Institution: University of Southampton		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: 01-10 Transforming standards of care and treatments for lymphoid cancers		
Period when the underpinning research was undertaken: 2000 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Peter Johnson	Professor	August 1998 – present
Francesco Forconi	Professor	October 2011 – present
Andrew Davies	Professor	January 2008 – present
Graham Packham	Professor	January 2000 – present
Andrew Steele	Associate Professor	March 2011 – February 2020
Terry Hamblin	Professor	August 1998 – February 2012
David Oscier	Professor	August 2012 – March 2015
Freda Stevenson	Professor	April 1997 – present (Honorary Fellow 1981–)
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Southampton (UoS) research has made seminal contributions to understanding the pathogenesis, prognosis and treatment of lymphoid malignancies. Investigating the structure and function of the tumour B-cell receptor provided the mechanistic rationale for the first tumour-eradicating cures in chronic lymphocytic leukaemia, and the development of targeted therapies that have achieved annual sales of more than GBP5 billion following regulatory approval during the impact period. Research into sequencing immunoglobulin genes resulted in new prognostic tools that were adopted as a standard of care by the NHS and in international guidelines for informing treatment selection. Leadership of large-scale clinical trials applying molecular phenotyping and functional imaging led to adoption of response-adapted therapy as the international standard of care in Hodgkin lymphoma and primary mediastinal lymphoma. It defined the optimum approach for antibody therapy in follicular lymphoma, resulting in further GBP billions of drug sales.

2. Underpinning research

University of Southampton research has provided novel insights into the pathogenesis, prognosis and treatment of two blood cancers: chronic lymphocytic leukaemia (CLL), the most common leukaemia with 3,700 new cases in the UK each year, and lymphoma, the fifth most prevalent cancer in the UK, with more than 14,000 new diagnoses annually. The new knowledge has been used to shape new standards of care internationally, develop new therapeutic drugs and optimise these treatments through clinical trials.

Chronic lymphocytic leukaemia

Stevenson and Hamblin were the first to identify two distinct immunogenetic subsets of CLL: Unmutated CLL (**U-CLL**) and Mutated CLL (**M-CLL**). U-CLL derives from B cells prior to entry to the germinal centre and carries no somatic mutations in the immunoglobulin (Ig) variable region genes. M-CLL derives from B cells that have traversed this site and accumulated mutations. U-CLL is the more aggressive subset, affecting 40% of CLL patients and having a mean survival of 8 years, compared to 25 years for M-CLL. Research [**3.1**, **3.2**] into biological processes underlying disease behaviour showed that the subsets differ in conformational structure and function of the immunoglobulin heavy chain variable region (IGHV) genes of the surface B-cell receptor (BCR). Patients with the more aggressive U-CLL were found to have higher levels of surface BCR engagement, and therefore responded preferentially to BCR-mediated signals. The discovery of this prognostic marker generated widespread interest in CLL among biologists and made possible new therapeutic strategies specifically targeting these signalling pathways.

Studies from 2011 [including under **G1**], led by Forconi and Packham, demonstrated that BCR signalling is vital to malignant B cells: CLL with high signal strength show more rapid disease progression [**3.3**]. Studies led by Steele between 2010 and 2020 explored the efficacy of different therapeutic treatments in interrupting this signalling. These included **ibrutinib**, a cell signal blocker that targets the Bruton's tyrosine kinase (BTK) protein [**3.4**], the dual Syk/JAK inhibitor cerdulatinib

and PI3-kinase inhibitor idelalisib. Recognition of the link between BCR signalling and apoptosis provided the rationale for clinical trials such as CLARITY (with Forconi as a leading contributor), which studied the efficacy of ibrutinib and venetoclax, a B-cell lymphoma 2 (BCL-2) inhibitor, when used in combination (details of the results in section 4).

Hodgkin and Non-Hodgkin Lymphoma (NHL)

Johnson has led international trials of new treatments for lymphoma over the last two decades. Beginning in 2008, the phase 3 RATHL trial [**G2**] in advanced Hodgkin lymphoma used FDG-PET imaging to modulate therapy and demonstrated the value of interim PET-CT scanning in guiding the intensification or de-escalation of chemotherapy to optimise the balance between efficacy and toxicity. The results were published in 2016 [**3.5**] (further details in section 4). Similar studies targeted primary mediastinal large B-cell lymphoma, a fast-growing type of NHL. Johnson and Davies led sequential phase 2 and 3 trials with the International Extranodal Lymphoma Study Group – IELSG 26 and IELSG 37 [**G3**] – to test the utility of PET imaging to guide the need for consolidation radiotherapy (details of the results in section 4).

