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Neurosurgery at the crossroads of immunology and nanotechnology. New reality in the COVID-19 pandemic

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ABSTRACT

Neurosurgery as one of the most technologically demanding medical fields rapidly adapts the newest developments from multiple scientific disciplines for treating brain tumors. Despite half a century of clinical trials, survival for brain primary tumors such as glioblastoma (GBM), the most common primary brain cancer, or rare ones including primary central nervous system lymphoma (PCNSL), is dismal. Cancer therapy and research have currently shifted toward targeted approaches, and personalized therapies. The orchestration of novel and effective blood–brain barrier (BBB) drug delivery approaches, targeting of cancer cells and regulating tumor microenvironment including the immune system are the key themes of this review. As the global pandemic due to SARS-CoV-2 virus continues, neurosurgery and neuro-oncology must wrestle with the issues related to treatment-related immune dysfunction. The selection of chemotherapeutic treatments, even rare cases of hypersensitivity reactions (HSRs) that occur among immunocompromised people, and number of vaccinations they have to get are emerging as a new chapter for modern Nano neurosurgery.

Contents

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1. Introduction

The term ‘‘nano neurosurgery ‘‘is less than two decades old. In 2003, Dunn and Black for the first time proposed it to use for glioma therapies on a molecular scale [1]. Nanomaterials for nano neurosurgery as imaging and treatment agents are selected for a number of criteria corresponding to the ‘‘brain rules”: 1. Neuroprotection and lack of neurotoxicity, 2. Ability to be delivered through BBB, 3. Pharmacological criteria, which are prolongation of plasma circulation, tumor accumulation and cancer cell retention, 4. Specific targeting of a brain cell type, 5. Immunomodulation of the brain privileged immune system, and 6. Resensitization to the other treatment’s effects (e.g., rendering more sensitive to radiation and chemo-, thermo-and immuno-therapy).

The tendency in modern neurosurgery is to minimize surgical invasiveness by incorporating novel imaging techniques and personalized surgical and treatment approaches. The theranostic approach, that is, the ability to deliver imaging and therapeutic agents to the tumor site and tumor cells using one nano agent hold great promise. Molecular imaging with the development of long-term circulating and targeting agents expands the options for both diagnostic and therapeutical strategies [2–4]. Nano-pharmacology in this setting allows for systemic drug administration to enhance drug concentrations in the tumors to maximize efficacy and minimize systemic and neuro toxicity. Nanotechnology may address a number of needs at the same time through the design of multifunctional agents able to act in the myriad of combinations of targeted and immune-therapeutical agents often needed to eradicate the existing tumors and prevent tumor growth and recurrence [5–9].

Development and optimization of effective delivery methods (e.g. convection-enhanced drug delivery) of nanoplatforms (synthetic or natural biodegradable carriers) may significantly improve the treatment of malignant gliomas and other brain tumors in the near future. This is achieved through facilitating *in vivo* therapeutic targeting of tumor endothelial system and parenchymal cells, thereby permitting access to the tumor microenvironment and its component immune system. With the advent of ‘‘nano neurosurgery,” targeted and efficient molecular therapeutics and immunotherapy would soon complement the current surgical, radiological, and chemotherapeutic approaches to the management of diseases in neurooncology.

This review discusses achievements of nanomedicine and immunology that could improve brain tumor treatment. Specifically, we focus on the clinical translation toward precision medicine to improve patient-specific therapeutic responses. We emphasize new biomaterials, drugs and bioengineering approaches aimed to overcome biological barriers and individual tumor heterogeneity. The classes and subclasses of nanomaterials that are currently under development or used in clinic for brain imaging and therapy are presented with evaluation of their physico-chemical properties that correspond to the clinical needs.

1.1. Precision medicine importance in neurosurgery

1.1.1. Concept of precision medicine

Precision medicine, or personalized medicine, calls for the development of patient-tailored treatments based on biomarkers or stratification by mutations or biomarkers. While not yet a clinical reality, the premise of precision medicine is that it will offer superior outcomes to the traditional treatment of disease rather than a one-treatment-per-disease approach to cancer management [10]. Patient stratification has already become a standard for new drug development, because anti-cancer therapeutics often show little efficacy in unstratified studies [11].

Although patient stratification is essential in the development of precision medicines, clinical trials for nanodrugs are currently conducted in unstratified populations [12]. This situation may soon change, as the importance of stratification becomes more obvious, and nanodrugs begin to gear toward specific patient populations. Nanodrugs can circumvent many current problems of delivery, which may potentially improve therapeutic efficacy of precision medicines. This may also allow more patients to receive individualized therapies.

1.1.2. Glioblastoma as the most common primary malignant brain tumor

Gliomas are the most common primary malignant brain tumors, comprising around 75% of all primary malignant brain tumors in adults [13]. Of various gliomas, glioblastoma (previously called glioblastoma multiforme, or GBM) is the most prevalent and the most lethal. The precise etiology of GBM is unknown, and the prevalence of GBMs is projected to increase in the United States

as the population ages. This may be due to increases in exposure to ionizing radiation and environmental factors that induce inflammation, as well as other sources of genomic insults [14–16]. Gliomas appear to be sex-dependent, with males having around 1.6-fold higher probability of acquiring this pathology than do females. In addition, females have a better response to therapy. The exact cause of sex dependence is not clear. A recent study has found molecular differences in gliomas depending on gender and suggests the need of further research to unravel their significance and potentially modify the treatment [17]. Gliomas of low grades (I-II) have a higher survival rate, although all gliomas including high grades (III-IV) eventually result in death [18]. The conventional standard of treatment including surgery followed by radiation and chemotherapy is decades old and only results in a modest survival benefit. The combination treatment using temozolomide (TMZ) with radiation therapy has led to a significant increase in patient survival rates [19]. Tumor resection is one of the primary treatment methods, though many risk factors may impact the patient's outcome, and prevention of novel neurological deficits as a result of tumor resection is placed at a higher value than the resection itself. While majority of cases of initial recurrence are in or in the vicinity of resection in patients with GBM, late recurrences typically involve diffuse infiltrating disease distant from site of origin and not easily amenable to surgical therapy. Standard of care remains safe resection of the enhancing region of the tumor on an MRI scan or reduction in volume size at the forefront (via temozolomide) [20]. Additionally, the extent of tumor resection was found to correlate with increased patient survival at a minimum resection amount of 78% [21].

Several known biomarkers, such as O^6-methylguanine-DNA methyltransferase (MGMT) methylation and isocitrate dehydrogenase (IDH) have been identified in terms of stratifying glioma response. Reduced MGMT protein expression regulated by its promoter methylation helps prevent cellular apoptosis caused by TMZ treatment. Therefore, tumor susceptibility to TMZ treatment is increased. Additionally, IDH mutations are present in many secondary GBM tumors, and in around 10% of all gliomas [22]. As of 2021, the updated WHO CNS tumor classification separates IDH mutated GBM as different astrocytoma grade II-IV. IDH mutated GBMs are their own separate entity and are grade IV [23]. Despite advances in cancer therapy, treatment of GBM remains a significant challenge due to the paucity of curative options [24]. One major hurdle is the inability of anticancer drugs to efficiently traverse the blood–brain barrier (BBB) to reach the tumor cells. Therefore, novel drug delivery methods that can easily cross the BBB and deliver anticancer drugs to tumor cells without affecting normal cells are desired [25]. It is hoped that Nanotechnology and nanoimmunology may significantly contribute to the future treatment of gliomas by facilitating BBB traversal to allow for novel brain cancer treatments, including both direct targeting of the tumor and perhaps in combination with immunotherapy.

1.1.3. Primary CNS lymphoma, a rare brain tumor

In addition to common primary brain tumors like GBM, a more rare and similarly deadly primary brain tumor is primary central nervous system lymphoma (PCNSL). Lymphomas are hematologic malignancies developing from lymphocytes. Within the four groups of non-Hodgkin lymphomas (NHL) there are over 60 specific types of tumors [26]. Lymphomas are considered as immunologically "hot" tumors, which will respond to immunotherapy. It was interesting to compare the PCNSL treatment response with other tumors, e.g., GBM, that are "cold" and do not respond easily to all kinds of immune stimulations. PCNSL represents only 4% to 6% of all extranodal lymphomas, but its incidence among immunocompetent patients is increasing, particularly among persons 65 years of age and older. This problem is getting more important nowadays with tendency to increasing longevity and geriatric population. Men are twice as likely to acquire this pathology than women [26,27]. PCNSL is encountered in the brain, eyes, and cerebrospinal fluid (CSF) but has no systemic manifestations, similar to the other brain primary glial tumor, GBM. About 95% of PCNSLs are diffuse large B-cell lymphomas that are typically highly infiltrative neoplasms, characterized as a "whole brain disease", particularly at relapse. Like malignant gliomas, PCNSL is not amenable to curative resection [28,29]. For treated lymphomas located outside the CNS, the 5-year survival is 67–79% (high-dose of methotrexate and radiation therapy or rituximab). However, treated PCNSL patients have 5-year survival rate of only 20–25% [30]. At present, there is no standard treatment for recurrent PCNSL. The median survival of patients with PCNSL did not change over the last 40 years and remains in the range of 6–7 months [31]. Lack of standard PCNSL treatment approach was confirmed in HOVON 105/ALLG NHL 24, phase III intergroup study [32,33]. This is another primary brain tumor where combination nanotechnology and immunotherapy will likely play a critical role to help neurosurgeons and neurooncologists to treat this deadly disease.

1.1.4. Nanotechnology for brain tumor personalized medicine

Nanotechnology is another branch focusing on development of therapeutic molecules that can combat cancer. The three main classes of nanoparticles used in CNS therapy are Lipid-based, polymeric, and inorganic nanoparticles. They have the ability to be adapted to the disease and to the patient and allow for many applications in targeting, treatment, nucleic acid and therapeutic delivery and imaging in the treatment of primary CNS tumors. These technologies will be discussed below in section 4.

2. Blood-Brain Barrier (BBB)

2.1. The cellular structure and functions of BBB

The BBB is composed primarily of endothelial cells, astrocytes, and pericytes to create a selective barrier where specific molecules may pass through to the brain cells (Fig. 1). The tight junctions in the endothelial cells are a major reason for the limitation on the entry of molecules and ions into the brain from blood vessels. Reese and Karnovsky in 1967 described these tight junctions between the cells in the BBB vessels as continuous and only having a small number of vesicles [34,35]. This is contrary to non-cerebral vessels where vesicles are more frequent and abundant. The sparsity of vesicles restricts the amount and kinds of materials that can pass through the BBB into the brain parenchyma [36]. The endothelial cell tight junctions are formed by the extracellular interaction of transmembrane proteins of two adjacent cells that link and bring each other's membrane together. These transmembrane proteins are selective and determine which molecules can be paracellularly permeable to the BBB [37].

The BBB selective permeability works primarily through the properties of its endothelial cells. Surrounding neurons, glia, astrocytes, pericytes, and circulating immune cells work together with the BBB in selective permeability, regulation of blood flow, angiogenesis, neuronal activity and development within the CNS [38]. (Fig. 1) The BBB interacts with its microenvironment in maintaining homeostasis. It works together with microglia, immune cells of the CNS, that constantly surveil the brain. They phagocytize toxic/unwanted materials as well as repair and support damaged vessels [38].

Given their exposure to blood from the periphery, the main structure of the BBB are endothelial cells, which line cerebral blood vessels [38]. They restrain the fast trafficking of materials between the brain and blood to control the quantity and identities of mole-

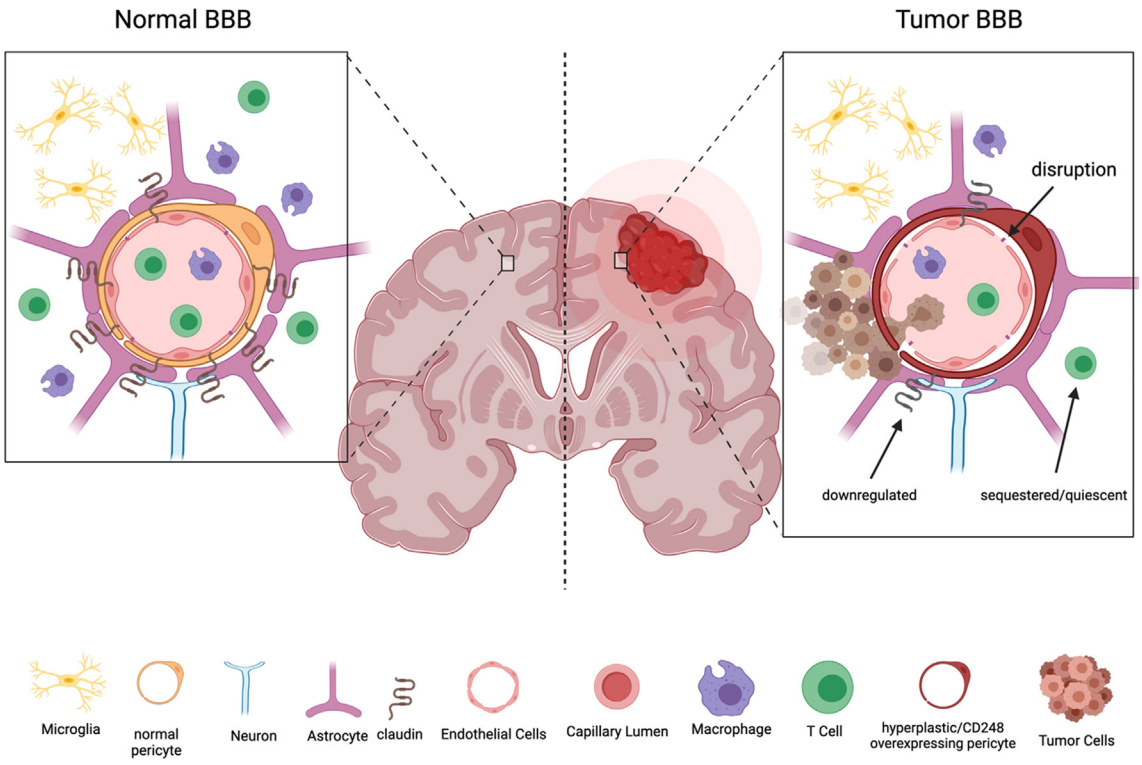

Fig. 1. Schematic demonstrating the normal vs tumor BBB architecture.

cules allowed in the brain. Polarized endothelial cells have different receptors on their extracellular and intracellular surface as well as various efflux and influx transporters that all together control the movement of materials [38]. They also have enzymatic barriers that inactivate and decompose various substances. This restricts certain molecules from carrying out their messages and/or performing their functions in the brain parenchyma. Endothelial cells possess a large number of mitochondria, which explains the greater use of energy for different ion gradients used for transport and enzymatic systems [38].

