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## **A Review on Nanocarriers Third Generation As Targeted Delivery Systems for Cancer Therapy**

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### **ABSTRACT**

Cancer is a leading cause of death worldwide. Currently available therapies are inadequate and spur demand for improved technologies. Nanomaterials are at the cutting edge of the rapidly developing area of nanotechnology. The potential for nanoparticles in cancer drug delivery is infinite with novel new applications constantly being explored. Targeted nanoparticles play a very significant role in cancer drug delivery. The promising implications of these platforms for advances in cancer diagnostics and therapeutics form the basis of this review. Targeted delivery systems of nano biomaterials are necessary to be developed for the diagnosis and treatment of cancer. Nano-based pharmaceuticals, or nanomedicines,” are engineered to either function as a drug or carry a drug while addressing these scientific challenges due to their nano-size.

**Keywords:** Nanomaterials, nanomedicines, Targeted delivery

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## INTRODUCTION

Nanoparticles have unique biological properties given their small size and large surface area-to-volume ratio, which allows them to bind, absorb, and carry compounds such as small molecule drugs, DNA, RNA, proteins, and probes with high efficiency. Their tunable size, shape, and surface characteristics also enable them to have high stability, high carrier capacity, the ability to incorporate both hydrophilic and hydrophobic substances and compatibility with different administration routes, thereby making them highly attractive in many aspects of oncology. Nanobiomaterials can be engineered to recognize cancer-specific receptors at the cellular levels and to deliver anticancer drugs into the diseased sites. In particular, nanobiomaterial-based nanocarriers, so-called nanoplatforms, are the design of the targeted delivery systems such as liposomes, polymeric nanoparticles/micelles, nanoconjugates, inorganic materials, carbon-based nanobiomaterials, and bio inspired phage systems, which are based on the nanosize of 1–100 nm in diameter. In this review, the first part, we examine cancer on the world stage, nanoparticles and their structure, functional properties, biomedical applications, nanomedicine, cancer drug delivery and drug delivery strategies using nanoparticles. In the second part, we focus on the various pathways available for cancer drug delivery and the role of nanoparticles in cancer drug delivery. In last part, the use of Nano devices in detection and imaging of cancer are discussed. The review provides recent advances in targeted cancer drug delivery.

Cancer is a worldwide disease with a leading cause of mortality, accounting for about 580,350 deaths, almost 1,600 people per day in 2014 from the statistical analysis of American Cancer Society in National Cancer Institute of the US (American Cancer Society, 2014). About 1,658,370 new cancer cases are expected to be diagnosed in 2015. This estimate does not include carcinoma in situ (non invasive cancer) of any site except urinary bladder, nor does it include basal cell or squamous cell skin cancers, which are not required to be reported to cancer registries (American Cancer Society. 2015).

The 5-year relative survival rate is still somewhat low, at 68% for all cancers diagnosed between 2002 and 2008, although it has been up from 49% in the period from 1975 to 1977. For this reason, it is essential for targeted therapy for cancer to reduce adverse reactions and mortality rate and to save costs in clinical practice. In 2005, a total of 7.6 million people died of cancer. More than 11 million people are diagnosed with cancer every year. It is estimated that there will be 16 million new cases every year by 2020. Cancer causes 7 million deaths every year or 12.5% of deaths worldwide. Some 60% of all these new cases will occur in the less developed parts of the world. Global cancer rates are expected to increase 50 percent by the year 2020, according to

the latest report from the International Agency for Research on Cancer (IARC), a branch of the World Health Organization. Cancer refers to a group of illnesses that result from cells in the body growing abnormally. These cells divide and produce new cells in an uncontrolled way that can spread throughout the body and cause damage to essential organs. When cancer spreads to other parts of the body, this is called metastasis. Metastases can occur when cancer cells enter the bloodstream or lymph system. These systems circulate all over the body and allow the cells to travel. Tumors are masses (or lumps) that can develop as abnormal cells accumulate. Not all tumors are cancer. Benign (non-cancerous or nonmalignant) tumors do not spread to other parts of the body and are rarely life-threatening. There are four main types of cancer: 1. Carcinomas – cancers of the organs 2. Sarcomas – cancers of the muscles, bone, cartilage, and connective tissue 3. Lymphomas – cancers of the lymphatic system 4. Leukemias – cancers of the blood-making system. Cancer cells vary in how fast they grow and how they spread in the body. Most cancers are defined by stage of growth using a system developed by the American Joint Committee on Cancer for solid tumors (like cancer of the lung, breast or colon).

