

Brain Cancer Study Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. The brain cancer occurs when abnormal cells form within the brain. There are two main types of tumors: malignant or cancerous tumors and benign tumors. Cancerous tumors can be divided into primary tumors that started within the brain and those that spread from somewhere else known as brain metastasis tumors. Treatment may include some combination of surgery, radiation therapy and chemotherapy. Anticonvulsant medication may be needed if seizures occur. This article introduces recent reports as references in the related studies.

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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. The brain cancer occurs when abnormal cells form within the brain. There are two main types of tumors: malignant or cancerous tumors and benign tumors. Cancerous tumors can be divided into primary tumors that started within the brain and those that spread from somewhere else known as brain metastasis tumors. Treatment may include some combination of surgery, radiation therapy and chemotherapy. Anticonvulsant medication may be needed if seizures occur.

The following introduces recent reports as references in the related studies.

Abbadi, S., J. J. Rodarte, et al. "Glucose-6-phosphatase is a key metabolic regulator of glioblastoma invasion." *Mol Cancer Res.* 2014 Nov;12(11):1547-59. doi: 10.1158/1541-7786.MCR-14-0106-T. Epub 2014 Jul 7.

Glioblastoma (GBM) remains the most aggressive primary brain cancer in adults. Similar to other cancers, GBM cells undergo metabolic reprogramming to promote proliferation and survival.

Glycolytic inhibition is widely used to target such reprogramming. However, the stability of glycolytic inhibition in GBM remains unclear especially in a hypoxic tumor microenvironment. In this study, it was determined that glucose-6-phosphatase (G6PC/G6Pase) expression is elevated in GBM when compared with normal brain. Human-derived brain tumor-initiating cells (BTIC) use this enzyme to counteract glycolytic inhibition induced by 2-deoxy-d-glucose (2DG) and sustain malignant progression. Downregulation of G6PC renders the majority of these cells unable to survive glycolytic inhibition, and promotes glycogen accumulation through the activation of glycogen synthase (GYS1) and inhibition of glycogen phosphorylase (PYGL). Moreover, BTICs that survive G6PC knockdown are less aggressive (reduced migration, invasion, proliferation, and increased astrocytic differentiation). Collectively, these findings establish G6PC as a key enzyme with promalignant functional consequences that has not been previously reported in GBM and identify it as a potential therapeutic target. IMPLICATIONS: This study is the first to demonstrate a functional relationship between the critical gluconeogenic and glycogenolytic enzyme G6PC with the metabolic adaptations during GBM invasion.

Addeo, R., S. Zappavigna, et al. "Erlotinib: early clinical development in brain cancer." *Expert Opin Investig Drugs.* 2014 Jul;23(7):1027-37. doi: 10.1517/13543784.2014.918950. Epub 2014 May 16.

INTRODUCTION: Glioblastoma (GBM) is the most common brain cancer in adults. It is also, unfortunately, the most aggressive type and the least

responsive to therapy. Overexpression of EGFR and/or EGFRvIII is frequently found in GBM and is frequently associated with the more malignant phenotype of the disease and a poor clinical outcome. EGFR-targeted therapy represents a promising anti-GBM therapy. Two EGFR kinase inhibitors, gefitinib and erlotinib have been tested in clinical trials for malignant gliomas. However, the clinical efficacy of EGFR-targeted therapy has been only modest in GBM patients. AREAS COVERED: The authors provide an evaluation of erlotinib as a potential therapy for GBM. The authors highlight experiences drawn from clinical trials and discuss the challenges, which include the insufficient penetration through the blood-brain barrier (BBB) and chemoresistance. EXPERT OPINION: Malignant brain tumours have a very complex signalling network that is not only driven by EGFR. This complexity dictates tumour sensitivity to EGFR-targeted therapies. Alternative kinase signalling pathways may be involved in parallel with the inhibited target, so that a single target's inactivation is not sufficient to block downstream oncogenic signalling. The use of nanocarriers offers many opportunities, such as the release of the drug to specific cells or tissues, together with the ability to overcome different biological barriers, like the BBB.

Bohmer, N. and A. Jordan "Caveolin-1 and CDC42 mediated endocytosis of silica-coated iron oxide nanoparticles in HeLa cells." *Beilstein J Nanotechnol.* 2015 Jan 14;6:167-76. doi: 10.3762/bjnano.6.16. eCollection 2015.

Nanomedicine is a rapidly growing field in nanotechnology, which has great potential in the development of new therapies for numerous diseases. For example iron oxide nanoparticles are in clinical use already in the thermotherapy of brain cancer. Although it has been shown, that tumor cells take up these particles in vitro, little is known about the internalization routes. Understanding of the underlying uptake mechanisms would be very useful for faster and precise development of nanoparticles for clinical applications. This study aims at the identification of key proteins, which are crucial for the active uptake of iron oxide nanoparticles by HeLa cells (human cervical cancer) as a model cell line. Cells were transfected with specific siRNAs against Caveolin-1, Dynamin 2, Flotillin-1, Clathrin, PIP5Kalpha and CDC42. Knockdown of Caveolin-1 reduces endocytosis of superparamagnetic iron oxide nanoparticles (SPIONs) and silica-coated iron oxide nanoparticles (SCIONs) between 23 and 41%, depending on the surface characteristics of the nanoparticles and the experimental design. Knockdown of CDC42 showed a 46% decrease of the internalization of PEGylated SPIONs within 24 h

incubation time. Knockdown of Dynamin 2, Flotillin-1, Clathrin and PIP5Kalpha caused no or only minor effects. Hence endocytosis in HeLa cells of iron oxide nanoparticles, used in this study, is mainly mediated by Caveolin-1 and CDC42. It is shown here for the first time, which proteins of the endocytic pathway mediate the endocytosis of silica-coated iron oxide nanoparticles in HeLa cells in vitro. In future studies more experiments should be carried out with different cell lines and other well-defined nanoparticle species to elucidate possible general principles.

Boice, J. D., Jr. "Radiation epidemiology and recent paediatric computed tomography studies." *Ann ICRP.* 2015 Mar 24. pii: 0146645315575877.

Recent record-linkage studies of cancer risk following computed tomography (CT) procedures among children and adolescents under 21 years of age must be interpreted with caution. The reasons why the examinations were performed were not known, and the dosimetric approaches did not include individual dose reconstructions or account for the possibility for missed examinations. The recent report (2013) on children by the United Nations Scientific Committee on the Effects of Atomic Radiation concluded that the associations may have resulted from confounding by indication (also called 'reverse causation'), and not radiation exposure. The reported cancer associations may very well have been related to the patients' underlying health conditions that prompted the examinations. Reverse causation has been observed in other epidemiological investigations, such as a Swedish study of thyroid cancer risk following I-131 scintillation imaging scans, and in studies of brain cancer risk following Thorotrast for cerebral angiography. Epidemiological patterns reported in the CT studies were also inconsistent with the world's literature. For example, in a UK study, teenagers had a higher risk of brain tumour than young children; in an Australian study, cancers not previously linked to radiation were significantly elevated; and in a Taiwanese study, the risk of benign tumours decreased with age at the time of CT examination. In all studies, solid tumours appeared much earlier than previously reported. Remarkably, in the Australian study, brain cancer excesses were seen regardless of whether or not the CT was to the head, i.e. a significant excess was reported for CT examinations of the abdomen and extremities, which involved no radiation exposure to the brain. In the UK study, the significance of the 'leukaemia' finding was only because myelodysplastic syndrome was added to the category, and there was no significance for leukaemia alone. Without knowledge of why CT examinations were performed, any future studies will be equally difficult to interpret. It is noteworthy that two recent studies of children in

France and Germany found no significant excess cancer risk from CT scans once adjustment was made for conditions that prompted the scan, family history, or other predisposing factors known to be associated with increased cancer risk. Nonetheless, such studies have heightened awareness of these relatively high-dose diagnostic procedures, and the need to reduce unnecessary examinations and lower the dose per examination commensurate with the desired image quality.

Booth, L., J. L. Roberts, et al. "GRP78/BiP/HSPA5/Dna K is a universal therapeutic target for human disease." *J Cell Physiol*. 2015 Jul;230(7):1661-76. doi: 10.1002/jcp.24919.

