Research Article ISSN 2639-9466

Nanotechnology & Applications

Advantages and Risks Involved In the Treatment of Brain and Nerve Related Diseases Using Nano Drug Delivery Systems

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Received: 04 Mar 2023; **Accepted:** 10 Apr 2023; **Published:** 15 Apr 2023

Citation: Wang Z, Sneed KB, Pathak Y. Advantages and Risks Involved In the Treatment of Brain and Nerve Related Diseases Using Nano Drug Delivery Systems. Nano Tech Appl. 2023; 6(1): 1-8.

ABSTRACT

Compared with traditional pharmaceutical preparations, nanomaterials have a wider range of variable structural design ideas and a higher ability to be controlled artificially, which leads to more advantages and opportunities for nanomaterials to overcome the disease fields and research directions that traditional drugs have been powerless for more than 100 years. Tumor, brain and nerve, the lesions that are difficult to reach by drugs in history, are expected to be broken through with the improvement of nano drug delivery system.

This review lists a variety of nano drug delivery systems with different design ideas, taking brain tumors as an example, including nano cars, nano robots, bionic nano drug delivery, intelligent nano drug delivery, light controlled nano drug delivery, macrophage nano drug delivery, biomaterial nano drugs represented by proteins, nanodrug immunotherapy, nanodrug gene therapy, etc. Otherwise, the advantages and special functions of nano drugs, as well as the safety risks of nano drugs under current research are listed. Finally, this review mentions the current problems that must be solved and the future direction of nano pharmaceuticals.

Keywords

Nano particulate drug delivery systems, Brain drug delivery, Brain tumors, Brain nerves, Cancer epidemiology.

Introduction

Brain tumors are usually classified as primary brain tumors or secondary brain tumors, and non-malignant brain tumors or malignant brain tumors. According to the worldwide statistics, the prevalence rate of intracranial tumors is 40 per 100000. The top three in terms of incidence rate and mortality are China, India and the United States, respectively [1]. At present, the incidence rate of secondary brain tumors accounts for about 15% of all cancer patients according to American social statistics. At the same time, the prognosis of brain tumors is not optimistic. The 5-year survival rate is about 34%, and the 10-year survival rate is about 30% [2]. There are many different types of brain tumors, and their incidence rate and survival rates vary greatly. The most common primary malignant brain and spinal cord tumor is glioblastoma, and the most common primary non-malignant brain and spinal cord tumor is meningioma. Brain tumors are usually induced by high intensity electron radiation. Because of the special and precise structure and function of the brain, even non-malignant brain tumors can cause death or permanent sequelae due to the damaged brain structures that are difficult to repair.

The incidence rate of secondary brain tumors is far higher than that of primary brain tumors, about 10 times that of primary brain tumors [3]. Cancer changes in any part of the body may spread to the whole body with blood and then transfer to the brain. The most common metastatic tumors usually come from breast cancer, colon cancer, kidney cancer, lung cancer, and melanoma.

According to the cancer epidemiological statistics in the United States and China, the incidence rate of brain tumors is still increasing year by year. The number of new brain tumor patients every year has caused a heavy burden to the medical system and society. Due to the special structure and function of the brain, the double-layer blockade of the blood-brain barrier and the blood-tumor barrier leads to the inability to break through the traditional drug delivery

system, resulting in high systemic blood concentration and low tumor site accumulation concentration, thus causing side effects of drugs that are far higher than the therapeutic effects, while seriously affecting the survival rate and quality of life of patients [4]. Therefore, developing a new nano drug delivery system has become an important mission in the field of nano pharmaceuticals.

In addition, it is worth noting that in addition to the special problems faced by brain tumors, the blood brain barrier, and the common difficulties to be solved by all tumor treatments, the blood tumor barrier and drug therapy also need to solve a barrier that does not exist in the physical level: the metabolic barrier. There are abundant transporters and transport cells in many biological tissues represented by the blood brain barrier. They do not prevent the drug particles from entering the tumor tissue, but they capture the drug particles that have entered the tissue and then discharge them, or make the drug particles lose biological activity and become harmless through the metabolism of tumor cells [5].

