Human Models for Human Disease: The Animal Replacement Centre of Excellence

Dr Alpesh Patel

There are very few topics that can initiate the same level of heated and polarised debate as when discussing the use of animals in medical research. I'm sure that many of us can recall such heated debates, either within the formal setting of a university debating society, sensationalised televised debates, or increasingly in modern times, through the various social media channels. During the course of these debates, even as an observer, one cannot help forming their own views and in decades gone by the argument would often centre on compassion and ethics. This ethical focus, whilst implicit, is changing and frequently the theme of discussion centres around that of animal 'alternatives' or the myriad of technologies now available to assist the accelerated field of 'animal replacement'.

It is important to appreciate that in this context 'animal-replacement' can be used as a suitable term to describe either the avoidance of using animals or replacement in a direct sense. Increasingly, animal-replacement features the avoidance of animal-models altogether to develop, validate and apply human models for human disease and consequently improve human relevancy or to address the issues surrounding the so called, 'translational-gap'.

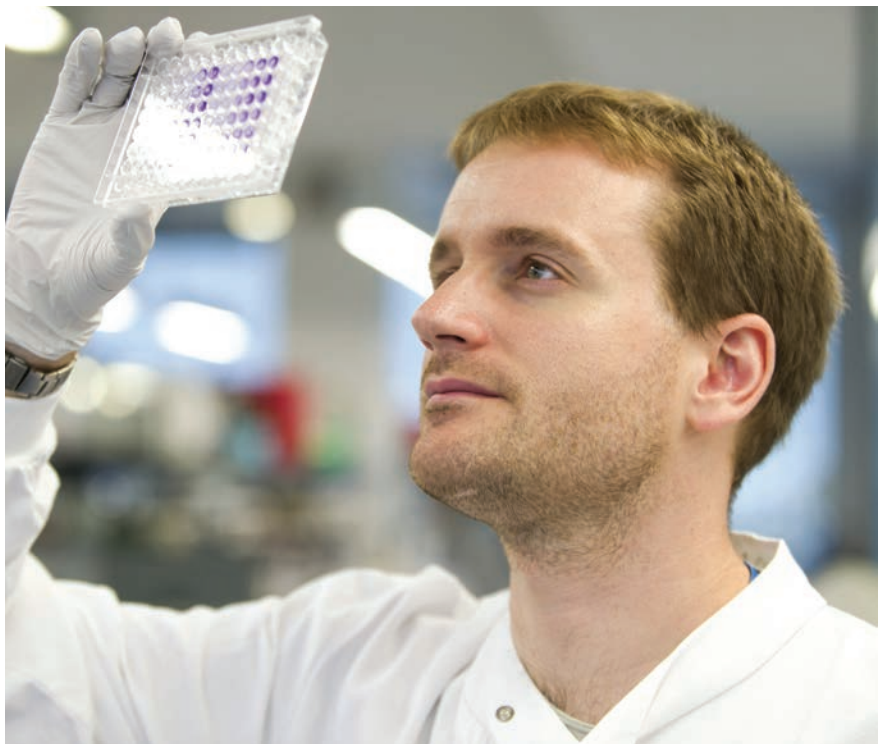
The DHT's Science Director Dr Brett Cochrane & Kerry McCarthy MP at the launch of The ARC

The evidence for the need to use "human-relevant methods" to understand human disease is growing. Over the past few years, many papers have been published, identifying the issues surrounding the use of animals in biomedical research as well as showing us how research can and should take place without the need to use animals (Akhtar, 2015; Pound & Bracken, 2014; Kehinde, 2013; Pound *et al*., 2004).

Artificially emulating human disease physiology or elucidating human toxicity pathways can be immensely complex and varied. It is imperative that to continue advancing our understanding of human biology and to ensure we have an increased approval rate of safe and effective drugs reaching the market we should fully embrace the ever-growing toolbox of non-animal technologies. Multidisciplinary research activities are now common place - biologists, chemists, physicists, engineers, mathematicians and computer scientists working together to implement the next generation of technologies to advance human health and reduce the reliance on often unreliable (and ethically questionable) animal-models. Many such approaches are already in existence and available to be used now or are in the later stages of official scientific validation (through official reference laboratories such as EURL-ECVAM) or scientific acceptance. There is still much work to be done, not only in animal-replacement technology development and validation but also to address societal norms and an institutionalised culture of animal-model reliance. A recent Ipsos MORI poll investigating public attitudes to animal research in 2016 reported that while 71% of the public accepted the use of animals in scientific research (featuring defined caveats), 74% of the public agreed that more work is needed into alternatives to animal research.

