



## Competition Title CRACK IT CHALLENGES

### INVITATION TO TENDER

This Invitation to Tender should be read in conjunction with other documents associated with this competition. These can be downloaded from

<http://www.innovateuk.org/content/competition/sbri/nc3rscrack-it-challenges.ashx>.

Applicants should also consult the NC3Rs CRACK IT website for additional information ([www.crackit.org.uk](http://www.crackit.org.uk)). The Guide for Participants ([www.crackit.org.uk/guideforparticipants](http://www.crackit.org.uk/guideforparticipants)) provides further details of the competition and includes the rules applying to the industry sponsors.

### SUMMARY

Applicants are invited to tender for projects under the SBRI Programme to develop technologies with potential **3Rs** (Replacement, Refinement and Reduction of animals in research) benefit into new products and methodologies for the global biosciences research community. The projects are detailed in the Challenges Brief (**see Appendix 1**).

### APPLICATION PROCESS

SBRI competitions are open to all organisations in the public and private sectors. The SBRI scheme is particularly suited to small and medium-sized business, as the contracts are of relatively small value and operate on short timescales. Academic organisations are equally eligible to apply under the scheme where the proposals are focused on delivery of solutions rather than on fundamental research. Developments are 100% funded and focused on specific identified needs, increasing the chance of exploitation. Suppliers for each project (the Contractors and its Subcontractors) will be selected by an open competition process and retain the intellectual property generated from the project, with certain rights of use retained by the contracting body (the NC3Rs) and the industry sponsors. This is an excellent opportunity to establish an early customer for a new technology and to fund its development.

Details of the Challenges and expected outcomes of the projects can be found in the Challenges Brief (below). All bids should be made using the Application Form (SBRI\_NC3Rs\_75\_004 Application Form), which can be accessed from <http://www.innovateuk.org/content/competition/sbri/nc3rscrack-it-challenges.ashx>. You are strongly advised to read the Guidance Notes (SBRI\_NC3Rs\_75\_003 Guidance Notes) before completing the Application Form.

## Key Dates:

|  |                               |
|--|-------------------------------|
| Application process opens                        | 20 September 2011             |
| Deadline for applications                        | 2 November 2011 at 12:00 noon |
| Applicants notified of Review Panel decisions    | 25 November 2011              |
| Presentations to Challenge Panel meetings        | 7 and 8 December 2011         |
| Applicants notified of Challenge Panel decisions | 16 December 2011              |
| Announcement of winners                          | 25 January 2012               |

## CHALLENGES BRIEF

### Background

The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) is an independent scientific organisation, tasked by Government with supporting the UK science base through the application of the 3Rs. It is the UK's largest funder of 3Rs research.

The biosciences sector faces significant scientific, industrial and regulatory challenges relating to the use of animals. This provides exciting opportunities to engage the scientific community in developing solutions to current problems which not only minimise animal use but also stimulate innovation. These problems are many: the decreasing productivity of the pharmaceutical industry with animal models often cited as bottlenecks in drug discovery and development; the complex regulatory environment surrounding the chemical and consumer products industries and conflicting pressures on animal use; and the increasing scrutiny of the quality and value of animal research in the public sector.

Radical solutions are required and as industry moves towards greater collaboration, both cross-company and with the public sector, there are new opportunities for problem solving. Harnessing the knowledge base and technologies in which the UK has significant investment and expertise can reduce reliance on animal use, improve animal welfare and deliver advanced tools and technologies to benefit the bioscience sector. This is the aim of [CRACK IT](#), the new research engine launched by the NC3Rs to exploit and commercialise science and technology for 3Rs benefits. CRACK IT is comprised of a research competition and an online resource to facilitate open access problem solving and collaboration on the 3Rs.

### The Challenges

The 2011 CRACK IT research competition consists of six Challenges identified jointly by the NC3Rs and industry sponsors to ensure that the aim of applying the 3Rs to the solving of technical problems is clearly defined. The industry sponsors are required to support the research through in-kind contributions that are indicated in the Challenges brief.

The brief includes a description of the problem to be solved, the 3Rs benefits, the names of the industry companies expressing interest in providing support, the nature of their proposed in-kind contributions, the notional financial cost of the project (the sum to be awarded by the NC3Rs), the potential timescale of the work, proposals for the organisation of the project and conditions of access by the industry sponsors to the results of the research. The Challenges are in **Appendix 1**.

## ASSESSMENT

Applications will be reviewed by selected panels of experts in a two stage process. Applications will be initially assessed by Review Panels consisting of representatives from the NC3Rs, the industry sponsors and others recruited for their expertise. The Review Panels will shortlist applications. Those selected will be invited to interview with the Challenge Panels. The Challenge Panels will consist of representatives from the NC3Rs, the industry sponsors, external experts and the relevant business community. Winning applicants will be awarded contracts shortly thereafter. Feedback to unsuccessful applicants will be given after contracts are awarded.

The assessment criteria are:

- Quality of the science and technological innovation
- Relevance to the Challenge
- Potential impact on the 3Rs
- Expertise and track record of the team
- Value for money

Successful applicants will be advised according to the published key dates, and organisations will be expected to mobilise rapidly to start the project.

## CONDITIONS

By applying, organisations are consenting to the terms and conditions contained in the Contract. The major considerations are summarised here.

**Eligibility:** The competition is open to any EU body, public or private. Applications from more than one eligible participant are encouraged and suggestions for the organisation of the project are detailed in each Challenge.

**Location:** Work funded by the NC3Rs should be carried out in the EU unless specifically indicated in the Challenge e.g. when work is required to be undertaken in one of the sponsor's laboratories outside the EU.

**Animal work:** All animal work to be undertaken in the project, whether by the applicants or the industry sponsors, must abide by the Guidance on Responsibility in the Use of Animals in Bioscience Research. The Guidance (SBRI\_NC3Rs\_75\_002 Guidance on Responsibility in the Use of Animals in Bioscience Research) and further information are available on the NC3Rs website (<http://www.nc3rs.org.uk/responsibility>).

