International Journal of Early Childhood Special Education (INT-JECSE)
DOI: 10.48047/intjecse/V12I1.201059 ISSN: 1308-5581 Vol 12, Issue 01 2020

PREPARE AND EVALUATE DRUG LOADED POLYMERIC NANO-FIBRES FOR THE TREATMENT OF BRAIN TUMOR

Dr Prashant Gahtori
Department of Pharmacy , Graphic Era Hill University, Dehradun, Uttarakhand, India 248002

Abstract

Due to poor diagnosis and profiling, brain tumors, particularly glioblastoma, continue to be the most aggressive type of all malignancies. The most difficult aspect of treating brain cancer is getting chemotherapeutic medicines and other anti-cancer substances across the blood-brain barrier and into the tumor cells where they can do the best. The strong, highly-tunable carrier systems known as polymeric nanoparticles (NPs) may be able to get around those challenges. Several studies have shown that properly built polymeric NPs may specifically target cancer cells in the central nervous system, enhance medication bioavailability, and decrease systemic toxicity by crossing the blood-brain barrier. While there are currently no clinical trials including the use of polymeric NPs for the treatment of brain cancer, there is growing preclinical evidence that they may be effective. This overview looks at several polymeric NPs and how their composition, surface changes, and administration mechanism affect their efficacy in treating brain tumors.

Keywords: Nanomaterials, nanoparticles; liposomes; blood–brain barrier; drug delivery;

INTRODUCTION

According to GLOBOCAN 2020, The brain is the primary site of genesis for CNS malignant tumors, which are the thirteenth leading cause of cancer mortality worldwide. Despite decades of study, the prognosis for people with GBM remains unchanged. Without surgical surgery followed by immediate starting of standard-of-care radiation and chemotherapy, the median survival time for patients globally is 8 months, and the 5-year survival rate is between 5% and 10%. In a similar vein, just 20% of those with initial malignant brain tumors survive for five years. There are several obstacles in the way of effective treatment for brain cancer. After being surgically removed, brain tumors often return. As a result, alternative or combination treatment methods are often required because they arise in locations where complete surgical resection would be too risky or impossible. Further, reliable research has shown that nanoparticles (NPs) are the most efficient means to penetrate the BBB and deliver drugs to the brain, where they may be used to treat cancer. Bypassing the BBB as nanocarriers, NPs do not interfere with the BBB's functionalization. In addition, by attaching the appropriate ligands, NPs provide delayed and sustained drug release directly into the brain, reducing the risk of peripheral toxicities. Anti-cancer drugs cannot cross the BBB without a mechanistic approach, and NPs provide this since their tiny size makes opening the tight junctions a realistic possibility. Finally, after NPs have crossed the BBB, endothelial cells will engulf them and release the medicine within the cell. Inhibiting P-glycoprotein (P-gp) efflux by conjugating NPs with thiolated and preactivated polymers has been proven to be an effective strategy for increasing medication half-life. Nanomedicine's contributions to the diagnosis of brain cancer include improved sensitivity, lower costs, and fewer false positives and negatives.

Thus, very stable, non-toxic self-assembled gadolinium chelates NPs have been added to the standard diagnostic method. The imaging effect may be maximized by maximally loading the chelates with gadolinium ions. Gadolinium may also be used in a different manner to improve targeting and imaging of tumors by conjugating it with interleukins, peptides, epidermal growth factor receptors, and specific antibodies. The utilization of gadolinium metallofullerene NPs is at the forefront of cutting-edge nano-diagnostics. The cage surface of gadolinium metallofullerene NPs is charged with an amino group (-

NH3 +), which results in high 1 H MR relaxivity. Hence, to sum up, it can be said that tailored NPs are more suited for comprehending the BBB's regulatory processes and exhibit promise delivery and detection to beat the mortality rate of deadly brain cancer.

In light of the foregoing, and as part of our research group's ongoing efforts to synthesize nanomaterials and investigate their potential bio applications, This article compiles the most up-to-date research available on the many nanomaterials that may be used in the detection and treatment of brain cancer. Thus, our review-style study brings the most up-to-date and pertinent material on NPs and brain cancer to the attention of all readers.

