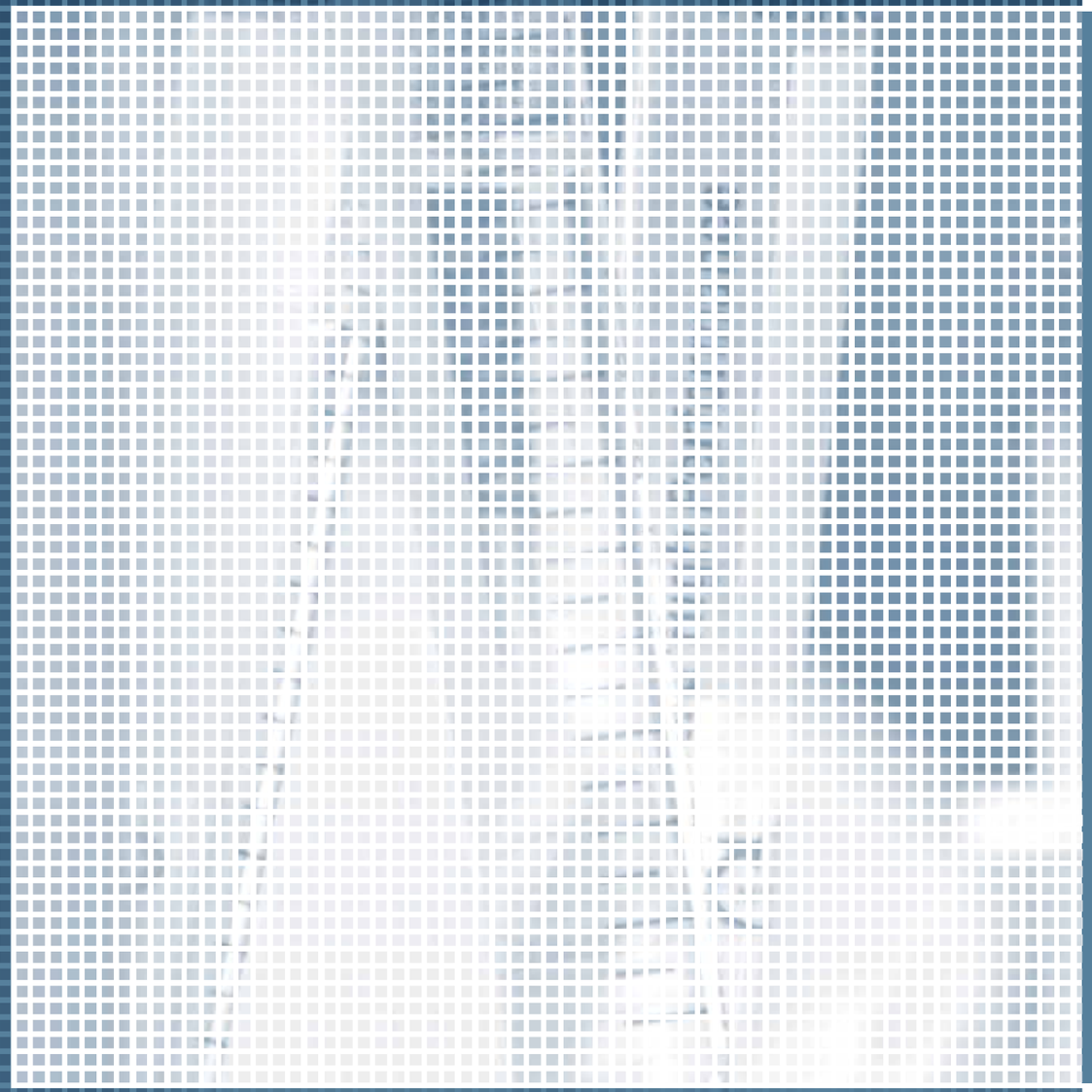
# ANNUAL REPORT 2011

NC3Rs



**THE NC3Rs LEADS THE DISCOVERY OF NEW WAYS TO REPLACE, REFINE AND REDUCE THE USE OF ANIMALS IN RESEARCH: CONNECTING SCIENCE WITH THE 3Rs.**

# FOREWORD

**VICKY ROBINSON**
Chief Executive

**IAN KIMBER OBE**
Chairman

For the past seven years we have shaped the scientific environment in which animal research is conducted in the UK. Our work has modernised the 3Rs agenda by focusing on changing attitudes and providing leadership. The 3Rs are no longer a marginal activity with little involvement from the mainstream bioscience community. Now they are widely recognised as a legitimate goal with important scientific and business benefits. This has created a more open approach to animal research issues. We have engaged a wide range of scientists and organisations resulting in exciting opportunities to minimise animal use and/or improve animal welfare. Maintaining this momentum will require the NC3Rs to continue to innovate and evolve – this has been our focus for 2011.

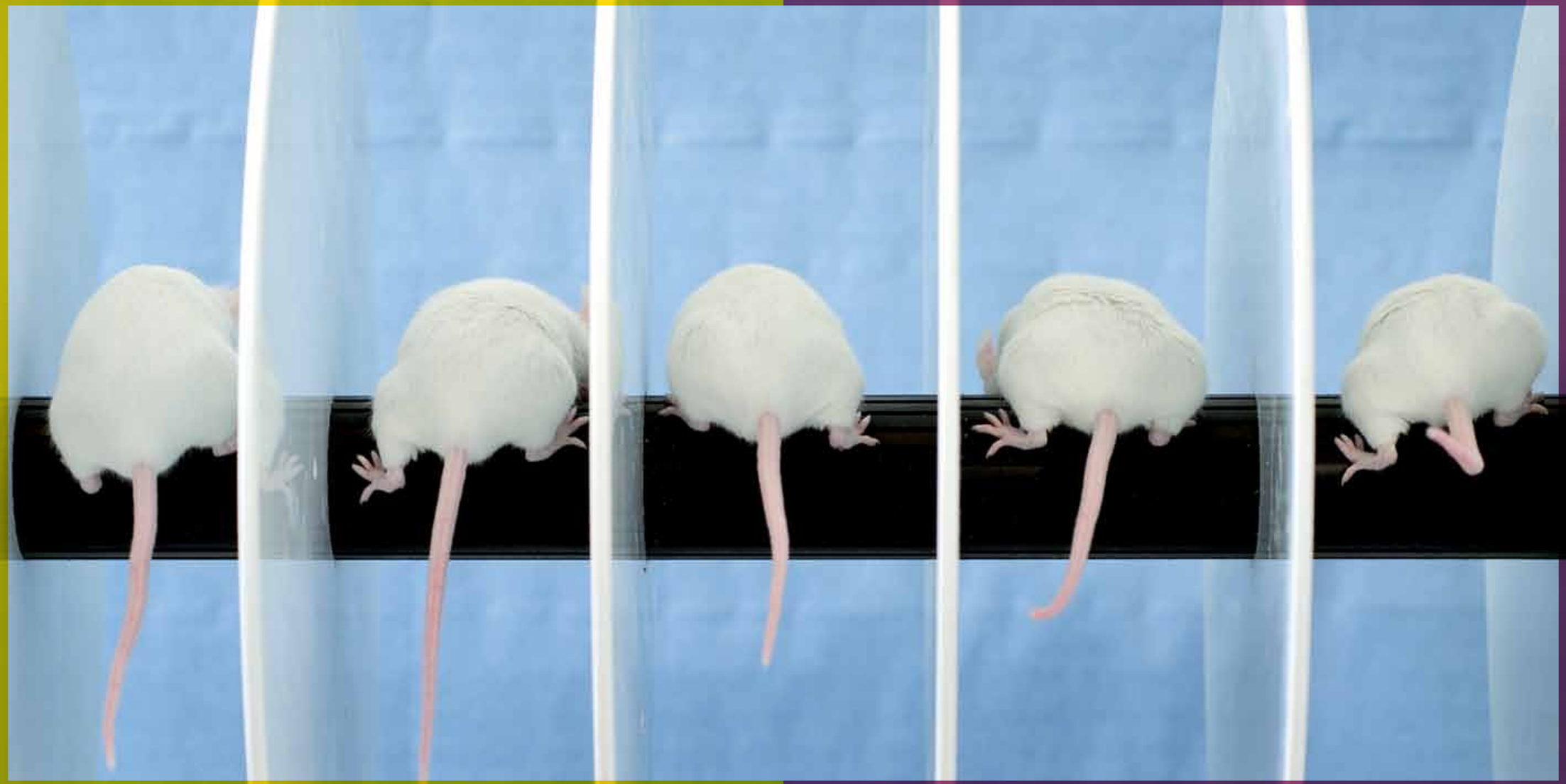
- We have launched CRACK IT – the world's first open innovation programme to connect scientists from universities, the SME sector and big business to focus on the 3Rs.
- We have made five CRACK IT Challenge awards totalling £3.5 million through our new research competition, with funding from the NC3Rs and in-kind contributions from industrial sponsors in the pharmaceutical, chemical and consumer product sectors.
- We have introduced the David Sainsbury Fellowships for exceptional early career scientists, ensuring that some of the most talented individuals are engaged in the 3Rs from the start of their independent research careers.



- We supported scientific and technological advances with £2.3 million for project and pilot study grants, and almost £1 million for strategic grants to develop human cell-based carcinogenicity assays.
- We trebled the number of PhD studentships awarded to 15, ensuring that we influence the training and development of the research leaders of the future.
- We have built new links with the mathematical modelling community in the UK in order to exploit opportunities for reducing the use of animals.
- We are leading an international programme to apply the 3Rs to the use of non-human primates in academic research and pharmaceutical discovery and development.
- We published our first review of our research portfolio highlighting the 3Rs impact of the science we fund and its wider implications in terms of providing new models and tools for industry and academia.
- We have 77 journals, including the *Nature* family, signed up to our ARRIVE guidelines for better reporting of animal research – up from 14 in 2010.
- We had 107,000 unique visitors – up 39% on the previous year – to our website which provides high quality 3Rs information and training resources.
- We have run 15 symposia and workshops – with over 1,300 delegates. These included events organised in collaboration with learned societies and research funders, and our first US workshop.

We recognise the importance of measuring and evaluating our impact. We have established a new expert group to help us review what metrics we should use. This is particularly important given the announcement last July that we would lead the Coalition Government's pledge to work to reduce the use of animals. Expectations from politicians and the public are high. We will continue to work closely with our scientific partners to provide the inspiration, infrastructure and investment necessary. The new regulatory framework which will be introduced to implement the EU Directive on the protection of animals used for scientific purposes should also provide an opportunity to support delivery of the Coalition pledge.