The nano drug delivery system is a drug delivery system that takes nano scale materials combined with drug particles as the basic unit, involves and is affected by a variety of human cells, and needs to break through multiple biological barriers. The goal is to target and identify drug particles and deliver them to designated organs and sites. As a result, drug therapeutic ingredients are stably released at designated sites under control. A successful nano drug delivery system should be to control the local drug concentration of the diseased part as stably as possible and reduce the systemic drug concentration outside the diseased tissue as much as possible, to meet the requirements of improving drug effectiveness and reducing adverse drug reactions. Nanodrug delivery systems have many different research directions. According to the selection of nano drug delivery platforms, they can be roughly classified into five categories: liposome nano drug delivery, polymer nano drug delivery, inorganic nanoparticles, nanoparticle albumin bond (nab) technology delivery, and bionic nano drug delivery. In addition to the five categories of the above classification methods, nano drug delivery systems based on tumor immunotherapy, nano drug delivery systems based on gene expression therapy, nano drug delivery systems based on photothermal imaging therapy, and the latest forms of intelligent nano drug delivery systems, nano cars, nano robots, nano chips and nano motors can also be classified according to the treatment schemes.

In the above classification, liposome nanoparticles and polymer nanoparticles are the major nano drug delivery system that has been successfully developed into a commercial product so far. Thanks to a clearer design idea, more definite efficacy and side effects, and a simpler production route, liposome nano drugs are easier to complete a full set of R&D-test-commercialization processes than other kinds of nano drug delivery systems. Most other nano drugs still need more data and experience accumulation before they are marketed.

Structure determines function. Because of the high degree of freedom in the field of structural design unique to nanomedicine, the new properties of materials in the nanoscale and the biological affinity of nanomedicine delivery systems, researchers have found that nanomedicine has an extremely broad application potential, which has not yet been discovered and developed. At present, the degree of exploration of nanomedicine delivery systems played by researchers in the design of nanomedicine application prospects is less than 1% of all. Although the research and development experience and commercialization experience of liposome nanoparticles are relatively mature, the development of nano pharmaceutical by researchers cannot stop in the field of liposome nanoparticles. This review discusses the significant advantages of the known nano drug delivery system under the current research progress, including reducing adverse reactions, improving treatment effect, suppressing cancer recurrence rate, blocking cancer metastasis, combating drug resistance of tumor tissue, etc. At the same time, it puts forward ideas for the future direction, including the integration trend of tumor monitoring imaging treatment in the direction of nano drug research and development, and the comprehensive nano trend of all serious disease treatment drugs, As well as the data and experience related to adverse reactions and risks of nano drugs that are seriously lacking at present, including material allergy, neurotoxicity, commercial development and abuse risks, and potential environmental hazards.

Basic Classification of Drug Targeting Types

Since 1906 Ehrlich P was the first to put forward the theory of drug targeted delivery. Today, in the more than 110 years of research process, researchers still have a very difficult way to explore and implement drug targeted delivery. The rapid development of nano pharmacy is more suitable for the application of drug targeting delivery theory than traditional pharmacy to a certain extent, but the process from experimental design to clinical application is still full of obstacles. In the past two decades, only 15 passive targeted drugs have been used in clinical treatment, while no active targeted drugs have been used in clinical treatment so far [6].

Passive targeting means that depending on the unique physiological and pathological characteristics of the tumor microenvironment and the differences between normal human tissues and organs, the tumor has enhanced permeability and retention effect (EPR effect), as well as the chemical and biological properties of nanoparticles, so that the nano drug delivery system can produce natural distribution differences and effectively accumulate in the tumor site [7].

Active targeting refers to modifying the structure of drug particles at the nanoscale through technical means, giving the drug or its carrier the ability to actively bind to the target, relying on the active recognition between specific molecules on the surface of the nano system and specific molecules and proteins at the tumor site, such as the chemical or physical coupling of probe molecules (such as antibodies, peptides, sugar chains and aptamers) that specifically bind to the target molecules and the drug or its carrier surface, in order to achieve the targeted effect and achieve the purpose of selective concentration of drugs in tumor tissues and cells [8].

Physical targeting refers to the use of light, heat, magnetic field, electric field, ultrasound and other physical signals on the tumor part of the patient to artificially affect the distribution of drugs in the body and activate the release characteristics, to achieve the target of the lesion [9].

So far, the maturity of passive targeting nano drug delivery system technology is ahead of that of active targeting, which benefits from the relatively easy design idea of passive targeting nano drug delivery system, more extensive experience and data accumulation, relatively low production cost, clear and controllable drug toxicity and side effects [10]. Correspondingly, the current defects of passive targeting nano drug delivery systems mainly focus on the unsatisfactory therapeutic effect and limited drug targeting specificity [11].

On the contrary, active targeting is expected to combine and accumulate specifically in target tissues and reduce residues in healthy tissues as much as possible to achieve the most perfect targeting state envisaged by drug delivery targeting theory. However, up to now, no clinical results have been achieved with high cost and high manpower input. Active targeting drug delivery system suffers from stronger than expected resistance from tumor tissue immune function (12). The immune and metabolic barrier in the tumor tissue will intercept and capture many nano drug particles. Some of these nano particles will be metabolized into metabolites that lose biological activity, and the other part will be expelled from the tumor tissue during exocytosis [13].