Astrocytes are glial cells that are a major part of the neurovascular unit. They are located between blood vessels and neurons, are intimately connected to the endothelial cells, share a common basement membrane (BM) with them and play a vital role in signalling [39]. Astrocytes are the connection between the BBB and neurons, explaining why both endothelial cells and astrocytes have receptors for neurotransmitters [39]. Astrocytes relay messages from neurons to endothelial cells to initiate signal transduction pathways within the BBB and to regulate blood flow [37]. They also upregulate many of the functions of the BBB: they signal the expression of specific enzymes for the enzymatic barrier of the BBB [39], they polarize transporters to increase the transport barrier [40], and they aid in creating stronger tight junctions between endothelial cells [41,42]. Astrocytes also function in the phenotypic makeup of the BBB. They release several molecules such as transforming growth factor-β (TGF-β), angiopoietin 1, glial-derived neurotrophic factor (GDNF), etc. that initiate these expressions [39,43,44].

2.2. BBB transport mechanisms

The BBB is not just a physical barrier between the cerebral blood vessels and the brain parenchyma; it also acts as a selective barrier in which specific substances can transport to and from the CNS via active and/or passive transport. The brain endothelial cells have abundant transporters that fall into two categories: efflux and solute transporters. Efflux transporters take molecules from the brain tissue and excrete them against their concentration gradient out into blood vessels. Solute transporters bring molecules and essential nutrients down their concentration gradient, through the BBB and into the brain [37]. The cerebral endothelial cells have specific carrier-mediated transporters (CMT) for molecules that have difficulty entering the membrane of the BBB cells but are still needed for survival of the brain. Molecules can also enter the BBB via receptor-mediated endocytosis from the surface of endothelial cells [38].

Gases such as oxygen passively diffuse across the BBB through a concentration gradient. In addition to gases, various lipid-soluble molecules can also enter the brain by simple diffusion; however, this depends on several factors such as their hydrogen bonding capacity, level of solubility, and molecular weight [45]. It would be convenient for drug delivery if these were the only constraints in passing through the BBB, but this is not the case. For instance, there are drugs that do not have any of these characteristics and can still enter the brain or may exhibit the same lipophilicity as some of these molecules but have a low rate of entrance into the brain [46].

Due to the high electability of the BBB, it has been estimated that approximately 98% of drugs have been rejected from the BBB, and thus were ineffective in targeting specific sites of the brain tissue and for gene delivery [47,48]. Only about 0.1% of intravenously administered therapeutic antibodies can enter the brain. To overcome this obstacle and to reach the concentration goal, higher doses of antibodies need to be administered, but this creates a greater risk of general toxicity and possibility of anaphylaxis development [49].

The net charge on the surface of endothelial cells is negative, allowing cations to easier cross the BBB than anions. Endothelial cells of the BBB also contain ATP-binding cassette (ABC) transporters, which are a type of efflux pump. They hydrolyze ATP to

expel toxins or unwanted molecules from the brain into the blood vessels [38].

All of these transport mechanisms contribute to the overall function of the BBB in its goal of maintaining normal brain function. Without it, humans would be probably unable to survive. However, these mechanisms are also creating great difficulty in manufacturing drugs to target specific areas of the brain and help treat diseases.

2.3. Brain cancer BBB structure

As the brain tumor grows, it disrupts the blood–brain barrier and triggers changes within its structures. When a primary or metastatic brain tumor grows within the brain parenchyma, it uses its surrounding environment to facilitate its own growth and survival through processes such as neoangiogenesis. As the tumor grows it creates changes in brain vasculature. These changes result in the compromised integrity of the BBB and its microenvironment, becoming an alternate form called the tumor BBB [50]. The tumor BBB is heterogeneous and usually leakier than the normal BBB. This is because the newly formed blood vessels have altered junctions and astrocytic contacts in the affected areas (sites of tumors), but at the unaffected areas (“normal” BBB) normal tight junctions are present [50,51]. At the affected sites, cancer cells may disrupt the normal BBB so that it can facilitate their proliferation, resulting in a lack of tight junction protein expression and creation of fenestrated endothelial cells. When a tumor grows, a number of changes in tight junctions occur such as protein expression dysregulation, which leads to impaired cell–cell contact/communication [52,53]. In the presence of a primary tumor, there is a decrease in the expression of occludin and claudins within the tight junction complex [54,55]. This results in a discontinuous and fenestrated endothelium with small openings [51,54]. These openings/pores are sites for passive diffusion of different manufactured drugs to target and destroy brain tumors. These changes in tight junction protein expression are seen in both primary and metastatic brain tumors. In highly metastatic brain tumors, there is a low expression in tight junction proteins, whereas for weaker metastatic brain tumors there may be an increase in tight junction expression [53]. In general, there is a negative correlation between the reduction of tight junctions and cancer metastasis development and tumor progression [53]. In human GBM, the changes from normal BBB to tumor BBB are also seen through changes in the molecular makeup of the basement membrane [52,56].

The tumor BBB has less connections and signaling with astrocytes and pericytes, altering its activity [50]. In normal brain, astrocytes secrete vascular endothelial growth factor (VEGF) to facilitate and manage vascular growth [50,57–59]. In brain cancer, VEGF is used by the tumors when they run low on oxygen and need to promote neoangiogenesis to grow and survive. These new tumor blood vessels are more permeable to substances than blood vessels of the BBB [50]. In brain tumors, there is noted hyperplasia of α-SMA-expressing pericytes and overexpression of CD248 by pericytes, which is believed to aid the formation of tumor microvasculature [60]. Astrocytes also secrete a trafficking molecule called major facilitator superfamily domain (Mfsd2a), which is important for the development of normal BBB [50,61]. In the tumor BBB, there is downregulation of Mfsd2a due to a decrease in the signaling from astrocytes to endothelial cells. This contributes to the tumor expansion in the brain and to the higher leakiness of tumor BBB [62].

Although this less restrictive BBB permeability in tumors increases the flow of molecules, many drugs still have difficulty passing through tumor BBB [63]. The tumor BBB has more active efflux pumps than the normal BBB, which remove the drugs from the brain to blood vessels. Additionally, regions of the brain that are left unaffected by the tumor also have efflux pumps that expel many molecules such as drugs and prevent them from entering [64–66].

Chemotherapeutic drugs can bypass the BBB by different ways including the use of iatrogenic agents or intrathecal drug administration. To allow drug passage through the BBB, it may be disrupted temporarily using osmotic means or administering vasoactive agents such as bradykinin [67], or by exposing the patient to high-intensity focused ultrasound (HIFU) [68]. Additionally, to bypass the BBB, endogenous transporters such as glucose and amino acid carriers, receptor-mediated transcytosis using insulin or transferrin (TfR) receptors, or inhibiting efflux transporters, e.g., p-glycoprotein may be used. However, some vectors targeting BBB transporters, such as TfR, may get entrapped in brain endothelial cells, instead of being transcytosed through the BBB into the tumor [69,70]. Preclinical and clinical methods for BBB passing also include intracerebral needle implantation and convection-enhanced drug administration. However, all the above pharmaceutical and “mechanical” mechanisms for the drug delivery through the BBB are not sufficient for efficient treatment of malignant gliomas [71].

3. Brain immune system as a dynamic component of microenvironment

3.1. Brain privileged immune system as a major regulator of physiological defense

Immunotherapy of brain tumors is evolving thanks to multifunctional therapies utilizing nanotechnology. The CNS immune system is unique because it depends on the interplay of the systemic and local immune systems. Since the 1940′s the brain was thought to be “immune privileged” with the landmark paper by Medawar where skin grafts implanted into brains did not elicit rejection compared to other locations in the body [72]. Many scientists attributed this to the BBB, which was thought to create a physical and biochemical wall [73]. The BBB capillary cell tight junctions create the physical barrier, whereas astrocytic foot processes interacting with the vascular basement membrane help tightly regulate small molecule movement [74]. More recently, this paradigm has significantly shifted based on the discovery of reciprocal orchestration of BBB capillary system, different immune cell migration, differentiation and involvement of extracellular matrix. In 2012, a novel glial-lymphatic or “glymphatic” system was discovered, which clears waste from the brain via aquaporin 4 mediated mechanism and was thought to be the surrogate lymphatic drainage of the brain [75]. Only in 2015, meningeal lymphatics vessels that drain into the cervical lymph node were discovered [76].

Another feature of the brain immune system is that it has resident microglial cells, which are the CNS equivalent of macrophages. The microglia’s myeloid progenitors arise from the yolk sac and form alongside the CNS where they continue to reside and replicate [77]. The microglia remain in their embryological state but get activated during inflammation, returning to quiescence after inflammation resolves. Furthermore, additional circulating monocytes are recruited in neuroinflammation on top of the brain’s resident microglia and disappear once the inflammatory process ceases [78]. Also, T cells have been noted to enter the brain under normal physiological conditions, further showing the dynamic brain immune system which was previously thought to be isolated [79]. As new discoveries are made, scientists are beginning to understand how unique and intricate the brain’s immune system is and how it connects with the rest of the human body’s immune system, which opens new doors for treatments. Nano immunology is rapidly becoming an important newest field to

understand, regulate and reverse the brain tumorigeneses for treatment of the CNS pathological conditions.

3.2. Cancer effects on the brain immune landscape

3.2.1. Tumor-induced changes in the brain immune microenvironment

In the presence of a tumor, the activity of immune cells such as NK and cytotoxic T cells in the brain microenvironment becomes suppressed. Brain tumors release various effector molecules that not only decrease the functionality of immune cells, but also inhibit antitumor activity [80–83]. These molecules include inflammation regulators that mediate inactivation of immune response to a tumor. Interestingly, in addition to T cell inactivation, synaptic activity to and from the glutamatergic synapses leads to tumor cell proliferation [84,85].

Programmed death ligand-1 (PD-L1) and its receptor PD-1 are proteins that normally function to aid and prevent immune cells from attacking healthy cells. In primary brain tumors, tumor-associated macrophages (TAMs) express PD-L1 and are thought to pass it via vesicles to regulatory cells resulting in the inhibition of CD8 + T cell activation, which is necessary for anti-tumor immunity [86]. In patients with glioma, surgical resection and immunotherapy with PD-L1 blockade results in improvement in survival rates [87,88]. Recently, scientists were able to manufacture a B cell vaccine able to perform antigen cross-penetration for glioma, resulting in greater survival and functionality of CD8 + T cells. This vaccine, in addition to radiation therapy and PD-L1 blockage, lead to death of tumor cells as shown in approximately 80% of treated animals with tumors [89].

Cancer immunotherapy has become one of the fastest developing approaches in oncology allowing successful treatment of various cancers [90–92]. The new trend in cancer treatment is a combination of immune checkpoint (CTLA and/or PD-1) inhibitors with targeted anti-cancer therapy [93]. Immunotherapy has recently been touted as the breakthrough strategy for oncology, and a wealth of data was accumulated in the last decade about therapy with checkpoint inhibitors and their side effects including systemic toxicity. These inhibitors include monoclonal antibodies (mAbs) to CTLA-4 or PD-1T cell receptors, which turn off the regulatory T cells (Tregs)-mediated inhibition of anti-tumor immune response, allowing cytotoxic T lymphocytes (CTL) and natural killer (NK) cells to eliminate cancer cells. Several humanized antibodies against immune system modulators (checkpoints) CTLA-4 and PD-1 have received FDA approval. Systemic administration of mAbs to CTLA-4 or PD-1 and to PD-L1 can suppress growth of some tumors but has low efficacy for brain tumors as these antibodies poorly cross the BBB [94–96]. Recent studies also highlighted significant roles of tumor-associated macrophages/microglia (TAMs) in cancer development and progression. TAMs produce PD-1, and its expression increases over time in mouse cancer models, and higher tumor stage in humans. PD-1 expression by TAMs was shown to suppress phagocytosis and tumor immunity [97–99]. Macrophage polarization into pro-inflammatory M1 and anti-inflammatory M2 phenotypes that have distinct functional characteristics is well established. M1 anti-tumor macrophages have been used in cancer immunotherapy [100,101]. In response to IFN-γ or TNF-α stimulation, M1 macrophages generate nitric oxide (NO) from arginine by inducible nitric oxide synthase (iNOS) to trigger anti-tumor action. M2 macrophages can be preferentially polarized by TGF-β and IL-10. Their accumulation in tumors is associated with induction of Treg cells that suppress CTLs. M2 macrophages can also suppress activation of NK cells through TGF-β. Overall, the immune reaction to tumors is mediated by the interactions among T cells (Tregs and effector cells), NK cells and TAMs [100,101].

