OUR Journal: ODU Undergraduate Research Journal

Volume 6 Article 5

2019

Can Nanotechnology be the Leading Method in Detecting and Treating Cerebral Tumors?

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Cover Page Footnote

Faculty Sponsor: Dr. Christopher Osgood

CAN NANOTECHNOLOGY BE THE LEADING METHOD IN DETECTING AND TREATING CEREBRAL TUMORS?

By Daniel Singh

ABSTRACT

Nanotechnology refers to the manipulation or design of materials and structures with desired features in the 1nm–1000 nm size range. The blood brain barrier (BBB) is a major obstacle that drugs must overcome in order to reach tumor cells. The role of this barrier is to transport essential nutrients while protecting and regulating the internal environment. Nanoparticles have been shown to transport drugs through this barrier and accumulate in tumor cells. This is significant since nanoparticles are drug carriers allowing chemotherapeutic drugs to accumulate in target areas (Sun et al., 2017). This is possible because they are able to be modified to overexpress specific peptides or membrane markers that are found in these target areas. Once the nanoparticle reaches these anatomical barriers they bind to the correct receptor and move into the area. They can then accumulate and drop their payload which may include a chemotherapeutic drug or contrast agent. This release is sensed by specific pH or temperature changes (Cheng, Morshed, Auffinger, Tobias, & Lesniak, 2014). Nanoparticles can contain different types of elements with unique properties. These properties can be optical, magnetic, or thermal resonating (Savale, 2015). They can be used in both imaging and treating tumors such as glioblastomas. However, there may be potential side effects that are currently not well understood (Wikipedia, 2019b). Nanoparticles are known to have a low toxicity when compared to other drugs (Wikipedia, 2019b). However, high toxicity levels can lead to alarming effects such as affecting other organs and their function (Savale, 2015). Cancer in the brain such as a glioblastoma (GBM) is one of the most active and lethal cancers.

Unfortunately, there is no known effective treatment; however, the use of nanoparticles has opened a new door into fighting this disease. This paper will discuss the relationships that nanoparticles have in treating cerebral tumors as well as imaging of cerebral tumors.

INTRODUCTION

The treatment and imaging of brain tumors is a difficult challenge faced in the neuro-oncology field. Tumors within the brain are very aggressive and usually once removed are able to recur and cause further problems in the future. To treat a glioblastoma surgically, margins of the tumor must be identified to differentiate diseased tissue from healthy tissue which is difficult without clear imaging (Cheng et al., 2014). Secondly, it is difficult for therapeutic drugs to reach target areas of tumor cells because of anatomical barriers such as the BBB. As a result, therapeutic drugs that are being used today have a difficult time accumulating and even reaching these target areas. In a clinical setting, an MRI (Magnetic Resonance Imaging) is used with a contrast media such as gadolinium to image a tumor found within the brain (Cheng et al., 2014). However, these molecules have a difficult time crossing the BBB because of the tight junctions that regulate what may enter and leave the brain. Also, extrusion pumps export drug out of the brain. Contrast media that is used in imaging typically depicts the areas where the BBB has been disrupted by the tumor cells and not the entire tumor itself. These molecules have a short half-life and usually require repeated injections of contrast media at higher doses which may result in harmful side-effects. These limitations have resulted in increased research in the neuro-oncology field for better techniques in imaging and targeting of brain tumors. Nanotechnology refers to the design, synthesis, and application of material within the size range of 1-1000 nanometers. Nanoparticles that contain properties such as optical, magnetic, and thermal resonance have gained interests in

the medical field and specifically oncology. Nanoparticles may have the opportunity to overcome the limitations discussed previously that typical drugs and imaging techniques face.

BACKGROUND OF NANOPARTICLES

The concept of the uniqueness of nanoparticles first began during a lecture at an American physical society meeting named, "There's Plenty Room at the Bottom," on December 29th, 1959 by Richard Feynman (Nanos, 2019). A Japanese scientist named Norio Taniguchi coined the termed nanoparticle in a 1974 conference (Wikipedia, 2019a). An American engineer named Eric Drexler was credited for the development of molecular nanotechnology (Nanos, 2019). Over the past few years, many kinds of nanoparticles have been produced. During this time, they have been used to create nanomaterials (MINATEC, 2016). These nanomaterials have then been used in areas such as: transportation, environment, healthcare, new energies, buildings, etc. (MINATEC, 2016). Nanoparticles also have physical properties like conductance, uniformity, and optical properties that make then useful in science (MINATEC, 2016).

