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Use of Lipid-Based Nanoparticles for the Treatment of Glioblastoma Multiform; A Review

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Abstract

A malignant brain tumor with a dismal prognosis and few available treatments is glioblastoma multiforme (GBM). The blood-brain barrier (BBB) poses challenges for therapeutic agents reaching the tumor site. Lipid-based nanoparticles (LBNPs) have emerged as a promising solution to get better outcomes in GBM therapy. LBNPs include liposomes, lipid nanoparticles (LNP), solid lipid nanoparticles (SLPs), lipid Nano emulsion (LNE), and nanostructured lipid carrier (NLC). The compromised BBB restricts the amount of medication that can flow through it and prevents it from reaching the tumor location. This review discusses the status of LNPs in GBM treatment, their types, and mechanisms of action, advantages and challenges, including toxicity, reproducibility and targeting ability. The review also explores the combination of LNPs with radiation therapy and immunotherapy to enhance therapy results.

Key Words: Glioblastoma Multiforme, Glioma, Nanoparticles, Blood-Brain Barrier, Brain tumor, Cancer. Liposomes, Nanotechnology, drug delivery, Blood-Brain Tumor Barrier, EPR effect, Gold NPs,

Introduction

Gliomas are malignant brain growth that develops in glial cells, which serve as the supportive tissues for the spinal cord and brain **(Kaur et al., 2024).** This subtype of tumor is managing tumor aggressiveness. A high-grade malignant primary brain tumor most known as glioblastoma multiforme or Grade IV glioma is the classification for GBM. due to rapid mitosis, necrosis, and angiogenesis **(Kaur et al., 2024)**. Oligodendroglia is more commonly seen in men of middle age and it is a particular kind of brain tumor that develops from oligodendrocytes, which are glial, cells that form myelin sheath. The most prevalent and combative kind of CNS tumor is glioblastoma multiforme, which some estimate life expectancy from 12 to 15 months duration **(X. Sun et al., 2023).** GBM patients are usually acquainted with the symptoms like dysphagia, drowsiness, and experiences of the cognitive and neurological deficits over time; as the disease progress they can also have, in addition to that **(Fritz et al., 2016).** Although glioblastoma multiforme (GBM) forms only 1.35% of all cancer cases and is a primary tumor in 54.4% of cases, it is one of the deadliest malignancies, causing 4% of the cancer mortality. GBM is more often found in the cerebellar area that is located 50-56 age-group patients; however, for those who are older (62-64 years), the cerebellar area is only detected in about 0.4-3.4% of cases. Furthermore, the disease that is lethal has got a very less time period of around 8 to 15 months because of improper treatment and diagnosis **(Louis et al., 2007).** The incidence of glioblastoma multiforme is not alienated since it fluctuates among the countries; the usual rates range from two to three cases per every 100, 00 individuals annually. Glioblastoma are classified in WHO's histological classification system as Grade IV, and this is why problems arise like, treatment options that are more complicated because of their cellular and molecular heterogeneity **(Tini et al., 2024).** It is estimated that population of Pakistan is 207.7 million, and it is growing at an ever-escalating rate. The people who sued and those who sued them had never conducted a clinical study on glioma cases in Pakistan **(Farshbaf et al., 2022)**. Gliomas account for 51% of malignancies the central nervous system, together with a frequency of 6.7/100, 000. The prevailing opinion is that by extrapolating the global population's incidence to the Pakistani population, up to 7097 people in Pakistan have fallen victim to glioma **(Abdullah et al., 2019)**.

MRI is the most reliable method for the diagnosis as well as observation newly discovered and recurring masses **(Queiroz, Veriato, Raniero, & Castilho, 2024)**. The conclusions reached with MRI are very important for identifying the patients before the beginning of the treatment and for the assessment of the course of treatment. However, the problems occur due to the fact that regular MRI does not make distinction between CNS masses, primary tumors, and metastases on one hand and real and psuedoprogression on the other **(Breen, Aryal, Cao, & Kim, 2024)**. The radiological characteristics of these diseases frequently overlap. The primary CNS lymphomas, metastatic lesions, and gliomas are typically seen as contrast-enhancing tumors that are encircled by T2-hyperintense oedema. Tumor recurrence for treating individuals with Glioblastoma (GBM), which have 14.6-month median survival have obtained conventional multimodal therapy **(Lei et al., 2024)**. The established treatment of GBM has drawbacks regarding the lack of its medicinal potential for instance neurotoxic side effects and inadequate loading efficiency **(Ghaznavi et al., 2024).** Many patients even after undergoing radiation, chemotherapy, and surgery still face local relapses. One specific of these naturally occurring plant-based chemicals which is known as Alkaloids has overnight become a significant point of research. It has been found in several studies that alkaloids (which are natural plant-based chemicals) might be utilized as potential drugs in the fight of cancer **(Shahcheraghi et al., 2024).**

Nanotechnology applications in medicine have been developing for the last few decades and today they are some of the most innovative technologies in medicine **(Wenqi, Lingxi, Mehmood, & Shah, 2024)**. Tumor targeting, diagnostics, and treatments of cancer among the other have in recent decades been greatly improved by the use of nanotechnology. Nanotechnology agents when treating cancer provide substantial benefits over conventional medicines which not only change the way this complex disease is treated but also revolutionize the whole

treatment protocol system by employing technology **(Ghosh, Ghosh, & Das, 2024).** Nanotechnology refers to the study of structures which measures one millionth of a millimeter in scale. This technology impacts sectors like electronics, energy, and medicine. Nano-sized objects, or nanometer-sized particles, have merged as a new frontier in scientific research. In the last few years, these applications have become commercial reality and have come to the forefront of research **(Cuenca et al., 2006).** Different class of nanoparticles results in different benefits and problems. Organic nanoparticles (ONPs) are under the searchlight for years, and a variety of drug delivery vectors are available for use. The examples include liposomes and vesicles, dendrimers, polymeric NPs (PNPs), and fluorescent organic nanoparticles (FONPs). The existence of many generations of ONP is the outcome of a multitude of years of study. The ability to change the structure of the materials by putting in place various deviations, such as imitating live cell's biophysical properties, promoting the effectiveness of the therapeutic drug delivery process is the result **(Yan et al., 2019).**

Liposomes are round structures made up of hydrophobic lipid tails and a polar head of phosphate groups, which are held together by phospholipids **(Large, Abdelmessih, Fink, & Auguste, 2021).** These are closed bilayer structure that can transport drugs contained within them without regard to the chemical properties of the drugs themselves. The main advantage of liposomes are that they are biocompatible, can encapsulated drugs of different polarities, and protect the medication from the outside environment **(Roque et al., 2023).** Lipids that maintain their solid- liquid state at physiological temperature are solid liquid nanoparticles. The lipid compact core with the phospholipid of these particles might be used that the encapsulation of the hydrophobic medications may be improves **(Ortega-Berlanga, Gonzalez, & Navarro-Tovar, 2021).** The current review is centered on the assessment of existing evidence regarding the progress and issues associated with the application of lipid nanoparticles (LNPs) as a therapeutic agent in GBM treatment. In this article, the author will explore the ways in which LNPs can facilitate drug administration into the CNS, increase treatment effectiveness, and bypass the blood-brain barrier. Also it will provide an overview of relevant studies conducted in laboratory animals and humans examine the potential applications of LNP to treat specific tumor cells and give outlook about improving the treatment strategy through changes in nanoparticles formulation.

Pathophysiology of Glioblastoma Multiforme

GBM that occurs primarily is recognized as the most subtype of GBM, and its expansion occurs within low previous low-grade lesions. Secondary GBM occurs as result of transformation of low-grade astrocytoma. Brain tumors are linked with various genetic and epigenetic modifications which play role in causing the affecting oncogenes and tumor suppressor genes, as well as genes responsible to cellular signaling, and DNA repair. The most prevalent genomic aberrations associated with GBM involves changes in genes such NF1, TP53, PTEN, EGFR, and IDH1 as shown in **(table1) (Alorfi, Ashour, Alharbi, & Alshehri, 2024)**. According to the WHO classification for 2016, primary glioblastoma (diffuse astrocytoma, IDH-wild type, grade IV) has been recognized as a different illness entity compared to IDH and grade II diffuse astrocytoma-wild type because it occurs rapidly de novo without an identified precursor lesion. For WHO Diffuse grading astrocytoma, IDH-wild type status, the existence of high-grade histopathology characteristics (Micro vascular proliferation and/or necrosis) is also the sole discrimination factor from a WHO-classified glioblastoma grade IV tumor **(Louis et al., 2007)**. This point of view has recently been challenged by the increasing appreciation of the molecular features of primary glioblastoma. Genomic research showed that primary glioblastoma, grade IV and most of IDH-wild type Grade II and III diffuse astrocytomas, have clinically similar outcomes, exhibit genetic changes, common features with the better-known IPs **(Gritsch, Batchelor, & Gonzalez Castro, 2022)**. On the 223 dead IDH1/2wt glioma patients, 165 (83.8%) were glioblastomas and 5(74.6%) astrocytoma WHO II and III cases with IDH1/2wt gene profile died before inclusion. All IDH1/2wt glioma patients possessed a median follow-up of 1.5 years (IDH1/2wt astrocytomas): 1.4; GBM: 1.5; IDH1/2wt astrocytomas WHO II and III: 2.9). Comparing the two other subtypes, the median overall survival (OS) of IDH1/2wt astrocytomas WHO II and III was noticeably longer; however, it was comparable to that of IDH1/2wt astrocytomas 47WHO IV (log-rank test: P=0.25) **(Tesileanu et al., 2020)**. According to WHO the diffusely infiltrating adult IDH-wild type astrocytic tumor is graded IV in cases where EGFR gene amplification, TRET promoter mutations or +7/-10 have a grade III IDH-wildtype astrocytomas with anaplastic characteristics. Naturally, "IDH-wildtype diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade IV" was the first entry in its convoluted categorization. 3 genetic abnormalities are the EGFR gene amplification, +7/10 chromosomes number of copies variations and mutation in TERT promoter that may result in micro vascular proliferation, necrosis or IDH-wildtype, WHO grade 4 conditions **(Louis et al., 2020).** Through molecular profiling, a comparable change in CNS WHO grade 2 or 3 diffuse astrocytic, IDH- wildtype glioma has significant predictive and clinical treatment implications. The 2021 WHO classification has removed diffuse astrocytoma as entity in a unitherapy: It is an uncommon situation with IDH-wildtype, CNS WHO 2 or 3 and no molecular characteristics of glioblastoma. Furthermore molecular testing for BRAF changes, histone mutations and methylome characteristics for glioblastoma to confirm the diagnosis **(Gritsch et al., 2022)**.

Table 1: The table was adapted from Louis et.al Neuro-Oncology. This displays the WHO classification for Tumor of the Central Nervous System for 2021.

