The impressive but sad list of over forty clinical studies using various cytotoxic chemotherapies published in the last few years has failed to increase median survival of glioblastoma beyond two years after diagnosis. In view of this apparent brick wall, adjunctive non-cytotoxic growth factor blocking drugs are being tried, as in the CUSP9* protocol. A related theme is searching for agonists at growth inhibiting receptors. One such dataset is that of melatonin agonism at M1 or M2 receptors found on glioblastoma cells, being a negative regulator of these cells’ growth. Melatonin itself is an endogenous hormone, but when used as an exogenously administered drug it has many disadvantages. Agomelatine, marketed as an antidepressant, and ramelteon, marketed as a treatment for insomnia, are currently-available melatonin receptor agonists. These melatonin receptor agonists have significant advantages over the natural ligand: longer half-life, better oral absorption, and higher affinity to melatonin receptors. They have an eminently benign side effect profile. As full agonists they should function to inhibit glioblastoma growth, as demonstrated for melatonin. A potentially helpful ancillary attribute of melatonergic agonists in glioblastoma treatment is an increase in interleukin-2 synthesis, expected, at least partially, to reverse some of the immunosuppression associated with glioblastoma.

Key words: agomelatine, CUSP9*, glioblastoma, interleukin-2, melatonin, ramelteon, temozolamide.

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Agomelatine or ramelteon as treatment adjuncts in glioblastoma and other M1- or M2-expressing cancers

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Preamble: an orthopaedic aphorism:
If a little force doesn’t work, maybe more force will.

Introduction
This paper presents some physiological data supporting adjunctive use of agomelatine or ramelteon in our ongoing effort to improve glioblastoma treatment, given that the current median overall survival remains less than two years [1]. An impressive but sad list of over forty clinical studies, using various cytotoxic chemotherapies and published in the last few years [1, 2], has failed to increase the median survival of glioblastoma beyond two years after initial diagnosis. Many of these studies imposed high side-effect burdens on patients. To redress this situation we took a new approach with the CUSP9* protocol [1, 2]. In CUSP9*, repositioned older drugs, drugs that have not traditionally been used in cancer chemotherapy, are used to block 17 different survival paths used by glioblastoma cells to survive, grow, and avoid cytotoxicity from traditional cytotoxic chemotherapy drugs. We now present past data and explain the rationale to indicate the potential for the benefit of the addition of currently marketed melatonin agonists agomelatine or ramelteon as adjuncts to a compatible, coordinated polypharmaceutical regimen during glioblastoma treatment.

Nile Distributary Problem
Recent oncology studies and thinking, both generally and regarding glioblastoma specifically [1–3], have drawn the conclusion that simultaneous blocking of multiple, cross-covering growth paths will be required for meaningful clinical benefit. This has been termed the Nile Distributary Problem (Fig. 1) [expanded in refs. 1 and 2]. Multiple cross-covering growth stimulating or growth enabling pathways imply a) non-existence of a single or crucial nodal flaw, and b) the consequent need of wide-net polypharmacy. A growth stimulating signalling system that we should inhibit and a growth inhibiting system that we should stimulate are considered functionally equivalent for the purposes of this discussion.

It is a widely implemented principle of modern engineering that if a single part or function of a well-engineered machine were to fail and result in catastrophic or significant harm, that part or function must be made redundant, often several times redundant. For example, many modern jet airliners would become unflyable without their computer’s help. Thus they have four redundant computers, any one of which can safely allow the plane to fly. After a thousand million years mammalian cells have become well-engineered entities and therefore have multiple redundant systems for crucial functions. Many of these go simultaneously awry in cancer, implying a need for multiple simultaneous interventions. The Nile Distributary Problem.
In light of and in recognition of the Nile Distributary Problem, agomelatine or ramelteon as treatment adjuncts during glioblastoma treatment are suggested only as a component of any larger CUSP-like regimen, not as a stand-alone option. According to this understanding, clinical control or cure will come when enough of the cross-covering growth paths are blocked so that glioblastoma cell survival is seriously impaired. To that end, this paper now reviews evidence for the role of agonism at the two currently recognised, widely expressed melatonin receptors, M1 and M2, in glioblastoma growth inhibition, and the potential for either of these two commercially approved and marketed M1/M2 agonists to enhance M1/M2-mediated growth inhibition – a counterweight to growth-stimulating paths.

Melatonin as a negative regulator of glioblastoma growth

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a 232 Da, short half-life hormone [4, 5] synthesised downstream from serotonin [6, 7] and found universally in mammals [8]. Melatonin signals through two outer surface membrane receptors, termed M1 and M2 [9]. Dietary tryptophan is used either i) in protein synthesis, ii) shunted along the kynurenine pathway, or iii) shunted to serotonin synthesis [10]. From the serotonin path melatonin is synthesised [11]. Melatonin as a pharmacological agent has several drawbacks, very short circulating half-life (Table 1) and erratic absorption [12] among them. Pharmacological melatonergic agonists were developed to circumvent these drawbacks and marketed to help initiate sleep during diurnal dysregulation states or to alleviate depression [13, 14].

