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Genetic Diversity of Glioblastoma Multiforme: Impact on Future Therapies

Franz-Josef Klinz[1], Sergej Telentschak[1], Roland Goldbrunner[2] and Klaus Addicks[1]
[1]*Department of Anatomy I, University of Cologne,*
[2]*Department of Neurosurgery, University of Cologne, Germany*

1. Introduction

Glioblastoma multiforme (GBM; WHO grade IV) is the most malignant type of glioma and in addition the most abundant malignant cancer of the adult human brain. Despite progress in diagnosis, surgery and chemotherapy, the median survival time of patients suffering from GBM is approximately 15 months (Stupp et al., 2005). The five years survival time is less than 5% (CBTRUS, 2010). Because glioblastoma cells show a highly infiltrating growth into the brain tissue, a total resection is not possible. In addition, glioblastoma cells are remarkably resistant to chemotherapy and ionizing radiation. In addition, the association of a portion of these cells with hypoxic and necrotic areas within the tumor increases their resistance.

Gliobastoma multiforme tumors can be classified:

1. by histopathology (WHO) in conventional glioblastomas (93%), giant cell glioblastoma (5%) and gliosarcoma (2%);
2. by pathogenesis in primary GBM (90%) and secondary GBM (10%);
3. by gene expression analysis in (I) classical, (II) mesenchymal, (III) proneural or (IV) neural type of GBM;
4. by genomic analysis in subgroups harboring specific mutations and/or altered gene dosage/chromosome number.

Conventional glioblastomas constitute approximately 93% of all glioblastomas and can be divided into primary or secondary tumors: primary glioblastomas represent approximately 90% and develop de novo, whereas the incidence of secondary glioblastomas that arise from astroyctomas WHO grade II and III is in the range of 5 to 10%. Primary and secondary glioblastomas differ in their genetic defects: for example 39% of primary glioblastomas harbor an amplification of the EGF receptor (EGFR) locus, whereas in secondary glioblastomas no amplification was detected. Mutations within the p53 gene are more abundant in secondary glioblastomas. Unconventional glioblastomas include giant cell glioblastomas, gliosarcomas and other rare types (for details see section 4).

	Conventional Glioblastoma		Giant cell glioblastoma	Gliosarcoma
	Primary glioblastoma	Secondary glioblastoma		
Frequency	93%		5%	2%
	90%	10%		
Clinical onset	de novo	secondary	de novo	de novo
Preoperative history (mo)	1,7	>25	1,6	2
Age at diagnosis (yr)	55	39	42	56

Table 1. Clinical profile of the common histopathological glioblastoma subtypes according to WHO. Modified from Kleihues et al., 2007; Peraud et al., 1997; Peraud et al., 1999 and Reis et al., 2000.

2. Genetics of glioblastoma multiforme

2.1 Genetic defects in human cancer

For an introduction into the history of this field the reader is referred to the review of Bignold et al. (2006). Abnormalities of mitoses and chromosomes in cancer cells were described in late 1880s and Hansemann (1890) suggested that cancer cells develop from normal cells due to a tendency to maldistribute chromosomes during mitosis. The term somatic mutation was introduced into tumor biology by Tyzzer (1916). To explain the complexity of cancer phenomena "multi-hit" models (Knudson, 1971) increased in popularity over "single-hit" models of somatic mutation. In the multistep progression model of sporadic colorectal carcinoma five to ten genetic alterations seemed to be necessary for generation of the malignant phenotype (for review see: Fearon and Vogelstein, 1990). The onset and extent of genetic alterations in progression of sporadic colorectal tumors was studied in detail by Stoler et al. (1999). Their observation of about 10,000 genomic alterations occurring per cancer cell has brought into attention the issue of genetic instability in human cancer. Genetic and phenotypic instability are hallmarks of cancer cells and appear early in tumor progression; most cancers are of clonal origin, but individual cancer cells are highly heterogenous. There are three major forms of genetic instability in cancer: (1) aneuploidy, in which entire chromosomes are lost or gained; (2) intrachromosomal instability, distinguished by insertions, deletions, translocations or amplifications and (3) point mutations, which accumulate in certain forms of hereditary cancer as well as in a small portion of sporadic cancers. Stanbridge et al. (1981) reported that specific chromosome loss is associated with the expression of tumorigenicity in human cell hybrids. It was published by Duesberg et al. (1998) that genetic instability of cancer cells is proportional to their degree of aneuploidy. Aneuploidy, an abnormal number of chromosomes, is the result of asymmetrical segregation of chromosomes to daughter cells during mitosis. Once aneuploid, cells will continue to segregate chromosomes asymmetrically during subsequent rounds of mitosis, a process that has been termed "chromosome error propagation" (for review see: Holliday, 1989).

Unlike oncogenes, tumor suppressor genes generally follow the "two hit" model, which implies that both alleles of a particular tumor suppressor gene have to be inactivated before an effect is manifested. If only one allele is inactivated, the second correct allele can still produce the correct protein. Whereas mutant oncogene alleles are typically dominant, mutant tumor suppressor genes are usually recessive.

The mutational activation of oncogenes induces loss of heterozygosity and genomic instability in mammalian cells. These results have used to formulate the oncogene-induced replication stress model (for review see: Halazonetis et al., 2008). In precancerous lesions with intact p53 gene, the oncogene-induced DNA damage leads to p53-dependent apoptosis and/or senescence. After the function of p53 is lost, cells are able to escape its apoptotic and/or senescence effects, and the precancerous lesion is predestinated to become cancerous (Gorgoulis et al., 2005; Bartkova et al., 2005; Bartkova et al., 2006; Di Micco et al., 2006). DNA damage has an important role in promoting polyploidization. If cells with altered DNA enter mitosis, defects in chromosomal segregation and cytokinesis occur (for review see: Chow and Poon, 2010).

The gene for the tumor suppressor protein p53 is mutated in about half of human cancers. It was shown recently by several groups, that eliminating p53 function by mutation leads to dramatically increased reprogramming efficiency of differentiated cells into induced pluripotent stem cells. Important for the field of cancer biology is the report of Mizuno et al. (2010), demonstrating that breast and lung cancers harboring TP53 mutations exhibit stem cell-like transcriptional signatures. These data suggest a role for active p53 in preventing the emergence of cancerous stem-like cells during tumor progression. Since TP53 mutations often arise in a late stage of tumor progression, when many cancer cells with different genetic alterations coexist, some cancer cells may be susceptible to reprogramming to generate stem-like cancer cells, leading to further tumor progression and cellular heterogeneity.

2.2 Genetic diversity of glioblastoma multiforme

DNA sequencing and gene dosage analysis of GBM revealed a high number of shared as well as individual-specific mutations, deletions and amplifications of DNA sequences. A hallmark of many primary GBMs is the loss of one copy of chromosome 10 harboring the locus for the PTEN tumor suppressor gene and/or amplification of the EGF receptor locus at chromosome 7. As a consequence, the Akt signalling pathway is often overactivated in GBM. Array comparative genomic hybridization (CGH) analyses revealed, that primary glioblastomas can be divided into three major genetic subgroups, i.e. tumors with chromosome 7 gain and chromosome 10 loss, tumors with chromosome 10 loss and tumors without copy number changes in chromosomes 7 or 10 (Misra et al., 2005).

Parsons et al. (2008) sequenced 20661 genes coding for proteins in 22 GBM samples and 1 normal sample. They observed that 685 genes contained at least 1 non-silent somatic mutation. 94% of these alterations were single base substitutions that were uniformly distributed among the 21 GBM samples, resulting in an average of 47 mutations per GBM. About 15% of the missense mutations were predicted to have a significant effect on protein function. The same 22 GBM samples were analysed for copy number alterations through hybridization of DNA samples to single nucleotide polymorphism (SNP) arrays, leading to the identification of 147 amplifications and 134 homozygous deletions.

Parsons et al. (2008) next studied the probabilities that the mutations were either "driver" or "passenger". Driver mutations may provide a selective advantage to the cancer cell, whereas passenger mutations arise by the instability of the tumor genome and have no effect on tumor growth. Analysis of all data was used to identify GBM candidate cancer genes that were likely drivers, pointing to alterations in several signaling pathways: CDKN2A (altered in 50% of GBMs); TP53, EGFR, and PTEN (altered in 30 to 40%); NF1, CDK4, and RB1 (altered in 12 to 15%); and PIK3CA and PIK3R1 (altered in 8 to 10%). By analysing additional gene members within signaling pathways affected by these genes, the authors identified alterations of critical genes in the RB1 pathway (RB1, CDK4, and CDKN2A; altered in 68% of GBMs), TP53 pathway (TP53, MDM2, and MDM4; altered in 64%), and the PI3K/PTEN pathway (PIK3CA, PIK3R1, PTEN, and IRS1; altered in 50%). Mutations in the NF1 gene (coding for neurofibromatosis-related protein NF-1 or neurofibromin 1, a stimulator of GTPase activity of ras proteins) were observed in 16 of 105 GBMs (15%). Mutations in the IDH1 gene (coding for the citric acid cycle enzyme isocitrate dehydrogenase 1) were reported in 18 of 149 GBMs (12%).

The Cancer Genome Atlas Research Network (2008) study analysed 91 GBM samples and found 453 non-silent somatic mutations in 223 genes. Affected signaling pathways include TP53, PTEN, NF1, EGFR, ERBB2, RB1, NF1, PIK3R1, and PIK3CA. High-level amplifications were observed frequently for EGFR, CDK4, PDGFR, MDM2, and MDM4 genes, whereas homozygous deletion events were often associated with CDKN2A/B and PTEN genes. In this study, GBMs from patients treated with temozolomide and/or lomustine were analysed for mutations. Treatment with alkylating agents resulted in more than tenfold increase in the number of mutations, that was dependent on the methylation status of the gene for the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT).

Bredel et al. (2009) published "A Network Model of a Cooperative Genetic Landscape in Brain Tumors". The authors demonstrate that a multigene risk scoring model based on gene dosis and expression of 7 landscape genes (POLD2, CYCS, MYC, AKR1C3, YME1L1, ANXA7, and PDCD4) is associated with the overall length of survival in 189 glioblastoma samples. Yadav et al. (2009) reported that loss of function of ANXA7 (annexin 7) stabilizes the EGFR protein and increases EGFR signaling in glioblastoma cells. ANXA7 haploinsuffiency doubles the tumorigenic potential of glioblastoma cells. The heterozygous loss of ANXA7 in about 75% of GBM in the Cancer Genome Atlas Research Network study (2008) plus the observed infrequent ANXA7 mutation in about 6% of GBM is indicative for its role as a haploinsuffiency gene. A multigene predictor model of outcome in GBM based on expression analysis of 9 genes was published by Colman et al. (2009).

Verhaak et al. (2010) used gene expression analysis to divide GBM into 4 subtypes: I. Classical, II. Mesenchymal, III. Proneural, and IV. Neural. The reproducibility of this classification was demonstrated in an independent validation set. To get insight into the genomic events, the authors used copy number and sequence data from the Cancer Genome Atlas Research Network (2008).

I. Classical subtype of GBM (21% of core samples):

Neural precursor and stem cell markers NES, as well as Notch and Sonic hedgehog signaling pathways were highly expressed in the Classical subtype. Chromosome 7 amplification paired with chromosome 10 loss was seen in 100% of the Classical subtype. High level EGF receptor (EGFR) gene amplification was observed in 97% of the Classical

subtype and infrequently in other subtypes. Even though TP53 is the most frequently mutated gene in GBM (Cancer Genome Atlas Research Network, 2008), there was a distinct lack of TP53 mutations in the Classical subtype samples sequenced. Deletion events at 10q23 harboring the PTEN locus were observed in 100% of the Classical subtype. Focal 9p21.3 homozygous deletion targeting CDKN2A (encoding for both p16INK4A and p14 ARF) was frequent and co-occurred with EGFR amplification in 94% of the Classical subtype.

II. Mesenchymal subtype of GBM (32% of core samples):

The Mesenchymal subtype displayed expression of mesenchymal markers as described earlier (Phillips et al. 2006). Genes in the tumor necrosis super family pathway are highly expressed in this subtype. Focal hemizygous deletion of a region at 17q11.2, containing the gene NF1 (coding for neurofibromatosis-related protein NF-1 or neurofibromin 1, a stimulator of GTPase activity of ras proteins) occurred predominantly in the Mesenchymal subtype. NF1 mutations were found in 20 samples, 14 of which were classified as Mesenchymal subtype, resulting in 53% of samples with NF1 abnormalities.