Since 2015 Johnson and Davies have led a national collaborative group to apply molecular phenotyping in aggressive lymphomas [**G4**]. The phase 3 REMoDL-B trial [**G5**] was the first to demonstrate the value of real-time gene expression profiling to stratify treatment for diffuse large B-cell lymphoma [**3.6**; details in section 4]. The translation of biological insights in B-cell-directed antibody therapy from the Southampton group led to the international phase 3 GALLIUM trial to assess the efficacy of anti-CD20 antibody **obinutuzumab** in combination with chemotherapy for the treatment of follicular lymphoma, a type of NHL. Davies led the correlative laboratory studies and identified that obinutuzumab-based therapy resulted in longer progression-free survival than the previous standard of **rituximab**-based therapy [**3.7**; details in section 4]. In SABRINA, another phase 3 trial in follicular lymphoma, a team led by Davies showed that rituximab given subcutaneously was as effective and safe as intravenous rituximab (the existing standard), thereby increasing patient convenience and reducing healthcare costs (details in section 4).

3. References to the research

3.1 Lanham S, Hamblin TJ, Oscier DG, Stevenson FK & Packham G. Differential signaling via surface IgM is associated with VH gene mutational status and CD38 expression in chronic lymphocytic leukemia. Blood 2003; 101:1087-1093. https://doi.org/10.1182/blood-2002-06-1822

3.2 Krysov S, Potter KN, Mockridge CI, Coelho V, Wheatley I, Packham G, Stevenson FK. Surface IgM of CLL cells displays unusual glycans indicative of engagement of antigen in vivo. *Blood* 2010; 15(21):4198-205. https://doi.org/10.1182/blood-2009-12-254847

3.3 D'Avola A, Drennan S, Tracy I, Henderson I, Chiecchio L, Larrayoz M, Rose-Zerilli M, Strefford J, Plass C, Johnson PW, Steele AJ, Packham G, Stevenson FK, Oakes CC, Forconi F. Surface IgM expression and function are associated with clinical behavior, genetic abnormalities, and DNA methylation in CLL. Blood. 2016 Aug 11;128(6):816-26. https://doi.org/10.1182/blood-2016-03-707786

3.4 Drennan S*, Chiodin G*, D'Avola A, Tracy I, Johnson PI, Trentin L, Steele AJ, Packham G, Stevenson FK, Forconi F. Ibrutinib therapy releases leukemic surface IgM from antigen drive in chronic lymphocytic leukemia patients. Clin Cancer Res. 2019 Apr 15;25(8):2503-2512. https://doi.org/10.1158/1078-0432.CCR-18-1286.

3.5 Johnson P, Federico M, Kirkwood A, Fosså A, Berkahn L, Carella A, d'Amore F, Enblad G, Franceschetto A, Fulham M, Luminari S, O'Doherty M, Patrick P, Roberts T, Sidra G, Stevens L, Smith P, Trotman J, Viney Z, Radford J, Barrington S. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. N Engl J Med. 2016 Jun 23;374(25):2419-29. doi: https://doi.org/10.1056/NEJMoa1510093

3.6 Davies A, Cummin TE, Barrans S, Maishman T, Mamot C, Novak U, Caddy J, Stanton L, Kazmi-Stokes S, McMillan A, Fields P, Pocock C, Collins GP, Stephens R, Cucco F, Clipson A, Sha C, Tooze R, Care MA, Griffiths G, Du MQ, Westhead DR, Burton C, Johnson PWM. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. Lancet Oncol. 2019 May;20(5):649-662. https://doi.org/10.1016/S1470-2045(18)30935-5

3.7 Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017 Oct 5;377(14):1331-1344. https://doi.org/10.1056/NEJMoa1614598

Key underpinning grants

The research was supported by programme grants from Cancer Research UK and Bloodwise; project grants from charities and foundations; clinical trial funding from Cancer Research UK, and collaborations with pharma partners totalling over GBP30m.

