PSM Journals

PSM
Veterinary Research

Review Article 2025 | Volume 10 | Issue 1 | 18-30

Open Access

Article Information

Received: August 2, 2025

Accepted: August 20, 2025

Published: August 24, 2025

Keywords

Central nervous system tumors, Personalized molecular imaging, Glioma biomarkers, Theranostic radioligands, Early clinical translation.

Authors' Contribution

AJA designed, AJA, and LMRM wrote and revised the paper. All authors read and approved the final manuscript.

Citation

Alkhatib, A.J., Mutlaq, L.M.R., 2025. Emerging Molecular Targets and Personalized Therapeutics in CNS Tumors. PSM Vet. Res., 10(1): 18-30.

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Emerging Molecular Targets and Personalized Therapeutics in CNS Tumors

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Abstract:
This is a review of the current preclinical data and early-phase clinical trials evaluating the use of personalized on-treatment molecular imaging in central nervous system tumors (CNS). Epigenetic modulators targeting IDH1-mutated, histone H3-mutated, or MGMT-methylated gliomas and "hot spot" mutations could increase the effectiveness of ICIs in glioma patients. Theranostic radioligands targeting somatostatin and prostate-specific membrane antigen could be of benefit in neuroendocrine CNS tumors and primary brain malignancies. In the presence of specific molecular features, these radioligands could be used for theranostic purposes. Recognizing IDH1-R132H mutation on brain cytopathological specimens allows for a tailored patient care approach by providing real-time diagnostics even if standard mutational analysis is uninformative. Including immunohistochemical testing in the routine intraoperative examination of benign oncological procedures for lesion excision would prevent multiple repeat surgeries in glioma patients and improve patient outcomes.

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INTRODUCTION

In recent years, the worldwide cancer incidence has remained high. Every year, tens of millions of Americans are given a new cancer diagnosis. Simultaneously, cancer kills millions, if not tens of millions, of people worldwide (Amjad *et al.*, 2020a; Chhikara and Parang, 2023). According to the current incidence rates, the world's top 10 cancers are female breast, lung, skin, prostate, colon, stomach, liver, rectum, esophageal, cervix uteri, and brain (Amjad *et al.*, 2020b; Iqbal, 2021; Sabarwal *et al.*, 2018). CNS tumors are diverse and present with unique characteristics influencing their response to treatment modality and patient outcome. CNS tumors have unique behavior, particularly when occurring in an immunologically privileged site such as the brain (Giotta Lucifero *et al.*, 2020). The treatments, therefore, may require a different approach compared to similar types of tumors outside the CNS (Ningaraj *et al.*, 2007). CNS malignancies can be primary tumors or metastases. Glial neoplasms account for about 40% of all primary CNS neoplasms, with glioblastoma multiforme (GBM) being the most common and an example of grade IV malignancy (Salari *et al.*, 2023). Accordingly, successful treatments for this cancer will likely necessitate the development of a multi-faceted approach for an individualized patient-based therapy (Ningaraj *et al.*, 2007). Within the field of neuro-oncology in the last years, much effort has been made for the discovery of novel approaches and personalized therapies intended to improve patient outcomes (Low *et al.*, 2022). The potential for targeting molecular aberrations in CNS tumors to improve treatment outcomes is discussed (Al-khatib, 2013). It is often difficult to treat many brain and spinal cord cancers due to the blood-brain barrier (BBB) that inhibits the entry of the majority of small- and large-molecule pharmaceuticals (Horbinski *et al.*, 2022). The current regimen for GBM consists primarily of using temozolomide as a chemotherapeutic agent and is given concurrently with radiotherapy, followed by adjuvant therapy (Ostrom *et al.*, 2021). This approach grants a slight increase in patient survival and increased 2-year survival compared to radiotherapy alone. However, the overall survival rate remains dismal with an average of 13.6 months (Smith *et al.*, 2022). It is suggested to use induced pluripotent stem cells as a model for BBB and BCSFB, both to comprehend the basal functioning and to potentially assess the implementation of newly developed brain drug delivery platforms such as nanoparticles and polymeric micelles. From the potential targets in brain tumors discussed, it appears that there is a diverse and versatile list of molecular targets whose exploitation may elicit a better treatment (McNamara *et al.*, 2022). Such targets include pathways currently investigated in trials focusing on other types of cancers which might be potentially investigated in CNS tumors (Smith *et al.*, 2022).

