Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study: Development and commercial exploitation of a novel diagnostic for early detection of lung cancers

1. Summary of the impact

Research directed by Professor John Robertson at The University of Nottingham led to the launch, in 2009, of the world's first autoantibody blood test for the detection of early-stage lung cancer. The *Early*CDT-Lung test has been commercialised through the spin-out company Oncimmune. [text removed for publication]. *Early*CDT-Lung is now used clinically in North and South America, the UK and the Middle East, generating revenue and saving lives.

2. Underpinning research

In the 1990s, established assays for tumour-secreted markers in bodily fluids focused on the detection of single proteins that reflected tumour bulk and were of value only late in the disease process. In the same period, circulating autoantibodies (AABs) were shown to be present before tumour-associated antigens (TAAs) could be detected. A research programme directed (since 1996) by Professor John Robertson in the Division of Surgery, University of Nottingham, identified that AAB response to specific panels of TAAs provides an indicator of disease at an early stage. Initial research in breast cancer showed that measurement of AABs in patient serum to a panel of TAAs, rather than to individual antigens per se, increased the sensitivity of detection such that it was possible to discriminate normal control individuals, primary breast cancer cases, metastatic cancers and asymptomatic BRCA1 mutation (at-risk) carriers with 95-100% confidence. Measurement of AABs provided enhanced sensitivity of detection compared with low levels of antigens. The technology also increased specificity compared with other methods since AABs distinguish normal and tumour isoforms of antigens. This research was disclosed in a patent filed by The University of Nottingham (Inventors: Professors Robertson and Mike Price, and Dr Ros Graves) in 1999[1]. The patent also included the observation that use of biotinylated TAAs expressed in bacteria could form the basis of a high throughput screening test. The diagnostic potential of this approach was further supported by evaluation of an appropriate TAA marker panel and insight into the type of TAA sequences required for efficient AAB detection[2].

The above research and four associated patent families (see section 5) from the group led the University to form the spin-out company, Oncimmune, in 2003. Oncimmune and University of Nottingham staff were co-located, and recruitment to the joint team of Dr Caroline Chapman (postdoctoral biochemist) in 2003 and Professor Herb Sewell (Professor of Immunology and Consultant Immunologist) in 2005, added significant expertise. Professor Robertson has been the Chief Scientific Officer of Oncimmune since the formation of the company, and both he and Dr Chapman are University of Nottingham inventors on three further patent families generated by Oncimmune.

The primary goal of Oncimmune was to develop a commercial AAB test for the early detection of lung cancer; much of the research to achieve this was done in collaboration with University of Nottingham researchers. Lung cancer is the largest cause of death from cancer worldwide (1.4 million deaths per year), and less than 13% of lung cancers in the UK are diagnosed at the earliest stages [National Lung Cancer Audit Report 2012]. This created a substantial market for an early detection test and facilitated Oncimmune raising investment that has funded £4.88M research in the University team.

Through European Union 5th Framework funding to Professor Robertson, the team demonstrated the potential value of an optimised panel of AABs as a means of early detection of lung cancer[3]. The technical validation of the lung cancer assay[4] and the first clinical evaluation of 655 patients to validate the lung cancer panel[5] was in collaboration with others, including Centres in the US (WC Wood, Emory School of Medicine) and Germany (S Holdenrieder, University Hospital Munich), and the University of Strathclyde (C Robertson: Statistics). These studies demonstrated the sensitivity and specificity of the technology in a high risk population. Further datasets including 574 patients from US, Canada and UK confirmed that 40% of all newly diagnosed lung cancer types could be detected reproducibly with very high specificity using *Early*CDT-Lung[6]. In the largest prospective cohort study of small cell lung cancer, the sensitivity of the test increased to 55% of patients,

irrespective of stage of disease[7]. These clinical studies were enabled through collaborations with Nottingham University Hospital NHS Trust (P Maddison, D Baldwin), British Columbia Cancer Agency (S Lam), International Prevention Research Institute, Lyon (P Boyle) and others. A prospective audit of the first 1,600 individuals in the USA to buy the test has shown that the test characteristics (i.e. sensitivity and specificity) in routine clinical practice[8] were precisely as predicted from the validation and further (post-validation) results. Similarly, an audit of 443 patients with lung nodules has shown that whatever the lung nodule size, a positive *Early*CDT-Lung test conveys an increased risk that the nodule is malignant (manuscript in preparation).