**Intellectual property:** IP developed within the project is the property of the Contractor and its Subcontractors, as described in the contract between the NC3Rs and the Contractor. One recipient of funding should be nominated as the IP manager for the project. The NC3Rs does not provide a model agreement but suggests as a default that IP arising from the research should be jointly owned by the Contractor and its Subcontractors in equal shares. Failing this, they should agree among themselves on the ownership of IP, for example, by adapting one of the Lambert Agreements (<http://www.ip.gov.uk/lambert>).

Although the NC3Rs is not a joint owner of any IP arising from a project, it is a condition of funding from the NC3Rs that work furthering the 3Rs must be made available to the rest of the bioscience sector. The protection of IP through filing of patents should therefore be pursued without unreasonable delay, and access by third parties to 3Rs benefits must be provided through publication and dissemination, or by appropriate licences, royalty-free or royalty-bearing on fair and reasonable terms. The exact

arrangements are detailed in the contract between the NC3Rs and the Contractor (SBRI\_NC3Rs\_75\_007 NC3Rs – Applicant Contract).

Industry sponsors are also not joint owners of any IP arising from a project. Sponsors benefit from early access to any new technology during the term of the project. Access beyond the project duration might be through granting of royalty-free licences or through favourable pricing for an agreed period. Expectations of the sponsors in this respect are detailed in the Challenge Briefs and included in the contract between the NC3Rs and the Industry Sponsor(s) (SBRI\_NC3Rs\_75\_017 NC3Rs – Industry Sponsor Contract)

**Project Management:** The NC3Rs requires the establishment of a Project Management Team whose members include representatives of the Contractor, the Subcontractor(s) and the industry sponsors. The Chair of the Project Management Team should normally be the representative of the Contractor, and will act as the liaison to the NC3Rs. The responsibilities of the Chair are described in the contract between the NC3Rs and the Contractor.

The Project Management Team should typically meet quarterly during the award period. A representative from the NC3Rs will attend every other meeting.

**Project reporting:** A brief progress report is required at least once during the lifetime of the project, following a request from the NC3Rs. An automatic notification is sent when this report is due.

A final scientific report will be required that describes the work undertaken, and the achievements and outcomes. This should include all information about how the project advanced the 3Rs. Automatic notification of the deadline for the final scientific report is sent to the chair of the Project Management Team to complete, approximately one month before the award ends.

**Publication and dissemination:** Holders of contracts are expected to disseminate their results by publishing in appropriate scientific journals and at relevant conferences, detailing the 3Rs impact of the work. Publications must have the prior agreement of the Project Management Team and in particular, publication timing must respect the need to protect intellectual property arising from the work. The NC3Rs funding through CRACK IT should be acknowledged in all publications and presentations and the NC3Rs should be informed of any publications or other promotional material or events arising from the award.

Animal-based studies must be reported in accordance with the [ARRIVE guidelines](#) (SBRI\_NC3Rs\_75\_015 ARRIVE Guidelines) as far as possible, taking into account the specific editorial policies of the journal concerned.

The NC3Rs organises Grant Holder meetings on a two yearly basis. If a meeting occurs within the term of the contract it is important that at least one member of the Project Management Team attends. This assists the NC3Rs in its strategic aim to forge links between researchers and improve dissemination of the research that is funded.

Industry sponsors are permitted to place company logos on promotional materials arising from the collaboration by prior agreement with the NC3Rs.

Further information on dissemination can be found in the contracts between the NC3Rs, the Contractor or the industry sponsors.

## DOCUMENTS ASSOCIATED WITH THIS COMPETITION

- SBRI\_NC3Rs\_75\_001 Invitation to Tender (this document)
- SBRI\_NC3Rs\_75\_002 Guidance on Responsibility in the Use of Animals in Bioscience Research
- SBRI\_NC3Rs\_75\_003 Guidance Notes (to be available by 20 September 2011)
- SBRI\_NC3Rs\_75\_004 Application Form (to be available by 20 September 2011)
- SBRI\_NC3Rs\_75\_005 FAQs (to be available by 20 September 2011)
- SBRI\_NC3Rs\_75\_007 NC3Rs – Applicant Contract (to be available before 2 November 2011)
- SBRI\_NC3Rs\_75\_015 ARRIVE Guidelines
- SBRI\_NC3Rs\_75\_016 Guide to Review Panel and Review Panel scoring (to be available by 20 September 2011)
- SBRI\_NC3Rs\_75\_017 NC3Rs – Sponsor Contract (to be available before 2 November 2011)
- SBRI\_NC3Rs\_75\_018 Guide to Challenge Panels (to be available by 25 November 2011)
- SBRI\_NC3Rs\_75\_019 Challenge Panel Presentation Template (to be available by 25 November 2011)
- SBRI\_NC3Rs\_75\_020 Presentation Template Guide for Completion (to be available by 25 November 2011)

## CONTACT POINTS

Questions and comments are very welcome while the competition is open. Questions on the overall SBRI programme should be addressed to [sbri@tsb.gov.uk](mailto:sbri@tsb.gov.uk); questions on the Challenges and scope of this competition should be addressed to the NC3Rs ([crackitenquiries@nc3rs.org.uk](mailto:crackitenquiries@nc3rs.org.uk)). Once the competition is closed, no further dialogue will be entered into.

## MORE INFORMATION

For more information about this and other competitions please see: <http://www.innovateuk.org/sbri>. For more information on the NC3Rs or CRACK IT Challenges please see [www.nc3rs.org.uk](http://www.nc3rs.org.uk) and [www.crackit.org.uk](http://www.crackit.org.uk) respectively.

## HELPLINE

TSB will provide a help desk for the application process and basic questions and feed any specific, complex or technical questions to the NC3Rs. Please contact the Business Support Group ([support@innovateuk.org](mailto:support@innovateuk.org); Tel. 0300 321 4357). Alternatively questions related to the Challenges themselves can be addressed directly to the NC3Rs at [crackitenquiries@nc3rs.org.uk](mailto:crackitenquiries@nc3rs.org.uk); Tel. 020 7611 2233.

