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New Views

Research and Application of Targeting Nano-Drugs

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Abstract

Nano-drug, a new type drug, is rapidly developing with nanotechnologies in biology and medicine field. The development of nano-drug s will cause the revolution of the diagnosis and treatment. Because Nano-drug carriers have high targeting, favorable sustained, controlled release capability and superior cell penetration ability, it can improve efficacy of drugs and reduce side effects. The role of the object from the target organ, target cell to the most advanced structure in the target cells. The three levels method of targeted therapy all could complete with nanotechnology. Nano-targeting drugs can be divided into passive targeting and active targeting. Current research focuses on the development of functionalized capsules for specific targeting of cancer or immune cells, and on controlling their release properties and targeting functionalities to develop new nano-drugs.

Keywords: Active targeting; biodistribution; drug delivery; Nano-drug; passive targeting; targeting function;

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Professor Liu Changxiao, Academician of Chinese Academy of Engineering, Doctorate Advisor, Research Fellow. Liu was born in Hunan, China, in 1942, and graduated from Beijing Medical College (now Peking University). Liu is honorary president and Director of Academic Committee of Tianjin Institute of Phamaceutical Research, Director of Biomedical Evaluation Center of National Institute of Nanotech and Engineering, Director of State key Laboratory of Drug Delivery Technology and Pharmacokinetics,Vice-chairman of Chinese Pharmacological society, and chairman of Tianjin Pharmacological society and Tianjin Pharmaceutical Society. In 1968, Liu set up the first pharmacokinetics laboratory in China. In 1980, he published the first book in China titled Drug Metabolism and Pharmacokinetics. In 1984, he published another new book, Introduction to Pharmacokinetics. Liu is the first among his Chinese peers to apply pharmacokinetics to the research of new drugs. Liu awarded 34 terms of Scientific and Technical Achievement Prizes. He published more than 320 papers and 16 books in English and in Chinese.

Introduction

Nanomedicine is the application of nanotechnology to medicine [1]. Nano-drug is taken into cells, to achieve the safe and effective targeted drug delivery and gene therapy. Because nano-drug carriers have high targeting, favorable sustained, controlled release capability and superior cell penetration ability, it can improve efficacy of drugs and reduce side effects. It is the production of nanotechnology combining with modern medicine. Polymeric nanoparticles, incorporating viral proteins have been shown to offer sustained release of antigen, with consequent prolongued stimulation of the respiratory immune system. In this paper the efficacy of two nanoparticle vaccines (poly-lactide-co-glycolide, PLGA; polymethylmethacrylate, PMMA), incorporating proteins of bovine parainfluenza type 3 virus (BPI-3) was investigated. As a preliminary to experiments in calves, it was considered essential to demonstrate immunogenicity of the experimental vaccine in mice. Mice immunised with PLGA nanoparticles, containing BPI-3 proteins, developed higher levels of virus-specific antibody than mice immunised with the PMMA vaccine or with soluble viral proteins alone. Immunoblotting using serum from the vaccinated mice, demonstrated strong reactions against the major BPI-3 proteins [2]. The plasmid DNA (pDNA)-coated nanoparticles significantly enhanced the specific serum IgG and IgA titres to an expressed model

antigen, beta-galactosidase, by 18-28 and 25-30 fold, respectively, when compared with naked pDNA alone. An enhanced splenocyte proliferative response was also observed after immunization with the pDNA-coated nanoparticles. It was concluded that these plasmid DNA-coated nanoparticles may have potential for immunization via the nasal route [3].

Nano-drugs can selective distribute the object, to enhance efficacy and reduce side effects. The role of the object from the target organ, target cell to the most advanced structure in the target cells. The three levels method of targeted therapy all could complete with nanotechnology. Nano-targeting drugs can be divided into passive targeting and active targeting. In the research, one of the key challenges in the field of bio-nanotechnology for drug delivery systems (DDS) is the development of nano- or micro-sized delivery carriers possessing both targeting functionalities for specific tissues or cells, and controlled release properties for encapsulated drug molecules, proteins and genes [4]. Current research focuses on the development of functionalized capsules for specific targeting of cancer or immune cells, and on controlling their release properties and targeting functionalities to develop new nanopharmaceuticals. The use of nanotechnology in drug delivery and imaging in vivo is a rapidly expanding field. The principles of passive and active targeting of nanosized carriers to inflamed and cancerous tissues with increased vascular leakiness, overexpression of specific epitopes, and cellular uptake of these nanoscale systems are discussed. Preparation methods and properties of nanoscale systems including liposomes, micelles, emulsions, nanoparticulates, and dendrimer nanocomposites, and clinical indications are outlined separately for drug delivery and imaging in vivo. Taken together, these relatively new and exciting data indicate that the future of nanomedicine is very promising, and that additional preclinical and clinical studies in relevant animal models and disease states, as well as long-term toxicity studies, should be conducted beyond the "proof-of-concept" stage. Large scale manufacturing and costs of nanomedicines are also important issues to be addressed during development for clinical indications [5].

