**Institution:** University of Southampton

**Unit of Assessment:** 01 Clinical Medicine

**Title of case study:** 01-07 Delivering clinical and commercial impact through novel monoclonal antibody cancer treatments

**Period when the underpinning research was undertaken:** 2000 – 2018

**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: |
|---|---|---|
| Martin Glennie | Professor in Immunochemistry | April 1983 – September 2018 |
| Mark Cragg | Professor in Experimental Cancer Biology | October 1997 – present |
| Stephen A Beers | Professor of Immunology and Immunotherapy | December 2002 – present |
| Sean H Lim | Associate Professor | January 2009 – present |
| Aymen Al-Shamkhani | Professor in Immunology | August 1998 – present |
| Juliet Gray | Associate Professor | September 2006 – present |
| Ali Roghanian | Lecturer | April 2009 – present |
| Peter W. M Johnson | Professor of Medical Oncology | August 1998 – present |
| Andrew Davies | Professor of Haematological Oncology | January 2008 – present |

**Period when the claimed impact occurred:** August 2013 – December 2020

**Is this case study continued from a case study submitted in 2014?** Y

## 1. Summary of the impact

University of Southampton research has underpinned the clinical development of anti-cancer monoclonal antibodies (mAb), including anti-CD20, anti-CD40, anti-CD27 and anti-FcγRIIB (CD32B). The most advanced are two anti-CD20 mAb: ofatumumab (trade name Arzerra) and obinutuzumab (trade name Gazyva), used to treat B-cell diseases such as chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL).

**Since August 2013:**

- Approvals of **ofatumumab (Arzerra)** for CLL grew from 27 countries to more than 60. It received FDA approval for two specific CLL treatments, generated more than GBP200m in revenue and been the subject of an acquisition by Novartis worth up to USD1bn. It has been used in 99 clinical trials in an increasing range of diseases, now including lymphoma, rheumatoid arthritis and multiple sclerosis (with positive phase III clinical trial data for the latter).
- **Obinutuzumab (Gazyva)** has been approved for use as a frontline treatment as monotherapy for FL and in combination with ibrutinib for CLL. It has generated revenues of CHF2.2bn (GBP1.7bn) and has been used in 175 clinical trials for multiple diseases, leading to an additional FDA designation for treatment of lupus nephritis.
- The patented **anti-FcγRIIB** research was collaboratively developed and licensed to a Swedish biotech firm, resulting in a clinical trial programme that led to a USD95m (GBP73m) commercial agreement.

## 2. Underpinning research

The University of Southampton has a distinguished history of research in immunotherapy, carrying out fundamental research into understanding the structure and function of antibodies, developing new therapeutic reagents and translating them into clinical practice. In 2002, Professors Martin Glennie and Mark Cragg discovered two distinct types of CD20 antibodies (CD20 being a marker for B cells and crucial in lymphoma diagnosis). The research [**3.1**] showed how mAbs bound to CD20 influenced the potency of the antibodies in vitro and in vivo. Papers published in *Blood* in 2003 and 2004 shaped the pharmaceutical industry's development of a new generation of drugs to target B cells for treating blood cancers like non-Hodgkin's lymphoma (NHL).

In 2004, Glennie joined Danish biotech firm Genmab for a six-month sabbatical, during which he led a small research team that developed a next generation CD20 mAb capable of replacing the first-in-class 'gold standard' therapeutic antibody rituximab. Glennie's team at the University went on to create and patent ofatumumab, which, unlike rituximab, is a human antibody, more potent and binds to a unique epitope containing both the small and large loops of the CD20 molecule on B cells [**3.1**]. Cragg and Glennie, alongside Professor Stephen Beers, continued to explore the relative potency of Type I and II mAbs and went on to show Type II reagents were five times more effective than rituximab in treating NHL [**3.2**]. This discovery spurred the development of a third generation anti-CD20 mAb, Roche's type II drug, obinutuzumab (GA101).