The chaperone GRP78/Dna K is conserved throughout evolution down to prokaryotes. The GRP78 inhibitor OSU-03012 (AR-12) interacted with sildenafil (Viagra) or tadalafil (Cialis) to rapidly reduce GRP78 levels in eukaryotes and as a single agent reduce Dna K levels in prokaryotes. Similar data with the drug combination were obtained for: HSP70, HSP90, GRP94, GRP58, HSP27, HSP40 and HSP60. OSU-03012/sildenafil treatment killed brain cancer stem cells and decreased the expression of: NPC1 and TIM1; LAMP1; and NTCPI, receptors for Ebola/Marburg/Hepatitis A, Lassa fever, and Hepatitis B viruses, respectively. Pre-treatment with OSU-03012/sildenafil reduced expression of the coxsakie and adenovirus receptor in parallel with it also reducing the ability of a serotype 5 adenovirus or coxsakie virus B4 to infect and to reproduce. Similar data were obtained using Chikungunya, Mumps, Measles, Rubella, RSV, CMV, and Influenza viruses. OSU-03012 as a single agent at clinically relevant concentrations killed laboratory generated antibiotic resistant *E. coli* and clinical isolate multi-drug resistant *N. gonorrhoeae* and MRSE which was in bacteria associated with reduced Dna K and Rec A expression. The PDE5 inhibitors sildenafil or tadalafil enhanced OSU-03012 killing in *N. gonorrhoeae* and MRSE and low marginally toxic doses of OSU-03012 could restore bacterial sensitivity in *N. gonorrhoeae* to multiple antibiotics. Thus, Dna K and bacterial phosphodiesterases are novel antibiotic targets, and inhibition of GRP78 is of therapeutic utility for cancer and also for bacterial and viral infections. *J. Cell. Physiol.* 230: 1661-1676, 2015. (c) 2014 The Authors. Journal of Cellular Physiology Published by Wiley Periodicals, Inc.

Bordji, K., A. Grandval, et al. "Hypoxia-inducible factor-2alpha (HIF-2alpha), but not HIF-1alpha, is essential for hypoxic induction of class III beta-tubulin expression in human glioblastoma cells." *FEBS J.*

2014 Dec;281(23):5220-36. doi: 10.1111/febs.13062. Epub 2014 Oct 13.

Glioblastoma multiforme (GBM) is the deadliest form of primary brain cancer. Several reports have indicated aberrant levels of betaIII-tubulin (betaIII-t) in human GBM. betaIII-t overexpression was linked to increasing malignancy in glial tumors and described to determine the onset of resistance to chemotherapy. Furthermore, a linkage was suggested between the induction of betaIII-t expression and hypoxia, a hallmark of GBM. We investigated the role of hypoxia-inducible factor (HIF)-1alpha and HIF-2alpha in the regulation of the betaIII-t gene (TUBB3) in GBM cells cultured in either normoxia or hypoxia. We report for the first time that HIF-2alpha, but not HIF-1alpha, is involved in hypoxia-induced betaIII-t expression in GBM cells. By gene-reporter experiments and site-directed mutagenesis, we found that two overlapping hypoxia response elements located in the 3' UTR of the gene were involved in the activation of TUBB3. This occurred through an enhanced binding of HIF-2alpha to the 3' region, as revealed by an electrophoretic mobility shift assay. Conversely, the promoter of TUBB3 was shown to be inactive. In addition, we observed that HIF-1alpha exhibits a repressive effect on betaIII-t expression in cells cultured in normoxia. These results show that both HIF-alpha isoforms have opposing effects on betaIII-t expression in GBM cells. Finally, we observed that hypoxia-induced betaIII-t expression is well correlated with the kinetics of HIF-2alpha protein stabilization. The evidence for a direct linkage between HIF-2alpha and increased expression of betaIII-t by hypoxia suggests that an anti-HIF-2alpha strategy (i.e. by downregulating betaIII-t) could be of potential interest for improving the treatment of GBM.

Brett-Morris, A., B. M. Wright, et al. "The polyamine catabolic enzyme SAT1 modulates tumorigenesis and radiation response in GBM." *Cancer Res.* 2014 Dec 1;74(23):6925-34. doi: 10.1158/0008-5472.CAN-14-1249. Epub 2014 Oct 2.

Glioblastoma multiforme (GBM) is the most common and severe form of brain cancer. The median survival time of patients is approximately 12 months due to poor responses to surgery and chemoradiation. To understand the mechanisms involved in radioresistance, we conducted a genetic screen using an shRNA library to identify genes in which inhibition would sensitize cells to radiation. The results were cross-referenced with the Oncomine and Rembrandt databases to focus on genes that are highly expressed in GBM tumors and associated with poor patient outcomes. Spermidine/spermine-N1-acetyltransferase 1 (SAT1), an enzyme involved in polyamine catabolism, was identified as a gene that promotes

resistance to ionizing radiation (IR), is overexpressed in brain tumors, and correlates with poor outcomes. Knockdown of SAT1 using shRNA and siRNA approaches in multiple cell and neurosphere lines resulted in sensitization of GBM cells to radiation in colony formation assays and tumors, and decreased tumorigenesis *in vivo*. Radiosensitization occurred specifically in G2-M and S phases, suggesting a role for SAT1 in homologous recombination (HR) that was confirmed in a DR-GFP reporter system. Mechanistically, we found that SAT1 promotes acetylation of histone H3, suggesting a new role of SAT1 in chromatin remodeling and regulation of gene expression. In particular, SAT1 depletion led to a dramatic reduction in BRCA1 expression, explaining decreased HR capacity. Our findings suggest that the biologic significance of elevated SAT1 expression in GBM lies in its contribution to cell radioresistance and that SAT1 may potentially be a therapeutic target to sensitize GBM to cancer therapies.

Cefalo, M. G., M. A. De Ioris, et al. "Wernicke encephalopathy in pediatric neuro-oncology: presentation of 2 cases and review of literature." *J Child Neurol.* 2014 Dec;29(12):NP181-5. doi: 10.1177/0883073813510355. Epub 2013 Nov 28.

Wernicke encephalopathy represents a well-known entity characterized by a set of cognitive and neurologic alterations. Wernicke encephalopathy is rare and under-recognized in childhood and may be fatal. Few cases have been documented in pediatric oncology. We report on 2 Wernicke encephalopathy cases that occurred in children having a brain tumor. The diagnosis of Wernicke encephalopathy was suggested by clinical manifestations associated with the typical radiologic findings and a laboratory evidence of thiamine deficiency. No large series have been published to support the evidence that pediatric malignancies represent a demonstrated factor of increased risk to develop a Wernicke encephalopathy. Moreover, the diagnosis may be even more difficult in brain tumors, considering the overlapping symptoms and the risk of encephalopathy related to both the disease and the treatment. Wernicke encephalopathy should be considered in all children with cancer presenting a neurologic deterioration, mainly in brain tumors. An early diagnosis is imperative for a prompt therapy that might prevent or minimize the irreversible brain damage related to this condition.

Chamberlain, M. C. "A selected review of abstracts from the 11th Congress of the European Association of Neuro-Oncology (EANO)." *CNS Oncol.* 2015;4(1):5-9. doi: 10.2217/cns.14.52.

The European Association of Neuro-Oncology (EANO) is the largest neuro-oncology

meeting in Europe that meets biannually and reproducibly provides an exciting forum to present new brain cancer clinical trials and research data. The EANO 2014 meeting in Turin, Italy (9-12 October 2014) was comprised of 3 days of presentation, nearly 50 oral presentations and nearly 350 abstracts provides a contemporary overview of neuro-oncology that includes both metastatic diseases of the CNS as well as primary brain tumors. This summary attempts to highlight select abstracts presented at the meeting of EANO 2014 in a short review that provides a portrait of a large and multifaceted meeting.

Deluche, E., S. Leobon, et al. "Two cases of cutaneous drug eruption associated with temozolamide therapy for glioblastoma." *Curr Oncol.* 2014 Dec;21(6):e779-81. doi: 10.3747/co.21.2133.

Glioblastoma is the most common form of primary brain cancer. Its treatment involves surgery, radiotherapy, and chemotherapy with temozolamide (tmz), which is an oral alkylating agent. To the best of our knowledge, few dermatologic side effects of tmz have been described. We report two cases of cutaneous drug eruption caused by tmz during and after radiochemotherapy treatment. In the first case, all tests were negative, but the clinical history and the time of onset supported an allergy to tmz. In the second case, an allergy to tmz was proved by a positive lymphocyte activation test. In this context, our study is one of a very few trying to determine dermatologic side effects by applicable tests used in routine practice.

Dewerchin, M. and P. Carmeliet "Placental growth factor in cancer." *Expert Opin Ther Targets.* 2014 Nov;18(11):1339-54. doi: 10.1517/14728222.2014.948420. Epub 2014 Oct 9.