## FAQS

Frequently asked questions are available at [www.crackit.org.uk/faqs1](http://www.crackit.org.uk/faqs1)

## **APPENDIX 1: THE CHALLENGES**



AstraZeneca



CRACK IT

**SBRI** Government challenges.  
Ideas from business.  
Innovative solutions.

## APPENDIX 1: CHALLENGE 1

### Title of Challenge

**A predictive *in vitro* screen for nephrotoxicity: from mice to men and back again**

### Background

The kidney, together with liver and heart, is among the most important target organs for the detection of undesired adverse effects during drug development. Kidney toxicity accounts for 2% of drug attrition during preclinical studies and 19% in phase 3 (1). There is a clear need for experimental models to both predict as well as to investigate drug-induced toxicities in the kidney. In recent years, significant progress has been made in the establishment and qualification of kidney toxicity biomarkers in rodents and in their transferability to man (2). However, there are no well established *in vitro* assays available to investigate kidney toxicity.

The aim of this challenge is to establish *in vitro* predictive assays that can provide reliable nephrotoxicity assessment. Such assays would allow information from several toxicologically relevant species (e.g. mouse, rat and dog) and from human-derived cells to be obtained. *In vitro* assays will also help understand the mechanistic basis of nephrotoxicity in different chemical classes of drug. Such systems would also allow a direct comparison of compound effects in rodent, non-rodent (e.g. dog) and human-derived cellular systems aiding compound selection and design of preclinical studies, e.g. species selection and appropriate dosing regimes.

### 3Rs Benefits

Assessing the safety of drug candidates accounts for approximately 10-20% of the animals used in the drug discovery and development process. Improved *in vitro* assays for predicting nephrotoxicity will avoid drugs destined to fail in development being tested in animals, and where animals are used, improved information on the underlying mechanisms of toxicity will help refine study designs, including dosing regimes and species selection.

### Need for collaboration

The kidney is a complex organ in terms of its multiple cell types and architecture. There are several kidney cell lines, mainly from the proximal tubule, that may provide a first indication of direct tubular toxicity. However, more complex systems such as co-cultures which include additional cell types and organotypical models need to be established, characterised and evaluated as possible test systems. The characterisation of such cell culture systems and the selection and establishment of suitable readouts require a diversity of expertise in the field of cellular and molecular assays (e.g. high content imaging, genomics, real-time read outs, etc). Collaboration between applicants with cell culture and assay expertise, and industry sponsors that can facilitate access to a selection of reference compounds with well characterized toxicological profiles derived from already performed *in vivo* experiments is essential. Technological expertise on the designated endpoints could be provided by both applicants and industry sponsors.

## **Overall objectives**

To develop an *in vitro* cell-based model for the testing of nephrotoxicity that allows inter-species comparisons between toxicologically relevant species including rodents, non-rodents and man. The model should include both predictive and mechanistic aspects.

## **Key deliverables**

- Identification and characterisation of appropriate cell types (cell lines and primary cells) to address kidney function;
- Establishment of appropriate endpoints for the detection of nephrotoxicity;
- Validation of the predictive performance of the assay by assessing a sufficient number of compounds and generating predictive statistical models with the obtained data;
- Demonstration that the model can provide mechanistic information on the underlying toxicological processes;
- Transfer of the assay(s) to industry standard platforms and initiating the process for formal validation (e.g. via ECVAM).

## **Industry sponsors**

Roche, AstraZeneca and UCB

## **In-kind contributions**

Projects of this nature require both toxicological expertise and availability of commercially available and proprietary compounds, as well as extensive analytical and instrumentation support. In-kind contributions from the pharmaceutical industry sponsors will include the provision of compound information and compounds for the assays being developed. In addition, access to instrumentation such as molecular biology platforms (e.g. microarrays), real-time read out (e.g. xCelligence), and high content imaging (HCI) platforms will be possible. Applicants could have access to these technologies at the site of the industry sponsor. The sponsor or the database-provider could perform the data analysis and models for the independent assessment of the model performance in terms of specificity and sensitivity.

## **Industry sponsor access to foreground Intellectual Property**

The companies participation is conditional on a provision entitling them to use the results of the programme in their research and development (R&D) activities, in the form of a non-exclusive, royalty-free usage right on the results obtained under such project for the purpose of carrying out R&D activities for discovering novel commercial pharmaceuticals.

## **Duration**

Up to three years

## **Budget**

Up to £750,000 in total, inclusive of VAT where applicable

## **Funding Model**

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise and applications are therefore welcomed from consortia in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors).

## **References**

1. Redfern W S *et al.* (2010) Impact and frequency of different toxicities throughout the pharmaceutical life cycle. *The Toxicologist* 114(S1): 1081.
2. Bai JP *et al.* (2011) Translational biomarkers: from preclinical to Clinical a Report of 2009 AAPS/ACCP Biomarker Workshop. *American Association of Pharmaceutical Sciences Journal* 13(2):274-83.

