NANOMATERIALS FOR DIAGNOSIS AND TREATMENT OF BRAIN CANCER

By

Tamanna Shahrin Tonny
18346077

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
March 2023

© 2023 Brac University
All rights reserved.

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Tamanna Shahrin Tonny
18346077

Approval

The thesis titled “Nanomaterials for Diagnosis and Treatment of Brain Cancer” submitted by Tamanna Shahrin Tonny (18346077) of Summer 2022, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Examining Committee:

Supervised By:

Kazi Fatema Rahman
Lecturer, School of Pharmacy
BRAC University

Approved By:

Program Coordinator:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir,
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study does not involve any kind of animal or human trial.

Abstract

Nanomaterials have shown significant promise in the diagnosis and treatment of brain cancer. These materials, because of their distinct physical and chemical properties, can be engineered to target specific molecules and tissues in the brain, making them useful in early diagnosis and targeted drug delivery. As a result, nanostructures with high specificity, such as metallic nanostructures, silica nano-vehicles, quantum dots, lipid nanoparticles (NPs), and polymeric NPs, can permeate the BBB. However, there are still some limitations to their use in the treatment of brain cancer, including toxicity, clearance, and stability. Despite these limitations, nanomaterials have been developed for a variety of purposes in the treatment of brain cancer, including drug delivery, imaging, photodynamic therapy, and hyperthermia. Nanoparticles can be designed to encapsulate therapeutic drugs and deliver them directly to brain cancer cells, potentially improving their efficacy and reducing toxicity to normal cells. This review provides a comprehensive overview of nanomaterials used for the treatment and diagnosis of brain cancer. This paper focuses on the application of liposomes, nanomicelles, dendrimers, carbon nanotubes, gold, silver nanoparticles.

Keywords: Nanomaterials, nanoparticles, nanobodies, brain cancer, blood–brain barrier, nano therapy.

Dedication

Dedicated To My Parents

Acknowledgement

This research could not have been completed without the help of numerous individuals who are gratefully acknowledged here. I would like to express my fullest gratitude to my supervisor, Kazi Fatema Rahman Ma'am, Lecturer, School of Pharmacy, BRAC University. She always supported and motivated me to finish this thesis paper. I am also thankful to Prof. Dr. Eva Rahman Kabir Ma'am, Honorary Chairperson, School of Pharmacy and BRAC University, Prof. Dr. Hasina Yasmin Ma'am, Program Director and Assistant Dean, School of Pharmacy, BRAC University, academic coordinator and all faculty members of School of Pharmacy.

Table of Contents

List of Tables

List of Figures

List of Acronyms

NPs	Nanoparticles
ZnO	Zinc Oxide
BBB	Blood-Brain Barrier
EPR	Enhanced permeability and retention
CT	Computed tomography
FUS	Focused ultrasound
MRI	Magnetic resonance imaging
AgNPs	Silver nanoparticles
PMA	Polymethacrylate
ROS	Reactive oxygen species
BTB	Blood-tumor barrier

Chapter 1

Introduction

Nanomaterials are materials that have at least one dimension that is on the nanoscale, which is about 1-100 nanometers. They have unique physical and chemical properties due to their small size, and have attracted a lot of attention for their potential use in various fields, including medicine (Miernicki et al., 2019). Brain cancer, also known as brain tumor, is a type of cancer that occurs in the brain or central nervous system (Piktel et al., 2016). It is a serious condition that can be difficult to treat and can have significant effects on a person's quality of life. There are several ways that nanomaterials are being used or investigated for the diagnosis and treatment of brain cancer. Nanoparticles can be designed to target specific cells or tissues in the body, which makes them useful for delivering drugs or other therapies directly to brain tumors (Quader & Kataoka, 2017). In addition, nanomaterials can be used to create imaging agents that can help doctors visualize brain tumors and monitor their response to treatment. Finally, nanomaterials are also being studied for their potential to be used in brain cancer prevention or as a tool for early diagnosis of the disease.

Brain cancer is a form of cancer that begins in the brain's cells. It is not as common as some other types of cancer, but it can be a serious and life-threatening disease. According to the National Cancer Institute, brain and other nervous system cancers make up about 2.5% of all cancers in the United States. The prevalence of brain cancer varies by age, with the highest incidence occurring in people over the age of 65 (Legler et al., 1999). The five-year overall survival rate for brain cancer is about 34%, although this can vary depending on the cancer's type and stage (Mukhtar et al., 2020). The mortality rate for brain cancer is the percentage of people with brain cancer who die from the disease.

It is important to note that the death rate for brain cancer can vary based on a variety of factors, including the type and stage of the tumor, the patient's age and overall condition, and treatment success (Legler et al., 1999). However, the survival rates can vary depending on the type and stage of the cancer. For example, the five-year survival rate for glioblastoma, a type of brain cancer, is typically less than 10% (Neganova et al., 2022). In contrast, the five-year survival rate for meningioma, another type of brain cancer, is typically more than 90% (Neganova et al., 2022). It is important to note that these survival rates are only estimates and cannot predict what will happen in any individual case (Neganova et al., 2022). Because of their unique physicochemical and biological properties, such as small sizes, large surface area, structural characteristics, ability to attach different molecules, ability to cross cell and/or tissue barriers, and long circulation time in the bloodstream, nanomaterials have a promising future in medicine. They have a wide range of biological uses, including medication delivery systems, contrast agents, and diagnostic instruments (Piktel et al., 2016). Early cancer detection is essential for better treatment since it minimizes the possibility of medication resistance (Jain, 2011). Nanoparticles have tremendous potential for molecular cancer cell targeting and drug administration, particularly in the CNS, where the BBB barrier is a major hindrance (Jain, 2008). Because of their tiny size, nanoparticles are utilized to treat CNS illnesses since they can penetrate the BBB and deliver medications to the target region (Jain, 2007). The distribution of medications in the brain is thus reliant on diffusion, which means that the concentration is highest at the administration site and decreases as one moves away from it. Yet, this technique has the advantage of allowing for site-specific administration, which reduces systemic toxicity (Jain, 2008). On the other hand, there are several reasons why brain cancers can be difficult to treat with chemotherapy. Initially, the blood-brain barrier (BBB) can make it difficult for chemotherapy medications to reach cancer cells in the brain. The BBB is a network of blood vessels that surrounds the brain and separates it from the rest of the body.

The cells that make up the BBB are tightly packed together, which makes it difficult for large molecules, such as chemotherapy drugs, to pass through (Jain, 2008). After that, brain tumors are often resistant to chemotherapy. This means that the cancer cells are able to survive and continue to grow despite treatment with chemotherapy drugs. Brain cancer is a highly challenging condition to treat, and there is a significant unmet clinical need in this field. However, the cancer population's heterogeneity in terms of site, type, and stage of disease, as well as the limited treatment options, variability in cancer treatment, and poor prognosis represents major difficulties in cancer patients (Giustozzi et al., 2022).

Despite advances in treatment, the survival rates for many types of brain cancer remain low. Finally, there is a need for better ways to diagnose and monitor brain cancer. Currently, brain cancer is often diagnosed using imaging tests, such as MRI and CT scans, and a biopsy may be needed to confirm the diagnosis (Butowski, 2015). However, these tests can be time-consuming and may not always provide a definitive diagnosis. Nanomaterials are also being explored as a way to deliver targeted therapies to cancer cells. Targeted therapies are designed to specifically target and attack cancer cells, leaving healthy cells unharmed. By attaching targeted therapies to nanomaterials, researchers hope to be able to more accurately deliver these therapies to cancer cells, which could improve their effectiveness and reduce side effects (Alja Zottel, Alja Videtic Paska).

Moreover, nanomaterials have the potential to revolutionize cancer therapy by improving the delivery of chemotherapy drugs, targeted therapies, and diagnostic tests. However, nanoparticles have the potential to revolutionize cancer treatment by improving the delivery and effectiveness of anti-cancer drugs (Martins et al., 2020). Conventional chemotherapeutic agents are often not specific to cancer cells and can have significant toxicities, but NPs can be designed to selectively target cancer cells and deliver drugs more effectively. The blood-brain barrier (BBB) and blood-tumor barrier (BTB) can be obstacles to delivering chemotherapy to

brain tumors, but NPs can be used as vehicles to help overcome these barriers (Mendiratta et al., 2019). NPs can also improve the delivery of hydrophobic drugs, which are not easily soluble in water, and can release drugs in a controlled and stimuli-responsive manner. NPs can be made using a variety of materials, including polymers, lipids, viruses, and organometallic compound nanotubes.

1.1 Aim and Objectives

- To provide the information on the use of nanomaterials in the treatment of brain cancer, including their properties, synthesis methods, and characterization techniques.
- To develop new nanomaterial-based solutions for crossing the blood-brain barrier and improving medication delivery to brain malignancies.
- To identify the challenges and future directions in the development of nanomaterial-based therapies for brain cancer.

1.2 Methodology

This paper has been written by using information from recently published articles, journals research papers. All necessary data and information were collected from authentic primary and secondary research articles indexed in PubMed, Google Scholar, ResearchGate and Scopus. The articles used to gather information for this review paper were published in journals like Chemosensors, Materials, Nature, and Frontiers. More than 50 articles have been studied to complete this review paper. For organizing the information of the selection topic in a systematic manner, an outline was formed with relevant heading headings and subheadings. The following keywords were used to search for relevant papers: “brain cancer” “nanomaterials” “recent,” “nanotechnology,” “diagnosis,” “treatment.”

Chapter 2

Nanomaterials in Biomedical Research

The ability to target complex molecular contents to tumor sites and cross the blood-brain barrier are just two of the many advantages that nanomaterials approaches have for brain cancer diagnosis and treatment (Saenz del Burgo et al., 2014). Nanomaterials can be made from a variety of materials, including metals, polymers, ceramics, and biological molecules. They can take many different forms, such as nanoparticles, nanotubes, nanofibers, and nanorods. The unique size-dependent properties of nanomaterials make them attractive for a huge range of uses, including medication administration and medical imaging, tissue engineering, biosensing, and cancer therapy (Romos et al., 2017). However, it is expected that bioactive nanomaterials will play a critical role in regenerative medicine, which seeks to repair or replace damaged or diseased tissues and organs. These materials have the potential to stimulate the body's own repair mechanisms and promote tissue regeneration, which could help to alleviate the strain on healthcare systems caused by an aging population and an increasing incidence of tissue injuries and pathologies (Uchegbu & Siew, 2013). The use of bioactive nanomaterials is expected to grow significantly in the coming years, with the market for these materials in the US alone predicted to increase from USD 70.03 billion to USD 130.17 billion by the end of 2021, representing a growth rate of 13.2%. Bioactive nanomaterials can be divided into two categories based on their origin: natural nanomaterials, which are derived from biological sources, and synthetic nanomaterials, which are artificially produced. Both types have unique properties and potential applications in the field of regenerative medicine (Mabrouk et al., 2021). The structures of several nanoparticles are shown schematically in Figure 1. Also, the Comparative distinctive features of various nanotherapy therapies for brain tumors are also mentioned in Table 1.

