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An update on applications of nanostructured drug delivery systems in cancer therapy: a review

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ABSTRACT

Cancer is a main public health problem that is known as a malignant tumor and out-of-control cell growth, with the potential to assault or spread to other parts of the body. Recently, remarkable efforts have been devoted to develop nanotechnology to improve the delivery of anticancer drug to tumor tissue as minimizing its distribution and toxicity in healthy tissue. Nanotechnology has been extensively used in the advance of new strategies for drug delivery and cancer therapy. Compared to customary drug delivery systems, nano-based drug delivery method has greater potential in different areas, like multiple targeting functionalization, *in vivo* imaging, extended circulation time, systemic control release, and combined drug delivery. Nanofibers are used for different medical applications such as drug delivery systems.

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Introduction

Cancer is a main public health problem and one of the world's most disturbing diseases. Systemic chemotherapy along with surgical resection or radiotherapy is the most generally used therapeutic strategy for cancer. A combination of radiation therapy and chemotherapy is commonly applied to raise survival rates of patients. However, the absence of selectivity for tumor tissues often leads to some adverse effect for the patients who undergo a chemotherapeutic method, including kidney malfunction, nausea and vomiting, nerve injury, impairment of sight, and bone marrow suppression (Saravanabhavan and Dharmalingam 2013, Zong et al. 2015). Although some progress has been made in cancer therapy, there are still numerous limitations including severe toxicity in normal cells, death caused by the systematic administration of anticancer drugs at extreme endurable doses (Piccolo and Kolesar 2014), limited distribution of chemotherapy drugs from the blood vessels into the solid tumors, (Postma et al. 2013) low resection rates and poor overall patient survival in surgery, (Langer 1998) and prominent clinical toxicities in radiotherapy (Minchinton and Tannock 2006). Recently, remarkable efforts have been devoted to develop nanotechnology to improve the delivery of anticancer drug to tumor tissue as minimizing its distribution and toxicity in healthy tissue (Panyam and Labhasetwar 2003). Nanotechnology has been extensively used in the advance of new strategies for drug delivery and cancer therapy. Compared to customary drug delivery systems, nano-based drug delivery method have greater potential in different areas, like multiple targeting functionalization, *in vivo* imaging, extended circulation time, systemic control release, and combined drug delivery (Liu et al. 2014). Polymeric nanofibers refers to fibers with diameters from 1 nm to 1 μm, closely matching the size scale of extracellular matrix (ECM) fibers (Dahlin et al. 2011, Ma and Zhang 1999). These nanomatertials are made of inorganic (i.e., titanium, silicon or aluminum oxides) or organic (polyvinyl alcohol, gelatin, poly(*N*-isopropylacrylamide, polycaprolactone, or polyurethane) materials. Nanofibers consist of low density, large surface area, tight pore size, and high pore volume (Díaz and Vivas-Mejia 2013). Nanofibers are used for different medical applications such as drug delivery systems. For instance, in one research Tseng and coworkers used biodegradable nanofibers to successfully deliver vancomicyn, an antibiotic, to the brain tissue of rats and decrease the toxicity related with parenteral antibiotic treatment (Tseng et al. 2013). Drug or other therapeutic agents may be integrated into electrospun nanofibers during blend electrospinning, chemical immobilization, co-axial electrospinning, physical adsorption, and emulsion electrospinning (Figure 1) (Huang et al. 2003).

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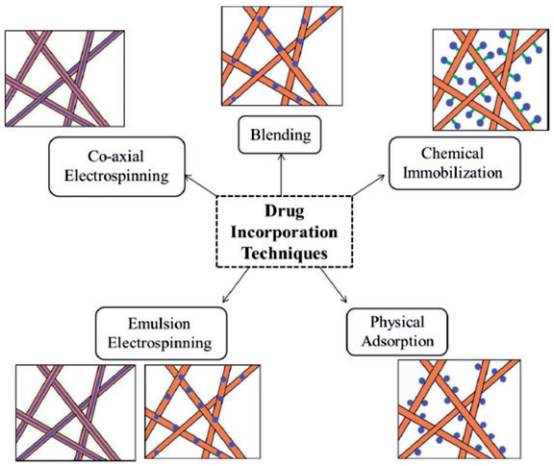

Figure 1. Drug incorporation techniques (Goonoo et al. 2014).