INTRODUCTION: Placental growth factor (PLGF) belongs to the VEGF family, which among the three VEGF receptors binds exclusively to VEGFR1, present on various cell types. Isoform PLGF-2 also binds the neuropilin co-receptors. PLGF is dispensable for development and health but has a prominent role in pathology including cancer. This has triggered the question whether PLGF targeting might offer an alternative to current antiangiogenesis therapy, which encounters problems of refractoriness and acquired resistance. **AREAS COVERED:** This article reviews the available literature on the characteristics of PLGF, its role(s) in cancer and the findings on PLGF inhibition in preclinical models with attention to as yet unresolved questions and summarizes data from initial clinical trials. **EXPERT OPINION:** Preclinical studies show that inhibition of PLGF, either by genetic inhibition or by pharmacological blockade using distinct independently generated anti-PLGF antibodies, slows down tumor growth and metastasis

and even induces regression of pre-existing medulloblastoma, the most frequent brain cancer in children. These promising preclinical findings, together with the acceptable safety profile of anti-PLGF administration in Phase I clinical trials, have attracted attention to PLGF as a potential target for therapy.

Dhruva, A., B. E. Aouizerat, et al. "Cytokine gene associations with self-report ratings of morning and evening fatigue in oncology patients and their family caregivers." *Biol Res Nurs.* 2015 Mar;17(2):175-84. doi: 10.1177/1099800414534313. Epub 2014 May 27.

The purpose of this study was to evaluate for differences in variations in pro- and anti-inflammatory cytokine genes between participants who were classified as having low and high levels of morning and evening fatigue and to evaluate for differences in phenotypic characteristics between these two groups. In a sample of 167 oncology outpatients with breast, prostate, lung, or brain cancer and 85 of their family caregivers, growth mixture modeling was used to identify latent classes of individuals based on ratings of morning and evening fatigue obtained prior to, during, and for 4 months following completion of radiation therapy. Differences in single nucleotide polymorphisms and haplotypes in 15 cytokine genes were evaluated between the latent classes. Multiple logistic regression was used to assess the effect of phenotypic and genotypic characteristics on morning and evening fatigue class membership. Associations were found between morning fatigue and number of comorbidities as well as variations in tumor necrosis factor alpha (TNFA) rs1800629 and rs3093662. Evening fatigue was associated with caring for children at home and variations in interleukin 4 (IL4) rs2243248 and TNFA rs2229094.

Dixit, S., T. Novak, et al. "Transferrin receptor-targeted theranostic gold nanoparticles for photosensitizer delivery in brain tumors." *Nanoscale.* 2015 Feb 7;7(5):1782-90. doi: 10.1039/c4nr04853a.

Therapeutic drug delivery across the blood-brain barrier (BBB) is not only inefficient, but also nonspecific to brain stroma. These are major limitations in the effective treatment of brain cancer. Transferrin peptide (Tfpep) targeted gold nanoparticles (Tfpep-Au NPs) loaded with the photodynamic pro-drug, Pc 4, have been designed and compared with untargeted Au NPs for delivery of the photosensitizer to brain cancer cell lines. In vitro studies of human glioma cancer lines (LN229 and U87) overexpressing the transferrin receptor (TfR) show a significant increase in cellular uptake for targeted conjugates as compared to untargeted particles. Pc 4 delivered from Tfpep-Au NPs clusters within vesicles after targeting

with the Tfpep. Pc 4 continues to accumulate over a 4 hour period. Our work suggests that TfR-targeted Au NPs may have important therapeutic implications for delivering brain tumor therapies and/or providing a platform for noninvasive imaging.

Hamed, H. A., S. Tavallai, et al. "Sorafenib/regorafenib and lapatinib interact to kill CNS tumor cells." *J Cell Physiol.* 2015 Jan;230(1):131-9. doi: 10.1002/jcp.24689.

The present studies were to determine whether the multi-kinase inhibitor sorafenib or its derivative regorafenib interacted with the ERBB1/ERBB2 inhibitor lapatinib to kill CNS tumor cells. In multiple CNS tumor cell types sorafenib and lapatinib interacted in a greater than additive fashion to cause tumor cell death. Tumor cells lacking PTEN, and anoikis or lapatinib resistant cells were as sensitive to the drug combination as cells expressing PTEN or parental cells, respectively. Similar data were obtained using regorafenib. Treatment of brain cancer cells with [sorafenib + lapatinib] enhanced radiation toxicity. The drug combination increased the numbers of LC3-GFP vesicles; this correlated with a reduction in endogenous LC3II, and p62 and LAMP2 degradation. Knock down of Beclin1 or ATG5 significantly suppressed drug combination lethality. Expression of c-FLIP-s, BCL-XL, or dominant negative caspase 9 reduced drug combination toxicity; knock down of FADD or CD95 was protective. Expression of both activated AKT and activated MEK1 or activated mTOR was required to strongly suppress drug combination lethality. As both lapatinib and sorafenib are FDA approved agents, our data argue for further determination as to whether lapatinib and sorafenib is a useful glioblastoma therapy.

Hammer, G. P., A. Auvinen, et al. "Mortality from cancer and other causes in commercial airline crews: a joint analysis of cohorts from 10 countries." *Occup Environ Med.* 2014 May;71(5):313-22. doi: 10.1136/oemed-2013-101395. Epub 2014 Jan 3.

BACKGROUND: Commercial airline crew is one of the occupational groups with the highest exposures to ionising radiation. Crew members are also exposed to other physical risk factors and subject to potential disruption of circadian rhythms. **METHODS:** This study analyses mortality in a pooled cohort of 93 771 crew members from 10 countries. The cohort was followed for a mean of 21.7 years (2.0 million person-years), during which 5508 deaths occurred. **RESULTS:** The overall mortality was strongly reduced in male cockpit (SMR 0.56) and female cabin crews (SMR 0.73). The mortality from radiation-related cancers was also reduced in male cockpit crew (SMR 0.73), but not in female or male

cabin crews (SMR 1.01 and 1.00, respectively). The mortality from female breast cancer (SMR 1.06), leukaemia and brain cancer was similar to that of the general population. The mortality from malignant melanoma was elevated, and significantly so in male cockpit crew (SMR 1.57). The mortality from cardiovascular diseases was strongly reduced (SMR 0.46). On the other hand, the mortality from aircraft accidents was exceedingly high (SMR 33.9), as was that from AIDS in male cabin crew (SMR 14.0).

CONCLUSIONS: This large study with highly complete follow-up shows a reduced overall mortality in male cockpit and female cabin crews, an increased mortality of aircraft accidents and an increased mortality in malignant skin melanoma in cockpit crew. Further analysis after longer follow-up is recommended.

Kerneis, S., L. H. Swift, et al. "Natural product extracts of the Canadian prairie plant, Thermopsis rhombifolia, have anti-cancer activity in phenotypic cell-based assays." *Nat Prod Res.* 2014 Nov 25:1-9.

Many plant species within the terrestrial ecological zones of Canada have not yet been investigated for anti-cancer activity. We examined the scientific literature describing the endemic flora from the prairie ecological zone and selected the species, Thermopsis rhombifolia, locally known as the buffalo bean, for investigation of its anti-cancer potential. We tested it in cell-based assays using phenotypic screens that feature some of the hallmarks of cancer. An ethanolic extract prepared from *T. rhombifolia* was cytotoxic to HT-29 (colon) and SH-SY5Y (brain) cancer cell lines, and showed little cytotoxicity to a normal human cell line (WI-38). In phenotypic assays, we identified activities in the extracts that target cell death, cell cycle and cell adhesion. These data highlight the anti-cancer potential of previously untested plants found in northern ecological zones and the feasibility of using pertinent phenotypic assays to examine the anti-cancer potential of natural product extracts.

Kondapalli, K. C., J. P. Llongueras, et al. "A leak pathway for luminal protons in endosomes drives oncogenic signalling in glioblastoma." *Nat Commun.* 2015 Feb 9;6:6289. doi: 10.1038/ncomms7289.

Epidermal growth factor receptor (EGFR) signalling is a potent driver of glioblastoma, a malignant and lethal form of brain cancer. Disappointingly, inhibitors targeting receptor tyrosine kinase activity are not clinically effective and EGFR persists on the plasma membrane to maintain tumour growth and invasiveness. Here we show that endolysosomal pH is critical for receptor sorting and turnover. By functioning as a leak pathway for

protons, the Na⁺/H⁺ exchanger NHE9 limits luminal acidification to circumvent EGFR turnover and prolong downstream signalling pathways that drive tumour growth and migration. In glioblastoma, NHE9 expression is associated with stem/progenitor characteristics, radiochemoresistance, poor prognosis and invasive growth in vitro and in vivo. Silencing or inhibition of NHE9 in brain tumour-initiating cells attenuates tumoursphere formation and improves efficacy of EGFR inhibitor. Thus, NHE9 mediates inside-out control of oncogenic signalling and is a highly druggable target for pan-specific receptor clearance in cancer therapy.

