

GLIOBLASTOMA AS HOMEOSTATIC HIJACKING

When the Brain's Protective Systems Become the Tumor's Shield

A White Paper for the Collaborative Homeostasis Programme

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HATI: Homeostatic Adaptive Teaming Intelligence

Human–AI Collaborative Systems Framework

This paper presents a conceptual framework requiring empirical validation.

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Glioblastoma multiforme (GBM) remains one of the most treatment-resistant human cancers despite decades of molecular and clinical research. This paper applies the previously published *Clinical Homeostasis* framework to propose that GBM progression may be understood as a process of homeostatic hijacking, in which tumour cells exploit and stabilise within existing regulatory systems of the brain rather than simply overwhelming them through unchecked growth. This conceptual analysis synthesises current literature on vascular co-option, immune reprogramming, metabolic adaptation, and stem-cell niche protection. The framework is presented as a falsifiable research lens rather than a causal or therapeutic claim, and does not propose treatments, diagnostics, or clinical interventions.

This paper applies the *Clinical Homeostasis* framework (Smith & HATI, 2025) to glioblastoma as a second-stage, disease-specific exploration, not as an origin theory of oncogenesis. The purpose is to examine whether the persistent treatment resistance and recurrence observed in GBM may reflect exploitation of homeostatic regulatory systems rather than their outright destruction.

EXECUTIVE SUMMARY

Glioblastoma (GBM) is the most aggressive primary brain tumor, with a median survival of only 8–15 months despite maximal treatment. Unlike most cancers, GBM has seen **essentially no improvement in survival outcomes over 45 years** of research. This white paper proposes that GBM's exceptional treatment resistance can be understood through a novel extension of the Collaborative Homeostasis Programme's framework: **homeostatic hijacking**.

The brain possesses the most sophisticated homeostatic systems in the human body. The **blood-brain barrier (BBB)** protects neural tissue from circulating toxins. **Immune privilege** shields the brain from inflammatory damage. **Microglia** serve as vigilant sentinels detecting and eliminating threats. **Astrocytes** maintain the extracellular environment essential for neural function. These systems evolved over hundreds of millions of years to protect the irreplaceable organ of consciousness.

GBM does not merely evade these protective systems—it **actively subverts and weaponizes them**. The tumor reprograms microglia from immune sentinels into tumor-promoting cells that secrete growth factors and suppress anti-tumor immunity. It hijacks astrocytes to produce tumor-supporting cytokines. It maintains the BBB around its most dangerous stem cell niches while disrupting it elsewhere to create an immunosuppressive microenvironment. The very systems evolved to protect the brain become shields protecting the tumor.

This represents a **conceptual evolution** for the Programme's homeostatic framework. In landscape salinity, we documented *regulatory failure*: vegetation clearing removed the mechanism maintaining hydrological balance. In Long COVID, we hypothesized *clearing failure*: fibrinolytic mechanisms unable to dissolve NET-microclot complexes. In glioblastoma, we observe something more sophisticated: *regulatory hijacking*—the tumor actively reprogramming protective mechanisms to serve its own survival and growth.

Critical caveats apply: This framework is proposed as a conceptual lens for understanding GBM biology, not as a proven mechanism. The therapeutic implications remain speculative until validated through clinical trials. The heterogeneity of brain tumors—particularly the profound differences between pediatric and adult cancers—means no single framework captures the full complexity. Nevertheless, understanding GBM as homeostatic hijacking may illuminate why conventional therapies fail and suggest novel intervention strategies targeting not the tumor directly, but the hijacked systems it depends upon.

CHAPTER 1: THE BRAIN'S EXCEPTIONAL HOMEOSTATIC SYSTEMS

1.1 Why the Brain Requires Extraordinary Protection

The brain represents approximately 2% of body weight but consumes 20% of metabolic energy. It contains 86 billion neurons, each forming thousands of synaptic connections in networks of staggering complexity. Unlike most tissues, neurons are largely post-mitotic—they do not divide and cannot be replaced if damaged. The brain's computational substrate is irreplaceable.

This irreplaceability drove the evolution of protective systems unparalleled elsewhere in the body. While other organs tolerate inflammatory responses that damage and regenerate tissue, the brain cannot afford such disruption. While other organs can be accessed by circulating immune cells and therapeutic drugs, the brain maintains strict barriers against intrusion. The result is a set of homeostatic mechanisms optimised for **protection at all costs**.

These protective systems—the blood-brain barrier, immune privilege, resident glial cells—normally serve essential functions. But their very sophistication creates a vulnerability: if a malignancy arises within the protected space, the same mechanisms that shield the brain from external threats can shield the tumor from the body's defences.

1.2 The Blood-Brain Barrier: Architecture of Exclusion

The blood-brain barrier (BBB) is not a single structure but a **neurovascular unit** comprising multiple cell types working in concert. Brain capillary endothelial cells are joined by tight junctions far more restrictive than those in peripheral vessels—essentially sealing the spaces between cells that would otherwise allow molecular passage. These endothelial cells are wrapped by pericytes (contractile cells regulating blood flow) and ensheathed by astrocyte end-feet that cover over 99% of the vascular surface.

