

ORAL PRESENTATIONS 10 JUNE 2016

Young Investigator Award Presentation

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Modelling Therapy Resistance for the Identification of Treatment-Refractory Cell Population(s) in Human Glioblastoma

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Despite aggressive multimodal therapy, human glioblastoma (hGBM), a highly malignant grade IV astrocytic tumour, remains incurable and inevitably relapses. Recent data has implicated intratumoral heterogeneity as the driver of therapy resistance and tumour relapse in hGBM. Thus models that capture the evolving hGBM biology in response to chemoradiotherapy will allow for the identification of cellular pathways that govern GBM therapy failure. In this study, we have developed a novel model to profile the clonal evolution of treatment naïve brain tumour initiating cell (BTIC) enriched hGBMs through chemoradiotherapy using: stem cell assays, BTIC marker expression and transcriptome analysis, immunohistochemistry, and cellular DNA barcoding technology. We report that treatment of hGBM BTICs leads to increased self-renewal capacity and higher transcript expression of stem cell genes *Bmi1* and *Sox2*. Based on global transcriptome analysis of the in vitro treated hGBM, we also identify a hyper-aggressive form of glioma. Using our therapy-adapted hGBM-mouse xenograft model, we discover that despite tumour regression and increased mouse survival post-therapy, tumour relapse remains inevitable. The treatment-refractory cells again have increased self-renewal capacity and higher expression of *Bmi1* and *Sox2*. Furthermore, by combining cellular DNA barcoding technology, which barcodes hGBM at single cell resolution, with our novel in vitro and in vivo therapy models, we are able to determine whether a pre-existing or a therapy driven subpopulation(s) seeds hGBM tumour relapse. Profiling the dynamic nature of heterogeneous hGBM subpopulations through disease progression and treatment may lead to the identification of novel therapeutic targets for the treatment of recurrent hGBM.

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Recruitment of Immune Effector Cells against Glioblastoma-Multiforme by a MHC-Chlorotoxin Chimeric Protein

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Glioblastoma Multiforme is the most common malignant primary brain tumor, having a mean overall survival <2 years. The lack of an

efficient immune response against the tumor have been attributed to its immunosuppressive capabilities and an immunosuppressing local environment. Aim: We set out to design a chimeric molecule that recognizes and binds tissue inducible metalloproteinase known to be induced in GBM cells (MMP-2) on one end. Its other end, the effector domain, mobilizes and recruits cytotoxic T-cells to mount an effective anti-tumor reaction. Methods: The targeting moiety is the small 36-amino acids Chlorotoxin, derived from the venom of the Israeli Yellow scorpion. The effector end is a single chain HLA-A2 (Human leukocyte antigen subtype A2) covalently bound to phosphoprotein-65 derived from the cytomegalovirus, to which most of the human population has developed a specific immune response. Results: The molecular construct was cloned and expressed in E.coli. The protein product was isolated, purified, and then folded in vitro. Various activity assays employed demonstrated retained activity of each domain, including flow-cytometry, intracellular staining, fluorescence immunohistochemistry, radiolabeled toxicity assays etc. Initial in-vivo studies show great promise. Conclusions: We present a proof of concept study for a new immunotherapy approach to battle GBM. A molecular construct which contains a non-antibody compact and highly specific targeting domain, combined with the ability to recruit anti-CMV T-cell lymphocyte population. The recruitment of potent memory CTL's to the tumor's milieu may prove resistant to the previously described local immunosuppressive environment brought about by the tumor.

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Time-Delayed Contrast Enhanced MRI Improves Detection of Brain Metastases: A Prospective Validation of Diagnostic Yield

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The radiological detection of BMs is essential for optimizing a patient's treatment. This statement is even more valid when stereotactic radiosurgery (SRS), a non-invasive image guided treatment that can target BM as small as 1-2mm, is delivered as part of that care. The timing of image acquisition after contrast administration can influence the diagnostic sensitivity of contrast enhanced MRI for BM. Objective: Investigate the effect of time delayed acquisition after administration of intravenous Atavist® (Gadobutrol 1mmol/ml) on the detection of BM. Methods: This is a prospective IRB approved study of 50 patients with BM who underwent post-contrast MRI sequences immediately after injection of 0.1 mmol/kg Gadavist® as part of clinical care (t0), followed by axial T1 sequences after a 10 minutes (t1) and 20 minute delay (t2). MRI studies were blindly compared by 3 neuro-radiologists. Results: Single measure intraclass correlation coefficients were very high (0.914, 0.904 and 0.905 for t0, t1 and t2 respectively), corresponding to a reliable inter-observer correlation. The t2 delayed sequences showed a significant and consistently higher diagnostic sensitivity for BM by every participating neuroradiologist as well as for the