Monoclonal antibody conjugated Nanoparticles targeted to Prostate tumor cells

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ABSTRACT

Novel approaches to drug delivery and formulation using nanotechnology are revolutionizing the future of medicine. The application of nanotechnology in medicine is offering many exciting possibilities in healthcare. Engineered nanoparticles and conjugation of monoclonal antibodies with anticancer drug Docetaxel have the potential to revolutionize the diagnosis and the therapy of its diseases, particularly by targeted delivery of anticancer drugs and imaging contrast agents. Prostate cancer, the second most common cancer in men, represents one of the major epidemiological problems, especially for patients in the advanced age. There is a substantial interest in developing therapeutic options for treatment of prostate cancer based on use of nanocarriers with the conjugation of drug and antibody, to overcome the lack of specificity of conventional chemotherapeutic agents as well as for the early detection of precancerous and malignant lesions. In this article, we highlight on the recent development of bioconjugation of drug with nanotechnology strategies adopted for the management of prostate cancer. In particular, the combination of targeted and controlled-release polymer nanocarriers have worked against prostate specific membrane antigen, a promising targeted Docetaxel-loaded nanoparticles, which can be validated for use in the prostate cancer therapy. However, several limitations facing nanoparticle delivery to solid tumors, such as heterogeneity of intratumoural barriers and vasculature, cytotoxicity and or hypersensitivity reactions to currently available cancer nanomedicines, and the difficult in developing targeted nanoparticles with optimal biophysicochemical properties, should be still addressed for successful tumor eradication.

Introduction

The American Cancer Society estimates that approximately 218,000 men will be diagnosed with, and 32,000 men will die of, prostate cancer in the United States in 2014[1]. To give these numbers context, prostate cancer (PCa) is the most commonly diagnosed cancer in men and is responsible for the second highest number of cancer related deaths in men in the United States. PCa represents 27.6% of new cancer cases in men and 10.7% of cancer related deaths in men [1]. An estimated 1 in 3 men will be diagnosed with PCa or a precancerous prostatic lesion in their lifetime [2]. In Europe, there are approximately 346,000 new PCa cases and 87,000 deaths per year [3]. PCa is largely dependent on androgens for growth and proliferation; hence, androgen deprivation therapy (chemical castration) is the standard of treatment, and it generally causes prostate tumors to regress. However, most PCa cases eventually recur after treatment. These more lethal cases generally have a high Gleason score and can be metastatic and/or refractory to androgen deprivation therapy (castration resistant). Skeletal metastasis is the most significant cause of morbidity and mortality in PCa [4]. Skeletal metastases are found in approximately 90% of patients who die of PCa [5]. This adds to the health burden of these patients while they are still alive, due to painful lesions that impair mobility and cause pathologic fractures, spinal cord compression, and symptomatic hypercalcemia [6]. The frequency of bone metastases in PCa indicates that the microenvironment of the bone may promote the growth of PCa cells. The proportion of active osteoblasts is usually
greater than that of active osteoclasts in PCa bone metastases, resulting in the net formation (rather than lysis) of bone in a majority of these lesions [7]. However, osteolysis is required for metastatic tumor cells to invade the bone matrix. Also, patients with bone metastases have a higher risk of fracture, indicating that bone destruction is occurring. One study suggests that there may be more bone lysis during prostate tumor metastasis than originally thought and that it might be more prevalent in PCa than other diseases [8]. While much work has been done in area of prostate tumor-bone crosstalk [9–11]. There is still much to learn in this area. Accordingly, there is an urgent need for new treatments and better experimental models for the study of PCa development, progression, and metastasis.

Prostate cancer is the second leading cause of cancer death in men and accounts for approximately 30% of all new cancer diagnoses in men. More than 70% of all cancer deaths in 2005 occurred in countries like India. Deaths from cancer in the world are projected to continue rising, with an estimated 9 million people dying from cancer in 2015 and 11.4 million dying in 2030. Prostate-specific membrane antigen (PSMA), also named glutamate carboxypeptidase II (GCPII), is a classic type II membrane glycoprotein and is perhaps the most important enzyme-biomarker and target in prostate cancer research. PSMA can be induced for internalization by bound antibodies or small-molecule inhibitors. Its extracellular domain possessing folate hydrolase and N-acetylated-alpha-linked- acidic dipeptidase (NAALADase) activities can serve as binding target for antibodies, inhibitors and aptamers. Every single cell that moves to other place may develop into new tumor giving rise to various necrotic regions. Upon treatment even if a single cell or colony is left out, it can again lead to entire tumor. Present cancer therapy should be based on the philosophy, “even a single cancer cell should not remain untreated in the body and nothing less than complete elimination of tumor from an individual can be accepted”. This forms the objective behind chemotherapy.