Tumor Type	Genes/Molecular Profiles Characteristically Altered
Astrocytoma, IDH-mutant	IDH1, IDH2, ATRX, TP53, CDKN2A/B
Oligodendroglioma. IDH-mutant, and 1p/19q-Codeeleted	IDH1, IDH2, 1P/19q, TERT promoter, CIC, FUBP1, NOTCH1
Glioblastoma, a IDH-wildtype	IDH-wildtype, TERT promoter, chromosomes 7/10, EGFR
Diffuse astrocytoma, MYB-or MYBL1-altered	MYB, MYBL1
Angiocentric glioma	MYB
Polymorphous low-grade neuroepithelial tumor of the young	BRAF, FGFR family
Tumor Type	Genes/Molecular Profiles Characteristically Altered
Diffuse low-grade glioma, MAPK pathway altered	FGFR1, BRAF
Diffuse midline glioma, H3 K27-altered	H3 G34, TP53, ACVR1, PDGFRA, MYCN, EGFR
Diffuse hemispheric glioma, H3 G34-mutant	H3 G34, TP53, ARTX
Diffuse pediatric-type high-grade glioma, H3-Wildtype	IDH-wildtype, H3-wildtype, MYCN, EGFR
Infant-type hemispheric glioma	NTRK family, ALK, ROS, MET
Pilocytic astrocytoma	KIAA1549-BRAF, BRAF, NF1
Chrodoid glioma	PRKCA

The main genetic mutations associated with GBM are loss of the PTEN gene that suppresses tumors, deletion or overexpression of the proto-oncogene EGFR, mutation of the TRET promoter, and mutation of the ATRX/TP53 as shown in (Table 1). For primary GBM (IDH- wildtype GBM), there was a higher likelihood of TRET promoter mutation, PTEN deletion, EGFR amplification, but for secondary GBM (IDH mutant-wildtype GBM), there was much a more highly likelihood to have ATRX and TP53 mutations as shown in (Table 1) **(del Pilar Guillermo Prieto & de La Fuente, 2021)**. Important genetic changes related to GBM have also been found for NF1, PDGFRA, MYCN, ACVR1, ROS, CDKN2A/B, BRAF, PRKCA, and FGFR1 as shown in (Table 1) **(Verdugo, Puerto, & Medina, 2022)**. Senescence avoidance, tumor growth beginning, and normal growth are the three primary biological processes that are generally indicative of genetic anomalies in GBM **(P. Y. Wen et al., 2020)**. Through the important signaling pathways, genetic abnormalities in each of these three processes appear necessary for gliomagensis **(Lan, Li, & Zhang, 2024)**.

Types of Lipid based Nanoparticles for Drug Delivery

These LBNPs are in essence spherical, nano-sized vessels carrying lipids and other structural elements. On the basis of composition and structure, Liposomal, lipid nanoparticles (LNP), solid lipid nanoparticles (SLNPs), lipid nano emulsion (LNE) and nanostructured lipid carrier (NLC) are the five kinds of LBNPs **(Hu, Li, You, Cai, & Chen, 2024)**.

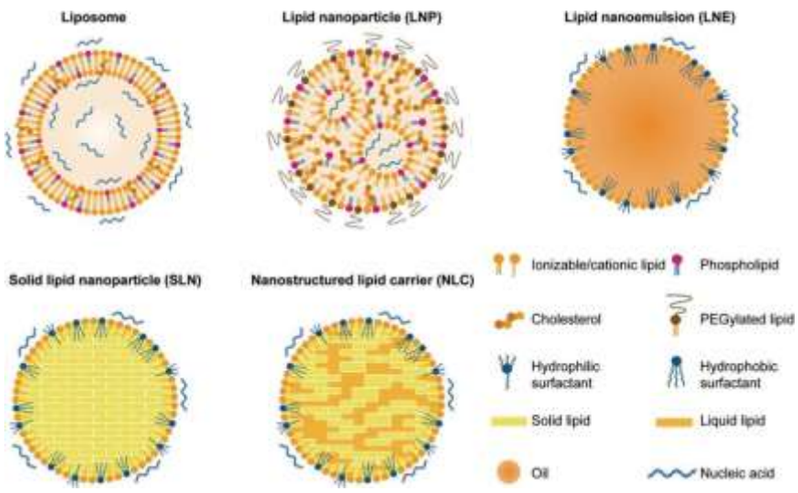


Figure 1: The five types of LBNP liposomes: lipid nanoparticles, lipid nanoemulsion, solid lipid nanoparticles, and nanostructured lipid carrier, liposomes are shown schematically **(Hu et al., 2024).**

Liposomes

Liposomes are categorized called SUVs, or tiny unilamellar vesicles or LUVs, or large unilamellar vesicles considering their size and numbers of bilayers, multivesicular vesicles and the multilammeter structures have resemblance to onion. Due to the smaller unilamellar vesicles that were found inside larger liposomes, MUV has a multilamellar configuration featuring phospholipid spheres that are concentric as shown in **(Figure 2) (Maja, Željko, & Mateja, 2020)**. Liposomes Lipid Bilayer Liposomes Size How Liposome penetrates to the skin Hydrophilic substances only. The dimensions and quantity of bilayers determine the amount of medicine

enclosed. When liposomes are used for medication transportation, the vesicles are 50- 150nm in size as intended. There are different beliefs liposome's interactions with cell membrane, include phagocytosis, membrane absorption, local fusion, and selective or nonspecific endocytosis **(Nsairat et al., 2022)**.

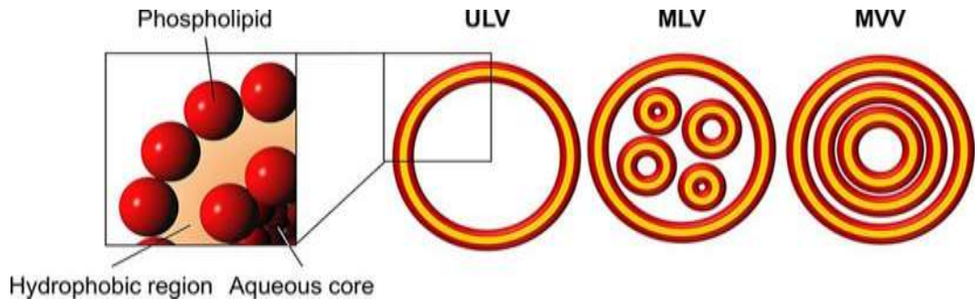


Figure 2: Overview of different type of liposomes **(Lai, Wong, & Rogach, 2020).**

The primary benefits of liposomes are their biocompatibility, ability to encapsulate a variety of compounds (polar and non-polar), and shielding the medicine within from outside influences as shown in (Figure 1). Liposomes' brief half-life while in use and propensity for quick removal by the RES is their drawbacks. PEGylation of liposomes inhibits RES absorption, hence preventing this fast clearance and increasing therapeutic efficacy **(Jaradat, Meziane, & Lamprou, 2024)**. The high expense of manufacturing these NPs is another significant drawback that prevents research into them from spreading and, as a result, delays our understanding of their potential therapeutic uses **(Ruiz-Garcia et al., 2021).** Concerning the creation of liposomes, it normally requires various successive phases. First, lipids are added to a uniform solvent solution at predetermined concentrations and temperatures **(J. Chen et al., 2024)**. Secondly, the solvent is eliminated, and an aqueous solution containing the lipids is combined. Lastly, the particles undergo purification and characterization. The following stages entails medication inclusion these nanoparticles contain might be either active or passive **(AbouSamra, 2024)**. Hydrophobic medications can be loaded into liposomes passively, which is best done when the liposomes are being constructed. However, active drug loading, which is typically utilized to encapsulate hydrophilic (polar) medications, is carried out after the liposomes have been created **(Zhu et al., 2021).**

Lipid Nanoparticles

Another is lipid nanoparticles class of nanoscale lipid-based systems that are derived from liposomes. In contrast, LNPs lack an internal aqueous core and closed lipid bilayer structure as shown in **(Figure 1) (Samaridou, Heyes, & Lutwyche, 2020)**. Depending on the formulation and payload, LNPs instead taken on self-assembled morphologies such as multilayer vesicles, homogenous core-shell, and nanostructured nuclei **(Pilkington et al., 2021)**.The most commonly recognized structural explanation of LNPs states that stable nanostructures are formed when inner NADs and lipids combine to create inverted micelle nuclei encircled by outside lipids **(Schoenmaker et al., 2021)**. However, further research is necessary to establish the morphology of LNPs because the nucleic acid-lipid complexes inside them are currently poorly known. Helper phospholipids, PEG-lipids, cholesterol, and ionisable lipids make up the four main parts of LNPs. The most significant elements of LNPs is ionisable lipids **(Eygeris, Gupta, Kim, &** Sahay, **2021)**.

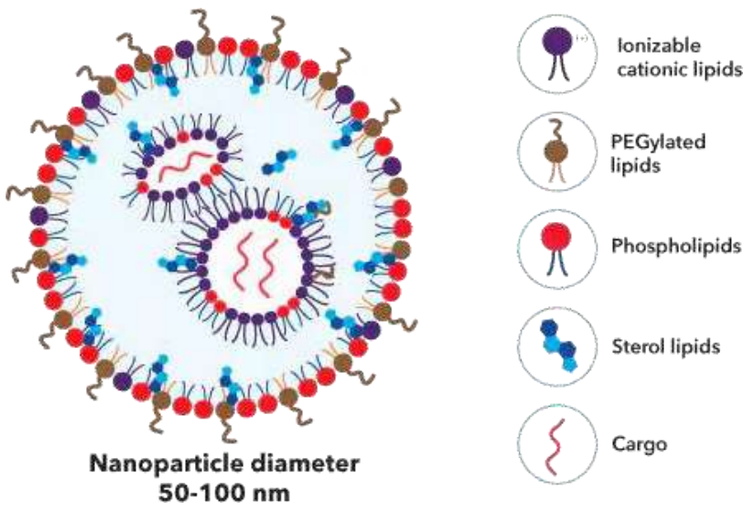


Figure 3: Schematic diagram of lipid nanoparticles. Besides improving uses in food and cosmetic industries, LNPs are crucial in modern medicine because they target certain cells for mRNA vaccines, gene therapy, cancer treatments, and protein replacement therapies. Ionisable lipids can be made to change state in a pH dependent manner, due to their pH dependent ionization behavior as shown in **(Figure 3)**. LNPs are cationic during lipoprotein precursor preparation and help to condense nucleic acids by electrostatic interaction. This is so they neutralize to become toxic at a physiological pH. However, once inside, acidic endosomal environments they became positively charged again to aid in the release of nucleic acids. Cholesrtol found in natural cell components and therefore in the typical LNPs may affect the fusion characteristics of particle membranes and enhance the stability of LNPs by modulating inter-lipid space, since cholesterol occupies this space **(S.-T. Yang,**

Kreutzberger, Lee, Kiessling, & Tamm, 2016). A second a type of structural lipid in LNPs is helper phospholipids. These amphiphilic lipids are essential to maintain the LNPs assembly and structure because they provide high phase transition temperature and can self-organize in a bilayer. Helper phospholipids also impacted the biological targeting and membrane fusion behavior of LNPs **(L. Zhang et al., 2019)**.What is an PEG-lipid? A compound with an anchor lipid and a PEG polymer, Q: Steric hindrance with the PG chain prevents LNP fusion and aggregation during preparation, facilitating formation of homogeneous and maintainable LPNs with long-term stability as shown in **(Figure 1)**. By changing the PEG-lipid ratio, we can modify the size of LNP particles as shown in **(Figure 3) (Albertsen et al., 2022)**.

