



## **A NATIONAL CENTRE FOR THE REPLACEMENT OF ANIMALS IN EXPERIMENTS**

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### **EXECUTIVE SUMMARY**

Public opinion and legislative imperatives demand that a sustained and directed effort be made to search for alternatives to animal experiments. A House of Commons Select Committee Report made a number of recommendations for the best way to seek viable alternatives to the use of animals in experiments, including the suggestion that a National Centre be set up to pursue effective ways of finding and developing replacements. A wide range of opinion canvassed by the Committee agreed that a hub and embedded spokes would be a cost effective way of designing such a Centre. We would recommend that a hub comprising a Director, scientific officers and administrative staff with the option of a specialist in library and information science, would be appropriate, at least in the early years of the Centre.

The mission of such a Centre would be:

- To encourage, fund, and stimulate research of the highest-quality in the UK with the aim of finding suitable replacements to the use of animals in research.
- To train in, advance and disseminate knowledge of, research without the use of animal experiments. In addition such a Centre would act as a focus for a paradigm shift in the way in which biomedical problems are conceived and researchers trained.

The spokes forming the other element of the Centre would be made up of groups of researchers, representing a wide range of expertise in the biomedical sciences and associated methodologies. The spokes would be recruited from already existing centres of national and international excellence and would bid for research funds for prioritised research themes. Bids would be judged on a competitive basis. Projects would normally be for three years and would be open to all groups within the UK research community.

A range of costs for the hub would be £281,000 to £354,000 in the first year and a option of an augmented information provision would add a further £25,000 to £28,000 to this estimate. There would be £2-4 million *per annum* for research projects.

Ideally, funding for both the hub and spoke research activities would come from a variety of sources, such as the Royal Society, Wellcome Trust, humane research organisations, an enhanced Home Office budget, and other Government Departments (such as the Department of Health), Association of Medical Research Charities (AMRC) members, Research Councils, Charitable Trusts and Foundations and industry. Many of the funders would also be represented on the Council of the Centre.

One of the possible obstacles to acceptance of a National Centre devoted to the search for non- animal methods is the need to make a paradigm shift away from the norm, of reliance upon the use of animals. A detailed case study involving the Pew-McDonnell initiative in cognitive neuroscience, is examined and this lends support to a close collaboration between all the various parties involved -- the funders, researchers and other stakeholders -- broadening the horizon to encompass new ways of pursuing research questions.

A suite of multidisciplinary and state-of-the-art research collaborative ventures are the most effective way to explore questions in science -- many examples from a wide range of topics are provided. A National Centre would both enrich the research community and demonstrate that the public's concerns are being addressed.

## **INTRODUCTION**

National and European legislation regulating animal experimentation demands that non-animal methods be sought before recourse to the use of animals whenever possible. In the UK, project licence applications require that the applicant demonstrates that the principles of refinement, reduction and replacement (the Three Rs) be fully considered before making an application. However, there are powerful disincentives to change from the use of animals; these include a lack of knowledge of the state of alternative approaches, a tradition of using animals to address certain areas despite other more powerful *in vitro* approaches and the scientific community's intrinsic conservatism.

Public opinion in the UK and across Europe strongly favours the use of non-animal approaches to medical research wherever feasible. A MORI poll undertaken for the MRC in 1999 indicated that of those polled 91% agreed that “there needs to be more research into alternatives to animal experiments”.

Home Office statistics on scientific procedures show that although there has been a slow decline in the total numbers of animals used, in 2001 630,759 procedures were conducted on genetically modified animals for a variety of experimental purposes, and indeed there has been a sustained increase, year on year, in the use of genetically modified animals over the past ten years.

In toxicology there has been a concerted and widespread drive to develop and use a variety of non-animal methods in order to replace animals. A climate for change arose because a number of salient issues came together -- these included growing public concern over cosmetic testing as disclosed by various animal protection organisations; impending European Union legislation to ban animal toxicity tests for cosmetics; a growing sense in the toxicology community of the severe shortcomings of certain test procedures which in turn led to a broadly-based consensus within the community that there were better ways to obtain reliable data of relevance to humans than the use of animals (*see Appendix 5* for a very brief history of alternatives).

## REPLACING ANIMALS IS THE KEY NEED

One of the recommendations of the House of Lords Select Committee on Animals in Scientific Procedures recently was that a “Centre for the Three R’s be set up, consisting of a small administrative hub which co-ordinates research units embedded in existing centres of scientific excellence”. The Report went on to say “We consider that the development of scientifically valid non-animal systems of research and testing is important, not just to improve animal welfare, but to provide substantial benefits for human health”<sup>1</sup>. There is a clear need for a Centre in order to stimulate, support, and communicate non-animal approaches to pressing research questions. Such a Centre would also raise the ‘critical mass’ of scientific expertise involved in researching non-animal methods, which will further provide the necessary impetus to develop a broad range of new means of addressing scientific questions. Although refinement and reduction may be important as temporary measures they simply do not address the long-term issue of animal experiments which most people, including those in research, say they would prefer not to continue.