**Tumor Physiology and Vasculature**

To understand prostate cancer, it helps to know something about the prostate and nearby structures in the body. The prostate is a gland found only in males. It is located in front of the rectum and below the urinary bladder. The prostate's job is to make some of the fluid that protects and nourishes sperm cells in semen, making the semen more liquid. Just behind the prostate are glands called seminal vesicles that make most of the fluid for semen. The urethra, which is the tube that carries urine and semen out of the body through the penis, goes through the center of the prostate. The prostate starts to develop before birth. It grows rapidly during puberty, fueled by male hormones (called androgens) in the body. The main androgen, testosterone, is made in the testes. The enzyme 5-alpha reductase converts testosterone into dihydrotestosterone (DHT). DHT is the main hormone that signals the prostate to grow. The prostate usually stays at

![Fig 1: Tumor physiology](image)
about the same size or grows slowly in adults, as long as male hormones are present. Under normal conditions, the cells reproduce, grow, divide, multiply and eventually undergo apoptosis. This maintains proper balance and functioning of the organs.

On the other hand tumors bear highly irregular complex architectural vasculature. The genesis of blood vessels is an abnormal state as there is abrupt formation of newer vessels and existing vessels tend to become disorganized. Such eruptions occur as a result of genetic aberrations from pre-existing vessels or in specialized microenvironment from endothelial cell progenitors of bone marrow [45-47]. Upon undergoing change in organizational pattern of a gene the normal cell cycle is disrupted. The gene (proto-oncogene) is thus converted into oncogene and loses its normal growth regulation. As a consequence of mutations abnormal growth and proliferation of cells begin along with the expression of various surface markers and proteins, which facilitate their growth and supplement the cells with necessary nutrients and oxygen at the expense of normal cells. The abnormal signal Nanoparticles proteins may induce faster proliferation of cells via transcription. Thus, a normal cell on being converted into oncogene proliferates under the stimuli of these agents and leads to metastatic tumors [48]. Blood from the capillaries may diffuse or drain out into a newer network consisting of vessels and lymph nodes called lymphatic system, which circulates like blood in various tissues and organs. Blood and lymph communicate to each other at lymph nodes and the lymph, via thoracic vein finally enters the general circulation. Lymphatic metastasis is characteristic of tumors. Metastasis is movement of tumors to other sites and is highly hazardous state of bio-system. Every single cell that moves to other place may develop into new tumor giving rise to various necrotic regions. Upon treatment even if a single cell or colony is left out, it can again lead to entire tumor.

The prostate is a secretary organ; it produces approximately 20% of the seminal fluid. Prostatic secretion contributes to sperm function, but is not mandatory to the fertilizing capacity of sperm. Progression of prostate cancer is a multistep process, and its mechanisms are poorly understood. Prostate cancer usually occurs in the peripheral zone [12], while BPH often occurs in the transition zone of the prostate. Commonly occurring chronic inflammation [13] may predispose the tissue to the development of malignant changes, although the concept that inflammation can promote prostate cancer is still highly speculative. Prostatic intraepithelial neoplasia (PIN) is considered a precursor of prostate cancer. Prostate cancer can be screened by means of the prostate-specific antigen (PSA) test; however, the actual cancer diagnosis is based on the histological or cytological examination of biopsy samples.

Cancer of the prostate gland is one of the most frequently diagnosed cancers amongst Western men, as well as men in most developing countries. According to figures available from the American Cancer Society, prostate cancer (PCA) has surpassed heart disease as the top killer of men over the age of 85 years [14]. Treatment of advanced PCAs relies mainly on non-specific therapies, such as chemotherapies and ionizing radiation, which have low efficacy and are highly toxic to normal tissues [15].

Role of tumor targeted therapy on prostate cancer

Targeted therapy is potentially an important means of attacking cancer. Better outcomes for hormone resistant tumors may be achieved by specifically delivering drugs, antigens or toxins to tumors to specifically kill tumor cells without affecting surrounding tissue. Targeted therapy is dependent on specific marker for the cancer cells that can be identified with affinity agents such as antibodies for antigens. One of the targeting agents associated with the prostate is prostate specific membrane antigen (PSMA). Several anti-PSMA monoclonal antibodies (MoAbs) that bind the extracellular PSMA domain have been developed. To improve the pharmacokinetics properties and the bioavailability of these chemo preventive agents, tremendous advancement has been made by making NP-based therapeutic products [16-17].

