



National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

Annual Report 2012

Pioneering Better Science

Foreword

The NC3Rs has a key role in supporting the delivery of the Coalition Government's pledge to work to reduce the use of animals in science. This report describes some of our main highlights from 2012 and the progress we are making to replace, reduce and refine animal use across academia and industry, nationally and internationally.

Over the last 12 months we have:

- Secured new funding to support our science from the Medical Research Council (MRC), the Biotechnology and Biological Sciences Research Council (BBSRC), the Engineering and Physical Sciences Research Council (EPSRC) and the Technology Strategy Board (TSB).
- Made our biggest single investment in 3Rs research to date with new grant awards of £5.1 million.
- Supported new approaches to replace animal use with £750k for interdisciplinary awards between toxicologists and mathematicians.
- Awarded the first four David Sainsbury Fellowships – the first dedicated 3Rs funding scheme for early-career scientists.
- Launched a new international initiative, with the Medicines and Healthcare products Regulatory Agency (MHRA), on minimising the use of recovery animals in pharmaceutical development.
- Evolved our 3Rs open innovation platform, CRACK IT, with the launch of two initiatives: the CRACK IT Mini Challenges funding scheme and the technology partnering hub CRACK IT Solutions.
- More than doubled the number of journals adopting our ARRIVE guidelines for better reporting of animal research.

We recognise the importance of measuring and assessing the impact of our work and this year we published the first 3Rs evaluation framework. The framework describes the metrics we use and how these are integrated to evaluate our strategy, the research we fund and the in-house programmes led by our own small team of scientists. Given the role of our organisation and societal concerns about animal use we believe that transparency about our work is essential. Over the next 12 months we will publish two new impact reviews, one on our initiatives with the pharmaceutical and biotechnology industries and the other on the research we have funded.

The latest Ipsos MORI survey on public attitudes to animal research also demonstrates the importance of openness and transparency. The survey shows a small decline in public support. This has triggered a commitment from the bioscience community to increased openness, which we welcome since it is consistent with the approach we have championed, for example with our ARRIVE guidelines. More broadly, a greater willingness to discuss openly the strengths and limitations of animal research is required to restore public confidence and to drive the development of 3Rs approaches from the scientific community.

Our partnership with the pharmaceutical industry demonstrates the value to the 3Rs in providing an environment for critiquing animal models and sharing data and knowledge. In 2012, we acted as an honest broker for data sharing on preclinical information from almost 300 compounds with new opportunities identified to reduce and refine animal use in safety and toxicity testing. The importance of data sharing should not be underestimated. We will now explore how we can facilitate this within the academic sector, where the potential is largely untapped.

The Ipsos MORI survey also illustrates the desire to know more about the work of the NC3Rs and during 2013 we will be placing more emphasis on public engagement and improving the information we provide about the 3Rs and our impact. We believe that we have some excellent examples of the 3Rs in practice, as we describe in this report.

Vicky Robinson, Chief Executive

Ian Kimber OBE, Chairman

First 3Rs summer school held

Nurturing the rising stars of the future

In 2012 we held our first 3Rs summer school for NC3Rs-funded PhD students. Attended by the ten students from award years 2009 and 2010, the course covered a diverse range of topics from experimental design through to working with the media.

We also awarded a further 12 PhD studentships. We received 53 applications from 31 institutions – a success rate of 23%. The awards include the development of an *in vitro* assay for studying melanomas and refinements to the mouse model of hypertension; 58% were for replacement projects, 17% for reduction and 25% for refinement.

A list of the awards can be found in the Annex on page 44.





Delegates at an
NC3Rs meeting.

Over one thousand delegates attended NC3Rs workshops and symposia

Supporting knowledge exchange and networking

This year we organised 12 workshops and symposia attended by approximately 1,200 delegates. Our events covered a range of topics from a joint meeting on implementing the 3Rs in behavioural and physiological research co-organised with the Association for the Study of Animal Behaviour and Society for Experimental Biology, through to a symposium with the Physiological Society and British

Pharmacological Society on experimental models of pain. The latter included a presentation on a £200k project that we funded in 2012 to use systematic reviews and meta-analysis to reduce and refine animal models of neuropathic pain.

A list of the events we organised in 2012 can be found in the Annex on page 42.

