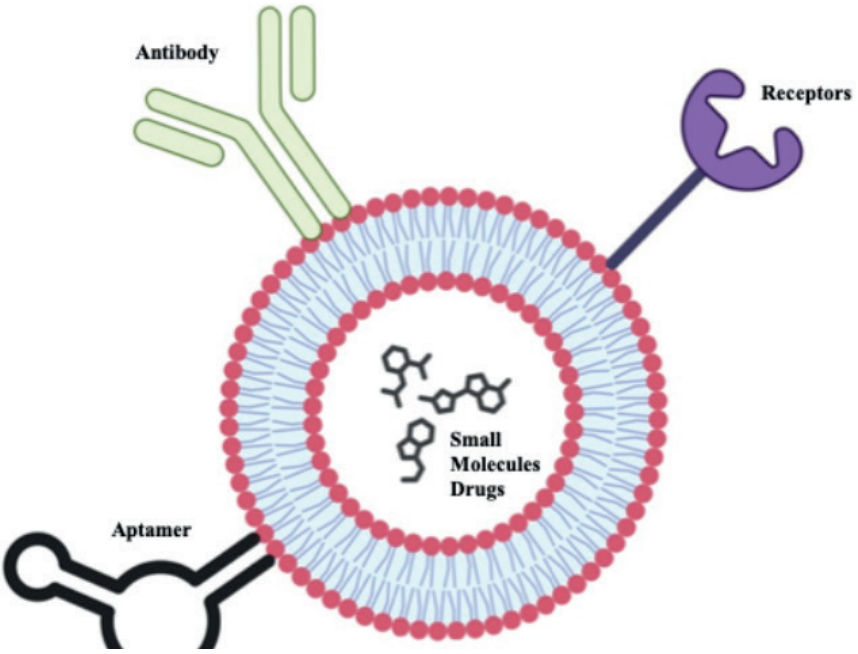

Figure 3. Functionalizing of liposomes to form drug-loaded complex.

2. Targeted Delivery

Drug targeting with nanoparticles can be divided into active and passive mechanisms. Active targeting involves using nanoparticles whose surfaces are selectively functionalized with specific agents. In contrast, passive targeting relies on the Enhanced Permeability and Retention (EPR) effect, which facilitates the accumulation of nanoparticles within tumour tissues due to leaky vasculature and impaired lymphatic drainage. EPR allows preferential localization of nanoparticles in tumour microenvironments, thereby increasing the effectiveness of drug delivery systems in oncology (Sun *et al.*, 2023).

In active targeting, drugs bind to receptors on the cancer cell surface and enter the cell by endocytosis. In passive targeting, drugs accumulate in the tumour tissue with the EPR effect. In fact, the most preferable targeting is active targeting. However, the fact that specific targets have not been discovered in some tumour tissues is the biggest obstacle to this. However, in such cases, it would be useful to take advantage of the EPR effect. For example, agents such as doxorubicin progress to brain tumours with the

EPR effect. Ultimately, both targeting aims to increase the accuracy of drug delivery and reduce toxicity (Zhang *et al.*, 2019; Rao *et al.*, 2022).

3. Nanoparticle-Mediated Synergistic Therapy

Combination therapy is the use of more than one drug together. The advantages of this treatment are to achieve the same or greater effect with a lower drug dose and to reduce side effects. Using two or more drugs affects different signalling pathways, thus preventing drug resistance (He *et al.*, 2016).

One of the advantages of nanoparticle drug delivery systems in combination therapies is that they allow multiple drug molecules to be loaded onto the same agent. In addition, they improve drug solubility, transport drugs to the target area, and protect the drug from immediate metabolism. Nanoparticles increase synergistic effects by providing more consistent pharmacokinetics of drugs. These nanoparticles can be administered orally, transdermal, or by injection. This increases patient compliance with treatment (Li *et al.*, 2024). Approved in 2017, Vyxeos is a liposomal formulation of cytarabine and daunorubicin loaded together. It has been approved for use in acute myeloid leukaemia and myelodysplasia (Krauss *et al.*, 2019).