Nanofiber in cancer therapy

More recently, nano carrier-based drug delivery systems have attracted more and more attention in overwhelming these limitations (Ferrari 2005, Jemal et al. 2006, Moses et al. 2003, O'Gorman et al. 2014, Peer et al. 2007). Newly, drug-eluting electrospun nanofibers as a novel dosage form have excited much exploration interest because they exhibited following benefits: high loading and encapsulation efficiency for physico-chemically diverse drugs; relatively prolonged residence time; desirable distribution and delivery of the active substance for an extended period at a predictable percentage; typical softness, flexibility, non-abrasion, and lack of sharp corners which enable them to realize various geometries (sheets, tubes, coatings) to fit the lesions; and finally low cost and easy application. These innovative systems have the capability to selectively carry drugs into the cancer tissues or into the targeted sites, which is in contrast to systematic treatment with free drugs. However, the efficacy of drug delivery and subsequently the specific selective effects are still main challenges of these intravenously delivered chemotherapeutics. Among these nanocarriers, polymeric micelles with distinct core/shell architecture which are self-assembled from amphiphilic copolymers have been extensively reported (Farokhzad and Langer 2009, Machado et al. 2013, Malcolm et al. 2010, Newland et al. 2012). They are in the center of attention because their exceptional advantages, such as the ability to improve the solubility of water insoluble drugs, prolonged blood circulation, and the easiness of functionalization (Blakney et al. 2013, Farokhzad and Langer 2009, Liu et al. 2013, Machado et al. 2013, Zhang et al. 2014). However, these nanocarriers will encounter various obstacles in route from the injection location to the target cell, such as mucosal barriers and nonspecific uptake (Kazunori et al. 1993, Zamani et al. 2013). Thus, the intravenously delivered micelles still show some defects, including fast clearance from the bloodstream, over gathering in non-target organs (Fox et al. 2009, Wang et al. 2012). Overreliance on the enhanced permeability and retention effect to deliver the nanocarrier into the tumor, and a modest increase in tumor accumulation (Nicolas et al. 2013). Unfortunately, the micelles' advantage-prolonging blood circulation, occasionally turns into a disadvantage that may result in extravasation of the encapsulated containing in unexpected locations due to the low stability of the micellar system (Moses et al. 2003).

To address some of these difficulties, localized drug delivery to the solid tumors is a worthy approach. By comparison to the systemic administration, the localized system has some gains such as ensuring prolonged therapeutic drug levels at the tumor location. Additionally, maintaining low systemic drug exposure, (Allen and Cullis 2004, Basarkar and Singh 2009) not only results in greater therapeutic efficacy and a lower toxicity, (Wang et al. 2014) but also reduces the requirement for repeating chemotherapeutic administrations and subsequently improving the quality of life and patient compliance (Allen and Cullis 2004).

In one efficacious previous study, implantable wafers found was on a polyanhydride polymer used to locally deliver chemotherapeutic drugs such as carmustine (BCNU) to treat brain cancer (Peer et al. 2007). The implantable bulk materials (like blocks, films, and wafers) and the conventional injectable hydrogel system are the most common forms for conventional localized drug delivery systems. For the implantable bulk materials, it is difficult to tune degradation rate. Conventional injectable hydrogel systems, which may improve patient compliance and ease, can be generally divided into two classifications including particle drug depots and semisolid drug depots (Couvreur and Vauthier 2006). The particle drug depots, (including emulsions, liposomes, biodegradable microspheres, and micelles) are relatively unstable and easy to migrate away from the tumor location. For the semisolid drug depots, the *in vivo* solidification of liquid hydrogel is inconvenient occasionally, and primary burst of drug may happen during the lag time between the injection and the formation of the solid hydrogel (Couvreur and Vauthier 2006).

Currently, the challenges of this localized drug delivery via polymers are the absence of control in drug release and distribution (Allen and Cullis 2004). And particularly targeting at tumor cells. Hence, the combination of the active targeting micellar system with the implantable "controllable" matrix may be a good choice to reach a high chemotherapy efficacy against tumors along with low side effects in normal tissues, and also to overcome the weaknesses of the conventional localized drug delivery systems.

In previous studies, researchers innovated a newly implantable active-targeting micelle-in-nanofiber device for efficient and harmless cancer therapy (Yang et al. 2015). This device can be prepared as illustrated in Figure 2.

First, the folate (FA)-conjugated polyε-caprolactone-polyethylene glycol (FA_PCL-PEG) copolymer was used to encapsulate doxorubicin (Dox), the anticancer drug model, by self-assembling into active-targeting micelles (FM). FA ligands can directly bind to the folate receptors (FR) that are over expressed on the surface of a majority of solid tumors (Low and Kularatne 2009). Then, these micelles are trapped in the core area of the core_shell polymeric nanofibers by coaxial electrospinning in which the inner phase is a mixture water solution of poly(vinyl alcohol) (PVA) and the micelles, and the outer phase is a gelatin solution. Electrospun fibers are identified to be excellent drug carriers with a higher surface area