Konno, S., K. Chu, et al. "Potent Anticancer Effects of Bioactive Mushroom Extracts (*Phellinus linteus*) on a Variety of Human Cancer Cells." *J Clin Med Res.* 2015 Feb;7(2):76-82. doi: 10.14740/jocmr1996w. Epub 2014 Nov 19.

BACKGROUND: Although several therapeutic options are currently available for patients with various cancers, the outcomes are often disappointing and a more effective modality needs to be promptly established. We have been exploring an alternative approach using natural agents and two bioactive mushroom extracts isolated from *Phellinus linteus* (PL), namely PL-ES and PL-I-ES, were of our interest. As anticancer effects of similar extracts have been reported in several cancers, we investigated whether PL-ES and PL-I-ES might have such anticancer activities on a variety of human cancer cells in vitro. **METHODS:** Ten different types of human cancer cell lines, including three metastatic prostate, bladder, kidney, lung, breast, stomach, liver, and brain cancer cells, were employed and tested with PL-ES or PL-I-ES. Cell growth/viability, exertion of oxidative stress, and induction of apoptosis were assessed by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay, lipid peroxidation (LPO) assay, and specific enzymatic assay, respectively. **RESULTS:** PL-ES (100 microg/mL) exhibited potent anticancer activity, resulting in a significant (40-80%) growth reduction in all 10 cancer cells at 72 hours. PL-I-ES (100 microg/mL) was effective on only four cancer cells but its higher concentration at 250 microg/mL led to a significant (25-90%) growth reduction in seven cancer cells. LPO assays indicated that such a significant growth reduction by PL-ES (100 microg/mL) or PL-I-ES (100 or 250 microg/mL) could result from cell death due to a cytotoxic effect of oxidative stress (through free radicals). Moreover, enzymatic assays for caspase-3 (Csp-3) and caspase-9 (Csp-9), the pro-apoptotic regulators, showed that both enzymes were significantly activated by PL-ES or PL-I-ES, indicating that cell death due to oxidative stress was more likely associated with apoptosis.

CONCLUSIONS: The present study shows that both PL-ES and PL-I-ES indeed have anticancer effects on a variety of cancer cells, although PL-ES appears to be more potent than PL-I-ES. Such an anticancer effect is presumably attributed to oxidative stress, which will ultimately lead to apoptosis. Therefore, these two bioactive mushroom extracts may have clinical implications in a more effective therapeutic option for a variety of human malignancies.

Madane, R. G. and H. S. Mahajan "Curcumin-loaded nanostructured lipid carriers (NLCs) for nasal administration: design, characterization, and in vivo study." *Drug Deliv.* 2014 Nov 4:1-9.

Abstract Cancer nanotherapeutics is beginning to overwhelm the global research and viewed to be the revolutionary treatment regime in the medical field. This investigation describes the development of a stable nanostructured lipid carrier (NLC) system as a carrier for curcumin (CRM). The CRM-loaded NLC developed as a particle with the size of 146.8 nm, a polydispersity index of 0.18, an entrapment efficiency (EE) of 90.86%, and the zeta potential (ZP) of -21.4 mV. Besides, the increased cytotoxicity of CRM-NLC than that of CRM to astrocytoma-glioblastoma cell line (U373MG) in the cancer cell lines was observed. Results of biodistribution studies showed higher drug concentration in brain after intranasal administration of NLCs than PDS. The results of the study also suggest that CRM-NLC is a promising drug delivery system for brain cancer therapy.

Man, J., J. D. Shoemake, et al. "Hyperthermia Sensitizes Glioma Stem-like Cells to Radiation By Inhibiting AKT Signaling." *Cancer Res.* 2015 Feb 20. pii: canres.3621.2014.

Glioma stem-like cells (GSCs) are a subpopulation of cells in tumors that are believed to mediate self-renewal and relapse in glioblastoma (GBM), the most deadly form of primary brain cancer. In radiation oncology, hyperthermia is known to radiosensitize cells and it is re-emerging as a treatment option for patients with GBM. In this study, we investigated the mechanisms of hyperthermic radiosensitization in GSCs by a phospho-kinase array that revealed the survival kinase AKT as a critical sensitization determinant. GSCs treated with radiation alone exhibited increased AKT activation, but the addition of hyperthermia before radiotherapy reduced AKT activation and impaired GSC proliferation. Introduction of constitutively active AKT in GSCs compromised hyperthermic radiosensitization. Pharmacologic inhibition of PI3K further enhanced the radiosensitizing effects of hyperthermia. In a preclinical orthotopic transplant model of human

GBM, thermoradiotherapy reduced pS6 levels, delayed tumor growth and extended animal survival. Together, our results offer a preclinical proof-of-concept for further evaluation of combined hyperthermia and radiation for GBM treatment.

Mazzacurati, L., M. Marzulli, et al. "Use of miRNA response sequences to block off-target replication and increase the safety of an unattenuated, glioblastoma-targeted oncolytic HSV." *Mol Ther.* 2015 Jan;23(1):99-107. doi: 10.1038/mt.2014.177. Epub 2014 Sep 9.

Glioblastoma multiforme (GBM) is an aggressive brain cancer for which there is no effective treatment. Oncolytic HSV vectors (oHSVs) are attenuated lytic viruses that have shown promise in the treatment of human GBM models in animals, but their efficacy in early phase patient trials has been limited. Instead of attenuating the virus with mutations in virulence genes, we engineered four copies of the recognition sequence for miR-124 into the 3'UTR of the essential ICP4 gene to protect healthy tissue against lytic virus replication; miR-124 is expressed in neurons but not in glioblastoma cells. Following intracranial inoculation into nude mice, the miR-124-sensitive vector failed to replicate or show overt signs of pathogenesis. To address the concern that this safety feature may reduce oncolytic activity, we inserted the miR-124 response elements into an unattenuated, human receptor (EGFR/EGFRvIII)-specific HSV vector. We found that miR-124 sensitivity did not cause a loss of treatment efficiency in an orthotopic model of primary human GBM in nude mice. These results demonstrate that engineered miR-124 responsiveness can eliminate off-target replication by unattenuated oHSV without compromising oncolytic activity, thereby providing increased safety.

McConnell, E. M., M. R. Holahan, et al. "Aptamers as promising molecular recognition elements for diagnostics and therapeutics in the central nervous system." *Nucleic Acid Ther.* 2014 Dec;24(6):388-404. doi: 10.1089/nat.2014.0492.

Oligonucleotide aptamers are short, synthetic, single-stranded DNA or RNA able to recognize and bind to a multitude of targets ranging from small molecules to cells. Aptamers have emerged as valuable tools for fundamental research, clinical diagnosis, and therapy. Due to their small size, strong target affinity, lack of immunogenicity, and ease of chemical modification, aptamers are an attractive alternative to other molecular recognition elements, such as antibodies. Although it is a challenging environment, the central nervous system and related molecular targets present an exciting potential area for aptamer research. Aptamers hold promise for targeted

drug delivery, diagnostics, and therapeutics. Here we review recent advances in aptamer research for neurotransmitter and neurotoxin targets, demyelinating disease and spinal cord injury, cerebrovascular disorders, pathologies related to protein aggregation (Alzheimer's, Parkinson's, and prions), brain cancer (glioblastomas and gliomas), and regulation of receptor function. Challenges and limitations posed by the blood brain barrier are described. Future perspectives for the application of aptamers to the central nervous system are also discussed.

McCray, A. N., S. Desai, et al. "The interruption of PKC-*iota* signaling and TRAIL combination therapy against glioblastoma cells." *Neurochem Res.* 2014 Sep;39(9):1691-701. doi: 10.1007/s11064-014-1361-8. Epub 2014 Jun 26.

