



DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEMS FOR TARGETED THERAPY

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Abstract:

The field of drug delivery systems has witnessed significant advancements in recent years, particularly in the development of novel approaches for targeted therapy. This review article provides a comprehensive overview of the latest innovations in drug delivery systems designed to enhance the efficacy and safety of targeted therapies. Various strategies, including nanotechnology, biomaterials, and personalized medicine, are discussed in detail. The importance of targeted drug delivery in minimizing off-target effects and improving patient outcomes is emphasized. Furthermore, the challenges and future directions in the development of novel drug delivery systems for targeted therapy are explored. Overall, this review aims to provide insights into the cutting-edge research in the field of drug delivery systems and its potential impact on the future of targeted therapy.

Keywords: Targeted therapy, Drug delivery systems, Nanotechnology, Biomaterials, Personalized medicine, Efficacy

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Introduction:

Targeted therapy and drug delivery systems have revolutionized the field of medicine by providing more precise and effective treatments for various diseases. These innovative approaches allow for the delivery of therapeutic agents directly to the site of action, minimizing side effects and improving patient outcomes [1].

Targeted therapy is a type of treatment that specifically targets the molecules or pathways involved in the growth and spread of cancer cells. Unlike traditional chemotherapy, which can affect both cancerous and healthy cells, targeted therapy selectively targets cancer cells, leading to fewer side effects and better treatment outcomes. This approach is based on the understanding of the molecular mechanisms underlying cancer development and progression, allowing for the development of drugs that can interfere with these specific targets [2].

One of the key advantages of targeted therapy is its ability to personalize treatment based on the genetic profile of the patient's tumor. By identifying specific genetic mutations or alterations in the tumor cells, clinicians can tailor treatment to target these specific abnormalities, leading to more effective and targeted therapy. This personalized approach has revolutionized cancer treatment and has significantly improved outcomes for patients with certain types of cancer, such as breast cancer, lung cancer, and melanoma [3].

In addition to cancer treatment, targeted therapy is also being explored for the treatment of other diseases, such as autoimmune disorders, inflammatory conditions, and infectious diseases. By targeting specific molecules or pathways involved in the disease process, targeted therapy can provide more effective and precise treatment options for patients with these conditions. This approach holds great promise for the development of new therapies that can improve patient outcomes and quality of life [4].

Drug delivery systems play a crucial role in the success of targeted therapy by ensuring the efficient and effective delivery of therapeutic agents to the target site. These systems are designed to overcome the barriers that limit the delivery of drugs to specific tissues or cells, such as poor solubility, rapid metabolism, and limited penetration into tissues. By using specialized drug delivery systems, clinicians can improve the bioavailability and efficacy of therapeutic agents, leading to better treatment outcomes and reduced side effects [5].

There are several types of drug delivery systems that are currently being used in targeted therapy, including nanoparticles, liposomes, micelles, and polymer-based delivery systems. These systems

can be engineered to encapsulate drugs, protect them from degradation, and release them at the target site in a controlled manner. By optimizing the properties of these drug delivery systems, researchers can enhance the therapeutic effects of drugs and improve their safety profile [6].

Nanotechnology-Based Drug Delivery Systems for Targeted Therapy:

Nanotechnology has revolutionized the field of drug delivery by offering innovative solutions for targeted therapy. Nanotechnology-based drug delivery systems have shown great potential in improving the efficacy and safety of therapeutic agents by delivering them directly to the target site. This essay will explore the various types of nanotechnology-based drug delivery systems, their advantages, challenges, and future prospects in the field of targeted therapy [7].

There are several types of nanotechnology-based drug delivery systems that have been developed for targeted therapy. These include liposomes, polymeric nanoparticles, dendrimers, and nanotubes, among others. Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs. Polymeric nanoparticles are particles made from biocompatible polymers that can release drugs in a controlled manner. Dendrimers are highly branched polymers that can carry drugs on their surface or within their structure. Nanotubes are cylindrical structures that can be used to deliver drugs to specific cells or tissues [8].

