Abstract. Glioblastoma is the most common type of malignant brain tumor among adults and is currently a non-curable disease due primarily to its highly invasive phenotype, and the lack of successful current therapies. Despite surgical resection and post-surgical treatment patients ultimately develop recurrence of the tumour. Several signalling molecules have been implicated in the development, progression and aggressiveness of glioblastoma. The present study reviewed the role of interleukin (IL)-6, a cytokine known to be important in activating several pro-oncogenic signaling pathways in glioblastoma. The current study particularly focused on the contribution of IL-6 in recurrent glioblastoma, with particular focus on glioblastoma stem cells and resistance to therapy.

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1. Introduction

Gliomas are histologically divided into four main grades based on World Health Organisation (WHO) criteria. Grade II astrocytomas are known as diffuse astrocytomas, while grade III are anaplastic astrocytomas (AA) and are considerably more proliferative and infiltrative than grade II gliomas (1). Yet, grade IV astrocytomas or glioblastoma, despite being histologically similar to AA, are notably more proliferative, invasive and angiogenic (2). Glioblastoma is the most common and aggressive tumour of the central nervous system, and it represents 17% of all primary intracranial tumours (3). The current standard of treatment for patients with glioblastoma is maximal surgical resection, concurrent and adjuvant temozolomide and radiotherapy (known as the Stupp protocol) (4). Despite this standard of care treatment, the median survival is less than 15 months, median progression-free survival is less than 7 months and 5-year survival rate of treated patients is about 10-20% (4,5).

The tumour microenvironment plays numerous key roles in cancer progression including the release of cytokines and other effectors that mediate responses and events that aid in tumour growth (6,7). These cytokines promote factors that are central to cancer formation and progression, incorporating sustained growth, cell migration, inhibition of apoptosis and differentiation of tumour cells. It is well established that the IL-6-STAT3 signalling pathway, along with other inflammatory cytokines such as IL-1β, IL-23 and TNFα has been implicated in cancer progression in many tumour types including glioblastoma contributing to tumour resistance and recurrence of glioblastoma (8).

2. Interleukin-6 signalling in glioblastoma

Interleukin-6 (IL-6). The ligand IL-6 is a pleiotropic cytokine of about 25 kDa (9). It was first discovered as a B cell differentiation factor (BSF-2), which induces maturation of B cells, but has since been identified as having an important role in inflammation-linked cancers, including prostate, breast, gastric, colon, lung and brain (10). IL-6 is often expressed when there are stimuli that are associated with tissue damage or stress, such as UV, viruses and the expression of other pro-inflammatory cytokines (11-13). It can be overexpressed during inflammation as an acute-phase response (14). During this inflammatory response, tumour necrosis factor alpha (TNFα) induces the expression of IL-6 (15). IL-6 subsequently regulates the inflammatory response by decreasing the expression of other pro-inflammatory cytokines along
with up-regulating anti-inflammatory cytokines, such as IL-1 (15,16). IL-6 has also been shown to inhibit TNFa expression (17), demonstrating its pleiotropic nature.

IL-6 is part of the IL-6 cytokine family, which consist of IL-11, IL-27, leukaemia inhibitor factor (LIF) and oncostatin M (OSM) (18). They share the common co-receptor (gp130 \( \beta \) subunit), which is expressed in almost every tissue and organ in the body. It is this subunit that is responsible for the transmission of signalling into the cell by activating associated cytoplasmic tyrosine kinases (e.g. JAK), resulting in the phosphorylation of various transcription factors including STAT3 (18,19). Among the family of IL-6 cytokines, attention has focussed on IL-6 itself, as its expression levels are highly up-regulated and has been shown to be correlated with poor survival in many cancers.

