Spectroscopic imaging with hyperpolarized [1-^{13}C]pyruvate shows an elevated lactate/pyruvate ratio in contrast enhancing and non-enhancing brain tumors of orthotopic patient-derived xenograft models of glioblastoma.

Richard Mair[1,2], Alan Wright[1], Kieren Allinson[3], Tiago Rodrigues[1], Colin Watts[2], and Kevin Brindle[1]

[1]CRUK Cambridge Institute, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom, [2]Division of Neurosurgery, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom, [3]Department of Pathology, Cambridge University Hospitals NHS Foundation Trust, Cambridgeshire, United Kingdom

Target Audience: Clinicians interested in brain tumor imaging and researchers working on applications of Dynamic Nuclear Polarized - (DNP) – metabolic tracers.

Purpose: Glioblastoma (GB) is the most common and aggressive primary cerebral neoplasm. Despite congruous histological analysis, these tumors are notorious for their varying behaviors following identical treatment regimes. DNP is a promising new technique that can be used to detect treatment response by interrogating 'real time' tumor metabolism. We present here the use of this technique in orthotopic, patient-derived xenograft models of GB that recapitulate the varied histopathological phenotypes of the disease.

Methods: Human GB-derived cells were harvested from patients and passaged <10 times to give three cell lines (defined here as GB1, GB2, and GB3) and stereotactically implanted into the right striatum of nude rats. T_2-weighted MR images were taken to monitor tumor growth using an Agilent 7T spectrometer. All cell lines generated tumors between 4 and 12 months following inoculation. On presentation of neurological deficit, or when the lesion on a T_2 weighted image exceeded 6 mm in diameter, mice were imaged using Chemical-Shift Imaging with hyperpolarized [1-^{13}C]pyruvate (5ml/kg of 184mM) (as described previously [1]) followed by contrast agent-enhanced (CE) MRI (T_1 weighted gradient echo imaging; 90s post a gadoterate meglumine (Guerbet) bolus: 200 µmole/kg). After imaging, the rats were sacrificed and their brains removed for hematoxylin and eosin (H & E) staining.
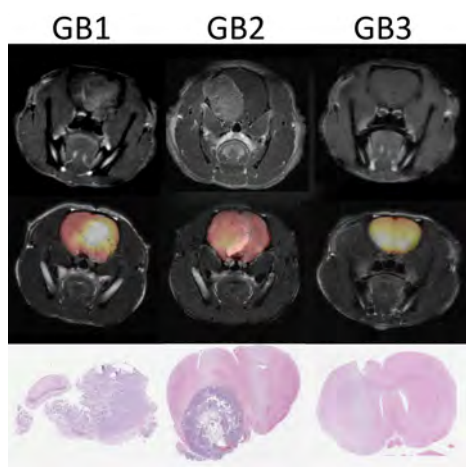

Figure1: MR and histopathological slices representative of each of the three tumour models. Row one: CE-MRI. Row two: Lactate/Pyruvate ratio maps overlaid on T_2 weighted images (red-0 : white-0.3). Row three: H & E staining showing the position of the solid mass in GB1 and GB2 plus regions of infiltrative growth that are at highest density in GB3.
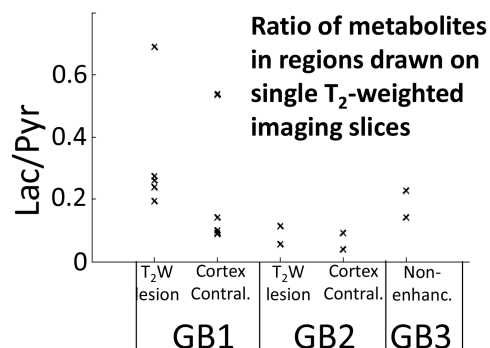

Figure 2: Metabolite ratios for regions of tumour in enhancing lesions and normal appearing brain/infiltrative growth in each rat.

Results: Five GB1, two GB2 and two GB3 rats were analyzed for the presence of GBs, with representative histopathology and MR imaging results given in Figure 1. T_1 weighted MR imaging showed 2 contrast enhancing phenotypes (GB1 and GB2) and one non-contrast enhancing phenotype (GB3). GB1s and GB2s grew as demarcated tumors with scattered invasive cells outside a single mass whereas GB3s grew in an infiltrative fashion. The highest lactate to pyruvate ratios were observed in GB1 tumors within the T_2-weighted lesion. GB3s showed an elevated lactate to pyruvate ratio across the whole brain that was consistent with the histopathologically verified infiltrative pattern of growth. This infiltration was not visible on T_2-weighted MRI (as observed previously in prostate cancer [2]). GB2s showed the lowest lactate to pyruvate level overall but with some regions of elevated lactate in the T_2-weighted-MRI enhancing lesion

Discussion: The different lactate to pyruvate ratios likely represent different metabolic phenotypes within the different cell lines but may also be influenced by the growth pattern, infiltrative vs demarcated (i.e. hypoxic), as well as the degree of perfusion and blood brain barrier disruption.

Conclusion: We have demonstrated the first use of hyperpolarized [1-^{13}C]pyruvate to interrogate patient derived orthotopic GB xenografts in vivo. Our models have successfully recapitulated the heterogeneity of the human disease whilst maintaining congruity within the cell line and the observation of hyperpolarized pyruvate metabolism to lactate. We have further observed an elevated lactate to pyruvate ratio in regions of infiltrative tumor growth beyond the T_2 weighted or CE-MRI detected lesion.

References: [1] Day S, et al. Detecting response of rat C6 glioma tumors to radiotherapy using hyperpolarized [1-^{13}C]pyruvate and ^{13}C magnetic resonance spectroscopic imaging. Magn Reson Med. 2011;65(2):557-63. [2] Nelson SJ, et al. Metabolic imaging of patients with prostate cancer using hyperpolarized [1-^{13}C]pyruvate. Sci Transl Med. 2013;5(198):198ra108.