Institution: University of Birmingham

Unit of Assessment: A1

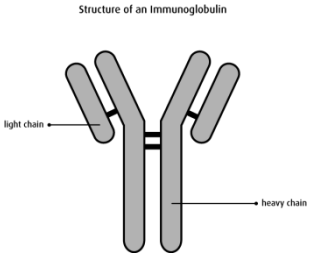
Title of case study:
Global health impact and economic impact from the development of Freelite®

1. Summary of the impact (indicative maximum 100 words)

Research conducted by Professor Jo Bradwell at the University of Birmingham provided the basis of the commercially available diagnostic test Freelite®, which quantifies free immunoglobulin light chains in serum and was the first and only assay for the diagnosis and monitoring of Multiple Myeloma (MM). MM is a cancer of immunoglobulin producing plasma cells in the bone marrow. Freelite® has markedly improved the diagnosis and management of MM, is helpful in the diagnosis of all B cell lymphoid neoplasias and provides prognostic information for premalignant conditions present in over 3% of people over 50 years of age. Freelite was commercialised by the University of Birmingham spinout company, the Binding Site, which has achieved worldwide sales, with over 360,000 tests being sold per month in 90 countries and an ongoing 25% annual growth in sales. The company provides annual revenue of £55m and employment for 620 people in the UK and abroad. An improved second generation of tests has been developed by Professor Mark Drayson at the University of Birmingham, which has been commercialised by a second University spinout company Serascience, which started marketing a point of care free light chain diagnostic test worldwide in April 2013.

2. Underpinning research (indicative maximum 500 words)

In the journal *Lancet* in 1847, Henry Bence Jones described the characteristics of the first cancer biomarker, a protein in urine from a patient who suffered with mollities and fragilitas ossium (myeloma). In the 1960s, the Bence Jones protein was identified as immunoglobulin free light chains (FLC), which when joined with the heavy chain make the whole immunoglobulin complex (see diagram below). FLCs and whole immunoglobulins are the products of normal polyclonal plasma cells (polyclonal immunoglobulin) and the neoplastic plasma cell clone of myeloma (monoclonal immunoglobulin – M-protein). Two forms of FLC are produced: kappa and lambda, with about twice as much being of the kappa type.



In healthy individuals the total body plasma cell pool produces about 0.5g/day of FLC, with a blood half-life of 2 to 4 hours. FLCs are removed from the blood by filtration into the kidneys and do not appear in the urine of healthy individuals because they are metabolised in the kidneys. In blood cancers such as MM, a single plasma cell gives rise to a greatly expanded neoplastic clone, which will secrete FLCs of either kappa or lambda type; it is this characteristic and the relative ratio of the two FLC types, which the diagnostic tests described in this case study are based. As a consequence of the increased level of FLCs being produced in diseases such as MM, the kidneys become saturated and FLC become detectable in the urine. A neoplastic clone of plasma cells must secrete more than 20g of FLC per day (40x the combined secretion of all the body's normal polyclonal plasma cells) to saturate the kidneys and for FLCs to become detectable in urine. Accordingly, it is preferable to assess FLC secretion by measurement of FLC in blood, not urine. A neoplastic clone of plasma cells only has to secrete 1g/day of monoclonal FLC to reveal its presence by distorting the normal blood serum FLC (SFLC) kappa to lambda ratio. Despite it being preferable to measure FLCs in the serum, it was technically challenging to develop such a test, this is because the level of SFLCs is 1000 fold less than the level of FLC in the bound form of the whole immunoglobulin. Thus antibodies for the clinical detection of SFLC must have a high specificity for epitopes (areas which antibodies bind) that are exposed on FLC, but are hidden on the form bound to the heavy chain in the whole immunoglobulin. Furthermore the FLC epitopes

that the diagnostic antibody recognises must be present on FLC from all patients and normal and neoplastic plasma cell clones.

In the late 1990s Professor Jo Bradwell, Senior Lecturer in the School of Immunity and Infection at the University of Birmingham (until September 2000) led a team to generate polyclonal antibodies in sheep for the development of laboratory assays to reliably quantitate FLCs in serum samples [1]. The diagnostic test was based on unique sheep polyclonal antibodies directed to either kappa or lambda FLC, which were conjugated to latex beads. Following the addition of FLC containing serum sample to these antibody conjugated beads, turbidimetry or nephelometry was used to measure the amount of cross linked antibody, which was directly correlated to the amount of SFLC. Professors Bradwell and Drayson (UoB from 1991) used serum samples from the national MRC myeloma trials to validate the clinical utility of the test from 2000 onwards. The greater sensitivity of measuring FLC in serum rather than urine was demonstrated in myeloma patients previously classed as non-secretory because the old gold standard methods for detecting monoclonal Immunoglobulin/FLC in serum and urine were negative [2]. Furthermore in myeloma patients who secreted large amounts of FLC with no whole monoclonal immunoglobulin detectable, the new serum FLC test was shown to be greatly more sensitive for detecting response to anti-myeloma treatment and relapse from remission than the old urine Bence Jones Protein test [3].

Prospective analysis of the SFLC test was made on 1,970 patients enrolled into the MRC Myeloma 9 trial, confirming and furthering the findings of the retrospective studies [4]. The results of this and use of the SFLC test in the MERIT trial proved for the first time that levels of nephrotoxic FLC could be lowered quickly resulting in renal recovery and improved patient survival and that the SFLC tests provide an early and accurate measurement of disease response and of relapse [5].