Traditionally, melatonin has been considered a pineal-synthesised hormone. Melatonin is found throughout vertebrates’ body and brain [15], but also in the brain of ancient, primitive life forms such as planaria [16] and marine zooplankton [17]. More recent evidence shows that lymphocytes can synthesise melatonin [18–20], as do other cells involved with innate immunity [21] and inflammation [22]. Normal brain astrocytes and glia also synthesise melatonin [23], as does the gut [24] and other organs [5].

Although best known for diurnal sleep-wake regulation and synthesis in the pineal gland [5], melatonin has significant physiological functions other than sleep-wake cycling [9, 25].

Multiple potential areas for melatonin’s anti-cancer action have been postulated by others [25–29]. Detailed below are data on melatonin function specifically in glioblastoma growth.

| Molecule   | T ½  | Animal | Reference |
|------------|------|--------|-----------|
| Agomelatine| 2 hours | human | 13        |
| Ramelteon  | ~1–2 hours | human | 67        |
| Ramelteon  | ~1–2 hours | human | 52        |
| Melatonin  | 23 min  | rat    | 68        |
| Melatonin  | < 20 min | hamster | 69       |
| Melatonin  | 40 min  | human | 42        |
| Melatonin  | ~30 min | human | 70        |
current concepts of glioblastoma, stem cells generally en-
compass four core cell attributes: i) relative quiescence,
ii) a sub-population from which post-chemotherapy (irra-
diation, resection) glioblastoma preferentially re-grows,
iii) enhanced in vitro clonogenicity where, relative to
the non-stem population, fewer cells are required to establish
three dimensional growth in soft agar, and iv) they can di-
vide symmetrically or asymmetrically to both stem or non-
stem daughter cells [3, 31–33].

Melatonin—whether by agonism at M1 or M2 or by both
is unclear—empirically lowers glioblastoma cell proliferation
generally and the stem sub-population plating efficiency
(clonogenicity) specifically [34]. The mode of glioblastoma
stem sub-population death is autophagy [34]. Melatonin
alone shows cytotoxicity to two glioma cell lines that also
lower IC₅₀ of temozolomide by 3 to 6 fold [35]. Temozolo-
amide is currently the mainstay cytotoxic drug in treating
glioblastoma [3, 36]. Under either hypoxia or normoxia,
melatonin slows centrifugal migration of glioblastoma cell
lines [37]. This would be of considerable benefit were this
to hold in vivo and in human disease, given that it is pre-
cisely these post-primary resection centrifugally migrating
cells that go on to kill patients.

A remarkable study from 1996 that does not seem to
have been followed up showed that of glioblastoma pa-

tients given 60 Gy irradiation plus 20 mg melatonin orally
daily for 1 year, 6 of 14 were alive, while in the control
group, given 60 Gy alone, only 1 of 16 was alive at 1 year
[38]. Two years later (in 1998) this same group published
a study in a group of various advanced stage cancers
claiming survival benefit from melatonin 20 mg orally per
day plus an aloe extract [39]. Procedural study weakness-
es and non-replication by others prevent analysis of this
data. Still, miraculous and unrefuted results, over a de-

cade old and neither replicated nor followed up, neither
widely instituted or acknowledged, should not, cannot, be
assumed just on that basis to be incorrect.

Agomelatine

Agomelatine is a 243 Da melatonin agonist licensed by
the EMA (but not the FDA) for treating depression [40]. It
has a higher affinity to both M1 and M2, with a pKi of about
10 nM, than does the natural ligand and longer half-life —
about two hours [4, 14, 41], see Table 1. The evanescent
nature of any circulating melatonin has been previously
noted as a clinical problem [4], an impediment to effective
treatment using exogenous melatonin itself. Added dis-
advantages include melatonin’s poor and erratic oral bio-
availability [12] with correspondingly highly variable blood
levels in subjects given identical doses [42].

Agomelatine is marketed as an antidepressant with
dual modes of action: a) agonism at M1 and M2 melatonin
receptors and and b) antagonism at serotonin 2 C recep-
tors (5-HT2C) [43–46]. It readily penetrates the blood-brain
barrier. The status or efficacy of agomelatine as an anti-
depressant is uncertain as of spring 2015, but its excellent
tolerability is unequivocal [41] as is its ability to improve
sleep during a major depression [47, 48], indicative of po-
tent M1/M2 agonism.

Ramelteon

Ramelteon is a 259 Da, brain-penetrant melatonin ago-


nist, FDA approved [but not approved by the EMA] to help
sleep initiation [49, 50]. It is remarkably free of side effects
[49–51], in part because of receptor agonism limited to M1
and M2 melatonin receptors. Also of note, ramelteon affinity
to M1 and M2 exceeds that of melatonin itself by an or-


der of magnitude, and oral absorption is good. Circulating
half-life of ramelteon is several times longer than that of
melatonin [52], see Table 1.

