Institution:
University of Cambridge

Unit of Assessment:
UoA4

Title of case study:
A highly effective therapy for active relapsing-remitting multiple sclerosis: from concept to drug licence

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

Starting from a mechanism-based hypothesis, Alastair Compston and colleagues in Cambridge have led the academic development of Alemtuzumab as a highly effective therapy for relapsing-remitting multiple sclerosis through Phase 1, 2 and two Phase 3 trials (1991-2012). The impacts to date are demonstration of the importance of the therapeutic 'window of opportunity' in treating multiple sclerosis; a product licence in the European Union (September 2013) for the commonest potentially disabling neurological disease of young adults; expansion of the work-force in industry to develop and market this initiative; and an estimated several-fold increase in revenue to the University of Cambridge (and other beneficiaries) from total royalties of £18.6M from 1997 to date.

2. Underpinning research (indicative maximum 500 words)

Alemtuzumab (originally Campath-1H) depletes lymphocytes and was the first therapeutic monoclonal antibody made using Milstein and Köhler's Nobel-prize winning technology and the humanisation technique of Sir Gregory Winter – each developed in Cambridge. Based on the hypothesis that T cell migration from the systemic circulation with infiltration of the CNS drives tissue injury, Alastair Compston, Professor of Neurology in Cambridge from 1989, initiated the use of Alemtuzumab in multiple sclerosis in 1991, being joined by Alasdair Coles (now University Lecturer in Clinical Neurosciences) from 1994. Together, they have since led the development of Alemtuzumab as a treatment of multiple sclerosis, working with a series of commercial partners (currently Genzyme, a Sanofi company). Open-label results with Alemtuzumab in progressive multiple sclerosis (1991-99: n=36) were disappointing: Alemtuzumab reduced clinical and radiological markers of brain inflammation but did not influence progression or brain atrophy.[1] Concluding that treatment earlier in the disease course might prove more effective, an open-label cohort with early relapsing-remitting disease (n=22) was then treated from 1999. The majority remain well in 2013 with no progression of disability at follow-up, now at 14 years. From this experience, the novel concept of a 'window of therapeutic opportunity', early in the disease and thereby limiting long-term disability, led to design of a Phase 2 randomised trial involving 334 patients with disease onset ≤3 years, high relapse rate and low disability (EDSS≤3). In head-to-head comparison with a standard licensed disease-modifying drug, Interferon beta-1a, Alemtuzumab reduced the relapse rate by 74%, and the risk of disability worsening by 71% over three years (CAMMS223). Mean disability improved in the Alemtuzumab group compared to a worsening after interferon beta-1a.[2] The superior efficacy of Alemtuzumab is maintained in the extension phase, most recently reported for ≥5 years follow-up.[3] This result led the group to design two multicentre phase III trials, CARE-MS1 (n=581: drug naive patients) and CARE-MS2 (n=840: cases already refractory to a first-line therapy), again testing Alemtuzumab *versus* an active comparator. In both trials, Alemtuzumab reduced the relapse rate by 49-55% compared to interferon beta-1a. In CARE-MS2, but not CARE-MS1, Alemtuzumab also significantly reduced the risk of accumulating disability by 42% and improved mean disability scores.[4, 5] MRI lesion formation and rates of cerebral atrophy were significantly reduced by Alemtuzumab, to levels expected in healthy adults, compared to Interferon beta-1a. Taken together, Alemtuzumab is the first therapy to show superior outcomes both for disability and MRI surrogates against an active comparator of proven efficacy.

Adverse effects of Alemtuzumab include mild infusion-associated symptoms and slightly increased risk of viral infections. One unexpected adverse effect has been a significant risk of secondary autoimmunity (30% thyroid disease, 1% immune thrombocytopenia, 0.1% anti-glomerular basement membrane disease) developing 1-4 years after treatment, and coinciding with lymphocyte reconstitution. This example of lymphopenia-associated autoimmunity is due to the homeostatic expansion of autoreactive T memory cells, driven by cytokines, especially IL-21, and the failure of thymic reconstitution. Indeed, high pre-treatment serum IL-21 levels identify patients

with multiple sclerosis at higher risk of autoimmunity after alemtuzumab.[6] Biomarkers are being developed to facilitate pre-treatment assessment and selection of patients, and for individualising regimes for monitoring and treatment.

