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ending animal experimentation

Advancing biomedical research through human-relevant research:

A business case for funding non-animal methodologies

February 2021

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INTRODUCTION

Humane Research Australia (HRA) is a not-for-profit organisation that challenges the use of animal experiments and promotes the use of more humane and scientifically valid non-animal methods of research.

We advocate the benefits of non-animal research methods to a range of stakeholders including Government agencies, research institutions and peak bodies. Whilst there are scientific and ethical reasons for a transition to non-animal research methodologies; we recognise that economic drivers remain a key factor. The adaption of non-animal research methods need not come at a cost; there are many savings that can be made when you consider the high costs of purchasing, caring for, and disposing of the animals used for animal research. Crucially, the costs of misleading animal experiments are immeasurable.

'If you sought out the wrong substances in drug development and they never make it to therapy because of a misleading animal experiment, then this is far more costly than any animal experiment you could possibly have done' (Thomas Hartung MD, Professor at Johns Hopkins Bloomberg School of Public Health).

The health and medical research industry is a multi-billion dollar industry in Australia. Researchers will 'follow the money', yet currently there is stagnation as no institution is taking responsibility for funding alternatives, despite a legislative obligation to only conduct research for which there is no alternative. If no funding is committed to develop, refine and validate alternatives, progress will remain stalled. HRA is calling for specific funding streams dedicated to the development and validation of non-animal research methods to ensure human-relevant and translational research.

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1. PROFILE OF BIOMEDICAL RESEARCH IN AUSTRALIA

Economic Profile

According to the Association of Australian Medical Research Institutes (AAMRI): (1)

- Australia's medical research institute sector has nearly 20,000 staff and students, including 11,841 researchers
- Australia's largest manufacturing export sector is Medical and Pharmaceutical products, worth $3.5 billion in 2016 (Australian Bureau of Statistics)
- Australia has over 50 pharmaceutical companies, 400 biotechnology companies and 500 medical technology companies, where over 100 are listed on the Australian Stock Exchange (MTP Connect, 2016).

A 2018 KPMG commissioned report analysing the economic impact of medical research in Australia (2) found that:

- Medical research from 1990 to 2004 has delivered net present gains of $78 billion from a net present cost of $20 billion — a return on historical investment of $3.90 for every dollar invested.
- Of the $78 billion in gains, $52 billion has been delivered in the form of health gains, and $26 billion in wider economic gains and from commercialisation of medical research.

Funding Profile

While only a relatively small proportion of health and medical research is undertaken directly by the Australian Government, it is responsible for providing the funding for a much larger proportion, particularly in higher education and Medical Research Institutes (MRIs). This includes funding provided through the National Health and Medical Research Council (NHMRC) and Australian Research Council (ARC). It also includes funding provided to universities through the block grants system, which is tied to the volume of each university's research and the number of research students.

Australian Government funding of HMR (health and medical research) through universities and MRIs (3)

NHMRC Funding	$845 million
ARC Funding contribution to HMR (10%)	$79 million
Research Block Grants contribution to HMR (34%)	$686 million
Medical Research Fund (MRFF)	$392 million
Total	$2,002 million

Source: Australian Government Science Research and Innovation Budget Tables 2018-19, estimated expenditure for 2019/20

This estimate assumes all MRFF funding in 2019/20 went to universities and MRIs as it is not possible to break this figure down. This estimate does not take into account taxation measures such as the R&D Tax Incentive and programs like the Department of Industry Innovation and Science Entrepreneurs Program, which support the development and commercialisation of research generally, including new medicines, medical devices and therapies. It also doesn't reflect other Commonwealth Government support provided to universities and MRIs which are used for new buildings and facilities that support HMR.

According to the AMRIi, the medical research institute sector revenue was $2.10 billion in 2018. (1)

2020-1 Federal Government Budget

The biggest funding announcement of the 2020-21 Budget was an additional $1 billion in research funding for universities provided through the Research Support Program (the university research block grant). The MRFF is now set to provide around $650 million in additional medical research investment each year. The additional funding will bring the MRFF disbursement for 2021-22 back up to $627.5 million. There are a series of smaller funding announcements which will be of interest to some parts of the medical research sector, including funding for preventative health initiatives, vaccine roll-out in the region and mental health research. (4)

State and territory governments are responsible for funding research undertaken within the state and territory hospital systems; the provision of support to MRIs for the indirect costs of research; and other programs to support R&D, a portion of which funds HMR. State and territory governments also provide capital funding for stand-alone research institutions (e.g. the South Australian Health and Medical Research Institute) and for organisations that combine research with health care delivery (e.g. the Victorian Comprehensive Cancer Centre).

The Not-for-Profit sector spent $1.27 billion in 2018/19 on medical research and development. (3)

Expenditure by Sector.