In 2008, The University of Nottingham and Professor Robertson established the UK's first academic Centre of Excellence for Autoimmunity in Cancer (CEAC). CEAC and Oncimmune R&D scientists have worked since 2008 to develop new AAB tests for hepatocellular and colon cancers that are in different stages of development. Their research has also identified that AABs provide an individual immune-profile which, when measured in a sequential manner, provides improved sensitivity and personalised risk assessment. Oncimmune's IP portfolio now has 169 patents currently enforceable in 12 Territories (Europe counted as a single Territory), with 49 pending applications in 12 Territories (Europe counted as one). This will help to guarantee investment for the second generation of *Early*CDT tests, with the launch for hepatocellular cancer on track for 2014.

3. References to the research

1) **Robertson JFR**, Graves CRL, Price MR. Tumour Markers US 7,402,403,B1. 1999. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=7402403.PN.&OS=PN/7402403&RS=PN/7402403

2) Chapman C, Murray A, Chakrabarti J, Thorpe A, Woolston C, Sahin U, Barnes A, **Robertson JFR.** Autoantibodies in breast cancer: their use as an aid to early diagnosis. Ann. Oncol. 2007 May;18:868-873 [**IF: 7.38**] http://dx.doi.org/10.1093/annonc/mdm007

3) Chapman CJ, Murray A, McElveen JE, Sahin U, Luxemburger U, Türeci O, Wiewrodt R, Barnes AC, **Robertson JFR**. Autoantibodies in Lung Cancer - possibilities for early detection and subsequent cure. Thorax. 2007;63:228-233 [**IF: 8.37**] http://dx.doi.org/10.1136/thx.2007.083592

4) Murray A, Chapman CJ, Healey G, Peek LJ, Parsons G, Baldwin D, Barnes A, Sewell HF, Fritsche HA, **Robertson JFR**. Technical validation of an autoantibody test for lung cancer. Ann Oncol. 2010; 21:1687-1693 [**IF: 7.38**] http://dx.doi.org/10.1093%2Fannonc%2Fmdp606

5) Boyle P, Chapman CJ, Holdenrieder S, Murray A, Robertson C, Wood WC, Maddison P, Healey G, Fairley GH, Barnes AC, **Robertson JF**. Clinical Validation of an Autoantibody Test for Lung Cancer. Ann Oncol. 2011 22:383-389 [**IF: 7.38**] http://dx.doi.org/10.1093%2Fannonc%2Fmdq361

6) Lam S, Boyle P, Healey GG, Maddison P, Peek L, Murray A, Chapman CJ, Allen J, Wood WC, Sewell HF, **Robertson JFR**. 2011. EarlyCDT-Lung: an Immuno-biomarker Test as an Aid to Early Detection of Lung Cancer. Cancer Prev Res 4;1126–1134 [**IF 4.9**] http://dx.doi.org/10.1158/1940-6207.CAPR-10-0328

7) Chapman CJ, Thorpe AJ, Murray A, Parsy-Kowalska CB, Allen J, Stafford KM, Chauhan AS, Kite TA, Maddison P, **Robertson JFR**. 2011. Immuno-biomarkers in small cell lung cancer: Potential early clinical signals. Clin. Cancer Res. 17:1474-1480 [**IF: 7.84**] http://dx.doi.org/10.1158/1078-0432.CCR-10-1363

8) Jett J, Peek LJ, Fredericks L, Jewell W, Pingleton WW, **Robertson JFR.** Audit of the autoantibody test, EarlyCDT®-Lung, in 1600 patients: an evaluation of its performance in routine clinical practice. Lung Cancer (in press).