Solid Lipid Nanoparticles

Submicron-sized spherical vesicles containing solid lipid core and surfactant monolayer shells are called solid lipid nanoparticles, or SLNs as shown in **(Figure 1)** the most important characteristics of SLNPs is that their lipid components, both at body temperature and room temperature are solid **(Naseri, Valizadeh, & Zakeri-Milani, 2015)**. Lipophilic medications are typically incorporated in a solid lipid core, which prevents drugs breakdown and produces effects of sustained release. SLNs are desirable substitute for liposomes and LNEs since they are also appropriate for extensive synthesis not using organic solvents and possess comparatively good strength **(Scioli Montoto, Muraca, & Ruiz, 2020)**. 3 β[N(NO,NO- dimethyaminomethane)carbonyl] cholesterol (DC-Chol), benzalkonium chloride (BA), cetylpyridinium chloride (CPC), cetrimide (CTAB), N,N-di-(β-stearoylethyl)-N,N- dimethylammonium chloride (Esterquat, EQ1), N-[1-(2,3-dioleoxyloxy) propyl] are examples of catalytic lipidic co-surfactants. Dimethyldioctadecylammonium bromide (DDAB) and N, N, N-trimethylammonium chloride (DOTAP) are occasionally employed as SLNs **(Kong et al., 2013)**. Lipids that stays solid at physiological temperatures make up solid lipid nanoparticles, or SLNs. The phospholipid coating on the lipidic (hydrophobic) compact core of these particles can improve the entrapment efficiency of hydrophobic medications **(Mehnert & Mäder, 2012)**. There is ongoing discussion over the processes that let SLNs to enter the central nervous system. While earlier research suggested that the primary channel for nanoparticle availability in the brain was paracellular entrance of the particles through transient relaxation of endothelial cells tight connections in the blood-brain barrier, more recent research indicates that NP endocytosis is the most common pathway **(Scioli Montoto et al., 2020).** A SLN encapsulating carmustine and another encapsulating temozolomide were created by Ak et al. and were subsequently employed in vitro in U87MG cells. Comparing this therapy method to unencapsulated temozolomide and unencapsulated carmustine, the authors demonstrated greater anticancer activity **(Ak et al., 2021).**

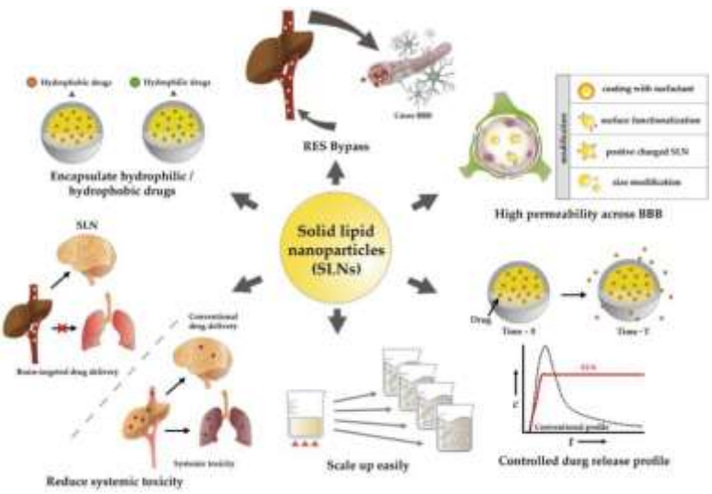


Figure 4: The following are the uses of SLNs and their derivatives: Because of its distinct physicochemical makeup, hydrophilic and lipophilic drug encapsulation can bypass the RES systemic toxicity, provide prolonged or regulated medication release that is scaled up in a time- dependent fashion economically. It is suitable for passing across the blood-brain barrier for medication administration to targeted targets **(Satapathy et al., 2021).** As a nontoxic method for medication carriers that successfully penetrates the BBB, SLNs enable regulated drug administration and decreased toxicity, which can be widely useful in the future clinical procedure for the management of a variety of neurological diseases (**Figure 4) (Saadh et al., 2024).** SLNs and NLCs are applied in order to keep up sustained therapeutic levels, increase the amount of bioavailable low-solubility medications, and control drug release. Their the capacity to entrap various medications, from tiny molecules to big biologics such as Nucleic acids and proteins expands the range of applications for pharmaceuticals in medicine **(Raj et al., 2021).**

Lipid Nanoemulsion

Phospholipids and emulsifiers stabilize the nanoscale droplets known as lipid nanoemulsions (LNEs), which usually take the form of oil in water. **(Figure 1) (Hörmann & Zimmer, 2016)**. To further enhance the therapeutic efficacy, lipophilic drugs such as squalene-an adjuvant proved to be safe and effective-can be introduced into the internal oil core of LNEs. In most case; DOTAP, a cationic lipid, is incorporated into the phase of oil to electro statistically add nucleic acids to the LNEs' surface **(Brito et al., 2014).** The benefits of LNE are numerous. Enzymatic breakdown of nucleic acids is prevented by the oil phase **(Ayer & Klok, 2017)**. LNEs have high adsorption rate in vivo due to their wide surface area, which lead to a high drug bioavailability **(Jaiswal, Dudhe, & Sharma, 2015)**. Aside from these, LNEs also have fusogenic properties that initiate a kind of particle-cell membrane contact that is not digested, thereby enhancing cellular uptake. According to our knowledge GEMCOVAC-19, which is produced by GENNOVA, is one of the limited numbers of NADs that

depend on LNEs which has successfully been employed in clinics so far. With mRNA encoding the S-protein of SARS-CoV-2 adsorbed on LNEs with polysorbate, DOTAP, and squalene, this forms the very first approved use by COVID19 as vaccine in India **(Blenke et al., 2023)**.

Nanostructured Lipid Carrier

As shown in **Figure 1**, nanostructured lipid carriers with a liquid oil phase and a solid lipid phase as the core of NLCs. The core is hybrid formulation between LNEs and SLNs. Actually it is acknowledged that NLCs are modified second-generation SLN **(Scioli Montoto et al., 2020).** The stability and loading capacity of drugs are improved by destroying the crystallinity of solid lipids by adding a liquid oil phase into the core **(Xu et al., 2022).** Like SLNs, cationic lipids, such as DOTAP, are typically added to NLCs to provide them the ability to transport nucleic acids. Yet, however, effective clinical application of NLSs for the administration of NAD has yet to realized **(Hu et al., 2024).**

Mechanism of Drug Encapsulation and Release

It is clear that apart from their lesser attraction to immune cells, PCNs can locally deliver highly specific therapies using endogenous (pH, redox, hypoxia, enzyme) or exogenous (light, ultrasonic, magnetic, temperature and radiation) stimuli as the catalyst for regulated drug release through hydrophobic/hydrophilic transition, degradability, ionizability etc. **(Chauhan, Basu, Yadava, Sarviya, & Giri, 2022).** The movement of these stimuli-active polymeric nanocarriers loaded with therapies are mostly likely capable of improving anti-GBM responses and prolonging survival in mouse models. The possibility to go through the BBB and specifically gathering in glioma cells were markedly improved by encoding targeting into these nanocarriers **(Hasan, Chauhan, Basu, & Giri, 2024).**

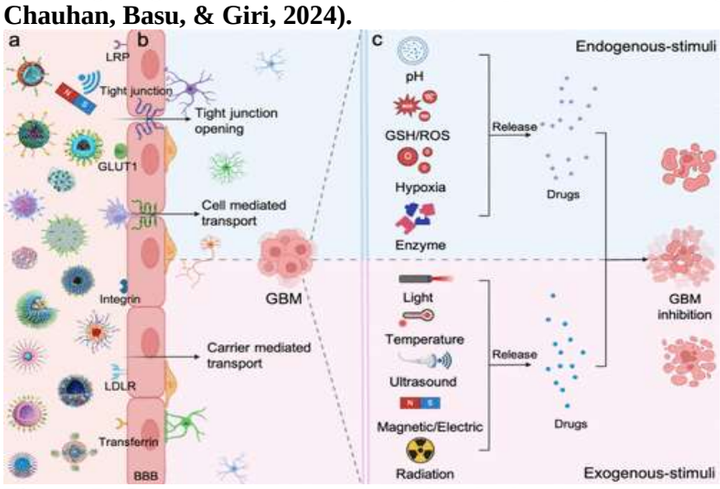


Figure 5: Schematic representation of multiple stimuli-active nanocarriers causing therapeutic drug release following successful blood-brain barrier **(Ismail et al., 2024).**

The nanocarriers will release drugs based on pH variations, which actually decrease the intracellular decrease the intracellular pH of the TMEC to an acidic condition. This is advantageous since the intracellular pH of the TME is lower compared to that in normal **(Meher & Poluri, 2020)**. The two main strategies in the design of pH-responsive polymeric nanocarriers are specific functional groups or chemical linkers sensitive to pH **(Meher & Poluri, 2020)**.

pH Responsive

Specific pH values because the pH-sensitive linkers used in pH-responsive polymeric nanocarriers to change shape or decompose, leading to medication release as shown in **(Figure 5) (Peng, Xiao, Chen, & Gao, 2022).** Tumors primarily generate a substantial amount of lactic acid because of their metabolic characteristics, resulting in a low pH and an acidic environment in the TME **(S. Thakkar, Sharma, Kalia, & Tekade, 2020).** The pH-sensitive linkers of pH- sensitive polymeric nanocarriers change shape or cleave at specific pH to release drugs. Since the metabolic profile of tumors primarily generates a tremendous amount of lactic acid, the TME is weakly acidic with a lower pH **(Ismail et al., 2024).**

Redox Responsive

Redox-sensitive nanocarriers take advantage of the redox potential gap between normal and tumorized brain tissues. The nanocarriers are engineered with redox-sensitive parts that would structurally change their conformations with alterations in redox potential. Therefore, it is possible to control the medicines release. In normal cells, redox processes tends to be in dynamic equilibrium **(Y. Yang, More, De Smet, De Vleeschouwer, & Agostinis, 2024).** However, the most important reason for this disequilibrium is the abnormal metabolism of tumors, which leads to environments around tumors that are dominated by hypoxia, overproduction of ROS, and very high levels of GSH as shown in **(Figure 5)**. Redox-sensitive polymeric materials in response to ROS and GSH and their characteristics and applications will be summarized in this section **(W. Liu et al., 2020)**.

