PORTFOLIO COMMITTEE NO. 2 – HEALTH

INQUIRY INTO USE OF PRIMATES AND OTHER ANIMALS IN MEDICAL RESEARCH IN NSW

HEARING – 1 JUNE 2022

SUPPLEMENTARY QUESTIONS TO MEDICAL ADVANCES WITHOUT ANIMALS TRUST (MAWA)

1. You say in your submission that, in your experience working with researchers in Australia, compliance with the 3R's often "falls short of what should be expected regarding the replacement of animals in medical research." Can you explain a bit more about what you mean by this? Can you provide any examples?

When working with researchers who wish to transition to animal-free research, or with students who wish to embark on a research career based on non-animal methods, MAWA often hears complaints that while universities and research institutions state their commitment to the 3Rs, their focus is principally on Refinement and Reduction with little, if any, focus on Replacement.

It has been suggested by many that alternative animal-free methods should be introduced to students in secondary science education, then taught in both undergraduate and post-graduate level courses as happens overseas. The Netherlands provides excellent examples of alternatives courses curricula at undergraduate and post-graduate levels.

Students express their frustration that many scientists have a mindset that animal research is essential for medical progress and that once reaching post-graduate level, there are not enough supervisors in Australia with expertise and experience in non-animal fundamental biomedical research to provide them with guidance and a career structure to advance in these fields. Many researchers and students report that without MAWA support and funding, conducting their animal-free research projects in Australia would not have been possible.

Additionally, researchers report inertia and a level of resistance to the use of non-animal models in their institutions. They believe that some scientists, especially some leading senior researchers who have based very successful careers on animal research, have become comfortable and quite conservative in considering new methods. This is, of course, understandable and MAWA appreciates the various costs that come with change. There must be significant incentives and a sufficient level of resources to enable a transition to the use of non-animal models.

Another issue that is regularly raised by researchers is the way that grants are currently reviewed and approved for funding in Australia. Many believe that this process is deeply flawed. We are informed that Australia has moved away from having grant panels sitting to discuss the strengths and weaknesses of research proposals, to a system where applications are reviewed by anonymous reviewers and grants are awarded simply on the score the project is given without real, focused discussion around the quality of the science, the strength of the project and whether the research could be done differently. Researchers have advised MAWA that this is not how funding reviews are conducted elsewhere in the world. There is also concern that reviewers may not declare conflicts of interest (eg when animal researchers are assessing animal-free methods) and that, unlike other countries, Australia does not have independent international experts sitting on grant review panels.

MAWA's position is that applications to the National Health and Research Council (NHMRC), the Australian Research Council (ARC) and the Medical Research Future Fund (MRFF) involving *in vivo* studies should be required to address Replacement in their applications and to state why animals are required and why a certain number are needed. Serious consideration of alternatives should be explored and rejected with critical evidence if animal use is to be supported. This should form part of the grant peer review process.

MAWA recognises that it is easier to build on existing data sets than to create new sets, and that it is difficult for researchers and Animal Ethics Committee (AEC) members to fully investigate alternatives given the speed with which replacement methods and technologies are emerging, and the fact that possible animal-free alternatives will often be developed outside of the researchers' disciplines. However, this problem could be overcome if Australian experts in alternatives were given a platform to provide constructive feedback, advice and training on approaches that could replace animal research.

Researchers and scholars funded by MAWA have developed, implemented or validated a range of alternative approaches to replace the use of animals or animal products in their research including: complex 3D tissue models: organ-on-chips/microphysiological systems; organoids; human cell and tissue cultures; stem cell platforms; plant tissue cultures; biobanking; bioprinting; genomics; proteomics; artificial intelligence, virtual reality and physical model-based simulators; imaging; *in silico*/computational tools; mathematical models and analytical technology; ethical clinical research with volunteer patients and healthy subjects; microdosing; bioinformatics; population studies (epidemiology); and post-mortem studies as well as using existing data. It is accepted that it is difficult to replace a whole living system, but researchers also use multiple animal-free alternative methods in combination taking advantage of the strengths of each to achieve experimental objectives and to decrease animal use.