The stage is based on the size of the tumor and on how much the cancer has spread. Stage I – Primary tumor only Stage II – Primary tumor, but larger than in Stage I Stage III – Primary tumor and metastasis to lymph nodes Stage IV – Primary tumor and distant metastasis (Dollinger *et al.*, 1997).

Cancer risk factors

- Tobacco use
  - High fat diet and being overweight
  - Excessive exposure to sunlight
  - Drinking too much alcohol
  - X-rays and other sources of radioactivity
  - Geographic area
  - Chemicals and other substances in the environment (carcinogens)
  - Unsafe sexual practices (through acquiring certain infections, such as HIV or genital warts)
  - Family members who have cancer (certain types of cancer are hereditary) (Dollinger, *et al.*, 1997).
- Diagnosing cancer Doctors use various means to make a diagnosis:
- Physical examination
  - Laboratory tests – such as blood and urine tests
  - Imaging – x-ray, CT scan, and MRI are examples of imaging

•Biopsy when a biopsy is done, tissue is examined directly to see if it has the characteristics of cancer. Tissue is obtained through a needle or a surgical procedure. Biopsy is a good method for diagnosing cancer with certainty. Cancer Treatment The good news is that about half of all cancers diagnosed are now curable. Even with cancers that cannot be cured, symptoms are often greatly diminished by treatment. Treatment options, which depend on the stage and type of cancer, include:

- Surgery
- Radiation therapy
- Chemotherapy Current treatment options for cancer include a combination of surgery, radiation therapy, and chemotherapy.

Over the past decade, our ability to design new treatments for cancer has been facilitated by a greater understanding of the tumor micro environment. Cancer tissue is composed of noncellular (ie, vascular and interstitial) and cellular compartments that differ remarkably compared with the surrounding normal tissue. Each of these compartments provides a challenge for the local delivery of drugs to tumor cells.

Within the noncellular compartment, tumor vascularity is markedly heterogeneous with densely vascularized areas supplying oxygen and nutrients to rapidly growing parts of the tumor while regions of tumor necrosis, in contrast, receive little blood supply. In addition, there is a decreasing amount of oxygen available to tumor cells which are further away from blood vessels; this is due in part to the increased distance over which oxygen has to diffuse to reach these cells as well as the consumption of oxygen by tumor cells that are closer to the blood vessels. New blood vessels are synthesized by tumors in a process known as angiogenesis; however, these vessels are abnormal with increased numbers of proliferating endothelial cells, increased vessel tortuosity, deficient pericytes, and abnormalities in the basement membrane with large gaps between adjacent endothelial cells ranging between 380 and 780 nanometers (nm) (Allen & Cullis, 2004, Brigger *et al.*, 2002). In addition, vascular endothelial growth factor, bradykinin, prostaglandins, and nitric oxide are all up regulated and contribute to the hyper permeable nature of tumors. Surrounding the tumor cells is the interstitial environment, which is composed of a collagen and elastic fiber network (Jain, 1987). Unlike normal tissues, the tumor interstitium has high interstitial pressure and a relative absence of a functioning lymphatic network.

