



Pharmacology and Drug Development

www.cambridgecancer.org.uk/duncanjodrell

Group Leader **Duncan Jodrell***

Senior Research Associate
Frances Richards*

The Cancer Research UK Pharmacology and Drug Development Group (PDDG) was based in Edinburgh until April 2008, when the Principal Investigator, Duncan Jodrell, relocated to a chair at the University of Cambridge.

The research aims of this group are to integrate and optimise the pre-clinical development and 'science-led' clinical application of novel therapies, including 'first into man' (phase I) and associated studies (Figure 1). To achieve these goals, a multi-disciplinary early phase clinical trials group is being established, based on the Cambridge Biomedical Campus, and a lab group is also being recruited, based in the CRI.

The clinical phase I evaluation of a XIAP anti-sense (AS) molecule (Dean et al., *J. Clin. Oncol.* 2009; in press) was completed in Edinburgh, in collaboration with the Christie Hospital, Manchester. The trial demonstrated anti-tumour activity associated with this novel compound. A linked laboratory project confirmed the potential for use of the AS in combination with other agents, such as taxanes and radiotherapy (Connolly et al, *Cancer Chemother. Pharmacol.* 2009; in press). A project evaluating *in vitro* models for the

assessment of the hepatotoxicity of novel anticancer agents was also completed. This demonstrated the utility of fresh hepatocytes, although inter-subject variability was significant and would need to be considered in their use as assessment tools for novel agents. The graduate students involved in these projects (Kate Connolly and Eilidh Reid) were awarded their doctorates (an MD and PhD respectively) for this work in 2008.

In association with the phase I clinical trial of the novel DNA minor groove binding pyrrolo-benzodiazepine (PBD), SJG 136 (Hochhauser et al., *Clin. Cancer Res.* 2009; in press), the characterisation of the ABC transporter substrate specificity of other novel PBDs was undertaken and will form the basis for a PhD thesis, to be submitted in 2009 by Maciej Kaliszczak. It is hoped that this work will lead to the design and synthesis of novel PBD compounds which are not substrates for the multi-drug resistance related ABC transporters, in collaboration with Spirogen Ltd.

Laboratory activities in the CRI are currently in development. A Senior Research Associate, Frances Richards, has been appointed and projects and resources (e.g. cell lines) are being moved from Edinburgh. Future priorities are the continuation of the group's work on the pharmacokinetics (PK) and pharmacodynamics (PD) of fluoropyrimidines, in particular, the orally administered agent, capecitabine (Guichard et al., *Eur. J. Cancer.* 2008; 44:310)(Figure 2). This work will be performed in collaboration with John Griffiths, investigating the role of non-invasive magnetic resonance spectroscopy (MRS) approaches to assess the metabolism and accumulation of the drug and its metabolites in both normal and tumour tissue. In addition to pre-clinical studies, clinical protocols are in development to assess the PK of capecitabine in specific sub-groups of patients post upper gastro-intestinal tract surgery and the PK of capecitabine in women with breast cancer, assessed using MRS.

Previously the PDDG had focussed on models of colorectal cancer; but following the move to Cambridge and development of a new pancreatic cancer clinic, the group will establish, in collaboration with David Tuveson (CRI), pre-clinical models of this disease. These models will be

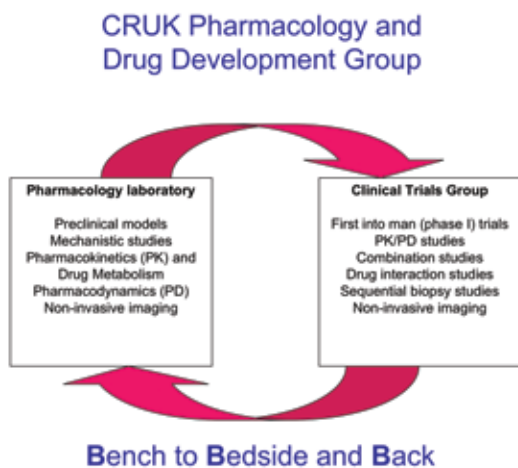
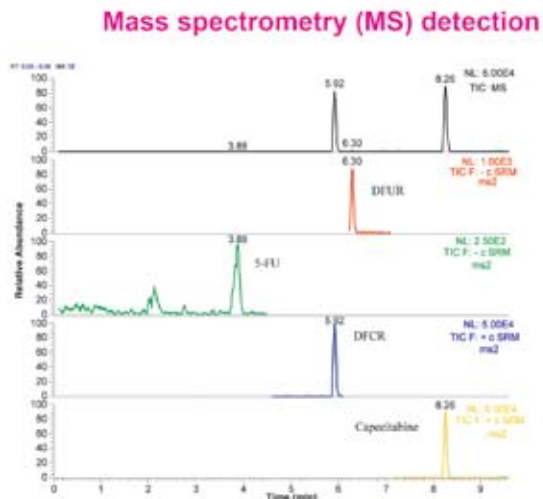


Figure 1. The research aims of the group.

*Joined during 2008



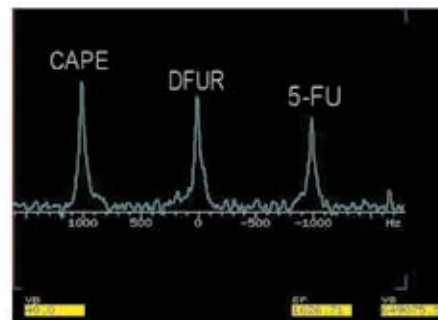
Guichard et al., *J. Chromatog. B* 2005; 826:232

Figure 2. Capecitabine and its metabolites identified by MS or MRS.

used to evaluate the impact of the tumour PK of established and novel agents on outcome in this disease, in order to improve and potentially individualise therapy for patients with pancreatic cancer. Novel combinations of gemcitabine, the current treatment of choice in this disease, and novel signalling inhibitors have been assessed by the Tuveson laboratory. These studies have led to the development of a clinical trial protocol, to be performed in Cambridge, which will commence in 2009.

In 2008 the clinical staff in the early phase clinical trials group in Cambridge have been involved in three phase I trials which have now closed to recruitment. These have included a novel oral kinase inhibitor; a novel antibody/cytokine construct and a new formulation of a taxane. In addition, 11 further trial protocols (five phase I, one phase II, two PK and three biomarker studies) are at various stages of development and will open for recruitment in 2009/early 2010.

Magnetic resonance spectroscopy (MRS)



Generated using a 7T magnet, in collaboration with Prof. Ian Marshall, University of Edinburgh.

One of these phase I studies in development is a combination of a novel agent with paclitaxel, a drug used widely in the treatment of many solid tumours. Combination studies will be a priority for the PDDG. Current clinical trial designs are sub-optimal and do not consider fully the potential interactions – both positive (i.e. synergy) and negative – of the combination being tested. We will undertake pre-clinical studies designed to inform the rational design of ‘science led’ clinical trials and will incorporate statistical approaches such as Bayesian design to maximise the information derived from early phase clinical trials and hence improve the treatment of patients.

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