Funding sources include: Funding for this work from 1993 to 2013 was awarded to Professor

Robertson from a number of sources (e.g. Susan Komen, Bayer Diagnostics, Cis Bio International, Nottingham University Hospitals [NUHs] Charity, AstraZeneca, Whitaker Charitable Fund, Oncimmune, European Union FP5, MRC) and has totalled over £4M.

4. Details of the impact

Beneficiaries of this research have been: 1) the patients who have benefited from earlier detection and therefore improved treatment options and outcomes, 2) clinicians who are able to offer their high-risk patients improved early detection, 3) shareholders in the spin-out company, and 4) the US and UK economies through taxation, legal fees and patent attorney and other services.

Clinical Impact

Treatment for lung cancer is more successful when the disease is diagnosed at an earlier stage. But, currently, 85% of patients with lung cancer remain undiagnosed until the disease has reached an advanced stage[a].

*Early*CDT-Lung detects all types and all stages of lung cancer, including Stage I and II, and is non-invasive, with no radiation risk for the patient. The test is currently marketed for use as 'a diagnostic test to aid in the early detection of lung cancer in your high-risk patients; most notably long-term smokers and ex-smokers'[b] (ie smokers and ex-smokers who quit <15 years previously). It is already influencing treatment decisions and saving lives in clinical practice. For example, in US pilot studies on smokers, the test 'either confirmed suspicions of a cancer, or prompted surgical intervention on a cancerous nodule previously thought to be benign'[c].

Our team have helped to develop *Early*CDT-Lung as an aid to diagnosis in the assessment of pulmonary lung nodules. Around 35-50% of individuals undergoing computerised tomography (CT) scanning have lung nodules, 96% of which are not malignant. CT scanning detects all of these nodules, whether malignant or benign. An *Early*CDT-Lung test significant improves the assessment of risk of malignancy of lung nodules, thereby impacting on the clinician's decision, and changing patient care. When used with CT, a positive *Early*CDT-Lung result can mean between a two-fold and five-fold increase in risk of cancer depending on the lung nodule size. Because of this, *Early*CDT-Lung is also now marketed as 'a new tool to stratify pulmonary nodules' for malignancy[b], especially in the indeterminate nodule (8-20mm) and/or where PET is not indicated or is inconclusive. According to a US clinician 'You see these indeterminate nodules, and they could be totally harmless and irrelevant to health and best left alone. But other patients will have ones that are small lung cancers. [The test] has dramatically changed our management of things, of how we make our decisions. For some of those patients who we had not planned to operate, we have then taken a different approach. When the nodules are studied afterwards it has confirmed that it was malignant'[c].

In 2011, the US National Lung Screening Trial (NLST) demonstrated that early detection with CT, followed by appropriate treatment, significantly reduces deaths from lung cancer by 20% [NEJM 2011; 365, 395-409]. But, CT screening has a high false positive rate, is expensive, and 'is unlikely to achieve a cost effective position to justify national screening'[a]. Commercialisation of the *Early*CDT-Lung test has therefore addressed an urgent and unmet clinical need for a pre-CT screening blood test – both to widen the entry criteria for CT, and to reduce the number of unnecessary CTs performed. '*Early*CDT-Lung will detect approximately half the cancers in the screened population and reduce the overall number to be followed up with CT to 7%. Having up to half the cancers in only 7% of the screening population should make the combination of *Early*CDT-Lung followed by CT highly cost effective'[a].