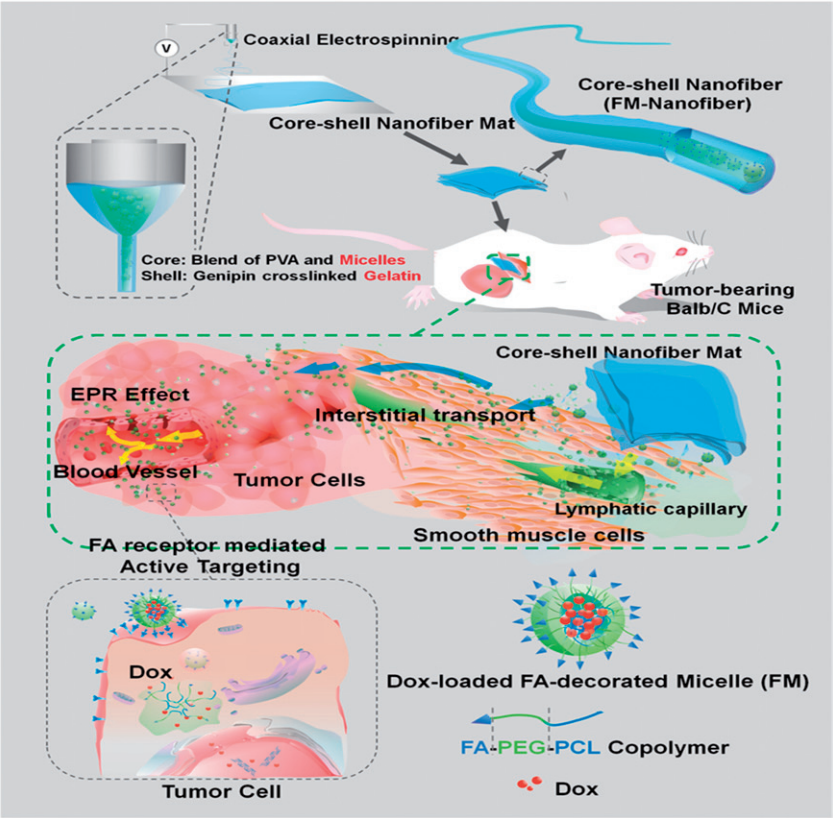

Figure 2. Schematic illustrations of the fabrication of the implantable active-targeting micelle-in-nanofiber device (FM-Nanofiber) and the delivery process of these Dox-loaded micelles (FM) from nanofiber matrix to tumor tissues and finally to tumor cells (Yang et al. 2015).

per mass, high drug loading, and encapsulation efficiency (Chakraborty et al. 2009, Joshi et al. 2014, Szentivanyi et al. 2011). They also have the potential as an implantable device for cancer chemotherapy of solid tumors either in the tumor or at the surgical resection margins (Kim et al. 2013, Ranganath and Wang 2008, Ranganath et al. 2010).

In summary, they have effectively developed a new localized drug delivery device by combination of active-targeting micellar system with implantable polymeric nanofibers (Madan et al. 2009). To date, many approaches have been proposed for the delivery of drugs, lysozymes, growth factors, and genes and siRNAs using forms of grapheme, polymers, and blends of these. It has been reported that these delivery systems have been used in diverse applications and post-surgical cancer therapies. Numerous drug delivery methods such as hydrogels, nanoparticles, polymer-drug conjugates, and microspheres have been advanced, which each of possesses its own advantages and disadvantages (Arnold and Ulbrich-Hofmann 2006, Charernsriwilaiwat et al. 2012, Chaturvedi et al. 2011, 2013, Kawashima et al. 2011, Neves et al. 2012, Rudzinski and Aminabhavi 2010). Of the diverse drug delivery systems, polymer nanofiber-drug conjugates have drawn interest between the scientists, as it could be delivered to targeted locations by passive or active targeting (Letchford and Burt 2007, Mora-Huertas et al. 2010).

A lot of systems have been developed for the administration of the drug, in which the polymeric drug-delivery systems have various merits compared to other conventional methods. Some of these advantages include dosage forms, therapeutic influence, non-toxicity, degradability, and so on. Despite these benefits, there are also some demerits, such as the low effectiveness of the drug delivery and burst release of drug at the beginning (Sokolsky-Papkov et al. 2007). The limitations associated with the existing treatment models and the requirement to overcome them acted as the catalyst for operating further investigation in these areas. In current years, electro spinning has gathered a lot of interest in the invention of ultrafine polymer fibers of diameters ranging from 20 to 2000 nm, as their fundamental properties provide an excellent environment for cell adhesion, proliferation, and differentiation. Some researchers have proposed the use of the fibers as an alternative for fabricating vascular scaffolds because of its low cost productivity, facile control of fiber diameter, and easiness in the setup. Furthermore, it mimics the natural ECM at nanoscale while possessing brilliant mechanical properties (Lin et al. 2013, Zeng et al. 2003).

It was obvious from the works of numerous researchers that the nanofiber scan be applied as typical carriers of the drug as they possess higher surface to the volume ratio along with improved antitumor efficacy and antimicrobial activity. Apart from drug delivery, much attention has been concentrated on the field of tissue engineering for maintenance and stimulation of tissue growth. This has always remained a very challenging application since the materials that are selected play a vital role. The materials used for tissue engineering must be biocompatible, biodegradable, non-toxic, and less immunogenic; moreover, it should be safe to implant or deliver the drug. Besides, it should also possess appropriate

mechanical properties and various other features that are required for drug delivery and tissue engineering applications (Peter et al. 2010, Zheng et al. 2013a, 2013b).