MAWA also recommends the establishment of more human tissue banks, and that support and resources are made available to overcome some of the obstacles to sourcing and using human tissue for research purposes. MAWA has provided funding support to the MS Brain Bank and the Sydney Heart Bank. MAWA Board members Professor Anne Keogh and Professor Cris dos Remedios believe that the use of human tissue in research can substantially reduce the use of animal models

Another concern regarding Replacement is that many AEC members have advised MAWA that very little evidence, if any, is provided by researchers seeking ethics approval to demonstrate that animal replacement alternatives have been investigated. A number of AEC members have reported to MAWA that some researchers simply make a statement that non-animal alternatives are not available without supporting evidence. When the UK Home Office introduced a very strict policy of increasing the need to address the replacement of animals for project licence applications, researchers stopped paying lip service to this requirement because their projects were not funded when proper consideration was not made. They then began to seriously consider other methods and technologies that might replace their use of animals resulting in a significant cultural shift.

Experts in the field recommend that researchers should list the biomedical bibliographic databases searched, and search strategies and terms used, to ensure their searches for alternatives have been thorough, and that research is not duplicative. They also recommend that a literature review of previous animal experiments be required to help assess whether the proposed animal experiments are needed. Such a pre-experimental exercise would enhance experimental design, produce higher quality results and ultimately save funds and time.

Additionally, the provision of a well-designed step-by-step guide on how to search for alternatives as well as accompanying worksheets as used in other countries, could make it much easier for researchers to adhere to both the NHMRC Code and Guidelines, and for AECs to properly assess and ensure compliance.

At present, compliance with the 3Rs regarding Replacement by researchers is not being properly assessed, and there is insufficient oversight of AECs to ensure compliance with the Code. The current system is not working for Replacement.

2. How is the lack of funding for alternatives in Australia affecting the quality of research we are able to produce, and the ability of research institutions to actually implement the 3Rs?

Unlike other countries, Australia does not have a federally funded specific grant category for developing and commercializing non-animal methods and no Australian government programme currently directs resources for the development of animal-free alternative approaches as a priority or specific policy aim.

The lack of specific funding for animal-free alternatives in Australia puts added pressure on current funding sources eg the Australian Research Council (ARC), and the National Health and Medical Research Council (NHMRC), which are already under funded. With a success rate of less than 10% (a success rate which is far less than in the UK, Europe and the US), resources through these bodies are far too stretched.

Specific funding for the 3Rs, through a new organisation or funding body, or via a series of specific Medical Research Future Fund (MRFF) calls, would lead to high quality applications designed to develop new approaches, policies, practices, and models across biomedicine. Excellence of science with significant 3Rs benefit can be achieved through a robust peer review process and a matrix scoring approach which is already in use in the UK with the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). Unfortunately, without funding to support new initiatives to address the 3Rs, implementation of alternatives in research and research institutions will be limited.

Another concern frequently expressed by researchers and scholars is that project reviewers favour animal-based research for the allocation of funding, and furthermore that they consider that the use of animals will increase their chances of publishing their research. This may not always be the case in fact, but it is most certainly the perception of many in the medical research community, and it is indeed concerning to MAWA that many students are advised that their chances of attracting funding, and publishing their research, are increased if they work with an animal model. Many researchers report that when attempting to secure funding, or when reporting their findings in journals, they are asked to provide animal data to support their research, even though it is not scientifically necessary. To really give animal replacement methods equal opportunity, this situation needs to be addressed.

MAWA grant recipients and Science Advisors to MAWA, Professor Alastair Sloan from the University of Melbourne, and Professor Wojciech Chrzanowski from the University of Sydney, also responded to this question and provided examples in their evidence at the NSW Inquiry's hearings.

Professor Sloan, along with his collaborators in Melbourne, have achieved significant advances with antimicrobial coatings for implants and the research is delivering some superb data. However, when they tried to publish their research in very good journals, they had reviewers' comments back, and editors agreeing with these comments, that "You must do an *in vivo* experiment. You must put this into an animal model." Professor Sloan's response is "No, we mustn't. We don't need to. That actually would not be a good scientific move." But this barrier to publish from the editors-in-chief and the editorial boards of some of these journals has two effects. It prevents researchers from driving cultural change, and it comes back to what we have mentioned previously in question 1 and in our MAWA submission - it has a negative impact on the publication ability of young, early-career researchers, and so the paradigm is perpetuated.

Professor Chrzanowski has reported that if his team applies for funding overseas, their alternative models are accepted because in the US, the UK and especially in the EU, there is a huge amount of funding for animal-free alternatives methods and technologies. However, when he applies for NHMRC funding, his experience is the same as Professor Sloan's. The response is, "You need an *in vivo* model. You cannot progress any work because you haven't done any animal research." He argues, however, that the animal model would be irrelevant. Professor Chrzanowski has said that when they tell him that he must use mice for his lab model, he refuses, but obviously this is a very big problem for researchers trying to avoid or replace the use of animals in their research.