Mutated Gene	Classical Subtype	Mesenchymal Subtype	Proneural Subtype	Neural Subtype	Approximate Overall Frequency
TP53	**0**%	32%	**54**%	21%	23%
PTEN	23%	32%	16%	21%	17%
NF1	5%	**37**%	5%	16%	13%
EGFR	32%	5%	16%	26%	13%
IDH1	0%	0%	**30**%	5%	8%
PIK3R	5%	0%	19%	11%	6%
RB1	0%	13%	3%	5%	5%
ERBB2	5%	3%	5%	16%	5%
EGFRvIII	**23**%	3%	3%	0%	5%
PIK3CA	5%	3%	8%	5%	4%
PDGFRA	0%	0%	**11**%	0%	3%

Table 2. Frequently mutated genes in Glioblastoma multiforme and their distribution among GBM subtypes according to Verhaak et al (2010). Outstanding frequencies are grayed out for comparison between subtypes. Modified from Verhaak et al. (2010).

III. Proneural subtype of GBM (31% of core samples):

The Proneural group showed high expression of oligodendrocytic genes, underlining its status as an atypical GBM subtype. The majority of TP53 mutations and TP53 loss of heterozygosity were found in Proneural samples. The classic GBM signature, chromosome 7 amplification associated with chromosome 10 loss was less prevalent and occurred in only 54% of the Proneural subtype. Focal amplifications of the locus at 4q12 harboring the PDGF Receptor A (PDGFRA) gene were seen in all subtypes of GBM but at a much higher rate

(35%) in Proneural samples. 11 of the 12 observed mutations in the isocitrate dehydrogenase 1 gene (IDH1) were found in this class.

IV. Neural subtype of GBM (16% of core samples):

The Neural subtype was typified by the expression of neuron markers. The two normal brain tissues samples examined in this data set were both classified as Neural subtype. Chomosome 7 amplification associated with chromosome 10 loss was prevalent in the Neural subtype.

		Known Cancer Gene in Region	Classical Subtype	Mesenchymal Subtype	Proneural Subtype	Neural Subtype
Amplification Events	7p11.2	EGFR	100%	95%	54%	96%
	7q21.2	CDK6	92%	89%	46%	96%
	7q31.2	MET	86%	91%	54%	92%
	7q34		86%	91%	52%	92%
	4q12	PDGFRA	5%	9%	35%	13%
Homo- and Hemizygous Deletion Events	17q11.2	NF1	5%	38%	6%	17%
	10q23	PTEN	100%	87%	69%	96%
	9p21.3	CDKN2A/CDKN2B	95%	67%	56%	71%
	13q14	RB1	16%	53%	52%	46%

Table 3. Frequency of copy number alterations in Glioblastoma subtypes according to gene expression. Modified from Verhaak et al. (2010).

2.2.1 Subtypes and clinical correlations

Three of four tumors classified as secondary GBMs were found in the Proneural group. The Proneural subtype was associated with younger age, PDGFRA abnormalities, IDH1 and TP53 mutations, all of which have been associated with secondary GBM in earlier studies (Arjona et al., 2006; Furnari et al., 2007; Kleihues and Ohgaki, 1999; Watanabe et al., 1996; Yan et al., 2009). Verhaak et al. (2010) concluded that tumors did not change class at recurrence, because recurrent tumors were found in all subtypes (Murat et al., 2008). Although statistically not significant, there was a trend towards longer survival for patients with a Proneural signature. Aggressive treatment significantly reduced mortality in Classical and Mesenchymal subtypes, had a less pronounced effect in the Neural subtype and did not alter survival in the Proneural subtype. There was no association of GBM subtype with methylation status of the DNA repair gene MGMT, which has been positively linked to therapy response (all data and conclusions from Verhaak et al., 2010).

Bredel et al. (2010) reported that NFKBIA (nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-α), an inhibitor of EGFR signaling pathway, is often deleted in GBM (Table 4). Most deletions occur in non-classical subtypes of GBM. Deletion and low expression of NFKBIA were reported to be associated with unfavorable outcomes. The authors present a two-gene model based on the expression of NFKBIA and MGMT that is strongly associated with the clinical course of GBM (Table 5).

Genetic Alteration	Classical Subtype	Nonclassical Glioblastomas		
		Mesenchymal Subtype	Proneural Subtype	Neural Subtype
NFKBIA deletion	**6**%	30%	39%	22%
EGFR amplification	**80**%	20%	11%	46%

Table 4. Relationship of four molecular subtypes of glioblastoma to gene-dosage profiles for NFKBIA and EGFR across 188 glioblastomas. NFKBIA deletions are rare in classical (6%) and more common in non-classical (32%) glioblastomas.

Irrespective of subtype a degree of mutual exclusivity between NFKBIA deletion and EGFR amplification was suggested: NFKBIA deletion or EGFR amplification were observed in 53%, whereas concomitant occurrence (NFKBIA deletion together with EGFR amplification) was observed only in 5%. All data and conclusions are from Bredel et al. (2010). Glioblastoma subtypes were classified according to Verhaak et al. (2010).

Risk Groups	NFKBIA and MGMT Expression	Median Survival	NFKBIA Expression and MGMT Promoter Methylation Status	Media Survival (Weeks)	With Radiotherapie and Temozolomide	
					NFKBIA Expression and MGMT Promoter Methylation Status	Median Survival (Weeks)
High-risk	Low NFKBIA, High MGMT	44	Low NFKBIA, Unmeth. MGMT	45	Low NFKBIA, Unmeth. MGMT	35
Inter-mediate-risk	Low NFKBIA, Low MGMT or High NFKBIA, High MGMT	59	Low NFKBIA, Meth. MGMT or High NFKBIA, Unmeth. MGMT	63	Low NFKBIA, Meth. MGMT or High NFKBIA, Unmeth. MGMT	71
Low-risk	High NFKBIA, Low MGMT	92	High NFKBIA, Meth. MGMT	91	High NFKBIA, Meth. MGMT	122

Table 5. The strong association of the clinical course of GBM with expression of NFKBIA and expression/methylation status of the promoter of O^6-methylguanine-DNA methyltransferase (MGMT). All data and conclusions are from Bredel et al. (2010).

To add an additional level of complexity, gene dosage analysis of separate tumor areas derived from one GBM revealed area-specific genomic imbalances (see chapter 5).

2.3 Correlation between genetic and histopathologic diversity in GBM

Glioblastomas are morphologically highly heterogeneous and in addition the histological features often vary in different areas of one tumor. Currently three distinct common histopathological variants of GBM are recognized by the actual World Health Organization classification scheme, including conventional glioblastoma, giant cell glioblastoma, and gliosarcoma.

Despite of lack of any histopathological difference, *primary* (de novo) and *secondary* (with an evidence of a lower-grade precursor) *conventional glioblastomas* harbor distinct molecular genetic abnormalities: Primary glioblastomas are characterized by relatively high frequencies of EGFR amplification, PTEN deletion, and CDKN2A (p16) loss, whereas secondary glioblastomas often contain TP53 mutations, especially those involving codons 248 and 273 or G:C->A:T mutations at CpG sites (Ohgaki et al., 2004).

Even within the conventional glioblastoma category, the cellular composition is heterogeneous and may include small or fibrillary, gemistocytic, granular, lipidized and occasional giant cells or oligodendroglial components. According to the predomination of one of these cell types indicating patterns of differentiation, the WHO distinguishes respective subtypes of glioblastoma such as small cell glioblastoma, glioblastoma with granular cell astrocytoma features, glioblastoma with lipidized cells; whereas giant cell glioblastoma is recognized as a distinct clinicopathologic entity (Kleihues et al., 2007; Miller and Perry, 2007).

Small cell astrocytoma is an aggressive histologic variant being often misdiagnosed as anaplastic oligodendroglioma because of considerable morphologic similarities. Despite of histological overlap clinicopathologic and genetic features are distinct: there are no small cell astrocytomas harboring 1p/19q codeletions, whereas vIII mutant form of EGFR, EGFR amplification and 10q deletions are present in 50%, 69% and 97% of small cell astrocytomas, respectively (Perry et al., 2004).

Once thought to represent a reactive component, *gemistocytes* have been found to harbor TP53 mutations and cytogenetic abnormalities (chromosome 7p gains and 10q losses); therefore, they are now thought to represent a true neoplastic component (Kros et al., 2000).

In rare cases *granular cells* may predominate and create the impression of a granular cell tumor. Similar to astrocytomas with non-granular cytology, these tumors may also harbor TP53 mutations, high-frequency loss of heterozygosity at 9p, 10q, and 17p, and less frequent loss of heterozygosity at 1p and 19q (Castellano-Sanchez et al., 2003). Brat et al. (2002) reported the largest series of such tumors to date (22 cases, including 4 grade II, 7 grade III, and 11 grade IV tumors) and found that these tumors were more aggressive than non-granular cell astrocytomas of the same grade.

Glioblastoma with oligodendroglioma component is an astrocytoma WHO-grade IV containing oligodendroglial areas varying in size and frequency (Kleihues et al., 2007). Despite of oligodendroglial component and in contrast to rather frequent codeletions in WHO grade III anaplastic oligodendroglioma (approximately 85%), deletion of either 1p (24%), 19q (43%), or combined 1p/19q (22%) is relatively infrequent in glioblastoma with oligodendroglioma component (Miller and Perry, 2007).

Giant cell glioblastoma is a rare variant that constitutes up to 5% of glioblastoma and is recognized as a distinct clinicopathologic entity in the WHO 2007 classification. Although occasional giant cells may be found in conventional glioblastoma, these cells are a predominating cytologic component in giant cell glioblastoma. As the name implies, the tumor cells are markedly enlarged and bizarre, often appear often multi-nucleated and

tumor masses are typically well-circumscribed. It occurs in younger patients (fifth decade) (Kleihues et al., 2007).
The molecular genetic features include relatively high frequencies of TP53 mutations (59% to 90%) and PTEN deletion (up to 33%), whereas EGFR amplification/overexpression and homozygous p16 deletion ($p16^{INK4a}$ gene at the CDKN2A locus, 9p21) are lacking in comparison to conventional glioblastoma (Meyer-Puttlitz et al., 1997; Peraud et al., 1997; Peraud et al. 1999; Temme et al. 2010). Therefore, giant cell glioblastomas contain clinical and molecular genetic features of both primary and secondary glioblastomas. Giant cell glioblastomas have an increased expression of Aurora Kinase B; combined with TP53 mutations this may be responsible in induce cytokinesis defects and the development of multinucleated cells (Temme et al., 2010).

	Gliosarcoma	Primary glioblastoma	Giant cell glioblastoma	Secondary glioblastoma
PTEN mutation	38%	32%	33%	4%
EGFR amplification	0%	39%	5%	0%
TP53 mutation	23%	11%	84%	67%
$p16^{INK4a}$ deletion	37%	36%	0%	4%
MDM2 amplification	5%	8%	0%	0%

Table 6. Genetic profile of the common histopathological glioblastoma subtypes. Similar tendencies are indicated by grayscale. Modified from Kleihues et al., 2007; Peraud et al., 1997; Peraud et al., 1999 and Reis et al., 2000.

