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Dual Antagonism of FGF2 and CSF1 by Computationally Designed Peptide-Ligand Conjugates for Targeted Glioblastoma Therapy

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Abstract

The cold brain tumor glioblastoma is one of the aggressive cancers that display infiltrative cells and chemoresistance. The reference treatment with Temozolamide unveiled a significant survival rate, while the specific targeted therapy, such as monoclonal antibodies, is hindered by impermeability through the blood-brain barrier. The present study aims to utilize the pharmacology of peptide-ligand conjugates (PLC) as a preferable targeted option for such a complex type of cancer. GGKRPAR and RPARPAR peptides were selected as carriers for antitumor natural products involving gingerol, mangiferin, quercetin, epigallocatechin gallate (EGCG), and curcumin. The ChemOffice 15 package was employed for linking, energy minimization, and DFT calculations. Afterward, docking to two novel targets, FGF2 and CSF1, followed by toxicity and allergenicity assessment. Results showed high docking scores against both targets in the range -7 to -8 kcal/mol. Numerous H-bonds, salt bridges, and hydrophobic forces account for the high docking scores. Furthermore, both peptide carrier was predicted to be safe in terms of toxicity as well as allergenicity. In conclusion, the dual-inhibiting, targeted therapy glorified in the present study shows potential promise in silico against glioblastoma, deserving in vitro as well as in vivo validation assays.

Keywords: Glioblastoma, Peptide-ligand conjugate, Natural products, Molecular docking

Introduction

Glioblastoma (GBM), categorized as a grade IV astrocytoma, represents an extremely aggressive form of brain tumor. It is characterized by a diverse array of genetically unstable and deeply infiltrative cells that exhibit resistance to chemotherapy (Mercatelli *et al*., 2017; Thakur *et al*., 2022; Lobach *et al*., 2023). Relying solely on surgical intervention is typically inadequate for the management of GBM due to the formidable challenge of complete tumor resection without causing harm to the surrounding healthy brain tissue. Given the cytological heterogeneity of GBM, a frequently employed approach known as optimal multimodality therapy encompasses surgical intervention coupled with chemotherapy and radiotherapy. Despite extensive endeavors aimed at establishing the most effective treatment regimens, GBM patients generally exhibit a grim prognosis, frequently experiencing tumor progression resulting in high mortality rates, with a median survival duration of only 12 to 15 months (Meng *et al*., 2018; Pinel *et al*., 2019). The established treatment protocol for GBM encompasses several key components: thorough surgical resection to the extent deemed safe, radiotherapy (RT), and chemotherapy utilizing the alkylating agent known as temozolomide (TMZ) (Weller *et al*., 2013). Within this regimen, both RT and TMZ exert their effects by initiating the demise of apoptotic cells through the induction of DNA double strand breaks (DSBs), thereby effectively targeting and eliminating GBM cells (Liu *et al*., 2022; Thabiani *et al*., 2022; Marian *et al*., 2024).

GBM displays three prominent pathways that are subject to dysregulation: firstly, the receptor tyrosine kinases (RTKs)/Ras/phosphatidylinositol 3-kinase (PI3K) pathway, which displays alterations in approximately 88% of GBM patients (Qin *et al*., 2021); secondly, the p53 pathway, exhibiting changes in 87% of patients (Zhang *et al*., 2018); and thirdly, the RB pathway, demonstrating alterations in 78% of patients (Chkheidze *et al*., 2021; Yurievna *et al*., 2023; Prada *et al*., 2024). Through a more extensive examination of sample data, it has been discerned that the most frequent amplification events on GBM chromosomes involve chromosome 7 (housing EGFR/MET/CDK6), chromosome 12 (encompassing CDK4 and MDM2), and chromosome 4 (containing PDGFRA). These pathway alterations serve as crucial discriminators for distinguishing between molecular and epigenetic subtypes of GBM, thereby contributing significantly to the development of targeted therapeutic approaches designed to impact clinical outcomes and the responsiveness of individual tumors to treatment (Yuan *et al*., 2022).