G1 Cancer Research UK: B-cell receptor signalling in B-cell malignancies: Identifying strategies for optimal therapeutic intervention based on common and distinct responses, 2017-2022, GBP**1.5**m
G2 Cancer Research UK: RATHL: A randomised trial to assess Response Adapted Therapy using FDG-PET imaging in patients with advanced Hodgkin Lymphoma, 2008-2016, GBP797,000
G3 Cancer Research UK: IELSG 37: A randomised phase III comparative study assessing the role of involved mediastinal radiotherapy after chemotherapy in patients with primary mediastinal B-Cell lymphoma, 2013-2023, GBP247,533
G4 Bloodwise 15002: Precision medicine for aggressive lymphoma, 2015-2018, GBP2.3m
G5 Janssen-Cilag: REMoDL-B: A Randomised Evaluation of Molecular guided therapy for Diffuse Large B-cell Lymphoma with Bortezomib, 2011-2017, GBP1.14m

Awards

Southampton's research was recognised between 2014 and 2018 with four international prizes in Haematology for Stevenson: *Jean Bernard Life Time Achievement Award:* European Haematology Association 2014; *Rai-Binet Medal:* International Workshop on Chronic Lymphocytic Leukemia 2015; *Lifetime Achievement Award:* British Society of Haematology 2020, and the *The Henry M Stratton Medal:* American Society of Hematology 2018. The citation for the latter noted that the research '*currently serves as a major indicator of prognosis and has also offered targets for drug therapies that are now demonstrating clinical efficacy*'.

4. Details of the impact

Research at Southampton has developed new understanding around the molecular classification and pathogenetic processes of lymphoid malignancies. This led to the development of new prognostic tools to inform the timing of early-stage treatment, regulatory approval of 'blockbuster' targeted therapies and changes to standards of care via large-scale, international clinical trials.

New prognostic tools and approaches to optimise early-stage CLL/lymphoma treatment

Patients with U-CLL have a worse prognosis than those with M-CLL in all studies investigating the significance of IGHV mutational status, and this classification, first described and elucidated by Southampton [**3.1**, **3.2**], is the dominant prognostic factor out of all those studied. This was confirmed in a 2016 meta-analysis of data from 4,933 patients with early-stage CLL, leading to the publication of an international prognostic index for CLL patients: CLL-IPI [**5.1**]. This tool stratifies CLL patients into four risk categories (ensuring high-risk patients are identified early) and provides a score to estimate prognosis and time to first treatment. It was published on MDCalc [**5.2**], the most broadly used medical reference for clinical decision tools (including by 65% of US physicians). The National Comprehensive Cancer Network (NCCN) updated its clinical practice guidelines in 2020 [**5.2**]; it recommended IGHV mutational status analysis for CLL prior to treatment if not done at diagnosis, and repetition of the test when considering treatment with chemoimmunotherapy instead of novel BCR inhibitors. In 2018 IGHV analysis was listed as a standard in NHS England's Genomic Test Directory for cancer [**5.2**].

Evidence from the UoS-led, phase 3 REMoDL-B trial [**3.6**, **G5**] identified a subgroup of diffuse large B-cell lymphoma (DLBL), *molecular high-grade (MHG) lymphoma*, determined by gene expression profiling, with a clearly inferior prognosis (progression-free survival of 37% compared to 72% from a study of 928 patients) [**5.3**]. Published in 2019, the results identified a new patient group that can benefit from intensified chemotherapy or novel targeted therapies [**5.3**].

Development and approval of novel therapies targeting BCR signalling pathways

A significant translational impact arising from Southampton's insights into the centrality of BCR signalling as a prognostic marker [**3.1**, **3.2**] is the development and regulatory approval of new

targeted therapies for CLL. The first-in-class ibrutinib, marketed as Imbruvica (AbbVie and Janssen), and the second generation acalabrutinib, marketed as Calquence (Astrazeneca and Acerta), specifically target BCR signalling pathways. Ibrutinib was first approved for CLL by the US FDA in 2014 and by NICE in 2017 for use on the NHS. Acalabrutinib received FDA approval in 2017 and EU approval in 2020. The clinical/patient benefits and economic impact of these BCR-inhibitor therapies, initially derived from Southampton's observations, has been vast, transforming CLL treatment by challenging the prior dominance of chemoimmunotherapy regimens. Annual sales revenues of ibrutinib alone reached USD7.24bn (GBP5,460,000,000) in 2019, with CLL the most profitable indication, while sales of acalabrutinib were USD522m (GBP382,000,000) in 2020 [**5.4**].