Only replacement has the potential to not only move away from reliance on the use of animals but in many instances provide a far more appropriate way of teasing apart the initiation and progression of human disease. Reduction and refinement do not call upon multidisciplinary research, but replacement has to surmount a number of hurdles within the research community and requires a national centre which is able to concentrate on a broad suite of approaches. In addition the MRC Centre for Best Practice in Animal Research proposes to tackle reduction and refinement but not replacement at a national level.

A major feature of the Centre would be its emphasis on building a responsive and growing research base and using transdisciplinarity -- bringing a suite of relevant approaches from nationally and internationally recognised research groups to scientific questions without recourse to animal experiments. A focus on transdisciplinarity is a key element because it is clear, from many fields of science, that having a team of the best researchers, from a number of areas working together on a specific method or problem, not only cross-fertilizes intellectually, but also throws up novel and innovative ways of approaching even well worked areas -- there are examples of such approaches on pages 6-8 and in *Appendix 3*.

There are many examples in the UK and the USA of centres which exploit a particular technology to study a range of biological processes or where a single process or disorder is addressed using a range of complementary techniques (examples are to be found later on pages 6-8). A national Centre such as is proposed would be a multi-stakeholder initiative, involving government and other parties who have both an interest and expertise in the area.

### **The Objectives And Mission Of Such A Centre Are In Summary:**

- To encourage, fund, and stimulate research of the highest-quality in the UK with the aim of finding suitable replacements to the use of animals in research.
- To train in, advance and disseminate knowledge of research without the use of animal experiments. In addition such a Centre would act as a focus for a paradigm shift in the way in which biomedical problems are conceived and researchers trained.

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<sup>1</sup> Report of the Select Committee on Animals in Scientific Procedures (ibid), 4.33, 2002.

The structure and function of the constituent parts of a Centre would broadly follow that recommended in the House of Lords Report. On the basis of contributions from a variety of interest and expertise groups, the Select Committee recommended that the most effective structure for a Centre would comprise a 'hub' and constituent 'spokes'. We recommend that, at a minimum, the hub could consist of a Director, at least two Scientific Officers together with an administrative secretary. The hub would implement the research funding and also frame and carry out a suite of information strategies. At a simple level this arrangement is very common within the research- funding community and works well for a variety of reasons.

If funds permit, a Library and Information Sciences (LIS) staff member would be especially advantageous. The budgetary implications of such added expertise are outlined in *Appendix 1*. With suitable expertise, such a team would form the necessary motive force for the major function of the hub -- to provide motivation and co-ordination as well as implementing the collation, distribution and operation of the funding mechanism for the research undertaken in the spokes.

We also recommend that the spokes comprise existing laboratories or research groupings having a nationally or internationally recognised level of expertise within an area of biomedical speciality or methodology and that they collaborate across disciplines. Communication across the constituent parts of the hub and spoke structure would need to identify research areas in need of alternative, non-animal approaches and suggest bids within these areas.

#### **The Structure Of The Centre For Replacement (*See Also Appendix 2*) Would Comprise:**

- A. An Executive Council -- a panel consisting of representatives from the funders of the Centre and scientists from the 'spokes' and from a range of disciplines from the wider scientific community. Such a Council would, together with the Director, prioritise research areas and outline suitable themes for research bids.
- B. The hub -- comprising Director, Scientific Officers and an administrative secretary as a minimum.
- C. Spokes -- discrete groups of recognised excellence, for example Groups, Units or programme grant holders funded by the research councils, private bodies or medical research charities.

Spokes would be recruited on the basis of successful project bids to the hub within prioritised research themes. Each successful application would represent outstanding science and feature collaboration between a number of groups. These applications would be highly competitive and would be assessed by the Executive Council, Director and other appropriate experts as independent peer reviewers, but it is envisaged that a small nexus of spokes would be in place when the Centre is launched in order to give advice and expertise to the Hub and Council.

- D. State-of-the-art communication strategies would be a major feature both within the Centre and in connection to the wider research community in order to maintain the momentum for alternatives to be researched, and used in place of animals. Within the Centre communication would be two-way between hub and the spokes, from spokes to spokes and from both the hub and spokes out to other players in the research, regulatory and implementation communities. Communication strategies would include:
  - i. An in-house specialist database or databases of existing alternatives and any unsuccessful approaches. An open-access database providing information on alternatives could also be part of the communication portfolio (if funds permitted) and would be available to

researchers; the Centre would become a portal for information on state-of-the-art research approaches using non-animal methods;

- ii. An electronic journal and/or web information bulletin boards which are regularly posted with news, regulatory matters and 'papers' for the research community;
- iii. Seminars and workshops -- perhaps in collaboration with other interested expert groups to explore newly emerging areas in alternatives research and to prioritise those areas in need of alternative approaches;
- iv. Annual Report of the Centre -- to also be available on the Centre's website.