The aggressive and recurrent nature of glioblastoma is multifactorial and has been attributed to its biological heterogeneity, dysfunctional metabolic signaling pathways, rigid blood–brain barrier, inherent resistance to standard therapy due to the stemness property of the gliomas cells, immunosuppressive tumor microenvironment, hypoxia and neoangiogenesis which are very well orchestrated and create the tumor's own highly pro-tumorigenic milieu (Lapointe *et al*., 2018; Spirito *et al*., 2022; Kushkhova *et al*., 2024). Once the relay of events starts amongst these components, eventually it becomes difficult to control the cascade using only the balanced contemporary care of treatment consisting of maximal resection, radiotherapy, and chemotherapy with temozolamide. Over the past few decades, the implementation of contemporary treatment modalities has shown benefit to some extent, but no significant overall survival benefit has been achieved. Therefore, there is an unmet need for advanced multi-faceted combinatorial strategies (Asija *et al*., 2022; Soininen & Valkama, 2022; AlHussain *et al*., 2023).

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The molecular diversity within GBM and the intricate nature of the human brain's anatomy pose significant challenges to the efficacy of drug treatments. However, the horizon for GBM research and drug development has been brightened by the emergence of innovative therapeutic strategies. These include cutting-edge approaches such as multi-specific 'off-the-shelf' cancer antigen receptor T cell (CAR-T) therapy, oncolytic viral therapy, and autologous dendritic cell vaccination (Waldman *et al*., 2020; Alharbi *et al*., 2022; Cui *et al*., 2023). While targeted therapy clinical trials have yielded discouraging outcomes, primarily due to the intricate interplay of signaling pathways and biological processes that drive drug resistance, it is now imperative to explore combination therapies and multi-modal treatment approaches (Gatto *et al*., 2023). One of the promising targeted therapies against GBM is the use of specific peptides to both deliver drugs and natural bioactive ligands and target them to the desired cancerous tissues. The formed complex is called a peptide-ligand conjugate (PLC) (Yang *et al*., 2022; Malinga & Laing, 2024; Perez *et al*., 2024).

This study sought to engineer first-in-class, dual-targeting PLCs as a transformative therapeutic paradigm for GBM. The central hypothesis is to achieve a synchronized, multi-mechanistic attack by directly inhibiting the pro-tumorigenic FGF2 signaling hub to induce cancer cell death, while simultaneously antagonizing the CSF1 pathway to disrupt the tumor's immunosuppressive niche. This approach employs the rational fusion of bioactive natural products with specialized brain-penetrating peptide carriers, a strategy critical for overcoming the fundamental limitation of BBB impermeability and ensuring the delivery of stabilized, targeted therapeutics with enhanced pharmacokinetic profiles, ultimately seeking to significantly outperform the singular efficacy of current standard-of-care treatments.

Materials and Methods

Study Design

The present study was designed via consecutive steps, deploying various programs and online servers to achieve the mentioned goals. The deployed strategy is illustrated in **Figure 1**.

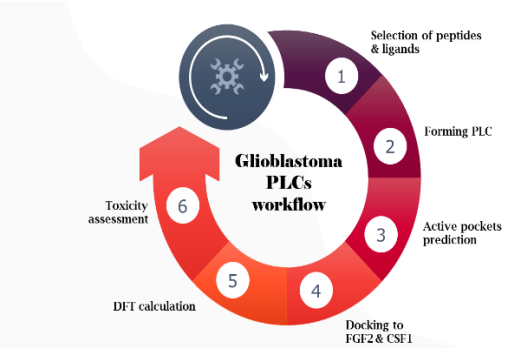


Figure 1. The main workflow for the design of this multi-step in silico study

Selection of Peptides and Ligands

The selection of the peptide is based on evidence from previous reports (Rico *et al*., 2022) indicating that these peptides are effective targeting molecules for brain cancers. Namely, two peptides, GGKRPAR and RPARPAR, were selected as carriers of the natural inhibitors of cancers (López-Martínez *et al*., 2022; Lambo *et al*., 2023). On the other hand, the natural ligands (flavonoids) were selected in essence of their reactivity against several types of cancers including GBM, namely, curcumin (Tomeh *et al*., 2019; Baldi *et al*., 2020; Ojo *et al*., 2022; Kinareikina & Silivanova, 2023), gingerol (Nafees *et al*., 2021; Zivarpour *et al*., 2021; Wala *et al*., 2022), epigallocatechin gallate (EGCG) (Bimonte *et al*., 2020; Chen *et al*., 2020; Ferrari *et al*., 2022), mangiferin (Mei *et al*., 2021; Morozkina *et al*., 2021; Maenpuen *et al*., 2023), and quercetin (Tang *et al*., 2020; Asgharian *et al*., 2022; Lotfi *et al*., 2023).

