Institution: University of Birmingham

Unit of Assessment: UoA 5 - Biological Sciences

Title of case study: Meeting clinical challenges in the UK and sub-Saharan Africa via drug redeployment.

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

The provision of effective and sustainable healthcare is a major challenge for society. In the developed world escalating costs are placing a huge burden on finite resources; in the developing world, where financial resources are often extremely limited, providing affordable healthcare is an even greater problem. One innovative route to help alleviate these problems is through drug redeployment, whereby existing drugs are employed in new ways to tackle serious diseases. Combining their knowledge of haematological disease gained from their research over the past 20 years together with a drug redeployment strategy, researchers in the School of Biosciences have developed and trialled new interventions for two blood cell cancers, Acute Myeloid Leukaemia (AML) and Burkitt's Lymphoma (BL), based on the administration of a combination of the lipid lowering drug *Bezalip* (Bez) and the female contraceptive *Provera* (MPA). As a result:

- Definitive significant outcomes have been demonstrated in terms of halting disease progression and / or diminishing disease load in patients suffering from AML and BL.
- Successful drug redeployment, on the basis of efficacy, absence of toxicity and low cost of drugs has been achieved.
- This intervention has created the means to reduce childhood mortality and improve the length and quality of life in areas of sub-Saharan Africa.

2. Underpinning research (indicative maximum 500 words)

The underpinning research that led to this impact were preclinical studies which began in 1994 conducted by Prof Chris Bunce (Research Fellow/Senior Research Fellow/Senior Lecturer/Reader 1987-2011 and subsequently Emeritus Professor of Experimental Haematological Oncology, School of Biosciences), Farhat Khanim (Research Fellow/Senior Research Fellow, School of Biosciences since November 2003) and colleagues at Birmingham. Studies using AML cell lines identified that a number of existing commonly used drugs have *in vitro* anti-leukaemic activity. These included; the common glucocorticoid steroid dexamethasone (Dex); the non-steroidal anti-inflammatory drug indomethacin (Indo); the female contraceptive medroxyprogesterone acetate (MPA; drug name *Provera*); and the lipid lowering drugs clofibrate (CF) and bezafibrate (Bez; drug name *Bezalip*)). These studies also identified that Dex, MPA and Indo shared a common target, the aldo-keto reductase AKR1C3.

AKR1C3 is a promiscuous enzyme that most likely performs different roles in a cell specific manner. The key function in AML cells was shown to be its prostaglandin D2 (PGD2) keto-reductase activity (ref. 2). Importantly this activity protects the cancer cells and promotes their inappropriate survival. Treatment of AML cells with AKR1C3 inhibitors reverses this process and induces many known downstream effector mechanisms resulting in AML cell death (ref. 2).

The inhibition of AKR1C3 leads to the accumulation of a highly biologically active metabolite (prostaglandin) called 15dΔ PGJ_2 .One of the recognised actions of 15dΔ PGJ_2 is as an activating ligand of the nuclear receptor PPARγ. There has been widespread interest in exploiting this as anti-cancer therapy. However 15dΔ PGJ_2 is an electrophile and covalently conjugates thiol groups on proteins; as such it cannot be administered as a drug due to its likely toxicity and low bioavailability.

The group's studies confirmed that the downstream consequences of AKR1C3 inhibition in AML cells included regulation of PPARγ target genes and therefore that inhibition of AKR1C3 provided the opportunity to deliver the same cytotoxic actions as 15dΔ PGJ_2 to AML cells (ref. 2) intrinsically rather than systemically.

The mode of action of fibrates in mediating control of lipid homeostasis is via acting as a pharmacological ligand of PPARα. It was therefore reasoned that **combining inhibition of AKR1C3 with the use of a fibrate** would co-stimulate PPAR-γ and -α **thereby exert a more stringent anti-leukaemic effect.** In addition, the possibility that PPARs are in part the targets of AKR1C3 inhibitor and fibrates extended the possibility that **these agents' efficacy may not be restricted to AML alone but extend to B-lymphoid malignancies, including Chronic Lymphocytic Leukaemia (CLL) and non-Hodgkin Lymphomas (NHL)**.