In a study conducted by Saravanabhavan and Dharmalingam (2013), scientists concluded that PSunanofibers were successfully fabricated with the incorporation of nHA into them by using the electro spinning technique as post-surgical implants in cancer therapy. The system exhibited a high potential in delivering the anticancer drugs to the target site, and it was also demonstrated that it could be used as a postsurgical implant.

In vitro studies on the drug release showed the prolonged pattern of release which allowed the spread of the drugs inside the target location wherever the tumor may exist. The results from the MTT assay showed that the metabolizing activity of the normal cells was not affected by the PSu; but the drug loaded composites decreased the metabolic activity of the cancerous cells. Thus, the prepared model could potentially be a carrier for anticancer drug, and it could also serve as a postsurgical implant (Ahmadi et al. 2014, Ebrahimnezhad et al. 2013, Mollazade et al. 2013, Nejati-Koshki et al. 2013, Pourhassan-Moghaddam et al. 2013, Saravanabhavan and Dharmalingam 2013, Zong et al. 2015).

In a study conducted by Zong et al. (2015), cisplatin-loaded poly (ethylene oxide)/polylactide composite electrospun nanofibers were prepared to seek the possibility and feasibility of nanofibers-based vaginal drug delivery system for local chemotherapy against the cervical cancer (Abbasi et al. 2014a, Alimirzalu et al. 2014, Alizadeh et al. 2014, Davoudi et al. 2014, Eatemadi et al. 2014, Ghasemali et al. 2013, Hosseininasab et al. 2014, Kouhi et al. 2014). The results showed that drug-loaded nanofibers is a hopeful dosage form for local therapy of cervical/vaginal cancers. It is appropriate for the treatment of incurable cervical/vaginal cancers, or even better as an auxiliary selection to surgical resection of these cancers (Abbasi et al. 2014b, Alizadeh et al. 2016, Chung et al. 2016, Daraee et al. 2014, Davoudi et al. 2014, Eatemadi et al. 2016, Effat et al. 2016, Elham et al. 2014, Eommolbanin et al. 2014, Fekri Aval et al. 2016, Hadis et al. 2016, Jin-Hwan et al. 2014, Mohammad et al. 2014, Nasrabadi et al. 2016, Tabatabaei Mirakabad et al. 2016).

Prevention of lung cancer recurrence by nanoparticle (nanofiber) technology

Lung cancer is the chief reason of cancer deaths in North America, with above 200,000 new cases identified every year and a gloomy five-year survival percentage of ~18% (Mollazade et al. 2013, Zong et al. 2015). One of the factors causative to poor survival is the lack of ability of a lot of patients to bear a "wide" local cutting out of their tumor, i.e., lobectomy, since elimination of the predictable 25% of whole lung function additional compromises previously restricted pulmonary function. Lesser, i.e., wedge, resections save lung parenchyma but are connected with a two-fold rise in local cancer return as an outcome of the microscopic disease remaining at the surgical resection border (Ebrahimnezhad et al. 2013, Nejati-Koshki et al. 2013). This is a serious choice since recent two-year survival in patients that grow recurrence drops to ~20% (Pourhassan-Moghaddam et al. 2013) for instance the mainstream of these patients are not candidates for added surgery, and radiation and/or chemotherapy are largely palliative (Ahmadi et al. 2014). Platinum based DNA-adducting agents, for instance cisplatin, are the in progress standard-of-care chemotherapy for lung cancer (Ghasemali et al. 2013, Kouhi et al. 2014). Even though these agents have dose-limiting side-effects such as nephrotoxicity (Abbasi et al. 2014a) and neurotoxicity (Hosseininasab et al. 2014) with systemic management, the expenditure of cisplatin has reached some enhancement in overall survival of lung cancer patients with metastatic disease. Cisplatin has furthermore been used in mixture therapy (Alimirzalu et al. 2014, Davoudi et al. 2014, Ghasemali et al. 2013, Kouhi et al. 2014) to attain a wider therapeutic window and therefore enhanced clinical results. Additional methods to increase cisplatin efficacy *in vivo* are also being explored. Nanoparticles and local drug delivery approaches such as chemotherapy-loaded films, foams, and gels are altogether being advanced to develop drug uptake while reducing systemic side effects (Eatemadi et al. 2014). In specific, cisplatin-loaded nanoparticles have been assessed in numerous clinical trials with hopeful outcomes, (Alizadeh et al. 2014, 2016) and other cisplatin drug delivery materials such as gels (Eatemadi et al. 2016), films (Davoudi et al. 2014), and glues (Effat et al. 2016) intended for local administration are gaining traction in the fight against lung and associated thoracic cancers. Though, a lot of local and systemic drug delivery systems possess burst release kinetics, which exposes drugs to tumors for merely a short period and highpoints the requirement for developed designs for sustained-release chemotherapy depots. In recent times, informed the fabrication of three-dimensional superhydrophobic microfiber meshes that make use of the metastable air barrier within these porous materials to drastically slow wetting and thus tolerate the release of encapsulated 7-ethyl-10-hydroxycamptothecin (HCPT) (Elham et al. 2014), an investigational lipophilic anticancer agent, for some weeks. Knowing the central character of cisplatin therapy in the treatment of lung cancer, this report concentrates on efforts using superhydrophobic materials to deliver this hydrophilic drug. Exactly, the current report defines the fabrication of cisplatin-loaded, three dimensional nanofiber meshes; reveals the sustained release of cisplatin *in vitro*; and applies the satisfactory physical and mechanical stuffs of these biodegradable meshes to an *in vivo* surgical model of destructive, initial-stage lung cancer, and local post-surgical cancer recurrence (Eommolbanin et al. 2014). Given the requirement to reduce the amount of lung removed and yet accomplish histologically negative margins, a local drug delivery tactic that supplements cytoreductive surgery with localized, sustained-release chemotherapy possibly will hold capacity by removing residual, microscopic tumor cells – mainly in patients impotent to endure more destructive resection. Such a local drug-delivery method is presently clinically implemented in the treatment of single one cancer: high-grade malignant glioma (Hadis et al. 2016, Tabatabaei Mirakabad et al. 2016). Afterward cytoreductive surgery, rigid, brittle carmustine (BCNU)-loaded polyanhydride (Daraee et al. 2014) wafers are located in the resected tumor beds, with BCNU release