Forming Peptide-Ligand Conjugates

The chemical structure of the selected peptides, as well as the natural ligands, was drawn using ChemDraw v. 2020. The linkage between the peptide and the natural ligands was through the formation of an ester bond between the carboxyl terminus of the peptides and the active hydroxyl groups of the ligands (only single-substitution was conducted). This represented the 2D structure, which was then imported to the Chem3D program to get the corresponding 3D architecture, followed by the MM2 energy minimization.

Molecular Docking

The prepared 3D structures of the PLC were then ready for molecular docking to two emerging receptors of GBM, fibroblast growth factor 2 (FGF2) and colony-stimulating factor 1 (CSF1). The two receptor crystal structures were downloaded from the Protein Data Bank (PDB) using the PDB accession codes 2FGF (Zhang *et al*., 1991) and 4WRL (Felix *et al*., 2015). All non-standard molecules were removed from the PDB file, followed by the addition of polar hydrogens and Gasteiger charges. These processes were performed through UCSF Chimera v.1.16. The receptors and the PLC were submitted to the DockThor web server (https://dockthor.lncc.br/v2/) (Guedes *et al*., 2021) to carry out the docking process. The docking options were selected as standard docking with 1.000.000 evaluations, population size of 750, and a number of runs of 24 via blind docking. These protocols were conducted after prediction and subsequent selection of the most potent active pocket to which docking will be done. This was accomplished through the DogSite 3 tool (https://proteins.plus/) belonging to the Proteins Plus portal (Graef *et al*., 2023).

DFT Calculation

The designed PCLs were investigated for their highest-occupied molecular orbitals (HOMO), lowest-unoccupied molecular orbitals (LUMO), and the gap between them (ΔE) in order to assess the reactivity/stability of the designed PCLs. This was accomplished by deploying Chem3D v. 2020.

Toxicity Profile

The potential toxicity of the two carrier peptides was predicted by using ToxinPred 3 web server

(https://webs.iiitd.edu.in/raghava/toxinpred3/index.html) (Rathore *et al*., 2024), whereas AllerCatPro 2.0 tool (https://allercatpro.bii.a-star.edu.sg/) (Nguyen *et al*., 2022) was used to assess the allergenicity. Default options were chosen for both servers.

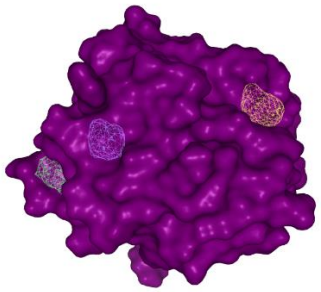
Results and Discussion

Active Pocket Prediction

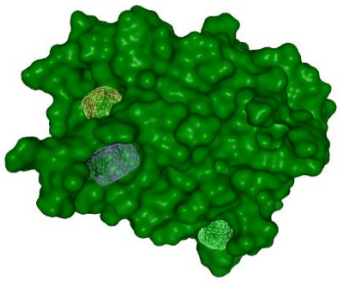
We obtained 3 major pockets of FGF2 occupying volumes of 41.98, 29.7, and 27.65. The surfaces of them are 213.42, 138.66, and 254.8 while the corresponding depths are 5.43, 4.38, and 4.93, respectively. Similarly, CSF1 pockets predicted using DogSite 3 were summarized in **Table 1**, including the volume, surface area, and depth of each pocket. The corresponding pockets are visualized in **Figure 2**.

Table 1. Predicted active pocket that can serve as a potential docking site, along with their volume, surface, and depth of the two targets

Receptor	Pocket	Volume (Å^3)	Surface (Å^2)	Depth (Å)
FGF2	P_1	41.98	213.42	5.43
	P_2	29.7	138.66	4.38
	P_3	27.65	254.8	6.08
CSF1	P_1	86.53	196.49	6.65
	P_2	83.46	245.91	5.77
	P_3	69.12	295.05	6.14



a)



b)

Figure 2. Three-dimensional visualization of the predicted pockets of the two targets: FGF2 (a) and CSF1 (b).

