Institution: University of Leicester

Unit of Assessment: 9: Physics

Title of case study: From space science to medicine; the application of novel sensor technologies in healthcare

1. Summary of the impact

Space science and medicine share a fundamental requirement for radiation sensors of the highest possible sensitivity. The development of imaging detectors for major X-ray observatories such as the European XMM-Newton and NASA's Chandra provided the impetus for a broad-based, intensive programme of deliberate technology transfer from the Unit's Space Research Centre (SRC) into the life sciences and medicine. The resulting impact now extends far beyond the exploratory provision of prototype sensor technologies for biomedical researchers into the full-scale commercial exploitation of those technologies with industry partners in the UK and Europe and, in three separate cases, to early-stage patient trials. Impact is being delivered in clinical specialisms from oncology to ophthalmology; from neurotoxicology to emergency medicine. The impact delivery mechanisms -- the hospital-based Diagnostics Development Unit (DDU) and the campus-based Bioimaging Unit -- are themselves novel and have achieved national prominence as examples of best practice in the drive for economic return even from established blue skies research.

2. Underpinning research

The establishment of "Detector Physics" as a distinct research discipline at Leicester dates from the early 1960s. The second use, exploitation or spin-off of detector technologies in fields outside X-ray astronomy began in the late 1970s, with a collaboration with AEA Harwell regarding background reduction in gas proportional counters for the location of nuclear materials. The principal researchers involved in detector technology transfer across the clinical interface in the timeframe of this Impact case study are, with their current positions in brackets:

Professor GW Fraser (Professor of Detector Physics 1999-date)
Professor MR Sims (Professor of Astrobiology 2008-date)
Dr JE Lees (Research Fellow, subsequently Reader 2010-date)
Dr JS Lapington (Research Fellow, subsequently Reader 2010-date)
Dr NP Bannister (Lecturer, subsequently Senior Lecturer 2009-date)

Dedicated technical staff support for the SRC's Bioimaging laboratory has been provided by D. Bassford. J. Holt has performed the same role for the DDU. Notable among the contributing PhD students and post-doctoral research associates is W. Ryder, who held a joint PhD studentship with the University of London Institute for Cancer Research / Royal Marsden Hospital, and the University of Leicester Space Research Centre, graduating in 2006.

Space science shares with both the life sciences and medicine a common set of requirements for its particle and photon detectors – large format, high spatial resolution, fast response, high detection efficiency for a wide range of particle / photon energies and low internal background. The cross-disciplinary use of imaging detector technologies perfected at Leicester for the X-ray Observatories XMM Newton [**1**] and Chandra [**2**] gave rise to the SRC's Bioimaging Unit as an internal focus for technology transfer into the life sciences and medicine. Initiated with the aid of a University Senate Development award, the success of the Bioimaging Unit means that it has been self-funding since 1997. Subsequent research in optical spectroscopy associated with a) the ground-based follow-up of the Gamma-ray Bursts (GRBs) observed by the US/Italy/UK Swift satellite mission [**3**] (2004-date) – for which Leicester supplied the Charge Coupled Device (CCD) X-ray camera and (b) basic laboratory studies for astrobiology and future planetary missions such as EXOMARS then gave rise to spin-off activities in Hyperspectral Imaging (the simultaneous recording of a scene in several optical passbands or "colours") and Hi-Content Biology (ultra-fast imaging, with ~100 pixels, binned every 100 ps, of biological processes) and to the formation of the

DDU in the A&E unit of Leicester's main hospital, the Leicester Royal Infirmary (LRI), now part of the University Hospitals Trust.

The transferred technologies in question have between them attracted over £2.0M of funding from a variety of agencies – MRC, BBSRC, DEFRA, STFC, NHS, Lachesis (the East Midlands Universities Venture fund) and the European Space Agency (ESA) Technology Transfer Office. The underpinning research, its subsequent use in medicine, together with brief summaries of the relevant funding sources, patents and industrial partners is described in detail below:

(a) Beta autoradiography using microchannel plate detectors developed for the Chandra High Resolution Camera (HRC) [**2**]
The NASA Chandra observatory is the highest resolution (0.5 arcsecond) X-ray telescope ever built. The HRC is one of only two interchangeable focal plane detectors; it is based on microchannel plate electron multipliers of very large area, fabricated from special radioisotope-free ("low noise") glass, developed within the Unit's laboratory programme. Our development of low-background microchannel plates for space astronomy then provides proteomics and other life science researchers with an instrument of unparalleled sensitivity to the radiolabel tritium, whose low-energy beta emission is otherwise difficult to detect. Two complete dedicated systems (one prototype, one production) capable of registering the patterns of radioactivity from DNA gels, protein gels and thin tissue sections have been built, the second of which is in daily use by neurotoxicology researchers in the Queen's Medical Centre, Nottingham. [Funding; BBSRC £160k (1998) ; Bayer Pharmaceutical £80k (1999) ; DEFRA £180k (2001) Companies engaged: Severn Science Ltd (Thornbury,Bristol) ; Lablogic (Sheffield)] Number of patents filed – one (A detector and Method for Autoradiography, GW Fraser and J.E. Lees (2000)].

