News & Views

UK Biobank Opens

Data on 500,000 middle-aged British individuals will become available to scientists in March.[1] The aim of the Biobank UK project is to improve the prevention, diagnosis and treatment of a wide range of serious diseases, including cancer, heart disease and depression.

The volunteers, who during the recruitment period (2006–2010) were aged between 40–69, gave blood, urine and saliva samples for future analysis, and provided medical and lifestyle details about themselves. From now on, their health will be followed in order to help scientists understand why some individuals develop certain diseases and others do not. Over the years, the not-for-profit database should develop into a powerful resource, available to biomedical scientists worldwide. According to Andrew Trehearne, Head of Communications at UK Biobank, "Anyone can apply to use the data, as long as their project is in the public interest and could bring health benefits". For researchers interested in accessing the data, the application procedure can be found at: http://www.ukbiobank.ac.uk/wpcontent/uploads/2011/11/Access_Procedures_Nov_2011.pdf

[1] Anon. (2012). *UK biobank opens in March.* [New Scientist, 07.01.2012]. Available at: http://www.newscientist.com/article/mg21328464.200-biobank-uk-prepares-to-open-for-business.html (Accessed 26.01.12).

InterNICHE Launches New Website

InterNICHE has a new website on alternatives to animal experiments in medical, veterinary medical and biological science education and training.[1]

The website has been developed to meet the needs of the international community for information on the use of alternative methods, including teachers, students and campaigners. It permits the upload of multi-language content from all parties, which will aid translation and encourage participation from the diverse international community that is involved in adapting curricular contents. Users are welcome to share news and information, and to contribute their skills, in order to build a useful repository of resources and experience. A role-based access facility defines each user's rights to view and publish data, reflecting their chosen degree of participation. New content and functionality will be announced on the *News* page.

According to the InterNICHE Co-ordinator, Nick Jukes, "A dynamic, sharing site and the decentralisation of resources and responsibilities will enhance the effectiveness and resilience of the movement for change. We are confident that the site demonstrates the viability of full replacement, and that its use will quicken the transformation of life science education and training to being fully humane and based on best practice."

One of the website's database resources is the InterNICHE *Alternatives Database*,[2] with descriptions, specifications and links for over 1000 alternatives, arranged by discipline and medium. This is available in several languages, and comprises alternatives first collated and detailed in the InterNICHE book, *From Guinea Pig to Computer Mouse*.

A novel free-access database, the InterNICHE *Studies Database*,[3] is also available to provide information on innovative and humane education and training, including alternatives to animal experiments in medicine, veterinary medicine and biological sciences.

The *Studies Database* aims to improve access to information that can support curricular transformation and replacement of animal experiments. It includes references, abstracts and other details for over 750 published studies, searchable by discipline, author and keyword. Its contents reflect major themes such as technological innovation, experience of implementation, and assessment and comparative studies. Since each study has been researched and included for its relevance to the pedagogical, ethical and economic issues presented by the use of animals, alternatives and technology in education and training, this resource can help identify specific alternative tools and approaches to enhance practical classes. A section for comments and the inclusion of some studies in favour of harmful animal use aims to encourage constructive critique and debate.

Studies on cutting-edge technology and of techniques used in medical training are also included, as they play a role in the replacement of animal experiments and in consolidating the implementation of non-animal training techniques. For example, the database provides an opportunity to research the evolution and assessment of virtual and augmented reality for laparoscopic surgical skills training.

In parallel with the InterNICHE *Alternatives Database*, the *Studies Database* can be linked into alternative search strategies. Furthermore, links to the PubMed database allow users to identify related references.

During 2012, the database is expected to double in size and new functionalities will be introduced. For example, studies will be linked to relevant products in the *Alternatives Database*, full-text versions of selected papers will be made available and more non-English studies will be included.

[1] Jukes, N. (2012). *InterNICHE*. Available at: www.interniche.org (Accessed 27.03.12).
[2] Anon. (2012). *InterNICHE Alternatives Database*. Available at: http://www.interniche.org/alternatives (Accessed 27.03.12).
[3] Anon. (2012). *InterNICHE Studies Database*. Available at: http://www.interniche.org/studies (Accessed 27.03.12).

Resignation of Director of Harvard Primate Center

Fred Wang, interim Director of The New England Primate Research Center at Harvard Medical School, resigned on 1 March 2012.[1] On 27 February, the US Department of Agriculture issued three citations for failure to comply with federal animal welfare regulations. Then, a cotton top tamarin died on 29 February, probably due to dehydration. This was the fourth monkey alleged to have died of negligence at the Center since June 2010. The Center houses more than 2,000 monkeys, and Wang had been appointed to deal with its ongoing animal welfare problems.

