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To the Editor,
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Thank you for looking at this and considering it for publication. We believe that this is important given the dismal prognosis of glioblastoma currently and the benign nature of the suggested augmentation method.
For all the authors,
Kind regards,
Richard
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Augmentation of the cytoidal effects of temozolomide by olanzepine and metformin in the treatment of histamine-1 receptor-positive glioblastomas

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ABSTRACT
As current standard treatments for glioblastoma commonly fail to cure, the need for more efficient therapeutic options is overwhelming. In this paper we summarize available experimental evidence to supporting the hypothesis that metformin and olanzepine have potential to augment the cytotoxic effects of temozolomide. Temozolomide is an alkylating chemotherapeutic agent commonly used to treat glioblastoma. Although the primary path leading to temozolomide induced cell death is formation of O6-methylguanine apoptotic signaling triggered by O6-methylG:T mispairs, that apoptotic signaling goes through an adenosine monophosphate protein kinase (AMPK) activation-mediated step. Metformin or olanzapine have been shown independently to enhance AMPK activation. Metformin to treat diabetes and olanzapine to treat psychiatric difficulties are eminently well-tolerated in normals and have been marketed and approved for use in humans for years. Based on evidence that proapoptotic effects of temozolomide go through an AMPK activation step we might be able to amplify that AMPK activation with metformin and olanzapine. Investigation of their potential as a synergistic combination therapy against glioblastoma is warranted.

Keywords: AMP kinase, chemotherapy, glioblastoma, metformin, olanzapine, temozolomide

Abbreviations: AMPK, adenosine monophosphate protein kinase; ATP, adenosine triphosphate; CXCR4, a chemokine receptor; H1, histamine receptor 1; K(Ca)3.1, intermediate conductance Ca2+ activated K+ channel; LKB1-MO25-STRAD, trimolecular kinase that activates AMP kinase; TMZ, temozolomide.

Acknowledgments and conflicts of interest:
This was unfunded research. All authors report no conflict of interest.
INTRODUCTION
Glioblastoma is a poor-prognosis cancer. Current treatments commonly use the alkylating drug temozolomide, \( \text{TMZ} \), in combination with irradiation after maximal surgical resection [Stupp et al. 2005, Stupp et al. 2009]. These interventions are extraordinarily rarely curative. More efficient and effective treatment options are urgently needed. In this short note, we discuss why olanzapine, a psychiatric drug used for over a decade to treat thought disorders, and metformin, the most commonly used drug for the initial treatment of type 2 diabetes, may enhance the cytocidal effect of \( \text{TMZ} \) against glioblastoma.

SYNOPSIS OF CURRENT EVIDENCE
AMPK
Adenosine monophosphate protein kinase, AMPK, is a heterotrimeric kinase that functions as an intracellular energy (adenosine triphosphate, ATP) sensor [Cantó and Auwerx, 2010]. When phosphorylated at its Thr-172, AMPK's activity is increased by a 1000-fold, leading to the phosphorylation of downstream target proteins that result in a metabolic shift away from ATP consuming processes. The trimolecular complex LKB1-MO25-STRAD is a primary kinase for phosphorylation of Thr-172 [Cantó and Auwerx, 2010]. The antidiabetes drug metformin enhances the formation of LKB1-MO25-STRAD [Shaw et al. 2005].

Recent data of Zhang et al. [2010] indicate that at least one path of TMZ-induced cell death employs an obligatory AMPK activation step. These authors showed AMPK activation after exposure to TMZ both in two glioblastoma cell lines and in explanted primary human glioblastoma cells [Zhang et al. 2010]. They provide evidence that the crucial link between AMPK and glioblastoma cell death is activated AMPK binding to and phosphorylating p53 [Zhang et al. 2010]. In their in vitro assay, the AMPK inhibitor rapamycin inhibited TMZ cytotoxicity, and an experimental AMPK-activating drug, 5-aminomidazole-4-carboxamide-1-beta-dribofuranoside, enhanced TMZ killing. Against this background, we may have ready means at hand to enhance TMZ-mediated glioblastoma cytotoxicity.

OLANZAPINE
Kim et al., in a 2007 study of the intracellular correlates of weight gain associated with the use of certain modern anti-psychotic medications,
showed that potent histamine receptor-1, H1, inverse agonism [in effect antagonism] by clozapine and olanzapine results in AMPK activation in the murine brain [Kim et al. 2007].

Hypothalamic tissue, in particular the arcuate and paraventricular nuclei, showed the greatest increases in AMPK activation, but at higher concentrations AMPK was activated in other cerebral areas as well [Kim et al. 2007]. The clozapine dose needed to raise general cerebral activated AMPK, 5 mg/kg, was well within the dose range used in humans (commonly 400 mg once at bedtime).

Since Kim et al. demonstrated that AMPK activation by clozapine or olanzapine is dependent on H1 inverse synergism, we would expect no augmentation of TMZ cytotoxicity in H1-negative glioblastomas. Evidence that glioblastoma cells commonly do bear H1 is listed below.

The growth enhancing role of histamine and its four receptors in cancer generally was recently reviewed [Medina and Rivera, 2010]. We have here outlined a previously unidentified specific mechanism of how H1 antagonism might augment cytotoxicity. H1 antagonism was on two other accounts previously suggested as treatment adjunct in glioblastoma:

1...H1 agonism is suspected to increase interleukin-6 signaling in glioblastoma [Altschuler and Kast 2005, Falus 1993, Kast and Altschuler 2006].