is responsible for the enhanced permeability and retention (EPR) effect (Koo H, *et al.*, 2011, Maeda , 2001). Although the EPR effect helps to deliver chemotherapeutic agents to well-vascularized parts of the tumor, drugs may not reach the poorly vascularized regions, thereby

preventing some cancer cells from receiving cytotoxic treatment. This effect is further compounded by low microvascular pressure in these regions, which reduces the extravasation of drugs from the vasculature given the surrounding high interstitial pressure. In addition, the reduction of available oxygen due to the lack of vasculature results in an acidic microenvironment from the buildup of lactic acid via anaerobic glycolysis, which, in turn, confers resistance against basic drugs that are ionized thereby preventing their diffusion across the cell membrane. Taken together, these factors likely account for the noncellular mechanisms of drug resistance. Recent studies have now shown that there are 2 distinct populations of cells within a tumor: a small rare and quiescent population known as cancer stem cells, and another larger population of rapidly proliferating cells that forms the majority of the tumor mass. While noncancer stem cells do not have the capacity to self-sustain or metastasize, cancer stem cells not only have the ability to regenerate the tumor but also retain their genetic programs for cell migration (ie, invasion and metastasis) and self-protection.

Because most therapeutic treatments mainly target noncancer stem cells, this leaves the cancer stem cells behind, which can then regenerate the tumor explaining why tumors often recur after treatment. Hence, new treatments are being designed to specifically target cancer stem cells, which are now believed to be the critical therapeutic target. The destruction of these cells will permanently eradicate cancer cells, thereby preventing local recurrence and metastasis (Niederhuber, 2007).

### **Surgery:**

About 60% of people with cancer have some sort of surgery. If the tumor is in one place and can be removed without interfering with body functions, then surgery may be the best approach.

### **Radiation therapy**

Radiation therapy is done to shrink tumors or to make them disappear. This can be done by directing beams of x-rays or other high-energy rays at the tumor site. Radioactive materials can also be placed in or near the tumor. Receiving radiation therapy is generally not painful but side effects can sometimes occur .Radiation

### **Side Effects**

- Fatigue or tiredness
- Nausea and vomiting
- Skin inflammation
- Appetite loss
- Dry mouth

- Changes in sense of taste

### **Chemotherapy:**

Radiation and surgery are often used to treat cancer that is in one part of the body. Chemotherapy may be used to treat cancer that has spread. Treatment can also be a combination of surgery, radiation and/or chemotherapy. The use of chemotherapy to treat cancer began at the start of the 20th century with attempts to narrow the universe of chemicals that might affect the disease by developing methods to screen chemicals using transplantable tumors in rodents. It was, however, four World War II–related programs, and the effects of drugs that evolved from them, that provided the impetus to establish in 1955 the national drug development effort known as the Cancer Chemotherapy National Service Center. The ability of combination chemotherapy to cure acute childhood leukemia and advanced Hodgkin’s disease in the 1960s and early 1970s overcame the prevailing pessimism about the ability of drugs to cure advanced cancers, facilitated the study of adjuvant chemotherapy, and helped foster the national cancer program. Today, chemotherapy has changed as important molecular abnormalities are being used to screen for potential new drugs as well as for targeted treatments (Cancer Res 2008).

### **FDA approve chemotherapeutics**

#### **Doxorubicin**

Doxorubicin, a very effective anticancer drug, is widely used in the treatment of breast, ovarian, bladder, and lung cancers(Tacar et al., 2013).Mechanism of action of doxorubicin is the blocker of topoisomerase II, which is an important enzyme in the DNA replication process that unwinds the DNA helix. The mechanisms of doxorubicin also include DNA cross-link and ROS generation besides inhibiting topoisomerase II. Based on these mechanisms of action, doxorubicin has a potent antitumor activity in tumor cells inducing cell death. However, doxorubicin is associated with the severe side effects on the heart including irreversible myocardio toxicity and fatal congestive heart failure (Volkova and Russell, 2011).