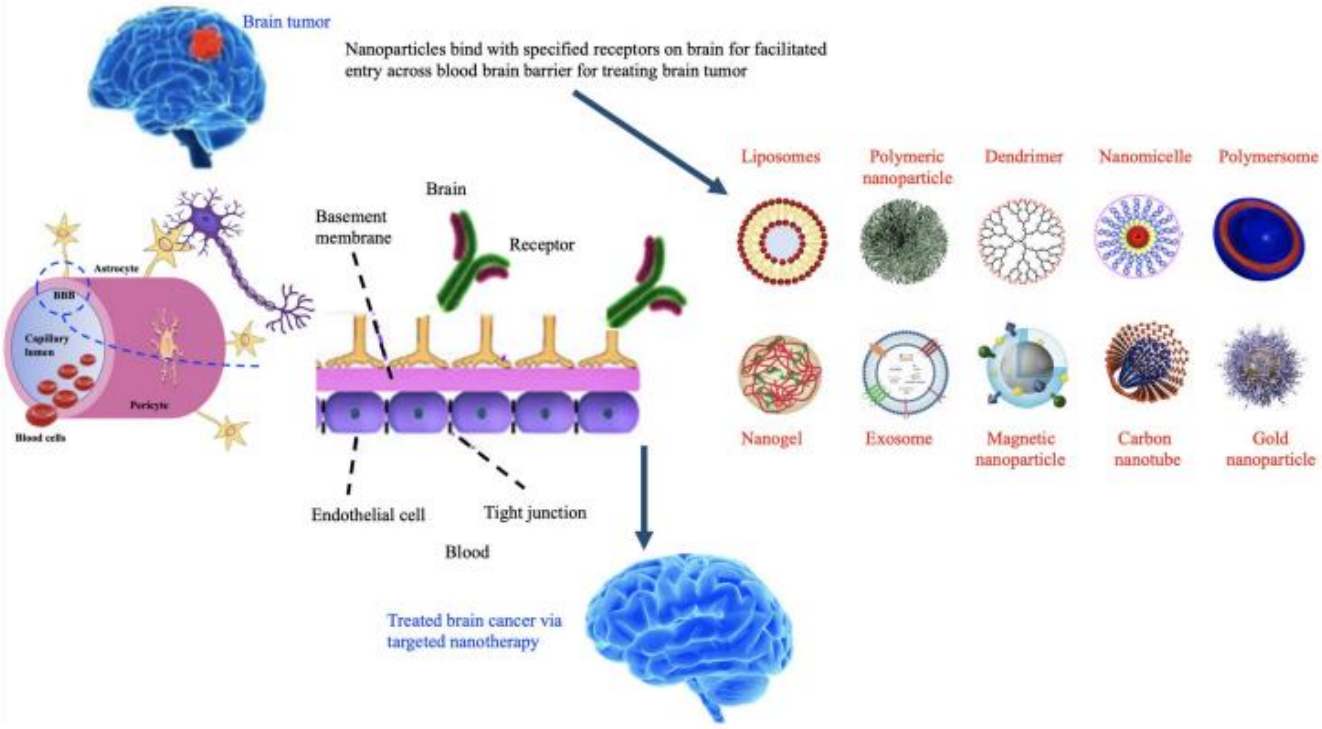

Figure 1: Brain cancer treated with novel nanoparticle (NP) therapy.

LITERATURE REVIEW

Duan, X., Chen, Hl. & Guo, C. (2019), Drug delivery systems (DDS) based on functional materials have emerged in recent years as a response to the shortcomings of conventional drug release formulations, such as the inability to precisely regulate drug concentration in the desired organs/tissues and the presence of undesirable side effects. Polymer nanofibers are employed in the creation of novel DDS because of their advantageous attributes, including as their low cost, high versatility, and high surface-to-volume ratio. The polymer nanofibers may be engineered to include a wide variety of medications. Its versatility stems from the fact that their release kinetics may be altered in accordance with the preparation's ingredients, quantities, and methods. So, there is a pressing need for an up-to-date, all-encompassing review of polymeric nanofibers for DDS. This review first explains the most frequent approaches to making polymer nanofibers, and then it presents managed strategies for loading drugs into and releasing them from these materials. Consequently, the roles of polymer nanofibers in DDS were reviewed, with an emphasis on the correlation between nanofiber physiochemical characteristics and DDS efficacy. Future prospects are outlined to round out the piece.

