Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

Total available funding for this competition was £4m from the Biotechnology and Biological Sciences Research Council; the Defence Science and Technology Laboratory; the Engineering and Physical Sciences Research Council; the National Centre for the Replacement, Refinement & Reduction of Animals in Research and the Technology Strategy Board.

Note: These proposals have succeeded in the assessment stage of this competition. All are subject to grant offer and conditions being met.

Participant organisation names	Project title	Proposed project costs	Proposed project grant
Asterand UK Acquisition Limited (lead) University of Manchester	Development of a 3D human cell-based model of liver fibrosis - a tale of two platforms	£190,132	£152,018

Project description - provided by applicants

Many liver diseases result in the development of fibrosis, the excessive accumulation of extracellular matrix proteins. Over time this process can lead to cirrhosis (severe scarring), liver failure and often requires liver transplantation. Currently the development of drugs to treat liver fibrosis is heavily reliant on animal studies to model the complex processes involved. Although animal models of liver fibrosis have proved invaluable in understanding the development and progression of the disease, we are yet to see an anti-fibrotic drug on the market.

This project aims to create a human 3D in vitro cell-based model of liver fibrosis. If successful, this model will allow the quicker evaluation of potential new anti-fibrotic drugs. In the longer term, this will hopefully lead to the development of more effective anti-fibrotic therapies, improved treatments for patients and ultimately a reduction in the use of animals in fibrosis research and drug discovery.

Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Aurelia Bioscience Limited (lead) The Electrospinning Company Limited	Development of phenotypic assays on novel 3-dimensional platforms for pharmacological profiling of compounds	£247,839	£185,880
Project description - provided by applicants			
This project aims to develop novel phenotypic screening systems in which cells are grown in 3D in electrospun polymer microscaffolds in suspension and to evaluate this system with stem cells, recombinant cells and primary cells in a suite of model assays using luminescence, fluorescence and imaging readouts. Adherent cells in 3D could be manipulated as if they were in suspension, providing convenience in passaging and plating, facilitating the adoption of more physiologically relevant 3D assays in high throughput systems. The project is led by Aurelia Bioscience, an SME Contract Research Organisation, with expertise in developing cell-based assays and in phenotypic screening, in collaboration with The Electrospinning Company, an SME with expertise in development and manufacture of polymer scaffolds for 3D cell culture. Takeda Cambridge will provide guidance to ensure the technology remains commercially relevant throughout the development project as well as transferring technology for specific assays of importance to their drug discovery programme.			

Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Avanticell Science Limited (lead) Tissue Click Limited University of Nottingham	Automation of 3D cell model assembly by additive printing	£249,801	£214,293
Project description - provided by applicants			
Cell-based analysis is a key technology in preclinical development of new drugs and healthcare products. By use of ethically-sourced human cells it is an attractive alternative to, and replacement for, animal testing. There is incentive to make cell-based analysis models as tissue-like as possible, making them 3-dimensional instead of conventional 2D cell cultures. This should confer analysis based on these models with high predictive value, but this increases the technical difficulty, and the time and resource needed to assemble the models. The project will test the feasibility of manufacturing cell-based analysis models by additive printing of both the cells and their supporting biological scaffolds into the multiwell culture dishes typically used in preclinical screening of candidate drugs. A successful demonstration of additive printing in this context will create opportunity to build new cost-effective, automatable manufacturing processes for cell-based systems. This innovation will have significant commercial value in a market sector worth >$2Bn world-wide; it will also increase end-user screening efficiency and, in so doing, reduce new drug development costs and shorten development time.			

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Cellesce Limited (lead) Cardiff University	Bioreactor and Bioprocessing of organoids to enable their market-wide drug screening application	£249,982	£218,733
Project description - provided by applicants			
Organoid culture is a new technique that, unlike the use of cell lines, maintains tumour properties in the lab. Organoid cultures should improve the rate at which new drugs are discovered since they should lower the number of ineffective drugs that make their way through animal testing; this will directly lead to new, more effective drugs plus reductions in animal usage in early-stage testing. Realising the potential of organoids in these roles is currently limited by the small numbers of organoids that can be grown in the lab and the expansion of organoid growth is a bottleneck in wider progress, i.e. the ability to supply organoids to pharmaceutical company customers. Therefore the aim of this new collaboration is to develop a bioreactor and accompanying bioprocess to scale up organoid culture. 3D cultures have been developed from a number of different tumour types; however we have chosen to focus initially on colorectal cancer. This particular tumour type is the third biggest cause of cancer morality within the U.K. with approximately 5,000 new cases per year in Wales alone. Ultimately we aim to expand this platform to other tumour types.			