Glioblastoma is a highly aggressive type of brain cancer which currently has limited options for treatment. It is imperative to develop combination therapies that could cause apoptosis in glioblastoma. The aim of this study was to characterize the effect of modified ICA-1, a PKC-*iota* inhibitor, on the growth pattern of various glioblastoma cell lines. T98G and U87 glioblastoma cells were treated with ICA-1 alone and the absolute cell numbers of each group were determined for cell growth expansion analysis, cell viability analysis, and cell death analysis. Low dose ICA-1 treatment alone significantly inhibited cell growth expansion of high density glioblastoma cells without inducing cell death. However, the high dose ICA-1 treatment regimen provided significant apoptosis for glioblastoma cells. Furthermore, this study was conducted to use a two layer molecular level approach for treating glioblastoma cells with ICA-1 plus an apoptosis agent, tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL), to induce apoptosis in such chemo-refractory cancer cells. Following ICA-1 plus TRAIL treatment, apoptosis was detected in glioblastoma cells via the TUNEL assay and via flow cytometric analysis using Annexin-V FITC/PI. This study offers the first evidence for ICA-1 alone to inhibit glioblastoma cell proliferation as well as the novel combination of ICA-1 with TRAIL to cause robust apoptosis in a caspase-3 mediated mechanism. Furthermore, ICA-1 plus TRAIL simultaneously modulates down-regulation of PKC-*iota* and c-Jun.

Miranda Filho, A. L., R. J. Koifman, et al. "Brain cancer mortality in an agricultural and a metropolitan region of Rio de Janeiro, Brazil: a population-based, age-period-cohort study, 1996-2010." *BMC Cancer.* 2014 May 6;14:320. doi: 10.1186/1471-2407-14-320.

BACKGROUND: Individuals who live in rural areas are at greater risk for brain cancer, and

pesticide exposure may contribute to this increased risk. The aims of this research were to analyze the mortality trends and to estimate the age-period-cohort effects on mortality rates from brain cancer in two regions in Rio de Janeiro, Brazil. **METHODS:** This descriptive study examined brain cancer mortality patterns in individuals of both sexes, >19 years of age, who died between 1996 and 2010. They were residents of a rural (Serrana) or a non-rural (Metropolitan) area of Rio de Janeiro, Brazil. We estimated mortality trends using Joinpoint Regression analysis. Age-period-cohort models were estimated using Poisson regression analysis. **RESULTS:** The estimated annual percentage change in mortality caused by brain cancer was 3.8% in the Serrana Region (95% confidence interval (CI): 0.8-5.6) and -0.2% (95% CI: -1.2-0.7) in the Metropolitan Region. The results indicated that the relative risk was higher in the rural region for the more recent birth cohorts (1954 and later). Compared with the reference birth cohort (1945-49, Serrana Region), the relative risk was four times higher for individuals born between 1985 and 1989.

Misuraca, K. L., K. L. Barton, et al. "Pax3 expression enhances PDGF-B-induced brainstem gliomagenesis and characterizes a subset of brainstem glioma." *Acta Neuropathol Commun.* 2014 Oct 21;2(1):134.

High-grade Brainstem Glioma (BSG), also known as Diffuse Intrinsic Pontine Glioma (DIPG), is an incurable pediatric brain cancer. Increasing evidence supports the existence of regional differences in gliomagenesis such that BSG is considered a distinct disease from glioma of the cerebral cortex (CG). In an effort to elucidate unique characteristics of BSG, we conducted expression analysis of mouse PDGF-B-driven BSG and CG initiated in Nestin progenitor cells and identified a short list of expression changes specific to the brainstem gliomagenesis process, including abnormal upregulation of paired box 3 (Pax3). In the neonatal mouse brain, Pax3 expression marks a subset of brainstem progenitor cells, while it is absent from the cerebral cortex, mirroring its regional expression in glioma. Ectopic expression of Pax3 in normal brainstem progenitors *in vitro* shows that Pax3 inhibits apoptosis. Pax3-induced inhibition of apoptosis is p53-dependent, however, and in the absence of p53, Pax3 promotes proliferation of brainstem progenitors. *In vivo*, Pax3 enhances PDGF-B-driven gliomagenesis by shortening tumor latency and increasing tumor penetrance and grade, in a region-specific manner, while loss of Pax3 function extends survival of PDGF-B-driven;p53-deficient BSG-bearing mice by 33%. Importantly, Pax3 is regionally expressed in human glioma as well, with high PAX3 mRNA characterizing 40% of human BSG, revealing a subset of tumors that significantly

associates with PDGFRA alterations, amplifications of cell cycle regulatory genes, and is exclusive of ACVR1 mutations. Collectively, these data suggest that regional Pax3 expression not only marks a novel subset of BSG but also contributes to PDGF-B-induced brainstem gliomagenesis.

Mlynarczyk, G. S., C. A. Berg, et al. "Salmonella as a biological "Trojan horse" for neoplasia: future possibilities including brain cancer." *Med Hypotheses*. 2014 Sep;83(3):343-5. doi: 10.1016/j.mehy.2014.06.009. Epub 2014 Jun 16.

This manuscript considers available evidence that a specific Salmonella strain could be used as an effective orally-administered option for cancer therapy involving the brain. It has been established that Salmonella preferentially colonizes neoplastic tissue and thrives as a facultative anaerobe in the intra-tumor environment. Although Salmonella accumulates in tumors by passive processes, it is still possible for lipopolysaccharide to cause sepsis and endotoxic shock during the migration of bacteria to the tumor site. An LPS-free version of a recently identified Salmonella isolate may have the capability to circumvent the blood brain barrier and provide a safer method of reaching brain tumors. This isolate merits further research as a "Trojan horse" for future oral biotherapy of brain cancer.

Mohamed, M. S., S. Veeranarayanan, et al. "Structurally distinct hybrid polymer/lipid nanoconstructs harboring a type-I ribotoxin as cellular imaging and glioblastoma-directed therapeutic vectors." *Macromol Biosci*. 2014 Dec;14(12):1696-711. doi: 10.1002/mabi.201400248. Epub 2014 Sep 2.

A nanoformulation composed of a ribosome inactivating protein-curcin and a hybrid solid lipid nanovector has been devised against glioblastoma. The structurally distinct nanoparticles were highly compatible to human endothelial and neuronal cells. A sturdy drug release from the particles, recorded upto 72 h, was reflected in the time-dependent toxicity. Folate-targeted nanoparticles were specifically internalized by glioma, imparting superior toxicity and curbed an aggressively proliferating in vitro 3D cancer mass in addition to suppressing the anti-apoptotic survivin and cell matrix protein vinculin. Combined with the imaging potential of the encapsulated dye, the nanovector emanates as a multifunctional anti-cancer system.

Moon, C. Y., J. W. Choi, et al. "Dual tumor targeting with pH-sensitive and bioreducible polymer-complexed oncolytic adenovirus." *Biomaterials*. 2015 Feb;41:53-68. doi: 10.1016/j.biomaterials.2014.11.021. Epub 2014 Dec 5.

Oncolytic adenoviruses (Ads) have shown great promise in cancer gene therapy but their efficacy has been compromised by potent immunological, biochemical, and specific tumor-targeting limitations. To take full advantage of the innate cancer-specific killing potency of oncolytic Ads but also exploit the subtleties of the tumor microenvironment, we have generated a pH-sensitive and bio-reducible polymer (PPCBA)-coated oncolytic Ad. Ad-PPCBA complexes showed higher cellular uptake at pH 6.0 than pH 7.4 in both high and low coxsackie and adenovirus receptor-(CAR)-expressing cells, thereby demonstrating Ad-PPCBA's ability to target the low pH hypoxic tumor microenvironment and overcome CAR dependence for target cell uptake. Endocytic mechanism studies indicated that Ad-PPCBA internalization is mediated by macropinocytosis instead of the CAR-dependent endocytic pathway that internalizes naked Ad. VEGF-specific shRNA-expressing oncolytic Ad complexed with PPCBA (RdB/shVEGF-PPCBA) elicited much more potent suppression of U87 human brain cancer cell VEGF gene expression in vitro, and human breast cancer MCF7 cell/Matrigel plug vascularization in a mouse model, when cancer cells had been previously infected at pH 6.0 versus pH 7.4. Moreover, intratumorally and intravenously injected RdB/shVEGF-PPCBA nanocomplexes elicited significantly higher therapeutic efficacy than naked virus in U87-tumor mouse xenograft models, reducing IL-6, ALT, and AST serum levels. These data demonstrated PPCBA's biocompatibility and capability to shield the Ad surface to prevent innate immune response against Ad after both intratumoral and systemic administration. Taken together, these results demonstrate that smart, tumor-specific, oncolytic Ad-PPCBA complexes can be exploited to treat both primary and metastatic tumors.

Motaln, H. and T. L. Turnsek "Cytokines Play a Key Role in Communication between Mesenchymal Stem Cells and Brain Cancer Cells." *Protein Pept Lett*. 2015 Jan 31.