[1] Waters, H. (2012). *Harvard primate director resigns*. [The Scientist, 05.03.2012]. Available at: http://the-scientist.com/2012/03/05/harvard-primate-director-resigns/ (Accessed 30.03.12).

A Model of Human Implantation

Suitable models for the study of human implantation would be useful. A recent paper by Hai Wang and colleagues describes the development of a human endometrium-like three-dimensional (3-D) *in vitro* model, in which certain elements of human implantation can potentially be investigated.[1]

In order to construct the 3-D endometrial cultures, epithelial and stromal cells from both primary cultures and cell lines were grown by using fibrin-agarose as the matrix scaffold. The structure of the resulting cultures resembled that of normal endometrium, with epithelial cells localised on top as a monolayer, and stromal cells concentrated within the matrix. An attachment assay that used Jar spheroids to mimic human trophoblast cells was developed to assess the potential of this system as an implantation model. Jar cells were allowed to grow into spheroids, which were shown to secrete human chorionic gonadotrophin into the medium. The spheroids were able to attach to the epithelium, but the adhesion was strongly correlated with the various cells types present in the 3-D culture.

[1] Wang, H., Pilla, F., Anderson, S., Martínez-Escribano, S., Herrer, I., Moreno-Moya, J.M., Musti, S., Bocca, S., Oehninger, S. & Horcajadas, J.A. (2012). A novel model of human implantation: 3D endometrium-like culture system to study attachment of human trophoblast (Jar) cell spheroids. *Molecular Human Reproduction* **18**, 33–43.

Empathically-motivated Behaviour in Rats

Empathically-motivated helping behaviour is widely acknowledged to be present in non-primates, and the results of a recent study suggest that it may also be present in rats.[1]

Although rats are known to share the distress of other rats, it was not known whether they would actually aid another individual. Therefore, a study was set-up to clarify whether rodents experience empathically motivated pro-social behaviour. During each test session, which involved placing pairs of rats in an arena, one of the animals was free to roam, while the other one was locked in a restrainer. After several sessions, the free rats eventually learnt to open the restrainer to release the locked animals, but they would not open empty restrainers or those containing objects. When the rats were presented with two restrainers in the arena — one trapping a rat and the other one chocolate — they typically opened both and shared the chocolate. When an empty restrainer was paired with a chocolate-containing one, the free rats ate all the chocolate. Collectively, these observations suggest that rats show empathically-motivated helping behaviour.[2]

[1] Bartal, I.B-A., Decety, J. & Mason, P. (2011). Empathy and pro-social behavior in rats. *Science* **334**, 1427–1430.
[2] Wein, H. (2011). *Rats show empathy, too*. [NHI Research Matters, 19.12.2011]. Available at: http://www.nih.gov/researchmatters/december2011/12192011empathy.htm (Accessed 22.02.12).

ICCVAM Recommends *In Vitro* Test Method for Endocrine-disruptors

The US Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) has recommended to Federal agencies that a non-animal test method can be used as a screening tool to identify substances that can induce, or inhibit, human oestrogen receptor (ER) activity *in vitro*.

Certain chemicals can interfere with the normal function of hormones in the endocrine system, potentially affecting growth, development or reproduction. Such substances are referred to as endocrine-disruptors. The BG1Luc ER transactivation (TA) test method, also known as the LUMI-CELL® ER test method, was developed by Xenobiotic Detection Systems, Inc. (Durham, NC, USA) with the purpose of identifying substances that can induce, or inhibit, human ER activity *in vitro*. This method relies on human ovarian cancer cells to assess whether, and to what extent, a substance interferes with TA activity via an ER-mediated pathway.

Following an international validation study, which also included European and Japanese agencies, the resulting documents — the background review document, test method performance standards and ICCVAM test method recommendations — were evaluated by an independent international panel.

ICCVAM concluded that the BG1Luc ER TA test method is at least as accurate as the only ER TA test method currently in a US regulatory test guideline, and that it offers some advantages. For example, the cell line used is available from more than one source, and the test has been validated for samples with a wider concentration range, can identify oestrogen receptor agonist and antagonist activities, and has the potential to detect a wider range of ER-active substances.

The BG1Luc ER TA test method has been adapted to a high-throughput format (on 1536-well plates) and, due to promising preliminary results, it is expected that this method will be incorporated into the Tox21 screening paradigm in 2012.

Further information can be found in the ICCVAM Test Method Evaluation Report, entitled *The LUMI-CELL® ER (BG1Luc ER TA) Test Method: An* In Vitro *Assay for Identifying Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals* (NIH Publication No. 11-7850).[1]

[1] Spranke, K. (2012). *ICCVAM recommends non-animal* in vitro *method to identify potential endocrine-active substances*. [AltTox.org, 15.02.2012]. Available at: http://forums.alttox.org/index.php?topic=781.msg1184#msg1184 (Accessed 29.02.12).