## **Additional suggested reading**

- Fragiadaki, M & Mason, RM (2011) Epithelial-mesenchymal transition in renal fibrosis - evidence for and against. *Int J Exp Pathol* 92(3):143-50.
- Gunness, P *et al.* (2010) Comparison of the novel HK-2 human renal proximal tubular cell line with the standard LLC-PK1 cell line in studying drug-induced nephrotoxicity. *Can J Physiol Pharmacol* 88(4):448-55.
- Gunness P *et al.* (2010) The effect of acyclovir on the tubular secretion of creatinine *in vitro*. *J Transl Med* 8: 139.
- Wu Y *et al.* (2009) Multiplexed assay panel of cytotoxicity in HK-2 cells for detection of renal proximal tubule injury potential of compounds. *Toxicol In Vitro* 23: 1170-8.
- Presnell S C *et al.* (2011) Isolation, characterization, and expansion methods for defined primary renal cell populations from rodent, canine, and human normal and diseased kidneys. *Tissue Eng Part C Methods* 17(3): 261-73.
- Rosines E *et al.* (2010) Constructing kidney-like tissues from cells based on programs for organ development: toward a method of *in vitro* tissue engineering of the kidney. *Tissue Eng Part A* 16(8): 2441-55.
- Subramanian B *et al.* (2010) Tissue-engineered three-dimensional *in vitro* models for normal and diseased kidney. *Tissue Eng Part A* 16(9): 2821-2831.
- Suzuki H *et al.* (2008) *In vitro* gene expression analysis of nephrotoxic drugs in rat primary renal cortical tubular cells. *J Appl Toxicol* 28(2): 237-48.
- Lash LH *et al.* (2008) Drug metabolism enzyme expression and activity in primary cultures of human proximal tubular cells. *Toxicology* 244(1): 56-65.
- Lash LH *et al.* (2005) Molecular markers of trichloroethylene-induced toxicity in human kidney cells. *Toxicol Appl Pharmacol* 206 157-168.
- Lash LH *et al.* (2007) Interactive toxicity of inorganic mercury and trichloroethylene in rat and human proximal tubules: effects on apoptosis, necrosis, and glutathione status. *Toxicol Appl Pharmacol* 221(13): 349-362.
- Dankers PY *et al.* (2011) Bioengineering of living renal membranes consisting of hierarchical, bioactive supramolecular meshes and human tubular cells. *Biomaterials* 32(3): 723-33.
- Ellis JK *et al.* (2011) Metabolic response to low-level toxicant exposure in a novel renal tubule epithelial cell system. *Mol Biosyst* 7(1): 247-57.
- Brown CD *et al.* (2008) Characterisation of human tubular cell monolayers as a model of proximal tubular xenobiotic handling. *Toxicol Appl Pharmacol* 233(3): 428-38.
- McGoldrick TA *et al.* (2003) Renal cysteine conjugate C-S lyase mediated toxicity of halogenated alkenes in primary cultures of human and rat proximal tubular cells. *Arch Toxicol* 77(7): 365-70.
- Burton CJ *et al.* (2001) Turnover of human tubular cells exposed to proteins *in vivo* and *in vitro*. *Kidney Int* 59(2): 507-14.

## **Keywords**

Kidney, toxicity, organotypical, cultures, mechanistic, human, rodent, biomarkers.



## APPENDIX 1: CHALLENGE 2

### Title of Challenge

#### **Wireless recording of the electrophysiology of cognition in psychiatric disease models**

### Background

Many brain disorders including schizophrenia and Alzheimer's disease are characterised by severe impairments in cognition that are still both poorly understood and treated. There is mounting evidence that some deficits in cognitive function arise through a break down in the coordinated activity of neuronal networks responsible for memory, learning and decision-making. The hippocampus and medial prefrontal cortex are two regions of the brain thought to be central to cognitive processes. The coordinated activity of hippocampal-prefrontal networks is specifically engaged in mice learning to navigate a maze to find food; a paradigm that measures hippocampus-dependent spatial working memory (1,2). It is possible to record both the individual activity of the hippocampal neurons involved as well as the rhythmic activity that arises within networks of neurons using multi-site *in vivo* electrophysiology. By implanting electrodes in multiple brain regions and then recording brain activity while mice run on a T-maze, the rhythms and oscillations that are essential for synchronisation can be identified. Such recordings, in conjunction with behavioural outcome (e.g. how long it takes to find the food, the acquisition of the task and the error rate), will provide for greater validity of the cognitive tasks and disease models employed in drug discovery and consequently, much greater certainty of clinical impact.

An automated, computer controlled, modular maze has recently been developed (3). In this apparatus, mice perform multiple trials with reduced variability and at a much greater rate. The scientific and welfare advantages of this apparatus can only be fully realised if the animals are freely moving. Therefore there is a need to monitor neuronal activity in the hippocampal-prefrontal networks without requiring the animals to be tethered in any way. Some progress in this respect has been made with the introduction of a wireless multi-channel system for mice and rats by Triangle BioSystems (4). However the performance characteristics of this system (weight, size and battery life) are not adequate to exploit fully the advantages of the automated T-maze. Furthermore, software needs to be developed linking electrophysiology with behaviour, not only for this challenge, but ideally in a manner that is readily adapted to the wider use of wireless electrophysiology in other behavioural paradigms e.g. those using operant lever pressing or touchscreen techniques.

### 3Rs benefits

Traditional T-maze rewarded alternation tasks require intense handling which may alter the affective state of the mouse and so alter cognitive performance. This has been confirmed in a recent study which showed that handling history modified stress levels and subsequent behavioural responses (5). In the automated maze both handling and tethering are avoided. The mouse is able to enter the maze at will at pre-programmed times during the light/dark cycle without any human intervention. This allows the mice to perform when they are naturally more active (i.e. in the dark period). Furthermore, the mouse remains in visual, auditory and olfactory contact with cage mates during the inter-trial interval, giving additional welfare benefits. Automation greatly increases the number of trials an animal can complete in a 24 hour period allowing greater statistical power from fewer animals. For long term recording, lighter and smaller devices with greatly increased battery life will minimise stressful handling. Finally, the potential reduction and refinement benefits of such a device could also be realised in other behavioural experiments if the software is sufficiently adaptable.

## **Need for collaboration**

This project will require a multidisciplinary approach with experts in rodent behaviour and electrophysiology helping mechanical and electrical engineering teams to reach a workable and successful prototype. Software development for data handling and statistical analysis also forms part of the proposal. Winning applications would typically have contributions from both the public and SME sectors with complementary expertise in the needed areas.

## **Overall objectives**

To develop a prototype of a wireless 16-32 channel recoding system that can acquire and transmit data for a minimum of 24 h but ideally for more than 10 days, that can be replaced or recharged with minimal discomfort for the animal and is small enough to be carried by a mouse without affecting its behaviour or welfare.