Nanotechnology based therapeutic systems have attracted tremendous attention as they have the potential to revolutionize cancer therapy and diagnosis owing to their tumor-targeting ability that allows anti-cancer drugs to be delivered more specifically to the cancer cells, thus greatly enhancing the therapeutic outcomes while minimizing any non-specific systemic toxicity [18]. Several recent studies have already demonstrated that prevention and therapy of PCAs using Nanomedicine may be a viable option for decreasing the mortality and morbidity associated with the disease [19]. NPs have the potential to offer solutions to the cur-rent obstacles in cancer therapies, because of their unique size (i.e. in general 1–1000 nm – or at least one dimension sized from 1 to 100 nm, preferably in the 5–200 nm range for medical purpose) and large surface-to-volume ratios. In fact, the size, surface characteristic and shape of a nanoparticle (NP) play a key role in its biodistribution in vivo [20].

Monoclonal antibodies

One way the immune system normally attacks foreign substances in the body is by making large numbers of different antibodies. An antibody is a “sticky” protein that targets a specific antigen. Antibodies circulate in the body until they find and attach to the antigen. Once attached, they recruit other parts of the immune system to destroy the cells containing the antigen. Many copies of a specific antibody can be made in the lab. These are known as monoclonal antibodies (MAbs). These antibodies can be useful in fighting diseases because they can be designed specifically to only target a certain antigen, such as one that is found on cancer cells. Monoclonal antibodies are now used to treat many diseases, including some types of cancer. A major advantage of these drugs is that because they are so specific, they may have only mild side effects, unlike some other cancer treatments. But
researchers first have to identify the right antigen to attack. For cancer, this is not always easy, and so far MAbs have proven to be more useful against some cancers than others. Over the past 15 years or so, the US Food and Drug Administration (FDA) have approved about a dozen mAbs to treat certain cancers. As researchers have found more antigens that are linked to cancer, they have been able to make monoclonal antibodies against more and more cancers. Clinical trials of newer mAbs are now being done on many types of cancer [49].

Types of monoclonal antibodies

Two types of monoclonal antibodies are used in cancer treatments:

- **Naked MAbs** are antibodies that work by themselves. There is no drug or radioactive material attached to them. These are the most commonly used MAbs at this time.

- **Conjugated MAbs** are those joined to a chemotherapy drug, radioactive particle, or a toxin (a substance that poisons cells). These mAbs work, at least in part, by acting as homing devices to take these substances directly to the cancer cells.

Naked monoclonal antibodies

Most naked MAbs attach to antigens on cancer cells, but some work by binding to antigens on other, non-cancerous cells, or to even free-floating proteins. Naked MAbs can work in different ways. Some may boost a person’s immune response against cancer cells. Others work by blocking specific proteins that help cancer cells grow. Some naked MAbs attach to cancer cells to act as a marker for the body’s immune system to destroy them. An example of this is alemtuzumab (Campath®), which is used to treat some patients with chronic lymphocytic leukemia. Alemtuzumab is an antibody that binds to the CD52 antigen, which is found on immune cells called B cells and T cells. Once attached, the antibody triggers the destruction of the cell by the immune system. Some naked mAbs work mainly by attaching to and blocking specific antigens that are important signals for cancer cells (or other cells that help cancer cells grow or spread). For example, trastuzumab (Herceptin®) is an antibody against the HER2/neu protein. A large amount of this protein is present on the cells in some types of cancer. When HER2/neu is activated, it helps these cells grow. Trastuzumab stops these proteins from becoming active. It is used to treat breast and stomach cancers that have large amounts of this protein.

Conjugated monoclonal antibodies

Monoclonal antibodies attached to a radioactive substance, drug, or toxin, are called conjugated MAbs. The MAb is used as a homing device to take one of these substances directly to the cancer cells. The MAb circulates in the body until it can find and hook onto the target antigen. It then delivers the toxic substance where it is needed most. This lessens the damage to normal cells in other parts of the body. Conjugated MAbs are also sometimes referred to as tagged, labeled, or loaded antibodies. They can be divided into groups depending on what they are linked to.

