Institution: University College London		
Unit of Assessment: 12 - Engineering		
Title of case study: Application of magnetic materials in the treatment of breast cancer		
Period when the underpinning research was undertaken: 2000 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Quentin Pankhurst	**Role(s) (e.g. job title):** Professor of Physics Director Institute of Biomedical Engineering	**Period(s) employed by submitting HEI:** 1993 - date
Period when the claimed impact occurred: 2013 - 2020		
Is this case study continued from a case study submitted in 2014? Y		

1. Summary of the impact

Ground-breaking UCL research in the field of biomedical applications of magnetic nanoparticles, led to the world's first licensed nanoparticulate injectable medical device in 2012 – the Sienna+/Magtrace tracer and its associated detection system, the Sentimag to better diagnose and treat cancer. As well as improving patient outcomes, this UCL system considerably improves hospital workflow and efficiency since, unlike radioisotopes, the injectable magnetic tracer is readily available and requires no special handling. The system gathered GBP9,800,000 turnover in 2020 and raised GPB32,000,000 from private investment. Worldwide over 60,000 breast cancer patients have been treated using SentiMag and Sienna+/Magtrace medica devices since August 2013.

2. Underpinning research

Quentin Pankhurst's interest in magnetism led him to pursue biomedical applications of magnetic nanoparticles, and to work on biomagnetics alternatives to radioisotopes in sentinel lymph node biopsy (SLNB, the recommended clinical method for determining the spread of cancers, including breast cancer). Pankhurst's approach to the biomagnetics field was revolutionary. It was based on a paradigm of 'sensing, moving and heating' as a rubric to motivate applications based on remote sensing (eg. the SLNB project), actuation (eg. targeted haemofiltration), and thermoablation (eg local heating treatments of pancreatic cancer). This paradigm has since been adopted worldwide, as evidence by the huge popularity of Pankhurst's 2003 review article (**R1**), which reached the milestone of 7,000 literature citations in 2020.

More specifically, Pankhurst pioneered the repurposing of already-validated biomaterials (such as the MRI contrast agent Endorem) to establish proof-of-principle in new contexts, and the adoption of system engineering approaches (to activate and monitor agents after their introduction into the body) for a variety of new biomedical applications. This allowed early-stage first-in-human studies to be performed with new devices and existing biomaterials; and supported the subsequent development of bespoke biomaterials (in the case of SLNB, the Sienna+/Magtrace 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 University of Houston to build a prototype SLNB detector. The design objective – based on metrics determined from consultation with surgeons – was a hand-held device/probe, suitable for use in an operating theatre, and capable of detecting 100 micrograms of magnetic tracer at a distance of 20 mm (the sensing equivalent of one millionth of the Earth's magnetic field at the probe).

The first prototype developed between 2004 and 2007 by Pankhurst and Simon Hattersley at UCL was based on a probe/cable/base-unit design. At the heart of the base-unit was a Superconducting Quantum Interference Device (SQUID) sensor, cooled by liquid nitrogen to 77K. This 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 UCL team had successfully incorporated the Houston SQUID into a prototype handheld instrument – the Sentimag device – by developing a new approach to at-source noise reduction and by paying unprecedented attention to the mechanical and thermal stability of the probe. This prototype was first used clinically in December 2006 by Michael Douek, a breast cancer surgeon from the UCL Department of Surgery. By the end of 2007, 12 subjects had been treated, with a detection rate equal to that achieved using the standard radioactive method (**R2**), thus establishing proof-of-principle. Throughout 2007, clinical tests illuminated a further set of engineering challenges, primarily around safety, stability and robustness, to be addressed to bring the Sentimag to an acceptable standard for routine hospital use.

In 2010-11, further work began on formulating a bespoke magnetic tracer to replace the MRI agent Endorem. The Sienna+ (now known as Magtrace following rebranding in 2018) tracer was formulated through a series of animal model biocompatibility experiments alongside a comprehensive clinical evaluation of previously published data. Sienna+/Magtrace differed from Endorem in that it was smaller, at approximately 60nm diameter, and was designed specifically for interstitial, rather than intravenous, injection (**R3**). As such it constituted an effective and optimised replacement for Endorem.