Nanotechnology-based drug delivery systems offer several advantages over conventional drug delivery methods. One of the key advantages is the ability to deliver drugs directly to the target site, reducing systemic side effects and improving therapeutic efficacy. Nanoparticles can also protect drugs from degradation in the body, prolonging their circulation time and enhancing their bioavailability. Additionally, nanotechnology-based drug delivery systems can be engineered to release drugs in a controlled manner, allowing for sustained drug release and improved patient compliance [9].

Despite their potential benefits, nanotechnology-based drug delivery systems face several challenges that need to be addressed. One of the main challenges is the potential toxicity of nanoparticles, which can cause adverse effects in the body. Nanoparticles can also be cleared from the body quickly, limiting their therapeutic effects. Furthermore, the scale-up and manufacturing of nanotechnology-based drug delivery systems can be complex and costly, hindering their widespread adoption [10].

Despite the challenges, nanotechnology-based drug delivery systems hold great promise for the future of targeted therapy. Researchers are actively working on developing novel nanocarriers that can overcome the limitations of current systems. These include hybrid nanoparticles, which combine the advantages of different types of nanoparticles, and smart nanoparticles, which can respond to specific stimuli in the body. Additionally, advancements in nanotechnology are enabling the development of personalized drug delivery systems that can be tailored to individual patients based on their genetic makeup and disease characteristics [11].

Nanotechnology-based drug delivery systems have the potential to revolutionize targeted therapy by improving the efficacy and safety of therapeutic agents. While there are challenges that need to be addressed, ongoing research and advancements in nanotechnology are paving the way for the development of innovative drug delivery systems. With continued investment and collaboration between researchers, clinicians, and industry partners, nanotechnology-based drug delivery systems have the potential to transform the treatment of a wide range of diseases and improve patient outcomes [12].

Biomaterials in Targeted Drug Delivery:

Biomaterials have revolutionized the field of medicine by offering innovative solutions for targeted drug delivery. Targeted drug delivery is a technique that involves delivering medication directly to the site of action in the body, thereby improving the therapeutic efficacy of the drug and minimizing side effects. Biomaterials play a crucial role in this process by serving as carriers for the drug molecules and facilitating their controlled release. In this essay, we will explore the different types of biomaterials used in targeted drug delivery and their applications in the field of medicine [13].

- **Types of Biomaterials in Targeted Drug Delivery**

There are several types of biomaterials that are commonly used in targeted drug delivery, each with its own unique properties and advantages. Some of the most commonly used biomaterials include liposomes, nanoparticles, hydrogels, and micelles [14].

Liposomes are small vesicles composed of lipid bilayers that can encapsulate drug molecules within their aqueous core. Liposomes are biocompatible and can be easily modified to target specific tissues or cells in the body. They are commonly used in cancer therapy to deliver chemotherapy drugs directly to tumor cells, thereby reducing systemic toxicity [14].

Nanoparticles are solid particles with a size range of 1-100 nanometers that can encapsulate drug molecules and protect them from degradation in the body. Nanoparticles can be made from a variety of materials, including polymers, metals, and ceramics. They are widely used in targeted drug delivery for a variety of applications, including treatment of infectious diseases, inflammatory disorders, and cancer [15].

Hydrogels are three-dimensional networks of crosslinked polymers that can absorb and retain large amounts of water. Hydrogels are biocompatible and can be engineered to release drugs in response to specific stimuli, such as changes in pH, temperature, or enzyme activity. They are commonly used in targeted drug delivery for sustained release of drugs over an extended period of time [15].

Micelles are self-assembled structures composed of amphiphilic molecules that can encapsulate drug molecules within their hydrophobic core. Micelles are stable in aqueous environments and can be easily modified to target specific tissues or cells in the body. They are commonly used in targeted drug delivery for delivery of hydrophobic drugs, such as anticancer agents [15].

