Exosomes Molecular Modifications for Drug Delivery: A Gleam of Hope in the Fight against Glioma

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ABSTRACT

Glioma treatment is constrained by two important factors: prompt and effective detection at commencement or recurrence, as well as drug entrance into the brain via the blood-brain barrier (BBB), which influences tumour growth. However, a safe BBB-crossing drug delivery system has given glioma treatment a new lease on life. Exosomes have a high cargo-loading capacity and the ability to pass across the BBB. They can also be given the power to send tailored messages. As a result, exosomes have a lot of promise as a targeted drug delivery vehicle. In this review, we discuss the most recent research on exosome-based drug delivery systems for cancer treatment, with a focus on the different types of exosomes used for delivering drugs. We also cover advancements in drug transport across the blood–brain barrier (BBB) and blood–brain tumour barrier, as well as progress in the development of new targeted drugs for glioblastoma (BBTB), and the limitations of currently available glioblastoma treatment, as well as the mechanism by which tumours become drug resistant. Finally, a model for the likely role of exosomes in delivering drug in glioma treatment is provided, based on knowledge of the most recent scientific research.

INTRODUCTION

Brain metastases are indeed a serious cancer side effect. Morbidity linked with brain metastasis is another critical problem, since patients with brain tumours have a significantly diminished quality of life [1]. As per research, around 20% of all cancer patients will eventually acquire brain metastasis [2-4]. It's worth noting that the occurrence of brain metastases in adult patients with renal cell carcinoma and colorectal cancer has risen dramatically in recent years, owing to advancements in cancer therapy and diagnosis in general [5]. As patient survival improves and our capacity to detect and control metastases in other organs improves, the overall number of persons known to be living with metastatic brain cancer is projected to climb. As a result, studying brain metastases is critical for preventing future cancer-related morbidity and mortality. Gliomas are the most common primary brain and spinal cord tumours. They share histological properties with normal glial cells and are given names based on these similarities [6]. Gliomas are classified as malignancy classes based on histological and genetic characteristics, ranging from confined type I to diffusely infiltrating type II-IV, according to WHO criteria (2016) [7]. Glioblastoma

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multiforme (GBM) is the most frequent and fatal kind of grade IV glioma. Surgical resection, chemotherapy, and radiotherapy are currently the standard GBM treatments, and they can improve the prognosis of low-grade gliomas to a degree [8]. High-grade glioma is one of the most destructive cancers that starts in the glial cells of the brain or spinal cord [9,10]. However, despite when many therapies are used, the median 5-year survival rate is just 3%-5% due to resistance mechanisms and low therapeutic penetrance to the tumour site due to hindering attributes of the blood-brain barrier (BBB) and blood-brain tumour barrier (BBTB) [11]. As a result, a novel class of drug delivery methods is urgently needed to efficiently circumvent the BBB and BBTB and deliver chemotherapeutics to glioblastoma [12]. The Blood brain barrier (BBB) is distinguished by its unique qualities of allowing central nervous system (CNS) to maintain homeostasis, which is critical for the CNS to execute precise neuronal action [13-15]. The major purpose of BBB is to provide protection from any infection and toxic agents by separating the brain from any form of connection with the rest of the body [16]. The confining character of BBB has become one of the reasons for drug delivery failure of drug delivery to Brain, as well as BBB contributing to functioning as an impediment by limiting the entrance of therapeutic pharmaceuticals, which provides a home for cancer cells [17-19]. Blood brain barrier system is made up of numerous blood arteries as well as tissue made up of tightly regulated cells that prevent dangerous from accessing the brain system. Several efforts are going on in order to achieve a method by which therapeutic drugs can be passed through BBB without facing any kind of restriction. Despite significant advances in our understanding of the mechanism of metastatic progression over the last few decades, metastasis remains the most perplexing aspect of cancer aetiology. The blood-brain barrier (BBB) and other components of the brain microenvironment shield tumour cells from immune surveillance, chemotherapeutics, and other potentially harmful substances, making the brain a haven for metastatic tumour growth. Three Extracellular vesicle have been reported to have the ability to diffuse through the BBB; however, our understanding of the mechanism that modulate the environment of BBB in order for them to dispersed into brain system is limited, and which types of extracellular vesicle can be used for therapeutics purpose is still being researched. Exosome is the most efficient at propagating into the BBB among three basic forms of extracellular vesicles. Because of their increasingly acknowledged physical and pathological roles, as well as their potential in diagnostic and therapeutic applications, exosomes have drawn great attention from both scientific disciplines and biomedical enterprises [20]. Exosomes have a tendency to move freely through the circulation and can access variety of tissues by avoiding variety of impediments. Because of their origin and propensity to duplicate the molecular contents of parent cells, Exosomes are in high demand [21]. Exosomes have been used to carry medications to the brain for long time, and many breakthroughs have been made. Many genes have been identified which mediates metastasis of cancer cells to the brains such as (ADAM8, cathepsin S, CEMIP, Angiopoietin-2 etc.), however no such genes have been identified that regulate the BBB, which is universal to all types of tumours [22-25]. It is critical to understand the underlying mechanisms involve in biogenesis of Exosome so that Exosomes can be employed to target the blood barrier in the treatment of the brain tumours in the near future. The goal of this study was to look over the literature and summarize what we know about exosome advancements in order to deliver therapeutic medications to patients with glioma, as well as to identify possible targets for preventive and therapeutic techniques and the role of exosomes in brain tumours. Exosome biogenesis in cancer Exosome secretion has emerged as an appealing therapeutic target because to the multiple ways exosomes

contribute to tumour growth, and it has been examined in a variety of circumstances. Exosomes are also thought to play a role in controlling communication between primary tumour cells and distant locations. Exosome secretion is necessary for the formation of invadopodia and invasive activity in breast cancer cells, which could help them exit the main tumour site [20]. Exosome biogenesis can occur via two separate pathways: ESCRT protein-dependent and ESCRT-independent. In early studies of exosome release, ceramide was discovered to be a regulator of exosome secretion. Ceramide is generated by neutral sphingomyelinase and is involved in endosome inward budding to form multivesicular bodies (MVBs) that contain exosomes [26]. Ceramide production has been linked to the secretion of exosomes by cancer cells in a number of different investigations [27-32]. Furthermore, at least one study demonstrated that ceramide is not required for exosome release [33]; as a result, it is unclear whether this pathway is a universal regulator of exosome secretion across all cancer types. The secretion of exosomes has been linked to a wide range of vesicle-trafficking genes. TBC1D10A is a protein that regulates Rab35 in oligodendrocytes to cause exosome extrusion [34]. Rab11 expression in K562 cells is associated with decreased exosome release and MVB interactions with autophagosomes [35]. In K562 cells, Rab11 appears to be necessary for 4 exosome release, although not for exosome secretion in HeLa cells. Rab27A and Rab27B stimulate the release of exosomes in HeLa cells. Rab27A regulates the size of MVBs, while Rab27B regulates their cellular position [36]. Rab27A/ B participation in exosome release has been validated in a variety of cancer cell types [20,37-39]. Rab27A regulates the stability of MVB docking sites in collaboration with cortactin and coronin 1b enabling the secretion of exosomes [39]. Furthermore, the involvement of Rab27A/B in exosome secretion is mostly based on in vitro investigations, and it is uncertain if Rab27A/B work in vivo in the same way. The tumor's microenvironment

also influences exosome release. Tumor cells battle for nourishment, oxygen, and growth factors as the tumour grows, and as a result, they create survival mechanisms to deal with the stress. Exosome secretion has been suggested as a way for tumour cells to survive in stressful settings [40,41]. By establishing a secretory lysosome phenotype, a hypoxic microenvironment boosts exosome secretion. Exosomes released in hypoxic conditions have higher levels of STAT3 and FAS, that can be forwarded on to other tumour cells to enable them to grow and spread [42]. Exosomes from hypoxia-cultured glioblastoma cells also induce angiogenesis and tumor progression, possibly by transferring hypoxia-related RNAs and proteins [43]. The expression of PKM2 (Pyruvate Kinase M2) can regulate exosome release, implying a relationship between cellular metabolism and exosome secretion. Through phosphorylation of synaptosome-associated protein 23, PKM2 regulates exosome secretion. (SNAP-23) [44]. Exosomes are also transported from cancer-associated fibroblasts (CAFs) to affect cancer cell metabolism and promote glycolysis, perhaps influencing exosome secretion further [45]. Increased glycolysis and lactate build up in the extracellular environment are frequently associated with hypoxia in tumours, resulting in an acidic microenvironment. Exosome biogenesis is also influenced by intracellular pH, with acidic pH (pH = 6. 0) boosting exosome secretion [46]. Exosome secretion, as well as exosomal protein and RNA, are reduced by alkaline pH [47]. In contrast; it has been shown that an acidic extracellular pH influences integrin activation. Integrins are important exosome uptake regulators [48]. As a result, exosome entrance into recipient cells may be influenced by the pH of the microenvironment. According to these findings, hypoxia stimulates the production of tumour cell-derived exosomes, which affect cell activity in the microenvironment. Exosomes in circulation are higher in tumor-bearing patients than in healthy patients, according to studies, implying that carcinogenesis is linked to

increased exosome release [49]. Exosome secretion is increased when oncogenic RAS is expressed in non-tumorigenic epithelial cells [50]. Exosome secretion is increased when oncogenic EGFRvIII is overexpressed in glioma cells. These vesicles can be transmitted to additional glioma cells that lack EGFRvIII, resulting in oncogenic activity being transferred [51]. Why exosomes? Exosomes obtained from both healthy and diseased cells could be used as medication delivery vehicles, immunomodulators, and other applications despite their role in tumour progression and metastasis [52-54]. Exosomes is the messengers that allow cells to 5 communicate with one another. Exosomes allow donor cells to transfer foreign molecules including proteins, mRNAs, microRNAs (miRNAs), and lipids to recipient cells. As a result, these naturally equipped nanocarriers have been used to carry drugs [55]. Exosomes derived from a patient's own cells offer superior biocompatibility and lower toxicity than synthetic medication carriers [56]. Exosomes have a variety of benefits over nanoparticles that

have been synthesised. Due to membrane proteins like tetraspanin and fibronectin, exosomes have a greater biocompatibility and cellular absorption than ordinary liposomes and artificial nanoparticles and can be easily altered to fit target cells [48,57]. Exosomes, which resembles liposomes in shape and function, are more stable in body fluids. Liposomes, for instance, can be easily eliminated either directly or indirectly by macrophages or reticulo-endothelial cells [58], but exosomes are known to be exceedingly biocompatible due to their endogenous origin. The potential of Exosomes to enter tissues, disperse into the circulation, and even breach the blood-brain barrier is their most promising feature (BBB) [59]. Exosomes have also been demonstrated in multiple studies to elude the immune system and extend circulation time in the body [60-62]. Exosomes can also be genetically modified. Exosomal surface protein engineering confers cell and tissue selectivity. Although, many researchers are interested in using exosomes as drug delivery vehicles.
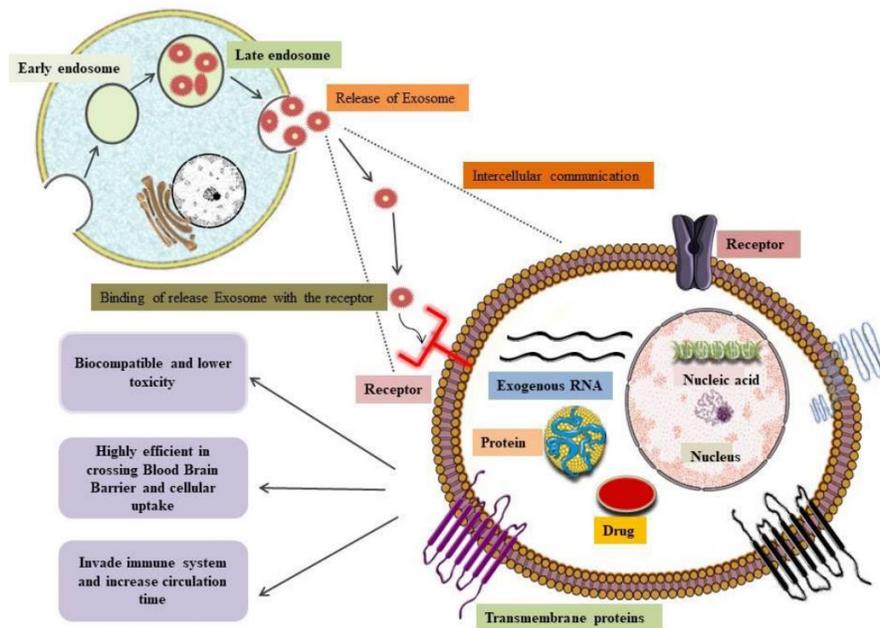
Figure 1: Exosome's influence in glioma advancement.