#### **Paclitaxel**

Paclitaxel is a chemotherapeutic agent for the ovarian, breast, and lung cancers as well as Kaposi's sarcoma(Cozzi et al., 2004).It is a mitotic inhibitor with a stabilizing activity of the microtubule assembly interfering the normal breakdown of microtubules during cell division. Paclitaxel was originally extracted from the Pacific yew tree, *Taxus brevifolia*. Bristol-Myers Squibb commercially developed paclitaxel, a famous trademark, Taxol. However, paclitaxel itself has severe adverse responses such as peripheral sensory neuropathy (Rowinsky et al., 1993,

Rowinsky and Donehower 1995) anaphylaxis, and hypersensitivity reactions due to its solubilizing materials (Cremophor EL and ethanol) (Rowinsky and Donehower 1995).

Therefore, the development of nanoplateforms is essential to overcome these problems of formulation for the improvement of pharmacokinetic parameters and the toxic adverse reactions in the normal tissues (Azim. and Awada 2012).

Platinum-Based Anticancer Drugs Cisplatin (cisplatinum or cis-diamminedichloroplatinum (II)) is also used in chemotherapy, which is a platinum-based anticancer drug for the treatment of various cancers including sarcomas, some carcinomas (e.g., small cell lung cancer and ovarian cancer), lymphomas, and germ cell tumors (Wang and Z.Guo, 2013, Butler and P. J. Sadler, 2013). Mechanism of action in platinum-based anticancer drug is DNA crosslinking to interfere with the cell division by mitosis triggering apoptosis or cell death. Oxaliplatin and carboplatinare also included in platinum-based anticancer therapeutics.

### **Camptothecins:**

Camptothecin and irinotecan, a water soluble derivative of camptothecin, are cytotoxic alkaloids isolated from *Camptotheca acuminata*. The target of these camptothecins and their derivatives is topoisomerase I to inhibit the replication in the cells. They bind to the topoisomerase I and DNA complex generating a stabilized ternary complex to prevent DNA religation and to cause DNA damage resulting in apoptosis. Camptothecin and its derivative are limitedly used due to lipophilicity and instability of the lactone ring structure by hydrolysis despite their superior anticancer activity (Zhang *et al.*, 2004).

### **Some limitations of chemotherapy**

Conventional chemotherapy employs drugs that are known to kill cancer cells effectively (Palacios *et al.*, 2013). But these cytotoxic drugs kill healthy cells in addition to tumor cells, leading to adverse side effects such as nausea, neuropathy, hair loss, fatigue, and compromised immune function. In addition, conventional chemotherapy suffers some limitations as:

- (a) Limited aqueous solubility: Most chemotherapeutics either from plant source or synthetic are hydrophobic and requires solvents to formulate the dosage form which contribute to severe toxicity,
- (b) Lack of selectivity of anticancer drugs: Most chemotherapeutics lack selectivity toward cancerous cells cause significant damage to rapidly proliferating normal cells
- (c) Multidrug resistance (MDR): MDR is mainly due to increased efflux pumps such as P-glycoprotein (Pgp) in the cell membrane which are responsible for transport of various

anticancer drugs out of cells (Kwon, 2003, Luo and Prestwich 2002, Simon Benita 2006, Stavrovskaya 2000).

### **Nan carriers in cancer therapy:**

Therefore current research has focused on developing more efficient local drug delivery or drug-targeted therapies to overcome these obstacles. New therapies are being designed to deliver chemotherapeutic drugs to the tumor at higher concentrations with minimal damage to normal tissues. Examples include drugs conjugated with monoclonal antibodies that bind to molecular targets that are solely expressed on cancerous cells. This allows the drug to be specifically directed to the tumor while limiting its exposure to normal cells that do not significantly bind with the attached antibody. Nevertheless, studies have shown that only 1 to 10 parts per 100,000 of intravenously administered monoclonal antibodies reach their parenchymal targets *in vivo*, with similar limitations noted for molecular imaging agents (Wang *et al.*, 2008, Ferrari 2005, Li KC *et al.*, 2004). A new emerging strategy to overcome these problems is to use nanoparticles for drug delivery, tumor therapy, and tumor follow-up using different imaging modalities.