This paper will focus on its application and abilities to the medical field specifically. Nanoparticles have gained interest since they have specific characteristics such as optical properties, heat transfer, and a small size (Pall et al., 2019). When light is shined on a nanoparticle it is able to be dispersed or absorbed (Aldrich, 2019). This is important for imaging of tumors. Heat transfer is another property that nanoparticles hold specifically magnetic nanoparticles (Pall et al., 2019). These particles generate heat once they are stimulated with some type of electromagnetic source such as light or a magnetic field (Pall et al., 2019). This property is emphasized in a study discussed later in this paper. However, once the particle reaches a tumor cell they then heat up and trigger mainly apoptosis (Pall et al., 2019). This can not only help in

treating cancers in the brain, but cancer found throughout the body. The small size of nanoparticles is discussed throughout this paper; it is very important to understand how their small size relates to their function.

STRUCTURE AND FUNCTION OF NANOPARTICLES

Nanoparticles are not simple molecules; they are complex mixtures (Christian, Von der Kammer, Baalousha, & Hofmann, 2008). There are few characteristics that all nanoparticles have in common such as they characteristically have a high surface area to volume ratio which play a role in why they are effective vehicles in treating and imaging of glioblastomas (Christian et al., 2008). Nanoparticles usually have a surface chemistry that differs from its core material (Christian et al., 2008). The surface of the nanoparticle plays a role in the environment and how it is able to transverse through the body. The surface of the nanoparticle also plays a role in its applicability and function. For example, the surface of the nanoparticle is where the overexpressed peptides or antibodies would be located that are able to specifically bind to certain obstacles like BBB and the tumor site. A nanoparticle can essentially be characterized into three layers: a functionalized surface, a shell that may be added intentionally depending on its task, and a core material such as a specific drug, contrast agent, or a metal (Christian et al., 2008).

The surface of a nanoparticle can be modified with the addition of small molecules, surfactants, peptides, or polymers. The charge of a nanoparticles surface may be modified allowing it to disperse in specific environments. For example, for a nanoparticle to disperse in an aqueous solution it must have a charged surface. Nanoparticles that do not have the ability to hold a charge on their surface may be modified with the addition of small molecules that are able to covalently bind to the surface of a nanoparticle which itself holds a charge. Examples of these molecules

include citrate stabilized gold, silver sols, and thiopropanic acid (Christian et al., 2008). The shell is the location where peptides are added that bind to receptors and are able to pass through anatomical barriers which is discussed in the next section (Christian et al., 2008).

The shell is the inner layer between the inner core and the outer surface (Christian et al., 2008). This layer is usually chemically different than the inner core (Christian et al., 2008). This layer may be prepared purposefully or can form through natural processes. An example of this is the formation of iron nanoparticles which form layers of iron oxide into their shell after they have been prepared (Christian et al., 2008).

The core of the nanoparticle is essentially the center of the nanoparticle. Many nanoparticles receive their name for what they hold in their core (Christian et al., 2008). Their core is what causes the side effect of nanoparticles such as toxicity. For the topic of neuro-oncology this is where the drug, contrast media, or metal is held.

SYNTHESIS OF NANOPARTICLES

Nanoparticles are synthesized through two different methods: top-down and bottom-up (Arolel, 2014). The particles are produced from materials such as polymers, lipids, proteins, metals, and semiconductors. The top-down method is usually the simplest way of fabricating nanomaterial in bulk. (Arolel, 2014). This method consists of mechanical processes known as ball milling in which energy of a grinding source is transferred to the substance being reduced. The material can then undergo processes known as compaction and consolidation in which it is then put back together with better characteristics (Arolel, 2014). There are many other top-down mechanical processes such as thermal methods in which heat is included in the form of electricity or solar energy.

Another form of a mechanical process is the lithography method (Arolel, 2014). This method works by adding patterns to the outside of the nanoparticle (Arolel, 2014).

The bottom-up approach is when nanoparticles begin as atoms or molecules and undergo processes that essentially build them up into functioning nanoparticles**.** Chemical vapor deposition is a common bottom up process that is a gas phase process (Arolel, 2014). This process begins with a reactive element which reacts over a templated surface to form a nanostructure. Examples of reactive elements used in this process include methane, acetylene, or other reactive carbon gases, and their catalysts include cobalt, iron, or nickel (Arolel, 2014). Other known bottom-up methods include atomic layer deposition, molecular beam epitaxy, liquid phase methods, and electroless deposition. All of these methods follow the same concept as the bottom-up approach beginning as small atoms or molecules and built up to larger structures up to 100 nanometers. Another process of the bottom-up method is the sol-gel process (Arolel, 2014). The sol-gel process is a wet chemical technique that is mostly used in nanotechnology and has multiple steps. These steps include hydrolysis and polycondensation, gelation, aging, drying, densification, and crystallization. This method is a synthetic way to create metal oxide nanoparticles (Arolel, 2014). Sol-gel process has a variety of advantages like easy modification as well as a changeable microstructure (Arolel, 2014).