Advantages and Limitations of Drug Delivery Nano Systems with Various Platforms

Polymer nanomedicine is a kind of intelligent drug delivery system that is created by self-assembly or other methods and connects polymers or drugs through chemical bonds. After entering the body, it uses exogenous or endogenous changes, such as pH, temperature, and redox environment, to break the chemical bonds and release drugs to targeted sites [14]. Polymer nano carriers can effectively reduce the side effects of drugs, improve the bioavailability, and have natural biological affinity. On the contrary, some polymer nano carriers may degrade too fast or too slowly, lack of modifiable end effectors, lead to accumulated toxicity due to difficulties in degradation *in vivo*, and difficult to prepare with high cost [15].

Liposome nanoparticles are drug particles that phospholipid materials self-assemble into spherical vesicles in aqueous solution, with a hydrophobic core surrounded by hydrophobic membranes, and can be used to load hydrophobic or hydrophilic molecules [16]. Liposome nanoparticles are the most advanced nano drug delivery system in the clinical application and commercialization of all nano drug delivery systems [17]. It has excellent biological affinity, stability, low toxicity, and controllability of drug release. Its shortcomings mainly lie in the unsatisfied targeting at present, and insufficient energy stored locally in the tumor [18].

Nanoemulsion, which is prepared by mixing oil, emulsifier and water into nanoscale emulsion droplets, can be used to transport drug particles [19]. The advantages of nano emulsion are good biological affinity and easy absorption by human tissues, satisfactory low toxicity and side effects, and good bioavailability. It can be made into different kinds of preparations, including sprays, oral liquids, creams, eye creams and other products for easy use [20]. The defect is that the stability is not ideal, and the emulsion particles may be destroyed [21].

The bionic nano drug delivery system, represented by virus coat vector, uses the shell structure of viruses or bacteria such as bacteriophages, makes use of the high binding rate of biological coat protein to cells and injects its own genetic material into cells to participate in gene expression, playing a role in tumor gene therapy [22]. However, because the antigen determinant contained in the viral coat is easy to cause human immune response, patients may have to use immune blocking drugs to inhibit adverse reactions [23].

Protein based nanoparticles are used to transport hydrophobic drug particles by non-covalent combination of protein and drug molecules. Its advantages are easy to be absorbed and degraded by human body, clear carrier structure activity relationship, easy production and low toxicity [24]. However, there are many kinds of proteins used in the Protein based nanoparticles delivery system. Each protein has different structures and properties, and a Protein based nanoparticle can use more than one protein to participate in assembly. The experience and understanding of researchers on Protein based nanoparticles still need to be accumulated [25].

Brain Tumor Microenvironment, Blood-Tumor Barrier and Blood-Brain Barrier

Blood brain barrier, blood tumor barrier, and tumor microenvironment of brain tumor tissue are not only the living space and nutrition source of brain tumor in physical sense, but also the main difference between brain tumor and other tumor types.

Blood-brain barrier (BBB)

The intermediate structure of neurovascular unit (NVU), which is composed of endothelial cells (EC), pericytes, astrocyte and other cells and tissues, is clear and stable, and its function is to prevent external substances from entering the BBB of central nervous system by regulating the permeability of endothelial cells and other structures. In brain tissue, many capillary networks, astrocytes around blood vessels, neuronal cell endings, and many microglia and monolayer brain endothelial cells are closely connected, and the membrane structure formed together forms the basal layer of BBB physical layer morphology [26]. BBB in normal form is a good protective layer, which can prevent 99% of substances in the blood, such as neurotoxic components and pathogens, from entering the central nervous system, and at the same time identify and release correct cells and nutrients into the central nervous system.

During the development of brain tumors, both primary brain tumors and brain metastatic tumors could invade the biological

structure of BBB, making the originally hierarchical and regular BBB become disordered, and local destruction and invasion lead to increased permeability. The nutrients and cells needed by the tumor enter the brain tumor tissue through the damaged BBB [27]. Different types and subtypes of brain tumors have different directions of erosion and transformation of BBB. For example, BBB modified by medulloblastoma has stronger ability to intercept chemotherapy drugs. BBB physiological ability varies greatly among patients due to different gene and cancer gene variations. However, the BBB permeability of anti-tumor drugs after BBB destruction has rarely been improved. One reason is that the invaded BBB only improves the selective permeability of some cells, rather than completely releasing all substances. On the other hand, the defective BBB and more microglia are used to form a new barrier: blood tumor barrier [28].