Passive Targeting

Common characteristics of polymeric nano-drugs with respect to passive targeting. It can be considered several biodegradable polymeric nanomedicines that are between 1 and 100 nm in size, and discuss the impact of this technology on efficacy, pharmacokinetics, toxicity and targeting. The degree of toxicity of polymeric nano-drugs is strongly influenced by the biological conditions of the local environment, which influence the rate of degradation or release of polymeric nano-drugs. The dissemination of polymeric nano-drugs in vivo depends on the capillary network, which can provide differential access to normal and tumor cells. The accumulation of nano-drugs in the microlymphatics depends upon retention time in the blood and extracellular compartments, as well as the type of capillary endothelium surrounding specific tissues. Finally, the toxicity or efficacy of intact nano-drugs is also dependent upon tissue type, i.e., non-endocrine or endocrine tissue, spleen, or lymphatics, as well as tumor type [1].

Studies found that small particle size passive targeting drugs can spontaneously gather the diseased region making use of EPR (Enhanced Permeability and Retention) to achieve the purpose of passive targeting [6]. Because the blood capillary permeability of the damage spot which caused by tumor, inflammation, hypertension and so on is higher than that of the normal blood vessel, simultaneous discharge capacity of lymph blood vessel is weaken. So long circulation in vivo the biological compatible macro-molecule, the medicine carrier, the molecular assembly is easier through blood vessel that injuries portion into the organization and assemble. The EPR is special useful to treat the tumor and blocks [7]. One of the ways to enhance EPR is strengthening the stability of drug to lengthen circulation time of drug in vivo. So the drug carriers have more opportunities to go through the target position and get together [8]. The passive targeting preparation include of micro-capsule, microsphere, nanopartiele，liposome and so on. The liquid crystal, fluid film, lipoid, protein and bio-degradation high polymer material is often used as carrier material.

Polymer conjugates are nano-sized, multi-component constructs already in the clinic as anticancer compounds, both as single agents or as elements of combinations. They have the potential to improve pharmacological therapy of a variety of solid tumors. Polymer-drug conjugation promotes passive tumor targeting by the enhanced permeability and retention (EPR) effect and allows for lysosomotropic drug delivery following endocytic capture. Greco and Vicent analyzed the promising results arising from clinical trials of polymer-bound chemotherapy. The experience gained on these studies provides the basis for the development of a more sophisticated second-generation of polymer conjugates. However, many challenges still lay ahead providing scope to develop and refine this field. The "technology platform" of polymer therapeutics allows the development of both new and exciting polymeric materials, the incorporation of novel bioactive agents and combinations thereof to address recent advances in drug therapy. The rational design of polymer drug conjugates is expected to realize the true potential of these “nanopharmaceuticals” [9].

Mitra et al [10] studied the tumor targeting using dextrandoxorubicin-chitosan nanoparticles and showed that nanoparticles was not only reducing peripheral side effects, but also greatly improving the treatment of solid tumors. Du et al [11] made the carrier complex system with cyclic arginine- glycine-aspartic acid and lipid and combined interferon-α1b to treat liver fibrosis in rats, showed that according to combine with carrier，the concentration of interferon-α1b in the liver of rats was

up to 10 times and the degree of liver fibrosis was significantly reduced comparing with non-carrier group. This illustrated the complex vector had a clear targeting to the liver. Briz et al [12-14] made two kinds of chelate compound with bile acid glycine-cisplatin and ursodeoxycholic acid-cisplatin, through the result of in vivo experiments showed that two complexes had a good affinity to the tumor cells of liver, and the absorbed dose was obvious higher than the original drug. Because of lower toxicity, these chelate compounds can extend more survival time of mice tumor transplant than the original drug. They also had effect to the chemical sproof tumor cells, and partly decrease physiological tolerance of tumor to the cisplatin.