Exosomes are a valuable addition to the complex mix of metabolites, growth factors, cytokines, and ions produced

by tumour cells [63]. Exosomes have been shown to transport histones, oncogenic species (EGFRvIII), non-coding RNA (miRNA), and tumour suppressors (PTEN) in

glioma cells [51,64-66]. Glioma cells produce exosomes, have been linked to a variety of events in the tumour microenvironment, including the transfer of functional RNA transcripts [67]. Exosomes from GBMs may potentially influence the immunological activities of the tumour microenvironment by altering immune cells' phagocytic capacity, as well as changing cell surface protein expression and cytokine production [68,69]. The extraordinarily invasive nature of GBM, as previously mentioned, is a major contributing factor in its likelihood of recurrence following surgical intervention, prompting investigation into the molecular reasons of this potent invasiveness [70]. Over the last 10 years - 15 years, researchers have discovered that various types of tumour cells with high invasive or metastatic potential have the ability to create invadopodia structures [71-74]. Exosomes have recently been demonstrated to mediate multiple phases of the invadopodia lifecycle, including their production, stability, and exocytosis of matrix degrading proteinases [20]. Exosomes can also help modify the microenvironment by switching the phenotype of nearby support cells to one that encourages tumour growth and invasion. Exosomes released by mesenchymal cells can assist tumour growth when cells are incubated with them. Exosomes originating from mesenchymal cells not only impaired normal support cells (astrocytes), but they also caused phenotypic abnormalities in the other molecular subtypes of GBM present. [68]. Angiogenesis is a crucial step in glioma growth, and GBM-derived exosomes contain multiple angiogenic factors that promote angiogenesis [75,76]. Tetraspanins preferentially feed proteins and mRNA to exosomes to mediate information flow between exosomes and vascular endothelial cells, hence boosting angiogenesis [77]. Glioma secrete a range of 6 angiogenic factors, the most common of which is epidermal growth factor receptor variant III [EGFRvIII]. Through a phosphatidylserine-dependent mechanism, the EGFRvIII can be "shared" across glioma cells via the intercellular transfer of exosomes [51]. Exosomes are important in tumour cell adaptation to hypoxia, which is linked to angiogenesis, tumour development, and metastasis. Hypoxia is a feature of the GBM microenvironment, influencing the transcriptome and proteome of tumour cells [76]. Thus, it modifies the protein content of GBM cell-derived exosomes in both a qualitative and quantitative manner by influencing the physiological activity of neighbouring or distant cells. The protein cargo in exosomes has different effects on the expression of different genes. The hypoxic condition of glioma cells is replicated in their cargo [43]. According to King et al., cancer cells respond to hypoxia by increasing the secretion of exosomes into the microenvironment, which increases their survival and invasiveness [78]. Furthermore, tumour growth in normoxic zones is aided by the exosomes produced by hypoxia cancer cells [79]. Exosomal miRNA content and release are regulated by hypoxia [80,81]. Under hypoxic conditions, GBM-derived exosomes have heightened autocrine and pro-migratory activities. Hypoxic exosomes are thus important for tumour vascularization, pericyte vessel coverage, and GBM cell proliferation [43]. Exosomes govern glioma cell proliferation and invasion, which are critical for glioma cell survival and recurrence [82]. Exosomes, which may export medicines from tumour cells, play a crucial role in glioma therapy resistance [83]. Exosomes can cause fibroblastic responses, which operate as a barrier to anticancer medicines by promoting the production of fibroblasts. Exosomes, on the other hand, can use biomolecules like the miRNA to turn drug-sensitive tumour cells into drug-resistant tumour cells [84,85]. In this light, exosome transport intercellular mechanisms can be considered a potential contribution to glioblastoma growth and biogenesis. Understanding the pathways through which exosomes are implicated in the evolution of GBM has established the framework for exploring a variety of potential clinical uses, ranging from prognostic

indications to targeted therapy. Exosome investigation in GBM is advancing in at least four therapeutic directions, with preclinical studies for brain tumour specific applications in: (i) employing exosomes as biological markers and in clinical diagnosis; (ii) hindering various signaling pathways by targeting exosomes; (iii) seeking to exploit exosome targeting and uptake systems that facilitate delivery of molecular or pharmacological therapeutics; and (iv) establishing cancer vaccines.
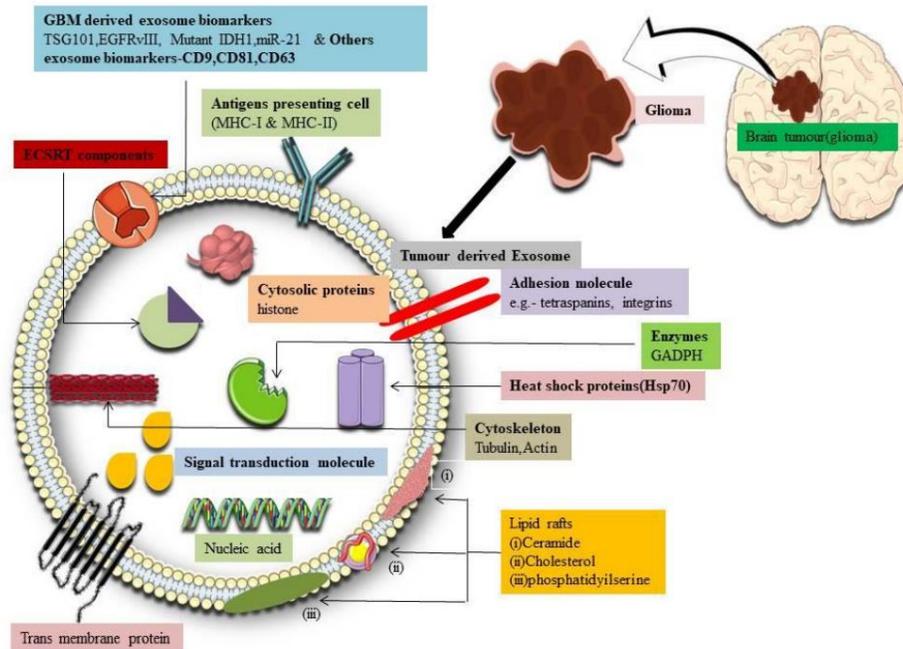
Figure 2: Structure of GBM derived exosomes.

Despite substantial breakthroughs in drug delivery, delivering anti-cancer drugs to the brain including central nervous system (CNS) illnesses remains a serious issue. The BBB is made up of neurons, astrocytes, pericytes, the endothelial basement membrane, and neighboring microvascular endothelial cells (BMECs). Tight junctions (TJs) and adherent's junctions (AJs) are found in the brain endothelial cells and serve an important function in regulating paracellular permeability [86]. Most molecules are blocked at these junctions, which illustrate 7 the BBB's changing properties as situations change, with the exception of those needed for homeostasis, such as feeding or bidirectional hormonal communication [87]. The BBB is a key impediment to effective and precise brain medication delivery. It makes drug transport from the bloodstream to the brain parenchyma extremely difficult

[88]. To begin with, the BBB's tight connections dramatically decrease ion and other hydrophilic material absorption through the intercellular space, producing a "physical barrier". Second, the "transport barrier" helps to remove metabolic wastes and other foreign chemicals from the brain parenchyma and convey them to the circulation. Furthermore, majority of hazardous chemicals are eliminated by extracellular and intracellular enzymes in the brain parenchyma, forming an "enzymatic barrier" [89]. Exosomes offer substantial benefits in terms of bypassing the BBB due to their small size and endogenous features. Exosomes can penetrate or bypass the BBB with or without surface change in vivo and in vitro, according to new findings. Various forms of natural exosomes can cling to or be picked up by various cells. Exosomes' natural targeting capacity is dependent on the components of

exosomes as well as the recipient cells' physiologic state. Experiments have indicated that under some conditions, certain types of natural exosomes can cross the BBB, according to a growing body of research. Internalization and functional activity of cancer cell exosomes were mediated by cell surface receptors such as HSPGs [90]. The key mechanism for enabling exosome to cross the BBB was proposed to be the interaction between exosome surface ligands and receptors on brain endothelial cells. Exosomes can also gain access to the brain by crossing the cerebrospinal fluid-brain barrier in the choroid plexus, in addition to the BBB-crossing entrance pathway [91]. These methods could possibly allow exosomes to pass across the BBB. Apart from natural exosome, modified exosome can also cross the BBB, by means of Receptor mediated transcytosis which is a naturally occurring approach that aids in the promotion of exosomes to overcome the BBB. A scientist combined methotrexate (MTX) with exosomes that were functionalized with therapy by targeting the low-density lipoprotein receptor, which is a BBB receptor, to construct a treatment for glioblastoma multiform. The peptide LDL facilitated both exosome extravasation across the BBB and drug accumulation in glioma sites, according to the study [92]. Transfecting progenitor cells with a fusion gene that encode a brain focused peptide along with a marker-encoding gene of exosomal protein results in exosomes enriched with the fusion protein and able to cross the BBB [93]. Because the transportation routes of EVs are unclear, the influence of EVs on ECs is also unknown. Five theoretical paths have been highlighted to date to characterize the interaction between EXOs and the receiving cell, with a focus on EXO [94]. The blood–brain barrier, which serves as a highway for EXOs, is potentially a freeway. The following are five routes for EXOs interacting with a receiving cell that have been described. (I) interaction with a cell surface protein G-coupled receptor, resulting in a signaling cascade; (II) EXOs are released into the cytoplasm after attachment and fusing to the cell surface, which can result in a variety of activities, including cell signaling. (III) macropinocytosis is a form of endocytosis that involves the nonspecific uptake of extracellular substances. (IV) It enters the cell through 8 endocytic pathways and is stored in the MVB via receptor-mediated transcytosis (V) nonspecific/lipid raft. No evidence of EXOs crossing the BBB via the paracellular route has been found. Exosome involvement in Brain metastasis Exosomes were once thought to be a way for cells to get rid of extra proteins [95,96]. However, there has been a significant advancement in the study of exosomes in recent decades, and it has now been established that these EVs play a vital role in intercellular communication, which is critical in the context of tumour progression and metastasis [97-99]. According to one recent study, exosomes generated from SK-Mel28 melanoma cells were taken up by a non-random process that relied on transmembrane proteins in human brain capillary endothelial cells (hCMEC/D3) [100]. Recent research has revealed that the successful growth of brain metastases is dependent on a complex intercellular communication mechanism that involves secreted proteins or small vesicles called exosomes that happens between metastatic cancer cells and brain stroma cells [101,102]. The involvement of multiple mechanisms by which exosomes can affect brain colonization by cancer cells in a malicious way demonstrates the significance of an enormous intercellular communication network that can be used as a target for therapeutic strategies perhaps as inspiration for novel drug delivery strategies. While confronting metastasis formation, it is vital to examine the TME's influence, as its dynamic nature allows tumour cells to alter their own habitat. According to emerging research, it is revealed that tumour derived exosome (TDEs) and exosomes generated by TME stromal cells are critical in tumour development, angiogenesis, invasion, survival, and metastasis formation [103,104]. Indeed, when attempting to define the involvement of exosomes in the creation of

brain metastases, the most crucial and exciting phase may be the transmigration of the BBB and subsequent brain parenchyma colonization by cancer cells. However, Tumor cells must first lose their adherence to the surrounding stroma and enter the bloodstream before reaching that stage in the metastatic cascade [105,106]. The TME initiates the metastatic cascade by activating the EMT process in neoplastic epithelial cells [105]. Cells undergoing EMT downregulate epithelial markers like cytokeratin and E-cadherin while upregulating mesenchymal markers like N-cadherin and vimentin [107]. Furthermore, when compared to those produced in a normoxic state, exosomes secreted during hypoxia, which has been linked to EMT and a high risk of metastasis, are richer in EMT inducers [105]. Exosomes produced from cancer-associated fibroblasts (CAFs) delivered miR-92a-3p to colorectal cancer cells, stimulating the Wnt/-catenin signalling pathway and triggering EMT [108].
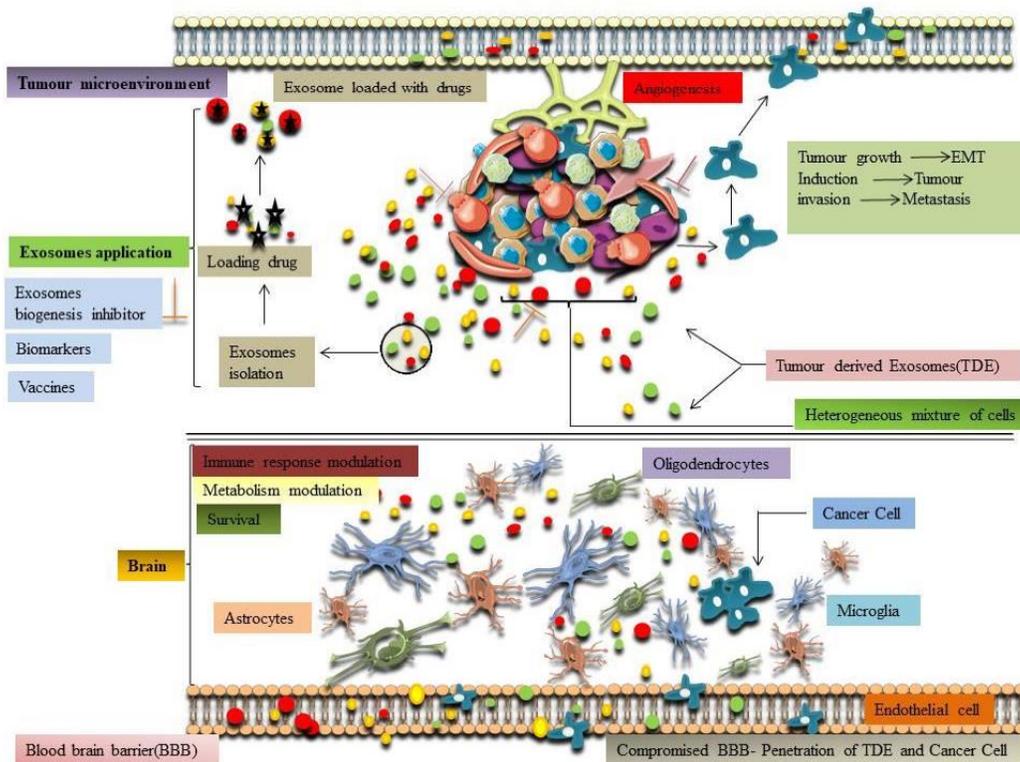
Figure 3: The following diagram depicts both stages of the metastases formation process with tropism to the brain: establishment of the tumour microenvironment (TME) and the pre-metastatic niche (PMN)/metastasis in the brain. TDEs are responsible for numerous of critical TME processes, such as epithelial–mesenchymal transition (EMT) and angiogenesis, which enhance tumor progression, infiltration, survival, as well as metastatic development. During this stage, exosomes can also promote endothelial barrier permeability, enabling cancer cells to more effectively enter the bloodstream. Exosomes from cancer cells trigger a plethora of alterations in the brain that contribute to PMN formation, including BBB permeability, metabolic and immune response modulation, and vascular co-option induction, which helps circulating tumour cells invade the brain parenchyma, generate metastases, and survive. Brain metastasis is aided by crosstalk between cancer cells and BBB cells such as astrocytes. Because of their critical involvement in metastasis formation, exosomes could be a potential target for metastatic cancer therapy using exosome production inhibitors. Extracellular vesicles, on the other hand, have been explored as biomarkers for the diagnosis and prognosis of metastatic cancer, as drug delivery systems (DDS) vehicles, and as cell-free therapeutic tools in anti-tumor vaccination.

