Annual Review of Medicine

New Approaches to Glioblastoma

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Annu. Rev. Med. 2022. 73:279–92

First published as a Review in Advance on October 19, 2021

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-042420-102102

Keywords

glioblastoma, precision medicine, immunotherapy

Abstract

Faced with unique immunobiology and marked heterogeneity, treatment strategies for glioblastoma require therapeutic approaches that diverge from conventional oncological strategies. The selection and prioritization of targeted and immunotherapeutic strategies will need to carefully consider these features and companion biomarkers developed alongside treatment strategies to identify the appropriate patient populations. Novel clinical trial strategies that interrogate the tumor microenvironment for drug penetration and target engagement will inform go/no-go later-stage clinical studies. Innovative trial designs and analyses are needed to move effective agents toward regulatory approvals more rapidly.

INTRODUCTION

Gliomas are among the most common primary tumors of the central nervous system (CNS) and are classified into World Health Organization (WHO) grades from grade I, most benign tumors, to grade IV, most aggressive (1). Approximately 50% of gliomas present as WHO grade IV glioblastoma, which are the most aggressive among gliomas. Glioblastoma accounts for 48.6% of primary malignant brain tumors, with an annual incidence of 3.23 per 100,000 in the United States (2). Despite the immense efforts made to cure this cancer over decades of effort, the prognosis remains dismal, with median overall survival (OS) of 15 months (3), and only 7.2% of patients surviving 5 years after diagnosis (2). The 2016 and 2021 WHO classification of tumors of the CNS uses both histological tumor typing and molecular markers such as genetic mutations in the metabolic enzymes isocitrate dehydrogenase (IDH) 1 and 2 genes, histone H3 genes, and codeletion of 1p19q (1). Glioblastoma designated as IDH-wildtype is distinct from IDH mutated astrocytoma, WHO grade IV, with the latter being much more prognostically favorable despite a similar histological appearance (4, 5).

The current standard of care for glioblastoma consists of maximal safe resection of the tumor followed by concurrent chemoradiation therapy using the alkylating agent temozolomide (TMZ) and an additional 6–12 cycles of adjuvant TMZ if tolerated (3). Tumor-treating fields (TTF) can be added to this regimen. TTF triggers tumor cell death by disrupting the microtubules in the mitotic spindle with alternating electrical fields. This strategy has been shown to prolong OS in a randomized controlled trial (6, 7), but the TTF device must be worn on the scalp 18 h/day, which limits patient compliance.

Despite these treatments, glioblastoma inevitably recurs because (*a*) genetic heterogeneity precludes a single, targetable oncogenic pathway (8); (*b*) aggressive and infiltrative tumor growth in an essential organ limits the curative potential of surgical therapy (9); (*c*) a blood–brain barrier (BBB) and chemotherapy-resistant mechanisms protect tumor cells (10); (*d*) glioma stem cells are resistant to chemotherapy and radiation therapy (11, 12); (*e*) a unique immune environment includes microglia that may be tumor supportive (13, 14); and (*f*) treatment modulates the tumor microenvironment (TME), which influences responses to therapy (13). For recurrent glioblastoma, no systemic therapy has been shown to improve survival since the introduction of TMZ in 2005 (15). In this review, we discuss new approaches to glioblastoma in the domains of surgery, chemotherapy, targeted molecular therapies, and immunotherapy.

SURGICAL ADVANCEMENTS: THE SUPER-RESECTION

The goals of surgery are to provide pathological tissue for diagnosis and potential precision medicine initiatives, to reduce the volume of the tumor tissue (cytoreduction) and tumor-mediated immune suppression, to decompress the normal brain and/or relieve neurological symptoms, and to maximize the effects of radiation and chemotherapy. The current standard of surgical care for glioblastoma is complete safe resection of the gadolinium-enhancing tumor (16). Given the prognostic influence of the IDH1 mutant in high-grade astrocytomas, a retrospective study showed that resection of both enhancing and non-enhancing tumors contributed to a better prognosis observed in the IDH1 mutant group (17). Supratotal resection is an emerging concept of glioma surgery that is defined as a resection beyond the T1 gadolinium-enhanced region, including the FLAIR (fluid-attenuated inversion recovery) abnormal region to maximize cytoreduction (18, 19). A single-center study evaluating supratotal resection found survival significantly increased with no significant differences in neurological deficits (20). In a second retrospective case series, a cutoff threshold of 45% or greater removal of the FLAIR residual tumor volume had an impact on