The functional consequence is extraordinary selectivity. Small lipophilic molecules can diffuse across; everything else requires active transport. Most circulating immune cells cannot enter. Most therapeutic drugs cannot penetrate. The brain maintains its own fluid composition (cerebrospinal fluid) distinct from blood plasma, creating an environment optimised for neural function but isolated from systemic circulation.

This barrier evolved to protect—but protection cuts both ways. When a tumor arises behind the barrier, many chemotherapeutic agents cannot reach it. When immune cells are needed to attack malignant cells, they cannot easily enter. The BBB becomes, in effect, a **fortress protecting the invader**.

1.3 Immune Privilege: The Double-Edged Shield

The concept of **immune privilege** emerged from Peter Medawar's observation in the 1940s that tissue grafts survive longer in the brain than elsewhere. The brain was thought to be 'immunologically isolated'—hidden from immune surveillance. While this view has been refined (the brain does have immune interactions), the central insight remains: inflammatory responses that would be tolerable elsewhere could be catastrophic in neural tissue.

Several mechanisms enforce this privilege. The BBB restricts immune cell entry. Brain cells express low levels of MHC molecules, reducing antigen presentation. The brain secretes immunosuppressive factors that dampen inflammatory responses. Lymphatic drainage was

long thought absent (recent discoveries of meningeal lymphatics have modified this view, but drainage remains limited compared to other tissues).

For tumor immunology, the implications are profound. Cytotoxic T cells that might eliminate a tumor elsewhere struggle to access and function within the brain. Natural killer cells face similar barriers. The immunotherapies revolutionising treatment of melanoma and lung cancer have shown limited efficacy against GBM—in part because the brain's immune privilege extends protection to the tumor within it.

1.4 Microglia: Sentinels Awaiting Instruction

Microglia are the brain's resident immune cells, comprising 10–15% of all cells in the central nervous system. Unlike other brain cells, microglia derive from embryonic yolk sac progenitors and represent a distinct lineage from peripheral immune cells. In their resting state, they maintain a characteristic branched morphology, their processes constantly surveying the local environment for signs of damage or infection.

When activated by pathological signals, microglia can adopt different functional states. The M1 phenotype is pro-inflammatory: microglia produce cytokines that recruit immune responses and can directly attack pathogens or damaged cells. The M2 phenotype is anti-inflammatory and reparative: microglia secrete factors that suppress inflammation and promote tissue remodelling. This plasticity allows microglia to respond appropriately to diverse challenges.

The vulnerability is this plasticity itself. Microglia respond to signals in their environment. If a tumor can generate the appropriate signals, it can instruct microglia to adopt states that benefit tumor growth rather than suppress it. The sentinels can be turned into collaborators.

1.5 Astrocytes: Metabolic Support and Beyond

Astrocytes are the most abundant glial cells, providing metabolic support to neurons, regulating extracellular ion concentrations, forming the BBB's outer layer via their end-feet, and modulating synaptic transmission. Their name derives from their star-shaped morphology, with processes extending to contact both blood vessels and neuronal synapses.

Like microglia, astrocytes can adopt reactive states in response to pathology. **Reactive astrocytes** undergo morphological and functional changes, upregulating various proteins and secreting cytokines. This reactivity can be protective (walling off damage) or detrimental (contributing to inflammation and scarring). In the context of brain tumors, reactive astrocytes become integrated into the tumor microenvironment, their normal supportive functions redirected to support malignant growth.

CHAPTER 2: THE BLOOD-BRAIN BARRIER PARADOX

2.1 Disruption and Preservation: The Heterogeneous Barrier

A common assumption holds that the BBB is 'broken' in glioblastoma—that the tumor's aggressive growth disrupts vascular integrity, making the brain accessible to drugs and immune cells. Contrast-enhanced MRI supports this view: gadolinium-based contrast agents, normally excluded from brain tissue, accumulate in GBM tumors, producing the characteristic bright enhancement used for diagnosis.

The reality is more complex and more troubling. The BBB is indeed disrupted within the tumor bulk, where abnormal angiogenesis produces leaky, disorganised vessels. But **the BBB remains largely intact at the tumor's invasive margins**—precisely where individual cancer cells infiltrate surrounding brain tissue. These infiltrating cells, protected by an intact barrier, are the seeds of inevitable recurrence.

Even more critically, **glioblastoma stem cells (GSCs)**—the most treatment-resistant and tumorigenic cell population—reside in perivascular niches where the BBB maintains relative integrity. Studies show that GSC-enriched regions are protected by a more competent barrier than bulk tumor. The cells most responsible for tumor maintenance and recurrence are the most shielded from therapeutic access.

2.2 Active Barrier Modulation by Tumor Cells

Recent research suggests that GBM does not passively experience BBB disruption—it **actively modulates barrier function** to serve its needs. Tumor cells secrete factors that can either tighten or loosen the barrier depending on context.

GSC secretomes have been shown to *decrease BBB permeability* in experimental models, upregulating tight junction proteins like claudin-5. Differentiated GBM cells, by contrast, tend to increase permeability through secretion of VEGF and inflammatory cytokines. This suggests a sophisticated division of labor: stem cells maintain protective niches while differentiated cells create the leaky, hypoxic environment that characterises bulk tumor.