The unique CNS immune environment and BBB physiology need to be considered for the design of glioma immunotherapy [102–104]. A recent review [94] summarized the data on the glioma immunotherapy trials. The authors analyzed the data from 28 vaccine clinical trials including peptide vaccines targeting EGFRvIII or IDH1; 13 clinical trials for oncolytic viruses; 15 clinical trials for checkpoint inhibitors (e.g., CheckMate 143 trial) and CAR-T cells, that are genetically engineered T cells with chimeric antigen receptors. It was concluded that none of these treatments have shown superior results to the GBM standard-of-care, with TMZ/radiation therapy [105]. CTLA-4 and PD-1 mAbs do not cross the BBB [104,106,107]; however, a modest efficacy against GBM was still observed in preclinical studies, apparently due to the general activation of the immune system upon intravenous antibody administration.

To increase checkpoint inhibitor efficacy against brain tumors, BBB-crossing nanoplatforms have been engineered that would deliver inhibitors through BBB after intravenous injections to match clinical administration of therapeutic antibodies [97]. The combination of nanotechnology and immunotherapy [108] has been shown to improve delivery of nanoscale immunoconjugate drugs across the BBB in animal models. An example of such drugs is a PMLA polymer with covalently conjugated CTLA-4 or PD-1 antibodies and a BBB-crossing antibody or a peptide [6,109]. To cross BBB, two mechanisms were used with similar results, that is, TfR-mediated transcytosis [2,109] or a synthetic low-density lipoprotein receptor (LRP-1) ligand [110], Angiopep-2 (AP-2) peptide. Intravenous use of these nano immunoconjugate drugs resulted in the activation of local brain immune system and increased survival of intracranial GBM GL261-bearing mice. This was a pioneering use of polymeric drug carriers with attached immunotherapeutic moieties to activate brain local immune system and successfully treat GBMs upon systemic therapy. Importantly, CTL fraction including CD8 + and especially proliferating CD8 + Ki67 + T cells was significantly increased in the treated groups. Additionally, the increase of macrophages, in particular, anti-tumor M1 population was observed after treatment, along with elevation of NK cells known as “tumor killers” [6]. These data open up new avenues for modulating local brain tumor immune system using clinically standard intravenous injection of nanodrugs so that they could help orchestrate immune attack on tumor cells and shrink the tumor to aid neurosurgeons in managing gliomas with additional treatments. It should be noted that this technology could be also applied to treat brain metastasis of other tumors, such as breast or lung cancer.

3.2.2. Cancer immunosuppression

Despite the brain immune system’s unique adaptations and newly discovered integration with the remainder of the body’s immune system, cerebral insults are known to induce immune suppression. Chongsathidkiet et al found that in GBM and other intracranial tumors, there is systemic T cell sequestration in the bone marrow [111]. This mechanism appears to be elicited by depletion of surface sphingosine 1 phosphate receptor 1 (S1P1) on T cells causing their internalization into bone marrow and out of circulation. When genetically stabilized to prevent internalization, the T cells remained in circulation. This alone did not confer any survival benefit but with additive stimulation of CD137(4-1BB) there was a synergistic effect and improved survival [111]. A linear correlation between tumor burden and degree of immunosuppression was described [112]. The authors postulated that a yet unknown soluble factor in circulation was responsible for these changes [112]. Additionally, other cerebral insults including stroke and trauma cause systemic immunosuppression [112]. This study also showed that once the damage is repaired, the immunosuppression resolves. Other studies found brain stromal cells secreting

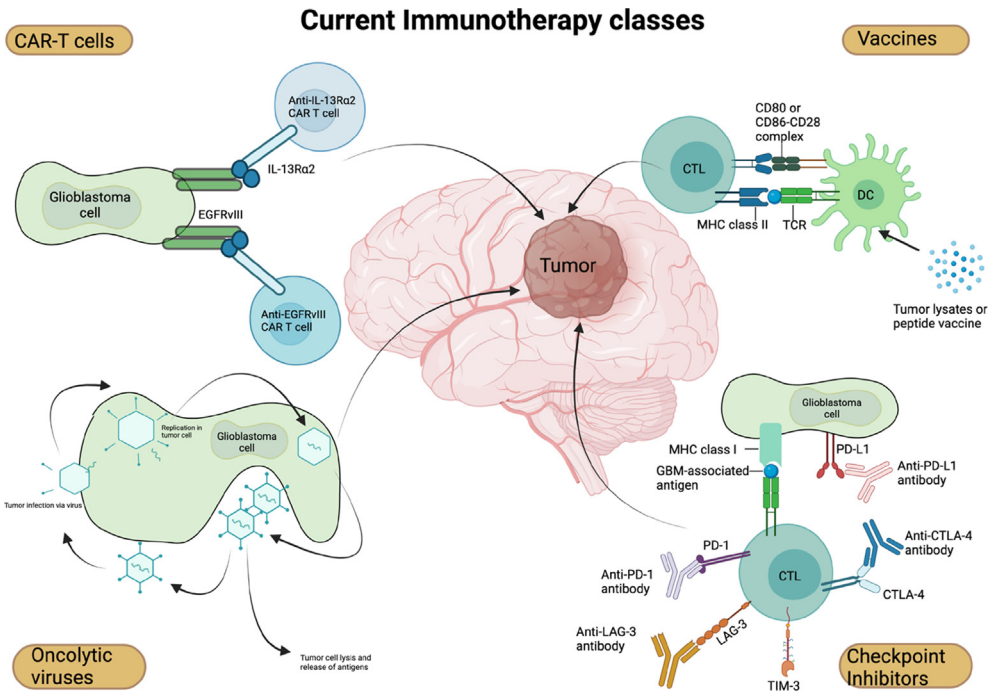

Fig. 2. Diagram demonstrating mechanisms of current immunotherapy for CNS tumors: CAR-T cells, tumor vaccines, checkpoint inhibitors, and oncolytic viruses.

TGF-β and interleukin-10 (IL-10) in response to inflammation, which cause immunosuppression by counteracting inflammatory cytokines [113,114]. These adaptative responses after cerebral insults may be triggered to prevent unrestricted inflammation and edema, thereby suppressing life-threatening increase in intracranial pressure [115]. However, tumors are also known to further cause immunosuppression via amino acid depletion mechanisms. Gliomas secrete indolamine 2,3-dioxygenase (IDO) which suppresses T cell activity by depleting tryptophan [116] and tumor-infiltrating myeloid cells secrete arginase, depleting arginine needed for T-cell proliferation [117]. These and possibly other yet unknown mechanisms may be one reason behind difficulties to treat primary malignant tumors of the brain. The described pathways and effectors may be valuable targets for future nanomedicines to relieve immunosuppression and help treat brain tumors.

3.3. Current immunotherapeutic approaches for brain tumors:

Modern immunotherapy falls into four categories: Tumor Vaccines, Oncolytic Viruses, CAR-T cells and Checkpoint Inhibitors (Fig. 2). In the following section, these type of treatment are discussed in more detail.

3.3.1. Tumor vaccines

Vaccines hold promise as another treatment methodology for GBM. Multiple trials are ongoing and more vaccine technologies are being developed. One such trial is PEPvIII, which is a vaccine targeting EGFRvIII mutant present in almost a third of GBM patients [118]. This vaccine showed efficacy in uncontrolled phase 2; however, it did not significantly improve survival in randomized phase 3 trials [119]. In addition, the majority of patients in EGFRvIII vaccine trials who developed recurrence had lost EGFRvIII expression [120]. Other single target vaccines include Wilms tumor 1 (WT1), IDH-R132H, and survivin. The WT1 peptide vaccine showed increased survival, but the trial was nonrandomized [121] requiring further testing. To circumvent these issues, trials were conducted with multi-peptide targeting vaccines. One such study looked at IMA950, which targets 11 GBM specific tumor peptides; however, there was no clear efficacy [122]. Other studies have tried to use personalized vaccines designed specifically to a patient's specific tumor antigens and genetic profiling [123]. Keskin et al. observed in their phase 1/1b personalized vaccine trial that corticosteroids, which are commonly given to patients to prevent tumor-associated vasogenic edema, appear to significantly inhibit its potency via systemic T-cell responses. Patients in the trial who did not receive steroids had an increase of antigen-specific CD4+ and CD8 + T cells with increase in tumor infiltrating T cells [124]. Another type of vaccine, dendritic cell (DC) vaccine, uses multiple antigens of various types to prime the immune system against tumors. The initial trail of DCs, ICT-107, where the cells were loaded with six GBM antigen peptides, suggested a survival benefit. However, there was no significant overall survival in a randomized phase II trial [125,126]. DCVax-L, an autologous tumor lysate-pulsed DC vaccine, recently completed a phase-3 clinical trial and, based on preliminary results, may increase progression-free survival. Unfortunately, the data are still limited, and it is too early to draw definitive conclusions [127].

There were attempts at improving tumor vaccine efficacy. In 2004, *in vitro* studies showed increased immunogenicity of DC vaccines after addition of polyinosininc-polycytidylic acid (poly(I:C)) and Toll-like receptor 3 (TLR3) among others [128]. These findings were corroborated in phase I/II clinical trial for glioma in 2011 where increased cytokine production and possible survival benefit [129]. Mitchell et al. used another strategy by inducing memory T cell activation with tetanus toxoid prior to CMV antigen-loaded DC vaccine treatment. This led to increased DC lymph node migration and may increase patient survival [130].

Another strategy to improve tumor vaccines is to activate the stimulator of interferon genes (STING) protein [see below section 4.4], an endoplasmic reticulum transmembrane protein, which is a critical part of STING pathway in antitumor immunity. Luo et al. used a STING activating nanoparticle vaccine (PC7A), which improved survival in multiple solid tumor mouse models as well as increased CD8 + T cells in tumors after combination therapy

Table 1
Current immunotherpy clinical trials for glioma .

1. VACCINES				
Trial Number Phase III	*Conditions*	*Interventions*	*Status*	*Results*
NCT01480479	Glioblastoma, Small cell glioblastoma, Giant cell glioblastoma, etc.	drug: CDX-110, temozolomide, KLH	completed	ongoing
PHASE II				
NCT00766753	Malignant Glioma	biological: dendritic vaccine, first and second booster vaccines	completed, has results	Median Time to Progression: Dose Level 1 WHO3 AG 5 mo, WHO4 GBM 4 mo; Dose Level 2 WHO3 AG 15 mo, WHO4 GBM 4 mo. Median OS: Dose Level 1 32.88 mo versus Dose Level 2 13.28 mo. 3/22 patients affected by serious AEs
NCT01635283	Adult Diffuse Astrocytoma, Adult Mixed Glioma, Adult Oligodendroglioma	biological: tumor lysate dendritic vaccine, other: laboratory biomarker analysis	completed, has results	OS: 5/5 survival, 3/5 patients affected by other not serious AEs
NCT00293423	Brain and Central Nervous System Tumors	biological: HSPPC-96, procedure: standard surgical resection	completed, has results	8/41 patients presented serious AEs upon Phase 2 Vaccination; 39/41 patients affected by all cause mortality
NCT00643097	Malignant Neoplasms of Brain	biological: PEP-3 vaccine, sargramostim; drug: temozolomide	completed, has results	1/18 patients affected by serious AEs upon Arm I, 3/10 patients affected by serious AEs upon ACT II DI; PFS values: Arm I 17.6 versus 9.9; Arm II 23.7 versus 10.5, Arm III 12.7 versus 8.1
NCT00323115	Glioblastoma Multiforme	biological: autologous dendritic cell, dendritic cell vaccine; drug: temozolomide; procedure: radiotherapy	completed, has results	1/10 patients had Grade 2 AE attributable to vaccine, Median PFS: 9.5, Median Survival Duration: 28 months (15 to 44)
NCT01280552	Glioblastoma Multiforme	biological: ICT-107, placebo DC	completed, has results	Median OS of patients with ICT-107 treatment compared to control dendritic cells: 18.3 versus 16.7, Median Overall Survival in HLA-A2 patients: 18.3 versus 12.9, Median PFS: 11.2 versus 9.0, Median PFS in HLA-A2 patients: 11.2 versus 7.2, Serious AEs in 8/80 treated with ICT-107 versus 7/43 in placebo group, survival still being tested
PHASE I				
NCT03615404	Glioblastoma, Malignant Glioma, Medulloblastoma Recurrent, etc.	biological: CMV-DCs with GM-CSF, Td (tetanus toxoid)	completed, has results	2/9 patients affected in All Cause Mortality, 0/9 patients affected by serious AEs, 9/9 patients affected by affected by other AEs
NCT02529072	Malignant Glioma, Astrocytoma, Glioblastoma	drug: nivolumab, biological: DC	completed, has results	Median OS of patients in Group I versus Group II: 8 versus 15.3, Median PFS Group I versus Group II: 4.3 versus 6.3, 1/3 patients affected by serious AEs in Group I, 2/3 patients affected by serious AEs in Group II; 3/3 Group I All Cause Mortality, 2/3 Group II All Cause Mortality