Breast cancer cells release exosomes, which activate the Wnt ligand Wnt5a in macrophages. Macrophages are then in charge of transporting Wnt5a to tumour cells, boosting their invasion [109]. Exosomes secreted by mesenchymal stem cells (MSCs)-derived adipocytes, on the other hand, were able to trigger EMT in breast cancer cells via the

Hippo pathway; additional research suggested that activation of the Hippo pathway could be caused by the transfer of exosomal miRNAs or proteins [110-113]. 9 A typical lymphatic system does not exist in the brain. In order to infiltrate this metastatic location, circulating tumour cells (CTCs) must cross the BBB and populate the brain parenchyma [114]. As a result, BBB transmigration is a crucial step in the metastization to the brain process [115]. Once cancer cells have crossed the BBB, they enter the brain parenchyma, where they may benefit from the metastatic niche's extensive intercellular communication network [116]. Several attempts have been made to characterize the role of exosomes in the process of cancer cells transmigrating over the BBB. Tominaga et al. found that EVs, including exosomes, released by brain metastatic derivative (BMD) cell populations chosen from breast cancer cells MDA-MD-231-luc-D3H2LN transmitted miR-181c to brain endothelial cells, resulting in increased BBB permeability (Figure 3).

The disruption of intercellular junctions caused by a shift in the position of tight junction proteins -Claudin-5, Occludin, and ZO-1-N-cadherin, and actin filaments was shown to cause BBB collapse [115]. Kinjyo and colleagues recently added to the evidence of exosomes contributing to BBB breaching by showing that precursor B acute lymphoblastic leukemia (BCP-ALL) blasts release exosomes into the blood, and that exosomes derived from BCPALL cells allowed leukemia cells to transmigrate through cultured endothelial monolayers [117]. The capability of CTCs to make contact with and proliferate along brain endothelial cells, known as vascular co-option, has also been linked to the metastization process [24,118]. The function of exosomal cell migration-inducing and hyaluronan-binding protein (CEMIP) in brain metastization by breast cancer cell was found by Rodrigues and colleagues. Brain-tropic breast cancer cells release CEMIP-enriched exosomes, which improve vascular cooption and, as a result, successful invasion and metastatic colonization of the brain. Exosomal CEMIP is also implicated in molecular pathways of brain endothelial cells and microglia that are linked to the formation of brain metastases, according to in vivo investigations [24]. What's wrong with conventional Glioma Treatment? Notwithstanding breakthroughs in diagnostic techniques and comprehensive treatment, all GBM patients eventually have tumour growth and nearly all die. Surgical excision of the majority of the tumour mass is now conventional treatment, followed by radiation therapy and long-term temozolamide (TMZ) therapy [119]. Despite the fact that this combinatorial technique has increased patients' progression-free survival time, overall survival has remained essentially unaltered [120].

Supplemental medicines, such as the novel MGMT inhibitors, have been explored in preclinical studies, however these inhibitors have a high risk of inactivating DNA repair mechanisms in healthy cells [121,122]. This has been attributed to the surviving tumour cells gaining resistance to TMZ by increased production of the O6methylguanine DNA methyltransferase (MGMT) [123-125]. Administering bevacizumab in combination to TMZ, in a different strategy, has indeed resulted in a prolonged disease-free timeframe, suggesting that other resistance mechanisms are quickly engaged [126,127]. The current treatment procedures endure a number of significant obstructions. The difficulty of establishing uniform therapy is exacerbated by genetic variation at both the intertumoral 10 and intratumoral levels [128]. Furthermore, the tumor's aggressive nature precludes surgery as a therapy option. Because tumour tissues have already expanded into surrounding healthy tissues, even high-precision Gamma Knife (radiosurgery) technology will not be able to completely eliminate malignant tissues [129]. The presence of the brain's inherent physiological barrier, the blood–brain barrier (BBB), obstructs the systematic transmission of medications to brain tumour locations, lowering chemotherapy's overall efficacy [130,131].

As a result, glioma treatment has tragically evolved into a question of purchasing more time for the patient to live rather than genuinely healing the patient. It is critical to devise a new strategy that will ultimately lead to the cure of the disease rather than simply acquiring additional time for the patient to survive. To improve a drug's therapeutic efficacy while reducing off-target effects, the drug molecules must concentrate in the affected area(s) in a controlled manner over a lengthy period of time. Despite significant advances in therapeutic technology, the BBB continues to obstruct the flow and accumulation of drugs from the blood to the tumour zone following surgical resection, offering a challenge. As a result, a new drug delivery system that can overcome the barrier and function effectively must be developed. Drugs currently used to treat GBM & underlying mechanism of resistance to them. One of the most significant barriers to successful cancer treatment is drug resistance. Exosomes have been demonstrated to be beneficial in treating cancers that are resistant to drugs. Temozolomide (TMZ) Temozolomide (TMZ), a prodrug that methylates DNA at the O6 position of guanine, is now one of the most effective chemotherapeutic drugs for GBM [132].

TMZ lowered Notch3 levels, which are elevated in gliomas, through activating CHAC1, according to transcriptome microarray and bioinformatic analysis. Because CHAC1 binds to the Notch3 protein and prevents it from activating, CHAC1-inhibited Notch3 signaling can affect TMZ-mediated cytotoxicity [133]. GBM becomes resistant to alkylating medications when phosphoinositide 3-kinase (PI3K) signaling is activated [134]. Small noncoding RNAs, like as miRNAs, have been demonstrated to play a role in TMZ resistance. Because its levels are adversely related with MGMT gene expression, miR-181d could be a possible measure of TMZ resistance in GBM [135]. It was discovered that epithelial-to-mesenchymal transition (EMT) is linked to poor TMZ responses using a gene set enrichment analysis (GSEA). Furthermore, miR-140 suppresses the mesenchymal transition and increases temozolomide cytotoxicity in GBM through targeting cathepsin B (CTSB) signaling [136].

In glioma cell lines, overexpression of FAM289 has recently been discovered to contribute to tumour growth. The association of FAM289 with galectin-1 enhances its entry into the nucleus, where it stimulates the extracellular signal-regulated kinase (ERK) pathway, upregulates DNA methyl transferase 1 (DNMT1) expression, and generates the CSCs 11 phenotype, which leads to TMZ drug resistance in glioma cells [137]. The activation of the transcription factors JUN and CEBPB is linked to cancer, while HDAC3 is linked to cell cycle suppression. The Jun proto-oncogene (JUN), transcriptional factors CCAAT/enhancer binding protein beta (CEBPB), and histone deacetylase 3 (HDAC3) were all shown to be implicated in the drug-resistant phenotype of hypoxia GBM cells in the transcriptome of hypoxic GBM cells [138]. It was discovered that honokiol boosted the effects of TMZ on GBM cell autophagy and apoptosis [139]. As a result, a better knowledge of the mechanisms underlying intrinsic TMZ resistance should aid in the creation of new anticancer medicines or adjuvant therapies to improve treatment outcomes.
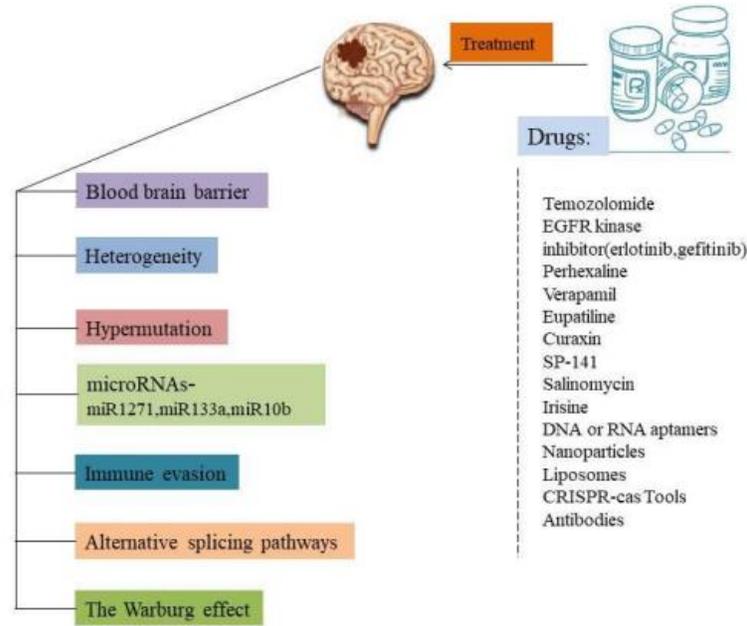
Figure 4: Mechanism by which glioma get resistant to treatment.

Other drugs various therapy techniques can be employed to treat glioblastomas, but each has its own set of limitations (Figure 4). Because of its essential function in GBM metabolism, the fatty acid oxidation (FAO) inhibitor Perhexiline could be a viable treatment medication. Perhexiline caused significant oxidative stress and apoptosis in GMM cells in vitro [140]. In the treatment of GBM, EGFR kinase inhibitors (erlotinib, gefitinib) are employed, however only 10% - 20% of patients respond. EGFR is typically increased, overexpressed, or mutated in glioblastomas, as previously stated [141]. Through the MAPK, phosphoinositide 3-kinase (PI3K)/AKT, and NF-B signalling pathways, the glioma cell line U-87 MG and patientderived CSCs were made more sensitive to therapy-induced senescence by combining the pan-adenosine triphosphate-binding cassette transporter and L-type voltage-dependent calcium channel inhibitor verapamil with carmustine and irradiation [142]. A number of potential medications have showed promise in in vitro or in vivo research, but their molecular mechanisms of action have yet to be studied, thus any predictions are premature. SP-141 was discovered to be cytotoxic for GBM cells due

to decreased MDM2, elevated levels of p53 and p21cip1, arrest of the G2/M cell cycle, and severe apoptosis [143] Sulforaphane (SFN), a compound found in cruciferous vegetables, was found to cause apoptosis in tumour tissues. Cysteine (SFN-Cys) has been added to this molecule to increase its half-life and consequently plasma enrichment [144]. The long-term activation of ERK1/2- and ERK1/2-mediated signalling pathways, such as the activation of caspase 3 and proteins associated with apoptosis, is required for the induction of cell apoptosis by this SFN-Cys. The curaxin CBL0137 upregulated p53 and downregulated nuclear factor-kappa B (NF-B) and Facilitates Chromatin Transcription by inactivating the chromatin remodelling complex (FACT) [145]. BEV is a VEGF-targeting monoclonal antibody that is used as a monotherapy or in combination with a secondary drug in the treatment of GBM [146]. A meta-analysis conducted by Diaz RJ et al. [147] based on 52 relevant studies of BEV found that while BEV could prolong PFS and OS in recurrent GBM patients either alone or in combination with cytotoxic agents, the survival advantage was limited to 4 months and there was no significant difference in survival

in the primary setting. BEV would also have a number of serious side effects, as well as the loss of the ability to use other therapeutic options. In vivo and in vitro studies, several other medications are increasingly incorporated into a variety of therapeutic pharmaceuticals or theranostics for glioblastoma. Table 1 listed out all the drugs currently undergoing clinical trials for Glioma treatment.

Drugs	Target	Mechanism	Clinical Trial Phase	Reference
Enzastaurin	target both PKC and PI3K/AKT pathways	suppress proliferation and tumor-induced angiogenesis	Phase III	[148,149]
Cilengitide	αvβ3 and αvβ5 integrin inhibitor	showed a PFS as well as an OS benefit	Phase II	[150]
Cediranib	vascular endothelial growth factor receptor (VEGFR)	tyrosine kinase inhibitor	Phase III	[151]
Everolimus	rapamycin (mTOR) inhibitor	restrict cell growth and proliferation, effective in reducing the volume of subependymal giant cell astrocytoma's	Phase III	[152]
Nimotuzumab	Epidermal growth factor receptor (EGFR)	Reduce oncogenesis and progression.	Phase III	[153,154]
Regorafenib	tyrosine kinase inhibitor	inhibits angiogenesis and other tumor-driven pathways, such as vascular endothelial growth factor receptor (VEGFR) 1-3, PDGFR, fibroblast growth factor receptor (FGFR), the angiopoietin receptor TIE-2, tyrosine kinase receptors, receptor tyrosine kinase genes, leukemia factor 1, the BRAF gene and other protein kinase activities	Phase II	[155,156]
Bortezomib	NF-κB pathway, cell cycle and apoptosis	inhibits cell adhesion, angiogenesis and cytokine-mediated intercellular communication, affects chemotherapy, increasing the sensitivity of tumors to chemotherapy	Phase II	[157]
Marizomib	proteasome inhibitor	blood-brain barrier permeability and obviously prolonged the survival time of animals with glioma	Phase II	[158]
Vemurafenib	Inhibitor of the V600E mutation.	prevent the occurrence and progression of tumors to a certain extent	Phase II	[159]
Onartuzumab	anti-MET pathway drug	Inhibit tumor proliferation, survival and metastasis	Phase II	[160]
APG101	bind to CD95L	blocks CD95L and can inhibit the effects of the binding of CD95 and CD95L	Phase II	[161]

Table 1: List of drug employ for glioma treatment and their clinical trial phase.