Augmenting the augmenter

Increasing ramelteon exposure

Ramelteon is metabolised primarily by hepatic CYP 1A2
[53, 54]. The antidepressant serotonin reuptake inhibitor
fluvoxamine is one of the most potent inhibitors known
of CYP 1A2 and empirically is found to increase circulating
ramelteon levels > 100 fold [54, 55], thus giving us the po-
tential to strongly stimulate M1 and M2 receptors on glio-


blastoma cells, augmenting the augmentation ramelteon
might offer when added to other glioblastoma treatments.

Interleukin 2 and melatonin receptors

Interleukin-2 (IL-2) is a 14 kDa protein that contributes
to driving T lymphocyte clonal expansion [56, 57]. Exog-


enous IL-2 is the first safe and effective pharmacological
agent augmenting immunological anti-cancer effects, of-
ten giving complete regression in metastatic melanoma
and renal cancer [56–58]. Interleukin-2 is in active study
for use in other cancers [59].

The wide array of proposed mechanisms by which
melatonin might exert its anti-cancer effects have been
reviewed elsewhere [60]. Increasing IL-2 might be one of
them. Lymphocytes bear melatonin receptors [61]. Of cen-
tral importance, melatonin exposure enhances lympho-

cyte’s IL-2 synthesis [62, 63]. Empirically, oral melatonin,
20 mg per day given to hepatocellular patients along with
transarterial catheter embolisation, increased circulating
IL-2 compared to those receiving embolisation alone [64].
We would expect agomelatine and ramelteon to be even
more potent and effective in this regard, given these drugs’
higher affinity to melatonin receptors and longer half-life
than the natural ligand.

Caveats

Cancers have multiple dysregulated physiological sys-
tems that act together as an ensemble to mediate malig-
nant behaviour. These dysregulated systems are different
over time and space and are different in different parts
of the same tumour, so single biopsy study will not give
an accurate picture of the complete array of dysregulated
systems active over time in a particular tumour. Growth
driving systems are not stable; they shift. These systems
cross-cover for each other when a pathway is blocked by
our drug treatment, others easily take over, compensating
for the inhibited pathway, implying a requirement for ex-
tensive polypharmacy for effective treatment, as in Nile
Distributary Problem.
Several non-oncology drugs with ancillary attributes that inhibit these pathways can be used simultaneously to block enough pathways to stop growth. This requires an admittedly unpleasant extensive polypharmacy. CUSPP9* [1] is the ten-drug treatment protocol for recurrent glioblastoma resulting from these considerations.

There is debate as to what degree the antioxidant effect of melatonin is mediated by the molecule itself or intracellular physiological events consequent to M1 or M2 agonism [65, 66]. Since several elements of CUSPP9* increase intracellular reactive oxygen species (ROS), and by design such an ROS increase contributes to anti-glioblastoma action, melatonin agonists like agomelatine or ramelteon might best be combined with polypharmaceutical regimens that do not rely on or mediate an increase in intracellular ROS as part of their mechanism of anti-cancer action, until this matter is settled. In other words, melatonin agonists might not be suitable for combination with CUSPP9* itself. Given the data on melatonin’s potent enhancing of temozolomide cytotoxicity to glioma cell lines [35], adjuvant agomelatine or ramelteon might be best used during initial Stupp Protocol treatment (temozolomide with 60 Gy irradiation) [3].

Conclusions

The limited progress in treating glioblastoma evident over the last decades prompts us to look beyond the traditional array of cytotoxic drugs for new paths to attack this hardy cancer. To augment the current standard cytotoxic drug in glioblastoma, temozolomide, we have briefly outlined past data showing how glioblastoma cells express both melatonin receptors M1 and M2, the stimulation of which seems to be a negative regulator of glioblastoma cell growth. We have readily available, potent, and well-tolerated M1 and M2 agonist drugs agomelatine [EMA approved, marketed in EU] and ramelteon [FDA approved, marketed in the USA]. These melatonin receptor agonists have significant advantages over the natural ligand: longer half-life, better oral absorption, and higher affinity to melatonin receptors.

The Stupp Protocol, maximal feasible resection, irradiation, and classic cytotoxic chemotherapy with temozolomide [3] is the current standard initial treatment for glioblastoma. As outlined, ideally agomelatine or ramelteon would be part of a coordinated polypharmacy. However, at the least, given three prominent facts: i) survival more than two years after diagnosis is still unusual, ii) agomelatine and ramelteon are exceptionally well-tolerated, very low risk medicines, and iii) the outlined data showing melatonergic agonism augments temozolomide cytotoxicity to glioblastoma cells, the risk/benefit of adding agomelatine or ramelteon to standard Stupp Protocol is highly skewed to proceeding to study such addition.

As in the Preamble, adjunctive agomelatine and ramelteon added during an appropriate phase of glioblastoma treatment might be an effective way to apply more force, making a dent in this heretofore intractable disease.

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