Institution: St George's, University of London

Unit of Assessment: A1 Clinical Medicine

Title of case study:

Discovery and development of thalidomide analogues for treatment of myeloma and other cancers.

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

Dalgleish proposed a programme to develop thalidomide analogues for their immunomodulatory and anti-neoplastic actions. Working with a small start-up company, Celgene, several analogues including lenalidomide and pomalidomide were developed and entered clinical trials. Both drugs significantly prolong patient survival in myeloma and myelodysplasia and have received FDA and NICE approval for these purposes. Celgene has grown into a large multi-national company with over 5000 employees. Lenalidomide sales were $3.8 billion in 2012.

2. Underpinning research (indicative maximum 500 words)

Following the serendipitous observation of improvement in leprosy in a patient taking Thalidomide in 1965, a number of clinicians reported beneficial effects of this drug on certain steroid-resistant diseases including graft-versus-host disease following organ transplantation. This prompted Dalgleish and colleagues working at St George's University of London to postulate that thalidomide had immunomodulatory actions in addition to its well-recognised sedative action. They conducted a clinical trial of thalidomide in HIV-positive patients in 1997 [1]. Although there was substantial dropout in both treatment and placebo limbs of the 24 week trial, it was evident that there were potentially important immunomodulatory effects of Thalidomide. However it was clear that its widespread use was likely to be impaired by its association with birth defects, significant neuropathy in some patients, and its tendency to induce somnolence.

Dalgleish therefore proposed a programme to develop a Thalidomide analogue, on the basis that a related drug that lacked these toxic actions could be developed. He entered into discussions with Celgene, a small start-up company, which synthesised a series of Thalidomide analogues that were tested by Dalgleish for *in vitro* anti-tumour necrosis factor activity [2]. Subsequently they screened these molecules for immunological and anti-cancer activities, and several groups of effective agents were identified [3] and patented jointly by Dalgleish and Celgene [4,5]. Amongst these, CC5013 / lenalidomide (Revlimid) and CC4047 / pomalidomide (Pomalyst) were the two analogues that had significant immuno-modulatory and immune stimulatory functions and anti-angiogenic activity [6], which led to these analogues going forward into the clinic.

Dalgleish administered lenalidomide to the first human subject and conducted the first phase I study in solid tumours [7]. A key observation they made at this time was that lenalidomide and pomalidomide appeared to be immunostimulatory, in addition to their anti-inflammatory properties [8]. This activity was confirmed in a pre-clinical model, where pre-treatment with these analogues greatly enhanced the effect of vaccines. This was subsequently confirmed in humans in 2010 when myeloma patients on these drugs were reported as responding preferentially to pneumococcal vaccines. It is now apparent that Lenalidomide is 50,000 times more potent than thalidomide in inhibiting tumor necrosis factor-alpha, and has less severe adverse drug reactions. This led to the development of lenalidomide as an oral adjuvant for therapeutic vaccines in HIV and cancer.

A second key insight was that the anti-inflammatory, co-stimulatory and anti-angiogenic activities of lenalidomide made it an ideal agent for combining with other classical therapies, such as Gemcitabine and Docetaxol, leading to clinical studies with these combinations in myeloma [9].

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

1. Marriott JB, Cookson S, Carlin E, Youle M, Hawkins DA, Nelson M, Pearson M, Vaughan AN, Gazzard M, **Dalgleish AG**. A Double-Blind Placebo-Controlled Phase II Trial of Thalidomide in Asymptomatic HIV-Positive patients: clinical Tolerance and Effect on Activation Markers and Cytokines. Aids Research and Human Retroviruses. 1997; 13: 1325-31. No DOI available.

2. Marriott, J.B., Clarke, I.A., Dredge, K., Muller, G., Stirling D & **Dalgleish, A.G**. Thalidomide and its Analogues Have Distinct and Opposing Effects on TNF-alpha and TNFR2 during Co-Stimulation of Both CD4(+) and CD8(+) T Cells. Clin Exp Immunol. 2002: 130, 75-84. DOI: 10.1046/j.1365-2249.2002.01954.x

3. Marriott JB, Clarke IA, Czajka A, Dredge K, Childs K, Man HW, Schafer P, Grovinda S, Muller GW, Stirling DI, **Dalgleish AG**. A novel subclass of thalidomide analogue with anti-solid tumor activity which caspase-dependent apoptosis is associated with altered expression Bcl-2 family proteins. Cancer Res. 2003:1:63(3):593-9. No DOI available.