- MAbs with radioactive particles attached are referred to as radio labeled, and treatment with this type of antibody is known as radio immunotherapy (RIT).
- MAbs with chemotherapy drugs attached are referred to as chemo labeled.
- MAbs attached to cell toxins are called immunotoxins.

Radio labeled antibodies

Radio labeled antibodies have small radioactive particles attached to them. Ibritumomab tiuxetan (Zevalin®) and tositumomab (Bexxar®) are examples of radio labeled mAbs. Both of these are antibodies against the CD20 antigen, but they each have a different radioactive particle attached. They deliver radioactivity directly to cancerous B cells and can be used to treat some types of non-Hodgkin lymphoma.

Chemo labeled antibodies

These MAbs have powerful chemotherapeutics drugs attached to them. The chemotherapeutic drug is often too powerful to be used on its own; it would cause too many side effects if not attached to a MAb. There are only 2 chemo labeled antibodies approved by the FDA to treat cancer at this time: brentuximab vedotin (Adcetris®) and ado-trastuzumab emtansine (Kadcyla®). Brentuximab vedotin is made up of an antibody that targets the CD30 antigen (found on B cells and T cells), attached to a chemo drug called MMAE. It is used to treat Hodgkin lymphoma and anaplastic large cell lymphoma that is no longer responding to other treatments. Ado-trastuzumab emtansine is made of an antibody that targets the HER2 protein attached to a chemo drug called DM1. It is used to treat advanced breast cancer in patients whose cancer cells have too much HER2.

Immunotoxins

These MAbs have cell poisons (toxins) attached to them, which makes them similar in many ways to chemo labeled mAbs. At this time no immunotoxins are approved to treat cancer, although many are being studied. However, a related drug known as denileukin diftitox (Ontak®) is being used to treat some cancers. It consists of an immune system protein known as interleukin-2 (IL-2) attached to a toxin from the germ that causes diphtheria. Although it’s not a MAb, IL-2 normally attaches to certain cells in the body that contain the
CD25 antigen, which makes it useful for delivering the toxin to these cells. Denileukin diftitox is used to treat lymphoma of the skin (also known as cutaneous T-cell lymphoma). It is also being studied to be used against a number of other cancers.

**Antibody-drug conjugates**

The first FDA approved ADC was Mylotarg (gemtuzumab ozogamicin) and was initially developed by Wyeth in 2000 for the treatment of acute myeloid leukemia. After a decade, it was withdrawn from the market due to an undesirable efficacy and safety profile. Mylotarg targeted the CD33 receptor which turned out to be nonselective for tumor cells [21]. Additionally, the linker used to attach the drug to the antibody was unstable and the drug was released prior to reaching its target [22]. Since this failure, huge strides have been made in the science of properly binding antibodies to drugs. By using linkers with an acceptable biological half-life, researchers ensure that ADCs can reach the targeted cell with limited side effects [23]. In 2011, the U.S. Food and Drug Administration (FDA) approved Seattle Genetics Adcetris (brentuximab vedotin) to treat Hodgkin’s lymphoma and systematic anaplastic large-cell lymphoma [24]. This ADC made about $34.5 million in the first quarter of 2012 and revenues continue to bolster. Use of ADCs is anticipated to increase nearly 50% over the next decade just in the oncology market. Roche and Genentech alone have over 25 ADCs in their pipeline, including nine in clinical trials [25]. The first potential blockbuster ADC reached the market in February 2013 when the Kadcyla (trastuzumab emtansine, T-DM1) was approved for the treatment of metastatic breast cancer. Kadcyla combines the breast cancer treatment antibody Herceptin (trastuzumab) with the cytotoxic payload mertansine (DM1), a drug licensed from ImmunoGen. The projected sales for the treatment are in the region of $2 to $5 billion per year. The continued success of the ADC technology platform is due to the collaborations within biopharma and the promising clinical trials [25]. These collective results indicate a commitment towards targeted therapeutic delivery using humanized monoclonal antibody technologies [26]. To date, most of the drugs utilized in the development of ADCs use auristatins (Seattle Genetics) or maytansine (ImmunoGen) [27] but other emerging payloads are in development from Spirogen such as pyrrolobenzodiazepines (PBDs) for the next generation of antibody-drug conjugates [28].