The patient benefits brought by *Early*CDT-Lung have led to the NHS-Scotland supported Early Cancer Detection - Lung Cancer Scotland (ECLS) study[d], which is assessing the test's feasibility as the basis for a national screening programme for lung cancer, as opposed to individuals having to request the test themselves. A health economic assessment from the US has shown that, on a population basis, use of the test as proposed in ECLS should save lives and money: the cost per life year gained of CT plus *Early*CDT-Lung was $20,044 (compared with no screening) and $19,293 (compared with CT alone)[e]. The group predicted that screening with CT plus *Early*CDT-Lung, or with CT alone, would lead to a gain of 6.3 and 5.7 life years, respectively[e].

[text removed for publication][f].

Commercial Impact

The Lachesis regional investment fund initially provided funding [text removed for publication] to support the company's goal of 'developing medical diagnostics for cancer screening, recurrence and therapeutic guidance through a patent protected 'autoantibody panel' of immunoassays'. [text removed for publication][g]. In 2006, a US subsidiary (Oncimmune LLC) was established to facilitate the FDA oversight and Clinical Laboratory Improvement Amendments lab approvals necessary to market the test in US federal health program Medicare/Medicaid cases. [text removed for publication]. On the basis of these sales, Health Diagnostics Laboratory inc. has acquired the rights to commercialise this test in the US[h]. Commercial utility is evidenced by the cost of the test being reimbursed by some private insurance companies and approval for reimbursement by Medicare. The test has now also been launched in Canada, South America and UK[i], with samples being sent to Oncimmune LLC for processing. [text removed for publication][h].

The key drivers for commercial success are:

i) UoN patents[j] which provide Oncimmune with a strong position particularly in the USA and Europe, the two largest oncology markets in the world. 169 patents are currently enforceable in 12 Territories, 73% of which have been granted since 2008, with 49 pending. These patents cover autoantibody assays to any cancer associated antigen. This width of patent protection provided a strong basis for securing the investment required to develop the test commercially.
ii) A solid reproducibility and precise *Early*CDT-Lung assay with a sustainable calibration and control system (which also has IP protection).

Professor Robertson has played a central role in bringing a new diagnostic test for lung cancer (*Early*CDT-Lung) to market. The technology behind *Early*CDT-Lung is applicable to all solid cancers. These relatively inexpensive blood tests could be taken up readily worldwide, even in resource poor/developing countries, in which around half of all cancers are diagnosed each year.

5. Sources to corroborate the impact

a. News article: http://www.obn.org.uk/obn_/news_item.php?r=PD4LIH840341
b. OncImmune: http://www.oncimmune.com/
c. 'New blood test detects cancer before it grows' and 'US lung patients already feeling the benefits'. The Times, 2010. (Articles available as a pdf on request.)
d. ECLS brochure (pdf available on request).
e. Weycker D, Jett JR, Detterbeck FC, et al. Cost-effectiveness of an autoantibody test (AABT) as an aid to diagnosis of lung cancer. J Clin Oncol (2010) 28(15) May 20 Supplement, 7030 http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7030?sid=91dc6c3d-b385-4e42-aa8a-c2ad35c3324c
f. Letter from Professor Frank Sullivan, Clinical Director, University of Dundee.
g. OncImmune factsheet and OncImmune accounts 2011/2012.
h. HDL press release.
i. *Early*CDT-Lung launch:
   Canada: http://www.marketwired.com/press-release/oncimmuner-earlycdt-lung-simple-blood-test-aid-early-detection-lung-cancer-now-available-1283347.htm
   UK: http://www.earlycdt-lung.co.uk/learn-more/test_providers-0/
   South America: http://www.auroramdx.com/index.php?country=CL&lang=en
j. 7 patent families giving rise to 169 granted patents in 12 Territories (36 countries) can be identified using: http://patentscope.wipo.int/search/en/search.jsf by entering the patent numbers:
   1. WO1999/58978 **2.** WO2000/34787 **3.** WO2004/044590 **4.** US20110086061
   5. WO2006/126008 **6.** WO2008/032084 **7.** WO2009/081165