We are a small organisation with big ambitions. We have established an excellent track record in delivering progress on the 3Rs. The challenges ahead are significant because many of the obstacles are scientific and technological. The benefits, however, go beyond the 3Rs, providing an opportunity to address some of the major issues facing the bioscience sector – from the utility of animal models through to the need for high-throughput systems to improve efficiency. We are using the 3Rs to shape science and drive innovation.



# WE ARE PIONEERING AN OPEN INNOVATION APPROACH TO 3Rs CHALLENGES



**We believe that a new model of working which facilitates greater sharing of ideas, knowledge and expertise across sectors is essential to revolutionise science in the 3Rs.**

In 2011 we launched CRACK IT, an ambitious open innovation programme designed to accelerate the application of the 3Rs by fostering and funding collaborations between disciplines and sectors and therefore broadening the expertise involved. Through CRACK IT we have provided a unique framework to facilitate efficient data and knowledge exchange, open new avenues for exploiting research and technologies, and ultimately deliver entrepreneurship in the 3Rs.

CRACK IT has two parts: a web-based hub to connect scientists, and a new challenge-led research competition.

**CRACK IT Challenges Competition**

The CRACK IT Challenges competition is a novel mechanism for funding research. In this competition, we have worked extensively with companies from the pharmaceutical, chemical, agrochemical and consumer product industries to identify business challenges with a 3Rs theme which could be solved by the academic or SME sectors (the 'crackers').

Research to solve the Challenges is supported with funding from the NC3Rs and in-kind contributions (for example, data, compounds, equipment) from the industry sponsors. The emphasis of this three-way partnership between the NC3Rs, the crackers and the sponsor(s) is on delivering solutions that have commercial potential or contribute to improving industry processes (for example, tackling bottlenecks in research and development). This marks a departure from our traditional role of funding grants to academia for discovery research. Instead we are encouraging applications with a greater emphasis on translation from both the public and private sectors and awarding contracts with payments linked to defined milestones.

The first CRACK IT Challenges competition was launched in September by the Minister of State for Universities and Science, David Willetts MP. There were six Challenges. These were identified with, and sponsored by, AstraZeneca, Huntingdon Life Sciences, Janssen, Lilly, Roche, Syngenta,

UCB and Unilever. The Challenges covered topics as diverse as improving the extrapolation to man of toxicity data from *in vitro* tests used for chemical risk assessment, to developing miniaturised devices for wireless recording of electrical signals from the rodent brain in psychiatric disease models.

The competition was run through the Technology Strategy Board's Small Business Research Initiative to allow us to award contracts to both universities and companies. In order to promote CRACK IT and foster a better understanding of industry needs we hosted seven regional roadshows during the summer and subsequently organised dedicated surgeries for future crackers to meet the sponsors of the Challenges and potential new collaborators. In total we received 41 applications for the Challenges, many from research groups and companies not normally involved in 3Rs research or that had not previously worked together.

The applications were reviewed by specialist Panels to short-list the best ones for Dragon's Den style interviews where the winners for each Challenge were selected. Five awards were made, totalling £3.5 million. These are described on pages 10 to 15. Four of the five awards include an SME partner, and four are new partnerships formed specifically for CRACK IT. None of the applications received for the Challenge to develop new *in vitro* systems for assessing kidney toxicity in preclinical drug testing sufficiently met the industry requirements. Our plan is to work with the renal biology community in 2012 to address this.

The next CRACK IT Challenges competition will be launched in the summer of 2012.

**CRACK IT Hub**

The CRACK IT website (www.crackit.org.uk) was also launched in September. Our aim is that this will be a hub for open innovation and collaboration in the 3Rs, providing an opportunity for broadening intellectual input and sharing ideas, knowledge and resources. Scientists and organisations from any discipline will be able to use the website as a platform to 'pose a challenge' from their own research area to the wider community for solving, or to 'share a solution', for example showcasing models or products that have potential 3Rs and scientific impacts to new users and markets. Individuals or organisations





using the hub will, if desired, be able to provide funding and in-kind contributions to those that they partner with. Over the next 12 months we will focus on promoting and expanding the CRACK IT hub.

**Capacity Building in New Disciplines**

In addition to CRACK IT as a catalyst for expanding the 'global 3Rs brain', we have focused on capacity building in disciplines not normally involved with the use of animals and the 3Rs. Our priority for 2011 was mathematical modelling. In May, we co-hosted with the EPSRC's Maths in Medicine Study Group a workshop to connect modellers and toxicologists from academia and industry. Our aim was to build new partnerships and raise awareness of the challenges of toxicology and the power of mathematical modelling. This has already had an impact with a new collaboration between a toxicologist and three mathematicians winning the CRACK IT Challenges competition on improved *in vitro* to *in vivo* extrapolation in chemical safety risk assessment of human toxicity.

The workshop has also led to a number of other collaborations and activities. The Maths in Medicine Study Group meeting in September included a problem presented by scientists from the crop protection company Syngenta, which arose from discussions at our workshop. This focused on reducing the use of animals through mathematical modelling to improve the prediction of the safety of new herbicides. Beyond toxicity testing, the Study Group also brainstormed the mathematical modelling of airway smooth muscle cell proliferation and apoptosis in asthma. This was a problem presented by the NC3Rs together with Professor Ian Hall from the University of Nottingham and followed on from the work we have done to stimulate new approaches to studying asthma without the use of animals, a review of which was published in *Drug Discovery Today* in 2011[1].

To continue building on our new partnership with the mathematical modelling community we will be investing further in its application to toxicity testing with a strategic call for proposals in 2012.



1. Holmes AM *et al* (2011). *Drug Discovery Today*, 16: 659–70.

# THE CRACK IT CHALLENGE WINNERS

# 2011





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

*Funded by the NC3Rs*
*Sponsored by Lilly*

Many psychiatric and neurological diseases, including schizophrenia and Alzheimer's disease, are characterised by impairments in cognitive function that are poorly understood and treated. Rodents are used extensively for studying cognition but can show poor prediction of clinical outcome.

A T-maze is a T-shaped apparatus used in neuroscience research, including drug discovery, to assess a rat or mouse's cognitive performance (spatial learning and memory). Typically the rodent is placed at the base of the T and allowed to explore the maze choosing to enter the right or left arms. Animals can be taught to respond to specific cues, visual or auditory for example, in return for food rewards. Various parameters can then be measured as an indicator of spatial learning and memory. Recordings of brain activity while mice 'run' on a T-maze improve the value of this behavioural task as a model of human cognitive function. The use of the traditional T-maze, however, requires intensive handling of the mice and tethering to allow brain recordings. Handling is known to stress mice and affect their cognitive performance whilst tethering requires single-housing, with animals being closely monitored to prevent them becoming entangled in the tether.

Variations on the maze have been developed including modular systems with multiple T-junctions and automation. Automated mazes have a number of animal welfare benefits. Mice are able to enter the maze at will, at pre-programmed times, during the light/dark cycle. This allows the mice to perform when they are naturally more active and without any human intervention. In addition, they are able to remain in visual, auditory and olfactory contact with cage mates between trials giving further welfare benefits. Automation has also been shown to reduce variability between experiments and to increase the number of trials an animal can complete in a 24 hour period, allowing greater statistical power from fewer animals.

The need for tethering of animals for brain recording restricts the use of the automated maze. Therefore its potential animal welfare benefits, over and above the traditional apparatus, cannot be fully realised. The aim of this Challenge is to address this by developing a wireless recording system which is small enough to be carried by the mouse without affecting its welfare, and can transmit data for a minimum of 24 hours without having to change batteries, in order to avoid handling of the mice. Funding of £0.5 million was allocated by the NC3Rs to support this Challenge, with in-kind contributions from Lilly, which includes the mazes, expertise in *in vivo* electrophysiology, and materials for the validation phase.

There were six applications received for this Challenge. The winning application was from a team of world experts in low power electronics and wearable systems for physiological monitoring in humans, led by Dr Esther Rodriguez-Villegas

from the Department of Electrical and Electronic Engineering at Imperial College London and Ervitech.

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

*Funded by the NC3Rs*
*Sponsored by AstraZeneca*

Many candidate drugs fail due to unanticipated safety concerns and there is a drive to improve the identification of adverse effects that are relevant to humans, during preclinical development. Rodents are used extensively in safety assessment studies with parameters such as changes in body temperature and activity levels used as indicators of adverse effects. Measuring these specific parameters can require rats and mice to be singly-housed, or undergo invasive surgery to implant telemetry devices, and therefore has animal welfare implications. The aim of this Challenge is to develop an automated, non-surgical system to measure activity and temperature in rats and mice whilst they remain group-housed in their home cage. Funding of £0.5 million was allocated by the NC3Rs to support this Challenge, with in-kind contributions from AstraZeneca, which includes the validation studies with the new system during in-house toxicity testing.

There were eight applications received for this Challenge. The winning application was from a team led by Professor Douglas Armstrong from Actual Analytics, a company specialising in animal behavioural analysis, his collaborators at TSE Systems, a world-leading provider of hardware to support animal behaviour and physiological studies, and Professor Judith Pratt, Professor of Systems Neuroscience at the University of Strathclyde. Over the next two years, the team will develop and test a new non-invasive tracking system for activities such as grooming, rearing, sleeping, eating and drinking, as well as abnormal behaviours. When combined with temperature measurement, this will provide a new approach that not only benefits the pharmaceutical industry but also has the potential to be applied to academic studies.





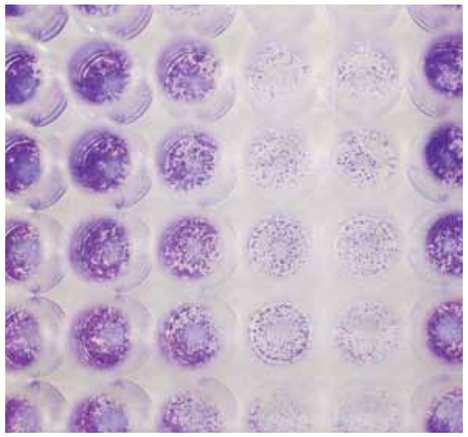
**Improving the predictive capacity of *in vitro* cytokine release assays to reduce animal use and drug attrition**

*Funded by the NC3Rs*
*Sponsored by Huntingdon Life Sciences*

Modulating the immune system with monoclonal antibodies has become an important strategy for the development of therapeutics for diseases such as rheumatoid arthritis and some types of cancer. A major challenge, however, is the risk of adverse immune reactions such as cytokine storms which can cause multiple organ failure and death. The non-human primate is commonly used for safety studies of monoclonal antibodies. However, because of differences in the immune system, it can be a poor predictor of cytokine storms in humans. A number of groups have developed *in vitro* assays using human leukocytes to detect antibody-induced cytokine release but these are limited by a lack of comparability of data between groups and correlation of performance with clinical data.