An Alternative to Rat Caries Testing

In compliance with the requirements of the US Food & Drug Administration (FDA), *in vivo* caries tests are conducted on all fluoride-containing toothpastes. Alternative methods can be used, but only if data demonstrating they provide results of "equivalent accuracy" are submitted to the FDA. Results from an investigation with an *in vitro* method, the Featherstone pH cycling model, exhibited excellent correlation with data from the currently accepted animal tests, demonstrating that the *in vitro* method fulfils the FDA's requirements.

In this investigation, which is published in the *American Journal of Dentistry*,[1] the alternative model performed similarly to the animal caries model with regard to the positive and negative controls and on the response to different and/or clinically relevant doses of fluoride. Furthermore, it provided an adequate representation of the caries process, and addressed concerns on the influence of salivary and abrasive agents.

Given this information, there are strong scientific grounds for the replacement of *in vivo* caries testing by the Featherstone laboratory pH cycling model, particularly for ionic fluoride-based toothpastes.

[1] Featherstone, J.D., Stookey, G.K., Kaminski, M.A. & Faller, R.V. (2011). Recommendation for a non-animal alternative to rat caries testing. *American Journal of Dentistry* **24**, 289–294.

Microfluidic Technology Used to Model Haematologic Diseases

An *in vitro* microvasculature-on-a-chip model has been developed that could be useful for the study of the biophysical interactions involved in haematologic diseases, and for testing potential drug candidates for treating them.

In certain haematologic disorders, abnormal interactions between blood cells, endothelial cells and soluble factors (such as cytokines) contribute to the pathogenesis by leading to microvascular occlusion and thrombosis. An *in vitro* microvasculature-on-a-chip model that mimics these processes and permits a quantitative analysis of how biophysical interactions influence pathology, has been described by Tsai and colleagues.[1]

The model system involves a single-mask microfabrication process and comprises microvascular-sized fluidic channels, which have their inner surfaces completely lined with endothelial cell monolayers. As it combines blood–endothelial cell adhesion, cellular aggrega-

tion and mechanical properties (e.g. size, deformability), microvascular geometry and haemodynamics, it is ideal for studying haematologic diseases where biological and biophysical elements contribute to the pathology. By using the microvasculature-on-a-chip model, the authors have shown that, for example, the activation of leukocytes and endothelial cells by TNF-α leads to an increased rate of microchannel obstruction than that resulting from the activation of endothelial cells alone. Experiments with blood from sickle cell disease patients suggested that the drug, hydroxyurea, promotes microvascular blood flow, a finding that is essential in order to understand the drug's clinical efficacy. In addition, with shiga toxin activation, the system can be a suitable *in vitro* model for haemolytic uremic syndrome, a thrombotic microangiopathy.

[1]Tsai, M., Kita, A., Leach, J., Rounsevell, R., Huang, J.N., Moake, J., Ware, R.E., Fletcher, D.A. & Lam, W.A. (2012). *In vitro* modeling of the microvascular occlusion and thrombosis that occur in hematologic diseases using microfluidic technology. *Journal of Clinical Investigation* **122**, 408–418.

Grant for Development of Replacement Methods

A research team at the University of Liverpool, led by Dr Dominic Williams, has been awarded a £1 million grant to develop tools for assessing the toxicity of chemicals without using animals.[1] The funding was given by the NC3Rs and Defra, and AstraZeneca, Syngenta and Unilever are providing an equivalent level of in-kind contributions, including human, animal and *in vitro* data. The project will also involve collaborators at the universities of Bath, Loughborough, Oxford and Strathclyde.

[1] Anon. (2012). *Reducing UK animal testing*. [University News, University of Liverpool, 12.03.2012]. Available at: https://news.liv.ac.uk/2012/03/12/reducing-uk-animal-testing/ (Accessed 30.03.12).

International Transport of Laboratory Animals

Early in March 2012, what seemed to be an orchestrated campaign, drew attention to the problems caused to animal users by the increasing reluctance of airlines and ferry companies to transport animals destined for laboratory use into the UK.

In an article in *The Times* on 14 March, Lord Drayson, a former Minister of Science, said that, if this continued, it would mean that "the search for cures will shift to other countries", "medical research will wither in our universities", and "more people will suffer and die".[1]

This led to some lively responses, including a letter to the editor of *The Times* on 15 March, by Professor Michael Balls, Chairman of the FRAME Trustees,[2] who accused Lord Drayson of scaremongering at its absolute worst, since only about 30,000 of the 3 million animals used in the UK each year are imported, and the vast majority of the best medical research does not involve the use of animals at all.