Despite showing a very poor prognosis giant cell glioblastoma appears to carry a slightly better prognosis than conventional glioblastoma (Burger and Vollmer, 1980; Margetts and Kalyan-Raman, 1989; Shinojima et al., 2004), perhaps because of a less infiltrative behaviour.
Gliosarcoma constitutes roughly 2% of GBMs and is also recognized as a distinct clinico-pathologic entity in the WHO 2007 classification. These tumors are characterized by their well-circumscribed, biphasic tissue pattern with clearly distinguishable areas of glial and mesenchymal differentiation. The glial component of gliosarcoma may display any of the aforementioned cytologic attributes and is typically immunoreactive for GFAP. The mesenchymal component is GFAP-negative and may also carry a wide variety of morphologic appearances, with evidence of differentiation along fibroblastic, cartilaginous, osseous, smooth and striated muscle, and adipose lines (Kleihues et al., 2007). There is a cytogenetic and molecular evidence for a monoclonal origin of both components (Actor et al., 2002; Paulus et al., 1994; Reis et al., 2000).
Exept for the infrequent EGFR amplification, gliosarcomas are genetically similar to primary glioblastomas: they harbor likewise low frequency of TP53 mutations (up to 24%) and similar rates of PTEN deletions (38%) as well as deletions of $p16^{INK4a}$ gene (at the CDKN2A locus, 9p21) in roughly 37% (Actor et al., 2002; Reis et al., 2000).
Comparative genomic hybridization analysis in 20 gliosarcomas by Actor et al. (2002) revealed such common chromosomal imbalances as gains on chromosomes 7 (75%), X (20%), 9q and 20q (15% each) as well as losses on chromosomes 13q (15%), 10 and 9p (35% each).

2.4 Area-specific genomic Imbalances in glioblastoma multiforme

Using flow cytometry data analysis Hoshino et al. (1978) reported that different tumor regions of one glioblastoma showed a highly variable distribution of ploidy. By use of a DNA fingerprinting technique Misra et al. (2000) analysed genetic alterations within two or three tumor areas from seven glioblastomas. In all cases except one, different areas of one tumor displayed different fingerprints, indicating a striking extent of intratumoral genetic heterogeneity. Conventional comparative genomic hybridization (CGH) was used to study the intratumoral patterns of genomic imbalance in Glioblastoma multiforme (Harada et al., 1998; Jung et al., 1999). Array comparative genomic hybridization was utilized by Nobusawa et al. (2010) to study in detail tumor area-specific genomic imbalances. Genetic alterations common to all the areas analyzed within a single tumor included gains at chromosomes 1q32.1 (PIK3C2B, MDM4), 4q11-q12 (KIT, PDGFRA), 7p12.1-11.2 (EGFR), 12q13.3-12q14.1 (GLI1, CDK4), and 12q15 (MDM2), and loss of chromosomes at 9p21.1-24.3 ($p16^{INK4a}/p14^{ARF}$ = CDKN2a), 10p15.3-q26.3 (PTEN, etc.), and 13q12.11-q34 (SPRY2, RB1). These alterations are likely to be causative in the pathogenesis of glioblastomas (driver mutations). Additionally, the authors reported numerous tumor area-specific genomic imbalances, which may be either nonfunctional (passenger mutations) or functional, but constitute secondary events reflecting clonal selection and/or progressive genomic instability, a hallmark of glioblastomas. Area specific-evolution of genomic imbalances in GBM may be comparable to the genetic evolution and genomic instability of metastatic pancreas cancer that has been studied in detail recently (Campbell et al., 2010; Yachida et al., 2010).

Loeper et al. (2001) reported that frequent mitotic errors occur in genetically micro-heterogenous glioblastomas. The authors used fluorescent in situ hybridization (FISH) to study chromosome numbers in a series of 24 glioblastomas. All examined chromosomes showed mitotic instability indicated by numerical aberrations within significant amounts of tumor cells. For chromosomes 10 and 17 only monosomy was observed, whereas chromosome 7 showed trisomy/polysomy. In contrast to other chromosomes displaying monosomy as well as trisomy, copy number changes of chromosomes 7, 10 and 17 seem to be the result of selection in favor of the respective aberration (Loeper et al., 2001). In this context it is interesting to note that neural stem and progenitor cells in the subventricular zone of mouse postnatal brain are frequently aneuploid (Kaushal et al., 2003) and that chromosome segregation defects contribute to aneuploidy in normal neural progenitor cells of the mouse cerebral cortex (Yang et al., 2003). Studies in mice and human demonstrate that chromosomal mosaicism is a prominent feature of neural stem cells, whereas interchromosomal translocations or partial chromosomal deletions or insertions are extremely rare (for review see: Peterson et al., 2008). Glioblastoma stem cells share several properties with neural stem cells, i.e. the growth in floating spheres under serum-free conditions, the expression of the stem cell marker nestin and the differentiation into neural cells like astrocytes or neurons. This similarity in marker expression and behaviour has led to the hypothesis that glioblastoma stem cells may be derived from NSCs (Berger et al., 2004; Sanai et al., 2005).

Recent research makes clear that GBMs do not behave as a whole; local heterogeneity may arise because the tumor regionally adapts to the microenvironment. The influence of microenvironment-induced stimuli may be the force behind clonal selection and acquisition of area specific genomic imbalances in GBM. In addition, regional genomic alterations may be associated with the development of resistance to irradiation and/or chemotherapy, resulting in tumor recurrence and/or progression.

2.5 Mechanisms leading to genetic alterations in glioblastoma multiforme

Analysis of copy number alterations showed an average of 7 amplifications and 6 homozygous deletions per GBM. In addition, an average of 47 mutations was reported (Parsons et al., 2008).

A characteristic feature of GBM is a chromosomal instability (CIN) phenotype distinguished by the loss or gain of complete chromosomes, for example by the gain of chromosome 7 and/or loss of chromosome 10. These chromosome copy number changes can be explained by merotelic spindle attachment that is associated with bipolar but more often with multipolar mitosis. Multipolar spindle pole coalescence in cells with supernumerary centrosomes has been reported as a major source of chromosomal misattachment and chromosome missegregation in colorectal cancer cell lines (Silkworth et al., 2009). Obviously, specific chromosome aberrations may be associated with growth advantage for clonal populations of cancer cells (for example by the loss of tumor suppressor genes).

In addition to its well-defined role in signal transduction at the plasma membrane, recent results have identified PTEN as a new guardian of the genome (for review see: Yin and Shen, 2008). Pten-deficient mouse embryo fibroblasts revealed an increased frequency of mitotic centromere-associated chromosomal instability as well as spontaneous DNA double-strand breaks (Shen et al., 2007). Li Li et al. (2008) developed a mouse model by infecting PTEN-/- neural precursor cells with an EGFRvIII expressing retrovirus and found that EGFRvIII expression and PTEN loss synergistically induced chromosomal instability and glial tumors.

Interestingly, polyploidization of mammalian hepatocytes occurs through failed cytokinesis and is followed by a process that was called reductive mitoses (Duncan et al. 2010). The authors postulate a dynamic model of hepatocyte polyploidization, ploidy reversal and aneuploidy (ploidy conveyor) and propose that this mechanism evolved to generate genetic diversity and permits adaptation of hepatocytes to xenobiotic and nutritional injury.

Several studies point to a link between centrosome amplification, chromosomal instability and the development of cancer (for review see: D´Assoro et al., 2002). Cells in resected high grade gliomas and cultured glioblastoma cells have been reported to exhibit often centrosome amplifications (Loh et al., 2010) and the centrosomal protein γ-tubulin is over-expressed and shows altered subcellular localization in GBM (Katsetos et al., 2006; Loh et al., 2010). Multipolar mitoses were occasionally observed in time lapse recordings of cultured glioblastoma cells (Hegedüs et al., 2000). Our laboratory used long term life cell imaging to study mitoses in a newly established glioblastoma cell line and found that cytokinesis defects followed by multipolar mitosis may be an important mechanism that is used by glioblastoma cells to reduce ploidy and generate viable daughter cells (our unpublished results).

2.6 Epigenetics in glioblastoma multiforme

To add another level of complexity, many types of cancer cells carry aberrant epigenetic modifications. Changes in epigenetic marks (caused or not caused by genetic alterations) may have an fundamental impact on tumor development and/or tumor progression. Epigenetic markers in human gliomas have been reviewed by Hesson et al. (2008). Two groups have studied in detail DNA methylation profiles in GBM (Etcheverry et al. 2010; Nousmehr et al., 2010). Hypermethylation at a large number of genetic loci occurred in a subgroup (proneural group) of glioblastoma patients and was associated with improved outcome (Nousmehr et al., 2010).

Epigenetic mechanisms like methylation of DNA have already an impact on chemotheraypy of GBM. Temozolomide (TMZ, Temodal®) is an orally administered alkylating drug that is often used for chemotherapy of GBM. O^6-Methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that specifically removes promutagenic alkyl DNA adducts from the O^6 position of guanine residues in DNA which are induced by alkylating agents like temozolomide (Goth and Rajewsky, 1974; Margison and Kleihues, 1975). Loss of MGMT expression may be caused by transcriptional silencing through hypermethylation of its CpG islands (Esteller et al., 1999; Qian & Brent, 1997), is frequently (45% to 75%) present in glioblastomas (Bello et al., 2004; Kamiryo et al., 2004; Nakamura et al., 2001) and results in improved survival of glioblastoma patients treated with the alkylating agent temozolomide (Fukushima et al., 2009; Hegi et al, 2005; Hegi et al., 2008). On the other hand not all glioblastoma patients with MGMT promoter methylation respond to alkylating agents and in addition responding GBMs cannot avoid eventual recurrence (Fukushima et al., 2009; Hegi et al., 2008). MGMT promoter methylation appears to occur with a higher frequency in secondary than in primary glioblastoma (Bello et al., 2004; Nakamura et al., 2001) but there is no evidence about its correlation with other histopathologic subtypes.

However, prospective randomized studies of EORTC (European Organisation for Research and Treatment of Cancer) and NCIC (National Cancer Institute of Canada) trial have revealed a significant prolongation of progression free and overall survival for patients with newly diagnosed glioblastoma treated by the concomitant and adjuvant temozolomide and irradiation. By this means median survival has been increased over one year (Stupp et al., 2005, 2009).

The methylation status of the MGMT gene promoter is being used as a biomarker for the potential benefit of the addition of temozolomide to the therapy because its epigenetic silencing has been identified as a strong and independent predictive factor of treatment response for anaplastic glioma patients undergoing chemotherapy with alkylating agents (Hegi et al., 2005; Wick et al., 2009). 3 to 5% of the GBM patients survive for more than 3 years. MGMT hypermethylation was reported to be significantly more frequent in the long-term survivor group (Krex et al., 2007).

The assumption that DNA methylation of CpG island on the MGMT promoter represses consecutively transcriptional activity of the MGMT gene and expression of MGMT protein has been used to explain the correlation between the positive promoter methylation status and favorable treatment response after chemotherapy with temozolomide (Kaina et al., 2007).

However, studies that were performed to validate a relationship between MGMT promoter methylation and protein expression have yielded contradictory results in brain tumors as well as in other neoplasms (Brell et al., 2011). While some studies report a significant correlation between MGMT protein expression analyzed by immunohistochemistry (IHC) and MGMT promoter status measured by methylation-specific polymerase chain reaction (MSP) in glioblastoma and brain metastases of various origin (Ingold et al., 2009; Spiegl-Kreinecker et al., 2009; Tang et al., 2011), other studies failed to detect correlations between both parameters (Brell et al., 2005, 2011; Christmann et al., 2010; Preusser et al., 2008).

In addition, there is increasing evidence that MGMT mRNA expression, unlike MGMT protein expression, could be a better predictor for tumor sensitivity to alkylating agents than MGMT methylation status (Everhard et al., 2009; Kreth et al., 2011). Kreth et al. (2011) provide not only evidence that the degree of MGMT mRNA expression is highly correlated with the MGMT promoter methylation status, but also that low MGMT mRNA expression is strongly

predictive for prolonged time to progression, treatment response, and length of survival. Furthermore, the authors found that in case of discordance the patients with methylated tumors combined with high MGMT mRNA expression did significantly worse than those with low transcriptional activity or unmethylated tumors with low MGMT mRNA expression. Finally Kreth et al. (2011) assume methylation-independent pathways of MGMT expression regulation; however, the exact role of DNA-methyltransferases DNMT1 and DNMT3b that are likely to be involved in methylation of CpG islands of MGMT gene promoter remains unclear.
In the Cancer Genome Atlas Research Network (2008) study, GBMs from patients treated with temozolomide and/or lomustine were analysed for mutations. Treatment with alkylating agents resulted in a more than tenfold increase in the number of mutations that was dependent on the methylation status of the MGMT gene. This phenotype seems to be caused by mutations in the MSH6 gene (Cahill et al., 2007; Hunter et al., 2006; Yip et al., 2009) and other genes of the DNA mismatch repair pathway (Cancer Genome Atlas Research Network, 2008). The loss of the mismatch repair protein MSH6 in GBM is associated with tumor progression during temozolomide treatment (Cahill et al., 2007; Hunter et al., 2006; Yip et al., 2009).