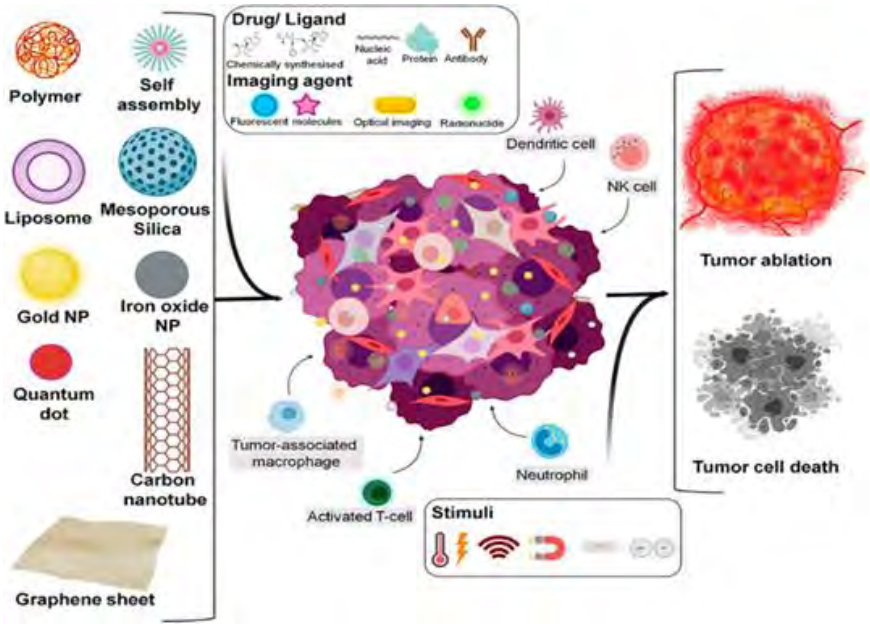

Figure 1: Brain cancer treated with novel nanoparticle therapy extracted from (Khan et al., 2021).

Table 1: Comparative characteristic features of different nanotherapy treatments of brain tumor.

Treatments of Brain tumor	Characteristics	Advantages	Disadvantages	Reference
Liposomes	A lipid bilayer membrane surrounds an aqueous compartment in liposomes, which are spherical structures. Phospholipids are amphiphilic molecules with a hydrophobic tail and	Liposomes have several important characteristics that make them a promising carrier for controlled and targeted drug delivery. Their ability to release drugs in response to various triggers, such as pH, temperature, and light, allows for more precise and effective delivery of therapeutic agents. In addition to their triggered release capabilities, liposomes also have several other	Poor solubility, a short half-life, high cost, and phospholipids that oxidize and undergo a hydrolysis-like process, leakage, and fusion of the	(Allen & Cullis, 2013) (S.-L. Huang et al., n.d.).

	a hydrophilic head that make up the lipid bilayer. This structure allows liposomes to mimic the structure of cell membranes, providing them suitable for a variety of biological applications, such as drug delivery and diagnostics.	properties that make them useful in different biomedical applications. Liposomes have been used in various therapeutic and diagnostic applications, Chemotherapeutic chemicals, therapeutic proteins, vaccines, radiopharmaceuticals, and nucleic acid-based drugs for gene therapy are all delivered in this manner. The versatility and specificity of liposomes make them a valuable tool in the field of medicine, and their use is expected to continue to grow in the future.	drug/molecules they encapsulate.	
Gold NPs	Gold nanoparticles (Au NPs) are particles with a size range of 1 to 100 nanometers and are composed of an ultrasmall gold core, usually surrounded by a stabilizing shell or coating. They have Unique optical properties, High surface area to volume ratio, Chemical stability, Biocompatibility, High thermal stability, Surface functionalization.	Gold nanoparticles (Au NPs) have several advantages likewise, Au NPs can be functionalized with targeting agents, such as antibodies or peptides that allow for targeted delivery of drugs to brain tumors. This improves the delivery's specificity and limits the exposure of healthy tissue to the therapeutic substance during MRI and computed tomography scans. This permits for improved visualization of the tumors, which can be beneficial for diagnosis and monitoring therapy efficacy.	There are also some challenges and limitations associated with their use. For example, Au NPs can cause toxicity in the brain, which can limit their use in therapy, the production of Au NPs is relatively expensive, and lack of standardization in the production and characterization of Au NPs.	(Meola et al., 2018).

Carbon Nanotubes	It obtains a special blend of stiffness, tenacity, and strength. As compared to other fiber materials, it has a high thermal and electrical conductivity (Kesharwani et al., 2015).	Greatest capacity for lipid bilayer penetration into the cytoplasm and nucleus, potentially utilized in drug delivery systems, biosensors, and biomedical equipment.Greater capacity for conjugation with different bioactive agents such as proteins, nucleic acids, peptides, therapeutic agents, acids.	Incredibly toxic to cultured cells like human kidney cells, T lympho-lympho- cytes, keratinocytes, alveolar endothelial cells and macrophages in vitro. Cellular oxidative stresses are reproduced by CNT.	(Kesharwani et al., 2015) (Kesharwani et al., 2012) (Monteiro-Riviere et al., 2005)
Dendrimers	Hyperbranched polymer having monodispersible changeable surface functionality, a well-defined size range, and various valency.	Effective medication delivery vehicle. Hydrophobic therapeutic agents have the potential to be entrapped in hydrophobic pockets, allowing hydrophobic medications to become water soluble. The best gene delivery platform is non-immunogenic and has the highest transfection efficiency.	Higher concentrations reduce cell suitability. Dendrimers' terminal-NH2 groups and numerous cationic charge are closely related with toxicity, limiting their appropriateness for medical applications, and proved different types of toxicity like immunogenicity, and in vivo toxicity etc.	(Dwivedi et al., 2016)

Zinc Oxide NPs	Zinc oxide nanoparticles have several unique characteristics like: have been shown to be biocompatible, meaning they are not toxic to living cells or organisms, making them suitable for use in biomedical applications such as drug delivery. Also, it has antimicrobial properties, can be functionalized with therapeutic drugs, designed to release drugs in a controlled manner (Mukhtar et al., 2020).	ZnO offers several advantages, including: Improved therapeutic efficacy by encapsulating therapeutic drugs within ZnO NPs, the drugs can be delivered directly to the target tumor site, leading to improved therapeutic efficacy and reduced side effects compared to systemic drug administration. ZnO NPs enhanced permeability and retention effect to penetrate the blood-brain barrier, which is a semi-permeable barrier that can limit the delivery of drugs to the brain. In addition, it can be functionalized with targeting moieties such as antibodies or peptides to help route the NPs to certain cells or tissues such as tumor cells for enhanced targeting and therapeutic effectiveness. Imaging-guided therapy by ZnO NPs which can be used as an MRI contrast agent, which can help to monitor the efficacy of drug delivery and the response of the tumor to treatment.	There are also several challenges and limitations that need to be addressed. For example, toxicity, ZnO NPs are foreign materials to the body and can be rapidly cleared from the circulation, which can limit their efficacy and duration of action as a drug delivery platform. Also, low drug loading and poor solubility.	(Mukhtar et al., 2020)

2.1 Nanomaterials in cancer treatment

The use of nanoscale materials for medication delivery to the brain has shown promise as a method of circumventing the blood-brain barrier, which can prevent pharmaceuticals from reaching the brain. Nanoparticles have the ability to traverse the BBB due to their small size, and they have the ability to carry medication molecules to their target location. With greater efficiency than larger particles. This can enable the administration of drugs at lower concentrations, reducing the risk of adverse effects and increasing the likelihood of therapeutic effectiveness. Some examples of nanomaterials that have been studied for drug delivery to the brain include gold nanoparticles, liposomes, dendrimers, carbon nanotubes, and micelles. The properties of NPs, such as their shape, size, surface area, drug loading capacity, and stability, can influence their effectiveness as drug delivery agents. It is essential to maintain these properties and reduce aggregation to achieve monodispersed NPs that can be efficiently internalized by cells. In addition, NPs can be functionalized or made from multiple materials in order to improve their physical qualities (Mukhtar et al., 2020).

2.2 Advantages of nanomaterial

Nanomaterials have shown promise as a means of improving the treatment of brain tumors, particularly glioblastoma, which is a type of aggressive brain cancer. Some potential advantages of using nanomaterials in the treatment of brain tumors include:

Nanoparticles have high surface-to-volume ratios in general, which contributes to their high loading capacity. Nanoparticles have been demonstrated to enhance medication solubility, extend blood circulation half-life, and regulate drug release when used as drug delivery systems (Farokhzad & Langer, 2009). Hydrophilic or hydrophobic medicinal compounds can be integrated into nanoparticles to increase systemic circulation half-life. Many nanoparticle delivery systems are built to respond to environmental cues like pH and temperature, allowing

for regulated therapeutic payload release. In other words, nanometer-sized particles collect specifically at the location of a brain tumor due to the improved permeability and retention (EPR) impact (Maeda et al., 2000). Surface functioning, which governs the interface between nanomaterials and biological systems, is a key component in influencing nanomaterial behavior and biomedical applications in vitro and in vivo. One can impact the half-life and localisation of nanoparticles during circulation by modifying their physicochemical characteristics (e.g., surface charge, hydrophobicity) (Cheng et al., 2014).

Chapter 3

Nanomaterials for Brain Cancer Diagnosis

Nanotechnology has potential for reliable imaging of cancerous brain areas in addition to improving medication delivery to treat diseases. Surface, chemistry, morphology, solubility, stability, and other physical properties of NPs made of biocompatible materials make them a good candidate for use as image contrast structures. In addition, NPs can improve the safety profile of drugs by reducing their toxicity and increasing their effectiveness. In the context of medical diagnosis, NPs have shown great potential for imaging and detecting malignant tissues. For example, the capacity of NPs to aggregate in tumor-associated cells and macrophages allows for sharp imaging of malignant tissues and differentiation from normal cells. Another way being researched to modify the medical identification of malignant tissues is the employment of specific coatings of peptides, bio-conjugates, and nucleotides to govern the tropism of the nanostructure for high-precision sensing of malignancies (Coates et al., 2011).

There are several techniques that are commonly used for the diagnosis of brain tumors and cancers, including optical imaging, photoacoustic imaging, computed tomography and fluorescence imaging. Magnetic resonance imaging is also frequently used to identify the tumor shape and the boundaries of malignant tissues during surgery, although it requires frequent administration of gadolinium chelates to maintain effective scanning. However, these techniques can be invasive and may not provide sufficient information about small or superficial tumors.

Nanotechnology has emerged in recent years as a technique for bioimaging and biosensing. Nanoarrays and nanochips, which combine optical and electrical features, are being developed as small-scale diagnostic and imaging tools for brain cancer and malignancies. These nanoparticles were chosen because of their biocompatibility and biodegradability. Overall, the

use of nanotechnology in conjunction with traditional diagnostic and imaging procedures, known as nanodiagnostics, has the potential to provide high precision and accuracy in cancer and tumor diagnosis without being invasive.

3.1 Nanodiagnostics

Nanodiagnostics is the application of nanotechnology in diagnostics, such as the detection of disease biomarkers or pathogen nucleic acids. This can be accomplished by combining nanodevices, such as nanochips or nanoarrays, with existing imaging methods for more precise diagnosis. The use of nanodiagnostics allows for the detection of biological molecules that may not be detectable using traditional methods. Currently, nanodiagnostic-based devices for detecting genetic diseases, SNPs, and pathogen nucleic acids are being developed. (Jain, 2003).