Despite the success of the original SFLC test, there are problems with the reliance on polyclonal antibodies which are difficult to produce and are very subject to batch to batch variation. In addition the sheep polyclonal antibody based tests (Freelite™) are restricted to use on expensive laboratory nephelometers and turbidimeters, have limited sensitivity and range of FLC level detection, along with antigen excess problems, where patients with exceedingly high levels of SFLC would be undetectable. The development of a second generation of FLC tests based on use of mouse monoclonal antibodies addresses the problems described above. Professor Mark Drayson led the development and clinical validation of the mouse monclonal antibody based, second generation SFLC tests over the last five years [6]. The use of monoclonal rather than polyclonal antibodies overcomes the long term problems of antibody production and batch to batch variation. Using competitive inhibition strategies overcomes the problem of antigen excess and greatly broadens the range of FLC levels that can be detected. The first of these tests to be described uses a flowcytometer platform with multiplexed beads enabling kappa and lambda FLC to be measured simultaneously, along with eight other immunoglobulin based analytes. The system has been adapted for nephelometry and turbidimetry platforms but also ELISAs allowing great flexibility on incorporation of the tests into different laboratory systems worldwide. Importantly the antibodies and the assay described above have been integrated into a point of care test which has been launched, bringing immediate improvement to patient diagnosis and management.

3. References to the research (indicative maximum of six references)

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6. Campbell JP, Cobbold M, Wang Y, Goodall M, Bonney SL, Chamba A, Birtwistle J, Plant T, Afzal Z, Jefferis R, **Drayson MT.** Development of a highly-sensitive multi-plex assay using monoclonal antibodies for the simultaneous measurement of kappa and lambda immunoglobulin free light chains in serum and urine. J Immunol Methods. 2013 Feb 3. *doi: 10.1016/j.jim.2013.01.014*

4. Details of the impact (indicative maximum 750 words)

The development of the freelight chain assays by Professors Bradwell and Drayson has had significant impact on the **clinical management of patients** with B cell lymphoid neoplasias and has led to changes in **clinical practice** and **commercial impact** through the success of the Binding Site and the formation of Serascience.

Clinical impact

The SFLC test has been adopted into worldwide clinical practice because of its importance in the diagnosis and management of myeloma, solitary plasmacytoma and light chain amyloidosis. This is evidenced by numerous review papers, national and international guidelines for the diagnosis and management of these diseases [1]. These guidelines continue to be updated as more scientific evidence becomes available about the use of the test. The SFLC test has been adopted as a prognostic marker for the whole range of B lymphoid cancers and premalignant conditions including monoclonal gammopathy of undetermined significance which occur in 3% of people aged >60 years [2]. More recently it has been adopted as a prognostic marker for survival in normal populations [2]. Use of the SFLC test in the MERIT trial and in the MRC Myeloma 11 trial has made it clear that the SFLC response to the first few weeks of anti-myeloma therapy reliably predicts final response [3]; this allows early identification of non-responders and change to a treatment more likely to be effective in identified individuals.

Impact on patients

The ability to measure serum FLC levels has had a major impact on the diagnosis and management of all patients with plasma cell dycrasias and B lymphoid lymphoma and leukaemia [4]. In non-secretory and light chain only myeloma and in many plasmacytoma and light chain amyloid patients SFLC tests allow diagnosis and detection of changes in disease activity that could not be achieved before. The second generation of these tests commercialised by Serascience is making these tests more widely available, in particular a point of care version, allowing patient management decisions to be made more reliably and immediately in the outpatient clinic, at the bedside or even at home [5].

Commercial impact

The Binding Site was formed in 1982 by a group of researchers from the University of Birmingham Medical School, to manufacture and supply antibodies, alongside developing a series of diagnostic tests. Following the development of the SFLC test the Binding Site incorporated the technology as a key part of its product portfolio. In October 2009 the Binding Site sold its autoimmune diagnostics business to the Werfen Group SA, based in Barcelona, Spain for £84 million in order to concentrate on Freelite which accounted for most of its other annual income and was growing at 40% per year [6]. The company's annual turnover in 2012 was £55 million and the company employs in excess of 550 people in the UK and abroad [7]. In 2012, 360,000 SFLC tests were sold each month in 90 countries, directly through offices in UK, USA, Canada, Germany, Austria, France, Spain, Italy, Czech Republic, Slovak Republic, Belgium, Netherlands and Luxembourg; and through a network of over 70 distributors [7].

In 2010, the Binding Site won The Queen's Award for Enterprise in the category International Trade, for its outstanding achievement in increasing export revenues by 74% to over £42

million/year in 3 years and selling more than 90% of its production overseas [8]. Aggregate exports over this period totalled £96 million. This growth is primarily driven by sales of Freelite®, which has grown to £36 million/year in 2012 [7]. New jobs have been created in sales, marketing, research and clinical education, both in the UK and internationally, to support this trade. In March 2011, the company moved its headquarters and 380 UK-based staff to larger premises in the centre of Birmingham. In April 2011 Nordic Capital Fund VII acquired the Binding Site for an undisclosed sum [9]. City analysts believe that sum to be in the region of £200 million [10].

A new University spinout company, SeraScience, was formed in 2011 to commercialise the monoclonal based SFLC assay. The company was formed as a result of significant investment from the University and UK based Healthcare company, Abingdon Health. The company has successfully developed a new range of "point of care tests" for FLC, which will mean that the SFLC assay can be undertaken within the clinic, providing rapid clinical assessment and immediate information for the patient and clinical teams. The new range was launched at the Biannual International Myeloma Conference in Kyoto, Japan in April 2013 [11]. The point of care test is manufactured by FORSITE in Yorkshire (a spinout company from DEFRA). The nephelometric and turbidimetric assays are being developed with Spinreact in Gerona, Spain.

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

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