ROS-Responsive Nanocarriers

The overexpression of superoxide dismutase causes the majority of cancer cells to produce significant amounts of reactive oxygen species (ROS) inside cells as shown in **(Figure 5) (Ismail et al., 2024).** ROS are also integral components in the initiation and progression of carcinogenesis, and their formation is further supported by alterations in the genetic and energy metabolic patterns of tumor cells. Tumorigenic conditions cause an increase in ROS generation within cancer cells due to intracellular redox imbalance **(N. Yang, Xiao, Song, Wang, & Dong, 2020).** Oxidation-sensitive linkers or groups can be introduced into these elevated ROS levels that act as endogenous initiators for drug release. Polymeric nanocarriers capable of responding to changes in ROS should be developed for the diagnosis and therapy of GBM **(Oddone et al., 2020).**

Hypoxia-Responsive Nanocarriers

An oxygen shortage, or hypoxia, is a typical characteristic of many malignancies, including GBM **(Stadlbauer et al., 2021).** The abnormal vascular structure and malfunctioning arteries in tumors cause hypoxic areas to emerge, which consequently change the metabolic pathways of malignant cells, in contrast to normal tissues as shown in **(Figure 5).** Oxygen-sensitive chemical linkages or groups form the backbone in the hypoxia responsive design of the polymers: for example, 2-nitroimidazole, nitrobenzene, and azobenezene. To put it in simple words, use of hypoxia-responsive polymeric nanocarriers offers bright promise for GBM therapy **(C.-S. Yuan et al., 2021).** Because the vascular structure of GBM is usually distorted with rapid growth, it commonly comprises hypoxic areas that constitute crucial factors involved in development and spread of tumor. The hypoxia-sensitive polymers contain hypoxia-active moieties or structures; hence they might become chemically or structurally susceptible to the hypoxic environment. The mainstay for the design of hypoxia responsive polymers contains oxygen-sensitive chemical bonds or groups such as 2-nitroimidazole, nitrobenzene, and azobenezene **(Kumari, Sunil, & Ningthoujam, 2020).** Hypoxia responsive polymeric nanocarriers show clear promises for application in GBM treatment. Due to their aberrant vascular architecture with fast growth, GBMs often feature hypoxic areas, which are crucial factors in tumor proliferation and metastasis. Hyposing-induced chemical or structural alteration under hypoxic conditions: polymers are conjugated to active moieties or structure-bearing hypoxia by these polymers **(Ismail et al., 2024).**

Enzyme-Responsive

Enzymes are involved in almost every biological and metabolic activity and are distinguished by their remarkable selectivity and effectiveness toward substrates as shown in **(Figure 5) (Mu, Lin, Huang, & Chen, 2018).** Remarkably, changes in the enzymatic environment have been noted in several disease-related environments, such as GBM TME **(J.-H. Choi & Choi, 2020).** An upward pace for researching enzyme-active polymeric nanocarriers is being placed toward treatment against GBM. Certain enzyme conventions, particularly those pertaining to the complex environment of GBM (namely MMPs, CatB, and phospholipases), deviate greatly from such customary levels in normal tissue regions. They are directly involved with various events related to angiogenesis and tumorigenic cell movement through cell migration and invasion **(Ismail et al., 2024).**

Exogenous Stimuli-Responsive Polymeric Nanocarrier Light Responsive:

It is a special type of energy owing to several wavelengths of light like ultraviolet (UV), infrared, and near-infrared (NIR) light. Photo responsive polymeric nanocarriers usually work through two distinct mechanisms: (1) they are loaded with a photosensitizer to allow for the activation/disassembly by photoresponse, or (2) they contain photoleveage/photoisomerization connections. Comarin **(Benoit et al., 2017),** o-nitrobenzyl **(Y. Yuan, Min, Hu, Xing, & Liu, 2014),** spiropyran **(S. Chen et al., 2016),** anthracene **(C.-C. Cheng et al., 2019)**, cinnamonyl **(Kitayama & Harada, 2021),** uracil **(Gebeyehu et al., 2018)**, and azobenezene **(Zhao et al., 2018)** are some of the photosensitive moieties that have been studied for regulated drug administration and are often included in the proposed light-responsive nanocarriers **(Mahdi, Parham, Soodeh, Mehdi, & Hamid, 2017).** Due to its noninvasive, cost-effective, and feasibility nature, light is employed in modern nanomedicine for the treatment is a number of diseases, including GBM, **(Jin et al., 2014)** used acid-labile β-thiopropionate couplings and o-nitrobenzyl as a light-cleavable linkage to generate light-responsive polymeric nanoparticles. When the NPs are exposed to ultraviolet light, the DOX-loaded NPs degrade to yield. The photo cleavage, breaking the o-nitrobenzyl linkage in a controlled manner, is utilized for medications. In the instance of glioma cell PDT, the polymer photosensitizer is activated by the visible light was up-converted to generate ROS **(Zhao et al., 2018).** Recent research has demonstrated that PDT/PTT has great promise for enhancing tumor therapeutic effectiveness and therefore, a lot of interest has been taken into these approaches, PDT is recognized as a potentially useful technique for treating cancers that generate ROS in situ by exposing a photosensitizer to a specific light wavelength. Clinical trials indicate that malignant glioma surgery under photosensitizer 5-aminolevulinic acid (5-ALA) improves the survival outcome of GVM patients more than the control group **(X. Li, Lovell, Yoon, & Chen, 2020).** A Phase I clinical study, NCT101682746 was initiated with a increase in photofrin dosage in combination with to ascertain the maximum tolerated dosage for children under a specified illumination intensity **(Gunaydin, Gedik, & Ayan, 2021).** Miraculously, three patients receiving 0.5mg/kg of Photofrin for infratentorial tumors experienced no adverse side effects with PDT. During the Phase I/II study, PDT was administered using incrementally low doses, eventually reaching 230J/cm2 for OS in the freshly diagnosed and the recurrently diagnosed GBM at a month rate of 14.3 and 13.5 respectively **(Gunaydin et al., 2021).** An additional, large clinical trial phase III is performed to investigate the safety profile and effectiveness of 5-ALA with PDT against HGG **(Mahmoudi et al., 2019).** To thermally kill the malignant cells without harming any of the adjacent healthy tissues, PTT uses photo thermal molecules to convert NIR light energy into heat, which is another non-invasive method of tumor treatment. Developed a photoacoustic imaging (PAI)-guided PTT that utilizes a second near-infrared (NIR-III) absorbent polymer (PDTP-TBZ) fused to an electron acceptor (thiadiazolobenzotriazole) and an electron donor (dinitheinopyrrole; DTP). Though the dual modification strategies of D-A units and pie conjugation implication, **(Guan et al., 2023)** successfully developed a perylene monoamide- based NIR-II PTA (N1) that exhibited NIR-II absorption. N1 was encapsulated in N1@2P NPs with a controlled size of around 26nm, and such NPs crossed the BBB. N1@2P NPs yielded strong PTT effects by increasing mobility and enrichment in orthotopic brain tumors **(Guan et al., 2023).**

Thermo Responsive:

Following the therapy, there was no discernible change in body weight, thus suggesting that N1@2P NPs and the PTT technique are safe **(C. Wang, Zhang, Liu, Hu, & Liu, 2017).** Meanwhile, systemically administered polymeric nanocarriers containing photosensitizer (ICG) have also shown promising results in GBM tumor models, **(Mi, 2020).** Theranostics approaches utilizing PTT and fluorescence imaging, as well as several other non-invasive therapies, have been described and hold much promise for GBM treatment **(Roussel, Udabe, Sabri, Calderón, & Donnelly, 2024).** In responding to mild hyperthermia, thermoresponsive nanocarriers can

switch between states by using heat as an initiation cue for their release by changing their chemical and physical properties. Even if the nanocarrier structure can change due to alterations in temperature, it is significantly stable at a specific temperature. PNIPAM is the common polymer with temperature-response activity, which has the LCST of 32 degree Celsius. The structure of poly (N-vinyl caprolactam) gradually transitions from coiled to globule in the temperature range 36-50 degree Celsius **(Kozlovskaya et al., 2019).** Temperature activated DOX release is observed in a study that investigates DOX-loaded PVS-b-PNVCL micelles; 90 percent was released at 37 degree Celsius with duration of 72 hours **(H. Wang, Xu, Chen, & Ullah, 2024).** Due to this swelling/collapse behavior by the polymer, thermodependent discharge was encountered with bupivacaine at 45 degree Celsius **(de Solorzano et al., 2019).** At pH 5, the DOX/ICG micelle encapsulated in HA-polyacrylamide-co-acrylonitrile showed a slow release of DOX; at 80.7 percent 45 degree Celsius **(G. Qiu et al., 2024).** At 45 degree Celsius, a DTX delivery platform based on a thermosensitive poly (NVCL-co-AAM)/PAMAM dendrimer showed greater release of DTX. For GBM patients, thermosensitive polymeric nanocarriers with controlled release properties may provide more reliable and effective treatment options **(Mohammad Asghari, Samadi Zadeh, Ahmad Panahi, Hesami Tackallou, & Safaeijavan, 2023).** Hydrophobic and hydrophilic moieties are combined to make the thermoresponsive hydrogels, which can turn a liquid into a gel state upon reaching a specific temperature. Different thermosensitive polymeric gel-based nanosystems have been used for medication delivery for the treatment of GBM.

Ultrasound Responsive

Many US-responsive nanocarriers, including micelles, microbubbles, nanobubbles, nanodroplets, liposomes, and emulsions, have been proposed as shown in (Figure 5) **(Abousalman-Rezvani et al., 2024).** US are critical in many fields of medicine **(Tu et al., 2021).** There is a surge of interest in US-driven drug release from polymeric nanocarriers using mechanical cultivation, thermal effects, or US-labile linkers **(Paris et al., 2018).** According to **(B. Liang, Wang, & Xia, 2020)**, in the presence of US radiation, a metal-supramolecular copolymer (PPG-Ru-PEG) was obtained that lead to scission at US-labile either linkage. **(J. Wang, Pelletier, Zhang, Xia, & Zhao, 2009)** prepared a diblock poly (ethylene oxide)-b-poly (2-tetrahydopyranyl methacrylate) copolymer that, upon exposure to US radiation, undergoes a chemical change leading to controlled disassembly by mechanical and thermal processes. **(Salgarella et al., 2018)** found that US therapy increased the release of Dex (dexamethasone) by 105% through mechanical effects. Under metastable conditions, homopolymeric nanocarriers of poly(amic acid) and poly(methoxyethyl methacrylate) showed US-responsiveness **(Dou et al., 2020).** This can be done by changing the self-assembly temperature control. Other research has shown that disulfides linkages **(Tong, Lu, & Xia, 2014),** ester **(F. Li, Xie, Cheng, & Xia, 2016),** and silicates **(J. Zhang et al., 2024)** network are US-responsive mechanophores. Many diseases have been diagnosed and treated using US technology, especially when it comes to deliver therapeutic medications to the brain through interfering with the blood brain barrier as shown in **(Figure 5)**. The tolerability and feasibility of delivering IMZ and liposomal DOX through the BBB opening were demonstrated in 2015 when the first noninvasive US-mediated BBB opening clinical studies were conducted on individuals with malignant GBM **(Mainprize et al., 2019).** An additional phase I–II clinical study enhanced the transport of carboplatin to the brain through the pre-treatment of GBM patients with US and systemically administering microtubules **(Cabral, Li, Miyata, & Kataoka, 2024). (T. Sun et al., 2023)** have demonstrated that US activation promotes drug delivery to GBM through BBB permeability. Moreover, sun utilized targeted US to deliver an injectable flexible hyaluronic acid construct carrying CPT and DOX in the brain. The research also proposed a new combination of a cationic microtubule and an anionic polyanion that contains boron to achieve targeted US-assisted to brain tumor **(Fan et al., 2019).**

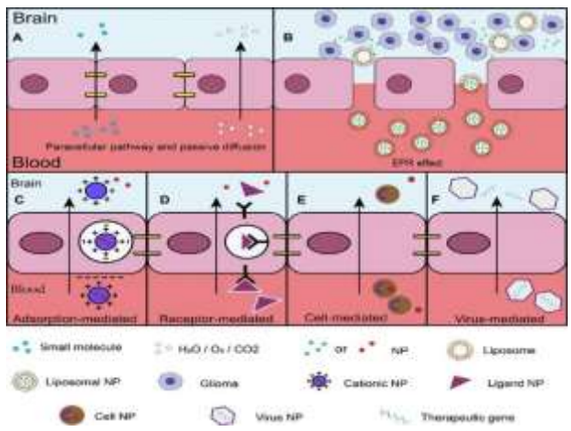
Targeted Delivery Strategies for Glioblastoma Multiforme

Probably, amongst all nondrug delivery technologies, liposomes are those most widely investigated and used. Liposomes are spherical vesicles having water-based core covered with one or more lipid layers; size of liposomes usually range from 20nm to 1 so they may be considered as monolayer or multilayer phospholipid bilayer materials **(ter Linden, Abels, van Solinge, Neefjes, & Broekman, 2024).** Liposomes possess many advantages: they are highly biocompatible, flexible, biodegradable, nonimmunogenic, and their toxicity is relatively low; in addition, liposomes protect their drugs against enzyme hydrolysis. In the general, low penetrability determines whether the treatment is successful. However, in comparison to this, in targeted drug delivery, it is claimed that the therapeutic agent is being accumulated at the target site through the circulation **(de Oliveira et al., 2024)**.