Twelve Exosome as an inspiration for drug delivery Exosomes' nanoscale capabilities have been employed in a rising number of studies to fully leverage the exosome potential in therapeutic applications and to encapsulate and distribute bioactive chemicals such as small molecules (anticancer drugs), proteins, and miRNAs [162]. Membrane decorated Exosome for drug delivery Exosomes are extracellular vesicles (EVs) that emerge from multivesicular bodies and therefore are not identified by the complement system, consequently they do not elicit unfavorable immunological responses. Exosomes, despite being natural vehicles, can have their surface altered. The objective of surface engineering is to confer cell type targeting specificity. Because the ideal drug delivery system should be able to deliver integrated therapeutics to specific sites while avoiding detection and early

degradation by the body's immune system, as well as regulated cargo molecule release in response to certain stimuli. Nanoscale medication delivery technologies have grown in popularity in recent years. Numerous nano-based medicine formulations have been designed to optimize the therapeutic efficacy of chemical and biomolecular treatments. Exosomes have sparked a lot of research interest since they were identified to serve as intercellular communication systems that deliver cargo to destination cells [163]. Furthermore; they show no long-term accumulation in any organ or tissue, as well as modest systemic toxicity and cellular uptake facilitation [164]. Exosomes can be modified using two approaches: genetic engineering and chemical alterations. Both approaches have their own limits. Chemical modification enables the display of a wide range of natural and synthesized ligands via crosslinking or lipid assembly. On the other hand, the use of genetic engineering to show peptides and proteins on the surface is effective. Crosslinking processes done by via chemical modification can irreversibly as well as firmly modify exosomal surface proteins, although overall efficiency is restricted by the intricacy of the exosome surface, and they typically lack site specificity control and the vehicles normal functioning could also be jeopardized by covalent alteration. Using genetic engineering, we can fuse the gene sequence of a guiding protein or polypeptide with that of a specific exosomal membrane protein. However, it is confined to targeting genetically encodable motifs [165]. Exosome genetic engineering is a convenient way for giving exosomes new features. To begin, ligands or homing peptides are coupled to transmembrane proteins produced on exosome surfaces. Donor cells that have been transfected with plasmids encoding the fusion proteins then produce modified exosomes with targeting ligands on their surfaces. Exosomes can be coupled with a pH-sensitive fusogenic peptide and a cationic lipid for cytosolic distribution [166,167]. Exosomes can also be engineered with PEG and AA for lung metastasis and medication

delivery [168,169]. Metal-organic frameworks (MOFs) have gained popularity among academics over the last two decades due to their interesting topologies, excellent crystallinity, outstanding porosity, and diverse modularity that may be used in a variety of sectors [170]. Table 2: update on engineered exosome for drug delivery purpose to treat cancer. 13 Drug delivery using Exosomes The permeability of the BBB is a significant barrier to the administration of chemotherapeutic medicines. Exosomes have features that make them suited for treating CNS tumours, and exosome-based combination medicines can address some of the problems with current GBM treatments [185,186]. Exosome-mediated transfers of lipophilic and hydrophilic medicines, such as curcumin [187] and doxorubicin [171], have been shown in previous investigations to not induce unfavorable immunological responses and are not recognized by the complement system. Temozolomide (TMZ) is a first-line anticancer medication that is commonly used in the treatment of GBM [188,189]. However, the alkylation damage induced by TMZ at the O6 position of DNA guanine can be repaired by O6-alkylguanine-DNA alkyl transferase (AGT), rendering tumour cells resistant to TMZ [190-195]. The combination of TMZ with BG20 reduces the maximum tolerated dose of TMZ, yet BG is not extensively utilized in anti-GBM therapy due to its side effects, which include liver toxicity, myelosuppression, pulmonary fibrosis, and poor BBB penetration [196,197]. To address these issues, a dual-receptor-specific exosome loaded with TMZ and BG (dubbed EXO-An2-AptTMZ and EXO-An2-Apt-BG) has been developed for the first time to maximize systemic TMZ and BG brain delivery for GBM treatment [198]. To conjugate exosomes with drugs, three techniques are used: incubation, which is the simplest method; electroporation, which involves the penetration of exosomes using short, high-voltage pulses; and sonication, which involves the loading of drugs (such as paclitaxel) into exosomes using effective sonication [199-201]. M. Zhuang et al.

administered exosomes containing the STAT3 inhibitor cucurbitacin I to mice with GBM through nasal, result in extending their survival from 20 days to 44.5 days without experiencing any negative consequences or behavioral problems [202]. Yang et al. [186] found that when anticancer medications were delivered by brain ECs-derived exosomes, the fluorescence intensity of xenotransplanted zebrafish cancer models and tumour development markers decreased. STAT3 is a protein that is found in a variety of cancers, including GBM. Exosomes have been found to contain hydrophilic and hydrophobic chemotherapeutic drugs such as Dox and PTX. Exosome-mediated chemotherapeutic administration has been established in a growing number of studies to improve anti-cancer efficacy [203-206]. Dox is a highly effective anti-cancer medicine that is used to treat leukemia, lymphoma, and a variety of solid tumours. However, due to their poor biocompatibility and substantial adverse effects such as bone marrow suppression and cardiotoxicity, Dox's clinical application is restricted. Exosomes generated from mesenchymal stem cells have recently been found to improve the cellular absorption rate and anticancer efficacy of Dox in osteosarcoma patients [207]. PTX is another anti-mitotic drug commonly used to treat malignant tumours like glioblastoma multiform and breast cancer [208]. PTX, on the other hand, has a dose dependent toxic effect and limited absorption, making it challenging to use in practice. In 14 numerous trials, PTX was likewise discovered to be unable to cross through the BBB [209- 211]. Furthermore, cancer-derived exosomes containing PTX may be able to directly target drug-resistant cancer stem cells, resulting in improved cytotoxicity against autologous cancer cells [212].

Therapeutics cargo	Target	Target cells	Function	Reference
KRAS siRNA	iRGD peptide	adenocarcinoma, human alveolar basal epithelial cells (A549)	Target oncogenic KRAS	[171]
DOX	iRGD peptide	breast cancer	Targeted delivery of DOX	[172]
SOX2 siRNA	Tlyp-1	non-small cell lung cancer, A549 stem cells	Gene delivery for cancer therapy	[173]
imatinib, BCR-ABL siRNA	IL-3	chronic myelogenous leukemia cells (LAMA84, K562, K562R)	Inhibit cancer cell growth	[174]
5-fluorouracil anti-miRNA-21	zHER affibody	colorectal cancer (HCT-116)	Reverse chemoresistance and improve cancer treatment efficiency	[175]
Tpd50 siRNA	DARPin	HER2-positive cells (SKBR3)	HER2-positive cells (SKBR3)	[176]
miRNA-let7a	GE11 peptide	breast cancer (HCC70)	Target EGFR- expressing tumor	[177]
Smart-exos	αCD3/αEGFR	T-cells (Jurkat), EGFR-positive breast cancer (MDA-MB-468)	Cell-free cancer immunotherapy	[178]
miRNA-26a	ApoA-1	hepatocellular carcinoma (HepG2)	Suppress tumor cell migration and proliferation	[179]
curcumin-SPION	neuropillin-1-targeted peptide	glioma (U251)	Simultaneous diagnosis and treatment of glioma	[180]
PTX	AA	murine lung cancer (3LL-M27), sigma	Improve drug circulation and inhibit pulmonary metastases	[170]
methotrexate, KLA (Lys-Leu-Ala)	ApoA-1 mimetic peptide	glioma	Selective brain tumor treatment	[171]
miRNA-let7, VEGF siRNA	AS1411 aptamer	nucleolin-positive cancer cells (MDA- MA-231)	Tumor-targeted small RNA delivery	[181]
aSIRPα, aCD47	antibodies	macrophages and tumor cells	s Enhance phagocytosis of cancer cells by blocking SIRPα– CD47 interaction	[182]
mannosamine	RGD	αvβ3 overexpressing cells (HUVEC)	Promote angiogenesis with targeted imaging	[183]
PTX, tirapazamine	D-CGKRK	B16F10	Hybrid membrane vesicles for targeted therapy	[184]

Table 2: Surface engineered exosome for drug delivery for cancer treatment.

Cargo	Cancer Type	Result	Reference
Doxorubicin	Breast cancer Ovarian cancer, Colon carcinoma	Tumor growth inhibition lowering medication toxicity, Suppression of tumor growth	[213-215]
Paclitaxel	Pancreatic adenocarcinoma, Prostate cancer, Pulmonary metastasis, Lung cancer, Glioblastoma-astrocytoma cancer	Improved anticancer effect, Drug resistance was overcome. On cancer cells, increased cytotoxicity, Drug resistance was overcome. On cancer cells, increased cytotoxicity, Suppression of tumor growth Lower systemic toxicity, On cancer cells, increased cytotoxicity. Passed through the BBB,	[215- 219]
TMZ	Glioma		[198]
Nucleic acid	Hepatocellular carcinoma, Brain tumor, Breast adenocarcinoma , Breast cancer Lung metastasis, Hepatocellular cancer, Breast cancer Leukemia	Chemosensitivity has been improved. Anticancer activity has been improved; Tumor development is inhibited. Passed through the BBB, Suppression of tumor growth Improved effect of tumor targeting, Increased the rate of cellular absorption Cancer cell migration and metastases are reduced, Suppression of tumor growth Promoted tumor cell apoptosis, Tumor growth inhibition Drug cytotoxicity is reduced.	[202,211215,22 2,223]
Protein	Pancreatic adenocarcinoma, Any type of cancer, Colon carcinoma, Colon carcinoma	Adenocarcinoma cells undergo induced apoptosis. Drug sensitivity has improved., Immunotherapy accumulation in lymph nodes, Enhanced phagocytosis of tumor cells Suppression of tumor growth, Proliferation and activation of immune cells Suppression of tumor growth	[224-226]

Table 3: Different cargo encapsulated using exosome.

The different types of exosomes in drug delivery systems (Table 3). Exosome pharmacokinetics are affected by physicochemical qualities that vary based on the type of exosome source [227,228]. As a result, it's crucial to investigate how distinct biochemical properties of exosomes are derived from various sources. Exosomes are a form of nano-sized extracellular vesicle (EV) that can be released by practically any type of cell. Exosomes have been extracted from human embryonic kidney (HEK) cells, cancer cells, immune cells, and stem cells by a number of research groups, and these exosomes have distinct features depending on their origin. Exosomes derived from HEK293T contain membrane resemblances to many organs in human body, according to prior studies [229-232]. Due to its desirable qualities such as ease of growth, low care requirements, and high transfection efficiency, the HEK cell line (HEK293T) is the most often used cell line in the field of biopharmaceutical manufacture [233]. This shows that HEK-derived exosomes can carry drugs to a variety of organs. Exosomes containing therapeutic membrane proteins have also been found to improve tumour penetration and anticancer effectiveness. Native

PH20 hyaluronidase expressing exosomes derived from HEK293T cells, according to Hong et al findings, inhibit tumour growth by degrading hyaluronan in the tumour extracellular matrix (ECM), which is a key component of the tumour microenvironment. When PH20 and doxorubicin (Dox) were delivered together in a tumor-bearing mouse model, the anticancer effects were dramatically improved compared to Dox-only administration groups [234]. Cancer cells are also considered good exosome producers because they overexpress two Rab protein subtypes involved in exosome release (Rab27a and Rab27b) [235]. Exosomes generated from cancer cells have shown potential as drug delivery vehicles, but there are fundamental limitations that must be overcome before they can be used to treat cancer [236]. To begin with, the pharmacokinetic profile of naive exosomes produced by cancer cells is less than ideal. Second, multiple studies suggest that cancer exosomes may contribute in tumour dissemination, thus all potential side effects should be considered before employing cancer exosomes as drug carriers [237]. Mesenchymal stem cells (MSCs), which can be extracted from a range of human

tissues and have a great capacity for ex vivo proliferation, are considered an ideal source for preparing exosomes for

therapeutic application among the numerous cell types known to secrete exosomes [238,239].