The aim of this Challenge is to develop robust human and monkey cell-based assays of cytokine release which can be scaled for high-throughput screening, and predict clinical outcome by comparison with historical data obtained from human studies. Such assays will reduce the number of monkeys used by avoiding the need for stand-alone studies for cytokine release, preclinical studies on drugs that fail later in development due to adverse immune reactions, and *in vivo* analysis of biosimilars.

Funding of £0.5 million was allocated by the NC3Rs to support this Challenge, with in-kind contributions from Huntingdon Life Sciences, which includes access to clinical antibodies, data, and technical support for the development of automation and scale-up. Five applications were received for this Challenge. The winning application was from a team led by Professor Martin Glennie from the University of Southampton and collaborators from the University of York. This internationally leading team of immunologists, clinicians, and statisticians will develop assays for different classes of monoclonal antibodies which can be integrated into a tiered strategy for the assessment of cytokine release. Importantly, the assays will take account of inter-patient variations and Fc receptor polymorphisms so that they are more predictive of the general human population.



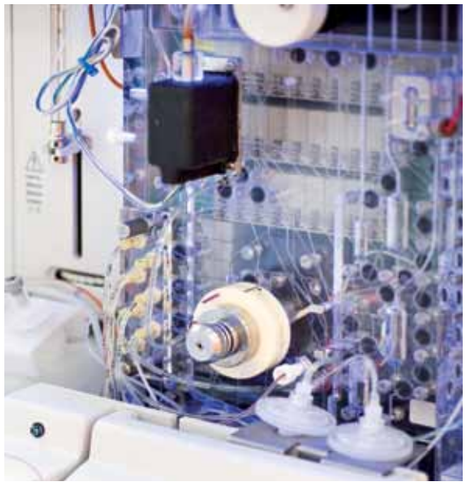
**Improved *in vitro* to *in vivo* extrapolation in chemical safety risk assessment of human systemic toxicity**

*Funded by the NC3Rs and Defra*
*Sponsored by AstraZeneca, Syngenta and Unilever*

Safety assessment of new chemicals across the chemical, agrochemical, pharmaceutical and consumer product sectors has long relied on high dose treatments in animals with default methods for extrapolating results to low level exposures in humans. Many thousands of animals are used and the results can sometimes be difficult to interpret with respect to human safety risk.

Increasingly emphasis has centred on the development of predictive *in vitro* models for safety assessment. Although progress has been made in developing *in vitro* models for some chemical toxicities, such as skin irritation and corrosion, models to detect systemic toxicity across multiple organs are not currently available. Approximately 16,000 animals are used in Great Britain each year for sub-chronic and chronic systemic toxicity testing.

In 2007, the US National Research Council published its landmark report on *'Toxicity Testing in the 21st Century: A Vision and a Strategy'*[2]. The report describes a future in which routine toxicity testing would not be conducted in animals. Instead, new *in vitro* and computational tools would be combined to evaluate cellular responses in a suite of 'toxicity pathway' assays using human cells and tissues. The aim of this Challenge is to investigate how a pathways approach to safety assessment can be put into practice. Funding of £1 million was allocated by the NC3Rs and Defra to support this Challenge, with in-kind contributions from AstraZeneca, Syngenta and Unilever. The companies will provide human, animal and *in vitro* data, aid access to specialised technologies and share expertise in modelling, risk assessment and toxicology.



There were 11 applications received for this Challenge. The winning application was from Dr Dominic Williams, University of Liverpool, who is working in collaboration with Dr Marianne Ellis, University of Bath; Dr John Ward, Loughborough University; Dr Rebecca Shipley, University of Oxford; Dr Steven Webb, University of Strathclyde; and Dr Iain Gardner, Simcyp. This is a new partnership formed as a result of the NC3Rs workshop on mathematical modelling. Using tissue engineered liver models, employing hollow fibre bioreactors with rodent and, ultimately, human cells, the team will examine effects upon biological pathways associated with liver toxicity. The data on these effects will then be used in mathematical models to extrapolate to what would happen *in vivo*.





**BADIPS: Generating human induced pluripotent stem cells to study bipolar affective disorder**

*Funded by the NC3Rs*
*Sponsored by Janssen and Lilly*

Approximately one to four percent of the world's population is diagnosed with the psychiatric condition bipolar affective disorder. Little is known about the causes although it is believed to have a genetic component since it runs in families. There are few effective treatments. Animal models of bipolar disorders have had limited impact on understanding the disorder and are poor predictors of clinical efficacy of potential therapeutics. The models typically involve the administration of compounds which cause psychosis in man or subjecting animals to stress (for example, by maternal or sleep deprivation) and are therefore associated with significant welfare concerns.

The aim of this Challenge is to exploit the potential of patient-derived induced pluripotent stem cells as an alternative to the use of animals, providing a new approach, with greater relevance to man, for discovering and screening drugs. Funding of £1 million was allocated by the NC3Rs to support this Challenge, with in-kind contributions from Lilly and Janssen including access to high-throughput assay systems, technology platforms and compound libraries to characterise and validate the model system. There were seven applications received. The winning application was from a team of psychiatrists, clinicians, geneticists and stem cell biologists from the Universities of Edinburgh and Cambridge and Roslin Cells. The team which is led by Professor Andrew McIntosh from the University of Edinburgh will develop a tool kit of stem cell-derived neural tissue assays from a family with bipolar affective disorder.

2. National Research Council (2007). http://www.nap.edu/catalog.php?record_id=11970

# WE ARE INSPIRING THE RESEARCH LEADERS OF THE FUTURE



**We believe that long term advances in the 3Rs are dependent on motivating the next generation of scientists from the start of their research careers.**

Our goal is to embed the 3Rs in the mindset of early career scientists. We are delivering this through our PhD studentship awards and our new David Sainsbury Fellowship scheme which was launched in 2011.

**PhD Studentships**

This year we have trebled, to 15, the number of PhD studentships we have awarded compared to 2010. This takes the total number of PhD studentships we have funded to 25. We now plan to develop additional opportunities and resources for our cohort of 3Rs ambassadors to ensure that they have a wide education in issues relating to animal use and the 3Rs, from experimental design to media training. This will commence with our first summer school in July 2012.

A full list of awards made in 2011 is shown in the Appendices. Included is a PhD studentship to Professor Alex Thiele and Dr Candy Rowe from Newcastle University to investigate key aspects of the use of fluid control in neuroscience experiments with non-human primates, where the monkeys perform various behavioural tasks for a fluid reward. Fluid control involves managing the animal's access to water. In the UK, this procedure typically involves the monkey obtaining the majority of its fluid intake during testing in the laboratory with additional fluid usually being provided for restricted periods in the home cage afterwards. Elsewhere in the world, the level of fluid control can be more severe. We have previously published a review of the use of fluid control and associated animal welfare concerns (such as thirst, dehydration and weight loss) which emphasised the importance of research to provide an evidence-base for refinements [3,4]. This studentship will address fundamental questions relating to the duration and level of fluid control and will ultimately provide an opportunity to improve animal welfare.

In 2011, we received 89 PhD studentship applications from 41 establishments: our award rate was 17%.



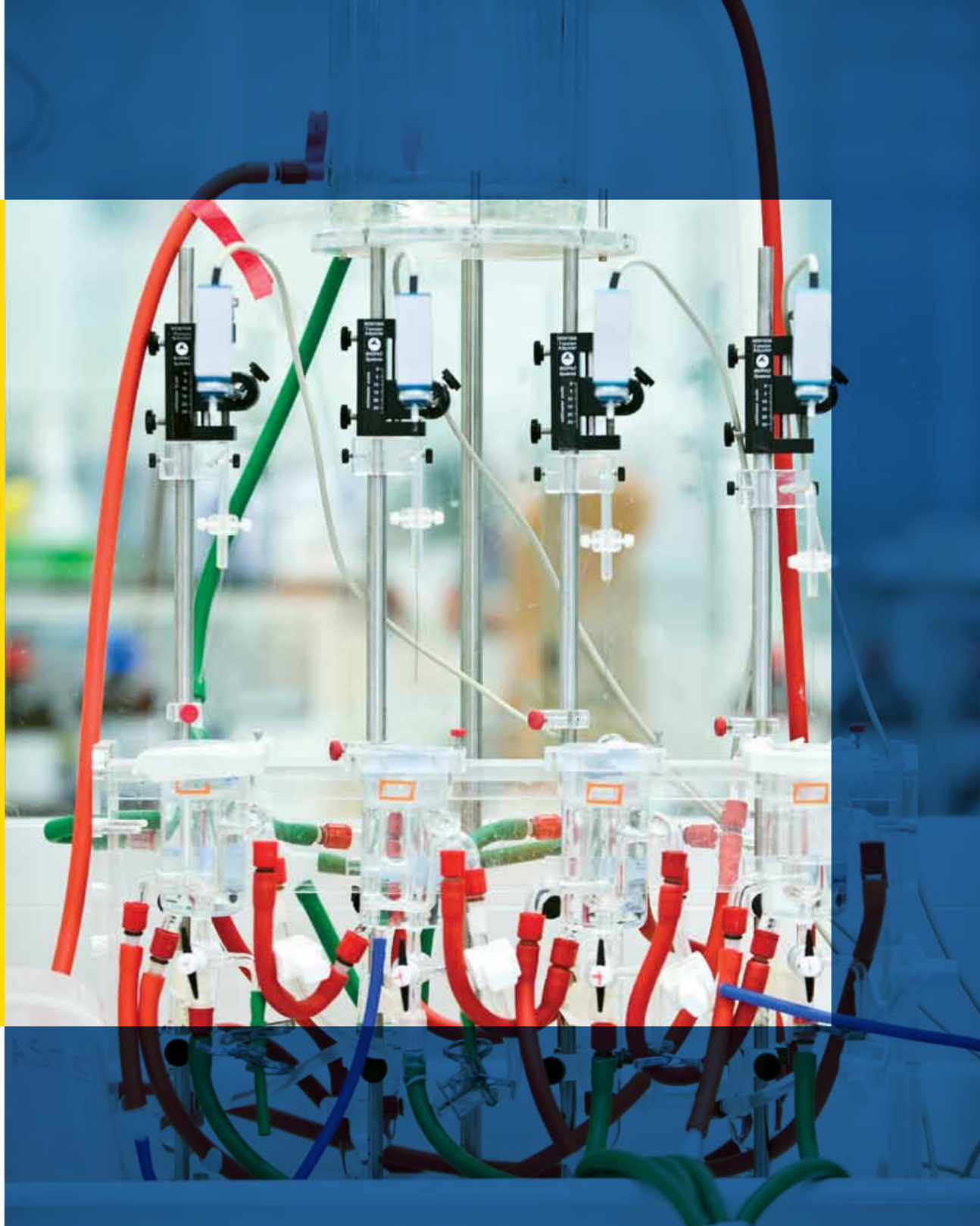
3. Prescott MJ *et al* (2010). *Journal of Neuroscience Methods*, 193: 167–88.