Abdelhakim, H.E; Li, J.; Liu, Y. (2018), Cancer is one of the worst illnesses, and the second leading cause of death worldwide; as the world's population ages and grows, so too will the prevalence and severity of problems related to cancer. Several treatments and medications specifically designed to

combat cancer have been created. While chemotherapy and related medications see extensive usage in therapeutic settings, they usually come with serious drawbacks. Nanotechnology has been used to enhance the medication delivery system in recent years, lowering the risk of unwanted side effects. Core-sheath nanofibres made by coaxial electrospinning stand out from the crowd because of their many desirable qualities. They include a high encapsulation efficiency, superior mechanical property, capacity for multiple drugs, and control over their release. Because of the benefits of regulated and prolonged drug release, encapsulating medicines in coaxial electrospun nanofibres is a promising approach. Coaxial electrospun nanofibres of varying topologies and medicines are discussed in this review for their potential use in the drug delivery of cancer therapies.

Singh, A.P., A. Biswas, and A. Shukla, et al (2019), Nanomedicines are becoming more popular as their promise of precise and efficient drug delivery is realized. Many clinical and preclinical studies have shown that the advantages of nanomedicines over traditional therapy, such as site-specific drug delivery, fewer adverse effects, and enhanced therapeutic efficacy, outweigh the risks. Nanomedicines aren't limited to pharmaceuticals or substances; peptides, nucleic acids (DNA and RNA), and genes have all showed promise as treatments for various long-term conditions. To guarantee the short- and long-term effects of nanomedicines on people, however, a vast number of thorough clinical studies are still required. This analysis compares and contrasts the merits of different drug delivery vehicles to help readers better comprehend their value in meeting the requirements of modern medicine. In addition, the use of several nanomedicines in the setting of important chronic illnesses is detailed.

Marta Cavo, Francesca Serio, Narendra R. Kale, (2017), Recently, More and more people are looking at how electrospun fibrous matrices might be utilized in cancer research, both as patches for delivering medicines in vivo and as scaffolds for simulating disease in the lab. We explain the impact that changing the process parameters has on the conformation and assembly of fibers, and provide a short introduction of the technique and most materials utilized in electrospinning. We next detail two ways in which electrospinning has been put to use in the field of cancer research: first, patches encasing anticancer medications for in vivo delivery, and as a method of generating 3D fibrous materials for use in in vitro pre-clinical cancer models.

B. Singh; K. Kim; M.-H. Park (2018), Nanofiber-based on-demand drug-delivery systems have broad therapeutic applications due to their ability to tailor medication release depending on a patient's specific anatomical and physiological needs. Changing the medicine in a nanofiber formulation that was originally developed for a different prescription may drastically alter the delivery system's rate of drug release. Nanofibers stand out from other materials due to their many useful characteristics, such as their huge surface area, complicated pore structure, and relative simplicity of production. In this review, we use the most up-to-date scientific literature to compare and contrast different types of nanofibers based on their chemical make-up and drug-release characteristics. The shape and composition of nanofibers are taken into account when categorizing them according to their ability to release drugs. An appropriate polymer, a high surface-to-volume ratio, and a highly porous nanofiber mesh are required for regulated drug release. This article classifies the characteristics of nanofibers for customized drug release into three broad categories: prolonged, stimulus-activated, and biphasic.

Receptor Targeting for Blood–Brain Barrier Penetration

When trying to treat tumors in the brain, the BBB stands as a major roadblock for NP delivery. As can be shown in the section under "Mechanisms of Delivery," NPs may be engineered to cross the BBB through a variety of transport modes, including adsorptive-mediated transcytosis (AMT), receptor-mediated transcytosis (RMT), and cell-based delivery. AMT occurs when positively charged ligands engage with the negatively charged membranes of brain capillary endothelial cells through electrostatic interactions. While NPs may benefit from this mechanism, whether or whether AMT plays a substantial role in the transport of endogenous substances through the BBB is not well

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understood. To improve medicine delivery to the brain parenchyma, several researchers have turned to targeting BBB endothelial cells for RMT. Receptor-mediated endocytosis occurs on luminal side BBB endothelial cells, which is then followed by trafficking and sorting before the contents are discharged into the brain parenchyma. Transferrin receptor (TfR), insulin receptor (IR), LDL receptor (LDLR), melanotransferrin (MT), complement receptor (CD), and others are among RMT's numerous targets. Figure 2 provides a summary of the many transport mechanisms that NPs may use to cross the BBB.