Inaugural David Sainsbury Fellowships announced

Creating early-career 3Rs champions

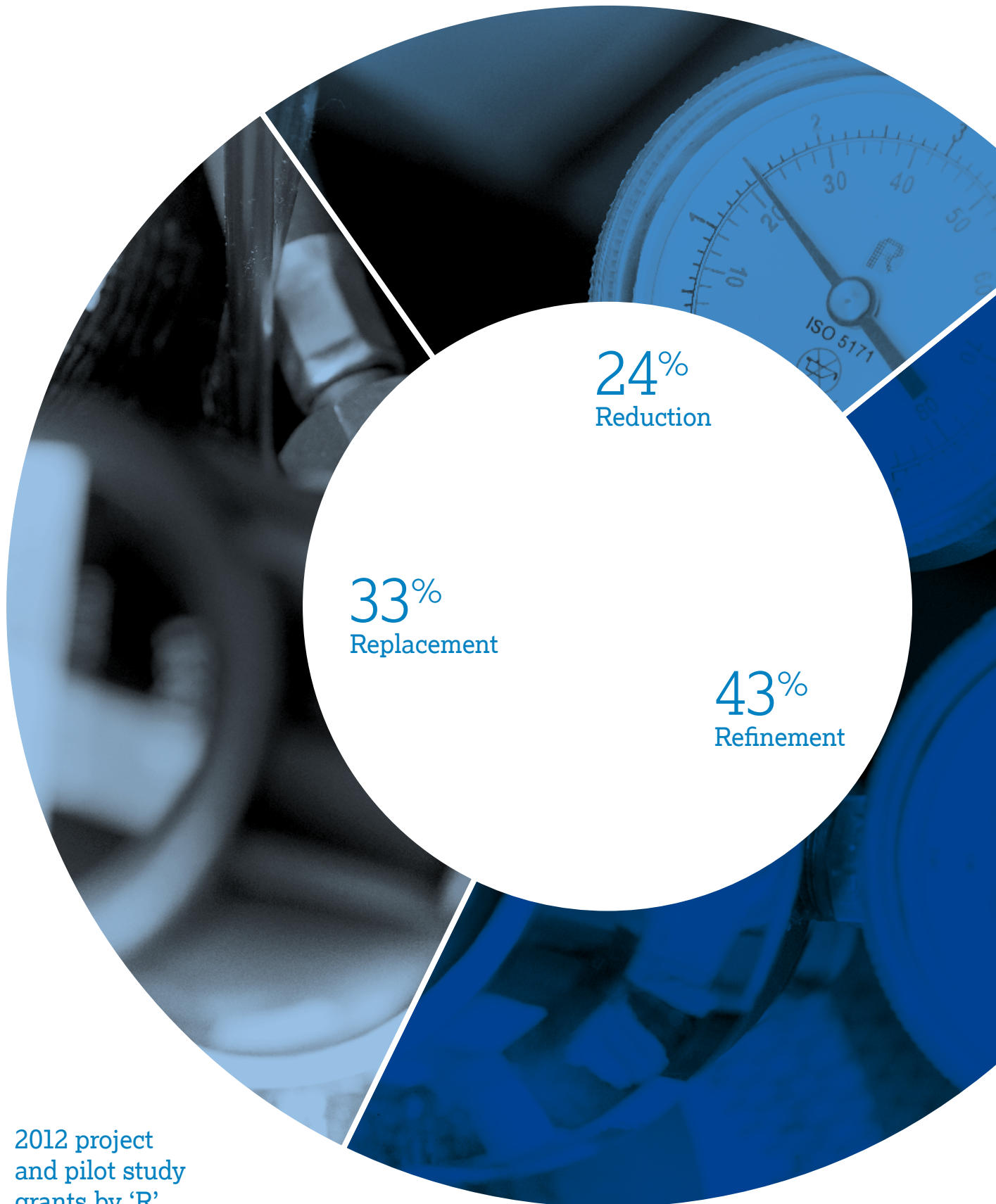
We have awarded the first four David Sainsbury Fellowships. These new awards are designed to fund talented early-career scientists with less than three years post-doctoral experience in the transition to independent researcher. We received 32 applications in total – a success rate of 13%. The four fellows will focus on 3Rs research in the areas of asthma, cancer stem cell biology, the function of the blood–brain barrier, and animal models of fatigue. The awards are named to reflect the central role of Lord Sainsbury of Turville in the establishment of the NC3Rs and are part of our strategy to embed the 3Rs in the training of the UK's future research leaders.

A list of the awards can be found in the Annex on page 45.

Dr Adrian Biddle,
David Sainsbury
Fellowship recipient.







2012 project
and pilot study
grants by 'R'



Record investment in 3Rs grants makes the news

New funding for 3Rs research and development

Radio 4's *Today* programme covered our announcement of £5.1 million to fund 21 project and pilot study grants. This is our biggest single investment in 3Rs research to date. We received 118 applications in total – a success rate of 18%. 33% of the awards were for replacement projects, 24% for reduction and 43% for refinement. The awards include a range of cutting-edge technologies from artificial human lymph nodes to computational models of bone formation. Eight of the awards, totalling £2.3 million, are for projects to develop novel ways to measure animal welfare, including an automated system to assess negative affective (emotional) state in rats and mice.

This record investment was facilitated by additional funding to the NC3Rs of £1 million from the MRC and £900k from the BBSRC.

A list of the awards can be found in the Annex on page 46.

First research paper published by NC3Rs PhD student

Reducing the use of rats in memory tests

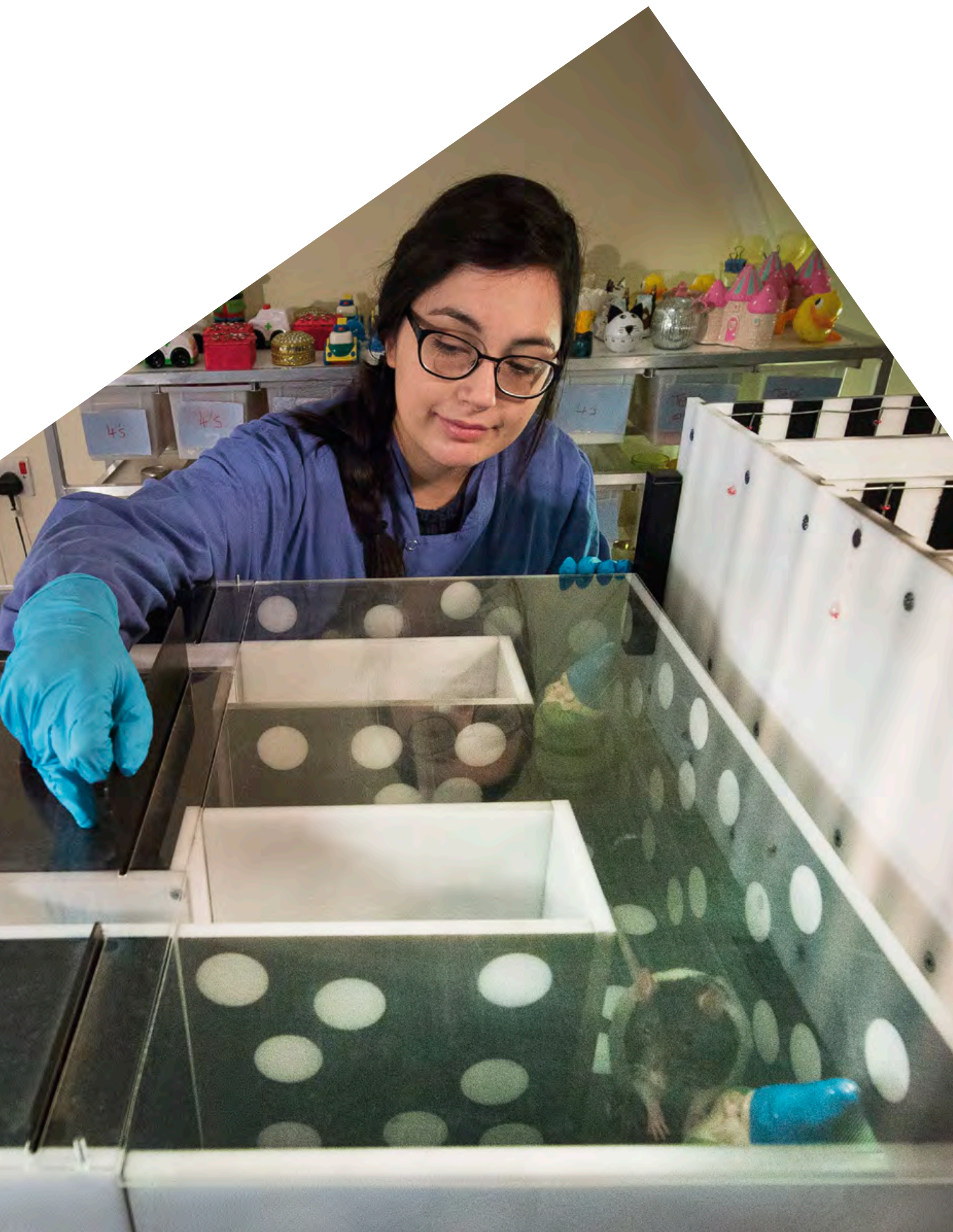
Kamar Ameen-Ali became the first PhD student funded by the NC3Rs to publish a paper on her research. A member of Dr Alex Easton's laboratory at Durham University, Kamar has developed a new testing paradigm for assessing complex memory in rats.