The Dr Hadwen Trust (DHT), a UK based charity dedicated to the promotion and funding of animal-replacement research activities has over the last 5 years alone invested in excess of £4 million addressing the public desire that more work should be done to reduce the reliance on animal-models through many different avenues. Late in 2016 the DHT and Queen Mary University of London, opened the Animal Replacement Centre of Excellence (The ARC) at their, world renowned, Blizard Institute.

The partnership between the DHT and the Blizard Institute to create the ARC was focussed around a shared ethos of scientific excellence and the continued development and application of human models for human disease. The initial research focus for this £1 million initiative over the next 5 years is cancer. In particular skin, head and neck cancers but with some aligned activities to breast and prostate cancers. Whilst this initial financial commitment is for 5 years, the vision is to continue expanding the ARC to advance the enormously skilled and multi-disciplinary team that it currently has.



Dr Adrian Biddle, DHT Lecturer ©NC3Rs

As stated by Rangarajan *et al*. in their 2003 Nature Reviews Cancer paper; "Laboratory mice have represented a powerful experimental system for understanding the intricacy of human cancer pathogenesis. Indeed, much of our current conceptualization of how tumorigenesis occurs in humans is strongly influenced by mouse models of cancer development. However, an emerging body of evidence indicates that there are

fundamental differences in how the process of tumorigenesis occurs in mice and humans." The theme of such comments is becoming more common place and Mestas & Hughes, in their 2004 Journal of Immunology paper stated; "As therapies for human diseases become ever more sophisticated and specifically targeted, it becomes increasingly important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with examples of therapies that work well in mice but fail to provide similar efficacy in humans" The Animal Replacement Centre of Excellence at Queen Mary's Blizard Institute is directly aiming to help address these issues through a number of techniques and approaches and all in a coordinated manner. With other important supporting activities at the Blizard Institute the ARC is already attracting attention from all over the capital which we hope will expand nationally.

The ARC will be led by Professor Mike Philpott with close academic support from DHT lecturer, Dr Adrian Biddle, and a team of post-doctoral research scientists all dedicated to the creation and success of this important animal-replacement facility. Using innovative scientific approaches, the ARC will accelerate the development of human models for human disease and help reduce the number of animals currently used in cancer research.

Peter Egan & QMUL's Professor Mike Philpott at the launch of the ARC

Additionally, the ARC aims to further develop the most robust and applicable non-animal research methods for human cancer by addressing the limitations of both poorly performing cell-based approaches and animal-models. As stated, the over-dependence on mouse models in particular has slowed progress in cancer research, and can provide misleading data. There is therefore a pressing need for human focussed non-animal technologies that have demonstrable relevance to human cancer – The ARC aims to directly address this issue.

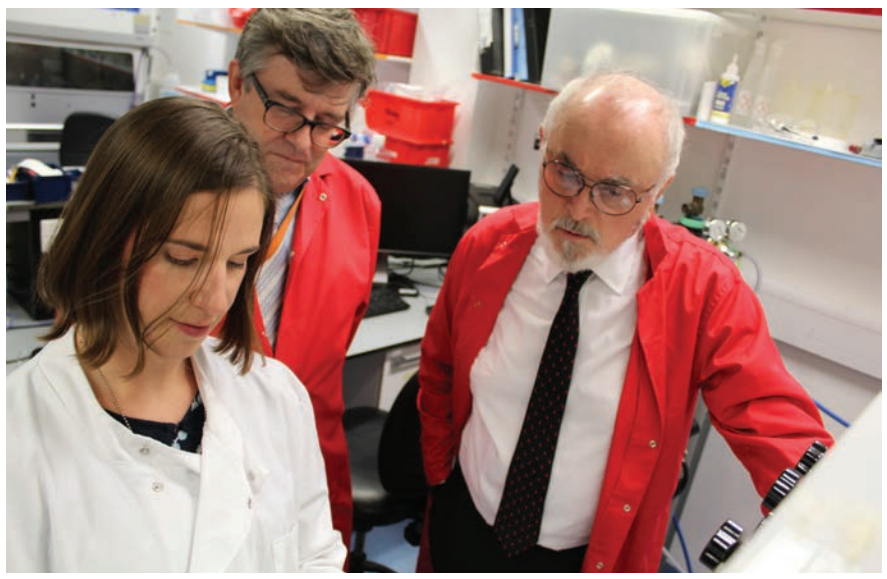
Professor Mike Philpott has been Professor of cutaneous biology at the Blizard Institute, Queen Mary, University of London (QMUL) since 2005. He has a long history of developing non-animal based research methods that are highly human-relevant. His PhD, from the University of Oxford, was entitled 'Studies on isolated hair follicles' from which he published on the *in vitro* culture and growth of human hair follicles now referred to as the 'Philpott model'. From Professor Philpott's early scientific research, the full focus is now on the role of 'Gli' in human skin cancer and *in vitro* modelling of skin carcinogenicity and human basal cell carcinoma.