happening over 2–3 weeks (Nasrabadi et al. 2016). Aimed at patients with lately identified malignant glioma, this treatment improved their median survival to 64.1 weeks, in comparison to 49.4 weeks with placebo (Chung et al. 2016, Nasrabadi et al. 2014). Additional success has been limited by the short time of drug release in this delivery system. Unlike static tissues, the practical difference of revocable tissue extension and contraction present on the lung surface requires the use of compliant materials for drug delivery. Hence, the design features for drug delivery to the lung requires a compliant, flexible material with a prolonged release profile. Therefore, formerly advanced paclitaxel-loaded PGC-C18 films for preventing local cancer recurrence in a parallel Lewis Lung Carcinoma (LLC) tumor resection model (Abbasi et al. 2014b). These films depend on their hydrophobicity to arrange for sustained drug release over ~90 days for lipophilic drugs (such as paclitaxel (Elham et al. 2014b)). Though, these films lacked the mechanical integrity to serve as buttressing materials themselves and were thus cast atop secondary scaffolds composed of de-cellularized bovine pericardium strips. In order to fabricate an all-in-one drug-device system that may well be stapled into the lung tissue by standard surgical staplers, as was designated the method of electrospinning. Electrospinning is a polymer processing procedure (Fekri Aval et al. 2016, Mohammad et al. 2014, Sill and von Recum 2008) that generates non-woven fiber meshes and involves the application of high voltage to a polymer solution at the tip of a syringe pump and needle assembly.

The communal chloroform/methanol solvent system for electrospinning PCL-based meshes was evaded for the reason that cisplatin is unsolvable in such nonpolar solvents, and solvent-drug compatibility has been exposed to affect drug release degrees and/or outcome in poor encapsulation (Zeng et al. 2005).

Nanofiber and tumor of central nervous system

Such as in other organs, malignant tumors are one of the greatest regularly studied target diseases of nanotherapeutics amongst brain diseases. Particularly, numerous pathological mechanisms as well as reactive oxygen species (ROS), biological actions of growth factors, and signaling pathways of proliferative potentials could be addressed with nanoparticle-based therapeutics (Arvizo et al. 2013, Kudgus et al. 2013). Furthermore, double functions of nanoparticles in together imaging and therapy, so called theranostics, are still attractive notions (Muthu et al. 2014). A prominent features of nanoparticles is that it is possible to increase bioavailability of therapeutic agents in brain tumors by way of conjugation of specific ligands on the surface of nanoparticles which are loaded with therapeutic materials. BBB could be a difficulty to therapeutic agents along with toxic materials (Kim et al. 2006). Bioavailability can be improved by ligand revision with peptides targeting cell surface receptors which are abundant in endothelial cells lining brain vasculatures, such as transferrin receptor and low-density lipoprotein receptor (Kuang et al. 2013, Zhang et al. 2013). Therapeutic materials as well as conventional chemotherapeutic agents and minor interfering RNA could be loaded in nanoparticles. Furthermore, ligand adjusted nanoparticles develops cellular uptake of therapeutic materials into malignant tumor cells by conjugation with ligands which fix to surface molecules specific to glioma cells (Gao et al. 2013). Packing with two or extra therapeutic materials into nanoparticles is also a plausible approach in the treatment of brain tumor (Lei et al. 2013).

