



Magnetic Resonance Imaging and Spectroscopy

www.cambridgecancer.org.uk/johngriffiths

Group Leader **John Griffiths**

Associate Scientist

Marion Stubbs

Postdoctoral Scientist

Davina Honess

Principal Scientific Officers

Madhu Basetti

Dominick McIntyre

Senior Scientific Officers

Marcus O'Brien

Loreta Rodrigues

Graduate Students

Leanne Bell*

Monika Golinska

Shen-Han Lee*

Staff Scientist

Mary McLean

Visiting Workers

Lorenzo Mannelli*

Alan Wright

Research Nurse

Charlotte Hodgkin*

Magnetic resonance imaging and spectroscopy (MRI and MRS) have many uses in cancer research. Our group uses these methods, both in the laboratory and in patients, to study basic cancer biology, to improve non-invasive methods for tumour diagnosis and grading, and to develop biomarkers for monitoring the action of anticancer drugs.

Tumour Cell Biology

The HIF-1 pathway, which allows normal cells to adapt to low oxygen concentrations, is upregulated in many cancers and accelerates their growth. It also upregulates the tumour glycolytic pathway (Evans et al., *Cancer Chemother. Pharm.* 2008; 61:377). Monika Golinska's PhD project is on Hepa c4 tumours that cannot activate HIF-1 or upregulate glycolytic enzyme expression but still perform glycolysis at normal rates, and even upregulate it in hypoxia. Strangely, the cells also have very low ATP levels. No other factors that can activate glycolysis independently of HIF (e.g. Akt or cMyc) are upregulated. We are currently testing the hypothesis that the low ATP and high ADP and AMP levels in Hepa c4 tumours upregulate glycolysis allosterically. Anti-HIF drugs are under development, so these results will have practical significance.

Several projects utilising metabolomic methods are under way or have been completed, notably a collaboration with Almut Shulze (Cancer Research UK London Research Institute) which demonstrated that SREBP activity is regulated by mTORC1 (Porstmann et al., 2008; *Cell Metab.* 8:224).

In a collaborative ¹H NMR metabolomic project with Masashi Narita (CRI), Madhu Basetti (who manages our ex vivo NMR instrument) is studying the metabolic profile of fibroblasts in which senescence has been induced by prolonged replication, oncogenic H-ras expression or DNA damage. These three physiological insults (and also malignant transformation) induce different metabolic patterns, and there seems to be no metabolic profile characteristic of senescence itself. In contrast, the metabolic profile of cellular quiescence (induced by serum starvation), was indistinguishable from that of normally-growing cells.

In a project in collaboration with Adrian Harris (University of Oxford), Shen-Han Lee, a graduate student, will study the role of the enzyme carbonic anhydrase IX (which is overexpressed in many cancers) on tumour extracellular pH.

Marc O'Brien has demonstrated that the MRI contrast in ex vivo tumour specimens in which all the tissue water has been replaced with alcohol is due to hydrogen bonds forming between tissue ligands and the alcohol hydroxyl groups. Tissue specimens stored in alcohol are nowadays often archived for future genomic studies, so imaging biopsies in ethanol could have a clinical application. Another study by Madhu Basetti has clarified the way that MRI contrast agents alter MRS signals (Madhu et al., *J. Magn. Reson. Imag.* 2008; 28:1201).

We are continuing our collaboration with Richard Syms and Ian Young (Imperial College, London) on their novel 'needle' MRS coils that can be inserted into tumours.

Anticancer drug studies

Dominick McIntyre, with Davina Honess, leads our laboratory MRI and MRS work. We continue to collaborate with the Tuveson laboratory on their autochthonous pancreatic