The tumor thus creates a **heterogeneous barrier landscape**: leaky enough in some regions to allow nutrient access and create the hypoxic conditions that drive malignant progression, yet intact enough in critical niches to protect the stem cell populations essential for tumor maintenance. This is not barrier failure—it is barrier manipulation.

2.3 Therapeutic Implications of the Barrier Paradox

The heterogeneous BBB creates a therapeutic dilemma. Conventional chemotherapy reaches the leaky tumor bulk but not the protected invasive margins. Surgical resection removes the enhancing tumor visible on MRI but cannot address infiltrating cells in apparently normal brain tissue. Radiation treats defined volumes but spares the scattered cells beyond treatment margins.

Strategies to 'open' the BBB—focused ultrasound, osmotic agents, tight junction modulators—may improve drug delivery to some regions but cannot selectively target the protected niches where GSCs reside. Worse, general barrier disruption might facilitate tumor spread by allowing cancer cells easier access to distant brain regions.

The barrier paradox suggests that **treating GBM requires not just reaching the tumor but understanding how the tumor controls its own accessibility**. Therapeutics must either

bypass the barrier entirely (e.g., local delivery) or address the mechanisms by which the tumor maintains protective niches.

It is important to distinguish between **adaptive selection** and **functional hijacking**. Glioblastoma does not require intentional or directed behaviour to exploit homeostatic systems. Rather, tumour cell populations that survive within existing regulatory constraints may be preferentially selected over time. In this sense, homeostatic hijacking may emerge through evolutionary selection processes rather than active biological intent. Both mechanisms may coexist, and this framework does not assume conscious or teleological action on the part of tumour cells.

CHAPTER 3: IMMUNE PRIVILEGE WEAPONIZED — THE MICROGLIA BETRAYAL

3.1 Glioma-Associated Microglia/Macrophages (GAMs)

Microglia and infiltrating macrophages together constitute **up to 30–50% of the cellular mass of glioblastoma tumors**—the largest immune cell population by far. This might suggest robust anti-tumor immunity. The reality is the opposite: these cells are predominantly tumor-promoting.

Glioma-associated microglia/macrophages (GAMs) are recruited to the tumor through chemokine signaling, particularly CCL2 and CSF-1 secreted by GBM cells. Upon arrival, they encounter a microenvironment saturated with immunosuppressive signals: TGF- β , IL-10, prostaglandin E2. Rather than attacking the tumor, GAMs undergo **phenotypic reprogramming** toward immunosuppressive, tumor-promoting states.

Reprogrammed GAMs secrete growth factors (EGF, VEGF) that promote tumor cell proliferation and angiogenesis. They produce matrix metalloproteinases that facilitate tumor invasion. They express checkpoint ligands (PD-L1) that suppress T cell function. They secrete immunosuppressive cytokines that further dampen anti-tumor immunity. The brain's immune sentinels become, in effect, **tumor support staff**.

3.2 The STAT3 Pathway: Master Switch of Reprogramming

A key molecular mechanism of GAM reprogramming involves the STAT3 signaling pathway. GBM cells, particularly GSCs, secrete factors that activate STAT3 in microglia and macrophages. STAT3 activation drives the immunosuppressive phenotype: upregulating IL-10 and TGF- β production, downregulating pro-inflammatory cytokines, and promoting the tissue-remodeling functions that support tumor growth.

Hypoxia—prevalent in the tumor microenvironment due to abnormal vasculature and rapid cell proliferation—enhances this process. Hypoxia-inducible factor 1 α (HIF-1 α) promotes GSC maintenance while simultaneously reinforcing the immunosuppressive GAM phenotype. The metabolic consequences of tumor growth thus feed forward into enhanced immunosuppression.

Experimental blockade of CSF-1R (the receptor through which CSF-1 promotes GAM recruitment and reprogramming) can reduce tumor growth in mouse models—demonstrating that GAMs are not merely bystanders but active contributors to tumor progression. However, clinical trials of CSF-1R inhibitors have shown limited efficacy, partly because tumors adapt by upregulating alternative survival pathways.

3.3 T Cell Exhaustion and Exclusion

Cytotoxic T cells—the immune cells most capable of killing cancer cells—face multiple barriers in GBM. Physical barriers (the BBB at tumor margins) limit their entry. Even when T cells infiltrate the tumor, they encounter an environment designed to neutralize them.

Tumor-infiltrating lymphocytes (TILs) in GBM show characteristic features of **exhaustion**: upregulation of inhibitory receptors (PD-1, LAG-3, TIM-3), reduced cytokine production (IFN- γ , IL-2), impaired proliferative capacity. They have been rendered functionally incapable of attacking the tumor.

GBM cells contribute directly to T cell suppression by expressing PD-L1 (the ligand for PD-1) and secreting immunosuppressive factors. Regulatory T cells (Tregs), recruited to the tumor

through CCL22 signaling, further dampen effector T cell function. The net effect is an immune environment where even the T cells present cannot mount effective anti-tumor responses.

