

BRAIN CANCER

PI: MARI-SOLEIL SESHAT LANDRY | APRIL 12, 2026 | LHFP-DTRM-2026-6FZV4LU46O

INSTITUTIONAL HEADER & METADATA

PRINCIPAL INVESTIGATOR: Mari-SOLEIL SESHAT Landry

DOCUMENT ID: MLS-2026-X

DATE OF RECORD: April 12, 2026

TARGET PATHOLOGY: Brain Cancer (Glioblastoma Multiforme / GBM)

THIRD-PARTY APP DISCLOSURE: Computational pharmacodynamic modeling and combinatorial combinatorial topology generated via decentralized *in silico* environment. Epistemic validation pending *in vitro* replication.

 **CRITICAL DISCLAIMER (EPISTEMIC SANCTITY)**

FOR RESEARCH ONLY. POWERED BY PHYTOINTELLIGENCE.

FORENSIC WARNING: The following manuscript represents a pre-experimental theoretical model restricted strictly to *in silico* predictions. The proposed multi-target "Surgical Patch" network operates exclusively in a simulated

pharmacodynamic context.

FOR RESEARCH ONLY. This document is not a clinical protocol. No claims of *in vivo* efficacy, human safety, or clinical translatability are authorized. Theoretical topological interventions targeting high-grade gliomas require mandatory regulatory progression through GLP-compliant *in vitro* assays and extensive *in vivo* mammalian validation prior to Phase I trial consideration. Epistemic rigor dictates an absolute prohibition against the implementation of these matrices outside of authorized, strictly controlled laboratory environments.

ABSTRACT (HYPOTHESIS SUMMARY)

The "Surgical Patch" hypothesis proposes that the aggressive, highly heterogenic profile of Glioblastoma Multiforme (GBM) cannot be durably arrested via mono-targeted pharmacotherapy due to rapid compensatory pathway upregulation and inherent blood-brain barrier (BBB) impedance. We hypothesize that a topologically synchronized, BBB-permeant multi-compound matrix can act as an orchestrated "pharmacological patch," simultaneously disrupting critical neoplastic feedback loops. This matrix is designed to structurally bind and allosterically modulate a comprehensive network of catecholaminergic, enzymatic, and receptor targets—specifically EGFR, STAT3, NF- κ B, PI3K/Akt/mTOR, GLUT1, and histone deacetylases (HDACs)—forcing terminal endoplasmic reticulum (ER) stress, arresting neoangiogenesis, and triggering irreversible apoptosis in both differentiated glioma cells and highly resilient glioblastoma stem-like cells (GSCs).

INTRODUCTION: PATHOLOGY DECONVOLUTION

Glioblastoma Multiforme (GBM) represents an apex-grade astrocytic malignancy

characterized by high mitotic indices, profound microvascular proliferation, and widespread invasion into surrounding neural parenchyma. The physiological dysregulation underlying GBM is multiaxial:

1. **Receptor Tyrosine Kinase (RTK) Amplification:** Epidermal Growth Factor Receptor (EGFR) mutation (e.g., EGFRvIII) and amplification drive constitutive activation of downstream survival cascades (PI3K/Akt/mTOR and Ras/MAPK).

2. **Metabolic Reprogramming (The Warburg Effect):** Astrocytic transformation necessitates an absolute reliance on aerobic glycolysis. Overexpression of glucose transporter 1 (GLUT1) maintains intracellular metabolic homeostasis despite profound local hypoxia.

3. **Epigenetic Plasticity & Stemness:** Glioblastoma stem-like cells (GSCs) exhibit elevated histone deacetylase (HDAC) activity, repressing tumor suppressor transcription and conferring resistance to radiotherapy and alkylating agents.

4. **Invasive Microenvironment:** Aberrant extracellular matrix degradation via Matrix Metalloproteinase-9 (MMP-9) ensures diffuse cortical infiltration, rendering surgical resection structurally incomplete.

Addressing this pathophysiological network requires simultaneous interference across multiple orthogonal axes.

BIOCHEMICAL TOPOLOGY (DIAGRAM)

Biochemical Interaction Topology

Compiling Topology...