4. Prescott MJ *et al* (2011). *Journal of Neuroscience Methods*, doi: 10.1016/j.jneumeth.2011.08.038.

**David Sainsbury Fellowships**

The David Sainsbury Fellowship scheme will fund, each year, five outstanding scientists with less than three years post-doctoral experience. There are few opportunities for autonomous funding at this early career stage. Our scheme will therefore support the transition to independent researcher, ensuring that some of the UK's most talented individuals are engaged in 3Rs research and have a subsequent competitive advantage over their peers when seeking other funding sources.

The scheme is named in recognition of the central role played by the former Science Minister, Lord Sainsbury of Turville, in the establishment of the NC3Rs. The scheme closed in November with 35 applications received. We will be announcing the first David Sainsbury Fellows in April 2012, following interviews of short-listed candidates. Awards will be £65k per annum for three years.



# WE ARE INVESTING IN WORLD LEADING SCIENCE AND TECHNOLOGY



**We believe in funding original ideas which will transform how science is done.**

We are the UK's main funder of 3Rs research with almost £24 million committed in grants. Our research funding schemes for project and pilot grants and strategic awards allow us to respond to and shape the research environment, supporting high quality science which delivers 3Rs benefits and provides new models and tools for scientists in academia and industry.

**Project and Pilot Study Grants**

In 2011, we awarded six project grants and three pilot study grants totalling £2.3 million through our response-mode scheme. We received 50 applications for project grants and 15 for pilot study grants: the award rates were 12% and 20% respectively. The award rate for our projects grants was lower than in previous years, partly reflecting the overall size of the grants made, with four of the six ranging from £436k to £470k (previously grants have typically been around £350k). A list of awards is shown in the Appendices. Three of the awards were for research with the primary goal of replacing animal use, one was for reduction and five for refinement.

Our pilot study scheme was introduced in 2011, reflecting our recognition of the importance of funding proof of concept work as a basis for a more substantive subsequent grant application. This year we also published our first review of our research portfolio. Fourteen of the awards we have made between 2005 and 2010 were showcased, focusing on areas such as metabolic disorders, inflammation and infections, and neurodegenerative diseases. The review highlights the impact we have had in delivering real 3Rs benefits in the laboratories of the scientists we sponsor and more broadly in their communities. Importantly, the review also demonstrates how our investment is delivering new scientific discoveries and technological innovations in areas of major human need. The review can be found at www.nc3rs.org.uk/researchreview.

**Strategic Funding**

This year we have committed almost £1 million in strategic awards. Our strategic award scheme has ring-fenced funding and is designed to invest in research we have identified as priority areas, either because there are

particular concerns about the number or suffering of the animals used or a belief that new thinking may reinvigorate 3Rs efforts.

The focus for our strategic award call for 2011 was to develop human cell-based carcinogenicity assays. The strategic call built on a workshop we co-hosted in 2010 with the UK Environmental Mutagen Society to review the status of cell transformation assays for carcinogenicity testing. The output of the workshop was published in *Mutagenesis* in 2011[5].

Assessing the potential for a substance to cause cancer is an integral part of the safety evaluation of chemicals, consumer products, agrochemicals and pharmaceuticals. Carcinogenicity testing requires a two year rodent bioassay using large numbers of rats and/or mice (up to 800 animals per species). Approximately 12,500 animals were used for carcinogenicity testing in Great Britain in 2010. Tests are also time consuming and expensive and are therefore impractical for large scale testing, for example, as required under the European chemicals legislation, REACH. Moreover, from 2013 the cosmetics industry will be banned from marketing products in Europe which are tested in animals. *In vitro* alternatives for assessing the potential for chemicals to damage DNA and/or cause mutations (genotoxicity assays) are already accepted for use in regulatory carcinogenicity test strategies, but these are limited as stand-alone tests: they have a high misleading positive rate, and they do not cover non-genotoxic mechanisms of carcinogenicity. Cell transformation assays using rodent cells show good correlation with the bioassay but a lack of mechanistic information limits their use for regulatory purposes.

Strategic awards were made to Professor Robert Newbold from Brunel University and Professor Gareth Jenkins from Swansea University. The former will build on previous NC3Rs-funded research that has helped to better define the molecular mechanisms of cell transformation. Working with collaborators from Queen Mary, University of London, AstraZeneca and the Lawrence Berkeley National Laboratory (University of California), Professor Newbold will develop assays that monitor the effects of chemicals on the two key molecular events known to be responsible for immortalisation of human cells.





Professor Jenkins' research, on the other hand, will explore how information on effects on cellular signalling pathways and cell behaviour, obtained using human cell lines, can be combined with data from currently used *in vitro* genotoxicity assays to provide a better prediction of which chemicals are potential carcinogens. The study, which is being conducted in collaboration with Roche and GE Healthcare, will also consider how concentrations causing effects *in vitro* can be extrapolated to doses likely to cause effects *in vivo*. These projects should provide the tools necessary to reduce animal use in carcinogenicity testing.

**Increasing Investment in Animal Welfare Science**

In June, we hosted a workshop with the BBSRC to stimulate research proposals on novel ways of measuring and assessing animal welfare. Approximately a quarter of all of the grants we have awarded to date are for refinement research. There is considerable scope to do more to improve the welfare of laboratory animals. In many cases, however, there is a lack of tools with which to objectively assess welfare and the impact of intended refinements. The UK, mainly through funding from the BBSRC, is a leader in the scientific study of animal welfare and our aim is to take some of the thinking and approaches that are emerging in this field to benefit laboratory animals. The workshop was designed to spark new ideas and collaborations, ahead of a joint research highlight notice from the NC3Rs and BBSRC in 2012.

**Research Portfolio Website**

Details of all of the grants we have awarded can be found on our new research portfolio website which was launched in 2011. This allows our research portfolio to be searched using key words, and other criteria such as award year, institution and 'R'. It also provides information on publications and other outputs from our grants. The research portfolio can be found at www.nc3rs.org.uk/researchportfolio.

Details of all of the NC3Rs funding schemes can be found at www.nc3rs.org.uk/fundingschemes.

**3Rs Prize**

Our annual prize recognises and rewards excellence in research. The prize, which is sponsored by GlaxoSmithKline, is for a paper published in the last three years which describes research that will advance the 3Rs. This year the value of the prize was increased to a £2k personal award and an £18k grant.



5. Creton S *et al* (2011). *Mutagenesis*, doi: 10.1093/mutage/ger053.

The winning paper, published in *The Journal of Clinical Investigation*, was from Dr Ludovic Vallier's team at the University of Cambridge[6]. It describes for the first time the differentiation of human induced pluripotent stem cells from patients with inherited liver disorders. The differentiated cells approximate liver cells in functionality and also display the key pathological features of inherited liver disease. The cells provide *in vitro* models for basic research and drug discovery, and have already reduced the use of animals for the production of primary hepatocytes in the laboratories that have adopted this technology. The cells could also transform the investigation of chemical and drug-induced liver injury, a major concern for the chemical and pharmaceutical industries, further helping to reduce the use of animals. The prize grant will be used to advance the production of hepatocytes with an adult metabolic phenotype which will be more useful for drug efficacy and toxicity screening.

**Runners-up**

This year we also awarded two runners-up prizes to Dr Stephen Pettitt from the Wellcome Trust Sanger Institute and Dr Anna Williams from the MRC Centre for Regenerative Medicine in Edinburgh. The paper from Dr Pettitt, published in *Nature Methods*, describes an important advance in the production of genetically modified mice[7]. The 129 embryonic stem cell line has for many years been the workhorse for production of knock-out and knock-in mice because of its ease of use and high frequency of germ-line transmission. Many researchers, however, prefer their animals to have a C57BL/6 (Black 6) genetic background. This requires lengthy breeding programmes, typically five to ten generations, to establish the mutation introduced in the 129 cells onto a pure C57BL/6 genetic background. Dr Pettitt and his colleagues have addressed this by isolating an efficient embryonic stem cell line from C57BL/6 mice. The stem cells have also had the agouti coat colour gene repaired – this allows the visualisation of embryonic stem cell-derived mice by coat colour and the recovery of pure inbred mice from crosses with C57BL/6 mice without the extensive back-crossing and concomitant high use of mice. The cells are now used by the International Knockout Mouse Consortium.

The paper from Dr Williams' group, published in *Experimental Neurology*, describes the development of an *in vitro* model of central nervous system remyelination[8]. In multiple sclerosis, loss of myelin leads to nerve damage





and motor deficits. Drugs which stimulate remyelination are being explored as possible treatment options. Such studies are usually conducted in rodents in which demyelination has been induced. The tests use up to 40 animals for each drug and are associated with suffering. Dr Williams has demonstrated that cultured brain slices from neonatal mice can be demyelinated, with spontaneous remyelination subsequently occurring. The new myelin has the same characteristics as repaired myelin formed *in vivo*. By combining the new *in vitro* model with automated analysis of the rate of remyelination, drugs can be tested for their effects very rapidly. The number of animals used can also be reduced by up to 95% with two neonatal mice providing enough tissue to test one drug.

29 applications were received for the 3Rs prize.



