Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: U: Invention, licensing and commercialisation of optical projection tomography microscopy

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

Impact: Commerce and professional services; the development of Optical Projection Tomography (OPT) – a technique for three-dimensional (3D) optical microscopy.

Significance: A step-change in scientific imaging; novel equipment and training services for imaging laboratories, offering a new standard in 3D microscopy. Over £2M in sales for the MRC.

Beneficiaries: Scientific institutions and imaging facilities, commerce.

Attribution: OPT was developed, by Sharpe, Baldock and Davidson, and commercialised at the MRC Human Genetics Unit, UoE.

Reach: World-wide: OPT instruments are used in Europe, America, Asia and Australia; chapters on OPT can be found in major microscopy textbooks.

2. Underpinning research (indicative maximum 500 words)

Scientists at the MRC Human Genetics Unit, UoE, (Director Professor Nick Hastie FRS, 1994–present) — Dr James Sharpe (Postdoctoral Fellow, 1998–2006), Professor Richard Baldock (Professor of Biomedical Systems Analysis, 1986–present) and Dr Duncan Davidson (Biomedical Systems Analyst, 1964–2010) — developed the OPT microscopy technique, which represented a step-change in biomedical scientific imaging.

Optical microscopy has contributed enormously to progress in science and technology and it is fair to say that the current state of biomedical research could never have been achieved without the availability of different types of microscopes. Despite more than four hundred years of history, optical microscopy continues to evolve. One of the clear challenges for microscopy in the postgenomic era is efficient mapping of gene expression patterns into 3D tissue descriptions.

When Sharpe joined the MRC Human Genetics Unit, UoE, in 1998 to work as a postdoctoral fellow with Baldock and Davidson, 3D optical imaging could be achieved using deconvolution, confocal microscopy and optical coherence tomography. None of these techniques allowed imaging of intact specimens to depths greater than 1–3 mm. A non-optical technique, magnetic resonance imaging, allowed visualisation to greater depths, but its complexity and expense combined with its inability to image commonly used coloured and fluorescent dyes made it unsuitable for general application.

With these limitations in mind, between August 1998 and November 2001, Sharpe, Davidson and Baldock conceived and developed a completely novel microscopy technique, Optical Projection Tomography (OPT) microscopy, to produce high-resolution 3D images of both fluorescent and non-fluorescent biological specimens with a thickness of up to 15 mm. The technique was used to analyse the expression of mRNA for the *Sox9* gene in a whole mouse embryo, and to identify new phenotypic abnormalities in Bapx1 (Nkx3.2)-null mice. OPT was described for the first time in a seminal paper in Science in April 2002 [3.1]. Subsequently, Sharpe and colleagues at the MRC Human Genetics Unit have applied this technique in many other biological settings, for example to image the human embryo and detect structures within the nervous system without the use of markers (2004) [3.2], to provide 3D imaging of the fruit fly *Drosophila melanogaster* (2007) [3.3] and to perform quantitative mapping of the normal tissue dynamics of an entire developing mammalian organ (2008) [3.4].

In parallel to academic development, several patent applications were filed between May 2002 and January 2005 [3.5]. Patents for OPT and associated technologies were granted between 2002 and 2011 in a wide range of countries (including the US, Europe, China, Australia, Canada and Japan), facilitating commercialization [3.6].

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

3.1 Sharpe J, Ahlgren U, Perry P,…Davidson D. Optical projection tomography as a tool for 3D microscopy and gene expression studies. Science. 2002;296:541-545. DOI: 10.1126/science.1068206.

3.2 Kerwin J, Scott M, Sharpe J, et al. 3 dimensional modelling of early human brain development using optical projection tomography. BMC Neurosci. 2004;5:27. DOI: 10.1186/1471-2202-5-27.

3.3 McGurk L, Morrison H, Keegan L, Sharpe J, O'Connell M. Three-dimensional imaging of Drosophila melanogaster. PLoS One. 2007;2:e834. DOI: 10.1371/journal.pone.0000834.

3.4 Boot M, Westerberg C, Sanz-Ezquerro J,…Sharpe J. In vitro whole-organ imaging: 4D quantification of growing mouse limb buds. Nat Methods. 2008;5:609–12. DOI: 10.1038/nmeth.1219.

3.5 Patent applications resulting from the work described, which were filed under the Patent Cooperation Treaty (PCT) scheme: PCT/GB02/02373, PCT/03/002570, PCT/03/003726, PCT/GB03/003746.

3.6 Examples of patents already granted for OPT technologies [available on request]:

- "Optical imaging apparatus and associated specimen support means". Europe, grant number 1530073, grant year 2007. USA, grant number 7,218,393, grant year 2007. Japan, grant number 4308535, grant year 2009. Australia, grant number 2002256798, grant year 2002. Canada, grant number 2,445,780, grant year 2010.
- "Laser scanning OPT system". China, grant number ZL03818363.3, grant year 2009.
- "Treatment of tissue specimens". Europe, grant number 1516183, grant year 2007. USA, grant number 7677197, grant year 2010. Japan, grant number 4129456, grant year 2008. Australia, grant number 2003280409, grant year 2008. Formal title: "Non focal optics for OPT system". Europe, grant number 1520173, grant year 2003. USA, grant number US8014063B2, grant year 2011. China, grant number ZL03818574.1, grant year 2009.

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

The work performed at the MRC Human Genetics Unit created the foundations of OPT and demonstrated the enormous potential of this technique in the biomedical sciences. Huge interest associated with the original publication (front cover of "Science" magazine and over 400 citations in the scientific literature [ISI Web of Knowledge]), together with the patents secured, rapidly translated into successful commercialisation and world-wide popularisation of this new technology.