2.7 Stem cells in glioblastoma multiforme

The cancer stem cell concept that is of importance for the genesis of many types of cancer receives increasing credit also in the field of GBM. A minor population of GBM cancer stem cells, which may be derived from genetically altered neural stem cells, is presumed to generate transit amplifying cells with high mitotic activity. Because these stem cells appear to have a low mitotic activity, they are difficult to target by radiotherapy and conventional chemotherapy.
For recent reviews on glioblastoma stem cells the reader is referred to Huang et al. (2010) and McLendon and Rich (2010). Ignatova et al. (2002) firstly described cells with stem-like properties in human cortical glial tumors. Singh et al. (2003) used the cell surface marker CD133 to isolate a clonogenic population of cells showing stem-like features in medulloblastomas and pilocytic astrocytomas. These cells were declared as tumor stem cells based on their capabilities of self-renewal and multilineage differentiation. Galli et al. (2004) and Yuan et al. (2004) confirmed these findings for glioblastomas. Bao et al. (2006a) selected CD133+ cells from glioblastoma biopsies that were capable of forming tumorspheres in vitro, demonstrated self-renewal and multilineage differentiation and resulted in tumours after transplantation into nude mice. In contrast, CD133- cells did not form tumorspheres in vitro und were not tumorigenic in nude mice. CD133+ cells proved to be a minor population of cells in GBM biopsies. Clinical studies suggested that the percentage of CD133+ cells (Zhang et al., 2008; Zeppernick et al., 2008) or the rate of tumorsphere formation in vitro (Laks et al., 2009; Panosyan et al., 2010) can be used to predict overall survival time of patients. However, it should be noted, that contrary results also exist (Phi et al., 2009; Kim et al., 2011). In recurrent glioblastomas the percentage of CD133+ cells is increased strongly when compared with primary glioblastomas (Pallini et al., 2010). Surprisingly, the increase in expression of CD133 after tumor recurrence was associated significantly with longer survival. Thon et al. (2008) described a correlation between the amount of CD133+ cells within the tumor mass and the WHO grade of glioma (WHO grade II, III and IV). Bao et al. (2006a) demonstrated that CD133+ cells constitutively expressed DNA repair genes at much higher levels that CD133- cells, mediating resistance to X-irradiation in CD133+ cells.

Brain tumor stem cells seem to be localized in a perivascular niche (Bao et al., 2006b; Calabrese et al., 2007; Shen et al., 2008) and low oxygen tension (hypoxia) is associated with its undifferentiated state. In glioblastomas, cancer stem cells express much higher levels of VEGF than non-stem cancer cells and show increased angiogenic potential in vivo (Bao et al., 2006b; Li et al., 2009). Because VEGF expression is under control of transcription factors of the hypoxia inducible factor (HIF) family, one should note that expression of HIF2α is unique to glioma stem cells and correlated with poor patient survival, whereas HIF1α is found in all malignant cells (Li et al., 2009). It has been reported that different human cancers (GBM, colorectal carcinoma, and NSCL carcinoma) converge at the HIF2α oncogenic axis (Franovic et al., 2009). The authors propose that inhibition of HIF2α may be of broad clinical interest in the treatment of cancers with different genetic signatures. Hjelmeland et al. (2010) published recently that acidic stress promotes a glioma stem cell phenotype by induction of HIF2α and other glioma stem cell markers. The authors suggest that an increase in intratumoral pH may be of benefit for targeting the stem cell phenotype.
Three recent papers demonstrate that stem-like cells in GBM are able to differentiate into endothelial cells and may give rise to tumor endothelium (Ricci-Vitiani et al., 2010; Thon et al., 2008; Wang et al., 2010). These results define a novel mechanism for cancer vasculogenesis and may help to explain the failure of currently used inhibitors of angiogenesis. Glioma stem cells as targets for novel strategies of treatment have been recently reviewed (Dietrich et al., 2010; Gilbert & Ross, 2011).

2.8 Promising targets for chemotherapy of glioblastoma multiforme

GBMs are highly infiltrative tumors that show resistance to conventional chemotherapy. Many chemotherapeutic agents are not able to reach the tumor in sufficient doses, because the blood brain barrier is at least partially intact in these tumors.
Most mitotic inhibitors used in clinic impair the function of mitotic spindles by targeting tubulins that are basic components of microtubules. Because microtubules in non-mitotic cells are also affected, these compounds often exhibit significant side effects (for example neurotoxicity). Future therapies of GBM may involve small molecules that inhibit the activity of aurora kinases A or B, polo kinases or the mitotic kinesin Eg5, all proteins that have specific functions in different phases of mitosis (for review see: Kaestner and Bastians, 2010; Sudakin and Yen, 2007). Pharmaceutical companies are on the way to develop selective inhibitors that target these proteins. Phase I and II studies on different forms of solid cancers are currently underway to study newly developed mitosis inhibitors and may also open the way for a more efficient therapy of GBM. Interestingly, it has been reported that in glioblastoma expression of aurora kinases A (Barton et al., 2010) and B (Zeng et al., 2007) were both associated with poor prognosis and may be targets for therapy. Among several other proteins also histone deacetylases (HDACs) may be promising targets for future therapy of GBM (Argyriou and Kalofonos, 2009). ABC transporters play an important role in the development of multidrug resistance. The role of ABC transporters in the resistance network of glioblastoma was reviewed by Bleau et al. (2009).
The humanized monoclonal antibody against vascular endothelial growth factor (Bevacizumab, Avastin®) has been approved by the FDA for treatment of GBM. Although targeting the tumor vasculature with Bevacizumab reduced the number of cancer-like stem cells in orthotopic brain tumor xenografts (Calabrese et al., 2007), a recent phase II study indicates that bevacizumab does not affect median survival of patients with recurrent GBM (Pope et al, 2011).

Potential targets for directed therapy of GBM may include extracellular matrix proteins of the perivascular niche that influence proliferation and/or migration of cancer stem cells. Targeting integrin α6 has recently been shown to inhibit self-renewal, proliferation, and tumor formation capacity of glioblastoma stem cells (Lathia et al., 2010). Cilengitide (Impetreve®) is a cyclic pentapeptide harboring a RGD sequence. RGD sequences present on extracellular matrix proteins mediate the binding to integrins, a class of cell surface receptors. Cilengitide is a selective inhibitor of αvβ3/5 integrins and currently under study as an inhibitor of angiogenesis in several types of solid cancer. Cilengitide monotherapy was well tolerated and exhibited modest antitumor activity among patients with recurrent GBM in a randomized phase II study (Reardon et al., 2008). Also targeting glioma stem cells through the neural cell adhesion molecule L1CAM has been reported to suppress glioma growth (Bao et al., 2008). Glioblastoma cells display complex surface structures with numerous microvilli and filopodia that resist the actions of cytolytic effector lymphocytes (Hoa et al., 2010). It should also be noted that gliomas are accompanied by numerous microglia/macrophages. As was recently reported, inhibition of microglia/macrophage activation may represent a new and effective strategy to suppress proliferation of glioma cells (Zhai et al., 2011).

Subtypes of breast cancer or leukemia can be efficiently treated by inhibiting the one excessively activated signal transduction pathway that is linked to malignancy. For GBM a monocausal therapy by inhibition of a single overactivated signaling pathway seems to be less promising, because cells or even regions with different genetic defects coexist in one tumor. A personalized therapy based on analysis of the individual genetic defects is not yet in sight for GBM.

3. Summary and perspective

Many types of cancer cells evolve through a multistep process in which genetic aberrations accumulate and finally lead to cells exhibiting aberrant gene expression programs. GBM has been considered as a system/network disease (Fathallah-Shaykh, 2010), because its phenotypes appear to be generated by several interconnected aberrant signal transduction pathways as well as numerous molecular abnormalities, thereby resulting in uncontrolled mitosis and migration of GBM cancer cells. In GBM local heterogeneity arises as the tumor regionally adapts to microenvironmental cues. Future molecular therapies of GBM should target its Achilles' heels: the elimination of the small intratumoral subpopulation of cells that exert stem cell properties and the inhibition of mitosis within the population of transit amplifying cells, which is responsible for forming the tumor mass.

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5. References

Actor, B.; Cobbers, J.M., Buschges, R., Wolter, M., Knobbe, C.B., Lichter, P., Reifenberger, G. & Weber, R.G. (2002). Comprehensive analysis of genomic alterations in gliosarcoma and its two tissue components. *Genes Chromosomes Cancer,* Vol.34, No.4, (December 2002), pp. 416–427, ISSN 1045-2257

Argyriou, A.A. & Kalofonos, H.P. (2009). Molecularly targeted therapies for malignant gliomas. *Mol Med*. Vol.15, No.3-4, (March-April 2009), pp. 115-22, ISSN 1076-1551

Arjona, D.; Rey, J.A. & Taylor, S.M. (2006). Early genetic changes involved in low-grade astrocytic tumor development. *Curr Mol Med.,* Vol.6, No.6, (September 2006), pp. 645-50, ISSN 1566-5240

Bao, S.; Wu, Q., McLendon, R.E., Hao, Y., Shi, Q., Hjelmeland, A.B., Dewhirst, M.W., Bigner D.D. & Rich, J.N. (2006a). Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature,* Vol.444, No.7120, (December 2006a), pp. 756-60, ISSN 0028-0836

Bao, S.; Wu, Q., Sathornsumetee, S., Hao, Y., Li, Z., Hjelmeland, A.B., Shi, Q., McLendon, R.E., Bigner, D.D. & Rich, J.N. (2006b). Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. *Cancer Res*., Vol.66, No.16, (August 2006b), pp. 7843-7848, ISSN 0008-5472

Bao, S.; Wu, Q., Li, Z., Sathornsumetee, S., Wang, H., McLendon, R.E., Hjelmeland, A.B. & Rich, J.N. (2008). Targeting cancer stem cells through L1CAM suppresses glioma growth. *Cancer Res.,* Vol.68, No.15, (August 2008), pp. 6043-6048, ISSN 0008-5472

Bartkova, J.; Horejsí, Z., Koed, K., Krämer, A., Tort, F., Zieger, K., Guldberg, P., Sehested, M., Nesland, J.M., Lukas, C., Ørntoft, T., Lukas, J. & Bartek, J. (2005). DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. *Nature,* Vol.434, No.7035, (April 2005), pp. 864-70, ISSN 0028-0836

Bartkova, J.; Rezaei, N., Liontos, M., Karakaidos, P., Kletsas, D., Issaeva, N., Vassiliou, L.V., Kolettas, E., Niforou, K., Zoumpourlis, V.C., Takaoka, M., Nakagawa, H., Tort, F., Fugger, K., Johansson, F., Sehested, M., Andersen, C.L., Dyrskjot, L., Ørntoft, T., Lukas, J., Kittas, C., Helleday, T., Halazonetis, T.D., Bartek, J. & Gorgoulis, V.G. (2006). Oncogene-induced senescence is part of the tumorigenesis barrier imposed by DNA damage checkpoints. *Nature,* Vol.444, No.7119, (November 2006), pp. 633-637, ISSN: 0028-0836

Barton, V.N.; Foreman, N.K., Donson, A.M., Birks, D.K., Handler, M.H. & Vibhakar, R. (2010). Aurora kinase A as a rational target for therapy in glioblastoma. *J Neurosurg Pediatr.,* Vol.6, No.1, (July 2010), pp. 98-105, ISSN 1933-0707

Bello, M.J.; Alonso, M.E., Amiñoso, C., Anselmo, N.P., Arjona, D., Gonzalez-Gomez, P., Lopez-Marin, I., de Campos, J.M., Gutierrez, M., Isla, A., Kusak, M.E., Lassaletta, L., Sarasa, J.L., Vaquero, J., Casartelli, C. & Rey, J.A. (2004). Hypermethylation of the DNA repair gene MGMT: association with TP53 G:C to A:T transitions in a series of 469 nervous system tumors. *Mutat Res.,* Vol.554, No.1-2, (October 2004), pp. 23-32, ISSN 0027-5107