### **Structure and Functional Properties of Nan carriers:**

A nanometer is one-billionth of a meter (10<sup>-9</sup>m); a sheet of paper is about 100,000 nanometers thick. These nanoparticles give us the ability to see cells and molecules that we otherwise cannot detect through conventional imaging. The ability to pick up what happens in the cell, to monitor therapeutic intervention and to see when a cancer cell is mortally wounded or is actually activated is critical for the successful diagnosis and treatment of this disease. For drug delivery in cancer we have Nano scale devices<sup>¶</sup>. Nanoscale devices (Yih and Wei 2005) are 10<sup>2</sup> to 10<sup>4</sup> times smaller than human cells but are similar in size to large biomolecules such as enzymes and receptors. Nanoscale devices smaller than 50 nm can easily enter most cells, and those smaller than 20 nm can move out of blood vessels as they circulate through the body. Nano devices are suitable to serve as customized, targeted drug delivery vehicles to carry large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells.

According to The National Cancer Institute, Nanoparticulate technology can prove to be very useful in cancer therapy allowing for effective and targeted drug delivery by overcoming the many biological, biophysical and biomedical barriers that the body stages against a standard intervention such as the administration of drugs or contrast agents. Nanoscale constructs can serve as customizable, targeted drug delivery vehicles capable of ferrying large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells, greatly reducing or eliminating the often unpalatable side effects that accompany many current

cancer therapies. Several nanotechnological approaches have been used to improve delivery of chemotherapeutic agents to cancer cells with the goal of minimizing toxic effects on healthy tissues while maintaining antitumor efficacy. Some nanoscale delivery devices, such as dendrimers (spherical, branched polymers), silica-coated micelles, ceramic nanoparticles, and cross linked liposomes can be targeted to cancer cells. This increases the selectivity of drugs towards cancer cells and will reduce the toxicity to normal tissue.

Rationale for the treatment of cancer using nanomedicine products

Nanocarriers present several advantages over conventional chemotherapy.

They can be:

1. Nanoparticle-based drug-delivery systems have made a remarkable difference in site-specific release of chemotherapeutic agents, owing to their physical and chemical characteristics and biological attributes.
2. The size and surface properties of nanomaterials can cause them to selectively accumulate in tumor tissue via what is termed the enhanced permeability and retention (EPR) effect making them potentially useful tumor delivery vectors.
3. NCs have shown many implications for the development and success of new therapeutic strategies for anticancer drug delivery, peptide and protein delivery and gene therapy. Furthermore, NPs and other colloidal drug-delivery systems modify the kinetics, body distribution and drug release of an associated drug.
4. Conjugation or encapsulation of drugs in PLGA nanocarriers reduces the undesirable shortcomings of these therapeutic agents, such as short circulation half-life and non-site-specific targeting.
5. Nanocarriers can be designed to release their payload upon a trigger resulting in stimuli-sensitive nanomedicine therapeutic. For example, drugs whose delivery is not primarily pH-dependent, such as doxorubicin, can be conjugated with a pH sensitive nanoparticle to increase cellular drug uptake and intracellular drug release.

### **Key principles of nanomedicine targeted strategies in cancer therapy**

Almost a century ago, Paul Ehrlich introduced the concept of targeted drug delivery. It was considered as a hypothetical 'magic bullet' as an entity consisting of two components the first one should recognize and bind the target, while the second should provide a therapeutic action in this target. Currently, the concept of 'magic bullet' includes a coordinated behavior of three components drug, targeting moiety and pharmaceutical carrier (Torchilin, 2000). Nanoparticles can be designed to have all three properties of the revised version of Ehrlich's magic bullet, and

they could be used as therapeutics and/or diagnostics. When designing the nano drugs it is essential to understand the target region. Target regions could be whole organs (heart, lung, brain, liver), tissues (muscle), cells (nerve, dendrite), dis-ease specific structures (tumor cells) or cellular components.