Many tests of memory use large numbers of animals to provide sufficient data for analysis. The new apparatus developed at Durham University uses less than a third of the number of rats typically required for traditional memory tests – a potential global reduction of around 3,400 animals a year. The test also provides the opportunity to study the neurobiology of complex forms of memory in rats, studies which are normally performed in non-human primates. Kamar's work was published in the *Journal of Neuroscience Methods*^[1] in 2012.



¹ Ameen-Ali KE, Eacott MJ, Easton A (2012). A new behavioural apparatus to reduce animal numbers in multiple types of spontaneous object recognition paradigms in rats. *Journal of Neuroscience Methods* 211: 66–76.

Kamar Ameen-Ali
NC3Rs-funded PhD student.



New 3Rs resource launched

Providing a first-class hub for learning and guidance

We have funded an online video resource on aseptic technique in rodent surgery. Asepsis during surgery is essential to avoid unnecessary suffering from post-operative infections. To support best practice we have worked with veterinarians and researchers from Newcastle University to provide guidance that can be implemented at any institute carrying out surgery on rodents. The guidance can be found on the NC3Rs-funded 'Procedures with Care' website (www.procedureswithcare.org.uk).

The NC3Rs website (www.nc3rs.org.uk) and our other online resources continue to provide comprehensive information on the 3Rs. We have seen a 22% increase in the total number of unique visitors – from 107,399 in 2011 to 131,488 in 2012, with almost 63% of the visitors from overseas. Over the next 12 months we will be developing a new NC3Rs website to improve accessibility for our range of stakeholders.

+22%

Unique visitors
to the NC3Rs website

2011

2012



Reducing fish use by one-third in agrochemical bioconcentration studies

Increasing our commitment to apply the 3Rs to the use of fish

We have published evidence to show that the use of fish in bioconcentration studies for pesticides can be reduced by one-third². Bioconcentration studies are carried out on most new pesticides and many substances under development worldwide. Two different concentrations are used – one low, one high, plus a control. Working with Syngenta and BASF we have analysed data on 55 pesticide active ingredients. Our analysis has demonstrated that bioconcentration factors do not differ between low and high concentrations and therefore only one concentration needs to be tested. This means that the number of fish used per test can be reduced from 108 to 72.

To complement this, we have also increased our investment in fish welfare with £878k for three new grants, including the development of an intelligent monitoring system to identify behaviours associated with pain and suffering.

² Creton S, Weltje L, Hobson H, Wheeler JR (2013). Reducing the number of fish in bioconcentration studies for plant protection products by reducing the number of test concentrations. *Chemosphere* 90(3): 1300–1304.



Improving the welfare of non-human primates

Providing advice and guidance in the UK and overseas

We provided 3Rs advice on 60 grant applications to the UK's major bioscience funders during 2012. This included 28 applications involving non-human primates; our advice influencing the use and welfare of around 250 animals in these proposals.

We have continued to drive changes in practice to improve the welfare of the thousands of non-human primates used worldwide. This includes organising two workshops: on training

the animals to cooperate with procedures in order to minimise stress, and refining the use of chronic implants to avoid infections and tissue damage. The workshops were each attended by over 100 delegates from academia and industry, with 40% from overseas institutes. We have now established an expert group to produce guidelines on refining the use of chronic implants in neuroscience studies.





First 3Rs evaluation framework launched

Measuring the output and impact of our activities

Our new 3Rs evaluation framework was launched by the Science Minister, David Willetts MP, at an event in the House of Commons hosted by Lord Willis of Knaresborough. The framework is the first published for measuring and evaluating progress in the 3Rs. It sets out a series of metrics for assessing the value and impact of our work. The metrics are subdivided into inputs (e.g. research funding and data sharing), outputs and outcomes, (e.g. publications and event attendance), interim impacts (e.g. changes in policy or regulatory guidelines) and mature impacts (e.g. actual impacts on animal numbers and welfare).

+129%

176 journals adopting
the ARRIVE Guidelines



Open letter in support of the ARRIVE guidelines published



2011

2012

Setting the standard for the reporting of animal research

An open letter signed by the chief executives of the UK's main bioscience funders – the MRC, BBSRC and Wellcome Trust – was sent to the Russell Group of universities and other research-intensive organisations urging them to ensure that their scientists comply with our ARRIVE guidelines for the reporting of animal research.

The ARRIVE guidelines were developed as part of our strategy to improve the design, analysis and reporting of animal experiments. The total number of journals adopting the guidelines reached 176 in 2012 – up from 77 in 2011 – with the BioMed Central family and journals of the American Physiological Society signing-up. We will continue to facilitate uptake and implementation of the guidelines, with a review of their impact planned for 2014.



