**Institution: Middlesex University**

**Unit of Assessment: 3 – Allied Health Professions, Dentistry, Nursing and Pharmacy**

**Title of case study:** Development of an anti-hCGβ cancer vaccine for the treatment of bladder cancer and other hCG/hCGβ secreting tumours.

## 1. Summary of the impact

Our research has underpinned the work of Celldex Therapeutics and other US based companies, in developing a vaccine directed against hCGβ for the adjuvant treatment of epithelial cancer. A number of Phase I trials indicated an improvement in survival of vaccinated patients and Phase II trials began for bladder cancer where early data showed promise by improving the survival time. This has had a significant impact on these patients, and has the potential to extend the life of many millions of cancer sufferers (around 32% frequency of hCGβ secretion by carcinomas). Our research input has helped prove the technology and further trials are awaiting finance.

## 2. Underpinning research

The research carried out by Dr Butler (Reader) and team of collaborators (including Profs Roitt & Iles and Drs Ghali (Principal Lecturer) and Naase (Senior Lecturer), Wen and Burczynska (Lecturers) at Middlesex University has, over fifteen years, been responsible for establishing that hCGβ was expressed by a malignant subset of bladder (and other) cancers. The team have proven the prognostic significance of detecting hCGβ in patient serum/urine/tissue by protein and gene expression studies, and have determined that hCGβ promotes malignancy by inhibiting apoptosis. Most significantly, they have shown how an anti hCGβ immunotherapy applied to humans can neutralise the anti-apoptotic effects of hCGβ and reduce cell survival in vitro and therefore propose to suppress tumour growth in vivo.

Prof. Roitt chaired the original WHO committee for the development of hCG vaccines for fertility and brought his expertise to Middlesex University to collaborate with Dr Butler and Prof. Iles. Dr Butler reviewed hCG vaccines in a chapter of his book on hCG in 2010 where more recently research had turned to modulating cancer metastases with hCG vaccines rather than fertility management. The original research carried out by Dr Butler demonstrated a specific role for hCGβ and paved the way for future studies on the effect of immunodepletion of hCGβ as an adjuvant treatment for advanced bladder and other epithelial cancers. Dr Butler's research continued to explore the structure function relationship of hCG variants in multiple cancer subtypes and demonstrated that by incubating cancer cells with antiserum, generated by hCGβ immunogen or vaccine, cells resumed their prospective apoptotic demise; hCGβ was protecting the cells which secreted it in an autocrine fashion.

Dr Butler and Iles' group investigated antiserum generated from various vaccinated sources and following Phase I studies by Celldex Therapeutics, tested the first human antiserum in 2010. It was demonstrated that the antiserum could effectively reduce hCGβ secreting cancer cell populations in vitro and that the vaccine generated a titre which was both elevated enough and specific enough to modulate tumour growth and metastasis in vivo. This specificity and efficacy data significantly lead to the publication of the Phase I data by Celldex Therapeutics and collaborators.

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

Outputs listed have been published in leading journals in the field with rigorous peer review systems. They are of at least internationally recognized quality.

1. **SA Butler**, MS Ikram, S Mathieu, RK Iles (2000) The increase in bladder carcinoma cell population induced by the free beta subunit of human chorionic gonadotrophin is a result of an anti-apoptosis effect and not cell proliferation. *British journal of cancer, 82* (9), 1553.

2. **SA Butler**, EM Staite EM, RK Iles. (2003) Reduction of Bladder cancer cell growth in response to hCGβ vaccinated mouse serum. *Oncology Research and Anti-Cancer Drug Design. 14*, 93-100.

3. LA Cole, **SA Butler**, SA Khanlian, A Giddings, CY Muller, MJ Seckl, EI Kohorn (2006) Gestational trophoblastic diseases: 2. Hyperglycosylated hCG as a reliable marker of active neoplasia. *Gynecologic oncology 102 (2),* 151-159

4. Delves PJ, Iles RK, **Roitt IM**, Lund T. (2007) Designing a new generation of anti-hCG vaccines for cancer therapy. *Mol Cell Endocrinol. Jan 2*; 260-262:276-81. Epub 2006 Oct 17. PubMed PMID: 17049720.

5. LA Cole, **SA Butler** (2012). Hyperglycosylated hCG, hCGβ and Hyperglycosylated hCGβ: Interchangeable cancer promoters. *Molecular and cellular endocrinology 349 (2),* 232-238.

6. Morse MA, Chapman R, Powderly J, Blackwell K, Keler, T, Green J, Riggs R, He LZ, Ramakrishna V, Vitale L, Zhao B, **Butler SA**, Hobeika A, Osada T, Davis T, Clay T, Lyerly HK. (2011) Phase I study utilizing a novel antigen-presenting cell-targeted vaccine with Toll-like receptor stimulation to induce immunity to self-antigens in cancer patients. *Clin Cancer Res., 17(14),* 4844-4853.