Active Targeting

Active targeting is that drug carriers through the surface of nano-ligand binding specificity of targeting delivers drugs to specific organizations or release drugs in vivo under the certain physical conditions. The conventional active targeting mechanisms include three kinds. The application of nanoparticulate systems that offer improved chemotherapeutic delivery through increased solubility and sustained retention times is an area of intense focus in nanomedicine. In addition, active targeting of nanoparticles through conjugation of tumor-specific cell surface markers such as tumor-specific antibodies or ligands can enhance the efficacy of nanoparticle drug delivery systems while significantly reducing toxicity [15]. Ocular drug delivery is an extremely challenging area due to its restrictive barrier functionalities. The ocular barriers are highly specialized and selectively control the inward/outward traverse of compounds, hence a better understanding of these biological obstacles would provide a platform to advance ophthalmic drug therapy towards specified delivery/targeting with minimal adverse consequences [16]. Most nano-drugs achieve selective tumor accumulation via the enhanced permeability and retention (EPR) effect or a combination of the EPR effect and active targeting to cell receptors. The fundamental physicochemical properties of a nano-drug (its size, charge, hydrophobicity, etc.) can dramatically affect its distribution to cancerous tissue, transport across vascular walls, and retention in tumors. The nanoparticle characteristics such as stability in the blood and tumor, cleavability of covalently bound components, cancer cell uptake, and cytotoxicity contribute to efficacy once the nanoparticle has reached the tumor's interstitial space. These properties (both of the nanoparticle and the cancer/tumor under study) can be used to design meaningful in vivo tests to evaluate nanoparticle efficacy [17].

1. Thermal-sensitive and pH-sensitive targeting

Thermal-sensitive and pH-sensitive targeting, that is, sufficiently use the changes of temperature and acidity that different body tissues and organs in the pathological process. Choose the polymer containing thermo-sensitive or pH-sensitive (such as N-isopropylacrylamide, etc.) component to form the polymer micelle. Drug-loaded micelles in the specific temperature or acidity can be easily depolymerized and released the drugs [18-20] reported a new type of temperature-sensitive nanoparticles. The critical solution temperature is 30°C. The drug was wraped in the nanoparticles and the slow releaseing could last one month in vitro. When the temperature was more than 37 °C, the nanoparticles could priority be uptaken by the MDA2MB2231 breast cancer cells. This temperature-sensitive nanoparticles has great potential in the treatment of thermal sensitivity targeting to the solid tumors.

Na et al [22] made PA-SDM nanoparticle with the amylopectin acetate (PA) and sulfanilamidesulfamidyl (SDM) that loadding adriamycin (ADR). The nanoparticles could change the rate of ADR release along with the alkalinity acidity change. As the pH value of the tumor spot was different from that of normal tissue, PA-SDM nanoparticles could selectively accumulate on the breast cancer cells MCF-7 and speed up the release, enhanced cytotoxicity to the tumor.

Yoo et al [23] got the pH-sensitive polymer micelles complex by linking ADR with acid-sensitive. Taking advantage of metaacid physiological characteristic of the tumor organization partial micro environment, adriamycin hydrolysis from the polymer micelles down when the drugs reached to the tumor site. Thereby enhanced the concentration of ADR in the tumor cells and increased efficacy of the drug. These belong to the studies of the targeted drug delivery that in response to the environment, when the drug carriers meet with environmental stimulative, they are depolymerized to the monomers and drugs releases out of the vector. When combine EPR effect, nano-drug carriers that environment respond can further enhance the efficacy of antineoplastic.

The polymer-drug linker must be stable in transit, but be degraded at an optimal rate intracellularly to liberate active drug. Duncan early studies designed two HPMA [N-(2-hydroxypropyl)methacrylamide] copolymer conjugates containing doxorubicin that became the first synthetic polymer-drug conjugates to be tested in phase I/II clinical trials. Since, a further four HPMA copolymer-anticancer drug conjugates (most recently polymer platinates) and the first polymer-based gamma-camera imaging agents followed. Polymer-drug linkers cleaved by lysosomal thiol-dependent proteases and the reduced pH of endosomes and lysosomes have been used widely to facilitate drug liberation. It is becoming clear that inappropriate trafficking and/or malfunction of enzymatic activation can lead to new mechanisms of clinical resistance. Recent studies have described HPMA copolymer conjugates carrying a combination of both endocrine and chemotherapy that are markedly more active than individual conjugates carrying a single drug [24].