It is, however, very encouraging to note that the many research groups around the world, including the prestigious Wyss Institute for Biologically Inspired Engineering at Harvard University (where organ-on-chips were first developed), are lobbying publishers to more readily accept research based on animal-free alternative models.

Prof Chrzanowski has also stated that funding is extremely limited in Australia and that, other than funding from MAWA and from Australian Ethical (which partners with MAWA to co-fund animal-free research), his team has never been successful in acquiring any major funding for alternative models in Australia. All his major funding has come from overseas sources. This funding is much sought after and is highly competitive internationally, so his success is a clear indication of the value of his non-animal models.

Prof Sloan, in his evidence at the hearing, highlighted other barriers to the implementation of alternatives as outlined in MAWA's submission. He also referred to the NC3Rs in the UK, and how they overcame a number of impediments by establishing a research funding stream for high-quality science addressing each of the 3Rs equally. He acknowledged that Replacement is the most difficult of the 3Rs, but that over time projects using animal replacement methods and different model systems have increased dramatically in the UK.

3. Some witnesses have suggested we should be increasing funding for animal research. Do you agree with this, or do you believe we should be targeting funding towards alternatives to animal research – and if so, why?

MAWA does not support an increase in funding for animal research, and believes that additional funding should instead be directed towards animal-free alternative methods and technologies in line with many other countries like the US, UK, Canada, the EU, and other European and Asian countries.

It is generally accepted in the medical research community that alternative non-animal methods can be less expensive, that results can often be obtained more rapidly and in many cases can more reliably be translated to the clinic. It is also recognised that in some cases, the discovery of treatments and cures for humans have been held back because they have either not worked well in the animal model, or have worked well in the animal model but not in humans, or have caused harm to humans due to species differences. It is important that these issues be considered.

There is now huge global interest in non-animal technologies. The use of alternative models has been a key contributory factor in drug discovery, therapeutics, diagnostics and medicines and has promoted creativity and innovation.

Professor Chrzanowski referred to the last World Congress on Alternatives and the Use of Animals in the Life Sciences in his evidence for the hearing. This conference in the Netherlands was the largest he had ever attended with 3,000 people participating from countries all around the world. However, what really struck him was that every big company producing pharmaceuticals or toiletries etc was attending and companies like Johnson & Johnson (the world's largest consumer health care company) stated that they don't want to test on animals anymore.

Professor Sloan also emphasised this in his evidence for the hearing when he said that "big global pharma" wants to avoid animal model systems. He works with large global institutions, including GSK, Phillips and Renishaw Limited, which fund his research, and he has stated that not one of them wants to support animal-based projects for fundamental research.

All major biomedical and pharmaceutical companies have now invested in the development of animal-free alternative models, which accelerates research and development, increases reliability and reproducibility, reduces costs and provides new opportunities for rapid translation of scientific discoveries.

At the same time the world's leading universities, eg Harvard, Massachusetts Institute of Technology (MIT), Stanford, Cambridge, Oxford and Imperial College London, have long standing programmes in developing non-animal alternative models. This demonstrates that this area of research and development is accepted and contributes to innovation and accelerates commercialisation.

Professor Sloan has pointed out that a significant amount of preclinical laboratory-based initial development can be performed on lab-based studies in cells, 3D model systems, algorithms and machine learning so that there is no need to use an *in vivo* animal system if appropriate animal-free alternative models can be developed.

Professor Sloan has developed systems that have been shown to make a 50% to 80% reduction in the use of animals for redeveloping his therapeutics. He has explained that an animal system gives one animal, one time point, or one animal, one dose point, whereas model systems can give you multiple dose points and multiple time points and are highly reproducible. It means when making the ultimate transition into a true preclinical environment, the right, very specific questions, are being asked, and the need for animals, if at all, is minimised. Professor Sloan believes that this is where research needs to progress to.

Professor Chrzanowski agrees. Instead of using one animal which provides one result, he can create hundreds of animal-free alternative models which mimic structures of human physiology to do high-throughput screening. This can be done more rapidly, and the models are more reproducible and reliable. He can develop personalised models by taking a patient's cells and recreating certain parts of the person's physiology in a dish to test whether treatments are effective or not for that particular individual. This is a huge advance for personalised medicine and cannot be done using an animal model. These animal-free alternative models provide more opportunities for fundamental discoveries, which can also drive commercialisation.