E. Transparency would be an essential feature of the functioning of the Centre, and would include the process of bidding for funds, the feedback from such activity, the publications from participant spokes and posting of various outcomes of these operations on the Centre's website. Additionally there would be an independent audit by an expert panel of the Centre's effectiveness.

### **Budgetary Considerations:**

The UK Government's national targeted budget for developing alternatives to animal experiments, administered through the Animal Procedures Committee is £280,000. To set the sums being requested in this proposal into a context, in 2001 the Joint Infrastructure Fund (JIF), which supports buildings and other 'structural' aspects of the research enterprise consisted of £750 million pounds – which included £300 million from the Wellcome Trust. Twenty five institutions received funding from JIF, the smallest amount was £1 million and the largest £58 million. This support was for mainstream research which would be improved by better buildings or similar facilities.

The National Centre for Replacement represents a concerted effort to find innovative ways of addressing fundamental questions with a suggested start-up research budget of £2 to 4 million (for about five to ten three-year projects) (*see Appendix 1*). The hub would disburse funds for research projects located in the spokes. The Wellcome Trust, one of the largest supporters of biomedical research, spent £2.2 million in 2001 on biomedical ethics and £4.4 million pounds on the history of medicine. Similarly a massive investment has been made over the years in the Human Genome Project and the ancillary sequencing programmes, one of the latest being that for the puffer fish at \$12 million.

Ideally, funding for both the hub and the spoke research activities would come from a variety of sources, such as the Royal Society, Wellcome Trust, humane research organisations, an enhanced Home Office budget, and other Government Departments (such as the Department of Health), Association of Medical Research Charities (AMRC) members, Research Councils, Charitable Trusts and Foundations and industry. Many of the funders would also be represented on the Council of the Centre.

Research funds will be targeted to those research areas prioritised by the Centre. They would be awarded for the development of alternatives to the use of animals in experiments and it is implicit that collaboration across traditional boundaries would be the rule rather than the exception.

Start-up costs for the hub are estimated to be a minimum of £281,000 to £354,000 in the first year depending upon location and the organisation of the office accommodation. It is assumed that there will be a long-term funding strategy (one which comprises a rolling programme of five-year periods, for instance).

A national Centre which stimulates, co-ordinates and funds research in alternative methods in biomedical science requires a fundamental shift in the mindset of both the research community and the funders of research. Such a Centre will draw upon a broad set of methods and approaches from the molecular, *in vitro* and clinical, to interacting systems using computational modelling. In Germany, for example, the Centre for Documentation and Evaluation of Alternatives to Animals Experiments (ZEBET -- [www.bgvv.de/tierschutz/zebet/index-e.htm](http://www.bgvv.de/tierschutz/zebet/index-e.htm)) was established by the Federal government in 1989 with the explicit goal of bringing about the replacement of animal experiments which used animals and to more generally pursue the Three Rs. The German government's investment overall in alternative research projects in the period 1980 to 1997 was £41 million. In contrast, the UK government's investment between 1986 and 2003, a similar time period, was £3.8 million. The structure of ZEBET includes a research arm as well as the provision of a rich array of information resources and databases of alternative approaches for the research community.

### **To Facilitate A Paradigm Shift -- A Case Study:**

It is useful to use as a conceptual case study the development of the cognitive neurosciences, which involved not only a paradigm shift within the biological sciences but also called upon multidisciplinary collaboration in the face of an often hostile research community. It is generally agreed that those engaged in cognitive neuroscience now produce research of the highest quality and seek answers to fundamental problems using novel approaches.

In the 1970s and 80s the biological and behavioural approaches to the study of the brain and behaviour operated very much in isolation, pursuing similar questions without recourse to the methods or results of the other. During the early 1980s the funding of the two disciplines showed a highly significant change when two funders decided to work together to create the multidisciplinary speciality of cognitive neuroscience. In 1986 John Bruer was appointed the president of the James S McDonnell Foundation and he discussed with other, enlightened, members of the board of trustees the idea of a Research Centre in cognitive neuroscience. Such a centre, it was planned, would involve collaboration across many disciplines -- computational modelling, cognitive psychology, ethology and basic neurobiology. It was envisaged that, like the Centre for replacement, such a group would have people from many disparate disciplines with different 'languages', orientations and conceptual frameworks brought together to look in new ways at often complex questions. The initiative called upon a conceptual framework that all of the various disciplines could accept, as well as techniques and methods to support the new structure. The research output would be peer reviewed and subjected to the same assessment processes as any other scientific area.