Glioblastoma multiforme (GBM) accounts for approximately 50% of Reported malignant brain tumors (Wen and Kesari 2008). GBM is a prime tumor of astrocytes that, in spite of years of investigation, remains resistant to treatment even with improvements in surgical methods, neuroimaging, and adjuvant modalities for instance chemotherapy and radiation (Bao et al. 2006, Sarkar and Chiocca 2011). Clinical observations recommend that these tumors migrate by way of single cells, chiefly along wihite matter tracts (Bellail et al. 2004, Louis 2006). Conventionally, cancer cell migration has been evaluated using a number of two-dimensional (2D) assays, such as the micro liter migration evaluate (Giese et al. 1995, Valster et al. 2005) or the wound healing assay (Valster et al. 2005). Particular to GBM migration, some brain mimetic hydrogels, as well as hyaluronic acid, have been working by ourselves (Rao et al. 2011) and others (Ananthanarayanan et al. 2011, Coquerel et al. 2009, David et al. 2008, Yang et al. 2011). Polymeric electrospun nanofibers are substitute neural tissue engineering substrates (Corey et al. 2008, Gerardo-Nava et al. 2009, Prabhakaran et al. 2009) that have been used as conductors for neural reparation and regeneration (Corey et al. 2008, Schnell et al. 2007, Wang et al. 2009) and substrates for Schwann cell maturation (Chew et al. 2008) and neural stem cell variation (Christopherson et al. 2009). Ranged electrospun nanofibers are mostly fascinating as neural guides because of their topographical resemblance to white matter (Jovanov-Milosevic et al. 2006). Moreover, aligned electrospun nanofibers (i.e., poly(ε-caprolactone) [PCL]) reproduce the morphological and molecular signs of glioma migration *ex vivo* (Agudelo-Garcia et al. 2011, Johnson et al. 2009). These tunable materials have not been employed formerly to survey the character of microenvironment, specifically mechanics and chemistry, on GBM behaviors (Rao et al. 2013).

Magnetic nanoparticle-based drug delivery for cancer therapy

Magnetic drug delivery systems

Greatly power has been made to address the diverse locations where tumors can happen and, therefore, numerous methods have been advanced. Magnetic implants are utilized to guide various magnetic drug-delivery applications, generally exploiting blood vessels, but with a little exceptions: One notion is created on intra the cal drug delivery and involves direct drug infusion into the spinal canal. It has become a standard training in order to treat various central nervous system diseases and in major tumors, also, due to the condensed systemic toxicity from the drug bypassing the blood–brain barrier. In order to overcome residual detriments, for example insufficient drug deposition at particular locations, ferric steel implants were located in the subarachnoid

space in an *in vitro* human spine model previous to nanoparticle administration into the spine. The consequences show that this method can improve the targeting abilities for intrathecal drug delivery (Lueshen et al. 2015). For treating lung cancer, the expiratory pathway appears to be the logical access for an sufficient targeting approach. Magnetizable aerosols can be used for inhalative magnetic drug targeting in order to improve the drug focus at a certain target place within the lung. Commercially accessible nebulizers are capable at making magnetic nanoparticle suspensions as aerosols for inhalation (Baumann et al. 2012). Joining both an implanted stable magnet in terms of dilute micro ferrio magnetic wires inserted within blood vessels and outside useful magnetic fields could provide specific enrichment of concurrently administered ferromagnetic nanoparticles (Hournkumnuard and Natenapit 2013). Within this setting, more than 60% of the injected concentration can be gathered in the area of interest. It has been, and still is, problematic to enrich magnetic nanoparticles three-dimensionally in the intersection of dissimilar magnetic fields. Enduring magnets are gaining attention for use in magnetic drug-targeting devices and can display convincing magnetic properties even at great depths deploying Halbach-like magnet arrays (He et al. 2014). Additional probability considers fast magnetic pulses on ferromagnetic rods that lead to reversing the indication of the potential energy term in Earnshaw's theorem, thus enabling a quasi-static, stable trap between magnets. *In vitro* investigating determine the possibility of making inward-pointing magnetic forces which cause the concentration of ferromagnetic rods on a central target (Nacev et al. 2015). An entirely different concept of magnetic drug targeting was done by Taherkani et al. using directional magneto taxis as an alternative to magnetic attraction. Bacteria can perform as self-propelling vehicles for reaching hard-to-treat hypoxic areas in solid tumors (Taherkhani et al. 2014). Drug-carrying liposomes were hence attached to the bacterium magnetococcus marinus MC-1 lacking countering the propelling properties. The total goal of the targeting plans should be their translation to clinics, and that depends on the possibility of Implementing both the synthesis of drug-carrying nanoparticles in a quality-controlled environment (GMP manufacturing) and the equipment essential for applying the system that can easily be performed in a clinical environment. The road to clinical implementation can be difficult and lengthy and several sophisticated methods providing very promising in-vitro and in-vivo results may fail under these presuppositions. A convincing concept that is close to clinical implementation is magnetic drug targeting based on intra-arterial administration of drug-loaded SPIONs and enrichment by externally applied magnetic fields that are generated by a tough electromagnet. The resistant of principle was proved in the worldwide major study concerning the positive pre-clinical application of SPIONs for cancer treatment (Tietze et al. 2013). In feature, instantaneous MTO-SPIONs injection into the tumor-supplying vessel in rabbits and application of a strong external magnetic field over a V2 squamous cell carcinoma located at the hind leg led to complete tumor remissions without side effects. Through applying only 5e10% of the conservative chemotherapeutic dose, complete tumor remissions were achieved. The distribution profile after MDT displayed 57.2% of the overall recovery of administered drug, with 66.3% of the particles localized in the tumor area, as compared to fewer than 1% of drug and particles reaching the tumor area during conventional intravenous application without magnetic targeting (Tietze et al. 2015).