## **Key deliverables**

A wireless recording device that has the following specifications:

- Capability equivalent to recording 16 channels at 32 kHz;
- Battery life of at least 24 hours and ideally more than 10 days to allow mice to learn multiple tasks within the T-maze uninterrupted and without stressful insults;
- Event tracking to allow the behavioural data to be linked to the electrophysiological data;
- Any part of the system carried by the mouse must not weigh more than 3g;
- Software for the collection, analysis, storage and interrogation of data, with flexibility for adaption to other behavioural paradigms;
- Performance in pre-agreed tasks in the automated T maze for validation of the technology e.g. demonstration of the relationship between hippocampal-frontal synchrony of theta oscillations as the mice make correct or incorrect choices in the maze (1).

## **Industry sponsor**

Eli Lilly

## **In-kind contributions**

Lilly will have 8 of the mazes in operation by early 2012. Lilly will make these mazes available for the project either by hosting visitors to its Erl Wood research laboratory, or by providing them for use by one or more of the applicants in their own laboratories. In addition Lilly has extensive expertise in *in vivo* electrophysiology and amperometry in rats performing complex cognitive tasks in operant chambers and is developing the approach for use in mice. Lilly will make available such experience as needed for the project. Within the company, software for data analysis is continuously evolving with input from internal experts and if the winning applications propose bringing in external software experts Lilly will offer opportunities for collaboration. In the validation phase, Lilly will provide appropriate materials for testing.

## **Industry sponsor access to foreground Intellectual Property**

There will be no restriction on IP exploitation. Applicants will be free to publish or commercialise where appropriate and no preferential access will be required by Lilly.

## **Duration**

Up to three years

## **Budget**

Up to £500,000 in total, inclusive of VAT where applicable

## **Funding model**

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise, and applications are therefore welcomed from consortia in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors). More than one such consortium could be funded, particularly if the proposed technologies take substantially different routes.

## **References**

1. Jones MW & Wilson MA (2005) Theta rhythms coordinate hippocampal–prefrontal interactions in a spatial memory task. *PLoS Biol* 3(12): e402.
2. Sigurdson CJ *et al.* (2010) Impaired hippocampal–prefrontal synchrony in a genetic mouse model of schizophrenia, *Nature* 464(7289): 763–7.
3. Gaskin BN *et al.* (2011) Little and often? Maintaining continued performance in an automated T-maze for mice. *Behav Processes* 86(2): 272–8.
4. Fan D *et al.* (2011) A Wireless Multi-Channel Recording System for Freely Behaving Mice and Rats. *PLoS ONE* 6(7): e22033.
5. Hurst JL & West RS (2010) Taming anxiety in laboratory mice. *Nature Methods* 7(10): 825-6.

## **Keywords**

Cognition, spatial navigation learning, telemetry, wireless, EEG, oscillations, psychiatric disease, animal behaviour, central nervous system.

## APPENDIX 1: CHALLENGE 3

### Title of Challenge

**Rodent Big Brother: automated recording of rodent activity and temperature in the home cage**

### Background

Measurement of the activity of individual rats or mice in their home cage provides useful information in studies from basic research through to drug discovery and development. This includes:

- Detecting and assessing toxicological effects (for example effects on the central nervous system) of candidate drugs, including physical dependence;
- Characterization of agents targeting disorders of the CNS;
- Behavioural phenotyping of genetically altered animals;
- Studies of circadian rhythms.

Measurement of body temperature in rodents may also be used in each of the research applications above; particularly for some toxicology studies (1) and the assessment of physical dependence.

Activity and temperature can currently only be measured separately, unless surgically implanted telemetry devices are used (e.g. 2, 3); however the surgery required places an additional welfare burden on the animals. Activity can be measured non-invasively using transparent cages and photocell beams or infrared movement sensors (e.g. 4), or by placing the cages on mechanical sensor platforms (e.g. 5). However, this requires animals to be singly housed, which is not ideal for social species such as rats and mice which live in groups.

Video tracking systems, with individuals marked with different colours, can be used for group-housed rodents but these methods are not readily incorporated into standard caging with wire mesh lids, especially when measuring simultaneously from multiple cages; also, video tracking in darkness requires infrared lighting, which would not enable discrimination between individuals marked with different colours.

The aim of this challenge is to develop an integrated system which combines measurement of activity and temperature in rodents that can be used with group housing and without surgery.

ID microchip transponders which measure temperature already exist and may potentially be utilised for this challenge. These chips are about 14 mm x 2 mm, and are injected subcutaneously in the nape of the neck. Examples include the IPTT-300 (PLEXX, Netherlands; BioMedic Data Systems Inc., USA) (6).

Accelerometers have been used to record and characterize behavioural movements in rodents (7), but so far only when worn externally.

### 3Rs benefits

The development of a non-surgical, automated approach to measure activity and temperature in animals supports reduction and refinement by avoiding the need for surgery or single housing. It would enable incorporation of these additional measurements into existing study types, thereby reducing the number of separate standalone studies. It could potentially impact on the welfare of thousands of animals.

More broadly, this technology could also be used to provide additional information for other studies where early identification of animals with subdued activity or changes in body temperature could be used to improve humane endpoints.

### **Need for collaboration**

The multi-disciplinary nature of this challenge means that expertise from a number of different sectors will be needed to provide a solution. It would be valuable to engage sectors that are not normally associated with the biosciences such as sensor electronics. Software development for data handling may also form part of the proposal.

### **Overall objectives**

To develop an automated non-surgical system, which can be used in rats and mice, to measure activity and temperature over a minimum of a 24 hour period.