Berger, F.; Gay, E., Pelletier, L., Tropel, P. & Wion, D. (2004). Development of gliomas: potential role of asymmetrical cell division of neural stem cells. *Lancet Oncol.,* Vol.5, No.8, (August 2004), pp. 511-514, ISSN 1470-2045

Bignold, L.P.; Coghlan, B.L. & Jersmann, H.P. (2006). Cancer morphology, carcinogenesis and genetic instability: a background. *EXS,* Vol.96, (2006), pp. 1-24, ISSN 1023-294X

Bleau, A.M.; Huse, J.T. & Holland, E.C. (2009). The ABCG2 resistance network of glioblastoma. *Cell Cycle,* Vol.8, No.18, (September 2009), pp. 2936-2944, ISSN 1538-4101

Brat, D.J.; Scheithauer, B.W., Medina-Flores, R., Rosenblum, M.K. & Burger, P.C. (2002). Infiltrative astrocytomas with granular cell features (granular cell astrocytomas): a study of histopathologic features, grading, and outcome. *Am J Surg Pathol.,* Vol.26, No.6, (June 2002), pp. 750-757, ISSN 0147-5185

Bredel, M.; Scholtens, D.M., Harsh, G.R., Bredel, C., Chandler, J.P., Renfrow, J.J., Yadav, A.K., Vogel, H., Scheck, A.C., Tibshirani, R. & Sikic, B.I. (2009). A network model of a cooperative genetic landscape in brain tumors. *JAMA*, Vol.302, No.3, (Juli 2009), pp. 261-75, ISSN 0098-7484

Bredel, M.; Scholtens, D.M., Yadav, A.K., Alvarez, A.A., Renfrow, J.J., Chandler, J.P., Yu, I.L., Carro, M.S., Dai, F., Tagge, M.J., Ferrarese, R., Bredel, C., Phillips, H.S., Lukac, P.J., Robe, P.A., Weyerbrock, A., Vogel, H., Dubner, S., Mobley, B., He, X., Scheck, A.C., Sikic, B.I., Aldape, K.D., Chakravarti, A. & Harsh, G.R. 4th. (2010). NFKBIA deletion in glioblastomas. *N Engl J Med.,* Vol.364, No.7, (February 2011), pp. 17627-17637, ISSN 0028-4793

Brell, M.; Ibáñez, J. & Tortosa, A. (2011). O6-Methylguanine-DNA methyltransferase protein expression by immunohistochemistry in brain and non-brain systemic tumours: systematic review and meta-analysis of correlation with methylation-specific polymerase chain reaction. *BMC Cancer,* Vol.11, No.1, (January 2011), pp. 35, ISSN 1471-2407

Brell, M.; Tortosa, A., Verger, E., Gil, J.M., Viñolas, N., Villà, S., Acebes, J.J., Caral Pons, J.J., Pujol, T., Ferrer, I., Ribalta, T. & Graus, F. (2005). Prognostic significance of O6 - Methilguanine DNA methyltransferase determined by promoter methylation and immunohistochemical expression in anaplastic gliomas. *Clin Cancer Res.*, Vol.11, No.14, (July 2005), pp. 5167-5174; ISSN 1078-0432

Burger, P.C. & Vollmer, R.T. (1980). Histologic factors of prognostic significance in the glioblastoma multiforme. *Cancer,* Vol.46, No.5, (September 1980), pp. 1179-1186, ISSN 1837-9664

Cahill, D.P.; Levine, K.K., Betensky, R.A., Codd, P.J., Romany, C.A., Reavie, L.B., Batchelor, T.T., Futreal, P.A., Stratton, M.R., Curry, W.T., Iafrate, A.J. & Louis, D.N. (2007). Loss of the mismatch repair protein MSH6 in human glioblastomas is associated with tumor progression during temozolomide treatment. *Clin Cancer Res.,* Vol.13, No.7, (April 2007), pp. 2038-2045, ISSN 1078-0432

Calabrese, C.; Poppleton, H., Kocak, M., Hogg, T.L., Fuller, C., Hamner, B., Oh, E.Y., Gaber, M.W., Finklestein, D., Allen, M., Frank, A., Bayazitov, I.T., Zakharenko, S.S., Gajjar, A., Davidoff, A. & Gilbertson R.J. (2007). A perivascular niche for brain tumor stem cells. *Cancer Cell,* Vol.11, No.1, (January 2007), pp. 69-82, ISSN 1535-6108

Campbell, P.J.; Yachida, S., Mudie, L.J., Stephens, P.J., Pleasance, E.D., Stebbings, L.A., Morsberger, L.A., Latimer, C., McLaren, S., Lin, M.L., McBride, D.J., Varela, I., Nik-Zainal, S.A., Leroy, C., Jia, M., Menzies, A., Butler, A.P., Teague, J.W., Griffin, C.A., Burton, J., Swerdlow, H., Quail, M.A., Stratton, M.R., Iacobuzio-Donahue, C. & Futreal, P.A. (2010). The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature*, Vol.467, No.7319, (October 2010), pp. 1109-1113, ISSN 0028-0836

Cancer Genome Atlas Research Network (2008). Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature,* Vol.455, No.7216, (October 2008), pp. 1061-1068, ISSN 0028-0836

Castellano-Sanchez, A.A.; Ohgaki, H., Yokoo, H., Scheithauer, B.W., Burger, P.C., Hamilton, R.L., Finkelstein, S.D. & Brat, D.J. (2003). Granular cell astrocytomas show a high frequency of allelic loss but are not a genetically defined subset. *Brain Pathol.,* Vol.13, No.2, (April 2003), pp. 185-194, ISSN 1015-6305

Central Brain Tumor Registry of the United States (2010) . Primary Brain and Central Nervous System Tumors Diagnosed in Unated States 2004-2006, In CBRUS Statistical Report (2010), 15.04.2011, Available from http://www.cbtrus.org/2010-NPCR-SEER/CBTRUS-WEBREPORT-Final-3-2-10.pdf

Chow, J. & Poon, R.Y. (2010). DNA damage and polyploidization. *Adv Exp Med Biol.,* Vol.676, (2010), pp. 57-71, ISSN 0065-2598

Colman, H.; Zhang, L., Sulman, E.P., McDonald, J.M., Shooshtari, N.L., Rivera, A., Popoff, S., Nutt, C.L., Louis, D.N., Cairncross, J.G., Gilbert M.R., Phillips, H.S., Mehta, M.P., Chakravarti, A., Pelloski, C.E., Bhat, K., Feuerstein, B.G., Jenkins, R.B. & Aldape, K. (2009). A multigene predictor of outcome in glioblastoma. *Neuro Oncol.,* Vol.12, No.1, (January 2010), pp. 49-57, ISSN 1522-8517

Christmann, M.; Nagel, G., Horn, S., Krahn, U., Wiewrodt, D., Sommer, C. & Kaina, B. (2010). MGMT activity, promoter methylation and immunohistochemistry of pretreatment and recurrent malignant gliomas: a comparative study on astrocytoma and glioblastoma. *Int J Cancer,* Vol.127, No.9, (November 2010), pp. 2106-2118, ISSN 0898-6924

D'Assoro, A.B.; Lingle, W.L. & Salisbury, J.L. (2002). Centrosome amplification and the development of cancer. *Oncogene,* Vol.21, No.40, (September 2002), pp. 6146-6153, ISSN 0950-9232

Di Micco, R.; Fumagalli, M., Cicalese, A., Piccinin, S., Gasparini, P., Luise, C., Schurra, C., Garre', M., Nuciforo, P.G., Bensimon A., Maestro, R., Pelicci, P.G. & d'Adda di Fagagna F. (2006). Oncogene-induced senescence is a DNA damage response triggered by DNA hyper-replication. *Nature.* Vol.444, No.7119, (November 2006), pp. 638-42, ISSN 0028-0836

Dietrich, J.; Diamond, E.L., & Kesari, S. (2010). Glioma stem cell signaling: therapeutic opportunities and challenges. *Expert Rev Anticancer Ther.,* Vol.10, No.5, (May 2010), pp. 709-22, ISSN 1473-7140

Duesberg, P.; Rausch, C., Rasnick, D. & Hehlmann, R. (1998). Genetic instability of cancer cells is proportional to their degree of aneuploidy. *Proc Natl Acad Sci U S A,* Vol.95, No.23, (November 1998), pp. 13692-13697, ISSN 0027-8424

Duncan, A.W.; Taylor, M.H., Hickey, R.D., Hanlon Newell, A.E., Lenzi, M.L., Olson, S.B., Finegold, M.J. & Grompe, M. (2010). The ploidy conveyor of mature hepatocytes as a source of genetic variation. *Nature,* Vol.467, No.7316, (October 2010), pp. 707-710, ISSN 0028-0836

Etcheverry, A.; Aubry, M., de Tayrac, M., Vauleon, E., Boniface, R., Guenot, F., Saikali, S., Hamlat, A., Riffaud, L., Menei, P., Quillien, V. & Mosser, J. (2010). DNA methylation in glioblastoma: impact on gene expression and clinical outcome. *BMC Genomics,* Vol.11, (December 2010), pp. 701, ISSN 1471-2164

Esteller, M.; Hamilton, S.R., Burger, P.C., Baylin, S.B. & Herman, J.G. (1999). Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia. *Cancer Res.*, Vol.59, No.4, (February 1999), pp. 793-797, ISSN 0008-5472

Everhard, S.; Tost, J., El Abdalaoui, H., Crinière, E., Busato, F., Marie, Y., Gut, I.G., Sanson, M., Mokhtari, K., Laigle-Donadey, F., Hoang-Xuan, K., Delattre, J.Y. & Thillet, J. (2009). Identification of regions correlating MGMT promoter methylation and gene expression in glioblastomas. *Neuro Oncol.*, Vol.11, (August 2009), pp. 348–356, ISSN 1522-8517

Fathallah-Shaykh, H.M. (2010). Malignant astrocytomas: a system disease. *Arch Neurol.*, Vol.67, No.3, (March 2010), pp. 353-355, ISSN 0003-9942

Fearon, E.R. & Vogelstein, B. (1990). A genetic model for colorectal tumorigenesis. *Cell,* Vol.61, No.5, (June 1990), pp. 759-767

Franovic, A.; Holterman, C.E., Payette, J. & Lee, S. (2009). Human cancers converge at the HIF-2alpha oncogenic axis. *Proc Natl Acad Sci U S A*, Vol.106, No.50, (December 2009), pp. 21306-21311, ISSN 0027-8424

Fukushima, T.; Takeshima, H. & Kataoka, H. (2009). Anti-glioma therapy with temozolomide and status of the DNA-repair gene MGMT. *Anticancer Res.,* Vol.29, No.11, (November 2009), pp. 4845-4854, ISSN 0250-7005

Furnari, F.B.; Fenton, T., Bachoo, R.M., Mukasa, A., Stommel, J.M., Stegh, A., Hahn, W.C., Ligon, K.L., Louis, D.N., Brennan, C., Chin, L., DePinho, R.A. & Cavenee, W.K. (2007). Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Dev.,* Vol.21, No.21, (November 2007), pp. 2683-2710, ISSN 0890-9369

Galli, R.; Binda, E., Orfanelli, U., Cipelletti, B., Gritti, A., De Vitis, S., Fiocco, R., Foroni C., Dimeco, F. & Vescovi, A. (2004). Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. *Cancer Res.,* Vol.64, No.19, (October 2004), pp. 7011-7021, ISSN 0008-5472

Gilbert, C.A. and Ross A.H. (2011). Glioma Stem Cells: Cell Culture, Markers and Targets for New Combination Therapies, In: *Cancer Stem Cells Theories and Prac*tice, S. Shostak (Ed.), InTech, Retrieved from http://www.intechopen.com/articles /show/title/glioma-stem-cells-cell-culture-markers-and-targets-for-new-combination-therapies

Gorgoulis, V.G.; Vassiliou, L.V., Karakaidos, P., Zacharatos, P., Kotsinas, A., Liloglou, T., Venere, M., Ditullio, R.A.Jr., Kastrinakis, N.G., Levy, B., Kletsas, D., Yoneta, A., Herlyn, M., Kittas, C. & Halazonetis, T.D. (2005). Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions. *Nature,* Vol. 434, No.7035, (April 2005), pp. 907-913, ISSN 0028-0836