Subsequent work by Beers and Cragg showed that Type I but not Type II mAbs are rapidly internalised from the cell surface and that this results in consumption of the mAb, reducing their efficacy. Dr Sean Lim, Glennie and Cragg demonstrated that this internalisation is precipitated by the expression of the inhibitory Fc gamma receptor (FcγRIIB/CD32B) [**3.3**]. The utility of high FcγRIIB expression as a poor prognosis biomarker has so far been established in subsequent studies. This work provided a novel mechanism of mAb-mediated resistance and was a key output from the Cragg FcγR programme [**A**]. The group developed these findings alongside Professor Björn Frendeus at a Swedish Biotech (BioInvent International), developing blocking FcγRIIB mAb that could overcome resistance from the inhibitory FcγRIIB and potentiate the killing of normal and malignant B cells with rituximab and other direct targeting therapeutic mAb (obinutuzumab and alemtuzumab) [**3.4**]). This internalisation of rituximab was also observed on B cells from autoimmune patients (RA and Lupus) and was correlated with impaired B cell depletion. Thus, it was considered that slower-internalizing type II mAb (such as Obinutuzumab) should be considered as alternative B cell-depleting agents for the treatment of RA and Lupus [**3.5**].

In another research strand Glennie and his team developed immunostimulatory antibodies, which trigger the body's immune system to provide long-lasting cancer protection, by targeting receptors on cells of the immune system. The team showed, using CD40 as a paradigm, that this approach provided protection for a range of tumour types and boosted cancer vaccines, opening up the development of a new class of immunostimulatory drugs. These receptor targets were explored within two large CRUK programmes [**B**]. Further work has revealed key findings for the field in terms of the FcγR dependence of these mAb as well as the unique contribution of epitope and isotype to deliver powerful agonism [**3.6**], as well as to combine with direct targeting antibodies such as anti-CD20 mAb [**3.7**]. This expertise has led to interaction with multiple biotech and pharma companies in order to deliver therapeutic mAb into the clinic [**C**].

## 3. References to the research

**3.1** Teeling JL, Mackus WJM, Wiegman LJJM, van den Brakel JHN, Beers SA, French RR, van Meerten T, Ebeling S, Vink T, Slootstra JW, Parren PWHI, Glennie MJ, van den Winkel JGJ. (2006) The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. Journal of Immunology. 177(1): 362-371. https://doi.org/10.4049/jimmunol.177.1.362

**3.2** Beers SA, French RR, Chan HTC, Lim SH, Jarrett TC, Vidal RM, Wijayaweera SS, Dixon SV, Kim H, Cox KL, Kerr JP, Johnston DA, Johnson PWM, Verbeek JS, Glennie MJ and Cragg MS (2010). Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. Blood. 115(25):5191-201. https://doi.org/10.1182/blood-2010-01-263533

**3.3** Lim SH, Vaughan AT, Ashton-Key M, Williams EL, Dixon SV, Chan HT, Beers SA, French RR, Cox KL, Davies AJ, Potter KN, Mockridge CI, Oscier DG, Johnson PW, Cragg MS, Glennie MJ. (2011) Fc gamma receptor IIb on target B cells promotes rituximab internalization and reduces clinical efficacy. Blood. 118(9):2530-40. https://doi.org/10.1182/blood-2011-01-330357

**3.4** Roghanian A, Teige I, Mårtensson L, Cox KL, Kovacek M, Ljungars A, Mattson J, Sundberg A, Vaughan AT, Shah V, Smyth NR, Sheth B, Chan HT, Li ZC, Williams EL, Manfredi G, Oldham RJ, Mockridge CI, James SA, Dahal LN, Hussain K, Nilsson B, Verbeek JS, Juliusson G, Hansson M, Jerkeman M, Johnson PW, Davies A, Beers SA, Glennie MJ, Frendéus B, Cragg MS. (2015) Antagonistic human FcγRIIB (CD32B) antibodies have anti-tumor activity and overcome resistance to antibody therapy in vivo. Cancer Cell. 27(4):473-88. https://doi.org/10.1016/j.ccell.2015.03.005

**3.5** Reddy V, Cambridge G, Isenberg DA, Glennie MJ, Cragg MS, Leandro M. (2015) Internalization of rituximab and the efficiency of B Cell depletion in rheumatoid arthritis and