Immune checkpoint inhibitors—the revolutionary drugs that have transformed treatment of melanoma and lung cancer by 'releasing the brakes' on exhausted T cells—have shown **disappointing results in GBM**. The CheckMate-143 trial of nivolumab (anti-PD-1) in recurrent GBM failed to improve survival over standard treatment. The immunosuppressive microenvironment appears to be too comprehensive to overcome with checkpoint blockade alone.

3.4 The Hijacking Framework: From Failure to Subversion

The immune landscape of GBM illustrates the distinction between *homeostatic failure* and *homeostatic hijacking*. In failure (as in Long COVID's proposed fibrinolytic dysfunction), the regulatory mechanism simply stops working—clots accumulate because they cannot be cleared. In hijacking, the regulatory mechanism continues to function but has been **redirected to serve the pathology**.

Microglia are not absent or non-functional in GBM—they are *hyperactive in tumor-promoting directions*. Immune privilege is not lost—it is *extended to protect the tumor*. The BBB is not uniformly broken—it is *selectively modulated* to serve tumor needs. The brain's protective systems are working—just not for the brain.

CHAPTER 4: THE TUMOR MICROENVIRONMENT — HIJACKED HOMEOSTASIS

4.1 Astrocyte Co-option

Astrocytes, like microglia, are reprogrammed by the tumor microenvironment. Reactive astrocytes in GBM lose their normal connections to blood vessel endothelium—disrupting BBB function in some regions—while simultaneously secreting factors that support tumor growth and invasion.

Key mechanisms include: astrocyte secretion of **IL-6 and CCL2**, which promote tumor cell migration and loosen the BBB; production of **tenascin C**, an extracellular matrix protein that blocks T cell migration into the tumor; and expression of **S1P receptors** that mediate tumor-astrocyte communication supporting invasion.

The astrocyte network—normally essential for maintaining the ionic and metabolic environment neurons require—becomes a **support infrastructure for tumor cells**. Metabolic substrates that should nourish neurons are redirected to fuel tumor growth. Protective barriers that should exclude threats are weakened to facilitate invasion.

4.2 Extracellular Matrix Remodeling

The brain's extracellular matrix (ECM) differs markedly from other tissues, containing high concentrations of glycoproteins, hyaluronic acid, and proteoglycans rather than the collagen-rich matrices found elsewhere. GBM extensively remodels this matrix to facilitate its spread.

Matrix metalloproteinases (MMP-2, MMP-9) secreted by tumor cells and GAMs degrade ECM components, creating paths for tumor invasion. Simultaneously, tumor cells deposit their own ECM proteins—periostin, tenascin C—that promote survival and inhibit immune attack. The matrix becomes **permissive for tumor and prohibitive for immune cells**.

Heparan sulfate proteoglycans (HSPGs), upregulated in GBM, sequester angiogenic growth factors (VEGF, FGF), creating local reservoirs that can be released to drive neovascularization as the tumor requires. The ECM is not merely structural—it becomes a **signaling platform controlled by the tumor**.

4.3 Hypoxia and Metabolic Reprogramming

GBM creates its own hypoxic environment through rapid proliferation outpacing blood supply. Rather than being fatal, hypoxia drives malignant progression through HIF-1 α -mediated transcriptional programs that promote angiogenesis, invasion, and treatment resistance.

Hypoxic zones become refugia for GSCs, which preferentially localize in low-oxygen niches. Hypoxia induces metabolic shifts toward glycolysis (the 'Warburg effect'), acidifying the microenvironment in ways that further suppress immune function. Acidic pH inhibits T cell cytotoxicity while promoting regulatory T cell function.

This creates a **self-reinforcing cycle**: tumor growth creates hypoxia; hypoxia promotes aggressive tumor phenotypes; aggressive tumors further outpace their blood supply. The metabolic microenvironment—normally maintained within tight homeostatic limits for neural function—is destabilized in ways that consistently favor tumor over host.

4.4 The Immunosuppressive Cytokine Milieu

The sum of these processes is an immunosuppressive cytokine environment unmatched in other cancers. Key players include:

- **TGF- β** : Suppresses T cell and NK cell function; promotes Treg differentiation; enhances tumor invasion through MMP activation
- **IL-10**: Suppresses Th1 responses; promotes tumor cell proliferation and migration; major product of reprogrammed GAMs
- **VEGF**: Promotes angiogenesis; inhibits dendritic cell maturation; maintains hypoxic niches
- **CSF-1**: Recruits and reprograms GAMs toward tumor-promoting phenotypes
- **IDO (indoleamine 2,3-dioxygenase)**: Depletes tryptophan, essential for T cell function; generates immunosuppressive metabolites

This is not a random collection of dysfunction—it is a **coordinated immunosuppressive program** that repurposes the brain's normal protective mechanisms for tumor benefit.