Passive Brain Targeted Drug Delivery

Under normal circumstances, drugs can passively enter the brain by way of paracellular pathways and passive diffusion. The connections between the densely packed endothelial cells, however, prohibit all big molecules and 98% of tiny molecules from passing through paracellular channels into the brain. In addition, only water, carbon dioxide, and oxygen can penetrate into the BBB passively because it is semi-permeable **(Khalil et al., 2024)**.The majority of drugs in formulations for passive targeting aggregate within macrophages due to tumors high retention effects and permeability, as well as the impact of medication surface and particle size characteristics; Less than 7 .When m, the spleen and livers macrophages often ingest it; 200- 400nm nanoparticles concentrate behind the liver and are promptly removed by it; In the bone marrow, nanoparticles less than 10nm gradually accumulate; Particles larger than 7 micrometer are typically captured by the lungs tiniest capillary bed through mechanical filtration, where they are then consumed by air bubbles or monocytes entering the lung tissue. There is one unique phenomenon called the EPR effect in tumour tissues **(Sripathi, 2024).** This was due to unique architectural and pathophysiological features of tumors through which nanomaterials could enter cancer tissues by large gaps between vascular endothelial cells of the tumour **(J. Fang, Islam, & Maeda, 2020)**. Additionally, the presence of obstructed lymphatic drainage in the tumor region allows NPs to reside within cancer tissues for an extended period, resulting in prolonged action of the drug. Therefore, in the last three decades, nearly all the NDDS used in tumor therapy have been closely linked to the EPR effect

(Mozhei, G. Teschemacher, & Kasparov, 2020). Notably, the EPR effect may be directly or indirectly influenced by the NPs' size, shape, softness, and surface characteristics **(Ikeda-Imafuku et al., 2022).** For an instance, NPs with a wavelength between 12 to 200 nm can efficiently target areas with cancer; NPs larger than 200nm are strip by a single phagocytic activity while NPs smaller than 12nm are cleared by kidneys **(Caro, Avasthi, Paez-Muñoz, Leal, & García-Martín, 2021)**. According to the studies, rod-shaped NPs collect more quickly in lung cancer, while spherical NPs aggregate fastest in breast cancer **(R. Zhang et al., 2021)**. Nonetheless, the EPR effect can reduce if cationic NPs aggregate with anionic proteins in blood. Even if the exterior charges of the majority of NPs are unlikely to influence the impact of EPR in most situations, there are



few that may counter the passive targeting in dependence of the EPR effect **(S. Thakkar et al., 2020).**

Figure 6: Varied mechanisms for Drug Delivery that targets the brain both passively and actively. (A) Paracellular pathways, where 2% of tiny molecules entering the brain, make up the BBB's semi-permeability, which permits passive diffusion of just oxygen, carbon dioxide, and water; (B) The primary mechanism of cell-mediated transcytosis (CMT) is determined by the characteristics of the cell itself. **(S. Thakkar et al., 2020).**

Active Brain Targeting

Incomplete targeting is a characteristic of all therapeutic dosages, and even if passive targeting has considerable edges in the therapy of tumors, some drug compounds tend to diffuse out surrounding normal tissue. The importance of the EPR impact in tumor therapy for NP drugs has been a matter of contention for several years **(Shi, van der Meel, Chen, & Lammers, 2020).** Interestingly, research has demonstrated that the majority of nanoparticles (roughly 97%) are taken to tumor sites by active transport mechanisms instead of using the augmented permeability and retention effects as shown in **(Figure 6)**. Consequently, due to the enhancement of the drug delivery accuracy, active targeting is becoming more and more common in practice **(Sindhwani et al., 2020).**

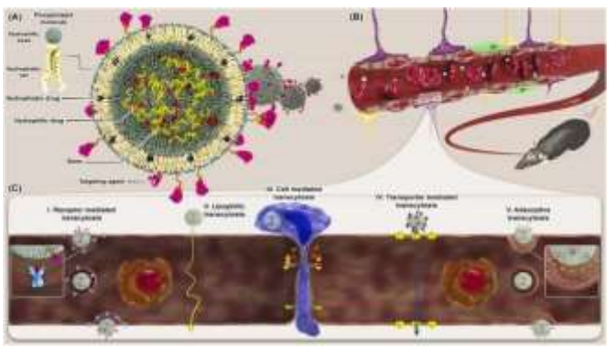


Figure 7: A schematic presentation comprising liposomes that have been functionalized and loaded with various therapeutics.**(Teixeira, Lopes, Amaral, & Costa, 2023).**

Adsorption-Mediated Transcytosis

The AMT has been thoroughly studied by the researchers as the main route in order to actively target the brain medication delivery **as shown in (Figure 6) (Song, Lu, Leszek, & Zhang, 2021).** The key mechanism is the cations and anions electrostatic interactions. In particular, there is a strong adsorption because of the electrostatic interactions between surface anionic epithelial cell membrane and cationic nanoparticles which lead to transcytotic vesicle production as shown in (Figure 7). Afterward these vesicles are incorporated into the cell membrane, transporting the NPs inside the brain **(W. Liu et al., 2020).** Eventually these vesicles fuse with plasma membrane and release the NPs across the blood-brain barrier (BBB). Hence, numerous NPs have been adapted to interstitialize through BBB by associated polymers with positive charge complimentary molecules such as cell-penetrating peptides (CPPS) or by simply surface modifying the NPs using commercially available cationic molecules like chitosan (CS) **(Gravina et al., 2022).**

Receptor-Mediated Transcytosis

RMT represents a potentially effective methodology for actively directing medication delivery to the brain as shown **(Figure 6)**. The main process of ligand binding involves certain receptors. AMT's cationic surface and electrostatic interactions may increase cytotoxicity are nonspecific **(Song et al., 2021).** RMT is safer, more precise, and more selective as a result. In the last years many receptors such as Tf (TfRs) **(Ramalho, Bravo, Loureiro, Lima, & Pereira, 2022),** Lf (LfRs) **(Janjua et al., 2021),** insulin (IRs) **(Kuo & Shih-Huang, 2013),**

lipoprotein receptors (LPRs) **(R. Wang et al., 2022),** expressed in brain tumor cell and the blood-brain barrier. Drug delivery by the use of certain ligands for these receptors is advantageous **as shown in (Figure 7) (R. Wang et al., 2022).**

Cell-Mediated Transcytosis

CMT is a potentially effective treatment strategy that makes use of a range of human brain cells. Some cells are recognized as "Trojan horse cells" because they are able to cross the blood-brain barrier and act as medication transporters **(Ayer & Klok, 2017).** Leukocytes, stem cells, and red blood cells are few examples. The drug half-life is prolonged by this delivery strategy because carrier cells have an innate ability to circulate for prolonged duration **(Azarmi, Maleki, Nikkam, & Malekinejad, 2020).** Furthermore, CMT has lesser immunogenicity and cytotoxicity as compared to other delivery modalities, which substantially reduces negative body reactions **as shown in (Figure 7) (Pawar et al., 2022).** Here, leukocytes are the main subject. You can find reviews alternatives drug delivery system according to various sorts of cells that are not included here **(Y. Chen et al., 2023).**

Viral-Mediated Transcytosis

Presently, nothing is known about how viruses act as carriers to cross the blood-brain barrier, maybe by RMT or other means **(W. Chen et al., 2021).** Viruses have the unique capacity to adhere to and enter host cells, it enables them to stay away from the host's immune system. The virus replicates through reverse transcription after host entering the host cell and releasing in DNA **(Loo, Bose, McCarthy, Azmi, & Madheswaran, 2021).** Thus, the use of viruses for medicine delivery has attracted a lot of attention. In gliomas, viruses has been employed as gene therapy carriers over the last 20 years **(Mozhei et al., 2020).** Immunogenicity, however, can result in severe side effects, including infrequent instances of treatment-related death **(Hamilton & Wright, 2021).** Thus the safety of viral carriers should be evaluated in detail before their employment. Among the current viral carriers, lentivirus (LVs), adenoviruses (Ads) and AVV are noteworthy, but AVV are the ones of interest **(Pena et al., 2020).**

Nanoparticle Penetration of Blood Brain Barrier BBB

GBM has emerged to be very heterogenic malignancy, which makes it extremely difficult in choosing treatment options. In administrating medication to the GBM tumor location, scientists have so far faced several problems. The BBB is a very unique vascular interface that restricts blood-borne chemicals from the neuronal environment as shown in **(Figure 8) (Kaur et al., 2024).** It has strong connections between capillary endothelium these cells, integrated microglia, pericytes, basement membrane and it is enveloped by a glial membrane surrounded by astrocytes that all play important notes in maintaining CNS homeostasis. Gliomas, place narrow interactions restrain flow of water soluble substances coming from the bloodstream into the brain include some of the pathological diseases that might compromise brain-blood barrier integrity. **(Z. Qiu et al., 2022).** In GBM, the BBB is significantly distorted and exhibits diffuse infiltration. Reactive oxygen species, TGF-B2, caveolin1, and other glioma-derived factors stimulate MMPs, which disrupt junctions in GBM. The formation of abnormal blood vessels is due to the degradation of the vessel basement membrane, the extracellular matrix surrounding it, and the migration of endothelial cells. Another possible hypoxia-inducible factor is vascular endothelial growth factor, or VEGF. is overexpressed when the body creates new blood vessels. Blood-brain barrier restrains medicine from entering the body, and simultaneously prevents it from reaching the tumor site, since the tumor in the case of GBM mangles this barrier at numerous sites **(Oberoi et al., 2015).**

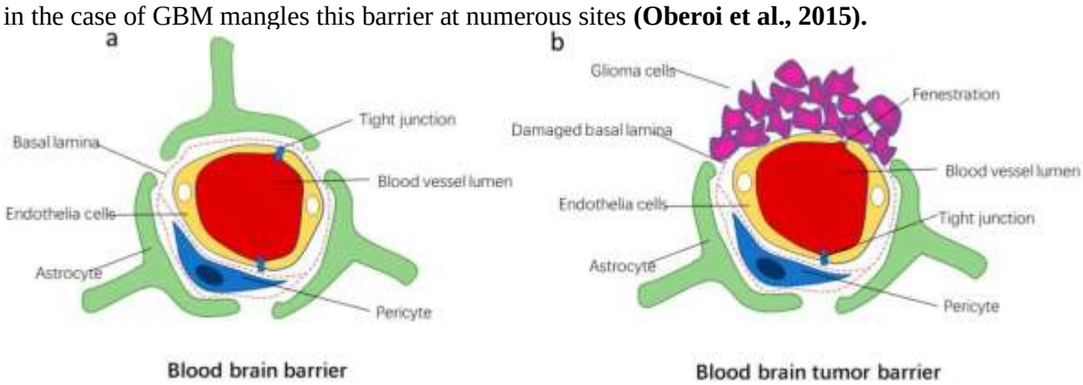


Figure 8: Diagram showing the anatomy and makeup of blood tumor and blood-brain barrier **(Z. Qiu et al., 2022).**