### **Key performance requirements**

A small, unobtrusive detector that:

- Does not require complex wiring to/from cages;
- Must work with standard rodent cages;
- Must detect both animal activity and temperature;
- Must be minimally invasive e.g. using a subcutaneous ID chip;
- Must allow normal use of cages (e.g. cages go through robotic cage washers);
- Can transmit wirelessly to a receiver that collates the data;
- Has a mechanism to automatically log the precise timing of the light-dark cycle;
- Has a mechanism to automatically log when technicians are in the room;
- Can measure time spent at each end of the cage (not necessarily X-Y co-ordinates);
- Can potentially measure rearing behaviour (i.e. rats standing on hind legs);
- Could potentially distinguish other types of motor activity and specific movements (e.g., eating; drinking; tremor; convulsions);
- Is quick to set up and start recording, with minimal configuration/adjustment;
- Is GLP/ 21 CFR Part 11-compliant to convert the proximity data from the detectors into activity counts and temperature measurements for each individual animal;
- Can detect and flag-up erroneous data;
- Data collection need not be continuous, minimum requirement would be collected, for example, in 5 minute bins every 30 minutes for 24 hours.

Final prototype that:

- Can be used to assess, optimize and validate the system using 4 cages, 12 animals;
- When scaled up should deliver recordings for several large, unrelated studies in parallel, in separate rooms (e.g. toxicology studies);
- Can incorporate the study design for toxicology studies (3-5 rats/cage or up to 6 mice per cage and between 24 to 80 animals in total per study).

### **Industry sponsors**

AstraZeneca

### **In-kind contributions**

AstraZeneca will run evaluation/optimization/validation studies in rats and mice in their laboratories, with a view to peer-reviewed publication. AstraZeneca has extensive experience in running and handling data from toxicology studies and will provide this expertise for the project.

## **Industry sponsor access to foreground IP**

AstraZeneca's participation is conditional on a provision entitling them to use the results of the programme in their research and development (R&D) activities, in the form of a non-exclusive, royalty-free usage right on the results obtained under such project for the purpose of carrying out R&D activities for discovering novel commercial pharmaceuticals.

## **Duration**

Up to three years

## **Budget**

Up to £500,000 in total, inclusive of VAT where applicable

## **Funding model**

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise, and applications are therefore welcomed from consortia in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors). More than one such consortium could be funded, particularly if the proposed technologies take substantially different routes.

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## **Keywords**

Activity, body temperature, home cage, rats, mice, automation.

## APPENDIX 1: CHALLENGE 4

### Title of Challenge

**Improving the predictive capacity of *in vitro* cytokine release assays to reduce animal use and drug attrition**

### Background

Cytokines are soluble signalling molecules which are released by cells of the immune system in response to antigen binding. Large molecule therapeutics such as antibodies can also trigger cytokine release and immune cell activation either directly by their V regions or by Fc regions binding to Fc receptors. A severe example of this was seen in the trial of TGN1412, an anti-CD28 IgG4, which activated T-cells resulting in massive cytokine generation and severe pathology in the volunteers that received it (1, 2).

The *in vivo* testing of biologics, such as monoclonal antibodies, is a regulatory requirement with the cynomolgus monkey being the most commonly used species. Whilst this monkey is used in toxicity studies for a range of drugs, it has poor predictivity for the potential of antibody-induced cytokine release in humans (3). This may be in part due to differences in the expression of antigens such as CD28, the lower affinity of the cynomolgus FcR for human Fc or the presence of regulatory signalling molecules that humans lack such as CD33-related Siglec (4).

A number of groups have developed *in vitro* assays using human leukocytes to detect antibody-induced cytokine release (for example; 5, 6). However, there is a divergence between groups in cellular preparation, antibody presentation and bioanalytical platform, which has led to poor comparability of data between groups. Whilst many groups have shown that their models produce the expected hierarchical responses to antibodies against antigens such as CD3 and CD28, there has not yet been an attempt to correlate this with clinical data to demonstrate the predictive value of these models. In addition to this, the majority of the current models neither make an attempt to measure the kinetics of the cellular cytokine response to antibody, nor cellular division, which are both important parameters in the assessment of the potential of an antibody to cause cytokine release syndrome.

The lack of a standard format for these assays in combination with the poor predictive value of the current models has highlighted the need for a new generation model that will be sensitive and predictive of clinical outcome, and will therefore inform both candidate selection and be predictive of toxicology in preclinical or clinical studies.

### 3Rs benefits

Biologics form approximately 30% of the global drugs pipeline. Immune responses caused by these drugs, including desired pharmacology and adverse events are assessed in preclinical studies, primarily using the cynomolgus monkey. Depending on the drug, the therapeutic area and company practices up to 144 monkeys may be used in a standard toxicology package for biologics (7). Immune responses are assessed either as part of the standard toxicology package or as standalone studies. *In vitro* assays which accurately predict immune responses, including the likelihood of a cytokine storm, would reduce the number of monkeys used by avoiding drugs which are destined to fail on safety or efficacy grounds being taken into preclinical studies.

Additional 3Rs benefits include:

- Screening and optimising molecules prior to preclinical studies to avoid unnecessary use of animals. For instance, a robust *in vitro* screen for a monoclonal antibody could show whether engineering was

needed to increase potency (if cytokine release is not stimulated enough) or reduce toxicity (if cytokine release is too high or not part of the expected pharmacology) prior to animal studies;

- Integration into the testing paradigm for biosimilars or manufacturing changes to use fewer (if any) animals for approval;
- Providing information on the mechanism of action and/or potency which could be used to inform study designs allowing fewer animals to be used and avoiding doses which result in significant adverse events or mortality.

### **Need for collaboration**

The events that control cytokine release are not well understood, yet underpin the development of predictive models for drug testing. The expertise to further understanding in this area and to develop conceptual models is probably within academia or SMEs, however, the expertise to develop these models into bioanalytical tools lies within industry.

### **Overall objectives**

- To develop *in vitro* human cell-based models for the testing of antibody-based therapeutics that will allow the prediction of human cytokine release.
- To develop a parallel assay with cells from non-human primate (e.g. cynomolgus monkey) to predict cytokine release in preclinical safety assessment.

