Institution: Edinburgh Napier University

Unit of Assessment: UoA 3

Title of case study: Developing improved pre-clinical testing strategies to reduce the drug attrition of inhaled drug compounds at pre-clinical assessment

1. Summary of the impact

Edinburgh Napier University is internationally recognised for its research into the mechanisms that drive the adverse health effects of inhaled particles. Pharmaceutical company GlaxoSmithKline (GSK) required early understanding of the likelihood that inhaled drug particulates, used in the treatment of asthma, would evoke an adverse biological response, thus compromising the development of any novel drug. Through collaboration, via a Knowledge Transfer Partnership (KTP), we were able to develop improved *in vitro* methodologies to study toxicity and, thus, predict pathologies reported *in vivo* with the aim of reducing both the use of animals and pre-clinical drug attrition.

2. Underpinning research

Much of the research that formed the basis of current nanoparticle hazard assessment originated from data generated from studies investigating mechanisms of particulate air pollution toxicity. Research led by Prof. Ken Donaldson, while at Edinburgh Napier University (1992 – 2002), pioneered the understanding behind the potential toxicological effects of exposure to the nano component of inhaled air pollution particulates. Work led by Prof. Vicki Stone, while at Edinburgh Napier University (1996 – 2010), Dr Gary Hutchison (2007 – present) and Dr Peter Barlow (2011 – present) demonstrated that increased lung inflammation and macrophage recruitment was driven by the production of reactive oxygen species (Source 3.2) within cells of the lung. Research published by the team has defined that *in vitro* toxicity assays are predictive of *in vivo* exposures, and can facilitate mechanistic studies and reduce the number of animals required for toxicity testing (Source 3.6).

The 2003 Department for Environment, Food and Rural Affairs (Defra) commissioned study (Source 3.7), conducted by Edinburgh Napier University, highlighted that the composition and size of the particles were important parameters in induction of inflammatory-driven pathologies in the lungs of animals, and that this toxicity could be predicted using cell models, and could be further correlated to the particles' physicochemical features. This research provided new evidence that particle characteristics drive toxicity, particularly via oxidative stress, often synergistically in the presence of metals. It was also noted that particle size, dose and geometry, could affect the deposition and clearance of material by host defence cells, in particular alveolar macrophages (Source 3.5).

GSK's dry powder drug formulations for inhaled delivery depend upon compound potency, coupled with the physicochemical properties of the molecule. Once administered to the lung, the drug properties have the potential to illicit a host defence mechanism resulting in drug failure. Many side effects that GSK reported in pre-clinical hazard assessment benefit from knowledge gained from the inhaled particle toxicology field. A Knowledge Transfer Partnership (KTP) was designed to investigate more effective and efficient screening of inhaled drug candidates. Development of inhaled therapeutics for asthma treatment involves assessment of targeted pharmacological activity *in vitro*, followed by assessment of pharmacological and toxicological impact *in vivo.* A significant number of drugs tested in animal models fail due to the development of delayed pathology associated with macrophage activation. Sometimes this pathology will be observed in one animal species (e.g. rodent) but not in another (e.g. dog). One of the primary cells involved in this response is the alveolar macrophage (the immune cell responsible for clearance of foreign particles and pathogens from the lung). The ability of macrophages to activate or phagocytose drug material could lead to reduced efficacy, or evoke an undesirable pro-inflammatory response, ultimately resulting in local toxicity leading to compound de-selection. The KTP project was set up

to better understand the use of assays designed to measure oxidative stress and toxicity in isolated macrophage cells, identify the most suitable cell system to carry out appropriate screening strategies for new inhaled molecules, and assess whether they could predict the response subsequently recorded in animal studies. The research and staff profiles of the team at Edinburgh Napier University were observed by GSK and resulted in this KTP project being developed.

3. References to the research

Key references all published (**Edinburgh Napier Staff at time of publication – highlighted in bold**) in peer-reviewed journals:

3.1 Lu S, Duffin R, Poland C, Daly P, Murphy F, Drost E, Macnee W, **Stone V,** Donaldson K. (2009) Efficacy of simple short-term in vitro assays for predicting the potential of metal oxide nanoparticles to cause pulmonary inflammation. Environ Health Perspect. 117(2):241-247.

3.2 Wilson MR, Lightbody JH, Donaldson K, Sales J, **Stone V.** (2002) Interactions between ultrafine particles and transition metals in vivo and in vitro. Toxicol Appl Pharmacol. 184(3):172-179.

3.3 Stone V, Donaldson K. (2006) Nanotechnology: Signs of Stress. Nature Nanotechnology 1(1):23-24.

3.4 Maynard AD, Aitken RJ, Butz T, Colvin V, Donaldson K, Oberdörster G, Philbert MA, Ryan J, Seaton A, **Stone V**, Tinkle SS, Tran L, Walker NJ, Warheit DB. (2006) Safe handling of nanotechnology. Nature 444(7117):267-269.

3.5 Barlow PG, Clouter-Baker A, Donaldson K, Maccallum J, Stone V. (2005) Carbon black nanoparticles induce type II epithelial cells to release chemotaxins for alveolar macrophages. Part Fibre Toxicol 2:11.

3.6 Brown DM, Hutchison L, Donaldson K, **Stone V.** (2007) The effects of PM10 particles and oxidative stress on macrophages and lung epithelial cells: modulating effects of calcium-signaling antagonists. Am J Physiol Lung Cell Mol Physiol 292(6):L1444-L1451.