4. Nanoparticle-Mediated Thermal Therapy

Nanoparticles designed to transmit heat to tumor cells aim to minimize damage to healthy tissues. The aim of the treatment is for the heat produced by the nanoparticles to kill cancer cells. Targetable nanoparticles heat the tissue locally. Nanoparticles that absorb light energy and convert this energy into heat at a specified wavelength are usually prepared using metals such as gold. Magnetic nanoparticles, on the other hand, bring tumor cells to a temperature where they can die when exposed to a magnetic field. Iron oxide nanoparticles are usually used in these cases. Although it may seem advantageous, it is very important for the tumor to reach the correct temperature and it is very difficult to monitor the situation (Bravo *et al.*, 2024).

Figure 4. Nanoparticle-mediated thermal therapy.

5. Personalized Nanomedicine

Personalized medicine aims to develop treatments tailored to each individual by addressing genetic and environmental factors that can affect the effectiveness and safety of treatment (Fornaguera and García-Celma, 2017).

The main goal of personalized medicine is to deliver the right drug to the right patient in the right dose. The targetability of nanoparticles makes them advantageous for personalized treatment because the dose can be easily adapted to the patient. In addition to all these, nanotechnology is also used to increase the bioavailability and binding affinity of the drug (Alghamdi *et al.*, 2022).

6. Future Perspective

As shown in Figure 5, there are many drugs approved for use in cancer treatment. Although the amount of these drugs is not large, many nanotechnological drug studies currently being studied are promising for the diagnosis and treatment of cancer. It is quite clear that nanotechnology, which offers more effective treatments with less toxicity and side effects as well as lower doses, will replace conventional treatment in the near future. In addition, drug resistance is a very big problem in cancer. Targetable treatments have been developed thanks to nanotechnology, and it is seen that resistance can be prevented thanks to these treatments (Puttasiddaiah *et al.*, 2025).

According to recent studies, new nanopharmaceuticals that elicit proptosis in cancer cells have been developed. These drugs increase selectivity

while minimizing unwanted effects and inflammation. In addition, these latest studies aim to examine and reveal the complex connections between proptosis, apoptosis and necrosis. The elucidation of these complex mechanisms with nanotechnology will bring significant success in cancer treatment in the future (Deivayanai *et al.*, 2024).

Approval (year)	Product	Nanoparticle material	Drug/Mechanism	Indication
EMA (2019)	Hensify (NBTXR3)	Hafnium oxide nanoparticle	Radiotherapy	Locally advanced soft tissue sarcoma (STS)
EMA (2019)	Pazenir	Nanoparticle-bound albumin	Paclitaxel	Metastatic breast cancer, metastatic adenocarcinoma of the pancreas, non-small cell lung cancer
FDA (2017) EMA (2018)	Vyxeos	Liposome	Cytarabine/Daunorubicin	Acute myeloid leukemia
FDA (2015)	Onivyde	Liposome	Irinotecan	Pancreatic cancer, colorectal cancer
EMA (2010, 2013)	NanoTherm	Iron oxide nanoparticles	Thermal ablation with magnetic field	Glioblastoma, prostate, and pancreatic cancer
FDA (2012)	Marqibo	Liposome	Vincristine	Acute lymphoblastic leukemia
EMA (2009)	Mepact	Liposome	Mifamurtide MTP-PE	Osteosarcoma
South Korea (2007)	Genexol-PM	PEG-PLA polymeric micelle	Paclitaxel	Breast, lung, ovarian cancer
FDA (1994, 2006)	Oncaspar	Polymer protein conjugate	Pegaspargase/L-asparaginase	Acute lymphoblastic leukemia
FDA (2005)	Abraxane	Nanoparticle-bound albumin	Paclitaxel	Breast and pancreatic cancer, non-small-cell lung cancer
FDA (1999)	DepoCyt	Liposome	Cytarabine	Neoplastic meningitis
FDA (1996)	DaunoXome	Liposome	Daunorubicin	Kaposi's sarcoma
FDA (1995, 1999, 2007), EMA (1996, 2000), Taiwan (1998)	Doxil, Caelyx, Myocet, and Lipo-Dox	Liposome	Doxorubicin	Metastatic breast cancer, ovarian cancer, Kaposi's sarcoma, multiple myeloma

Figure 5. Approved nanotechnological drugs used in cancer treatment.

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