**IL-6 triggered JAK-STAT3 signaling in glioblastoma.** IL-6 binds and signals through its own distinct receptor alpha subunit (IL-6R\( \alpha \); 80 kDa) on the plasma membrane (20). This IL-6/IL-6R\( \alpha \) complex then associates with the shared IL-6 family co-receptor gp130, resulting in an activated hexameric complex (two molecules of IL-6, two molecules of IL-6R\( \alpha \) and two molecules of gp130). There are two types of IL-6 mediated signalling: Classical and trans-signalling. Classical IL-6 signalling is the major form of IL-6 signalling and the membrane-bound IL-6R (mIL-6R\( \alpha \)) which is only expressed in certain tissues such as hepatocytes, some epithelial cells and leukocytes (21). Alternatively, the trans-signalling mechanism allows IL-6 signalling to occur in more cell types, as gp130 is expressed ubiquitously. This occurs due to trans-signalling of soluble IL-6R\( \alpha \) (sIL-6R\( \alpha \)), which lacks the trans-membrane domain, through the interaction with gp130. sIL-6R\( \alpha \) is then generated by the alternative splicing of the IL-6R\( \alpha \) mRNA by cytoplasm-bound metalloproteinases (ADAM10 and ADAM17) (18,22-24). As a result, the presence of sIL-6R\( \alpha \) permits IL-6 signalling to occur in adjacent cells. Both signalling pathways lead to the activation of JAK proteins, which are responsible for intracellular signalling and the subsequent phosphorylation of STAT transcription factors, in particular STAT3 (25).

Several studies demonstrate a correlation with IL-6 expression with glioma tumour grade and overall patient survival. IL-6 mRNA expression was found to be significantly greater in glioblastoma patient samples compared to those with lower histopathological grade (including Grade II and III astrocytomas and Grade I pilocytic astrocytomas; Table I) (26). In addition, no IL-6 gene amplification was detected in low-grade or anaplastic tumors (0/17), whereas amplification was found in 15 out of 36 (42%) glioblastoma sections (27). Importantly, this IL-6 gene amplification correlated with significantly shorter survival compared to glioblastoma patients without amplification (27).

In addition, immunohistochemistry analysis identified the IL-6 receptor expression in 6/6 (100%) patient glioblastoma samples compared to 0/7 (0%) in normal brain tissue (28). IL-6 has also been detected in the cerebrospinal fluid of 11/13 (85%) and the tumor cyst fluid of 5/5 (100%) glioblastoma patients (29). In contrast, only 3/16 (19%) cerebrospinal Fluid (CSF) samples obtained from control patients had detectable IL-6 levels (29).

Once IL-6 has bound, the \( \beta \) subunit (gp130) homodimerises and the receptor-associated Janus Kinase (JAK1, JAK2 and Tyk2) become activated (18). Activated JAKs act as a platform for phosphorylation of STAT3. Two STAT3 monomers can form a dimer and up-regulate STAT3 target genes in the nucleus (Fig. 1). The STAT protein family is a group of transcription factors that play crucial roles in the transmission of extracellular signals into the nucleus for the transcription of a variety of genes (30,31). In cancer research, there is particular focus on STAT3 because of its oncogenic abilities. STAT3 up-regulates genes that can facilitate tumour survival, angiogenesis, resistance to cell death and cell cycle progression. Target genes of STAT3 include vascular endothelial growth factor (VEGF), Bcl-2, Bcl-xL, cyclin D1, human telomerase reverse transcriptase and c-myc (30).

Involvement of STAT3 in tumourigenesis was first described in fibroblasts and epithelial cells that were transformed by Src tyrosine kinase, where constitutive STAT3 activity was first observed (32,33). This was further supported in transgenic mice (transformed with v-src), where they developed astrocytoma that led to secondary glioblastoma (34). It only became clear that STAT3 itself could be implicated in cancer when it was found that dominant-negative STAT3 decreased tumourigenesis behaviour of src-transformed cells, whereas constitutively active STAT3 enhanced tumourigenesis (32,35,36). Interestingly, mutations within the STAT3 gene are rare, indicating that constitutive activation of STAT3 is usually due to abnormal signalling from upstream regulators, such as IL-6 (33).

STAT3 is activated in a high percentage of glioblastoma (37-39). It contributes to tumourigenesis in glioblastoma by inhibiting apoptosis, which has been demonstrated by the use of RNAi knockdowns and STAT3 inhibitors (39,40). It has also been observed that recurrent glioblastoma tumours exhibit increased phosphorylated STAT3 levels when compared with primary glioblastoma (41). Moreover, tumours which exhibited greater nuclear localization of STAT3 correlated with lower rates of recurrence-free survival and overall patient survival.

