Institution: University College London

Unit of Assessment: 15 – General Engineering

Title of case study: Application of magnetic nanoparticles in the treatment of breast cancer

1. Summary of the impact

Groundbreaking UCL research and development of magnetic nanoparticles for biomedical applications led to the introduction in 2012 of the world's first licensed nanoparticulate injectable medical device, the Sienna+ tracer, and its associated detection system, the SentiMag. A UCL spinout company, Endomagnetics Ltd., has introduced this new technology to better diagnose and treat cancer without the need for invasive surgery. The system uses magnetic materials, rather than radioisotopes, to locate the sentinel lymph nodes that are the key indicators of the spread of cancer away from the primary tumour site. As well as improving patient outcomes, the system considerably improves hospital workflow and efficiency since, unlike radioisotopes, the injectable magnetic tracer (Sienna+) is readily available and requires no special handling

2. Underpinning research

In 2003/4 Quentin Pankhurst (joined UCL 1993, now Director of the Institute of Biomedical Engineering) started work with the UCL Healthcare Biomagnetics Laboratory (HBL) on biomagnetic alternatives to the use of radioisotopes in sentinel lymph node biopsy (SLNB), currently the recommended clinical method for determining the spread of cancers, including breast cancer. Pankhurst's interest in magnetic nanoparticles had developed towards engineering-based problems, moving from research in 1994 on the physics of protein-encapsulated magnetic particles [1] through to work in 1998 on stabilising factors in biocompatible magnetic fluids [2]. By 2001, when he won an MRC Discipline Hoppers grant to study the magnetic properties of the Alzheimer brain [3], healthcare biomagnetics had become the focus of his research, and he formed the HBL.

At that time, biomedical engineering approaches to the use of magnetic nanoparticles in healthcare were unheard of. The field was focused firmly on the intravenous injection of magnetic particles as MRI contrast agents or drug delivery vectors. In contrast, the HBL method brought together systems engineering, hardware development and materials engineering to meet carefully targeted (and achievable) clinical goals. The HBL established the paradigm – now used by research teams all over the world – of 'sensing, moving and heating' as a rubric to motivate applications based on remote sensing (as with the SLNB project); actuation (as with *in vivo* stem cell targeting); and thermoablation (as with local heating treatments of prostate cancer). This new paradigm was expounded in a 2003 review article by Pankhurst [4], since cited more than 3,000 times.

Pankhurst and his team have remained at the forefront of the new field of biomedical engineering with biomagnetics. In particular, they have pioneered the repurposing of clinically validated commercial biomaterials (such as the MRI contrast agents Endorem and Resovist) to establish proof-of-principle in a given biomedical context, and the adoption of system engineering approaches (to activate and monitor them after their introduction into the body) for sensing, moving, and heating applications. This has allowed early-stage first-in-man studies to be performed with new devices and existing biomaterials, and supported the subsequent development of bespoke biomaterials; in the case of SLNB, these have included the Sienna+ tracer.

In 2003/04 Pankhurst received funding from the Department of Trade and Industry, under the UK-Texas Bioscience Initiative, for a project with the Texas Center for Superconductivity at the University of Houston to build a prototype SLNB detector. In the collaboration, the Houston team was responsible for supplying a novel sensor for the device, and the HBL team was responsible for everything else – ca. 85% of the work. The objective was to build a device with a hand-held probe, capable of detecting 100 micrograms of magnetic tracer at a distance of 20 mm (the equivalent of one millionth of the Earth's magnetic field at the probe tip), suitable for use in an operating theatre.

The original design, developed between 2004 and 2007 by Pankhurst and Simon Hattersley (UCL Research Fellow, Department of Physics), was based on a probe–cable–base-unit design wherein a probe comprising sense and drive coils arranged as first-order gradiometers acted as a magnetic susceptometer. The cable was flexible and carried both the drive and sense signals, in an unbroken loop, to the base-unit. At the heart of the base-unit was a superconducting quantum interference device (SQUID) sensor, cooled by liquid nitrogen to a temperature of 77 K. This prototype design presented a host of major mechanical, electrical, and systems engineering

challenges: the use of liquid cryogens, the tiny sense currents, the substantial drive currents, and major issues related to thermal expansion, all within the same system.

Despite these challenges, by 2006 the HBL team managed to incorporate the Houston SQUID into a prototype SentiMag device [5]. A patent was filed disclosing the invention and its unique features, namely a transformative approach to at-source noise reduction and unprecedented attention to the mechanical and thermal stability of the ceramic rod onto which the electromagnetic sense and drive coils were wound. Also in 2006, a clinical investigator-led, pre-certification human trial began, generating real patient data and insight into the treatment pathway. The SentiMag was first used clinically in December 2006 by Michael Douek, a breast cancer surgeon from the UCL Department of Surgery. The SLNB procedure was successfully tested using the SentiMag and the commercial tracer, Endorem. By the end of 2007, 12 subjects had been treated with a 100% detection rate, equal to that achieved using the standard radioactive method [6].