2-year OS (21). Tumor visualization adjuncts such as 5-ALA may provide additional intraoperative guidance for achieving these supratotal resections. The evidence to support the emerging concept of supratotal resection is limited and requires prospective multicenter studies with larger cohorts to be established as a standard of care. Cumulatively, the data support maximal safe resection to achieve long-term disease control, improve quality of life, and prolong OS (21, 22). More recently, there has been a shift toward considering the volume of residual tumor post resection as being a more valuable and accurate metric in determining outcomes (23, 24).

COMBINATORIAL CHEMOTHERAPY WITH ESTABLISHED AGENTS

TMZ is the first-line chemotherapy treatment for patients with glioblastoma and provides a therapeutic benefit of an increase in OS to approximately 2.5 months when added to radiotherapy (3). There is a greater benefit in patients whose O(6)-methylguanine-DNA methyltransferase gene (*MGMT*) is silenced through methylation in the promoter (25). However, given the lack of other treatment options, TMZ is generally given to all patients regardless of *MGMT* status. In patients with an unmethylated *MGMT* promoter gene, who are less likely to respond to TMZ, omission of TMZ would be justifiable to allow evaluation of experimental therapies without additional toxicities from TMZ or potentially inducing hypermutation (26, 27). Gliomas may be especially prone to subclonal mutations, which can induce resistance to therapies such as immune checkpoint blockade (28). This increase in mutational burden can be induced by TMZ, which causes defects in DNA mismatch repair genes. This is also associated with an increased degree of intratumoral heterogeneity that may also pose challenges to antigen-specific immunotherapies. Lomustine (CCNU), like TMZ, is an alkylating agent and was commonly given with procarbazine and vincristine (a combination known as the PCV regimen) for glioblastoma. An open-label phase III trial has shown that the addition of lomustine to TMZ chemo-radiotherapy may increase survival for patients with primary *MGMT*-methylated glioblastoma (29). This study was terminated early due to slow accrual and lack of statistical power. A larger study is being planned to confirm the findings.

Poly ADP-ribose polymerase inhibitors (PARPi) block the PARP-1 and PARP-2 enzymes (30, 31), which are important in repairing DNA damage, and data suggest that they can be effective radiosensitizers (32, 33). The combination of the PARPi veliparib and TMZ demonstrates synergistic activity when used to treat *MGMT*-methylated glioblastoma cell lines (34, 35). There were also encouraging responses when this combination was applied to *MGMT*-unmethylated cell lines, especially in those with elevated baseline expression levels of DNA repair genes (35), consistent with the proposed mechanism of veliparib (36, 37). The brain-to-plasma concentration ratio of veliparib was substantially higher relative to other PARPi such as olaparib, rucaparib, and talazoparib (38). However, the triplet combination of veliparib, radiation, and TMZ was toxic when administered concurrently in clinical trials, causing severe thrombocytopenia (39). As such, veliparib has been further studied in *MGMT*-methylated glioblastoma in the ongoing A071102 trial (NCT02152982), added to adjuvant TMZ after completion of the concurrent radiation/TMZ therapy. A parallel trial in patients with newly diagnosed glioblastoma with unmethylated *MGMT* promotor in which veliparib was combined with only radiation (no concurrent TMZ), followed by adjuvant TMZ and veliparib, demonstrated an acceptable safety profile but no survival advantage (40). Several other PARPi including olaparib and pamiprab (BGB-290) have better BBB penetration and are being developed in early-phase studies in glioblastoma, in a variety of combinations with radiation/TMZ and other therapies (NCT03212742, NCT03150862, and PARADIGM-2).

PRECISION ONCOLOGY AND TARGETED THERAPY IN GLIOBLASTOMA

Advances in sequencing technology have enabled a greater understanding of the genomic landscape of glioblastoma (41). Identifying targetable and actionable driver genomic alterations promises to expand the list of potential therapies. One of the strongest selective pressures may occur early during glioblastoma development (42). The epidermal growth factor receptor variant III (EGFRvIII), which is a constitutively active form of the EGFR (43), has been the focus of many targeted therapies with tyrosine kinase inhibitors (TKIs) such as erlotinib and others. These therapies have largely failed to demonstrate significant efficacy (44, 45) as a function of insufficient drug penetration and target engagement. Depatux-M, an antibody-drug conjugate targeting EGFR, has shown activity in a phase II trial in combination with TMZ in recurrent *EGFR*-amplified glioblastoma. However, it has failed to demonstrate a benefit in a larger confirmatory trial in newly diagnosed glioblastoma (46, 47). Peptide vaccine strategies also failed at late-stage clinical trials secondary to target heterogeneity and target loss (48).