- **Applications of Biomaterials in Targeted Drug Delivery:**

Biomaterials have a wide range of applications in targeted drug delivery, with potential benefits for a variety of medical conditions. Some of the key applications of biomaterials in targeted drug delivery include [16]:

- **Cancer therapy:** Biomaterials are widely used in targeted drug delivery for cancer therapy, where they can deliver chemotherapy drugs directly to tumor cells while minimizing damage to healthy tissues. This approach can improve the therapeutic efficacy of the drugs and reduce systemic toxicity [16].

- **Infectious diseases:** Biomaterials can be used in targeted drug delivery for treatment of infectious diseases, such as bacterial or viral infections. By delivering antimicrobial drugs directly to the site of infection, biomaterials can improve the effectiveness of the treatment and reduce the risk of drug resistance [17].

- **Inflammatory disorders:** Biomaterials can be used in targeted drug delivery for treatment of inflammatory disorders, such as rheumatoid arthritis or inflammatory bowel disease. By delivering anti-inflammatory drugs directly to the inflamed tissues, biomaterials can reduce inflammation and improve the patient's quality of life [16].

- **Chronic conditions:** Biomaterials can be used in targeted drug delivery for treatment of chronic

conditions, such as diabetes or cardiovascular disease. By delivering drugs in a controlled and sustained manner, biomaterials can improve patient compliance and reduce the frequency of drug administration [17].

Biomaterials have emerged as powerful tools in targeted drug delivery, offering new possibilities for improving the efficacy and safety of drug therapies. By harnessing the unique properties of biomaterials, researchers and clinicians can develop innovative drug delivery systems that target specific tissues or cells in the body, while minimizing side effects and improving patient outcomes. As the field of biomaterials continues to advance, we can expect to see even more exciting developments in targeted drug delivery and personalized medicine [17].

Personalized Medicine Approaches for Targeted Therapy:

Personalized medicine, also known as precision medicine, is an innovative approach to healthcare that takes into account an individual's unique genetic makeup, lifestyle, and environment in order to tailor medical treatment to their specific needs. This approach has revolutionized the field of medicine, particularly in the realm of targeted therapy [18].

Targeted therapy is a type of cancer treatment that specifically targets the cancer cells while minimizing damage to normal, healthy cells. This approach is made possible through the use of personalized medicine, which allows healthcare providers to identify specific genetic mutations or biomarkers that are driving the growth of the cancer cells. By targeting these specific mutations or biomarkers, targeted therapy can be more effective and less toxic than traditional chemotherapy or radiation therapy [19].

There are several different approaches to personalized medicine for targeted therapy. One approach is to use genomic testing to identify specific genetic mutations that are driving the growth of the cancer cells. This information can then be used to select a targeted therapy that is designed to specifically target those mutations. For example, if a patient's cancer cells have a mutation in the BRAF gene, they may be a candidate for a targeted therapy that inhibits the BRAF protein [20].

Another approach to personalized medicine for targeted therapy is to use liquid biopsies to monitor the levels of circulating tumor DNA in a patient's blood. By monitoring these levels over time, healthcare providers can track the progression of the cancer and identify potential resistance mechanisms that may develop. This information

can then be used to adjust the patient's treatment plan and potentially switch to a different targeted therapy if the cancer becomes resistant to the current treatment [21].

In addition to genomic testing and liquid biopsies, other personalized medicine approaches for targeted therapy include immunotherapy and combination therapy. Immunotherapy is a type of cancer treatment that uses the body's own immune system to fight cancer cells. By identifying specific biomarkers on the surface of the cancer cells, healthcare providers can tailor immunotherapy treatments to target those specific biomarkers [22]. Combination therapy is another approach to personalized medicine for targeted therapy that involves using multiple targeted therapies in combination to treat the cancer. By targeting multiple pathways that are driving the growth of the cancer cells, combination therapy can be more effective than using a single targeted therapy alone [23].

