Institution:
University of Cambridge

Unit of Assessment:
UoA5

Title of case study:
Technology for real time clinical imaging of tumour metabolism using hyperpolarized 13C magnetic resonance spectroscopy

1. Summary of the impact (indicative maximum 100 words)

Response to treatment is the most important prognostic factor for a cancer patient. Conventional morphological imaging methods do not give an early indication of treatment response. Professor Kevin Brindle and colleagues demonstrated how hyperpolarised 13C magnetic resonance spectroscopic imaging (MRSI) could be used to determine treatment response in preclinical animal models of disease, and have identified metabolites that facilitate this imaging, which are now being used in clinical trials. As a direct result of this work, GE Healthcare founded a spin-out company that commercialises the hyperpolarised 13C-MRSI technology. Three hyperpolarisers, that can produce metabolites containing hyperpolarised 13C, have been sold, and a further 10 are on order, at a sales value of $2.2M / £1.41M each. Revenue and employment have been generated in the UK at Oxford Instruments, who build the cryomagnets for the hyperpolarisers.

2. Underpinning research (indicative maximum 500 words)

Throughout cancer therapy, it is important to detect response to therapy as early as possible, so as to target effective treatment to responding patients and to spare non-responders from expensive, toxic and unnecessary treatment. The conventional way to assess treatment response in the clinic has been to look for evidence of tumour shrinkage in Computed Tomography (CT) or Magnetic Resonance (MR) images. However it is clear that these measurements cannot give an early indication of treatment response. For this reason, Kevin Brindle, (Professor of Biomedical Magnetic Resonance at the Department of Biochemistry since 2005, Lecturer 1993-2001, Reader 2001-2005), and his group have sought to develop imaging techniques that measure tumour function. Such imaging methods have potential use in clinical trials, as early indicators of therapeutic efficacy, as well as in tailoring an individual patient's therapy.

Introduction of a ^{13}C-labelled substrate and detection of the ^{13}C-labelled metabolites formed from it, using ^{13}C-MRSI, can provide information on metabolic flux. Amersham Health Research and Development AB, Sweden (collaborators of the Brindle group) showed in 2003 that the inherently low sensitivity of ^{13}C in MRSI can be overcome by hyperpolarisation of the ^{13}C nucleus through dissolution dynamic nuclear polarisation (DNP), which enhances its sensitivity to detection by more than 10,000-fold. This allowed dynamic imaging of cellular metabolic fluxes *in vivo*, in the absence of any background signal.

Research led by Brindle between 2006 and 2007, in collaboration with GE Healthcare, UK, and Imagnia AB, Sweden (formerly Amersham Health Research and Development AB), showed that flux of hyperpolarised ^{13}C label between pyruvate and lactate, catalysed by lactate dehydrogenase (LDH), could be imaged in lymphoma-bearing mice and was decreased in mouse lymphoma cells *in vitro* and in lymphoma tumours *in vivo* after drug-induced cell death. The work suggested that the technique could be used for early treatment response monitoring in the clinic (Ref. 1, Section 3).

Additional experiments carried out in the Brindle group between 2007 and 2008, in collaboration with GE Healthcare, UK, and Imagnia AB, Sweden, show that tissue pH can be imaged *in vivo* from the ratio of the signal intensities of hyperpolarized bicarbonate ($H^{13}CO_3^-$) and $^{13}CO_2$ following intravenous injection of hyperpolarized $H^{13}CO_3^-$. The technique was demonstrated in a mouse tumour model, which showed that the average tumour interstitial pH was significantly lower than the surrounding tissue. The work suggested that this technique could be used clinically to image pathological processes that are associated with alterations in tissue pH, such as cancer, ischaemia and inflammation (Ref. 2, Section 3), and attracted considerable attention in the media.

Further work carried out by the group of Prof Brindle between 2006 and 2009 demonstrated that flux of hyperpolarised ^{13}C label between pyruvate and lactate, measured by ^{13}C-MRSI, showed similar sensitivities for detecting response to drug treatment in a murine lymphoma model as the currently clinically used ^{18}F-labelled 2-fluoro-2-deoxy-D-glucose (FDG) in conjunction with Positron Emission Tomography (PET). The results indicated that ^{13}C-MRSI of hyperpolarised ^{13}C-pyruvate could be an alternative to FDG PET for imaging tumour treatment response in the clinic; allowing the use of ionizing radiation to be avoided, and treatment response to be measured in tumours of the brain and prostate, where FDG PET is ineffective (Ref. 3, Section 3).

Further work, carried out between 2008 and 2011, in collaboration with Alan Koretsky (NIH in Bethesda, Maryland), demonstrated that metabolism of hyperpolarized pyruvate could also detect treatment response in a rat model of glioma, a tumour where treatment response in the clinic is difficult to detect using traditional FDG PET (Ref. 4, Section 3).

While both FDG PET and the hyperpolarised pyruvate experiment detect tumour cell damage following treatment, they do not necessarily detect tumour cell death, which is the most important parameter to determine since there is a strong correlation between tumour cell death early during treatment and subsequent clinical outcome.