2. ONCOLYTIC VIRUSES				
Trial Number Phase II	*Conditions*	*Interventions*	*Status*	*Results*
NCT02986178	Malignant glioma	biological: PVSRIPO	active, not yet recruiting	ongoing
NCT00028158	Glioma, astrocytoma, glioblastoma	drug: G207	completed	ongoing
NCT02798406	Brain Cancer, Brain Neoplasm, Glioma	biological: DNX-2401, biological: pembrolizumab	active, not yet recruiting	ongoing
NCT04758533	Diffuse Intrinsic Pontine Glioma, Medulloblastoma	biological: AloCELYVIR	not yet recruiting	ongoing
NCT04482933	Neoplasms, High Grade Glioma, Glioblastoma Multiforme	drug: biological G207	not yet recruiting	ongoing
NCT03294486	Glioblastoma, Brain Cancer	drug: combination of TG6002 and 5-FC, Ancotil	recruiting	ongoing
NCT01582516	Brain Tumor, Recurring Glioblastoma	biological: delta-24-RGD adenovirus	completed	ongoing
NCT01301430 Phase I	Glioblastoma Multiforme	drug: H-1PV	completed	ongoing
NCT03178032	Brainstem Glioma, Neoadjuvant Therapy	biological: DNX-2401	active, not recruiting	ongoing
NCT03896568	IDH1 wt Allele, Recurrent Anaplastic Astrocytoma, Recurrent GBM	biological: oncolytic adenovirus Ad5-DNX-2401	recruiting	ongoing
NCT03072134	Glioma, Anaplastic Astrocytoma, Anaplastic Oligodendroglioma	biological: neural stem cells with oncolytic adenovirus	active, not recruiting	ongoing
NCT00528684	Malignant glioma	biological: REOLYSIN	completed	ongoing
NCT03043391	Malignant glioma, Anaplastic Astrocytoma, Anaplastic Oligoastrocytoma	biological: PVSRIPO	recruiting	ongoing
NCT01491893	GBM, Glioblastoma, Glioma, Malignant Glioma	biological: PVSRIPO	active, not recruiting	DLT observed in 1/4 patients at Dose Level 5; serious AEs observed in
NCT00028158	Glioma, astrocytoma, glioblastoma	drug: G207, an oncolytic virus	completed	ongoing
NCT02197169	Glioblastoma or Gliosarcoma	drug: single intratumoral injection of DNX-2401, interferon-gamma	completed	ongoing
NCT01956734	Glioblastoma Multiforme, Recurrent Tumor	procedure: DNX2401 and Temozolomide	completed	ongoing

3. CAR-T				
Trial Number Phase II	*Conditions*	*Intervention*	*Status*	*Results*
NCT01454596	Malignant Glioma, Glioblastoma, Brain Cancer, Gliosarcoma	biological: (EGFRv)III (CAR) transduced PBL, drug: Aldesleukin, Fludarabine, Cyclophosphamide	completed, has results	
NCT04077866	Recurrent Glioblastoma, Refractory Glioblastoma	drug: temozolomide; biological: B7-H3 CAR-T	recruiting	ongoing
PHASE I				
NCT03726515	Glioblastoma	biological: CART-EGFRvIII T cells, pembrolizumab	completed	ongoing
NCT04185038	Central nervous system tumor, Diffuse Intrinsic Pontine Glioma, Diffuse Midline Glioma	biological: SCRI-CARB7H3(s); B7H3-specific CAR T cell	recruiting	ongoing
NCT03392545	High grade glioma, Glioblastoma, Glioma of the brainstem, Glioma malignant	combination product: combined immune adjuvants and radiation	recruiting	ongoing
NCT04214392	Recurrent glioblastoma, Recurrent malignant glioma, Recurrent WHO Grade II glioma, Recurrent WHO grade III glioma	biological: chlorotoxin(EQ)-CD28-CD3zeta-CD19t-expressing CAR T-lymphocytes	recruiting	ongoing
NCT02208362	Recurrent glioblastoma, Recurrent malignant glioma, Recurrent WHO grade II glioma, etc.	biological: IL13Ralpha2-specific Hinge-optimized 4-1BB-co-stimulatory CAR/Truncated CD19-expressinng Autologous TN/MEM cells	recruiting	ongoing

4. CHECKPOINT INHIBITORS				
Trial Number Phase III	*Conditions*	*Interventions*	*Status*	*Results*
NCT04396860	Gliosarcoma, MGMT-unmethylated Glioblastoma	biological: Ipilimumab, Nivolumab; device: NovoTTF-100A Device, etc.	recruiting	ongoing
PHASE II				
NCT03925246	High Grade Glioma, Brain Cancer	drug: Nivolumab	active, not recruiting	ongoing
NCT02798406	Brain Cancer, Brain Neoplasm, Glioma, etc.	biological: DNX-2401, pembrolizumab	active, not yet recruiting	ongoing
NCT03047473	Glioblastoma Multiforme of the Brain	biological: avelumab	active, not recruiting	ongoing
NCT03491683	Glioblastoma	biological: INO-5401, INO-9012, Cemiplimab, etc.	active, not recruiting	ongoing
PHASE I				
NCT03576612	Glioma, Malignant	biological: AdV-tk, Valacyclovir; radiation: radiation	active, not recruiting	ongoing

with radiation showing a synergistic effect [8]. It was an important demonstration that a synergistically acting combination of radiation and stimulation of STING pathway using a nanovaccine leads to a long-term regression of large mouse tumors, with a significant increase of the fraction of CD8 + T cells. These results suggest that combination of local radiotherapy with systemic PC7A nanovaccine is a promising approach to improve therapy of late-stage solid tumors. The same group further showed that their PC7A was able to stimulate prolonged production of pro-inflammatory cytokines via binding of a non-competitive surface site on STING, compared to activation with its native activator, cGMP, and an even more potent effect when both PC7A and cGMP were used. This led to significant survival increases in lung and colon tumor bearing animals. This therapy also significantly upregulated cytokine expression in cultured resected human squamous cell carcinoma, cervical tumor tissue, and sentinel lymph nodes [5]. This promising technology could also be useful for CNS tumor treatment as the STING pathway was noted to be dysfunctional in gliomas [131]. Current clinical trials using vaccines are listed in Table 1, section 1.

3.3.2. Oncolytic viruses

Oncolytic viruses are another branch of immunotherapy where viruses are modified to stimulate an immune response, cause destruction of cancer cells or deliver therapeutics into targeted cells [132]. Viruses activate the immune system through pattern recognition receptors, pathogen associated molecular patterns, and activate macrophages via toll-like receptors (TLRs) [133]. Viruses can also promote an inflamed microenvironment in tumors due to activated myeloid cells improving T cell infiltration, offering an interesting workaround for combating tumor immunosuppression often seen in GBM [94]. Oncolytic viral therapy has evolved since its conception with the initial trials using replication incompetent viruses [134] to the current employment in clinical trials of replication competent viruses such as adenoviruses, measles virus, herpes simplex virus, and polio virus among others [135,136].

One of the first viruses for GBM treatment was a recombinant oncolytic poliovirus PVSRIPO (clinical trial NCT01491893). The virus modifies the internal ribosome entry site with a human rhinovirus type 2 to prevent attack on the CNS. This therapy capitalized on the fact that GBMs often express high levels of poliovirus receptor CD155, allowing the virus to infect GBM cells. In the published studies [137,138], overall survival plateaued at 21% of patients in the dose-expansion phase at 24 months and was sustained at 36 months, with 19% having grade 3 or higher drug related adverse event. Another early trial was a virus Toca 511, a non-lytic replicating retrovirus derived from Moloney murine leukemia virus. The virus has a modified cytosine deaminase, allowing it to preferentially infect tumor cells [139], although it also infects normal cells. The advantage of this virus is that unlike normal cells, tumor cells have impaired defense mechanisms allowing the virus to integrate into their genome more easily [140]. The trial was done in 45 patients with the virus injected into the resection cavity at the time of surgery and 6 weeks later had intravenous injection of Toca FC, an extended release 5-fluorocytosine. In infected tumor cells this prodrug was converted to its active form of 5-fluorouracil. The overall survival was 13.6 months, which was superior to matched controls. Aside from the direct tumoricidal effect, the virus also stimulated the immune system for improved response, and likely the synergy of both effects were the cause of this improved survival. Despite its initial success, the larger phase 3 trial, NCT02414165 ultimately did not show significant benefit based on data presented at the 2019 Society of Neuro-Oncology (SNO) meeting [141,142].

Adenoviruses are another class of viruses studied for oncolytic therapy for many years and have well established protocols for *in vitro* modifications [142]. One adenovirus, DNX2401, has been

investigated in combination therapy with TMZ, pembrolizumab (NCT02798406), and IFN-γ (NCT02197169). DNX2401 targets tumor cells through a 24-base pair deletion of transforming protein E1A and insertion of an Arg-Gly-Asp motif onto a viral capsid protein, improving α_v integrin targeting [143]. The company behind DNX2401 announced at the 2019 SNO meeting that their phase II trial with DNX2401 and pembrolizumab showed a median OS of 12.5 months in patients with recurrent glioma, with four patients surviving more than 23 months. They announced a phase III study being planned [144].

Another aspect of oncolytic viral therapy is the ability of viruses to function as gene delivery vectors. These genes can be tumoricidal, such as those delivered by the replication-incompetent adenovirus aglatimagene besadenovec (AdV-tk). AdV-tk expresses HSV thymidine kinase (HSV-TK) which is able to convert ganciclovir into a toxic compound to kill tumor cells [145]. After being found safe in a phase I clinical trial [146], two phase II trials, BrTK02 [145] and HGG-01 [147], using AdV-tk intratumoral injection along with either valacyclovir or ganciclovir, respectively, were conducted. The trials demonstrated favorable progression-free and overall survival.

Measles virus has also been used in GBM treatment. An engineered measles virus that produced carcinoembryonic antigen (MV-CEA) showed regression in flank tumors and increased survival in GBM-bearing mice [148]. This ultimately led to a clinical trial, NCT00390299; however, the trial went suspended for unknown reasons.

Another group of viruses tested are Herpes simplex viruses (HSV). These viruses had great success in pre-clinical studies, especially when engineered to selectively attenuate genes, such as lacZ gene insertions into viral ribonucleotide reductase promoter, thymidine kinase deletions, among others, so that the virus targets replicating cells in the CNS [149,150]. These preclinical studies demonstrated low toxicity and high anti-GBM effects. Multiple trials are testing different modifications of HSV.

Overall, oncolytic viruses are an interesting branch of immunotherapy and seem to work synergistically with other immune therapies such as checkpoint inhibitors, which is where the future direction of research and trials are headed, such as those with DNX-2401. Many clinical trials are currently ongoing, and it may become clear soon whether these therapies provide safe and efficient treatment in clinical setting [151]. Current clinical trials using oncolytic viruses are listed in Table 1, section 2.

3.3.3. Chimeric antigen receptor T cells - CAR-T cells

One promising immune therapy direction is adoptive T cell therapy. The most successful development is currently chimeric antigen receptor T cells (CAR-T cells). CD19 targeting CAR-T cells are currently approved for treatment of B cell leukemia and lymphoma [152]. Multiple trials for GBM have been initiated, with currently 3 antigens being targeted: EGFRvIII, ERBB2 and IL-13Rα2 [153–155]. However, these therapies have a significant obstacle to overcome, which is the heterogeneity of these tumors. GBM has heterogenous cell population and therefore varying antigen expression. In the case of EGFRvIII targeting CAR-T cells, there was a significant decrease of EGFRvIII; however, wild-type EGFR was unaffected [156]. Similarly, after administration of IL-13Rα2 targeted CAR-T cells, a patient had significant regression of his tumor burden, however, soon relapsed and his tumor became IL-13Rα2 negative [155]. CAR-T cell therapy designs will have to adapt to this heterogeneity and likely broaden their effects, which increases the risk for creating a larger non-specific immune response that may affect normal tissues. One study used an EGFRvIII specific CAR-T cell and a bispecific T cell engager (BiTE) against EGFR (together, CART-BiTE), which was able to target EGFRvIII in tumors as well as recruit untransduced bystander T cells against wild-type EGFR. This caused heterogenous tumor elimination in mouse models without toxicity against human skin grafts *in vivo* [157].

In addition to targeting, CAR-T cells have to deal with immunosuppressive effects. By themselves, CAR-T cells trigger an influx of Treg cells as well as immunosuppressive factor release from the brain [156]. CAR-T cell therapy design has to account for these factors to improve efficacy. Interestingly, Fraietta et al. described a patient treated with CD19 targeting CAR-T cells for chronic lymphocytic leukemia (CLL). At peak efficiency, the majority of the T cells originated from one clone that had a disruptive mutation in methylcytosine dioxygenase TET2 gene [158]. This mutation greatly increased the CAR-T cell efficacy, which opens up the possibility of TET2 inhibition to further boost CAR-T cell therapy.

Another related strategy to CAR-T cells is transducing cloned T cell receptors (TCRs) into T cells, expanding them, and using them for treatment. One such treatment targets pediatric diffuse pontine gliomas (DIPG). TCRs targeting DIPG mutation H3.3K27M showed efficacy in a mouse model with DIPG xenografts [159]. CAR-T cells targeting disialoganglioside GD2, a protein expressed in DIPG, also had significant tumor clearance in a mouse DIPG xenograft model [160]. This evidence holds promise for future refinement of CAR-T strategy to treat not only hematogenous malignancies but solid tumors as well including brain gliomas. Such therapy could become more efficient when combined with other treatment modalities including radiation and surgery. Current clinical trials using CAR-T cells are listed in Table 1, section 3.

3.3.4. Checkpoint inhibitors

In recent years, immune checkpoint blockade that boosts antitumor immunity, particularly the inhibition of CTLA-4 and receptor-ligand system PD-1–PD-L1, has revolutionized solid tumor treatment [161–163]. However, this treatment did not show significant success for gliomas. The CheckMate-143 clinical trial compared the efficacy of anti-PD-1 antibody nivolumab with anti-VEGFA antibody bevacizumab for recurrent GBM and found no overall survival benefit [164]. A more recent trial, CheckMate-498, dealt with MGMT unmethylated GBM using nivolumab plus radiation vs. standard therapy of radiation with TMZ and again found no improvement in overall survival [165]. The latest trial, CheckMate-548 combining TMZ with nivolumab in MGMT-methylated GBM has been stopped by Bristol-Meyer-Squibb. The company issued a press release again stating that no significant overall survival benefit was obtained, with formal results still pending [166,167]. Although some success has been observed with checkpoint blockade for intracranial metastatic melanoma [168], GBM's characteristics make it an elusive target. With the lack of efficacy in GBM, many groups turned to causes of checkpoint blockade failure and to novel methods of checkpoint inhibitor delivery. The significant intratumoral heterogeneity of GBM is likely one of the challenges that needs to be overcome. GBM heterogeneity has been shown on a single cell level with single cells expressing significant oncogenic transcription variations [169]. Another aspect is the dysfunction of T cells in GBM, which prevents success with checkpoint blockade [170].

