Institution: The University of Manchester

Unit of Assessment: 4

Title of case study:
BIOXYDYN: Magnetic Resonance Imaging Biomarkers

1. Summary of the impact

Magnetic resonance imaging (MRI) provides measurements for quantitative, non-invasive, diagnostic, repeatable monitoring of disease. MRI biomarkers research at the University of Manchester (UoM) spans cancer, lung disease, neurology and more. Our research has produced methods that are widely used by the pharmaceutical industry for drug development decision-making (including ≥ seven AstraZeneca development molecules, plus other pharma), leading to economic benefit, and for healthcare impact (e.g., influencing diagnostic MRI tools introduced by Philips and creating new tools via spin-outs). The methods have been delivered in part via an award-winning UoM spin-out SME, Bioxydyn (incorporated 2009; 2012 turnover £630K; employing 12 staff).

2. Underpinning research

See section 3 for references 1-6. UoM researchers are given in bold.

The impact is based on research that took place in Manchester from 2001-date. The key researchers were:

- **Geoff Parker** (Research Fellow, 2001-2005; Senior Fellow, 2005-6; Reader, 2006-7; Professor, 2007-date)
- **Alan Jackson** (Professor, 2001-date)
- **John Waterton** (Professor 20%, 2007-date)
- **Josephine Naish** (PG Fellow, 2001-2005; full-time industry, 2005-2006; PG Fellow, 2006-2009; Lecturer, 2009-date)

The aim of the research was (and continues to be) to develop quantitative MRI biomarkers for use in the pharmaceutical industry and in healthcare. We were one of the pioneering groups in the targeted development of MRI biomarkers, working in close collaboration with industry. The key milestones were:

1. In 2001, UoM researchers established the Quantitative Biomedical Imaging Lab (QBI Lab), initially funded by industrial research income, to develop imaging biomarkers. The initial focus was cancer. In collaboration with UoM clinical groups, we provided advanced MRI for approximately 20 clinical drug trials sponsored by industry. Since creation, QBI Lab has received ~£12.5m funding from industry, charities and research councils.
2. We developed advanced neuro MRI tools, focussing on making diffusion MRI tractography a better characterised tool for neuroscience (e.g., 1, 3). We patented aspects of this work (PCT/GB2008/001533) and applied these methods to help understand the healthy and diseased brain (e.g., 4, 5).
3. We developed improved dynamic contrast-enhanced MRI tools (e.g., 2) for application in cancer (e.g., 6) and inflammatory conditions (e.g., rheumatoid arthritis, lung disease).
4. We developed novel approaches for monitoring tissue oxygenation non-invasively using MRI and 16-O_2 as a contrast agent. We patented aspects of this work (PCT/GB2008/001390, PCT/GB2009/000979, PCT/GB2010/001989) and applied these methods to cancer and lung disease.

Our research is still extremely productive and continues to feed into the impact. We have recently extended our activities to cardiac MRI and foetal MRI, and anticipate that this will lead to new industrial and healthcare improvement opportunities.

3. References to the research

The research was published in leading methodological and applied (clinical) journals. Outputs 1-3 are papers describing examples of important methodological developments that have had subsequent impact. Outputs 4-6 are illustrative applications papers that use developments from this period in clinical research. The supporting letter from AstraZeneca (see S5 below) quotes a series of additional papers in which the methods developed have influenced strategic decision-making at the company.

1. **Parker GJM**, Haroon HA, Wheeler-Kingshott CAM. A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements. *Journal of Magnetic Resonance Imaging*. 2003;18(2): 242-254. DOI: 10.1002/jmri.10350
2. **Parker GJM**, Roberts C, Macdonald A, Buonaccorsi GA, Cheung S, Buckley DL, **Jackson A,** Watson Y, Davies K, Jayson GC. Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. *Magnetic Resonance in Medicine*. 2006;56(6): 993-1000. DOI: 10.1002/mrm.21066
3. **Parker GJM**, Alexander DC. Probabilistic anatomical connectivity derived from the microscopic persistent angular structure of cerebral tissue. *Philosophical Transactions of the Royal Society B – Biological Sciences*. 2005;360(1457):893-902. DOI: 10.1098/rstb.2005.1639
4. **Parker GJM**, Luzzi S, Alexander DC, Wheeler-Kingshott CAM, Clecarelli O, Lambon Ralph MA. Lateralization of ventral and dorsal auditory-language pathways in the human brain. *NeuroImage*. 2005;24(3): 656-666. DOI: 10.1016/j.neuroimage.2004.08.047
5. Powell HW, **Parker GJM**, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CAM, Barker GJ, Noppeney U, Koepp MJ, Duncan JS. Hemispheric asymmetries in language-related pathways: A combined functional MPI and tractography study. *NeuroImage*. 2006;32(1):388-399. DOI: 10.1016/j.neuroimage.2006.03.011
6. Buckley DL; Roberts C; **Parker GJM**; Logue JP; Hutchinson CE. Prostate cancer: Evaluation of vascular characteristics with dynamic contrast-enhanced T1-weighted MR imaging - Initial experience. *Radiology*. 2004; 233(3):709-715. DOI: 10.1148/radiol.2333032098

4. Details of the impact

See section 5 for corroborating sources S1-S5.