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

1. Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, Hale G, Miller D, Waldmann H, Compston A. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol. 1999; 46(3): 296-304.
2. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, Norris K, Tandon PK. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008; 359(17): 1786-801.
3. Coles AJ, Fox E, Vladic A, Gazda SK, Brinar V, Selmaj KW, Skoromets A, Stolyarov I, Bass A, Sullivan H, Margolin DH, Lake SL, Moran S, Palmer J, Smith MS, Compston DA. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial. Neurology. 2012: 78; 1069-78.
4. Cohen JA*, Coles AJ* [joint first author], Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012; 380(9856): 1819-28.
5. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Miller T, Fisher E, Sandbrink R, Lake SL, Margolin DH, Oyuela P, Panzara MA, Compston DA. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012; 380(9856): 1829-39.
6. Jones JL, Phuah CL, Cox AL, Thompson SA, Ban M, Shawcross J, Walton A, Sawcer SJ, Compston A, Coles AJ. IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H). J Clin Invest. 2009; 119(7): 2052-61.

Grants:
Medical Research Council Training Fellowship for Dr Alasdair Coles: 1994-1997, £98,906
Wellcome Trust Advanced Training Fellowship for Dr Alasdair Coles: 2000-2004, £285,339
Mechanisms of axonal protection after suppression of inflammation in multiple sclerosis.
Multiple Sclerosis Society of Great Britain and Northern Ireland: 2003-2006, £89,813
Benefactions:
Novel antibody based treatments in multiple sclerosis. MuSTER: 1996-1998, £39,210
Fellowship for Dr Amanda Cox, Patrick Berthoud Trust: 2002-2005, £150,750
A pilot study combining monoclonal antibody treatment in early active relapsing-remitting multiple sclerosis using Campath-1H with its non-binding form, SM3. Moulton Charitable Trust: 2004-2006, £221,96
Industry sponsored:
CAMS223. A single blind randomised trial comparing CAMPATH-1H and IFN beta in early active multiple sclerosis. Ilex Biotechnology Company: 2002-2005, £1,007,238
An investigator sponsored study of rescue therapy using Campath-1H in patients with multiple sclerosis failing treatment with IFN-beta. Ilex Biotechnology Company: 2002-2005, £468,350
CARE-MS1 and CARE-MS2. Genzyme Corporation: 2007-2009, £440,000

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

1. Licensing of an effective therapy for multiple sclerosis: The efficacy of Alemtuzumab, as demonstrated in the Phase 2 and 3 trials, is unprecedented. No other trial of a drug in multiple sclerosis, used as monotherapy, has shown superior outcomes in terms of disability compared to an active licensed drug. Natalizumab only showed improved efficacy against an active comparator when added to interferon-beta (Rudick et al., *New Eng. J. Med* 2006); and, in a trial of only one year, there was no significant difference in the effect of Fingolimod on disability compared to interferon (Cohen et al., *New Eng. J. Med* 2010). Although the adverse effects of Alemtuzumab are significant, Alastair Compston and colleagues have shown that it can be used safely, if appropriate

risk-monitoring programmes are adopted over the first 3-4 years following treatment, as developed in the Phase 2 and 3 trials. Alemtuzumab offers highly-effective suppression of inflammatory disease activity, with consequent improvement or stabilisation of disability over several years, albeit with significant but manageable adverse effects. Alternative available treatments are problematic - from the inferior efficacy with the well-established Beta-interferon (Rebif) compared to Alemtuzumab; to Natalizumab, carrying a risk of up to 1/200 for a potentially fatal complication, progressive multifocal leucoencephalopathy.

Alastair Compston, and (subsequently) Alasdair Coles, led the clinical development of Alemtuzumab from first concept as a treatment for multiple sclerosis in 1991 to the publication of Phase 3 trials in 2012. Over that period, the drug had 11 commercial owners, not all of whom were enthusiastic to develop it as a treatment of multiple sclerosis. There is no other example, in the successful licensing of a drug for multiple sclerosis, for all phases of the development to have been led by the same investigators based in an academic institution - in the UK, or elsewhere. In June 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion for approval of LEMTRADA™ (alemtuzumab) 'for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features'; and a product licence was approved by the European Commission on 17 September 2013.[1,2] Of the 100,000 people with multiple sclerosis in the UK, approximately 30,000 have relapsing-remitting disease and 4500 are newly diagnosed with the disease each year; the estimate is that 5-15,000 each year could benefit from Alemtuzumab.[3]