Nanoparticles are an important component of nanodiagnostics, as they can be engineered to specifically target and detect certain biological molecules or structures. For example, gold nanoparticles can be used to detect DNA fragments on the sensor's surface via a process known as application, which happens only in the presence of complementary DNA (K. K. Jain, 2008). This allows for more sensitive detection than traditional enzyme-linked immunosorbent assays (ELISAs). Inorganic fluorophores known as quantum dots are also promising for diagnosis and have been employed in sentinel lymph node biopsy to detect cancer cells in a single lymph node.

After that, Iron nanoparticles have several potential applications in nanodiagnostics for cancer detection. They have the ability to localize within neoplasms, which can result in images with sharp margins when used as a contrasting agent in MRI. Unlike gadolinium-based treatments, which can disperse fast owing to tumor vascular leakage and produce fuzzy pictures, iron nanoparticles have no substantial effect on cell viability. Proliferation, differentiation, or function when attached to cells. This makes them a promising tool for detecting cancer earlier

than is possible with conventional techniques, and for the detection of metastatic and latent tumors (Kewal K. Jain, 2012).

Although nanodiagnostics has the potential to revolutionize molecular diagnostics, it is still a long way from being a common component of clinical practice. This is due to the complexity of translating research findings into healthcare services, which necessitates thorough performance assessment, validation, and testing to guarantee that the findings are accurate and can be used in the clinic without producing false positives. Moreover, there is currently a dearth of understanding regarding the interactions of nanoscale materials with biological systems, which might make the application of nanotechnology for diagnostics more difficult. However, once these challenges are addressed, nanodiagnostics has the potential to improve sensitivity and specificity, reduce the need for large sample sizes and large amounts of reagents, and provide a non-invasive method for diagnosis and disease monitoring, particularly at the single-cell level. Single-cell analysis, also known as "single-cell genomics," allows for analysis at a cellular level without the need for amplification or cloning, which can lead to quicker outcomes. This could enable the detection of diseases in their early stages, when they are still manageable, and ultimately lead to increased patient survival (Alja Zottel, Alja Videtic Paska, 2019).

3.2 Metallic Nanoparticles

Gold nanoparticles (AuNPs) have been used in the past for diagnostic and therapeutic applications in the treatment of rheumatological disorders and infections, cancer cells. One of the key advantages of AuNPs is their optical properties, particularly plasmon resonance, which can be used to image biological disorders. In addition, AuNPs are biocompatible and easily detectable using imaging techniques such as computed tomography (CT), focused ultrasound (FUS), and magnetic resonance imaging (MRI). MRI can be particularly useful for detecting

and monitoring cancerous and tumorous tissues using AuNPs due to their tunability and biocompatibility (Bagheri et al., 2018).

Gold nanoparticles (AuNPs) have been explored for use in imaging brain tumors, particularly gliomas. They can be synthesized and characterized using a variety of ligands, like chlorotoxin peptides, to improve their imaging properties and cytocompatibility. One study demonstrated the use of AuNPs labeled with radionuclide 131I for CT imaging and simultaneous radionuclide therapy in a rat glioma model (Zhao et al., 2019). Additionally, it has been demonstrated that AuNPs have favorable biocompatibility profiles for in vivo imaging of brain tumors. Furthermore, they can be functionalized with a variety of BBB-crossing enhancers, including transferrin, fibroblast growth factors, and antibodies to enhance their capacity to target and view subcellular brain cancer or tumors using methods like multiphoton microscopy and scanning electron microscopy (Meola et al., 2018). In one study, AuNPs were coated with the short peptide CBP4 to target CD133 on tumor cells, and the peptide-coated AuNPs displayed biocompatibility and stimulus-responsive fluorescence when localized in the cytosol (Cho et al., 2017). Silica-based iron oxide nanocomposites are a sensitive imaging tool that can be used for accurate delineation of glioblastomas (GBMs). In both in vitro and in vivo fluorescent imaging, they can detect tumor-associated macrophages. Their nanoparticles' ability to dissolve in water and serve as multimodal contrast agents is a plus (Lee et al., 2018). A near-infrared nanoprobe incorporating organoplatinum (II) metallocycles and the FDA-approved polymer Pluronic F127 has also been developed as a cancer theragnostic for gliomas. This nanoprobe is photostable and can be used for real-time monitoring of cancer therapeutics, and has been shown to be efficiently internalized in cancer cells while not being internalized in non-cancerous cells (Ding et al., 2019).

3.3 Quantum Dots

Quantum dots are nanoscale materials that have unique electrical and optical properties due to their size, which makes them useful for a variety of applications. Due to their adjustable qualities and adaptability to be employed with fluorescent characteristics, such as significant Stokes shifts and narrow emission bands for high-resolution images, they offer an appealing platform for imaging malignancies and tumors. Moreover, they can be utilized during surgery as dual-modality pictures to map brain abnormalities (McHugh et al., 2018). The figure demonstrates the key features of QDs for improved imaging as well as the method of contact with cell membrane surface receptors.

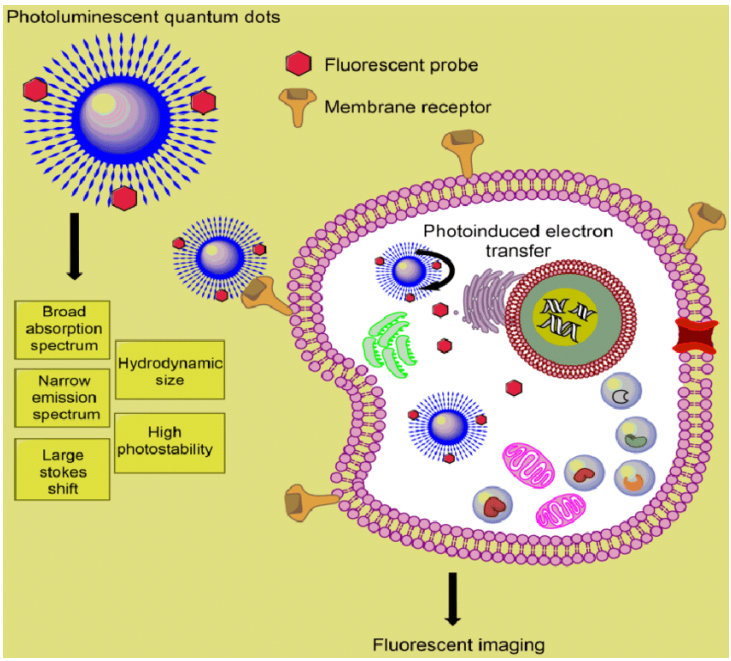

Figure 2: Quantum dots interaction with membrane receptors and the mechanism of fluorescence production within the cell for imaging extracted from (Mabrouk et al., 2021).

QDs have many potential applications in biomedicine, including use as fluorescent probes, drug delivery vehicles, and imaging agents. Their unique optical properties make them particularly useful for imaging and diagnosis, as they can emit bright fluorescence over a wide

range of wavelengths (Mabrouk et al., 2021). The effectiveness of PEG-coated QDs based on CdSe/ZnS as new glioma imaging nanoprobes was reviewed. Asparagines-glycine-arginine peptides (NGR), which are included in these QDs, target the CD13 glycoprotein on tumor cells. The effective targeting of CD13 on glioma tissues by these NGR-PEG-QDs resulted in fluorescence during an in vivo examination, which may facilitate the surgical removal of gliomas (Huang et al., 2017). The nanobubbles can be activated by ultrasound and accumulate in brain tumor tissues, and can be imaged using both optical and ultrasound imaging techniques (Mukhtar et al., 2020).

In another study, a QD-labeled aptamer was designed for use in fluorescence-guided surgery for tumor resection. In mice with the epidermal growth factor receptor variation III (EGFRvIII), the QD-Apt nanoprobes were able to attach precisely to the tumor's surface, were non-toxic, and could image tumor tissues by crossing the blood-brain barrier. This technology has potential as a diagnostic tool for glioma and other types of cancer (Tang et al., 2017). Another type of inorganic compound called MXenes, which are two-dimensional materials, have also been studied in combination with QDs for use in photothermal therapy and imaging of glioma cells. The use of QDs for image-guided therapy in the near-infrared bio windows is a promising approach for the diagnosis and treatment of glioma and other types of cancerQDs are excellent for usage in vivo for the imaging of glioma and other disorders because they are biodegradable, programmable, and biocompatible (Shao et al., 2020).

3.4 Polymeric nano vehicles

Polymeric nanoparticles (NPs) have been developed for the treatment of central nervous system tumors, and have been changed with different components to enable them to interact with BBB and tumor cells. Different subtypes of polymeric NPs can be selected based on their pharmacokinetics, modifiability, and payload delivery, and Polymers can also be modified to

produce various nanoparticles that could be used in medicine, such as optical nanofibers for use in phototherapy, drug delivery, and sensing. In order to improve the delivery of innovative noninvasive therapies to brain tumors, several researchers have loaded polymeric nanoparticles (NPs) into neutrophils or monocytes. Preclinical studies have shown indications that polymeric NPs may be useful in the treatment of CNS malignancies despite the fact that there are still many obstacles to overcome (Caraway et al., 2022). Another study showed that Semiconducting polymers have been developed for the accurate diagnosis of brain tumors using a fluorination strategy to produce fluorescence. These polymers, known as polymer dots, have been proven to create pictures that are three times better than non-fluorinated equivalents (Mukhtar et al., 2020).

3.5 Biomimetic Nanocomposites

New functional materials are being created in advanced biomedical engineering by simply imitating the properties of natural materials on a chemical, physical, or biological level such as biomimetic nanocomposites (Kumar et al., 2022). In order to actively target tumors, biomimetic nanocomposites were also coated with cRGD, an endothelial integrin receptor-targeting peptide. The biomimetic contrast NPs that were cRGD-labeled localized in the tumor tissue and offered real-time guided resection. By the use of cells produced from tumor cells as the coat, BBB penetration was made possible for improved targeting using multimodal imaging (Duan et al., 2020). To improve in tumor cell imaging and phototherapy, the membrane of a brain metastatic tumor cell was coated on the nanocarriers and embellished with indocyanine green. The biomimetic NPs showed excellent BBB permeability and were discovered to be non-toxic (C. Wang et al., 2020). To overcome this barrier, NPs have been modified with various moieties that allow them to interact with the BBB and cancer cells (Mukhtar et al., 2020).

Chapter 4

Blood Brain Barrier – A Major Obstacle for Anticancer Drug Delivery to Brain

There are various "barriers" that must be overcome in order to get anti-cancer medications to the brain. Both the blood brain barrier and the blood cerebro-spinal fluid barrier (BCSFB) surround the brain. Because of their physical or molecular properties, approximately 95% of medication substances are unable to cross the BBB. Therefore, the blood-brain barrier is a membrane that protects the brain from the bloodstream. It is composed of a web of blood vessels that are bordered by densely populated cells known as endothelial cells, which provide a physical barrier that stops many things from entering from the blood into the brain. The chemical environment of the brain is maintained by doing this, and it also serves to shield the brain from potentially dangerous compounds that may be present in the blood (Lesniak & Brem, 2004). However, it also poses a problem for drug delivery because getting therapeutic molecules into the brain can be challenging. Amphiphilic compounds with both hydrophilic (loving water) and hydrophobic (hating water) sections can traverse the BBB via carrier-mediated transport, in which specialized carrier proteins transport the molecules over the barrier (Deeksha et al., n.d.). Polar and large molecules, such as proteins, peptides, lipoproteins, and antibodies, may be capable of crossing the BBB through receptor-mediated transcytosis, in which the molecules attach to specific receptors on the endothelial cell surface and are carried across the barrier. Non-specific adsorptive mediated transcytosis is another way for chemicals to cross the BBB, although it is less selective and less efficient than receptor-mediated transcytosis (Cecchelli et al., 2007).