Goth, R. & Rajewsky, M.F. (1974). Persistence of O6-ethylguanine in rat-brain DNA: correlation with nervous system-specific carcinogenesis by ethylnitrosourea. *Proc Natl Acad Sci U S A.* Vol.71, No.3, (March 1974), pp. 639-43, ISSN 0027-8424

Halazonetis, T.D.; Gorgoulis, V.G. & Bartek, J. (2008). An oncogene-induced DNA damage model for cancer development. *Science,* Vol.319, No.5868, (March 2008), pp. 1352-5, ISSN 0193-4511

Hansemann, D. (1890). Ueber asymmetrische Zellteilung in Epithelkrebsen und deren biologische Bedeutung [On the asymmetrical cell divisions in epithelial cancers and

its biological significance]. *Arch Pathol Anat etc., Berlin (Virchow´s Arch),* Vol.119, (1890), pp. 299-326

Harada, K.; Nishizaki, T., Ozaki, S., Kubota, H., Ito, H. & Sasaki, K. (1998). Intratumoral cytogenetic heterogeneity detected by comparative genomic hybridization and laser scanning cytometry in human gliomas. *Cancer Res.* Vol.58, No.20, (October 1998), pp. 4694-700, ISSN 0008-5472

Hegedüs, B.; Czirók, A., Fazekas, I., B'abel, T., Madar'asz, E. & Vicsek, T. (2000). Locomotion and proliferation of glioblastoma cells in vitro: statistical evaluation of videomicroscopic observations. *J Neurosurg.,* Vol.92, No.3, (March 2000), pp. 428-34, ISSN 0022-3085

Hegi, M.E.; Diserens, A.C., Gorlia, T., Hamou, M.F., de Tribolet, N., Weller, M., Kros, J.M., Hainfellner, J.A., Mason, W., Mariani, L., Bromberg, J.E., Hau, P., Mirimanoff, R.O., Cairncross, J.G., Janzer, R.C. & Stupp, R. (2005). MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.,* Vol.352, No.10, (March 2005),pp. 997-1003, ISSN 0028-4793

Hegi, M.E.; Liu, L., Herman, J.G., Stupp, R., Wick, W., Weller, M., Mehta, M.P. & Gilbert, M.R. (2008). Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity. *J Clin Oncol.,* Vol.26, No.25, (September 2008), pp. 4189-99 ISSN 0732-183X

Hesson, L.B. ; Krex, D. & Latif, F. (2008). Epigenetic markers in human gliomas: prospects for therapeutic intervention. *Expert Rev Neurother.,* Vol.8, No.10, (October 2008), pp. 1475-96, ISSN 1473-7175

Hjelmeland, A.B.; Wu, Q., Heddleston, J.M., Choudhary, G.S., Macswords, J., Lathia, J.D., McLendon, R., Lindner, D., Sloan, A. & Rich, J.N. (2010). Acidic stress promotes a glioma stem cell phenotype. *Cell Death Differ.,* [Epub ahead of print], ISSN 1476-5403

Hoa, N.; Ge, L., Kuznetsov, Y., McPherson, A., Cornforth, A.N., Pham, J.T., Myers, M.P., Ahmed, N., Salsman, V.S., Lamb, L.S.Jr., Bowersock, J.E., Hu, Y., Zhou, Y.H. & Jadus M.R. (2010). Glioma cells display complex cell surface topographies that resist the actions of cytolytic effector lymphocytes. *J Immunol.,* Vol.185, No.8, (October 2010), pp. 4793-803, ISSN 0022-1767

Holliday, R. (1989). Chromosome error propagation and cancer. *Trends Genet.* Vol.5, No.2, (February 1989), pp. 42-5, ISSN 0168-9525

Hoshino, T.; Nomura, K., Wilson, C.B., Knebel, K.D. & Gray, J.W. (1978). The distribution of nuclear DNA from human brain-tumor cells. *J Neurosurg.,* Vol.49, No.1, (July 1978), pp. 13-21, ISSN 0022-3085

Huang, Z.; Cheng, L., Guryanova, O.A., Wu, Q. & Bao, S. (2010). Cancer stem cells in glioblastoma-molecular signaling and therapeutic targeting. *Protein Cell,* Vol.1, No.7, (July 2010), pp. 638-55, ISSN 1674-800X

Hunter,C.; Smith, R., Cahill, D.P., Stephens, P., Stevens, C., Teague, J., Greenman, C., Edkins, S., Bignell, G., Davies, H., O'Meara, S., Parker, A., Avis, T., Barthorpe, S., Brackenbury, L., Buck, G., Butler, A., Clements, J., Cole, J., Dicks, E., Forbes, S., Gorton, M., Gray, K., Halliday, K., Harrison, R., Hills, K., Hinton, J., Jenkinson, A., Jones, D., Kosmidou, V., Laman, R., Lugg, R., Menzies, A., Perry, J., Petty, R., Raine,

K., Richardson, D., Shepherd, R., Small, A., Solomon, H., Tofts, C., Varian, J., West, S., Widaa, S., Yates, A., Easton, D.F., Riggins, G., Roy, J.E., Levine, K.K., Mueller, W., Batchelor, T.T., Louis, D.N., Stratton, M.R., Futreal, P.A. & Wooster R. (2006). A hypermutation phenotype and somatic MSH6 mutations in recurrent human malignant gliomas after alkylator chemotherapy. Cancer Res., Vol.66, No.8, (April 2006), pp. 3987-91, ISSN-0008-5472

Ignatova, T.N.; Kukekov, V.G., Laywell, E.D., Suslov, O.N., Vrionis, F.D. & Steindler, D.A. (2002). Human cortical glial tumors contain neural stem-like cells expressing astroglial and neuronal markers in vitro. *Glia,* Vol.39, No.3, (September 2002), pp. 193-206, ISSN 0894-1491

Ingold, B.; Schraml, P., Heppner, F.L. & Moch, H. (2009). Homogeneous MGMT immunoreactivity correlates with an unmethylated MGMT promoter status in brain metastases of various solid tumors. *PLoS ONE,* Vol.4, No.3, (March 2009), pp. e4775, ISSN 1932-6203

Jung, V.; Romeike, B.F., Henn, W., Feiden, W., Moringlane, J.R., Zang, K.D. & Urbschat, S. (1999). Evidence of focal genetic microheterogeneity in glioblastoma multiforme by area-specific CGH on microdissected tumor cells. *J Neuropathol Exp Neurol.,* Vol. 58, No.9, (September 1999), pp. 993-9, ISSN 0022-3069

Kaestner, P. & Bastians, H. (2010). Mitotic drug targets. *J Cell Biochem.,* Vol.111, No.2, (October 2010), pp. 258-65, ISSN 0730-2312

Kaina, B.; Christmann, M., Naumann, S. & Roos, W.P. (2007). MGMT: key node in the battle against genotoxicity, carcinogenicity and apoptosis induced by alkylating agents. *DNA Repair (Amst)*, Vol.6, No.8, (August 2007), pp. 1079–1099, ISSN 1568-7864

Kamiryo, T.; Tada, K., Shiraishi, S., Shinojima, N., Kochi, M. & Ushio, Y. (2004). Correlation between promoter hypermethylation of the O6-methylguanine-deoxyribonucleic acid methyltransferase gene and prognosis in patients with high-grade astrocytic tumors treated with surgery, radiotherapy, and 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea-based chemotherapy. *Neurosurgery,* Vol.54, No.2, (February 2004), pp. 349-57, ISSN 0148-396X

Katsetos, C.D.; Reddy, G., Dráberová, E., Smejkalová, B., Del Valle, L., Ashraf, Q., Tadevosyan, A., Yelin, K., Maraziotis, T., Mishra, O.P., Mörk, S., Legido, A., Nissanov, J., Baas, P.W., de Chadarévian, J.P. & Dráber, P. (2006). Altered cellular distribution and subcellular sorting of gamma-tubulin in diffuse astrocytic gliomas and human glioblastoma cell lines. *J Neuropathol Exp Neurol.,* Vol.65, No.5, (May 2006), pp. 465-77, ISSN 0022-3069

Kaushal, D.; Contos, J.J., Treuner, K., Yang, A.H., Kingsbury, M.A., Rehen, S.K., McConnell M.J., Okabe, M., Barlow, C. & Chun, J. (2003). Alteration of gene expression by chromosome loss in the postnatal mouse brain. *J Neurosci.,* Vol.23, No.13, (July 2003), pp. 5599-606, ISSN 0270-6474

Kim, K.J.; Lee, K.H., Kim, H.S., Moon, K.S., Jung, T.Y., Jung, S. & Lee, M.C. (2011). The presence of stem cell marker-expressing cells is not prognostically significant in glioblastomas. *Neuropathology,* (January 2011), [Epub ahead of print], ISSN 0919-6544

Kleihues, P.; Burger, P.C., Aldape, K.D., Brat, D.J., Biernat, W., Bigner, D.D., Nakazato, Y., Plate, K.H., Giangaspero, F., von Deimling, A., Ohgaki, H., Cavenee, W.K. (2007).

Glioblastoma. In: *Classification of Tumors of the Central Nervous System*, Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K., pp. 33-49, WHO, ISBN 978-92-832-2430-2, Lyon: IARC

Kleihues, P. & Ohgaki, H.(1999). Primary and secondary glioblastomas: from concept to clinical diagnosis. *Neuro Oncol.,* Vol.1, No.1, (January 1999), pp. 44-51, ISSN 1522-8517

Knudson, A. (1971). Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A,* Vol.68, No.4, (April 1971), pp. 820–3, ISSN 0027-8424

Kreth, S.; Thon, N., Eigenbrod, S, Lutz, J., Ledderose, C., Egensperger, R., Tonn, J.C., Kretzschmar, H.A., Hinske, L.C. & Kreth, F.W. (2011). O-Methylguanine-DNA Methyltransferase (MGMT) mRNA Expression Predicts Outcome in Malignant Glioma Independent of MGMT Promoter Methylation. *PLoS One*, Vol.6, No.2, (February 2011), pp. e17156, ISSN 1932-6203

Krex, D.; Klink, B., Hartmann, C., von Deimling, A., Pietsch, T., Simon, M., Sabel, M., Steinbach, J.P., Heese, O., Reifenberger, G., Weller, M. & Schackert, G. (2007). German Glioma Network. Long-term survival with glioblastoma multiforme. *Brain*, Vol.130, No.10, (October 2007), pp. 2596-606, ISSN 0006-8950

Kros, J.M.; Waarsenburg, N., Hayes, D.P., Hop, W.C. & van Dekken, H. (2000). Cytogenetic analysis of gemistocytic cells in gliomas. *J Neuropathol Exp Neurol.,* Vol.59, No.8, (August 2000), pp. 679–686, ISSN 0022-3069

Laks, D.R.; Masterman-Smith, M., Visnyei, K., Angenieux, B., Orozco, N.M., Foran, I., Yong, W.H., Vinters, H.V., Liau, L.M., Lazareff, J.A., Mischel, P.S., Cloughesy, T.F., Horvath, S. & Kornblum, H.I. (2009). Neurosphere formation is an independent predictor of clinical outcome in malignant glioma. *Stem Cells*, Vol.27, No.4, (April 2009), pp. 980-7, ISSN 0250-6793

Lathia, J.D.; Gallagher, J., Heddleston, J.M., Wang, J., Eyler, C.E., Macswords, J., Wu, Q., Vasanji, A., McLendon, R.E., Hjelmeland, A.B. & Rich, J.N. (2010). Integrin alpha 6 regulates glioblastoma stem cells. *Cell Stem Cell,* Vol.6, No.5, (May 2010), pp. 421-32, ISSN 1934-5909

Li, Z.; Bao, S., Wu, Q., Wang, H., Eyler, C., Sathornsumetee, S., Shi, Q., Cao, Y., Lathia, J., McLendon, R.E., Hjelmeland, A.B. & Rich, J.N. (2009). Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. *Cancer Cell*, Vol.15, No.6, (June 2009), pp. 501-13, ISSN 1535-6108