The pathway from which cognitive neuroscience emerged has a number of pointers for a national Centre for replacement:

- an initial workshop was organised to bring together, in a relaxed fashion, those from various backgrounds to identify research themes -- these groups would then become the initial spokes
- collaboration between the various funders followed -- the Pew Charitable Trusts and the McDonnell Summer Institutes targeted where funding could be usefully applied to those themes which were previously identified
- key players in the funding and research communities nurtured and fleshed out the original plans for a centre and this support helped to bridge the various scientific cultures which existed in the biological and behavioural sciences.

The McDonnell Foundation and the Pew Trusts then agreed to launch an initiative that would:

- fund the creation of research groups which could investigate cognitive neuroscience from a multidisciplinary perspective.
- fund training and research in order to bring investigators from other disciplines into the emerging cognitive neuroscience. By bringing young scientists into this new field the funders were creating a change in mindset -- diversity of approach replaced the reliance on narrow, conventional approaches; this is especially important in difficult areas

Despite many serious and often hostile doubts about the wisdom of the approach taken, the funders and the key players in the research community persisted.

### **The Results:**

A rigorous programme of evaluation and investment followed from the initial ideas. Workshops, summer schools and conferences spread not only the research findings supported by the initiative but also the culture of cognitive neuroscience. By 1998 the programme had built a research base, trained investigators, supported novel and innovative research and built a new discipline. A key element was the use of multidisciplinary centres within a high risk area. The research groupings set up under the McDonnell-Pew partnership now attract funding from national and international funders and governments.

### **Lessons For A Centre For Replacement:**

1. A small nucleus of enlightened and motivated individuals within funding bodies and the research community can progress an idea even in the face of hostile criticism from sections of the research community.
2. All involved in the creation of the cognitive neuroscience community realised from the start that the goal was the formation of a community of individuals, each with specific areas of expertise, who were prepared to utilise their areas of competence to build collaboration with others in different areas of expertise.
3. The original ideas for research topics came from the research community itself and were taken up by the funders -- this approach could also be used to stimulate the initial research programme for the Centre for replacement. See page 4 for further details.
4. Frequent feedback and evaluation in the early days allowed the knowledge base to grow and set new research questions.
5. Multidisciplinary approaches were a keynote feature of the process throughout the initial 12 years of the programme.

As a result of the collaboration of funders, members of various research communities and young researchers, a new discipline has been established which has addressed fundamental questions in novel ways and thrown light on human neurobiology in ways which were never previously conceived.

Over the period from 1986 to 1998 the Pew Trusts and the McDonnell Foundation invested research funding of \$47.2 million which established eight research groups for cognitive neuroscience and made 198 grants available for training and research.

## Other Specialist Centres:

The concept that specialist centres should be established in order to create a 'critical mass' which is capable of advancing specific areas of science has been widely and successfully used over the past twenty years.

In Germany the **ZEBET** centre has eleven permanently funded staff and the research programme is separately funded using at present a small proportion of that staff figure -- two full-time staff members and various visiting post-doctoral and senior scientists. ZEBET has a vigorous prevalidation and validation programme for non-animal techniques which has made substantial progress, for instance in the last year, major methods to replace animal use in skin and eye irritation, phototoxicity and embryological toxicity have been accepted by regulatory authorities. Collaboration with other funding agencies is a marked feature of the ZEBET research programme.

There are now in the UK a great many specialist centres which span all areas of science, where various disciplines collaborate to investigate complex questions.

The **Leverhulme Centre for Innovative Catalysis** ([www.liv.ac.uk/LCIC/](http://www.liv.ac.uk/LCIC/)) at the University of Liverpool is an academic centre investigating catalytic science: an area of fundamental importance in biology, chemistry, engineering and medicine. The centre uses industrial collaboration across many departments to carry out research which is not "biased by a limited knowledge or understanding".

Also at the University of Liverpool is the **Surface Science Research Centre** ([svr.ssci.liv.ac.uk](http://svr.ssci.liv.ac.uk)) which involves collaboration between chemists, physicists, engineers, and industrial researchers to probe events at the molecular level which occur on various surfaces. A wide range of techniques are harnessed by the centre.

The **Wellcome Trust Centre for Human Genetics** ([www.well.ox.ac.uk](http://www.well.ox.ac.uk)) at Oxford University explores all aspects of human susceptibility to disease, especially the role of genes. The centre houses multidisciplinary research teams in human genetics, functional genomics, bioinformatics, statistics and structural biology.