**Antibody-drug conjugates mechanism of action**

A typical ADC consists of a monoclonal antibody which is capable of binding to the surface of tumor cell-specific antigens [29]. These can include proteins on the surface of the B and T cells of the immune system, such as CD20 and CD22, the human epidermal growth factor receptor 2 (HER2), or prostate-specific membrane antigen (PSMA) [30]. This specific antibody is attached to a cytotoxic drug via a cleavable linker [31]. The drug is designed to induce tumor cell death by causing irreversible DNA damage or interfering with cell division [32]. The mechanism of action of ADCs is the ability of the antibody to recognize and bind with a specific antigen. This binding initiates a cascade of events (Stages 1 to 5) via the process called endocytosis whereby the cell’s lysosomal enzymes release the cytotoxic drug to kill tumor cells (Figure 2) [33].

Fig 2: Schematic representation of the ADC internalization process

**Nanotechnology approaches to target to Prostate Tumor**

In this context, Sanna et al.2011 [34], developed novel targeted polymeric encapsulated NPs, densely decorated by low molecular weight organic molecule as targeting ligands in their polymeric [poly(lactide-co-glycolide)-PEG, PLGA-PEG] shell surface, to selectively bind to prostate specific membrane antigen (PSMA) [35]. These functionalized NPs exhibited a selective in vitro efficacy against PSMA-expressing Prostate Cancer cells PC3 and DU145 with respect to the non-
functionalized ones, without affecting normal cell viability. Other different nanosystems, such as polysaccharide NPs, were studied as drug delivery vehicles for chemoprotective agents [36]. These NPs retained biological activity, thus reducing the cell viability and inducing apoptosis of PC3 and DU145 cells. In vitro assay further demonstrated that encapsulation of monoclonal conjugated Nanoparticles enhanced its inhibitory effect on cell proliferation at lower concentrations, compared with free antigens.

As for the development of “nanobiocoupled tumor targeted therapy” to be used in PCa therapy, a major effort has been done by the team led by Langer and Farokhzad, that designed customized controlled-release NPs, loaded with the chemotherapeutic agent Docetaxel (DTXL), constituted by several safe or Food Drug Administration (FDA) approved materials as biocompatible polymers (PLGA, PEG, etc.), each one performing a specific function in the final NP prototype [37-38]. For example, hydrophilic spacer (i.e. PEG) were incorporated into the NP’s outer shell, in order to have a minimal self–self and self–nonself interaction, to prevent NP loss to undesired location, and to escape macropage capture, enabling “stealth” properties for immune evasion. The results indicated that the encapsulated drug efficiently interacted to the tumor and selectively delivered DTXL to PCa cells. This approach strongly contributed to the development of targeted NPs as highly selective and effective therapeutic modalities for PCa treatment.

The researchers observed that injection of NP-gene complexes led to significant decrease in the sizes of the prostate gland and the prostate tumor, whereas direct injection of the gene construct alone produced no effects on the tumor growth. A novel method for combining Taxol (Paclitaxel) chemotherapy and Herceptin (a monoclonal antibody) to generate a treatment for advanced PCa has been developed by the Goldstein’s group [34, 39]. Since the HER2 receptor is over expressed in some PCa cells, the Herceptin (Trastuzumab) antibody has been considered as a putative targeting agent.

General nanoparticle characteristics

The size, surface characteristics and shape of a nanoparticle play a key role in its biodistribution in vivo. Spherically shaped, passively targeted, nanoparticle less than 5 nm in diameter are rapidly cleared from circulation via extravasations or renal clearance, and as particle size increases from the nanometer range to ~15 micrometers, accumulation occurs primarily in the liver, spleen and bone marrow. Nanoparticle behavior in the size range ~10 nm to ~15 micrometers varies widely in terms of biodistribution and cellular uptake of nanoparticle in this range is heavily dependent on cell type. Under normal circumstances, nanoparticle are mechanically filtered by sinusoids in the spleen and removed from circulation via cells of the reticuloendothelial system (RES). In addition, Kupffer cells in the liver, also part of the RES, play a key role in particle removal [42]. The propensity for accumulation of nanoparticle in cells of the RES is dictated by specific proteins adsorbed in vivo to the particle surface, which can be influenced through modifications of surface characteristics. This process of protein adsorption, known as opsonization, begins immediately after particles come in contact with plasma. The exact nature of the types and quantities of proteins and their conformations dictate the body’s reaction. The mechanisms involved in this process are not well understood; however, the major opsonins are known. Immunoglobulin (Ig) and complement proteins are the predominant contributors to the recognition of foreign particles by the cells of the RES (that is, macrophages). Complement activation can further complicate targeted drug delivery by inducing hypersensitivity reactions. Finally, particulate matter larger than ~15 micrometers is removed from circulation via mechanical filtration in capillaries and can be lethal depending on dose [43].