Exosome donor	Exosome Acceptor	Exosome loaded	Result	Reference
HEK-293T cells	U87-MG, C6 and rat model	miR-21 sponge construct	Tumor volume is reduced by miR-21 down-regulation and overexpression of miR-21 target genes (PDCD4 and RECK)	[240]
hBMSCs	U251	miR-199a	Down-regulate the expression of AGAP2, in turn inhibits tumour development, invasion, and migration	[241]
hBMSCs	Glioma cells (SHG44, C6, U87, and U251) and nude mice	miR-375	Encourages apoptosis and inhibits growth, migration, and infiltration via Suppressing SLC31A1	[242]
DCs carried CRCLs with GL261 glioma cells	6-weekold female C57BL/6 mice	CRCLs	As a result of modulating Cbl-b and c-Cbl signaling, it exacerbates the longevity of tumor-bearing mice and inhibits tumour progression.	[243]
MSCs	male Fischer rats	miR-146b	Inhibits the expression of EGFR due to which Glioma growth is halted.	[244]
hBMSCs	U87 cells; T98G cells	Anti-miR-9	Reduces GBM cell chemoresistance to TMZ by decreasing miR9 levels and drug transporter expression in GBM cells. MDR1	[245]
Human GBM cells	CTLs obtained from PBMCs	Tumor antigen	Kills autologous glioma cells by inducing the production of glioma-specific CD8+ CTLs.	[246]
GL26 cells	Microglial cells	Cucurbitacin	By selectively decreasing the activity of STAT3 and diminishing the expression of IL-1b and IL-6, it promotes tumour cell death and decreases tumour cell proliferation.	[202]
SMA560vIII	VM/Dk mice		Reduces tumorigenesis and prolongs survival by producing immune memory, improving T cell function, and stimulating antibody production.	[247]

Table 4: Types of different exosome from different source for treating cancer.

Future perspective Exosomes have demonstrated their full capacity for medication delivery in order to overcome any limitations. Because of their unique features, such as endogenous origin and tissue tropism, exosomes hold promise for improving therapeutic delivery. Furthermore, exosomes 15 could be easily modified to improve medication loading and targeting efficiency. Despite the benefits of exosomes, thorough knowledge of exosome biology is still in its infancy, and more study remains to be done in the future. The choice of exosome source for therapeutic applications must be decided with great care. In this sense, strategies for identifying and removing or adding exosomal components are crucial for exosome-based drug delivery for cancer treatment, and they may one day allow us to overcome limitations posed by heterogeneous exosome subpopulations.

The loading efficiency necessary for clinical applications is not met by current exosome cargo loading techniques. The basic incubation approach, in particular, is relatively limited in terms of the sort of cargo that may be loaded, and its efficiency is too low to be used in clinical applications, so new approaches are needed to develop. Exosomes offer limitless promise as biomarkers for cancer detection and prognosis, in addition to their potential as medication carriers. Exosomes have been studied extensively in order to better understand their varied profiles and roles, as well as to facilitate their clinical uses. Exosomes have ushered in a new age in drug delivery, owing to their low immunogenicity and high biocompatibility. Due to in vivo degradation of the therapeutic substance and a lack of targeting ability, traditional delivery techniques of anticancer drugs, nucleic acids, and proteins for cancer treatment frequently fail to produce desired effects.

Although there are still a few challenges and roadblocks to overcome in developing a commercial exosome-based drug delivery system, a better understanding of exosomes' detailed biological mechanisms and more clinical research will allow them to emerge as a next-generation comprehend for cancer therapy. In our lab, we're experimenting with exosomes as a drug delivery system to see if we can design a system that is both effective and resistant to degradation. Conclusion Glioblastoma treatment is complicated by resistance to standard medicines and recurrent recurrence. To overcome these obstacles and improve treatment outcomes, new therapeutic strategies must be developed. Internal factors like the blood–brain barrier (BBB), the blood-brain tumour barrier (BBTB), genetic molecular characteristics (heterogeneity, the Warburg effect, oncologically activated alternative splicing pathways), and external factors like a therapeutic agent or the immune system can all contribute to resistance (immune evasion). Because GBM is so heterogeneous, the most promising therapeutic strategy for treating it is to use a combination of methods and treatment regimens. Drugs that penetrate the BBB (upon chemical modification, use of substrates for carrier-mediated and receptor-mediated transcytosis, virus-mediated and exosome-mediated blood-brain barrier delivery) in combination with hyperosmotic agents and focused ultrasound, for example, will be useful with an intact BBB.

REFERENCES

1. Wong J, Hird A, Kirou-Mauro A, et al. (2008) Quality of life in brain metastases radiation trials: A literature review. Current Oncology 15(5): 25-45.

2. Nayak L, Lee EQ, Wen PY (2012) Epidemiology of brain metastases. Current Oncology Reports 14(1): 48-54.

3. Tabouret E, Chinot O, Metellus P, et al. (2012) Recent trends in epidemiology of brain metastases: An overview. Anticancer Research 32(11): 4655-4662.

4. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. (2004) Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. Journal of Clinical Oncology 22(14): 2865-2872.

5. Nieder C, Spanne O, Mehta MP et al. (2011) Presentation, patterns of care, and survival in patients with brain metastases. Cancer 117: 2505-2512.

6. Modrek AS, Bayin NS, Placantonakis DG (2014) Brain stem cells as the cell of origin in glioma. World Journal of Stem Cells 6(1): 43.

7. Louis DN, Perry A, Reifenberger G, et al. (2016) The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathologica 131(6): 803-820.

8. Hu X, Martinez-Ledesma E, Zheng S, et al. (2017) Multigene signature for predicting prognosis of patients with 1p19q co-deletion diffuse glioma. Neuro-oncology 19(6): 786-795.

9. Bush NAO, Chang SM, Berger MS (2017) Current and future strategies for treatment of glioma. Neurosurgical Review 40(1): 1-14.

10. Gao H (2017) Perspectives on dual targeting delivery systems for brain tumors. Journal of Neuroimmune Pharmacology 12(1): 6-16.

11. Wu M, Zhang H, Tie C, et al. (2018) MR imaging tracking of inflammation-activatable engineered neutrophils for targeted therapy of surgically treated glioma. Nature Communications 9(1): 1-13.

12. Ruan H, Chen X, Xie C, et al. (2017) Stapled RGD peptide enables glioma-targeted drug delivery by overcoming multiple barriers. ACS Applied Materials & Interfaces 9(21): 17745-17756.

13. Zlokovic BV (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 57(2): 178-201.

14. Daneman R (2012) The blood-brain barrier in health and disease. Annals of Neurology 72(5): 648-672.

15. Larsen MJ, Martin RD, Byrne EM (2014) Recent advances in delivery through the blood-brain barrier. Current Topics in Medicinal Chemistry 14(9): 1148-1160.

16. Cheng H, Perez-Soler R (2018) Leptomeningeal metastases in non-small-cell lung cancer. The Lancet Oncology 19(1): e43-e55.

17. Arvanitis CD, Ferraro GB, Jain RK (2020) The blood-brain barrier and blood - tumour barrier in brain tumours and metastases. Nature Reviews Cancer 20(1): 26-41.

18. Fares J, Kanojia D, Rashidi A, et al. (2020) Landscape of combination therapy trials in breast cancer brain metastasis. International Journal of Cancer 147(7): 1939-1952.

19. Lakhal S, Wood MJ (2011) Exosome nanotechnology: An emerging paradigm shift in drug delivery: Exploitation of exosome nanovesicles for systemic in vivo delivery of RNAi Heralds new horizons for drug delivery across biological barriers. Bioessays 33(10): 737-741.

20. Hoshino D, Kirkbride KC, Costello K, et al. (2013) Exosome secretion is enhanced by invadopodia and drives invasive behavior. Cell Reports 5(5): 1159-1168

21. Lai RC, Yeo RWY, Tan KH, et al. (2013) Exosomes for drug delivery - A novel application for the mesenchymal stem cell. Biotechnology Advances 31(5): 543-551.

22. Conrad C, Götte M, Schlomann U, et al. (2018) ADAM8 expression in breast cancer derived brain metastases: Functional implications on MMP-9 expression and transendothelial migration in breast cancer cells. International Journal of Cancer. 142(4): 779-791.

23. Sevenich L, Bowman RL, Mason SD, et al. (2014) Analysis of tumour-and stroma-supplied proteolytic networks reveals a brain-metastasis-promoting role for cathepsin S. Nature Cell Biology 16(9): 876-888.

24. Rodrigues G, Hoshino A, Kenific CM, et al. (2019) Tumour exosomal CEMIP protein promotes cancer cell colonization in brain metastasis. Nature cell biology 21(11): 1403-1412.

25. Avraham HK, Jiang S, Fu Y, et al. (2014) Angiopoietin-2 mediates blood-brain barrier impairment and colonization of triple- negative breast cancer cells in brain. The Journal of Pathology 232(3): 369-381.

26. Trajkovic, K, Hsu C, Chiantia S, et al. (2008) Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science 319(5867): 1244-1247.

27. Cheng Q, Li X, Wang Y, et al. (2018) The ceramide pathway is involved in the survival, apoptosis and exosome functions of human multiple myeloma cells *in vitro*. Acta Pharmacologica Sinica 39(4): 561-568.

28. Ostenfeld MS, Jeppesen DK, Laurberg JR, et al. (2014) Cellular disposal of miR23b by RAB27-dependent exosome release is linked to acquisition of metastatic properties. Cancer Research 74(20): 5758- 5771.

29. Lee HY, Chen CK, Ho CM, et al. (2018) EIF3C-enhanced exosome secretion promotes angiogenesis and tumorigenesis of human hepatocellular carcinoma. Oncotarget 9(17): 13193.

30. Matsumoto A, Takahashi Y, Nishikawa M, et al. (2017) Accelerated growth of B16 BL 6 tumor in mice through efficient uptake of their own exosomes by B16 BL 6 cells. Cancer Science 108(9): 1803-1810.

31. Datta A, Kim H, Lal M, et al. (2017) Manumycin A suppresses exosome biogenesis and secretion via targeted inhibition of Ras/Raf/ERK1/2 signaling and hnRNP H1 in castration-resistant prostate cancer cells. Cancer Letters 408: 73-81.

32. Madeo M, Colbert PL, Vermeer DW, et al. (2018) Cancer exosomes induce tumor innervation. Nature Communications 9(1): 1-15.

33. Phuyal S, Hessvik NP, Skotland T, et al. (2014) Regulation of exosome release by glycosphingolipids and flotillins. The FEBS Journal 281(9): 2214-2227.

34. Hsu C, Morohashi Y, Yoshimura SI, et al. (2010) Regulation of exosome secretion by Rab35 and its GTPase-activating proteins TBC1D10A-C. Journal of Cell Biology 189(2): 223-232.

35. Savina A, Vidal M, Colombo MI (2002) The exosome pathway in K562 cells is regulated by Rab11. Journal of Cell Science 115(12): 2505-2515.

36. Ostrowski M, Carmo NB, Krumeich S, et al. (2010) Rab27a and Rab27b control different steps of the exosome secretion pathway. Nature Cell Biology 12(1): 19- 30.

37. Bobrie A, Krumeich S, Reyal F, et al. (2012) Rab27a supports exosome-dependent and-independent mechanisms that modify the tumor microenvironment and can promote tumor progression. Cancer Research 72(19): 4920-4930.

38. Zheng Y, Campbell EC, Lucocq J, et al. (2013) Monitoring the Rab27 associated exosome pathway using nanoparticle tracking analysis. Experimental Cell Research 319(12): 1706-1713.

39. Sinha S, Hoshino D, Hong NH, et al. (2016) Cortactin promotes exosome secretion by controlling branched actin dynamics. Journal of Cell Biology 214(2): 197-213.

40. Kucharzewska P, Belting M (2013) Emerging roles of extracellular vesicles in the adaptive response of tumour cells to microenvironmental stress. Journal of Extracellular Vesicles 2(1): 20304.

41. De Maio A (2011) Extracellular heat shock proteins, cellular export vesicles, and the stress observation system: A form of communication during injury, infection, and cell damage. Cell Stress and Chaperones 16(3): 235-249.

42. Dorayappan KDP, Wanner R, Wallbillich JJ, et al. (2018) Hypoxia-induced exosomes contribute to a more aggressive and chemoresistant ovarian cancer phenotype: A novel mechanism linking STAT3/Rab proteins. Oncogene 37(28): 3806-3821.

43. Kucharzewska P, Christianson HC, Welch JE, et al. (2013) Exosomes reflect the hypoxic status of glioma cells and mediate hypoxia-dependent activation of vascular cells during tumor development. Proceedings of the National Academy of Sciences 110(18): 7312-7317.

44. Wei Y, Wang D, Jin F, et al. (2017) Pyruvate kinase type M2 promotes tumour cell exosome release via phosphorylating synaptosome-associated protein. Nature Communications 8(1): 1-12.

45. Zhao H, Yang L, Baddour J, et al. (2016) Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism. Elife 5: e10250.

46. Parolini I, Federici C, Raggi C, et al. (2009) Microenvironmental pH is a key factor for exosome traffic in tumor cells. Journal of Biological Chemistry 284(49): 34211-34222.

47. Ban JJ, Lee M, Im W, et al. (2015) Low pH increases the yield of exosome isolation. Biochemical and Biophysical Research Communications 461(1): 76- 79.

48. Mulcahy LA, Pink RC, Carter DRF (2014) Routes and mechanisms of extracellular vesicle uptake. Journal of Extracellular Vesicles 3(1): 24641.

49. Silva J, Garcia V, Rodriguez M, et al. (2012) Analysis of exosome release and its prognostic value in human colorectal cancer. Genes, Chromosomes and Cancer 51(4): 409-418.

50. Lee TH, Chennakrishnaiah S, Audemard E, et al. (2014) Oncogenic ras-driven cancer cell vesiculation leads to emission of double-stranded DNA capable of interacting with target cells. Biochemical and Biophysical Research Communications 451(2): 295-301.

51. Al-Nedawi K, Meehan B, Micallef J, et al. (2008) Intercellular transfer of the oncogenic receptor EGFRvIII by microvesicles derived from tumour cells. Nature Cell Biology 10(5): 619-624.