Current challenges in treatment

Central nervous system (CNS) tumors constitute a diverse unit of malignancies that includes the various gliomas, medulloblastomas, ependymomas, and other less prevalent histologic types of tumors within the CNS (Al-khatib, 2013). Primary glial tumors are generally classified as gliomas, which in turn account for approximately 30% of all primary CNS tumors and about 80% of all malignant brain tumors (Ostrom *et al.*, 2021). Despite ongoing investigations and the approach of combining modalities for treatment, the outcome of patients diagnosed with anaplastic gliomas or the most malignant gliomas (GBM) invariably results in treatment failure, particularly due to local recurrence (Ghiaseddin *et al.*, 2021). Therefore, the need for novel approaches in the treatment of CNS tumors is as urgent as it gets (Iqbal and Ashraf, 2020; Wang *et al.*, 2015). Given the limitations regarding surgical removal and radiotherapy and the anti-proliferative characteristics exhibited by the chemotherapeutics used to treat these tumors, a better understanding of the molecules involved in the pathogenesis and progression of CNS tumors would provide a basis for the development of more successful targeted strategies of treatment (Ghiaseddin *et al.*, 2021). Efforts to clarify the genetic alterations of CNS tumors have shown that they have a high frequency of genetic alterations that are exclusive to each CNS tumor type (Louis *et al.*,

2021). Such genetic alterations are responsible for activating several different types of proteins, which have the potential to serve as effective and exclusive therapeutic targets (Wang *et al.*, 2015). Correspondingly, several molecular abnormalities in CNS tumors have been described that represent feasible targets for the use of new drugs (Miller *et al.*, 2021).

Emerging molecular targets

The treatment of nervous system tumors has markedly evolved over the last decade with the identification of both common and less commonly recognized molecular targets (Horbinski *et al.*, 2022). These improvements have culminated in a greater understanding of the biology of primary brain tumors across multiple histologic subtypes and the ability to provide more personalized, targeted, and active systemic therapies, often as part of multimodal therapeutic strategies (Batchelor, 2022). In parallel, evolving central nervous system cancer biology research provides intriguing areas for future therapy development, particularly as it pertains to overcoming significant treatment challenges, including an understanding of persistent resistance to therapy in cells in the tumor-infiltrated zone, and the study of active modes of brain-tumor communication as possible additional targets (Poon *et al.*, 2021). The embracing of vaccination strategies to generate T-cell responses to tumor neoantigens is also an encouraging sign that these types of resistant tumors, especially glioblastomas, do not represent an insurmountable challenge for immunotherapeutic approaches. Here, recent progress identifying the genetic and non-genetic architecture of immune responses in breast cancer brain and spinal metastases, how these dynamics change with therapy, and implications for their resistance to various modes of treatment will be examined, along with open questions in the field that are relevant for designing new therapeutic strategies moving forward (Santoni *et al.*, 2022).

Personalized therapeutics

Molecular genetic investigations have unveiled a panoply of driver mutations and altered molecular pathways that contribute to the pathogenesis of a wide range of cancerous tumors (Li *et al.*, 2024). Randomized controlled trials dictate the current clinical approach to cancer therapy, but these do not closely account for intertumor and intratumor heterogeneity or tumor evolution through time (Nkune *et al.*, 2021). In the era of precision medicine, understanding of tumor biology is being rapidly transformed into novel and highly needed targeted therapies and highly sensitive companion diagnostics for specific histological and molecular tumor subtypes (Wang *et al.*, 2022). This approach has been particularly productive for melanoma and hematologic malignancies (Pratyasha *et al.*, 2022). In contrast to other brain tumors, these carry a low average number of protein-altering mutations overall and a low number of mutations that drive tumor formation (Ari Yuka *et al.*, 2023). As an example, glioblastomas typically display alterations in the tumor suppressor encoded by the TP53 gene, retinoblastoma 1, and Cyclin-dependent kinase inhibitor 2A and CDKN2B genes, as well as amplification of the gene encoding EGFR or fusions involving Neurotrophic receptor tyrosine kinase genes (Valido *et al.*, 2024).

