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Dendrimer-based Diagnostic Applications and Therapeutic for Anti-Cancer Therapy

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Abstract

This review reviews diagnostic applications and therapeutic on the use of based of dendrimer systems for anti-tumour therapy. Recent studies have shown that dendrimers are ideal delivery vehicles for explicit studies of the effects of polymer size, charge and composition and structure on biorelated properties like lipid bilayers interaction,plasma retention time, tumor absorption, biodistribution, cytotoxicity, and internalization. In the past few years, significant advances have been made in the treatment and diagnosis of dendrimers in the field of anticancer therapy. In this report, recently achievements in dendritic molecules in cancer therapy and diagnosis will be introduced, as well as the applications of dendritic molecules as a therapeutic platform for a variety of cancers, including chemotherapy, radiation therapy, photothermal therapy, photodynamic therapy, gene therapy and some other techniques.

Keywords

Dendrimer, Anti-Cancer; Dendrimer-Based Systems; Drug, Diagnostic Applications; Cancer Therapy; PAMAM.

1. Introduction

1.1 Characteristics and Advantages of Dendrimer

The word "dendrimer" comes from the Greek word "dendrons," which literally means trees or branches. [1]The dendrimers are highly branched macromolecules with well defined and uniform dimensions and shapes. Their basic structure have three main components: a repetitive branching unit, a terminal group and a central core, which can make variable surface functions. The formation of dendrimer macromolecules depends on the number of repeated scoring units and is also related to the formation of spherical structures. What makes dendrimer attractive for drug and gene delivery applications is the high control of its structure. Medicines can be encapsulated in their inner brightness or linked to their surfaces by hydrophobic or electrostatic interactions. Also medicines can form covalent bonds by reacting with terminal functional groups.

Dendritic macromolecules have been recognized as the most promised and effective cancer therapy platforms in the world due to their unique three-dimensional structure, good water soluble, low immunity and facilitation of functionalization. At same time, dendritic macromolecules are considered to be one of the most promising carriers of drugs, proteins and other treatment of drugs due to their close monodispersity and controllable structure, nanometer size and shape. Dendrimers must undergo some surface modification before they can be applied in biomedicine. For example, pegylation makes the system have prolongation of blood circulation time, good biocompatibility and stability. In nanomedical areas, dendrimers can be used as carriers for loading medicines via electrostatic interactions or hydrophobic interactions, to covalent bond drug molecules around the dendrimers, to compress genetic material through electrostatic interactions, to capture or stabilize

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inorganic NPs within the dendrimers. These approaches are currently used in a variety cancer therapies, including chemotherapy, radiation, PDT , PTT, gene therapy,and combination therapy.

1.2 Different Dendrimers

Various dendrimers have been developed and used since the 1980s and polyamide (PAMAM) are undoubtedly the most widely used (Figure 1A).They are hydrophilic, biocompatible and non-immunogenic systems, which promote their use in the supply of medicines.

Polymers (propylene immine) (PPI) dendrimers (Figure 1B) were the first to be reported by Buhleier et al. in 1978. [2] They called them a cascade of molecules. Together with PAMAM, they were also extensively studied.

Polyl-lysine (PLL) dendrimers (Figure 1C) are a type of polypeptide dendrimers that are primarily used as gene carriers because they condense well with oligonucleotides. Similar to other dendritic macromolecules, they have good water soluble, , flexibility, biodegradability and biocompatibility. In their structure they have peptide bonds , and the branching units and core are usually based on the lysine.

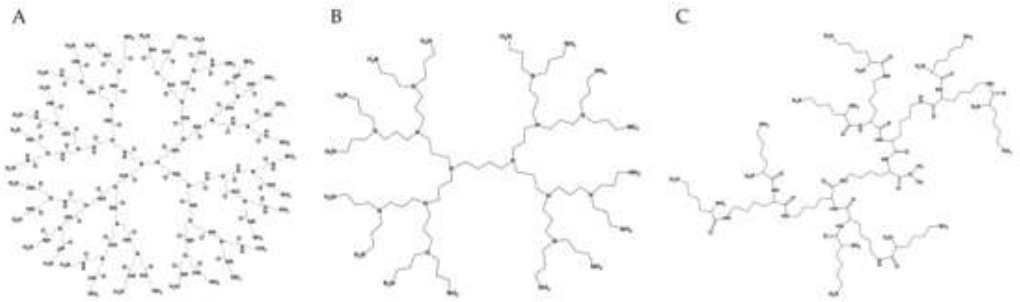

Figure 1. Different schematic representation of dendrimers. (A) PAMAM (B) PPI; (C) PLL . Illustrations generated by ChemDraw Professional Version 16.0.1.4