PHASES OF DEVELOPMENT

Figure 1 depicts various nanoparticles that are being used today such as their uses and phases of development (Cheng et al., 2014). Currently there are many possible nanoparticles that are being used in treating cancers in the brain. Three main materials used for nanoparticles are organic, inorganic, and hybrid (Cheng et al., 2014). Organic materials are formed from particles like

liposomes and micelles. Both of these nanoparticles are used for transporting drugs (Cheng et al., 2014). Inorganic materials are materials like iron oxide and quantum dots. Iron oxide are also used as drug carriers but are also used in MRI imaging. Quantum dots are used for florescence imaging (Cheng et al., 2014). Hybrid materials are a combination of more than one type of nanomaterial. These structures normally form barge or tanker designs (Cheng et al., 2014). A barge design is when the entity is stuck onto the outer surface of the nanoparticle. On the other hand, a tanker design is when the entity being carried is inside of a porous capsule like structure. Determining which design to use is based on what is being transported (Cheng et al., 2014). Delicate drugs that are possibly unstable or can easily be altered should be placed in a vessel (tanker) until it reaches its destination. In another situation an imaging medium should be placed on the outside of the nanoparticle (Cheng et al., 2014). This allows for it to be easily found and used, which is return allows for a faster release of the package when met with a stimulus. Unfortunately, both of these designs have a common flaw when it comes to carrying capacity. Based on a spherical model, more substances can be placed inside of the nanoparticle than can be placed on the surface area. The transportation design method used is based on the size of the substance being carried (Cheng et al., 2014).

How Nanoparticles Enter Into the Body/Modes of Delivery to the Brain

A. Ingestion

When the nanoparticles are ingested, there are two pathways it can take (Teleanu, Chircov, Grumezescu, Volceanov, & Teleanu, 2018). If the nanoparticle is small enough it can pass through the empty areas between the cells (paracellular absorption). They can also be taken across cells by enterocytes with no energy required or by being bound to specifically instructed receptors (Teleanu

et al., 2018). Depending on the size, charge, and the ability to be dispersed, nanoparticles can go through the gastrointestinal tract (Teleanu et al., 2018). From here they can be pulled into the systemic circulation and get spread out to other organs (Teleanu et al., 2018). If the size is small enough these nanoparticles can then cross the BBB and build up in the brain (Teleanu et al., 2018). Also, nanoparticles can be engulfed through cell mediated endocytosis where the cells are able to recognize the nanoparticle and then take it in through phagocytosis. From here it travels until it can reach the BBB.

B. Inhalation

Another option for delivering these nanoparticles and their drugs so that they reach the brain is thorough inhalation. Once inhaled they will either go to the upper respiratory tract or the lower respiratory tract (Oberdörster, Elder, & Rinderknecht, 2009). From either of these two locations they will be transported to the lymph and then into the blood, or directly to the blood. Once in the blood they will eventually reach the BBB (Oberdörster et al., 2009). Nanoparticles that are in the blood were also found to be located in other organs like the liver and spleen (Heath, 2019). Where these particles end up is based on their size. The smallest sizes (10nm) are capable of spreading to almost all organs (Heath, 2019). Larger nanoparticles (100nm or more) are mainly kept within the liver and spleen because they cannot make it through the smaller pores (Heath, 2019). If the nanoparticles are hydrophilic based, they will stay inside of the body longer as well as carry a positive charge. While held in the spleen and liver these nanoparticles are easily eliminated due to the phagocytes and other cells that aid in the digestion of foreign matter (Heath, 2019).

C. Skin Absorption

In this technique the nanoparticle is held within the lipid configuration that the skin has, or in the connections of the skin (Teleanu et al., 2018). From here they ideally can be released slowly into the deeper skin layers like the dermis (Teleanu et al., 2018). More research and trials need to be done with this method (Teleanu et al., 2018). More research will allow for a better understanding of what specific nanoparticles can be used in skin penetration as well as which will affect this technique (Teleanu et al., 2018). When using this technique there is a possibility of irritation and sensitivity to the nanoparticles (Teleanu et al., 2018). This sensitivity and irritation can cause allergic reactions from the release of various metals used in the process (Larese Filon, Mauro, Adami, Bovenzi, & Crosera, 2015). Research must still be done on nanoparticles used for skin absorption specifically the effects of size, shape, surface receptors on how nanoparticles can pass through the skin and into the blood stream (Teleanu et al., 2018).