Significance of personalized medicine in CNS tumors

Central Nervous System (CNS) tumors are the formation of abnormal cells in the brain and the spinal cord (Smith *et al.*, 2022). CNS tumors encompass a wide range of disease entities with diverse biological behaviors and responses to therapy (Daron-Mathis, 2015). There are over 120 different types of primary malignant or benign brain and CNS tumors, as well as CNS metastases originating outside the CNS region (Levine, 2020). In general, tumors are formed when the molecular machineries that govern the dynamics of the cellular life cycle are disrupted (Xiong *et al.*, 2020). There are a number of mutations and amplifications in genes involved in cell-cycle regulation, such as the cyclins, cyclin-dependent kinases, and retinoblastoma (Orr *et al.*, 2020). Also, suppressors of the cell cycle-regulated transition, known as tumor suppressor genes, like p53, are mutated (Kim *et al.*, 2020). About 70% of patients with CNS

tumors have mutations in p53 (Daron-Mathis, 2015). Generally, three types of therapy are used to treat CNS tumors: chemotherapy, radiotherapy, and surgery. The main limit of chemotherapy is its toxicity (Pinto and Zambetti, 2020). In fact, classic chemotherapy does not distinguish between cancer cells and normal fast-growing cells, leading to severe side effects (Cacciotti *et al.*, 2020). Moreover, due to the protective effect of the Blood-Brain Barrier (BBB), very few drugs can reach a therapeutic concentration in the brain (Qi *et al.*, 2024). Most chemotherapeutics consist of alkylating agents, DNA intercalators, topoisomerase inhibitors, and antimetabolites (Cash *et al.*, 2021).

Genetic involvement of CNS tumors

Recent progress regarding the genetic architecture of CNS tumors has paved the way for the development of interventions that are selectively geared towards key oncogenes and pathways implicated in the progression of the tumor, along with preclinical tests of potential drugs, patient trials, currently approved targeted treatments, and a series of unresolved concerns that might potentially be targeted in the future (Xiao *et al.*, 2020). Awareness of the molecular pathways of CNS tumors has drastically increased recently. This comes secondarily from comprehensive genotype research initiatives (Iqbal, 2020; Pichaivel *et al.*, 2022). In-depth molecular knowledge of specific CNS tumors has been achieved through mutation screenings and laboratory assessments in different research institutes. In the case of diseases that are biologically and/or genomically diverse, like gliomas, this data has triggered the classification of new tumor entities with relevant clinical consequences (Ott *et al.*, 2021). The most critical actionable alterations have been identified in a considerable number of cases of different CNS tumors, such as amplifications, mutations or fusions that lead to oncogenic activation of receptor tyrosine kinases such as ERBB2, ALK, and MET, mutations in RAS and PI3K pathway genes such as NF1 and BRAF, some mutations affecting the epigenetic machinery such as mutations in IDH, H3F3A, and ATRX, or BRAF fusions or mutations in specific malignant glioma entities (Karschnia *et al.*, 2021). Interfering pharmacologically with the enzymes or proteins of these pathways results in direct targeting, which constitutes a clinical benefit for the patient (Ramkissoon *et al.*, 2020). Furthermore, improved comprehension of the mechanisms that underlie how cancer cells eventually gain drug resistance has led to the development of compounds that might counteract or prevent the emergence of resistant tumor clones, like AURK inhibitors in glioblastoma (d'Amati *et al.*, 2024). This review discusses the growing knowledge of molecular targets discovered in the pathogenesis of nervous system tumors, from the standpoint of their basic principles, translational research, current and potential personalized treatments, and unresolved vital questions for the future (Pellerino *et al.*, 2022).

Background on CNS tumors

Central nervous system (CNS) tumors have been treated with surgery, radiotherapy, and chemotherapy, like most other tumors (Delgado - Martín and Medina, 2020). Evaluating the effectiveness of treatment for cancer patients in general has traditionally been done based on oncologic assessment of tumor shrinkage (Torp *et al.*, 2022). In the clinical evaluation of the treatment effect of CNS tumors, radiologic studies have been used to evaluate changes in size based on criteria like the Macdonald and the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Wang *et al.*, 2015). Changes in the size of the fluid-attenuated inversion recovery (FLAIR) images or within lesions that show tumor characteristics are regarded as indicators of treatment effect (Torp *et al.*, 2022). The apparent diffusion coefficient (ADC) is used as a tool to monitor tumor response to therapy. This measure assesses the mobility of water within tissues (Jiang *et al.*, 2020). Water diffuses more easily in tissues with lower cell density or low nucleus: cytoplasmic ratios (Kwon *et al.*, 2021).