In 2012-13, a multicentre clinical trial involving 160 patients was undertaken (**R4**). This was an "equivalence trial", designed to objectively compare the clinical outcomes of the standard-of care and magnetic methods. The clinical team concluded that: "*the magnetic technique is a feasible technique for SLNB, with an identification rate that is not inferior to the standard technique*." In the understated language of such reports, this was a resounding endorsement of the approach. Subsequently, several other clinical studies have been completed, both for breast cancer, and also for melanoma (**R5**), all of which have seen similarly positive outcomes.

3. References to the research

R1. **Pankhurst QA**, Connolly J, Jones SK, Dobson J. (2003) *Applications of magnetic nanoparticles in biomedicine*, *J. Phys. D* **36**, R167-R81. doi.org/fkrj4d. (A review article with more than 7,000 citations.)

R2. Joshi T, **Pankhurst QA**, Hattersley S, Brazdeikis A, Hall-Craggs M, De Vita E, Bainbridge A, Sainsbury R, Sharma A, Douek M. (2007) *Magnetic nanoparticles for detecting cancer spread*, Breast Cancer Research and Treatment, S129. doi.org/fc2tpz. (First report on the clinical pilot study, N = 7 patients, UK.)

R3. Mayes E, Douek M, **Pankhurst QA.** (2012) in *Magnetic Nanoparticles: From Fabrication to Clinical Applications*, ed. N. T. K. Thanh (CRC Press, 2012), pp. 541-55. ISBN: 1439869324. (Overview of the technical development of the SentiMag).

R4. Douek M, Klaase J, Monypenny I, Kothari A, Zechmeister K, Brown D, Wyld L, Drew P, Garmo H, Agbaje O, **Pankhurst QA**, Anninga B, Grootendorst M, Ten Haken B, Hall-Craggs MA, Purushotham A, Pinder S. (2014), Sentinel node biopsy using a magnetic tracer versus standard technique: the SentiMAG Multicentre Trial. *Annals of Surgical Oncology* **21**, 1237-45 (2014). doi.org/10.1245/s10434-013-3379-6. (First major breast cancer clinical trial: N = 160 patients, UK/Netherlands.)

R5. Anninga B, White SH, Moncrieff M, Dziewulski P, Geh J, Klaase J, Garmo H, Castro F, Pinder S, **Pankhurst QA**, Hall-Craggs MA, Douek M. (2016) Magnetic technique for sentinel lymph node biopsy in melanoma: the MELAMAG trial, *Annals of Surgical Oncology* **23**, 2070-8 (2016). http://doi.org/10.1245/s10434-016-5113-7. (First major melanoma clinical trial: N = 129 patients, UK.)

Patents

Hattersley SR, **Pankhurst QA**, Brazdeikis A. Apparatus and method for determining magnetic properties of materials. US2012229130A1. Priority date 2005-04-29, issued 2012-09-13.

Hattersley SR, **Pankhurst QA**, Magnetic probe apparatus. USPTO: US20110137154A1. Priority date 2009-12-04, issued 2011-06-09.

4. Details of the impact

Over 2,100,000 new cases of breast cancer are diagnosed annually around the world. 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 (EORTC) currently recommends sentinel lymph node biopsy (SLNB), wherein the sentinel lymph nodes are removed and inspected under a microscope. The procedure provides certainty regarding the localised or metastatic state of the cancer, which informs the post-surgery treatment pathway, and leads to an overall improvement in outcomes.

Despite this minimally invasive procedure being the preferred standard of care in breast cancer operations, current methods of sentinel node detection are not easy to use as they involve injection of radioactive isotopes with a blue dye as a tracer. Because the isotopes are potentially hazardous they must be injected in the nuclear medicine department, rather than by surgeons, and the isotopes' six-hour half-life presents challenges and limitations for theatre scheduling. Mandatory handling and waste disposal regulations add to the overheads, as does the training and licensing of operating theatre staff in the handling of radioisotopes. 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.