6. Rashid TS *et al* (2010). *The Journal of Clinical Investigation*, 120: 3127–36.

7. Pettitt SJ *et al* (2009). *Nature Methods*, 6: 493–7.

8. Zhang H *et al* (2011). *Experimental Neurology*, 230: 138–48.

# WE ARE INFLUENCING ANIMAL RESEARCH POLICY AND PRACTICE IN ACADEMIA



**We believe the 3Rs should be embedded in the policies of research funders and science journals.**

To foster the integration of the 3Rs into the academic research process we work closely with major funders and leading scientific journals to ensure that their policies encourage and support good practice in the use of animals.

**Working with the Research Funders**

This year the number of grant, fellowship and studentship applications we reviewed for the MRC, BBSRC and the Wellcome Trust increased by 43% compared with 2010. Our reviews have identified new opportunities for implementing the 3Rs, highlighting where standard good practice was not being adopted, and recommending conditions for grant funding. In total, we reviewed 25 proposals involving the use of monkeys and 38 with cats, dogs, equines or other animals. Moreover, as part of the peer review process we visited two overseas facilities to provide advice on compliance with the guidelines *'Responsibility in the use of animals in bioscience research: expectations of the major research councils and charitable funding bodies'* and *'Primate accommodation, care and use'* which we have previously published as a benchmarks to promote high standards.

The peer review process came under further scrutiny this year when an analysis of the justification and utility of research using non-human primates, conducted between 1997 and 2006, was commissioned by the MRC, BBSRC and the Wellcome Trust[9]. We were involved in advising the funders on the scope and nature of the review which was chaired by Professor Sir Patrick Bateson FRS. During 2012, we will be working with the funders to consider how the recommendations published in the Bateson Review can be best implemented, particularly those focusing on the 3Rs.

**Working with the Science Journals**

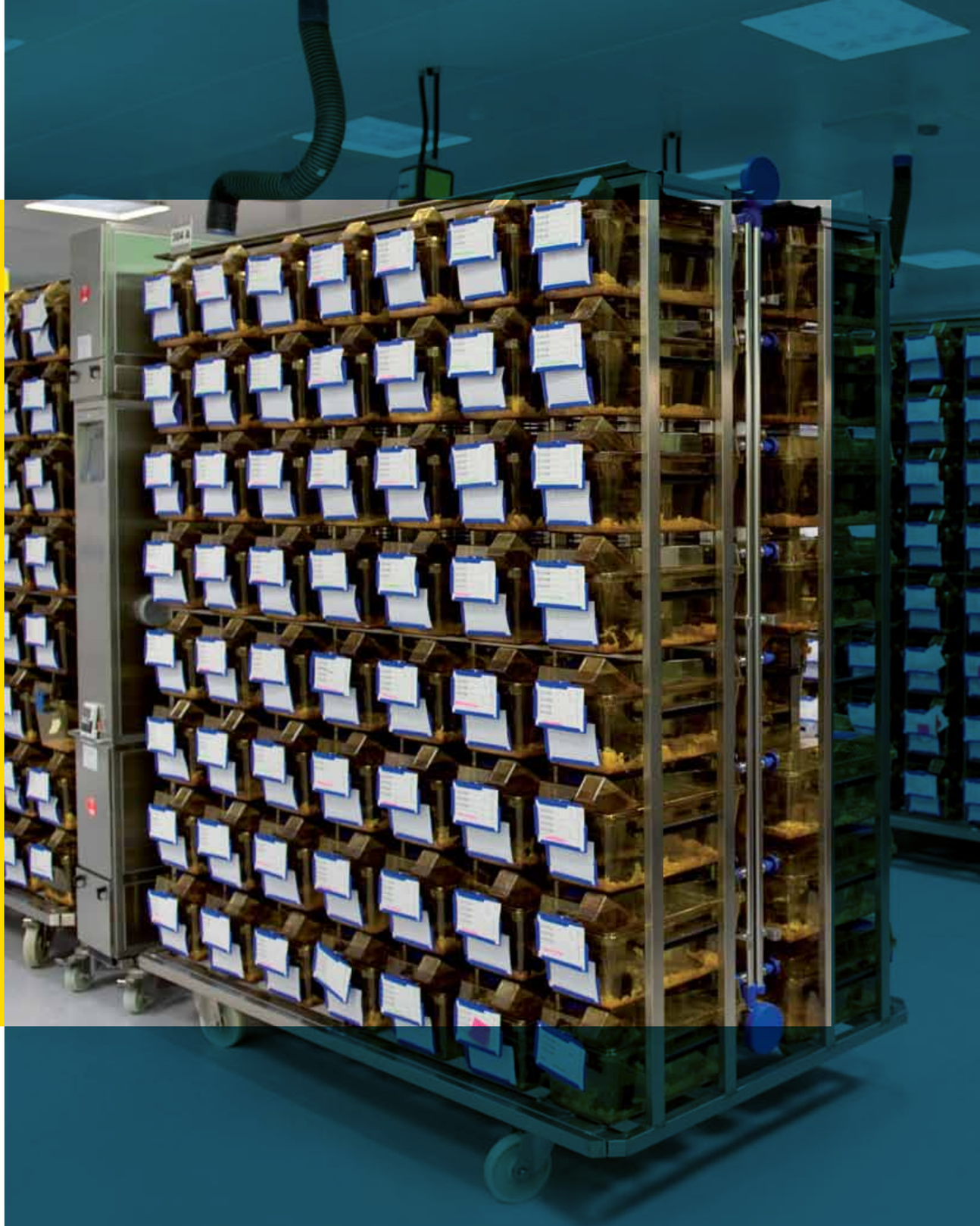
Over the last 12 months we have increased from 14 to 77 the number of journals that have adopted our ARRIVE guidelines, for example, by incorporating them into guidance to authors. Seven editorials on the ARRIVE guidelines have also been published.



9. Bateson P *et al* (2011). www.nc3rs.org.uk/batesonreport

The ARRIVE guidelines are intended to improve the reporting of animal research, providing greater transparency in terms of experimental design and analysis and maximising the knowledge gained from *in vivo* studies[10]. They were developed following our earlier work which highlighted deficiencies in the design, analysis and reporting of publicly funded research using rodents or non-human primates. The guidelines include a checklist of key information which should be included in publications, such as number and strain of the animals used, randomisation and statistical methods.

Publications signed up to the ARRIVE guidelines now include high impact journals such as the *Nature* family through to specialist publications such as *Gastroenterology* and the *Journal of the National Cancer Institute.* Our aim over 2012 is to continue to expand the number of journals using the guidelines.





10. Kilkenny C *et al* (2010). *PLoS Biology,* 8: e1000412 doi:10.1371/journal.pbio.1000412.

# WE ARE LEADING THE 3Rs IN NON-HUMAN PRIMATE RESEARCH



**We believe that greater implementation of the 3Rs in research using monkeys is achievable.**

Around 3,000 non-human primates are used in Great Britain each year, the majority for safety testing of potential new drugs. We have implemented a comprehensive programme focusing on applying the 3Rs to the use of monkeys in academic and pharmaceutical research. This includes sponsoring research. In 2011, two project grants and one pilot study grant were awarded to scientists at Newcastle University to investigate potential refinements in neuroscience research, an automated system for positive reinforcement training, and the assessment of pain using facial expressions.

**Championing the 3Rs in Pharmaceutical Development**

This year we have published four papers on reducing the use of non-human primates in pharmaceutical discovery and development, specifically in studies of abuse potential[11], assessment of candidate pharmacokinetics[12] and the testing of monoclonal antibody therapeutics[13,14]. The latter builds on our previous work which identified the potential to reduce by 64% the number of monkeys used per monoclonal antibody in drug development. The new paper includes an analysis of data from ten companies on 58 antibodies currently in development and provides an evidence-base for practical guidance on how to design studies to implement reduction strategies. Many of the international companies involved in our initiative are now using the guidance to inform their internal practice. This work has been presented at five meetings this year including the American Association of Pharmaceutical Scientists National Biotechnology Conference in San Francisco, the British Toxicology Society autumn meeting in Nottingham and the inaugural European Biosafe meeting in Cambridge. During 2012 we will review our priorities in this area, with a greater focus on refinement.

**A Forum for the Exchange of Best Practice**

Our annual non-human primate welfare meeting continues to be an important event for sharing best practice on monkey welfare internationally, with over 20% of the delegates coming from outside of the UK.

In 2011, the meeting focused on welfare assessments, captive management and refining scientific procedures. It included a presentation on a study, led



11. O'Connor EC *et al* (2011). *Neuroscience & Biobehavioural Reviews*, 35: 912–38.
12. Beaumont K *et al* (2011). *Journal of Pharmaceutical Sciences*, 100: 4518-35.
13. Chapman KL *et al* (2011). *Regulatory Toxicology and Pharmacology*, doi:10.1016/j.yrtph.2011.10.016.
14. Buckley LA *et al* (2011). *International Journal of Toxicology*, 30: 583–90.

by the NC3Rs, on the impact of weaning policy on the behavioural and physiological development of macaques. The study, which was published in *Applied Animal Behaviour Science*, involved a literature review and analysis of production data from a small breeding colony of rhesus macaques (Centre for Macaques, UK) and a large breeding colony of cynomolgus monkeys (Bioculture, Mauritius)[15]. The analysis challenges the common view that early weaning, at least before the natural weaning age, increases the productivity of the colony, and provides further evidence that early weaning can also negatively affect the behavioural and immunological competence of young macaques and therefore may ultimately influence the science the animals are used for.

**New Website on Marmoset Care**

A new website on the care and welfare of the common marmoset was also launched at the meeting. The website, which was developed by Professor Hannah Buchanan-Smith and colleagues at the University of Stirling, was funded by the NC3Rs and the Primate Society of Great Britain. Approximately 600 marmosets are used in scientific procedures in Great Britain each year and the new website provides a wealth of information for scientists and animal care staff, as well as zoos and private owners. The website can be found at www.marmosetcare.com.



15. Prescott MJ *et al* (2011). *Applied Animal Behaviour Science*, doi:10.1016/j.applanim.2011.11.001.

# WE ARE PROVIDING THE RESOURCES TO PUT THE 3Rs INTO PRACTICE



**We believe that easy access to information underpins uptake of the 3Rs.**

We are committed to providing a range of resources to maximise the dissemination of the 3Rs and their translation into practice. Our aim is to provide high quality, relevant, evidence-based material which informs and inspires. Over the last year we have delivered this through our online resources, publications and events which target the scientific community.