The following table is an estimate of where HMR expenditure occurs in Australia: (3)

Location of expenditure $million					
Aust. Govt. (including agencies)	States & Territories	Higher Education	Not For Profit	Business	Total
128	**598**	**4,132**	**1118**	**1958**	**7,934**
2%	**7%**	**52%**	**14%**	**25%**	**100%**

Global Animal Testing Market

The global animal testing market size was valued at $10.74 billion in 2019 and the market is expected to grow at a Compound Annual Growth Rate (CAGR) of 4.27% during 2019-2025 and at a CAGR of 2.46% during 2025-2035. On the other hand, the global non-animal alternatives testing market was valued at $1.11 billion in 2019. The market is expected to grow at a CAGR of 10.40% during 2019-2025 and at a CAGR of 11.62% during 2025-2035. (5)

3Rs

The universally-accepted 3R's principle (Replace, Reduce and Refine animal experiments) was adopted by the National Health and Medical Research Council (NHMRC) in 1984 and underpins the Australian Code for the Care and Use of Animals for Scientific Purposes which is adopted through state and territory legislation. (6)

The 3Rs aim to guide the humane treatment of animals used in experiments, whilst ultimately seeking their replacement. A NHMRC Information Paper on the implementation of the 3Rs in Australia published in September 2019 (7) indicated that most investigators and AEC members agreed that 3Rs methods are recognised throughout the Australian scientific community Cases of 'incidental' 3Rs development and implementation were provided such as the below:

- The development of organoids — miniature organs derived from human cells and grown in culture dishes — that allow studies outside a human or animal and replace the use of animal
- The use of cancer tumours sourced from humans and grown in a gelatin sponge platform in the laboratory instead of in mice to investigate new cancer therapies
- Collaborative work between laboratory-based researchers and mathematical modellers where computer simulation is leading to improvements in the design of studies using animals, so that the minimum numbers of animals are used to produce useful high-quality data

However, whilst these are promising, it can be argued that Australia has made very little progress in replacing animals in research, as illustrated by the vast numbers of animals used. Australia has been cited as the fourth highest user of animals in research globally despite a proportionally low population. (8)

The 2017 statistics collated by HRA indicate that over 20 million animals were used for research and teaching in Australia (noting that nearly 5 million of these were for the purpose of environmental study and may be observational only, and there were 12 million domestic fowl, used in Queensland in non-invasive research).

Research funding is not broken down to animal/non animal research and certainly much of the research does not use any animals. Previous disclosures on the number of NHMRC funded research projects requiring animal ethics approval ranges from 40 to 50% of total funding.

Public Opinion

Public acceptance of the use of animals in biomedical research is conditional on it producing benefits for humans. Pandora Pound and Michael Bracken argue that *"the benefits remain unproved and may divert funds from research that is more relevant to doctors and their patients."* (9)

67% of Australians support allocating a proportion of medical research grants to funding scientific alternatives to animal experiments (10). Researchers have also expressed support for funding to develop alternatives to animal use in personnel communications with HRA. See Appendix 1 for a list of researchers who have expressed interest in the provision of funding incentives to develop alternatives to animal experiment, and Appendix 2 for supporting statements from researchers. Despite this demand, currently, there is no federal funding dedicated to the development of alternatives to animal research, and at present, only the South Australian Government has provided funding, with the establishment of a research scholarship for the 3Rs, but not research into alternatives specifically.

2. LIMITATIONS OF ANIMAL RESEARCH

Predictability

Scientific literature raises questions about the reliability and predictive value of animal testing in research for humans (11), (12). Systematic reviews continue to show that animal experiments are not sufficiently predictive of human outcomes and can be dangerously misleading.

Humans differ from animals anatomically, genetically and metabolically, and interspecies variations are a high cause of clinical trial failure of pharmaceutical products. Not only does this mean that results cannot be accurately extrapolated to humans, but it also means that some possibly successful treatments are being ruled out pre-clinically due to adverse reactions or responses in animals. Animal use in research and safety studies is therefore misleading and causes abandonment of effective therapeutics. (14)

Additionally, not all drugs approved following animal testing are safe in human patients. Many currently used medicines have suboptimal efficacy, while others may cause adverse effects which restrict their use and can result in serious illnesses. (15) It has been estimated that adverse drug reactions (ADRs) kill more than 10,000 people in the UK and 100,000 in the United States each year.(17)