Glioblastoma is a highly vascular tumor with overexpression of vascular endothelial growth factor (VEGF). Bevacizumab is a monoclonal antibody against VEGF-A that has been investigated in multiple large clinical trials in glioblastoma, also demonstrating no benefit on OS (49). However, bevacizumab has steroid-sparing effects on surrounding edema, allowing for reduced steroid use and consequent reduced immunosuppression (50). Dexamethasone, if given during vaccine priming, may induce systemic depletion of memory and naïve CD4/CD8 T cells, rendering immunotherapy ineffective (51). In this context, bevacizumab is worth re-evaluating, specifically for its ability to reduce the need for immunosuppressive corticosteroids (52, 53). Given that VEGF is a good target in glioblastoma, there have been several trials of VEGF or multi-kinase TKIs directed to the TME. Cediranib, an oral VEGF TKI, failed to show a survival benefit in a randomized phase III trial, either as monotherapy or in combination with lomustine in recurrent glioblastoma (54). Trials of other agents such as tivozanib (55), pazopanib (56), and sunitinib (57) have shown minimal activity, indicating that VEGF monotherapy has a limited role in an unselected population. More recently, a phase II trial of regorafenib in the relapse setting showed an efficacy signal with a survival benefit compared to lomustine (58). To confirm this finding, regorafenib is now under evaluation in the Adaptive Global Innovative Learning Environment for Glioblastoma (AGILE) trial (27). AGILE is a Bayesian multi-arm clinical platform that can nimbly test multiple therapies at the same time against standard of care (**https://www.gcaresearch.org**). Other targeted agent studies in AGILE (NCT03970447) currently include (*a*) the bi-alkylating agent dianhydrogalactitol, Val-083, which induces interstrand crosslinks at N7-guanine leading to persistent DNA double-strand breaks and cell cycle arrest in a p53-dependent or p53-independent manner (59) and (*b*) the brain penetrant PI3K/mTOR inhibitor Paxalisib (GDC-0084) (60). The PI3K/mTOR pathway is frequently dysregulated in glioblastoma (61), although previous trials targeting this pathway have not shown efficacy. For example, buparlisib, a pan-PI3K TKI, demonstrated minimal single-agent efficacy in recurrent PI3K-activated glioblastoma patients (62). mTOR inhibitors, such as temsirolimus, have also demonstrated a lack of efficacy in phase II trials (63).

Less frequently targeted than EGFR and VEGF are the *BRAF* V600E activating mutations present in approximately 6% of glioblastomas (64), with a predominance in the epithelioid glioblastoma histological variant. Preliminary data from studies of vemurafenib indicated modest activity in *BRAF* V600E mutant glioblastoma (65). However, combination BRAF/MEK inhibition with dabrafenib and trametinib may be more promising (66). Gene fusions are also detected in rare subsets of glioblastoma patients, and they can be targeted with NTRK TKIs such as larotrectinib and entrectinib. These have already received tumor-agnostic approval from the US Food and Drug Administration (FDA) for patients with solid tumors, including a small number of

glioblastomas harboring NTRK fusions, based on impressive response rates in early basket trials (67, 68). Subgroup analyses suggest benefit for NTRK inhibitors in patients with gliomas in the aforementioned trials. Alterations in the cyclin D1-cyclin-dependent kinase 4/6-retinoblastoma 1 pathway in glioblastoma have also been targeted with a CDK4/6 inhibitor in glioblastoma (69). Alterations in the CDK4/6 proteins and RB1 are reportedly involved in over 78% of glioblastomas, mainly in the classical and mesenchymal subtypes (70). Abemaciclib is currently being evaluated in the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) (71).