systemic lupus erythematosus. Arthritis Rheumatol. 67(8):2046-55. https://doi.org/10.1002/art.39167
**3.6** Yu X, Chan HTC, Orr CM, Dadas O, Booth SG, Dahal LN, Penfold CA, O'Brien L, Mockridge CI, French RR, Duriez P, Douglas LR, Pearson AR, Cragg MS, Tews I, Glennie MJ, White AL (2018) Complex Interplay between Epitope Specificity and Isotype Dictates the Biological Activity of Anti-human CD40 Antibodies. Cancer Cell. 33(4):664-675. https://doi.org/10.1016/j.ccell.2018.02.009
**3.7** Turaj AH, Hussain K, Cox KL, Rose-Zerilli MJJ, Testa J, Dahal LN, Chan HTC, James S, Field, VL, Carter MJ, Kim HJ, West JJ, Thomas LJ, He LZ, Keler T, Johnson PWM, Al-Shamkhani A, Thirdborough SM, Beers SA, Cragg MS, Glennie MJ, Lim SH (2017) Antibody Tumor Targeting is Enhanced by CD27 Agonists through Myeloid Recruitment. Cancer Cell. 32(6):777-791. https://doi.org/10.1016/j.ccell.2017.11.001

**Grants**
**A.** Bloodwise Specialist Programme: 2013 – 2017. Optimising antibody therapy for Lymphoma. PI: Cragg. CO PIs: Ashton-Key, Beers, Strefford, Glennie, Johnson & Davies. GBP1.1m plus associated clinical trial 2015 – 2020 Davies, Frendeus and Cragg. Bloodwise First in Man Trial grant BI-1206-01: A Phase I/IIa Study with BI-1206, an antibody to Fc gamma receptor IIB (Fc RIIB), and rituximab in patients with CD32+ B cell malignancy GBP0.5m = GBP1.6m in total.
**B.** CRUK funding for antibody development projects (including three programmes). PIs: Glennie, Cragg, Al-Shamkhani, Beers, and Lim. 2015 – present: ~ GBP8.3m.
**C.** Biotech funding for Glennie, Beers, Lim, Roghanian, Cragg and Shamkhani as PIs. 2015 – present: ~ GBP5m.

## 4. Details of the Impact

Biologics are large biomolecular drugs, now ubiquitous in the treatment of human disease ranging from cancer to autoimmune disorders, comprising half of the top-ten blockbuster pharmaceuticals and grossing around USD30billion/year worldwide. Eighty per cent of these biologics are mAb. Researchers at Southampton have played a leading role in bringing two types of anti-CD20 mAb from lab to clinic to treat B cell disorders and inspiring the development of a new class of immunostimulatory mAb to treat cancer.

### Clinical and commercial impact of ofatumumab (Arzerra)

Ofatumumab, marketed under the name Arzerra, was developed and patented by Glennie and colleagues in 2004 and licensed from Genmab to GSK in 2006. It was approved by the FDA in 2009 and the EU in 2011 for the most prevalent form of leukaemia, CLL, after Southampton researchers proved it was able to kill target cells resistant to similar drugs (covered in REF2014).

Globally, leukaemia accounts for some 300,000 new cases each year with 222,000 deaths, giving Ofatumumab a wide reach in its first approved indication. In 2016 it was approved by the FDA as a treatment for recurrent or progressive CLL [**5.1**] and for relapsed CLL in combination with Fludarabine and Cyclophosphamide [**5.2**]. Since August 2013 it has been assessed in 99 clinical trials [**5.3**], including in autoimmune conditions such as rheumatoid arthritis, which affects more than 400,000,000 patients worldwide, and multiple sclerosis (MS), which affects 2,100,000 patients worldwide. In MS, exciting phase 3 data (involving 1,882 patients), published in August 2019, was observed (ASCLEPIOS I and II trials), showing that ofatumumab reduced the annualised relapse rate over current treatment (teriflunomide) in patients with relapsing forms of MS [**5.4**].

Ofatumumab's commercial impact since August 2013 has been highly significant, achieving sales revenues of more than GBP200,000,000, translating to GBP41,000,000 in royalties for Genmab [**5.5**]. GSK's rights to its use in cancer were acquired by Novartis in August 2015 in a deal worth up to USD1billion (GBP6,500,000,000) [**5.6**].

### Clinical and commercial impact of obinutuzumab (Gazyva)

The same programme of Southampton research was instrumental in the selection of a second anti-CD20 mAb, obinutuzumab (GA101, trade name Gazyva). The Head of Oncology at Roche Pharmaceutical Research and Early Development said: "The characterisation of type I and II CD20 mAb by the Southampton Lab and their clear demonstration of increased potency by type II reagents was an important factor in our decision to select GA101 for clinical development.