Joint international project with the UK's medicines regulator

Optimising preclinical testing in partnership with industry and regulators

In partnership with the UK's MHRA, we have launched an initiative to reduce the use of recovery animals in pharmaceutical development. Recovery animals – rats, dogs and non-human primates – are used in many toxicology studies to determine whether it is possible to recover from any adverse effects caused by the drug being tested. The new initiative, which is focusing on data sharing and analysis, includes representatives from 15 pharmaceutical companies and contract research organisations across the UK, Europe and the USA, and the major medicine regulatory agencies such as the US Food and Drug Administration. It has the potential to save the use of tens of thousands of animals worldwide.

Location of companies working in partnership with the NC3Rs

- Pharmaceutical companies
- Contract research organisations
- Biotechnology companies



Limiting body weight loss to refine high dose toxicity studies

Sharing data to benefit animal welfare

We have identified new opportunities to refine short-term toxicity studies using body weight loss as an indicator of animal welfare. Such studies are used in pharmaceutical development to establish the highest dose of a drug that can be tolerated without major adverse effects (the maximum tolerated dose or MTD) and to set dose levels for subsequent toxicity studies. They involve the use of thousands of animals each year. We have

facilitated data sharing on 151 compounds from 13 pharmaceutical companies and contract research organisations to identify ways to minimise suffering. Our work shows that the MTD can be determined without exceeding body weight loss of 10% in rats and dogs, and 6% in non-human primates – lower limits than in current practice.




Promoting stem cell and tissue engineering technologies

Utilising the latest medical advances to develop replacement solutions

We have continued to champion stem cell and tissue engineering technologies to replace animal use. This includes a £400k grant to develop cardiomyocytes and hepatocytes from human pluripotent stem cells with engineered genotypes. These cells will provide a testing platform for pharmaceutical safety evaluation that mirrors the genetic diversity of human populations and could replace the use of a significant number of animals in the drug development process.

To date we have committed over £9 million for stem cell and tissue engineering technologies. Some of the science we fund, including the development of high-throughput 3D tumour assays to reduce animal use in the preclinical testing of anti-cancer drugs, was showcased at a symposium we organised with the BBSRC in 2012³.



Dr Sue Eccles and Dr Maria Vinci, NC3Rs-funded researchers at the Institute of Cancer Research.

³ Vinci M, Gowan S, Boxall F, Patterson L, Zimmermann M, Court W, Lomas C, Mendiola M, Hardisson D, Eccles SA (2012): Advances in establishment and analysis of three dimensional tumor spheroid-based functional assays for target validation and drug evaluation. *BMC Biology* 10: 29.

Unique maths and toxicology collaborations funded

Leveraging mathematical modelling to reduce animal experiments

Working with the EPSRC we have invested £750k in four interdisciplinary grants which bring together mathematicians and toxicologists and collaborators including AstraZeneca, GlaxoSmithKline, Syngenta and Unilever to exploit the use of mathematical modelling for replacing animals in the testing of pharmaceuticals and chemicals. The awards follow a workshop that we organised to foster new partnerships between toxicologists and the mathematical modelling community.

Around 400,000 animals are used in safety testing in the UK each year. Our new awards provide the long-term innovation required for alternatives to be adopted.

A list of the awards can be found in the Annex on page 48.

New data sharing projects provide evidence-base for change

Improving the translation to humans

We have continued to provide scientists with a forum to share data and critique the use of animals and potential alternative approaches – challenging the status quo and facilitating an evidence-based paradigm shift away from ‘gold standard’ animal models. We have established an expert group, with representatives from eight universities and four pharmaceutical companies, to promote the 3Rs in asthma research. This builds on the £1.5 million we have invested in asthma research to date, including the fellowship awarded in 2012 to apply the 3Rs to studies of asthmatic airway re-modelling.

Our expertise as an honest broker for data sharing has been extended to include an initiative with seven pharmaceutical companies to assess animal models for safety pharmacology studies. Focusing on central nervous system and respiratory tests, we have compared preclinical and clinical data for over 100 compounds, providing an evidence-base to rationalise the use of animals.

Dr Huw Golledge, Newcastle University, NC3Rs strategic award holder.



Funding a centre of excellence in animal welfare

Developing insights in pain recognition and alleviation

Scientists funded by the NC3Rs are providing new insights into the assessment and alleviation of pain in animals. In 2012, Dr Matt Leach, Newcastle University, published the rabbit grimace scale, a new method of assessing pain based on facial expressions⁴. This is the first time that such an approach has been used in rabbits – potentially improving the welfare of the hundreds of thousands of rabbits used worldwide.

The Newcastle University Pain and Animal Welfare Sciences Group is recognised as an international centre of excellence. Around 90% of its funding is from the NC3Rs. We support projects on alleviating pain in mouse models of cancer, assessing cumulative severity in non-human primates used in neuroscience experiments and refining the use of gaseous euthanasia in rodents. The latter is supported by an NC3Rs strategic award to Dr Huw Golledge and has implications for the welfare of the millions of laboratory rats and mice worldwide that are killed by this method each year.

⁴Keating SCJ, Thomas AA, Flecknell PA, Leach MC (2012): Evaluation of EMLA cream for preventing pain during tattooing of rabbits: Changes in physiological, behavioural and facial expression responses. *PLoS ONE* 7(9): e44437.



3Rs Prize goes international

Rewarding and recognising 3Rs research

We have opened our annual prize to international applications to help raise the profile of the 3Rs globally. The £20k prize, which is sponsored by GlaxoSmithKline, is for an original contribution to scientific and technological advances in the 3Rs published within the last three years. We received 23 applications, almost half from researchers outside of the UK.

The winning application was from Professor Donald Ingber, from the Wyss Institute for Biologically Inspired Engineering at Harvard University, USA, for his publication in *Science Translational Medicine*⁵. Many existing cell culture models fail to recapitulate complex, organ-level disease processes in humans and cannot be used to replace animals in preclinical research. The publication shows how this can be addressed using biomimetic microdevices, in this case to study pulmonary edema. The so-called lung-on-a-chip reconstitutes the alveolar-capillary interface of the human lung providing new insights into disease and allowing for *in vitro* drug screening. This innovative technology is also being applied to other organ systems and has the potential to revolutionise the replacement of animal experiments.

Three highly commended awards were also made for publications describing opportunities to replace and reduce the use of animals for studying spinal cord injury, screening anti-cancer drugs and investigating the neuropharmacology of the gut.