Professor Chrzanowski also provided an example of a company he has been working with in Korea on bioprinting. ROKIT is a 3D printing company. Today they have a very large factory that is producing skin replacement for burns after injuries. The company started with only one bioprinter, but after only five years they now have hundreds of bioprinters for printing skin and their premises is the size of a large university building.

A lack of investment in our country will have a significant impact on the competitiveness of Australian science. Researchers argue that in many areas they are forced into the role of underfunded followers in animal-free alternatives, rather than role models and inspiring influencers leading the world in these areas of research. As Professor Chrzanowski said at the Inquiry's hearing, we have two options - watch what the world is doing, and in a few years wake up and follow what they have done, or be leaders with alternative models in the life sciences.

4. What recommendations would you like to see from this Inquiry in terms of alternatives to animal research?

MAWA would like to see the following statement and recommendations from the Committee conducting this Inquiry.

To support the development and implementation of alternatives to the use of animals in medical research in NSW, and as a result of this Inquiry, the Portfolio Committee No 2 recommends that the NSW Government:

1. Provides leadership and action, by developing a vision and strategy for decreasing animal usage and for implementing alternatives, including a roadmap with established targets and an allocation of sufficient funding, research support and other incentives, to bring about cultural change and a shift away from animal research as the dominant paradigm.

2. Formally recognises:

    a. the rapidly increasing economic value and investment potential of developing animal-free alternatives in the medical technology and pharmaceutical sector given Australia's world class universities and research institutions and Australia's achievements in medical research
    b. that there can be issues with research reproducibility and clinical translation with using animal models for medical research and that animal-free approaches can offer scientific value by way of improved physiological relevance and advanced solutions for modelling human biology and predicting interactions to external challenges
    c. that there are many Australian researchers who would like to make non-animal model development a key focus of their research portfolio and to be a part of a community of like-minded researchers

3. Establishes an expert advisory body at state level with a high level of expertise in animal-free biomedical research to:

    a. develop new policy and legislation with stronger regulation for the implementation of animal-free alternatives
    b. develops a roadmap with milestones, timelines, funding and deliverables to guide the efforts of those involved in advancing non-animal technologies
    c. provide thought leadership and advice to industry, academia and regulatory bodies to advance the development and validation of new methods and technologies
    d. Facilitate partnerships between government, academia, industry, regulators and other stakeholders to stimulate innovation and growth in this area
    e. Encourage coordination of cross disciplinary mechanisms for research groups using animal-free alternatives
    f. Facilitate information exchange and open dialogue among stakeholders and the pooling of knowledge and data from different models and test methods to accelerate the transition to animal-free methods through collaborations between various sectors
    g. Create opportunities to showcase new animal-free alternative models and highlight work that can drive innovation and facilitate commercialization of animal-free methods and technologies
    h. Provide information on international organisations funding animal replacement research which accept applications from Australia
    i. Provide resources and information on alternatives journals, websites, 3Rs Centres, search engines, databases, and step-by-step guides on how to search for alternatives with accompanying work sheets to make it easier for researchers to adhere to the NHMRC Code and the Guidelines, and for AECs to properly assess and ensure compliance

4. Supports the establishment of a national multi-disciplinary research institute for alternatives focused on research to develop methods and techniques to replace animals, with states and territories establishing a network of centres to contribute to, and complement, the work of the national institute.

5. Establishes a world class discovery centre, or an innovation precinct, in NSW to develop multidisciplinary scientific skills in animal-free alternatives, such as in biology, chemistry, engineering, mathematics and computer science.

6. Recognises that upscaling what MAWA provides in Australia, that is research, development and equipment grants, research fellowships, a range of scholarships, travel bursaries and sponsorships, plus prizes for excellence in emerging fields, is urgently needed.

7. Provides strategic funding, supportive infrastructure and resources to:

    a. support the development, validation, implementation and commercialization of animal-free methods
    b. establish seed funding to assist researchers to gain access to other funding streams for animal-free approaches
    c. establish top up or dedicated funding for NSW scientists who are successful in participating in EU, US or any other overseas funding schemes or international programmes
    d. provide long-term funding (say 10 years) for consortia and other commercial entities to develop methods and strategies for manufacturing and commercialising animal-free models
    e. provide education and training in alternatives for students, researchers and Animal Ethics Committee (AEC) members to increase awareness, knowledge and expertise in animal-free methods and technologies