Also at Oxford is the **Oxford Centre for Molecular Sciences** ([www.ocms.ox.ac.uk](http://www.ocms.ox.ac.uk)) which takes an interdisciplinary approach to an array of biological processes from the 3-D structure of complex biological molecules to the ways in which cells pass information to each other. Departments liaising through the Centre include Chemistry, Biology and Medicine.

The **Centre for Nonlinear Dynamics and its Applications** ([www.ucl.ac.uk/CNDA/](http://www.ucl.ac.uk/CNDA/)) at University College London involves researchers using the study of nonlinear dynamic behaviour in order to understand of complex systems as disparate as the weather, machinery behaviour, turbulence in body systems, economic phenomena and crowd behaviour. Collaboration across the corresponding specialities is co-ordinated by researchers in the Department of Civil and Environmental Engineering at University College London.

Also at University College London is the **Nuclear Magnetic Resonance Physics Group** ([www.ion.ucl.ac.uk/nmrphysics/index.html](http://www.ion.ucl.ac.uk/nmrphysics/index.html)) which is located at the Institute of Neurology and is focussed on ways to investigate multiple sclerosis and epilepsy in humans. Liaison between various departments across University College and internationally involves physicists, clinicians, computer experts as well as those in the functional imaging field.

There are many other examples in the UK and the rest of the world of centres being established to promote and develop research applications in a diverse range of applications by fostering collaboration across scientific fields.

Many comprise disparate groupings of expertise where collaboration focuses on a single topic such as genetics, biological structure or a specific disorder such as diabetes or brain disease. The search for a range of alternative approaches to the use of animal experiments to seek answers to scientific questions involves both a paradigm shift -- from an ends-driven to a methods-driven approach – but also calls upon collaboration across many disciplines. But paradigm shifts and multidisciplinary are the hallmarks of the very best of science. It is obvious that in the life sciences there is an exponential growth in the technologies becoming available for a host of research uses.

Clearly, centres which use multidisciplinary approaches are neither new nor especially high-risk endeavours. A Centre investigating and promoting replacement of animals would not only enrich research practice but would also produce ethically-inspired researchers trained in cutting edge cellular and molecular techniques.

A National Centre would provide a critical mass to develop high quality non-animal approaches across a broad range of needs, and also addresses the public's desire for a far more humane science. It is also a move which would fulfil the intention embodied in European legislation (especially Directive 86/609). The European Commission, in their submission to the European Parliament, have stressed the importance of the life sciences and biotechnology, properly regulated, in the creation of the next wave of the knowledge-based economy. The submission states<sup>2</sup> that “Europe is faced with a major policy choice: either accept a passive and reactive role, and bear the implications of the development of these [life sciences and biotechnology] technologies elsewhere, or develop proactive policies to exploit them in a responsible manner, consistent with European values and standards”. The UK is in a similar position with respect to developing and applying new methods to replace animal experiments. The creation of a National Centre of Excellence in the UK would go some way toward fulfilling a serious need to be more proactive in this field.

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<sup>2</sup> Towards a strategic vision of life sciences and biotechnology: consultation document COM(2001)454 – September 2001. Also at <http://europa.eu.int/comm/biotechnology>.

## Appendix 1

This Appendix illustrates a suggested *per annum* budget for the provision of a hub and a research programme (within the spokes). Research funding would be awarded on the basis of competitive bids. Two scenarios for the hub are provided. Scenario 1 assumes a minimum communications strategy, whilst scenario 2 includes a specialist library and information sciences officer and an enhanced information and communications strategy.

	<b>Scenario 1</b>	<b>Scenario 2</b> (enhanced information & communications)
<b>Hub Staff</b>		
Director	£55,000 - £60,000	£55,000 - £60,000
Scientific Officer 1	£30,000 - £40,000	£30,000 - £40,000
Scientific Officer 2	£30,000 - £40,000	£30,000 - £40,000
Admin. Secretary	£15,000 - £20,000	£15,000 - £20,000
Library & Information Sciences Officer	n/a	£22,000 - £25,000
Staff recruitment	£4,000 - £5,000	£4,000 - £5,000
<b>Hub</b>		
Premises rental	£20,000 - £30,000	£20,000 - £30,000
Office equipment (including computers etc)	£10,000	£10,000
Utilities (telephone, electricity etc)	£6,500 - £9,000	£6,500 - £9,000
Information & communications*	£106,000 - £126,000	£106,000 - £126,000
Council & expert committee meetings	£4,500 - £9,500	£4,500 - £9,500
<b>Hub Database of Alternatives</b>		
Database start-up**	n/a	£3,100
Database operation#	n/a	£1,200
<b>Hub total</b>	£281,000 - £354,000	£306,000 - £382,000
<b>Research Funding###</b> (awarded to the spokes)	£2 million - £4 million	£2 million - £4 million
<b>Grand total</b>	£2,281,000 - £4,354,000	£2,306,000 - £4,382,000

\*Information and communications include: website design and maintenance, electronic journal and bulletin boards, workshops, seminars, launching the Centre, advertising grants etc.