A list of the awards can be found in the Annex on page 50.

⁵ Huh D, Leslie DC, Matthews BD, Fraser JP, Jurek S, Hamilton GA, Thorneloe KS, McAlexander MA, Ingber DE (2012): A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. *Science Translational Medicine* 4(159): 159ra147.





New funding for 3Rs open innovation

Brokering collaborations across industry and academia

Our open innovation competition, CRACK IT Challenges, was supported with new funding to the NC3Rs of £3 million from the MRC and £1 million from the TSB. The Challenges were sponsored by five companies from the pharmaceutical and chemical sectors and for the first time an academic organisation – MRC Harwell. Two of the Challenges primarily focused on replacing animal use, one on reduction and one on refinement.

This year the competition has been divided into two phases, with Phase 1 for proof-of-concept studies providing a gateway to full funding in Phase 2. A total of 24 applications were received and ten Phase 1 contracts totalling £1 million awarded – a success rate of 40%. Nine of the ten winners included Small and Medium-sized Enterprises (SMEs).

A list of the awards can be found in the Annex on page 49.

CRACK IT

CRACK IT is our open innovation platform launched in 2011 to bridge the gap between scientific research and its wider use and commercialisation for 3Rs purposes. It is designed to tackle global 3Rs challenges, focusing on improving business processes and/or developing marketable products. Our aim is to increase scientific and technological innovation in the 3Rs by connecting the industrial, academic and SME sectors.

This year we have continued to evolve CRACK IT with new investment for our main competition CRACK IT Challenges; a new funding scheme, CRACK IT Mini Challenges; and a new technology partnering hub, CRACK IT Solutions.





NC3Rs-funded researcher.

CRACK IT Challenges

CRACK IT Challenges is a 3Rs innovation competition. The Challenges are defined by the NC3Rs in partnership with sponsors from the commercial and academic communities who provide support through in-kind contributions (such as data, compounds, expertise and equipment).

New sponsors from industry and academia

In 2012, 13 proposals were submitted as potential Challenges by sponsors predominantly from the pharmaceutical and chemical industry sectors. We selected four Challenges for the competition based on their potential for both 3Rs and commercial impacts. For the first time one Challenge was from an academic sponsor – MRC Harwell.

New proof-of-concept stage introduced

This year, the competition was divided into two phases to allow a number of approaches to be initially explored for each Challenge. Phase 1 is for six month proof-of-concept studies, of up to £100k per award. The Phase 1 winners are subsequently subject to a Dragons' Den-style interview to select one winner per Challenge to receive Phase 2 funding of up to £1 million.





New investment from the MRC and TSB

New funding of £1 million was provided to the NC3Rs by the TSB for the Phase 1 studies and £3 million by the MRC for the Phase 2 studies. The competition was run through the TSB's Small Business Research Initiative allowing us to award contracts to universities, spin-off companies and SMEs and therefore support the UK business sector.

Phase 1 winners identified

The 2012 Challenges were launched at an event in September which provided an opportunity for potential applicants to meet the sponsors and new collaborators. In total 24 Phase 1 applications were received. These were reviewed by expert panels and ten were selected for proof-of-concept funding – a success rate of 40%. Of the winners, nine included at least one SME.

The Phase 2 awards will be decided by a Dragons' Den-style interview in July 2013.

Details of the Phase 1 awards can be found in the Annex on page 49.



2012 Challenges

PREDART: Prediction of human developmental and reproductive toxicity through non-mammalian assays

Funded by the NC3Rs and sponsored by Shell and Syngenta

The goal of this Challenge is to develop a screen for reproductive and developmental toxicity, for example using cell-based assays or invertebrates, to eliminate many of the mammalian studies which are currently conducted.

Evidence of developmental or reproductive toxicity can significantly affect the potential use of a chemical, including its restriction from occupational and/or consumer use. Studies are therefore conducted early in the product development pipeline to identify those chemicals with adverse effects. The standard tests use a large number of animals, around 2,500 per chemical, typically rats and rabbits. Around 90% of the 54 million animals predicted to be used under the European chemicals regulations, REACH, will be for this purpose.

Three Phase 1 awards were made for the PREDART Challenge.

DRGNET: Enabling access to primary human dorsal root ganglion neurones for drug target identification and pharmacological testing

Funded by the NC3Rs and sponsored by Pfizer Neusentis and Grünenthal

The goal of this Challenge is to develop a viable system for the supply and use of human, rather than animal, dorsal root ganglia (DRGs) for testing potential analgesic drugs.

Animals including mice, dogs and non-human primates are used as a source of DRGs – the group of nerve cells which lie in the spinal column and are involved in processing sensory information including pain signalling. Receptors and ion channels expressed on the DRGs are targets for new analgesics and DRGs from animals are used in a range of *in vitro* experiments to assess potential drugs. There have, however, been a number of high-profile drug failures in clinical trials which had looked promising in animal studies and this has driven a demand for more physiologically relevant systems to assess efficacy, including the use of DRGs from human post-mortem or surgery tissue.

Two Phase 1 awards were made for the DRGNET Challenge.

ProBE IT: Determining the biodistribution properties of biological entities through the use of advanced imaging techniques

Funded by the NC3Rs and sponsored by GlaxoSmithKline

The goal of this Challenge is to reduce the use of animals in biodistribution studies by up to 85% by developing a non-invasive imaging approach for detecting and quantifying large biomolecules.

Large biomolecules such as monoclonal antibodies represent a growing proportion of the drugs in pharmaceutical development. Unlike traditional small molecule drugs there are no general methods for measuring how biomolecules distribute into tissues after administration to an animal. Such information is important for understanding drug effects and can help in the selection of drugs with the greatest chance of clinical success. Currently, the distribution of biomolecules can only be assessed in *ex vivo* studies. These require large numbers of animals to be dosed (around 70 mice or rats per drug) and culled at specific time points for organs to be removed for analysis.

Two Phase 1 awards were made for the ProBE IT Challenge.

Rodent Little Brother: Measurement of mouse activity, behaviour and interaction in the home cage

*Funded by the NC3Rs and sponsored
by MRC Harwell*

The goal of this Challenge is to improve the welfare of the hundreds of thousands of mice used in behavioural tests worldwide by developing non-invasive monitoring systems for tracking, recording and analysing a range of behaviours whilst mice are housed in groups, undisturbed in their home cage environment.