Tumor targeting approaches

In this section, we will argue diverse (active) targeting plans that force the tumor-selective enrichment of active agents. Numerous tumor properties are exploited to improve the buildup of drugs in tumor cells. Generally, they are attributed to particular components on the surface of tumor cells, but there are numerous extra mechanisms. One pattern of particular binding on tumor cells is the tactic of Shvetsov et al. using heat shock protein HSP 70 connected to the surface of SPIONs that are talented to attach to the CD 40 receptor that is expressed on glioma cells (Shevtsov et al. 2014). The particular overexpression of Endoglin (CD105) receptors in actively proliferating single-walled carbon nanotube (CNT) that is moreover attributed with Dox as a chemotherapeutic agent. The application in a murine breast cancer model yielded significantly increased cell death (Al Faraj et al. 2015). The FA receptor is a very frequently addressed tumor target, as the application of FA-functionalized copolymers of poly(ethylene glycol), subsequent self-assembly into nanoscaled micelles and encapsulation with a hydrophobic model drug and SPIONs indicate (Zhang et al. 2014). Many cancer cells overexpress avb3/5 integrins, which can specially identify the short peptide motif Arg–Gly–Asp (RGD). Based on this biological feature of cancer, particle surfaces were spread with this peptide and thus a formulation of siRNA/RGD gold nanoparticles was able to target tumor cells in a lung cancer syngeneic orthotopic murine model (Conde et al. 2013). A dissimilar notion exploits the distinct microenvironment in the tumor region as it refers to dynamic cellular and extracellular components surrounding tumor cells at each phase of carcinogenesis. Many investigators assume that this aspect is a better mechanism than antibody recognition because of its relative genetic stability with lesser probability for the development of drug resistance. LyP-1, a nine residue peptide, has been exposed to target tumor-associated macrophages. As a result, LyP-1 was spread on hollow mesoporous silica nanoparticles and confirmed improved uptake into MDA-MB-231 cells (Liu et al. 2015). Hypoxia is a significant factor of the tumor microenvironment and has been the target of drug discovery efforts for nearly half an era. An remarkable study considers the uptake of charged nanoparticles that were far enlarged for positively charged nanoparticles in comparison to negatively charged ones. Similar phenomena were detected in both iron oxide nanoparticles and gold nanoparticles (Chen et al. 2013). These results will be significant for adjusting nanodrug carriers for well uptake efficacy. A novel pH and redox dual-responsive targeting nanoparticle is planned as a drug carrier. The peptide RGDFFFFC is anchored on the surface of mesoporous silica nanoparticles via disulfide bonds, that are redox-responsive, as a gatekeeper as well as a tumor targeting ligand. The

peptide and monomethoxypolyethylene glycol (MPEG) with a benzoic-imine bond, which is pH-sensitive, are then connected via "click" chemistry. *In vitro* cell research shows that the targeting possessions is switched off in typical tissues with a neutral pH, and switched on in tumor tissues with an acidic pH after elimination of the MPEG segment by hydrolysis of the benzoic-imine bond under acidic conditions (Xiao et al. 2014).

Use of CNT and lipid nanoparticles based delivery system

Recently in order to prepare novel drug delivery devices, the use of, polymers, silicon materials, carbon materials, and metals has been proposed. The carbon-nanotubes composites and hybrid materials that couple the benefits of polymers (biodegradability and biocompatibility) with those of CNTs (cellular uptake, stability, electromagnatic, and magnetic behavior) are one of the furthermost talented materials in this field.

There are three pre-requisites for a perfect transporter for target drug delivery systems functions: (1) they themselves have target effects; (2) they have adequately strong adsorptive special effects for anticancer drugs to make sure they can transfer the drugs to the effect-relevant locations; and (3) they can release the drugs from them in the effect-relevant locations, and only in this way can the treatment sound effects grow. The transferring abilities of CNTs combined with suitable surface modifications and their unique physicochemical properties demonstrate great potential to meet the three pre-requisites (Zhang et al. 2011).