Laboratory facilities at the Blizard Institute where the Animal Replacement Centre of Excellence is based

The programme of work at the ARC is a continuation of *in vitro* research from both Professor Mike Philpott and Dr Adrian Biddle, where they have identified heterogeneous cancer stem cell sub-populations in human cancer cell lines growing in 2D culture, fresh tumour specimens transplanted into 2D culture, and in direct analysis of fresh tumour specimens. They have shown that cancer stem cell sub-populations differ in both their invasive ability and their resistance to chemotherapeutic drugs (Biddle *et al*., 2011; Biddle *et al*., 2016). The demonstration that cancer stem cell sub-populations can be modelled using cell lines *in vitro* provides an opportunity for the development of novel therapeutic strategies targeting cancer stem cell sub-populations that may otherwise survive therapeutic intervention and drive tumour recurrence.

Given the similar underlying biology of human epithelial tumours, these findings are likely to also be relevant to other cancers. However, there is currently some uncertainty over the relevance of cell culture models to human cancer, and this has driven an increase in the use of mouse models for studies of this kind. In the UK alone, approximately half a million mice are used in non-toxicological cancer research each year. As previously stated, mouse models are slow, expensive, and provide a paucity of useful data. There is therefore a pressing need for cell culture models that have demonstrable relevance to human cancer.

The research focus at the ARC is not only concerned with developing non-animal based research models but also ensuring that human-based research models are as accurate and representative of humans as possible. Together with Professor Philpott's development of relevant models for cancer, Dr Adrian Biddle will also be discerning why the current cell culture models are not fully representative of human cancer and what can be done to improve those models for drug discovery. Dr Biddle, in 2012, was awarded an NC3Rs David Sainsbury fellowship that enabled him to establish an independent research program around the theme of cancer stem cell heterogeneity and plasticity in cancer and in 2016, he was appointed to the DHT lectureship in animal replacement science within the Blizard Institute.



QMUL's Dr Ros Hannen with QMUL's Professor Mike Philpott and DHT Patron Peter Egan in one of the labs at the Blizard Institute in QMUL

Dr Biddle's work research will characterise the cellular heterogeneity of various cancer cell lines that are in current use and identify the most suitable lines for drug discovery, taking into account the relevance to the tumour of interest. Therefore, there is much that can be done to improve the use of human cell lines in cancer research and demonstrate their efficacy for therapeutic development.

Developing and applying non-animal approaches to medical research benefits both animals and humans alike and we sincerely hope that while animal experimentation will not end overnight, or unfortunately any time soon, we will soon realise the benefits of such technologically innovative and creative approaches to further advance, 'human models for human diseases'.

References

Ipsos MORI Poll: Attitudes to animal research in 2016: https://www.ipsos-mori.com/researchpublications/publications/1858/Attitudes-to-animal-research-in-2016.aspx

Akhtar A., The flaws and human harms of animal experimentation., Camb Q Healthc Ethics. 2015 Oct;24(4):407-19. doi: 10.1017/S0963180115000079.

Biddle A, Gammon L, Liang X, Costea DE, Mackenzie IC., Phenotypic Plasticity Determines Cancer Stem Cell Therapeutic Resistance in Oral Squamous Cell Carcinoma., EBioMedicine. 2016 Jan 9;4:138-45. doi: 10.1016/j.ebiom.2016.01.007. eCollection 2016.

Biddle A, Liang X, Gammon L, Fazil B, Harper LJ, Emich H, Costea DE, Mackenzie IC., Cancer stem cells in squamous cell carcinoma switch between two distinct phenotypes that are preferentially migratory or proliferative., Cancer Res. 2011 Aug 1;71(15):5317-26. doi: 10.1158/0008-5472.CAN-11-1059. Epub 2011 Jun 17.

Kehinde EO., They see a rat, we seek a cure for diseases: the current status of animal experimentation in medical practice., Med Princ Pract. 2013;22 Suppl 1:52-61. doi: 10.1159/000355504. Epub 2013 Nov 9.

Mestas J, Hughes CC., Of mice and not men: differences between mouse and human immunology., J Immunol. 2004 Mar 1;172(5):2731-8.

Pound P et al., Where is the evidence that animal research benefits humans? BMJ. 2004 Feb 28;328(7438):514-7.

Pound P, Bracken MB., Is animal research sufficiently evidence based to be a cornerstone of biomedical research?, BMJ. 2014 May 30;348:g3387. doi: 10.1136/bmj.g3387.

Rangarajan A, Weinberg RA., Opinion: Comparative biology of mouse versus human cells: modelling human cancer in mice., Nat Rev Cancer. 2003 Dec;3(12):952-9.