CHAPTER 5: AGE-DEPENDENT PATTERNS — WHY PEDIATRIC ≠ ADULT

5.1 The Age Distribution of Brain Tumors

Brain tumors are not uniformly distributed across age. Different tumor types predominate at different life stages:

Age Group	Common Tumor Types	Key Characteristics
Pediatric (0–14)	Medulloblastoma, pilocytic astrocytoma, embryonal tumors	Different molecular drivers; better treatment response; #1 cancer cause of death in children
AYA (15–39)	Diffuse astrocytoma, oligodendroglioma, transitional to GBM	Unique molecular profiles; often 'fall through cracks' between pediatric/adult care
Adult (40–64)	Glioblastoma predominates; meningioma	Peak GBM incidence; median age 62; worst prognosis
Elderly (65+)	GBM, meningioma	Poorest survival; treatment-limiting comorbidities

The WHO CNS5 classification (2021) formally recognises this distinction, introducing categories of 'adult-type' and 'pediatric-type' diffuse gliomas with different molecular criteria and clinical behavior.

5.2 Molecular Differences: Pediatric vs. Adult

Pediatric and adult brain tumors arise through different molecular pathways. **Pediatric high-grade gliomas** frequently harbor mutations in histone genes (H3F3A, particularly the K27M and G34R/V mutations) that alter chromatin structure and gene expression—epigenetic rather than purely genetic drivers.

Adult GBM is characterised by different alterations: EGFR amplification/mutation, PTEN loss, TERT promoter mutations, and in a subset, IDH1/2 mutations that define a distinct (and slightly more favorable) entity. The molecular landscapes are sufficiently different that treatments effective in one population often fail in the other.

These differences may reflect the cellular context of tumor origin. Pediatric tumors may arise from developmental cell populations with distinct vulnerabilities. Adult tumors emerge in a mature brain with different cell populations and accumulated genetic damage. The **homeostatic systems being hijacked differ between age groups**.

5.3 Treatment Response and Survival

Pediatric brain tumors, despite being the leading cause of cancer death in children, are generally more treatment-responsive than adult GBM. Five-year survival for childhood brain tumors overall exceeds 70%; for adult GBM, it is under 10%. Medulloblastoma, the most common malignant pediatric brain tumor, has 70–75% five-year survival with appropriate treatment.

This difference may reflect the different hijacking strategies employed. Pediatric tumors may less effectively subvert the brain's protective systems—or may subvert different systems with different susceptibilities to therapeutic intervention. Understanding these age-dependent patterns may reveal vulnerabilities that could be exploited therapeutically.

The AYA (adolescent and young adult, 15–39) population faces particular challenges: their tumors often have molecular features distinct from both pediatric and older adult tumors, yet they receive care designed for one of these populations. Over 200,000 AYAs in the United States are living with primary brain tumors—a population whose unique needs are only beginning to be recognized.

CHAPTER 6: SEX DIFFERENCES — HORMONAL AND GENETIC MODULATION

6.1 Incidence and Outcome Disparities

GBM shows consistent sex differences across populations. **Males have approximately 1.6× higher incidence** than females (3.97 vs. 2.53 per 100,000 in US data). This difference persists across age groups and geographic regions.

Beyond incidence, males experience **worse outcomes**: shorter median survival, earlier recurrence, reduced response to treatment. This survival disadvantage persists even after adjusting for known prognostic factors. Females with GBM simply do better than males with otherwise similar tumors.

Tumor localization also differs by sex. Population studies show women have higher incidence in the right temporal lobe; men show higher incidence in the frontal lobe and left temporal lobe. Whether these differences reflect distinct tumor biology or different environmental exposures remains unclear.

6.2 Hormonal Influences

Sex hormones may contribute to the observed differences. Estrogen has documented neuroprotective effects and may modulate immune function in ways that enhance anti-tumor immunity. Some studies suggest estrogen inhibits GBM cell proliferation in vitro. Progesterone may have similar protective effects.

Androgens, conversely, may promote tumor growth. Androgen receptors are expressed in GBM cells, and testosterone may enhance proliferation in some contexts. However, the evidence is mixed, and hormonal influences likely interact with genetic and microenvironmental factors in complex ways.

Interestingly, meningioma—the most common primary brain tumor overall—shows the opposite sex distribution, with females having approximately 2× higher incidence. Meningioma frequently expresses progesterone receptors and has been linked to hormone replacement therapy. Different brain tumors may respond to hormonal environments in opposite directions.

6.3 Immune and Genetic Factors

Sex differences in immune function may contribute to GBM disparities. Females generally mount stronger immune responses than males—a difference that increases autoimmune disease risk but may enhance anti-tumor immunity. The immunosuppressive microenvironment of GBM may be more effectively established in the context of male immune function.

Genetic factors on the X chromosome may also play a role. Some tumor suppressor genes are located on the X chromosome; females, with two copies, may retain function even if one copy is lost. X-linked immune genes may contribute to differential immune responses. The molecular basis of sex differences in GBM remains an active area of investigation.

From the hijacking perspective, sex differences suggest that **the brain's homeostatic systems may be differentially susceptible to tumor subversion** depending on hormonal milieu and genetic background. Understanding these differences may reveal intervention opportunities—perhaps hormonal modulation could enhance treatment response in some patients.

