

Conclusion: We have discovered novel drugs that can significantly inhibit the viability and growth of human glioma stem cells. These findings are expected to either replace or complement existing therapies within a clinical setting in due course.

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POSTER

NPAS3 is a Negative Prognostic Survival Marker in Glioblastomas

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Background: Glioblastomas, the most common primary brain tumours in adults, still continue to have a predominantly fatal outcome. We previously cloned NPAS3 (Neuronal PAS 3), a gene which is among the largest genes in the human genome, and encodes a transcription factor. We recently discovered NPAS3 drives the progression of malignant astrocytomas, as a tumour suppressor, by modulating the cell cycle, proliferation, apoptosis, cell migration/invasion, and with a further influence on angiogenesis. In human glioblastoma surgical specimens, up to 75% demonstrate aberrant NPAS3 protein expression. In this study, we evaluated the expression of NPAS3 in the overall survival of patients diagnosed with glioblastomas.

Methods and Results: We examined a panel of glioblastomas from 77 post-operative patients who had total resection of the tumour. Post-operative patients were treated by standard adjuvant radiation therapy (60 Gy, 6 to 7 weeks) combined with chemotherapy, with a study follow up not exceeding 30 months. Among the glioblastomas, 28 had absent, 18 had elevated and 31 had normal NPAS3 expression. 54 males and 23 females were used in this study with a median age of 59 years. From this study, patients with glioblastomas having absent NPAS3 expression were identified with the poorest overall survival in comparison to patients with glioblastomas having normal or elevated NPAS3 expression (Log-rank P-value <0.001). Such trend is still maintained even when patients are stratified among different age groups (<60, >60 years). However, no significant difference in overall survival among patients with glioblastomas having either normal or elevated NPAS3 expression was noted (Log-rank P-value >0.05). Likewise, no significant difference in gender verses overall survival noted.

Conclusion: Our findings are of clinical importance by demonstrating that NPAS3 is an informative negative prognostic survival marker in patients with glioblastomas.

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POSTER

Correlation of Epidermal Growth Factor Receptor and Phosphatase and Tensin Homolog Status With Treatment Outcome in Postoperative Glioblastoma Patients Treated With Chemoradiotherapy

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Background: To study the impact of Epidermal Growth Factor Receptor (EGFR) overexpression and loss of phosphatase and tensin homolog (PTEN) expression on treatment outcome in Glioblastoma (GBM) patients.

Materials and Methods: Twenty patients of GBM treated with maximal safe resection followed by concurrent chemoradiotherapy were analyzed in this prospective single arm study. All patients underwent a maximal safe resection. Clinical Target Volume (CTV) for radiotherapy included the pre-operative tumour volume and surrounding edema with 2.5 cm margin. A uniform 5 mm expansion was used to generate Planning target volume (PTV). A dose of 60 Gy to the PTV was prescribed at 95% isodose level with 6MV photons using conformal radiotherapy. All patients received concurrent Temozolomide at 75 mg/m² daily during the whole course of radiotherapy and six courses of adjuvant chemotherapy with Temozolomide 175–200 mg/m² D1–5 given every 4 weeks. EGFR and PTEN assessment was done by Immunohistochemistry(IHC). Proteinase-K (DAKO) and antigen retrieval buffer citrate(Neo-marker) were used for EGFR and PTEN respectively. Response evaluation was done one month after completing treatment using RECIST criteria for solid tumours version 1.1.