Peer-reviewed grant applications that supported this work:

Dr Hutchison and Prof. Stone – Host institution, Edinburgh Napier University
The impact of in vitro models on drug attrition
KTP programme. January 2010 – February 2012 (£143,232).

Prof. Stone and Dr Hutchison – Host institution, Edinburgh Napier University
Contract research: In vitro acute hazard assessment of six GSK samples
GSK. August 2009 – February 2010 (£63,000).

Prof. Donaldson and Prof. Stone – Host institution, Edinburgh Napier University
Molecular mechanisms of nanoparticle induced toxicity
Colt Foundation Trust (£287,282).

4. Details of the impact

Research into particle hazard assessment in relation to human health, carried out at Edinburgh Napier University over the past 20 years, has informed policy and funding strategy for the European Commission, Non-Governmental Organisations, and the United Kingdom Government. For example, numerous scientific reports commissioned by Defra – REFNANO, HARN, CELLPEN and EMERGNANO (all published online), were completed by Edinburgh Napier University. This work contributes to, and raises the profile of, our other work in providing expert advice on particle toxicology to the World Health Organisation and evidence for the Government-commissioned

reports published by the Royal Society/Royal Academy of Engineering (2003), the Royal Commission, and the Department of Health's Committee on the Medical Effects of Air Pollution (COMEAP).

The KTP has demonstrated that a number of different *in vitro* screening assays can be applied to potential inhaled candidate molecules. Although relatively few assays that were examined appeared predictive of an *in vivo* effect, they permitted a ranking of risk factors among potential candidates. The KTP also demonstrated that *in vitro* cell lines produce similar results to primary cells isolated from a rat and dog, which allows more efficient screening of molecules and reduction in animal usage. The impact of the project resulted in reduction and replacement of animals in pre-clinical testing, by providing *in vitro* models that reflect the *in vivo* responses GSK had previously observed. Overall, the partnership delivered on its objectives set by GSK (Sources 5.1, 5.2 and 5.3).

The transfer of knowledge from Edinburgh Napier University to GSK informs the pre-clinical team as to the selection of potential drug candidates. This was achieved by providing biological data to underpinning physiological responses to drug substances, and identifying potential differences in response between animal test species. The longer term impact is that candidate compounds not suitable for clinical use are taken out of the production line much earlier, reducing cost and accelerating patient access to new therapeutics. The KTP facilitated the development of experimental methodology, the training of five GSK personnel in harvesting of pulmonary macrophages via bronchoalveolar lavage (BAL), and in the analysis of BAL samples in animal safety studies. The contribution and impact to GSK, having implemented study KTP recommendations (Source 5.2, KTP published report, 2012), has resulted in a shift in approach to earlier hazard assessment by the inhaled sciences division of the company (Source 5.1). The identified benefit from the KTP will reduce drug development costs and reduce attrition, delivered via data-driven development decisions. Savings will span company functions. This is estimated to be approximately £7 million over a five-year period if the decision to cease progression of just one molecule was made, based on the result of the research conducted (Source 5.2).

The extent of the impact generated from the KTP is two-fold. The first activity directly changed was screening strategies carried out within the company line functions (Source 5.1 and 5.2). Secondly, the KTP associate presented orally at internal line meetings, and larger company symposia, which allowed the findings and key messages to percolate through the company to key stakeholders (Source 5.4). As highlighted in GSK's KTP report, this work will influence programme teams across the United Kingdom (UK) and US arms of the company (Source 5.2). The project has had wider impact and Dr Hutchison, from Edinburgh Napier University, has been recognised for his significant research into the field of hazard assessment, particularly the work of the collaborative KTP project, and was invited (December 2012) to become a member of Defra's new Hazardous Substances Advisory Committee (HSAC; source 5.5). The Committee remit is to inform and guide UK Government Ministers on policy such as pharmaceutical testing strategies and their impact on the environment. HSAC will also lead on developing a stance, and guiding policy, on issues surrounding new emerging technologies and their impact on society. Dr Hutchison has already contributed to the guidance document "Hazard and Risk Assessment of Substances: The HSAC Approach", published June 2013, to advise Defra's Chief Scientific Advisor and the Minister responsible for HSAC.

Collectively, these pieces of evidence demonstrate the real world impact, above and beyond academic beneficiaries, that Edinburgh Napier University's research, in the area of particle toxicology assessment, has had.

5. Sources to corroborate the impact

5.1 Testimonial from GSK towards the impact of the work *(document can be made available to the panel on request)*.

5.2 KTP published report: Hutchison GR (2012) Knowledge Transfer Partners Final Report

KTP007664 (special reference to the section completed by GSK as company partner) *(document can be made available to the panel on request).*

5.3 Independent assessment of the success of the KTP. http://forms.ktponline.org.uk/printtemplates/store/CL_KTP0076645fa3188d-b127-4115-a421-a86b95fee39e.pdf.

5.4 GSK research findings presented at the international EUROTOX 2012 meeting, in Stockholm. The EUROTOX 2012 scientific programme spans the variety of interests for academia, industry and regulatory agencies from around the world, and covers the significant developments and achievements in science, and in regulation.

EUROTOX 2012, Stockholm, "Safety science serving society", 48th Congress of European Societies of Toxicology, 17-20 June 2012, Stockholm Waterfront Congress Centre, Sweden *(document can be made available to the panel on request).*

5.5 Dr Hutchison being invited to become a member of UK Government HSAC committee based in Defra – Letter from the Parliamentary Under Secretary in recognition of expert knowledge *(document can be made available to the panel on request).*

5.6 HSAC approach on hazard and risk assessment of substances. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/209709/hsac-hazard-risk-assessment-substances.pdf.