Current methods for addressing the negative attributes associated with opsonization have focused almost exclusively on slowing the process by rendering the particle surface more hydrophilic or by neutralizing surface charge. The predominant strategy has been to adsorb or graft a hydrophilic polymeric coating, such as polyethylene glycol (PEG) to the surface of the particle. These polymer chains, depending on density, act as a steric brush that imparts resistance to protein adsorption. However, the PEG effect is transient, so eventual opsonization and macrophege clearance still occur [44].

**Nanocarrier Conjugates**

Due to their unique architecture and available surface groups, (PLGA) [poly (lactide-co-glycolide) nanocarriers have been used as a backbone for the attachment of several types of biologic material. The resulting conjugates have applications in a number of different areas of biology and medicine. Some of the earlier work done in this area documented that antibodies can direct nanocarrier-associated therapeutic agents to antigen-bearing tumors. Nanocarriers have also been conjugated to fluorochromes and shown to enter cells and can be detected. The current work combines these features to show that anti-PSMA antibody dendrimer conjugates can be used for targeting prostate cancer cells.

**Ultimate outcomes**

Major progress in the recombinant gene technology has opened access to human-compatible MAb, which provides significant advantages for the MAb-based tumor targeting. The validity of this approach has been proven by the success of Mylotarg, which was approved by the FDA as well as the fact that more than several MAb-drug conjugates are in various stages of human clinical trials. Major challenges for MAb-based drug delivery include the identification of target antigens that are over expressed specifically on the tumor surface, the circumvention of potential immunogenicity of the conjugates, and the determination of the right size of the conjugates that can penetrate into tumors, yet not to be cleared by kidneys too fast.
Monoclonal antibody based targeting has a high potential for tumor specific drug delivery of cytotoxic agents. Since most prostate cancers are difficult to treat due to their multidrug-resistance, this approach may shed a light on the development of efficacious chemotherapy. One of the inherent problems is the stability of these peptides in circulation, although this can be solved by appropriate design and modifications to prevent or slow down the amide hydrolysis. The efficacies demonstrated in the animal models show great promise in this approach. However, the detailed mechanism of tumor-targeting by biodegradable polymeric nanoparticles needs to be clarified.

As described above, tumor-targeting drug delivery in cancer therapy has been evolving from the traditional chemotherapy with the hope to minimize undesirable side effects and improve the quality of life of cancer patients. The authors sincerely hope that some breakthroughs come out of this line of approaches for new and efficacious cancer chemotherapy.

Conclusions and perspectives

Nanotechnologies are demonstrating significant impact on drug delivery over about the last 20 years; several first-generation of therapeutic NP products are commercially available. Active targeting via the inclusion of a specific ligand on the NPs is envisioned to provide an effective strategy, and some ligand-targeted nanotherapeutics are either approved or under clinical evaluation. Focusing on PCa, the pioneering work of Farokhzad *et al.* [37, 41] led to proof-of-concept for the development of drug delivery vehicles that were composed of biocompatible polymeric NPs and aptamers to target PSMA. The therapeutic potential of these NPs has been explored by in vitro and in vivo studies for targeted delivery and uptake of DTXL by PCa cells. The translation of these bioconjugates into clinical practice resulted in targeted polymeric NPs that have recently entered clinical trials. More complex targeted NP systems addressed to the PCa, as well as to many cancer diseases, which combine diagnostic and therapeutic agents, or that can trigger drug release at the target site when exposed to external stimuli, are also going ahead in the development process. Despite the great potential of nanosystems, there is an increasing effort to overcome several limitations that prevent therapeutics and imaging agents from reaching target tumors in sufficient concentration. In fact, a succession of several membrane layers as biological barriers, and a plethora of cellular processes, constitutes important obstacles for chemotherapeutic or imaging agents attempting to target solid tumors [40-42].

NP surface charge is an important factor for activation of the complement system, and some polymer coatings were shown to reduce complement activation by NPs. Therefore, for NPs moving into the clinical evaluation, it is important that nanotoxicology research uncovers and understands how these factors influence the toxicity of such nanosystems, to avoid their undesirable properties. In conclusion, the “magic bullet” concept, the first description of the drug-targeting paradigm, is beginning to be also applied for treating PCa disease, and continued research and development efforts in the nanotechnology arena will provide major goals for cancer therapy and for human health in the next future.

Conflict of interest statement

We declare that we have no conflict of interest.

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