Docking

It is obvious from **Table 2** that the peptides belonging to sequence 1 are more potent than the conjugates bridged to sequence 2 in terms of binding affinity toward the GBM druggable target FGF2. The binding affinity of the sequence 1 conjugates ranges from -7.49 to -8.62 kcal/mol, while PCL 2 conjugates range from -6.76 to -7.72 kcal/mol. This is indicative of the partial involvement of the peptide carrier in the binding to the receptor besides the natural ligand payload. Quercetin bound to both sequences was the most powerful PCL FGF2 antagonist.

Table 2. The docking scores of the two PLC families against FGF2 ranked according to the binding affinity

No.	PCL1	Binding affinity	No.	PCL2	Binding affinity
1	Quercetin	-8.622	1	Quercetin	-7.728
2	EGCG	-7.963	2	Curcumin	-7.637
3	Mangiferin	-7.615	3	Gingerol	-7.203
4	Gingerol	-7.545	4	Mangiferin	-6.802
5	Curcumin	-7.49	5	EGCG	-6.767

On the flip side, CSF1 docking of the two sets of PCLs was relatively comparable, albeit the PCL2 set was slightly higher than the PCL1. The binding affinity of the two PCL sets is provided in **Table 3**. Curcumin in the PCL1 set was the most potent lead candidate (binding affinity -8.38 kcal/mol) when compared to the other conjugates. Conversely, EGCG was the top-ranked PCL as CSF1 antagonist with a binding affinity of -8.81 kcal/mol.

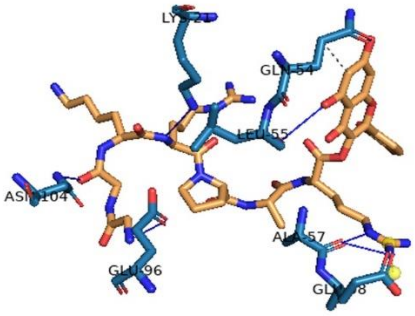
Table 3. The docking scores of the two PLC families against CSF1 ranked according to the binding affinity

No.	PCL1	Binding affinity	No.	PCL2	Binding affinity
1	Curcumin	-8.385	1	EGCG	-8.819
2	EGCG	-8.099	2	Mangiferin	-8.294
3	Gingerol	-8.058	3	Quercetin	-7.954
4	Mangiferin	-7.181	4	Gingerol	-7.402
5	Quercetin	-6.991	5	Curcumin	-7.038

Interaction Investigation

The interaction between PLC and the FGF2 protein involved various types of bonds and attractions, including hydrophobic interactions, hydrogen bonds, and ionic interactions (salt bridges). For example, the interaction between quercetin and FGF2 involved the formation of 8 H-bonds with Lys 21, Gln 54, Leu 55, Ala 57 (2 H-bonds), Glu 96 (2 H-bonds), and Asn 104. Additionally, a hydrophobic attraction with Gln 54 as well as a salt bridge with Glu 58. Similarly, quercetin 2 formed 10 H-bonds with the same amino acids besides Arg 97, Leu 98, Tyr 106, and Arg 107. Two hydrophobic interactions and two salt bridges were constituted with Ala 57, Arg 60, and Glu 96, respectively. On the flip side, curcumin 1, four H-bonds with Gln 26, Glu 36, Asp 59, and Lys 100, two salt bridges with Glu 62 and Asp 63 were observed. EGCG 2, on the other hand, is richer in interactions compared to curcumin 1 in terms of the number of H-bonds (8 vs 4), salt bridges (3 vs 2), and the presence of hydrophobic interaction. The detailed

interactions of the best four complexes as predicted through the PLIP server are depicted in **Figure 3**.



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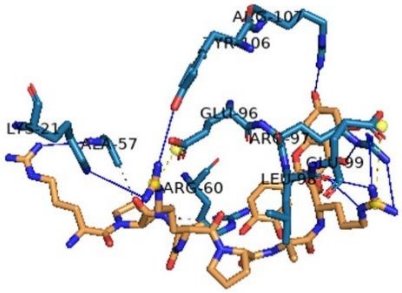

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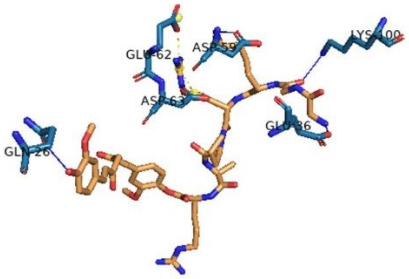