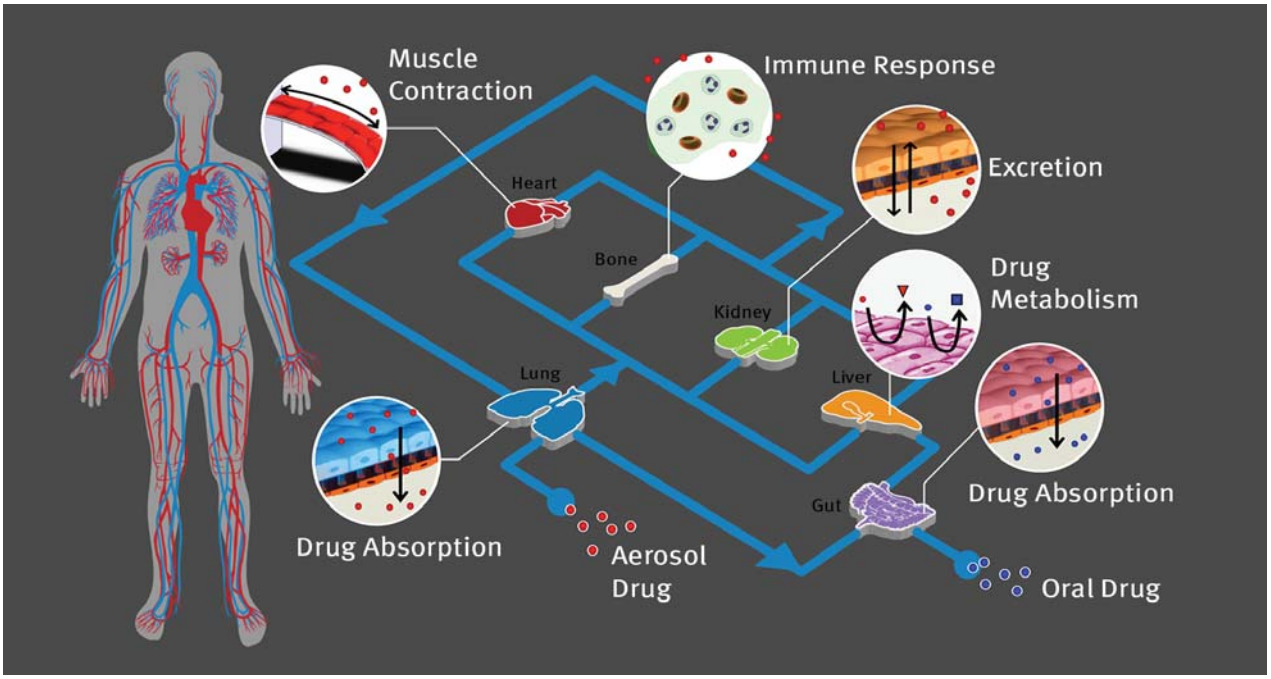
Research Translation

'We are so ingrained in trying to cure mice that we forget we are trying to cure humans' - Dr. Ronald Davis, Genomics Professor, Stanford University, USA. (18)

According to FDA (U.S. Food and Drug Administration), in spite of huge research effort and expense, development of new treatments has slowed, as preclinical success has not followed through into clinical trials. (19) **Indeed, a 95% failure rate of clinical trials following 'successful' animal trials is reported.** (20)

Many disease areas have seen little progress, despite decades of intensive animal research. For example:

- Out of more than 1,000 potential drugs for stroke tested in animals, only 1 of these have proved effective in patients
- Only two new classes of asthma treatment have become available for patients in the last 50 years



Human-on-a-Chip, Wyss Institute

In a discussion paper addressing health and medical research, the Victorian government recognises that *'Australia punches far above its weight by producing 3 per cent of global research publications with only 0.3 per cent of the world's population. However, compared with international standards,* ***Australia has a poor record of commercial translation...'*** (21).

A presentation delivered by the NSW Office for Health and Medical Research (22) identified Australia as ***'Poor at translating research innovation into economic benefit for Australia'*** with an Innovation Efficiency Index of 73 (of 128 OECD countries).

Similarly, the KPMG report on the economic value of Australia's medical research (2) concludes that with an increased focus on translation and commercialisation of medical research, return on investment will increase. **HRA proposes that intensifying efforts to develop, validate and implement human-relevant research will result in increased translation and commercialisation of medical research.**

Cost

'If you sought out the wrong substances in drug development and they never make it to therapy because of a misleading animal experiment, then this is far more costly than any animal experiment you could possibly have done' (Thomas Hartung MD, Professor at Johns Hopkins Bloomberg School of Public Health) (23).
The self-reported challenges of the Australian Healthcare system are as listed below (24):

- an ageing population and increasing demand on health services
- increasing rates of chronic disease
- **costs of medical research and innovations**
- making the best use of emerging health technologies
- making better use of health data

In the light of the high investment in medical research, it is reasonable that there should be thorough scrutiny of the translational relevance of this research.

As such, the pharmaceutical industry has recognised the limitations of animal research **and is now using about one-sixth the number of animals that they used in the past for drug studies** (25).

Whilst Australia's medical research industry is hugely profitable, indications are that the return on investment may be hindered by animal research. **With the average time and cost to develop and test a single drug now between 10-13 years and $US 1 billion, new drug development decreasing, more drugs being withdrawn, and 9 out of 10 new drug candidates that appear safe and effective in animal studies failing subsequent clinical trials it is time to find a new 'gold standard.'**

3. FINANCIAL IMPLICATIONS OF TRANSITIONING TO NON-ANIMAL RESEARCH

Animal research incurs the high ongoing costs of purchasing, caring for and disposing of animals. Alternatives are more cost efficient, as well as more effective. As with any transitioning industry, there are costs associated with training staff in new methods, especially taking into consideration that some fields will be outside the skill set of many researchers, and any potential investment in technology or infrastructure, dependent on the alternative method that it to be used.

However, any initial costs outlaid can be returned over the long term. For example, tissue culture requires a high infrastructure and high level of training. On the other hand, automation of processes and testing of thousands of substances in parallel can be undertaken.

To compare costs; for one fifth of the cost of a single rodent cancer test, then US National Institutes of Health Chemicals Genomics Center can screen 100 chemicals in 200 different robot automated call tests in as little as 2 weeks (15).

Recent breakthroughs have demonstrated reduced costs in drug testing, resulting in cheaper medicine costs. For example, a new device simulating the gut accurately simulates the gastro-intestinal tract and how it absorbs medication. This means that the cost of clinical trials, as well as the use of animals in testing, could be greatly reduced (26).
As previously explained cost savings would also be made from redirecting funding into human-relevant research instead on continuing to fund animal models of research with extremely low validation rates at clinical trial.