The efficacy of the therapeutics, effectiveness of the diagnostics, safety, affordability and access will measure the final success of nanoparticles in medicine in regard to its applied value to the patients. General strategies and advanced functionalities of nanomedicine products to improve the drug's therapeutic index are discussed below:

- Passive targeting
- Active targeting
- Stimuli-responsive systems/triggered release
- Multi-functionality/theranostics

### **First generation cancer nanomedicines passive targeting**

Most clinically available nanocarrier-based cancer therapeutics are passively targeted first-generation nanomedicine drugs. First generation nanomedicine drugs mainly rely on controlling the pharmacokinetics and biodistribution of a compound by modulating its physicochemical properties (Golden, et al., 1998). For example, pegylated liposomal doxorubicin (Doxil®/Caelyx®) (Fig. 6D) and nab-paclitaxel (Abraxane®) are first generation nanomedicine drugs based on passive targeting. First generation cancer nanomedicine US food and drug administration

### **Strategy to increase bioavailability of nanocarriers s:'**

Stealth coating 'To take advantage of the EPR effect, NPs need to circulate for a prolonged period. One significant obstacle to the long-term circulation of NPs is clearance by the reticuloendothelial system (RES)(Kao and Juliano 1981,Senior 1987)whose main role is to protect the body from the invasion of extraneous particles. The removal of NPs is initiated by interactions between foreign particles and the phagocytic cells in the blood (e.g., monocytes, neutrophils) and tissues (e.g., Kupffer cells, dendritic cells, macrophages)(Pratten and Lloyd 1986, Bartneck et al., 2009, Dobrovolskaia et al., 2008) .This process is facilitated by adsorption of plasma proteins (opsonins), such as IgG or complement fragments, onto the particle surface, which labels the NPs as a foreign substance(Moghimi 1998, Essa et al., 2011, Moghimi and Patel 1998).

The opsonized NPs are ultimately eliminated by receptor-mediated phagocytosis. Many studies have shown that NPs administered intravenously are cleared from the blood by RES within minutes, if the NP surface is not protected from opsonization.

## **SECOND GENERATION NANOMEDICINE**

### **Active targeting strategy**

Second generation nanomedicine primarily focused on the development of new nanocarriers, which were specifically targeted at cancer cells, without affecting the function normal cells (Jong and Borm 2008). New generation nanomedicine comprises nanocarrier loaded with one or more cancer therapeutics, chemosensitizer, imaging components and an active targeting element such as folate receptor (Visaria *et al.*, 2006). Albumin-based nanoparticle carriers have been extensively studied by various groups (Shapira *et al.*, 2011, Basu *et al.*, 2009, Pinhassi *et al.*, 2010). Pegylated liposome encapsulated doxorubicin, carbon nanotubes, micellar NPs etc are also extensively studied nanoformulations for targeted delivery. A combination of cancer diagnostic aid and therapeutic agent loaded onto same NP system called theranostic NPs are also studied.

### **Conclusion**

Anti-cancer drug delivery specifically to cancer cells remains major challenge. Due to the lack of drug availability, adverse side effects and drug resistance, the conventional therapy failed to achieve proper treatment of cancer. Nanotechnology has great potential to radically improve current approaches to the diagnosis and treatment of patients with various types of cancer. Nanotechnology has already begun to have a significant impact on the treatment of patients by improving major challenges for the future including optimization of design and engineering of cancer targeted materials. In order to realize the potential of nanoparticle strategies, an improved understanding of the tumor specific, tumor site, and host factors which influence the delivery of nanomaterials specifically to sites of cancer causing cell will be necessary. Because of appropriate size and surface chemistry, allowing conjugation to biologically active molecule, several NPs are being investigated for more efficient targeted delivery of chemotherapeutic agents. Protein and liposome based nanomedicines formulation is already in clinical use, and many new formulations are in the phase 2 and phase 3 stages of evaluation. The future of nanomedicine will no doubt yield innovative

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