Comparing the BTB in gliomas to the healthy BBB, several features are evident **(Steeg, 2021).** Aberrant blood vessel production brought on by chaotic and uncontrolled angiogenesis, aberrant pericytes distribution, and astrocytic end-feet and neuronal connections are lost are all characteristics of gliomas **(Arvanitis, Ferraro, & Jain, 2020).** The disruption of astrocytic end- feet by invasive glioma cells results in the development of extremely permeable, leaky blood vessels with atypical shape and function **(Arvanitis et al., 2020).** Because Tj integrity is weakened, there are more fenestrations and gaps which improve the permeability of molecules into the tumor tissues **(Kadry, Noorani, & Cucullo, 2020).** Additionally, microvessels exhibit a significant regulation of occludin and claudin-5 expression but a loss of claudin-1 expression **(Kadry et al., 2020).** The notable up-regulation of AQP4 may be responsible for the characteristic of malignant tumor, similar to brain metastasis; brain edema **(Kadry et al., 2020).** These alternations make BTB of gliomas permeable. Gadolinium-based contrast agents diffuse out from the arterial lumen to enter the extravascular extracellular space, which makes this visible as a hyperintense region on terms of contrast-enhancing by T1-weighted (T1W) magnetic resonance imaging (MRI). **(Sarkaria et al., 2018).** It is important to stress that, even in cases where low-grade lesions have nearly fully functional BBBs, enhanced permeability will only be observed in certain areas of high-grade gliomas (HGG) **(Sarkaria et al., 2018).** There are several MRI and PET studies that reveal HGG regions with different levels of BBB breakdown and vascular permeability **(Steeg, 2021).** The peritumoral region and

the surrounding brain microenvironment often maintain a nearly perfect blood-brain barrier, whereas the tumor core typically exhibits more leakiness **(Arvanitis et al., 2020).** Many malignant tumors, including most HGG tumors, showed highly infiltrative tumor cells observed by the FLAIR sequence on the MRI scan, extending outside the primary mass to invade the edema around it **(Fortin, 2019).** Because of their high levels of metabolic flexibility and transcriptional diversity, these distant tumor locations protect the invasive GSCs through an intact blood-brain barrier. Thus, GSCs are the main reason GBM occurs and is resistant to therapy. Patients with gliomas have little prospect of enhancing their chemotherapeutic results as long as medications do not build up in peripheral glioma areas that are encircled by an undamaged blood-brain barrier **(Pinkiewicz, Pinkiewicz, Walecki, & Zawadzki, 2022).**

Blood Brain Tumor Barrier (BBTB) in GBM

A leaky and heterogeneous vasculature known as the blood-brain tumor barrier (BBTB) forms as glioma cells proliferate and encourage neovascularization, weakening the BBB's strong connections as shown in **(Figure 8) (J. P. Thakkar et al., 2014).** Many recent innovative clinical trials of chemotherapeutic therapy for GBM were unsuccessful as their inability to attain medication concentrations that work well when BBTB is present in invasion sites and at the tumor's edge. Chemotherapy medications must thus be administered to the most internal regions of GBM, with the exception of the tumor's periphery. To overcome the challenges posed by BBTB in the therapeutic management of GBM, a number of approaches have been considered **(Z. Qiu et al., 2022).**

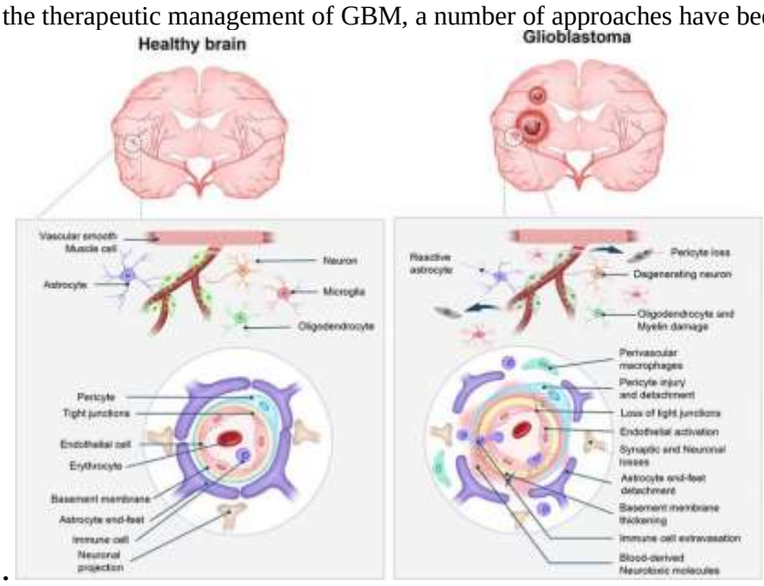


Figure 9: Diagram showing distinction between the blood-brain tumor barrier (BBTB) and the blood-brain barrier (BBB) (a). All things considered, the connections between GBM and BBB are a multifaceted and intricate combination of direct and indirect processes. It will be easier to create effective GBM treatment strategies if these interactions are understood **(Lim, Yee, & Khang, 2024).** The BBB and GBM interact in several ways **as shown in (Figure 9)**. One of the most important ways is the formation of certain cell surface receptors, which may bind to proteins located within the extracellular matrix of BBB **(Cabral-Pacheco et al., 2020).** In the extracellular matrix of blood-brain barrier, integrins such avβ3 and a5β1 may interact with laminin and fibronectin, respectively, and are known as overexpressed on GBM cells **(Ellert-Miklaszewska, Poleszak, Pasierbinska, & Kaminska, 2020).** In addition, other cell surface receptors that mediate interactions with GBM-BBB are shown to include platelet-derived growth factor receptors and epidermal growth factor receptor. Activation of the latter down-stream cascade results in the breakdown of blood-brain barrier and angiogenesis **(An, Aksoy, Zheng, Fan, & Weiss, 2018).** GBM cells also secrete a variety of factors that could influence the functioning of BBB. For example, it has been shown that the overexpression of VEGF in GBM lead to disruption of tight junctions between endothelial cells forming the BBB, thereby increasing its permeability **(L. Wen et al., 2017).** The BBB's basement membrane components and extracellular matrix proteins can be broken down by other substances like matrix metalloproteinases (MMPs), which increase permeability **(Rempe, Hartz, & Bauer, 2016).** These interactions can directly affect the function of BBB besides direct action. For example, GBM cells can attract with immune cells in the brain, including macrophages and microglia, which may release cytokines and chemokines that impact the function of blood-brain barrier **(Ma, Chen, & Li, 2021).** Angiogenesis is a process where the tumor cells alter the pre-existing microvasculature of the brain, due to the increased oxygen and nutrients requirements when glioma cells proliferate outside the blood-brain barrier. Simultaneously, angiogenesis will provide cancer cell with the required nutrients to sustain proliferation **(Monteiro, Hill, Pilkington, & Madureira, 2017).** Fenestrations and the lack of tight junctions' protein complexes characterize juvenile blood vessels at all the stages of the angiogenesis process. This is because of structural immaturity of the vessels, making it easy for the substances to flow through due to increased permeability. These capillaries are immature and 'leaky' compared to normal BBB capillaries. The environment surrounding the tumor become increasingly hypoxic as the tumor lesion progresses and extends. In response to this hypoxic condition, tumor cell will produce more of the vital angiogenic molecule VEGF **(Blethen et al., 2021).**

Mechanism of Penetration of Blood Brain Barrier in GBM

Membrane Camouflage for Brain Targeting

Nanotechnology has promised a whole range of biological applications within the last few decades, starting from therapeutic to diagnostic; however, once they arrive in the body, it stops most of them working because of natural immunity of the body **(Mundt, Greter, & Becher, 2022).** Through strategies including particle surface

modification, researchers have tried to escape immune system capture in order to prevent identifications and eliminations **(Y. Li et al., 2023).** An instance of an "invisible coating" maybe polyethylene glycol (PEG) applied on the surface of nanoparticle **(X. Fang et al., 2023).** While half-lives of most of the nanoparticles can be extended through PEGylation, acquired immunity is still likely to be demonstrably accelerated with more frequent injection. In addition, identification, characterization, and manufacture of specific ligands have been the subject of much research aimed at enhancing the focal targeting and specificity of nanoparticles. As nanocarriers' production becomes increasingly sophisticated, it will become inventible that the process of ligand modifications becomes more challenging to regulate. In recent years, natural membrane materials such as exosomes and cell membranes have been used to modify nanoparticles. Since this (biomimetic) nanoparticles interface with platforms formed from cell membranes, the immune system is unable to eliminate them. However, they include inherent targeting capabilities that allow them to move across the intricate biological milieu and concentrate in certain areas. **(Figure 10) (Qu et al., 2024).**

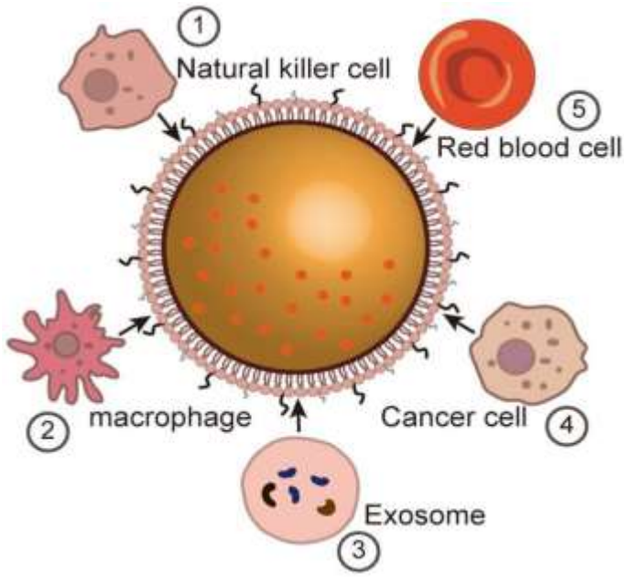


Figure 10: Brain targeted through membrane camouflage. 1) NK cells, immune cell based membrane camouflage, 2) Macrophage, vesicle-based membrane camouflage, 3) The Exosomes,
4) Membrane camouflage on cancer cell, 5) Membrane-based camouflage on red blood cell **(Qu et al., 2024).**