Currently, several basket trials are evaluating targeted therapies based on molecular signatures in solid tumors including glioblastoma. These include Lung-MAP (NCT02154490), NCI-MATCH (NCT02465060), and My Pathway (NCT02091141). Moreover, adaptive trial designs have been used in recent trials, such as the aforementioned INSIGhT adaptive platform trial (NCT02977780) and the glioblastoma AGILE adaptive platform trial (NCT03970447) (27, 72). Similarly, the Neuro Master Match–N^2M^2 (NOA-20) (N^2M^2) umbrella phase I/IIa trial NCT03158389 evaluates novel therapies in a tumor-specific manner based on molecular characterization and includes combinations of targeted therapies such as palbociclib and immune checkpoint inhibitors such as atezolizumab (73, 74). These designs are increasingly used for targeted therapies to circumvent lengthy pauses between trial phases. Their usage still lags behind for immunotherapies (75).

THE IMMUNOTHERAPY CONUNDRUM FOR CENTRAL NERVOUS SYSTEM TUMORS

The CNS has been traditionally considered immune-privileged due to the presumed BBB and absence of a conventional lymphatic drainage system. These notions have been dismantled (76, 77) and refuted by immune checkpoint inhibitor therapeutic efficacy against CNS brain metastases (78, 79). This is in direct contrast with the lack of therapeutic effect of this strategy in the vast majority glioblastoma patients (80). There are multiple explanations, including infrequent expression of immune checkpoint biomarkers such as PD-1 and PD-L1 (81, 82), low tumor mutation burden and mismatch repair (83), and minimal infiltrating T cells in glioblastoma compared to other malignancies (14, 84). Furthermore, there are many redundant mechanisms of tumor-mediated immune suppression in glioblastoma (85, 86).

Immune cells in the glioblastoma microenvironment mainly consist of macrophages and microglia, which account for up to 30–50% of the total cellular composition (87). Myeloid cells predominate over lymphoid lineage cells in glioblastoma, in contrast to other solid tumors (88). Glioblastoma is known as a "cold tumor" because of its immunosuppressive TME. Possible reasons are paucity of effector T cells (89); presence of tumor-associated macrophages (TAMs); expansion of regulatory T cells; impaired antigen presentation due to impaired upregulation of major histocompatibility (MHC) class II (90); increased expression of checkpoint receptors, such as PD-1 or PD-L1, on T cells and TAMs (81); and expression of multiple immune suppressive mechanisms, such as the signal transducer and activator of transcription 3 (STAT3) (91) and indoleamine 2,3-dioxygenase (92). The T cells in glioblastoma patients are sequestered in the bone marrow (93) and are typically refractory to the restoration of effector responses regardless of the immune therapeutic strategy used (94, 95), indicating that alternative strategies will be needed for the unique immunobiology of glioblastoma.

To overcome the challenge of an immunologically cold tumor, various oncolytic viral therapies have been devised and tested (96). Oncolytic viruses are tumor selective because the tumor cells express viral entry receptors and rapid cell division in tumor cells makes it easier for the virus to replicate. Many tumor cells have deficiencies in pathways that eliminate virus, such as type I

interferon signaling through the Janus kinase (JAK)-STAT axis or cGAS-STING (cyclic GMP-AMP synthase–stimulator of interferon genes) pathway for DNA viruses (97). These viruses can induce the release of tumor-associated antigens and trigger immune activation that may ultimately confer responses to immune checkpoint inhibitors (97). Talimogene laherparepvec has received FDA approval for advanced melanoma (98). In various solid tumors (99, 100) including glioblastoma (NCT02798406), strategies include adenovirus (99), poliovirus (101), reovirus (102), and retrovirus (103), alone or in combination with immune checkpoint inhibitors. Although there have been some long-term responders, a number of challenges remain to be overcome, including clearance of virus due to host immunity, insufficient access to tumor, and infectivity throughout the TME (104). An alternative strategy is the development of STING agonists. The cGAS-STING pathway is a component of innate immunity that detects the presence of cytosolic DNA and, in response, triggers production of proinflammatory cytokines and type I interferon by myeloid cells that, in turn, trigger T cell recruitment and activation (105, 106). Although several promising STING agonists have been developed to activate macrophages in the TME, none of them have demonstrated therapeutic efficacy in early clinical trials in immune checkpoint–refractory solid tumors (107). This strategy has not been tested yet in human glioblastoma, which is markedly enriched for the cGAS-STING target myeloid immune cell population but has demonstrated marked radiographic regression of canine glioblastoma (108).

