**Institution:** University of Nottingham

**Unit of Assessment:** 5 - School of Life Sciences

**Title of case study:**

*Early cancer detection: Life changing diagnosis and intervention in patients with high risk for lung cancer.*

## 1. Summary of the impact

A research team, led by Professor John Robertson, was joined by Professor Herb Sewell as lead collaborator. They developed a blood test that permitted early detection of lung cancer in high risk patients, allowing earlier and more successful treatment. The *Early*CDT-Lung test was commercialised by the university spin-out, Oncimmune, and launched in 2010. It is in clinical use in North and South America, in private clinics in the UK and in some Middle East countries, generating employment and revenues for the company, and is starting to bring mortality and lifestyle benefits to patients and their families.

## 2. Underpinning research

### i) Development, commercialisation and clinical introduction of *Early*CDT-Lung

The underpinning research conceived and initiated by Professor Robertson (Professor of Surgery, Faculty of Medicine and Health) at the University of Nottingham demonstrated that patients at high risk of developing lung cancer developed auto-antibodies (AAbs) to a range of tumour-associated antigens (TAAs). Detecting the presence of these AAbs was developed by Robertson's group as a potential clinical diagnostic test, termed '*Early*CDT-Lung'.

Progress of the *Early*CDT-Lung diagnostic test to clinical utility was accelerated when Professor Sewell (Professor of Immunology, Infection and Immunity group, School of Life Sciences) joined the group in 2003, bringing his immunological expertise and longstanding research on human immune responses in cancer[1]. Sewell, as Medical Consultant, has led for more than 20 years a Diagnostic Immunology laboratory in Nottingham that is recognised nationally as a leading department in the speciality. His key contributions to development of *Early*CDT-Lung from 2003 onwards helped to enhance the test to deliver a very high specificity (>90%) by defining use of the best anti-immunoglobin isotype (anti-human IgG) to use for detecting the presence of AAbs in human serum that specifically bind to TAAs, whilst minimising the detection of cross-reactive poly-specific IgM natural antibodies also present in test samples that bind more weakly to many antigens. High specificity is the crucial requirement for the *Early*CDT-Lung blood test in order for it to complement existing x-ray computed tomography (CT) scans, which contrastingly have very high sensitivity for detecting lung nodules and abnormalities, but poor specificity/predictability for reliable identification of those that are cancerous.

Professor Sewell has contributed continuously since 2003 to guiding the technical[2] and clinical[3] development to the point of commercial roll out of *Early*CDT-Lung test by the university spin-out company, Oncimmune, in 2009. The group demonstrated in publications from 2010 to 2012[2-5], that the diagnostic test does indeed aid the early detection of lung cancer. Professor Sewell has also worked with the Scientific Advisory Board of Oncimmune to design and execute major retrospective clinical studies to validate the use of the test in practice.

### ii) Centre of Excellence for Autoimmunity in Cancer (CEAC)

Based on its international leading position, the University of Nottingham created the Centre of Excellence for Autoimmunity in Cancer (CEAC) in 2008. Professor Sewell sits on the CEAC Scientific Research Committee (SRC) and has been involved in three significant aspects of CEAC's work: 1) Clinical trials testing of *Early*CDT-Lung at the National Jewish Hospital (Colorado, USA) and the Early lung Cancer detection test – Lung cancer Scotland (ECLS) trial. 2) He played a critical role in coordinating the wide portfolio of collaborative studies with international centres of excellence in Europe and North America using retrospective analysis of blood sample banks. Professor Sewell demonstrated significant variation in protein degradation in stored samples,

revealing the importance of testing sample quality to detect potential reductions of AAb titre, from which AAb detection thresholds could be adjusted to discriminate positive and negative samples more reliably. 3) Professor Sewell also guided development of techniques for generating panels of TAAs in high throughput systems[4,5], as well as refining the ELISA assay used for detecting AAbs in various patient groups[2]. Most recently Professor Sewell has developed new micro-array formats for the cancer detection assays, based on principles from his earlier work using AAb selection in phage libraries to define antigen epitopes in autoimmune disease[6].