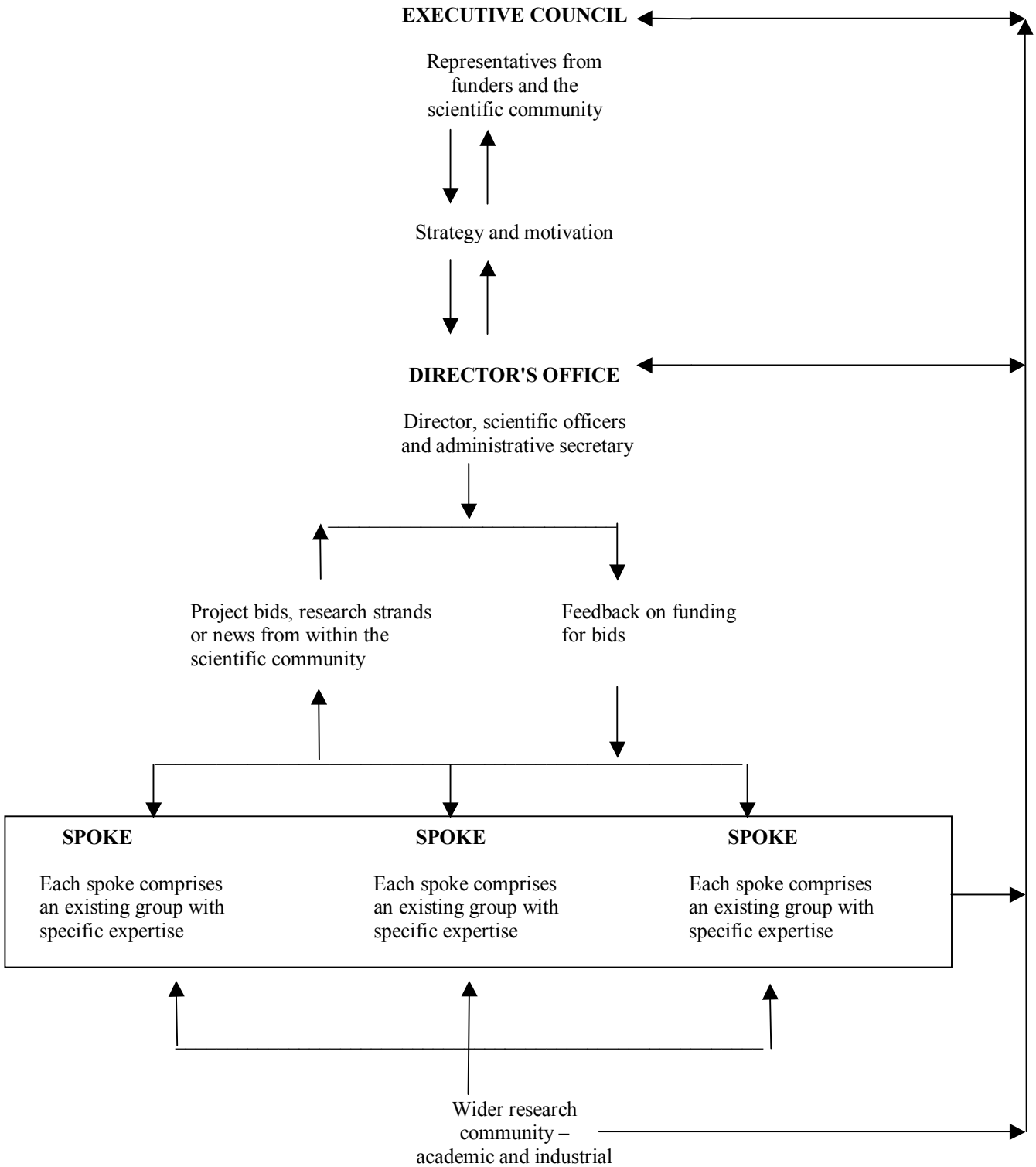
\*\*Year one only: to include keying in information (outsourced), consumables and promoting the database (staff costs are in Hub Staff section).

#Year two onwards: keying in (outsourced), updating, consumables.

###The research budget is awarded via the hub to the spokes (researchers). This sum, awarded *per annum*, would fund a projected five to ten three-year projects.

## Appendix 2

### A possible structure for a National Centre for Replacement of Animals in Experiments



## Appendix 3

**This Appendix lists very briefly examples of some successful replacements of animals by non-animal methods.** The large range of appropriate methods described indicates that a diversity of approaches are gathered together under the rubric of alternatives.