D. Injection

Hexapeptide dalargin, the first drug used with nanoparticles, was injected intravenously in 2005 (Wikipedia, 2019b). This process was a breakthrough for nanoparticle in the medical field. This opened the doors for other options and other attempts to be made (Teleanu et al., 2018; Wikipedia, 2019b). This type of exposure is most used in the field of nanomedicine and used for brain cancer and central nervous diseases such as Alzheimer's, Schizophrenia, and Parkinson's (Teleanu et al., 2018). This pathway injects nanoparticles directly into the blood stream and if small enough can pass through the BBB mainly through cell mediated endocytosis and accumulate in target sites (Wikipedia, 2019b).

MODIFICATIONS TO NANOPARTICLES

Drugs must be able to overcome the obstacle of the BBB (illustrated in figure 2 and 3) to reach the target site (Cheng et al., 2014). As stated before, nanoparticles have gained much attention through the capability of adding modifications to their surface. These modifications allow them to overexpress particular peptides or antibodies which can then bind to receptors found in the BBB or tumor cells allowing them to pass by cell mediated endocytosis. This is a great advantage that nanoparticles have over other drugs and imaging techniques. An experiment was done to assess the endocytosis efficiency of macrophages loaded with gold nanoparticles. These gold nanoparticles were used to kill glioblastoma cells through mainly apoptosis and small amounts of necrosis (Pall et al., 2019). Apoptosis is known as programmed cell death. During this time the cell begins to break apart and the DNA forming "blebs" or small vesicles where they are located are phagocytized by macrophages. However, necrosis is known as abnormal cell death in which the small vesicles are formed, but they then fuse with other vesicles and rupture releasing cell contents which can result in an unwanted inflammation response. This unwanted response can cause major undesirable consequences such as brain damage, coma, or even death (Fellizar, 2018).

These macrophages were previously known to transverse the BBB which allowed them to be recognized and cross the barrier (Pall et al., 2019). NHE9 is a sodium hydrogen exchanger which has been known to be a driver for glioblastoma progression (Pall et al., 2019). NHE9 overexpression had been previously shown to increase accumulation in glioblastoma cells. These gold nanoparticles contained NHE9 overexpression on their surfaces which allowed them to accumulate in the tumor cells (shown in figure 4) (Pall et al., 2019). Once the nanoparticles had accumulated within the tumor cells a new technique known as Gold Nanoparticle Enabled Photothermal Therapy (NEPTT) was used (Pall et al., 2019). This technique uses infrared light

which the nanoparticles then turn into heat which triggers apoptosis and small amounts of necrosis (Pall et al., 2019). This temperature change can be seen in the graph in figure 5 (Pall et al., 2019).

OTHER METHODS OF NANOPARTICLE TRANSPORT

This paper focuses mainly on how nanoparticles are able to pass through the BBB through cell mediated endocytosis. However, figure 3 illustrates other mechanisms for nanoparticles to cross the BBB (Pall et al., 2019). Mechanisms worth noting include adsorbtive transcytosis and the transcellular lipophilic pathway (Pall et al., 2019). Adsorbtive transcytosis includes the binding of cation (positively charged) molecules to the BBB which the brain then recognizes and absorbs (Curley & Cady, 2018). The transcellular lipophilic pathway is currently not well understood, however this pathway uses lipohilic molecules (loaded with nanoparticles) that are known to be able to cross the barrier (Curley & Cady, 2018).

NANOPARTICLES USED FOR DRUG DELIVERY

Nanoparticles used for drug delivery are natural and biodegradable to reduce the risk of side effects and toxicity (Wikipedia, 2019b). Nanoparticles used as drug carriers include; liposomes, micelles, polymeric nanoparticles, gold nanoparticles, iron oxide nanoparticles, and ceramic nanoparticles (Cheng et al., 2014). These different types of nanoparticles no matter if they're organic or inorganic function in the same way. Nanoparticles high surface area allows them to hold high amounts of the chemotherapeutic drugs or contrast media. Many hydrophobic drugs that normally would not be able to pass the BBB are able to when used with a nanocarrier. As discussed earlier, modifications to the surface of nanoparticles allow for an effective delivery system for brain

tumors. Liposomes, spherical phospholipid bilayers have received lots of attention through their ability to pass the BBB and enhance the pharmacological effects of the drug.

NANOPARTICLES USED FOR IMAGING

Research is being done to design nanoparticles that include multiple imaging modalities. Different imaging modalities include MRI, PET, optical, and SPECT. Since each modality has its advantages and drawbacks, when they are used in combination this may result in a better chance for earlier detection and imaging of the tumor cells. These images may help in every step of cancer treatment including pre-op, intra-op, and post-op. Many nanoparticles serve as both drug carriers and imaging probes such as gold nanoparticles. Gold nanoparticles have surface plasmon characteristics. This is caused by oscillations of electron charge that is in resonance with the frequency of visible light. The surface plasmon resonance can be determined by the size or shape of the nanoparticle. This allows the nanoparticle to be tailored for imaging of specific tumor cells.