### **Key deliverables**

An assay to predict *in vivo* cytokine release.

Phase 1:

- Must generate detectable cellular cytokine release in response to antibody binding;
- Must be formatted appropriately to allow the collection of time-course data for cytokine release;
- Must be amenable to measurement of the division of responder cells. Demonstrate that the assay predicts clinical outcome e.g. through comparison of currently marketed drugs with historical preclinical and clinical data.

Phase 2:

- Should be able to demonstrate the use of both fresh and frozen material as a source of responding cells;
- Should be amenable to medium to high throughput screening and allow for multiplex analysis;
- Must contain suitable controls and replicates to allow validation as described in FDA guidance document (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf>).

### **Industry sponsor**

Huntingdon Life Sciences (HLS)

## **In-kind contributions**

Projects of this nature require extensive analytical and instrumentation support, especially in the latter stages during validation and conversation to higher throughput platforms. In-kind contributions from HLS will be the provision of clinical antibodies where appropriate, multiplex analysis platforms (Cytometric Bead array, MSD platforms), automation (liquid handling robots) and tissue banking facilities. HLS has extensive experience in high throughput *in vitro* screening strategies and will provide this expertise for the project. There may be also the potential for the academic partners to participate in bulk ordering of reagents with the other partners to reduce reagent costs.

## **Industry sponsor access to foreground Intellectual Property**

There will be no restriction on IP exploitation. Applicants will be free to publish or commercialise where appropriate and no preferential access will be required by Huntingdon Life Sciences.

## **Duration**

Up to three years

## **Budget**

Up to £500,000 in total, inclusive of VAT where applicable

## **Funding model**

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise, and applications are therefore welcomed from consortia, in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors). More than one such consortium could be funded, particularly if the proposed technologies take substantially different routes.

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## **Keywords**

Biologics, cytokine release, *in vitro*, non-human primate, human, toxicology.



## APPENDIX 1: CHALLENGE 5

### Title of Challenge

**Improved *in vitro* to *in vivo* extrapolation in chemical safety risk assessment of human systemic toxicity**

### Background

The safety assessment of new chemicals across the industrial chemical, agrochemical, pharmaceutical and consumer product sectors has long relied on high dose treatments in animals with default methods for extrapolating observed results to low level exposures in human populations. These traditional 'whole-animal' methods are expensive, can use many animals, and can sometimes be misleading with respect to human safety risk. As a result, increasing emphasis has centred on the development of predictive *in vitro* models for endpoints of toxicity, and their use to provide mode-of-action understanding within the risk assessment process. Although progress has been made in developing *in vitro* models to predict some chemical toxicities such as skin irritation and corrosion, models to detect systemic toxicity across multiple organs are not currently available. Recently published opinions by the EU Scientific Committee on Consumer Safety (1) and a review by experts selected by the European Commission (2) indicate that, in the future, greater priority needs to be given to developing non-animal approaches which provide biological and chemical concentration-response data that can be integrated into consumer exposure and safety risk assessments.

In 2007 the US National Research Council (NRC) issued its landmark report on "Toxicity Testing in the 21st Century: A Vision and a Strategy" (TT21C; (3)). The report sees a future in which routine toxicity testing would be conducted in human cells, human tissue surrogates, or human cell lines *in vitro* by evaluating cellular responses in a suite of toxicity pathway assays. These tools would enable risk assessors to predict regions of exposure that are expected to be without adverse consequences, rather than making predictions on the incidence of specific adverse responses in human populations. A key element to the realisation of this vision is the development of systems to understand exposure parameters *in vitro* and their extrapolation to inform safe *in vivo* exposure/in use scenarios. This will be the focus for this challenge.

### 3Rs benefits

Historically, 'alternative' methods in toxicology have aimed to reproduce data generated using animal-based models. The aim of this challenge is not to predict animal toxicity data but rather focus on safety risk assessment based on data relevant to human use as outlined in the TT21C vision (3). As such, if successful long term, the challenge will ultimately provide tools and a means to address safety without use of animals.

### Need for collaboration

As outlined in (3) a pathways approach to safety risk assessment will require a truly multi-disciplinary collaborative effort. Modelling approaches have been used with success in the pharmaceutical industry (e.g. 4) to predict human-drug kinetics (predominantly via oral routes of exposure). There are opportunities to broaden the applicability of these approaches to other areas of chemical space and to bridge the gap between *in vitro* concentration responses (toxicity pathways) and the relevance of these concentrations to human safety. There is already considerable on-going effort in this area (e.g. 5). However, this is predominantly led by traditional toxicology expertise. We would welcome the opportunity to work with scientists able to bring new perspectives to the challenge (e.g. partnerships with SMEs and academic groups with expertise in cell biology, physiology, mathematical modelling, chemical analyses etc).

## **Overall objectives**

- Develop a model that provides understanding of the relevance of toxicity concentration response data from human *in vitro* systems to predictions of safety following relevant *in vivo* human exposure. This should focus on assessment of systemic toxicity rather than localised endpoints such as skin or eye irritation.
- This challenge should deliver new understanding of exposure parameters *in vitro* and how these relate to safe human doses.

## **Key deliverables**

- For a defined toxicity pathway (applicants choice\*), establish concentration response information in human *in vitro* system(s) relevant to that pathway.
- Based on the above, establish a model(s) to predict the concentration effect and dose response in the human *in vivo* for the chosen pathway.
- Application of the above to safety decision making (e.g. would the predicted changes in the identified pathway result in an adverse health effect?).
- To provide proof of concept, consideration should be given to the validation of the proposed approach.

## **Industry sponsors**

Unilever, Syngenta and AstraZeneca.

## **In-kind contributions**

AstraZeneca, Syngenta and Unilever would be happy to provide relevant human, animal and *in vitro* data to which they have access, to aid access to specialised technologies, and to share expertise in modelling, risk assessment and toxicology.