8. Establishes protocols and provides resources to:

    a. Increase monitoring of compliance to current codes and standards and institutes stronger enforcement measures
    b. Facilitate systematic reviews and the implementation of a critical cost-benefit analysis system for research involving animals, such as is used in the UK
    c. Review complicated bureaucratic processes for regulatory acceptance of animal-free alternative test methods following the scientific processes of development and validation
    d. Require researchers seeking ethics approval to demonstrate at an early stage in the process that animal replacement alternatives have been fully investigated, and to provide evidence, in order to avoid the problem of researchers, faculties and institutions having so much time and energy invested by the time proposals reach Animal Ethics Committees
    e. Require and facilitate the pre-registration of all animal experiments and establishment of a national database of all research on animals, including research that fails to achieve expected results and require researchers to consult this database before submitting a protocol
    f. Require researchers to list the biomedical bibliographic databases searched, and the search strategies and terms used, to ensure their searches for alternatives have been thorough, and that research is not duplicative. A literature review of previous animal experiments should also be provided to assist AEC members to assess whether the proposed animal experiments are truly needed
    g. Require action to ensure that animal replacement methods are given equal opportunity by providing access to experts, resources and training in alternatives for grant and journal reviewers, to avoid the common perception that reviewers favour animal-based research in regard to the allocation of funding, and that the use of animals will increase the chances of publishing research

9. Encourages the establishment of more human tissue banks and resources to overcome some of the obstacles regarding sourcing and using human tissue for research purposes

10. Encourages NSW universities and research institutions to follow the example of the University of Wollongong, and the University of NSW, which have committed funding specifically for the 3Rs

11. With other Australian governments, engages and works with world leaders in alternatives to contribute to, and promote, international acceptance of high-tech non-animal replacement methods and technologies based on human biology for biomedical research.

5. You note in your submission that by the time a research proposal comes before an animal ethics committee, it generally already has funding from a group like NHMRC. Do you think this puts pressure on an animal ethics to approve research, even if a non-animal alternative might be available? If so, how can we fix that?

To the first part of the question, the answer is yes, AEC members have advised MAWA that they sometimes feel immense institutional pressure to approve research projects despite their reservations for a range of reasons, including their disquiet that animal replacement alternatives might be available.

Please refer back to MAWA's response to question 1 where we note concern from AEC members that researchers do not provide sufficient evidence that they have investigated animal-free alternatives, and in many cases, they just assert, without evidence, that there are none. In response to this situation, MAWA has passed on expert advice that AEC members should require researchers to search biomedical bibliographic databases, and to provide the search strategies and terms they used, to ensure their searches for animal-free alternatives have been thorough, and that research is not duplicative. MAWA also suggests that AEC members request a literature review of previous animal experiments to help assess whether the proposed animal experiments are needed.

MAWA is aware that ethical decision making is a difficult process and, as mentioned in MAWA's submission, AEC members have stated that timing can be important too as once a proposal is presented to an AEC, it often has funding approval and that issues regarding animal ethics are among the last to be considered. In other countries there is ethical screening before funding decisions are made which avoids the problem of researchers, faculties and institutions having so much invested by the time the AEC is required to assess whether alternatives have truly been investigated. This would be preferable for the Australian situation as well.

It seems to MAWA that AEC members would appreciate a lot more training not only to increase their knowledge and understanding of scientific research, but also in ethical decision making and the availability of non-animal methods and technologies.

MAWA believes that experts in alternatives, and in ethics, should be brought on to AEC panels, and that all universities and research institutions should provide researchers with comprehensive step-by-step guides on how to search for alternatives and accompanying worksheets as used in other countries. The worksheets could then be provided to AEC members to make it easier for them to assess projects and ensure that researchers are complying with the NHMRC Code and Guidelines.

MAWA would also like to see more frequent reviews of AECs, as the current regime of every 4 years is far too long for sufficient oversight.

6. You note in your submission that MAWA is often approached by research facilities and animal ethics committees for support and assistance with alternatives to animal experimentation, but you don't have the capacity to assist with every request – what kind of support are these groups looking for? What does the Government need to do to ensure animal ethics committees receive the support and advice they need?

MAWA receives countless enquiries from research facilities. These usually come from university research offices, development offices, advancement departments or philanthropy departments, asking for support for their students and researchers, or requesting support for a range of sponsorships. Similarly research institutions are continually reaching out to seek funds for their researchers interested in animal-free alternatives, or for specific programmes. Additionally, universities and research institutions approach MAWA for speakers for conferences, seminars, workshops, training courses etc.

Government departments and professional associations also approach MAWA for members to join committees, consultancies, reference groups etc.