4.1 Mechanism of Nanomaterials Transport across the Blood Brain Barrier

Cerebral endothelial cells are unique in that they form complex tight junctions (TJs) by the interaction of multiple transmembrane proteins, essentially closing the paracellular pathway. These complicated molecular junctions make the brain essentially inaccessible to polar molecules unless they are transported via BBB transport channels that govern the brain's microenvironment. Adherens junctions (AJ) are another type of junction that helps to stabilize cell-cell connections in the junctional zone. Furthermore, the presence of internal and extracellular enzymes such as monoamine oxidase (MAO), - glutamyl transpeptidase (-GT), alkaline phosphatase, peptidases, nucleotidases, and many cytochrome P450 enzymes provides metabolic activity to this dynamic interface. Large molecules, including as antibodies, lipoproteins, proteins, and peptides, can also be transported to the central compartment by receptor-mediated or non-specific adsorptive transcytosis. Transcytosis is mediated by insulin, low-density lipoprotein (LDL), iron transferrin (Tf), and leptin receptors. P-gp stands for P-glycoprotein, and MRP stands for multidrug resistance-associated protein family (Cecchelli et al., 2007). Here, in Figure 3 represents schematically the mechanisms available for nanomaterial transport across the BBB.

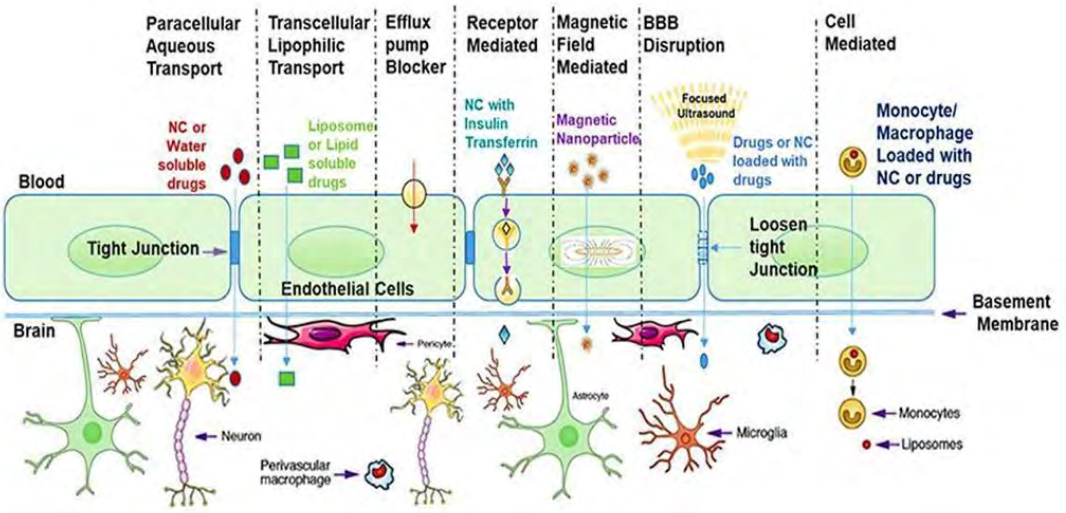

Figure 3: Schematic representation of mechanisms available for nanomaterial transport across the BBB (Bagchi et al., 2019)

Chapter 5

Nanomaterials use for Treatment of Brain Cancer

Nanotechnology involves the direct delivery of medications to cancer cells using extremely small, nanoscale particles. Due to their small size, nanoparticles can more efficiently penetrate the BBB and reach cancer cells in the brain. Additionally, they can be made to specifically target cancer cells, minimizing their negative impact on healthy cells. For the treatment of brain cancer, a variety of nanoparticles have been created, including liposomes, polymeric nanoparticles, and inorganic nanoparticles like gold and quantum dots. These nanoparticles can be utilized to deliver chemotherapeutic medications or other therapeutic substances directly to cancer cells. Although the use of nanoparticles in brain cancer therapy is still in its early phases, preclinical research and early clinical trials have yielded some encouraging outcomes. Nanotechnology, it is believed, will eventually lead to more effective and less hazardous therapies for brain cancer (Rajabi, 2020).

5.1 Liposomes

Liposomes are spherical particles with water compartments and biodegradable natural or synthetic phospholipid bilayers. These nanospheres form spontaneously due to the amphiphilic nature of phospholipids (Malam et al., 2009). Based on their synthesis procedures and post-formation processing, they are classified as lipid vesicles. ULVs have a large aqueous core and are best suited for encapsulating hydrophilic drugs, whereas MLVs preferentially encapsulate lipid-soluble medications. Unilamellar liposomes, which have two to three lamellar bilayers and a hydrodynamic diameter of 250 nm, release at a much faster pace than MLVs while having a higher entrapped volume (Torchilin, 2005). Tumors can be actively or passively targeted by liposomes. It is useful to target micrometastases, vasculature, and blood cancers even if active tumor targeting isn't always more successful than passive tumor targeting (Bozzuto & Molinari,

2015). Liposome engineering with polyethylene glycol coating can lower toxicity while boosting biocompatibility, water solubility, targeted drug administration, controlled release, and half-life. To boost blood circulation length and brain-oriented medication delivery, the liposome surface may also be functionalized by including a wide range of macromolecules such as antibodies, peptides, aptamers, polymers, or polysaccharides (Allen & Cullis, 2013). In figure 4 schematically represents the main liposomal medications and targeted substances that enhance liposome affinity and selectivity for delivery to the brain.

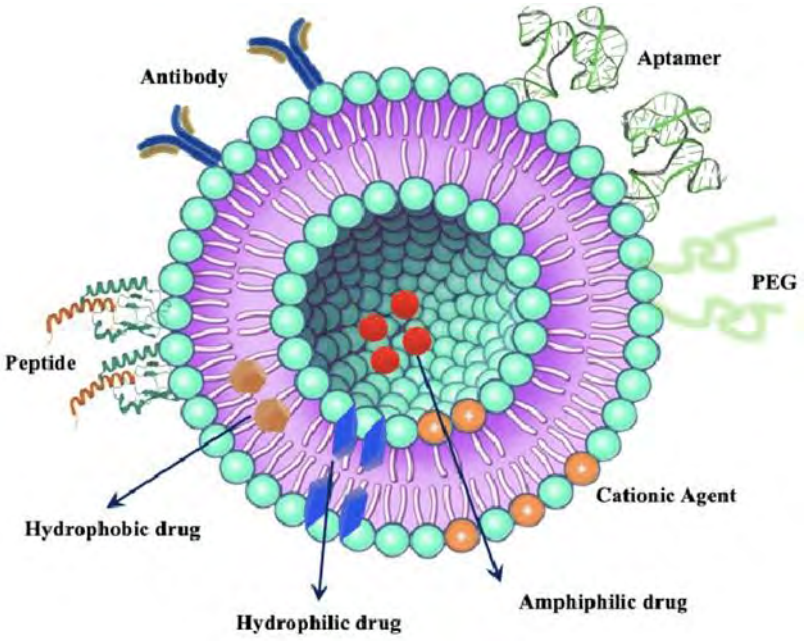

Figure 4: The main liposomal drugs and targeting agents that improve liposome affinity and selectivity for brain delivery extracted from (Mukhtar et al., 2020)

Due to its substantial potential to enhance vitamin E's therapeutic effects, polyethylene glycolated (PEGylated) vitamin E (also known as D-tocopherol polyethylene glycol 1000 succinate or TPGS) is often used in the food and pharmaceutical sectors. The effectiveness of the created nano-liposomal systems was compared to that of plain and covert liposomes (PEG-coated liposomes). Using C6 glioma cells, the liposomes were produced using a solvent injection approach, described, and their cellular uptake and cytotoxicity were examined. TPGS-

coated liposomes had particle sizes ranging from 126 to 191 nm. The IC50 values for naked, commercial Taxotere-, PEG-, and TPGS-coated liposomes after 24 hours of incubation with C6 glioma cells were 31.04, 37.04, 7.70, and 5.93 g/mL, respectively. PEG liposomes were surpassed in vitro by TPGS-capped nanoliposomes (Muthu et al., 2011).

5.2 Gold and Silver Nanoparticles

There are many different forms and special characteristics of gold-based nanoconjugates made on Au cores that can be utilized to treat brain cancers. In addition to their optimum size, Au NPs may be nanoengineered for time- and dose-optimized drug release. They can also be coupled with appropriate cell-targeting ligands (Norouzi, 2020) (Chan et al., 2018). There are several applications of smart Au-based hybrid NPs in neuro-oncology research in the recently published literature. Thus, an anti-transferrin receptor (Cabezón et al., 2015) and glucose (Gromnicova et al., 2016) were used to transport Au NPs to the mouse brain. It has also been demonstrated that epidermal growth factor (Feng et al., 2017) and chlorotoxin peptide-functionalized (Zhao et al., 2019) Au NPs are suitable for enhanced tumor retention in the mouse brain. For glioma accumulation and treatment, intranasally administered immunotherapeutic oligonucleotide-functionalized Au NPs and anti-EphA3 antibody-functionalized (L. Wang et al., 2021) Au NPs have been used successfully. Additionally, Au NPs have been used for in vivo targeted miRNA-mediated gene therapy of glioma cells (Kouri et al., 2015). Using hybrid polyethyleneimine-entrapped Au NPs functionalized with RGD peptide, glioblastoma cells (Kong et al., 2017) were made lethal via siRNA-mediated gene therapy. To efficiently penetrate glioma spheroids, macrophages were placed in hybrid nanoshells with a silica dielectric core covered with Gold. In addition, the Au coating absorbed near infrared light and converted it to heat for photothermal ablation of the cancer cells. In conclusion, it is abundantly obvious that Au-based NPs, especially those designed for optimal

biostability, targeting, and delivery, offer a wide range of therapeutic and imaging alternatives in neuro-oncology research (Ahmad et al., 2022).

Because of their unique physical, chemical, and biological features, as well as their potent anti-cancer and antibacterial effects, silver nanoparticles (AgNPs) have been the focus of much investigation (Giesen et al., 2020). AgNP disintegration, which results in the release of silver particles/ions in cells and the large-scale creation of reactive oxygen species, is primarily responsible for the anti-cancer and antibacterial properties of it. This production of ROS has the potential to harm biological substances including DNA, proteins, and lipids, which might ultimately lead to cell death (Dayem et al., 2017). Studies have shown that AgNPs have toxic effects against cancer cells, such as C6 rat glioma cells. A 24-hour treatment with AgNPs has been found to reduce the viability of the cancer cells by 21%. AgNPs have also been used as a component of multifunctional nanoplatforms in combination with drugs and targeting peptides to enhance their efficacy in treating brain tumors. The therapeutic efficacy of these nanoparticle-based systems has been shown to significantly reduce tumors both in vivo and in vitro (Locatelli et al., 2014). However, it's important to note that the toxicity and efficacy of AgNPs depend on many factors such as shape, concentration, size, route of ingestion, and biological target and need more research to be fully understood (Mukhtar et al., 2020)

5.3 Carbon nanotubes and carbon dots

Carbon nanotubes have potential as a theranostic agent for cancer, including brain tumors. CNTs are a form of carbon with unique electronic and mechanical properties and they can be used to improve the chemotherapy of cancer. The intrinsic near-infrared light absorption property of CNTs can be used to destroy cancer cells in vitro and their NIR photoluminescence property can be used for in vitro cell imaging and probing. Studies have shown that CNTs have a significant potential for therapeutic usage and can improve brain tumor treatment (Mahajan

et al., 2018). Another study showed Treatment for brain glioma using oxidized MWCNTs (O-MWNTs) based on PEG coupled with angiopep-2. For a cytotoxicity investigation, the effectiveness of doxorubicin (DOX) loaded O-MWNTs in treating gliomas was assessed. However, It is also reported that the slower biodegradation rate of CNTs, which might result in toxicity during in-vivo nanotheranostic applications, limits their clinical value. The use of CNTs is still under research and it need more extensive studies to prove their safety and the long-term benefit before they could be used in clinical practice (Ren et al., 2018).