To characterise and investigate mouse models of human neurological and psychiatric diseases it is necessary to be able to measure the activity, behaviour, social interactions and cognitive function of individual mice. This often requires animals to be singly housed or moved to unfamiliar environments – both of which can be stressful for mice and lead to more animals being used due to data variability. Many behavioural tests are also invasive, labour intensive and use subjective scoring systems.

Three Phase 1 awards were made for the Rodent Little Brother Challenge.



CRACK IT Mini Challenges

New 'close to market' funding scheme

For Challenges involving the development of an already proven concept or prototype we have introduced a new funding scheme, CRACK IT Mini Challenges, with awards of up to £50k and 12 months duration.

In 2012 there was one Mini Challenge, RETINAS, sponsored by GlaxoSmithKline to refine techniques used in rabbits for intravitreal injection. Treatment of diseases of the eye, such as macular degeneration and diabetic retinopathy, is becoming more common. Drugs often have to be injected into the eye, and as a result the use of intravitreal injection is increasing in preclinical development. Rabbits are used due to the broad anatomical similarity of their eyes to human eyes.

The optimal site for intravitreal injection in the rabbit is very small (approximately 1mm) and the angle of needle insertion is critical to avoid rupturing the lens or tearing the retina. Although there are devices available in the clinic to minimise the likelihood of damaging the eye, they are not suitable for use in the rabbit. The goal of this Mini Challenge is to develop an injection aid suitable for the rabbit in order to avoid potential adverse effects associated with current procedures.

There were four applications for the RETINAS Mini Challenge. The Challenge winner will be announced in February 2013.





CRACK IT Solutions

New technology partnering hub launched

CRACK IT Solutions provides a route for academics and SMEs to showcase research and technology with 3Rs potential to the wider scientific community, including industry, enabling them to find new partners for adoption, validation, further development and commercialisation.

3Rs Solutions are advertised via the CRACK IT website (www.crackit.org.uk) and actively promoted by the NC3Rs through various specialist networks, forums and social media. To date eight Solutions, including five from SMEs, have been showcased with at least one potential new partner identified for seven of them. The Solutions range from using *Dicytostelium* for emetic liability studies through to small bioreactor-type devices for culturing multiple cell types in a perfusion system.

The scheme is beginning to generate wide interest and gather momentum with a further 18 Solutions currently in the pipeline. To catalyse the development of productive collaborations, in 2013 we will introduce a new scheme for short-term awards of up to £30k.

Financial summary

Background

This annual report describes our activities for the calendar year 2012. Our financial accounting period runs from 1 April to 31 March each year. The Research Councils UK (RCUK) Shared Service Centre provides the NC3Rs with accounting and budget management services, with additional support from the MRC. The financial information provided covers the period 1 April 2011 to 31 March 2012 and has been compiled using data from the RCUK Shared Service Centre.

Income

Total income for this financial period was £5.71 million, an increase of 3% from the previous period.

Income from 'Government' comes from the Department for Business, Innovation and Skills (through the MRC and BBSRC) and the Home Office. In 2011/12 there was a 3% increase in funding from the MRC and the BBSRC. Funding from the Home Office remained level at £250k.

Income from 'Charities' increased by £10k in the financial year ending 31 March 2012.

Income from 'Industry' includes sponsorship from the pharmaceutical, chemical, agrochemical and consumer product industries – this remained level.

Income	2011/12 £ million	2010/11 £ million
Government	5.46	5.32
Charity	0.11	0.10
Industry	0.14	0.14
Total	5.71	5.56

Expenditure

The annual budget is agreed by the NC3Rs Board.

Total expenditure was increased from £5.06 million in 2010/11 to £6.47 million in 2011/12.

Programme costs include initiatives led by 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 2011/12, expenditure on programme costs was £1.10 million, up from £730k in the previous financial year. This increase of 51% reflects costs associated with the appointment of new staff, the development and launch of CRACK IT and the number of scientific events.

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 2011/12, expenditure on operating costs was £400k – 3% higher than in the previous financial year.

Expenditure	2011/12 £ million	2010/11 £ million
Board Costs	0.01	0.01
Programmes Costs	1.10	0.73
Operating Costs	0.40	0.39
Grant Costs	4.96	3.93
Total	6.47	5.06

Research funding expenditure

Research funding expenditure covers awards made in 2007, 2008, 2009, 2010 and 2011. This was £4.96 million in the period 2011/12 – 26% higher than in the previous financial year. This is due to the increased number and value of the awards made.

Expenditure on studentships was £225k in the year 2011/12, up from £75k in the previous financial year. This is included in the grant costs below.

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

Financial year	Commitments made on new awards £ million	Spend on awards £ million
2007/08	2.47	1.28
2008/09	2.65	1.93
2009/10	4.86	1.86
2010/11	6.13	3.93
2011/12	9.18	4.96

NC3Rs Events

Science Review meeting

28 February

Annual event providing an overview of the NC3Rs activities and future plans, including presentation of the 3Rs prize

Mathematical modelling and toxicology workshop

2 March

Workshop to foster new collaborations between mathematicians and toxicologists and to launch joint NC3Rs/EPSRC strategic call on mathematical modelling in toxicology

Regulatory dialogue on alternative approaches for environmental safety assessment

22 May

Reception held at the Society of Environmental Toxicology and Chemistry (SETAC) World Congress in Berlin to promote cross-sector discussion on recent research on alternative approaches for environmental safety assessment. Jointly hosted with the SETAC Animal Alternatives in Environmental Science Advisory Group

Symposium on tissue engineering: the third dimension to animal replacement

12 June

Joint event with the BBSRC to showcase tissue engineering and stem cell solutions for replacing animal use, included an industry session with speakers from the pharmaceutical, consumer product, chemical and agrochemical sectors

PhD student summer school

26–28 June

3Rs educational event for NC3Rs-funded PhD students

Parliamentary event

2 July

Held at the House of Commons to launch the NC3Rs report on 'Evaluating progress in the 3Rs: the NC3Rs framework'