**Website**

Our website continues to be a well used comprehensive 3Rs resource. There were almost 158,000 visits to the site from over 107,000 unique visitors in 2011, an increase of 21.5% and 39% respectively on the previous year. Around 40% of the visits are from the UK, 16% from the rest of Europe and 25% from North America. Traffic to the website is supported by our newsletter which has over 2000 subscribers and by our new presence on Twitter and LinkedIn. We recognise that although the website content and functionality have evolved since the site was launched in 2005 they nevertheless require updating to improve the site's overall usability. This will be our focus next year with the aim of launching a new site early in 2013.

We also have started to develop a new online knowledge-based tool which will guide researchers through the design of their experiments, helping to ensure that they use the minimum number of animals consistent with their scientific objectives. The Experimental Design Assistant (EDA) is intended to be operational by the end of 2013. We have established an expert working group of statisticians and other experimental design specialists to help us develop the content and rules underpinning the EDA. To support this we have carried out a scoping exercise with 20 early career scientists to ensure that the EDA responds to the needs of researchers. A specialist Information Technology company will be appointed in 2012 to build the EDA with user testing expected to commence early in 2013.

**Publications**

This year we have authored or co-authored 17 papers, presented our work at 40 national and international events and organised 15 workshops, symposia and other events (see Appendices). Our publications cover a wide range of topics from predicting emetic liability[16] to a cross-company review of



16. Percie du Sert N *et al* (2011). *British Journal of Pharmacology*, doi: 10.1111/j.1476-5381.2011.01669.x.

opportunities to minimise animal use in pharmaceutical regulatory toxicology[17]. The latter, which was conducted under the auspices of an NC3Rs/LASA working group and published in *Regulatory Toxicology and Pharmacology*, highlighted the variation in the number of animals used for standard toxicity tests between companies and proposes new study designs which could reduce animal use by up to 40%.

**Events**

Our wide range of specialist and general 3Rs events continue to attract large audiences with over 1,300 delegates attending in 2011. Many of our meetings, such as the joint symposium with the Society of Biology, are becoming a fixture in the science calendar. This year, we have paid particular attention to ensuring that as many scientists as possible are able to attend a 3Rs event via our regional roadshows. In October we hosted our first US event in Virginia in partnership with Charles River Laboratories, focusing on improving the efficiency of pharmaceutical drug development and reducing animal use. We have also presented our work widely at scientific conferences such as EUROTOX – the Congress of the European Societies of Toxicology in Paris and the PRIM&R IACUC Conference in Chicago. During 2012 we will continue to host a range of workshops and symposia to increase the profile of our work, motivate participation in the 3Rs and encourage new networks.




17. Sparrow SS *et al* (2011). *Regulatory Toxicology and Pharmacology*, 61: 222–9.

## FINANCIAL SUMMARY

This annual report describes our activities for the calendar year 2011. Our financial accounting period runs from 1 April to 31 March each year. The RCUK Shared Services Centre Limited provides the NC3Rs with accounting and budget management services, with additional support from the MRC. The financial information provided covers the period 1 April 2010 to 31 March 2011 and has been compiled using data from the RCUK Shared Services Centre Limited.

### Income

Total income received in this financial period was £5.56 million, an increase of 16% from the period April 2009 to March 2010.

Our income from Government comes from the Department for Business, Innovation and Skills (through the MRC and BBSRC) and the Home Office. In 2010/11 there was an 18% increase in funding from the MRC and the BBSRC. Funding from the Home Office remained level at £0.25 million.

Income from charities remained level.

Income from industry includes sponsorship from the pharmaceutical, chemical, agrochemical and consumer product industries. This decreased slightly in 2010/11 due to specific projects ending.

FOR THE YEAR ENDED 31 MARCH 2011

| **Income** | **2010/11 £ million** | **2009/10 £ million** |
|---|---|---|
| Government | 5.32 | 4.52 |
| Charity | 0.10 | 0.10 |
| Industry | 0.14 | 0.16 |
| **Total** | **5.56** | **4.78** |





### Expenditure

Our annual budget is agreed by the NC3Rs Board.

Total expenditure was increased from £3.15 million in 2009/10 to £5.06 million in 2010/11.

Board costs include travel for members to meetings and associated honorariums. In the period 2010/2011, Board costs were £8,393, 24% lower than in the previous financial year. In 2009/10 Board costs included recruitment costs.

Programme costs include initiatives led by the NC3Rs staff. This covers the costs for events, working groups and the salaries of scientific and business staff who support these initiatives. In the period 2010/11, expenditure on programme costs was £0.73 million, a decrease of 24% over the previous financial year. The main factor causing this decrease was staff losses and the recruitment freeze.

Operating costs include staff salaries for core administrative duties, staff travel and training, recruitment, stationery, rental and service charges and publishing costs. In the period 2010/11, expenditure on operating costs was £0.39 million, 13% higher than in the previous financial year. This is due to the costs associated with the relocation of the NC3Rs Office to the Wellcome Trust's Gibbs Building.

FOR THE YEAR ENDED 31 MARCH 2011

| **Expenditure** | **2010/11 £ million** | **2009/10 £ million** |
|---|---|---|
| Board Costs | 0.01 | 0.01 |
| Programme Costs | 0.73 | 0.95 |
| Operating Costs | 0.39 | 0.33 |
| Grant Costs | 3.93 | 1.86 |
| **Total** | **5.06** | **3.15** |

### Research Funding Expenditure

Research funding expenditure covers grants awarded in 2006, 2007, 2008, 2009 and 2010. This was £3.93 million in the period 2010/2011, 111% higher than in the previous financial year. This is due to the increased commitments in the previous year and expenditure starting on the new grants awarded.

Expenditure on studentships was £0.075 million in the year 2010/11. There was no expenditure the previous year. This is included in the grant costs above.

Grants awarded typically commit expenditure over a three year period. Commitments for future years are covered by agreed funding from the MRC and BBSRC.

RESEARCH FUNDING PROFILE

| **Financial Year** | **Commitments made each year on new grants £ million** | **Actual spend on grants in year £ million** |
|---|---|---|
| 2005/6 | 0.99 | 0.27 |
| 2006/7 | 1.47 | 0.82 |
| 2007/8 | 2.47 | 1.28 |
| 2008/9 | 2.65 | 1.93 |
| 2009/10 | 4.86 | 1.86 |
| 2010/11 | 6.13 | 3.93 |
| **Total** | **18.57** | **10.09** |

## STUDENTSHIPS AWARDED IN 2011

**Professor Sue Barnett**
**Dr Mathis Riehle**
**University of Glasgow**

£90,000

The development of an *in vitro* model of spinal cord injury to study aligned neurite outgrowth.

**Professor Timothy Barraclough**
**Professor Gary Frost**
**Imperial College London**
**Professor Glenn Gibson**
**University of Reading**

£120,000

*In vitro* and *in silico* models of gut bacterial diversity and its impacts on human health.

**Professor Mark Dunne**
**Dr Karen Cosgrove**
**University of Manchester**

£90,000

Reducing animal dependency in diabetes research through pancreatic stem cells.

**Professor Christopher Elliott**
**Dr Katrina Campbell**
**Queen's University Belfast**

£90,000

Development of non-radioactive labels for a receptor binding assay for paralytic shellfish poisoning toxin testing.

**Dr Amir Ghaemmaghami**
**Professor Cameron Alexander**
**Dr Felicity Rose**
**University of Nottingham**

£120,000

Construction of a miniaturised human lymph node model as an alternative to the Local Lymph Node Assay.

**Dr Robert Harrison**
**Professor Richard Pleass**
**Liverpool School of Tropical Medicine**

£90,000

Refining, reducing and replacing *in vivo* WHO-standard preclinical assays of snake venom pathology and anti-venom efficacy.

**Dr Petros Ligoxygakis**
**University of Oxford**

£120,000

A *Drosophila* model of *Candida albicans* gastrointestinal infection.

**Dr Kevin Murphy**
**Imperial College London**

£90,000

Developing a novel model to assess the specificity of appetite-reducing agents.

**Dr Istvan Nagy**
**Dr Elizabeth Want**
**Dr Laki Buluwela**
**Imperial College London**

£90,000

Improving the principles of the 3Rs through new integrative metabolomic and gene expression resources for signalling studies in burn injuries.

**Dr Wendy Noble**
**Dr Diane Hanger**
**King's College London**

£90,000

Characterisation and validation of an organotypic slice culture model of Alzheimer's disease.

**Professor Richard Oreffo**
**Dr Nicholas Evans**
**University of Southampton**

£120,000

Bone healing and regeneration in an *ex vivo* bioreactor – evaluation of angiogenesis and reparation for clinical application.

**Dr Catherine Pears**
**Professor Louis Mahadevan**
**University of Oxford**
**Dr Robin Williams**
**Royal Holloway, University of London**

£90,000

Development of a non-animal model for characterising drug-resistant tumours.





**Professor Alex Thiele**
**Dr Candy Rowe**
**Newcastle University**

£120,000

Refinement of the use of fluid control as a motivational tool for non-human primates in neuroscience research.

**Dr John Ward**
**Loughborough University**
**Dr Dominic Williams**
**University of Liverpool**

£120,000

Combinatorial mathematical modelling and novel toxicological profiling of drug-induced hepatotoxicity.

**Dr Helen Wheadon**
**Dr Mhairi Copland**
**University of Glasgow**

£120,000

Using induced pluripotent stem cells as a replacement for *in vivo* models to screen novel therapies which target self-renewal pathways in chronic myeloid leukaemia.

## PILOT STUDY GRANTS AWARDED IN 2011

**Dr Andrew Jackson**
**Mr Jonas Zimmermann**
**Newcastle University**

£73,516

A fully-automated system for positive reinforcement training of group-housed non-human primates.

**Dr Roland Ashford**
**Dr Mark Chambers**
**Ms Charlotte Cooke**
**Dr William Newell**
**Animal Health and Veterinary Laboratories Agency**

£38,244

The use of gene expression profiles to predict protective immunity without the need for disease challenge.

**Dr Eric Hill**
**Dr Rhein Parri**
**Aston University**

£73,520

Investigating the use of human stem cell-derived neurons in toxicity testing.