Consistent with this, the group demonstrated the improved *in vitro* anti-neoplastic actions of the combination of Bez and MPA (termed **BaP**) in BL, CLL and AML (refs. 1-3). The availability of Bezalip and Provera as currently used drugs of known high tolerability and low toxicity facilitated the translation of the preclinical studies into phase1 & 2 trials of the combination of these drugs (BaP) as potential novel anti-cancer therapy.

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

1. Fenton SL, Luong QT, Sarafeim A, Mustard KJ, Pound J, Desmond JC, Gordon J, Drayson MT, Bunce CM. Fibrates and medroxyprogesterone acetate induce apoptosis of primary Burkitt's lymphoma cells and cell lines: potential for applying old drugs to a new disease. Leukemia.(2003) 17: 568-75. PubMed PMID: 12646946
2. Hayden RE, Pratt G, Davies NJ, Khanim FL, Birtwistle J, Delgado J, Pearce C, Sant T, Drayson MT, Bunce CM. Treatment of primary CLL cells with bezafibrate and medroxyprogesterone acetate induces apoptosis and represses the pro-proliferative signal of CD40-ligand, in part through increased 15dDelta12,14,PGJ2. Leukemia. (2009a) 23: 292-304. doi: 10.1038/leu.2008.283
3. Khanim FL, Hayden RE, Birtwistle J, Lodi A, Tiziani S, Davies NJ, Ride JP, Viant MR, Gunther UL, Mountford JC, Schrewe H, Green RM, Murray JA, Drayson MT,Bunce CM. Combined bezafibrate and medroxyprogesterone acetate: potential novel therapy for acute myeloid leukaemia. PLoS One. (2009b) 4(12):e8147. doi 10.1371/journal.pone.0008147.

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

Significant new drug discoveries for cancer in general and for haematological malignancies have been sporadic. **Acute myeloid leukaemia** (AML) is an aggressive cancer that mostly affects individuals over the age of 60. The outlook for the majority of patients with acute myeloid leukaemia has remained unchanged for more than twenty years with significant numbers dying within six months of diagnosis and overall survival remaining dismal**. Burkitt's Lymphoma (BL)** is endemic in sub-Saharan Africa. The geography of this endemic form of the disease (eBL) coincides with some of the poorest countries in the world. Similarly new curative measures for lymphoma and multiple myeloma have been seriously lacking. In addition, the situation in poorer countries is significantly worse, where those drugs that have been recently derived (such as imatinib for chronic myeloid leukaemia and rituximab for B-cell lymphoid malignancies), are prohibitively expensive. Even in Europe and the USA many new drugs are not widely available because of their expense. Hence, Bunce and colleagues have adopted a novel strategic approach to address these issues by exploiting combinations of existing drugs not originally developed as anticancer agents. As result they have improved survival and the quality of life for patients with haematological malignancies and revealed the benefits of this approach for less developed regions such as sub-Saharan Africa.

Initial confirmation of the efficacy of the drug repurposing strategy to treat Acute Myeloid Leukaemia and Burkitt's Lymphoma came with the analysis and publication in 2010 of an AML patient trial conducted by Prof Bunce and Prof Drayson (Medical School, University of Birmingham) (www.controlled-trials.com/ISRCTN50635541). As it is not ethical to deny AML patients who are likely to benefit from conventional chemotherapy access to those treatments, radically novel AML treatments have to be first tested in those end stage patients for whom only palliative care is available. Consequently, the patients represented an elderly group with an extremely poor prognosis whose disease would be expected to be progressive and in none of whom would an improvement in haemopoiesis or reduction in disease activity be expected without effective anti-AML therapy.