Li, L.; Dutra, A., Pak, E., Labrie, J.E. 3rd, Gerstein, R.M., Pandolfi, P.P., Recht, L.D., Ross, A.H(2008). EGFRvIII expression and PTEN loss synergistically induce chromosomal instability and glial tumors. *Neuro Oncol*. Vol.11, No.1, (February 2009),pp. 9-21, ISSN 1522-8517

Loeper, S.; Romeike, B.F., Heckmann, N., Jung, V., Henn, W., Feiden, W., Zang, K.D. & Urbschat, S. (2001). Frequent mitotic errors in tumor cells of genetically micro-heterogeneous glioblastomas. *Cytogenet Cell Genet.*, Vol.94, No.1-2, (2001), pp. 1-8, ISSN 0301-0171

Loh, J.K.; Lieu, A.S., Chou, C.H., Lin, F.Y., Wu, C.H., Howng, S.L., Chio, C.C. & Hong, Y.R. (2010). Differential expression of centrosomal proteins at different stages of human glioma. *BMC Cancer*, Vol.10, (June 2010); pp. 268, ISSN 1471-2407

Margetts, J.C. & Kalyan-Raman, U.P. (1989). Giant-celled glioblastoma of brain. A clinico-pathological and radiological study of ten cases (including immunohistochemistry and ultrastructure). *Cancer*, Vol.63, No.3, (Feb 1989), pp. 524-31

Margison, G.P. & Kleihues, P. (1975). Chemical carcinogenesis in the nervous system. Preferential accumulation of O6-methylguanine in rat brain deoxyribonucleic acid during repetitive administration of N-methyl-N-nitrosourea. *Biochem J.,* Vol.148, No.3, (June 1975), pp. 521-5, ISSN 0264-6021

McLendon, R.E. & Rich, J.N. (2010). Glioblastoma Stem Cells: A Neuropathologist's View. *J Oncol.*, Vol.2011, (2011), pp. 397195, ISSN 1687-8450

Meyer-Puttlitz, B.; Hayashi, Y., Waha, A., Rollbrocker, B., Boström, J., Wiestler, O.D., Louis, D.N., Reifenberger, G., von Deimling, A. (1997). Molecular genetic analysis of giant cell glioblastomas. *Am J Pathol.,* Vol.151, No.3, (September 1997), pp. 853–857, ISSN 0002-9440

Miller, C.R. & Perry, A. (2007). Glioblastoma. Morphologic and Molecular Genetic Diversity. *Arch Pathol Lab Med.,* Vol.131, No.3, (March 2007), pp. 397-406, ISSN 0003-9985

Misra, A.; Chattopadhyay, P., Dinda, A.K., Sarkar, C., Mahapatra, A.K., Hasnain, S.E. & Sinha, S. (2000). Extensive intra-tumor heterogeneity in primary human glial tumors as a result of locus non-specific genomic alterations. *J Neurooncol.* Vol.48, No.1, (May 2000), pp. 1-12, ISSN 0167-594X

Misra, A.; Pellarin, M., Nigro, J., Smirnov, I., Moore, D., Lamborn, K.R., Pinkel, D., Albertson, D.G. & Feuerstein, B.G. (2005). Array comparative genomic hybridization identifies genetic subgroups in grade 4 human astrocytoma. *Clin Cancer Res.*, Vol.11, No.8, (April 2005), pp. 2907-18, ISSN 1078-0432

Mizuno, H.; Spike B.T., Wahl, G.M. & Levine, A.J. (2010). Inactivation of p53 in breast cancers correlates with stem cell transcriptional signatures. *Proc Natl Acad Sci U S A,* Vol.107, No.52, (December 2010), pp. 22745-50, ISSN 0027-8424

Murat, A.; Migliavacca, E., Gorlia, T., Lambiv, W.L., Shay, T., Hamou, M.F., de Tribolet, N., Regli, L., Wick, W., Kouwenhoven, M.C., Hainfellner, J.A., Heppner, F.L., Dietrich, P.Y., Zimmer, Y., Cairncross, J.G., Janzer, R.C., Domany, E., Delorenzi, M., Stupp, R. & Hegi, M.E. (2008). Stem cell-related "self-renewal" signature and high epidermal growth factor receptor expression associated with resistance to concomitant chemoradiotherapy in glioblastoma. *J Clin Oncol.,* Vol.26, No.18, (June 2008), pp. 3015-24, ISSN 0732-183X

Nakamura, M.; Watanabe, T., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (2001). Promoter methylation of the DNA repair gene MGMT in astrocytomas is frequently associated with G:C --> A:T mutations of the TP53 tumor suppressor gene. *Carcinogenesis*, Vol.22, No.10, (October 2001), pp. 1715-9, ISSN 0143-3334

Nobusawa, S.; Lachuer, J., Wierinckx, A., Kim, Y.H., Huang, J., Legras, C., Kleihues, P. & Ohgaki, H. (2010). Intratumoral patterns of genomic imbalance in glioblastomas. *Brain Pathol.,* Vol.20, No.5, (September 2010), pp. 936-44, ISSN 1015-6305

Noushmehr, H.; Weisenberger, D.J., Diefes, K., Phillips, H.S., Pujara, K., Berman, B.P., Pan, F., Pelloski, C.E., Sulman, E.P., Bhat, K.P., Verhaak, R.G., Hoadley, K.A., Hayes, D.N., Perou, C.M., Schmidt, H.K., Ding, L., Wilson, R.K., Van Den Berg, D., Shen, H., Bengtsson, H., Neuvial, P., Cope, L.M., Buckley, J., Herman, J.G., Baylin, S.B., Laird, P.W. & Aldape, K. (2010). Cancer Genome Atlas Research Network.

Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer Cell,* Vol.17, No.5, (May 2010), pp. 510-22, ISSN 1535-6108

Ohgaki, H., Dessen, P., Jourde, B., Horstmann, S., Nishikawa, T., Di Patre, P.L., Burkhard, C., Schüler, D., Probst-Hensch, N.M., Maiorka, P.C., Baeza, N., Pisani, P., Yonekawa, Y., Yasargil, M.G., Lütolf, U.M. & Kleihues, P. (2004). Genetic pathways to glioblastoma: a population-based study. *Cancer Res.,* Vol.64, No.19, (October 2004), pp. 6892-9, ISSN 0008-5472

Pallini, R.; Ricci-Vitiani, L., Montano, N., Mollinari, C., Biffoni, M., Cenci, T., Pierconti, F., Martini, M., De Maria, R. & Larocca, L.M. (2010). Expression of the stem cell marker CD133 in recurrent glioblastoma and its value for prognosis. *Cancer,* Vol.117, No.1, (January 2011), pp. 162-74

Panosyan, E.H.; Laks, D.R., Masterman-Smith, M., Mottahedeh, J., Yong, W.H., Cloughesy, T.F., Lazareff, J.A., Mischel, P.S., Moore, T.B. & Kornblum, H.I. (2010). Clinical outcome in pediatric glial and embryonal brain tumors correlates with in vitro multi-passageable neurosphere formation. *Pediatr Blood Cancer,* Vol.55, No.4, (October 2010), pp. 644-51, ISSN 1545-5009

Parsons, D.W., Jones, S., Zhang, X., Lin, J.C., Leary, R.J., Angenendt, P., Mankoo, P., Carter, H., Siu, I.M., Gallia, G.L., Olivi, A., McLendon, R., Rasheed, B.A., Keir, S., Nikolskaya, T., Nikolsky, Y., Busam, D.A., Tekleab, H., Diaz, L.A.Jr., Hartigan, J., Smith, D.R., Strausberg, R.L., Marie, S.K., Shinjo, S.M., Yan, H., Riggins, G.J., Bigner, D.D., Karchin, R., Papadopoulos, N., Parmigiani, G., Vogelstein, B., Velculescu, V.E. & Kinzler, K.W. (2008). An integrated genomic analysis of human glioblastoma multiforme. *Science,* Vol.321, No.5897, (September 2008), pp. 1807-12, ISSN 0036-8075

Paulus, W.; Bayas, A., Ott, G. & Roggendorf, W. (1994). Interphase cytogenetics of glioblastoma and gliosarcoma. *Acta Neuropathol (Berl),* Vol.88, No.5, (1994), pp. 420–425, ISSN 0001-6322

Peraud, A.; Watanabe, K., Plate, K.H., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1997). p53 mutations versus EGF receptor expression in giant cell glioblastomas. *J Neuropathol Exp Neurol.,* Vol.56, No.11, (November 1997), pp. 1236-41, ISSN 0022-3069

Peraud, A.; Watanabe, K., Schwechheimer, K., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1999). Genetic profile of the giant cell glioblastoma. *Lab Invest,* Vol.79, No.2, (February 1999), pp. 123–129, ISSN 0023-6837

Perry, A.; Aldape, K.D., George, D.H. & Burger, P.C. (2004). Small cell astrocytoma: an aggressive variant that is clinicopathologically and genetically distinct from anaplastic oligodendroglioma. *Cancer*, Vol.101, No.10, (November 2004), pp. 2318-26

Peterson, S.E., Westra, J.W., Paczkowski, C.M. & Chun, J. (2008). Chromosomal mosaicism in neural stem cells. *Methods Mol Biol.* Vol.438, (2008), pp. 197-204, ISSN 1064-3745

Phi, J.H.; Park, S.H., Chung, C.K., Wang, K.C., Cho, B.K. & Kim, S.K. (2009). Atypical cell clusters expressing both neuronal and oligodendrocytic markers: novel histological pattern of glioneuronal tumors? *Pathol Int.,* Vol.59, No.10, (October 2009), pp. 735-43, ISSN 1320-5463

Phillips, H.S.; Kharbanda, S., Chen, R., Forrest, W.F., Soriano, R.H., Wu, T.D., Misra, A., Nigro, J.M., Colman, H., Soroceanu, L., Williams, P.M., Modrusan, Z., Feuerstein, B.G. & Aldape, K. (2006). Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell,* Vol.9, No.3, (March 2006), pp. 157-73, ISSN 1535-6108

Pope, W.B.; Xia, Q., Paton, V.E., Das, A., Hambleton, J., Kim, H.J., Huo, J., Brown, M.S., Goldin, J. & Cloughesy, T. (2011). Patterns of progression in patients with recurrent glioblastoma treated with bevacizumab. *Neurology*, Vol.76, No.5, (February 2011), pp. 432-7, ISSN 028-3878

Preusser, M.; Charles, J.R., Felsberg, J., Reifenberger, G., Hamou, M.F., Diserens, A.C., Stupp, R., Gorlia, T., Marosi, C., Heinzl, H., Hainfellner, J.A. & Hegi, M. (2008). Anti-O6-methylguanine-methyltransferase (MGMT) immunohistochemistry in glioblastoma multiforme: observer variability and lack of association with patient survival impede its use as clinical biomarker. *Brain Pathol.,* Vo.18, No.4, (October 2008), pp. 520–532, ISSN 1015-6305

Qian, X.C. & Brent, T.P. (1997). Methylation hot spots in the 5' flanking region denote silencing of the O6-methylguanine-DNA methyltransferase gene. *Cancer Res.*, Vol.57, No.17, (September 1997), pp. 3672-7, ISSN 0008-5472

Reardon, D.A.; Fink, K.L., Mikkelsen, T., Cloughesy, T.F., O'Neill, A., Plotkin, S., Glantz, M., Ravin, P., Raizer, J.J., Rich, K.M., Schiff, D., Shapiro, W.R., Burdette-Radoux, S., Dropcho, E.J., Wittemer, S.M., Nippgen, J., Picard, M. & Nabors, L.B. (2008). Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. *J Clin Oncol.*, Vol.26, No.34, (December 2008), pp. 5610-7, ISSN 0732-183X

Reis, R.M.; Konu-Leblebliciogl u, D., Lopes, J.M., Kleihues, P. & Ohgaki, H. (2000). Genetic profile of gliosarcomas. *Am J Pathol.,* Vol.156, (2000), pp. 425–432

Ricci-Vitiani, L.; Pallini, R., Biffoni, M., Todaro, M., Invernici, G., Cenci, T., Maira, G., Parati, E.A., Stassi, G., Larocca, L.M. & De Maria, R. (2010). Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells. *Nature,* Vol.468, No.7325, (December 2010), pp. 824-8, ISSN 0028-0836

