

Impact case study (REF3b)

Institution: University of Southampton
Unit of Assessment: 01 Clinical Medicine
Title of case study: 01-20 Treatment of cancer with monoclonal antibodies
<p>1. Summary of the impact</p> <p>Southampton research underpins the clinical development of a new class of anti-cancer monoclonal antibodies (mAb), such as anti-CD40, anti-CD27 and anti-CD20. The most advanced is a next generation, fully human drug, ofatumumab (commercialised by GlaxoSmithKline/Genmab; trade-name Arzerra) approved in Oct 2009 to treat advanced chronic lymphocytic leukaemia. Its approval was based on a 42% response rate in patients who had failed current 'best in class' treatment. Arzerra is now a multi-million dollar drug, launched in 26 countries (and growing) and is being used in 19 on-going clinical trials worldwide for diseases ranging from lymphoma to rheumatoid arthritis and multiple sclerosis. Southampton's work has inspired follow-on funding from government and industry in excess of £12m.</p>
<p>2. Underpinning research</p> <p>The University of Southampton has a long and distinguished history of research into the underlying immunological causes of disease. Work in this field began in the 1970s when Professors George and Freda Stevenson identified the first antibodies to treat B-cell lymphomas. They received the Armond Hammer prize for cancer treatment in 1982.</p> <p>Since the early 1980s Martin Glennie, Professor of Immunochemistry (1982-present), and his team have continued research into understanding the structure and function of antibodies, developing new therapeutic treatments and translating them into clinical practice. In 2002 Glennie and Mark Cragg, Professor of Experimental Cancer Research (2004-present), discovered two types of anti-CD20 antibody (CD20 being a marker for B cells and crucial in lymphoma diagnosis). The research [3.1] showed how mAbs bound to the CD20 within the surface membrane influenced the potency of the antibodies in vitro and in vivo. Papers published in <i>Blood</i> in 2003 and 2004 shaped the pharmaceutical industry's development of a new generation of drugs to treat blood cancers like non-Hodgkin's lymphoma.</p> <p>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 anti-CD20 mAb capable of replacing the drug rituximab, the 'gold standard' therapeutic treatment for B-cell lymphomas. Rituximab is a part human, part mouse chimeric antibody, which is not ideal for certain patients who become unresponsive due to drug resistance. Glennie's team went on to create and patent ofatumumab which, unlike rituximab, is fully human, more potent and binds to a unique epitope containing both the small and large loops of the CD20 molecule on B cells [3.2, 3.3].</p> <p>Southampton's Cancer Research UK (CR UK) Centre was one of the first to test ofatumumab. Peter Johnson, Professor of Medical Oncology (1998-present), was the UK Lead investigator for clinical testing [3.4], which led to ofatumumab's approval by the US Food and Drug Administration (FDA) in 2009. Cragg and Glennie, alongside Dr Stephen Beers, Senior Research Fellow (2009-present), had 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 non-Hodgkin's lymphoma. This discovery spurred the development of a third generation anti-CD20 mAb, Roche's type II drug, obinutuzumab (GA101), which is expected to receive FDA approval soon.</p> <p>In another research strand stemming from the original work on the mechanisms of antibodies, Glennie and his team have developed immunostimulatory antibodies, which trigger the body's immune system to provide long-lasting cancer protection. In 1999, <i>Nature Medicine</i> published the critical observation that mAbs targeting CD40, an immune stimulatory receptor, result in a marked increase in anti-cancer killer T cells, curing and providing lasting immunity against tumours [3.5]. The team went on to show that this treatment provided protection for a range of tumour types and</p>

boosted cancer vaccines, opening up the development of a new class of immunostimulatory drugs. Translation of these observations into the clinic has been achieved through the development of a novel chimeric reagent, LobChi 7-4, in the CR UK Centre, and anti-CD27 under a licensing agreement with Celldex Therapeutics, a USA-based biotechnology firm [3.6].

3. References to the research

- 3.1** Cragg MS, Morgan SM, Chan HTC, Morgan BP, Filatov AV, Johnson PWM, French RR, Glennie MJ. Complement-mediated lysis by anti-CD20 mAb correlates with segregation into lipid rafts. *Blood* 2003; 101:1045-1052.
- 3.2** Teeling JL, French RR, Cragg MS, van den Brakel J, Pluyter M, Huang H, Chan C, Parren PW, Hack CE, Dechant M, Valerius T, van de Winkel JG, Glennie MJ. Characterization of new human CD20 monoclonal antibodies with potent cytolytic activity against non-Hodgkin lymphomas. *Blood* 2004; 104:1793-1800
- 3.3** Teeling JL, Mackus WJM, Wiegman LJJM, van den Brakel JHN, Beers SA, French RR, van Meerten T, Ebeling S, Vink T, Slootstra JW, Parren PW, Glennie MJ, van den Winkel JGJ. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *Journal of Immunology* 2006;177(1): 362-371
- 3.4** A. Hagenbeek, O. Gadeberg, P. Johnson, L.M. Pedersen, J. Walewski, A. Hellmann, B.K. Link, T. Robak, M. Wojtukiewicz, M. Pfreundschuh, M. Kneba, A. Engert, P. Sonneveld, M. Flensburg, J. Petersen, N. Losic, J. Radford. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase I/II trial. *Blood* 2008; 111:5486-5495.
- 3.5** French RR, Chan HT, Tutt AL, Glennie MJ. CD40 antibody evokes a cytotoxic T-cell response that eradicates lymphoma and bypasses T-cell help. *Nat Med* 1999; May 5(5):548-553
- 3.6** French RR, Taraban VY, Crowther GR, Rowley TF, Gray JC, Johnson PW, Tutt AL, Al-Shamkhani A, Glennie MJ. Eradication of lymphoma by CD8 T cells following anti-CD40 monoclonal antibody therapy is critically dependent on CD27 costimulation. *Blood* 2007; 109(11): 4810-4815