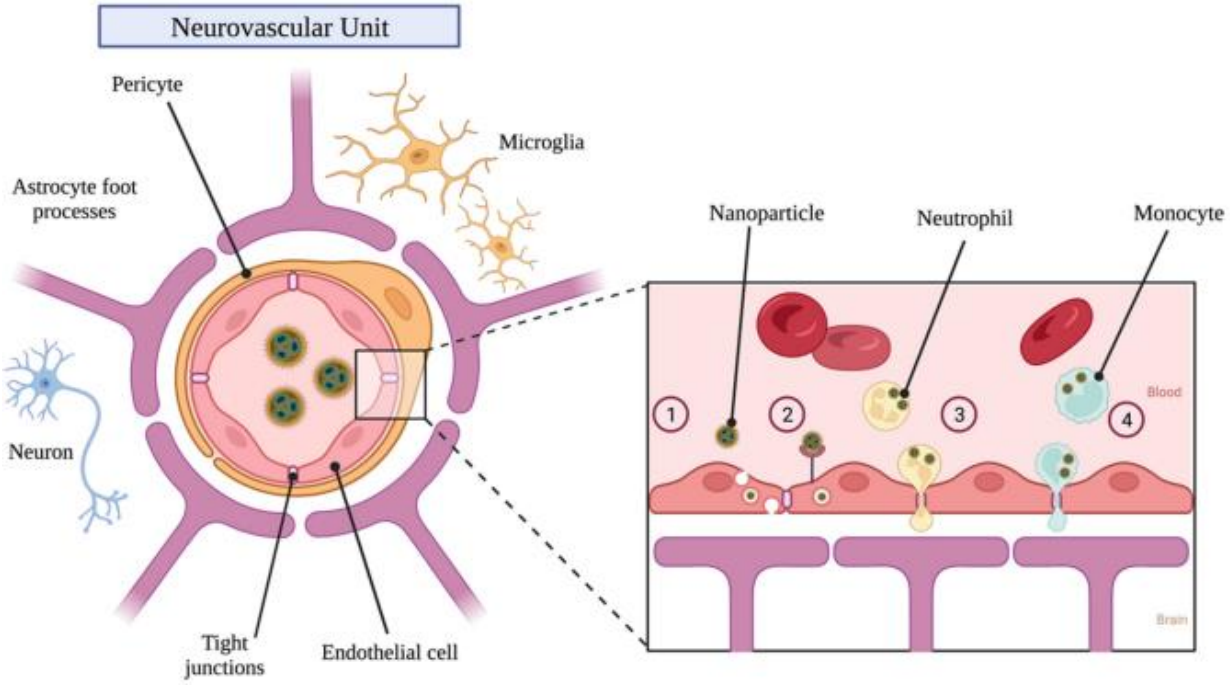

Figure 2. Nanoparticle transport across the blood–brain barrier.

Receptor Targeting for Delivery to Brain Cancer Cells

Vascular endothelial growth factor (VEGF) is an angiogenic mitogen that promotes blood vessel formation. Endothelial cells and numerous kinds of tumor cells are among the many cell types that express it. Despite the fact that VEGF is secreted, you may often find it in membranes and intracellular matrices. Antibodies against VEGF have been used to treat several types of cancer, including many types of brain cancer, for quite some time. Tumor cell VEGF overexpression is critical for tumor progression and metastasis due to enhanced angiogenesis.

Epidermal Growth Factor Receptor

Afatinib, dacomitinib, and cetuximab are tyrosine kinase inhibitors that target epidermal growth factor receptor (EGFR), panitumumab, and nimotuzumab, are only a few of the many cancer therapies that have been developed over the years to target EGFR and its variations in various tumors across the body. Unfortunately, difficulties in transporting these drugs over the blood-brain barrier (BBB) have prevented their clinical efficacy from being established against GBM and other brain malignancies. In their 2017 comprehensive review of EGFR-targeted therapies for GBM, Westphal et al. once again highlighted brain delivery as the most prevalent stumbling block.

In an effort to improve tumor-specific delivery and inhibition, In recent years, scientists have focused on NPs that are coupled to EGFR-targeting antibodies or loaded with EGFR inhibitors.