52. Campanella C, Caruso Bavisotto C, Logozzi M, et al. (2019) On the choice of the extracellular vesicles for therapeutic purposes. International Journal of Molecular Sciences 20(2): 236.

53. Liu C, Su C (2019) Design strategies and application progress of therapeutic exosomes. Theranostics 9(4): 1015.

54. Sun YZ, Ruan JS, Jiang ZS, et al. (2018) Extracellular vesicles: A new perspective in tumor therapy. BioMed Research International 2018:2687954.

55. Batrakova EV, Kim MS (2015) Using exosomes, naturally-equipped nanocarriers, for drug delivery. Journal of Controlled Release 219: 396-405.

56. Quah BJ, O'Neill HC (2005) The immunogenicity of dendritic cell-derived exosomes. Blood Cells Mol Disorders 35(2): 94-110.

57. Purushothaman A, Bandari SK, Liu J, et al. (2016) Fibronectin on the surface of myeloma cell-derived exosomes mediates exosomecell interactions. The Journal of Biological Chemistry 291(4): 1652-1663.

58. Soltani F, Parhiz H, Mokhtarzadeh A, et al. (2015) Synthetic and biological vesicular nano-carriers designed for gene delivery. Current Pharmaceutical Design 21(42): 6214-6235.

59. Zheng M, Huang M, Ma X, et al. (2019) Harnessing exosomes for the development of brain drug delivery systems. Bioconjugate Chemistry 30(4): 994-1005.

60. Gutiérrez-Vázquez C, Villarroya-Beltri C, Mittelbrunn M, et al. (2013) Transfer of extracellular vesicles during immune cell-cell interactions. Immunological reviews 251(1): 125-142.

61. Haney MJ, Klyachko NL, Zhao Y, et al. (2015) Exosomes as drug delivery vehicles for Parkinson's disease therapy. Journal of Controlled Release 207: 18-30.

62. Whiteside TL (2013) Immune modulation of T-cell and NK (natural killer) cell activities by TEXs (tumour-derived exosomes). Biochemical Society Transactions 41(1): 245-251.

63. Belting M, Wittrup A (2008) Nanotubes, exosomes, and nucleic acid-binding peptides provide novel mechanisms of intercellular communication in eukaryotic cells: Implications in health and disease. The Journal of Cell Biology 183(7): 1187.

64. Schiera G, Di Liegro CM, Saladino P, et al. (2013) Oligodendroglioma cells synthesize the differentiation-specific linker histone H1 and release it into the extracellular environment through shed vesicles. International Journal of Oncology 43(6): 1771-1776.

65. Li CC, Eaton SA, Young PE, et al. (2013) Glioma microvesicles carry selectively packaged coding and non-coding RNAs which alter gene expression in recipient cells. RNA Biology 10(8): 1333-1344.

66. Putz U, Howitt J, Doan A, et al. (2012) The tumor suppressor PTEN is exported in exosomes and has phosphatase activity in recipient cells. Science Signaling 5(243): ra70-ra70.

67. Skog J, Würdinger T, Van Rijn S, et al. (2008) Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nature Cell Biology 10(12): 1470-1476.

68. de Vrij J, Maas SN, Kwappenberg KM, et al. (2015) 21 Glioblastoma-derived extracellular vesicles modify the phenotype of monocytic cells. International Journal of Cancer 137(7): 1630-1642.

69. Ge R, Tan E, Sharghi-Namini S, et al. (2012) Exosomes in cancer microenvironment and beyond: Have we overlooked these extracellular messengers?. Cancer Microenvironment 5(3): 323-332.

70. Giese A, Westphal M (2001) Treatment of malignant glioma: A problem beyond the margins of resection. Journal of Cancer Research and Clinical Oncology 127(4): 217-225.

71. Artym VV, Matsumoto K, Mueller SC, et al. (2011) Dynamic membrane remodeling at invadopodia differentiates invadopodia from podosomes. European Journal of Cell Biology 90(2-3): 172-180.

72. Bergman A, Condeelis JS, Gligorijevic B (2014) Invadopodia in context. Cell Adhesion & Migration 8(3): 273-279.

73. Hoshino D, Branch KM, Weaver AM (2013) Signaling inputs to invadopodia and podosomes. Journal of Cell Science 126(14): 2979-2989.

74. Paz H, Pathak N, Yang J (2014) Invading one step at a time: The role of invadopodia in tumor metastasis. Oncogene 33(33): 4193-4202.

75. Sanner T (1975) Formation of transient complexes in the glutamate dehydrogenase catalyzed reaction. Biochemistry 14(23): 5094-5098.

76. Kore RA, Edmondson JL, Jenkins SV, et al. (2018) Hypoxia-derived exosomes induce putative altered pathways in biosynthesis and ion regulatory channels in glioblastoma cells. Biochemistry and Biophysics Reports 14: 104-113.

77. Filipazzi P, Bürdek M, Villa A, et al. (2012) Recent advances on the role of tumor exosomes in immunosuppression and disease progression. In Seminars in Cancer Biology, Academic Press 22(4): 342-349.

78. King HW, Michael MZ, Gleadle JM, et al. (2012) Hypoxic enhancement of exosome release by breast cancer cells. BMC Cancer 12(1): 1-10.

79. Roma-Rodrigues C, Fernandes AR, Baptista PV (2014) Exosome in tumour microenvironment: Overview of the crosstalk between normal and cancer cells. BioMed Research International 2014: 179486.

80. Li L, Li C, Wang S, et al. (2016) Exosomes derived from hypoxic oral squamous cell carcinoma cells deliver miR-21 to normoxic cells to elicit a prometastatic phenotype. Cancer Research 76(7): 1770-1780.

81. Shaimardanova AA, Solovyeva VV, Chulpanova DS, et al. (2020) Extracellular vesicles in the diagnosis and treatment of central nervous system diseases. Neural Regeneration Research 15(4): 586.

82. Basu B, Ghosh MK (2019) Extracellular vesicles in glioma: From diagnosis to therapy. Bio Essays 41(7): e1800245.

83. Yue X, Lan F, Xia T (2019) Hypoxic glioma cell-secreted exosomal miR-301a activates Wnt/β-catenin signaling and promotes radiation resistance by targeting TCEAL7. Molecular Therapy 27(11): 1939-1949.

84. Corcoran C, Rani S, O'Brien K, et al. (2012) Docetaxel-resistance in prostate cancer: Evaluating associated phenotypic changes and potential for resistance transfer via exosomes. PloS One 7(12): e50999.

85. Azmi AS, Bao B, Sarkar FH (2013) Exosomes in cancer development, metastasis, and drug resistance: A comprehensive review. Cancer and Metastasis Reviews 32(3): 623-642.

86. Wolburg H, Lippoldt A (2002) Tight junctions of the blood-brain barrier: development, composition and regulation. Vascular Pharmacology 38(6): 323-337.

87. Banks WA (2016) From blood-brain barrier to blood-brain interface: New opportunities for CNS drug delivery. Nature Reviews: Drug Discovery 15(4): 275-292.

88. Abbott NJ (2-13) Blood-brain barrier structure and function and the challenges for CNS drug delivery. Journal of Inherited Metabolic Disease 36(3): 437-449.

89. Ghosh C, Puvenna V, Gonzalez-Martinez J, et al. (2011) Bloodbrain barrier P450 enzymes and multidrug transporters in drug resistance: A synergistic role in neurological diseases. Current Drug Metabolism 12(8): 742-749.

90. Christianson HC, Svensson KJ, Van Kuppevelt TH, et al. (2013) Cancer cell exosomes depend on cell-surface heparan sulfate proteoglycans for their internalization and functional activity. Proceedings of the National Academy of Sciences 110(43): 17380-17385.

91. Grapp M, Wrede A, Schweizer M, et al. (2013) Choroid plexus transcytosis and exosome shuttling deliver folate into brain parenchyma. Nature Communications 4(1): 1-13.

92. Ye Z, Zhang T, He W, et al. (2018) Methotrexate-loaded extracellular vesicles functionalized with therapeutic and targeted peptides for the treatment of glioblastoma multiforme. ACS Applied Materials & Interfaces 10(15): 12341-12350.

93. Alvarez-Erviti L, Seow Y, Yin H, et al. (2011) Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nature Biotechnology 29(4): 341-345.

94. Chen CC, Liu L, Ma F, et al. (2016) Elucidation of exosome migration across the blood-brain barrier model *in vitro*. Cellular and Molecular Bioengineering 9(4): 509-529.

95. Harding C, Heuser J, Stahl P (1983) Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. Journal of Cell Biology 97(2): 329-339.

96. Pan BT, Teng K, Wu C, et al. (1985) Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. The Journal of Cell Biology 101(3): 942-948.

97. Kahlert C, Kalluri R (2013) Exosomes in tumor microenvironment influence cancer progression and metastasis. Journal of Molecular Medicine 91(4): 431-437.

98. Harding CV, Heuser JE, Stahl PD (2013) Exosomes: Looking back three decades and into the future. The Journal of Cell Biology 200(4): 367.

99. Raposo G, Stoorvogel W (2013) Extracellular vesicles: Exosomes, microvesicles, and friends. Journal of Cell Biology 200(4): 373-383.

100. Kuroda H, Tachikawa M, Yagi Y, et al. (2018) Cluster of differentiation 46 Is the major receptor in human blood-brain barrier endothelial cells for uptake of exosomes derived from brain-metastatic melanoma cells (SK-Mel-28). Molecular Pharmaceutics 16(1): 292-304.

101. Hoshide R, Jandial R (2017) The role of the neural niche in brain metastasis. Clinical & Experimental Metastasis. 34(6): 369-376.

102. Shumakovich MA, Mencio CP, Siglin JS, et al. (2017) Astrocytes from the brain microenvironment alter migration and morphology of metastatic breast cancer cells. The FASEB Journal 31(11): 5049-5067.

103. Conigliaro A and Cicchini C (2019) Exosome-mediated signaling in epithelial to mesenchymal transition and tumor progression. Journal of Clinical Medicine 8(1): 26.

104. Roma-Rodrigues C, Fernandes AR, Baptista PV (2014) Exosome in tumour microenvironment: Overview of the crosstalk between normal and cancer cells. BioMed Research International 2014: 179486.

105. Syn N, Wang L, Sethi G, et al. (2016) Exosome-mediated metastasis: From epithelial-mesenchymal transition to escape from immunosurveillance. Trends in Pharmacological Sciences 37(7): 606-617.

106. Steinbichler TB, Dudás J, Riechelmann H, et al. (2017) The role of exosomes in cancer metastasis. Seminars in Cancer Biology 44: 170-181.

107. Onder TT, Gupta PB, Mani SA, et al. (2008) Loss of E-cadherin promotes metastasis via multiple downstream transcriptional pathways. Cancer Research 68(10): 3645-3654.

108. Hu JL, Wang W, Lan XL, et al. (2019) CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial mesenchymal transition in colorectal cancer. Molecular Cancer 18(1): 91.

109. Menck K, Klemm F, Gross JC, et al. (2013) Induction and transport of Wnt 5a during macrophage-induced malignant invasion is mediated by two types of extracellular vesicles. Oncotarget 4(11): 2057-2066.

110. Wang S, Su X, Xu M, et al. (2019) Exosomes secreted by mesenchymal stromal/stem cell-derived adipocytes promote breast cancer cell growth via activation of Hippo signaling pathway. Stem Cell Research & Therapy 10(1): 1-12.

111. Qu Z, Wu J, Wu J, et al. (2017) Exosomal miR-665 as a novel minimally invasive biomarker for hepatocellular carcinoma diagnosis and prognosis. Oncotarget 8(46): 80666.

112. Hu Y, Yang C, Yang S, et al. (2018) miR-665 promotes hepatocellular carcinoma cell migration, invasion, and proliferation by decreasing Hippo signaling through targeting PTPRB. Cell Death & Disease 9(10): 1-13.

113. Corrado C, Saieva L, Raimondo S, et al. (2016) Chronic myelogenous leukemia exosomes modulate bone marrow microenvironment through activation of epidermal growth factor receptor. Journal of Cellular and Molecular Medicine 20(10): 1829-1839.

114. Fazakas C, Kozma M, Molnár K, et al. (2021) Breast adenocarcinoma-derived exosomes lower first-contact de-adhesion strength of adenocarcinoma cells to brain endothelial layer. Colloids and Surfaces B: Biointerfaces 204: 111810.

115. Tominaga N, Kosaka N, Ono M, et al. (2015) Brain metastatic cancer cells release microRNA181c-containing extracellular vesicles capable of destructing blood-brain barrier. Nature Communications 6(1): 1-12.

116. Eichler AF, Chung E, Kodack DP, et al. (2011) The biology of brain metastases - translation to new therapies. Nature Reviews: Clinical Oncology 8(6): 344-356.

117. Kinjyo I, Bragin D, Grattan R, et al. (2019) Leukemia-derived exosomes and cytokines pave the way for entry into the brain. Journal of Leukocyte Biology 105(4): 741-753.

118. Kuczynski EA, Vermeulen PB, Pezzella F, et al. (2019) Vessel co-option in cancer. Nature Reviews: Clinical Oncology 16(8): 469-493.

119. Fernandes C, Costa A, Osório L, et al. (2017) Current standards of care in glioblastoma therapy, Glioblastoma. Exon Publications 197-241.

120. Stupp R, Mason WP, Van Den Bent MJ, et al. (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. New England Journal of Medicine 352(10): 987-996.