## **Industry sponsor access to foreground Intellectual Property**

Applicants free to publish or commercialise where appropriate. Access to IP will be through a non-exclusive licence to the sponsors for R&D purposes.

## **Duration**

Up to three years

## **Budget**

Up to £1 million in total, inclusive of VAT where applicable

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\* Clearly, many different toxicity pathways exist associated with a large variety of adverse health outcomes. The selection of 'case study' pathways to explore the 'Toxicity Testing in the 21<sup>st</sup> Century' concept is currently the subject of much discussion (e.g. 6). For example Bhattacharya et al. (7) are currently exploring a case study (DNA-damage-induced carcinogenicity) to evaluate the potential application of a toxicity pathways-based approach within a risk assessment context for repeat dose toxicity. Some examples of toxicity pathways are listed in (8); applicants may select from this list or focus on a different pathway of their own selection.

## **Funding model**

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is possible that an applicant from a single organisation with departments covering a wide range of disciplines would be able to access all the required expertise. However, applications would also be welcomed from consortia of smaller more focused enterprises but this would require a strong scientific lead and vision. More than one such consortium could be funded, particularly if the proposed approaches take substantially different routes. Under such circumstances, the budget will be divided between the successful applicants who will need to identify shorter term milestones appropriate to the budget available.

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## **Keywords**

Toxicity pathways, *in vitro in vivo* extrapolation, PBPK modelling, concentration response, human safety, risk assessment.

## APPENDIX 1: CHALLENGE 6

### Title of Challenge

**BADIPS – Generating human induced pluripotent stem cells (iPS cells) to study bipolar affective disorder**

### Background

Mental disorders, including bipolar affective disorder (BAD), are a serious burden on society, including in the UK, and there is a large unmet medical need for novel, more efficacious treatment options (1). Current treatments for BAD originated serendipitously, or secondarily from approaches originally developed to treat schizophrenia or major depression. A key issue is the lack of valid animal models for BAD (2-4), despite the generation of a whole series of genetically altered animals (3). Current animal models have limited impact on the understanding of the disorder and do not predict clinical efficacy of novel treatment options.

Over the last few years, in parallel with other fields, human genetic studies for BAD have been dominated by genome-wide association studies (GWAS), and to a lesser extent by copy-number variant (CNV) studies. These GWAS have identified some polymorphisms but few findings have been reproduced as statistically significant in independent studies (2).

An alternative approach is the use of patient-derived cell models of brain diseases that are relevant and robust enough to produce the large quantities of cells required for molecular and functional analyses, including induced pluripotent stem (iPS) cells (5-8).

### 3Rs benefits

Current animal models used to study BAD include genetically altered mice and rodent models of schizophrenia or major depression. The latter involves the administration of drugs which cause psychosis in man, or subjecting animals to stress (e.g. maternal deprivation) and are therefore associated with significant welfare concerns. Using iPS cells from BAD patients as screening tools for the development of novel treatment options, it will be possible to reduce the dependence on animal models, improve the predictive validity of the assays, and possibly even make some of the present *in vivo* testing obsolete. Specifically this will include reducing the use of:

- Standard rodent models for novel drug screening, which attempt to mimic some elements of BAD and rely on reference drugs to provide some predictive value. Typically dose-response curves are generated in these models using 7 to 15 animals per treatment concentration;
- Classical behavioural testing in transgenic animals where specific genetic factors derived from GWAS or disease pathway analysis are modified;
- Drug testing in transgenic models;
- *Ex vivo* tissue from transgenic animals.

### Need for collaboration

The generation of iPS cells from patient material is a multicentre task, involving clinical scientists who have access to well-defined patient populations, preclinical scientists who can generate and validate the cellular assays, and industrial scientists who will develop these assays to allow high-throughput screening.

## **Overall objectives**

The development of relevant phenotypical high throughput screens for the discovery of new treatments for BAD.

## **Key deliverables**

- Generate viable iPS cells from 5-10 clearly defined BAD patients, ideally carrying polymorphisms in coding regions of risk genes or CNVs that will allow directed investigation of cellular properties as proof of concept;
- Identify phenotypic characteristics of these cells (iPS or differentiated into neurones) that are specifically related to BAD;
- Generate a robust and validated assay suitable for screening in an industrial setting.

## **Industry sponsors**

Janssen and Eli Lilly

## **In-kind contributions**

This will include

- Gene expression profiling;
- High content characterization of iPS derived neurons: antibody labelling and imaging, *in vitro* electrophysiological support;
- Testing human cells and if applicable, cells from rodents carrying mutations in the genes of interest with the aim of building a screening platform;
- Provision of shRNA or siRNA for knock-down of gene expression;
- Access to compound libraries and reference drugs for validation.
- Differentiation of the iPS cell lines into different types of neurons (e.g., GABA, glutamate, dopamine phenotypes);
- Genomic characterization (e.g., mRNA, miRNA, candidate gene expression);
- Functional characterization of the cells using biochemical, electrophysiological and imaging technologies with and without functional genomics and pharmacological tools/probes;
- Testing human cells and if applicable, cells from rodents carrying mutations in the genes of interest with the aim of building a screening platform;
- Access to public domain compounds/reference drugs.

## **Industry sponsors access to foreground Intellectual Property**

Janssen's and Eli Lilly's participation is conditional on a provision entitling Janssen and its Affiliates and Eli Lilly and its Affiliates to use the results of the programme in its research and development (R&D) activities, in the form of a non-exclusive, royalty-free usage right on the results obtained under such project for the purpose of carrying out R&D activities for discovering novel commercial pharmaceuticals.

## **Duration**

Up to three years

## **Budget**

Up to £1 million in total, inclusive of VAT where applicable

## **Funding model**

Although success in the project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise and applications are therefore welcomed from teams forming consortia in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors). More than one such consortium could be funded, particularly if the proposed approaches take substantially different routes.

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## **Keywords**

iPS cells, neuronal culture, bipolar affective disorder, assay development, phenotypic screen.