Mechanisms of Delivery

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Focused Ultrasound

Brain illnesses are among those that may benefit from focused ultrasound (FUS), a promising therapy that employs a less invasive approach [128]. FUS may temporarily and reversibly open the BBB, allowing more medicines to enter areas of the brain that are ordinarily inaccessible. There were no negative radiological findings during the 3-month follow-up, supporting the result of several previous clinical investigations. Under normal conditions, the BBB prevents all but the smallest molecules and those that are channel-mediated from crossing into the brain. Endothelial cells lining capillaries, axon terminals of astrocytes, and pericytes are major contributors. While its primary role is to prevent brain injury, the BBB also limits the kinds of medications that may enter the brain. FUS improves drug delivery, and drugs mixed with microbubbles, which are roughly the same size as red blood cells at around 10 m in diameter, have a greater chance of crossing the BBB. Using FUS prior to administering NPs increases NP uptake by cancer cells.

Nose-to-Brain Delivery

The nasal route to the brain is an easy and non-invasive way to administer NP. Unlike oral administration, nasal administration of drugs may be absorbed directly into the central nervous system through the olfactory and trigeminal pathways, resulting in improved pharmacokinetics and pharmacodynamics. Mucociliary clearance and the presence of degrading enzymes such cytochrome P450 reduce drug retention and absorption through these pathways, presents a difficulty for nasal administration of medications. Bioavailability is often limited for medicinal compounds that are nose-to-brain administered, despite the fact that it is known that certain chemicals may go from the olfactory and trigeminal routes to the brain parenchyma and CSF.

Studies have shown that modified NPs successfully shield their payloads from enzyme degradation and ciliary clearance. Polymeric NPs such as chitosan, PLGA, and PLA have been explored for possible intranasal administration; nevertheless, it is unlikely that therapeutic dosages would be achieved in the CNS via this route alone.

Intracranial Hydrogel Delivery

Benefits of hydrogels include passively regulated drug release, localized drug delivery in response to stimuli, and little toxicity. NP-based treatment systems offer the same potential benefits, and numerous research have looked into using NP-loaded hydrogel hybrids to treat brain cancers. Using hydrogels in chemotherapeutics may be difficult due to the hydrophobic nature of most chemotherapeutic medicines, which is fundamentally incompatible with the hydrophilic feature of the gels. Polymeric NPs, which are extremely modifiable, may be used to avoid this problem since they may be designed with hydrophilic shells filled with hydrophobic medicines. Several gel matrices have been demonstrated to be stable habitats for NPs, making hydrogels an attractive choice for incorporating NPs before, during, or after the gelation process.

Cell-Based Delivery

Monocytes, neutrophils, and stem cells may all take up NPs for transport to the brain tumors there. Particularly attractive is the use of immune cells as vectors for NP administration, monocytes and neutrophils, for example, are able to rapidly traverse the BBB and arrive to sites of injury, inflammation, or tumor growth. This cell-based strategy may make it unnecessary for NPs to cross the BBB in order to reach the brain parenchyma. The quick absorption and removal from circulation by the reticuloendothelial system, which includes monocytes/macrophages in the liver, spleen, and other fixed tissues, presents another significant barrier in delivering NPs to brain tumor locations. Intravenous injection of a patient's own monocytes, macrophages, and neutrophils that have been loaded with drug-containing NPs in vitro might be used to treat a variety of inflammatory diseases.

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Since MSCs are hypoimmunogenic and have been shown to migrate toward tumor cells, they have been widely investigated as possible vectors for glioma therapy. In the same study, researchers demonstrated that MSCs injected intra-arterially or intracranially migrated toward human glioma cells in a mouse model. Similarly, Clavreul et al. showed that the survival of U87MG-bearing mice was considerably enhanced in comparison to the survival of animals injected with the lipid nanocapsules alone after injecting an MSC subpopulation harboring an organometallic complex into the striatum. According to the findings from 2018, After injecting paclitaxel-primed MSCs or paclitaxel-containing PLGA NPs alone into the brains of an orthotopic glioma rat model, researchers found that MSCs loaded with paclitaxel dramatically increased survival. The same team of scientists showed that these MSCs could deliver paclitaxel to glioma cells, killing the tumor cells in vitro. While just a small number of studies have shown that NPs may be delivered to brain tumor tissue through cells, this strategy shows promise for improving patient outcomes and should be further explored. Table 1 provides a comparison of the different administration methods considered in this article.