Brain Targeting Based on Cell Membrane Encapsulation

Erythrocytes provide good 'shells' for secure and immunologically compatible delivery of drugs system because of their inherent characteristics and stability **(Cui et al., 2020).** Additionally, erythrocytes membranes are easily prepared, evenly sized, and accessible. The neruprotectant NR2B9C is delivered specifically to the brain by bioengineered ROS-responsive nanocarriers that target the upregulation of ROS in ischemic neurons to lessen the severity of ischemia- induced brain damage **(Lv et al., 2018)**. This makes medications used to treat ischemic strokes more effective. The dextran polymer core of this nanocarrier has been modified using ROS- responsive borate while the stroke homing peptide (SHp) has been incorporated into the membrane shell of the red blood cell (RBC) as shown in **(Figure 10) (Lv et al., 2018).** Consequently, this nanoparticle, SHp-RBC-NP, controls the release of NR2B9C when it enters ischemic brain region that is caused by elevated ROS. The rat middle cerebral artery occlusion (MCAO) model and in vitro tests were used to evaluate the therapeutic efficacy of SHp-RBC-NP in treating ischemic stroke. In vitro test revealed that SHp-RBC-NP was effectively protected against glutamate-induced cytotoxicity. Additionally, nanoparticles improved active targeting to ischemic areas, reduced ischemic brain damage in MCAO mice, and considerably extended the systemic circulation of NR2B9C, according to in vivo PK/PD tests **(Qu et al., 2024).** Leukocytes, including NK cells, dendritic cells (DCs), and macrophages as shown in **(Figure 10)** can permeate the blood-brain barrier and reach the location of the brain injury. Immune cell membranes are therefore advantageous membrane-encapsulated materials due to their improved biocompatibility and the negative consequence of normal cells not being recognized **(Hilligan & Ronchese, 2020)**. Macrophage membrane contain endogenous substances that can confer nanoparticles that are encapsulated by the membrane with a variety of properties, such as immune evasion, brain tissue targeting, and penetration across the BBB, for instance, C-C chemokine receptor 2(CCR2) **(Quaranta et al., 2023)** and ICAM-1, an intercellular adhesion molecule **(Soldati et al., 2023),** The macrophage membrane capped nanoparticles can guide to the location of the tumor. In addition, the integrins α4 and β1 on the macrophage membrane can attach to the VCAM-1 on the cancer cell membrane, allowing targeting and metastasis of the cancer cells. **(V. W. Cheng et al., 2019).** It was shown that the nanoparticles could cross the blood-brain barrier and get to the tumor site by using different chemokines on the surface of the macrophage membranes. Upon reaching this area, they were released through morphological changes which were activated by the activation of extracellular milieu of the tumor. Upon the internalization the medication escapes the nanoparticles. very fast due to the pH of the endosomes, hence enhancing the tumor killing efficacy. The host an efficient drug delivery system customized for the tumor microenvironment by using cascade-responsive nanoparticles and bionic cell membranes **(Qu et al., 2024).** NKG2D is one of several different ways that natural killer cells, which are important immune cells and physically large granular lymphocytes, might detect malignant cells due to the absence of cell surface receptors specific to the tumor antigens. **(H. Liu et al., 2019),** NKp44, NKp46, and DNAM-1 **(Cifaldi et al., 2023),** They are highly effective in targeting cancers and combining biocompatibility. Through aggregating a membrane derived from NK cells, Tang et al. produced nanorobots that look like NK cells. Emission induced

by-NK. An active polymer endoskeleton **(Su et al., 2021).**

Brain Targeting Based on Exosomes

When internal multivesicular bodies (MVB) unite with the cell membrane, they release membranous vesicles called exosomes into the extracellular matrix **(Y. Zhang et al., 2020).** Virtually all cell types that can generate and secrete exosomes are nanoscale lipid inclusion structures that range from 30 to 100nm in diameter. Their tissue-organ targeting and outstanding biocompatibility stem from their parental cell origin **(Ocansey et al., 2020).** Thus, the exosomes biological origin might be a useful tactic to promote distribution that is specifically targeted to the brain **(R. Yang et al., 2024).** When compared to MSC-derived EVs, neural stem cells derived EVs showed an increased efficacy of transport in a mouse stroke model to the CNS. However, when these exosomes from different cell types were injected systemically without any modification, it showed that the delivery to the brain was less than 1% indicating that exosomes naturally ignore the blood-brain barrier **(Y. Liang, Duan, Lu, & Xia, 2021).** Because of this, scientists have attempted a myriad of changes to the exosomes' surface that increase their capacity to target the brain among others, including the one mentioned above receptor-mediated transcellular transporter activity. Kim et al., using transferrin receptor (TfR)-modified exosomes, developed TfR-exo. Through the conjugation of the T7 peptide to Lamp2, TfR-exo achieved better penetration of the BBB and glioma targeting as compared to the unaltered exosome **(H. Choi et al., 2022).**

Recent Advance in Lipid Based Nanoparticles in the treatment of GBM

GBM is a very invasive and lethal reuse IV principal brain tumor. Surprisingly, now there is no remedy for it. That is why standard of care, which includes surgical treatment, radiotherapy, chemotherapy, and targeted drug therapy, offers a survival rate of only 4-5% **(Buchalska, Kamińska, Owe-Larsson, & Cudnoch-Jędrzejewska, 2024).** Surgery is not easily accomplished in GBM because the tumor cells are invasive and growing around the brain; hence, complete resection of the tumor is very rare. Available chemotherapeutic treatments of GBM include alkylating agents such as methylating agents, carmustine, nimustine, and lomustine agents such as Temozolomide **(Shao et al., 2023).** The best practice entails using TMZ in the postsurgery for 6 weeks then using radiation every 28 days for 6 cycles. Nonetheless, potential severe complications arising from this treatment are thrombocytopenia and hematologic damage, which have been noted in 10-20% of patients in phase 2 trials **(Krauze et al., 2015).** Additionally, an alkylating agent called Carmustine (BCNU), is utilized to treat gliomas, can be given systematically with less toxicity or delivered locally through biodegradable wafers placed in the tumor resection cavity during neurosurgery. Although evidence exists for improved overall survival in glioblastoma patients when carmustine wafers are used, questions remain concerning their safety, especially the effect on postoperative infection, and quality of life along with subsequent therapies **(Xiao et al., 2020).** These wafers may cause complications such as seizures, intracranial infections, brain edema, and delays in healing, cerebrospinal fluid leaks, and cyst formation **(Kuramitsu, Motomura, Natsume, & Wakabayashi, 2015).**

The intravenous Bevacizumab, a monoclonal antibody that targets VEGF-A, is administered to patients with recurrent GBM and is thought to be an antiangiogenic drug. Prolonged survival without progression, but does not increase overall survival of newly diagnosed GBM patients, hypertension, and leukopenia are tendencies of side effects **(Diaz et al., 2017).** In recurrent GBM, a phase II trial examined the outcome associated with the combination of Cetuximab with irinotecan and bevacizumab. Cetuximab was administered once per week, whereas bevacizumab and irinotecan were given once every two weeks 34 of the 43 enrolled patients were assessable for radiographic response; the majority of these patients had both minor and major improvements on radiographic examination for a radiographic response rate of 34% **(Ezzati, Salib, Balasubramaniam, & Aboud, 2024)**. The overall median survival was 29 weeks, and at six months, the progression-free survival rate was 30%. The most frequent problem with the combined use of these drugs was skin toxicity, although it was usually mild **(Hasselbalch et al., 2010).** Currently, there are a number of studies in clinical trials in relation to the use of drugs in conjunction with radiation and immunotherapy. But these treatments have side effects, poor drug delivery across the BBB and possibility of off-target toxicity. The current diagnosis of glioma entails MRI, and computerized tomography (CT scan).

Combinational Therapy: Lipid Nanoparticles with Other Modalities:

Malignant brain tumors called gliomas are quite common worldwide and affect a number of individuals globally. The main challenges involved in treating these tumors include the ability of chemotherapy drugs to pass through the blood brain barrier and the various harmful side effects they entail **(Sun, Li, Zheng, Zou, & Shi, 2024).** Thanks, to the advancement of nanoparticle drug delivery systems (NDDS) glioma treatment could see changes in times. These NDDS offer toxicity levels, strong biocompatibility and high stability, with side effects. Nanogel (NG) stands out as a choice, for drug delivery purposes with a focus on time administration due to its unique combination of hydrogel and nanoparticles properties that offer excellent drug holding capabilities and compatibility with the body while being responsive to external stimuli **(as mentioned by Zhang H., et al., 2016).** This makes nanogels ideal, for transporting medications. An examination resulted in the creation of a nanogel coated with a blood cell membrane, named ARNGsthTMZhICGi. It was equipped with TMZ and the photosensitizer indocyanine green as reported by Zhang et al. In 2022. Exposure, to light triggers the production of oxygen species in ICG **(Trivedi, Hussain, Agade, & Belgamwar, 2024).** These discoveries indicate that this biomimetic NG could enhance drug efficacy in targeting tumors prolong the drugs lifespan and ultimately boost survival rates. However there are downsides to utilizing NGs such as responses and instability in colloidal form. Therefore continuous refinement is essential for the use of these technologies, in healthcare settings **(Sarkar, Kumar, Saha, Basu, & Ghosh, 2024).** Because NPs can minimize off-target effects, get beyond issues with targeted delivery, and potentially work well with other modalities, they hold the promise to revolutionize radiotherapy. There is an observed effect of radiation enhancement by NPs **(Ahmed, Canney, Carpentier, Thanou, & Idbaih, 2023).** Upon exposure to radiation, NPs may initiate chemical and physical reactions around localized sites, thus (Chernov et al., 2024)enhancing the radiation energy that is deposited inside the cells. For example, energetic electrons produced by metal NPs from exposure to radiation can induce damage to

surrounding DNA and cell membranes, perhaps making their side effects on radiotherapy more potent **(Corvo et al., 2016)**. Additionally, in the event when NPs and radiation interact, they could create a hyperthermia effect that makes cells sensitive and results in localized heating. A study has illustrated that iron oxide NPs enhance the radiosensitivity of cancer cells to X-rays **(Ostrom et al., 2013).** This proof represents a new proof that will be used to show that nanoparticles may be employed as a novel adjuvant radiation therapy. It is evident that radiation particle therapy heavily relies on the enhancement effect of radiation, which makes NPs a potential adjuvant for the treatment of radiation. Researchers have found that the efficiency of treatment in radiation therapy is increased and the process of damage due to radiation is accelerated by radiation sensitizing designed nanoparticles (NPs) **(Wu et al., 2020).** Furthermore, it is important to note that NP interactions with radiation may depend significantly on a number of parameters such as their size and shape, composition, etc. Thus, the best treatment outcomes in NP-guided radiation particle therapy will be highly dependent on a detailed research into these interaction processes **(Ostrom et al., 2014).**