Carbon dots (CDs) are a type of nanomaterial that have been investigated for their potential use as drug delivery systems, particularly in the treatment of brain tumors. CDs are small, fluorescent particles made of carbon, and they have several properties that make them attractive for use in drug delivery. One of the main advantages of CDs is that they are biocompatible, which means they do not cause harm to the body's cells and tissues. They also have good stability and are able to withstand harsh environments, such as high temperatures and pressures. Additionally, CDs can be functionalized with various molecules, such as proteins and polymers, which can be used to target specific cells or tissues. In the context of brain tumors, CDs have been studied for their ability to target and accumulate in tumor tissues. Research has shown that CDs can cross the blood-brain barrier, which is a protective barrier that surrounds the brain and prevents the passage of certain substances from the bloodstream into the brain. Once in the tumor tissue, the CDs can release their payload of drugs, leading to a more targeted and effective treatment. It is also being studied that CDs can be used as a contrast agent in imaging of tumors and could be used to monitor the progression of the disease as well as the effectiveness of the treatment (Calabrese et al., 2021).

Another study showed the state of CDs' tumor theranostics research at this time with the intention of providing critical viewpoints to motivate future research on CDs for biomedical applications. Several reviews have already been published that focus on various areas of CDs,

including preparation, optical property, sensing, and imaging capabilities. Another study discusses the most recent developments in CD production, hydrophilicity, biotoxicity, and optical properties as well as their evolution from multifunctional tumor theranostic systems to bioimaging probes at their core. Also presented are the remaining challenges and probable consequences of CD-based theranostics (Wu et al., 2021). In figure 5 schematically illustrated the properties and recent trends in applications of carbon dots (CDs) in biomedicine.

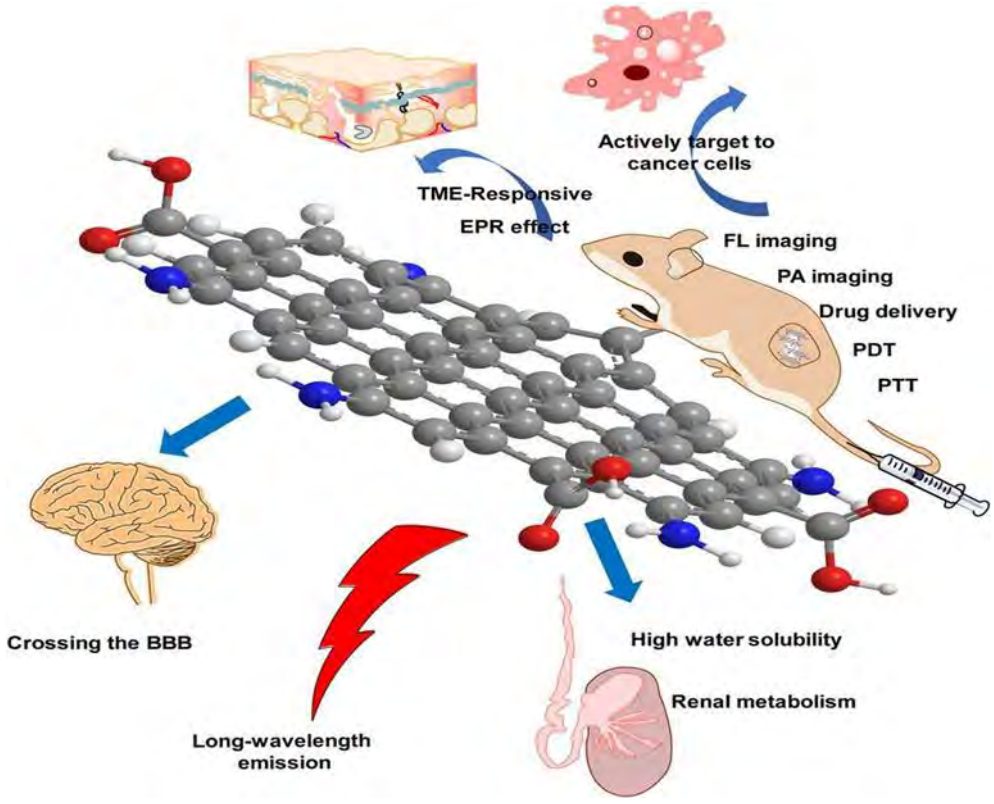

Figure 5: Schematic illustration of the properties and recent trends in applications of carbon dots (CDs) in biomedicine extracted from (Wu et al., 2021).

Ruan et al. suggests that the C-dots (or C-dot/Gly) produced using a thermal treatment on glycine have potential as a targeted imaging agent for glioma, a type of brain tumor. The in vitro experiments with C6 glioma cells showed that these C-dots were not highly toxic and that their uptake into the cells increased with both time and concentration. The in vivo studies further supported these findings, as the C-dots were found to accumulate specifically in the

glioma tissue and had a stronger fluorescence intensity than normal brain tissue. These findings are exciting because targeted imaging agents are an important tool for early detection and monitoring of cancer, and there is a need for better imaging agents that can specifically target brain tumors. The fact that these C-dots are biocompatible, non-toxic and have a strong fluorescence suggests that these C-dots may be a promising candidate for targeted imaging in glioma. However, further research is needed to confirm their safety and effectiveness in vivo and to better understand their mechanism of action (Ruan et al., 2014).

5.4 Dendrimers

Dendrimers may entrap bioactive molecules and have a lot of hydrophobic pockets, allowing for regulated and prolonged medication release. (Kesharwani et al., 2014). Dendrimers are a type of highly branched, nanoscale polymer with a well-defined, monodisperse structure (Kesharwani et al., 2015). They are synthesized through a stepwise process that involves the growth of repetitive branches emanating from a central core. As the number of generations of a dendrimer increases, its shape tends to become more spherical, and its drug loading affinity also increases proportionally (Dwivedi et al., 2016).

When delivering medications or genes to cancerous cells or tissues, nanocarrier systems can focus their delivery either passively or actively (Iyer et al., 2014). Drug or drug carrier system accumulation from passive targeting occurs at a particular location, where it manifests its physicochemical, pathophysiological, and pharmacological effects (Iyer et al., 2006). Active targeting, on the other hand, involves particular modifications to the carrier system that result in the attachment of active ligands that bind to a certain cell type, tissue, or organ with high affinity in the body. The improvement of drug molecule features such as solubility, plasma circulation time, and polymeric carrier system facilitates passive targeting of drug matrix at the site of solid tumor shown in Figure 6 (Islam & Josephson, 2009), (Teow & Valiyaveettil, 2010).

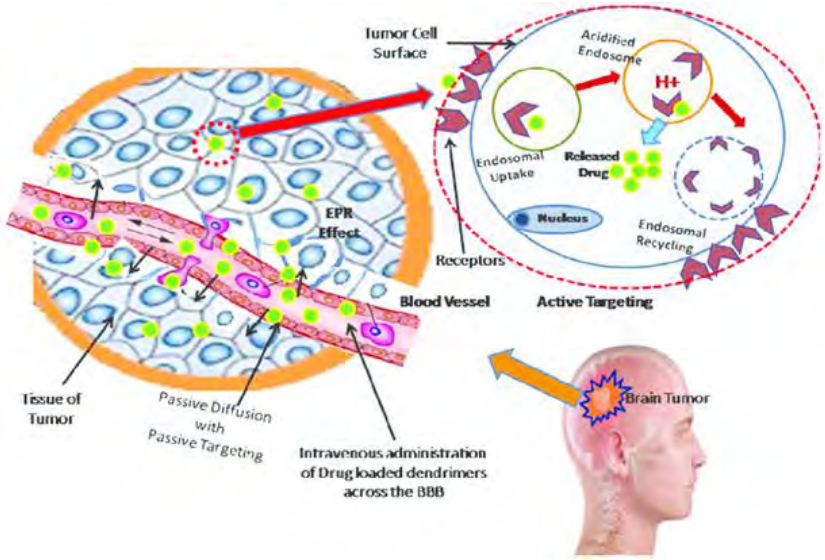

Figure 6: Mechanism involved in active and passive targeting mediated by dendrimers extracted from (Dwivedi et al., 2016).

Increased tumor vascular permeability and restricted medication lymphatic leakage can both result in dendrimers and other polymeric carriers, which improves therapy effectiveness (Matsumura & Maeda, 1986). AdditionallyWhen medications are enclosed in dendrimers, CNTs, polymeric nanoparticles, or polymeric micelles, for example, the concentration selectivity in solid tumors might result in passive targeting or EPR effects. It has been discovered that a polymer's molecular weight, such as N-(2 hydroxypropyl) methacrylamide (HPMA), is a crucial factor in passive targeting via the EPR effect (Omayra L. Padilla De Jesús et al., 2002). In addition, the size of dendrimers also plays a critical role in passive tumor targeting, with dendrimers ranging from 10 to 20 nm being suitable candidates for this purpose (She et al., 2013). Dendrimer-conjugated heavy plasma proteins and other biomolecules prolong therapeutic medication half-lives and enable prolonged, precise drug delivery to tumor locations. Cisplatin-loaded 3.5G PAMAM dendrimer, as an illustration, demonstrated a 50 times greater accumulation of the drug at the tumor location as a result of passive targeting via the EPR effect (DUNCAN & IZZO, 2005).

5.5 ZnO Nanoparticles

Zinc oxide nanoparticles (ZnO-NPs) are a type of inorganic nanomaterial that has a wide range of potential applications due to its unique properties (Jin et al., 2000). Several techniques, such as hydrothermal synthesis, ultrasonication, and thermal evaporation, have been developed for the creation of various forms of zinc oxide nanostructures, including nanowires, nanotubes, nanorods, nanobridges, nanobelts, nanoribbons, and nano-nails (Lao et al., 2003). Zinc oxide nanoparticles have been found to reach the brain following oral ingestion, either through neural transportation or by crossing the blood-brain barrierAccording to studies, ZnO-NPs can have harmful effects on the brain and blood when they interact with the plasma and brain (Shim et al., 2014). Research has also suggested that ZnO-NPs can cause energy depletion and oxidative stress in microglia cells, leading to cell death (Sharma et al., 2017). ZnO-NPs have also been found to have toxic effects on brain cancer cells in mice, when compared to other nanoparticles such as Al2O3, TiO2, CrO3, and Fe3O4 (Jeng & Swanson, 2006).