Bispecific antibodies are designed to bind to a tumor-associated antigen with one arm in order to guide and accumulate them in the TME and then to activate T cells locally via a T cell receptor agonist arm in order to engage their cytotoxic effector function against the tumor. Bispecific fully human antibodies targeting EGFRvIII and T cells have been tested in preclinical models of glioblastoma and demonstrated the ability to evoke an immune response strong enough to cure established and invasive patient-derived xenografts engrafted into the brains of mice (109). Bispecific antibodies against another glioma target, interleukin (IL)-13Rα2, have been shown to activate peripheral blood and tumor-infiltrated lymphocytes harvested directly from patients' tumors and kill glioma cells. A single injection of neural stem cells engineered to secrete this therapeutic protein directly to the tumor bed significantly improved the survival of mice bearing patient-derived glioma xenografts (110). Eventually, targeting both EGFRvIII and IL-13Rα2-expressing tumors should provide broader antigenic tumor coverage. The bispecific antibodies engaging T cells are translatable, off-the-shelf therapeutics and less costly than adoptive cellular therapies. Combined with other therapeutic modalities for maximal therapeutic efficacy, these molecules are poised to improve outcomes in patients affected by glioblastoma.

ADOPTIVE IMMUNOTHERAPY CELLULAR STRATEGIES TO OVERCOME T CELL DEFICIENCY

Lack of antigen-presenting dendritic cells (DCs) in the TME contributes to the cold tumor state, and, therefore DC immunotherapy typically utilizes DCs collected from the patient periphery or generated ex vivo from patient tissue. The DCs are then loaded with the target protein or derivative peptides or, alternatively, transduced or transfected with DNA or RNA coding for the target. Cytomegalovirus phosphoprotein 65 (CMV pp65) is widely expressed in glioblastoma and, when pulsed onto DCs, can generate potent tumor-targeted cytotoxic $CD8^+$ T lymphocyte (CTL) responses (111, 112). This strategy has been tested in multiple clinical trials and has been shown to be safe, with a signal of response in subjects (113, 114). In contrast, when adoptive CMV-specific T cells are administered to glioblastoma, there is insufficient maintenance of immune effector activity and insufficient distribution throughout the TME (115). This has now given rise to efforts to use concurrent BBB opening ultrasound in combination with either immune

checkpoint inhibitors or adoptive immunotherapy in the setting of glioblastoma since preclinical models indicate this approach enhances therapeutic activity (116). Although pp65 expression is common in the TME, it is heterogeneous. To provide additional antigenic coverage, multiepitope vaccine-based approaches have been tested in glioblastoma [e.g., in the GAPVAC trial (NCT02149225)], but it should be noted that many tumor antigens are not particularly immunogenic and fail to elicit sufficient T cell clonotypic expansion (117, 118). An alternative strategy would be targeting a shared clonal neo-epitope such as IDH1-R132H to overcome tumor heterogeneity (NCT02454634). In a phase Ib trial of neoantigen vaccination for glioblastoma, patients who generated neoepitope-specific systemic immune responses were found to have an increased level of infiltrating T cells, although these expressed multiple coinhibitory receptors (119). Synergistic effects have been observed in preclinical models where multivalent neoantigen vaccines combined with checkpoint blockade were found to generate superior efficacy, even in models with reduced anti-PD-L1 sensitivity (120). Vaccination, when combined with checkpoint blockade, has been shown preclinically to expand the memory T cell compartment, which may help to induce more durable antitumor responses (121).

As an alternative to DC vaccines, a subset of activated B cells has been identified as having potent anti-glioblastoma activity, and these B cells are a new potential source for cellular-based therapy (122). This B-cell-based vaccine induces both cellular immunity (antigen presentation and activation of T cells) and humoral immunity (production of tumor-reactive antibodies). Similar to many DC-based vaccines, B cell vaccines are pulsed with tumor lysates to act as T cell activators. In preclinical models, B cell vaccines have demonstrated high in vivo persistence, capacity to migrate to secondary lymphoid organs and tumors, and resistance to glioblastoma immunosuppressive pressure, known to inhibit function of tumor-infiltrating B cells (123). Effective therapeutic results were obtained in glioma-bearing mice treated with B cell vaccines pulsed with tumor lysates, radiation/TMZ, and PD-L1 blockade; these results lay the groundwork for eventual combinatorial clinical trials. The B cell vaccine is currently under development for clinical application.