Historical treatment approaches

Primary central nervous system lymphoma (PCNSL) affects primarily elderly patients and comprises 5% of all primary brain tumors with

predominant histology of diffuse large B-cell lymphoma (DLBCL) (Pirozzi and Yan, 2021). Due to the exclusion of PCNSL from programs of high-level evidence clinical trials, most therapeutic decisions for patients with PCNSL are based on data from retrospective studies and prospective phase II trials (Komori, 2022). Whole-brain radiotherapy (WBRT) does not provide durable remission and is involved in the development of leukoencephalopathy with delayed neurotoxicity, especially in elderly patients (Pirozzi and Yan, 2021). Thus, more attention has been paid to regimens excluding WBRT, out of which high-dose methotrexate (HD-MTX)-based immunochemotherapy is being introduced recently (Komori, 2022). BBB-penetrating HD-MTX-based multiagent immunochemotherapies have shown high activities as induction regimens, followed by high-dose chemotherapy with autologous stem-cell transplant (HDC/ASCT) in healthy patients with early relapse. Nevertheless, patients with poor performance or very late relapse often do not implement this regimen, and for them, there is no standard second-line therapy (Poetsch *et al.*, 2021). Therefore, exploration of innovative therapeutic strategies, including the application of molecular targeted therapies against key signaling molecules, is sought after. There is recent progress in understanding the molecular pathogenesis of PCNSL, and this knowledge can be exploited to develop novel molecular targeted therapies against key signaling molecules activated by these genetic changes (Lombardi *et al.*, 2020). The molecular genetic understanding of nervous system tumors has expanded rapidly during the past decade, with some alterations offering insight into potentially targetable oncogenic driver alterations (Correia *et al.*, 2021). Furthermore, larotrectinib has been FDA-approved for use in gliomas that harbor certain NTRK fusions. Others are exploring rational combinations to inhibit downstream pathway signaling to counteract mechanisms of resistance (Reuss, 2023).

Shift towards personalized therapeutics

Recent focus on targeted treatments has drastically reshaped the therapeutic landscape of the majority of solid tumors; the manifold and cell-specific molecular alterations characterizing their onset and progression have provided the groundwork for focused therapies that are currently being assessed in an array of clinical trials (Han and Brastianos, 2017). With an increasing number of studies dissecting the complex molecular scene of primary CNS and metastatic brain neoplasms and allowing a more precise dissection of the underlying biology, research now strives to keep up with the advancements made across other tumors (Ghiaseddin *et al.*, 2021). The understanding of the cryptic tumorigenic mechanisms underpinning the onset and progression of gliomas is expanding, though much remains to be elucidated; this being so, refinement is ongoing for the tools allowing the study of molecular processes within gliomas (Richards *et al.*, 2021). The immediate follow-up to this improved knowledge is the identification of potentially targetable vulnerabilities in tumor cells that apparently do not affect neural and glial cells (Han and Brastianos, 2017).

Molecular targets in CNS tumors

Several new opportunities in the treatment of CNS tumors have now arisen with the development of molecular genetic profiling techniques that enable them to be tailored to the individual patient (Malone *et al.*, 2020). Here, several personalized therapeutic approaches are discussed in the context of brain tumors (Park *et al.*, 2021). These approaches aim to optimize the beneficial effects of treatment by taking account of the individual characteristics of the tumor; the intrinsic genetic profile or predominant pathway activation within the tumor, the extent to which a drug or agent enters the tumor mass or intracellular compartment, subsequent evidence of drug pharmacokinetics within the individual tumor, and the tumor's inherent resistance capabilities or outcome effects on cellular population kinetics (Reuss, 2023).

Best outcomes in the targeted treatment against nervous system tumors have been realized by the development of molecularly targeted agents or small molecule inhibitors (Ningaraj *et al.*, 2007). These drugs are particularly effective

against brain tumors because, in the majority of cases, it is not possible to surgically extirpate the neoplastic tissue in CNS primary tumors (Correia *et al.*, 2021). The current molecular signatures from the nervous and extraneural system tumors obtained from large-scale next-generation sequencing efforts revealed, however, that the translational potential of these insights is still largely unfulfilled or even declining compared to other cancer types or pediatric brain and spinal cord tumors (Pichaivel *et al.*, 2022). Tuning state-of-the-art mouse modeling of human tumors is manifest as faithful to histopathology, genomics, and epigenomics (Pellerino *et al.*, 2022). Conversely, many results generated in experimental animals remain relentlessly preclinical, disconnected from validated therapeutic paradigms in human cancer (Mayo *et al.*, 2021). The genomics of human nervous system tumors portrays agglomerates of driver mutations conglomerated through stochastic or probabilistic events and physiologically opposed in cancer (Panwar *et al.*, 2023).