Paclitaxel (Tx)-loaded anti-HER2 immunonanoparticles (NPs-Tx-HER) were prepared by the covalent coupling of humanized monoclonal anti-HER2 antibodies (trastuzumab, Herceptin) to Tx-loaded poly (dl-lactic acid) nanoparticles (NPs-Tx) for the active targeting of tumor cells that overexpress HER2 receptors. The physico-chemical properties of NPs-Tx-HER were compared to unloaded immunonanoparticles (NPs-HER) to assess the influence of the drug on anti-HER2 coupling to the NP surface. The immunoreactivity of sulfo-MBS activated anti-HER2 mAbs and the in vitro efficacy of NPs-Tx-HER were tested on SKOV-3 ovarian cancer cells that overexpress HER2 antigens. Tx-loaded nanoparticles (NPs-Tx) obtained by a salting-out method had a size of 171±22 nm (P.I.=0.1) and an encapsulation efficiency of about of 78±10%, which corresponded to a drug loading of 7.8±0.8% (w/w). NPs-Tx were then thiolated and conjugated to activated anti-HER2 mAbs to obtain immunonanoparticles of 237±43 nm (P.I.=0.2). The influence of the activation step on the immunoreactivity of the mAbs was tested on SKOV-3 cells using 125I-radiolabeled mAbs, and the activity of the anti-HER2 mAbs was minimally affected after sulfo-MBS functionalization. Approximately 270 molecules of anti-HER2 mAbs were bound per nanoparticle. NPs-Tx-HER exhibited a zeta potential of 0.2±0.1 mV. The physico-chemical properties of the Tx-loaded immunonanoparticles were very similar to unloaded immunonanoparticles, suggesting that the encapsulation of the drug did not influence the coupling of the mAbs to the NPs. No drug loss was observed during the preparation process. Aanalysis showed that encapsulated Tx is in an amorphous or disordered-crystalline phase. These results suggest that Tx is entrapped in the polymeric matrix and not adsorbed to the surface of the NPs. In vitro studies on SKOV-3 ovarian cancer cells demonstrated the greater cytotoxic effect of NPs-Tx-HER compared to other Tx formulations. The results showed that at 1 ng Tx/ml, the viability of cells incubated with drug encapsulated in NP-Tx-HER was lower (77.32±5.48%) than the viability of cells incubated in NPs-Tx (97.4±12%), immunonanoparticles coated with mabthera, as irrelevant mAb (NPs-Tx-RIT) (93.8±12%) or free drug (92.3+/-9.3%) [25].

2. Special targeting ligand

Drug carriers can be modifed by combining with special targeting ligand (antibodies, lectins, sugars, hormones, etc.). Thereafter, this carrier-ligand complexity can be specifically identified by the epicyte receptors and accurately transmitted to the target spot. Xiao et al [26] made the starch nanoparticles (StNP) charged negative electricity with reverse microemulsion and cross-linking methods, after StNP was modificed by a folic acid active substances (FA-PEG-NH2) modifiction, they successfully prepared the folic acid-starch nanoparticles (FA-PEG/StNP) which the average diame-ter was about 130 nm. FA-PEG/StNP was combined with the anti-cancer drug doxorubicin (DOX) through penetration and got nano-drug containing folic acid-starch. Compared with StNP through hepatoma cells (BEL7404) culture experiments found that the cell lethality of using FA-PEG/StNP carrier was 3 times higher than that of StNP carrier. The result proved that FA was modified on the particles can significantly increased the particle targeting to the liver targeting cancer cells, made more drugs actting on the tumor cells and enhanced the drug's effect. Pan and Feng [27] synthesized nanoparticles (NPs) of the blend of a component copolymer for targeted chemotherapy with paclitaxel used as model drug. The component was poly (lactide)-D-α-tocopheryl polyethylene glycol succinate (PLA-TPGS), which was of desired hydrophobic-lipophilic balance, which facilitates the folate conjugation for targeting. The nanoparticles were decorated by folate. The drugs were evidently promoted to targeting gather the surface of the breast cancer cells (MCF-7) and C6 glioma cells, thereby enhancing its efficacy.

Since inflammatory bowel disease (IBD) represents a state of dysregulated inflammation, drugs that augment the anti-inflammatory response have the potential to downregulate inflammation and thereby hopefully modify the disease. Tumor necrosis factor (TNF) is a major target of research and clinical investigation. TNF has proinflammatory effects in the intestinal mucosa and is a pivotal cytokine in the inflammatory cascade. Certolizumab pegol (CDP870) is a PEGylated, Fab' fragment of a humanized anti-TNF-α monoclonal antibody. PEGylation increases the half-life, reduces the requirement for frequent dosing, and possibly reduces antigenicity as well. Certolizumab has been shown in Phase III trials to achieve and maintain clinical response and remission in Crohn's disease patients. It improves the quality of life. It is not possible to construct an algorithm for treatment, but when compared with infliximab the two principal advantages are likely to be lower immunogenicity (as shown by anti-drug antibodies, absence of infusion reactions, and low rate of antinuclear antibodies), and a subcutaneous route of administration. These two factors may be sufficient to promote it up the pecking order of anti-TNF agents [28].