Throughout 2007, clinical tests and discussions with Mr Douek illuminated a further set of engineering challenges, primarily around safety, sterilisability and robustness, to be addressed to bring the SentiMag to an acceptable standard for routine hospital use. One of these was the need to find a replacement for the liquid-nitrogen-cooled Houston SQUID sensor, because of the danger posed by its use of cryogens. This challenge was met by systems engineer Hattersley, who developed an entirely electronic system able to meet the detector's sensitivity requirements [7].

In 2010-11, further work began on formulating a bespoke magnetic tracer to replace Endorem. The Sienna+ tracer was formulated through a series of animal model biocompatibility experiments alongside a comprehensive clinical evaluation of previously published data. Sienna+ differed from Endorem in that it was smaller, at ca. 60 nm diameter, and was designed specifically for interstitial, rather than intravenous, injection [7].

3. References to the research

References [3] [4] and [7] best demonstrate the quality of the research.

[1] Q. A. Pankhurst, S. Betteridge, D. P. E. Dickson, T. Douglas, S. Mann, and R. B. Frankel, *Mössbauer spectroscopic and magnetic studies of magnetoferritin*, Hyper. Interact. 91, 847-51 (1994). doi.org/bv587c

[2] Q. T. Bui, Q. A. Pankhurst, and K. Zulqarnain, *Inter-particle interactions in biocompatible magnetic fluids*, IEEE Trans. Magn. 34, 2117-9 (1998). doi.org/dffgfb

[3] D. Hautot, Q. A. Pankhurst, N. Khan, and J. Dobson, *Preliminary evaluation of nanoscale biogenic magnetite in Alzheimer's disease brain tissue*, Proc. R. Soc. Lond. Ser. B-Biol. Sci. **270**, S62-S4 (2003). doi.org/bt4pjs

[4] Q. A. Pankhurst, J. Connolly, S. K. Jones, and J. Dobson, *Applications of magnetic nanoparticles in biomedicine*, J. Phys. D **36**, R167-R81 (2003). doi.org/fkrj4d >3000 citations

[5] U. A. Gunasekera, Q. A. Pankhurst, and M. Douek, *Imaging applications of nanotechnology in cancer*, Targeted Oncology **4**, 169-81 (2009). doi.org/fjv7x7

[6] T. Joshi, Q. A. Pankhurst, S. Hattersley, A. Brazdeikis, M. Hall-Craggs, E. De Vita, A. Bainbridge, R. Sainsbury, A. Sharma, and M. Douek, *Magnetic nanoparticles for detecting cancer spread*, Breast Cancer Research and Treatment, S129 (2007). doi.org/fc2tpz

[7] E. Mayes, M. Douek, and Q. A. Pankhurst, in *Magnetic Nanoparticles: From Fabrication to Clinical Applications*, ed. N. T. K. Thanh (CRC Press, 2012), pp. 541-55. ISBN: 1439869324. Copy available on request.

4. Details of the impact

More than 1.38 million new cases of breast cancer are diagnosed around the world each year, a figure that is currently increasing by 20,000 year on year. In almost all cases, surgery is required to remove the tumour. To determine whether the disease has spread to other sites, the European Organisation for Research and Treatment of Cancer currently recommends sentinel lymph node biopsy (SLNB), wherein the sentinel lymph nodes are removed and inspected under a microscope. This minimally invasive procedure is the preferred standard of care in breast cancer operations; in the UK, around 80% of all operations for that cancer include SLNB.

Despite this, current methods of sentinel node detection are not easy to use, involving the injection

of radioactive isotopes, along with a blue dye as a tracer. A surgeon then uses a hand-held Geiger counter to locate the node or nodes closest to the tumour. Because the isotopes are potentially hazardous they must be injected in the nuclear medicine department, rather than by surgeons. The injection itself is painful and distressing, and the isotopes' six-hour half-life presents challenges and limitations for theatre scheduling. Mandatory handling and waste disposal regulations add to the overheads for this procedure, as does the training and licensing of operating theatre staff in the handling of these radioactive materials. Furthermore, patients themselves may have reservations about the use of nuclear medicine. Together, these factors present a significant barrier to the widespread adoption of SLNB. For hospitals or clinics without ready access to radioisotopes, SLNB is not performed at all. As a result, 40% of all breast cancer procedures performed in the West and almost 85% of operations in the rest of the world simply do not include SLNB.

The research described above has had direct and significant impacts on this particular healthcare problem through the commercial production of the award-winning SentiMag device and the Sienna+ tracer [a], which have been used to treat more than 850 breast cancer patients since 2008. Together, these new technologies make SLNB available to more patients and at a lower cost than the limited availability radioisotope-based method. The magnetic approach to SLNB is straightforward, and minimal clinician training is required for its administration. Sienna+, a fluid containing a solution of coated iron oxide particles, each around 60 nanometres in diameter, is injected near the tumour to provide a trackable signal, as lymph capillaries easily absorb particles of this size. Surgeons then use the SentiMag to locate the lymph node or nodes closest to the tumour in order to determine whether or how far the cancer has spread. In contrast to the radioactive tracer, the Sienna+ device has a shelf life of several years, enabling its use much more widely than just at centres with access to nuclear medicine. The new technology poses no staff safety issues, and therefore no regulatory burden.