CHAPTER 7: THE GLIOBLASTOMA STEM CELL PROBLEM

7.1 Stem Cells as the Root of Resistance

Glioblastoma stem cells (GSCs) represent a small fraction of tumor cells but are responsible for tumor maintenance, therapy resistance, and inevitable recurrence. They possess properties analogous to normal neural stem cells: self-renewal capacity, multipotent differentiation, and expression of stemness markers (CD133, SOX2, Nestin, OCT4).

GSCs are **intrinsically resistant to conventional therapies**. They express high levels of DNA repair enzymes, allowing survival of radiation damage. They express drug efflux pumps that export chemotherapy before it can act. They can enter quiescent states that render them invisible to treatments targeting dividing cells. Even when the tumor bulk is destroyed, surviving GSCs regenerate the tumor.

This explains the clinical pattern of GBM: initial treatment reduces tumor volume dramatically (visible on imaging), but recurrence is essentially universal. The treatments eliminate the differentiated tumor mass while sparing the stem cell population that will reconstitute it.

7.2 Protected Niches Within Disrupted Barriers

GSCs localize to specific microenvironmental niches: **perivascular niches** (close to blood vessels, with access to nutrients and oxygen), **hypoxic niches** (low oxygen zones that promote stemness), and **invasive margins** (the frontier of tumor expansion into normal brain).

Critically, these niches are **protected by relatively intact BBB**. GSC secretomes, as noted earlier, actually decrease BBB permeability—the stem cells create their own protective barriers. This creates the paradox that the most treatment-resistant cells are also the least accessible to treatment.

The niche is not merely physical location—it is active signaling. Endothelial cells in perivascular niches provide factors that maintain GSC stemness. Hypoxia activates HIF-1 α , which promotes GSC phenotype. The invasive margin provides contact with normal brain tissue that may support stem cell identity. **The niche hijacks normal stem cell support mechanisms to maintain the tumor's regenerative core.**

7.3 Stem Cell-Mediated Immune Suppression

GSCs are not merely passive beneficiaries of immunosuppression—they actively create it. GSCs modulate GAMs through STAT3 signaling, inducing the tumor-promoting phenotype. They recruit Tregs through chemokine secretion. They express PD-L1 at higher levels than differentiated tumor cells, directly suppressing T cell function.

GSCs also secrete periostin, which recruits tumor-associated macrophages from peripheral circulation. These GSC-recruited macrophages differ from brain-resident microglia but undergo similar reprogramming toward tumor-promoting phenotypes. The stem cells thus orchestrate the immunosuppressive microenvironment that protects the tumor as a whole.

This places GSCs at the center of the hijacking network. They do not merely benefit from subverted protective mechanisms—**they are the primary agents of subversion**. Therapeutic strategies targeting GSCs may therefore have outsized effects on the entire tumor ecosystem.

CHAPTER 8: THERAPEUTIC IMPLICATIONS — RESTORING VS. BYPASSING HOMEOSTASIS

8.1 Current Standard of Care and Its Limitations

The current standard treatment for GBM—maximal safe surgical resection, followed by radiation with concurrent and adjuvant temozolomide—has remained essentially unchanged since the Stupp protocol was established in 2005. This regimen extends median survival from approximately 12 months (radiation alone) to approximately 15 months. No subsequent therapy has significantly improved on these outcomes for the general GBM population.

Each component of treatment faces the barriers described in this paper:

- **Surgery:** Cannot remove infiltrating cells beyond the visible tumor; cannot access deep or eloquent brain regions
- **Radiation:** Kills differentiated tumor but spares radiation-resistant GSCs; cannot treat beyond defined margins
- **Chemotherapy:** Limited by BBB penetration; limited by GSC efflux pumps and DNA repair
- **Immunotherapy:** Limited by immunosuppressive microenvironment; limited by BBB restriction of immune cell access

The hijacking framework suggests why: **each therapy fights not only the tumor but the tumor's appropriated protective systems.** The tumor has turned the brain's defenses into its own.

8.2 Targeting the Hijacked Systems

The hijacking framework suggests an alternative strategy: rather than attacking the tumor directly (which must overcome the hijacked defenses), **target the hijacked systems themselves.** If the tumor depends on reprogrammed microglia, restore microglial anti-tumor function. If the tumor maintains protective BBB niches, disrupt those specifically. If the tumor generates immunosuppressive cytokines, neutralize them.

Emerging approaches aligned with this strategy include:

GAM reprogramming: Agents targeting CSF-1R to block GAM recruitment; TLR agonists to shift GAMs toward anti-tumor phenotypes; STAT3 inhibitors to disrupt the reprogramming pathway

Barrier modulation: Focused ultrasound with microbubbles for transient, targeted BBB opening; nanoparticle delivery systems designed to cross intact barrier; convection-enhanced delivery to bypass barrier entirely

Microenvironment normalization: Anti-VEGF therapy (bevacizumab) to normalize vasculature and reduce hypoxia; IDO inhibitors to restore tryptophan and T cell function; TGF- β blockade to reduce immunosuppression

GSC targeting: Agents targeting stemness pathways (Notch, Hedgehog, Wnt); differentiation therapy to force GSCs into treatment-sensitive states; niche disruption to expose GSCs to therapeutic attack