In pharmacokinetics, Certolizumab pegol has been constructed by grafting the short, hypervariable complementarity-determining regions (CDRs) derived from the murine monoclonal antibody HTNF40 onto an otherwise virtually human immunoglobin (Ig) Fab' fragment. The engineered Fab' fragment retains the biological potency of the original antibody, but lacks the Fc portion of the parent IgG4 antibody. The Fab' fragment is linked to two cross-linked chains of PEG each of which has a molecular weight of 20 kDa. This site-specific polyethylene glycolation increases the half-life of the antibody fragment to approximately 2 weeks in plasma, thereby increasing the interval between dosing required dosing. Certolizumab pegol is administered as a 400-mg subcutaneous injection, initially every 2 weeks for the first three doses and subsequently every 4 weeks for maintenance. Subcutaneous administration of

certolizumab pegol has been shown in Phase III trials to be clinically effective with good tolerability in patients with moderate-to-severe Crohn's disease and rheumatoid arthritis. It is possible that the subcutaneous route of drug administration could contribute to the good tolerability because peak serum concentrations are lower than would be achieved after intravenous delivery. Certolizumab pegol is a Fab' fragment that has been designed not to fix complement. It is possible that the absence of the Fc fragment, which is the reason that it does not activate complement-dependent cytotoxicity effector mechanisms, could enhance therapeutic safety and reduce adverse events compared with other anti-TNF agents [28].

Terada et al [29] established the specific targeting drug delivery system to the human hepatoma cell line (HCC). Through amino of dioleoyl phosphatidylethanolamine (DOPE) linked to substrate peptide of peginterferon matrix metalloproteinase-2 that was modified by PEG and obtained PEG-PD, which could be enzymed cut by matrix metalloproteinase-2, then integrated the PEG-PD into the galactose-liposome and got the GaL-PEG-PD-liposomes. Because the steric effect caused by PEG shielding the galactosyl of the surface of liposome complex, GaL-PEG-PD-liposomes could not be uptaken by the normal liver cells. But there was has high concentration of secreted matrix metalloproteinase-2 around the HCC cells and could hydrolysis the peptide of Gal- PEG-PD-liposomes to remove the polyethylene glycol, relief the steric effects of polyethylene glycol, exposure the galactose residues of liposome surface. At this time the liposome could be recognised and uptaken by HCC cells and got the purpose of specific targeting to HCC cells.

Liang W et al [30] research results on doxorubicin-containing PEG-PE micelles are an important contribution to nanomedicine development (which is called "nanoparticles carry chemotherapy drug deeper into solid tumors"). Encapsulation of doxorubicin into PEG-PE micelles increased its accumulation and penetration in tumors in terms of both the percentage of cells that were reached by the drug and the intracellular levels that were attained. This increased accumulation and penetration can be attributed to the efficient internalization of the drug-containing micelles by the endocytotic cell uptake mechanism and enhanced permeability and retention of tumors with leaky vasculature. High intracellular retention is especially important because doxorubicin must be internalized into tumor cells to realize the effective therapy for tumors. The metabolism of nanoparticles in the body strongly depends on the surface characteristics of the nanomaterials. A threshold limited size of nanoparticles may exist for restricting the movement of nanoparticles in various parts of body. The pharmacokinetic behaviors of different types of nanoparticles require thorough investigation. The biological effects associated with different nanoparticles should be studied at the target organs, tissues and cellular levels. The assessment of biological effects in cardiopulmonary system is necessary for every new nanoparticle to be used for medical application. The available information on most nanoparticles indicates that certain nanoparticles may be genotoxic and phototoxic and photogenotoxic. There are only a few long term studies reported that are related to nanomaterials including SiO_2, CNT, and TiO_2. Nanoparticles may have potential for generating free radicals and exhibit oxidative tendency depending on their surface characteristics.