4. REPLACING ANIMAL RESEARCH

Non-animal alternatives

As new technologies emerge, the range of non-animal methods continues to grow, which are more dependable and produce more accurate results than tests on species who differ from humans in their metabolism of toxins, absorption of chemicals, mechanisms of DNA repair and lifespan – all factors that have a profound effect on the efficacy of drugs.

Some examples are listed below:

- Microdosing - involves giving research participants miniscule doses of an experimental drug then tracking the drug's movement through the body by radio labelling. Its distribution and metabolism in bodily fluids is measured and enables researchers to quantify its concentrations in blood, urine, saliva and white blood cells.
- Microfluidic chips - consist of a network of interconnected reservoirs mimicking the organ systems of a living being. Researchers can place lung, liver, fat, gastric or heart cells inside the reservoirs, add a particular drug and quickly evaluate how the chemical is distributed, metabolised and excreted
- Transcranial Magnetic Stimulation (TMS) - a non-invasive treatment using a magnetic field to stimulate nerve cells in areas of the brain. It has been shown to affect mood, motor and cognitive functioning. TMS has few side effects and is also used as a treatment for mental illness.

For more in-depth information about replacements for animals, see the HRA publication 'Better Ways to Do Research' available at:
www.humaneresearch.org.au/wp-content/uploads/2020/06/BetterWaysToDoResearch.pdf

5. GLOBAL PERSPECTIVE

Around the world, government-funded initiatives are acknowledging the need to further develop and validate non-animal methods of research, investing millions of dollars in alternatives and reflecting practical commitment to the replacement of animal research.

This may be enshrined in legislation. In South Korea new federal legislation has been proposed that would prioritise funding for human biology-based approaches in biomedical research; whilst the UK Animals in Scientific Procedures Act 2012 revision has enshrined the concept of the development of 'alternatives' as a legal requirement. The wording in ASPA 2012 reads:

20B Alternative strategies

(1) The Secretary of State must support the development and validation of alternative strategies.
(2) In particular, the Secretary of State must—
(a) assist the European Commission in identifying and nominating suitable laboratories to carry out validation studies on alternative strategies;
(b) nominate a person the Commission may contact for advice on the regulatory relevance and suitability of alternative strategies proposed by the Commission for validation;
(c) take such other steps as the Secretary of State considers appropriate to encourage research into alternative strategies;
(d) ensure the promotion of, and dissemination of information about, alternative strategies.
(3) The Secretary of State may make grants to any person concerned with the development, promotion or validation of alternative strategies.

The Dutch government recently announced its plan to phase out toxicology tests for chemicals, food ingredients, pesticides, veterinary medicines, and vaccines by 2025.

Their Transition Program for Innovation without the use of Animals sets out the means to achieve this through collaboration between the science, health care, government and business community.

- **BraCVAM** – BRA: Brazilian Center for Validation of Alternative Methods.
- **CaCVAM** - Canadian Centre for the Validation of Alternative Methods
- **ECVAM** - The European Centre for the Validation of Alternative Methods.
- **ICCVAM** - the Interagency Coordinating Committee on the Validation of Alternative Methods (U.S.).
- **NKCA** – The National Knowledge Centre on Alternatives to Animal Experiments (Netherlands).
- **JaCVAM** - Japanese Center for the Validation of Alternative Methods.
- **NC3RS** – National Centre for the 3Rs (UK)
- **SKoCVAM** - the Korean Center for the Validation of Alternative Methods.
- **Swiss 3R Competence Centre**
- **ZEBET** - the Centre for Documentation and Evaluation of Alternatives to Animal Experiments (Germany).

It is not only the benefits to human health that are identified as supporting drivers, but also the potential for economic growth.

There are increasing examples of private and philanthropic funding for the development of non-animal research approaches. In 2020, a 50 million $US Wellcome Leap Program in Human Organs, Physiology, and Engineering (HOPE) was announced, stating that there is a need for better models of human physiology.

A non-animal technologies roadmap for the UK concludes that 'Non-animal technologies could replace the use of animals in testing the safety and efficacy of new products including pharmaceuticals, veterinary medicines, agrichemicals, chemicals and consumer products, and are one of a series of emerging technologies that could drive future UK economic growth.' Indeed, the 3D Cell Culture market was estimated to be over US$ 718.8 M in 2018. It is anticipated to grow at a compound animal growth rate of 19.8% from 2019 to 2030 (28).

While other nations forge ahead in the area of alternatives research, **Australia is missing an opportunity to excel in clinical translation and technological innovation.**

6. IMPEDIMENTS TO PROGRESS

Over 30 years ago, In 1989, the Senate Select Committee on Animal Welfare, in its report to the Australian Government, recommended 'that the Commonwealth Government establish a separate fund for research into the use of alternatives to animal experimentation and that grants be disbursed from this fund by a board composed of representatives from the scientific community, animal welfare organisations, ACCART [now ANZCCART] and government authorities.' As confirmed by ANZCCART, this fund has never been established (29).

Currently, Australian researchers interested in the field of alternatives are reliant on limited overseas funding and whilst there are some exciting projects underway in Australian via this funding source, (30, 31) additional funding would facilitate more innovative research of this nature.

It is acknowledged that Australian funding bodies will accept applications for '3R's research', however their systems of application review mean that those applications do not stand a realistic chance of success, which is why we only see incidental progression of alternatives. Therefore, the only way such applications would succeed through the system would be for dedicated funds being set aside specifically for this area of research, as other countries have done. This specific purpose 'pot' would be in addition to funding for any proposals that are accepted through the current system as 'incidental 3Rs'.