However, there are other immune checkpoints that may be targeted for GBM treatment. Two checkpoints under heavy investigation and ongoing clinical trials in GBM patients are T cell immunoglobulin and mucin domain-containing protein 3 (TIM3) and lymphocyte activation gene 3 (LAG3). LAG3 is being tested alone or in combination with anti-PD-1 for recurrent glioma [171], and TIM3 is being tested in combination with anti-PD-1 and stereotactic radiosurgery [172]. One aspect of immune checkpoint therapy that appears to improve efficacy is neoadjuvant administration. A trial of neoadjuvant nivolumab created a power-

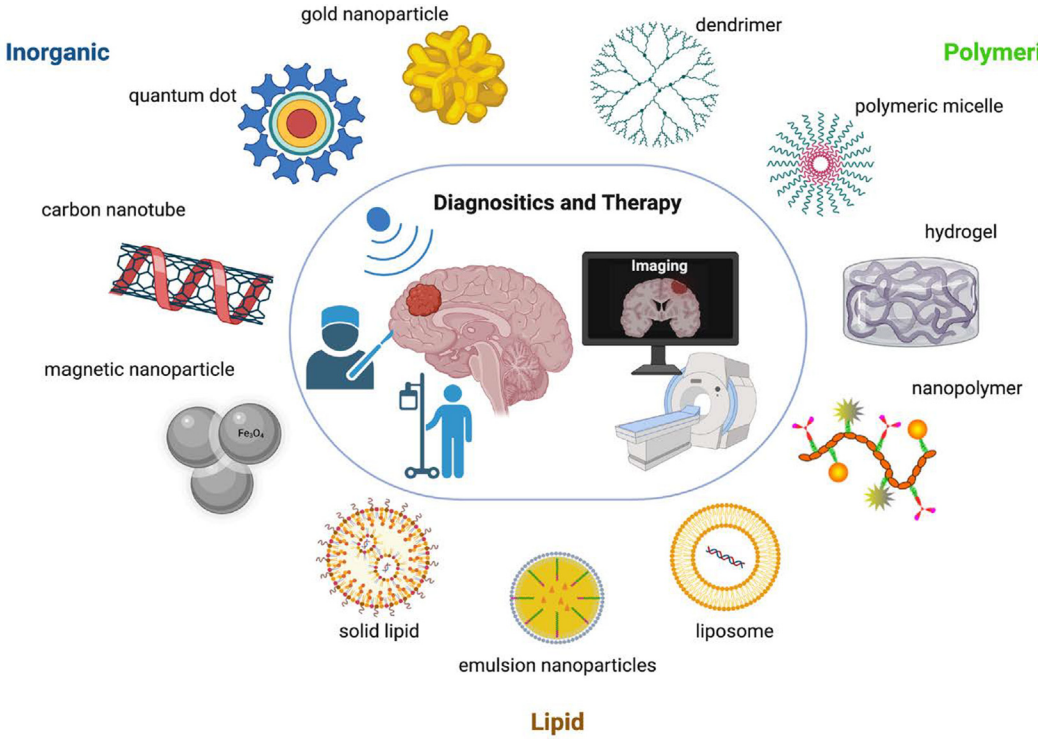

Fig. 3. Schematic showing the categories of nanoparticles used for CNS tumor treatment, with uses in diagnostic imaging and therapy.

ful pro-inflammatory response and altered the GBM microenvironment, however, without a significant survival benefit [87].

There is still some hope coming from a recent trial where a single dose of neoadjuvant anti-PD-1 pembrolizumab extended survival to 417 days compared to 228.5 in control arm in patients with recurrent GBM associated with a more profound immune response [88]. Another immune checkpoint, glucocorticoid-induced tumor necrosis factor related protein (GITR) is expressed in Treg cells. Novel antibody checkpoint inhibitor targeting GITR receptor induces anti-tumor effects in GBM. The treatment was shown to promote CD4 Treg differentiation into CD4 effector T cells and to reduce Treg mediated suppression of immune response in tumors. These effects caused Treg cells to increase cytokine production and gain cytotoxic activity against tumor cells, while no longer causing immune suppression. Furthermore, there was a synergistic effect with PD-1 inhibitors, and the combination of GITR with PD-1 conferred significant survival benefit in GBM-bearing mice [173].

Overall, traditional checkpoint blockade failed to prolong survival of GBM patients. However, new immune system targets and new inhibitor combinations are being actively tested to improve this treatment approach. Encouraging data in preclinical models on the use of checkpoint inhibitors directly delivered to glioma tissue using nanoplatforms passing through BBB are also emerging [6]. Development of this nano delivery approach may significantly increase the efficacy and reduce systemic toxicity of new generation checkpoint inhibitors and their combinations. Current clinical trials using checkpoint inhibitors are listed in Table 1, section 4.

4. Classes of nanoparticles used in CNS therapy

4.1. Lipid-based nanoparticles (NPs).

Currently, many lipid-based NPs are already approved by FDA for clinical use. Lipid-based NPs have different structures but are usually spherical platforms with at least one lipid bilayer around an aqueous compartment. For drug delivery, these NPs have considerable advantages, such as simple formulation, self-assembly, biocompatibility, good bioavailability, large payload size and a number of controllable physico-chemical properties that may be modulated and customized. Liposomes that also belong to lipid-based NPs are typically composed of phospholipids, with unilamellar and multilamellar vesicular structures. This feature allows the liposomes to carry various drugs (hydrophilic, hydrophobic and lipophilic). Hydrophilic and lipophilic agents can be entrapped in one liposome, thereby expanding the use of this class of NPs. Another variant of lipid-based NPs is commonly called lipid nanoparticles (LNPs). They are similar in structure to liposomes and frequently utilized for nucleic acids delivery [174] (Fig. 3, Table 2).

4.2. Polymeric NPs

Polymeric NPs are produced from natural or synthetic materials and have a number of variable structures and characteristics (Fig. 3, Table 2). Their synthesis can enable precise control of various features. They constitute good delivery systems because of their biocompatibility, simple formulation and variable drug delivery abilities. Drugs can be encapsulated in the NP core, or trapped in the polymer matrix, or covalently bound either to the polymer or to the NP surface. Polymeric NPs can deliver various hydrophobic and hydrophilic drugs of different size, including small molecules, macromolecules, proteins and vaccines [175–180], making them very suitable for co-delivery [181].

The most common polymeric NPs are nanocapsules that have cavities surrounded by a polymeric membrane or shell and nanospheres that have solid matrix. Polymeric micelles that are also block copolymers can self-assemble to nanospheres with a hydrophilic inner core and a hydrophobic outer coating. This structure protects aqueous cargo and helps improve circulation time.

Table 2
Selected nanoparticles and its subclasses used in CNS translational study.

Class of nanoparticles	Applications	Concerns
I. Inorganic Nanoparticles	**Ability to cross BBB for payload delivery**	**Toxicity issues**
1. Quantum dots [198–201] Colloidal seminconductor crystals with metalloid crystalline core. They can be coated or conjugated with a number of different molecules Size: 2 – 10 nm	Labeling of intracranial and spinal tumors Tunable emission and long fluorescence half-life. May be used for imaging but mostly for *in vitro* applications	Limited data from *in vivo* studies make it is difficult to assess toxicity and predict clinical usefulness
2. Magnetic nanoparticles [3,202–205] Magnetites (Fe_3O_4) & Maghemites (Fe_2O_3) Superparamagnetic iron oxide size: 50 – 150 nm Ultrasmall size: 10 – 14 nm	Retention effect in tumors May be promising contrast agents due to paramagnetic properties	Potential toxicity and sequestration in the body
3. Carbon nanotubes and graphene [206–212] Nano cylinders of graphene sheets wrapped onto themselves	Potential scaffold for neuroregeneration due to biocompatibility and stretch	Unclear genotoxic and cytotoxic effects
4. Gold nanoparticles [189,213–216] Size: 2.5 nm	Small size is favorable for delivery. Important photothermal and radiosensitising NPs useful for theranostic applications (imaging and treatment)	Potential problems with toxicity, biodistribution, and pharmacokinetics
II. Polymeric Nanoparticles	**Ability to improve BBB delivery; Retention effect in tumors; Multifunctional properties**	**Potential toxicity due to early payload release**
1. Micelles [4,7,217–219] Hydrophobic core is stabilized by hydrophilic shell Size:10 – 150 nm	Hydrophobic core accommodates drugs with poor water solubility Hydrophilic shell provides escape from immune mechanisms and ensures longer circulation	They may leak cargo if dissociate too early. Due to strong crosslinking may not dissociate well causing inadequate drug release
2. Dendrimers [4,7,217–219] Spheroids made up of repetitive branched three-dimensional structures Sizes depend on the number of generations	Direct delivery of anti-tumors agents to tumor cells Good capacity for surface functionalization resulting from high surface to volume ratio Used to deliver drugs and nucleic acids	Targeted therapy via conjugated antibodies or other moieties, systemic injection or stereotactic implantation Membrane interaction with cationic surface groups may cause cytotoxicity
3. Hydrogels [4,7,217–219] Composed of cross-linked polymers, both ionic and non-ionic <150 nm	Provide controlled drug release, which is stimulus-responsive. Usable as neural tissue scaffolds due to good mechanical strength.	May retain unwanted reactivity after synthesis resulting from non-cross-linked small molecules
4. Nanopolymers [4,7,174,217–219] Solid natural or synthetic biocompatible nanopolymers Size: 10 – 100 nm	Easy manipulation of chemistry for diagnostic and treatment (theranostic) needs, with various materials and functions. Biodegradability makes them useful as drug delivery vehicles, scaffolds etc.	Toxicity profiles may be regulated with specific moieties. Ability to reduce drug resistance
III. Lipidic Nanoparticles	**Big size might be problematic for BBB delivery**	**Potential toxicity**
1. Liposomes [4,7,174,217–219] Bilayered lipid or phospholipid vesicles with aqueous core 2. Unilamellar or multilamellar Size: 20 – 500 nm	Biocompatible and biodegradable; this makes them attractive carriers for hydrophilic and lipophilic drugs. Liposomes often have special surface modifications aimed at extending their circulation and enhancing delivery. These properties enable clinical use	Rapid uptake by the reticuloendothelial system; low solubility and short half-life; may undergo oxidation and hydrolysis; may leak drug molecules
2. Solid lipid NPs [4,7,174,217–220] Lipid NPs (LNPs) are liposome-like structures for nucleic acids delivery. They are colloidal carriers composed of physiological lipid, dispersed in water or in an aqueous surfactant Size: 40 – 1000 nm	Targeted drug delivery and good physical stability	Insufficient loading capacity Drug may get expulsed during storage upon polymeric transition
3. Emulsion [174,221]	Simple to formulate; have a number of useful physico-chemical properties. Possess high bioavailability and payload flexibility	Low encapsulation efficiency

Polymeric micelles have been used as delivery vehicles for cancer drugs in clinical trials [182].

Dendrimers consist of hyperbranched polymers with complex architecture allowing for the mass, size, shape and surface modifications to be well controlled. Active groups on the dendrimer exterior enable chemical conjugation of biological or contrast agents to the surface whereas drugs can reside in the interior. Dendrimers can carry various drugs, most commonly nucleic acids and small molecules [183,184]. For these applications, charged dendrimers including poly(ethylenimine) (PEI) and poly(amidoamine) (PAMAM) are utilized. Dendrimer-based compounds are currently in clinical trials testing them as theranostic, contrast and transfection agents, as well as topical gels [184–186]. Generally, polymeric NPs are great candidates for drug delivery because of their superior features including biodegradability, water solubility, biocompatibility, and stability during storage. The possibility of easy modification for targeting [187] allows polymeric NPs to deliver proteins, chemical agents, and genetic material to specific tissues, making them attractive systems for cancer diagnostics, treatment, and gene therapy. However, polymeric NPs possess an increased risk of particle aggregation and toxicity, which is a known drawback for their use. For this reason, only a few polymeric nanomedicines are FDA-approved, and these nanocarriers are currently being evaluated in clinical trials [188].

4.3. Inorganic NPs

Gold, iron and silica have been used to produce nanostructured materials for drug delivery and imaging (Fig. 3). Inorganic NPs can be precisely formulated and engineered to have various sizes and structures. Gold NPs (AuNPs) exist in various forms including nanospheres, nanoshells, nanorods, nanostars, and nanocages [189]. Inorganic NPs possess unique properties including physical, magnetic, electrical, and optical. For instance, AuNPs have free electrons at their surface that continually oscillate at a frequency dependent on their size and shape, conveying them photothermal

properties [190]. Also, AuNPs can be easily functionalized to expand their properties and delivery abilities [189].

Iron oxide is also a popular material for inorganic NPs; most FDA-approved inorganic nanomedicines belong to this category [191] (Table 2). Magnetic iron oxide NPs composed of magnetite (Fe_3O_4) or maghemite (Fe_2O_3) is superparamagnetic at certain sizes and is a valuable contrast agent, drug delivery system and thermal-based therapeutic [192]. Other inorganic NPs made of calcium phosphate and mesoporous silica have been also successfully used for gene and drug delivery [193,194]. Semiconducting quantum dots made of silicon are unique NPs used for *in vitro* imaging applications and are also promising for *in vivo* diagnostics [195,196].