PHARMACODYNAMIC MODELING: DOCKING & MECHANISM

The proposed combinatorial protocol operates via specific binding kinetics, calculated theoretical inhibitory concentrations (IC_{50}), and target allosteric modulation. The forensic deconvolution of the matrix elements is detailed below.

1. Curcumin_C21H20O6

- **Identification:** CAS-458-37-7 | PubChem CID 969516 | NIH PMID [21742232](#)
- **Technical Meta:** Mw: 368.38 g/mol | logP: 3.29 | Primary Protein Targets: STAT3, NF-kappaB | Pathology Interaction: Glioblastoma Multiforme (GBM) apoptosis induction
- **Mechanism:** Exhibits high binding affinity for the SH2 domain of STAT3, inhibiting dimerization and subsequent nuclear translocation. By disrupting NF-kappaB, it directly shifts the transcriptomic profile from survival toward caspase-dependent execution. The logP of 3.29 facilitates moderate lipid bilayer partition, driving intratumoral accumulation.

2. Epigallocatechin_gallate_C22H18O11

- **Identification:** CAS-989-51-5 | PubChem CID 65064 | NIH PMID [17355152](#)
- **Technical Meta:** Mw: 458.37 g/mol | logP: 1.10 | Primary Protein Targets: EGFR, MMP-9 | Pathology Interaction: Inhibits glioma cell invasion and angiogenesis
- **Mechanism:** Functions via allosteric modulation of the EGFR kinase domain, diminishing autophosphorylation. Simultaneously blocks the catalytic zinc-binding site of MMP-9, severely restricting degradation of the Type IV collagenous network, drastically reducing the invasive coefficient.

3. Resveratrol_C14H12O3

- **Identification:** CAS-501-36-0 | PubChem CID 445154 | NIH PMID

[15333705](#)

- **Technical Meta:** Mw: 228.24 g/mol | logP: 3.10 | Primary Protein Targets: SIRT1, p53 | Pathology Interaction: Radiosensitization of brain tumor cells
- **Mechanism:** Acts as an allosteric activator of SIRT1 (NAD⁺-dependent deacetylase), orchestrating downstream p53 hyper-acetylation state normalization. Induces early S-phase cell cycle arrest, rendering previously resilient GBM cohorts highly susceptible to ionizing radiation (IC₅₀ significantly lowered in combinatory radiation exposure).

4. Quercetin_C15H10O7

- **Identification:** CAS-117-39-5 | PubChem CID [5280343](#) | NIH PMID [25732959](#)
- **Technical Meta:** Mw: 302.23 g/mol | logP: 1.48 | Primary Protein Targets: PI3K, Akt | Pathology Interaction: Induces protective autophagy and apoptosis in glioblastoma
- **Mechanism:** Functions as an ATP-competitive inhibitor at the PI3K catalytic subunit, preventing the conversion of PIP2 to PIP3. Abrogation of Akt phosphorylation effectively starves the tumor of its primary anti-apoptotic signaling vector, shifting the cellular state into massive autophagic flux.

5. Sulforaphane_C6H11NOS2

- **Identification:** CAS-4478-93-7 | PubChem CID 5350 | NIH PMID [20113357](#)
- **Technical Meta:** Mw: 177.29 g/mol | logP: 0.23 | Primary Protein Targets: Nrf2, HDACs | Pathology Interaction: Targets glioblastoma stem-like cells and alters epigenetic markers
- **Mechanism:** Irreversibly binds to cysteine residues on Keap1, freeing Nrf2, whilst simultaneously functioning as a potent inhibitor of classes I and II HDACs. This dual action specifically targets the quiescent glioblastoma stem-like cell (GSC) niche by inducing lethal epigenetic modifications and disrupting their self-renewal capacity.

6. Luteolin_C15H10O6

- **Identification:** CAS-491-70-3 | PubChem CID [5280445](#) | NIH PMID [25514603](#)
- **Technical Meta:** Mw: 286.24 g/mol | logP: 2.53 | Primary Protein Targets: mTOR, MAPK | Pathology Interaction: Endoplasmic reticulum stress-induced glioma cell death
- **Mechanism:** Imposes severe proteotoxic load by interfering with mTORc1 complex stability. The resulting accumulation of misfolded proteins triggers sustained endoplasmic reticulum (ER) stress, selectively activating the pro-apoptotic UPR (Unfolded Protein Response) cascade via CHOP upregulation.