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These benefits derived principally from the success of the clinical work in 2006-07, which led to the decision to take the SentiMag all the way 'from bench to clinic'. With seed investment from UCL Business plc, the Bloomsbury Bioseed Fund and the Central London Universities Challenge Fund, Endomagnetics Ltd. was formed as a spin-out company in April 2007. After the initial patent filing in 2006, a portfolio of five further patents was generated, currently at different stages of prosecution in Europe, the USA, Canada, Japan and Australia. Between 2008 and 2010, the Technology Strategy Board supported a collaborative research project linking Endomagnetics with Integrated Technologies Ltd, a medical devices manufacturer; this resulted in a prototype SentiMag trialled on 50 subjects [outputs 6, 7, above]. The pilot model differed from the original prototype in its incorporation of the new room temperature sensor and an optimised control circuit designed by Hattersley. With a fully validated technical file for the hardware, firmware and software components of the SentiMag system resulting from the trial, in December 2010 Endomagnetics was able to secure CE marking for the SentiMag as a Class IIa medical device, as required for its use throughout Europe [e].

Growth followed in August 2011 with the completion of an additional round of private investment, and the appointment of three full-time company employees – a CEO, and technical and operational staff. In November 2011 a second CE mark was issued to the company for the production of its own tracer, Sienna+, for on-label use as an interstitial injectable marker for lymph node detection [f]. The two products were launched in the European market in 2012, and in February 2013 a distribution agreement was signed between Endomagnetics Ltd and Sysmex Europe GmbH to supply the products into the Europe, Middle East and Asia region [g].

Endomagnetics Ltd is currently working with the FDA and with American regulatory consultants to establish its entry into the United States market. Here, despite the extremely high quality of major city-based cancer centres, the more rural, outlying hospitals are almost entirely cut off from a source of radioisotopes, so for them, there is a definite clinical need to be addressed.

Clinical trials: The technology has been tested with patients in a number of clinical trials [h]. The cryogen-free SentiMag was first tested in clinical studies on 43 patients in 2009-10 by Mr Douek (who by then had moved to Guy's Hospital London), using Endorem. This was designed to assess safety and to be a *prima facie* measurement of efficacy. The study found no adverse reactions, and

the observed detection rate was high: 87% in patients that were injected less than an hour before the operation, and 93% for those that were operated on after an hour or more [output 7]. This difference was taken as an indication that the 150 nm diameter of the Endorem particles was inhibiting their lymphatic flow, and led to the development of the 60 nm Sienna+ particles [output 7]. An added benefit was also noted: that the presence of magnetic particles in the excised nodes gave them a brown/black colouration that aided intraoperative identification [i].

In 2012-13 Mr Douek led a 160-patient clinical evaluation that involved six UK hospitals and one Dutch hospital. This was designed to be a statistically significant comparative study of the radioisotope and magnetic methods. The result was conclusive: a Sienna+ identification rate of 94% was recorded, compared to 95% with the radioisotopes, so that at the statistical power of 80% it was concluded that the magnetic technique was non-inferior to the radioactive technique [j].

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

[a] European Innovation Board's Academic Enterprise Life Sciences Award for Endomagnetics Ltd, February 2012. http://www.sciencebusiness.net/news/75686/ACES-winner-shows-how-magnetic-particles-can-fight-cancer

[b] [text removed for publication]

[c] [text removed for publication]

[d] [text removed for publication]

[e] Endomagnetics Achieves CE Mark Approval for SentiMag™, December 2010, http://www.endomagnetics.com/?p=1115

[f] Endomagnetics Achieves CE Approval for Sienna+™ Tracer, November 2011, http://www.endomagnetics.com/?p=1092

[g] Endomagnetics Ltd secures strategic distribution agreement, February 2013, http://www.uclb.com/news-and-events/news-post/endomagnetics-ltd-secures-strategic-distribution-agreement

[h] Details of clinical trials: Sentimag Multicentre Trial http://www.kcl.ac.uk/medicine/research/divisions/cancer/research/sections/researchoncology/bcsurgery/sentimag/professionals.aspx; http://www.cancerresearchuk.org/cancer-help/trials/a-study-looking-new-way-find-sentinel-lymph-nodes-breast-cancer-sentimag;

[i] Corroboration that the magnetic particles in excised nodes aided intraoperative identification, see page 1888 of: L. Johnson. G. Charles-Edwards and M. Douek, *Nanoparticles in sentinel node assessment in breast cancer*, Cancers **2**, 1884-94 (2010). http://doi.org/fmjmfk

[j] For the clinical evaluation showing that the magnetic technique was non-inferior to the radioactive technique, see pages 15-17 of: M. Douek et al., *The SentiMAG multicentre trial primary outcome*, Annals of Oncology (2013). At press: copy provided.