Inorganic NPs have special magnetic, radioactive or plasmonic properties and are uniquely suitable for diagnostics, imaging and photothermal therapy. They usually possess good biocompatibility and stability and are being used in applications requiring properties that organic materials do not have. Their disadvantages limiting clinical applications include low solubility and some toxicity, especially when heavy metals are used [192,197].

5. Treatment of brain tumors based on molecular tumor profiles

Recently, gliomas have been well characterized by genomic and molecular marker analysis under The Cancer Genome Atlas (TCGA) project [128,222,223]. These studies have highlighted GBM heterogeneity and the necessity for the development of new treatment strategies. Such strategies not only target cancer cells but are also directed to critical components of brain tumor microenvironment that facilitate malignant growth, invasion and escape from immune surveillance [224]. They are also part of the niche for cancer stem cells (CSCs) that are thought to be responsible for tumor therapy resistance and recurrence development [224–226]. Tumor blood vessels are key part of this niche in gliomas and provide structural and functional support to perivascular CSCs [225–229]. The available evidence emphasizes the importance of tumor extracellular matrix (ECM), vascular system, immune environment in GBM growth and recurrence, and suggests that new therapies could target this niche in addition to cancer cells for inhibiting glioma growth and CSCs [224,226,230]. Recent preclinical evidence showed the ability of nanoformulations to successfully modulate GBM microenvironment including ECM [7] and brain local immune system [6] to inhibit GBM growth. This gives hope for the development of clinically relevant combinations of nanodrugs targeting both cancer cells and tumor microenvironment in a multiprong effort to increase glioma treatment efficacy while maintaining safety due to direct nanodrug delivery to the tumors.

5.1. Molecular targets for drug development to treat tumors

Targetable molecular glioma markers that are used in preclinical and clinical studies include EGFR, tenascin-C, bcl-2 family of antiapoptotic proteins, survivin, Rho proteins, p53, MMPs, VEGF and its receptors [231–233]. Increased expression of some proteins (EGFR, tenascin-C, survivin, laminins) is associated with poor survival of patients [7,234–237]. Some drugs aimed at modulating the expression levels of such markers are being used in clinic; however, there are no clinically approved nanodrugs in this class. Nonetheless, preclinical studies are constantly expanding to develop nanoplatforms able to pass through BBB and change the expression of glioma markers in the desirable direction. For instance, our group has found that vascular BM protein laminin-411 ($\alpha4\beta1\gamma1$) was overexpressed in 92% of GBM cases, and this correlated with shorter time to glioma recurrence and poor survival. It was proposed as a marker for prediction of recurrences and patient survival, based on the analysis of several hundred GBM samples [7,238]. Laminins are major BM components important for cell adhesion, migration, and angiogenesis, as well as for the maintenance of the BBB [239,240]. Dysregulation of cell-laminin interactions is found in various cancers. In GBMs, this dysregulation is associated with increased Notch signaling and high expression of CSC markers [7]. In several mouse models of intracranial GBM, selective inhibition of laminin-411 by specific antisense attached to PMLA-based nanoconjugate reduced Notch signaling and the expression of CSC markers with significant increase of survival in tumor-bearing animals. Suppression of GBM growth and survival increase were similar in animals treated with nanoconjugate and untreated animals that were inoculated with GBM cells where laminin-411 expression was blocked by CRISPR-Cas9 [7]. These data attested to the high efficacy of the used nanoconjugate able to pass through BBB and block a GBM protein laminin-411. These studies illustrate the high potential of nanotechnology for developing new pharmacological therapies against gliomas that could be used alone or in combination with other treatment modalities.

5.2. Blood-Brain Barrier (BBB) role in drug delivery

The BBB is a complex barrier structure formed by tight-junction connected brain capillary endothelial cells surrounded by pericytes and astrocytes—all three contributing significantly to the integrity of this structure. BBB also protects the brain from various harmful agents including pathogens. It is important to fully understand the functions and components of the BBB to create the most effective drugs that can be delivered to specific targets in the brain and overcome the obstacles posed by the BBB. The BBB controls which molecules can enter/exit the brain as well as maintain a homeostatic environment. It acts as a highly selective barrier between the cerebral blood vessels and the brain parenchyma. The BBB maintenance of homeostasis allows CNS structures to perform their functions properly without facing any interruptions from other processes carried throughout the body, and to maintain normal brain function as a highly specialized neurovascular unit [241]. The BBB permits passing oxygen and other necessary nutrients needed for survival into brain cells, but rejecting harmful and/or unknown molecules from entering.

Nanodrug delivery approaches including specific delivery to the brain represent a significant portion of biopharma research and offer many promising applications. Current developments are aimed to improve controlled drug release, target cell-specific drug release and efficacy, and reduction of systemic side effects [9,242,243].

A significant advantage of nano drug delivery vehicles is their ability to pass through biological barriers, especially important for the CNS and gastrointestinal tract [244–247]. Growing tumors release angiogenic factors and build new vasculature inside them with often abnormal extracellular matrix. Brain tumor vessels unlike normal ones that characteristically have tight junctions forming the BBB, may have 600 to 800 nm gaps between adjacent endothelial cells. Such abnormal vessels may not completely preclude passage of macromolecular drug carriers through the BBB into the brain parenchyma. Such nonspecific, "passive" targeting was described by Maeda as the enhanced permeability and retention (EPR) effect [248]. Because of altered tumor lymphatic drainage, EPR effect allows macromolecular drugs to reach high tumor drug concentrations (10-fold or higher) compared with free drug administered at r the same dose [249]. However, EPR effect seems to be less important in case of poorly vascularized tumors or necrotic tumors with little angiogenesis. Many drugs including antibodies are still unable to enter the brain tumors even with

morphological and physiological changes of the tumor vasculature allowing passive EPR effect-mediated passage. For this reason, new drug delivery systems have specific moieties targeting brain endothelial cell surface proteins that enables them to pass through BBB by transcytosis and reach tumor cells. This process is called "active" or ligand-mediated targeting. Some of these promising medicines are being used in clinic (Ambisome, Doxil, DepuCyt, Bexxar), with active development of many others [250].

5.3. BBB crossing nanotechnological systems

Nanotechnology for the generation of drug delivery devices requires a platform that is able to carry multiple components, such as a drug, a targeting agent, and a tracking agent, as well as allow for controlled and target-specific drug release and have a good safety profile [250]. Additional moieties may be needed for drug delivery through BBB and blood–brain tumor barrier that exists in brain tumors.

Polymers able to deliver drugs to tumor cells rather than to the whole brain are gaining momentum partly due to lower immunogenicity than viral vectors that renders them more useful for multiple treatments [251–254]. The advantages of macromolecular therapeutics compared to low molecular mass drugs also include increased efficacy and maximum tolerated dose, lower non-specific toxicity and activity toward multidrug resistant cells, increased solubility and tumor targetability, enhanced accumulation in solid tumors, induction of tumor cell apoptosis, and activation of different signaling pathways. These therapeutics are exemplified by the extensively characterized system to treat GBMs that is based on a natural polymer, poly(b-L-malic) acid (PMLA). The beneficial properties of PMLA as a carrier platform for modern drugs are its high loading capacity, lack of toxicity and immunogenicity, biodegradability, stability in the bloodstream (avoiding long term storage), and ready cellular uptake [255–259].

Nanotherapy is a mechanism that has been proven successful in targeting brain tumors. Nanodrugs can not only cross the BBB, which is one of the greatest obstacles that drugs have to overcome to be considered effective, but they can also activate anti-tumor immune responses in the brain when loaded with therapeutic antibodies. This is engineered using covalently bound antibodies on the nanoplatform such as PMLA or others as part of the delivery system crossing BBB. Activation of the anti-tumor immune response results in an increase in immune cells (NK cells, CD8 + T cells, macrophages) in the microenvironment of gliomas [6]. Therapy with these nanodrugs greatly increased animal survival and treatment efficacy of primary brain tumors compared to treatments with free immune response-stimulating antibodies, such as anti-CTLA-4 anti-PD-1 [6]. Such nanodrugs cross the BBB via receptor-mediated transcytosis and then can be released into the brain parenchyma [260–262]. This process of BBB crossing may be achieved through various ligands on the nanodrugs, e.g., MiniAp-4 (M4), Angiopep-2 (AP2), transferrin and insulin receptor ligands, glucose transporters, vascular cell adhesion molecule 1, etc.[4,263]. One complication of receptor mediated transcytosis across the BBB is the heterogeneous composition of various receptors [264].

Even though nanodrugs are able to cross the BBB, they may fail in entering the brain parenchyma due to a non-specific binding to the extracellular matrix [265,266]. To overcome this challenge, scientists have explored changing the surface of the nanodrugs, such as creating a dense PEG coating. This modification greatly improved delivery because the nanodrugs are more evenly distributed throughout the brain and can better penetrate GBMs [265–267]. It should be noted, however, that despite these advances and emerging clinical trials, the BBB still remains a major challenge for drug delivery and efficient targeting of tumors even for newer nanoformulations.

To avoid the BBB overall, scientists have explored another possible route, which is to administer drugs intranasally to the brain [268,269]. This circumvents the limitations posed by the BBB and systemic delivery. However, like any other option, this method has its problems too. Administering drugs intranasally can only be done in a limited dosing volume, whereas congestion and mucus become an additional obstacle for a drug to overcome [270,271].

5.4. Anti-angiogenesis therapy for brain tumors

Angiogenesis is the process of new blood vessel formation from pre-existing vasculature. Angiogenesis is triggered by angiogenic growth factors and their receptors in concert with ECM and its integrin receptors. ECM can activate intracellular signaling pathways mediating endothelial cell survival, proliferation, migration, morphogenesis, and blood vessel organization [272]. ECM and growth factor receptors can potentiate each other's effects. For instance, activated $\alpha_v\beta_3$ integrin promotes phosphorylation and activation of VEGF receptor [(VEGFR)-2], augmenting VEGF mitogenic activity [252]. Gliomas are highly vascularized tumors and are known to promote angiogenesis during their growth [273]. This property makes these tumors attractive targets for antiangiogenic therapy. This is why the angiogenic growth factors and vascular ECM, as well as technologies for inhibiting them are important for further development of brain tumor treatments.

Because angiogenesis is an integral part of tumor development, angiogenic biomarkers are considered important for cancer treatment. In the last two decades, antiangiogenic therapy emerged as one of the winners among FDA-approved biological drugs: Avastin (Genentech), Sorafenib (Nexavar, Onix Pharmaceuticals), Sunitinib (Sutent, Pfizer). Antiangiogenic therapy alone or most often in combination with other drugs significantly increases the cancer patient's longevity and quality of life [274–277]. Engineering a novel antiangiogenic drug with precise tumor delivery by using peptides or pegylated polymers is thus considered a high priority [251,278–280]. In 2009, FDA granted accelerated approval to bevacizumab (anti-VEGF mAb) for glioma treatment. VEGF is arguably the best studied angiogenic growth factor that mediates the formation of new blood vessels under both physiologic and pathologic conditions. However significant side effects seen with bevacizumab are hypertension, proteinuria including nephrotic syndrome, venous and arterial thrombosis including cerebral and myocardial infarction, transient ischemic attacks, bleeding and hemorrhage, impaired wound healing, and congestive heart failure [281]. For these reasons, the use of this therapy requires close patient monitoring and caution, and imposes constraints on dosage. It may be assumed that targeted delivery of bevacizumab to brain tumors using nanosystems could significantly alleviate systemic toxicity and would allow increasing the dose for a maximum anti-tumor effect.

To target tumor vasculature, several polymeric nanoplatforms have been proposed. PMLA-based polymers delivering laminin-411 inhibitors to GBM have been described above [6,7]. Another promising nanopolymeric drug based on a synthetic polymer, N-(2-hydroxypropyl)methacrylamide [282], conjugated with O-(chloracetyl-carbamoyl) fumagillol (TNP-470) has also been extensively used in preclinical studies including inhibition of GBM growth [283,284]. Polymers that deliver drugs to tumors are poorly immunogenic and suitable for multiple treatment, which may be necessary to eradicate the tumor [283,285].

5.5. Nano immunology approaches in tumors

One of the difficult-to-treat brain tumors is primary CNS lymphoma (PSNSL) belonging to the group of non-Hodgkin lymphomas (NHL). This group comprises heterogeneous diseases 85–90% of which originate from B lymphatic cells where CD20 receptor is overexpressed [286]. Anti-CD20 mAb rituximab (RTX) has revolutionized the therapeutic landscape for B-cell malignancy [287]. Among the RTX mechanisms of action, direct induction of apoptosis remains far from being fully exploited. Hyper-crosslinking of CD20 induces apoptosis, but the ligation of CD20 by RTX itself is very limited [288].

To improve the efficacy of anti-CD20 approach in NHL, Kopeček's group designed nanopolymeric drugs for lymphoma treatment. His approach was based on crosslinking of CD20 antigens. The used nanoconjugates for direct and enhanced induction of apoptosis in NHL cells used drug-free macromolecular therapeutics (DFMT). One design was a composition of multiple anti-CD20 antibody Fab' fragments attached to *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer [289,290]. In another design, receptor crosslinking was mediated by the biorecognition of binding motifs (coiled-coil peptides, or complementary oligonucleotides) at the cell surface [291–307]. Crosslinking of CD20 initiates apoptosis by calcium influx and mitochondrial signaling pathway without the involvement of toxins or cytotoxic drugs [305,307]. The DFMT was effective *in vitro* [291–293,295–303,305,307], *in vivo* [294,296,301], and on cells isolated from patients diagnosed with various subtypes of B cell malignancies [300,301,304]. DFMT induced apoptosis in 65.9% cells from patients irrespective of genomic aberrations (13q14; 17p13; and 11q22 deletions) [304]. Kopeček's team also elucidated the ability of DFMT to treat rituximab-resistant NHLs by: a) upregulating CD20 receptors by gemcitabine pretreatment, and b) covalent conjugation of anthracyclines or other agents to the DFMT. The latter can integrate the advantages of both chemosensitization function and improved intracellular drug delivery into a single system, resulting in maximum effect of chemotherapy and receptor-mediated apoptosis [306]. This interesting concept could be used in design of nanoconjugates for the treatment of PCNSL using a delivery vehicle that will mediate the transcytosis of the nanoconjugates through the BBB. The incorporation of special moieties for transcytosis across the BBB is imperative since intravenous RTX alone is not effective [308].