Another potential treatment modality for gliomas is photodynamic therapy, which employs a photosensitizer activated by laser light. Once activated, the photosensitizer interacts with oxygen and other substrates to generate ROS; these can help kill the malignant cells. The current study assessed the efficacy of PDT for rats carrying 9L gliosarcoma using a photofrin encapsulated in a liposome delivery system **(Mitusova et al., 2022).** The theory behind it was that the liposome vehicle would increase the concentration of photofrin in the tumor tissue, increasing the effect of treatment. As is evident from the results, PDT with liposomes loaded with Photofrin induced significantly higher damage in tumors (22% necrosis) than dextrose infusion caused spotty damage. The concentration of photofrin in tumors was significantly higher with liposome administration **(Jeon et al., 2021)**.PDT for brain cancer however poses serious difficulties: poor selectivity, poor penetration of light in brain tissue and photosensitizer administration. Researchers have produced nanoliposomal benzoporphyrin derivative (Nal-BPD) and nanoliposomal protoporphyrin IX (Nal-PpIX) and assessed the photodynamic effects in rat brains. They showed that the PDT effect of Nal-BPD at a depth of 2 cm in brain tissues **(Inglut et al., 2020).** Although some of the patients responded with a tumor, the formulation's cause Liposomes is one of the formulations based on lipids that are authorized for the use in clinical investigation. In PEG-liposomal doxorubicin plus oral topotecan for relapsed malignant brain tumors, a study evaluated the combination use of topoisomerase I and II chemotherapeutic drugs. The study found significant levels of toxicity, mainly as grade III/IV hematotoxicity, stomatitis, and infections. It is now suggested to escalate PEG-liposomal doxorubicin to 10–20 mg/m2 every two weeks due to the substantial toxicity that the previously proposed dose scheme entails **(Wagner et al., 2008).** Another Ongoing study using CED to deliver liposomal formulation radiolabeled with 186Re, for the treatment of recurrent glioblastoma and others malignancies. The results from this study demonstrated enhanced drug delivery by means of the multi-catheters model, long-term retention of drugs applied to the tumor, promising preliminary treatment results, including survival rates that increase upon the delivery of intense radiation, directly to the tumors **(Uccelli et al., 2022)**. A total of 23 patients with recurrent high-grade gliomas received PEG-DOX either alone or in combination with tamoxifen (TAM). Compared to other studies, an overall response rate of 40% was achieved in this study, with survival extended by **(Ruiz-Molina et al., 2022).** Patients with grade III tumors generally did better than those with grade IV tumors; some grade III patients actually had better quality of life and more durable disease control. In Trial 2, TAM did not improve PEG-DOX efficacy; the combination was ineffective. The most prominent toxicities of PEG-DOX were cutaneous problems and mild myelosuppression. The drug was not toxic

Toxicity, biocompatibility and safety of LNPs

Most GBM drugs have low therapeutic effectiveness due to the BBB challenges, leading to required high dosages that accelerate the process of toxicity and side effects **(Ou, Yung, & Majd, 2020)**. Smart drug delivery devices in the form of cleverly engineered different NPs have been designed to address these issues for the treatment of GBM. NPs have the capability to effectively sequester a variety of drugs to enhance their stability and solubility **(Iturrioz- Rodríguez, Bertorelli, & Ciofani, 2021)**. And either passively or actively targets them to make it easier for them to pass through the BBB. Lipid-based NPs (LBNPs) provide a number of benefits over other NPs including decreased immunogenicity, toxicity and improved biodegradability and biocompatibility. LBNPs have therefore become the industry standard for drug delivery nano-carriers **(Liao et al., 2019)**. The term "blood-brain barrier" or BBB applies to the summation of two separate barriers, namely, that produced by neurological cells and capillary barriers between the plasma of blood vessels and the other one generated by the choroid plexus between its plasma and the cerebrospinal fluid **(Pandit, Chen, & Götz, 2020)**. The primary type of brain cancer tumor, GBM, causes alterations to the blood-brain barrier surrounding brain parenchymal capillaries. This result in the creation of a new structure called the BBTB that delineates the altered BBB and is localized to regions of the brain tumor that are affected **(Bagchi, Moriyama, & Shahidi, 2012)**. Tumor cells cause changes in the drug transport pathways along with increased permeability due to damage to the integrity of the blood-brain barrier. Other characteristics that differentiate GBM from other tumors are its noticeable vascularization, which is a result of abnormal expansion of the lymphatic vasculature. A characteristic feature of such a process includes endothelial hyperplasia, the formation of pinocytic vesicles, fenestrations, and the breaking down or dissociation of tight connections between endothelial cells (ECs) **(Ganipineni, Danhier, & Préat, 2018)**. Although these vascular changes make the BBTB more permeable, GBM is less permeable due to its special properties and the cranial environment. Thus, only fewer therapeutic drugs reach intracranial tumors **(Farshbaf et al., 2022)**. To attain high-quality-of-life improvement in patients and efficient treatment of GBM, this challenge has to be broken. Neves et al. Created SLNs modification by ApoE that demonstrated their ability to cross BBB model without losing their structural integrity, as demonstrated in a number of research studies. Simultaneously, their study revealed that ApoE- modified SLNs were internalized by their cells more than their non-functionalized counterparts **(Neves, Queiroz, Lima, & Reis, 2017)**. Together with p-hydroxybenzoic acid (pHA), having a penetration ability through the BBB, the D-peptide ligand VAP, ability to specifically bind the 78-kDa

glucoseregulated protein, which is overexpressed on glioma cells, vasculogenic mimicry and BBTB, has become a potent tool. Wu et al had created a liposome enclosed in cabazitaxel that was altered using a VAP and pHA composite ligand (pV-Lip/cNC). The significant glioma targeting, effective barrier-penetrating and spheroid tumor penetration properties if pV-Lip/cNC were validated by in-vitro investigations. PV-Lip/cNC substantially increased the intratumoral concentration of CBZ inside gliomas, thereby improving the anti-glioma effectiveness and increasing the survival period in a mouse orthotopic GBM model by up t0 53 days. Survival times for the liposomes loaded with single ligands, cNC/VAP or pHA, were 42 and 45 days, respectively **(Wu et al., 2022).** These results validate the proposed mechanism of crossing the BBB and the BBTB, leading to complete killing of glioma cells, so holds promise for all-inclusive treatment for GBM **(Wu et al., 2022)**. Determination of an appropriate lipid mixture or a physical phase before the production of LBNPs will be very important to ensure the highest drug loading capacity and guarantee stability of structure throughout the time before its production. **Salunkhe et al.** also studied the liquid lipids surfactant system that include Tween 80 and Labrasol in combination with the solid lipids Precirol ATO 5 and oil Miglyol 840 noted a notable rise in the bioavailability within the brain compartment up to 2.8-folds greater than plain drug-loaded aqueous dispersions **(Salunkhe, Bhatia, & Bhatia, 2016)**. According to their research, the liquid Miglyol 840 can be replaced by the solid lipid Precirol ATO 5; the particle diameter obtained is smaller than 200 nm, and the particles are negatively charged. This helps maintain nanostructure integrity and prevents blood flow and inhibits capability of hepatocytes cells to capture and ingest RES. The lipid matrix structure was extremely chaotic and flawed as a result of the binary merging of liquid and solid lipids, this does increase more space for stabilized and high encapsulation of drugs. **Rehman et al** synthesized a liquid/solid fatty acid mixture at a concentration of 0.1:1 to 2:1 to prepare a thermosensitive liposome. The liquid/solid fatty acid mixture showed a phase shift from the solid to liquid state at 39 °C, and its formulation was reported. . The synthesized lipids sensitive to heat showed improved permeability at 39 °C in the in vitro model of the BBB because of a state deformation that enables the material to permeate across the BBB's transmembrane gap **(Rehman et al., 2017)**. These thermosensitive deformable lipids' in vivo BBB permeability should be looked into.

Challenges and Future Directions

A few factors approaching the clinical applications of nanotherapeutics are potential toxicity, repeatability, variability from batch-to-batch production on a large scale, and target capability **(Tan et al., 2020)**. Many new materials are being produced as nanotechnology progress with the aim of using them as nanocarriers. It can take some time to get clinical approval for these novel materials, because of the researchers typically focus on utilizing biomaterials that are already well-established and authorized, which impedes the use of novel materials in clinical settings **(Ghiaseddin, Shin, Melnick, & Tran, 2020)**. Manufacturing nanotherapeutics on a large scale is complicated, by repeatability concerns **(Stupp et al., 2017)**. While several methods exist for the synthesis of NPs for many types of therapy including therapies aimed at GBMs, these processes are not always be able to produce consistent outcomes **(Davies, Weinberg, & Palti, 2013)**. As a result additional adjustments and revisions to published protocols are required for every unique solution **(Rosenblum et al., 2020).** However, treatment of GBM is a complex and formidable but not unsolvable problem. Lipid nanoparticles in brain tumor theranostics hold significant promise, especially for the development of more personalized and targeted treatments **(Slika et al., 2023)**. Advances in nanotechnology and molecular biology are likely to lead to the design of LNPs with enhanced specificity, making it easier for move across to the blood-brain barrier with greater efficiency and provide direct delivery of medicinal medicines to tumor cells, while reducing unintended consequences **(Stepanenko et al., 2024)**. The development of "smart" LNPs that respond to tumor microenvironment stimuli could enable more precise drug release and imaging agent. Moreover, the incorporation of advanced imaging methods utilizing LNP-based delivery systems could revolutionize tracking delivery of drugs in real-time and treatment efficacy, paving the way for more dynamic and responsive therapeutic strategies **(B. D. Choi et al., 2019).** Also, codelivery of multiple therapeutic agents, including chemotherapeutics, gene therapies, and immunomodulators, may offer synergistic effects, reduce the chances of drug resistance, and improve overall survival rates **(Polychronidou et al., 2023)**. Furthermore, personalized LNP formulations could be optimized for individual tumor characteristics and treatment needs by leveraging advances in tumor profiling and patient specific biomarkers**(Mao, Wu, et al., 2022)**. While LNPs for brain tumor theranostics show immense potential, several critical challenges must be addressed. One of the primary obstacles is the ability of LNPs to effectively cross the BBB, which is selective and major barrier to drug delivery **(Mao, Calero-Pérez, et al., 2022)**. Despite ongoing research, many LNP formulations continue to face challenges to achieve therapeutic concentrations within the brain and the risk of systemic toxicity due to off-target accumulation. Moreover, the heterogeneity of brain tumor is another challenge **(Hua, De Matos, Metselaar, & Storm, 2018)**. Tumor types can vary significantly, even within a single patient, presenting different molecular profiles that make it challenging to create an LNP-based therapies from preclinical to clinical settings is hindered by complex manufacturing, stability issues, patient variability, BBB penetration challenges, limited clinical experience, ethical and legal concerns, and competition with established therapies **(Kumar, Pattnaik, Satapathy, Swapna, & Mohanty, 2021)**. By addressing these critical issues, LNP-based theranostics could revolutionize brain tumor treatment, offering more effective, personalized and less invasive options for patients in the future **(Hegde et al., 2022).**

Conclusion

The current GBM treatment is challenging because of the heterogeneity, aggressiveness, resistance, and invasiveness of the tumor along with drug delivery into the brain. One area of research that shows promise is the use of slid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) as drug delivery vehicles for treatment of GBM. There is published body of literature regarding the process of getting ready and using of NLCs and SLNs for the treatment of GBM with diverse drugs, materials, and types regarding functionalization, as far as we are aware, no pharmaceutical firm created or released any of these carriers onto the market. RMT is

a drug delivery strategy to the brain, which primarily targeting specific receptors Tf and Lf which overexpress safety, selectivity, and specificity. In our opinion, these methods for generating nanocarriers with repetition patterns or large-scale production demand more emphasis. More research is also expected to dispel some of the controversies surrounding the safety of nanoparticles about their nano-sized characteristics and their potential permeability across cell membranes of biological systems. This might be investigated through in vivo tests that could aid in toxicity prediction of the nanoparticles in all organs. For safety, a long-term evaluation of lung toxicity is necessary for nanoformulations intended for nose-to-brain transmission. Considering all these disconcerting aspects can lead to significant breakthroughs in the exploitation of SLNs and NLCs serves as advanced systems of medication administration to treat malignant GBM

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