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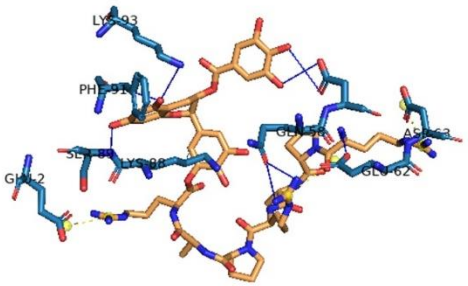

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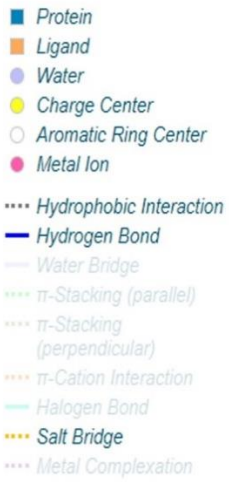
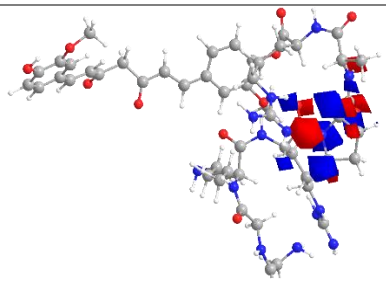
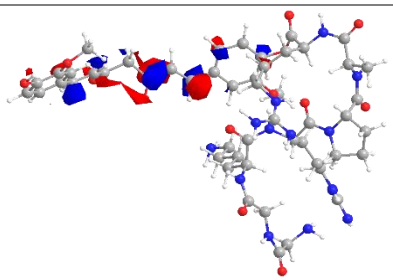


Figure 3. 3D representation of the best PLCs against FGF2 (a, b) and CSF1 (c&d), along with the legend showing the type of interaction

DFT

The DFT calculations of the best potential PLC were analyzed and summarized in **Table 4**. Results have shown that the HOMO of curcumin PLC2 was -10.117 eV, while its LUMO was -5.709 eV. Hence, the energy gap (ΔE) was 4.408 eV, which is considered a quite large energy gap reflecting a great stability profile.

Table 4. DFT calculations of curcumin PLC2 showing the respective HOMO, LUMO, and the energy gap

PCL	HOMO	LUMO	ΔE
Curcumin 2			4.408 eV
	-10.117 eV	-5.709 eV	

Toxicity and allergenicity profile

Both carrier peptides (GGKRPAR and RPARPAR) displayed no toxicity nor allergenicity against the available data. The obtained findings are theoretically accurate, given the high confidence (E-value < 0.001) and the high threshold (0.5).

As a result of the immune-deficient nature of the brain, neurologists have classified GBM as a "cold tumor," where existing immunotherapies have not yielded definitive survival benefits. Compounding this complexity is the formidable presence of the blood-brain barrier (BBB), which constrains drug access to the brain, consequently restricting available therapeutic avenues. Consequently, extensive endeavors are currently underway to advance the creation of innovative nanomedicines capable of traversing the BBB and selectively homing in on cancer cells, thus addressing this formidable challenge in glioblastoma treatment (Mo *et al*., 2021; Yeini *et al*., 2021).

In response to certain constraints associated with small-molecule drugs, alternative chemotherapeutic agents have been devised, employing a peptide-linked mechanism known as peptide drug conjugates (PDCs). These PDCs, akin to ADCs (Antibody-Drug Conjugates), consist of three essential components: (i) a peptide carrier, (ii) a cytotoxic payload, and (iii) a linker. In essence, the peptide carrier serves to enhance tumor targeting, the payload (which is the therapeutic element) supports anti-cancer biological effects, and the linker establishes the connection between the peptide carrier and the payload (Fu *et al*., 2023; Heh *et al*., 2023).

We aimed to develop a new targeted therapy for glioblastoma by linking natural compounds to brain-penetrating peptides. Our strategy is unique because it addresses two problems at once: it directly targets the FGF2 protein in cancer cells while also blocking CSF1, which suppresses the immune system around the tumor. This dual approach could potentially overcome the limitations of current treatments by simultaneously fighting the cancer and boosting the body's natural defenses against it.