Symposium on implementing the 3Rs in behavioural and physiological research

4–5 July

Joint event with the Association for the Study of Animal Behaviour and Society for Experimental Biology to explore opportunities for applying the 3Rs in behavioural and physiological research

Symposium for animal technicians

11 September

Event to support the professional development of animal technicians, included presentations on breeding strategies for genetically altered mice and the welfare of minipigs



Launch of the CRACK IT 2012 Challenges
12 September

Formal launch of the 2012 competition, including networking opportunities for potential applicants with industry sponsors

Symposium on models of experimental pain: opportunities and challenges
11 October

Joint event with the British Pharmacological Society and the Physiological Society to discuss opportunities for developing new models of experimental pain, with reduced reliance on animal models

Non-human primate training workshop: meet the trainers
19 November

Co-organised with Huntingdon Life Sciences to share information on solving common problems encountered when training non-human primates for co-operation with husbandry and scientific procedures

Non-human primates chronic implants workshop: let's share what works
21 November

Co-organised with the University of Oxford to share information on the challenges of working with chronic implants used in neuroscience studies with non-human primates and the opportunities for refinement

2012 Awards: PhD Studentships

All awards were
£90k over three years

Dr Philip Biggin

University of Oxford

Using molecular simulation to improve prediction of drug export

Dr Joan Boyes

University of Leeds

Development of an *in vitro* system to determine the causes of aberrant, leukaemogenic V(D)J recombination reactions

Professor Susan Brain

King's College London

Refining an established model of hypertension in the mouse

Dr Robert Busch

University of Cambridge

Single-cell analysis of replicative fate *in vivo* by heavy water labelling of DNA and mass spectrometry

Professor Margaret Dallman

Imperial College London

Live imaging of mucosal and vascular inflammation in zebrafish in response to a high cholesterol diet

Dr James Dear

University of Edinburgh

Development of urinary exosomes as biomarkers of drug-induced kidney injury

Dr Paul Genever

University of York

3D gene knockout tissue models using adult human stem cells

Dr Pierre Guermonprez

King's College London

Development of an *in vitro* culture system generating haematopoietic dendritic cells (DCs) from mouse embryonic stem cells

Dr Nicholas Lakin

University of Oxford

Dictyostelium as non-animal model to identify DNA repair pathways as targets for cancer therapy

Dr Richard Mort

University of Edinburgh

An integrated platform to assay melanoblast and melanoma invasion of epidermis *in vitro*

Dr Tao Wang

University of Manchester

A disease model to investigate vascular endothelial function for genetic stroke CADASIL

Professor Christine Watson

University of Cambridge

Recapitulating the adult stem cell and cancer stem cell niche *in vitro* using 3D engineered matrices

David Sainsbury Fellowships

All awards were
£195k over three years

Dr Adrian Biddle

Queen Mary University of London

In vitro methods for replacement of current *in vivo* assays for development of drugs against heterogeneous cancer stem cell population

Dr Adjanie Patabendige

University of Liverpool

Optimisation of a flow-based human *in vitro* blood–brain barrier model to replace animal models for studying immunopathogenesis of viral brain infections

Dr Clare Richardson

Newcastle University

Refining the study of fatigue in mouse models of chronic liver disease

Dr Amanda Tatler

University of Nottingham

The role of bronchoconstriction in the development of airway remodelling and its effects upon lung function

Project and pilot study grants

Project grants

Professor Wendy Barclay

Imperial College London

Developing an *in vitro* approach to study transmission of respiratory viruses

£399,896

Professor Melissa Bateson

Newcastle University

Assessing cumulative severity in macaques used in neuroscience research*

£484,656

Dr Ilaria Bellantuono

University of Sheffield

Development of computational models of bone formation and resorption to predict changes in bone in preclinical intervention studies

£364,835

Professor Hannah Buchanan-Smith

University of Stirling

Validating reward-related behaviour for welfare assessment, and improving welfare through increased predictability of events*

£168,345

Dr Raymond Bujdoso

University of Cambridge

Use of PrP transgenic *Drosophila* to measure mammalian prion infectivity

£261,755

Dr Mark Coles

University of York

Human and mouse artificial lymph nodes: novel technology to reduce and replace the use of animal models in clinical and developmental immunology

£418,976

Professor Andrew Cossins

University of Liverpool

The detection, assessment and alleviation of pain in laboratory zebrafish*

£445,398

Professor Chris Denning

University of Nottingham

Human pluripotent stem cell cardiomyocytes and hepatocytes with engineered genotypes for drug safety evaluation

£414,536

Dr Charlotte Hosie

University of Chester

Establishment of consensual husbandry protocols for laboratory *Xenopus laevis* using novel physiological and behavioural techniques*

£318,366

Dr Ioanna Katsiadaki

Centre for Environment, Fisheries and Aquaculture Science (Cefas)

Assessing welfare in fish: the answer is in the water!*

£363,346



Dr Jan-Ulrich Kreft
University of Birmingham

eGUT: a tool for predictive computer simulation of the gut microbiota and host interactions
£259,264

Professor Michael Mendl
University of Bristol

Development and validation of an automated test of animal affect and welfare for laboratory rodents*
£323,338

Dr Emily Sena
University of Edinburgh

Reduction and refinement in animal models of neuropathic pain: using systematic review and meta-analysis
£208,908

Dr Sarah-Jane Vick
University of Stirling

Quantifying the behavioural and facial correlates of pain in laboratory macaques*
£177,449

Pilot study grants

Ms Gidona Goodman
University of Edinburgh

Investigation of behavioural and physiological responses to fin-clipping in zebrafish*
£74,406

Dr Francois Lassailly
Cancer Research UK

Non-invasive imaging to reduce and refine the use of animals and monitor their welfare during the course of experimentations in oncology
£72,702

Professor Mark Lewis
Loughborough University

CRANNME: The complete removal of animal use for neuromuscular effectors testing
£73,737

Dr Donna MacCallum
University of Aberdeen

Live real-time imaging of life-threatening invasive fungal infections
£76,139

Dr Fiona Oakley
Newcastle University

Optimising liver equivalents to model liver fibrosis
£75,300

Dr Christopher Petkov
Newcastle University

Individually customisable, non-invasive head immobilisation for primates with the option for voluntary engagement
£75,191