CNTs are lengthy carbon-based tubes which can be either single or multiwalled and have the potential to perform as bio persistent fibers. Nanotubes for single-walled carbon nanotubes (SWCNT) and multiwalled carbon nanotubes (MWCNT) have feature ratios >100, with measurements of numerous mm and widths of 0.7–1.5 nm and 2–50 nm, respectively (Shvedova et al. 2003). Based on current investigation with carbon derived nanomaterials revealed that both single and multi-wall CNTs induced platelet aggregation, but not by the C60-fullerenes that are used as building blocks for these CNT (Radomski et al. 2005). Recently study informed that cisplatin, a small molecule, can be loaded into SWCNTs with a diameter of 1.3–1.6 nm (Tripisciano et al. 2009). The cisplatin incorporated into the tubes was demonstrated with, infrared spectroscopy, Raman spectroscopy and high-resolution communication electron microscopy (TEM). Drug-release study using dialysis membrane technique has shown that cisplatin was frequently released for almost a week, with maximum release during 72 h and up to one week. Wu et al. effectively created a new MWCNT based drug delivery system by tethering anticancer agent HCPT onto the surface of MWCNTs. CNTs were surface-functionalized, which was followed by amidation with a hydrophilic diaminotriethylene glycol, and subsequent conjugation of by carboxyl enhancement via heightened oxidization treatment, succinylated HCPT to hydroxyl derivatized MWCNTs was attained via a cleavable ester linkage (Wu et al. 2009). Of specific attention here are lipid-based nanoparticles (LNPs) that are genuine particles (about 100 nm in dimension) accumulated from diversities of lipid and other chemical modules that perform cooperatively to overcome biological barriers for LNPs in order to specially accumulate in or around disease-target cells for the functional delivery of therapeutic agents in order to cure or of imaging agents for diagnosis. The abilities of these LNPs will obviously vary depending on practical necessities, but the nanoscale permits for an impressive level of variety in abilities to permit corresponding LNPs to address a similarly varied range of functional necessities. Consequently, LNPs should be considered as suitable vehicles to make available an integrated, personalized method to cancer diagnosis and therapy in future cancer disease management. There is one aspect that is very much in favor of multifunctional LNP use in terms of diagnosis of cancer and therapy. LNPs ordered in the blood stream (i.v. administration) regularly gather in tumors anyway due to the improved penetrability and retention (EPR) effect, a performance that was recognized by Matsumura and Maeda as a means to target anticancer therapeutic agents to tumors (Matsumura and Maeda 1986). LNP accumulation in tumors takes place by reason of the attendance of highly penetrable blood vessels in tumors with great fenestrations (>100 nm in size), a consequence of quick, faulty angiogenesis. Furthermore, tumors are considered by dysfunctional lymphatic drainage that assistances the retention of LNPs in tumor for long sufficient to permit local nanoparticle to disintegrate in the locality of tumor cells (Thanou and Duncan 2003).

Micelles' advantage, extending blood circulation, occasionally turns into a problematic that may result in extravasation of the encapsulated cargos in unexpected locations due to the little firmness of the micellar system (Peer et al. 2007). To address some of these problems, localized drug delivery to the solid tumors is a good approach. By comparison to the systemic administration mentioned to beyond, the localized system has several advantages such as confirming therapeutic drug levels at the tumor location for prolonged times of time while keeping low systemic drug exposure which not only consequences in advanced therapeutic effectiveness of the drugs to cancer and a lower toxicity (Ho et al. 2007). But also decreases the need for repeat chemotherapeutic administrations, improving the quality of life and enhancing patient compliance. The implantable bulk materials (like blocks, films, wafers and so on) and the conventional injectable hydrogel system for conventional localized drug delivery systems, are the furthermost communal methods. The degradation rate is hard to be tuned in order to the implantable bulk materials. For the conventional injectable hydrogel systems, which can improve patient compliance and ease, it can be approximately divided into two categories: particle drug depots and semisolid drug depots (Hatefi and Amsden 2002). The particle drug depots, including emulsions, liposomes, biodegradable microspheres and micelles, are comparatively unbalanced and easy to transfer away from the tumor location, while, for the semisolid drug depots, the solidification of liquid hydrogel *in vivo* is problematic sometimes, and an primary burst of drug may happen during the lag time between the injection and the formation of the solid hydrogel. Presently, the challenges of this localized drug delivery using polymers are the lack of control in drug release and distribution (Wolinsky

et al. 2012) and specific targeting to tumor cells. Consequently, the incorporation of the active targeting micellar system into the implantable, "controllable" matrix may be a good optimal to attain a high chemotherapy effectiveness against tumors and low side effects in normal tissues and overcome the drawbacks of the conventional localized drug delivery systems.

Conclusion

In the past few years, a number of approaches have been demonstrated to obtain aligned polymer fibers. Numerous anticancer drugs include Dox, paclitaxel (PTX), platinum complexes, and dichloroacetate have been electrospun into fibers and used for postoperative local chemotherapy. For example, preparation of ultrafine Dox-containing PEG–PLLA fibers by electrospinning a water-in-oil emulsion, in which the aqueous phase contained the water-soluble drugs and the oily phase was a chloroform solution of PEG–PLLA. The consequences showed that the Dox was entirely encapsulated inside the electrospun fibers. Then; they successfully loaded hydrophobic PTX and hydrophilic Dox at the same time into PEG–PLLA nanofiber mats by the emulsion-electrospinning method, and recognized multi-drug delivery

Authors' contributions

AA conceived of the study and participated in its design and coordination. SD, and YP participated in the sequence alignment and drafted the manuscript. All authors read and approved the fi nal manuscript.

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The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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