To address this, Brindle also developed the technique, using another substrate, hyperpolarised [1,4-$^{13}C_2$]fumarate,– in collaboration with Imagnia AB, Sweden – and demonstrated detection of cell death directly, in the form of cellular necrosis, using a murine lymphoma model (Ref. 5, Section 3), and a murine xenograft model of breast adenocarcinoma (Ref. 6, Section 3).

3. References to the research (indicative maximum of six references)

1. Day, S. E., Kettunen, M. I., Gallagher, F. A., Hu, D.-E., Lerche, M., Wolber, J., Golman, K., Ardenkjaer-Larsen, J. H. and Brindle, K. M. (2007) Detecting tumor response to treatment using hyperpolarized ^{13}C magnetic resonance imaging and spectroscopy. Nature Med. **13**, 1382-1387. DOI 10.1038/nm1650
2. Gallagher F.A., Kettunen M.I., Day S.E., Hu D.-E. , Ardenkjær-Larsen J.H., in 't Zandt R., Jensen P.R., Karlsson M., Golman K., Lerche M.H. and Brindle K.M. (2008) Magnetic resonance imaging of pH in vivo using hyperpolarized ^{13}C-labelled bicarbonate. Nature 453, 940-943. DOIL10.1038/nature07017
3. Witney, T., Kettunen, M., Day, S., Hu, D., Neves, A., Gallagher, F., Fulton, S. and Brindle, K. (2009) A comparison between radiolabeled fluorodeoxyglucose uptake and hyperpolarized C-13-labeled pyruvate utilization as methods for detecting tumor response to treatment. Neoplasia. **6**, 574-582. DOI 10.1593/neo.09254
4. Day, S. E., Kettunen, M. I., Cherukuri, M. K., Mitchell, J. B., Lizak, M. J., Morris, H. D., Matsumoto, S., Koretsky, A. P. and Brindle, K. M. (2011) Detecting Response of Rat C6 Glioma Tumors to Radiotherapy Using Hyperpolarized [1-C-13]Pyruvate and C-13 Magnetic Resonance Spectroscopic Imaging. Magnetic Resonance in Medicine. **65**, 557-563. DOI 10.1002/mrm.22698
5. Gallagher, F. A., Kettunen, M. I., Hu, D. E., Jensen, P. R., in't Zandt, R., Karlsson, M., Gisselsson, A., Nelson, S. K., Witney, T. H., Bohndiek, S. E., Hansson, G., Peitersen, T., Lerche, M. H. and Brindle, K. M. (2009) Production of hyperpolarized [1,4-^{13}C)]malate from [1,4-^{13}C)]fumarate is a marker of cell necrosis and treatment response in tumors. Proc. Natl Acad. Sci. U.S.A. **106**, 19801-19806. DOI:10.1073/pnas.0911447106
6. Witney, T. H., Kettunen, M. I., Hu, D.-E., Gallagher, F. A., Bohndiek, S. E., Napolitano, R. and Brindle, K. M. (2010) Detecting treatment response in a model of human breast adenocarcinoma using hyperpolarised [1-^{13}C]pyruvate and [1,4-$^{13}C_2$]fumarate. Brit. J. Cancer. **103**, 1400-1406. DOI:10.1038/sj.bjc.6605945

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Recipient: Kevin Brindle; *Sponsor:* Cancer Research UK; *Title:* Molecular Imaging in Cancer

Dates: 01/11/03- 31/10/08; *Value:* £640,628.00
Recipient: Kevin Brindle; *Sponsor:* BBSRC (CASE partner GE Healthcare)
Title: CASE studentship for Timothy Witney: Detection of Apoptosis Using MRI
Dates: 01/10/06- 30/09/10; *Value:* £46,919.00

4. Details of the impact (indicative maximum 750 words)

Impact on Commerce

A new business has been created and established its viability by generating revenue or profits

The research led by Brindle has had a direct commercial impact. It has led to three international patents ("^{13}C MR imaging or spectroscopy of cell death", 2006; "Imaging medium comprising lactate and hyperpolarised ^{13}C-pyruvate", 2006; and "Hyperpolarized lactate contrast agent for determination of LDH activity", 2010; Refs 1-3, Section 5), on which Prof. Brindle is the named inventor, filed by GE (who funded the research and were assigned the right to resulting IP in the collaboration agreement).

As a result of this research and in order to commercialise the application, GE founded the spin-out company, Research Circle Technologies Inc. (RCT) in 2011. This spin-out commercialises the IP around the concept of 'metabolic magnetic resonance', from the Brindle lab, and other academic collaborators which are part of their "Research Circle". Commercialisation requires assembling "wetware", hardware and software. The wetware is the contrast agent, which has to be tailored to fit the biochemical process that is being monitored. The hardware is the MRSI equipment that traces the contrast agents, and the hyperpolariser that produces the contrast agent. The software interprets the images that the MRSI delivers. The research and IP generated in the Brindle group relates to the "wetware", *i.e*. it has provided proof *in vitro* and *in vivo* in animal models of several cancers that hyperpolarised ^{13}C-pyruvate and ^{13}C-fumarate in ^{13}C-MRSI can be used to assess early response to drug treatment. As the MD of RTC testifies, this proof of concept has been instrumental to GE developing the 'Spinlab' hyperpolariser as a new product, and Prof Brindle's leadership in the field and involvement in the project has aided in developing sales (Refs 4 and 5, Section 5). So far three 'Spinlab' machines have been sold and installed (1-USA, 1-Canada 1-United Kingdom), and a further 10 machines are on order (6-USA, 2-Denmark, 1-United Kingdom and 1-Switzerland), each at a sales value of $2.2M / £1.41M. RCT testify that Prof. Brindle and his lab have played a critical part in the development of the Metabolic Industry (Ref. 4, Section 5).