Impact on commerce

In response to the discovery of OPT, MRC Technology — the exclusive technology transfer agent for the UK's Medical Research Council — formed MRCT Bioptonics. MRCT Bioptonics was responsible for the promotion and licencing of OPT technology, the manufacturing and distribution of OPT equipment and the provision of OPT scanning services [5.1, 5.2]. Five people in full-time employment managed the development and marketing of OPT between 2008 and 2012. In addition, a significant part of the manufacturing work was outsourced to the Belgian company SkyScan (employment figures unavailable; SkyScan was acquired in 2012 by Bruker Corporation adding ~$13M to Bruker's annual revenue [5.3]). In 2006, MRCT Bioptonics developed a commercial OPT scanner, the OPT 3001. Since January 2008, more than 30 instruments have been sold to multiple countries around the world including in the UK, USA, Canada, Sweden, Finland and Switzerland. During this period, MRCT Bioptonics staff provided specialist training in the use of OPT technology to approximately 50 users from multiple countries including the UK, USA, Spain, Singapore, Canada, and Germany. The sales figures for MRCT Bioptonics in the

period 2008–2012 were as follows: £775,129 (financial year 2008–9), £523,736 (financial year 2009–10), £194,977 (financial year 2010–11) and £773,054 (financial year 2011–12) [5.2].

In addition, in November 2008, the MRC licenced OPT technology to a major international microscopy manufacturer (name withheld because of a confidentiality agreement). Three of the patents are licensed to this company for further development and manufacture [5.2].

MRC and MRC Technology have also invested in OPT's potential use in pathology diagnostics. As a pilot, they have developed a sponsored collaboration of £190,000 with the University of Dundee, NHS Tayside and Oxford University to investigate OPT use in the diagnosis of colonic polyps [5.2].

Impact on professional services

Chapters on OPT are now a standard part of major international microscopy textbooks [5.4] and OPT technology was a feature at the EMBO Practical Course on 3D developmental imaging in 2009 and 2010 [5.5]. OPT instruments are available at scientific institutions in multiple countries and have become a routine service offered by their imaging facilities [5.6 a–e]. It is difficult to estimate the number of people using OPT on regular basis but it must be substantial judged by the number of OPT-based publications available in the public domain (over 100 papers are listed on the MRCT Bioptonics web-site alone; two of the Wellcome Image awards in 2011 were given for images produced using OPT [5.1]).

In April 2012, the International Mouse Phenotyping Consortium (IMPC) workshop supported by the European Union's InfraCoMP programme agreed on a common strategy to undertake phenotyping of embryonic lethal lines. The IMPC aims to create 20,000 knockout mouse strains over the next ten years and it is estimated that at least 30% of all these strains will die during the embryonic or perinatal periods. The IMPC listed OPT as one of the leading 3D imaging techniques considered for high-throughput screening of embryonic phenotypes in its Bloomsbury report on mouse embryo phenotyping [5.7]. OPT is already used in several other "atlas-type" projects including EMAP - the e-Mouse Atlas Project [5.8], the Interactive 3D Mouse Limb Anatomy Atlas [5.9] and the e-Chick Atlas of Gene Expression [5.10].

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

5.1 MRCT Bioptonics web-site. http://www.bioptonics.co.uk/.

5.2 Letter from MRC Technology. *[Available on request. The letter provides information about the production of OPT equipment and training provided by MRCT Bioptonics. It also confirms the sales, employment figures and licencing of OPT technology to a major international manufacturer.]*

5.3 "Bruker announces acquisition of SkyScan", news release from Bruker Corp., 2 Apr 2012. http://ir.bruker.com/phoenix.zhtml?c=121496&p=irol-newsArticle&ID=1678843&highlight.

5.4 Examples of international microscopy textbooks containing chapters on OPT [available on request]:

- Molecular Imaging: Principles and Practice. Editors: Weissleder R, Ross B, Rehemtulla A, Gambhir S. PMPH-USA, 2010.
- Advanced Imaging in Biology and Medicine. Editors: Sensen C, Hallgrimsson B. Springer, 2009.

5.5 Research Changes Lives. 2009–2014 mid-term update on progress against objectives. Medical Research Council report, July 2012. http://mrcblogs.helpfulclients.com/comment/files/2012/11/Mid-term-progress-reA33730.pdf.

5.6 Examples of imaging facilities that offer OPT as a service:

a) University College London (UCL) Centre for Advanced Biomedical Imaging, UK. http://www.ucl.ac.uk/cabi/imaging/imaging_techniques/opt.

b) Medical Center at Erasmus University, Holland, Applied Molecular Imaging Erasmus

MC (AMIE). http://www.erasmusmc.nl/amie/instrumentation/opt/?lang=en.

c) Institute of Translational Health Sciences, Washington State University, USA, Small Animal Tomographic Analysis Facility (SANTA). https://www.iths.org/resource-centers/small-animal-tomographic-analysis-facility-santa-0.

d) Institute of Development, Aging and Cancer, Tohoku University, Japan, Center of Research Instruments. http://www.idac.tohoku.ac.jp/en/activities/research/common_ic/.

e) Singapore Bioimaging Consortium, Singapore. http://www.sbic.a-star.edu.sg/resources/equipment.php#.

5.7 Adams D, Baldock R, Bhattacharya S, et al. Bloomsbury report on mouse embryo phenotyping: recommendations from the IMPC workshop on embryonic lethal screening. Dis Model Mech. 2013; 6:571–579. DOI: 10.1242/dmm.011833.

5.8 e-Mouse Atlas Project. http://www.emouseatlas.org/emap/home.html.

5.9 Interactive 3D Mouse Limb Anatomy Atlas. http://www.nimr.mrc.ac.uk/3dlimb.

5.10 e-Chick Atlas of Gene Expression. http://www.echickatlas.org/ecap/home.html.