Results: Twenty biopsy proven GBM patients included in the study (male: Female-3:1). Median age 45 years (range: 18–57 years). Commonest presentation was headache (11) followed by seizure (9). Frontal lobe (9) was the commonest site followed by temporal lobe(7). The median KPS was 90 (Range-70–100). Thirteen patients underwent a complete resection and partial resection was possible in seven. Sixteen blocks were retrieved with adequate specimen for IHC. In this cohort four (25%) cases were found to over express EGFR protein whereas loss of PTEN

expression was noted in one (6.25%) case only. 95% of our patients completed the planned treatment one patient defaulted after two cycles. One patient developed grade IV thrombocytopenia and another patient developed grade III thrombocytopenia. The overall grade III and grade IV thrombocytopenia was noted in 10% of patients. In our study complete response was noted in 45% patients whereas 15% had a partial response only. After a median follow-up of 15.7 months the median survival found to be 17.7 months (range-6 months-27 months) and disease free survival was 21.9 months. We found a trend towards overall survival benefit for patients who underwent a complete resection but due to small sample size the p value was not significant. OS and DFS were found to differ significantly with KPS, age, EGFR overexpression and loss of PTEN.

Conclusion: Only a small subgroup of Indian patients with GBM may show EGFR over expression and loss of PTEN. Combining targeted therapy to radiotherapy may help improve treatment results in this subgroup. A larger prospectively designed study is needed to answer this question.

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POSTER

Intrathecal Sodium Butyrate for Neoplastic Meningitis- Experimental Study and Clinical Trial

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Background and Purpose: The prognosis of neoplastic meningitis (NM) is still extremely poor, and thus a new treatment method has been anticipated. Sodium butyrate (SB)-C-4 saturated fatty acid present in the human bowel membrane in high concentration (2mM) as food metabolite, has been reported as biological inducer of differentiation of several cancer cells resulting in growth arrest. However, the precise mechanism has not been fully elucidated. Here, we firstly investigated the role of this natural chemical on cancer cell motility and invasion. Secondly, continuous intrathecal administration of SB for rat NM was evaluated, and finally we performed clinical study under the permission of local ethics committee.

Experimental Design and Results: In vitro, we examined the cytotoxicity, colony formation in soft agar, neurotoxicity using a primary culture of ED14 neurons and cultured astrocytes. We also investigated the inhibitory effect of this compound on tumour cell invasion with the Matrigel invasion assay. As a result, SB inhibited rat breast cancer (Walker 256) and human glioblastoma (A172) cell motility and invasiveness, decreased 2D cell growth and colony formation in soft agar in a dose-dependent fashion, and showed minimal neurotoxicity as well as same grade of influence on cultured astrocytes. SB also affected the morphology of cells namely spread out, decreased peripheral ruffling and increased stress fiber formation. The phosphorylation level of focal adhesion kinase (FAK, pY577 and pY397 sites) was increased, but that of myosin light chain was not affected. All of these biological effects of SB were reversible, and recovered after withdrawal. In addition, A172 cells treated with SB showed positivity for senescence-associated b-gal staining with elevated expression level of p53 and p21 proteins in a dose-dependent manner. In vivo, neurotoxicity was evaluated by continuous intrathecal administration of SB using osmotic pump in syngeneic normal rat, and no abnormal findings were observed. Moreover, invasion of cells into brain parenchyma was inhibited and the extended animal survival was observed in experimental rat NM model using Walker 256 cells. Finally, clinical study was performed in patients with NM, and continuous intrathecal administration showed good treatment effect without severe adverse effects.

Conclusion: SB induced cellular senescence, inhibited invasion and growth, and would be a good candidate for NM without severe adverse effects.

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POSTER

B-Aware – a Unique Patient Awareness Campaign to Improve Outcomes in Patients With Metastatic Brain Tumours

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Background: More than 1 million Americans are diagnosed with cancer every year and up to 200,000 of these patients develop metastatic brain tumours (MBTs) during the course of their illness. Early diagnosis of MBTs and improving the patient's awareness of potential treatment options is likely to improve the outcomes of these patients. We report on a direct-to-cancer patient education program on the risks, symptoms and treatment options regarding MBTs.

Method: The campaign, called B-AwareSM (B is for brain), is the first program of its kind, launched by Cleveland Clinic in partnership with the Northern Ohio American Cancer Society. The program strives to educate cancer patients and their families about the risk as well as common signs and symptoms of MBTs with the goal that this awareness may