The other elegant system published by Gao's group describes the nano immune approach by using synthetic polymeric nanoparticle, PC7A NP, based on monomer 2-(hexamethyleneimino) ethyl methacrylate (C7A-MA**)** to modulate the stimulator of interferon genes (STING) pathway in antitumor immunity [5,8]. These data show promise for the future use of nanoformulations able to pass through the BBB to stimulate local immune response for a more efficient treatment of brain tumor of various etiologies.

6. RNA nanomedicine therapy

6.1. RNA delivery

RNA therapy is a relatively new mechanism in nanomedicine (using mRNA, siRNA, miRNA) that has gained popularity in recent years. Compared to the delivery of plasmid DNA, RNA therapeutics do not need to enter the cell's nucleus, and do not run the risk of insertional mutagenesis [309].

In order for mRNA to be delivered properly and effectively into the targeted site, it must have a vehicle of delivery that not only protects mRNA from the natural degradation by endonucleases, but also has specificity to send it to its destined location [310,311]. To target brain tumors, it must be able to also cross the BBB. Currently, about 70% of clinical trials with RNA delivery use recombinant viruses as the delivery vehicles [312]. This is because new generation recombinant viruses have a high cell transduction rate, don't affect the products of the mRNA translation, and present virtually no oncogenic and minimal immunogenic potential. They do however have a limited capacity of nucleic acids in which they can carry [313]. When the mRNA is being delivered, there must be a sufficient intracellular arrangement of the nucleic acids so that the translation can occur, all the while preventing the activation of the body's immune response [310,311].

Non-viral vectors are another vehicle system that can be used in gene delivery. They have clear advantages as a delivery mechanism because they are safe and easy to be produced. The amount of nucleic acids they can potentially carry is not a major obstacle, and they are economically and reproducibly more advantageous than viral vectors. Although there are still issues with cell transfection efficiency, methods have been developed that have improved this part of their use [314–316].

It is very important to have the most effective and efficient vehicle for the delivery of mRNA. Selection of the right vehicle would prevent the major complications [317]. Direct intravenous delivery of mRNA (with no vehicle) by microinjections into the body has been tested [318,319]. This is an ineffective method since mRNA is degraded by ribonucleases and the body's immune response is activated. The half-life of the naked mRNA once intravenously delivered is less than 5 min [320].

Through extensive research of nucleic acids and materials science, it has been suggested that a universal delivery system is not probable [321]. It should be designed and catered to the specific disease and target. Such vehicles can vary in physicochemical characteristics, shape, size and ionization potential in order to most efficiently carry the naked mRNA to the designated target. These delivery systems can also be designed to initiate different bodily responses such as a reduction of toxicity to healthy tissues, an increase in blood circulation, etc. [310,322]. These factors are important to consider when targeting brain tumors and protecting the healthy cells surrounding the lesion.

Lipid-based vectors are the most commonly used non-viral vehicles for naked mRNA delivery [323]. Due to the hydrophobic nature of the lipid bilayer of the BBB endothelial cells, this allows for the passive diffusion of highly lipophilic substances to pass through [324,325]. Nanoparticles are modified to have lipid-based vectors in order to enter through the BBB and target tumors [324]. Unfortunately, a highly hydrophobic nanoparticle is not the most effective in passing through the BBB; these types of nanoparticles tend to be retained in the lipid bilayer and not permeate through [324,326]. This can result in cellular toxicity through the excretion or uptake by the cell transporters [324]. Thus, it is important to construct a nanodrug that is the perfect balance between being lipophilic and hydrophilic, so that it can effectively cross the BBB and target brain tumors [327].

The major component of these lipid-based vectors are cationic lipids, which form electrostatic bonds with mRNA [323]. Cationic lipids can also be designed to form lipid nanoparticles (LNPs) as well as cationic nanoemulsions (CNEs) [314]. CNEs are mainly used to create mRNA vaccines, and have a droplet size distribution of 200 nm [328,329]. LNPs are currently one of the most advanced systems for mRNA delivery [330]. FDA-approved drugs contain an ionizable lipid, Dlin-MC3-DMA (MC3), which is used as a vehicle for mRNA delivery [331,332]. In order to have the maximum mRNA release into the targeted site, the delivery system must have more phospholipid and polyethylene glycol (PEG) than cholesterol and ionizable lipids [333]. LNPs are typically composed of ionizable lipids with other helper lipids that aid in maintaining vehicle structure and facilitate endocytosis, cholesterol that also helps stabilize

the vehicle structure, and PEG lipids [334–336]. The use of LNPs as a delivery mechanism for mRNAs has been increasingly used to treat cancer since its first study in 1999 [337]. LNP mRNA vaccines contain tumor-associated antigens (TAAs). An immune response is initiated by these vaccines once the antigen is expressed in the antigen-presenting cells (APCs or macrophages) [338]. The most common procedure used for mRNA vaccination in cancer is *ex vivo* therapy with transfected DCs (strongest APC of the immune system) [339].

The very first trials with mRNA delivery as a form of cancer immunotherapy showed that direct injections of naked mRNA resulted in rapid degradation, which emphasizes the importance of a delivery system [340]. Today, lipids are the most commonly used system which are then followed by polypeptides. Vaccines with mRNA encoding antigens are developed in the lipid nanosystems [309]. Current clinical trials are designed to treat GBM with mRNA delivery and find the most successful sequence and mechanism of delivery. Some of these trials include mRNA encoding Survivin and hTERT, vaccines with TAA mRNA, and mRNA encoding WT1. Some trials also include the intravenous therapy of mRNA CAR-T cells for treatment [309].

6.2. Structural properties of nano LNP-mRNA vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

During the COVID-19 era the importance of mRNA delivery technologies was demonstrated with the development of mRNA vaccines saving millions of lives. Some of these successful formulations are LNP-mRNA vaccines. Although they are used against a specific viral pathogen, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), they are important for brain field as they may protect brain cells from the viral assault as discussed below. The COVID-19 disease and vaccines against it are also important for the brain tumor field as more and more patients with brain cancer present with viral infection that could potentially alter the course of malignant disease and of its surgical and therapeutic management.

Respiratory infections from viral pathogens (e.g., influenza, respiratory syncytial virus, and SARS-CoV-2 that causes COVID-19 disease) result in significant morbidity and mortality worldwide and seriously affect endothelial system including the brain vasculature as a high vascular density [341].

Clinical trials by Pfizer-BioNTech and Moderna using mRNA nano vaccines showed significant protection against hospitalization from COVID-19 in 94% of vaccinated people. The protection was lower against newer SARS-CoV-2 mutated variants but still remained high. Both Pfizer-BioNTech and Moderna vaccines approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency use LNPs as delivery vehicles for mRNA. Pfizer-BioNTech (BNT162b2) has recently received full FDA approval. In both vaccines, viral Spike protein mRNA chain contains modified nucleoside 1-methyl-pseudouridines instead of uridine, to increase protection against RNAse degradation. The construct is able to express full-length Spike glycoprotein. Two proline additions are served to fix S1-S2 Spike protein subunits in a prefusion conformation. The ionizable cationic LNP carriers have pKa values between 6 and 7, and contain cholesterol, 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), and a poly(ethylene glycol) (PEG)-conjugated lipid, which prevents LNP aggregation during storage. Pfizer-BioNTech and Moderna formulations have different PEG terminal groups and different lipid conjugated to PEG. The quantity of vaccine per Pfizer-BioNTech dose is 30 μg, compared to Moderna's 100 μg [220,342].

7. SARS-CoV-2 infection necessitates emergency care for patients with CNS disorders

The COVID-19 pandemic caused by SARS-CoV-2 virus has created a global need for not only treating infected patients but to also rapidly develop new approaches on how to take care of immune deficient categories of patients suffering from cancer, diabetes, autoimmune diseases, as well as of aged population and several other categories. It has been shown that the spike protein of SARS-CoV-2 has high affinity for human angiotensin-converting enzyme 2 (ACE2) [343,344]. ACE2 is the main entry receptor for SARS-CoV-2 and is expressed on the surface of various human cells, such as lung, heart, kidney, neurons, and endothelial cells.

There are a number of data that have not been systemically sorted out yet, which show how the CNS is affected in COVID-19 patients, how the virus may be entering the brain and the role of inflammation, systemic and local brain immune systems and impaired BBB for progression of brain tumors and cancer patient's survival.

7.1. Brain endothelial system after SARS-CoV-2 infection induces an aberrant immune reaction

COVID-19 patients usually show an altered inflammatory response with the immune system overactivation [345,346]. Cytokine storm, which may develop during severe infection, increases endothelial cell permeability and promotes pathophysiological changes in the brain. The endothelial injury may result more from host inflammatory responses because of epithelium infection than from viral replication or increased viral load in endothelial cells. Summarizing these results, Barbosa et al. indicated that direct or indirect activation of endothelial cells by SARS-CoV-2 infection leads to pulmonary edema and may trigger a coagulation cascade seen in severe COVID-19 with further damage of multiple organs [347].

Patients with severe COVID-19 have decreased interferon (IFN) production, as well as aberrant polarization of Th cells (predominantly Th17), increased expression of exhaustion-related surface markers, such as TIM3 and PD-1, and altered cytokine secretion pattern [348–350]. Pulmonary epithelial cells may act as a gateway for SARS-CoV-2 infection, but alveolar problems may be mediated mainly by endothelial damage, resulting in cytokine and chemokine activation and immune system cell recruitment [350]. SARS-CoV-2 infection may thus not be the primary cause of tissue damage in COVID-19 [351,352]. COVID-19 has been associated with the significant recruitment of immune cells directly affecting endothelial cells. The tissue damage may result from the excessive immune response causing acute inflammation mediated by massive release of cytokines, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) [351]. These cytokines affect lung parenchyma, oxygen uptake and endothelial cells, leading to endotheliitis, thrombotic events and intravascular coagulation [353].

Clinical evidence points to the frequent impact of the central nervous system (CNS) by SARS-CoV-2 infection, either direct or indirect, although the underlying mechanisms remain obscure. One such mechanism may involve pericytes that are contractile perivascular cells in tissues including the brain that have been proposed as SARS-CoV-2 infection points. Wang et al. have shown that pericyte-like cells (PLCs), when integrated into a cortical organoid, are capable of being infected with original SARS-CoV-2 [354]. They developed an experimental model for studying neural infection, PLC-containing cortical organoids, which served as viral 'replication hubs', and tracking virus spreading to astrocytes and mediating inflammatory type I IFN transcriptional responses.

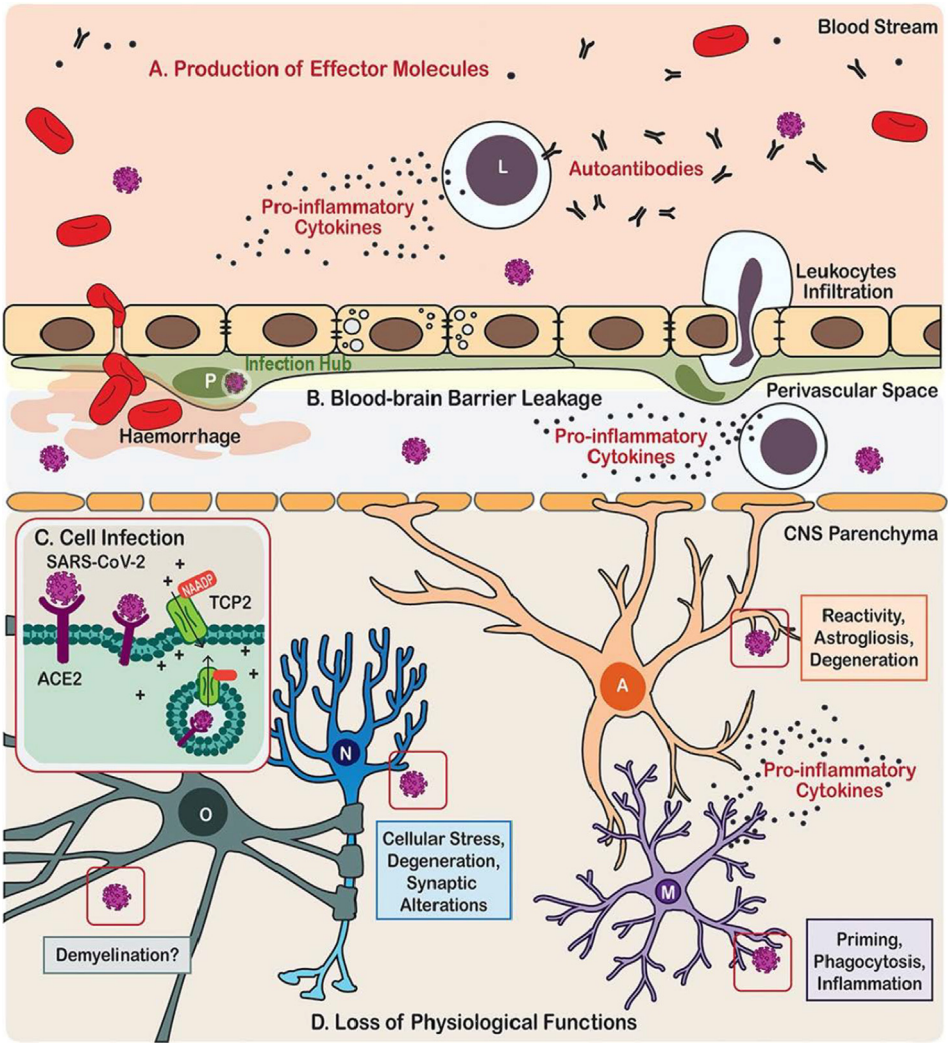

Fig. 4. Scheme illustration of the neurotropism, neuroinflammatory processes, BBB leakage and effects on different brain cells triggered by COVID-19 in patients. (A) Immune cells from the periphery and the central nervous system (CNS) produce effector molecules that include pro-inflammatory cytokines and autoantibodies. (B) SARS-CoV-2 infection also causes leakage of the blood–brain barrier leading in some cases to hemorrhage and cerebral infarct, as well as eliciting leukocytes infiltration. (C) In the parenchyma, the CNS cells become infected by SARS-CoV via angiotensin-converting enzyme 2 (ACE2) endocytosis mediated by the two-pore channel 2 (TCP2). (D) SARS-CoV-2 infection leads to loss of physiological functions of the brain cells, including neurons, astrocytes, microglia, pericytes and oligodendrocytes. Cell types are identified in the following manner; A, Astrocyte; L, Leukocyte; M, Microglia; N, Neuron; O, Oligodendrocyte; P, pericyte. Reproduced with slight modification from: Tremblay ME, Madore C, Bordeleau M, Tian L, Verkhratsky A. Neuropathobiology of COVID-19: the role for glia. Front Cell Neurosci. 2020;14, 592214.