Although there has been enthusiasm for chimeric antigen receptor (CAR) T cells in glioblastoma, clinical trials to date have shown modest effects. In the case of EGFRvIII-specific CAR T cells, tumor recurrence was associated with antigen escape (124)—similar to observations of peptide vaccine strategies 10 years earlier. The intended selective targeting of cells or spontaneous elimination of target cells at recurrence produces an outgrowth of antigen-negative cells resulting in relapse (48, 124, 125). A novel approach that may help to address heterogeneity is to use therapeutic T cells with synthetic Notch (synNotch)–controlled expression (126) or tandem CAR approaches with receptors that recognize multiple tumor antigens (127). Another approach is the development of chlorotoxin (scorpion venom protein with a high affinity for glioblastoma tumor cells) targeted CAR T cells that can engage the majority of tumor cells and mediate potent activity even in tumors lacking expression of other glioblastoma-associated antigens, resulting in tumor regression in orthotopic xenograft glioblastoma tumor models with no reported off-target effect (128). Despite these advances, CAR immunotherapy still faces significant challenges, including time to generate the product, cost, and dependence on fitness of patient T cells (which is often compromised by the disease or previous treatment).

Given the lack of glioblastoma-specific antigens, alternative adoptive immunotherapy strategies such as natural killer cell immunotherapy may overcome some barriers, since they do not require broadly expressed, tumor-specific antigens for targeting. In order to overcome their deactivation by transforming growth factor (TGF)-β, allogeneic natural killer cells were combined with either genetic or pharmacological blockade of the TGF-β pathway enabling them to elicit marked therapeutic responses in glioblastoma stem cell orthotopic preclinical models (129). Clinical trials of this strategy are now under way (NCT04489420).

DISCUSSION

Glioblastoma continues to have one of the poorest outcomes in oncology. Unique challenges, including immunosuppression and heterogeneity, remain considerable barriers to progress. Gliomas are especially prone to subclonal mutations, which can induce resistance to immune checkpoint blockade. Treatment-induced intratumoral heterogeneity and extensive steroid utilization in the glioma patient population indicate that more trials in the newly diagnosed setting are warranted. Targeted and immunotherapeutic strategies will continue to be challenged by the fundamental issues of target heterogeneity, immune suppression, immune editing, and TME distribution. Prior to proceeding to larger later-stage clinical trials, window-of-opportunity analysis can be informative, not only for drug concentrations and target engagement but also for interrogation of mechanisms of treatment resistance. After a multitude of recent phase III clinical trial failures, it is increasingly apparent that monotherapy approaches with a single targeted therapy or immunotherapy are unlikely to suffice. Novel strategies and combinations with additive or synergistic mechanisms, including conventional chemotherapy and radiotherapy as well as immunotherapies, will be required.

KEY TAKE-HOME POINTS

- Because of fundamental differences in the biology of glioblastoma relative to other malignancies, we cannot necessarily apply or extrapolate from therapeutic approaches or biomarkers used in other malignancies
- Immune therapeutics need to consider modulation of other antitumor immune effector populations besides T cells for glioblastoma or devise strategies that enrich the T cells in the TME.

DISCLOSURE STATEMENT

M.K. reports grants from BMS and grants and personal fees from AbbVie, as well as personal fees from Roche, Ipsen, Specialized Therapeutics, Janssen, and JAX lab for genomic research. C.L.-C. has a pending international patent application on BVax for the treatment of glioblastoma and other cancers. I.V.B. has a patent on IL-13Rα2 binding agents and their use in cancer treatment. A.B.H. receives monetary reimbursement for serving on the scientific advisory board of Caris Life Sciences and WCG Oncology Advisory Board, has received research support from Codiak Biosciences and Celularity, has received royalty payments from Celldex Therapeutics and DNAtrix, and has received nonfinancial clinical trial support from Moleculin.

ACKNOWLEDGMENTS

This study was supported in part by National Institutes of Health grants R37CA258426 (C.L-C.), R33NS101150 (I.V.B.), R01 NS106379 (I.V.B.), R01 NS122395 (I.V.B.), 5P50CA190991 (A.B.H.), R01CA120813 (A.B.H.), R01 NS120547 (A.B.H.), and the Remisson Alliance (A.B.H.).

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