8.3 Combination and Sequence Strategies

No single agent is likely to overcome GBM's comprehensive hijacking. The field is moving toward **rational combinations** that address multiple hijacked systems simultaneously:

1. BBB opening + chemotherapy: Focused ultrasound to transiently breach barrier, followed by systemic drug administration
2. Immunotherapy + microenvironment modulation: Checkpoint inhibitors combined with agents that reduce immunosuppression
3. GSC targeting + radiation: Radiosensitizers that specifically affect GSCs, combined with standard radiation
4. Vascular normalization + multiple modalities: Anti-VEGF to normalize vessels, improving delivery and efficacy of subsequent treatments

Sequencing also matters: some interventions may need to precede others. Opening the BBB before immunotherapy might allow T cell infiltration. Normalizing the microenvironment before targeting GSCs might make stem cells accessible. The temporal orchestration of combination therapies is an emerging area of investigation.

The research directions discussed in this section are presented **solely as conceptual implications** of the framework. They do not predict clinical success, recommend interventions, or imply that regulatory disruption will overcome treatment resistance. Any translational relevance remains contingent on extensive experimental validation and clinical trial evidence.

This framework should not be interpreted as identifying therapeutic targets or strategies, but rather as a lens for understanding why many existing approaches fail.

CHAPTER 9: LIMITATIONS AND FALSIFIABILITY

9.1 Conceptual Framework vs. Proven Mechanism

The 'homeostatic hijacking' framework presented in this paper is a **conceptual lens for understanding GBM biology**, not a proven mechanism with established therapeutic implications. Several important limitations apply:

Descriptive vs. explanatory: The framework describes what GBM does (subvert protective systems) but does not explain *how* it evolved this capacity or *why* some tumors hijack more effectively than others. It organizes observations without providing mechanistic depth.

Post-hoc interpretation: The framework was developed after observing GBM biology. It risks 'just-so story' reasoning where any observation can be fitted to the narrative. A good framework should make predictions, not merely accommodate existing data.

Heterogeneity: GBM is not a single disease. Different molecular subtypes may hijack different systems through different mechanisms. The framework may apply variably across the heterogeneous GBM population.

9.2 What Would Falsify This Framework?

For the framework to be scientifically useful, we must specify what evidence would contradict it:

1. **Passive evasion sufficient:** If GBM survival can be explained entirely by passive immune privilege and BBB exclusion—without active tumor manipulation of these systems—the 'hijacking' concept is unnecessary.
2. **Reprogramming not tumor-dependent:** If GAM reprogramming occurs identically in response to any brain injury (stroke, trauma, infection), it may reflect generic reactive responses rather than tumor-specific hijacking.
3. **System-targeting fails:** If therapies targeting hijacked systems (GAM reprogramming, BBB modulation) consistently fail to improve outcomes, the therapeutic premise is wrong.
4. **Non-hijacking GBMs:** If a subset of GBMs lacks the hijacking phenotype yet behaves similarly to hijacking tumors, the framework fails to distinguish biologically meaningful categories.
5. **Better alternative framework:** If an alternative conceptualization explains GBM biology more parsimoniously or generates more productive therapeutic hypotheses, it should replace this framework.

9.3 Relationship to Prior Programme Work

This paper extends the Programme's homeostatic framework in a new direction—from *failure* to *hijacking*. This extension requires justification:

System	Pattern	Mechanism
Landscape salinity	Regulatory failure	Vegetation removed → balance lost
Long COVID (proposed)	Clearing failure	Fibrinolysis impaired → microclots accumulate
Glioblastoma (proposed)	Regulatory hijacking	Protection reprogrammed → shields tumor

The progression from failure to hijacking represents increasing sophistication of pathology. Salinity is a passive consequence of disruption; Long COVID may involve pathological structures that resist clearing; GBM involves active reprogramming of protective systems. Whether this progression represents genuine biological unity or forced analogy remains to be determined.

CHAPTER 10: CONCLUSIONS AND PROGRAMME INTEGRATION

10.1 Summary of the Hijacking Framework

This white paper has proposed understanding glioblastoma through the lens of **homeostatic hijacking**—a conceptual framework in which the tumor actively subverts the brain's protective systems rather than merely evading them:

1. The brain possesses extraordinary homeostatic systems (BBB, immune privilege, glial support) evolved to protect irreplaceable neural tissue.
2. GBM does not merely evade these systems—it reprograms microglia into tumor-promoting cells, manipulates BBB permeability to create protective niches, and co-opts astrocytes for metabolic support.
3. Glioblastoma stem cells reside in protected niches and orchestrate the hijacking program, making them the root of treatment resistance.
4. Age and sex differences in GBM may reflect differential susceptibility of homeostatic systems to tumor subversion.
5. Therapeutic strategies targeting hijacked systems—rather than the tumor directly—may overcome resistance mechanisms that defeat conventional approaches.

10.2 Programme Evolution: From Failure to Hijacking

This analysis extends the Collaborative Homeostasis Programme's framework in a new direction. The Programme has documented homeostatic failure across scales—from molecular (Long COVID microclots) through organismal (koala disease, devil cancer) to continental (landscape salinity). GBM adds a more sophisticated pattern: **hijacking**.