Interestingly, another study reported that the down-modulation of pSTAT3-Y705 resulted in resistance to Temozolomide, as it was able to minimise O\(^4\)-methylguanine DNA methyltransferase (MGMT) expression post-transcriptionally in recurrent glioblastoma (41). It was observed in this study that STAT3 inhibition reduced MGMT levels, which led to the re-sensitisation to Temozolomide treatment (41). Potential therapies utilising STAT3 as a target are currently being investigated and clinical trials are underway for pSTAT3-Y705 inhibitors (42).

**IL-6 signalling in glioma development and cell invasion and migration.** It is well established that IL-6 signalling plays a crucial role in a variety of cancers, whereby expression levels of IL-6 mRNA and protein are significantly increased in colorectal (43), prostate (44), breast (45), ovarian (46), pancreatic (46,47), lung (48) and cervical cancer (49). Weissenberger and colleagues showed the importance of IL-6 signalling in glioma and its impact on the tumorigenicity in glioblastoma, using transgenic mice (50). Mice expressing the GFAP-v-src\(^+\) transgene develop spontaneous astrocytomas with a penetrance of around 21% (12 out of 56). However, only 1 out of 35 transgenic mice (3%) that lack IL-6 developed astrocytic tumour formation (50).
IL-6 signalling promotes a variety of activities that support gliomagenesis including cell invasion and migration, contributing to the invasive nature of glioblastoma, resulting in reduced treatment efficacy and high rates of recurrence. STAT3 activation induced by IL-6 signalling has been shown to promote cell invasion and migration in U251 and T98G glioblastoma cells (51). In a study by Liu et al (51), increased levels of IL-6 positively correlated with the levels of matrix metalloproteinase-9 (MMP-9) expression. MMPs belong to a family of proteases responsible for degrading extracellular matrix proteins and play a major role in migration (both adhesion and dispersion) as well as cell proliferation. Similarly, a study by Li et al (52), demonstrated IL-6 stimulation of U87MG glioblastoma cells resulted in increased MMP-2 expression and secretion and enhanced cell invasion.

Furthermore, IL-6 signalling correlates with increased fascin-1 expression. Fascin-1 is involved in cell invasion by the formation of actin-based protrusions known as invadopodia and the subsequent degradation of the extracellular matrix to promote migration and invasion (52). Immunofluorescence staining of fascin-1 revealed that the number of protrusions increased and fascin-1 protein was localised to the peripheries of the cell when glioblastoma cells were treated with IL-6. This study demonstrated that IL-6 signalling influences the distribution of fascin-1 and alters the structural aspects of the cell to become a more invasive phenotype in glioblastoma cells (51).
IL-6 signalling and tumour angiogenesis. Tumour angiogenesis is another crucial process that is required for the growth and invasion of tumours. Angiogenesis requires migration of vascular endothelial cells into the tumour bulk (51). This process involves the release of mediators such as TNF-β, TNF-α, MMP-9, MMP-2 and VEGF (53). The STAT3 transcription factor is known to up-regulates the expression of VEGF-2 and its receptor, VEGFR-2, contributing to invasion through the action of IL-6 signalling and subsequent JAK-STAT3 activation (54-56). IL-6 secretion into neighbouring cells further induces this behaviour, thereby promoting cell migration through these vascular endothelial cells (51).

VEGF is an important mediator in tumour-induced angiogenesis. It has been observed that high expression of VEGF correlates with higher tumour grade and shorter survival (57,58), while one of the mechanisms of progression in glioblastoma is postulated to involve tumour resistance to anti-angiogenic treatments (59,60). This may be due to these angiogenic switches and up-regulation of different angiogenic pathways (57,61-63) as well as mesenchymal cell transition (64).