(b) Hybrid Mini Gamma Camera [**1,3**]
Two of the three focal plane CCD cameras on the XMM Newton observatory and the single CCD X-ray detector on Swift were designed and built at Leicester. Out of this strand of detector research has emerged an important technology for cancer treatment. A major challenge in oncology is to reduce the mortality rate for breast, skin and other cancers through the use of interventional imaging techniques to assist the surgeon. Based on the CCD detector research for X-ray astronomy carried out in the SRC, a new type of hybrid camera – combining optical and gamma imaging [**4,5**] – has been developed to the clinical prototype stage in collaboration with the Queen's Medical Centre, Nottingham (Professor Alan Perkins).

(c) Ophthalmic Spectrometry
In July 2009 the UoA was contacted by ophthalmologists at the Leicester Royal Infirmary seeking advice on optical spectrometry. The LRI team was interested in the potential of spectroscopy as a tool for early detection of sight-threatening conditions. Once the technical feasibility of the approach was established, an Innovation Fellowship from the East Midlands Development Agency funded the design and production of an instrument that was installed on a standard slit lamp at LRI, to allow precise, selective measurements of the reflectance spectrum of the sclera of the eye. With medical ethics committee approval, patients presenting conditions affecting the sclera were assessed using the device. The results showed a consistently reproducible, characteristic signature for the eye condition scleritis [**6**]. The technique is now being extended, using STFC innovation funding, to corneal ulcers. A laboratory system has been constructed, and preliminary testing on agar-plate cultures began in June 2013. Pending the results of this work, new medical ethics committee approval will be sought for the first dedicated corneal patient trials in 2014/15. [Funding ; EMDA £16k (2010); STFC Mini Innovations Partnership £120k (2012)]

(d) Diagnostics Development Unit (DDU)
The DDU has been established by in a bay within the A&E Department of the Leicester Royal Infirmary. Its location within A&E of a major inner-city hospital is itself unique, and has attracted much media attention. It employs non-contact, non-invasive Visible/IR imaging and spectroscopic techniques adapted from the SRC's laboratory and flight experiment programmes to detect the physiological status of an individual. Mass spectrometry of exhaled breath and reflectance measurements of skin colour, along with body temperature information from thermal infrared

imaging, provide invaluable diagnostic information. [Funding : HEFCE CIF £420k (2008)]

3. References to the research

1. M.J.L. Turner et al., Astronomy and Astrophysics 365 (2001) L27
2. S.S. Murray et al., Proc. SPIE 4012 (2000) 68.
3. N. Gehrels et al., Astrophysical Journal 611 (2004) 1005.
4. J. E. Lees, G. W. Fraser, A. Keay, D. Bassford, R. Ott and W. Ryder, The High Resolution Gamma Imager (HGRI): a CCD based camera for medical imaging Nucl. Inst.Meth A, 513 (2003) 23-26
5. J E Lees, DJ Bassford, OE Blake, PE Blackshaw, AC Perkins, A Hybrid Camera for simultaneous imaging of gamma and optical photons, J. Inst. 7 (2012) P06009
6. N.P. Bannister et al., Journal of Opthalmology (Innovations) (2013), in press

4. Details of the impact

In the particular case of the transfer of sensor technology from the physical sciences to medicine, the full-scale realisation of impact depends finally on the clinical acceptance and widespread use of the technology. Full impact is therefore approached asymptotically over many years. Here we report the impact has been achieved for multiple detector technologies and that the results of a coordinated programme of detector development over nearly two decades, based on a Bioimaging Unit with its own dedicated laboratory space, include the following significant achievements:

(i) Initial patient trials of a portable gamma camera (in clinic, Queens Medical Centre, Nottingham)