The doxorubicin-containing PEG-PE micelles had greatly increased antitumor activity in both subcutaneous and lung metastatic LLC tumor models compared with free doxorubicin. However, mice treated micelle-encapsulated doxorubicin showed fewer signs of toxicity than those treated with free doxorubicin. This drug packaging technology may provide a new strategy for design of cancer therapies [31]. J Natl Cancer Inst gave a high evaluation for their research [32]. Wei et al carried out study on comparative pharmacokinetics of nanoparticle mic3lle-encapsulated doxorubicin (M-Dox), liposome encapsulated doxorubicin (L-Dox0 with general doxorubicin (G-Dox). Their results indicated that M-Dox had a similar pharmacokinetic characteristics to G-Dox, but L-Dox was significant different from G-Dox, which had smaller Vd and CL, and higher AUC based on plasma level than those for G-Dox [33]. Our laboratory studied the accumulation of doxorubicin nanoparticles in tissues of tumor-bearing mice. Compared with general doxorubicin preparation, which is a marketed product, nanoparticle micelle of doxorubicin has the similar pharmacokinetics in the tissue, and the similar concentrations in the tumor tissue. However, the accumulation of doxorubicin in the heart, spleen, kidney, lung, tumor, muscle and skin decreased significantly after three intravenous injections, showing that the nanomicelle can improve the elimilation of doxorubicin in most tissues. It is deduced that the side-effects of doxorubicin after clinical use may be reduced significantly [34]. Li et al studied the pharmacokinetics and tissue distribution of micelle encapsulated alprostadil (M-Alp) and free alprostadil (F-Alp) by intravenous injection of 200 μg/kg in rats. The pharmacokinetic results showed that the Apl was eliminated quickly with half-life time of 4.39 min and 4.76 min, for M-Apl and F-Apl, respectively. The tissue distribution results indicated that the novel M-Apl tended to accumulate into tissues such as heart, liver etc. This nanocarrier assembling technology may provide a new strategy for delivery of Apl for the treatment of chronic arterial obstruction and microcirculation dieturbance [35].

3. Suitable adjuvant

A major limitation inherent to most conventional anticancer chemotherapeutic agents is their lack of tumor selectivity. One way to achieve selective drug targeting to solid tumors is to exploit abnormalities of tumor vasculature, namely, hypervascularisation; aberrant vascular architecture; extensive production of vascular permeability factors stimulating extravasation within tumor tissues; and lack of lymphatic drainage. Maeda and

his colleagues have extensively studied tumor vascular abnormalities in terms of active and selective delivery of anticancer drugs to tumor tissues, notably defining the enhanced permeability and retention effect (EPR effect) of macromolecular drugs in solid tumors. Due to their large molecular size, nanosized macromolecular anticancer drugs administered intravenously (i.v.) escape renal clearance. Often they can not penetrate the tight endothelial junctions of normal blood vessels, but they can extravasate in tumor vasculature and become trapped in the tumor vicinity. With time the tumor concentration will build up reaching several folds higher than that of the plasma due to lack of efficient lymphatic drainage in solid tumor; an ideal application for EPR-based selective anticancer drug delivery. Establishing this principle hastened development of various polymer conjugates and polymeric micelles as well as multifunctional nanoparticles for targeted cancer chemotherapy. Indeed this selective high local concentration of nanosized anticancer drugs in tumor tissues has proven superior in therapeutic effect with minimal side effects in both preclinical and clinical settings [36].

Suitable adjuvant was encapsulated into the micelles with physical method. The micellar will pulse release drug under the influence of the external excitation conditions (such as IR light, magnetic field). The adjuvant does not affect performance of micelles (stability, permeability, etc.), but impact the performance of the drug that is wrapped up in micellars (under certain conditions, hydrophilic can be converted to lipophilic, etc.). For example, Sershen and co-workers [37] prepared N-isopropylacry- lamide hydrogel could encapsulate γ-Fe_2O_3. Under the effect of outside magnetic field, when the temperature of hydrogel rised 10 °C and is higher than the critical solution temperature, hydrogel will rupture and sudden release the drugs. Nanoparticles interacte with electromagnetic pulse or ultrasonic pulse can also enhance the release of drug. When the nanoparticles reach to the tumor vascular sys-tem and was adsorbed to the vessel wall, because elec-tromagnetic pulse or ultrasonic pulse lead to the local thermal effects and further caused cavitation, tumor cell membrane is perforated, large molecular drugs enter into the cancer cells from blood, play the therapeutic effect.

Effect of nanoparticle sizes on targeting distribution

Structures of nanoparticles general have following kinds, including nanocapsules, nanotubes, nanogels, dendrimers, nanoshells, and other structures. Encapsulated structures protect drugs, allow for surface modification, it considered fully enclosed structures nanocapsules, partially enclosed and plugged structures will be dealt with under nanoshells and nanotubes. Lipisomes are closed, continuous bi-layered structure, can synthesized with polymers, and liked to make them stable for storage and application. Advantages of nanoparticles as drug carriers to exhibit the targeting delivery are presented in 5 aspects: (1) large surface-to-volume ratio resulting enhanced interaction sites,; (2) surface functionalization for targeting, (3) suitable encapsulation; (4) release drugs in controlled manner, and (5) more efficient uptake by cells.