Overall, personalized medicine approaches for targeted therapy have revolutionized the field of cancer treatment by allowing healthcare providers to tailor treatment plans to the specific needs of each individual patient. By identifying specific genetic mutations, monitoring circulating tumor DNA, using immunotherapy, and combining multiple targeted therapies, healthcare providers can improve outcomes for cancer patients and minimize the side effects of treatment. As personalized medicine continues to advance, the future of targeted therapy looks promising, with the potential to revolutionize cancer treatment and improve patient outcomes [24].

Overcoming Challenges in Targeted Drug Delivery Systems:

One of the main challenges in targeted drug delivery systems is achieving specificity in drug delivery. Traditional drug delivery methods often result in the drug being distributed throughout the body, leading to potential side effects and decreased efficacy. Targeted drug delivery systems aim to deliver the drug directly to the site of action, minimizing systemic exposure and maximizing therapeutic effects. However, achieving this level of specificity can be challenging, as it requires the drug to be delivered only to the target cells or tissues while avoiding off-target effects [25].

Another challenge in targeted drug delivery systems is overcoming biological barriers. The body has several defense mechanisms in place to prevent foreign substances from entering cells and tissues, making it difficult for drugs to reach their intended target. For example, the blood-brain barrier is a highly selective barrier that prevents

many drugs from crossing into the brain, limiting the effectiveness of treatments for neurological disorders. Overcoming these biological barriers is crucial for the success of targeted drug delivery systems [26].

In addition, the stability and pharmacokinetics of the drug are important considerations in targeted drug delivery systems. Drugs must be stable in the body and have the right pharmacokinetic profile to ensure optimal delivery to the target site. Formulating drugs in a way that allows for controlled release and sustained drug levels at the target site can be challenging, but is essential for the success of targeted drug delivery systems [27]. Despite these challenges, researchers and scientists are developing innovative strategies to overcome them and improve the effectiveness of targeted drug delivery systems. One such strategy is the use of nanotechnology to enhance drug delivery. Nanoparticles can be engineered to encapsulate drugs and target specific cells or tissues, allowing for more precise drug delivery and improved therapeutic outcomes. Nanoparticles can also help overcome biological barriers, such as the blood-brain barrier, by facilitating drug transport across these barriers [28].

Another innovative strategy for targeted drug delivery is the use of ligand-targeted drug delivery systems. Ligands are molecules that can bind to specific receptors on target cells, allowing for targeted drug delivery. By conjugating drugs to ligands that target specific cells or tissues, researchers can achieve greater specificity in drug delivery and reduce off-target effects. This approach has shown promise in improving the efficacy of targeted drug delivery systems for various diseases, including cancer and inflammatory disorders [29].

Furthermore, advances in drug delivery technology, such as microfluidic devices and implantable drug delivery systems, are also helping to overcome challenges in targeted drug delivery. Microfluidic devices allow for precise control over drug delivery parameters, such as flow rate and drug concentration, enabling tailored drug delivery to specific target sites. Implantable drug delivery systems, such as drug-eluting stents and implants, provide sustained release of drugs at the target site, reducing the need for frequent dosing and improving patient compliance [30].

Targeted drug delivery systems hold great promise for improving the efficacy and safety of drug treatments for various diseases. However, developing these systems comes with its own set of challenges, including achieving specificity in drug delivery, overcoming biological barriers, and optimizing drug stability and pharmacokinetics.

Through innovative strategies, such as nanotechnology, ligand-targeted drug delivery, and advanced drug delivery technology, researchers are making significant progress in overcoming these challenges and improving the effectiveness of targeted drug delivery systems. By continuing to address these challenges and develop new technologies, we can unlock the full potential of targeted drug delivery systems and revolutionize the field of medicine [31].