Grants

- A. 2009-2015 Martin Glennie, Professor Aymen Al-Shamkhani (Joint Principal Investigators) Dr Mark Cragg (Co-investigator), Prof Peter Johnson (Co-investigator) CR UK, 6-year programme grant Immunomodulating Monoclonal Ab for the Promotion of Anti-Cancer T-cell Immunity £3 million
- B. 2010-2014 Beers SA (PI), Glennie MJ, Cragg MS (Co-investigators) CR UK 3-year Project Grant In vivo manipulation of Fc gamma Receptor expression and activity through macrophage polarization £320,258
- C. 2012-2015 Glennie MJ, White A. CR UK 3-year Project Grant Role of Fc gamma receptor II in the immunostimulatory and therapeutic activity of anti-CD40 mAb Year 1 £69,392
- D. 2012-2015 Glennie MJ, Williams AP. Crack-It NC3Rs Improving the predictive capacity of in vitro cytokine release assays to reduce animal use and drug attrition £500,000
- E. 2013-2015 Gray J (PI), Beers SA (Co PI), Chowdhury F, Cragg MS, Glennie MJ, SPARKS Enhancing anti-GD2 immunotherapy for neuroblastoma by manipulating Fc gamma receptors £91,000
- F. 2013-2017 Leukaemia Lymphoma Research Specialist Programme: Optimising antibody therapy for Lymphoma. PI Professor Mark Cragg. CO PIs Margaret Ashton-Key, Stephen Beers. Jonathan Strefford, Martin Glennie, Peter Johnson & Andrew Davies. £1,116,000
- G. 2013-2017 Glennie MJ et al. EU Framework HEALTH-2013-INNOVATION-1 Proposal No: 602262-2 Immunostimulatory Agonist antibodies for Cancer Therapy €5,995,747

4. Details of the impact

Monoclonal antibodies represent a multi-billion dollar industry with at least five attaining blockbuster drug status (> one billion dollars/year). Researchers at Southampton have played a leading role in bringing two types of anti-CD20 drugs from lab to market/clinic to treat resistant leukaemia and inspiring the development of a new class of immunostimulatory anti-cancer antibodies to protect against cancerous diseases.

Ofatumumab, marketed under the name Arzerra, was patented by Glennie and colleagues and approved by the FDA in 2009 after Southampton researchers proved it was able to kill target cells resistant to similar drugs [5.1], and granted marketing authorisation by the European Medicines Agency in 2011. Only eight years elapsed between its discovery and FDA approval, reflecting its impact on cancer treatment. It was licensed from Genmab to GlaxoSmithKline (GSK), after Prof Glennie returned to Southampton, in a package reported to total more than \$2 billion, the largest known settlement for a mAb at the time. Ofatumumab's initial approval was for the most prevalent form of leukaemia, chronic lymphocytic leukaemia, where it demonstrated a 42% response rate in patients who had failed to respond to the 'best in class' treatments. Ofatumumab has been the subject of more than 90 clinical trials. It has been launched in 26 countries [5.2] and has annual sales of over \$70 million. It also won the Galien Prize in the Netherlands for the "Year's Best Medicine" in 2011 [5.3].

Globally, leukaemia accounts for some 300,000 new cases each year with 222,000 deaths giving Arzerra a wide reach even in its first approved indication. However, it is currently in 19 further clinical trials for other B-cell disorders including follicular lymphoma, diffuse large B-cell lymphoma, rheumatoid arthritis (>400 million patients worldwide), and multiple sclerosis (2.1 million patients worldwide). The full clinical and economic impact of ofatumumab is thus increasing rapidly and given that rituximab, its less potent prototype, has annual revenue in excess of \$6 billion and treats most B-cell disorders, the impact is far-reaching.

The same programme of Southampton research has also been instrumental in the selection of a second anti-CD20 mAb, named GA101 or obinutuzumab (named in 2009), by Roche. This 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, it is currently in multicentre phase III trials, including a head-to-head trial against rituximab in lymphoma and leukaemia. GA101 combined with chlorambucil demonstrated a significant 86% reduction in the risk of leukaemia progression, relapse or death [5.4, 5.5]. It is expected that Roche/Genentech will replace rituximab with obinutuzumab once FDA approval has been obtained.