## 3. References to the research

Publications (UoN authors in bold, key author(s) underlined)


1. **Sewell HF**, Halbert CF, Robins RA, Galvin A, Chan S, Blamey RW (1993). Chemotherapy-induced differential changes in lymphocyte subsets and natural-killer-cell function in patients with advanced breast cancer. Int J Cancer. 11;55(5):735-8. doi: 10.1002/ijc.2910550506
2. Murray A, **Chapman CJ**, Healey G, Peek LJ, Parsons G, Baldwin D, Barnes A, **Sewell HF**, Fritsche HA, **Robertson JF (2010)**. Technical validation of an autoantibody test for lung cancer. Ann Oncol. 21(8):1687-93. doi: 10.1093/annonc/mdp606
3. Lam S, Boyle P, Healey G, Maddison P, Peek L, Murray A, Chapman CJ, Allen J, Wood WC, **Sewell HF**, **Robertson JFR** (2011). *Early*CDT–Lung: An immunobiomarker Test as an Aid to Early Detection of Lung Cancer. Cancer Prev Res. 4(7):1126-34. doi: 10.1158/1940-6207.CAPR-10-0328
4. Macdonald IK, Allen J, Murray A, Parsy-Kowalska CB, Healey GF, **Chapman CJ**, **Sewell HF**, **Robertson JF** (2012). Development and validation of a high throughput system for discovery of antigens for autoantibody detection. PLoS One. 7(7):e40759. doi: 10.1371/journal.pone.0040759
5. Macdonald IK, Murray A, Healey GF, Parsy-Kowalska CB, Allen J, McElveen J, Robertson C, **Sewell HF**, **Chapman CJ**, **Robertson JF** (2012). Application of a High Throughput Method of Biomarker Discovery to Improvement of the *Early*CDT(®)-Lung Test. PLoS One.7(12):e51002. doi: 10.1371/journal.pone.0051002
6. **Shakib F**, **Hooi DS**, **Smith SJ**, **Furmonaviciene R**, **Sewell HF** (2000). Identification of peptide motifs recognized by a human IgG autoanti-IgE antibody using a phage display library. Clinical and Experimental Allergy. 30(7), 1041-6. doi: 10.1046/j.1365-2222.2000.00852.x


Key Research Grants

**2004 to present: Sewell HF**, in collaboration with **Robertson JF**, **>£20 million** investment has been raised from the Biotechnology Industry and from venture capital to support the work in autoimmunity and cancer early detection.

**2012-2014: Sewell HF**: Co-investigator on Medical Research Council 'Confidence in Concept' scheme, Biomedical Catalyst award, **£400,000**, to investigate the use of human autoantibodies in the early diagnosis and screening for Colorectal cancer.

## 4. Details of the impact

Lung cancer causes more deaths than breast, colon and prostate cancer combined, and its incidence will increase further up to 2030. The National Lung Screening Trial (NLST) spiral CT lung cancer screening study (NSLT Research Team, et al; 2011. N Engl J Med. 365(5):395-409)[A], indicated that early detection of lung cancer by low-dose CT scan (when identified as small lung nodules and treated accordingly), leads to a 20% reduction in lung cancer deaths, and a 6.7% reduction in overall mortality compared to later stage detection by chest X-ray (when the tumour is often larger and palliative care is often the only treatment option available). At this late stage, lung cancer survival rates are as low as 15%.

*Early*CDT-Lung is the first (and currently the only) autoantibody blood test for detecting lung cancer in people identified as being at high risk (e.g. aged over 40 with more than 20 pack-years history of smoking). The test detects AABs to TAAs from an early stage when the cancer (observed by CT-scan) is small, often asymptomatic, and is also potentially curable[B] (e.g. by surgery or

stereotactic radiotherapy). This leads to better patient risk assessment, closer surveillance and less invasive treatment options, resulting in greater survival rates and better patient quality of life.

**Impact 1: Foundation of Oncimmune and Commercialisation of *Early*CDT-Lung**

Professor Sewell's contribution to establish a commercially-viable diagnostic test was central to the University's decision in 2003 to support the generation of spinout company, Oncimmune (based in the UK and USA), to exploit the commercial value of the 4 patent families arising from the UoN research, to which Oncimmune has added 3 others. Oncimmune has attracted investment of £30.5 million to date, and generated 15 jobs in the UK and 28 jobs in the US within the company[C], as well as helping to secure positions within suppliers and distributers[C]. The *Early*CDT-Lung test is available in multiple continents (North & South Americas, Europe, Middle East), with sales of upwards of 6,000 tests per month, generating substantial revenues for the company. Oncimmune is therefore the principal beneficiary of the University's research.