Blood-tumor barrier (BTB)

After brain tumors invade and damage BBB, more cells and tissues are used to regenerate BTB. BTB also could intercept and eject substances. The BTB tissues of some brain tumors represented by glioblastoma may even contain complete BBB tissue structures, including transporters that discharge drug particles [29]. The abnormal disconnection of the original tight connection between the nerve cell tip and outer membrane and the astrocyte cell membrane, and the invasion of glioma cells into BBB and replacement of the original astrocytes, led to the increase of the permeability of the original barrier structure, decreased the interception function, and the increase of cell permeability was the main feature of BTB.

Although the permeability of BTB to cells and substances needed for brain tumors has increased, the permeability of anticancer drugs has not increased significantly. This means that brain tumor anticancer drugs may experience double interception of BBB and BTB before entering brain tumor tissue, making drug treatment more difficult than other cancer types.

Tumor microenvironment (TME)

The tumor microenvironment is the living environment of tumor tissue, which is usually composed of tumor cells and tissues, tumor related cells and tumor affected cells, immune cells, extracellular matrix, and signal molecules. It usually contains rich abnormally hyperplastic vascular tissue, accompanied by hypoxia, abnormal acidic environment, and some necrotic cells. Due to the proliferation and abnormal metabolic activity of cell tissues, TME may have local necrosis, hydrops and edema, which may change the physical properties of TME. TME contains a variety of lymphocytes and immune cells, including an abnormal number of macrophages, other bone marrow cells, T cells, and B cells [30]. However, TME contains various signal molecules at the same time to play a strong immunosuppressive role, making lymphocytes lose their original immunity and ability to kill tumor tissues.

In normal state, brain tissue and the periphery of central nerve contain abundant extracellular matrix, also known as ECM. ECM is rich in proteins, mainly including tendinosis and lectin. The invasion of tumor will change the normal components and physiological functions of ECM [31]. The original regular and clear ECM structure will become disorganized and disordered, and become hard with the proliferation of tumor tissue. ECM after tumor invasion and change contains abnormal signal molecules, which can affect and inhibit the activity of human immune system. The expression level of integrin and fibronectin increased which improved the mobility and invasion of tumor cells [32].

Macrophages (MDMs) differentiated from monocytes in bone marrow are recruited into TME by abnormal signals sent by tumor ECM, which can reach 30% of the total weight of brain tumor tissue [33]. Microglia are the macrophage group with the second highest content of TME. They are recruited into TME by ECM signal molecules such as granulocyte macrophage colony stimulating factor (GM-CSF), matrix derived factor-1 (SDF-1) and glial cell line derived neurotrophic factor (GDNF), accounting for 30% of the total weight. Microglia entering TME can interact with cancer cells, cancer cells release cytokines and chemokines, microglia express tumor promoting and survival promoting factors, promote the proliferation of cancer cells, immune cells and other anti-tumor activities [34]. Stimulated by TME, these macrophages changed the direction of gene expression and biological function, not only lost the ability of immunity and killing antigens, but also gathered in large numbers to protect cancerous cells from being destroyed. MDMs and microglia are collectively referred to as tumor associated macrophages (TAM). Due to the different tumor types and subtypes, as well as the individual differences of patients, the different types of gene variation and expression directions, the TAM induced by different kinds also changes in different directions, resulting in functional diversity and plasticity. The soluble factor secreted by TAM is one of the important sources of TME immunosuppression [35].

The tumor cells represented by glioma stem cells (GSCs) have been proved to secrete angiogenesis promoting factors, can recruit monocytes into TME, and generate active factors such as CCL2 and CSF-1, which can induce monocytes to differentiate into tumor promoting phenotype, inhibit the proliferation, differentiation and killing ability of T cells, and induce apoptosis of T cells. GSC can also affect neutrophils [36]. Neutrophils in TME can promote brain tumor metastasis and enhance the ability of brain tumor metastasis and post metastasis colonization. In addition, GSC can help tumor cells hide and escape NK cell-mediated cytotoxicity by secreting NK cell inhibitory ligand HLA-G [37]. In addition, GSC has a special ability to promote the differentiation and proliferation of vascular system in TME to generate small space for endothelial cells and protect the proliferation of GSC.

Dendritic cells (DCs) are important antigen presenting cells, which are responsible for endocytosis, processing and presenting antigens to immune cells to activate the immune response. However, TME will release CCL5, XCL1 and other chemokines to recruit DC and NK cells after brain tumor invasion. DCs stimulated to inhibit immunity activate Treg and further inhibit T cell activity [38].