Future Perspectives and Emerging Trends in Targeted Drug Delivery Systems:

Targeted drug delivery systems have revolutionized the field of medicine by allowing for more precise and effective treatment of various diseases. These systems use nanotechnology to deliver drugs directly to the site of action, reducing side effects and improving therapeutic outcomes. As technology continues to advance, future perspectives and emerging trends in targeted drug delivery systems are shaping the way we approach drug delivery and treatment [32].

One of the key future perspectives in targeted drug delivery systems is the development of personalized medicine. With advancements in genomics and proteomics, researchers are able to tailor drug delivery systems to individual patients based on their genetic makeup and specific disease characteristics. This personalized approach allows for more targeted and effective treatment, leading to better patient outcomes and reduced side effects [33].

Another emerging trend in targeted drug delivery systems is the use of biomaterials for drug delivery. Biomaterials are materials that interact with biological systems, making them ideal for drug delivery applications. These materials can be engineered to release drugs in a controlled manner, ensuring optimal drug concentrations at the target site. Additionally, biomaterials can be designed to biodegrade once the drug has been released, reducing the risk of toxicity and improving patient safety [34].

Nanotechnology is also playing a crucial role in the future of targeted drug delivery systems. Nanoparticles can be engineered to encapsulate drugs and deliver them to specific cells or tissues, allowing for precise drug targeting. Additionally, nanoparticles can be functionalized with targeting ligands that recognize specific cell surface markers, further enhancing drug delivery to the desired site. With continued advancements in nanotechnology, targeted drug delivery systems are becoming increasingly sophisticated and effective [35].

In addition to personalized medicine, biomaterials, and nanotechnology, other future perspectives in

targeted drug delivery systems include the use of stimuli-responsive drug delivery systems and the development of novel drug delivery platforms. Stimuli-responsive systems are designed to release drugs in response to specific stimuli, such as changes in pH, temperature, or enzyme activity at the target site. These systems allow for on-demand drug release, improving drug efficacy and reducing side effects [36].

Novel drug delivery platforms, such as microfluidic devices and implantable drug delivery systems, are also being developed to improve targeted drug delivery. Microfluidic devices can be used to precisely control drug release rates and concentrations, while implantable systems can provide sustained drug delivery over extended periods of time. These platforms offer new opportunities for targeted drug delivery in a variety of disease settings, including cancer, infectious diseases, and chronic conditions [37].

Overall, the future of targeted drug delivery systems is bright, with continued advancements in personalized medicine, biomaterials, nanotechnology, stimuli-responsive systems, and novel drug delivery platforms. These emerging trends are shaping the way we approach drug delivery and treatment, leading to more effective and precise therapies for patients. By harnessing the power of technology and innovation, targeted drug delivery systems hold great promise for the future of medicine [38].

Conclusion:

In conclusion, targeted therapy and drug delivery systems represent a groundbreaking approach to treating diseases by delivering therapeutic agents directly to the site of action. These innovative strategies have the potential to revolutionize the field of medicine by providing more effective and personalized treatment options for patients. By understanding the principles behind targeted therapy and drug delivery systems, exploring their applications in different medical conditions, and investing in research and development efforts, we can harness the full potential of these technologies to improve patient outcomes and quality of life.

The future of targeted therapy and drug delivery systems is promising, with ongoing research and development efforts focused on improving the effectiveness and specificity of these treatments. Advances in nanotechnology, biomaterials, and drug design are enabling the development of innovative drug delivery systems that can overcome the limitations of traditional therapies and provide more targeted and personalized treatment options for patients. With continued investment and collaboration in this field, targeted

therapy and drug delivery systems have the potential to transform the way we treat a wide range of diseases and improve patient outcomes in the years to come.