Genomic alterations

Accumulating evidence of significant genomic heterogeneity intratumorally as well as across different metastatic sites in patients diagnosed with brain metastases has emerged. With advancements in cancer therapy, enabling prolonged survival of patients with advanced cancer, the incidence of brain metastases is on the rise (Ali *et al.*, 2021). Despite standard treatment modalities, including surgical resection, brain radiotherapy, and systemic chemotherapy, prognosis remains poor (Shih *et al.*, 2020). Genomic analyses of brain metastases often harboring actionable driver mutations not present in the primary tumors or other synchronous brain metastases have been reported, raising the possibility for expanded irradiation of these potential targets in the brain (Morgan *et al.*, 2021). Moreover, findings of amplifications in the receptor tyrosine kinases (RTKs) erBB2 (HER2) and c-Met in the brain metastases of breast cancer or non-small cell lung cancer (NSCLC) patients have renewed interest in the evolving 'seed-and-soil' hypothesis in the context of potential drug resistance consortia of RTKs facilitating brain colonization (Kim *et al.*, 2020). In patients with melanoma brain metastases, constitutively activated extracellular signal-regulated kinases (ERK) pathways have been linked to an en masse quiescence of these brain metastases (Morgan *et al.*, 2021). Although still largely underrecognized, advancements in cancer genomic analysis using innovative, less invasive techniques in CM may be informative for personalized therapeutic decisions (Gonzalez *et al.*, 2022). Moreover, they are more practical, even in patients not amenable to surgical procedures or whose BMs recur with intolerable brain toxicity. Collectively, these results suggest that multi-targeted, comprehensive genomic assessments are of paramount importance in CM (Cosgrove *et al.*, 2022). Vascular endothelial growth factors (VEGF) targeting agents administered alone or in association with other drugs are used to stop the cancer progression (Irfan *et al.*, 2016). As linked biomarkers and trials are essential, much work remains to be effused into refining their role and utility in the design of therapeutic interventions (Li *et al.*, 2024).

Epigenetic modifications

Tumors of the central nervous system (CNS) comprise a heterogeneous group of lesions arising in the brain and spinal cord that can be broadly categorized as primary CNS and metastatic tumors (Poetsch *et al.*, 2021). Tumors of the CNS constitute approximately 2% of all human cancers, with a wide range of histopathological and clinical properties (Reuss, 2023). In the pediatric population, CNS tumors are the most common types of childhood cancer (Horbinski *et al.*, 2022). Despite significant advances in the early detection, multimodal therapy, and understanding of cancer, CNS malignancies, considered collectively, still have met with a considerable clinical challenge, and their overall prognosis is generally very poor (Lambrou *et al.*, 2021). The standard approaches for the treatment of CNS tumors include surgery, radiotherapy, and chemotherapy when feasible (Cosgrove *et al.*, 2022). During the past years, significant progress in understanding the cellular and

molecular pathogenesis of CNS tumors led to the identification of several genetic and epigenetic modifications (Bale and Rosenblum, 2022). Currently, there is a great interest and emphasis on molecular targeting of CNS tumors, taking into account that many small molecules, along with immune-based therapeutic approaches, have demonstrated encouraging results and significantly affected the management and outcome of cancer patients (LeBlanc and Mazcko, 2020).