Another essential pro-angiogenic factor is fibroblastic growth factor-2 (FGF-2), which is a heparin-binding protein that has a range of roles, including serving an important pathway in tumorigenesis (65). Recent research has indicated that both VEGF and FGF2 work together to influence the process of angiogenesis. It has been shown that when both factors are expressed in mouse models, there is enhanced tumour growth coupled with the presence of high density vessels. When either FGF2 or VEGF signalling is inhibited, the rate of the tumour growth decreases significantly (65-67). Although an early study (20) showed that IL-6 acts as a growth factor in glioblastoma, a more recent study did not reach this conclusion and demonstrated that IL-6 did not have a proliferative effect in GBM cell lines, but instead promoted a more invasive phenotype by increasing the migration ability of cells (51).

IL-6 signalling promotes resistance to cell death. In addition to evading growth suppression signaling through the loss of TP53 function, tumours such as glioblastoma are also associated with an increase in the expression of anti-apoptotic regulators or down-regulation of pro-apoptotic factors. IL-6 signalling disrupts the balance between anti- and pro-apoptotic protein expression by favouring anti-apoptotic signalling through JAK-STAT3 activation, as well as NF-kB signalling, which activates the expression of many anti-apoptotic proteins such as Bcl-2, Bcl-xL and Mcl-1 (51,68). These anti-apoptotic proteins are also important in cell proliferation as they are direct targets of STAT3 (69). Other than increased Bcl-2 and Bcl-xL expression, IL-6 also promotes the expression of survivin through JAK-STAT3 activation (69,70). It has been found that the downregulation of survivin by inhibiting STAT3 induces apoptosis in tumour cells (70).

3. Glioblastoma stem cells

Cancer stem cells (CSCs) are a group of tumour cells that have stem cell-like properties and are capable of self-renewal. Studies have shown that CSCs are critical in the progression of cancer and resistance to various therapies in different types of solid tumours, including brain tumours (71-76). In recent years the cancer stem cell (CSC) hypothesis has grown in popularity. This states that a small group of cells can maintain the cancer growth and survival, whilst providing resistance to therapy. It has been established that gliomas are one of the tumours where cancer stem cells, or glial stem cells (GSCs) has been established (77,78). Subsequently, GSCs have been intensely studied for understanding their capacity for self-renewal and importantly, their contribution to therapeutic resistance as well as tumour recurrence (79). GSCs are thought to play important roles in gliomagenesis, recurrence and aggressiveness (80,81).

In other cancers, IL-6 is also implicated in promoting STAT3 mediated CSC expansion, such as in prostate and breast CSCs (82-84). Through the activation of JAK-STAT3 signalling (mainly from IL-6 signalling), hypoxic conditions activate these CSCs and promote self-renewal (85). It was found that upon STAT3 inhibition, GSCs lose their stem-cell phenotype permanently, suggesting that STAT3 is required for the self-renewal and growth of stem cells within glioblastoma (40,86). The contribution of CSCs to the difficulty of cancer treatment and therapy is crucial, and targeting the JAK-STAT3 pathway may therefore become a potential mechanism to overcome CSC-mediated Temozolomide resistance in glioblastoma and other solid tumours.

Several studies have found that GSCs express the IL-6 receptor and ligand, which indicates that IL-6 could be a potential cytokine to contribute to the tumourigenicity of these GSCs. Wang et al (2009) (87) found that GSCs co-expressed elevated levels of IL-6Ra and gp130 (β subunit), as demonstrated by immunofluorescence staining, although they also showed that IL-6 mRNA levels were lower in GSCs than non-GSCs. Knockdown of IL-6 or IL-6Ra by shRNA led to reduced cell growth, neurosphere formation and increased cell death in GSCs isolated from D456MG human glioma xenografts. IL-6 or IL-6Ra suppression also led to reduced tumour growth and increased survival of mice bearing intracranial xenografts (87). IL-6 has also been shown to induce the expression of glioma pathogenesis-related 1 (GPR1, also known as RTVP1) via the STAT3 pathway (88). GPR1 plays an important role in GSCs, contributing to migration, resistance to therapy and tumour recurrence. GPR1 was originally discovered in glioblastoma as one of the target genes of the tumour suppressor gene p53, one of the most commonly mutated genes in human cancer.