4. Bartlett JB, Muller GW, Schafer PH, Galustian C, **Dalgleish AG**, Meyer B: Immunological uses of immunomodulatory compounds for vaccine and anti-infectious disease therapy. March 2007: US 20070048327

5. Bartlett JB, Muller GW, Schafer PH, Galustian C, **Dalgleish AG**, Meyer B: Immunological uses of immunomodulatory compounds for vaccine and anti-infectious disease therapy. July 2012: US 20120190110

6. Bartlett JB, Michael A, Clarke IA, Dredge K, Nicholson S, Kristeleit H, Polychronis A, Pandha H, Muller GW, Stirling DI, Zeldis J, **Dalgleish AG.** Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers. Br J Cancer. 2004 March 8; 90(5): 955–961. doi: 10.1038/sj.bjc.6601579.

7. Schey SA, Fields P, Bartlett JB, Clarke IA, Ashan G, Knight RD, Streetly M, **Dalgleish AG**. A Phase I Study of an Immunomodulatory Thalidomide Analog, CC-4047, in Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2004 Aug. (22) 3269-76. DOI: 10.1200/JCO.2004.10.052

8. Dredge, K., Marriott, J.B., Todryk, S.M., Muller, G.W., Chen, R., Stirling, D.I. & **Dalgleish, AG** Protective antitumour immunity induced by a Costimulatory Thalidomide Analog in Conjunction with Whole Tumour Cell Vaccination is Mediated by Increased Th1-type Immunity. J Immunol. 2002: 168: 4914-9. No DOI available.

9. Liu WM, Nizar S, **Dalgleish AG**. Gemcitabine and lenalidomide combination in a patient with metastatic pancreatic cancer: a case study. Med Oncol. 2010;27:430-3. doi: 10.1007/s12032-009-9228-6.

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

Multiple myeloma is a relatively common haematological malignancy accounting for ~2% of all cancer deaths. Several large-scale clinical trials demonstrated the efficacy of lenalidomide in treating myeloma. Prior to the advent of thalidomide analogues the median one- and five-year survival figures for myeloma were 60% and 20% respectively, and treatment required use of toxic chemotherapeutic agents such as melphalan. With thalidomide or lenalidomide the one- and five-year survival figures increased to 70% and 37% respectively. The use of lenalidomide for this indication in the USA was approved by the FDA in 2006 [A]. Its use in the UK was delayed largely by concerns over treatment costs. However, NICE developed a novel cost-sharing scheme with the manufacturer Celgene and approved the drug for use in myeloma patients who had received two or more prior therapies in 2010 [B,C]. The development of this cost-sharing scheme and the highly influential role of patient representatives in this agreement was explored in a BBC

documentary by Adam Wishart on drug rationing in the NHS [D].

Whilst the immediate beneficiaries of lenalidomide have been patients who suffered from myeloma or myelodysplasia [E], this drug is now being found to be effective in chronic leukaemias and lymphomas. Pomalidomide, the second analogue originally developed by Dalgleish in conjunction with Celgene has a more potent immune co-stimulatory action than lenalidomide and received approval by the FDA in February 2013 for relapsed multiple myeloma [F]. It is now being trialled for use in other tumours .

Impact on economy and commerce

The development of lenalidomide has had a major impact on the growth of Celgene. From being a small non-clinical research organisation when the collaboration with Dalgleish started in 1993 it is now a worldwide corporation based in New Jersey, USA, employing over 5,700 employees [G]. Many of these employees are in Europe and the U.K. in particular, and this has led to the funding of many other research groups and clinical trials throughout the U.K. The excellent future investment prospects for Celgene were discussed in several for a including [H] Lenalidomide sales worldwide generated $3.8 billion USD in 2012 and U.S sales have increased 16% this year and international sales 8% [I].

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

A http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm095626.htm

B www.nice.org.uk/nicemedia/pdf/TA171

C http://publications.nice.org.uk/lenalidomide-for-the-treatment-of-multiple-myeloma-in-people-who-have-received-at-least-one-prior-ta171

D. http://www.adamwishart.info/2009/06/the-price-of-life-bbc-documentary.html

E http://www.cancer.gov/cancertopics/druginfo/fda-lenalidomide

F http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm339286.htm

G http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-irhome

H 2012 - Morning Star article Revlimid-1.pdf

I http://newsroom.celgene.com/press-release/corporate/celgene-reports-strong-third-quarter-2013-operating-and-financial-results