Astrocytes, responsible for the specific communication of brain tissue and information exchange between brain cells, regulate the blood brain barrier, are the unique and highest content glial cells in the central nervous system. However, astrocytes can bind to tumor cells in TME, and this newly generated functional channel can transmit the oncogenic factors expressed and secreted by tumor cells. At the same time, astrocytes can also provide neurotrophic factors, growth factors, cytokines and metalloproteinases to tumor cells through this channel to support tumor cell proliferation and invasion. In addition, astrocytes can also express programmed death ligand 1 (PD-L1) to enhance the immunosuppressive ability of TME [39]. It is worth mentioning that the reflex of the nervous system and the signal molecules secreted by the synapses of nerve cells have been found to have the ability to stimulate the proliferation of tumor cells.

The vascular endothelial cells stimulated by tumor cells begin to express integrin in TME αvβ 3. Promote the proliferation of vascular network in tumor tissue. With the proliferation and progress of brain tumors, vascular tissue will become abnormal. Many vascular endothelial growth factor (VEGF) rich in tumor tissue will induce many new immature blood vessels with abnormal distorted shape, weak tube walls and high drug permeability, which are called dystrophic growth [40]. Compared with the canceration of other parts, the malnourished growth of the blood vessels of brain tumors will repair as mature blood vessels with low drug permeability at a faster rate. Therefore, the tumor tissue of glioblastoma usually has more abundant reticular vascular system than other types of tumor tissue.

As a result of the above research results on brain tumor mechanism, some brain tumor treatment strategies are inferred:

1. Using the recruitment effect of TME on macrophages, designing a nano drug delivery system that is easy to combine with macrophages, and the macrophages will bring drug particles into tumor tissue.

2. Design immune activating drugs, through the nano drug delivery system that is easy to combine with immune cells, to re-awake immune cells that are immune suppressed by TME signal molecules and fall into sleep [41].

3. Design anti-angiogenesis drugs to inhibit the proliferation of blood vessels in the tumor tissue, leading to the tumor tissue necrosis due to lack of nutrients. At the same time, vascular inhibitors can also prevent the immature high permeability new blood vessels from continuing to become complete, keep the blood vessel wall ultra-thin and do not block the drug permeability, so that anti-cancer drugs can easily enter TME from the blood.

Intelligent Nano-Drug Delivery System

In the context of current technology research and development, the design of nano drug delivery system has fallen into a two-way difficulty. Targeting delivery of nano drugs can be divided into active targeting and passive targeting. However, the current accumulation of technology cannot support the active targeting of R&D drugs into clinical practice. At the same time, the research and development of passive targeting drugs is not satisfactory because of its low targeting. Drugs cannot be accurately delivered to targeted organs without spreading to the whole body. At this time, the intelligent nano drug delivery system has opened up a new road in the two-way obstacles. The intelligent nano drug delivery system does not rely on active or passive targeting to deliver drugs to the correct targeted organs and tissues. Instead, it uses a designed polymer nano carrier to lock the active ingredients of the drug [42]. Only when the drug diffuses into tumor targeted tissues. Only when the polymer nano carrier is opened, can the effective components of the drug be released to the correct position. The drug active ingredients sealed by polymer nano carriers have no biological activity, and even if they spread to the whole body, they will not cause adverse reactions in other organs [43]. When nano drug carriers are stimulated by endogenous or exogenous stimuli, including special PH, enzyme, redox activity. As well as light, temperature, magnetic field, electric field, wave, polymer nano carriers will open and release drugs, so that the active ingredients of drugs can play a role [44].

Brain tumor tissues have many specific properties, including slightly lower PH than normal tissues, and specific enzymes and signal molecules in the tumor microenvironment. Glutathione GSH is a tripeptide used to remove excess ROS. The levels of GSH and ROS in tumor cells were much higher than those in normal cells. Therefore, it is a very good group of endogenous stimuli. In addition, light, magnetic field, electrical signal and other stimuli can also be triggered artificially. To induce polymer nano drug particles in the correct position of tissues and organs, and release drug active ingredients [45].

In addition, polymer nano carriers can also be used to design nano cars and nano robots. This is a new nano carrier technology, which is characterized by the ability of nano cars and nano robots to move independently in the body [46]. They can be programmed. It can automatically move to the correct part of brain tumor tissue, even to the tumor cells [47]. Until the nano car accident robot enters the correct target cell. Only these smart carriers can release effective components of drugs and play a role in killing tumors [48].

Biomimetic Nanoparticle Drug Delivery System

Some cells of the human body, even some viruses and bacteria, have natural immune hiding ability and are not recognized, discovered and captured by the immune system. When these bio-membranes are separated and extracted, the specific recognition factors and proteins on the surface of these bio-membranes still retain the ability to hide themselves from the recognition of the immune system. Using these bio-membranes as bionic carriers to carry effective drug ingredients can also prevent drugs from being captured by the immune system and sent to the corresponding target organs and tissues [49].