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
CN Bio Innovations Limited (lead) XenoGesis	3D cell culture model for studying Non-Alcoholic Fatty Liver Disease (NAFLD).	£145,802	£100,211

Project description - provided by applicants

Non-alcoholic fatty liver disease (NAFLD) encompasses a range of conditions from fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH). NAFLD is a condition affecting around 30 % of the general population and 70 % of obese and diabetic patients. The prevalence of NAFLD is set to rise as the obesity and diabetic pandemic escalates.

It is therefore important that there are tools available to investigate this disorder; however current in vitro models for NAFLD research are limited. To address this we aim to create models to study NAFLD using CN Bio's proprietary 3D in vitro primary human hepatocyte culture system, LiverChip.

The goals of this project are to generate and characterise commercially viable models for NAFLD research, which will then be exploited for xenobiotic studies. This project will be a collaborative work between CN Bio and Xenogesis.

Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

Note: These proposals have succeeded in the assessment stage of this competition. All are subject to grant offer and conditions being met.

Participant organisation names	Project title	Proposed project costs	Proposed project grant
Gentronix Ltd (lead) University of Swansea	Reducing animal use through more accurate in vitro mutagenicity testing	£248,982	£210,463
Project description - provided by applicants			
Continued innovation by the diverse chemical sectors is expected to provide new, better and more effective medicines, herbicides, pesticides and consumer products. The public expects these to be safe as well as effective. Cancer risk is perhaps the most concerning. The most potent carcinogens are mutagens: compounds that alter the DNA sequences in our cells. Tests that identify mutagens using bacteria or human/animal cells grown in laboratories have been in use since the 1970s, and they have been effective in ensuring chemical safety. However, these tests often produce positive results for non-mutagens - 'false positive'. This means that many potentially useful or even life-saving chemicals will have been lost due to misplaced safety concerns. To identify false positives, the number of animals used before exposing humans, is increased - often finding that the compounds are indeed carcinogens. The obvious solution is the development of more accurate cell-based tests, which will reduce this use of animals and bring more useful and safe products for people to use: and that is the ambition of this project.			

Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Inocardia Limited (lead) Coventry University	InoCardia: Human Traberculae Work-Loop Feasibility	£247,898	£206,229
Project description - provided by applicants			
When drugs are developed to treat a particular disease they sometimes have side effects that cause damage to the heart. Occasionally these dangerous side effects are only recognised after the drug has been marketed and thousands of patients have been treated. This is a significant risk to human health and causes very high costs to the pharmaceutical industry when a potentially dangerous product is withdrawn from market. Although side effects of drugs can be caused by many things, one area of great concern is the effects of drugs on the force that that heart muscle can produce during its role in pumping blood around the body. Current drug testing relies mainly on the use of animals, often via tissue taken from animals, such that the tests do not do well in predicting the effect on humans. Therefore, we need to develop a test that uses human heart muscle tissue in a way that can efficiently test many drugs to reduce the risk of any approved drugs causing damage to the heart.			

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

Note: These proposals have succeeded in the assessment stage of this competition. All are subject to grant offer and conditions being met.

Participant organisation names	Project title	Proposed project costs	Proposed project grant
Kirkstall Limited (lead) ELISHA Systems Ltd Manchester Metropolitan University	CVTox - Development of a Co-Culture Cardiovascular Toxicological Model	£249,359	£212,219
Project description - provided by applicants			
Cardiovascular diseases account for more than 150,000 annual deaths in UK, affect more than 5 million people and cost more than £30bn a year to treat. To tackle this problem, drug companies and academics are trying to find new ways to expand our understanding of the causes of cardiovascular disease, and develop new ways of treating them. Usually, this research involves the use of animal models. Tests in animals are often unable to accurately predict what will happen in a human when a drug is given, leading to unexpected harmful effects in patients. The aim of our project is to develop a model of the cardiovascular system, using human cells, in a circulating system to allow the cells to communicate and detecting their response to drugs using state-of-the-art biosensor chips. This physiologically-relevant model will be a major step towards study of cardiovascular diseases and therapies in the laboratory without using animals. The models developed in this project could help drug companies identify which drugs are going to be useful and which drugs will be harmful, helping them to develop safe and effective new treatments for cardiovascular diseases, and saving human and animal lives.			

Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

Note: These proposals have succeeded in the assessment stage of this competition. All are subject to grant offer and conditions being met.