The 2019 NHMRC Information Paper on the Implementation of the 3Rs in Australia identified barriers to implementation (7) *'All participant groups identified the lack of appropriate scientific or technological innovation as the primary barrier to implementation of the 3Rs. Other key barriers included comparability of data (identified by investigators) and insufficient funding available (identified by institutional representatives).'* The paper states *'The project's scope did not include funding of projects for the development of the 3Rs, identification of prospective research areas for the 3Rs, and the benefits or otherwise of specific 3R methods or techniques'* yet *'Increased funding to develop replacement options'* was identified as a key enabler to implement the 3Rs.

Researchers will 'follow the money' yet currently there is stagnation as no institution is taking responsibility for funding alternatives, despite a legislative obligation to only conduct research for which there is no alternative. If no funding is committed to develop, refine and validate alternatives, progress will remain stalled. Whilst it is argued that Australian researchers can rely on international alternatives data, a cultural change is needed to encourage adoption of alternatives and that can only be achieved through leadership, commitment and mentorship of Australian researchers, leading to generational change in research practices. Funding is a crucial first step.

7. RECOMMENDATIONS

Considering the public interest in ethical treatment of animals, the likelihood of non-animal alternatives providing more beneficial outcomes for public health and the legislation itself requiring adherence to the 3R's, Australia's peak funding bodies are duty-bound to allocate meaningful financial support to the development of non-animal models.

The use of animals in research is, according to the code, for cases where no alternative exists, **but alternatives will never be adopted without support for the development of non-animal based scientific testing.** Australian researchers therefore need dedicated funds earmarked specifically for the development of non-animal methods of research – as occurs in other nations.

Australian federal, state and territory governments should now be making a commitment to fund research into seeking alternatives to animal use – as is already the case in other countries.

It should be noted that HRA's call for increased transparency in animal research and investment in funding for 'alternatives' research has been supported by a Motion in the Senate (32) and as such tangible action is required to ensure this call is met in practice.

HRA is calling for:

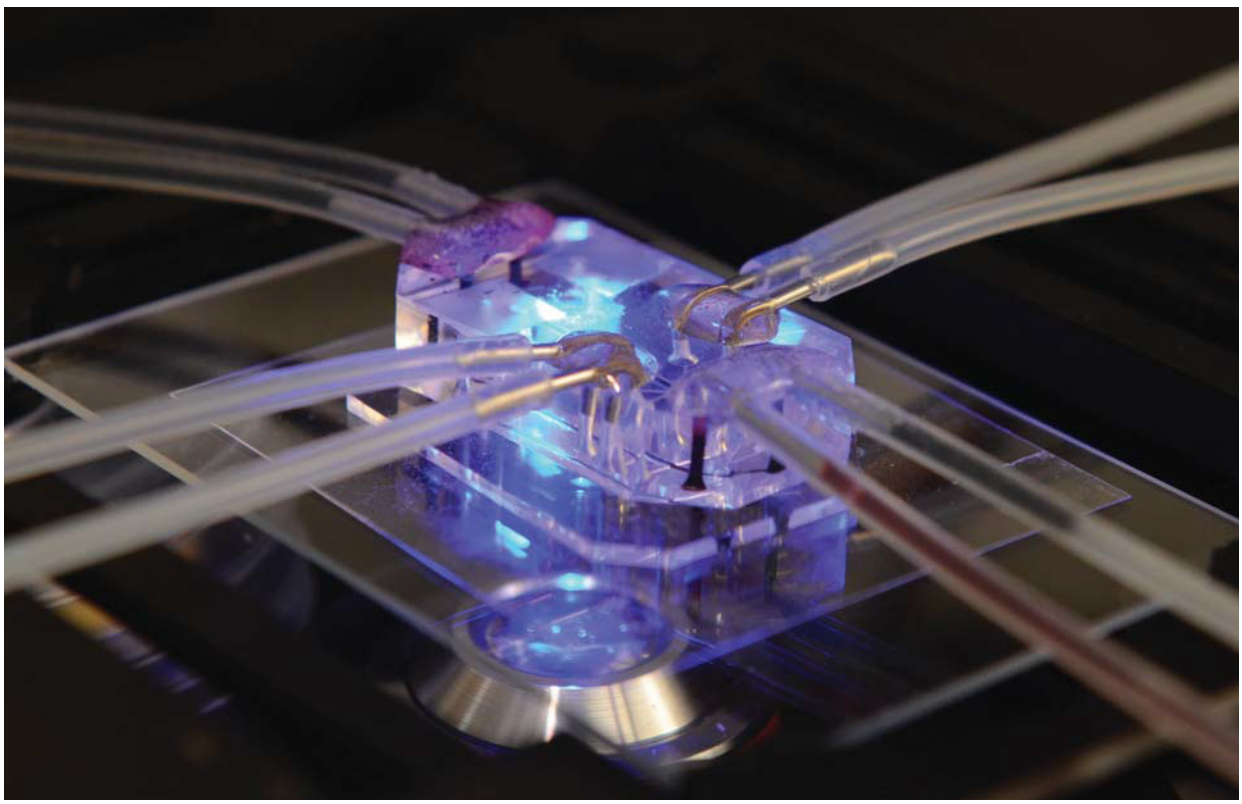
- **An ongoing federally funded research funding stream for the development of non-animal based scientific testing via the NHMRC and the Australian Research Council**
- **A targeted call for research for the development of non-animal based scientific testing via the Medical Research Future Fund, to be identified as a priority**
- **A commitment to developing an Australian Centre for the Development and Validation of Alternatives.**
- **State and territory funding for the development of non-animal based scientific testing via incentives such as awards, scholarships or research grants.**

Appendix 1: Researchers in Support of the Need for Funding Alternatives

The following individuals have confirmed to us that their research (and in many cases that of their colleagues) would benefit from the availability of funding to replace animals in medical research.