- a non-invasive brain imaging technique called synthetic aperture magnetometry (SAM) is capable of collecting data on electrical activity in the human brain. This technique was developed by collaboration across several departments. Using SAM a model of human gut hypersensitivity was produced which identified various regions of the brain responsible for the interpretation of signals from the gut and their role in the gut hypersensitivity syndrome and the characteristics of certain forms of chest pain. Such research has previously been undertaken on cats, rabbits and primates.
- Pregnancy testing once involved injecting urine samples into rabbits, who were killed several days later in order for their ovaries to be examined for signs of egg development. Using a fast and reliable *in vitro* method dependent upon monoclonal antibodies produced by cell cultures obviates the need for any reliance on the use of living animals. This approach means that cheap and reliable kits can be produced for use in poorer communities.
- Using a tissue bank which comprised cultured human liver cells derived from partial liver removal from fully consenting patients, information has been produced on the various mechanisms of tumour formation and spread. Using these cells in culture clues have been discovered about how cellular and molecular interactions involving liver and blood vessel cells might be implicated in metastasis. Rodents are routinely used to understand tumour behaviour.
- Monoclonal antibodies are used widely in medical treatment and diagnosis. Such antibodies were derived from painful tumours induced in the abdomen of rats and mice. Cell culture techniques are now rapidly replacing the animal method and in the UK the use of animals for monoclonal antibody production has dropped by 87% since 1990 when more than 45,000 animals were used every year.
- Programmed cell death (apoptosis) is an important, natural event in growth, development and possibly cancer. Although many clues about apoptosis have been gained from the study of yeast, there has been a reliance on animals to understand its role in humans. The use of a suite of *in vitro* techniques have uncovered the likely role of apoptosis in human male infertility. Using human biopsied testicular tissue new data has been obtained about the role of cell membranes and the passage of certain ions. Such information sheds light on the cellular events controlling fertility in the male, helping to replace farm and laboratory animals used in fertility studies
- Disturbances of calcium balance are found in a number of human diseases. The parathyroid glands play a fundamental role in calcium balance and the establishment of a human tissue bank of biopsied parathyroid material has given a number of important clues as to function of the gland. Using this tissue bank molecular events and the role of genes have been followed and obviated the use of rodents with the attendant problems of species variation.
- The production and testing of polio vaccine in the UK and USA once used around 55,000 monkeys annually. In 1980 the World Health Organisation recommended that specific cell

culture tests which had been developed were more reliable and ensured a higher level of safety testing for polio vaccine than reliance upon the use of primates.

- The implanting of human tumours into various animals, who are often genetically modified, has been widely used to attempt to understand how tumours grow, develop and spread. Therapies often depend upon the use of such tumour-bearing animal ‘models’ to derive treatment regimes for various forms of cancer. Using mathematical modelling it has been possible to use data from cell cultures in combination with human clinical information to predict the optimal combination of treatments. This approach has been used to significant effect in the treatment strategies for certain childhood cancers -- including neuroblastoma and non-Hodgkins lymphoma. These approaches did not use animals at any stage.
- Another example of non-invasive brain imaging is magnetoencephalography (MEG). Using this method researchers have been able to detect activity in areas of the brain known to be involved with activities such as vision, memory. Use of MEG can also be extended to studies of the diseases of the brain. Basic understanding of brain function has formerly relied upon using primates, cats and other vertebrates. Using MEG, insights into human epilepsy have been gained without use of animals with the attendant difficulties of cross-species interpretation.
- Fundamental research into pain uses a wide variety of animals. Using a suite of imaging techniques such as EEG, PET and fMRI researchers have been able, using fully informed volunteers, to obtain data about pain perception in the brain using painful stimulation calibrated by means of a specially developed laser device. Whilst primarily developed to understand and design treatments for rheumatic pain this approach has far wider applications in understanding human pain and its appropriate therapy.
- A cell culture method has been developed in order to investigate how tumours are linked up to the blood system and thus grow and develop. Using cells derived from human umbilical cords, which are usually destroyed as waste, cultures have been derived which can be cultured in ways which closely mimic those found in tumours. Using a range of molecular techniques the interactions between blood cell and tumour tissue have been characterised and ways of designing successful therapies sought without recourse to the use of rodents or other species.

## Appendix 4

**This Appendix describes briefly a number of examples of first-class science where researchers have used methods which have not depended upon animal experiments.** Whilst the primary intention was not to find non-animal alternatives, nonetheless, major medical advances have followed independent of the experimental use of animals.