Dr Jurgen Schneider
University of Oxford

Feasibility of replacing invasive heart pressure measurements with non-invasive MR Elastography to reduce rodent numbers in pre-clinical research
£73,962

Mathematical modelling in toxicology Strategic Awards

Dr Michael Chappell

University of Warwick

Structural identifiability and indistinguishability analysis as tools for quantitative and systems pharmacology to support the 3Rs

£245,378

Dr John Gosling

University of Leeds

Uncertainty and confidence in applying mathematical models and *in vitro* data in toxicological safety assessments

£81,195

Dr Gary Mirams

University of Oxford

Prediction of human cardiotoxic QT prolongation using *in vitro* multiple ion channel data and mathematical models of cardiac myocytes

£176,136

Dr Jonathan Pitchford

University of York

Imprecision and importance: probabilistic graphical models in toxicology

£221,894



CRACK IT Challenges Phase 1 Awards

PREDART

Professor Wayne Glasse-Davies
Brainwave-Discovery Ltd
£96,600

Dr Nils Klüver
Helmholtz Centre for Environmental Research
GmbH – UFZ
£99,957

Professor Raymond Pieters
Institute for Risk Assessment
Sciences/ Toxicology
£100,000

DRGNET

Professor Praveen Anand
Imperial College London
£99,359

Professor Andrew Hart
University of Glasgow
£99,997

ProBE IT

Professor Neil Williams
KWS BioTest
£99,938

Dr James McGinty
Imperial College London
£98,439

Rodent Little Brother

Professor Douglas Armstrong
Actual Analytics
£100,000

Dr Valter Tucci
Istituto Italiano di Tecnologia
£99,150

Professor York Winter
PhenoSys GmbH
£100,000

3Rs Prize Awards

Winner

Professor Donald Ingber

Wyss Institute for Biologically Inspired Engineering at Harvard University

Huh D, Leslie DC, Matthews BD, Fraser JP, Jurek S, Hamilton GA, Thorneloe KS, McAlexander MA, Ingber DE (2012). A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. *Science Translational Medicine* 4(159): 159ra147

Highly commended

Professor Susan Barnett

University of Glasgow

Boomkamp SD, Riehle MO, Wood J, Olson MF, Barnett SC (2012). The development of a rat *in vitro* model of SCI demonstrating the additive effects of Rho and ROCK inhibitors on neurite outgrowth and myelination. *Glia* 60(3): 441–456

Professor Gareth Sanger

Queen Mary University of London

Broad J, Mukherjee S, Samadi M, Martin JE, Dukes GE, Sanger GJ (2012). Regional- and agonist-dependent facilitation of human neurogastrointestinal functions by motilin receptor agonists. *British Journal of Pharmacology* 167(4): 763–774

Professor Shuichi Takayama

University of Michigan

Tung YC, Hsiao AY, Allen SG, Torisawa Y, Hoc M, Takayama S (2011). High-throughput 3D spheroid culture and drug testing using a 384 hanging drop array. *Analyst* 136(3): 473–478

NC3Rs Board and Panel members

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University of Manchester

Professor Jamie Davies (Deputy Chair)
University of Edinburgh

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Syngenta

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MRC

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Independent

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NC3Rs

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University of Oxford and NC3Rs Board

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Professor Paul Bolam
MRC Anatomical Neuropharmacology Unit

Professor Tracy Hussell
University of Manchester

Dr Marcus Tindall
University of Reading

Professor Dominic Wells
Royal Veterinary College

Co-opted members

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Pfizer Neusentis

Professor Owen Sansom
University of Glasgow

Professor Phil Stephens
Cardiff University

Dr Carl Westmoreland
Unilever

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Professor Chris Denning
University of Nottingham

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Professor Ian Jackson
University of Edinburgh

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University of Manchester and NC3Rs Board

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Dr Cahir O'Kane
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Dr Lucy Walker
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Professor Susan Wray
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University of Cambridge

Dr Timothy Ebbels
Imperial College London

Dr Sue Eccles
Institute of Cancer Research

Professor Roger Lemon
University College London

Mr Terry Priest
University of Manchester

Dr Roberto Solari
Imperial College London

Professor Dominic Wells
Royal Veterinary College

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Dr Matthias Heil
University of Manchester

Dr Kevin Painter
Heriot-Watt University

Dr John Pinney
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Dr Heather Wallace
University of Aberdeen

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For ProBE IT and Rodent Little Brother

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MRC Harwell

Professor Kurt Anderson

University of Glasgow

Professor Richard Bayford

Middlesex University

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University of Manchester and NC3Rs Board

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Netherlands Vaccine Institute
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Dr Kathryn Chapman
Head of Innovation and Translation

Dr Mark Prescott
Head of Research Management
and Communications

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Programme Manager, Research Funding

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Programme Manager,
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Dr Tim Francis (until June 2012)
CRACK IT Manager

Dr Anthony Holmes
Programme Manager,
Technology Development

Dr Nathalie Percie du Sert
Programme Manager, Experimental Design,
Analysis and Reporting

Mr Dan Richards (from December 2012)
Communications Manager

Ms Ashley Scott
Business Manager

Dr Fiona Sewell (from August 2012)
Science Manager

Ms Caroline Shriver (from July 2012)
Operations Support Manager

Ms Dianne Stilwell (until June 2012)
Communications Manager

Ms Emma Stokes
Website and Design Manager

Acronyms

3Rs

Replacement, Reduction and Refinement of animal research

ARRIVE

Animal Research: Reporting *In Vivo* Experiments

BBSRC

Biotechnology and Biological Sciences Research Council

DRG

Dorsal Root Ganglia

EPSRC

Engineering and Physical Sciences Research Council

MHRA

Medicines and Healthcare products Regulatory Agency

MRC

Medical Research Council

MTD

Maximum Tolerated Dose

NC3Rs

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

RCUK

Research Councils UK

SETAC

Society of Environmental Toxicology and Chemistry

SMEs

Small and Medium-sized Enterprises

TSB

Technology Strategy Board



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MRC

BBSRC

Department for Environment,
Food and Rural Affairs

Home Office

Wellcome Trust

Association of the British
Pharmaceutical Industry*

GlaxoSmithKline

SC Johnson

Shell

Syngenta

The Dow Chemical Company

Unilever

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