Their pre-clinical work has now been validated in several phase 3 trials and has supported our expansion to new diseases such as lupus" [**5.7**].

Gazyva was the first type II anti-CD20 mAb to be humanised for clinical work. Capable of killing a significantly higher number of cancerous cells than its type I counterpart, and being less subject to internalisation, it was assessed in several multicentre phase III trials involving Southampton lead investigators (e.g. Professor Andrew Davies), head-to-head against rituximab in FL and CLL. Gazyva was shown to provide significantly better responses than rituximab in combination with chlorambucil in CLL and in previously untreated advanced FL patients. As a consequence of this phase III study, the drug was FDA-approved for CLL in November 2013 [**5.8**] and FL in November 2017 [**5.9**], changing frontline clinical treatment of these diseases. It was also approved as the first Non-Chemotherapy Combination Regimen for Treatment-Naïve Patients with CLL, alongside ibrutinib in 2019 [**5.10**].

Since August 2013 there have been 68 clinical trials assessing Gazyva [**5.11**] in multiple settings, from post-transplant lymphoproliferative disorder and renal disease, to lupus where the FDA granted Breakthrough Therapy Designation for adults with lupus nephritis based on data from the phase II Nobility study [**5.12**]. In adult patients with proliferative lupus nephritis, Gazyva, in combination with standard of care, demonstrated enhanced efficacy compared to placebo plus standard of care alone in achieving complete renal response at one year.

The commercial impact has again been highly significant. Sales of Gazyva have grown considerably year-on-year since its FDA approval in November 2013, reaching CHF632m (GBP515,000,000) in 2020 and giving a total of CHF2.2bn (GBP1,700,000,000) over the period. [**5.13**]

**Clinical and commercial impact of work involving FcγRIIB mAbs**

The added insight from the Southampton team also revealed a novel and unexpected mechanism of resistance for CD20 (and other) mAb through the inhibitory FcγRIIB. The pre-clinical work and partnership with BioInvent International led to the development and characterisation of new fully human FcγRIIB mAb and a first-in-human trial [**5.14**] assessing its safety and utility in B cell malignancies with promising safety and therapeutic profiles in patients.

Patents around this biology have been granted and licensed to BioInvent [**5.15**]. These approaches are also being explored in mantle cell lymphoma and in solid tumours in combination with checkpoint inhibitors such as anti-PD-1 including with a new FcγRIIB reagent (BI-1607) following pre-clinical evidence and mechanistic insight from Southampton. This work led to a deepened association with BioInvent, leading to GBP3,140,000 in funding since 2014. An example of the significant commercial impact arising from this clinical trial programme came in October 2020 when BioInvent and US-based CASI Pharmaceuticals announced an exclusive licensing agreement worth up to USD95m (GBP73,000,000) for the development and commercialisation of novel anti-FcγRIIB antibody, BI-1206, in mainland China, Taiwan, Hong Kong and Macau. [**5.15**]

Promising results from the phase 1/2a clinical trial of BI-1206, in combination with rituximab, for relapsed NHL were published in *Blood* in November 2020 [**5.16**]. In total 15 NHL patients were recruited to the Phase I trial, all of whom were late stage and had failed conventional treatments, including several lines of rituximab-containing therapies. Notably, of the 9 patients who completed the induction cycle, 6 patients showed either complete or partial responses several of which are still ongoing. Remarkably, two patients achieved a complete response, which continues to be sustained 12 and 24 months later. [**5.14**]

**Clinical and commercial impact of the Southampton immunomodulatory antibody programme**

Under its immunomodulatory antibody programme, Southampton has developed a range of novel immunostimulatory mAb (CD40, CD27, OX40, 4-1BB) and protein engineering approaches to boost their activity. This led to the discovery and patenting of several of these reagents, including a novel target CD27, immunostimulatory mAb which can promote anti-cancer immunity [**5.17**]. This intellectual property is licensed exclusively to Celldex Therapeutics, USA, who have undertaken several trials with a fully human mAb, varlilumab in combination with nivolumab/atezolizumab/ipililumab etc. in haematological and solid malignancies [**5.18**].