Employment in the UK

The UK-based company Oxford Instruments plc, (on behalf of RCT) builds the cryomagnet systems which are used in the 'Spinlab' clinical hyperpolariser machines. Their Group Business Development Manager testifies:

"Orders for this machine which RCT receives result in orders (at RTC's discretion) for our company. Hence the orders to RCT for hyperpolarisers, facilitated through the work of Prof Brindle as explained in Jonathan's letter [*letter of support from RCT, Ref. 4, Section 5*], result in income for our company and in securing work for our employees. […] Oxford Instruments also build a pre-clinical version of the hyperpolariser, the HyperSense, under license from RTC's parent company GE Healthcare, for *in vitro* use. We have sold 42 of these to date globally at an average sales price […] of about £230k. Although our licence only covers *in vitro* work, a number of our HyperSense customers have sought and obtained from GE Healthcare a licence from them to use these machines for preclinical *in vivo* applications. […] Prof Brindle's work and leadership in the field has contributed to the uptake of the technology, and therefore has had a positive impact on our HyperSense sales figures. This again has had a tangible impact on securing employment in our company."

Impact on Health

A new clinical technology has been trialled with patients

A Phase I trial (NCT01229618; US-based; *trial period:* 01/10/2010-01/12/2015; *sponsor:* UCSF;

collaborator: GE Healthcare) is being carried out with prostate cancer patients using the hyperpolariser technology (Ref. 7, Section 5). A total of 31 patients have so far successfully received an injection of the hyperpolarized agent. The data obtained up to now demonstrate that pyruvate not only reached the prostate but that its metabolic product lactate could be observed (Ref. 8, Section 5).

Impact on Society

The research findings on hyperpolarised MRSI by the Brindle group and their down-stream benefits for cancer patients has been brought to the attention of the public through a wide range of media coverage following the publication of the Nature paper "Magnetic resonance imaging of pH *in vivo* using hyperpolarized ^{13}C-labelled bicarbonate" in May 2008 (Ref. 2, Section 3). Several million readers came into contact with the research findings through coverage eg in the BBC News, the Washington Post, the Daily Mail (Refs 9-11, Section 5), the Telegraph, Reuters as well as a range of online media.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. International patent. ^{13}C MR imaging or spectroscopy of cell death. Priority date: 18th August 2006. Application no. WO 2008/020764. Inventors KMB, M.I. Kettunen, S. E. Day.
2. International patent. Imaging medium comprising lactate and hyperpolarised ^{13}C-pyruvate. Priority date: 18th August 2006. Application no. WO 2008/020765. Inventors KMB, S. E. Day. (patent protection has been discontinued in 2011 due to internal reasons / economic optimisation)
3. International Patent. Hyperpolarized lactate contrast agent for determination of LDH activity. 3rd May 2010. Application no. WO 2011/138269A1. Inventors KMB, M.I. Kettunen, BWC Kennedy.
4. Letter of support, Managing Director at Research Circle Technologies, Inc.
5. Press release highlighting link between work of Prof Brindle and foundation of Research Circle Technologies, Inc.: http://www.businesswire.com/news/home/20110909005844/en/GE-Launches-Company-Enhance-Development-Innovative-Technology
6. Letter of support, Group Business Development Manager at Oxford Instruments plc
7. *Drug*: Hyperpolarized Pyruvate (13C) injection. *Study title*: A Phase 1 Ascending-dose Study to Assess the Safety and Tolerability and Imaging Potential of Hyperpolarized Pyruvate (13C) Injection in Subjects with Prostate Cancer. *Sponsor / collaborators*: University of California, San Francisco / GE Healthcare. *Trial period:* 01/10/2010-01/12/2015. *Trial information link*: http://clinicaltrials.gov/ct2/show/record/NCT01229618
8. Nelson SJ et al, Metabolic Imaging of Patients with Prostate Cancer Using Hyperpolarized [1-^{13}C] Pyruvate (2013) Sci Transl Med 5, 198ra108, 1-10. DOI: 10.1126/scitranslmed.3006070
9. BBC News 28 May 2008 http://news.bbc.co.uk/1/hi/health/7423304.stm
10. Washington Post 29 May 2008 http://www.washingtonpost.com/wp-dyn/content/article/2008/05/29/AR2008052902090_3.html?nav=hcmodul
11. Daily Mail 29 May 2008 http://www.dailymail.co.uk/health/article-1022702/New-MRI-scanner-detect-cancer-early-8230-pinch-baking-soda.html