1.3 Toxicity of Dendrimers

Many research groups are currently studying the nanotoxicity of dendritic macromolecules in vitro and in vivo. On a molecular level, dendrimers have a strong binding affinity for heavy metal ions, amphyllic lipids, bile acids, vitamins, proteins and nucleic acids, suggesting that therapeutic physiological systems based on dendrimers may lead to the reduce of function of molecules and ions.

The surface function of dendrimers largely determines their molecular toxicity. For example, acetylcholinesterase shows conformational changes in the presence of PAMAM. Although there is little literature on the toxicity of dendrite molecules, we should focus on these problems in the long-term safety assessment dendrimer nanomedicines.

The cytotoxicity of dendrite macromolecules is the most common method for early screening of toxic or biocompatible drugs. It is widely believed that the main factor that determines the cytotoxicity of dendrite macromolecules may be the surface charge properties. According to research, neutral PAMAM are minimal toxic dendrimers of hydroxyl, carboxyl and amino terminus PAMAM .[3] The toxicity of dendritic macromolecules to specific tissues or organs has not been reported, but spleen, liver and kidney toxicity need to be considered.

Finally, the excretion of dendrite molecules is also an important issue. The dendrimer should be degraded into non-toxic compounds and excreted from the body. Over time, the accumulation of non-degradable dendritic molecules in the body may cause adverse symptoms. At present, the urgent need to prepare dendrimer nanomedicine is to design degradable or self-cracking dendrimers with potential triggers such as acids, light, reductants and enzymes.

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2. Cancer Therapy

2.1 Gene Therapy

Studies have shown that for electrostatic compression, nucleic acid containing anions can be easily condensed by the cationic dendritic macromolecules containing a large number of amine groups. Nucleic acid/dendrimer complexes formed in this way can be surface modified to enable them to perform different functions, can be protected nucleic acids from enzymatic degradation which are all compressed. In addition, dendrimers such as PAMAM, PPI and polyether imines with numerous tertiary amine groups can play proton sponge effects to make the polymerget away from nucleic acid lysosomes. For these reasons, nucleic acids may adequately protected and effectively released into the cytoplasm for expression.[4].

Among these dendrimers, PAMAM dendrimers, phosphorus dendrimers and PPI dendrimers are the three most widely used. To reduce the cytotoxicity of dendrimer, a range of modification strategies, such as dodecylation can be used. At the same time, it should be noted that some studies have shown that Au NPs retain their three-dimensional spherical structure well after encapsulation within the dendrimer, thus having more DNA binding sites than the dendrimer without Au nucleus. For this reason, the ability of dendrimers to compress pDNA is significantly improvements that are important for improved gene delivery. So the crucial question for improving gene delivery is how to significantly improve the ability of dendrimers to compress pDNA.

2.2 PTT (Photothermal Therapy)

Appearance and photothermal therapy of metal nanoparticles in the 1990s, has rapidly developed into a new field of tumor therapy. Traditional photothermal therapy uses the heat between 41 and 45 degrees Celsius induced by photothermal therapy that can convert near-infrared laser light (NIR) into thermal energy to remove cancer cells. [5] On the other hand, gold nanoparticles have been developed to absorb light strongly in the near infrared region and promote light penetration into the swollen tissue. The tumor site produces a locally lethal dose of heat to kill tumor cells.

In order to achieve photothermal therapy for tumors, dendrite macromolecules can modify photothermal therapy drugs to form functional nanohybrid. The preparation of Metal encapsulated dendron Lima for biomedical applications is aimed at adding a more refined degree of control to regulate biological interactions caused by metal particles, including improved ease of surface modification, ease of retention, contrast agents, biomarkers, biocompatibility and use as photothermal therapy. Among them, dendrimers have been identified as potentially useful in the treatment of malignant tissues by light and heat. (Figure 2) Recognition of the applicability of these particles in target hyperthermia and electron density contrast agents is now under way.