## 5. Sources to corroborate the impact

**5.1** FDA approval of Arzerra as an extended treatment for recurrent or progressive CLL (January 2016). https://www.drugs.com/newdrugs/genmab-announces-u-s-fda-approval-arzerra-ofatumumab-extended-recurrent-progressive-cll-4327.html

**5.2** FDA approval of Arzerra in combination with Fludarabine and Cyclophosphamide for Relapsed CLL (August 2016). https://www.drugs.com/newdrugs/genmab-announces-u-s-fda-approval-arzerra-ofatumumab-combination-fludarabine-cyclophosphamide-4425.html
**5.3** Clinical trials of ofatumumab between August 2013 and December 2020 https://www.clinicaltrials.gov/ct2/results?term=ofatumumab&strd_e=12%2F31%2F2020&prcd_s=01%2F08%2F2013
**5.4** Positive phase 3 data in MS: https://www.novartis.com/news/media-releases/novartis-ofatumumab-demonstrates-superiority-versus-aubagio-two-head-head-phase-iii-multiple-sclerosis-studies
**5.5** Genmab annual reports 2013-2019 (extracts and calculations supplied).
**5.6** Sale of Arzerra to Novartis: http://www.pmlive.com/pharma_news/novartis_buys_rights_to_gsks_arzerra_in_ms_for_$1bn_805063
**5.7** Corroborating statement from Head of Roche Glycart AG, Switzerland.
**5.8** FDA approves Gazyva for CLL (November 2013) https://www.roche.com/media/releases/med-cor-2013-11-01.htm
**5.9** FDA Approves Gazyva for Previously Untreated Advanced Follicular Lymphoma (Aug 2017) https://www.drugs.com/newdrugs/fda-approves-genentech-s-gazyva-previously-untreated-advanced-follicular-lymphoma-4643.html
**5.10** FDA Approves Imbruvica (ibrutinib) Plus Obinutuzumab as First Non-Chemotherapy Combination Regimen for Treatment-Naïve Patients with Chronic Lymphocytic Leukemia https://www.drugs.com/newdrugs/fda-approves-imbruvica-ibrutinib-plus-obinutuzumab-first-non-chemotherapy-combination-regimen-na-ve-4906.html (January, 2019)
**5.11** Clinical trials of Obinutuzumab between August 2013 and December 2020 https://www.clinicaltrials.gov/ct2/results?term=obinutuzumab&strd_s=08%2F01%2F2013&prcd_e=12%2F31%2F2020
**5.12** FDA grants Breakthrough Therapy Designation for Roche's Gazyva (obinutuzumab) in Lupus Nephritis https://www.roche.com/media/releases/med-cor-2019-09-18.htm (Sept 2019)
**5.13** Roche annual results 2013-2020 (extracts and calculations supplied).
**5.14** https://clinicaltrials.gov/ct2/show/NCT02933320
**5.15** Corroborating statement from BioInvent
**5.16** M Jerkeman et al. (2020) 17-BI-1206-02 Phase 1/2a Clinical Trial of BI-1206, a Monoclonal Antibody to Fcgriib, in Combination with Rituximab in Subjects with Indolent B-Cell Non-Hodgkin Lymphoma That Has Relapsed or Is Refractory to Rituximab. Blood. 136 (Supplement 1): 36-37. https://doi.org/10.1182/blood-2020-140219
**5.17** Patent applications of reagents including CD40 and CD27:
**a)** Human Therapies Using Chimeric Agonistic Anti-Human CD40 Antibody; MJ Glennie: https://worldwide.espacenet.com/patent/search?q=pn%3DUS2009074711A1
**b)** Immunomodulatory Antibodies; A Al-Shamkhani, HT Chan, MS Cragg, RR French, MJ Glennie, JE Willoughby: https://worldwide.espacenet.com/patent/search?q=pn%3DUS2018327504A1
**c)** Cancer And B-Cell Related Disease Therapy; A Al-Shamkhani, MS Cragg, MJ Glennie, SH Lim: https://worldwide.espacenet.com/patent/search?q=pn%3DUS2019169306A1
**d)** Human Immune Therapies Using A CD27 Agonist In Combination With Another Immune Agonist To Treat Cancer; A Al-Shamkhani, MJ Glennie, AL Tutt: https://worldwide.espacenet.com/patent/search?q=pn%3DUS2018273631A1
**5.18** Clinical trials with anti-CD27 mAb from Celldex Therapeutics run under a license from the University of Southampton http://www.clinicaltrials.gov/ct2/results?term=CDX-1127+&Search=Search; https://www.celldex.com/pipeline/cdx-1127.php