It is worth mentioning that some special viruses have extremely special shell structures, which enable them to penetrate BBB

naturally and enter the central nervous system [50]. These viral shells were isolated and purified as carriers of nano drugs. Carrying active ingredients of drugs. It can enable these nano drug particles to penetrate BBB, which is beneficial to the treatment of brain tumors [51].

One of the advantages of biomimetic nano drug carriers is that there is no need to worry about human metabolism. It is different from the shell of nano carrier composed of some heavy metals. Biomimetic nano drug carriers come from biological natural components, so the human body can also metabolize these biofilm tissues and convert them into the components it needs. It will not accumulate in individual organs, causing cumulative toxicity.

Conclusions

So far, the contribution made in the research field of nano drug delivery system is worthy of recognition. In a completely different direction. It includes polymer nano drug delivery system, liposome nano drug delivery system, biomaterial nano drug delivery system and bionic nano drug system. In addition, the intelligent nano drug delivery system, nano chip, nano motor, nano robot, etc. that are still under development. From the perspective of different therapeutic directions, there are still more directions in the process of research and development, such as the nano drug delivery system with macrophages as the carrier cells, the nano drug delivery system with the goal of activating immune activity, and the nano drug delivery system with the goal of gene therapy. Although many research products are still under test, there are still many difficulties to be solved in the process of clinical application and market commercialization, and there is a long way to go. However, it can be predicted that these drugs all have the advantages of nano drug delivery systems. It includes high biological compatibility, high bioavailability, effectiveness, low toxicity and targeting. They have enough potential to solve the disease fields that traditional medicine can't conquer for hundreds of years.

Future trends

With the current progress of nano pharmaceutical research and development. And experience. In addition to continuing to improve their own direction and research products so that they can be promoted to clinical applications and market productization, there are several trends that will occur in the future

Multi in One Research Direction of Nano Drugs.

At present, researchers have found that two or more effective components of drugs are sealed in the same nano carrier. At the same time, the design of multiple factors to stimulate the opening of the nano carrier shell can enable the same nano drug product to have multiple functions. Other studies have also found that the shell of nano carrier is not only a function of loading effective drug ingredients, but also can play a role in drug activity, monitoring the internal environment, and sensitivity to light and heat. Therefore, it can be boldly inferred that one of the future directions of nano drug research and development will be multi in one nano drug products. Cancer monitoring, tumor imaging, drug therapy, chemotherapy and radiotherapy have the opportunity to be realized through the same nano drug preparation, which has the advantages of convenience and efficiency.

Large-Scale Nano Scale of Existing Therapeutic Drugs.

According to the current experience in nano drug research, it is found that the manufacturing process of some nano drugs is not necessarily complicated, difficult and costly, but it has a strong ability to improve the toxicity, stability and targeting of drug effectiveness. Once the research of nano drug delivery system is mature. At that time, it will no longer be difficult to determine the appropriate nano encapsulation of known active ingredients of drugs. Therefore, it may promote the nano upgrading of drug products in the existing market.

Estimation of Harmfulness and Risk of Nanomaterials.

At present, the clinical use experience of nano drugs is extremely lacking, which leads to insufficient experience and data on adverse reactions of nano drugs to human body. In particular, the awareness of allergy and inflammation, neurotoxicity, abuse risk and environmental hazards is very insufficient.

Up to now, medical research has not fully understood the deep mechanism of allergy and inflammation, but it can be found that there are strong individual differences in allergy. Even food that is completely harmless to the vast majority of people in life, including vegetables and fruits, also has the risk of disease or even death for special populations. It is necessary to do a good job in the research and development of nanomaterials to prepare for the response and treatment of patients with nanomaterial allergy.

It is necessary to make a more detailed assessment of the potential neurotoxicity of nano drugs and attach great importance to the review and evaluation in the process of nano drug research and development. Due to the small size and special physical and biological functions of nano drugs, nano drugs are naturally easier to enter the central or peripheral nervous system through biological barriers than other drug materials. Therefore, nano particles have the potential to cause neurotoxicity.

Some nano drug materials and by-products in the production process of nano drugs may cause harm to the environment. It is known that the toxicity of heavy metal nanoparticles, including gold nanoparticles and silver nanoparticles, to the environment, especially aquatic animals, deserves attention.