121. Kaina B, Mühlhausen U, Piee-Staffa A, et al. (2004) Inhibition of O6-methylguanine-DNA methyltransferase by glucoseconjugated inhibitors: Comparison with nonconjugated inhibitors and effect on fotemustine and temozolomide-induced cell death. Journal of Pharmacology and Experimental Therapeutics 311(2): 585-593.

122. Bobustuc G, Donohoe D, Bosenko D, et al. (2017) Exth-24. Mgmt inhibition by disulfiram/copper complex restores veliparib enhancing temozolomide effect in unfavorable glioblastoma multiforme. Neuro-Oncology 19(suppl 6): vi77.

123. Kitange GJ, Carlson BL, Schroeder MA, et al. (2009) Induction of MGMT expression is associated with temozolomide resistance in glioblastoma xenografts. Neuro-Oncology 11(3): 281-291.

124. Lee SY (2016) Temozolomide resistance in glioblastoma multiforme. Genes & Diseases 3(3): 198-210.

125. Yu T, Wang X, Zhi T, et al. (2018) Delivery of MGMT mRNA to glioma cells by reactive astrocyte-derived exosomes confers a temozolomide resistance phenotype. Cancer Letters 433: 210-220.

126. Gilbert MR, Dignam JJ, Armstrong TS, et al. (2014) A randomized trial of bevacizumab for newly diagnosed glioblastoma. The New England Journal of Medicine 370(8): 699-708.

127. Chinot OL, Wick W, Mason W, et al. (2014) Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. The New England Journal of Medicine 370(8): 709-722.

128. Phillips HS, Kharbanda S, Chen R et al. (2006) Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. Cancer Cell 9(3): 157-173.

129. (2018) Glioma brain tumors (Astrocytoma, oligodendroglioma, glioblastoma).

130. Cowles AL, Fenstermacher JD (1974) Theoretical considerations in the chemotherapy of brain tumors. In Antineoplastic and Immunosuppressive Agents Part I: 319-329.

131. Groothuis DR (2000) The blood-brain and blood-tumor barriers: A review of strategies for increasing drug delivery. Neuro-oncology 2(1): 45-59.

132. Margison GP, Santibáñez Koref MF, Povey AC (2002) Mechanisms of carcinogenicity/chemotherapy by O 6-methylguanine. Mutagenesis 17(6): 483-487.

133. Chen PH, Shen WL, Shih CM et al. (2017) The CHAC1-inhibited Notch3 pathway is involved in temozolomide-induced glioma cytotoxicity. Neuropharmacology 116: 300-314.

134. Haas B, Klinger V, Keksel C et al. (2018) Inhibition of the PI3K but not the MEK/ERK pathway sensitizes human glioma cells to alkylating drugs. Cancer Cell International 18(1): 1-14.

135. Zhang X, Yu J, Zhao C et al. (2019) MiR-181b-5p modulates chemosensitivity of glioma cells to temozolomide by targeting Bcl-2. Biomedicine & Pharmacotherapy 109: 2192-2202.

136. Ho KH, Cheng CH, Chou CM et al. (2019) miR-140 targeting CTSB signaling suppresses the mesenchymal transition and enhances temozolomide cytotoxicity in glioblastoma multiforme. Pharmacological Research 147: 104390.

137. Guo XR, Wu MY, Dai LJ, et al. (2019) Nuclear FAM289-Galectin-1 interaction controls FAM289-mediated tumor promotion in malignant glioma. Journal of Experimental & Clinical Cancer Research 38(1): 1-19.

138. Gao Y, Liu B, Feng L, et al. (2019) Targeting JUN, CEBPB, and HDAC3: A novel strategy to overcome drug resistance in hypoxic glioblastoma. Frontiers in Oncology 9: 33.

139. Chio CC, Chen KY, Chang CK, et al. (20180 Improved effects of honokiol on temozolomide-induced autophagy and apoptosis of drug-sensitive and-tolerant glioma cells. BMC Cancer 18(1): 1-12.

140. Kant S, Kesarwani P, Guastella AR, et al. (2020) Perhexiline demonstrates FYN-mediated antitumor activity in glioblastoma. Molecular Cancer Therapeutics 19(7): 1415-1422.

141. Luo S, Lei K, Xiang D, et al. (2018) NQO1 is regulated by PTEN in glioblastoma, mediating cell proliferation and oxidative stress. Oxidative medicine and cellular longevity 2018.

142. Ham SW, Jeon HY, Kim H (2017) Verapamil augments carmustine-and irradiation-induced senescence in glioma cells by reducing intracellular reactive oxygen species and calcium ion levels. Tumor Biology 39(5): 1010428317692244.

143. Punganuru SR, Arutla V, Zhao W, et al. (2020) Targeted brain tumor therapy by inhibiting the MDM2 oncogene: In vitro and in vivo antitumor activity and mechanism of action. Cells 9(7): 1592.

144. Wu S, Zhou Y, Yang G, et al. (2017) Sulforaphane-cysteine induces apoptosis by sustained activation of ERK1/2 and caspase 3 in human glioblastoma U373MG and U87MG cells. Oncology Reports 37(5): 2829-2838.

145. Barone TA, Burkhart CA, Safina A, et al. (2017) Anticancer drug candidate CBL0137, which inhibits histone chaperone FACT, is efficacious in preclinical orthotopic models of temozolomide-responsive and-resistant glioblastoma. Neuro-oncology 19(2): 186-196.

146. Ferrara N, Hillan KJ, Novotny W (2005) Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. Biochemical and Biophysical Research Communications 333(2): 328-335.

147. Diaz RJ, Ali S, Qadir MG, et al. (2017) The role of bevacizumab in the treatment of glioblastoma. Journal of Neuro-oncology 133(3): 455-467.

148. Graff JR, McNulty AM, Hanna KR, et al. (2005) The protein kinase Cβ–selective inhibitor, enzastaurin (LY317615. HCl), suppresses signaling through the AKT pathway, induces apoptosis, and suppresses growth of human colon cancer and glioblastoma xenografts. Cancer Research 65(16): 7462-7469.

149. Keyes KA, Mann L, Sherman M, et al. (2004) LY317615 decreases plasma VEGF levels in human tumor xenograft-bearing mice. Cancer Chemotherapy and Pharmacology 53(2): 133-140.

150. Smith JW (2003) Cilengitide merck. Current opinion in investigational drugs (London, England: 2000) 4(6): 741-745.

151. Batchelor TT, Mulholland P, Neyns B, et al. (2013) Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. Journal of Clinical Oncology 31(26): 3212.

152. Franz DN, Belousova E, Sparagana S, et al. (2013) Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): A multicentre, randomised, placebo-controlled phase 3 trial. The Lancet 381(9861): 125-132.

153. Maire CL, Ligon KL (2014) Molecular pathologic diagnosis of epidermal growth factor receptor. Neuro-oncology 16(suppl_8): viii1-viii6.

154. Westphal M, Heese O, Steinbach JP, et al. (2015) A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. European Journal of Cancer 51(4): 522-532.

155. Wilhelm SM, Dumas J, Adnane L, et al. (2011) Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. International Journal of Cancer 129(1): 245-255.

156. Wilhelm SM, Carter C, Tang L, et al. (2004) BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Research 64(19): 7099-7109.

157. Yin D, Zhou H, Kumagai T, et al. (2005) Proteasome inhibitor PS-341 causes cell growth arrest and apoptosis in human glioblastoma multiforme (GBM). Oncogene 24(3): 344-354.

158. Di K, Lloyd GK, Abraham V, et al. (2016) Marizomib activity as a single agent in malignant gliomas: Ability to cross the blood-brain barrier. Neuro-oncology 18(6): 840-848.

159. Kaley T, Touat M, Subbiah V, et al. (2018) BRAF inhibition in BRAFV600-mutant gliomas: Results from the VE-BASKET study. Journal of Clinical Oncology 36(35): 3477.

160. Cloughesy T, Finocchiaro G, Belda-Iniesta C, et al. (2017) Randomized, double-blind, placebo-controlled, multicenter phase II study of onartuzumab plus bevacizumab versus placebo plus bevacizumab in patients with recurrent glioblastoma: efficacy, safety, and hepatocyte growth factor and O (6)-methylguanine-DNA methyltransferase biomarker analyses. Journal of Clinical Oncology 35(3): 343-351.

161. Wick W, Fricke H, Junge K, et al. (2014) A phase II, randomized, study of weekly APG101+ reirradiation versus reirradiation in progressive glioblastoma. Clinical Cancer Research 20(24): 6304-6313.

162. Ha D, Yang N, Nadithe V (2016) Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: Current perspectives and future challenges. Acta Pharmaceutica Sinica B 6(4): 287-296.

163. Luan X, Sansanaphongpricha K, Myers I, et al. (2017) Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacologica Sinica 38(6): 754-763.

164. Goh WJ, Zou S, Ong WY, et al. (2017) Bioinspired cell-derived nanovesicles versus exosomes as drug delivery systems: A cost-effective alternative. Scientific Reports 7(1): 1-10.

165. Liang Y, Duan L, Lu J, et al. (2021) Engineering exosomes for targeted drug delivery. Theranostics 11(7): 3183.

166. Kobayashi S, Nakase I, Kawabata N, et al. (2009) Cytosolic targeting of macromolecules using a pH-dependent fusogenic peptide in combination with cationic liposomes. Bioconjugate chemistry 20(5): 953-959.

167. Sakurai F, Nishioka T, Saito H, et al. (2001) Interaction between DNA–cationic liposome complexes and erythrocytes is an important factor in systemic gene transfer via the intravenous route in mice: The role of the neutral helper lipid. Gene Therapy 8(9): 677-686.

168. Liu R, Wang X, Curtiss C, et al. (2018) Monoglyceride lipase gene knockout in mice leads to increased incidence of lung adenocarcinoma. Cell Death & Disease 9(2): 1-15.

169. Kim MS, Haney MJ, Zhao Y, et al. (2018) Engineering macrophage-derived exosomes for targeted paclitaxel delivery to pulmonary metastases: *In vitro* and *in vivo* evaluations. Nanomedicine: Nanotechnology, Biology and Medicine 14(1): 195-204.

170. Zhou Z, Xing X, Tian C, et al. (2018) A multifunctional nanocage-based MOF with tri-and tetranuclear zinc cluster secondary building units. Scientific Reports 8(1): 1-8.

171. Tian Y, Li S, Song J, et al. (2014) A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. Biomaterials 35(7): 2383-2390.

172. Bai J, Duan J, Liu R, et al. (20200 Engineered targeting tLyp-1 exosomes as gene therapy vectors for efficient delivery of siRNA into lung cancer cells. Asian Journal of Pharmaceutical Sciences 15(4): 461-471.

173. Bellavia D, Raimondo S, Calabrese G, et al. (2017) Interleukin 3-receptor targeted exosomes inhibit in vitro and in vivo Chronic Myelogenous Leukemia cell growth. Theranostics 7(5): 1333.

174. Liang G, Zhu Y, Ali DJ, et al. (2020) Engineered exosomes for targeted co-delivery of miR-21 inhibitor and chemotherapeutics to reverse drug resistance in colon cancer. Journal of Nanobiotechnology 18(1): 1-15.

175. Limoni SK, Moghadam MF, Moazzeni SM, et al. (2019) Engineered exosomes for targeted transfer of siRNA to HER2 positive breast cancer cells. Applied Biochemistry and Biotechnology,187(1): 352-364.

176. Ohno SI, Takanashi M, Sudo K, et al. (2013) Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells. Molecular Therapy 21(1): 185-191.

177. Cheng Q, Shi X, Han M, et al. (2018) Reprogramming exosomes as nanoscale controllers of cellular immunity. Journal of the American Chemical Society 140(48): 16413-16417.

178. Liang G, Kan S, Zhu Y, et al. (2018) Engineered exosome-mediated delivery of functionally active miR-26a and its enhanced suppression effect in HepG2 cells. International Journal of Nanomedicine 13: 585.

179. Jia G, Han Y, An Y, et al. (20180 NRP-1 targeted and cargo-loaded exosomes facilitate simultaneous imaging and therapy of glioma in vitro and in vivo. Biomaterials 178: 302-316.

180. Ye Z, Zhang T, He W, et al. (2018) Methotrexate-loaded extracellular vesicles functionalized with therapeutic and targeted peptides for the treatment of glioblastoma multiforme. ACS Applied Materials & Interfaces 10(15): 12341-12350.

181. Pi F, Binzel DW, Lee TJ, et al. (2018) Nanoparticle orientation to control RNA loading and ligand display on extracellular vesicles for cancer regression. Nature Nanotechnology 13(1): 82-89.

182. Koh E, Lee EJ, Nam GH, et al. (2017) Exosome-SIRPα, a CD47 blockade increases cancer cell phagocytosis. Biomaterials 121: 121-129.

183. Wang J, Li W, Lu Z, et al. (2017) The use of RGD-engineered exosomes for enhanced targeting ability and synergistic therapy toward angiogenesis. Nanoscale 9(40): 15598-15605.

184. Lee J, Lee H, Goh U, et al. (2016) Cellular engineering with membrane fusogenic liposomes to produce functionalized extracellular vesicles. ACS Applied Materials & Interfaces 8(11): 6790-6795.

185. Jiang XC, Gao JQ (2017) Exosomes as novel bio-carriers for gene and drug delivery. International Journal of Pharmaceutics 521(1-2): 167-175.

186. Yang T, Martin P, Fogarty B, et al. (2015) Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in Danio rerio. Pharmaceutical Research 32(6): 2003-2014.

187. Sun D, Zhuang X, Xiang X, et al. (2010) A novel nanoparticle drug delivery system: The anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Molecular Therapy 18(9): 1606-1614.