*Joined during 2008

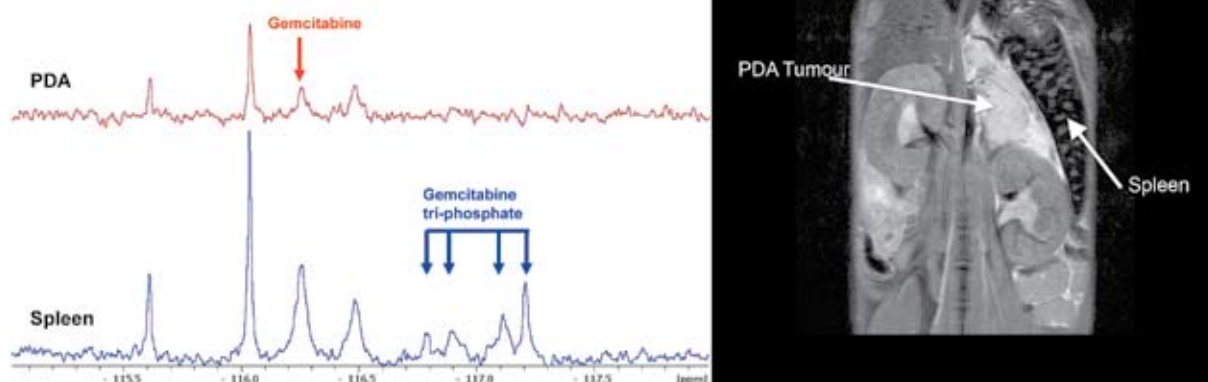


Figure 1. ^{19}F NMR spectra (left) demonstrating that the anticancer drug gemcitabine is not activated in the KPC model of pancreatic ductal adenocarcinoma whereas it is in the host's spleen (both shown in the MRI image on the right). The spleen tissue extract contains activated gemcitabine tri-phosphate (dFdCTP) whereas the KPC extract does not. Other ^{19}F NMR signals seen in the above spectra are from the breakdown products of gemcitabine in the tissue. Collaborative study with the Tuveson laboratory.

tumour models, which (like human pancreatic tumours) sometimes respond to gemcitabine but are usually resistant. Our DCE-MRI studies suggest that vascular insufficiency contributes to their chemoresistance. A new graduate student, Leanne Bell, is applying quantitative diffusion-weighted MRI and magnetisation transfer MRI to see whether this vascular insufficiency could be due to changes in the tumour matrix. Madhu Basetti has also developed improved ^{19}F NMR methods for monitoring gemcitabine uptake and metabolism in the tumour cells (Figure 1).

Our group has also completed a study on monitoring antivascular drugs (Howe et al., *Int. J. Radiat. Oncol. Biol. Phys.* 2008; 71:1470) and developed a liver tumour model for use in certain types of drug study (Kalber et al., 2008; *J. Magn. Reson. Imag.* 28:1451).

We are continuing our joint programme with Martin Leach and Ian Judson (Institute of Cancer Research) on monitoring the actions of novel anticancer drugs by MRS and MRI in order to develop non-invasive biomarkers for use in drug trials or in the clinic (Chung and Griffiths, *Ernst Schering Found. Symp. Proc.* 2007; 4:55). A study has been completed on the novel histone deacetylase inhibitor, LAQ824 (Chung et al., *Neoplasia* 2008; 10:300).

Clinical MRI and MRS

Mary McLean leads our work on tumours in patients. We are collaborating with James Brenton (CRI) and Evis Sala (Department of Radiology, University of Cambridge) in an MRI and MRS study on response to chemotherapy of cancer of the ovary. We have scanned 20 patients, and two papers are in preparation. We have also begun a study on the response of prostate tumours to androgen ablation therapy in collaboration with David Neal (CRI) and Evis Sala.

We are continuing a NCI-funded international collaboration (CoGMAC) aimed at individualising therapy for patients with non-Hodgkin's lymphomas using MRS to predict response. We scanned seven patients for this project in 2008.

Brain cancer is another major topic for the group. A large EU-funded international collaboration (eTumour) is developing a non-invasive diagnostic method using MRS. We have scanned a further eight patients for this study in 2008 in collaboration with Stephen Price (Department of Neurosurgery, Addenbrooke's Hospital, Cambridge), and we have developed the automated quality control protocol for the cooperative group (Wright et al., *Magn. Reson. Med.* 2008; 59:1274). We have developed techniques for better measurement of lactic acid and are about to begin a project establishing the repeatability of the measurements in brain tumours *in vivo* in collaboration with Merck & Co., Inc. We have also completed several NMR studies on spectroscopy of brain tumour biopsies *ex vivo* (Opstad et al., *Magn. Reson. Med.* 2008; 60:1237; Opstad et al., *NMR Biomed.* 2008; 21:1138; Opstad et al., *NMR Biomed.* 2008; 21:677; Opstad et al., *J. Magn. Reson. Imag.* 2008; 27:178).

We are collaborating with David Lomas and Lorenzo Mannelli (Department of Radiology, University of Cambridge) in a new project on blood oxygen level dependent (BOLD) MRI studies of hepatocellular carcinoma, both in patients and using a laboratory model of the disease.

Publications listed on page 57