Based on brain ACE2 expression data, it was reported [355–357] that in rodents and humans ACE2 is expressed in the brain gate entry as oral and nasal mucosa, nasopharynx, and directly in brain tissues as the substantia nigra, choroid plexus, non-neuronal cells and many neurons, both excitatory and inhibitory. Brain ACE2 could contribute to the neurological symptoms in COVID-19 [358] including neurogenic hypertension [359]. The damage reported in the oral and nasal mucosal epithelium may also be a result of SARS-CoV-2 interaction with ACE2 and/or other receptors [358,360–363].The presence of SARS-CoV-2 particles in brain neurons of infected patients has also been documented.

All these observations suggest a mechanism of SARS-CoV-2 entry into the brain that might underlie neurovascular and vascular symptoms clinically seen in some COVID-19 patients [347]. The epithelial/endothelial lesions mediated by cytokines/chemokines could potentially damage the BBB, promoting vascular permeability, leukocyte and macrophage infiltration, and hypoxia [348].

Loss of smell is a frequent symptom in COVID-19, with yet unknown etiology. Cell types in the olfactory cells that express SARS-CoV-2 cell entry molecules have been identified [364]. Molecular sequencing has shown that olfactory mucosa in several species including human expresses two key genes involved in SARS-CoV-2 entry, that is, ACE2 and transmembrane serine protease 2 (TMPRSS2). Single cell sequencing supported by immunostaining showed ACE2 expression in support cells, stem cells, and perivascular cells, as well as in dorsally-located olfactory epithelial sustentacular cells and olfactory bulb pericytes in the mouse. It has been suggested that anosmia and other problems with odor perception in COVID-19 patients may be due to SARS-CoV-2 infection of non-neuronal cell types.

In samples from the patients who died from COVID-19, brain hyperemic and edematous tissue and degenerated neurons have been found [365]. Neurological analyses of COVID-19 patients in Wuhan, China, found neurologic manifestations, such as stroke or cerebral hemorrhage, in 36% of SARS-CoV-2 patients treated for severe infection [365]. These cerebrovascular manifestations may be due to the BBB and brain vasculature impairment [366]. Changes in the BBB may lead to alternative functions of tight junctions, which prevent free passage through the vessel wall, and expression of transporters regulating the entry and exit of various

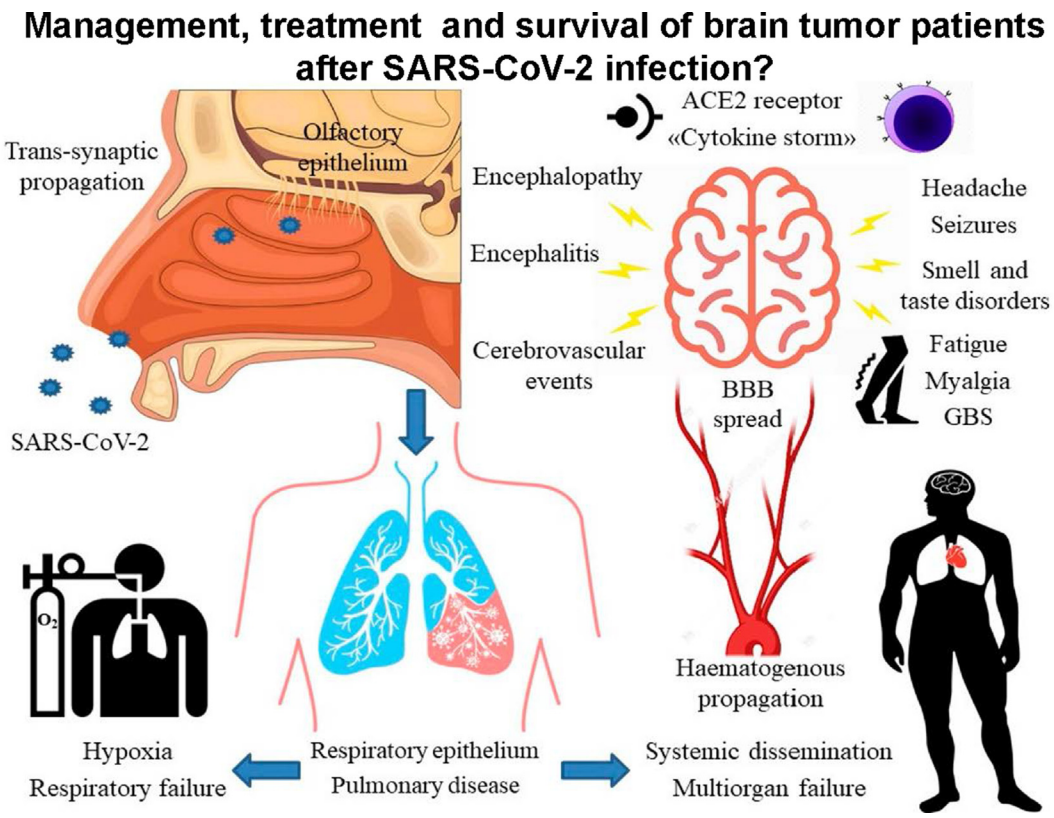

Fig. 5. Main neurological manifestations of COVID-19 and proposed mechanisms of SARS-CoV-2 neuroinvasion. ACE2: angiotensin II converting enzyme receptor-2; BBB: blood–brain barrier; GBS: Guillain-Barré syndrome. Reproduced from: Pennisi M, Lanza G, Falzone L, Fisicaro F, Ferri R, Bella R. SARS-CoV-2 and the nervous system: from clinical features to molecular mechanisms. Int J Mol Sci. 2020;21(15), 5475.

substrates. Tight junctions also limit transcellular transport through the capillary wall that maintains low levels of leukocyte adhesion molecules expression limiting the entry of immune cells into the brain [367–370].

Neurotropic respiratory viruses appear to enter the CNS via the two main pathways, that is, hematogenous and neuronal [371]. Currently, the mechanism by which SARS-CoV-2 achieves neuroinvasion is still unclear. It was postulated that this occurs through olfactory nerve *trans*-synaptic transfer, with vascular endothelium infection or immune cells migration through the potentially compromised BBB [354]. The expression of ACE2 was found in the brain tissue capillaries and cultured primary human brain microvascular endothelial cells [372], in line with detection of virus-like particles in the frontal lobe endothelium [373].

Brain vascular endothelial cells highly express SARS-CoV-2 entry-associated protease cathepsin B (CTSB) but not TMPRSS2 [355,366]. Viral invasion of the CNS could lead to the release of viral proteins that affect the structure and function of endothelial cells, degrade tight junction proteins, and lead to BBB permeability [366,374].

7.2. Neurosurgery directions in the era of COVID-19

In the era of COVID-19, the total coronavirus cases in the world are over 214 million, with 4.47 million deaths as of August 25, 2021 [375]. Based on these figures, the neurosurgical and neurooncological management of brain tumor patients should be quickly adapted to the future needs of COVID-19 affected cancer patients. Neovascularization is a major characteristic of brain cancer. The patient's risk of SARS-CoV-2 infection could be associated with overexpression of ACE2 on endothelial cells and altered immunity. Also, both cancer therapeutics and tumor microenvironment can cause immunosuppression and vascular complications, with modulation of ACE2 levels in cancer patients [347]. Cancer cells with altered immunogenicity may cause immune cells to produce immunosuppressive effectors, such as TGF-β, VEGF, PGE2, IL-10, and iNOS, inhibiting the proliferation and the cytotoxic response from T lymphocytes and leading to a prevalence of anti-inflammatory phenotype (T regs, M2 macrophages). Immunosuppressive microenvironment can induce the recruitment/polarization of anti-inflammatory M2 TAMs and immature dendritic cells [376]. However, COVID-19 and cancer patients may also develop altered immune and inflammatory reactions with high expression of IL-2 and IL-6 receptors, and possible changes in the prothrombotic state, such as elevation of prothrombin time [377–380]. This may negatively affect the course of disease. (Fig. 4)

Chronic immunosuppression in tumor patients could facilitate the infection by SARS-CoV-2 and increase COVID-19 severity. However, very little is known about ACE2 and other virus entry receptor levels on endothelial cells in brain cancer patients. ACE2 is a regulator of tumor angiogenesis [381], and this receptor has abnormally high expression in lung tumors [382]. Additionally, higher levels of VEGF were found in COVID-19 patients compared with healthy controls [383]. Based on these limited data, Barbosa et al. hypothesized that the level of ACE2 in the vascular endothelium of cancer patients may influence the risk associated with COVID-19 [347].

It was recently published that cancer patients infected with SARS-CoV-2 have a high chance of serious disease, a high risk of mortality, and a worse prognosis [378,379,381,384–386]. It was

reported that cancer patients had a higher risk of serious COVID-19 than patients without cancer (39% vs. 8%, P = 0.0003) [377]. Lung tumors were the most common form (28%). Clinical outcomes of patients with hematological malignancies were also worsened, with 2-fold increased mortality compared with patients with solid tumors (50% vs. 26.1%) [378]. However, available statistical data are not sufficient to conclude whether cancer is an independent risk factor, or the observed differences would mainly be due to gender, age, obesity, uncontrolled diabetes, cardiovascular disease, and/or therapy, in particular for brain tumors [387,388]. All the above should alert the physicians when treating cancer patients who were infected with SARS-CoV-2 virus (Fig. 5).

Several drugs including chemotherapeutics, such as cisplatin, can modulate ACE2 levels in cells [389]. In addition, the action of the chemotherapeutic anti-VEGF bevacizumab in SARS-CoV-2 patients is currently being evaluated in a clinical trial (NCT04275414) [383]. However, many chemotherapeutics including antiangiogenic drugs inhibiting VEGF are also associated with systemic cardiovascular toxicity. Hypertension, thrombosis, heart failure, cardiomyopathy, and arrhythmias all increase cardiovascular risk in cancer patients [390,391]. Moreover, these examples indicate that invasive surgical, radiological and pharmaceutical management should be adapted to the new situation that affects millions of people with extra caution in cancer patients compromised by COVID-19.

8. Future directions

The comprehensive analyses of primary brain tumor biology demonstrates that discovery of tumor specific targets, immunotherapy with optimal BBB delivery systems together with effective combination therapy are the main directions to win the battle against poorly treatable brain tumors. Nanomedicine treatment approaches open new horizons for creation of multifunctional drugs and novel nano immunotherapies. The expected goals for the neurosurgery and neuro oncology would be to translate innovation in nanotechnology and its novel opportunities to the clinical arena. Through continued mutual effort of multidisciplinary scientists, physicians, chemists, pharmacologists, molecular biologists, immunologists, and engineers, the future of nanomedicine and nano neurosurgery will be shaped towards clinical benefits. To fulfill the need for new effective nanomedicines combating brain cancer, the neurosurgery and neuro oncology also need newer preclinical models with personalized approach. The development of these models using patient-derived tumors has already allowed to successfully test some nanodrug treatments for GBM [7]. Recently developed new animal models utilize molecularly characterized cancer cells bearing the same oncogene mutations that are found in individual patients with gliomas [392,393]. They may constitute next generation of testing systems for the emerging nanomedicines aimed at helping neurosurgery to successfully fight deadly gliomas.

To curb the COVID-19 pandemic, WHO calls for 50–80% of the world population to be vaccinated against SARS-CoV-2 virus, where mRNA nanoparticles are currently playing the dominant role. Given the intrinsic relationship between endothelial system including the brain endothelium and the pathophysiology of SARS-CoV-2, endothelial-related therapies such as anticoagulants, fibrinolytic drugs, immunomodulators, and molecular therapies have been proposed and should be aligned with brain cancer patient treatment. The available evidence emphasizes an increasing role of vascular system in the understanding and treatment of inflammation and edema that often occur in the brain tumor, the disseminating coagulation processes, ACE2 target positive cancer patients, and suggests the need for combined anti-cancer and endothelial cell-associated therapies to treat brain cancer in conjunction with COVID-19 [347].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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