References:

1. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol.* 2015;33(9):941-951.
2. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. *Nat Rev Drug Discov.* 2014;13(11):813-827.
3. Davis ME, Chen Z, Shin DM. Nanoparticle therapeutics: an emerging treatment modality for cancer. *Nat Rev Drug Discov.* 2008;7(9):771-782.
4. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm Res.* 2016;33(10):2373-2387.
5. Hua S. Targeted drug delivery strategies for improved therapeutic efficacy. *J Control Release.* 2014;188:1-16.
6. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. *Nat Rev Mater.* 2016;1:16014.
7. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol.* 2007;2(12):751-760.
8. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Adv Drug Deliv Rev.* 2013;65(1):36-48.
9. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano.* 2009;3(1):16-20.
10. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer.* 2017;17(1):20-37.
11. Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. *Nat Rev Clin Oncol.* 2010;7(11):653-664.
12. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J Control Release.* 2000;65(1-2):271-284.
13. Danhier F, Feron O, Pr at V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *J Control Release.* 2010;148(2):135-146.
14. Maeda H. The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular

- drug targeting. *Adv Enzyme Regul.* 2001;41:189-207.
15. Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A, Liang XJ. pH-sensitive nano-systems for drug delivery in cancer therapy. *Biotechnol Adv.* 2014;32(4):693-710.
 16. Bae YH, Park K. Targeted drug delivery to tumors: myths, reality and possibility. *J Control Release.* 2011;153(3):198-205.
 17. Guo S, Huang L. Nanoparticles containing insoluble drug for cancer therapy. *Biotechnol Adv.* 2014;32(4):778-788.
 18. Dhar S, Gu FX, Langer R, Farokhzad OC, Lippard SJ. Targeted delivery of cisplatin to prostate cancer cells by aptamer functionalized Pt(IV) prodrug-PLGA-PEG nanoparticles. *Proc Natl Acad Sci U S A.* 2008;105(45):17356-17361.
 19. Peer D, Margalit R. Loading mitomycin C inside long circulating hyaluronan targeted nano-liposomes increases its antitumor activity in three mice tumor models. *Int J Cancer.* 2004;108(5):780-789.
 20. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for imaging and therapy. *Nanomedicine (Lond).* 2011;6(4):715-728.
 21. Farokhzad OC, Cheng J, Teply BA, et al. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. *Proc Natl Acad Sci U S A.* 2006;103(16):6315-6320.
 22. Farokhzad OC, Jon S, Khademhosseini A, Tran TN, Lavan DA, Langer R. Nanoparticle-aptamer bioconjugates: a new approach for targeting prostate cancer cells. *Cancer Res.* 2004;64(21):7668-7672.
 23. Kirpotin DB, Drummond DC, Shao Y, et al. Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. *Cancer Res.* 2006;66(13):6732-6740.
 24. Yu MK, Park J, Jon S. Targeting strategies for multifunctional nanoparticles in cancer imaging and therapy. *Theranostics.* 2012;2(1):3-44.
 25. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. *Nat Mater.* 2013;12(11):991-1003.
 26. Lammers T, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. *J Control Release.* 2012;161(2):175-187.
 27. Chauhan VP, Stylianopoulos T, Boucher Y, et al. Delivery of molecular and nanoscale medicine to tumors: transport barriers and strategies. *Annu Rev Chem Biomol Eng.* 2011;2:281-298.
 28. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. *Nat Rev Mater.* 2016;1:16014.
 29. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for imaging and therapy. *Nanomedicine (Lond).* 2011;6(4):715-728.
 30. Hrkach J, Von Hoff D, Mukkaram Ali M, et al. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. *Sci Transl Med.* 2012;4(128):128ra39.
 31. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Mol Pharm.* 2008;5(4):505-515.
 32. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res.* 1986;46(12 Pt 1):6387-6392.
 33. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer.* 2017;17(1):20-37.
 34. Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date. *Pharm Res.* 2016;33(10):2373-2387.
 35. Hrkach J, Von Hoff D, Mukkaram Ali M, et al. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. *Sci Transl Med.* 2012;4(128):128ra39.
 36. Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. *Nat Rev Mater.* 2016;1:16014.
 37. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for imaging and therapy. *Nanomedicine (Lond).* 2011;6(4):715-728.
 38. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer.* 2017;17(1):20-37.