Name	Email	Institution	Area of research
Joseph Cashmore	joseph.cashmore@gmail.com		Student in Wildlife and Conservation Biology
Jessica Cowie	jessica.cowie@hotmail.com		Science student in final year of degree
A/Prof Aeron Hurt	Aeron.hurt@influenzacentre.org	WHO Collaborating Centre for Reference and Research on Influenza, at the Peter Doherty Institute, Parkville	Infectivity and transmissibility of influenza viruses
Dr Gabrielle Musk	gabrielle.musk@uwa.edu.au	University of Western Australia	Veterinary Anaesthesia and Analgesia
Dr Brett Lidbury	brett.lidbury@anu.edu.au	The National Centre for Epidemiology and Population Health, College of Health and Medicine, ANU	Alternatives research
Dr Raf Freire	rfreire@csu.edu.au	Charles Sturt University	Animal and Veterinary Sciences
Prof. Paul Fisher	P.Fisher@latrobe.edu.au	Discipline of Microbiology; Department of Physiology, Anatomy and Microbiology; La Trobe University.	neurodegenerative and neurological disorders
Robin L Anderson, PhD	Robin.Anderson@onjcri.org.au	Olivia Newton-John Cancer Research Institute	Head, Translational Breast Cancer Program
Dr. Sarah Annesley	S.Annesley@latrobe.edu.au	LaTrobe University	Mitochondrial and neurodegenerative diseases
Dr Normand Pouliot	Normand.Pouliot@onjcri.org.au	Olivia Newton-John Cancer Research Institute	Head, Matrix Microenvironment & Metastasis Laboratory
Dr David Ascher	david.ascher@unimelb.edu.au	Bio21 Molecular Science and Biotechnology Institute, University of Melbourne	The development of computational tools to predict pharmacokinetic and toxicity properties
A/Prof Alex Hewitt	hewitt.alex@gmail.com	Centre for Eye Research Australia	Eye diseases
Prof Ian Macreadie	ian.macreadie@rmit.edu.au	RMIT	Alzheimer's disease, proteostasis and aging

Dr Raymond Wong	wongcb@unimelb.edu.au	Center for eye research Australia, University of Melbourne	stem cells, neuroscience, retinal biology, cell reprogramming
Dr Peter Gibbs	Gibbs.P@wehi.edu.au	Walter & Eliza Hall Institute	Cancer
Dr Martha Lappas	mlappas@unimelb.edu.au	University of Melbourne	gestational diabetes; obesity in pregnancy; preterm birth
Prof. Michael Stear	M.Stear@latrobe.edu.au	LaTrobe University	Creating mathematical models of the infection process (livestock)
Associate Professor Bryan G. Fry	bgfry@uq.edu.au	University of Queensland	Paralytic neurotoxins
Dr Marnie Winter	Marnie.Winter@unisa.edu.au	University of South Australia	nanotechnology and bioengineering approaches to address pre-eclampsia
Sarah Stuart	sstuart@student.unimelb.edu.au	University of Melbourne, Royal Melbourne Hospital	Brain cancer- Using brain tumor organoids to evaluate efficacy of novel inhibitors
Dr Hugo Morandini	hmorandini90@gmail.com	Institution Perth Children's Hospital	Clinical Neuroscience



Lung on a chip - close up on microscope - Wyss Institute

Appendix 2: Supporting Statements from Researchers

The need for a dedicated fund to support alternatives to use of animals in scientific research, Malcolm Caulfield BSc (Hons); PhD; LLB

The implementation of Reduction, Replacement and Refinement in relation to animal use in science (3Rs) is a legal requirement in Victoria. To advance this, I feel it is imperative that there should be allocation of research funds specifically for projects which set out to implement the 3Rs. From my experience in the pharmaceutical industry and in studying basic mechanisms of neuronal function, I firmly believe that with modern techniques and knowledge, it is almost impossible to justify using animals in scientific experiments. Understanding of basic physiology and pathology comes from an understanding of molecular processes in normal and aberrant situations. Today, with knowledge of human gene sequences for all human proteins, and the ability to express those human genes in immortalised cells or in primary cultures, it is possible to study every aspect of these key basic systems, such as neurotransmitter receptors, ion channels and enzymatic pathways, without the need to use animals; indeed, such studies are more informative and relevant than animal studies.

