Institution: University of Salford

Unit of Assessment: A5 Biological Sciences

Title of case study: Cancer Research

1. Summary of the impact

Cancer research at the University of Salford focuses on developing new and improved treatments for cancer, particularly for children with cancer, demonstrating the following impact:

- The development of RH1, a novel anticancer drug and a second generation novel agent, Es5, arising from RH1;
- Participation in clinical studies in paediatric and adult cancers with North West, UK and international partners in the health, charitable and commercial sectors to trial and develop the technologies;
- The establishment of spin-out company, *Onco-NX* to develop and exploit the technologies and IP arising from the research;
- The establishment of Kidscan, a University-based registered charity to support research into new and improved treatments for children with cancer and generating dedicated support for and commitment to cancer research among North West UK communities.

2. Underpinning research

The key researchers and positions they held at the institution at the time of the research are as follows: Professor R. Bisby, Professor of Biochemistry (from 1976), Dr J. Butler (until 2006), Dr E. Elkord, Senior Lecturer in Biomedical Sciences & Immunology (from 2010), Dr J. Hadfield, Senior Lecturer in Medicinal Chemistry (from 2001), Professor A. McGown, Professor of Molecular Drug Design (from 2002), Dr I Podmore, Senior Lecturer in Analytical Bioscience from 2001, Prof G Warhurst visiting Professor (from 2007), School of Environment and Life Sciences. Cancer research at the University of Salford was established in 2002 with the Centre for Molecular Drug Design and the impact described in this case study is underpinned by the following research:

- **2002-onwards:** The 'holy grail' of cancer therapy is to produce a drug which will specifically target cancer cells without any damage to healthy tissue. DT-diaphorase, an obligate 2 electron reducing enzyme, is over-expressed in tumours. The novel agent RH1 was designed and patented by Butler [**1**] as an inactive prodrug that is activated to a potent cytotoxic drug by DT-diaphorase within tumour cells, thus reducing the possibility of off-target side effects (toxicity). The synthesis and development of the novel anticancer agent RH1 was undertaken as a joint project between the University of Salford and the Paterson Institute. (Butler/McGown [**2**]).
- **2003-2005**: A collaboration (McGown with K. Flower, University of Manchester) has resulted in a patent (WO/2005/058421) for novel gold anti-tumour agents that restore sensitivity to tumours that have acquired resistance to cisplatinum. Pre-clinical development of these agents was funded by Modern Biosciences Ltd.
- **2008-onwards:** Elkord has demonstrated that CD8(+) T cells recognizing h5T4 can be generated in the absence of CD4(+) T cells from peripheral blood lymphocytes of human healthy individuals and the existence and expansion of human CD4(+) T cells against h5T4 by stimulation with autologous monocyte-derived dendritic cells infected with a replication defective adenovirus encoding the h5T4 cDNA (Ad-h5T4). The h5T4-specific T-cell responses in normal individuals are enhanced by initial depletion of CD25(+) cells (putative T regulatory cells) prior to the in vitro stimulation. The research identified a novel h5T4-derived 15-mer peptide recognized by CD4(+) T cells in HLA-DR4 positive healthy individuals. CD4(+) T cells spontaneously recognizing a different 5T4 epitope restricted by HLA-DR were identified in tumour-infiltrating lymphocytes isolated from a regressing renal cell carcinoma lung metastasis. Data show that CD4(+) T cells recognizing h5T4 can be expanded and detected in healthy individuals and a renal cell carcinoma patient. Such h5T4-specific CD4(+) T cells boosted or induced by vaccination could act to modulate both

cell or antibody mediated anti-tumour responses [**3**]. In addition, Elkord et al show that h5T4 oncofetal antigen is expressed in high risk of relapse childhood pre-B acute lymphoblastic leukemia and is associated with a more invasive and chemotactic phenotype [**4**].

- **2009-2012:** A series of novel kinase inhibitors designed at Salford (Hadfield/McGown) have shown the ability to restore communication between cancer cells and surrounding normal cells, thus restoring the normal phenotype. These agents have been patented (WO/2011/023986) and are currently being evaluated [**5**].
- **2012-onwards:** Second generation analogues of RH1 are in development in the form of Es5, a prodrug that is selectively activated within the cancer itself: Tumour vasculature represents a new and important target for cancer therapy as the destruction of a single vessel within a tumour would kill thousands of cancer cells that depend on the vessel for oxygen and nutrition. Hadfield/Bisby/McGown have patented drugs that have been shown to destroy tumour vasculature with the development of inactive pro-drugs that can be activated *in situ* within the tumour (WO/2013/021208).
- The conversion of inactive *trans*-stilbenes to highly potent *cis*-stilbenes is efficiently achieved using light [**6**] allowing the administration of inactive drug which is converted to active drug only where light is administered, maximising activity whilst reducing toxicity (Bisby/Hadfield/McGown). A clinical trial designed to determine if it is possible to predict response to anti-tumour agents is nearing completion (McGown/Carlson/Warhurst). The research uses a novel technology which measures the electrical potential of tumour cells and how this responds to treatment with anti-cancer drugs. The research involves obtaining tumour at the time of surgery and testing the tumour against a panel of clinically used drugs and correlating this with response. McGown et al have demonstrated that this technology can be predictive of response. Trials in colon and oesophageal cancer are being completed.