Drugs and food with new technologies are particularly vulnerable to abuse by users. Therefore, it is necessary to pay attention to the abuse of nano drugs. Users should be educated to follow the doctor's instructions and use the correct dosage for the correct symptoms to take nano drugs. It should not be used privately or change the drug dosage, nor should it be taken as a nutrient or health care product for a long time. At present, there are many cases in different countries where patients overdose certain drugs and mistakenly believe that drugs should be taken as often as food. Nanodrugs are usually more stable. Once the patient overdoses, it

may be difficult to rescue, and it is difficult to quickly metabolize the drugs already taken, which increases the difficulty of rescue. Therefore, the prevention and rescue measures for nano drug abuse should be paid enough attention and improved as soon as possible.

References

1. GBD 2016 Brain and Other CNS Cancer Collaborators. Global, regional, and national burden of brain and other CNS cancer, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. Neurology. 2019; 18: 376-393.
2. Huang J, Li H, Yan H, et al. The comparative burden of brain and central nervous system cancers from 1990 to 2019 between China and the United States and predicting the future burden. *Frontiers in public health*. 2022; 10: 1018836
3. Fortin D. The blood-brain barrier: its influence in the treatment of brain tumors metastases. Current cancer drug targets. 2012; 12: 247-259.
4. Furtado, Björnmalm M, Ayton S, et al. Overcoming the Blood–Brain Barrier: The Role of Nanomaterials in Treating Neurological Diseases. Advanced Materials. 2018; 30.
5. DePeaux K, Delgoffe GM. Metabolic barriers to cancer immunotherapy. Nat Rev Immunol. 2021; 21: 785-797.
6. Rosenblum D, Joshi N, Tao W, et al. Progress and challenges towards targeted delivery of cancer therapeutics. Nature communications. 2018; 9: 1410.
7. Torchilin VP. Passive and active drug targeting: drug delivery to tumors as an example. Handbook of experimental pharmacology. 2010; 197: 3-53.
8. Pérez-Herrero E, Fernández-Medarde A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik. 2015; 93: 52-79.
9. Polyak B, Friedman G. Magnetic targeting for site-specific drug delivery: applications and clinical potential. Expert opinion on drug delivery. 2009; 6: 53-70.
10. Golombek SK, May JN, Theek B, et al. Tumor targeting via EPR: Strategies to enhance patient responses. Advanced drug delivery reviews. 2018; 130: 17-38.
11. Shi Y, van der Meel R, Chen X, et al. The EPR effect and beyond: Strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. Theranostics. 2020; 10: 7921-7924.
12. Li R, Zheng K, Yuan C, et al. Be Active or Not: the Relative Contribution of Active and Passive Tumor Targeting of Nanomaterials. Nanotheranostics. 2017; 1: 346-357.
13. Rosenblum D, Joshi N, Tao W, et al. Progress and challenges towards targeted delivery of cancer therapeutics. Nature communications. 2018; 9: 1410.
14. De R, Mahata MK, Kim KT. Structure-Based Varieties of Polymeric Nanocarriers and Influences of Their Physicochemical Properties on Drug Delivery Profiles. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2022; 9: 2105373.
15. Ahlawat J, Henriquez G, Narayan M. Enhancing the Delivery of Chemotherapeutics: Role of Biodegradable Polymeric Nanoparticles. Molecules (Basel, Switzerland). 2018; 23: 2157.
16. Mukherjee A, Waters AK, Kalyan P, et al. Lipid-polymer hybrid nanoparticles as a next-generation drug delivery platform: state of the art, emerging technologies, and perspectives. International journal of nanomedicine. 2019; 14: 1937-1952.
17. Fan Y, Marioli M, Zhang K. Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. Journal of pharmaceutical and biomedical analysis. 2021; 192: 113642.
18. Alavi M, Hamidi M. Passive and active targeting in cancer therapy by liposomes and lipid nanoparticles. Drug metabolism and personalized therapy. 2019; 34.
19. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015; 5: 123-127.
20. Ashaolu TJ. Nanoemulsions for health, food, and cosmetics: a review. Environmental chemistry letters. 2021; 19: 3381-3395.
21. Attia MF, Anton N, Wallyn J, et al. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. The Journal of pharmacy and pharmacology. 2019; 71: 1185-1198.
22. Chen YH, Keiser MS, Davidson BL. Viral Vectors for Gene Transfer. Current protocols in mouse biology. 2018; 8: 58.
23. Shirley JL, de Jong YP, Terhorst C. Immune Responses to Viral Gene Therapy Vectors. Molecular therapy: the journal of the American Society of Gene Therapy. 2020; 28: 709-722.
24. DeFrates K, Markiewicz T, Gallo P, et al. Protein Polymer-Based Nanoparticles: Fabrication and Medical Applications. International journal of molecular sciences. 2018; 19: 1717.
25. Tarhini M, Greige-Gerges H, Elaissari A. Protein-based nanoparticles: From preparation to encapsulation of active molecules. International journal of pharmaceutics. 2017; 522: 172-197.
26. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nature reviews. Cancer. 2020; 20: 26-41.
27. Mo F, Pellerino A, Soffietti R, et al. Blood-Brain Barrier in Brain Tumors: Biology and Clinical Relevance. International journal of molecular sciences. 2021; 22: 12654.
28. Quail DF, Joyce JA. The Microenvironmental Landscape of Brain Tumors. Cancer cell. 2017; 31: 326-341.
29. Tomaszewski W, Sanchez-Perez L, Gajewski TF, et al. Brain Tumor Microenvironment and Host State: Implications for Immunotherapy. Clinical cancer research: an official journal of the American Association for Cancer Research. 2019; 25: 4202-4210.
30. Klemm F, Maas RR, Bowman RL, et al. Interrogation of the Microenvironmental Landscape in Brain Tumors Reveals Disease-Specific Alterations of Immune Cells. Cell. 2020; 181: 1643-1660.