Clinical trials have demonstrated the significant clinical benefit of targeting BCR signalling using ibrutinib-based regimens over immunochemotherapy, particularly for the U-CLL group. In a phase 3 trial of previously untreated CLL receiving either ibrutinib-based therapy or standard chemoimmunotherapy, ibrutinib-based therapy resulted in much better progression-free survival: 90.7% vs. 62.5% at 3 years; hazard ratio for progression or death at 3 years, 0.26; 95% CI, 0.14-0.50 [**5.5**]. Southampton was the leading centre in the phase 2 CLARITY trial, reporting the remarkable efficacy and low toxicity of ibrutinib in combination with BH3-mimetic venetoclax in patients with recurrent CLL. This combination has shown unprecedented efficacy, with eradication of the disease in more than 60% of patients. The study marked the first demonstration that combining BCR targeting with BH3 mimetics can result in molecular eradication of CLL [**5.6**]. In Diffuse Large B Cell Lymphoma, Acerta invested GBP800,000 for Southampton to carry out the phase 1/2 ACCEPT trial of acalabrutinib in combination with standard chemoimmunotherapy (2018) and Astrazeneca invested GBP3,200,000 in Southampton-led phase 2 trial REMoDL-A to to establish whether this combined approach may become the new standard of care [**5.7**].

Changing standards of care and validating new treatments through large-scale trials

Southampton has led practice-changing trials that have demonstrated the value of FDG-PET imaging in lymphoma therapy. The phase 3 RATHL trial [**3.5**, **G2**] showed that negative PET imaging after the first 2 months of treatment in **advanced Hodgkin lymphoma** could predict 5-year progression-free survival of 82%. For this group, the RATHL findings demonstrated that incidence of lung toxicity could be reduced without compromising cure rates by omitting the drug bleomycin, a treatment that had been used in chemotherapy for 30 years but which can cause long-term lung damage. This finding translated into changes to clinical practice, as recommended in NHS guidelines, the 2018 European Society for Medical Oncology (ESMO) Guidelines and the US National Comprehensive Cancer Network (NCCN) guidelines [**5.8**]. The overall RATHL results showed 5 year survival of 95%, leading to adoption of treatment modulated according to PET results in the UK, wider Europe and US [**5.8**].

In **primary mediastinal lymphoma**, the international IELSG 26 trial of PET imaging led by Southampton showed 95% 5 year survival. This defined the response criteria to be used in this illness (cited in 2016 ESMO guidelines [**5.9**]). In **follicular lymphoma**, the GALLIUM study [**3.7**], for which Southampton led the correlative laboratory studies, demonstrated that progression-free survival for patients treated with the novel anti-CD20 antibody obinutuzumab (80%) was superior to that seen with the previous standard rituximab (73%) when given with chemotherapy. This changed practice internationally. Citing the Gallium results, the US FDA and the EU approved obinutuzumab (tradename: Gazyva in US; Gazyvaro in Europe; Roche) as a treatment, in combination with chemotherapy, for follicular lymphoma in 2017. In March 2018 NICE recommended obinutuzumab '*as an option for untreated advanced follicular lymphoma in patients at higher risk*' [**5.10**]. This led to significant commercial impact too. As an indication, when obinutuzumab was approved with bendamustine for follicular lymphoma in 2016, the media reported a likely sales uplift for Roche of USD500m to USD1bn [**5.11**]. In phase 3 UoS-led trial SABRINA, the maintenance antibody therapy for follicular lymphoma – rituximab (marketed by Roche as MabThera in Europe and Rituxan in US) – was shown to be equally effective and safe when given subcutaneously as intravenously (published in *Lancet Haematology*, 2017 [**5.12**]). This was shown to increase convenience for patients and reduce healthcare costs by 25%, from EUR1,956 per cycle to EUR1,460, or a total of EUR6,000 for the full course of treatment [**5.13**]. As a direct result of SABRINA, the subcutaneous version of rituximab received approval for common forms of NHL from the EU in 2014 and the US in 2017. In 2014 NICE cited SABRINA as providing key evidence for its use [**5.14**]. The commercial

impact was significant; as an indication, rituximab has been one of Roche's best-selling drugs, with USD7.39bn (GBP5,010,000,000) in global sales in 2015 [**5.15**] and in 2016 Roche said the subcutaneous version of MabThera had secured an average 35% market share [**5.16**].