3. References to the research

Key outputs:

1. Ross, D**,** Butler, J, Hargreaves, R H J, Siegel, D & Beall, H D. (*DT-diaphorase directed anti-tumour agents* 2000). US patent: A61K 31396; C07D40302; C07D40308.
2. Ward T. H., Danson S., McGown A. T., Ranson M, Coe N.A., Jayson G., Cummings J., Butler J. (2005). Pre-clinical evaluation of the pharmacodynamic properties of RH1 (2,5-diaziridinyl-3-(hydroxymethyl)-6-methyl-1,4-benzoquinone). *Clinical Cancer Research*, 11: 2695-2701. doi: 10.1158/1078-0432.CCR-04-1751 DOI
3. Elkord, E, Burt, D. J, Drijfhout, J.W, Hawkins, R. E, Stern, P. L. (2008). CD4+ T-cell recognition of human 5T4 oncofoetal antigen: implications for initial depletion of CD25+ T cells. *Cancer Immunology, Immunotherapy,* 57:833-47. DOI
4. Castro, F V, McGinn, O J, Krishnan, S, Marinov, G, Rutkowski, A, Elkord, E, Burt, D, Holland, M, Gallego, A, Saha, V and Stern, P L. (2012). '5T4 oncofetal antigen is expressed in high risk of relapse childhood pre-B acute lymphoblastic leukemia and is associated with a more invasive and chemotactic phenotype', *Leukemia,* 26, pp.1487-1498. DOI
5. Hampson, L. He X.T., Oliver A.W., J. Hadfield, T. Kemp, J. Butler, A. McGown, H.C. Kitchener, I.N. Hampson. (2009). 'Analogues of Y27632 increase gap junction communication and suppress the formation of transformed NIH3T3 colonies.' *British Journal of Cancer,* 101: 829-839**.** DOI **(REF 2)**
6. Bisby, R. H, Botchway SW, Hadfield JA, McGown AT, Parker AW, Scherer KM.(2012). Fluorescence lifetime imaging of E-combretastatin uptake and distribution in live mammalian cells. *European Journal of Cancer*, 48: 1896-1903. DOI **(REF 2)**

Key grants:

7. **2009:** Two-photon activation of stilbene-based drugs targeted at the vasculature. STFC, £30,420.00 Principal Investigator: R Bisby (50%). Co-Investigators: J Hadfield (25%), A McGown (25%).

8. **2008:** Use of Tissue Models in Predicting Oral Drug Absorption, BBSRC, £117,952.00 Investigators: A McGown (50%), G Warhurst (50%).
9. **2005:** Evaluation of novel anti-vascular agents (extension to STRN47) Cancer Research UK, £60,453.00 Investigator: A McGown (100%).
10. **2004:** UK childhood acute lymphoblastic leukemia randomised trial (UKALL 2003) MRC, £131,598.00 Investigators: J Butler (25%), A McGown (25%), A Gernaey (25%), I Podmore (25%).
11. **2004:** Evaluation of Novel Anti-Vascular Agents, Cancer Research UK, £46,118.00 Investigators: A McGown (35%), J Hadfield (35%), J Butler (30%).
12. **2004:** Methotrexate-mediated modulation of methionine synthase activity, 06-alkylguanine DNA-alkyltransferase and glutathione levels as a means to optimise therapy for childhood central nervous system tumours, RMCH, £30,000.00 Investigators: J Butler (10%), I Podmore (80%), A McGown (10%).