STAT3 has been shown to be highly expressed in GSCs, and inhibition of STAT3 levels has led to decreases in the proliferation of these GSCs (40). Furthermore, inhibition of STAT3 also diminishes the multipotency characteristic of these GSCs. STAT3 has been identified as a potential target for CSC-mediated therapy as it is the convergence point for many signalling pathways. It has been found that inhibition of STAT3 using a shRNA approach prevented proliferation and formation of neurospheres in GSCs (30,40,89). Moreover, leukaemia inhibitory factor (LIF), a member of the IL-6 family, has been found to be responsible for the tumour development of GSCs via the JAK-STAT pathway (90).

4. Therapeutic targets in recurrent glioblastoma

The importance of targeting the STAT3 signalling pathway due to its function in recurrence, GSCs and resistance to
The disruption of upstream receptor tyrosine kinases is one of the potential methods for inhibiting STAT3 activity. By inhibiting JAKs, growth factor receptors, receptor tyrosine kinases (RTKS) and cytokine receptors, it would be possible to alter downstream STAT3 activity. However, STAT3 is the convergence point of several oncogenic signalling pathways, including EGFR, heregulin-2/neuregulin receptor (Her2/Neu), Platelet Derived Growth factor receptor, IL-6R/gp130, c-Met, Abelson Leukemia protein (Abl), and Src tyrosine kinases. Therefore, it would be probable that a compensatory pathway could override the initial inhibition of STAT3 (94-98). On the other hand, preventing homodimerisation of STAT3 involves blocking the SH2 domains from coming together after STAT3 phosphorylation, and ultimately inhibiting STAT3’s transcription capabilities. Thus far, studies have targeted the SH2 domain to prevent homodimerisation (99-102). Two groups (100,101) have shown that blocking the phosphorylated tyrosine peptide at position 705 was able to prevent STAT3 from binding to DNA in the nucleus and furthermore, the SH2 domain of STAT3 has been shown to interact with upstream signalling proteins to STAT3, including EGFR and IL-6 and its receptor. Studies that have targeted this particular homodimerisation have generated positive results, yet they have yet to be translated into an in vivo setting (28,103-105).

5. Mechanism of STAT3 action in recurrent glioblastoma

JAK/STAT activation. There is a lack of evidence regarding the mechanism of action of over-activation of STAT3 in recurrent glioblastoma. The STAT3 signalling pathway has been extensively investigated in primary glioblastoma, but it has not yet been shown why phosphorylated STAT3 is overexpressed in recurrent glioblastoma compared to primary glioblastoma (44). Furthermore, increased phosphorylation of STAT3 has been correlated with increased grade of astrocytoma (106,107). Based on this evidence, it is possible that STAT3 could be considered as a prognostic factor. Tu et al (107), have demonstrated that

<table>
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<tr>
<th>Author, date</th>
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<th>Target</th>
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<tr>
<td>Ashizawa et al, 2013</td>
<td>STX-0119</td>
<td>STAT3</td>
<td>Reduced cell growth and induced apoptosis in vitro, reduced tumour growth in vivo</td>
<td>(30)</td>
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<td>Rahaman et al, 2002</td>
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<td>JAK2/STAT3</td>
<td>Reduced cell growth in vitro and in vivo</td>
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<td>(116)</td>
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<td>Reduced cell growth in vitro and in vivo</td>
<td>(117)</td>
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<tr>
<td>McFarland et al, 2011</td>
<td>AZD1480</td>
<td>JAK1/2</td>
<td>Reduced cell growth and induced apoptosis in vitro, reduced tumour growth in vivo and enhanced survival of mice bearing intracranial tumours</td>
<td>(119)</td>
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<td>He et al, 2013</td>
<td>G5-7</td>
<td>JAK2</td>
<td>Reduced cell growth in vitro and in vivo</td>
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<td>Senft et al, 2011</td>
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<td>JAK2</td>
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<td>Fuh et al, 2009</td>
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<td>Cpd188</td>
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JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3.