- Using human biopsy material the bacteria *Helicobacter pylori* was found to be closely associated with the formation of gastric ulcers. This discovery (which was initially made over a century ago in human post-mortem tissue) of the trigger for ulceration was ignored for some time. Attempts to rely upon the induction of ulcers in animals by using *H. pylori* failed, but large scale clinical studies confirmed the link.
- Chronic Obstructive Pulmonary Disease COPD is a major lung disease with high levels of mortality and morbidity. The triggering event and the subsequent progression of the disease has been elucidated using biopsies from patients together with detailed epidemiological studies.
- The National Cancer Institute in the USA has, since 1990, used sixty human cancer cell lines to screen potentially new and effective drugs for cancer treatment. Five new compounds have been identified and have progressed to clinical trials. This approach has been shown to be more effective than the previous reliance upon rodent screening programmes.
- Vaccine development and screening has been revolutionised by the use of cell culture techniques. Rabies and polio vaccine have been produced using *in vitro* methods. The resultant vaccines are superior in purity and the lack of side effects to the previously animal-based compounds.
- Long-term epidemiological studies of low-birth-weight babies has shed new light on the susceptibility to heart disease, high blood pressure, stroke and diabetes in adults. It is now clear that low birth weight is a significant risk factor for these diseases in later life.
- Yeast and bacteria have been used to unravel genetic processes and their possible role in human disease. Yeast were studied to elucidate the various events which culminate in ageing and conditions such as Werner's Syndrome - a form of premature ageing. Bacteria, genetically modified, have been used to produce human antibody fragments in place of monoclonal antibodies from mice.
- A Europe-wide tissue bank comprising various kinds of cells obtained from human donors has been made available to researchers. About 750 genetic disorders are represented in the bank, which currently houses samples from over 40,000 donors. Highly targeted lines can be produced which enable fine resolution genetic analysis of a wide range of human diseases such as Type I diabetes, Alzheimer's Disease and stroke.
- The part played by environmental triggers and their interaction with other elements such as genes has been elucidated using biopsies from patients suffering from a severe lung disease – cryptogenic fibrosing alveolitis. The ways in which variations in a particular cluster of genes, enzymes and pollutants interact to produce this disease allow both an understanding of those at risk and the possible treatments to be developed.

- The Nobel Prize is widely acknowledged to be the ultimate accolade for excellence. The awards for medicine or physiology are given in recognition of research of the highest calibre and most enduring influence to biomedical science. From 1901 to 1996 (no prizes were awarded 1940-42), and more recently, Nobel Prizes in medicine or physiology were given to many researchers who used methods which can be defined as alternative. That is, where no animals were used in the work celebrated, or where 'lower' animals were used or where clinical material was used for the fundamental breakthrough. From 1965 to 1985, nineteen out of 20 of the Prize winners used such non-animal approaches. More recent examples are:

2001 -- L H Hartwell, T Hunt and P Nurse for their work on cell cycle regulation used yeast and in vitro techniques

2002 -- S Brenner, H R Horvitz and J E Sulston for studies on organ development and various cellular processes used *Caenorhabditis elegans* a simple worm, as their 'model' organism.

## **Appendix 5**

### **Landmarks in the search for alternatives to animal experiments**

We list below some of the many notable landmarks in the search for viable alternatives to the use of animals in experiments.

#### **1959**

The publication of the book *The Principles of Humane Experimental Technique* by W M S Russell and R L Burch which detailed the Three Rs -- Reduction, Refinement and Replacement

#### **1971**

The Council of Europe Resolution 621 which suggested that an alternatives database be set up

#### **1979**

In the USA the Research Modernization Act was passed which directed that funds be devoted to alternatives to the use of animals in research

#### **1980**

Henry Spira in the USA launched a public campaign to ban the Draize Eye Test -- this signalled the start of the Johns Hopkins Centre for Alternatives

#### **1983**

The Swiss government allocated SFr 2 million over two years for alternatives research

#### **1986**

The UK Animals (Scientific Procedures) Act became law. The Industrial in vitro Toxicology Society was set up

#### **1989**

The Centre for Documentation and Evaluation of Alternatives to Animals Experiments (ZEBET) was established by the Federal government in Germany

#### **1992**

The European Centre for Validation of Alternative Methods (ECVAM) was established

#### **1994**

The Interagency Co-ordinating Committee on the Validation of Alternative Methods (ICCVAM) was set up by the United States government

The Netherlands Centre for Alternatives to Animal Use was set up to provide information on animal alternatives

#### **1997**

The Institute for In Vitro Sciences launched in the USA

#### **1999**

ICCVAM endorsed Corrositex for skin corrosivity and the mouse local lymph node assay for the assessment of allergic contact dermatitis potential

**2000**

The Organisation for Economic Co-operation and Development (OECD) announced plans to delete the LD50 test in favour of three alternative methods

**2002**

The OECD agreed to delete the LD50 test. New *in vitro* methods for skin corrosion and phototoxicity were accepted by the OECD

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