2...H1 agonism opens the intermediate conductance Ca2+ activated K+ channel [K(Ca)3.1] also commonly found on glioblastoma cells [Fioretti et al. 2009].

3...In the current short note, we add a third rationale for H1 antagonism as treatment adjunct in glioblastoma. The chemokine receptor CXCR4, important in directing migration and triggering mitosis in glioblastoma cells [Zagzag et al. 2008] signals through opening of the K(Ca)3.1 [Kast 2010, Sciaccaluga et al. 2010] as does H1.

K(Ca)3.1 is a voltage-insensitive K+ egress channel, tending to hyperpolarize cells when open [Kast 2010, Bradding and Wulff 2009, Chou et al. 2008]. K(Ca)3.1 opens in response to a local increase in Ca2+
concentration. Since signaling by the cell surface receptor CXCR4 is one of the major determinants of glioblastoma cells' centrifugal migration [Zagzag et al. 2008] and CXCR4 uses K(Ca)3.1 as does H1, by inhibiting H1's contribution to total K(Ca)3.1 opening with potent antihistamines like olanzapine, we could potentially up-bias the threshold for CXCR4 to create a given K(Ca)3.1 opening degree [Kast 2010].

Olanzapine is simpler than clozapine to use clinically and would be the drug of choice in the role suggested here also due to attributes in normals potentially of benefit to glioblastoma patients. Olanzapine has been extensively studied in people without psychiatric difficulties where sleep continuity, sleep efficiency, and increased stage III/IV sleep are seen [Cohrs 2008]. These attributes would be salutary. Also olanzapine has potent serotonin-3 receptor antagonism resulting in anti-nausea/ anti-emesis effects [Kast and Foley 2007] as in the 'setron class antagonists such as ondansetron and others.

METFORMIN
Since both clozapine and olanzapine increase appetite and are therefore associated with weight gain and attendant diabetes, metformin is commonly used with these drugs [Baptista et al. 2007, Carrizo et al. 2009, Chen et al. 2008, Wu et al. 2008]. The combination is well tolerated. Fortuitously for therapeutic purposes in glioblastoma, metformin also tends to increase AMPK activation via enhancement of formation of the activating kinase LBK1-MO25-STRAD [Shaw et al. 2005].

Suggesting metformin as treatment adjunct in cancer is not new [Ben Sahra et al. 2010, Jalving et al. 2010, Zadra et al. 2010]. Indeed, metformin is in one phase III and six phase II trials in this role. However, the work of Zhang et al. [2010] provides a new and specific rationale for adding metformin to olanzapine and TMZ AMPK activation by TMZ, AMPK activation by H1 blockade with olanzapine, and AMPK activation by the metformin-enhanced LBK1-MO25-STRAD complex are potentially synergistic and may yield enhanced cytotoxic effects against glioblastoma cells.

DISCUSSION
Good evidence from studies on glioblastoma cell lines [Hishinuma et al. 1995, Clark et al. 1971, Fioretti et al. 2009, Falus 1993, Li et al. 2003] and
patient biopsies [Weydt et al. 1997, Li et al. 2003] show that H1 is commonly expressed on glioblastoma cells. That AMPK increases by olanzapine would be expected only in cells expressing H1 would mean that only in H1 expressing cells would TMZ cytotoxicity be augmented.

TMZ is thought to exert tumor cytotoxic effects by generating O(6)-methylguanine [Roos et al, 2007]. O(6)-methylguanine-DNA methyltransferase, MGMT, is one of the repair proteins after DNA such damage by TMZ [Lai et al. 2011, Vassella et al. 2010]. The gene for MGMT tends to be repressed when its promoter has been methylated, clinically translating into somewhat longer survival of glioblastoma patients with the methylated promoter treated with TMZ and related alkylating agents. The study of Lai et al is typical for example, where median overall survival was 24.7 months in patients with MGMT promoter methylation and 15.9 months in patients without promoter methylation. The corresponding progression free survival was 17.5 with and 10.5 without promoter methylation [Lai et al. 2011].

Efforts to improve TMZ cytotoxic effects in glioblastoma by inhibiting MGMT function have been hampered by increased haematopoetic toxicity when bone marrow is fully exposed to the TMZ augmentation maneuver [Hegi et al. 2008]. In contrast, TMZ augmentation by olanzapine would be restricted to cells that are both H1-bearing and proliferating. Because bone marrow cells tend to be H1-negative, the proposed approach has potential for less bone marrow toxicity than the combination of TMZ and MGMT inhibitors. This statement holds true for other tissues with the exception of mucosae.

Even glioblastoma patients with low levels of MGMT due to good MGMT promoter gene methylation have been seen to poorly respond to TMZ, the AMPK amplification proposed in this communication constitutes an independent previously unexplored path to enhancing TMZ cytotoxicity.

CONCLUSION

If, as recent work suggests, at least some of TMZ's cytotoxicity during the treatment of glioblastoma goes through an obligatory AMPK activation step, then adding metformin and olanzapine should augment such cytotoxicity. Metformin and olanzapine are already being combined in the treatment of psychotic illnesses. Such combination is well-known and
well-tolerated and would therefore not be expected to add to TMZ's side effect burden or patient morbidity.

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