The research at UCL by Pankhurst and his team led to the realisation of a hand-held probe capable of working at the unprecedented levels of sensitivity and selectivity required for the SLNB application. This innovation has had direct and significant impacts in the field through the commercial production of the award-winning Sentimag device and the Sienna+/Magtrace tracer (**S1**). The magnetic approach to SLNB is straightforward: the Sentimag is a direct replacement for the Geiger counter, and the Sienna+/Magtrace is a direct replacement for the radioisotope – and minimal clinician training is required for its adoption.
Sienna+/Magtrace has a shelf life of three years, enabling its use much more widely than just at centres with access to nuclear medicine. The new technology pioneered from UCL – compared to the incumbent standard-of-care use of radioisotopes – presents fewer staff safety issues, and a lower regulatory burden. As such it significantly overcomes the barriers to uptake inherent in the current approach and makes SLNB available to all.

In 2006-07, based on its success in early clinical studies, Pankhurst's SentiMag was developed "from bench to clinic" . With seed investment from UCL Business plc and others, Endomagnetics Ltd was formed as a spin-out company in April 2007. 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 that was first trialled on 160 subjects and subsequently on many hundreds more. The Sentimag and Sienna+/Magtrace products were CE marked in Europe in 2011 and 2012 respectively, and together achieved Investigational Device Exemption (IDE) accreditation in the USA in 2017.

Between 1 August 2013 and 31 December 2020, through Endomagnetics Ltd, the UCL-led innovations have (**S2**):

- **60,000+ breast cancer** patients treated using the SentiMag and Sienna+/Magtrace medical devices;

- **600+** SentiMag base units and 45,000+ vials of Sienna+/Magtrace sold; resulting in **GBP9,800,000 turnover** in 2019/20, with 10% year-on-year growth;
- **GPB32,000,000 private investment** raised;
- **61 full-time** jobs created (54 in the UK and 7 in the USA) with a 43%/57% female/male gender balance; plus **11FTE** part-time/associated posts generated;
- 51 granted/allowed patents from a family of 21; with 13 in the US;
- ranked **43rd in the 2020 Sunday Times' Tech Track 100 league table** – a ranking of the UK's fastest-growing tech companies (**S3**); and
- receipt, in 2018, of the **Queen's Award for Enterprise** (**S4**).

Endomagnetics Ltd is now a mature company endorsed by the clinical community "*by moving breast cancer treatment forward and it's really doing things patients are happy with*" – Leading Breast Surgeon, from the University of California, San Francisco (**S5**). In 2018 it established a US operation base, with 5 staff permanently based there for sales and marketing.

In 2020 Endomagnetics Ltd has been active in responding to the special challenges brought on by the Covid-19 pandemic. In the UK, the crisis forced breast cancer centres to change their ways of working, in many cases moving from large hospitals to smaller Covid-free facilities. An example of this was the relocation of cancer services from the Greater Manchester region to the Rochdale Infirmary (**S6**). Given that these smaller units did not have regular access to nuclear medicine for breast cancer staging, it was vitally important that these affected facilities should be helped so that they could continue to offer access to the best standard of care available.

Endomagnetics stepped in by providing over GBP150,000 worth of free vials of Sienna+/Magtrace to the NHS, plus free guidance and support to anyone that wanted it (**S7**). The move has been welcomed by UK surgeons, as evidenced by the testimonials of four of London's most highly recognised consultant oncoplastic breast surgeons given in response to the establishment of new Covid-free 'hubs' in the city (**S8**). This promoted "*fantastic cooperation between NHS and the private sector*" (Consultant Oncoplastic Brest Surgeon) and has allowed highly recognised consultants to continue working "*in the best possible way … delivering the best-and the faster- possible care"* (Oncoplastic Breast Surgeon and Clinical Lead) (**S8**).

5. Sources to corroborate the impact

S1. Endomagnetics Ltd. has received multiple awards, most recently the Barclays Entrepreneur Award for 'International Expansion of the Year, 2019'.
S2. Statement from the CEO of Endomagnetics confirming company details (number of patients treated, units sold, revenue, funding, employment).
S3. Ranked 43rd in the Sunday Times' Tech Track 100 league table.
S4. Queen's Award for Enterprise 2018, Endomagnetics Ltd, April 2018.
S5. Testimonials to the efficacy of the SentiMag approach:.
S6. Press report on Covid-19 impact on breast cancer care in Greater Manchester.
S7. Press report on Endomagnetics donation of £150,000 worth of Sienna+/Magtrace to the NHS.
S8. Surgeon testimonials on the Endomagnetics contribution to London's new Covid-free hubs.