The head of Roche Glycart said: "*The characterisation of type I and II CD20 mAb by the Glennie lab in Southampton and their clear demonstration of increased potency by type II reagents was a key factor in our decision to select GA101 for clinical development.*" [5.6].

Under its antibody discovery programme Southampton [grant A] has developed one of the first anti-human CD40 mAbs, ChiLob 7-4, to be tested clinically; work presented at the 2010 annual conference of the American Society of Clinical Oncology, held in Chicago [5.7]. This came despite a series of regulatory delays following a failed clinical trial of the mAb at London's Northwick Hospital. Southampton is measuring its activity in a phase I clinical trial, and a licensing agreement is currently under confidential negotiation with a German Biotech company. This development will be part of a recent E6 million EU Framework 7 [grant G], announced in 2013, to develop ChiLob 7-4 in both pancreatic and head and neck cancer across Europe.

In addition to ChiLob 7-4, three other CD40 reagents have undergone clinical trials; the most advanced is Pfizer's product CP-870,893 which shows promise in the treatment of pancreatic cancer (NCT00711191 commenced 2008), a highly aggressive disease with poor prognosis which results in around 300,000 deaths per year worldwide [5.8]. Anti-CD40 mAbs are the forerunners of a new range of immunostimulatory mAb and many of these have entered the clinic in the last

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decade. The most successful to date, ipilimumab (anti-CTLA-4) (Bristol-Myers Squibb) was approved (2011) for the skin cancer metastatic melanoma (>200,000 new cases each year worldwide), the first time any drug has improved survival in this devastating disease. The pivotal trial for ipilimumab (2008-2010) was conducted in multiple centres, including Southampton (Professor Christian Ottensmeier), with over 600 patients, and opens the way for immunostimulatory mAbs in cancer and other diseases where immune modulation is therapeutic. Finally, Southampton's antibody research has led to the discovery and patenting (issued July 2013) of a novel cancer target, CD27, for immunostimulatory mAbs that can promote anti-cancer immunity. This intellectual property is licensed exclusively to Celldex Therapeutics, USA, who are undertaking a phase I trial with a fully human mAb, CDX-1127 [5.9, 5.10].

Collectively, Southampton's mAb research has underpinned the development of clinical mAb, including delivery of two clinical drugs (Arzerra and GA101), one approved and one soon to be approved, which together are protecting thousands of patients from B-cell disorders ranging from leukaemia to autoimmunity and earning millions of dollars worldwide, and which stand to replace rituximab the prototype anti-B-cell mAb. It is also the basis of a range of immune stimulating drugs (anti-CD27, -CD40 and clinical testing of ipilimumab), which have revitalised the immunotherapy field and demonstrated the first increase in survival of metastatic melanoma ever recorded.

5. Sources to corroborate the impact

5.1 Status of clinical trials of ofatumumab conducted by Genmab and GlaxoSmithKline (currently showing 94 trials): <http://www.clinicaltrials.gov/ct2/results?term=ofatumumab&Search=Search>

5.2 Genmab Annual Report 2012 (latest)

http://files.shareholder.com/downloads/AMDA-KPIBN/2146582313x0x643344/0FBC01BB-9C50-4F55-BOA6-FE3314170787/06_Genmab_AR2012_UK_070313.pdf

5.3 Arzerra Wins Galien Prize as Year's Best Medicine in the Netherlands

The Galien prize, awarded each year in the Netherlands for the most innovative and important new medicine on the market has been won by Arzerra (ofatumumab). Arzerra is now in the running for the International Prix Galien, considered the pharmaceutical industry's equivalent to the Nobel Prize. For more information on the Prix Galien visit:

<http://www.prixgalien.com/en/01/introduction.htm>

5.4 Type II nature of Ab—as defined in Southampton: latest press release on success with GA101: http://www.roche.com/investors/ir_update/inv-update-2013-07-24.htm

5.5 Clinical trial status of GA101:

<http://www.clinicaltrials.gov/ct2/results?term=obinutuzumab&Search=Search>

5.6 Head of Roche Glycart AG, Switzerland

5.7 Active ChiLob 7-4 anti-CD40 mAb trial in Southampton:

<http://www.clinicaltrials.gov/ct2/results?term=Chilob&Search=Search>

5.8 The current status of anti-CD40 mAb development:

<http://www.clinicaltrials.gov/ct2/results?term=CP-870&Search=Search>

5.9 Celldex Therapeutics CD27 mAb programme:

<http://www.celldextherapeutics.com/clinical-trials/lymphoma-leukemia-cdx-1127.php>

5.10 The first clinical trial with anti-CD27 mAb from Celldex run under a license from the University of Southampton and CR UK

<http://www.clinicaltrials.gov/ct2/results?term=CDX-1127+&Search=Search>