## PROJECT GRANTS AWARDED IN 2011

**Dr Bertrand Collet**
**Marine Scotland Science**
**Professor Alexandra Adams**
**Dr Kim Thompson**
**University of Stirling**
**Miss Milena Monte**
**Professor Christopher Secombes**
**University of Aberdeen**

£435,700

Development of a non-lethal sampling method to monitor immune response and disease progression in salmonid fish.

**Professor Stuart Baker**
**Dr Graeme Chester**
**Newcastle University**
**Professor Nicholas Donaldson**
**University College London**

£71,994

Wireless high-bandwidth transcutaneous signal transmission.

**Dr Matthew Leach**
**Professor Paul Flecknell**
**Newcastle University**

£247,800

The assessment of pain using facial expressions in laboratory mice, rats, rabbits and macaques.

## PROJECT GRANTS AWARDED IN 2011

**Dr Gisli Jenkins**
**Professor Ian Hall**
**Dr Simon Johnson**
**Professor Thomas Meersmann**
**University of Nottingham**
**Dr Robin McAnulty**
**University College London**

£443,900

Refining models of fibrotic lung disease.

**Professor John Greenman**
**Mrs Marina Flynn**
**Professor Stephen Haswell**
**Dr Leigh Madden**
**Dr Anthony Maraveyas**
**University of Hull**

£450,852

Replacement of animal models for tumour biology with a multifunctional microfluidic-based approach.

**Dr Ezio Rosato**
**Dr Flaviano Giorgini**
**Professor Charalambos Kyriacou**
**University of Leicester**

£470,368

An advanced model for neurodegeneration studies in the fruit fly *Drosophila melanogaster*.

## STRATEGIC GRANTS AWARDED IN 2011

**Professor Robert Newbold**
**Brunel University**
**Professor Martha Stampfer**
**Lawrence Berkeley National Laboratory**
**Professor E Kenneth Parkinson**
**Queen Mary, University of London**
**Professor Michael R O'Donovan**
**AstraZeneca**

£499,736

Development of human epithelial cell transformation models for carcinogen screening, employing defined phenotypic endpoints mechanistically representative of rate-limiting events in human carcinogenesis.

**Professor Gareth Jenkins**
**Dr Shareen Doak**
**Dr George Johnson**
**Swansea University**

£379,306

Developing an integrated '*in vitro* carcinogenicity predictive tool' utilising *in vitro* cell signalling and cell behaviour assessment coupled with *in vitro* genotoxicity data.

## CRACK IT CHALLENGES AWARDS IN 2011

**Dr Esther Rodriguez-Villegas**
**Dr David Yates**
**Professor Andrew Holmes**
**Dr Alex Casson**
**Imperial College London**
**Mr Guangwei Chen**
**Ervitech**

£500,000

A miniature wireless EEG system for continuous monitoring of mice brainwave activity.

**Professor Douglas Armstrong**
**Mr James Heward**
**Actual Analytics**
**Dr Holger Russig**
**TSE Systems**
**Professor Judith Pratt**
**University of Strathclyde**

£ 500,000

The Trurat Show.

**Professor Martin Glennie**
**Dr Tony Williams**
**Professor Peter Johnson**
**Dr Ali Roghanian**
**Dr Stephen Beers**
**Dr Isabel Reading**
**University of Southampton**
**Dr Mark Coles**
**University of York**

£ 452,000

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





**Dr Dominic Williams**
**University of Liverpool**
**Dr Marianne Ellis**
**University of Bath**
**Dr Steven Webb**
**University of Strathclyde**
**Dr John Ward**
**Loughborough University**
**Dr Rebecca Shipley**
**University of Oxford**
**Dr Iain Gardner**
**Simcyp**

£ 997,634

Development and mathematical modelling of zonated hollow fibre bioreactors for *in vitro* to *in vivo* extrapolation of systemic chemical toxicity.

**Professor Andrew McIntosh**
**Dr Paul de Sousa**
**Professor David Porteous**
**Dr Kathy Evans**
**Professor Siddharthan Chandran**
**Professor Douglas Blackwood**
**University of Edinburgh**
**Dr Ludovic Vallier**
**University of Cambridge**

£998,586

An iPS model of Bipolar Disorder based on a large family with a highly penetrant mutation.

## EVENTS ORGANISED BY THE NC3Rs

**Science review meeting**
25 January, London

Annual event providing a scientific overview of the NC3Rs progress and future plans, including presentation of the 3Rs prize.

**Mathematical modelling and toxicology workshop**
10-11 May, London

Workshop organised jointly with the EPSRC's Maths in Medicine Study Group initiative to bring together the mathematical modelling and toxicology communities to consider how modelling could be applied to reduce animal use in toxicological testing.

**Joint workshop with the BBSRC on animal welfare**
6 June, London

Workshop to bolster the number of applications received from the animal welfare sciences community, with specific emphasis on proposals to improve measures and assessment of animal welfare.

**NC3Rs roadshows**
16 (Cardiff), 20 (Sheffield) and 28 (Nottingham) June; 6 (Manchester), 13 (Edinburgh) and 20 (London) July; 1 August (Southampton)

A series of regional roadshows to showcase the benefits of 3Rs research and to raise awareness on CRACK IT.

**Joint symposium with the Society of Biology**
22 June, London

Annual symposium focusing on a range of topics relevant to the 3Rs, including selection of control animals, imaging and the impact of neonatal stress on experimental variability.

**CRACK IT launch**
20 September, London

Formal launch of CRACK IT, by David Willetts MP, Minister for Universities and Science. Also featured the publication of the first review of the NC3Rs research portfolio.

**NC3Rs grant holders' meeting**
13 October, London

An event to bring together all of the scientists funded by the NC3Rs to promote their role as ambassadors for the Centre.

**Joint Charles River Laboratories/ NC3Rs toxicology workshop**
24-25 October, Virginia, USA

A trans-Atlantic programme focusing on designing pharmaceutical toxicology studies to minimise animal use and improve translation in man.

**Non-human primate welfare meeting**
29 November, London

Annual event, sponsored by the Wellcome Trust, providing a forum for scientists, veterinarians and animal care staff to discuss non-human primate use and welfare.

## PUBLICATIONS FROM THE NC3Rs STAFF

*NC3Rs staff are highlighted in bold.*


Adler S, Basketter D, **Creton S**, Pelkonen O, van Benthem J, Zuang V, Andersen KE, Angers-Loustau A, Aptula A, Bal-Price A, Benfenati E, Bernauer U, Bessems J, Bois FY, Boobis A, Brandon E, Bremer S, Broschard T, Casati S, Coecke S, Corvi R, Cronin M, Daston G, Dekant W, Felter S, Grignard E, Gundert-Remy U, Heinonen T, Kimber I, Kleinjans J, Komulainen H, Kreiling R, Kreysa J, Leite SB, Loizou G, Maxwell G, Mazzatorta P, Munn S, Pfuhler S, Phrakonkham P, Piersma A, Poth A, Prieto P, Repetto G, Rogiers V, Schoeters G, Schwarz M, Serafimova R, Tahti H, Testai E, van Delft J, van Loveren H, Vinken M, Worth A & Zaldivar JM (2011). Alternative (non-animal) methods for cosmetics testing: current status and future prospects-2010. *Archives of Toxicology* 85: 367–485.

Bateson P, Johansen-Berg H, Jones DK, Keverne EB, Matthews PM, Milner ADM, **Prescott MJ**, Ragan CI, Shattock R, Strauss J & Peck H (2011). Review of research using non-human primates: report of a panel chaired by Professor Sir Patrick Bateson FRS, London, *BBSRC/MRC/NC3Rs/Wellcome Trust*. www.nc3rs.org.uk/batesonreport.

Beaumont K, Gardner I, **Chapman K**, Hall M & Rowland M (2011). Toward an integrated human clearance prediction strategy that minimises animal use. *Journal of Pharmaceutical Sciences* 100: 4518-35.

Buckley LA, **Chapman K**, Burns-Naas LA, Todd MD, Martin PL & Lansita JA (2011). Considerations regarding nonhuman primate use in safety assessment of biopharmaceuticals. *International Journal of Toxicology* 30: 583–90.

**Chapman KL**, Andrews L, Bajramovic JJ, Baldrick P, Black LE, Bowman CJ, Buckley LA, Coney LA, Couch J, Dempster MA, de Haan L, Jones K, Pullen N, de Boer AS, Sims J & Ragan CI (2011). The design of chronic toxicology studies of monoclonal antibodies: Implications for the reduction in use of non-human primates. *Regulatory Toxicology and Pharmacology* Epub ahead of print. doi:10.1016/j.yrtph.2011.10.016.

**Creton S**, Aardema MJ, Carmichael PL, Harvey JS, Martin FL, Newbold RF, O'Donovan MR, Pant K, Poth A, Sakai A, Sasaki K, Scott AD, Schechtman LM, Shen RR, Tanaka N & Yasaei H (2011). Cell transformation assays for prediction of carcinogenic potential: state of the science and future research needs. *Mutagenesis* Epub ahead of print. doi: 10.1093/mutage/ger053.

**Creton S**, Saghir SA, Bartels MJ, Billington R, Bus JS, Davies W, Dent MP, Hawksworth GM, Parry S & Travis KZ (2011). Use of toxicokinetics to support chemical evaluation: Informing high dose selection and study interpretation. *Regulatory Toxicology and Pharmacology* Epub ahead of print. doi: 10.1016/j.yrtph.2011.12.005.

**Holmes AM**, Solari R & Holgate ST (2011). Animal models of asthma: value, limitations and opportunities for alternative approaches. *Drug Discovery Today* 16: 659–70.

O'Connor EC, **Chapman K**, Butler P & Mead AN (2011). The predictive validity of the rat self-administration model for abuse liability. *Neuroscience & Biobehavioural Reviews* 35: 912–38.

**Percie du Sert N** (2011a). Improving the reporting of animal research: when will we ARRIVE? *Disease Models & Mechanisms* 4: 281–2.

**Percie du Sert N** (2011b). Systematic review and meta-analysis of pre-clinical research: the need for reporting guidelines. *European Heart Journal* 32: 2340.







**Percie du Sert N**, **Holmes AM**, Wallis R & Andrews PL (2011). Predicting the emetic liability of novel chemical entities: a comparative study. *British Journal of Pharmacology* Epub ahead of print. doi:10.1111/j.1476-5381.2011.01669.x.