4. Details of the impact

The development of new and improved treatments for cancer remains challenging. Treatments are often associated with side effects that arise because of damage that occurs to healthy cells, particularly in children with cancer, where treatment can damage normal tissues leading to impairment of physical, educational and emotional development (even where treatment of the cancer is successful.) University of Salford researchers have developed a number of novel approaches aimed at maximising the desired effect against the cancer whilst minimizing damage to normal health tissues. These approaches include light activation of antivascular agents and Es5; a prodrug that is selectively activated within the cancer itself:

- **2004-2011:** RH1 was licensed to Allos Therapeutics in 2004 Allos Therapeutics Inc., announced the initiation of patient enrollment in a Phase 1, non-randomized, open-label, multi-centre dose escalation study of the Company's targeted chemotherapeutic agent RH1 in patients with advanced solid tumors or non-Hodgkin's lymphoma (NHL). "*We are pleased to advance the development of this agent,*" said Pablo J. Cagnoni, M.D., Chief Medical Officer of Allos. "*RH1 is a small molecule chemotherapeutic agent that is bioactivated by the enzyme DT-diaphorase (DTD), which is over-expressed in many tumours, including lung, colon, breast and liver tumours. We believe that because RH1 is bioactivated in the presence of DTD, it has the potential to preferentially target certain tumours while limiting the amount of toxicity to normal tissue*." [**A**] RH1 completed Phase I clinical trials both in the UK and the USA in 2011.
- **2009:** The Clinical and Experimental Pharmacology Group, Paterson Institute for Cancer Research, Manchester, UK evaluated the preclinical efficacy of the RH1 against paediatric tumours concluding that the demonstration of RH1 efficacy against paediatric tumour cell lines suggests that this agent may have clinical usefulness in childhood cancer.
- **2011:** Second generation drugs based on RH1 (Es5) are currently under development by Onco-NX, a spin out company of the University of Salford formed by Hadfield and McGown to exploit the oncology research within the University [**B**]. Onco-NX received £50k funding in 2011 from the North West Fund for Biomedical (venture capital investor). The North West Fund for Biomedical is managed by early-stage venture capital firm SPARK Impact and is part of the £185 million evergreen fund provided jointly by the European Investment Bank and European Regional Development Fund, to supply equity funding to small and medium-sized enterprises (SMEs) in the North West. In 2012 Onco-NX secured a further £100k from the Fund based on positive results of in-vivo testing of the efficacy of Es5 [**C**].
  Current: Research into light activated antivascular prodrugs (Hadfield/Bisby/McGown) in collaboration with the STFC Lasers for Science Facility and the Rutherford Appleton Laboratory is continuing, with the aim of developing a new area of laser surgery for both cancer patients and also those with vascular proliferative disease (e.g. macular degeneration). Drug synthesis and screening are undertaken at Salford whilst the laser facilities at Oxford are used for analysis of the effects at the cellular level. The potential of

this technology to treat both cancer and other diseases associated with abnormal vascular proliferation (e.g. macular degeneration) is great.

- Expertise in cancer within the University of Salford resulted in the establishment of Kidscan, a charity based at the University of Salford, whose work is focused on developing new and improved treatments for children with cancer [**D**]. Local people directly and personally affected by childhood cancer are able to access opportunities for active fundraising in their own communities, directly contributing to research undertaken in the region and which attracts venture capital and Research Council funding; building personal investment and agency in innovation in treatment among North West communities.
- Kidscan has raised over £2M to date and £275k in 2012-2013, to fund research both at the University and in other centres throughout the NW of England, at a time of significant economic pressure affecting communities in the region. Kidscan not only supports work on new and improved pharmaceutical interventions but also into research aimed at establishing the factors that determine quality of life, health status, psychological wellbeing and self-esteem for children undergoing treatment for central nervous system (CNS) tumours.
- Kidscan's work has been the subject of a recent Granada TV news report, showcasing the approach to engaging local communities and developing their stake in cutting edge technology for improving cancer treatment, demonstrating public interest in and commitment among communities in the North West for locally grown fundraising into research and development in the biomedical sectors in the region [**E**].
- The charity has supported student/ industrial placements, technical support, equipment purchase and maintenance, and consumables. Funding of projects is decided by an independent scientific committee. In addition the charity provides speakers (members of staff of the University) to increase public awareness of the causes, prevention and treatment of cancer (paediatric and adult) throughout the North West of England. The fundraising events organised by Kidscan are designed to encourage public participation and the development of a charity ethos, bringing together communities, corporate partners and students, whilst raising public awareness of cancer and the role of Universities in the development of new treatments.
- The charity has initiated a healthy lifestyle campaign backed by the celebrity nutritionist Jeanette Jackson with the development of an innovative campaign where ten celebrities have donated a healthy recipe compiled into a book with all proceeds going to Kidscan [**F**].

5. Sources to corroborate the impact

a) Allos Therapeutics Initiates Study of RH1 in Patients with Advanced Solid Tumours or non-Hodgkin's Lymphoma
b) Link to University of Salford spin-out company, Onco-NX
c) Link to the North West Fund for Biomedical report into investment in Onco-NX
d) Link to the University of Salford fundraising charity Kidscan
e) Link to Granada Reports segment on community fundraising and cancer research in the North West UK
f) Link to Star Bites fundraising campaign for Kidscan