Sanai, N.; Alvarez-Buylla, A. & Berger, M.S. (2005). Neural stem cells and the origin of gliomas. *N Engl J Med.*, Vol.353, No.8, (August 2005), pp. 811-22, ISSN 0028-4793

Shen, W.H.; Balajee, A,S., Wang, J., Wu, H., Eng, C., Pandolfi, P.P., Yin, Y (2007) Essential role for nuclear PTEN in maintaining chromosomal integrity. Cell. Vol.128, No.1, (January 2007), pp. 157-70, ISSN:0092-8674

Shen, Q.; Wang, Y., Kokovay, E., Lin, G., Chuang, SM., Goderie, S.K., Roysam, B. & Temple, S. (2008). Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell-cell interactions. *Cell Stem Cell,* Vol.3, No.3, (September 2008), pp. 289-300, ISSN 1934-5909

Shinojima, N.; Kochi, M., Hamada, J., Nakamura, H., Yano, S., Makino, K., Tsuiki, H., Tada, K., Kuratsu, J., Ishimaru, Y. & Ushio, Y. (2004). The influence of sex and the presence of giant cells on postoperative long-term survival in adult patients with supratentorial glioblastoma multiforme. *J Neurosurg.,* Vol.101, (2004), pp. 219–226

Silkworth, W.T.; Nardi, I.K., Scholl, L.M. & Cimini, D. (2009). Multipolar spindle pole coalescence is a major source of kinetochore mis-attachment and chromosome mis-

segregation in cancer cells. *PLoS One*, Vol.4, No.8, (August 2009), pp. e6564, ISSN 1932-6203

Singh, S.K.; Clarke, I.D., Terasaki, M., Bonn, V.E., Hawkins, C., Squire, J. & Dirks, P.B. (2003). Identification of a cancer stem cell in human brain tumors. *Cancer Res.*, Vol.63, No.18, (September 2003), pp. 5821-8, ISSN 0099-7013

Spiegl-Kreinecker, S.; Pirker, C., Filipits, M., Lötsch, D., Buchroithner, J., Pichler, J., Silye, R., Weis, S., Micksche, M., Fischer, J. & Berger, W. (2009). O6-Methylguanine DNA methyltransferase protein expression in tumor cells predicts outcome of temozolomide therapy in glioblastoma patients. *Neuro Oncol.,* Vol.12, No.1, (January 2010), pp. 28-36, ISSN 1522-8517

Stanbridge, E.J.; Flandermeyer, R.R., Daniels, D.W. & Nelson-Rees, W.A. (1981). Specific chromosome loss associated with the expression of tumorigenicity in human cell hybrids. *Somatic Cell Genet.,* Vol.7, No.6, (November 1981), pp. 699-712, ISSN 0098-0366

Stoler, D.L.; Chen, N., Basik, M., Kahlenberg, M.S., Rodriguez-Bigas, M.A., Petrelli, N.J. & Anderson, G.R. (1999). The onset and extent of genomic instability in sporadic colorectal tumor progression. *Proc Natl Acad Sci U S A,* Vol.96, No.26, (December 1999), pp. 15121-6, ISSN 0027-8424

Stupp, R.; Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J., Belanger, K., Brandes, A.A., Marosi, C., Bogdahn, U., Curschmann, J., Janzer, R.C., Ludwin, S.K., Gorlia, T., Allgeier, A., Lacombe, D., Cairncross, J.G., Eisenhauer, E. & Mirimanoff, R.O. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med,* Vol. 352, No.10, (March 2005), pp. 987–996, ISSN 0028-4793

Stupp, R.; Hegi, M.E., Mason, W.P., van den Bent, M.J., Taphoorn, M.J., Janzer R.C., Ludwin, S.K., Allgeier, A., Fisher, B., Belanger, K., Hau, P., Brandes, A.A., Gijtenbeek, J., Marosi, C., Vecht, C.J., Mokhtari, K., Wesseling, P., Villa, S., Eisenhauer, E., Gorlia, T., Weller, M., Lacombe, D., Cairncross, J.G., Mirimanoff, R.O., European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups & National Cancer Institute of Canada Clinical Trials Group. (2009). Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.*, Vol.10, No.5, (May 2009), pp. 459-66, ISSN 1470-2045

Sudakin, V. & Yen, T.J. (2007). Targeting mitosis for anti-cancer therapy. *BioDrugs*, Vol.21, No.4, (2007), pp. 225-33, ISSN 1173-8804

Tang, K.; Jin, Q., Yan, W., Zhang, W., You, G., Liu, Y. & Jiang, T. (2011). Clinical correlation of MGMT protein expression and promoter methylation in Chinese glioblastoma patients. *Med Oncol.,* (Mar 2011), [Epub ahead of print], ISSN 1357-0560

Temme, A.; Geiger, K.D., Wiedemuth, R., Conseur, K., Pietsch, T., Felsberg, J., Reifenberger, G., Tatsuka, M., Hagel, C., Westphal, M., Berger, H., Simon, M., Weller, M. & Schackert, G. (2010). Giant cell glioblastoma is associated with altered aurora b expression and concomitant p53 mutation. *J Neuropathol Exp Neurol.*, Vol.69, No.6, (June 2010), pp. 632-42, ISSN 0022-3069

Thon, N.; Damianoff, K., Hegermann, J., Grau, S., Krebs, B., Schnell, O., Tonn, J.C. & Goldbrunner, R. (2008). Presence of pluripotent CD133+ cells correlates with malignancy of gliomas. *Mol Cell Neurosci.,* Vol.43, No.1, (January 2010), pp. 51-9, ISSN 1044-7431

Tyzzer, E.E. (1916). Tumor immunity. *J Cancer Res.,* Vol.1, (1916), pp. 125-155

Verhaak, R.G.; Hoadley, K.A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M.D., Miller, C.R., Ding, L., Golub, T., Mesirov, J.P., Alexe, G., Lawrence, M., O'Kelly, M., Tamayo, P., Weir, B.A., Gabriel, S., Winckler, W., Gupta, S., Jakkula, L., Feiler, H.S., Hodgson, J.G., James, C.D., Sarkaria, J.N., Brennan, C., Kahn, A., Spellman, P.T., Wilson, R.K., Speed, T.P., Gray, J.W., Meyerson, M., Getz, G., Perou, C.M., Hayes, D.N., Cancer Genome Atlas Research Network. (2010). Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell,* Vol.17, No.1, (January 2010), pp. 98-110, ISSN 1535-6108

Wang, R.; Chadalavada, K., Wilshire, J., Kowalik, U., Hovinga, K.E., Geber, A., Fligelman, B., Leversha, M., Brennan, C. & Tabar, V. (2010). Glioblastoma stem-like cells give rise to tumour endothelium. *Nature,* Vol.468, No.7325, (December 2010), pp. 829-33, ISSN 0028-0836

Watanabe, K.; Tachibana, O., Sata, K., Yonekawa, Y., Kleihues, P. & Ohgaki, H. (1996). Overexpression of the EGF receptor and p53 mutations are mutually exclusive in the evolution of primary and secondary glioblastomas. *Brain Pathol.*, Vol.6, No.3, (July 1996), pp. 217-23, ISSN 1015-6305

Wick, W.; Hartmann, C., Engel, C., Stoffels, M., Felsberg, J., Stockhammer, F., Sabel, M.C., Koeppen, S., Ketter, R., Meyermann, R., Rapp, M., Meisner, C., Kortmann, R.D., Pietsch, T., Wiestler, O.D., Ernemann, U., Bamberg, M., Reifenberger, G., von Deimling, A. & Weller, M. (2009). NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *J Clin Oncol*, Vol.27, No.35, (December 2009), pp. 5874-80, ISSN 0732-183X

Yachida, S.; Jones, S., Bozic, I., Antal, T., Leary, R., Fu, B., Kamiyama, M., Hruban, R.H., Eshleman, J.R., Nowak, M.A., Velculescu, V.E., Kinzler, K.W., Vogelstein, B. & Iacobuzio-Donahue, C.A. (2010). Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature*, Vol.467, No.7319, (October 2010), pp. 1114-7, ISSN 0028-0836

Yadav, A.K.; Renfrow, J.J., Scholtens, D.M., Xie, H., Duran, G.E., Bredel, C., Vogel, H., Chandler, J.P., Chakravarti, A., Robe, P.A., Das, S., Scheck, A.C., Kessler, J.A., Soares, M.B., Sikic, B.I., Harsh, G.R. & Bredel, M. (2009). Monosomy of chromosome 10 associated with dysregulation of epidermal growth factor signaling in glioblastomas. *JAMA,* Vol.302, No.3, (July 2009), pp. 276-89, ISSN 0098-7484

Yan, H.; Parsons, D.W., Jin, G., McLendon, R., Rasheed, B.A., Yuan, W., Kos, I., Batinic-Haberle, I., Jones, S., Riggins, G.J., Friedman, H., Friedman, A., Reardon, D., Herndon, J., Kinzler, K.W., Velculescu, V.E., Vogelstein, B. & Bigner, D.D. (2009). IDH1 and IDH2 mutations in gliomas. *N Engl J Med.,* Vol.360, No.8, (February 2009), pp. 765-73, ISSN 0028-4793

Yang, A.H.; Kaushal, D., Rehen, S.K., Kriedt, K., Kingsbury, M.A., McConnell, M.J. & Chun, J. (2003). Chromosome segregation defects contribute to aneuploidy in normal neural progenitor cells. *J Neurosci.,* Vol.23, No.32, (November 2003), pp. 10454-62, ISSN 0270-6474

Yin, Y & Shen, W.H. (2008). PTEN: a new guardian of the genome. Oncogene. Vol.27, No.41, (September 2008), pp. 5443-53, ISSN 0950-9232

Yip, S.; Miao, J., Cahill, D.P., Iafrate, A.J., Aldape, K., Nutt, C.L. & Louis, D.N. (2009). MSH6 mutations arise in glioblastomas during temozolomide therapy and mediate temozolomide resistance. *Clin Cancer Res.,* Vol.15, No.14, (July 2009), pp. 4622-9, ISSN 1078-0432

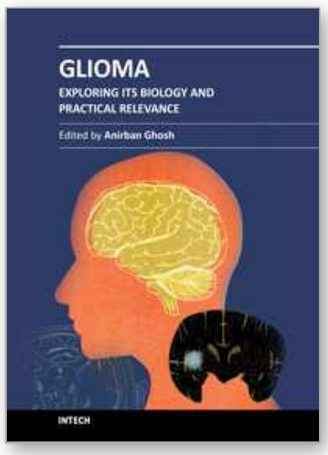
Yuan, X.; Curtin, J., Xiong, Y., Liu, G., Waschsmann-Hogiu, S., Farkas, D.L., Black, K.L. & Yu, J.S. (2004). Isolation of cancer stem cells from adult glioblastoma multiforme. *Oncogene*, Vol.23, No.58, (December 2004), pp. 9392-400, ISSN 0950-9232

Zeng, W.F.; Navaratne, K., Prayson, R.A. & Weil, R.J. (2007). Aurora B expression correlates with aggressive behaviour in glioblastoma multiforme. *J Clin Pathol.,* Vol.60, No.2, (February 2007), pp. 218-21, ISSN 0021-9746

Zeppernick, F.; Ahmadi, R., Campos, B., Dictus, C., Helmke, B.M., Becker, N., Lichter, P., Unterberg, A., Radlwimmer, B. & Herold-Mende, C.C. (2008). Stem cell marker CD133 affects clinical outcome in glioma patients. *Clin Cancer Res.,* Vol.14, No.1, (January 2008), pp. 123-9, ISSN 1078-0432

Zhai, H.; Heppner, F.L. & Tsirka, S.E. (2011). Microglia/macrophages promote glioma progression. *Glia*, Vol.59, No.3, (March 2011), pp. 472-85, ISSN 0894-1491

Zhang, M.; Song, T., Yang, L., Chen, R., Wu, L., Yang, Z. & Fang, J. (2008). Nestin and CD133: valuable stem cell-specific markers for determining clinical outcome of glioma patients. *J Exp Clin Cancer Res.,* Vol.27, (December 2008), pp. 85, ISSN 0392-9078



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