**Impact 2: Accelerating Development and Clinical Validation of Early Cancer Detection Tests**

The *Early*CDT-Lung test took almost a decade to bring to market. Further tests for other tumour types require a considerably shorter development timeline to be commercially viable. Professor Sewell's research within CEAC, using high throughput screening and micro-array technology as the next generation platform for detecting autoantibodies to cancer antigens, has achieved a reduction in technical development time (and hence, cost) for Oncimmune, with the next *Early*CDT test for hepatocellular cancer planned for launch after only 5 years in development. This will allow faster world-wide commercialisation of the autoantibody approach for diagnosis of all solid tumours. CEAC has also designed and initiated a prospective randomised clinical trial of *Early*CDT-Lung in the USA with Chief Investigator Dr James Jett (National Jewish Hospital, Colorado), and is involved in the NHS-Scotland-supported ECLS trial that is randomising 10,000 individuals at increased risk of lung cancer to have the *Early*CDT-Lung test or not. Both of these studies are expected to accelerate clinical validation of the test to support its commercialisation. Oncimmune is therefore the beneficiary of ongoing non-clinical and clinical research developments from the university.

**Impact 3: Clinical use of *Early*CDT-Lung to save lives**

From the 7 year NLST study showing that early detection and treatment of lung cancer improves survival outcomes [see above], the *Early*CDT-Lung test, which has been in use in the US since 2010, is expected to have at least a similar long-term patient benefit to CT screening, but with an improved safety profile because it is a simple blood test and does not involve patient exposure to x-rays. It is known that repeated CT scans have an increased risk, albeit low, of possible secondary cancers associated with radiation exposure. By using *Early*CDT-Lung to screen high risk people, the number of individuals who will require follow-on CT scans using repeated exposure to radiation is decreased. *Early*CDT-Lung test has been shown to be cost effective and beneficial from a healthcare economics perspective (Weycker et al, 2010)[D] to save lives and money. Many patients and their clinical practitioners in the US have already reported transformation in life styles and quality of life due to the physician's use of the *Early*CTD-Lung test in clinical management; testimonials available on the Oncimmune UK (and US) web site[E] attest to the benefits it has already brought to individuals. On-going studies have also demonstrated its usefulness in the follow up of patients with indeterminate lung nodules that have been identified by CT scans. Thus, in conjunction with diagnostic imaging, *Early*CTD-Lung has shown its potential to aid in the identification of lung cancer at a very early stage when treatment can be most successful. The expectation is that a 10 year follow-up will show a significant improvement in patient survival.

The on-going NHS-Scotland-supported ECLS clinical trial is expected to produce the same positive outcome seen so far in the US, leading to adoption of the test for population screening by the NHS in the UK. The positive healthcare and reduced mortality benefits for patients, as well as the health economic value, are likely to lead to a change in healthcare policy on lung cancer screening and risk assessment. Impact on public awareness of the ECLS clinical trial and its healthcare benefits has already been made through newsprint[F] articles in 2010 and a television broadcast[G] in 2012.

Patient risk assessment, early detection and diagnosis of lung cancer in high risk patients, and changes to healthcare policy are therefore the ultimate benefits that are progressing from development of the *Early*CTD-Lung test by researchers at the University of Nottingham.

In summary the primary impacts and beneficiaries derived from this ongoing research are:

a. Commercialisation of university research by foundation of the spin-out company, Oncimmune
b. Job creation, revenue generation, and further technical and clinical developments for Oncimmune.
c. Changes to clinical practice and healthcare policy to improve lung cancer risk assessment and early diagnosis, bringing benefits to clinicians and healthcare funders.
d. Transformation of patient outcomes to reduce mortality and improve health and quality of life.

**5. Sources to corroborate the impact**

A. http://www.nejm.org/doi/full/10.1056/NEJMoa1102873

B. www.nottingham.ac.uk/impactcampaign/campaignpriorities/healthandwell-being/cancerearlydetection/cancerearlydetection.aspx Robertson, Sewell and Chapman explaining development of *Early*CDT-Lung and patient experiences.

C. Information provided by Chief Scientific Officer of Oncimmune.

D. Weycker D et al, 2010. Cost-effectiveness of an autoantibody test (AABT) as an aid to diagnosis of lung cancer. J Clin Oncol 28(15 suppl): 7030.

E. http://www.earlycdt-lung.co.uk/testimonial-videos/ Patient and Physician testimonies are included in links to videos on this page.

F. Times news articles and testimonials from 01 June 2010, and the 'Eureka' supplement on 03 June 2010, about use of the *Early*CDT-Lung test in the UK.

G. Channel 4 News report about announcement of major Lung Cancer Screening Trial by the NHS in Scotland using *Early*CDT-Lung blood test: http://www.channel4.com/news/breakthrough-cancer-bloodtest-to-be-made-available-in-uk.

Corroborative documents and copies of webpages are held on file and are available on request.