There are already several FDA approved nanoparticle-based cancer therapies on the market and in clinical trials (Tables 1 and 2). In most therapeutic nano-drugs, a toxic drug is either encapsulated within the core of a nanoparticle or conjugated to the surface. For optimal

Table 1. Clinically Approved Nanoparticle-Based Therapeutic Drugs and Imaging Agent for Cancer Application [17]

Compound	Carrier/size	Indication	Clinical Status	Route of Administration
Doxorubicin (Doxil/Caelyx)	PEGylated liposome/100 nm	Breast, ovarian cancer	Kaposi sarcoma	i.v.
Daunorubicin (DaunoXome)	Liposome/45 nm	Kaposi sarcoma	Approved	i.v.
Doxorubicin (Myocet)	Liposome/150 nm	Metastatic breast cancer	Approved	i.v.
Paclitaxel (Genexol-PM)	Methoxy-PEG-poly(D,L)-lactide/30– 60 nm)	Metastatic breast cancer	Approved	i.v.
L-Asparaginase (Oncaspar)	PEGylated	Acute lymphoblastic leukemia	Approved	i.v., i.m.
Abraxane	Albumin/130 nm	Metastatic breast cancer	Approved	i.v.
AMI-227 (GastroMark)	Poly [N-(2-aminoethyl) aminoproyl] siloxane/300 nm	Gastrointestinal cancer	Approved	Oral

Table 2. Selected Nanoparticle-Based Drugs in Clinical Trials [17]

Compound	Carrier/size	Indication	Clinical Status	Route of Administration
Cisplatin (SPI-077)	Liposome	Head and neck cancer, Lung cancer	Phase I/II	i.v.
Cisplatin (Lipoplatin)	Liposome	Several cancer	Phase II/III	i.v.
Camptothecin analog (S-CKD602)	Liposome	Several cancer	Phase I	i.v.
Oxaliplatin analog (Aroplatin)	Liposome	Colon cancer	Phase II	i.v.
Vincristine (Onco-TCS)	Liposome	Non-Hodgkin's lymphoma	Phase II/III	i.v.
L-Annamycin (Annamycin)	Liposome	ALL/AML	Phase I	i.v.
Cisplatin (SLIT Cisplatin)	Liposome	Lung	Phase II	Aerosol
Lurtotecan (OSI-221)	Liposome	Head and neck cancer, ovarian cancer	Phase II	i.v.
Paclitaxel (LEP-ETU)	Liposome	Breast, ovarian, and lung cancer	Phase I	i.v.
Doxorubicin (Sarcodoxome)	Liposome	Soft tissue sarcoma	Phase I/II	i.v.
Oxaliplatin analog (ProLindac)	HPMA copolymer	Ovarian cancer	Phase II	i.v.
Arginine deaminase (Hepacid)	PEGylated	Heptocellular carcinoma	Phase I/II	i.v.
Campothecin (Prothecan)	PEGylated	Several cancer indications	Phase I/II	i.v.
Doxorubicin (SP1049C)	Pluronic block-copolymer	Esophageal carcinoma	Phase II	i.v.
Camptothecin (IT-101)	Polycyclodextrin	Metastatic solid tumors	Phase II	i.v.
t-retinoic acid(Atragen)	Liposome	Acute pro-myelocytic leukemia, advanced renal cell carcinoma	Phase I/II	i.v.
Aurimune	Colloidal gold	Solid tumors	Phase I/II	i.v.
AuroShell	Gold-coated silica	Refractory head and neck cancer	Phase I	i.v.

efficacy, a systemically administered nanomedicine should: (1) reach cancer cells in adequate quantities to deliver a sufficient dose of drug, and (2) assume its active form within the tumor (e.g., the nanoparticle platform should not interfere with the release or efficacy of the drug inside the tumor). Fulfilling each of these requirements involves an interplay between the properties of the nanomedicine and the characteristics of the tumor under treatment. That is the nanoparticle must be engineered to match the specific tumor it is intended to treat [17].

The physicochemical characteristics of nanomaterials (e.g., size, surface charge, hydrophobicity) must be tuned to exploit the EPR effect and to minimize nonspecific interactions with noncancerous cells and uptake by the immune system[17]. Nanoparticle size, an important characteristic, is significant affect the circulation time (Table 3). Nanoparticle size. Systemically administered

Table 3. Relationship of Long circulation time with Particle size

particles	Size	Circulation time
Small particles	<10 nm	lost to extravasation (absorption into tissue)
Targeting particles	10 and 70 nm	penetrate capillary vessels
	70 and 200 nm	show longest circulation time
Large Particles	>200 nm	quickly captured and excreted

nano-drugs should have diameters ranging from 10 to 200 nm. Reaching certain areas of the body, such as the brain, may impose even narrower size requirements [38], and smaller than 200 nm to avoid sequestration by sinusoids in the spleen and fenestra of the liver, which are approximately 150–200 nm in diameter [39]. This size range is prescribed by human anatomy nanomaterials must be larger than 10 nm in diameter to avoid first-pass elimination through the kidneys [40].