**Prescott MJ**, Brown VJ, Flecknell PA, Garrod K, Lemon RN, Parker AJ, Ryder K, Schultz W, Scott L, Watson J & Whitfield L (2011). Response to Westlund's commentary: 'Can conditioned reinforcers and variable-Ratio Schedules make food- and fluid control redundant?' *Journal of Neuroscience Methods* Epub ahead of print. doi: 10.1016/j.jneumeth.2011.08.038.

**Prescott MJ**, Nixon ME, Farningham DAH, Naiken S & Griffiths M-A (2011). Laboratory macaques: when to wean? *Applied Animal Behaviour Science* Epub ahead of print. doi:10.1016/j.applanim.2011.11.001.

Price C, Stallard N, **Creton S**, Indans I, Guest R, Griffiths D & Edwards P (2011). A statistical evaluation of the effects of gender differences in assessment of acute inhalation toxicity. *Human & Experimental Toxicology* 30: 217–38.

Sparrow SS, Robinson S, Bolam S, Bruce C, Danks A, Everett D, Fulcher S, Hill RE, Palmer H, Scott EW & **Chapman KL** (2011). Opportunities to minimise animal use in pharmaceutical regulatory general toxicology: a cross-company review. *Regulatory Toxicology and Pharmacology* 61: 222–9.

Stallard N, Price C, **Creton S**, Indans I, Guest R, Griffiths D & Edwards P (2011). A new sighting study for the fixed concentration procedure to allow for gender differences. *Human & Experimental Toxicology* 30: 239–49.

## NC3Rs BOARD

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University of Nottingham

## NC3Rs STAFF

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Chief Executive

**Dr Rubina Ahmed**
Research Funding
(From February 2011)

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Pharmaceutical Industry

**Dr Stuart Creton**
Chemicals and Consumer
Products Industries

**Dr Tim Francis**
Innovation and Translation
(From September 2011)

**Dr Anthony Holmes**
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**Dr Nathalie Percie du Sert**
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**Dr Mark Prescott**
Animal Welfare

**Ms Ashley Scott**
Business Manager

**Ms Dianne Stilwell**
Communications Manager
(From September 2011)

**Ms Emma Stokes**
Web Manager
(From August 2011)

## PhD STUDENTSHIP ASSESSMENT PANEL

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NC3Rs Board and GlaxoSmithkline

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University of Oxford

**Professor Bill Dawson**
Bionet Ltd

**Professor Tracy Hussell**
Imperial College London

**Professor Christine Nicol**
University of Bristol

**Dr Sally Robinson**
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**Professor Dominic Wells**
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### Co-opted Members

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**Professor Jamie Davies**
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of Edinburgh

**Professor Sue Kimber**
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**Dr Kevin Painter**
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**Dr Marcus Tindall**
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**Dr James Wheeler**
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**Professor Susan Wray**
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## PILOT STUDY AND PROJECT GRANTS ASSESSMENT PANEL

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NC3Rs Board and
University of Oxford

**Professor Verity Brown**
University of St Andrews

**Professor Peter Clegg**
University of Liverpool

**Professor Chris Denning**
University of Nottingham

**Dr Colin Dunn**
Charles River Laboratories

**Professor Nigel Gooderham**
Imperial College London

**Professor Tom Hutchinson**
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and Aquaculture Science

**Professor Ian Jackson**
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**Professor Ian Kimber OBE**
NC3Rs Board and University
of Manchester

**Professor Mike Mendl**
University of Bristol

**Dr Cahir O'Kane**
University of Cambridge

**Dr Nick Pullen**
Pfizer

**Dr Carl Westmoreland**
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### Co-opted Members

**Professor Tim Hardingham**
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**Professor Tracy Hussell**
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## STRATEGIC AWARD PANEL

**Professor Ian Kimber OBE** (Chair)
NC3Rs Board and University
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**Dr Raffaella Corvi**
European Commission

**Dr Marilyn Aardema**
Marilyn Aardema Consulting

**Dr James Harvey**
GlaxoSmithKline

**Dr Michael Routledge**
University of Leeds

## CRACK IT CHALLENGES COMPETITION

### Review Panel A

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

**Professor Nigel Gooderham** (Chair)
Imperial College London

**Dr Melvin Andersen**
The Hamner Institutes for Health Sciences

**Dr Paola Cassanelli**
Defra

**Dr Tim Ebbels**
Imperial College London

**Dr David Hay**
MRC Centre for Regenerative Medicine

**Professor Malcolm Rowland**
University of Manchester (Professor Emeritus)

**Dr Domingo Salazar**
Syngenta

**Dr Andy Scott**
Unilever

**Dr James Sidaway**
AstraZeneca

**Dr Marcus Tindall**
University of Reading

### Review Panel B

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

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

**Dr Ian Ragan** (Chair)
NC3Rs Board

**Dr Mathieu Albasser**
Lilly

**Professor Richard Bayford**
Middlesex University

**Dr Peter Brennan**
University of Bristol

**Dr Paul Brooker**
Huntingdon Life Sciences

**Dr James Brusey**
Coventry University

**Professor Kevin Fox**
Cardiff University

**Dr John Huxter**
Lilly

**Dr David Jones**
Medicines and Healthcare Products Regulatory Agency

**Dr Keith Phillips**
Lilly

**Dr Leann Quinn**
Porsolt & Partners

**Dr Will Redfern**
AstraZeneca

**Dr Mark Tricklebank**
Lilly

### Review Panel C

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

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

**BADIPS: Generating human induced pluripotent stem cells to study bipolar affective disorder**

**Professor Jamie Davies** (Chair)
NC3Rs Board and University of Edinburgh

**Professor Steve Anderton**
University of Edinburgh

**Professor Sue Barnett**
University of Glasgow

**Dr Davide Danovi**
University College London

**Professor Chris Denning**
University of Nottingham

**Dr Helga Gerets**
UCB

**Professor Fiona Karet**
Cambridge University

**Dr Chris Kirton**
Huntingdon Life Sciences

**Dr Tilo Kunath**
University of Edinburgh

**Dr Anke Luhe**
Roche

**Professor Tom MacDonald**
Queen Mary, University of London





### Review Panel C (continued)

**Dr Stephen Madden**
Charles River Laboratories

**Professor Angela Mally**
Universität Würzburg

**Professor Theo Meert**
Janssen

**Dr Jill Norman**
University College London

**Dr Rony Nuydens**
Janssen

**Dr Klaus Okkenhaug**
Babraham Institute

**Dr Emanuele Sher**
Lilly

**Dr Sally Price**
AstraZeneca

**Professor Walter Pfaller**
Innsbruck Medical University

**Dr Stuart Watson**
Newcastle University

### Challenge Panels

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

**Professor Jamie Davies** (Chair)
NC3Rs Board and University of Edinburgh

**Professor Bill Dawson**
Bionet Ltd

**Dr Stephane Dhalluin**
UCB

**Dr Jill Norman**
University College London

**Dr Sally Price**
AstraZeneca

**Dr Laura Suter-Dick**
Roche

**Dr Julian White**
White Rose University Consortium

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

**Dr Ian Ragan** (Chair)
NC3Rs Board

**Dr Mathieu Albasser**
Lilly

**Professor Richard Bayford**
Middlesex University

**Professor Paul Bolam**
University of Oxford

**Dr John Huxter**
Lilly

**Dr Keith Phillips**
Lilly

**Dr James Rimmell**
Lilly

**Dr Peter Stern**
Science

**Dr Mark Tricklebank**
Lilly

## CRACK IT CHALLENGES COMPETITION

### Challenge Panels

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

**Dr Malcolm Skingle CBE** (Chair)
NC3Rs Board and GlaxoSmithKline

**Dr Mike Capaldi**
Edinburgh BioQuarter

**Professor Nick Donaldson**
University College London

**Professor Steve Morgan**
University of Nottingham

**Mr Terry Priest**
University of Manchester

**Dr Leann Quinn**
Porsolt & Partners

**Dr Will Redfern**
AstraZeneca

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

**Dr Ian Ragan** (Chair)
NC3Rs Board

**Dr Lee Coney**
Huntingdon Life Sciences

**Professor Sir Gordon Duff**
University of Sheffield

**Dr Chris Kirton**
Huntingdon Life Sciences

**Professor Tom MacDonald**
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**Dr Martino Picardo**
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**Improved *in vitro* to *in vivo* extrapolation in chemical safety risk assessment of human systemic toxicity**

**Professor Ian Kimber OBE** (Chair)
NC3Rs Board and University of Manchester

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**Professor David Delpy**
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**Dr Domingo Salazar**
Syngenta

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**Dr David Tosh**
University of Bath

**Dr Carl Westmoreland**
Unilever

**Dr Jayne Wright**
Syngenta





## 3Rs PRIZE PANEL

**BADIPS: Generating human induced pluripotent stem cells to study bipolar affective disorder**

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NC3Rs Board

**Dr Mark Braganza**
TPG Capital

**Dr Tilo Kunath**
University of Edinburgh

**Professor Theo Meert**
Janssen

**Dr Rory Nuydens**
Janssen

**Dr Pieter Peeters**
Janssen

**Dr Emanuele Sher**
Lilly

**Dr Stuart Watson**
Newcastle University

**Professor Lorraine Young**
University of Nottingham

**Professor Ian Kimber OBE** (Chair)
NC3Rs Board and University of Manchester

**Professor Douglas Kell**
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**Professor Paul Matthews OBE**
Imperial College London and GlaxoSmithKline

**Dr Declan Mulkeen**
MRC

**Professor Bernard Silverman**
Home Office

**Professor Mike Stratton**
Wellcome Trust Sanger Institute

## GLOSSARY

**ARRIVE**
Animal Research: Reporting *In Vivo* Experiments

**BBSRC**
Biotechnology and Biological Sciences Research Council

**Defra**
Department for the Environment, Food and Rural Affairs

**EDA**
Experimental Design Assistant

**EPSRC**
Engineering and Physical Sciences Research Council

**IACUC**
Institutional Animal Care and Use Committee

**LASA**
Laboratory Animal Science Association

**MRC**
Medical Research Council

**NC3Rs**
National Centre for the Replacement, Refinement and Reduction of Animals in Research

**PRIM&R**
Public Responsibility in Medicine and Research

**RCUK**
Research Councils UK

**REACH**
Registration, Evaluation, Authorisation and restriction of Chemicals

**SME**
Small and Medium-sized Enterprises

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National Centre for the Replacement, Refinement
and Reduction of Animals in Research