5. Sources to corroborate the impact

5.1 International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016 Jun;17(6):779-790. https://doi.org/10.1016/S1470-2045(16)30029-8

5.2 Corroboration of the clinical impact of IGHV mutational status analysis for CLL:

- CLL-IPI available via MDCalc: https://www.mdcalc.com/international-prognostic-index-chronic-lymphocytic-leukemia-cll-ipi;
- NCCN Clinical Practice Guidelines in Oncology: CLL/SLL, Version 4.2020 (available as PDF);
- NHS England National Genomic Test Directory for cancer: https://www.england.nhs.uk/publication/national-genomic-test-directories/

5.3 Molecular High-Grade B-Cell Lymphoma: Defining a Poor-Risk Group That Requires Different Approaches to Therapy. J Clin Oncol. 2019 Jan 20;37(3):202-212. https://doi.org/10.1200/JCO.18.01314

5.4 Corroboration of the commercial revenues associated with ibrutinib and acalabrutinib: https://www.fiercepharma.com/special-report/imbruvica-top-10-drugs-by-sales-increase-2020; https://news.cision.com/astrazeneca/r/azn--full-year-2020-results,c3284624

5.5 Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019 Aug 1;381(5):432-443. https://doi.org/10.1056/NEJMoa1817073

5.6 Ibrutinib Plus Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia: The CLARITY Study. J Clin Oncol. 2019 Oct 20;37(30):2722-2729. https://doi.org/10.1200/JCO.19.00894

5.7 Corroboration of investment by the pharma industry in UoS-led clinical trials for acalabrutinib: https://clinicaltrials.gov/ct2/show/NCT03571308; https://clinicaltrials.gov/ct2/show/NCT04546620

5.8 Examples of international guidelines changed by the RATHL trial findings:

- Haematology Cancer Clinical Trial Guidelines, Northern Cancer Alliance (2020): https://www.northerncanceralliance.nhs.uk/wp-content/uploads/2020/09/Haematology-Cancer-Clinical-Guidelines-S12-Management-of-Classical-Hodgkin-Lymphoma-2-3.pdf (RATHL cited 8 times);
- Pan-London Haemato-Oncology Clinical Guidelines (2020): https://www.kingshealthpartners.org/assets/000/003/344/Pan_London_Hodgkin_Guidelines_Jan_2020_original.pdf (RATHL cited 13 times);
- Hodgkin Lymphoma, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology: https://jnccn.org/view/journals/jnccn/18/6/article-p755.xml (RATHL cited 4 times);
- Hodgkin Lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: https://www.annalsofoncology.org/article/S0923-7534(19)31690-4/pdf (RATHL cited 3 times).

5.9 Extranodal Diffuse Large B-Cell Lymphoma and Primary Mediastinal B-Cell Lymphoma: ESMO Clinical Practice Guidelines. Ann Oncol (2016) 27 (suppl 5): v91-v102 (Cites IELSG 26/37). https://doi.org/10.1093/annonc/mdw175

5.10 Obinutuzumab for untreated advanced follicular lymphoma. NICE Technology appraisal guidance [TA513]: https://www.nice.org.uk/guidance/ta513/chapter/1-Recommendations

5.11 Corroboration of the commercial impact of Obinutuzumab approvals for Roche: http://www.pmlive.com/pharma_news/roches_gazyvaro_cleared_for_follicular_lymphoma_in_europe_1041358

5.12 Lancet Haematol. 2017 Jun;4(6):e272-e282 https://doi.org/10.1016/S2352-3026(17)30078-9.

5.13 Comparative Cost Analysis Of Intravenous And Subcutaneous Administration Of Rituximab In Lymphoma Patients. ClinicoEcon Outcomes Res. 2019 Nov 18;11:695-701. https://doi.org/10.2147/CEOR.S212257

5.14 NICE evidence summary for subcutaneous rituximab maintenance: https://www.nice.org.uk/advice/esnm46/chapter/full-evidence-summary#evidence-review-2

5.15 https://www.fiercepharma.com/special-report/rituxan-1

5.16 https://www.outsourcing-pharma.com/Article/2016/07/25/Roche-getting-under-the-skin-of-biosimilar-competition