Personalized therapeutics

Emerging novel insights into the molecular genetics of underlying nervous system tumors have led to therapies targeting actionable oncogenic drivers, and technological advancements in engineering preclinical model systems have enabled rapid assessment of promising new drugs with potential application to targeted therapy of children's neuro-oncology (Tan and Tan, 2022). Dynamic developments in understanding the molecular genetic diversity of tumors underlying the nervous system provide powerful insights into the characteristic alterations in known oncogenic drivers that drive tumorigenic initiation, maintenance, and progression (Hasanli and Günay, 2023). Over the past decades, an extensive array of distinct classes of targeted drugs has been developed that specifically inactivate the oncogenic driver via diverse mechanisms of interference (Chevallier *et al.*, 2021). The tumor shrinkage is substantially reduced due to selective inhibition of tumor-specific growth and survival signals, excluding damage to normal signaling pathways, leading to fine tolerability compared with non-selective chemo and radiation therapy (Genova *et al.*, 2020). The lessons learned from the elucidation of the molecular genetics might foster the repurposing of clinically approved drugs to treat the usual tumors of the nervous systems featuring comparable driver mutations, utilizing vulnerabilities of the tumor's addiction network(s). Such advancement of novel drug design designates immense possibilities to treat tumors with genomic landscapes that have hitherto been without a course of action, and ultimately to eradicate cancer as a likely deadly disorder (Mutebi, 2024).

CNS tumors are the deadliest brain cancers. The CNS includes the brain and spinal cord and their adjacent structures within the skull or spine (Shobeiri *et al.*, 2023). New genomic technologies make a difference in the detection and treatment of brain cancers (Deng *et al.*, 2022). Many tumors have been linked to gene alterations (Ghiaseddin *et al.*, 2021). Novel molecular target developments evolve new detection and treatment methods against brain cancers. Effective target-based therapies have much lower side effects than conventional treatments (Alkhatib, 2019). For this reason, tumors are analyzed at a molecular level to identify useful targets for the development of personalized treatments. Treatment with rising technology involves personalized therapeutic methods for the relief of CNS tumors (Riedl *et al.*, 2024). Central nervous system (CNS) tumors represent a diverse group of tumors, each with unique morphologies, gene expression patterns, and treatment responses (Abou-Mrad *et al.*, 2021). Increased understanding of this intratumoral heterogeneity has led to the evaluation and discoveries of newer therapeutic targets beyond the traditional cytotoxic agents and kinase inhibitors (Kamath and Kumthekar, 2018).

Radiological advances in CNS tumors

Multiparametric MRI is an MRI that includes diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI, like DSC, DCE), MR spectroscopy (MRS), and high-field-strength imaging. The diagnostic accuracy of MRI is enhanced when these modalities are added. Further characterization of lesion cellularity, vascularity, metabolism, and microstructural heterogeneity is determined. One example includes automatic quantification methods using multi-sequence MRI have improved residual tumor detection, and their combination with clinical variables such as age and performance status improved prognostication (Park *et al.*, 2020; Sawlani *et al.*, 2020). Precise and accurate delivery of radiation to the target cancerous tissue reduces the relapse and increases the overall survival (Din *et al.*, 2016). Radiomics is a noninvasive method that extracts high-dimensional quantitative imaging features

from modalities (MR, PET), allowing for tumor phenotyping, insights into prognosis, and therapeutic response (Rogers *et al.*, 2020; Sabeghi *et al.*, 2024). Radiogenomics goes further by exploring the correlations between imaging features and crucial molecular biomarkers like EGFR, MGMT, and IDH1. Research has shown that MRI-based imaging patterns are significantly related to these molecular alterations, opening the doors for personalized management (Seow *et al.*, 2018). Deep learning and machine-learning models have efficiently predicted molecular status directly from imaging with high accuracy (Jiang *et al.*, 2023).

CONCLUSION

Effective treatment requires targeting tumor-initiating events. In the context of the rapidly and persistently evolving mutational and nefarious tumor microenvironment, unlocking the brain's capacity to fight back is expected to significantly enhance the efficacy of other therapeutic measures. This volume presents the challenges and some of the recent advances in identifying brain features, biomarkers, and possible physiological strategies to intervene promptly to fend off emerging tumors. The few potential therapeutic interventions directed at mechanisms that are neither mutated nor different in brain samples are highlighted. Although these approaches would not provide a comprehensive understanding of fundamental brain-specific events, they can provide a useful basis to investigate how cancer-type-specific mechanisms differ from other features and infer potential brain-specific alterations in signal transduction. The avoidance of the mitigation of general features will be required to effectively prevent opposite effects, or not to wipe out protective features that are still missing in the current comprehension of brain-specific signaling. To this end, the recent exploration of drug repurposing opportunities that would provide a needed safe and cheap physical approach could shed light on such protective mechanism candidates that would then require an intensification of efforts to characterize brain-specific functional infrastructures.

CONFLICT OF INTEREST

The authors hereby state that they do not have any conflicts of interest to declare.

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