Hypothesis: A Paradigm Shift in Glioblastoma Treatment and Research: A Multi-mechanistic, Multi-agent Approach to Target Glioblastoma Multiforme

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ABSTRACT

The majority of patients with glioblastoma multiforme (GBM) suffer dismal outcomes. Adopting a broader, multi-mechanistic, multi-agent approach targeting GBM using readily available and fairly benign agents in combination with standard therapy may improve outcomes. Such agents include fluoxetine, fenofibrate, cimetidine, citrulline, valacyclovir, 1-3, 1-6 β-glucan, and tadalafil, among others. In the context of in vitro and animal studies, these agents appear to target GBM cells and modify the tumor microenvironment. The current approach to GBM treatment focuses on limited molecular attributes of the condition. The following article highlights the relevance of the aforementioned agents in GBM treatment and proposes a multi-mechanistic, multi-agent paradigm shift, addressing a broader range of molecular attributes in the quest to improve patient outcomes.

Glioblastoma multiforme (GBM) is a devastating diagnosis with a dismal prognosis. In spite of best efforts, most patients' life expectancy is measured in months. Given the expanding knowledge base on common agents and the recent idea of repurposing older agents for new uses, I hypothesize improving outcomes with consideration of standard radiation, chemotherapy, and surgery in combination with repurposing older agents that have established track records for safety.

Fluoxetine is a common drug used for depression, also it selectively kills GBM cells [1]. It induces transmembrane calcium influx with subsequent GBM cell death via interactions with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR). Fluoxetine does so by interacting with GluR-1 subunit of the AMPAR and causes mitochondrial membrane damage and sets off the intrinsic apoptosis pathways with increased caspase 3, 9 and cytochrome C and poly (ADPribose) polymerase (PARP). The AMPARs are overexpressed in GBM so the killing is selective to GBM cells [1]. Fluoxetine is also known to markedly decrease expression of O6-methylguanine-DNA methyltransferase (MGMT) in GBM cells, disrupt NfkB/p65 signaling, and decrease GBM activity through

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Downregulating MGMT expression in GBM cells while additionally sensitizing the GBM to temozolomide [2]. This research highlights the mechanisms through which fluoxetine may positively impact the GBM outcomes.

Fenofibrate is a common drug used in the treatment of hypertriglyceridemia. When it interacts with a GBM cell, forces it to make use of beta oxidation instead of glycolysis, then damages Complex I of the electron transport chain making it impossible for the GBM to make use of the electron transport chain. By 72 hours of 50 microM exposure, a metabolic catastrophe impacts the GBM cells [3].

Fenofibrate effects are selective to GBM cell, most likely due to the inability of GBM cells to convert the fenofibrate to fenofibric acid, resulting in fenofibrate accumulation in the mitochondrial fraction which leads to Complex I damage [4]. Fenofibrate also 'reprograms' the GBM cells' metabolic pathways such that the GBM cells suffer from an energy deficit but are still forced to produce ketone bodies, which GBM cells cannot metabolize for their own benefit [5]. Those ketone bodies can, however, act as fuel for normal neurons and also act as cytoprotective signaling molecules for the normal neurons [5].

Cimetidine is a common drug used to decrease acid production in the stomach. It has immunomodulatory properties. It will decrease the number of myeloid derived suppressor cells via activation of intrinsic apoptosis in the myeloid derived suppressor cells (MDSCs), increase number of natural killer cells, decrease T-regulatory cells (Tregs), and increase interleukin 2 and interferon-gamma levels [6, 7]. I believe the accumulation of MDSCs in the blood of GBM patients constitutes a significant tumor immunosubversive strategy. Depleting MDSCs and impairing their internal functions could potentially improve immunotherapy effectiveness, and cimetidine may play a key role. Cimetidine has antiadhesive and antimigratory effects on glioma cells [8]. The combination of cimetidine and temozolomide increases survival rate in mice with GBMs [8]. Surgery results in an expansion of MDSC numbers. Dosing cimetidine before and after surgery prevents MDSC expansion and blunts post-surgery immune suppression [9].

MDSCs use arginine and cysteine depletion as major immunosuppressive mechanisms to impair T-cell functions [10-11]. Citrulline is an amino acid that can be used to provide arginine to the T-cells in MDSC induced arginine depleted states. The T-cells can import the citrulline and convert it to arginine using their arginosuccinate synthase pathway [12].

Tadalafil is a common drug used to treat male reproductive dysfunction. It will also inhibit the function of arginase I within the MDSC, making it more difficult for the MDSC to induce an arginine depleted state within the T-cells. It will also impair MDSC NOS2 functioning. Tadalafil will also decrease Treg cell numbers. The exact mechanism is unknown [14-15].

Because of its effect on MDSCs and Tregs, tadalafil may improve immune therapies such as ipilimumab and pembrolizumab [15-16]. As a PDE5 inhibitor, tadalafil should improve transport of chemotherapy across the blood brain barrier and blood tumor barrier [25].

Valacyclovir, an acyclovir prodrug, is a common antiviral agent. It will also inhibit indoleamine 2,3-dioxygenase (IDO) [24]. IDO is an immunosubversive factor and will increase Treg cell number in GBM and contribute to other issues in GBM [17-18]. Valacyclovir also has some activity against cytomegalovirus [19].

1-3,1-6 β-Glucan is a polysaccharide found in bakers' yeast that has immune modulating properties [20, 23]. When given orally, the macrophages in the Peyer's patches sample the β-glucan and share the information with key parts of the immune system [21, 22]. The result is reprogramming of the immune system to express strong TH1 attributes. I believe monoclonal antibodies will work better in a system with stronger TH1 attributes [21, 24]. Glioblastoma probably manipulates immune checkpoints, programmed cell death-1 (PD-1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4) to induce T-cell exhaustion. Ipilimumab is a monoclonal antibody for CTLA-4 and pembrolizumab is a monoclonal antibody for PD-1. When researchers blocked CTLA-4 and PD-1 and IDO, all the mice in the study, with established GBM, became long-term survivors [13].

Despite all these, the questions do remain. Are the animal/lab studies translatable to humans? Can the required CNS concentrations of the agents be attained and maintained? Would including sertraline with tadalafil further improve blood brain barrier and blood tumor barrier permeability? Will drug interactions become a problem? How long does one stay on the nonchemotherapy agents? Would including metformin and sulforaphane, or disulfiram be a more effective way to deal with the cancer stem cell issues, given the effect these agents have on signaling systems within the cancer stem cells [25]? Would different combinations of other agents already on the shelf work better? Should transcranial cryoablation of unresectable or recurrent GBMs be employed

more frequently given the immune stimulation aspects of cryoapototic cell death?

In the quest to improve outcomes for patients with GBMs, we should take a broad based and multi-mechanistic approach that employs multiple agents in addition to standard treatment to maximize tumor destruction, revert tumor induced immune distortions and resolve the cancer stem cell issues in the patient.

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Conflict of Interest

The author declared no Conflict of Interests.

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