31. Lah TT, Novak M, Breznik B. Brain malignancies: Glioblastoma and brain metastases. Seminars in cancer biology. 2020; 60: 262-273.
32. Perus LJM, Walsh LA . Microenvironmental Heterogeneity in Brain Malignancies. Frontiers in immunology. 2019; 10: 2294.
33. Charles NA, Holland EC, Gilbertson R, et al. The brain tumor microenvironment. Glia. 2012; 60: 502-514.
34. Cole AP, Hoffmeyer E, Chetty SL, et al. Microglia in the Brain Tumor Microenvironment. Advances in experimental medicine and biology. 2020; 1273: 197-208.
35. Andersen BM, Faust Akl C, Wheeler MA, et al. Glial and myeloid heterogeneity in the brain tumour microenvironment. Nature reviews. Cancer. 2021; 21: 786-802.
36. Boyd NH, Tran AN, Bernstock JD, et al. Glioma stem cells and their roles within the hypoxic tumor microenvironment. Theranostics. 2021; 11: 665-683.
37. Dapash M, Hou D, Castro B, et al. The Interplay between Glioblastoma and Its Microenvironment. Cells. 2021; 10: 2257.
38. Le Rhun E, Preusser M, Roth P, et al. Molecular targeted therapy of glioblastoma. Cancer treatment reviews. 2019; 80: 101896.
39. Boire A, Brastianos PK, Garzia L, et al. Brain metastasis. Nature reviews. Cancer. 2020; 20: 4-11.
40. Charles N, Holland EC. The perivascular niche microenvironment in brain tumor progression. Cell cycle (Georgetown, Tex.). 2010; 9: 3012-3021.
41. Ou A, Yung WKA, Majd N. Molecular Mechanisms of Treatment Resistance in Glioblastoma. International journal of molecular sciences. 2020; 22: 351.
42. Tarantino P, Carmagnani Pestana R, Corti C, et al. Antibody-drug conjugates: Smart chemotherapy delivery across tumor histologies. CA: a cancer journal for clinicians. 2022; 72: 165-182.
43. Wang X, Li C, Wang Y, et al. Smart drug delivery systems for precise cancer therapy. Acta pharmaceutica Sinica. B. 2022; 12: 4098-4121.
44. Mitchell MJ, Billingsley MM, Haley RM, et al. Engineering precision nanoparticles for drug delivery. Nature reviews. Drug discovery. 2021; 20: 101-124.
45. Bai, Zhang Y, Li D, et al. Gain an advantage from both sides: Smart size-shrinkable drug delivery nanosystems for high accumulation and deep penetration. Nano Today. 2021; 36: 101038.
46. Wang, Dong Y, Ma P, et al. Intelligent Micro-/Nanorobots for Cancer Theragnostic. Advanced Materials. 2022.
47. Wang, Kostarelos K, Nelson BJ, et al. Trends in Micro-/Nanorobotics: Materials Development, Actuation, Localization, and System Integration for Biomedical Applications. Advanced Materials. 2021; 33.
48. Van der Meel R, Sulheim E, Shi Y, et al. Smart cancer nanomedicine. Nature nanotechnology. 2019; 14: 1007-1017.
49. Chen L, Hong W, Ren W, et al. Recent progress in targeted delivery vectors based on biomimetic nanoparticles. Signal transduction and targeted therapy. 2021; 6: 225.
50. Suh S, Jo A, Traore MA, et al. Nanoscale Bacteria-Enabled Autonomous Drug Delivery System (NanoBEADS) Enhances Intratumoral Transport of Nanomedicine. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2018; 6: 1801309.