Numerous small molecules including cytokines that have primarily been associated with immune response, have been shown to play a role in normal mesenchymal stem cell (MSC) and tumour cells' communication. One characteristic that distinguishes MSC from fibroblast and other cells of mesenchymal origin is their pro-tumour migratory behaviour. Recognizing the cytokines as key players of the MSC and tumour cell cross-talk and understanding their intracellular signaling, should lead to a development of more efficient anti-tumour therapies. Those are urgently needed to possibly improve the treatment of patients with glioblastoma multiformae (GBM) that are suffering from most

aggressive and incurable type of brain tumours. So far, the "cytokine signalling interference" approach, employing genetically modified MSCs and GBM cells in animal xenograft models pointed to the mechanisms underlying tumour - directed migration and immunomodulatory role of MSCs. There, MSC's effects on tumour cells growth were shown to vary substantially, and to depend on the type of cells and animal model used. This review is focusing on the MSC produced cytokines and their involvement in proliferation, migration, angiogenesis, apoptosis and immune cell infiltration into the tumour mass. Recently, targeted therapies have emerged as a promising modality for GBM treatment. New approaches, combining these with MSCs as cellular vectors for modulating cytokines and cytokine receptors' signalling in GBM may thus prove more efficient at inhibiting glioma progression.

Rutka, J. T., B. Kim, et al. "Nanosurgical resection of malignant brain tumors: beyond the cutting edge." *ACS Nano*. 2014 Oct 28;8(10):9716-22. doi: 10.1021/nn504854a. Epub 2014 Sep 18.

Advances in surgical procedures and improvements in patient outcomes have resulted from applications of new technologies in the operating room over the past three decades. All surgeons would be excited about the possibilities of improving their resections of tumors for patients with cancer if a new technology were introduced to facilitate this. In this issue of ACS Nano, Karabeber et al. use a hand-held Raman scanner to probe the completeness of resection of glioblastoma multiforme (GBM), the most malignant brain cancer, in a genetically engineered mouse model. They show that the hand-held scanner could accurately detect gold-silica surface-enhanced Raman scattering nanoparticles embedded within the GBM, resulting in a complete tumor resection. In this Perspective, we review potential applications of nanotechnologies to neurosurgery and describe how new systems, such as the one described in this issue, may be brought closer to the operating room through modifications in nanoparticle size, overcoming the obstacles presented by the blood-brain barrier, and functionalizing nanoparticle conjugates so that they reach their target at highest concentrations possible. Finally, with adaptations of the actual hand-held Raman scanner device itself, one can envision the day when "nanosurgical" procedures will be a part of the surgeon's armamentarium.

Sacar, M. D., C. Bagci, et al. "Computational prediction of microRNAs from Toxoplasma gondii potentially regulating the hosts' gene expression." *Genomics Proteomics Bioinformatics*. 2014

Oct;12(5):228-38. doi: 10.1016/j.gpb.2014.09.002. Epub 2014 Oct 28.

MicroRNAs (miRNAs) were discovered two decades ago, yet there is still a great need for further studies elucidating their genesis and targeting in different phyla. Since experimental discovery and validation of miRNAs is difficult, computational predictions are indispensable and today most computational approaches employ machine learning. *Toxoplasma gondii*, a parasite residing within the cells of its hosts like human, uses miRNAs for its post-transcriptional gene regulation. It may also regulate its hosts' gene expression, which has been shown in brain cancer. Since previous studies have shown that overexpressed miRNAs within the host are causal for disease onset, we hypothesized that *T. gondii* could export miRNAs into its host cell. We computationally predicted all hairpins from the genome of *T. gondii* and used mouse and human models to filter possible candidates. These were then further compared to known miRNAs in human and rodents and their expression was examined for *T. gondii* grown in mouse and human hosts, respectively.

Sandholm, J., J. Tuomela, et al. "Hypoxia regulates Toll-like receptor-9 expression and invasive function in human brain cancer cells in vitro." *Oncol Lett*. 2014 Jul;8(1):266-274. Epub 2014 Apr 25.

Toll-like receptor-9 (TLR9) is a cellular DNA sensor of the innate immune system. TLR9 is widely expressed in a number of tumors, including brain cancer; however, little is known regarding its regulation and involvement in cancer pathophysiology. The present study demonstrated that hypoxia upregulates and downregulates TLR9 expression in human brain cancer cells in vitro, in a cell-specific manner. In addition, hypoxia-induced TLR9 upregulation was associated with hypoxia-induced invasion; however, such invasion was not detected in cells where hypoxia had suppressed TLR9 expression. Furthermore, suppression of TLR9 expression through TLR9 siRNA resulted in an upregulation of matrix metalloproteinase (MMP)-2, -9 and -13 and tissue inhibitor of matrix metalloproteinases-3 (TIMP-3) mRNA, and a decreased invasion of cells in normoxia, in a cell-specific manner. In cells where hypoxia induced TLR9 expression, TLR9 expression and invasion were reduced by TLR9 siRNA. The decreased invasion observed in hypoxia was associated with the decreased expression of the MMPs and a concomitant increase in TIMP-3 expression. In conclusion, hypoxia regulates the invasion of brain cancer cells in vitro in a TLR9-dependent manner, which is considered to be associated with a complex expression pattern of TLR9-regulated mediators and inhibitors of invasion.

Santagata, S., L. S. Eberlin, et al. "Intraoperative mass spectrometry mapping of an onco-metabolite to guide brain tumor surgery." *Proc Natl Acad Sci U S A.* 2014 Jul 29;111(30):11121-6. doi: 10.1073/pnas.1404724111. Epub 2014 Jun 30.

For many intraoperative decisions surgeons depend on frozen section pathology, a technique developed over 150 y ago. Technical innovations that permit rapid molecular characterization of tissue samples at the time of surgery are needed. Here, using desorption electrospray ionization (DESI) MS, we rapidly detect the tumor metabolite 2-hydroxyglutarate (2-HG) from tissue sections of surgically resected gliomas, under ambient conditions and without complex or time-consuming preparation. With DESI MS, we identify isocitrate dehydrogenase 1-mutant tumors with both high sensitivity and specificity within minutes, immediately providing critical diagnostic, prognostic, and predictive information. Imaging tissue sections with DESI MS shows that the 2-HG signal overlaps with areas of tumor and that 2-HG levels correlate with tumor content, thereby indicating tumor margins. Mapping the 2-HG signal onto 3D MRI reconstructions of tumors allows the integration of molecular and radiologic information for enhanced clinical decision making. We also validate the methodology and its deployment in the operating room: We have installed a mass spectrometer in our Advanced Multimodality Image Guided Operating (AMIGO) suite and demonstrate the molecular analysis of surgical tissue during brain surgery. This work indicates that metabolite-imaging MS could transform many aspects of surgical care.

Santiago-Dieppa, D. R., J. Steinberg, et al. "Extracellular vesicles as a platform for 'liquid biopsy' in glioblastoma patients." *Expert Rev Mol Diagn.* 2014 Sep;14(7):819-25. doi: 10.1586/14737159.2014.943193.

Extracellular vesicles (EVs) are cell-secreted vesicles that range from 30-2000 nm in size. These vesicles are secreted by both normal and neoplastic cells. Physiologically, EVs serve multiple critical biologic functions, including cellular remodeling, intracellular communication, modulation of the tumor microenvironment and regulation of immune function. Because EVs contain genetic and proteomic contents that reflect the cell of origin, it is possible to detect tumor-specific material in EVs secreted by cancer cells. Importantly, EVs secreted by cancer cells transgress anatomic compartments and can be detected in the blood, cerebrospinal fluid, and other biofluids of cancer patients. In this context, there is a growing interest in analyzing EVs from the biofluid of cancer patients as a means of disease diagnosis and

therapeutic monitoring. In this article, we review the development of EVs as a diagnostic platform for the most common form of brain cancer, glioblastoma, discuss potential clinical translational opportunities and identify the central challenges associated with future clinical applications.

Seyfried, T. N., R. Flores, et al. "Metabolic therapy: a new paradigm for managing malignant brain cancer." *Cancer Lett.* 2015 Jan 28;356(2 Pt A):289-300. doi: 10.1016/j.canlet.2014.07.015. Epub 2014 Jul 25.

Little progress has been made in the long-term management of glioblastoma multiforme (GBM), considered among the most lethal of brain cancers. Cytotoxic chemotherapy, steroids, and high-dose radiation are generally used as the standard of care for GBM. These procedures can create a tumor microenvironment rich in glucose and glutamine. Glucose and glutamine are suggested to facilitate tumor progression. Recent evidence suggests that many GBMs are infected with cytomegalovirus, which could further enhance glucose and glutamine metabolism in the tumor cells. Emerging evidence also suggests that neoplastic macrophages/microglia, arising through possible fusion hybridization, can comprise an invasive cell subpopulation within GBM. Glucose and glutamine are major fuels for myeloid cells, as well as for the more rapidly proliferating cancer stem cells. Therapies that increase inflammation and energy metabolites in the GBM microenvironment can enhance tumor progression. In contrast to current GBM therapies, metabolic therapy is designed to target the metabolic malady common to all tumor cells (aerobic fermentation), while enhancing the health and vitality of normal brain cells and the entire body.