Table 1. Comparison of polymeric NP mechanisms of delivery

Mechanism of Delivery	Type(s) of Polymeric NPs Used	Advantages	Limitations
Focused Ultrasound	PLGA	Can reversibly open BBB; targeted delivery; safety supported via clinical trials; minimal systemic effects	Acute complications such as microhemorrhages reported; invasive
Convection Enhanced Delivery	PLGA, PBAE, Chitosan, PAMAM, PCL	High volume of distribution reported; targeted delivery; multiple ongoing clinical trials; potential for use post-resection; minimal systemic effects	No definitive increase in glioma patient survival time reported; infection; limited therapeutic administration windows; invasive
Nose-to-Brain Delivery	PLGA, Chitosan, PCL	Minimally invasive; easier to study in vivo; bypasses BBB; minimal systemic effects	Exact delivery mechanism and clearance pathways unclear; non-targeted delivery; bioavailability can be low compared to other delivery mechanisms; limited NP clinical studies

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Intracranial Hydrogel Delivery	PLGA, Chitosan, PCL	Potential for use post-resection; targeted delivery; passively controlled drug release; variety of potential approaches; minimal systemic effects	Difficult to use with hydrophobic NPs; invasive; non-targeted delivery
Cell-Based Delivery	PLGA	Minimally invasive; limited clearance via reticuloendothelial system compared to other systemic delivery approaches	Limited NP clinical studies; non-targeted delivery

Diagnosis and Biosensing of Brain Cancer

Nanotechnology has the potential to enhance both the precise imaging of cancerous tissues in the brain and the efficient delivery of drugs to treat illness. Biocompatible NPs have the desirable physical features for usage as image contrast structures, including the right surface chemistry, topology, morphology, solubility, stability, etc. The nanoscale size of biocompatible nanomaterials improves both their safety profile and the time they remain in circulation. Nanodiagnostics decrease signaling frequency in brain malignancies and tumors produced by leaky vasculature due to phagocytosis by tumor cells. Exciting new approaches to medically identifying malignant tissues are now being explored. One such strategy is to use peptides, bio-conjugates, and nucleotides to modulate the nanostructure's tropism for high-precision monitoring of the tumors.

Intraoperative ultrasonography is another non-optical approach that may be used to generate integrated pictures of brain tissue. Nevertheless, the method does not provide sufficient data for identifying subclinical or superficial brain tumors. Other intrusive methods to gather information on brain malignancies and tumor tissues include the use of neurophotonic technologies including Raman spectroscopy, optical coherence tomography, fluorescence spectroscopy, and thermal imaging. Delineating a cancerous or malignant tumor is a delicate process that calls both precise imaging before surgery and sensitive, non-invasive imaging thereafter to provide real-time data. Recent imaging methods fall short in terms of precision, responsiveness, and specificity. The fields of bioimaging and biosensing have been more interested in nanotechnology in recent years (Figure 3). Nanodiagnostics integrates nanotechnology with established medical imaging and diagnosis methods. Because to nanotechnology, it's now possible to gather data with unprecedented specificity and accuracy, without resorting to any kind of intrusive methodology. Nanoarrays/nanochips are a recent technological advancement in this area; they combine optical, magnetic, and electrical features into tiny instruments for detecting and imaging malignant brain tumors. The imaging and sensing of brain tumors and cancer are two areas where multimodal/multifunctional NPs are showing promise. Several methods have been used to modify NPs for use as specialized imaging-guided therapies. The biocompatibility and biodegradability of nanomaterials have recently come under scrutiny. The numerous nanotechnology-based imaging and diagnostic methods are summarized in Table 2.