Numerous studies have used different particle sizes to bring about selective targeting to tumors [41-43]. Nanocarrier size has been shown to influence circulation half-life [44] and tumor accumulation [45]. Such as PEG 5000-PHDCA (80 nm) exhibited significantly longer circulation times, decreased liver uptake, and greater accumulation in tumor as compared to larger particle sizes (170 and 240 nm). This is because of decreased serum protein adsorption and phagocytic uptake of the smaller particle. Tumor vasculature fenestrations vary depending on a myriad of factors including cancer type, stage of disease, site in the body, and host species (see Section Tumor Characteristics), but usually have sizes not exceeding several hundred nanometers. The size of the fenestrations in tumor vasculature also puts an upper limit on the size of nanomedicines that use the EPR effect to accumulate in tumors.

Discussion

Nano-drugs based on nanoscience and nanotechnology are medicinal products for drug delivery, nanoscale drugs and therapies, in vivo imaging, in vitro diagnostics, biomaterials, and active implants. In the field of nano-drug, these countries like USA, Japan, Canada, China, India, Korea, Russia, Singapore, and Switzerland firstly started the research on the drug delivery in early 1980-1990s by employing dendritic nano architecture for the controlled and targeted delivery of anticancer bioactivities. Many laboratories and institutions in these countries also initiated the research and development of nano-drug products since 1990s [46-59].

Nanoscience and nanotechnology in China become ever more consequential in our lives, all members of the scientific community should better inform and educate the public about the great changes this new nano era is likely to bring. Here we review some main advances on the research and development of nanomaterials, nanotechnology and nano-drugs in China [60,61]. In recent years we have been watching the development of nanotechnology and nano-drugs, and have paid special attention on its development of risk analysis, safety issues and biomedical evaluations. Nanotechnology manifests that itself can be used for medical application in a wide range of materials. The unprecedented freedom to design and modify nanomaterials to target cells, chaperone drugs, imaging biomolecular processes, sense and signal molecular responses to therapeutic agents, and guide surgical procedures is the fundamental capability offered by nanotechnology, which promises to impact drug development, medical diagnostics, and clinical applications profoundly [56-59].

Nano-drug, a new type drug, is rapidly developing with nanotechnologies in biology and medicine field. Many researchers have done a lot of research in nanotechnologies, such as in synthesis, preparation, and characterization of nanoparticles on biological and electrochemical behaviors, adsorption, and targeted nanocarriers biodistribution and their application [62-84]. they carried out the results of nano-drug targeting for the study provides useful help. The development of nano-drugs will cause the revolution of the diagnosis and treatment. However, at present, the basic theory of nanotechnology applied in medicine and the preparation of nano-drugs are still incomplete, especially the safety of nano-drugs has many problems remain to be explored in depth. Therefore, the research in the field of nanotechnology applied in pharmaceutical industry has a great deal of work needs to be done, but the superior capability that nano-drugs owns indicates a very wide range of applications in the clinical disease treatment [85]. Because Nano-drug carriers have high targeting, favorable sustained, controlled release capability and superior cell penetration ability, it can improve efficacy of drugs and reduce side effects. Therefore, we believe that drug research and development in nanotechnology will be greater progress.

Conclusions

Nano-drug, a new type drug, is rapidly developing with nanotechnologies in biology and medicine field. The development of nano-drugs will cause the revolution of the diagnosis and treatment. Because Nano-drug carriers have high targeting, favorable sustained, controlled release capability and superior cell penetration ability, it can improve efficacy of drugs and reduce side effects. The role of the object from the target organ, target cell to the most advanced structure in the target cells. The three

levels method of targeted therapy all could complete with nanotechnology. Nano-targeting drugs can be divided into passive targeting and active targeting. Current research focuses on the development of functionalized capsules for specific targeting of cancer or immune cells, and on controlling their release properties and targeting functionalities to develop new nano-drugs. However, at present, the basic theory of nanotechnology applied in medicine and the preparation of nano-drugs are still incomplete, especially the safety of nano-drugs has many problems remain to be explored in depth.

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