Swartling, F. J., S. Bolin, et al. "Signals that regulate the oncogenic fate of neural stem cells and progenitors." *Exp Neurol.* 2014 Oct;260:56-68. doi: 10.1016/j.expneurol.2013.01.027. Epub 2013 Jan 31.

Brain tumors have frequently been associated with a neural stem cell (NSC) origin and contain stem-like tumor cells, so-called brain tumor stem cells (BTSCs) that share many features with normal NSCs. A stem cell state of BTSCs confers resistance to radiotherapy and treatment with alkylating agents. It is also a hallmark of aggressive brain tumors and is maintained by transcriptional networks that are also active in embryonic stem cells. Advances in reprogramming of somatic cells into induced pluripotent stem (iPS) cells have further identified genes that drive stemness. In this review, we will highlight the possible drivers of stemness in medulloblastoma and glioma, the most frequent types of primary malignant brain cancer in children and

adults, respectively. Signals that drive expansion of developmentally defined neural precursor cells are also active in corresponding brain tumors. Transcriptomal subgroups of human medulloblastoma and glioma match features of NSCs but also more restricted progenitors. Lessons from genetically-engineered mouse (GEM) models show that temporally and regionally defined NSCs can give rise to distinct subgroups of medulloblastoma and glioma. We will further discuss how acquisition of stem cell features may drive brain tumorigenesis from a non-NSC origin.

Tajes, M., E. Ramos-Fernandez, et al. "The blood-brain barrier: structure, function and therapeutic approaches to cross it." *Mol Membr Biol.* 2014 Aug;31(5):152-67. doi: 10.3109/09687688.2014.937468. Epub 2014 Jul 21.

The blood-brain barrier (BBB) is constituted by a specialized vascular endothelium that interacts directly with astrocytes, neurons and pericytes. It protects the brain from the molecules of the systemic circulation but it has to be overcome for the proper treatment of brain cancer, psychiatric disorders or neurodegenerative diseases, which are dramatically increasing as the population ages. In the present work we have revised the current knowledge on the cellular structure of the BBB and the different procedures utilized currently and those proposed to cross it. Chemical modifications of the drugs, such as increasing their lipophilicity, turn them more prone to be internalized in the brain. Other mechanisms are the use of molecular tools to bind the drugs such as small immunoglobulins, liposomes or nanoparticles that will act as Trojan Horses favoring the drug delivery in brain. This fusion of the classical pharmacology with nanotechnology has opened a wide field to many different approaches with promising results to hypothesize that BBB will not be a major problem for the new generation of neuroactive drugs. The present review provides an overview of all state-of-the-art of the BBB structure and function, as well as of the classic strategies and these appeared in recent years to deliver drugs into the brain for the treatment of Central Nervous System (CNS) diseases.

Ugarte, M. D., A. Adin, et al. "On fitting spatio-temporal disease mapping models using approximate Bayesian inference." *Stat Methods Med Res.* 2014 Dec;23(6):507-30. doi: 10.1177/0962280214527528. Epub 2014 Apr 7.

Spatio-temporal disease mapping comprises a wide range of models used to describe the distribution of a disease in space and its evolution in time. These models have been commonly formulated within a hierarchical Bayesian framework with two main

approaches: an empirical Bayes (EB) and a fully Bayes (FB) approach. The EB approach provides point estimates of the parameters relying on the well-known penalized quasi-likelihood (PQL) technique. The FB approach provides the posterior distribution of the target parameters. These marginal distributions are not usually available in closed form and common estimation procedures are based on Markov chain Monte Carlo (MCMC) methods. However, the spatio-temporal models used in disease mapping are often very complex and MCMC methods may lead to large Monte Carlo errors and a huge computation time if the dimension of the data at hand is large. To circumvent these potential inconveniences, a new technique called integrated nested Laplace approximations (INLA), based on nested Laplace approximations, has been proposed for Bayesian inference in latent Gaussian models. In this paper, we show how to fit different spatio-temporal models for disease mapping with INLA using the Leroux CAR prior for the spatial component, and we compare it with PQL via a simulation study. The spatio-temporal distribution of male brain cancer mortality in Spain during the period 1986-2010 is also analysed.

Vidone, M., R. Clima, et al. "A comprehensive characterization of mitochondrial DNA mutations in glioblastoma multiforme." *Int J Biochem Cell Biol.* 2015 Feb 7. pii: S1357-2725(15)00037-0. doi: 10.1016/j.biocel.2015.01.027.

Glioblastoma multiforme (GBM) is the most malignant brain cancer in adults, with a poor prognosis, whose molecular stratification still represents a challenge in pathology and clinics. On the other hand, mitochondrial DNA (mtDNA) mutations have been found in most tumors as modifiers of the bioenergetics state, albeit in GBM a characterization of the mtDNA status is lacking to date. Here, a characterization of the burden of mtDNA mutations in GBM samples was performed. First, investigation of tumor-specific vs. non tumor-specific mutations was carried out with the MToolBox bioinformatics pipeline by analyzing 45 matched tumor/blood samples, from whole genome or whole exome sequencing datasets obtained from The Cancer Genome Atlas (TCGA) consortium. Additionally, the entire mtDNA sequence was obtained in a dataset of 104 fresh-frozen GBM samples. Mitochondrial mutations with potential pathogenic interest were prioritized based on heteroplasmic fraction, nucleotide variability, and in silico prediction of pathogenicity. A preliminary biochemical analysis of the activity of mitochondrial respiratory complexes was also performed on fresh-frozen GBM samples. Although a high number of mutations was detected, we report that the large majority of them does not pass the prioritization filters.

Therefore, a relatively limited burden of pathogenic mutations is indeed carried by GBM, which did not appear to determine a general impairment of the respiratory chain. This article is part of a Directed Issue entitled: Energy Metabolism Disorders and Therapies.

Vijayalaxmi and T. J. Pihoda "Mobile phones, non-ionizing radiofrequency fields and brain cancer: is there an adaptive response?" *Dose Response*. 2014 Apr 22;12(3):509-14. doi: 10.2203/dose-response.14-012. Vijayalaxmi. eCollection 2014 Jul.

There is widespread concern among the general public regarding the ever increasing use of mobile phones. The concern is mainly because the antenna which transmits nonionizing radiofrequency fields is held close to the head during use and thus might cause brain cancer. By far, the largest epidemiological study was conducted by the INTERPHONE study group and the results were published in 2011. The author's conclusions were (i) no increased risk of meningioma and glioma in mobile phone users and (ii) there were suggestions of an increased risk for glioma at the highest exposure levels but, bias and error prevented a causal interpretation. We have carefully examined all of the odd ratios presented in the INTERPHONE study publication: our results showed 24.3% decreased and 0.7% increased risk for meningioma and 22.1% decreased and 6.6% increased risk for glioma. Hence, we hypothesize that the overwhelming evidence for the decreased risk for both diseases may be due to the induction of 'adaptive response' which is well-documented in scientific literature.

Vymazal, J. and E. T. Wong "Response patterns of recurrent glioblastomas treated with tumor-treating fields." *Semin Oncol*. 2014 Oct;41 Suppl 6:S14-24. doi: 10.1053/j.seminoncol.2014.09.009. Epub 2014 Sep 16.

Glioblastoma multiforme (GBM) is the most common form of primary malignant brain cancer. Median overall survival (OS) for newly diagnosed patients is only about 12 to 18 months. GBM tumors invariably recur, and there is no widely recognized and effective standard treatment for recurrent GBM. NovoTTF Therapy is a novel and US Food and Drug Administration (FDA)-approved antimitotic treatment for recurrent GBM with potential benefits compared with other options. Recurrent GBM patients from two prior trials with demonstrated radiologic tumor response to single-agent NovoTTF Therapy were analyzed to better characterize tumor response patterns and evaluate the associations between response, compliance, and OS. In addition, a compartmental tumor growth model was developed and evaluated for

its ability to predict GBM response to tumor-treating fields (TTFields). The overall response rate across both trials was 15% (4% complete responses): 14% in the phase III trial (14/120) and 20% (2/10) in a pilot study. Tumor responses to NovoTTF Therapy developed slowly (median time to response, 5.2 months) but were durable (median duration, 12.9 months). Response duration was highly correlated with OS ($r^2 = .92$, $P < .0001$), and median OS for responders was 24.8 months. Seven of 16 responders exhibited initial tumor growth on magnetic resonance imaging. Compliance appeared to be linked with both improved response and survival. The tumor growth model predicted tumor arrest and shrinkage only after several weeks of continuous NovoTTF Therapy, consistent with the observed clinical findings of initial transient tumor growth in some patients. NovoTTF Therapy is a novel antimitotic treatment for recurrent GBM associated with slowly developing but durable tumor responses in approximately 15% of patients. Some responders exhibit initial tumor growth before shrinkage, indicating treatment should not be terminated prior to allowing for the full effect of NovoTTF Therapy to be realized. OS is longer in responders than in nonresponders. High daily compliance rates may be associated with increased likelihood of an objective response and are predictive of improved survival.