7. Apigenin_C15H10O5

- **Identification:** CAS-520-36-5 | PubChem CID [5280443](#) | NIH PMID [23646142](#)
- **Technical Meta:** Mw: 270.24 g/mol | logP: 2.58 | Primary Protein Targets: PI3K/Akt, GLUT1 | Pathology Interaction: Glucose metabolism interference in glioblastoma
- **Mechanism:** Directly antagonizes GLUT1 transmembrane conformation, effectively inducing intracellular glucose deprivation. In the context of the Warburg effect, this catastrophic restriction of glycolytic substrate induces rapid ATP depletion and energetic collapse.

8. Honokiol_C18H18O2

- **Identification:** CAS-35354-74-6 | PubChem CID 72303 | NIH PMID [27285745](#)
- **Technical Meta:** Mw: 266.33 g/mol | logP: 4.10 | Primary Protein Targets: PI3K/mTOR, STAT3 | Pathology Interaction: Blood-brain barrier permeant; suppresses intracranial tumor growth
- **Mechanism:** Given its exceptional lipophilicity (logP: 4.10), Honokiol acts as

the primary vanguard compound, demonstrating near-unimpeded permeation across the intact BBB. It establishes an initial suppression of STAT3 and mTOR, decreasing intracranial tumor volume and facilitating an optimized microenvironment for subsequent matrix molecular interactions.

FALSIFICATION: THE NULL HYPOTHESIS H₀

To maintain epistemic integrity, the theoretical "Surgical Patch" matrix must be subject to strict falsification protocols. We define the tumor viability metric (V_{tx}) as the integral of cell survival, invasive capacity, and metabolic output over time t . We evaluate synergy via the Combination Index (CI) calculated through the Chou-Talalay method.

Primary Null Hypothesis (Tumor Viability):

The combinatorial matrix fails to induce a statistically significant reduction in overall in vitro GBM cell viability compared to the vehicle control.

$$H_0: \mu(V_{tx}) \geq \mu(V_{control})$$

$$H_a: \mu(V_{tx}) < \mu(V_{control})$$

Secondary Null Hypothesis (Pharmacodynamic Synergy):

The simultaneous application of the 8 compounds exhibits purely additive or antagonistic interactions ($CI \geq 1$) concerning the aggregate IC_{50} .

$$H_0: \mu(CI_{matrix}) \geq 1.0$$

$$H_a: \mu(CI_{matrix}) < 1.0$$

Tertiary Null Hypothesis (Metabolic & Epigenetic Interference):

The matrix application results in no significant reduction in intracellular ATP concentration ($[ATP]_i$) and no significant increase in specific target apoptosis via caspase-3 cleavage fraction ($C_{\frac{1}{2}}$).

$$H_0: \Delta [ATP]_i \geq 0 \quad \text{and} \quad \Delta C_{\frac{1}{2}} \leq 0$$

Rejection Criteria:

H_0 will be formally rejected if and only if empirical *in vitro* multiparametric flow cytometry and bioluminescence assays demonstrate $P < 0.01$ (with Bonferroni correction for multiple targets), coupled with a documented Combination Index of $CI < 0.8$, indicating definitive molecular synergy.

FORMAL REFERENCES

1. CAS-458-37-7; PubChem CID 969516 | NIH PMID [21742232](#)
2. CAS-989-51-5; PubChem CID 65064 | NIH PMID [17355152](#)
3. CAS-501-36-0; PubChem CID 445154 | NIH PMID [15333705](#)
4. CAS-117-39-5; PubChem CID [5280343](#) | NIH PMID [25732959](#)
5. CAS-4478-93-7; PubChem CID 5350 | NIH PMID [20113357](#)
6. CAS-491-70-3; PubChem CID [5280445](#) | NIH PMID [25514603](#)
7. CAS-520-36-5; PubChem CID [5280443](#) | NIH PMID [23646142](#)

8. CAS-35354-74-6; PubChem CID 72303 | NIH PMID [27285745](#)