Temozolomide is well established (90). Therapeutic targets of STAT3 have been investigated, but only a small number has been tested against glioblastoma (summarised in Table II). Furthermore, there has not been much success at preventing downstream nuclear signalling (91). Studies into STAT3 inhibitors should continue, as the importance of this pathway is continually being demonstrated (92,93). Furthermore, the inhibitors that have been investigated with glioblastoma generally have had significant challenges in the translation into clinical practice, mainly because of the form of administration, toxicity, cell permeability and non-selective activity (91).
JAK/STAT activation is correlated to higher grade gliomas, and furthermore, it was shown that JAK/STAT activation is a prognostic indicator of decreased survival. One potential mode of action is through a mutated MSH6 gene, which has been correlated with a methylated O6-methylguanine-DNA transferase (MGMT) promoter, whose cellular levels are known to be regulated by STAT3 through IL-6 (41). This potential mechanism is outlined in the next section.

IL-6-STAT3 signaling and MGMT. Currently, the DNA repair protein, MGMT, is the most studied predictive biomarker of response to temozolomide treatment in patients with glioblastoma. Temozolomide exerts its cytotoxic activity by methylating specific DNA sites including the O6 position of the nucleotide guanine, resulting in cell death (108). MGMT directly inhibits the cytotoxic effect of temozolomide by removing the methyl group off the O6 position of guanine in DNA (109,110). Thus, patients with glioblastoma that expressed reduced MGMT due to epigenetic methylation of the MGMT promoter have better response rates to temozolomide and are associated with longer overall survival (Fig. 2) (111).

A study by Piperi et al (112) identified methylation of MGMT in 58.8% of tissue surgically resected from 23 glioblastoma patients. Patients with tumour tissue containing MGMT methylation had a poorer overall median survival of 12 months compared to patients with tissue absent of MGMT methylation (16 months). Importantly, MGMT methylation in this study was found to also correlate with IL-6 expression (112). Despite this paper not examining STAT3 activity, one can speculate that enhanced STAT3 activation (through increased IL-6 expression) may mediate temozolomide sensitivity and poorer overall outcomes.

In support of this notion is the study from Koksaka and colleagues who did indeed evaluate a potential correlation between phosphorylated STAT3 and MGMT expression (41). In this paper, a significant correlation was observed between pSTAT3 staining intensity by immunohistochemistry with MGMT expression in 44 surgically resected human glioma specimens. Koksaka and colleagues also generated a U87MG sub-population that was temozolomide-refractory after 3 weeks of continuous exposure to low-dose temozolomide. These resistant cells designated U87R displayed greater expression of IL-6, STAT3 and MGMT compared to their sensitive parental counterparts. Importantly, pharmacological inhibition of STAT3 or STAT3 knockdown with shRNA resulted in reduced MGMT expression in the U87R cells and other glioblastoma cell lines. STAT3 inhibition also re-sensitized cells to temozolomide (41).

Taken together, these articles strongly link IL-6-STAT3 signaling with MGMT expression and methylation and to temozolomide sensitivity. However, further studies are required to investigate the mechanisms of action for the epigenetic control of tumour cell functions by IL-6. Overall, it would be advantageous to extensively study the potential of IL-6/STAT3 inhibitors on MGMT expression levels, and determine if this could potentially aid in overcoming temozolomide resistance in glioblastoma considering that MGMT requires STAT3 activation to modulate cellular levels of MGMT.
6. Conclusions

Understanding how overexpressed or over-active signaling pathways promote recurrent glioblastoma progression may lead to the development of new therapies. In particular, targeting the important IL-6-JAK/STAT3 signaling pathway should result in reduced tumour proliferation and invasion and improved patient outcomes. In addition, therapeutic targeting of STAT3 and its components may provide a basis for sensitising these recurrent tumours to the currently available treatments for glioma. For this strategy to proceed, further preclinical research into how IL-6-STAT3 promotes glioblastoma recurrence and progression is still required.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

AJW, VT and RBL contributed to the writing of this manuscript, while HPTN, SSS, APM, AHK and RBL contributed the conception design and editing of the manuscript.

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Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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human brain tumors


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Author/s:
West, AJ; Tsui, V; Stylli, SS; Nguyen, HPT; Morokoff, AP; Kaye, AH; Luwor, RB

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