Wade, A., J. R. Engler, et al. "Measuring sulfatase expression and invasion in glioblastoma." *Methods Mol Biol*. 2015;1229:507-16. doi: 10.1007/978-1-4939-1714-3_39.

Extracellular sulfatases (SULF1 and SULF2) selectively remove 6-O-sulfate groups from heparan sulfate proteoglycans (HSPGs) and by this process control important interactions of HSPGs with extracellular factors including morphogens, growth factors, and extracellular matrix components. The expression of SULF1 and SULF2 is dynamically regulated during development and is altered in pathological states such as glioblastoma (GBM), a highly malignant and highly invasive brain cancer. SULF2 protein is increased in an important subset of human GBM and it helps regulate receptor tyrosine kinase signaling and tumor growth in a murine model of the disease. By altering ligand binding to HSPGs, SULF2 has the potential to modify the extracellular availability of factors important in a number of cell processes including proliferation, chemotaxis, and migration. Diffuse invasion of malignant tumor cells into surrounding healthy brain is a characteristic feature of GBM that makes therapy challenging. Here, we describe methods to assess SULF2 expression in human tumor tissue and cell lines and how to relate this to tumor cell invasion.

Waghmare, I., A. Roebke, et al. "Intercellular cooperation and competition in brain cancers: lessons from *Drosophila* and human studies." *Stem Cells Transl Med.* 2014 Nov;3(11):1262-8. doi: 10.5966/sctm.2014-0086. Epub 2014 Sep 17.

SUMMARYGlioblastoma (GBM) is a primary brain cancer with an extremely poor prognosis. GBM tumors contain heterogeneous cellular components, including a small subpopulation of tumor cells termed glioma stem cells (GSCs). GSCs are characterized as chemotherapy- and radiotherapy-resistant cells with prominent tumorigenic ability. Studies in *Drosophila* cancer models demonstrated that interclonal cooperation and signaling from apoptotic clones provokes aggressive growth of neighboring tumorigenic clones, via compensatory proliferation or apoptosis induced proliferation. Mechanistically, these aggressive tumors depend on activation of Jun-N-terminal kinase (upstream of c-JUN), and *Drosophila* Wnt (Wg) in the apoptotic clones. Consistent with these nonmammalian studies, data from several mammalian studies have shown that c-JUN and Wnt are hyperactivated in aggressive tumors (including GBM). However, it remains elusive whether compensatory proliferation is an evolutionarily conserved mechanism in cancers. In the present report, we summarize recent studies in *Drosophila* models and mammalian models (e.g., xenografts of human cancer cells into small animals) to elucidate the intercellular interactions between the apoptosis-prone cancer cells (e.g., non-GSCs) and the hyperproliferative cancer cells (e.g., GSCs). These evolving investigations will yield insights about molecular signaling interactions in the context of post-therapeutic phenotypic changes in human cancers. Furthermore, these studies are likely to revise our understanding of the genetic changes and post-therapeutic cell-cell interactions, which is a vital area of cancer biology with wide applications to many cancer types in humans.

Wang, B., W. Xu, et al. "Integrative genomic analyses of a novel cytokine, interleukin-34 and its potential role in cancer prediction." *Int J Mol Med.* 2015 Jan;35(1):92-102. doi: 10.3892/ijmm.2014.2001. Epub 2014 Nov 12.

Interleukin-34 (IL-34) is a novel cytokine, which is composed of 222 amino acids and forms homodimers. It binds to the macrophage colony-stimulating factor (M-CSF) receptor and plays an important role in innate immunity and inflammatory processes. In the present study, we identified the completed IL-34 gene in 25 various mammalian genomes and found that IL-34 existed in all types of vertebrates, including fish, amphibians, birds and mammals. These species have a similar 7 exon/6

intron gene organization. The phylogenetic tree indicated that the IL-34 gene from the primate lineage, rodent lineage and teleost lineage form a species-specific cluster. It was found mammalian that IL-34 was under positive selection pressure with the identified positively selected site, 196Val. Fifty-five functionally relevant single nucleotide polymorphisms (SNPs), including 32 SNPs causing missense mutations, 3 exonic splicing enhancer SNPs and 20 SNPs causing nonsense mutations were identified from 2,141 available SNPs in the human IL-34 gene. IL-34 was expressed in various types of cancer, including blood, brain, breast, colorectal, eye, head and neck, lung, ovarian and skin cancer. A total of 5 out of 40 tests (1 blood cancer, 1 brain cancer, 1 colorectal cancer and 2 lung cancer) revealed an association between IL-34 gene expression and cancer prognosis. It was found that the association between the expression of IL-34 and cancer prognosis varied in different types of cancer, even in the same types of cancer from different databases. This suggests that the function of IL-34 in these tumors may be multidimensional. The upstream transcription factor 1 (USF1), regulatory factor X-1 (RFX1), the Sp1 transcription factor 1, POU class 3 homeobox 2 (POU3F2) and forkhead box L1 (FOXL1) regulatory transcription factor binding sites were identified in the IL-34 gene upstream (promoter) region, which may be involved in the effects of IL-34 in tumors.

Webb, A. J. and R. J. Butterworth "Determinants of clinical effectiveness and significant neurological diagnoses in an urgent brain cancer referral pathway in the United Kingdom." *Clin Neurol Neurosurg.* 2015 Feb 25;132:37-40. doi: 10.1016/j.clineuro.2015.02.014.

BACKGROUND: Cerebral tumours can rapidly progress to life-threatening complications yet referral pathways often result in non-significant diagnoses. We aimed to identify the determinants of referrals resulting in significant neurological diagnoses after specialist review. **METHODS:** We reviewed all urgent brain cancer referrals to the neurology service at a British district general hospital between January 2009 and September 2013. Time to appointment, frequency of significant neurological diagnoses, appropriateness of referrals and referral heterogeneity across GP practices were measured as determinants of non-significant diagnoses. **RESULTS:** 31/105 patients received significant neurological diagnoses (29.5%), including ten (9.5%) tumours (7 malignant), although 2 patients were admitted prior to clinic. There was significant heterogeneity between primary care physicians in referral frequency ($p=0.008$) and significant diagnoses ($p=0.005$). Non-significant diagnoses were more common in inappropriate

referrals and if patients were unaware of the potential diagnosis. Seizures or subacute focal symptoms were more likely to result in a significant neurological diagnosis than isolated headache syndromes (odds ratio 3.45, 1.34-18.4, p=0.008).

Yeom, S. Y., D. H. Nam, et al. "RRAD promotes EGFR-mediated STAT3 activation and induces temozolomide resistance of malignant glioblastoma." *Mol Cancer Ther.* 2014 Dec;13(12):3049-61. doi: 10.1158/1535-7163.MCT-14-0244. Epub 2014 Oct 13.

Glioblastoma multiforme (GBM) is an extremely aggressive brain cancer with a median survival of less than 2 years. GBM is characterized by abnormal activation of receptor tyrosine kinase and constitutively activated STAT3. Although EGFR phosphorylation and STAT3 activation are essential for the maintenance of GBM cancer stem cells, the molecular mechanism underlying endosome-mediated STAT3 activation is not fully understood. In the current study, we showed that GTP-binding protein RRAD (RAS associated with diabetes, RAD) physically associates with EGFR, and EEA1, enhancing the stability and endosome-associated nuclear translocation of EGFR. Functionally, RRAD contributes to the activation of STAT3 and expression of the stem cell factors OCT4, NANOG, and SOX2, thereby enhancing self-renewing ability, tumor sphere formation, EMT, and in vivo tumorigenesis. Most importantly, RRAD contributes to poor survival in patients with GBM. RRAD expression is correlated with temozolomide resistance, and, conversely, depletion of RRAD leads to sensitization of highly temozolomide-resistant GBM cells.

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