**4. Details of the impact**

The work of this team has established through a number of peer reviewed publications that hCGβ is expressed by many aggressive human tumours and that it is required for rapid cell growth. They extended this in further publications to show that hCGβ expression could be used as a diagnostic tool to establish tumour type and indicate potentially useful therapies, and to show that antibodies could be used to block the action of hCGβ *in vitro*, which decreased tumour cell growth by preventing the hCGβ mediated inhibition of apoptosis. The group continued this work to develop modified forms of hCGβ that could be used for immunotherapy or vaccine development.

Building on this work, and that of others, Celldex Therapeutics (Needham, MA, USA) have developed an anti-hCGβ cancer vaccine based on their patented technology for targeting antigen presenting cells (APC) - (Keler *et al.,* 2007). Termed CDX-1307, this vaccine has completed Phase 1 development and is planned to be marketed as a treatment for colorectal, pancreatic, bladder, ovarian and breast cancers, with the potential for others. CDX-1307 couples the entire beta chain of hCG to an APC specific adjuvant antibody and induces both humoral and cell mediated response to the complete molecule and not just the CTP. These Phase I trials showed a halting of tumour progression for many patients, and their serum was demonstrated by Dr Butler to significantly reduce cell number *in vitro* (Morse et al., 2011). A Phase II study in patients with invasive bladder cancer began in May 2010. The N-ABLE Trial (Neoadjuvant and Adjuvant Bladder Cancer Trial), was proposed to evaluate CDX-1307 in both neoadjuvant and adjuvant settings in patients with newly diagnosed muscle-invasive bladder cancers with inclusion dependent on demonstrating hCGβ expression by the tumour. Preliminary data was expected by the end of 2011. However, while initial data was very encouraging and positive data was presented from three product candidates in four presentations at the American Society of Clinical Oncology annual meeting, recruitment of suitable patients was slow. Coupled with the financial crisis slowing progress even further the trial was halted in 2011.

However, Celldex and other companies are well positioned to continue this work when circumstances are right. Therefore, current benefits include possible increased survival time for patients within the trial, and a significant financial impact on whichever company runs the trial. As an indication of the impact this may make, other US based companies have received significant government funding to extend this work using other immunotherapy approaches although no data have been presented as yet. The results reported in this trial show the vaccine approach has the potential to make significant advances in the treatment of this invasive cancer. From our data we know that antisera appears to block anti-apoptotic activity of hCGβ, which in turn reduces the growth and spread of tumours to distant organs. This has a profound effect on survival and the

vaccine may target these metastatic cells directly.

Current plans are that the vaccine will be trialled over a five-year period, amongst a group of 60 newly-diagnosed patients with the cancer. The same molecule occurs in many epithelial cancers (32% by meta analysis) (Butler & Iles, 2010). In time, therefore, this type of vaccine could also offer treatment benefits across a range of other highly invasive cancers. Bladder cancer affects four times as many men as women with 10,000 new cases a year in the UK. It is the fourth most common cancer and the sixth most common cause of cancer death in UK men. At present, 75% of cases are lethal. The potential beneficiaries therefore number in the millions worldwide, with the nature of the impact being increased survival times, and possibly long term cures of cancers.

**5. Sources to corroborate the impact**

i) **Dr Michael Morse** at Duke University in North Carolina, Michael.Morse@duke.edu.
As the first and corresponding author for Morse et al., Phase I Study, Clinical Cancer Research.17(14):4844-53, 2011, Dr Morse is prepared to corroborate the involvement of Dr Butler of Middlesex University in conjunction with Celldex Therapeutics and the CDX1307 trials in demonstrating the specificity of the vaccine for hCGbeta.

ii) The **Celldex Therapeutics** Cancer vaccine Web page is: **http://www.celldextherapeutics.com/wt/page/cancer** and this contains press releases and publications on the vaccine trials.
These include the following press releases:

- Celldex Press Release mentions conference presentation of poster which includes Iles/Butler data: http://ir.celldextherapeutics.com/releasedetail.cfm?releaseid=715948
- Celldex Press Release of Trial – Mentions Middlesex University and a quote from Prof. Ray Iles: http://ir.celldextherapeutics.com/releasedetail.cfm?ReleaseID=715947
- Celldex Press Release mentioning recruitment to Trial and success so far:
- *http://ir.celldextherapeutics.com/releasedetail.cfm?releaseid=715938*

**Other Press releases and articles:**
Examples of other on-line sources specifically referring to the vaccine development and Middlesex University:

- http://www.vaccinationcouncil.org/2010/07/17/toxic-cancer-vaccine-being-developed-will-destroy-human-fertility/
- http://finance.paidcontent.org/paidcontent/news/read?GUID=13086514&ChannelID=3191
- http://www.thehealthage.com/2010/07/jab-halt-deadly-forms-cancer/
- http://www.dailymail.co.uk/health/article-1293927/Jab-halt-deadly-forms-cancer.html
- http://www.nydailynews.com/life-style/health/shot-stops-deadly-forms-cancer-ready-5-years-scientists-article-1.468328
- http://cancersupport.aarogya.com/year-2010/now-a-jab-to-stop-cancer-in-tracks