Chapter 6

Challenges of Using Nanomaterials

Nanoparticles synthesis is an expensive and difficult procedure that necessitates certain components, tools, and appropriate circumstances, particularly for multifunctional NPs. (Cheng et al., 2021). Many laboratory and clinical investigations have demonstrated that NPs are an important tool in clinical practice and diagnosis. NPs have the advantage of being specialized to a particular work, illness, or organ, overcoming the drawbacks of conventional drugs. This technique makes it possible to combine macromolecules, medications, and imaging agents to create functional NPs that help in medication delivery and diagnostics. Another advantage that NPs contribute to nanotherapy is their enormous surface area, which allows for increased drug payload delivery to action sites. Furthermore, NPs can precisely target certain cells and transfer their load accordingly. Despite these multiple benefits, additional research is needed to optimize the large-scale manufacture of these dosage forms and their pharmacokinetic properties. To yet, sufficient evidence has accumulated demonstrating the presence of a variety of downsides of NPs when employed to treat brain illnesses. (Hanif et al., 2021), (Neganova et al., 2022). The use of nanomaterials for brain treatments can have rapid and toxic effects. Another study shows that the first generation of nanomedicines, liposomal formulations, have been utilized thus far without harm. Other nanomedicines, such as phospholipids or biodegradable polymers, may add harmful effects, though researchers are not yet aware of them (Jain, 2008). The source of the nanomaterial will probably play a significant role in determining any potential harmful effects. Although there is currently no proof that carbon nanotubes are toxic to humans, it is expected that they can cause inflammation similar to that caused by asbestos, while tissue-specific toxicity may occur from the heavy metal

content of nanomaterials and their ability to infiltrate and perhaps accumulate in important organs (Alja Zottel, Alja Videtic Paska, 2019).

As a result, future experimental investigations should try to reduce the cost-benefit ratio when applying nanotechnology in clinical settings, as they will be used in patient medical treatment. The route of administration of NPs has a substantial impact on medication bioavailability in the brain and demands special consideration. (Ling et al., 2021). Another potential concern is intellectual property. Because nanomedicines are complicated structures made up of multiple components, it is necessary to clarify who owns the intellectual property rights (Hua et al., 2018).

Chapter 7

Conclusion and Future Directions

In the last few decades, there has been a major breakthrough in nanotechnology. It is thought to have a significant capacity for the creation of current and creative clinical oncology methods. New cancer treatment ideas are desperately needed because the 5-year survival rate for cancer patients is still so low. The use of nanotechnology in diagnostic, therapy, and treatment offers enormous potential from the perspective of customized medicine. It presents unique alternatives for controlling therapy of impenetrable tumors and for targeting and eliminating remaining tumor mass and/or cells that are the principal culprits in cancer recurrence. Additionally, it allows for the customization of individualized therapy plans for each patient (Alja Zottel, Alja Videtic Paska, 2019). Prior to considering clinical implications, the most recent developments and safety issues must be addressed. This review discusses the latest developments in a variety of nanomaterials for effective drug administration in the treatment of brain cancer, including liposomes, nano-micelles, dendrimers, carbon nanotubes, carbon dots, and NPs (gold, silver, and zinc oxide NPs). The use of nanostructured materials for medication delivery to the brain is a promising strategy since they are small enough to easily penetrate the BBB and can deliver drug molecules to the desired location. The fact that therapeutic chemicals or medications can reach the brain at far lower concentrations than the normal doses of the free drugs is significant since it enables safe drug delivery to achieve therapeutic effectiveness (Mukhtar et al., 2020).

To minimize damaging effects on healthy tissues, it is difficult to define molecular targets correctly and to guarantee that these molecules are expressed exclusively in the targeted organs. Second, it is crucial to comprehend what happens to drugs after they enter sensitive cell compartments like the nucleus. Furthermore, because nanosystems improve drug delivery

efficiency, doses may need to be recalculated. Finally, because of the push to accelerate development, novel technologies such as synthesis and screening automation are required to accelerate the discovery process.

References

Schiavi, S., Ocampo-Pineda, M., Barakovic, M., Petit, L., Descoteaux, M., Thiran, J. P., & Daducci, A. (2020). A new method for accurate in vivo mapping of human brain connections using microstructural and anatomical information. Science Advances, 6(31). https://doi.org/10.1126/sciadv.aba8245

Wang, X., Yu, Y., Zang, L., Zhang, P., Ma, J., & Chen, D. (2020). Targeting Clusterin Induces Apoptosis, Reduces Growth Ability and Invasion and Mediates Sensitivity to Chemotherapy in Human Osteosarcoma Cells. Current Pharmaceutical Biotechnology, 21(2), 131–139. https://doi.org/10.2174/1389201020666190821151112

Jena, L., McErlean, E., & McCarthy, H. (2019). Delivery across the blood-brain barrier: nanomedicine for glioblastoma multiforme. Drug Delivery and Translational Research, 10(2), 304–318. https://doi.org/10.1007/s13346-019-00679-2

Zhou, Y., Peng, Z., Seven, E. S., & Leblanc, R. M. (2018). Crossing the blood-brain barrier with nanoparticles. Journal of Controlled Release, 270, 290–303. https://doi.org/10.1016/j.jconrel.2017.12.015

Mendiratta, S., Hussein, M., Nasser, H. A., & Ali, A. A. A. (2019). Multidisciplinary Role of Mesoporous Silica Nanoparticles in Brain Regeneration and Cancers: From Crossing the Blood–Brain Barrier to Treatment. Particle &Amp; Particle Systems Characterization, 36(9), 1900195. https://doi.org/10.1002/ppsc.201900195

Neves, A. R., Queiroz, J. F., Lima, S. A. C., & Reis, S. (2017). Apo E-Functionalization of Solid Lipid Nanoparticles Enhances Brain Drug Delivery: Uptake Mechanism and Transport Pathways. Bioconjugate Chemistry, 28(4), 995–1004. https://doi.org/10.1021/acs.bioconjchem.6b00705

Ramos, A. P., Cruz, M. A. E., Tovani, C. B., & Ciancaglini, P. (2017). Biomedical applications of nanotechnology. Biophysical Reviews, 9(2), 79–89. https://doi.org/10.1007/s12551-016-0246-2

Mabrouk, M., Das, D. B., Salem, Z. A., & Beherei, H. H. (2021). Nanomaterials for Biomedical Applications: Production, Characterisations, Recent Trends and Difficulties. Molecules, 26(4), 1077. https://doi.org/10.3390/molecules26041077

Quader, S., & Kataoka, K. (2017). Nanomaterial-Enabled Cancer Therapy. Molecular Therapy, 25(7), 1501–1513. https://doi.org/10.1016/j.ymthe.2017.04.026

Jain, K. (2007). Nanobiotechnology-Based Drug Delivery to the Central Nervous System. Neurodegenerative Diseases, 4(4), 287–291. https://doi.org/10.1159/000101884

Teleanu, D., Chircov, C., Grumezescu, A., Volceanov, A., & Teleanu, R. (2018). Impact of Nanoparticles on Brain Health: An Up to Date Overview. Journal of Clinical Medicine, 7(12), 490. https://doi.org/10.3390/jcm7120490

Yasui, T., Kaji, N., & Baba, Y. (2013). Nanobiodevices for Biomolecule Analysis and Imaging. Annual Review of Analytical Chemistry,6(1),83–96. https://doi.org/10.1146/annurev-anchem-062012-092619

Pillay, V., Frank, D., Tyagi, C., Tomar, L. K., Choonara, Y. E., du Toit, L. C., Kumar, P., & Penny, C. (2014). Overview of the role of nanotechnological innovations in the detection and treatment of solid tumors. International Journal of Nanomedicine, 589. https://doi.org/10.2147/ijn.s50941

Gatoo, M. A., Naseem, S., Arfat, M. Y., Mahmood Dar, A., Qasim, K., & Zubair, S. (2014). Physicochemical Properties of Nanomaterials: Implication in Associated Toxic Manifestations. BioMed Research International, 2014, 1–8. https://doi.org/10.1155/2014/498420

Cheng, Y., Morshed, R. A., Auffinger, B., Tobias, A. L., & Lesniak, M. S. (2014). Multifunctional nanoparticles for brain tumor imaging and therapy. Advanced Drug Delivery Reviews, 66, 42–57. https://doi.org/10.1016/j.addr.2013.09.006

Jain, K. (2003). Nanodiagnostics: application of nanotechnology in molecular diagnostics. Expert Review of Molecular Diagnostics, 3(2), 153–161. https://doi.org/10.1586/14737159.3.2.153

Alharbi, K. K., & Al-sheikh, Y. A. (2014). Role and implications of nanodiagnostics in the changing trends of clinical diagnosis. Saudi Journal of Biological Sciences, 21(2), 109–117. https://doi.org/10.1016/j.sjbs.2013.11.001

Jain, K. (2008). Nanomedicine: Application of Nanobiotechnology in Medical Practice. Medical Principles and Practice, 17(2), 89–101. https://doi.org/10.1159/000112961

Jain, K. K. (2012). Role of Nanodiagnostics in Personalized Cancer Therapy. Clinics in Laboratory Medicine, 32(1), 15–31. https://doi.org/10.1016/j.cll.2011.10.001

Bagheri, S., Yasemi, M., Safaie-Qamsari, E., Rashidiani, J., Abkar, M., Hassani, M., Mirhosseini, S. A., & Kooshki, H. (2018). Using gold nanoparticles in diagnosis and treatment of melanoma cancer. Artificial Cells, Nanomedicine, and Biotechnology, 46(sup1), 462–471. https://doi.org/10.1080/21691401.2018.1430585

Perry, H. L., Botnar, R. M., & Wilton-Ely, J. D. E. T. (2020). Gold nanomaterials functionalised with gadolinium chelates and their application in multimodal imaging and therapy. Chemical Communications, 56(29), 4037–4046. https://doi.org/10.1039/d0cc00196a

Zhao, L., Li, Y., Zhu, J., Sun, N., Song, N., Xing, Y., Huang, H., & Zhao, J. (2019). Chlorotoxin peptide-functionalized polyethylenimine-entrapped gold nanoparticles for glioma SPECT/CT imaging and radionuclide therapy. Journal of Nanobiotechnology, 17(1). https://doi.org/10.1186/s12951-019-0462-6

Cho, J. H., Kim, A. R., Kim, S. H., Lee, S. J., Chung, H., & Yoon, M. Y. (2017b). Development of a novel imaging agent using peptide-coated gold nanoparticles toward brain glioma stem cell marker CD133. Acta Biomaterialia, 47, 182–192. https://doi.org/10.1016/j.actbio.2016.10.009

Cho, J. H., Kim, A. R., Kim, S. H., Lee, S. J., Chung, H., & Yoon, M. Y. (2017c). Development of a novel imaging agent using peptide-coated gold nanoparticles toward brain glioma stem cell marker CD133. Acta Biomaterialia, 47, 182–192. https://doi.org/10.1016/j.actbio.2016.10.009

Lee, C., Kim, G. R., Yoon, J., Kim, S. E., Yoo, J. S., & Piao, Y. (2018). In vivo delineation of glioblastoma by targeting tumor-associated macrophages with near-infrared fluorescent silica coated iron oxide nanoparticles in orthotopic xenografts for surgical guidance. Scientific Reports, 8(1). https://doi.org/10.1038/s41598-018-29424-4