From the obtained docking output, a clear and target-dependent profile of efficacy emerges for the two PCLs. For the FGF2 target, the PCL1 series demonstrated superior binding affinity compared to PCL2, suggesting the peptide carrier in PCL1 plays a partial role in receptor binding, with Quercetin conjugates being the most potent FGF2 antagonists across both sequences. In contrast, for the CSF1 target, the binding affinities of both PCL sets were relatively comparable, with PCL2 exhibiting a slight advantage; here, the most potent leads were target-specific, as Curcumin in the PCL1 set and EGCG in the PCL2 set emerged as the top-ranked CSF1 antagonists.

Next, the types of bonds and forces that contribute to the docking score were explored. The molecular interactions underpinning the binding of the PLCs to the FGF2 target were deconstructed to reveal a sophisticated and multi-valent binding architecture, dominated by an extensive network of hydrogen bonds, strategic hydrophobic contacts, and stabilizing salt bridges. This is epitomized by the Quercetin conjugates, which act as molecular anchors by forming a dense web of up to 10 highly specific hydrogen bonds, complemented by hydrophobic interactions and critical salt bridges with key residues. The comparative analysis further illuminates a direct correlation between binding robustness and interaction complexity; for instance, EGCG 2, with its richer tapestry of bonds compared to the more sparsely interacting Curcumin 1, demonstrates how superior affinity is achieved through synergistic, multi-modal contact. This intricate characterization moves beyond mere docking scores, providing a definitive structural rationale for the observed potency and revealing the precise chemical blueprint for high-affinity antagonism, thereby establishing a foundational framework for the rational design of next-generation FGF2 inhibitors.

Regarding the energy gap (ΔE) of curcumin 2, it was calculated to be 4.408 eV, which is considered quite large and reflects a high stability profile. This means that it requires a significant amount of energy (4.408 eV) to excite an electron from the highest occupied orbital to the lowest unoccupied one. This makes the molecule unreactive in processes that involve this kind of electron excitation (Nakata & Tsuneda, 2013). Accordingly, this PLC is likely stable and not prone to uncontrolled decomposition or reaction under ambient conditions. It will not readily participate in reactions that involve its π-system or frontier orbitals.

Both carrier peptides (GGKRPAR and RPARPAR) were predicted to be safe in terms of toxicity as well as allergenicity.

All of the discussed results of the present in silico study suggest it as a promising strategy to combat such an aggressive form of brain tumor. Our unique idea was to create something new – molecular carriers by attaching these natural compounds to special peptides that can carry them into the brain. But we didn't stop there. We designed them to address two major problems in glioblastoma simultaneously. First, they directly target FGF2, a key protein that drives the cancer cells themselves (Przystal *et al*., 2021). Second, and this is the really clever part, they also target CSF1, which is like cutting the fuel line to the immune-suppressing cells that protect the tumor (Naik *et al*., 2025). Thus, it is considered a one-two punch.

Conclusion

In summary, this study successfully demonstrates the rational design and in silico investigation of novel peptide-ligand conjugates (PLCs) as promising therapeutic candidates against glioblastoma. By strategically conjugating antitumor natural products to brain-penetrating peptide carriers, we have engineered a class of molecules that effectively surmounts the critical challenge of blood-brain barrier impermeability, which plagues conventional targeted therapies. The robust binding affinities, substantiated by multi-faceted molecular interactions with the druggable targets FGF2 and CSF1, coupled with favorable safety profiles, underscore the therapeutic potential of this approach. These computationally optimized PLCs represent a significant stride beyond the limitations of temozolomide, laying a solid foundation for the development of a new generation of targeted, effective, and safe treatments for this devastating malignancy. Following the computational validation, the therapeutic potential of the lead conjugates should be assessed through a tiered experimental pipeline. In vitro, their binding affinity and target engagement must be confirmed via surface plasmon resonance against FGF2 and CSF1R, followed by functional assays in patient-derived glioblastoma stem cells to evaluate cytotoxicity,

clonogenic inhibition, and downstream pathway suppression. Concurrently, an in vitro blood-brain barrier model using human brain microvascular endothelial cells will validate enhanced permeability. For in vivo translation, biodistribution and efficacy should be tested in orthotopic glioblastoma mouse models, in which systemic administration of the conjugates will be evaluated for brain tumor accumulation, inhibition of tumor growth via bioluminescence imaging, and, ultimately, a significant survival benefit.

AI usage

This study used DeepSeek AI to enhance language and grammar only

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Conflict of interest: None

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Ethics statement: None

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