However, the majority of requests for support come from researchers, students and AEC members, plus other organisations such as animal protection groups, health charities and other non-profit organisations. These mostly include requests for resources, guidance and information about:

- non-animal replacement methods, technologies and models
- alternatives to animal products such as animal tissue, animal cells, animal antibodies, animal serum, animal derived stains or reagents, animal bioinks and a range of other animal media used in medical research.
- funding bodies for alternatives research - domestic and international.
- research groups developing, utilising or validating alternatives throughout Australia
- universities and research institutions most supportive of alternatives
- potential supervisors for students undertaking post-graduate research
- MAWA's networks - general or discipline specific, disease or disorder specific and domestic and international

In response MAWA provides helpful contacts, examples of animal replacement research and information on: international 3Rs centres; journals; websites; search engines; databases; step-by-step guides on how to search for alternatives; and international organisations promoting alternatives and funding animal replacement research. Given many countries provide such resources through government funded bodies, it would bring Australia into line with current advances if the states and territories could also assist and encourage researchers, students and AEC members by providing similar support and guidance.

7. Do you think state and federal Governments need to play a greater leadership role in reducing the number of animals being used in research, and put forward some kind of roadmap or plan for how we will get there, including funding but also potentially targets for reducing animal usage? What would this look like?

Yes, absolutely, there should be a much greater leadership role by governments at both state and federal levels. It is clear to MAWA that while there is valuable expertise across a range of alternative approaches to animal research methods throughout Australia, a coordinated national and state approach is required for widespread implementation.

A roadmap with milestones, timelines, funding and deliverables to increase non-animal technologies and decrease animal use in research is essential to guide the efforts of those involved. An inquiry by an All-Party Parliamentary Group (APPG) established in the UK to accelerate innovation and create change in biomedical research and testing concluded that targets and government deadlines were needed in addition to incentivisation to change the behaviour of researchers, funders and regulators. The APPG's legal expert noted that "paradigm shifts rarely happen in a policy vacuum".

However, while MAWA sees a value in setting targets for reducing the numbers of animals used in research, we believe that first targets should include establishing critical mass (knowledge, personnel, capabilities) to enable the development, validation and manufacturing of alternatives, plus broader education and promotion for the acceptance of alternative models by regulatory agencies in line with other countries. This will naturally lead to the reduction of animal research.

The ideal situation would be the establishment of a national multi-disciplinary research institute for alternatives focused on research to develop methods and techniques to replace animals, with states and territories establishing a network of centres to contribute to, and complement, the work of the national institute thereby improving awareness and knowledge of non-animal technologies.

NSW could lead the way with a world class discovery centre, or an innovation precinct, to develop multidisciplinary scientific skills in alternatives, such as in biology, chemistry, engineering, mathematics and computer science. Advancing fundamental knowledge in alternatives and establishing a central place for research and development will attract industry partners to establish world class manufacturing capabilities. Some research groups supported by MAWA in NSW have advised of several companies who have already expressed their interest.

As Professor Sloan has stated in his evidence at the hearings, if NSW leadership results in a significant step-change in culture or practice, and NSW researchers are winning highly competitive grants, then this would send a shock wave across the biomedical sector and encourage the federal and other state governments to take notice. This would also attract researchers and students who want to focus on non-animal approaches to NSW from other states, encouraging them to follow suit and go in the same direction.

Even if the federal government continued with a lack of interest in establishing a national research institute, they could still provide funding through the National Health and Medical Research Council (NHMRC), the Australian Research Council (ARC) or the Medical Research Future Fund (MRFF) by creating targeted calls for animal-free alternatives research.

Engagement with international programmes and open data sharing should also be facilitated. The development of databases of validated alternatives will build confidence for their implementation and enable knowledge exchange.

NSW could also provide an upscaling of MAWA's funding initiatives as mentioned previously. There is always strong interest from researchers and students in NSW for MAWA's research and development grants, equipment grants, fellowships, scholarships, travel and conference bursaries, sponsorships, prizes and awards etc.

8. What developments from the European Union in terms of supporting the development of alternatives would you like to see adopted in Australia, and why?