Tamba, B., Streinu, V., Foltea, G., Neagu, A., Dodi, G., Zlei, M., Tijani, A., & Stefanescu, C. (2018). Tailored surface silica nanoparticles for blood-brain barrier penetration: Preparation and in vivo investigation. Arabian Journal of Chemistry, 11(6), 981–990. https://doi.org/10.1016/j.arabjc.2018.03.019

Ding, F., Chen, Z., Kim, W. Y., Sharma, A., Li, C., Ouyang, Q., Zhu, H., Yang, G., Sun, Y., & Kim, J. S. (2019). A nano-cocktail of an NIR-II emissive fluorophore and organoplatinum(ii) metallacycle for efficient cancer imaging and therapy. Chemical Science, 10(29), 7023–7028. https://doi.org/10.1039/c9sc02466b

Huang, N., Cheng, S., Zhang, X., Tian, Q., Pi, J., Tang, J., Huang, Q., Wang, F., Chen, J., Xie, Z., Xu, Z., Chen, W., Zheng, H., & Cheng, Y. (2017). Efficacy of NGR peptide-modified PEGylated quantum dots for crossing the blood–brain barrier and targeted fluorescence imaging of glioma and tumor vasculature. Nanomedicine: Nanotechnology, Biology and Medicine, 13(1), 83–93. https://doi.org/10.1016/j.nano.2016.08.029

Chan, M., Liu, R., & Hsiao, M. (2019). Light/Ultrasound Responsive 750 nm-Emitted Non-toxic Indium Phosphide Quantum Dots Hybrid Nanobubble for Brain Tumor Imaging. The FASEB Journal, 33(S1). https://doi.org/10.1096/fasebj.2019.33.1_supplement.662.6

Tang, J., Huang, N., Zhang, X., Zhou, T., Tan, Y., Pi, J., Pi, L., Cheng, S., Zheng, H., & Cheng, Y. (2017). Aptamer-conjugated PEGylated quantum dots targeting epidermal growth factor receptor variant III for fluorescence imaging of glioma. International Journal of Nanomedicine, Volume 12, 3899–3911. https://doi.org/10.2147/ijn.s133166

Perini, G., Palmieri, V., Ciasca, G., De Spirito, M., & Papi, M. (2020). Unravelling the Potential of Graphene Quantum Dots in Biomedicine and Neuroscience. International Journal of Molecular Sciences, 21(10), 3712. https://doi.org/10.3390/ijms21103712

Jovanović, S. P., Syrgiannis, Z., Marković, Z. M., Bonasera, A., Kepić, D. P., Budimir, M. D., Milivojević, D. D., Spasojević, V. D., Dramićanin, M. D., Pavlović, V. B., & Todorović Marković, B. M. (2015). Modification of Structural and Luminescence Properties of Graphene Quantum Dots by Gamma Irradiation and Their Application in a Photodynamic Therapy. ACS Applied Materials &Amp; Interfaces, 7(46), 25865–25874. https://doi.org/10.1021/acsami.5b08226

Shao, J., Zhang, J., Jiang, C., Lin, J., & Huang, P. (2020). Biodegradable titanium nitride MXene quantum dots for cancer phototheranostics in NIR-I/II biowindows. Chemical Engineering Journal, 400, 126009. https://doi.org/10.1016/j.cej.2020.126009

Caraway, C. A., Gaitsch, H., Wicks, E. E., Kalluri, A., Kunadi, N., & Tyler, B. M. (2022). Polymeric Nanoparticles in Brain Cancer Therapy: A Review of Current Approaches. Polymers, 14(14), 2963. https://doi.org/10.3390/polym14142963

Mukhtar, M., Bilal, M., Rahdar, A., Barani, M., Arshad, R., Behl, T., Brisc, C., Banica, F., & Bungau, S. (2020). Nanomaterials for Diagnosis and Treatment of Brain Cancer: Recent Updates. Chemosensors, 8(4), 117. https://doi.org/10.3390/chemosensors8040117

Verma, S., Utreja, P., & Kumar, L. (2020). Role of Nanomedicine in Treatment of Brain Cancer. Current Nanomedicine, 10(2), 105–129. https://doi.org/10.2174/2405461503666181119103142

Barani, M., Mirzaei, M., Torkzadeh-Mahani, M., & Adeli-sardou, M. (2019). Evaluation of Carum-loaded Niosomes on Breast Cancer Cells:Physicochemical Properties, In Vitro Cytotoxicity, Flow Cytometric, DNA Fragmentation and Cell Migration Assay. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-019-43755-w

Jia, Y., Wang, X., Hu, D., Wang, P., Liu, Q., Zhang, X., Jiang, J., Liu, X., Sheng, Z., Liu, B., & Zheng, H. (2018). Phototheranostics: Active Targeting of Orthotopic Glioma Using Biomimetic Proteolipid Nanoparticles. ACS Nano, 13(1), 386–398. https://doi.org/10.1021/acsnano.8b06556

Grosu, F., Ungureanu, A., Bianchi, E., Moscu, B., Coldea, L., Stupariu, A. L., Pirici, I., & Roman-Filip, C. C. (2017). Multifocal and multicentric low-grade oligoastrocytoma in a young patient. *Romanian Journal of Morphology and Embryology*, *58*(1), 207–210.

Wang, X., Hu, Y., Wang, R., Zhao, P., Gu, W., & Ye, L. (2020). Albumin-mediated synthesis of fluoroperovskite KMnF3 nanocrystals for T1-T2 dual-modal magnetic resonance imaging of brain gliomas with improved sensitivity. Chemical Engineering Journal, 395, 125066. https://doi.org/10.1016/j.cej.2020.125066

Rajabi, T. (2020). Application of Nanomaterials in Brain Cancers Diagnosis and Treatment: A Mini-Review. American Journal of Biomedical Science &Amp; Research, 11(1), 83–86. https://doi.org/10.34297/ajbsr.2020.11.001591

Sonali, Viswanadh, M. K., Singh, R. P., Agrawal, P., Mehata, A. K., Pawde, D. M., Narendra, Sonkar, R., & Muthu, M. S. (2018). Nanotheranostics: Emerging Strategies for Early Diagnosis and Therapy of Brain Cancer. Nanotheranostics, 2(1), 70–86. https://doi.org/10.7150/ntno.21638

Calabrese, G., De Luca, G., Nocito, G., Rizzo, M. G., Lombardo, S. P., Chisari, G., Forte, S., Sciuto, E. L., & Conoci, S. (2021). Carbon Dots: An Innovative Tool for Drug Delivery in Brain Tumors. International Journal of Molecular Sciences, 22(21), 11783. https://doi.org/10.3390/ijms222111783

Wu, H., Su, W., Xu, H., Zhang, Y., Li, Y., Li, X., & Fan, L. (2021). Applications of carbon dots on tumour theranostics. View, 2(2), 20200061. https://doi.org/10.1002/viw.20200061

Ruan, S., Qian, J., Shen, S., Zhu, J., Jiang, X., He, Q., & Gao, H. (2014). A simple one-step method to prepare fluorescent carbon dots and their potential application in non-invasive glioma imaging. Nanoscale, 6(17), 10040–10047. https://doi.org/10.1039/c4nr02657h

Ahmad, F., Varghese, R., Panda, S., Ramamoorthy, S., Areeshi, M. Y., Fagoonee, S., & Haque, S. (2022). Smart Nanoformulations for Brain Cancer Theranostics: Challenges and Promises. Cancers, 14(21), 5389. https://doi.org/10.3390/cancers14215389

Dwivedi, N., Shah, J., Mishra, V., Mohd Amin, M. C. I., Iyer, A. K., Tekade, R. K., & Kesharwani, P. (2016). Dendrimer-mediated approaches for the treatment of brain tumor. Journal of Biomaterials Science, Polymer Edition, 27(7), 557–580. https://doi.org/10.1080/09205063.2015.1133155

Wang, Z. L. (2004). Nanostructures of zinc oxide. Materials Today, 7(6), 26–33. https://doi.org/10.1016/s1369-7021(04)00286-x

Ostrovsky, S., Kazimirsky, G., Gedanken, A., & Brodie, C. (2009). Selective cytotoxic effect of ZnO nanoparticles on glioma cells. Nano Research, 2(11), 882–890. https://doi.org/10.1007/s12274-009-9089-5

Sharma, A. K., Singh, V., Gera, R., Purohit, M. P., & Ghosh, D. (2016). Zinc Oxide Nanoparticle Induces Microglial Death by NADPH-Oxidase-Independent Reactive Oxygen Species as well as Energy Depletion. Molecular Neurobiology, 54(8), 6273–6286. https://doi.org/10.1007/s12035-016-0133-7

JENG, H. A., & SWANSON, J. (2006). Toxicity of Metal Oxide Nanoparticles in Mammalian Cells. Journal of Environmental Science and Health, Part A, 41(12), 2699–2711. https://doi.org/10.1080/10934520600966177

Wahab, R., Kaushik, N. K., Verma, A. K., Mishra, A., Hwang, I. H., Yang, Y. B., Shin, H. S., & Kim, Y. S. (2010). Fabrication and growth mechanism of ZnO nanostructures and their cytotoxic effect on human brain tumor U87, cervical cancer HeLa, and normal HEK cells. JBIC Journal of Biological Inorganic Chemistry, 16(3), 431–442. https://doi.org/10.1007/s00775-010-0740-0

Zottel, A., Videtič Paska, A., & Jovčevska, I. (2019). Nanotechnology Meets Oncology: Nanomaterials in Brain Cancer Research, Diagnosis and Therapy. Materials, 12(10), 1588. https://doi.org/10.3390/ma12101588

Invernici, G., Cristini, S., Alessandri, G., E. Navone, S., Canzi, L., Tavian, D., Redaelli, C., Acerbi, F., & A. Parati, E. (2011). Nanotechnology Advances in Brain Tumors: The State of the Art. Recent Patents on Anti-Cancer Drug Discovery, 6(1), 58–69. https://doi.org/10.2174/157489211793979990

Allen, T. M., & Cullis, P. R. (2013). Liposomal drug delivery systems: From concept to clinical applications. *Advanced Drug Delivery Reviews*, *65*(1), 36–48. https://doi.org/10.1016/j.addr.2012.09.037

O'Sullivan, B., McPherson, D. D., & Macdonald, R. L. (2008). A Method to Co-Encapsulate Gas and Drugs in Liposomes for Ultrasound-Controlled Drug Delivery. *Ultrasound in Medicine and Biology*,*34*(8),1272–1280. https://doi.org/10.1016/j.ultrasmedbio.2008.01.005

Kesharwani, P., Mishra, V., & Jain, N. K. (2015). Validating the anticancer potential of carbon nanotube-based therapeutics through cell line testing. *Drug Discovery Today*, *20*(9), 1049–1060. https://doi.org/10.1016/j.drudis.2015.05.004

Kesharwani, P., Ghanghoria, R., & Jain, N. K. (2012). Carbon nanotube exploration in cancer cell lines. *Drug Discovery Today*, *17*(17–18), 1023–1030. https://doi.org/10.1016/j.drudis.2012.05.003

Monteiro-Riviere, N. A., Nemanich, R. J., Inman, A. O., Wang, Y., & Riviere, J. E. (2005). Multi-walled carbon nanotube interactions with human epidermal keratinocytes. *Toxicology Letters*, *155*(3), 377–384. https://doi.org/10.1016/j.toxlet.2004.11.004