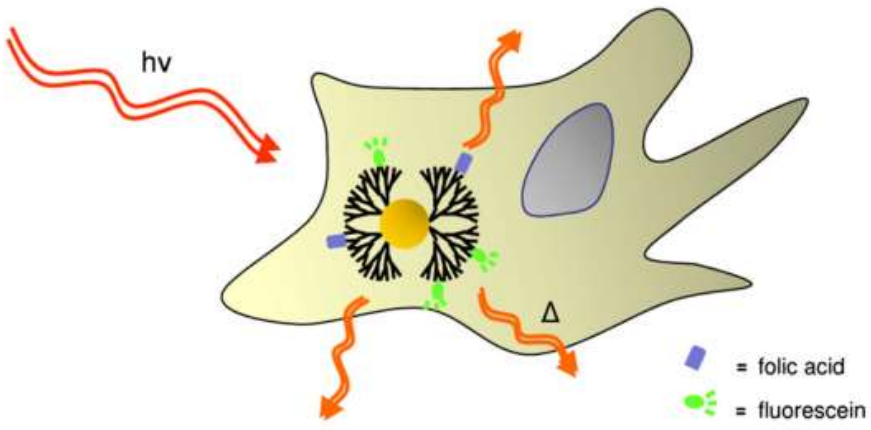

Figure 2. PTT. Concept expression of photothermal therapy using dendrimer capture gold nanoparticles. Nano particles target tumor cells through folate receptors, and when exposed to near-infrared light, gold particles generate heat and kill host cells.

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2.3 Chemotherapy

Cancer chemotherapy is a way that use chemicals to control invasion, proliferation and metastasis of tumour cells. At the same time, cancer chemotherapy also has many drawbacks, such as low specificity leading to dosedependent side effects, short time of blood circulation and high drugsresistance. Dendritic macromolecules can overcome these drawbacks for three reasons :1) multiple modifications of dendritic macromolecules terminators make them specific to tumour cells; 2) Special dendritic platforms can effectively delay the drug release rate, prolong blood circulation time and improve the pharmacokinetics; 3) The introduction of specific medicines can inhibit drug resistance.[6].

Zhu et al. [7]discovered a method of costly linking dendritic macromolecules with α -reproductive phenol succinate (α -TOS), that is, combining with dendrite macromolecules to kill tumour cells. The resulting Au-ToS-FA DENPs or Au-ToS-RGD DENPs can be used for targeted chemotherapy and CT imaging of tumor cells.

For Au-TOS-FA DENPs (Figure. 3), the IC 50 of α-TOS was 19.2 μmol L −1, is a bit more than those of Au-TOS-RGD DENPs[8] , presumably derived from different target change .This demonstrates the targeting and effectiveness of dendritic drug.

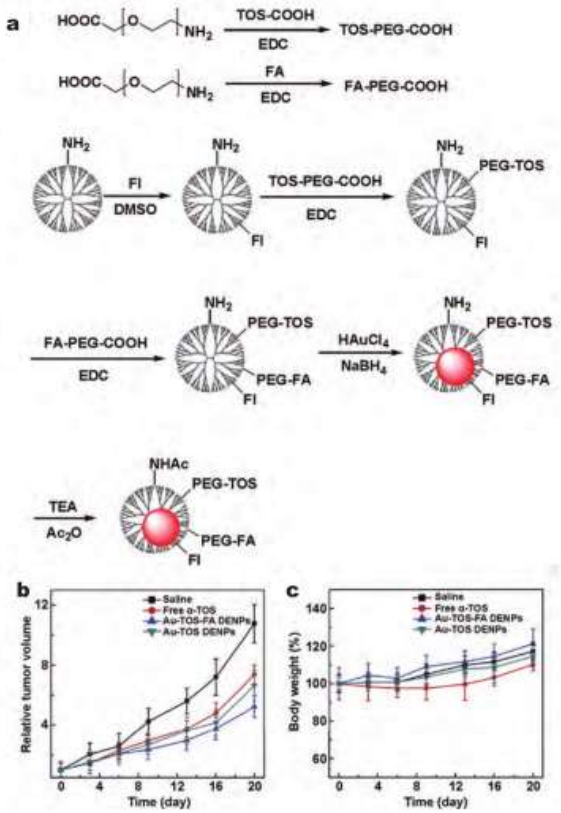

Figure 3. Schematic illustrating the DENP Au-TOS-FA (a), U87MG after various treatments (b); body weight of U87MG (c).Reproduced with the permission of Ref..Copyright 2015, Elsevier.