While the European Union has been leading the way with many 3R initiatives like:

- The establishment of the European Partnership for Alternative Approaches to Animal Testing (EPAA) in 2005
- The adoption of the *Directive for the Protection of Animals used for Scientific Purposes* by the European Parliament and the Council of the European Union in 2010
- The *Review of Advanced Non-Animal Models in Biomedical Research* undertaken by the European Union Reference Library (EURL), of the European Centre for the Validation of Alternative Methods (ECVAM) in 2020
- The adoption by the European Parliament of a resolution calling on the European Commission to establish an *EU-wide Action Plan for the Active Phase out of the Use of Animals in Experiments* in 2021

MAWA is also impressed by developments in countries such as:

- The Netherlands with the introduction of their *Transition Programme for Innovation Without the Use of Animals* in 2018, and their plan to phase out animal testing by 2025
- The UK's innovation platform Crack IT, introduced in 2011 to fund collaborations to deliver 3Rs benefits
- The UK's development of a roadmap for non-animal technologies in 2015
- The UK's partnership between their NC3Rs and the World Health Organisation with funding from the Gates Foundation in 2021 to enable vaccines manufacturers and regulators to apply the latest non-animal testing approaches
- The UK's collaboration between the NC3Rs and the Biotechnology and Biological Sciences Research Council in 2022, focussed on supporting alternatives to *in vivo* models in bioscience research
- The US's establishment of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in 2000
- The US's development of a strategic roadmap for establishing new animal-free approaches in 2018

- The US Environment Protection Agency's initiative in 2019 to reduce the use of animals in research with a goal to eliminate safety tests on mammals by 2035
- The introduction of the US Food and Drug Administration (FDA) Modernisation Act to end animal testing mandates in 2021.

These programmes and initiatives for the implementation and commercialisation of non-animal methods are all described in MAWA's submission and are in addition to the establishment of Centres for Alternatives in the EU and many countries around the world including the UK, US, Canada, Netherlands, Norway, Denmark, Switzerland, Germany, Italy, Poland, Brazil, Romania, Japan and Korea which are also described in MAWA's submission.

The European Union has certainly led the way for the replacement of animals in toxicology with the development and validation of non-animal technologies as alternatives to animal testing for the safety of cosmetics, toiletries, pharmaceuticals, chemicals etc and in many areas of replacement, refinement and reduction for the use of animals for teaching and training. However, MAWA's focus is on the more challenging area of the replacement of animals in fundamental biomedical research where the vast majority of animals are used. MAWA, therefore, needs to look beyond initiatives addressing toxicology and animal testing to focus more on replacing the use of animals in medical research designed to improve understanding of human illnesses, their causes, progression, and the underlying features to facilitate prevention, early diagnosis and effective treatment.

It would be hugely beneficial if Australia could follow the EU's example of:

- Establishing Centres for Alternatives
- Providing infrastructure, resources and specific funding streams for the development and validation of non-animal technologies
- Providing education and training opportunities for new non-animal technologies
- Forming partnerships between governments, academia, industry and a range of other stakeholders to phase out the use of animals in research and to encourage the implementation of animal-free alternative methods and technologies
- Recognising the scientific value of animal-free approaches which offer improved physiological relevance and advanced solutions for modelling human biology and predicting interactions to external challenges
- Appreciating that non-animal technologies can reduce costs and offer economic value with their investment potential
- Reviewing regulatory requirements for research involving animals and pharmaceutical approval

Currently, Australia lags behind with no government commitment or significant plan to phase out animal testing other than for cosmetics, or to develop alternatives to the use of animals in medical research.

Professor Sloan suggests that funding for non-animal alternatives is key to progress and that Australia should look to the UK's National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) as an excellent example of what can be achieved with government leadership.

The NC3Rs is funded by the UK government and has been in operation since 2004, following the recommendation of a House of Lords Select Committee report on Animals in Scientific Procedures published in 2002. The NC3Rs was established with funds from the government's Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). The NC3Rs is governed by a board which reports to the Science Minister as do all UK Research and Innovation bodies.

The NC3Rs supports research into alternatives while ensuring scientific excellence is maintained. It operates in the same way as the MRC, the BBSRC and other funding bodies with a grant assessment panel to review and award funding through a competitive process.

The NC3Rs has led the creation and implementation of the *Animal Research: Reporting of In Vivo Experiments* (ARRIVE) guidelines for appropriate animal use, and it's CRACK IT scheme has built partnerships between academic researchers and industry to address problems and 3Rs needs in the biotech, biomedical and pharmaceutical sciences industries. As such it leads the implementation of the 3Rs in science through engagement, academic/industry partnerships and with significant research funding for the development of model systems and approaches to address the 3Rs.

The NC3Rs does not work in isolation, which is a real strength. It works in partnership with other government funding bodies, not-for-profit organisations and charities, and has strong connections with Animal Free Science UK (AFRUK), as well as the Fund for the Replacement of Animals in Medical Experiments (FRAME).