Confirmation of diagnosis in breast cancer, melanoma and in certain other cancers is achieved using “sentinel node biopsy”. This requires the surgeon to locate and remove relevant lymph nodes so that they can be tested to see if the cancer has spread. The position of the lymph nodes is usually detected by injecting a short-half-life radioactive substance into the tumour, which then drains away via the lymphatic system. The location of the first (sentinel) node is usually detected with a non-imaging gamma probe, with low precision. The new camera provides the surgeon with a visible light image overlaid with the pattern of uptake of a radioactive tracer such as 99mTc (a short-lived emitter of 140 keV gamma rays). The gamma channel of the camera provides both sub-mm spatial resolution and sufficient energy resolution to discriminate against scattered photons, which would otherwise blur the image structure. Early collaborative work in this area with Prof. Robert Ott (Institute of Cancer Research) led to a patent originally filed in Dec 2000 (Devices for imaging radionuclide emissions, Lees, Fraser and Ott). This patent has now been granted in Australia and Canada. A second patent covering the concept of simultaneous optical and gamma-ray imaging “Imaging Device and Method” was filed on May 16th 2005 and has now been granted in the USA, Europe, Australia and Japan with the application still pending in Europe and the USA. [Funding : MRC Discipline Hopping Award, in collaboration with Leicester Royal Infirmary £50k (2002) ; European Space Agency Technology Transfer Office, €50k (2002) ; Lachesis Venture Fund Pathfinder Award £25k (2004) ; UHL NHS Trust Charitable Fund £10k (2004) ; Lachesis Pathfinder Award £25k (2006) ; Lachesis Supplemental Award £50k (2010) ; Lachesis Large Award £200k (2007): East Midlands Development Agency £121.6k (2009); MRC Discipline Hopping award £90k (2009) ; STFC CLASP award £147k (2011)].

The hybrid camera will improve sentinel node localisation, reduce surgical trauma, improve patient outcomes and reduce healthcare costs. To date, images of 12 patients (**a**) presenting with a number of cancer types had been recorded in clinic at the Queen’s Medical Centre. Ethics approval has been received for up to 100 patients in the period 2013-15.

*(ii) Commercialisation of the small format, high resolution gamma camera (**b**)*

In September 2007, the University of Leicester formed a spin-out company, Gamma Technologies

Limited (GTL), to begin commercialisation of the camera technologies. GTL has raised over £250k first stage venture funding and is currently seeking second-round funding for safety certification and the manufacture of early-adopter prototypes. A UK-based medical devices company is currently performing due diligence on GTL with a view to investing £900k in by the end of 2013.

(iii) Design, manufacture and delivery of novel tools for (a) proteomics and so for the field of neurotoxicology (**c**) and (b) for the detection of scleritis in ophthalmology.

(iv) Patient trials of said opthalmology spectrometer, involving ~15 individuals to date.

(v) Establishment of a novel sensor-based unit within a large, working Hospital A&E Department, involving over 100 patients in two distinct clinical studies.

(vi) Contributions to the evidence base that space science and astronomy can have significant economic and societal impact beyond their blue skies research agenda (**d,e**).

5. Sources to corroborate the impact

(a) Patient images (anonymised) from the hybrid gamma camera can be made available to the panel on request. DDU data are available on the same basis.
(b) Although there is considerable information in the public domain concerning the main applications for large format gamma cameras, little has been published concerning small format gamma cameras. An independent market research report from the consultants Bridgehead International Limited was commissioned by GTL in 2009. The study initially comprised desk research utilising in-house databases and specialist commercial sources. The findings were then followed by detailed interviews with breast surgeons and radiologists. Half the interviewees were in the USA, and the remainder mainly in the UK, with some from key European countries. Interviewees provided up to date opinion and information on requirements, unmet needs and potential opportunities in target markets. This independent market assessment indicated a potential market for our gamma cameras in excess of £400 million worldwide. The report can be made available to the panel on request.
(**c**) A recent paper (M.H. Tarhoni et al, *Molecules* 16 (2011) 6535: Detection, Quantification, and Microlocalisation of Targets of Pesticides Using Microchannel Plate Autoradiographic Imagers) contains the following testimonial from clinical neurotoxicology users of our microchannel plate imager system:
"*The study of protein post-translational modifications has been advanced by the commercial availability of radiochemical ligands. The relative ease of synthesis and a relatively long half-life, render tritium incorporation into radiochemicals a suitable tracer ligand to study many biological processes. However, tritium usage may be hindered by the limit in the detection threshold and signal linearity of conventional film autoradiography. MCP digital autoradiography displays superior detection sensitivity and over a more comprehensive signal magnitude than that of film autoradiography. These traits may be exploited for the detection and quantification of protein modifications that lie well below protein visibility levels, such as the protein modifications by pesticides detailed in this manuscript. The MCP devices also possess useful spatial resolution to enable microlocalisation of small molecule radioligands, and collectively these qualities will continue to assist with the dissection and understanding of biological systems."*
(d) The work of the Unit areas covered by this case study features prominently in an "Innovation from UK astronomy" brochure, published in June 2013 by the Royal Astronomical Society (brochure editor, Dr Sue Bowler, University of Leeds). See "Beyond the stars: why astronomy matters" http://www,ras.org.uk/images/stories/publications/beyondthestars.pdf)
(e) Other examples of influential outreach related to this case study are to be found in both print (e.g.Rebecca Wilson, "Medical marvels from space", The Irish Times, 11th October 2012) and broadcast media (e.g. the DDU's appearance on BBC1 TV's "One Show", 19th May 2013).