Saeedi, M., Eslamifar, M., Khezri, K., & Dizaj, S. M. (2019). Applications of nanotechnology in drug delivery to the central nervous system. *Biomedicine & Pharmacotherapy*, *111*, 666–675. https://doi.org/10.1016/j.biopha.2018.12.133

Malam, Y., Loizidou, M., & Seifalian, A. M. (2009). Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. *Trends in Pharmacological Sciences*, *30*(11), 592–599. https://doi.org/10.1016/j.tips.2009.08.004

McHugh, K. J., Jing, L., Behrens, A. M., Jayawardena, H. S. N., Tang, W., Gao, M., Langer, R., & Jaklenec, A. (2018). Biocompatible Semiconductor Quantum Dots as Cancer Imaging Agents. Advanced Materials, 30(18), 1706356. https://doi.org/10.1002/adma.201706356

Bozzuto, G., & Molinari, A. (2015). Liposomes as nanomedical devices. International Journal of Nanomedicine, 975. https://doi.org/10.2147/ijn.s68861

Norouzi, M. (2020). Gold Nanoparticles in Glioma Theranostics. Pharmacological Research, 156, 104753. https://doi.org/10.1016/j.phrs.2020.104753

Chan, T., Morse, S. V., Copping, M. J., Choi, J. J., & Vilar, R. (2018). Targeted Delivery of DNA-Au Nanoparticles across the Blood-Brain Barrier Using Focused Ultrasound. ChemMedChem, 13(13), 1311–1314. https://doi.org/10.1002/cmdc.201800262

Cabezón, I., Manich, G., Martín-Venegas, R., Camins, A., Pelegrí, C., & Vilaplana, J. (2015). Trafficking of Gold Nanoparticles Coated with the 8D3 Anti-Transferrin Receptor Antibody at the Mouse Blood–Brain Barrier. Molecular Pharmaceutics, 12(11), 4137–4145. https://doi.org/10.1021/acs.molpharmaceut.5b00597

Gromnicova, R., Yilmaz, C., Orhan, N., Kaya, M., Davies, H. A., Williams, P., Romero, I. A., Sharrack, B., & Male, D. (2016). Localization and mobility of glucose-coated gold nanoparticles within the brain. Nanomedicine, 11(6), 617–625. https://doi.org/10.2217/nnm.15.215

Feng, Q., Shen, Y., Fu, Y., Muroski, M. E., Zhang, P., Wang, Q., Xu, C., Lesniak, M. S., Li, G., & Cheng, Y. (2017). Self-Assembly of Gold Nanoparticles Shows Microenvironment-Mediated Dynamic Switching and Enhanced Brain Tumor Targeting. Theranostics, 7(7), 1875–1889. https://doi.org/10.7150/thno.18985

Zhao, L., Li, Y., Zhu, J., Sun, N., Song, N., Xing, Y., Huang, H., & Zhao, J. (2019). Chlorotoxin peptide-functionalized polyethylenimine-entrapped gold nanoparticles for glioma SPECT/CT imaging and radionuclide therapy. Journal of Nanobiotechnology, 17(1). https://doi.org/10.1186/s12951-019-0462-6

Wang, L., Tang, S., Yu, Y., Lv, Y., Wang, A., Yan, X., Li, N., Sha, C., Sun, K., & Li, Y. (2021). Intranasal Delivery of Temozolomide-Conjugated Gold Nanoparticles Functionalized with Anti-EphA3 for Glioblastoma Targeting. Molecular Pharmaceutics, 18(3), 915–927. https://doi.org/10.1021/acs.molpharmaceut.0c00911

Kouri, F. M., Hurley, L. A., Daniel, W. L., Day, E. S., Hua, Y., Hao, L., Peng, C. Y., Merkel, T. C., Queisser, M. A., Ritner, C., Zhang, H., James, C. D., Sznajder, J. I., Chin, L., Giljohann, D. A., Kessler, J. A., Peter, M. E., Mirkin, C. A., & Stegh, A. H. (2015). miR-182 integrates apoptosis, growth, and differentiation programs in glioblastoma. Genes & Development, 29(7), 732–745. https://doi.org/10.1101/gad.257394.114

Kong, L., Qiu, J., Sun, W., Yang, J., Shen, M., Wang, L., & Shi, X. (2017). Multifunctional PEI-entrapped gold nanoparticles enable efficient delivery of therapeutic siRNA into glioblastoma cells. Biomaterials Science, 5(2), 258–266. https://doi.org/10.1039/c6bm00708b

Giesen, B., Nickel, A., Meischein, M., Toscano, A. V., Scheu, C., Janiak, C., & Janiak, C. (2020). Influence of synthesis methods on the internalization of fluorescent gold nanoparticles into glioblastoma stem-like cells. Journal of Inorganic Biochemistry, 203, 110952. https://doi.org/10.1016/j.jinorgbio.2019.110952

Dayem, A. A., Hossain, M. A., Lee, S. B., Kim, K., Saha, S. K., Yang, G., Choi, H. J., & Cho, S. (2017). The Role of Reactive Oxygen Species (ROS) in the Biological Activities of Metallic Nanoparticles. International Journal of Molecular Sciences, 18(1), 120. https://doi.org/10.3390/ijms18010120

Locatelli, E., Naddaka, M., Uboldi, C., Loudos, G., Fragogeorgi, E., Molinari, V., Pucci, A., Tsotakos, T., Psimadas, D., Ponti, J., & Franchini, M. C. (2014). Targeted delivery of silver nanoparticles and alisertib: in vitro and in vivo synergistic effect against glioblastoma. Nanomedicine, 9(6), 839–849. https://doi.org/10.2217/nnm.14.1

Hanif, S., Muhammad, P., Niu, Z., Ismail, M. H., Morsch, M., Zhang, X., Li, M., & Shi, B. (2021). Nanotechnology-Based Strategies for Early Diagnosis of Central Nervous System Disorders. Advanced NanoBiomed Research, 1(10), 2100008. https://doi.org/10.1002/anbr.202100008

Hsu, J., Chu, S., Liao, C., Wang, C., Wang, Y., Lai, M., Wang, H., Huang, H., & Tsai, M. (2021). Nanotechnology and Nanocarrier-Based Drug Delivery as the Potential Therapeutic Strategy for Glioblastoma Multiforme: An Update. Cancers, 13(2), 195. https://doi.org/10.3390/cancers13020195

Hsu, J., Chu, S., Liao, C., Wang, C., Wang, Y., Lai, M., Wang, H., Huang, H., & Tsai, M. (2021b). Nanotechnology and Nanocarrier-Based Drug Delivery as the Potential Therapeutic Strategy for Glioblastoma Multiforme: An Update. Cancers, 13(2), 195. https://doi.org/10.3390/cancers13020195

Jain, K. K. (2008). Nanomedicine: Application of Nanobiotechnology in Medical Practice. Medical Principles and Practice, 17(2), 89–101. https://doi.org/10.1159/000112961

Cl, V. (2017). Progress in Nanomedicine: Approved and Investigational Nanodrugs. P & T : A Peer-Reviewed Journal for Formulary Management, 42(12), 742–755.

Cheng, Z., Li, M., Dey, R., & Chen, Y. (2021). Nanomaterials for cancer therapy: current progress and perspectives. Journal of Hematology & Oncology, 14(1). https://doi.org/10.1186/s13045-021-01096-0

Ling, T. L., Chandrasegaran, S., Xuan, L. Z., Suan, T. K., Elaine, E., Nathan, D. V., Chai, Y. H., Gunasekaran, B., & Salvamani, S. (2021). The Potential Benefits of Nanotechnology in Treating Alzheimer's Disease. BioMed Research International, 2021, 1–9. https://doi.org/10.1155/2021

Cl, V. (2017b). Progress in Nanomedicine: Approved and Investigational Nanodrugs. P & T : A Peer-Reviewed Journal for Formulary Management, 42(12), 742–755.

Kesharwani, P., Tekade, R. K., & Jain, N. K. (2014). Generation dependent cancer targeting potential of poly(propyleneimine) dendrimer. Biomaterials, 35(21), 5539–5548. https://doi.org/10.1016/j.biomaterials.2014.03.064

Kesharwani, P., Tekade, R. K., & Jain, N. K. (2015). Dendrimer generational nomenclature: the need to harmonize. Drug Discovery Today, 20(5), 497–499. https://doi.org/10.1016/j.drudis.2014.12.015

Islam, T., & Josephson, L. (2009). Current state and future applications of active targeting in malignancies using superparamagnetic iron oxide nanoparticles. Cancer Biomarkers, 5(2), 99–107. https://doi.org/10.3233/cbm-2009-0615

De Jesus, O. P., Ihre, H. R., Gagne, L., Fréchet, J. M. J., & Szoka, F. C. (2002). Polyester Dendritic Systems for Drug Delivery Applications: In Vitro and In Vivo Evaluation. Bioconjugate Chemistry, 13(3), 453–461. https://doi.org/10.1021/bc010103m

She, W., Li, N., Luo, K., Guo, C., Wang, G., Geng, Y., & Gu, Z. (2013). Dendronized heparin−doxorubicin conjugate based nanoparticle as pH-responsive drug delivery system for cancer therapy. Biomaterials, 34(9), 2252–2264. https://doi.org/10.1016/j.biomaterials.2012.12.017

Duan, Y., Wu, M., Hu, D., Pan, Y., Hu, F., Liu, X., Thakor, N. V., Ng, W. T., Liu, X., Zheng, H., & Liu, B. (2020). Biomimetic Nanocomposites Cloaked with Bioorthogonally Labeled Glioblastoma Cell Membrane for Targeted Multimodal Imaging of Brain Tumors. Advanced Functional Materials, 30(38), 2004346. https://doi.org/10.1002/adfm.202004346

Wan, Y. Z., Huang, Y., Yuan, C. Z., Raman, S. R., Zhu, Y. S., Jiang, H., He, F., & Gao, C. S. (2007). Biomimetic synthesis of hydroxyapatite/bacterial cellulose nanocomposites for biomedical applications. Materials Science and Engineering: C, 27(4), 855–864. https://doi.org/10.1016/j.msec.2006.10.002

Lao, J., Huang, J., Wang, D., & Ren, Z. L. (2003). ZnO Nanobridges and Nanonails. Nano Letters, 3(2), 235–238. https://doi.org/10.1021/nl025884u

Jin, B., Bae, S. C., Lee, S. H., & Im, S. (2000b). Effects of native defects on optical and electrical properties of ZnO prepared by pulsed laser deposition. Materials Science and Engineering: B, 71(1–3), 301–305. https://doi.org/10.1016/s0921-5107(99)00395-5

Kachroo, P., Singh, V., Gera, R., Purohit, M. P., & Ghosh, D. (2017). Zinc Oxide Nanoparticle Induces Microglial Death by NADPH-Oxidase-Independent Reactive Oxygen Species as well as Energy Depletion. Molecular Neurobiology, 54(8), 6273–6286. https://doi.org/10.1007/s12035-016-0133-7

Jeng, H. A., & Swanson, J. M. (2006). Toxicity of Metal Oxide Nanoparticles in Mammalian Cells. Journal of Environmental Science and Health, Part A, 41(12), 2699–2711. https://doi.org/10.1080/10934520600966177