Professor Sloan has reported that over the last 18 years the number of applications to the NC3Rs has increased significantly and the quality of the science has been outstanding. He believes that the establishment of the NC3Rs, along with other UK government and non-government initiatives, has really shifted the culture in the medical research community.

Professor Chrzanowski, upon considering this question relating to the European Union, has suggested that it might be useful for the Inquiry's Committee to consider a case study which he believes with provide some insight into the disadvantages Australian scientists are faced with when competing for international funding.

Case study: European Commission's Horizon Europe Programme
Horizon Europe is the European Union's key funding programme for research and innovation with a budget of 95.5 billion Euro.

Professor Chrzanowski initiated a European Union (EU) consortium of universities, research institutes and industry partners which recently received 3 million Euro from Horizon Europe to develop alternative models and new characterisation tools to assess the impact and influence of nanomaterials on the central nervous system (CNS) over a four-year period. This is the world's first programme in this area, so very exciting news and a major achievement by this impressive consortium, but while Prof Chrzanowski initiated this program, the EU does not provide funds to an Australian partner, therefore there is no funding to execute this research in Australia. NHMRC programs https://www.nhmrc.gov.au/funding/find-funding/2021-nhmrc-european-union-collaborative-research-grants are very limited, selective and unaligned with EU funding in terms of dates.

Previously Professor Chrzanowski received EU funding of 1.7 million Euro, but the NHMRC announced that the scheme he participated in is not eligible to apply for additional funding in Australia, which forced him to resign from the consortium and jeopardizes his reputation and relationship with multiple, top universities in Europe.

Professor Chrzanowski also points out that there is only one round of funding in Australia for the National Health and Medical Research Council-European Union Collaborative Research Grants, and researchers must wait nine months for the announcement of the awards. The preparation of applications for these grants requires a substantial amount of work - approximately 100 pages for an EU application. These applications go through a rigorous assessment process by leading international experts. In other countries if a researcher is awarded an EU grant, they automatically receive funds from their own country for such project.

Professor Chrzanowski recommends that funding from the NHMRC, the ARC, or perhaps a new scheme funded by the State Government should be provided automatically if an application has already been favourably evaluated by leading international experts acting on behalf of the European Commission. Australian researchers will have dedicated months to planning and writing an EU grant requiring many meetings with EU colleagues during the night due to time differences. To have to write a second grant, and then wait sometimes for over a year to hear the outcome is unreasonable and unworkable for Australian researchers. Professor Chrzanowski asks, how can they be competitive globally?

Many Australian researchers believe that our country should align fully with EU funding dates. If not, Australian institutions/universities and researchers will not be attractive as EU partners as they cannot bring any funds and therefore cannot conduct the relevant partner research in which they excel.

Professor Chrzanowski maintains that the lack of schemes, capabilities and long-term strategy means Australian researchers could end up only as observers and hopeful future followers of frontier technologies. He believes that some large spending now will provide huge benefits for medical research in Australia into the future saving lives and meeting the health needs of our society.

9. We have received evidence during this inquiry about human 'lifesaving' research –what percentage of animal research do you think is being conducted that will be human lifesaving or have a good chance of being human lifesaving?

This is a very difficult question to answer and quantify given the simple phrase "lifesaving" and MAWA is not in a position to provide information of this nature. There is no doubt that animal experiments have led to the introduction of medications which have benefitted human life, and modelled disease states which have led to better therapeutic interventions. However, translation from animals to humans, is not straightforward and has sometimes led to unfortunate and lethal consequences and slowed progress considerably in some instances.

Problems with research reproducibility and clinical translation of basic research have been highlighted by Professor Francis Collins, in an article in the top-ranking science journal *Nature* where he states, "Preclinical research, especially work that uses animal models, seems to be the area that is most susceptible to reproducibility issues." Professor Collins was then Director (2009-2021) of the US National Institute of Health (NIH), the largest biomedical research agency in the world.

MAWA has established relationships with the research community developing and utilising alternative methods and technologies. MAWA funding is much sort after so MAWA can testify to the interest of researchers, and that there are many scientists in Australia who would like to make non-animal model development a key focus of their research portfolio and to be a part of a community of like-minded researchers.

If a percentage of what animal research is lifesaving was arrived at, most researchers would see their work as lifesaving and arguments about how to move forward would be unproductive. A better approach would be to provide supportive infrastructure, strategic funding, education, training and collaboration opportunities for researchers and industry to develop and validate animal-free alternative methods, technologies and models.

Sharyn Watson
Executive Director
The MAWA Trust

MEDICAL ADVANCES WITHOUT ANIMALS