2. Demonstration of the importance of the therapeutic 'window of opportunity' in using drugs in multiple sclerosis: The differential effects of alemtuzumab on early relapsing-remitting and secondary progressive disease shown in the pre-clinical trials work of Alastair Compston and Alasdair Coles (see ref [1] above; and Coles et al., *J Neurology* 2006) are still widely quoted as evidence for the importance of early treatment in multiple sclerosis: see, for example, Stys et al., *Nature Reviews Neuroscience* 2012: 13; 507-14 and Saidha *Ann New York Acad. Sci.* 2012: 1247; 117-37. These data have contributed to the change in basic understanding of the pathogenesis of multiple sclerosis from the late 1990s, alongside histological studies from Oxford and the US emphasising the importance of axon degeneration in the lesions of multiple sclerosis. It is now axiomatic that, for immunotherapies to be effective, they need to be given early in the course of the disease. It is significant that, for the first time, the Committee for Medicinal Products for Human Use recommendation (and the licence in the European Union) moves away from escalation therapy to the concept of early aggressive therapy aimed at modifying the course of the disease in patients not yet disabled, based on the submitted evidence from the use of Alemtuzumab in Phase 2 and 3 trials, and the background information dating from 1991. This decision has significant commercial implications.[4,5]

3. A considerable expansion of the work-force in industry and related sectors worldwide to develop and market this initiative: Anticipating sales in the US, 'Genzyme recently employed about 200 people in areas such as sales, marketing and reimbursement teams', Bill Sibold, Genzyme's Head of MS, said in an interview to Bloomberg News (October 2012).[6] Dr Sibold added in august 2013: 'Genzyme expects to employ over 400 people globally in support of Lemtrada™ by the end of 2013. Although Genzyme has not publicly disclosed sales estimates for Lemtrada™ in MS, the average consensus estimates of Wall Street analysts suggest cumulative European sales potentially in excess €2.0B from 2013 through 2018. After September Genzyme will disclose more details on total spend for the program and some other relevant facts'. Referring to acquisition of Genzyme and the multiple sclerosis portfolio, including Alemtuzumab, Mr Chris Viehbacher, chief executive of Sanofi reported that 2.5 years after buying Genzyme Corporation for $20.1 billion, the deal has added $40 billion to the international pharmaceutical giant's market value: 'once we had Genzyme, that changed investor perception about Sanofi with the company's share price climbing more than 50 percent since the buyout. Genzyme's experimental multiple sclerosis drug Lemtrada — a focal point of negotiations that followed Sanofi's takeover bid in 2010 — won approval from European regulators and is awaiting an OK from Food and Drug Administration by the end of the year'.[7]

4. The first tranche of revenue and a contribution to 'Business and Innovation' in the UK from existing royalties and patents:

- A proportion of earnings from the sale of Alemtuzumab is paid in Royalties to the inventors (each of whom is a UK resident) and to the University of Cambridge. [**Commercial in Confidence**: the University has received a total of £18.6M in revenues since the launch of Campath-1H for the treatment of chronic lymphocytic leukaemia (information from Cambridge Enterprise)].
- Alemtuzumab has become a significant commercial property. When Sanofi bought Genzyme in 2011, there was a significant difference in projections for the sales of Alemtuzumab for multiple sclerosis, but both were high: Genzyme at $3.5 billion a year and Sanofi at around $700 million a year (Reuters: 4.9.12). This led to a complex financial agreement, which has already 'paid out' in that Sanofi has bought $152 million of contingent value rights from Genzyme.[4,5]
- In 2011, Genzyme submitted a patent application for a specific dosing regimen of Alemtuzumab in multiple sclerosis, with Alastair Compston and Alasdair Coles named as inventors.

The discovery of the utility of pre-treatment serum IL-21 as a predictive biomarker of autoimmunity after Alemtuzumab has led to a patent filing (US 2011/0229470 A1) with ourselves, and Dr Joanne Jones, as inventors, through Cambridge Enterprise.

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

1. Committee for Medicinal Products for Human Use recommendation on licensing Alemtuzumab http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003718/smops/ Positive/humansmop000544.jsp&mid=WC0b01ac058001d127
2. Genzyme comment on CHMP recommendation http://genzyme.newshq.businesswire.com/press-release/genzyme-receives-positive-chmp-opinion-lemtrada-alemtuzumab-europe
3. Contact: Director of Policy and Research MS Society
4. Reuters report on Sanofi buyback of Genzyme contingent value rights, 4th September 2012 http://www.reuters.com/article/2012/09/04/us-sanofi-buyback-idUSBRE88306Y20120904
5. Sanofi interview with Bloomberg News October 2012 http://www.businessweek.com/news/2012-10-12/sanofi-aims-to-add-second-generation-lemtrada-to-pipeline
6. Contact: Senior Vice President; Head of Multiple Sclerosis, Genzyme
7. The Boston Globe: http://www.bostonglobe.com/business/2013/09/18/sanofi-chief-executive-said-acquisition-genzyme-has-paid-off-for-french-drug-maker/mCXJJATbWTBLAErkbD9iXP/story.html