Hijacking may represent the most challenging form of homeostatic disruption to address therapeutically. In failure, restoring the regulatory mechanism may restore function. In hijacking, the regulatory mechanism is present and functional—just redirected. Therapy must not only reach the tumor but must also **reprogram the reprogrammed systems**.

Whether hijacking is unique to cancer—or whether other conditions involve similar active subversion of protective mechanisms—remains an open question. The framework may illuminate other treatment-resistant conditions where pathology seems to 'take over' host systems rather than simply damaging them.

10.3 Recommendations

For Research:

1. Systematically characterise the 'hijacking signature' in GBM: which systems are subverted, by what mechanisms, with what variation across patients and tumor subtypes.
2. Develop combination therapies targeting multiple hijacked systems simultaneously, with attention to sequencing and timing.
3. Investigate age and sex differences to identify factors that modulate hijacking susceptibility.
4. Explore whether the hijacking framework applies to pediatric brain tumors or whether their different biology requires different conceptualization.

For Clinical Practice:

- Recognise that GBM treatment faces not only the tumor but its appropriated defenses; manage patient expectations accordingly.
- Consider clinical trials of combination approaches targeting tumor microenvironment rather than tumor cells alone.
- Attend to sex-specific outcomes data as evidence accumulates regarding differential treatment responses.

For the Collaborative Homeostasis Programme:

- Position the hijacking framework as conceptual extension requiring validation, not established fact.
- Explore whether other treatment-resistant conditions (chronic infections, autoimmune diseases) might involve hijacking patterns.
- Develop clearer criteria distinguishing failure, clearing failure, and hijacking as distinct homeostatic disruption types.

10.4 Closing Statement

Glioblastoma remains one of medicine's most formidable challenges—a cancer whose treatment resistance has defied 45 years of research progress. The homeostatic hijacking framework offers a perspective on why: **the tumor has not merely survived within the brain but has taken control of the brain's protective infrastructure**. Fighting GBM means fighting the tumor's appropriated allies as much as the tumor itself.

This framework does not promise immediate therapeutic breakthroughs. But it may reorient research toward the systems the tumor depends upon rather than the tumor alone. It may explain why immunotherapies that work elsewhere fail in the brain. It may suggest combination strategies targeting multiple hijacked systems. And it may connect GBM to broader patterns of homeostatic disruption the Programme has documented across biological scales.

For the hundreds of thousands of patients diagnosed with GBM each year, and the families who watch them struggle against a disease that turns the brain's defenses into the tumor's shields, any new perspective that might accelerate progress toward effective treatment is worth pursuing. The hijacking framework is offered in that spirit—not as final truth, but as a lens that may reveal vulnerabilities currently obscured.

This analysis does not claim that glioblastoma arises from homeostatic dysfunction, but explores whether tumour persistence and resistance may reflect stabilisation within regulatory systems that normally support tissue integrity.

METHODOLOGY AND AI ATTRIBUTION STATEMENT

This white paper was developed using the HATI (Homeostatic Adaptive Teaming Intelligence) collaborative synthesis framework.

AI Contribution: Claude (Anthropic) contributed to literature synthesis, framework development, and document preparation. Prior collaboration with ChatGPT (OpenAI) on the Long COVID white paper informed the approach to epistemic humility and falsifiability criteria applied here.

Human Authority: All interpretive conclusions, editorial decisions, and responsibility for claims rest with the human author. AI systems functioned as epistemic collaborators, not autonomous authors.

Medical Disclaimer: This document presents a conceptual framework for understanding glioblastoma biology. It does not constitute medical advice. The framework is proposed, not proven. Patients should consult qualified healthcare providers for diagnosis and treatment decisions.

Epistemic Status: This paper presents a *conceptual framework* based on synthesis of published research. Key claims represent interpretation, not established consensus. Limitations and falsification criteria are explicitly specified.

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ABOUT THE COLLABORATIVE HOMEOSTASIS PROGRAMME

The Collaborative Homeostasis Programme is an independent research initiative dedicated to understanding and restoring homeostasis across biological, ecological, and human systems.

Published Research:

- **Glioblastoma as Homeostatic Hijacking** — Tumor subversion of brain protective systems (Human medicine)
- **Long COVID as Vascular Homeostatic Failure** — Microclots and fibrinolytic dysfunction (Hypothesis)
- **Australia's High Salinity Lands** — Dryland salinity as landscape homeostatic failure
- **Saudi Arabia's High Salinity Lands** — Fossil aquifer depletion
- **Argentina's High Salinity Lands** — Dual mechanisms in Pampas and Chaco
- **The Fernbrook Protocol** — Koala genomic resilience
- **The Devil Homeostasis Project** — Transmissible cancer
- *Additional works on dolphins, coral, and cross-species patterns*

Evolving Thesis: Health is homeostasis; disease is its disruption. The pattern of regulatory failure—or now, regulatory hijacking—operates across scales of biological organisation.

Framework: HATI (Homeostatic Adaptive Teaming Intelligence)

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