2.4 PDT (Photodynamic Therapy)

Photodynamic therapy is based on visible light or near infrared (NIR) photoactivating photosensitizers. When the light is excited, it forms a high energy state, which reacts with oxygen to produce highly active singlet oxygen, thus inducing tumor cell necrosis and apoptosis. In recent years, the use of dendrimers for drug delivery has been widely studied in photodynamic therapy to improve tumor selectivity, retention and pharmacokinetics.

PS / dendrimer nano formulation can be formed by covalently bonded, physical encapsulation, and electrostatic interactions between PS and dendrimer. On the other hand, we can use PS to make a

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branching unit and synthesize which PS-based dendrimers for PDT of cancer. Bastien et [9] discovered photosensitizer chlorine-e6 (CE6) and PAMAM G4.5 dendritic Lima conjugates (Figure.4).

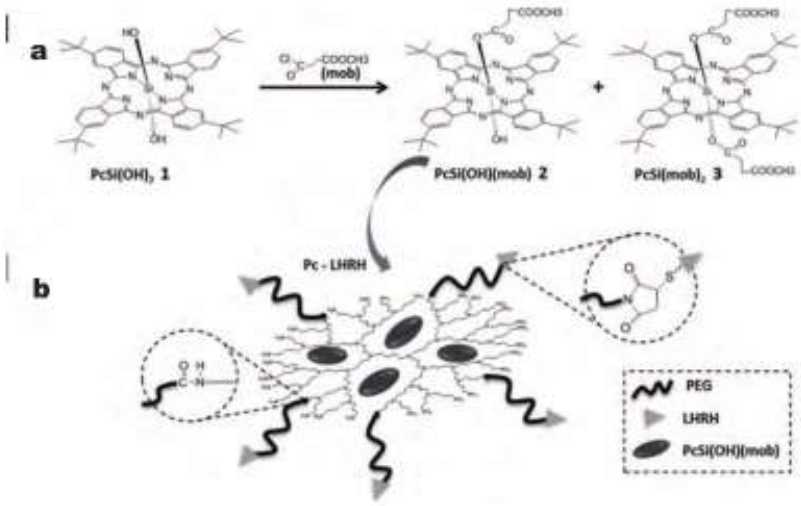

Figure 4. (a) synthesis of mono (pcsI (OH) (mob), 2) disubstituted (pcsI (mob) 2,3) derivatives of silicon phthalocyanine (pcsI (OH) 2, 1). A schematic expression of a tumor targeted pyrolytic platform based on a phthalocyanine loaded dendrimer is reproduced with permission from the luteinizing hormone releasing hormone. Copyright 2013, American Chemical Society.

2.5 Radiotherapy

Cytotoxic radiation levels can be passed to the place of tumour by radionuclides labelled on the dendromer tray. Many kinds of radionuclides such as 131I, 90Y,177Lu, 188 Re and 89Sr are used in radiation therapy at clinics. Among them, 177 Lu and 131 I can be labelled to dendrite molecules and used in cancer radiotherapy. In addition, different targeting agents can also be used to modify the periphery of dendrite molecules, including FA and chlorotoxin (CTX)[10]. (Figure.5).