Not surprisingly, *Nature* rushed to the support of the animal users, in an editorial,[3] and the Association of the British Pharmaceutical Industry issued a Parliamentary briefing to emphasise the importance of maintaining the flow of animals.[4]

This incident revealed the gulf which still exists between those who want to defend the use of laboratory animals at all costs and those who want to see it replaced as quickly as possible.

The next issue of *ATLA* will contain detailed comments on what took place.

[1] Drayson, Lord. (2012). *Speaking out to defend science and democracy*. [The Times, 14.03.2012].
[2] Balls, M. (2012). *Animal transport and experiments*. [Letters to the Editor, The Times, 15.03.2012].
[3] Anon. (2012). Flight risk. *Nature, London* **483**, 373–374.
[4] Callaghan, A. (2012). *Parliamentary briefing. Transporting animals for research purposes.* London, UK: ABPI.

Debate on Transposition of *Directive 2010/63EU*

On 27 March 2012, Nic Dakin MP, Chair of the All Party Parliamentary Group for the Replacement of Animals in Medical Experimentation (APPRG), for which FRAME provides the Secretariat, led a Westminster Hall Adjournment Debate on the transposition of the new EU directive on animal experimentation into UK law.[1] His main point was that there is widespread concern, not only among animal welfare groups, but also among organisations representing the main users of laboratory animals, that the UK Government might take the opportunity to water down the provisions of the UK legislation to harmonise with an EU minimum. In the absence of the Home Office Minister responsible for this area, Lynne

Featherstone MP, another Home Office Minister, Damian Green MP, the Minister of State (Immigration) replied, giving assurance that the Government is "strongly committed to ensuring the best possible standards of animal welfare and protection for animals used for scientific purposes". However, he dodged the question of whether the Home Office Inspectorate would now be run centrally from London, without the three regional offices which have functioned well for many years.

A detailed report on the debate and its aftermath will be published in the next issue of *ATLA*.

[1] Dakin, N. and others (2012). House of Commons Hansard Debates for 27 March 2012, Columns 366WH to 373WH. Available at: http://www.publications.parliament.uk/pa/cm201212/cmhansrd/cm120327/halltext/120327h0002.htm#12032751000001 (Accessed 30.03.12).

Ban on the Use of Great Apes

Great apes had not been used as laboratory animals for many years, when the then Home Secretary said, in 1998, that no licences would be issued for the use of these higher primates, man's closest relatives. However, that such use is not specifically banned by law has long been seen as a weakness, especially as organisations such as the Research Defence Society and, more-recently, Understanding Animal Research, have said that they could envisage circumstances where a case could be made for such use.

These concerns have been heightened by the inclusion in *Directive 2010/63/EU* of a clause which bans such use, but would permit Member States to seek a derogation from the Commission to permit the use of great apes, in circumstances where it could be considered essential.

The All Party Parliamentary Group for the Replacement of Animals in Medical Experimentation (APPRG) wrote to the Home Office Minister, Lynne Featherstone MP, to suggest that the UK position against the use of great apes would be weakened, if the Government did not take advantage of another clause in the Directive, by putting a ban on the face of the revised UK legislation. At about the same time, the British Union for the Abolition of Vivisection (BUAV) and FRAME made a joint submission to the Government, spelling out the unanswerable ethical welfare, scientific and logistical reasons why the ban should be made legally binding in the UK (published in this *ATLA*[1]).

Unfortunately, in her replies to both the APPRG and BUAV/FRAME, Lynne Featherstone said that, while the Government could not foresee any circumstances in which the use of great apes would be permitted in UK laboratories, the intention was to copy the derogation clause in the Directive directly into the revised UK legislation.

This point was raised by Nic Dakin MP during the Westminster Hall Debate, and Damian Green MP, standing in for Lynne Featherstone MP, said,[2] "We will continue to prohibit the use of great apes. There has been concern — the hon. Gentleman expressed it earlier — that the directive weakens the protection of those animals by providing a derogation allowing their use in exceptional circumstances. I can assure him and the House that we foresee no circumstances in which we would use that derogation, and we will put the ban in the legislation, as he asked. That is a full assurance such as he sought."

Thus, at the time of writing, the Home Office appears to be sending out two very different messages. Attempts will be made to sort out the confusion, so that a full report can be given in the next issue of *ATLA*.

[1] Thew, M., Bailey, J., Balls, M. & Hudson, M. (2012). *The Ban on the Use of Chimpanzees in Biomedical Research and Testing in the UK Should Be Made Permanent and Legally Binding*. A joint submission to the Coalition Government by the BUAV and FRAME. *ATLA* **40**, 3–8.

[2] Green, D. (2012). House of Commons Hansard Debates for 27 March 2012, Column 371WH. Available at: http://www.publications.parliament.uk/pa/cm201212/cmhansrd/cm120327/halltext/120327h0002.htm#12032751000001 (Accessed 30.03.12).