Participant organisation names	Project title	Proposed project costs	Proposed project grant
Kirkstall Limited (lead) Queen Mary University of London Foundation University of Leeds	Neuro-Tox: A novel integrated BBB-brain model for comprehensive drug permeability and toxicity testing	£249,999	£218,737

Project description - provided by applicants

The blood–brain barrier (BBB) is composed of different specialised cell types and regulates exchange of substances between the blood and the brain. There are a large number of diseases including stroke, brain trauma and tumours in which the permeability of the BBB is increased. Conversely, many drugs are unable to cross the BBB to reach the brain making the BBB one of the major obstacles in the treatment of the brain diseases. Proper regulation and maintenance of BBB is, therefore, essential for effective drug delivery to the brain to cure brain diseases and preventing its further damage.

In this project we aim to develop a three dimensional in vitro BBB model using the Kirkstall Quasi-Vivo system which allows multiple cell types to be cultured in inter-connected culture chambers and a method of assaying the passage of potential drugs across the BBB by electrochemical and laser biosensors. This in vitro model will be an important tool for investigation of different aspects of BBB function and testing potential drugs for their permeability and toxicity and reducing animal usage in this area. Human cell based models should be more accurate and predictive than animals.

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
MIca Biosystems (lead) Keele University XenoGesis	Development and validation of a dynamic drug screening platform for ADME testing.	£243,838	£172,761
Project description - provided by applicants			
The Caco-2 cell line is the gold standard for the prediction of drug absorption and permeability in vitro by mimicking the small intestine. However, this model lacks the dynamic motion which represents one of the physiological functions of the small intestine (peristalsis). In our research, we investigate the possibility the similarity between the static Caco-2 cell model and the dynamic intestine by creating a dynamic in vitro environment using MICA technology. Our results to date have shown that MICA' technology improves the absorption of the selected drugs, and their permeability is more similar to that found in the human intestine. Our data suggests that MICA' technology applied to Caco-2 drug permeability assay could be used to a better predict, using in vitro assays, the in vivo human drug absorption rates. This feasibility study will enable us to test rigorously against the gold standards and generate a new assay for the pharmaceutical market. Our research will lead ultimately to a reduction in animal research and more drugs coming through the pipeline to applications in healthcare.			

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
NPL Management Limited (lead) Epistem Limited	Evaluating spectroscopic imaging of living skin equivalents as a new approach for topical formulations research	£244,221	£166,197

Project description - provided by applicants

In vitro product testing is a vital part of product development for topical applications and devices and this project seeks to establish a powerful non-animal approach as a new method for providing a greater understanding of percutaneous absorption of topical formulations in pre-clinical studies.

This project aims to develop label free imaging of drugs by mass spectrometry imaging (MSI) and stimulated Raman spectroscopy (SRS) in human living skin equivalents (HSLEs). We propose to undertake the first comparison of each of these techniques for imaging of drugs and to gather data to allow a robust evaluation of the penetration profiles of pharmaceutical compounds in human and pig ex vivo skin, and in an HLSE.

In addition, we will introduce significant novelty and new metrology to support the application of the HLSEs and spectroscopic imaging to provide reliable and transferable protocols. The ultimate aim of this project is to support the 3Rs via the delivery of a non-animal model and novel chemical imaging protocols which are validated for topical formulation testing to allow reliable predictions of safety and efficacy in clinical studies.

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Renishaw PLC (lead) Clyde Biosciences Ltd Heriot-Watt University	3D Stem Cell Printing for Animal-Free Drug Development	£249,735	£205,959
Project description - provided by applicants			
Printing tissues and mini-organs has recently been achieved by using modified ink-jet printer technology in the field of biofabrication. The novel method of direct printing live cells opens up new paradigm in tissue science for drug discovery and therapeutic applications. This project aims to develop the first commercial stem cell bioprinter based on the valve-based printing methods pioneered at Heriot-Watt University, capable of printing human embryonic stem cells without damage. We will develop a new printer by integrating a 3D printing platform with optimised valve based cell printing technology. The new platform will then be validated for producing human heart tissues using human induced pluripotent stem cells by leading specialists Roslin Cellab Ltd. The new tool will not only allow us to produce high quality human tissue for potentially more reliable animal free drug testing, but also enable a range of high throughput applications for pharmaceutical industry, biotechnology companies and stem cell biologists.			

Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Sirius Analytical Instruments Limited (lead) University of Bath	Evaluation of in-vitro tests to reduce animal testing in drug toxicology studies	£249,229	£208,559
Project description - provided by applicants			
Tens of thousands of animals are sacrificed every year in the UK during drug toxicity testing; many more worldwide. Toxicity testing is an important part of drug development. Newly discovered molecules are tested, as well as metabolites and new formulations. The tests are generally done on rats, mice and dogs. Many of these tests are not actually done to test toxicity, but in preliminary studies to gather data used to design the final toxicity study. This preliminary data is used to design fit-for-purpose formulations, mainly for orally-administered drugs. We believe that most preliminary experiments using animals could be replaced by in-vitro tests. In this project, Pfizer will supply data from completed toxicological studies. Sirius will re-create the formulations and run in-vitro experiments to assess physicochemical characteristics and bioavailability. Scientists at the University of Bath will analyse the in-vitro data and look for IVIVC (in-vitro/in-vivo correlation). If the project is able to demonstrate that fit-for-purpose formulations can be assessed using in-vitro experiments, some 50% of animal experiments for testing drug toxicity could be eliminated.			

Technology Strategy Board
Driving Innovation

Results of competition: Advancing the development and application of non-animal technologies - Feasibility studies

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Unilever Research and Development Colworth (lead) University of Bath	Capillary Bed Bioreactor: Improved Estimation Of Dermal Bioavailability	£248,428	£198,199
Project description - provided by applicants			
Historically, animal testing has been used to support risk assessment related to cosmetic ingredients. However, in recent years, there has been a continuous drive to reduce the level of animal testing undertaken to support risk assessments for new cosmetic products, and a move towards a mechanistic understanding of human toxicology (incorporating exposure-based risk assessment). Consequently, the development of non-animal models for predicting the safety of new chemicals is necessary to generate data leading to increased confidence in predictions of in vivo scenarios. The model used by Unilever to assess dermal bioavailability utilises skin (from elective cosmetic surgery procedures) in diffusion cells, and the permeation of a test item through the skin is monitored over time. While this has proved to be an adequate model, little is known regarding chemical clearance via dermal capillaries. The proposed capillary bed bioreactor (CBB) better replicates the in vivo environment of the skin and its blood supply by providing a bed of pseudovascularisation in the form of hollow fibre membranes.			

Technology Strategy Board
Driving Innovation

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
Unilever Research and Development Colworth (lead) University of Cardiff	3D-DIP-ChIP: an 'omics'-based method for measuring genotoxin induced DNA damage	£211,192	£173,790
Project description - provided by applicants			
Industries across a broad spectrum of sectors are now generating increasing numbers of innovative and novel compounds and products, which have the potential to bring enormous benefits to society. Many of these novel compounds will become incorporated into products that will bring continued economic growth and improve global living standards. However, the safe introduction and release of these new materials into the world requires safety assessment prior to their use. At the moment, many of the methods employed to do this were developed in the middle of the last century, and rely heavily on the use of animals. It has become increasingly clear that these methods have limitations, including their speed, scale of use, accuracy and predictivity of various outcomes and relevance to the human context. There is now a concerted global effort to develop novel non-animal methods that will more quickly and accurately predict the safety of novel compounds being produced. The work described in this project will evaluate the potential of a novel method developed in the UK using genomic technology to be used in the assessment of novel materials.			

Technology Strategy Board
Driving Innovation

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Participant organisation names	Project title	Proposed project costs	Proposed project grant
XCellR8 Limited (lead) Frame Inventya Limited Lush Retail Limited	Non-animal replacement tests for acute toxicity testing	£235,418	£181,944

Project description - provided by applicants

The Cosmetics Regulation prohibits the testing of cosmetic products and their ingredients on animals, as well as the marketing of cosmetics and their ingredients that have been tested on animals for cosmetic purposes. The ban came into full effect on 11 March 2013 and was the culmination of several decades of campaigning with huge public support.

This progress is now under threat by the EU REACH regulations, which still require certain animal tests to be performed. This regulatory clash presents the UK / EU cosmetics industry with an enormous dilemma and places the future of the industry under significant threat. Animal testing has long been a highly emotive issue in the cosmetics sector and a major market driver. REACH is broadly supportive of alternatives to animal testing, but still requires animal tests where there are currently no validated alternatives available. Non-animal replacement tests are urgently needed which are both scientifically advanced and ethically sound.

The project partners will explore the feasibility of developing replacement tests for acute toxicity that are scientifically relevant and sufficiently robust and reproducible for (ultimate) adoption as OECD Test Guidelines.