In my experience, non-clinical scientists will continue to claim that they need to use animals, and that use is justified by being necessary to advance knowledge of physiology or pathology. The classic argument is that the complexity of what goes on in humans (be it physiology or disease) can only be understood by studies in other complex organisms, that is, animals. This argument is weak, as the key statement concerns the lack of understanding of complexity in man. That understanding will only come from a reductionist approach, with study of individual components of the complex system, and an understanding of their interaction. Studies in animals will tell you much about the complexity of animals, but little about the complexity in man. Furthermore, I believe that another major motivator of this scientific conservatism is fear of the unknown. Most scientists have their favourite techniques, which will in all likelihood involve animal use. Familiarity with those techniques allows easier production of data and more data means more publications, which is necessary for career progression. Whilst it can be argued that the requirement for justification removes this need to maintain the status quo, I think that justification, for a grant-writing scientist, is relatively easy. Almost anything can be justified. Furthermore, I do believe (having seen it at first hand) that the grant awarding system is somewhat incestuous, and those who sit in judgment on whether or not grants get awarded again tend to look after their own, so to speak. All of this creates a culture which operates against the active pursuit of non-animal approaches.

A dedicated fund for research which promotes the 3Rs approach will encourage scientists to step away from animal-based research, and engage in research which, while still cutting edge, focuses more on (for example) cell culture systems, or the measurement of relevant parameters related to disease in patients.

Biographical Note: Malcolm Caulfield has over 25 years experience working in biological sciences. He has led research groups in industry (Glaxo Group Research) and in academia (University College London; Dundee University). He has published over 30 scientific papers, which have been cited more than 3,400 times in the scientific literature. He has served on the editorial board of the British Journal of Pharmacology and Pharmacology and Therapeutics. Since 2002 he has worked in the field of animal welfare.

Funding for Animal Alternatives in Scientific Research – Victorian Government Investigation, Associate Professor Brett A. Lidbury, National Centre for Epidemiology and Population Health, RSPH, The Australian National University

Victoria currently has a leadership role in biomedical research, as well as an international reputation as an innovation hub in health and medicine (for example, the Parkville precinct).

Therefore, it is appropriate that Victorian leadership develops on the timely topic of animal alternatives, with this concentration of institutions and expertise traversing fundamental biomedicine, clinical research and research translation to the clinic.

With limited funding and greater calls for the translation of fundamental research discoveries to health application, developing replacement alternatives that allow and encourage the direct study of human biology and pathology will be key to progress in this realm. From as early as 2004, the Food and Drug Administration (FDA) in the United States has questioned, in the context of the increasing fundamental research effort, the slower than anticipated development of new drugs; part of their answer was "... the over reliance on animal models ..." (of human disease). This issue is discussed further in reference (1), including links to the FDA report and other relevant publications.

Since this report, a significant number of academic studies have examined broader issues in research practice, including the efficacy of animal models in discovery research and then pre-clinical studies, and have confirmed concerns on the efficacy of non-human animals to predict human outcomes.

Adding extra weight to the need to rethink animals in research, was the announcement in late 2015 that the National Institutes of Health (NIH) in the United States retired their remaining chimpanzees from biomedical experimentation (2). According to NIH Director, Dr Francis Collins, while chimps and other animals had value in the past, modern methods are "... probably more reliable in terms of their predictability ... (for) what would happen in a human being ..." Basically, the decision to retire the chimps was based on the evidence that alternatives to animals are now available, and more "reliable" in terms of understanding and predicting human disease.

Commentaries by Pandora Pound from 2004 and 2014 (3) also offer compelling reasons to consider a significant rethink on animals in biomedical science, and identified that while a pressing need continues in this area, little is being done to address solutions; one of which is dedicated funding to develop and validate animal alternatives in biomedical experimentation and testing.

References and additional resources:
(1) Animal Instincts: MJA InSight (14) 20 April 2015
(www.doctorportal.com.au/mjainsight/2015/14/brett-lidbury-animal-instincts/);
(2) NIH ends all medical testing on chimpanzees (Story via YouTube)
-www.youtube.com/watch?v=MX6EQ7bO5-c&feature=youtu.be
(3) Is animal research sufficiently evidence based to be a cornerstone of biomedical research? Commentary by Pandora Pound and Michael Bracken (www.bmj.com/content/348/bmj.g3387). (Access May need subscription log in).

The need for replacement of animals used for scientific purposes, Simon Bain, BVSc MANZCVS, Animal Ethics Consultant

I speak as one who attended six World Congresses on Alternatives and the Use of Animals in the Life Sciences between 1996 and 2011. These congresses are about significantly improving the welfare of animals used for scientific purposes in terms of application of the 3 R's.

Congresses demonstrated significant replacement of animals occurring in the field of toxicology, particularly within the EU and USA. They of course have significant cosmetics industries and the need for animal replacement started within that sector. It extended to industry in general and progress re animal replacement was impressive to see. In Australia it is not apparent that we use animals at all for cosmetic testing. Any use of animals used for toxicological testing relate to environmental concerns (eg water quality, air quality) and the testing of animal vaccines which we use in significant numbers in the agricultural sector. Australia is making progress re the replacement of use of animals in some of these areas. In the last 20 years Australia has made significant to excellent progress in replacement of animals used for education purposes.

I am a veterinarian who was for 23 years (2001-2014) the Executive Officer of the Australian National University Animal Experimentation Ethics Committee. Attendance at the World Congresses resulted in the introduction of a number of refinement measures at ANU and an increased consciousness and encouragement of the need for replacement and reduction. My personal ethos is that as far as biomedical research and wildlife research is concerned much advancement of relevance has been achieved by the use of animals, however the veterinarian that I am and a wish for more humane research pushes me towards strongly supporting the replacement of animals where scientifically feasible in biomedical research. In the field of biomedical research we need to look more determinedly at animal replacement. It will need political leadership for this to occur. A good overseas example where this occurred was with NC3Rs Centre in the UK (https://www.nc3rs.org.uk/our-science). The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) was established in May 2004, following the recommendation of a House of Lords Select Committee report on Animals in Scientific Procedures, published in July 2002.