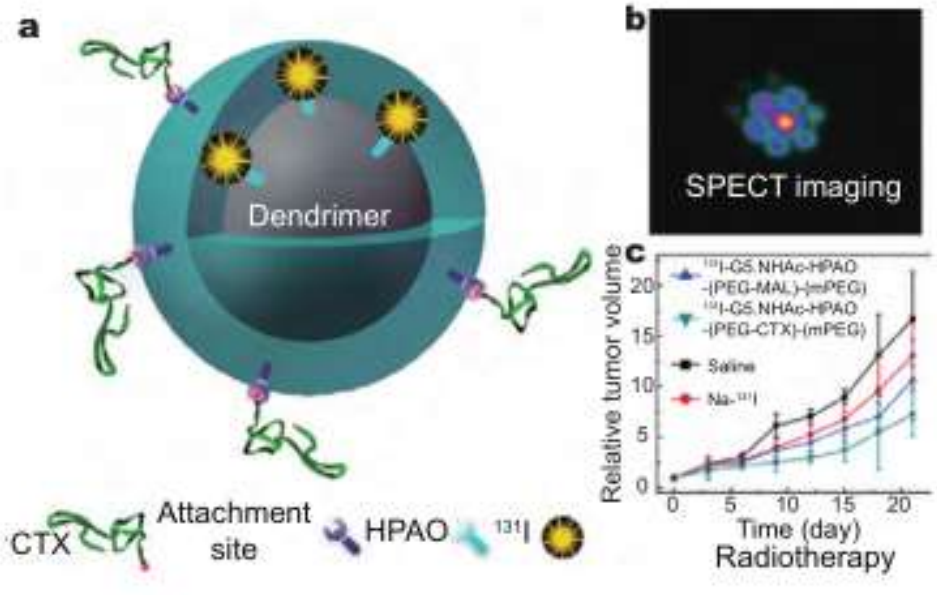

Figure 5. The structure of multifunctional dendrometers, combined with chlorotoxin, labelled 131 I (a), the tumours SPECT images (b) and volume (c) of mice suffering from C6 tumours .Reproduced with permission of Ref. Copyright 2015, American Chemical Society.

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2.6 Combination Therapy

Common used chemotherapeutic agents often have adverse reactions, multipharmacological resistance and poor drug delivery efficiency in solid tumors due to tumor vascular abnormalities and hypoxia microenvironment [11], resulting in very limited efficacy. Radiation therapy, photothermal therapy, photodynamic therapy and gene therapy have their own disadvantages and limitations due to their simple treatment methods. Therefore, in order to improve the effectiveness of treatment, combination therapy must be used. For example, studies have shown that photothermal therapy combined with photo-thermo-chemotherapy has been shown that much more effective than their monotherapies. That is because both have an additive or synergistic effect in the treatment approach. At the same time, dendrimers can also be a valuable carrier for combined cancer therapy.

On the other hand, for radio-photothermal combination therapy, dendrimer nanoplatforms are designed to label radioisotopes and capture or stabilize nano-photothermal therapy drugs, for example, Au NPs [12]. In addition to the above two combination therapies, photothermo-photodynamic therapy, genetic-chemotherapy therapy, genetic-photodynamic therapy[13] and genetic-photothermal therapy are being studied or have been used in clinical treatment.

3. Conclusions and Perspectives in Dendrimer-based Anti-Cancer Therapy

This review reviews recently progress of different dendritic macromolecular platforms in cancer therapy. Dendrimer is a newly discovered carrier and that means it can serve as a carrier for drug dissolution and nucleic acid concentration to increase the efficacy meanwhile reduce the cancer therapy toxicity compared to traditional chemotherapy. Their structural characteristics and their almost precise control during synthesis help their developments in the field of tumour delivery.

The high level of control over size, density, shape, structure, and branch length, and surface function of dendrimers make them ideal vectors for biomedical applications such as drug delivery and gene delivery. The bioactive agent will optionally embedded within the dendrimer. Then, chemically or physically adsorbed on the dendrimer's surface, depending on the specific situation of the active material and their applications. The unique structural properties of dendritic macromolecules allow drugs to be physically loaded inside dendrite molecules through hydrophobic or surface-related interactions of dendrite molecules through covalent reactions. At the same time, other chemicals and radioisotopes capable of being introduced into a surface of dendrimer for PTT, PDT and radiotherapy therapy. In addition, the high-density surface groups of dendrimers can also attach target groups and a group that modifies solution behavior or toxicity in dendrites. The surface modified dendrimers can be used effectively means against viruses, bacteria andtumors.