Five patients took BaP for <4 weeks because of complicating co-morbidities and 4 more received other concomitant therapies. For these patients it was not possible to assess the anti-AML activity of BaP. Nonetheless, 15 patients took BaP as the sole therapy for between 4.5->200 weeks without toxicity (1 patient stopped BaP therapy because of depression, athough a possible side effect of the treatment this patient had had a torrid disease history). **Amongst these 15 patients, 4 achieved stable disease for 5-39 weeks and a further 4 showed improved haemopoiesis for 22->200wks. Only 2/15 patients had progressive disease whilst on BaP therapy.** Thus the importance of this study is that it demonstrated the safety of BaP in elderly patients with AML combined with strong evidence of both anti-AML activity and improved haemopoiesis. In stark contrast to cytotoxic chemotherapy, BaP had no haematological toxicity and can be administered continuously. The innovation in this approach was the introduction of the concept that complete ablation of the leukaemia cells (complete remission) by BaP may not be necessary to allow haemopoiesis to recover towards normal, improving both quality and duration of life.

Based on this successful outcome a further trial using this strategy is underway focussing on not only AML, but also B cell Chronic Lymphocytic Leukaemia (CLL) and B cell Non Hodgkins Lymphoma (BNHL) (http://www.controlled-trials.com/ISRCTN99131400). The trial started in December 2011 and is being led by Prof Drayson.

Endemic Burkitt's lymphoma is the most common childhood malignancy in malaria-endemic areas of sub-Saharan Africa where it is 50 fold more common than elsewhere. It accounts for about half the cancers that present to the Queen Elizabeth Central Hospital (QECH), Blantyre in Malawi. The treatment of BL at QECH is limited by several factors including cost. Malawi is one of the poorest nations in the world, the resultant lack of supportive medical care and poor nutritional status of patients mean that conventional chemotherapy would lead to unacceptable toxicity. Despite this, current low grade, chemotherapy available at QECH cures around 50% of children and rescue therapy salvages approximately one third of those patients who relapse or present with primary resistant disease. The preclinical studies identified BaP to have anti-BL activity (2003). In collaboration with Prof, Elizabeth Molyneux, these agents have been added to the rescue protocol for relapsed and primary resistant patients at QECH since 2006.

The trial (www.controlled-trials.com/ISRCTN34303497) which ran from 2007-2012 was conducted in a total of 96 patients (median age of 9 years old) and tested three escalating doses of BaP in a total of 96 patients. The trial treated patients for a week on BaP alone and then in combination with rescue therapy. In those patients that showed progression on BaP alone, rescue therapy was started immediately. The trial **clearly identified that the higher doses of BaP ceased lymphoma progression in all patients** and furthermore reduced tumour size in almost a third of patients. At the end of all therapy, complete remissions were present in 41%, 43% and 66% (p=0.04) of low,

intermediate and full dose BaP. The analysis of the trial data has been accepted for publication in the British Journal of Haematology.

Impact from the phase 1 & 2 trial in relapsed and primary resistant eBL in Malawi demonstrated:

- BaP has significant activity against eBL *in vivo*
- The absence of toxicity
- At the maximum dose tested BaP alone halted disease progression and or diminished disease load in **all** patients
- When combined with standard local low grade rescue chemotherapy this same dose of BaP significantly increased complete remissions from 41% to 66%.
- The cost of BaP adjunctive therapy alongside standard rescue therapy is just £72 as compared to ~£10-20K in the UK, EU and USA.
- The cost of the quality adjusted life years (QALY) for a Malawi patient who is cured after BaP therapy is <£2 (given life expectancy is 52 years).

Following this outcome a new drug combination currently in phase I/II, if safe, will be combined with BaP to determine the best treatment to take to phase III trials in relapsed and primary resistant BL. Longer term, there are also plans for a randomised trial of BL at first diagnosis and to set up a national centre for drug redeployment across all diseases.

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

s1. Published AML results Murray JA, Khanim FL, Hayden RE, Craddock CF, Holyoake TL, Jackson N, Lumley M, Bunce CM, Drayson MT. Combined bezafibrate and medroxyprogesterone acetate have efficacy without haematological toxicity in elderly and relapsed acute myeloid leukaemia (AML). Br J Haematol. 2010 Apr;149(1):65-9. doi:10.1111/j.1365-2141.2009.08055.x. Epub 2010 Jan 13. PubMed PMID: 20067564.

s2. BL Trial: Corroborating statement received from Head of Paediatric Department, College of Medicine, Box 360, Blantyre, Malawi (dated 28/06/13)