In Australia the lack of progress in replacing animals in biomedical research is largely a result of the mentoring of new generations of scientists. Post-graduate students, the scientists of the next generation, are taught by their supervisors that the use of animal models is the only way to achieve scientific progress in the biomedical research disciplines. Many alternatives to the use of animals for biomedical research do exist and in the interests of brevity I will not repeat them here.
Victoria and Melbourne in particular, have long been recognised as a centre of excellence in Australian biomedical research. Agriculture Victoria administrates the use of animals for research and teaching. Its Bureau of Animal Welfare had a particularly strong effective reputation in this area in terms of administration of all aspects of the use of animals for scientific purposes, and ran particularly good training courses for all involved, including investigators and AEC members. It does need a government in Australia prepared to take leadership in this role. It would be particularly appropriate were the Victorian Government to take a leadership role in the progressive replacement of animals used in biomedical research.

Resourcing 3R-based activity in wildlife research and pest management in Australia, Dr Clive A Marks

The Australian Code for the Care and Use of Animals for Scientific Purposes (COP) employs the 3Rs (Replacement, Reduction and Refinement) as a governing principle. Under the COP institutions must demonstrate compliance by the diligent application of the 3Rs in order to obtain approval for animal experimentation. However in several research areas (e.g. conservation, pest control and wildlife research generally) there remains a practical barrier to developing new methods consistent with these obligations. No Australian program currently directs resources for the development of alternative approaches as a priority or specific policy aim.

Today, only an ad hoc capacity to progress Refinement and Replacement exists in this area. Given both the increasing scale of wildlife and pest management programs in Australia and New Zealand (e.g. with lethal population control of exotic and feral species being undertaken or proposed on a landscape scale) and the growing popularity of wildlife research in the university and government sector, this arrangement is inconsistent with the intention of the COP. Currently the pursuit of Refinement and Replacement is a passive process largely contingent upon an individual researcher's initiative and the willingness of the funding agencies to resource R3-related developments.

Historically there has been little emphasis upon the need to deliver better animal welfare outcomes in these areas. For instance, state government conservation and pest management legislation does not mandate continuous improvement of animal welfare outcomes under their provisions, nor does product registration via the APVMA demand progressive improvements. As a consequence research methods have lagged behind other industries that have been more actively encouraged to progress 3R outcomes. In contrast, pest management in Australia and New Zealand has continued to embrace older methods. For example, in vivo bioassays have been routinely used for the prospecting and development of lethal control agents and for the assessment of non-target risk and provision of regulatory data. However, non-lethal and in vitro methods offer far greater utility compared to bioassays, yet there has been no capacity to develop this approach as a replacement method despite in vitro approaches also offering far greater cost-effectiveness, less resource-intense research and greater public acceptability.

Modelling and in vitro approaches have been embraced by other industries for some time now given that they are suited to high through-put assays and bio-prospecting that is not possible or economic using older bioassay methods. A wide range of other non-traditional technologies offer scope to deliver improved welfare outcomes in wildlife health, animal population survey and control, diagnostics and basic research methods. Yet by failing to develop appropriate policies to augment targeted pursuit of 3R outcomes, wildlife and pest research has not yet lived up to the spirit of the COP. Without a demonstrable capacity to pursue 3R outcomes it is arguable whether any area of research can be thought of as capable of long-term compliance with the COP.

Dr John Lai, PhD (Honorary Fellow of the University of Melbourne, and Senior Development Scientist at Genetic Technologies)

I am writing to follow up on Humane Research Australia's (HRA) recent communications with the Victorian Government to incentivise alternative non-animal research methods in medical research. I have spent over 10 years researching cancer genetics during my academic career, which includes postdoctoral training at the Norris Cancer Center, University of Southern California.

The issue of research reproducibility and clinical translation of basic research is gaining a lot of attention in the science community in recent years. This is highlighted by an article published in one of the premier science journals. This article was written by Prof. Francis Collins, the Director of the National Institute of Health in the United States of America, which is equivalent to the NHMRC in Australia. In this article, Prof. Collins notes that "Preclinical research, especially work that uses animal models, seems to be the area that is currently most susceptible to reproducibility issues".

Recent discoveries in genetics research highlight the complexities of many human diseases such as cancer. These studies show that tumours are very different between individuals, let alone between species. As such, using animals and/or cell lines to model human tumours will always be much less effective than profiling tumours straight from human patients. Therefore, It is essential that public funding for medical research is efficiently directed to studies that have real world value to our community, rather than carrying out mechanistic studies in animals which have questionable relevance to human biology.

To conclude, I encourage the Victorian Government to work with HRA to promote alternative research methods that do not use animal models, as I (and other researchers) propose that animal models are flawed in many circumstances, which results in delaying the translation of therapeutic diagnostics and/or drugs. Regardless of the ethical considerations in medical research, the ultimate outcome must be to ensure that government funds are directed to real-world translational research that will benefit society.

Thank you for your time,
John Lai

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