IMAGING TECHNIQUES USED IN CONJUNCTION WITH NANOPARTICLES

A variety of imaging modalities are being used including Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) (Z. Cheng, Yan, Sun, Shen, & Gambhir, 2016), Optical imaging, and single-photon emission computerized tomography (SPECT) (Clinic, 2019). MRI's are precise in imaging and allow for the detection of minute lesions; however, they are at a high cost and take longer in time (Cheng et al., 2016). PET scans allow for the imaging of specific organs and tissues compared to an MRI which images joints, cartilage, ligaments, and tendons. SPECT integrates computer tomography and a radioactive tracer. The tracer allows the ability to see where blood is flowing to tissues and organs (Cheng et al., 2016). With the combination of

these imaging techniques may allow for earlier detection of cancer and better characterization of molecular and metabolic features of a brain tumor (Cheng et al., 2016).

FUTURE WORKS

Based on what has been learned in this field some problems must be solved in the future. In the oncoming years it is expected that there will be the creation of nanodevices that are able to deliver to the cancer preventing substances as well as anticancer vaccines (Savale, 2015). It is also suggested that molecular sensors that can be implanted should be created to detect biomarkers known to be associated with cancer (MEMS). Nanoparticles are also being improved to efficiently deliver medication that will help to reduce the side effects from cancer fighting therapies (Savale, 2015). Better imaging diagnostics such as targeted contrast agents that improve imaging and resolution of tumors (quantum dots) (Savale, 2015). Continued research that integrates imaging and therapeutic function into nanoparticles (Savale, 2015). To advance this research interdisciplinary training from engineering, biology, nanotechnology, and oncology can accelerate our understanding of nanoparticles help answer question that are currently not completely understood (Savale, 2015).

DISCUSSION

Many challenges are faced in overcoming the BBB and then targeting of brain tumor cells (Cheng et al., 2014). Also, the ability for nanoparticles to target only tumor cells is a difficult task because normal cells found in the brain may also express targeted receptors that the nanoparticle is modified to attach to (Cheng et al., 2014). Nanoparticles that have shown the most promising results are those that express multiple peptides that allow for recognition of tumor cells (Cheng et al., 2014). Another challenge that is faced is the control of drug release. For the particle to function

optimally it must deliver the drug inside the tumor cells (Cheng et al., 2014). Not only should these particles sense change in pH or temperature, but they could also include enzyme degradable attachments as well as chemical linkers that are capable of cleaving the particle once it arrives in the correct location (tumor cells) (Cheng et al., 2014). Nanotoxicology is a growing subject in the medical field because the use of nanoparticles in the medical field has increased in interest and possible application. Specifically, safety is a major concern in nanomedicine because the effects of these particles are not well known (Cheng et al., 2014). Concerns of applying these particles to actual patients start to arise. Nanoparticles are known to have a low toxicity compared to other forms of cancer treatment; however, the long-term side effects are not well known (Cheng et al., 2014). Currently, nanoparticles are being used to treat patients with aggressive recurring glioblastomas who have a low quality of life (Cheng et al., 2014). The central nervous system is one of the most complex specialized systems in the body, and the use of nanoparticles in the brain may be unpredictable and not fully understood when interacting with healthy cells (Cheng et al., 2014).

Nanoparticles are still in the beginning stages of research and are still a relatively new idea. Few nanoparticles are being used in clinical trials and on patients with the worst prognoses (Cheng et al., 2014). To fully understand the effects of nanoparticles will require large amounts of studies, research, and testing which may take a substantial amount of time.

CONCLUSION

The use of nanoparticles to treat brain cancer is still a new and emerging field. This idea originated in 1959 at a meeting of American physical scientists. After work was done, it was discovered that nanoparticles all have a few characteristics in common. All nanoparticles have a large surface area and surface chemistry that is different from its core. Nanoparticles are made from two main

methods: top-down and bottom-up. Top-down is the easiest and simplest whereas bottom-up is when they start off as atoms and are built up to become nanoparticles that can be used. A common process of bottom-up is the sol-gel process that is often used in nanotechnology. Currently there are three materials that are used for nanoparticles: organic, inorganic, and hybrid. Each of these are based on what the particle will be used for. Nanoparticles used in drug therapy can be administered in various ways such as ingestion, inhalation, skin absorption, and injection. Although nanoparticles are very upcoming and promising there is still work that needs to be done. These nanoparticles must be able to overcome the BBB to be effective in administering the drugs. Fortunately, these nanoparticles are able to have modifications made to their surface. Overall, nanoparticles are a promising idea to use in treating brain cancers, other various diseases, and imaging methods. In the future, it is speculated that nanodevices will be created to deliver anticancer substances, and molecular sensors will be used in implant form as biomarkers for cancer. Not only this, but they will also be constructed to better deliver medications that would help reduce side effects of cancer therapies.