188. Nieder C, Adam M, Molls M, et al. (2006) Therapeutic options for recurrent high-grade glioma in adult patients: Recent advances. Critical Reviews in Oncology/Hematology 60(3): 181-193.

189. Wong ML, Kaye AH, Hovens CM (2007) Targeting malignant glioma survival signalling to improve clinical outcomes. Journal of Clinical Neuroscience 14(4): 301-308.

190. Bobola MS, Blank A, Berger MS, et al. (1995) Contribution of O^6-methylguanine-DNA methyltransferase to monofunctional alkylating-agent resistance in human brain tumor-derived cell lines. Molecular Carcinogenesis 13(2): 70-80.

191. Bobola MS, Berger MS, Silber JR (1995) Contribution of O^6-methylguanine-DNA methyltransferase to resistance to 1, 3-(2-chloroethyl)-1-nitrosourea in human brain tumor-derived cell lines. Molecular Carcinogenesis 13(2): 81-88.

192. Bobola MS, Tseng SH, Blank A, et al. (1996) Role of O^6-methylguanine-DNA methyltransferase in resistance of human brain tumor cell lines to the clinically relevant methylating agents temozolomide and streptozotocin. Clinical Cancer Research 2(4): 735-741.

193. Bacolod MD, Johnson SP, Pegg AE, et al. (2004) Brain tumor cell lines resistant to O^6-benzylguanine/1, 3-bis (2-chloroethyl)-1-nitrosourea chemotherapy have O^6-alkylguanine-DNA alkyltransferase mutations. Molecular Cancer Therapeutics 3(9): 1127-1135.

194. Friedman HS, Stephen K, Anthony EP, (2002) "O^6-Benzylguanine-mediated Enhancement of Chemotherapy 1 This work was supported by NIH Grants NS30245 (to HSF), NS20023 (to HS F), CA57725 (to AEP, HSF, and MED), and CA81485 (to MED). Drs. Pegg, Moschel, and Dolan have a financial relationship with Access Oncology, the company that is presently licensing O^6-benzylguanine. Dr. Friedman is a paid consultant for Access Oncology. 1." Molecular Cancer Therapeutics 1(11): 943-948.

195. Kokkinakis DM, Bocangel DB, Schold SC, et al. (2001) Thresholds of O^6-alkylguanine-DNA alkyltransferase which confer significant resistance of human glial tumor xenografts to treatment with 1, 3-bis (2-chloroethyl)-1-nitrosourea or temozolomide. Clinical Cancer Research 7(2): 421-428.

196. Berg SL, Gerson SL, Godwin K, et al. (1995) Plasma and cerebrospinal fluid pharmacokinetics of O^6-benzylguanine and time course of peripheral blood mononuclear cell O^6-methylguanine-DNA methyltransferase inhibition in the nonhuman primate. Cancer Research 55(20): 4606-4610.

197. Roy SK, Gupta E, Dolan ME (1995) Pharmacokinetics of O6-benzylguanine in rats and its metabolism by rat liver microsomes. Drug Metabolism and Disposition 23(12): 1394-1399.

198. Liang S, Xu H, Ye BC (2021) Membrane-Decorated Exosomes for Combination Drug Delivery and Improved Glioma Therapy. Langmuir.

199. Kim MS, Haney MJ, Zhao Y, et al. (2016) Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells. Nanomedicine: Nanotechnology, Biology and Medicine 12(3): 655-664.

200. Gehl J (2003) Electroporation: Theory and methods, perspectives for drug delivery, gene therapy and research. Acta Physiologica Scandinavica 177(4): 437-447.

201. Alvarez-Erviti L, Seow Y, Yin H, et al. (2011) Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nature Biotechnology 29(4): 341-345.

202. Zhuang X, Xiang X, Grizzle W, et al. (2011) Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. Molecular Therapy 19(10): 1769-1779.

203. Giallombardo M, Taverna S, Alessandro R, et al. (2016) Exosome-mediated drug resistance in cancer: The near future is here. Therapeutic Advances in Medical Oncology 8(5): 320-322.

204. Song H, Liu B, Dong B, et al. (2021) Exosome-based delivery of natural products in cancer therapy. Frontiers in Cell and Developmental Biology 9: 366.

205. Wang J, Zheng Y, Zhao M (2017) Exosome-based cancer therapy: Implication for targeting cancer stem cells. Frontiers in Pharmacology 7: 533.

206. Zhang HD, Jiang LH, Hou JC, et al. (2018) Exosome: A novel mediator in drug resistance of cancer cells. Epigenomics 10(11): 1499-1509.

207. Wei H, Chen J, Wang S, et al. (20190 A nanodrug consisting of doxorubicin and exosome derived from mesenchymal stem cells for osteosarcoma treatment in vitro. International Journal of Nanomedicine 14: 8603.

208. Salarpour S, Forootanfar H, Pournamdari M, et al. (2019) Paclitaxel incorporated exosomes derived from glioblastoma cells: Comparative study of two loading techniques. DARU Journal of Pharmaceutical Sciences 27(2): 533-539.

209. Mu Q, Jeon M, Hsiao MH, et al. (2015) Stable and efficient Paclitaxel nanoparticles for targeted glioblastoma therapy. Advanced Healthcare Materials 4(8): 1236-1245.

210. Wang P, Wang H, Huang Q, et al. (2019) Exosomes from M1-polarized macrophages enhance paclitaxel antitumor activity by activating macrophages-mediated inflammation. Theranostics 9(6): 1714.

211. Xin H, Sha X, Jiang X, et al. (2012) Anti-glioblastoma efficacy and safety of paclitaxel-loading Angiopep-conjugated dual targeting PEG-PCL nanoparticles. Biomaterials 33(32): 8167-8176.

212. Saari H, Lázaro-Ibáñez E, Viitala T, et al. (2015) Microvesicle-and exosome-mediated drug delivery enhances the cytotoxicity of Paclitaxel in autologous prostate cancer cells. Journal of Controlled Release 220: 727-737.

213. Jang SC, Kim OY, Yoon CM, et al. (2013) Bioinspired exosome-mimetic nanovesicles for targeted delivery of chemotherapeutics to malignant tumors. ACS Nano 7(9): 7698-7710.

214. Wei H, Chen J, Wang S, et al. (2019) A nanodrug consisting of doxorubicin and exosome derived from mesenchymal stem cells for osteosarcoma treatment in vitro. International Journal of Nanomedicine 14: 8603.

215. Pascucci L, Coccè V, Bonomi A, et al. (2014) Paclitaxel is incorporated by mesenchymal stromal cells and released in exosomes that inhibit in vitro tumor growth: A new approach for drug delivery. Journal of Controlled Release 192: 262-270.

216. Agrawal AK, Aqil F, Jeyabalan J, et al. (2017) Milk-derived exosomes for oral delivery of paclitaxel. Nanomedicine: Nanotechnology, Biology and Medicine 13(5): 1627-1636.

217. Gan HK, Rosenthal MA, Cher L, et al. (2015) Management of glioblastoma in Victoria, Australia (2006–2008). Journal of Clinical Neuroscience 22(9): 1462-1466.

218. Lou G, Song X, Yang F, et al. (2015) Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma. Journal of Hematology & Oncology 8(1): 1-11.

219. Kim G, Kim M, Lee Y, et al. (2020) Systemic delivery of microRNA-21 antisense oligonucleotides to the brain using T7-peptide decorated exosomes. Journal of Controlled Release 317: 273-281.

220. Yang Z, Xie J, Zhu J, et al. (2016) Functional exosome-mimic for delivery of siRNA to cancer: In vitro and in vivo evaluation. Journal of Controlled Release 243: 160-171.

221. Zhao L, Gu C, Gan Y, et al. (2020) Exosome-mediated siRNA delivery to suppress postoperative breast cancer metastasis. Journal of Controlled Release 318: 1-15.

222. Chen W, Quan Y, Fan S, et al. (2020) Exosome-transmitted circular RNA hsa_circ_0051443 suppresses hepatocellular carcinoma progression. Cancer Letters 475: 119-128.

223. Usman WM, Pham TC, Kwok YY, et al. (2018) Efficient RNA drug delivery using red blood cell extracellular vesicles. Nature Communications 9(1): 1-15.

224. Aspe JR, Diaz Osterman CJ, Jutzy JM, et al. (2014) Enhancement of Gemcitabine sensitivity in pancreatic adenocarcinoma by novel exosome-mediated delivery of the Survivin-T34A mutant. Journal of Extracellular Vesicles 3(1): 23244.

225. Park O, Choi ES, Yu G, et al. (2018) Efficient delivery of tyrosinase related protein-2 (TRP2) peptides to lymph nodes using serum-derived exosomes. Macromolecular Bioscience 18(12): 1800301.

226. Cho JA, Yeo DJ, Son HY, et al. (2005) Exosomes: A new delivery system for tumor antigens in cancer immunotherapy. International Journal of Cancer 114(4): 613-622.

227. Charoenviriyakul C, Takahashi Y, Morishita M, et al. (2017) Cell type-specific and common characteristics of exosomes derived from mouse cell lines: Yield, physicochemical properties, and pharmacokinetics. European Journal of Pharmaceutical Sciences 96: 316-322.

228. Vader P, Mol EA, Pasterkamp G, et al. (2016) Extracellular vesicles for drug delivery. Advanced Drug Delivery Reviews 106: 148-156.

229. Jurgielewicz BJ, Yao Y, Stice SL (2020) Kinetics and specificity of HEK293T extracellular vesicle uptake using imaging flow cytometry. Nanoscale Research Letters 15(1): 1-11.

230. Kanada M, Bachmann MH, Hardy JW, et al. (2015) Differential fates of biomolecules delivered to target cells via extracellular vesicles. Proceedings of the National Academy of Sciences 112(12): E1433-E1442.

231. Vilanova-Perez T, Jones C, Balint S, et al. (2020) Exosomes derived from HEK293T cells interact in an efficient and noninvasive manner with mammalian sperm in vitro. Nanomedicine 15(20): 1965-1980.

232. Li J, Chen X, Yi J, et al. (2016) Identification and characterization of 293T cell-derived exosomes by profiling the protein, mRNA and microRNA components. PloS One 11(9): e0163043.

233. Zhu X, Badawi M, Pomeroy S, et al. (2017) Comprehensive toxicity and immunogenicity studies reveal minimal effects in mice following sustained dosing of extracellular vesicles derived from HEK293T cells. Journal of Extracellular Vesicles 6(1): 1324730.

234. Hong Y, Nam GH, Koh E, et al. (2018) Exosome as a vehicle for delivery of membrane protein therapeutics, PH20, for enhanced tumor penetration and antitumor efficacy. Advanced Functional Materials 28(5): 1703074.

235. Ostrowski M, Carmo NB, Krumeich S, et al. (2010) Rab27a and Rab27b control different steps of the exosome secretion pathway. Nature Cell Biology 12(1): 19-30.

236. Smyth T, Kullberg M, Malik N, et al. (2015) Biodistribution and delivery efficiency of unmodified tumor-derived exosomes. Journal of Controlled Release 199: 145-155.

237. Qiao L, Hu S, Huang K, et al. (2020) Tumor cell-derived exosomes home to their cells of origin and can be used as Trojan horses to deliver cancer drugs. Theranostics 10(8): 3474.

238. Giordano A, Galderisi U, Marino IR (2007) From the laboratory bench to the patient's bedside: An update on clinical trials with mesenchymal stem cells. Journal of Cellular Physiology 211(1): 27-35.

239. Noort WA, Scherjon SA, Kleijburg-Van Der Keur C, et al. (2003) Mesenchymal stem cells in human second-trimester bone marrow, liver, lung, and spleen exhibit a similar immunophenotype but a heterogeneous multilineage differentiation potential. Haematologica 88(8): 845-852.

240. Monfared H, Jahangard Y, Nikkhah M, et al. (2019) Potential therapeutic effects of exosomes packed with a miR-21-sponge construct in a rat model of glioblastoma. Frontiers in Oncology: 782.

241. Yu L, Gui S, Liu Y, et al. (2019) Exosomes derived from microRNA-199a-overexpressing mesenchymal stem cells inhibit glioma progression by down-regulating AGAP2. Aging 11(15): 5300.

242. Deng SZ, Lai MF, Li YP, et al. (2020) Human marrow stromal cells secrete microRNA-375-containing exosomes to regulate glioma progression. Cancer Gene Therapy 27(3): 203-215.

243. Bu N, Wu H, Zhang G, et al. (2015) Exosomes from dendritic cells loaded with chaperone-rich cell lysates elicit a potent T cell immune response against intracranial glioma in mice. Journal of Molecular Neuroscience 56(3): 631-643.

244. Katakowski M, Buller B, Zheng X, et al. (2013) Exosomes from marrow stromal cells expressing miR-146b inhibit glioma growth. Cancer Letters 335(1): 201-204.

245. Munoz JL, Bliss SA, Greco SJ, et al. (2013) Delivery of functional anti-miR-9 by mesenchymal stem cell-derived exosomes to glioblastoma multiforme cells conferred chemosensitivity. Molecular Therapy-Nucleic Acids 2: e126.

246. Bu N, Wu H, Sun B, et al. (2011) Exosome-loaded dendritic cells elicit tumor-specific CD8+ cytotoxic T cells in patients with glioma. Journal of Neuro Oncology 104(3): 659-667.

247. Graner MW, Alzate O, Dechkovskaia AM, et al. (2009) Proteomic and immunologic analyses of brain tumor exosomes. The FASEB Journal 23(5): 1541-1557.