Context

MRI is increasingly acknowledged as a tool for the provision of quantitative measurements of tissue structure and function. It is used as diagnostic marker and a tool for monitoring disease. The market for imaging biomarkers is global and growing, with estimated value of $400m (S1). We established a programme to develop translational imaging biomarkers for industry and healthcare that probe the pathophysiology and morphology of disease. We demonstrated that focussed effort on the development and characterising of MRI methods allows application in a wide range of diseases with clinical and industrial relevance.

Pathways to impact

In 2001, a gap was identified in the growing academic and industrial interests in quantitative imaging methods. These interests were brought together at UoM to provide concerted action to address the development and application of MRI biomarkers. The QBI Lab was set up with

industrial research income to develop imaging biomarkers. Since its creation, the QBI Lab has received ~£12.5m funding from industry, charities and research councils.

Methodological developments were initially presented at leading conferences organised by The International Society for Magnetic Resonance in Medicine (ISMRM), the Organisation for Human Brain Mapping (OHBM) and Information Processing in Medical Imaging (IPMI), with subsequent journal publication.

IP protection and industry take up: This dissemination of our methods development led to further significant interest from the pharmaceutical industry and for clinical research applications. Patent protection was obtained, in particular relating to lung imaging and tissue oxygenation. Potential routes to market were explored by Visual Automation Ltd, a company wholly-owned by the University, which is embedded in the research group, and which specialises in transferring imaging science research into practical applications, licensing arrangements and new business opportunities.

The period 2001-2008 included an expansion of research work funded by the pharmaceutical industry and clear evidence of commercial demand for MRI biomarkers for clinical trials. Software tools developed within the QBI Lab were licensed to industry in 2011 at £5k per licence per annum.

Incorporation: The spin-out Bioxydyn Limited (S2) was created in 2009, with initial investment from University's intellectual property venture capital fund. The company, with 12 staff and turnover of £630k in 2012, has provided an important route to market for the research, providing specialist imaging services for numerous clinical trials and currently developing diagnostic imaging products for general healthcare (S3).

Reach and Significance of the Impact

Workflows

The major medical imaging companies are increasingly focussed on adding value to their imaging products by delivering MRI data acquisition and analysis solutions to support clinical workflows; specialised SMEs and not-for-profit open source initiatives also address this market. Impacts of our research in this field include:

1. Siemens, Philips and GE all have large MRI development teams that develop acquisition and analysis components for clinical workflow products. For example, between 2006 and 2013 our work on perfusion and diffusion MRI has enabled development and refinement of Philips' MRI tools in this area. A Philips Healthcare Clinical Scientist comments that: 'as part of our active research collaboration with the University of Manchester, we request and receive expert feedback and direction regarding the utility of both product and research (prototype) options on Philips MRI systems. This informs our Clinical Science organisation which contributes to decisions on future product developments.' (S4)
2. Bioxydyn has received ~£2.6m investment to develop MRI-based diagnostic imaging products for lung disease, based on oxygen-enhanced MRI methods transferred to the company from our research group (2007-2013). These tools are being developed for CE marking and FDA clearance to allow marketing to clinical centres for diagnostic use within the EU and USA within the next 2-3 years (S3).

Imaging Biomarkers for pharma

Major pharmaceutical companies also make significant use of quantitative MRI measurements as they provide sensitive, non-invasive, repeatable, non-ionising probes of physiological and morphological change associated with drug action and disease progression. This contributes critically, therefore, to decisions on continuing or halting development of a given compound, with significant financial implications (potentially £100s millions; S5). They also provide tools for patient selection/stratification, thereby maximising the value of medicines in the healthcare environment and thus overall improving the business proposition for pharma. This also facilitates more agile drug development strategies (particularly shorter, smaller trials), leading to savings when bringing

each drug to market. There is particular demand for imaging biomarkers in chronic diseases, such as dementias, rheumatoid arthritis, type II diabetes and lung disease, alongside continuing needs for biomarkers in cancer. The imaging biomarkers market is estimated at ~$400m (S1).

Specific impacts based on the research include:

3. Investment of ~£10m by AstraZeneca, in partnership with spin-out companies (including Bioxydyn) and the University, to develop, validate and de-validate imaging biomarkers of disease to enable rapid and cost-effective drug development (2007-2013) (S5).
4. University and Bioxydyn delivery of imaging biomarkers for cancer, neurological disease, lung disease, inflammatory conditions in multiple phase 0-phase III clinical trials for AstraZeneca, Merck-Serono, Roche, Amgen, Synageva, BMS, Centocor, UCB-Celltech, Cytopia, GSK, Pfizer, Genentech (2001-2013). Each of these trials was industry-led and designed to provide commercially-critical information, typically in the form of internal decision-making information with which the companies can inform go/no-go decisions relating to continuing the development of specific candidate pharmaceuticals. In the case of AstraZeneca, this activity had direct impact on the development of at least seven different molecules (S5).

5. Sources to corroborate the impact

S1. VirtualScopics Inc. annual report 2012: http://quicktake.morningstar.com/stocknet/secdocuments.aspx?symbol=vscp

S2. www.bioxydyn.com; http://umip.com/pdfs/case-studies/Bioxydyn.pdf

S3. Letter from CEO, Bioxydyn.

Development of the company based on University research; company service provision to pharma; company development of diagnostic tools for healthcare; company job creation and turnover.

S4. Letter from Clinical Scientist-MR, Philips Healthcare.

Use of UoM research contributions to Philips MRI-related products.

S5. Letter from Chief Scientist, Personal Health Care and Biomarkers, AstraZeneca.

Investment in imaging biomarkers and their impact on AstraZeneca drug development.