Figure 1

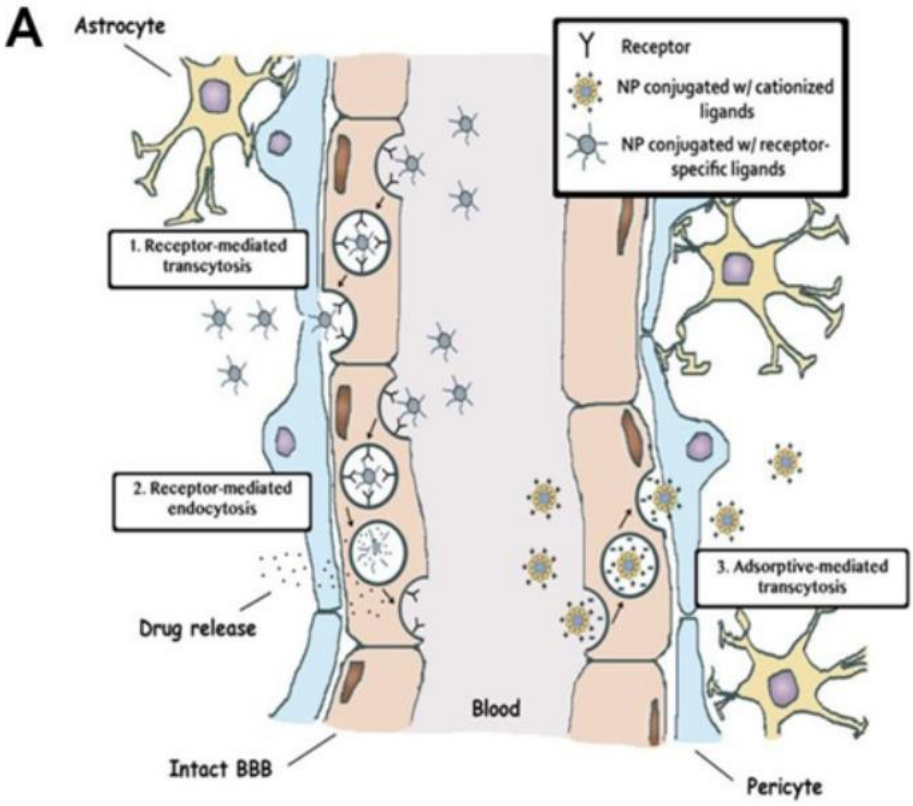
Table 1

Examples of nanoparticle platforms for brain tumors

Material	Particle Type	Structure Formed	Size	Main component	Main Applications	Phase of development	Ref.
Organic	Liposomes	Colloid vesicular strucutre	10nm–1000 nm	Lipid	Drug carrier	Phase I, II Clinical Trials	[63]
	Micelles	Nanosphere; cylinder	20nm–200 nm	Polymer	Drug carrier	Preclinical	[64]
	Polymeric nanoparticles	Nanosphere; nanocapsules	10nm–1000 nm	Polymer	Drug carrier	Preclinical	[59]
	Dendrimers	Branch	> 5 nm	poly(amidoamine)	Drug carrier	Preclinical	[62]
Inorganic	Gold nanoparticles	Nanosphere; nanorod; nanoshell	1nm–100nm	Gold	Drug carrier; photothermal therapy; photoacoustic imaging	Preclinical	[58,71]
	Iron oxide nanoparticle	Nanosphere	10nm–50nm	Iron oxide	Drug carrier; magnetic hyperthermia; MRI	Phase I, II Clinical Trials	[57,60]
	Ferromagnetic discs	Microdisk	lμm	Iron, nickel	Magnomechanical stimulation	Preclinical	[61]
	Ceramic nanoparticle	Nanosphere	20nm–100nm	Silica	Drug carrier	Preclinical	[235]
	Quantum dots	Nanosphere; nanorod	2–20nm	Cadmium selenide	Fluorescence imaging	Preclinical	[66]
	Titanium dioxide nanocrystals	Sphere	5 nm	Titanium dioxide	Photodynamic therapy	Preclinical	[67]
Hybrid	More than one type of nanomaterials	Barge or tanker	Range depends on materials selected	Core-metallic and polymeric; corona-single or multiple lipid layers	Theranostics	Preclinical	[168]

This figure depicts the many various types of nanoparticle and importantly for this paper their material, applications, and phases of development. *Note*. From “Multifunctional Nanoparticles for Brain Tumor Diagnosis and Therapy” by (Cheng et al., 2014).