It has been demonstrated that well-designed dendritic structures can undergo a series of adjustments aimed at achieving ideal biocompatibility, bioavailability, pharmacokinetics and local treatment of malignant tumors. Cationic amines, a substance inherent in the surface of dendrimers, can not only perform a variety of modifications, but also concentrate nucleic acid materials for gene transport. Above all, dendrimers function as a platform for tumour therapy, inducing synergistic effects or combined effects. Thus, dendrimers really can proven to be unique platforms for building different multifunctional nanoscale cancer therapeutic platforms.

However, it is worth noting that many studies have focused on improving and optimizing dendrimer-based cancer therapeutic platforms, while dendrimer systems with greater biocompatibility, reinforcement therapeutic effectiveness, metabolic mechanisms stay to bestudied. On the other hand, there is still much room to explore and solve in improving the therapeutic effect of dendritic macromolecules and discovering the safety of their metabolic mechanism. That is, the clinical transformation of dendrite macromolecules has not been realized. Therefore, the clinical application and effective development of dendritic macromolecules still have a long way to go. At present, it is possible to further design a suitable multi-functional platform based on dendritic molecules for intensive therapy by in-depth understanding of tumor microenvironment, tumor metabolism and tumor metastasis.

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References

[1] Tomalia DA, Naylor AM, Goddard WA. Starburst dendrimers: molecular-level control of size, shape, surface chemistry, topology, and flexibility from atoms to macroscopic matter. Angew Chem Int Ed, 1990, 29: 138-175.

[2] Buhleier, E.; Wehner, W.; VÖGtle, F. “Cascade”- and “Nonskid-Chain-like” Syntheses of Molecular Cavity Topologies. Synthesis 1978, 1978, 155-158. [CrossRef].

[3] R. Duncan and L. Izzo, Adv. Drug Delivery Rev., 2005, 57, 2215.

[4] Yang J, Zhang Q, Chang H, et al. Surface-engineered dendrimers in gene delivery. Chem Rev, 2015, 115: 5274-5300.

[5] Ait-Mohand S, Fournier P, Dumulon-Perreault V, et al. Evaluation of 64 Cu-labeled bifunctional chelate–bombesin conjugates. Bioconjugate Chem, 2011, 22: 1729–1735.

[6] Pooja D, Kulhari H, Singh MK, et al. Dendrimer–TPGS mixed micelles for enhanced solubility and cellular toxicity of taxanes. Colloids Surfs B-Biointerfaces, 2014, 121: 461-468.

[7] Zhu J, Fu F, Xiong Z, et al. Dendrimer-entrapped gold nano- particles modified with RGD peptide and alpha-tocopheryl suc- cinate enable targeted theranostics of cancer cells. Colloids Surfs B-Biointerfaces, 2015, 133: 36-42.

[8] Zhu J, Zheng L, Wen S, et al. Targeted cancer theranostics using alpha-tocopheryl succinate-conjugated multifunctional dendrimer-entrapped gold nanoparticles. Biomaterials, 2014, 35: 7635-7646.

[9] Bastien E, Schneider R, Hackbarth S, et al. PAMAM G4.5- chlorin-e6 dendrimeric nanoparticles for enhanced photodynamic effects. Photochem Photobiol Sci, 2015, 14: 2203–2212.

[10] Zhu J, Zhao L, Cheng Y, et al. Radionuclide 131 I-labeled multi- functional dendrimers for targeted SPECT imaging and radiotherapy of tumors. Nanoscale, 2015, 7: 18169–18178.

[11] Kala S, Mak ASC, Liu X, et al. Combination of dendrimer-na-novector-mediated small interfering RNA delivery to target Akt with the clinical anticancer drug paclitaxel for effective and potent anticancer activity in treating ovarian cancer. J Med Chem, 2014, 57: 2634–2642.

[12] Hutnick MA, Ahsanuddin S, Guan L, et al. PEGylated dendrimers as drug delivery vehicles for the photosensitizer silicon phthalocyanine Pc 4 for candidal infections. Biomacromolecules, 2017, 18: 379–385.

[13] Yang Z, Gao D, Cao Z, et al. Drug and gene co-delivery systems for cancer treatment. Biomater Sci, 2015, 3: 1035–1049.