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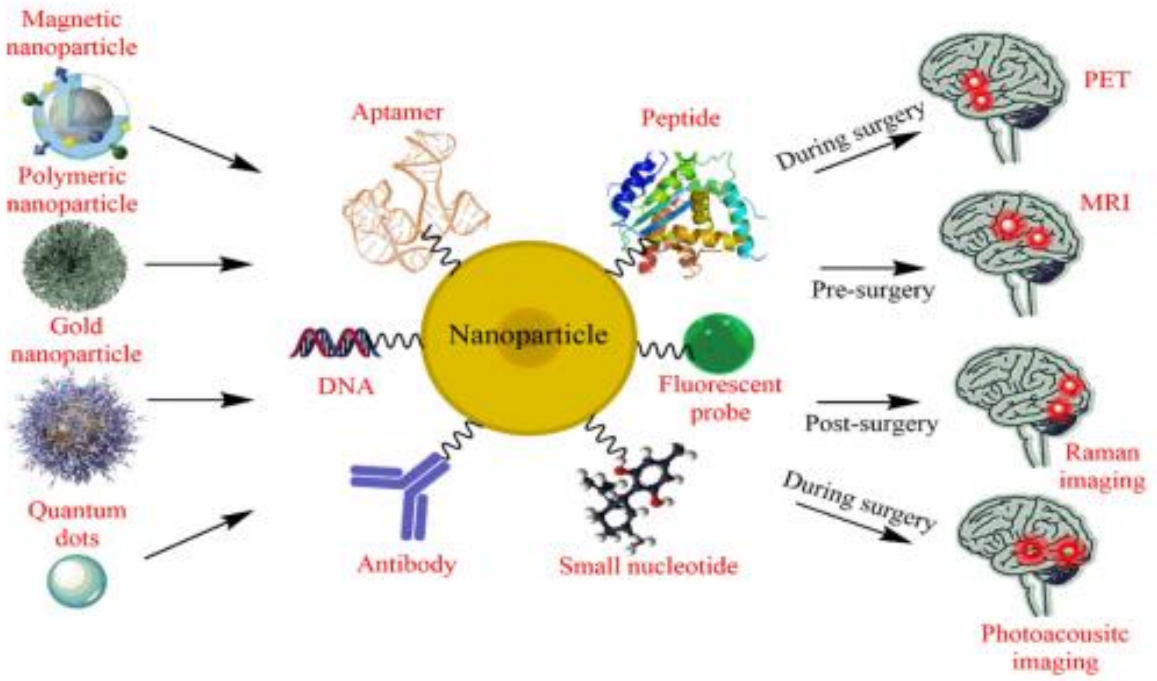

Figure 3: Nanomaterial-based imaging technology for improved diagnosis and surgery

Table 2: Different technologies utilizing nanostructures

Imaging Technique	Selection Parameters Based on Characteristics	Nanostructures Used
Surface-enhanced resonance Raman scattering imaging (SERRS)	High specificity and provides data about the location of biochemical components of cells.	SERRS NPs with 68Ga comprised of gold core and silica shell
Magnetic resonance imaging (MRI)	Sensitive to changes in the cartilage and bone and provides an elaboration of the anatomical structure of the brain with high soft-tissue contrast.	Iron oxide NPs' surface decorated with peptides; gadolinium oxide-based NPs
Photoacoustic (PA) imaging	Acquires molecular data with high resolution in real-time and can be used simultaneously with other imaging techniques.	Silicon quantum sheets, molybdenum di-sulfide nanosheets conjugated with indocyanine green
Fluorescence (FL) imaging	Non-invasive with low spatial resolution.	Gold NPs
Focused ultrasound (FUS)	Real-time visualization of neural anatomy with 3D contrast-enhanced images.	Cisplatin gold NP conjugates, mesoporous organo-silica NPs

Multimodal imaging	Possibility to map cell density to understand heterogeneity of the tissues; high sensitivity and specificity.	SERRS-MSOT*-nanostar with gold core embedded in silica coat functionalized with PEG, SERRS-MRI gold nanoprobes
Positron emission tomography (PET)	Nuclear imaging technique to identify pathophysiological changes in the brain; unlimited penetration.	Alanine modified gado-fullerene NPs, self-assembled amphiphilic dendrimer nano-system
Computed tomography (CT)	Able to provide electron density differences among tissues to establish diagnosis.	Transferrin conjugated liposome, Lanthanide NPs

CONCLUSION

Brain tumors and cancer have an intricate pathophysiology that defies observation by current imaging techniques. Yet, recent advances in nanotechnology have made high-resolution, sensitive imaging of brain regions feasible via selectively targeting cancer cells. In order to accomplish their diagnostic and imaging functions, many NPs have been developed to cross the BBB. If polymeric NP-based drugs are to be used in the treatment of brain cancer, obstacles like limited therapeutic administration and inconsistent trial findings must be resolved. There is no agreement on the best polymer for treating brain cancer since its composition affects the targeted ligands, contents, delivery methods, tumor characteristics, and other elements chosen for each study. PLGA is the most popular polymeric platform utilized in studies of nanocarriers for the treatment of neurological illnesses. Similar studies have revealed conflicting results when it comes to NP size and form, as well as BBB and tumor localisation. The difficulties in standardizing effective polymeric NP properties are likely partly attributable to the known discrepancies in physiology and permeability across different in vivo and in vitro models compared to people. Polymeric NPs continue to show therapeutic promise, although further research is needed. Further information on the ideal polymeric NP composition for treating brain cancer should be gleaned from ongoing clinical trials and future research.

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