Figure 2



This figure helps in proving the point that the BBB does a great job at protecting itself from foreign molecules. Astrocytes as well as pericytes are shown wrapping around the endothelial cells forming tight junctions that create a barrier. *Note*. From "Multifunctional Nanoparticles for Brain Tumor Diagnosis and Therapy" by (Cheng et al., 2014).

Figure 3

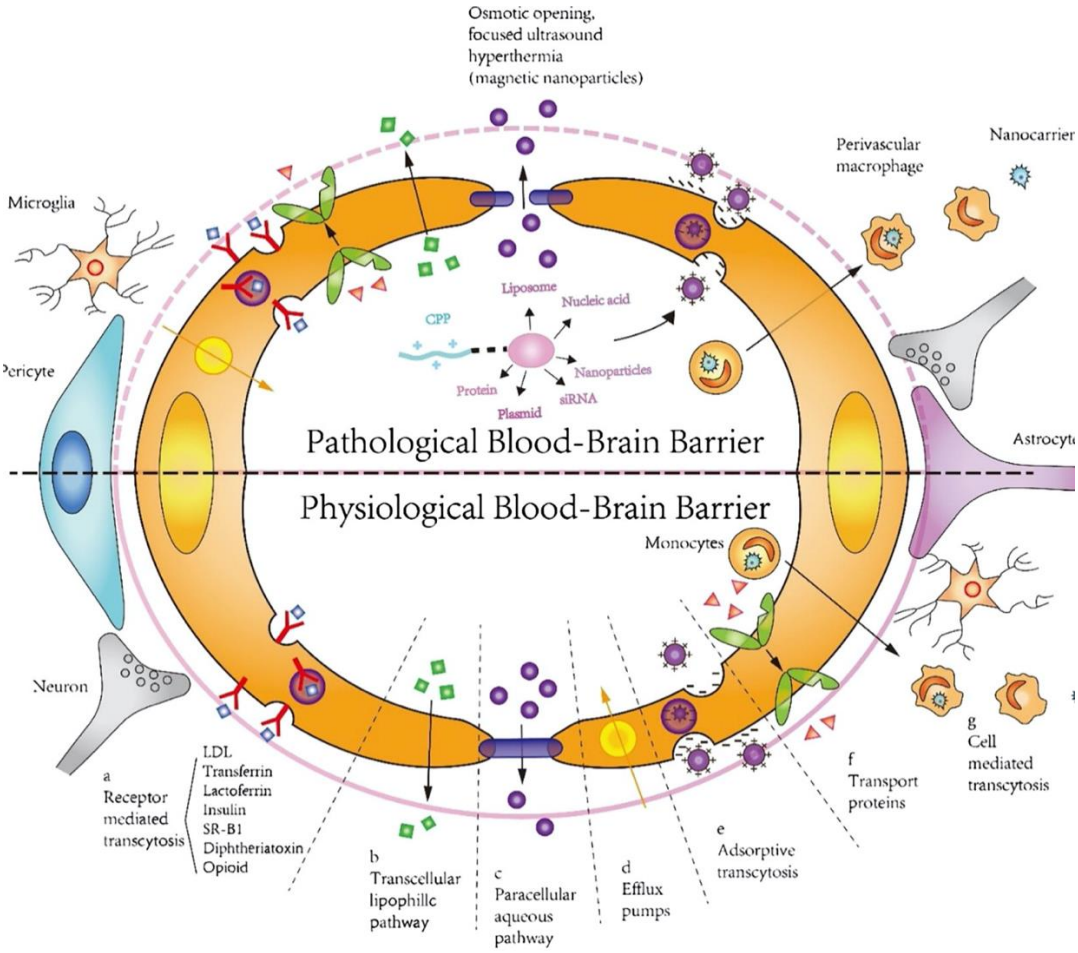
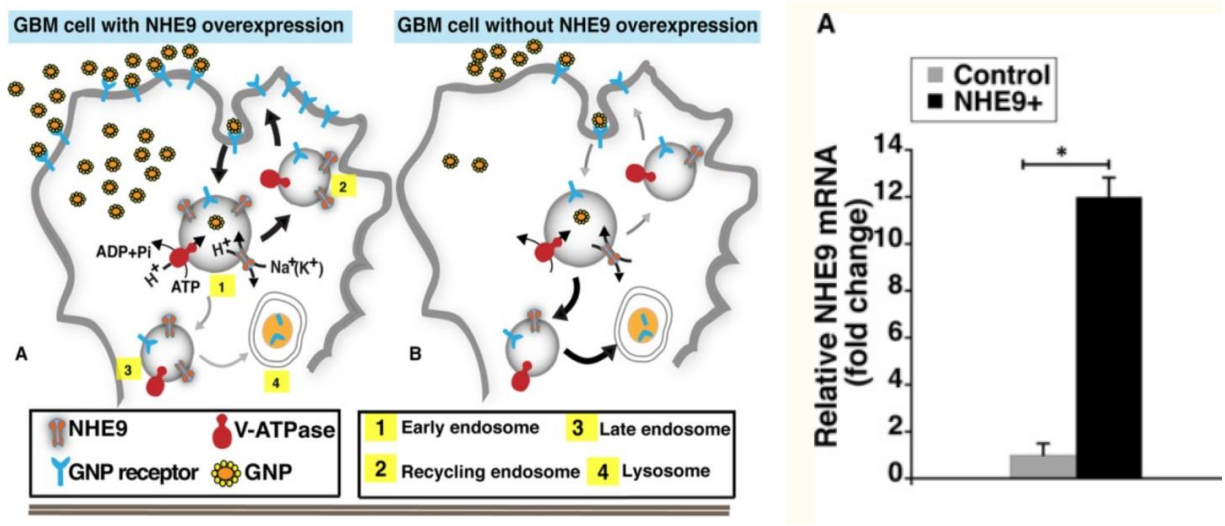


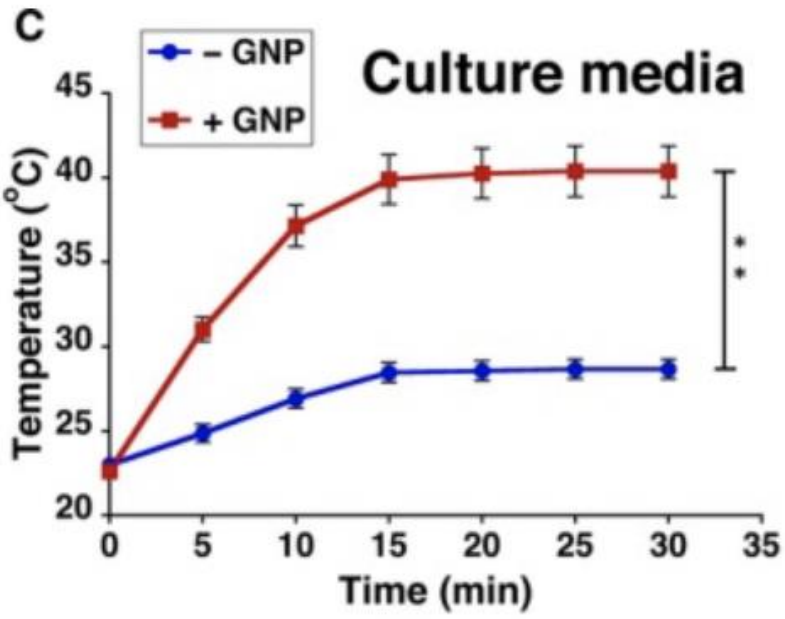
Figure 1: This paper focuses on receptor mediated endocytosis; however, nanoparticles have other methods of overcoming the BBB. This figure illustrates other methods that are not discussed in this paper (Sun et al., 2017).

Figure 4



This figure depicts the effectiveness of external modifications on nanoparticles. This figure is from the study that was previously discussed. As shown when the gold nanoparticles had NHE9 overexpression they were more likely to be accumulated within the glioblastoma cell (tumor cell). The bar graph on the right depicts the measured results from a control compared to a nanoparticle with NHE9. As shown, a 12-fold increase can be seen with those expressing NHE9 compared to the control with around a 1-fold increase. *Note*. From "A gain of function paradox: Targeted therapy for glioblastoma associated with abnormal NHE9 expression" (Pall et al, 2019).

Figure 5



This figure shows the change in temperature once the gold nanoparticles were accumulated in the tumor cells. Gold Nanoparticle Enabled Photothermal Therapy (NEPTT) was used. This used infrared light which the nanoparticles then turn into heat which trigger apoptosis and small amounts of necrosis. This line graph illustrates the temperature change with gold nanoparticles vs. without non-gold nanoparticles. Up to an 18° Celsius temperature change can be seen with gold nanoparticles present. *Note*. From "A gain of function paradox: Targeted therapy for glioblastoma associated with abnormal NHE9 expression" by (Pall et al, 2019).

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