Submission No 226

INQUIRY INTO USE OF PRIMATES AND OTHER ANIMALS IN MEDICAL RESEARCH IN NEW SOUTH WALES

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SUBMISSION

NSW LEGISLATIVE COUNCIL INQUIRY: USE OF PRIMATES AND OTHER ANIMALS IN MEDICAL RESEARCH IN NEW SOUTH WALES

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1 About AAMRI

The Association of Australian Medical Research Institutes (AAMRI) is the peak body for medical research institutes (MRIs) across Australia. Our 58 member organisations, which includes 20 institutes in New South Wales, work on a broad spectrum of human health issues such as preventive health, chronic disease, mental health, immunology, and Indigenous health. Their research ranges from fundamental biomedical discovery through to clinical research and the translation of research findings into new drugs, devices, and other therapies.

AAMRI welcomes this inquiry and is pleased to provide the Committee with the following information relating to the essential role of animals in medical research.

2 Recommendations for the NSW Government

1. **Work with stakeholders to develop accredited training standards and training programs for staff working with animals in research.**
2. **Fund initiatives that can help develop alternative methodologies to replace or reduce the number of animals used in medical research.**
3. **In conjunction with the federal and other state governments establish a National Centre for the Replacement, Refinement and Reduction of Animals in Research.**

3 Introduction – the use of animals in research has delivered major advances for human health

Most major advances and breakthroughs in health and medical research have been developed through medical research undertaken with animals.

- The development of insulin administration as an effective therapy was only made possible by using animals in research, not only saving countless lives but also improving the quality of life of many more people.
- The cervical cancer vaccine, developed in Australia, was based on research studies using mouse models establishing a link between the papilloma virus (HPV) and cancer. This discovery paved the way for further research establishing the link in humans too, leading to the development of a vaccine that dramatically reduces the risk of contracting HPV, and therefore developing cancer. Organ transplants have only been made possible through research with animals, which has allowed for the development and constant improvement of the surgical and pharmacological techniques that are now routinely employed.
- Deep brain stimulation, which is one of the most effective treatment options for Parkinson's disease, was also developed by studies employing animals, and specifically non-human primates.

In each of these cases, animal-based research, often initiated with the desire to understand a biological phenomenon (discovery research) was the seed that initiated the long road to translation to human health. While these are well known historical examples there are many research projects underway working towards the same goal: improving patient outcomes

through research. Examples of this are provided through three cases studies in response to term of reference F.

It should be noted that in New South Wales the use of animals in medical research is highly regulated by both legislation and national guidelines. This ensures the highest possible welfare for animals, as well as a robust ethical framework that ensures animals are only used when there are no other alternatives. While alternative techniques are emerging and have allowed for a reduction in the use of animals, they are not sufficiently advanced to allow for the complete replacement of animals in medical research.

In this submission, AAMRI responds to the inquiry's terms of reference by outlining the nature and use of animals in medical research, the benefits it delivers for human health, the progress made in reducing the number of animals used, and the challenges of eliminating animal use entirely.

4 Terms of reference A: the nature, purpose and effectiveness of medical research being conducted on animals in New South Wales, and the potential public health risks and benefits posed by this research.

4.1 Nature, purpose and effectiveness of medical research conducted on animals

The nature, purpose and effectiveness of medical research being conducted on animals in New South Wales is similar to that in the rest of Australia, and in other leading medical research nations. Broadly speaking the use of animals in medical research is usually serves one of the two following purposes:

- to make new discoveries that advance our scientific knowledge (sometimes referred to as discovery, fundamental or basic research),
- or to conduct pre-clinical studies that test the efficacy of new drugs, medical devices, and other therapeutic treatments and ensure they can be used to treat humans.

As noted above, these two types of scientific activity using animals are deeply intertwined, with the successful application of knowledge to human health and wellbeing typically depending on the combination of many fundamental research discoveries, often made independently, and covering different fields of investigation.

The development of new scientific knowledge is crucial to making advances in medical research, and ultimately the development of new vaccines, drugs, medical devices, and other treatments. This discovery research typically studies life at the cellular and molecular level to identify and characterise the mechanisms and metabolic pathways involved in the essential life processes of living organisms.[i] Major developments on our current understanding of biological systems and their functioning have been made from discovery research involving animals. While the initial goal of discovery research might have been to advance scientific knowledge, it also provides the fundamental building blocks needed to develop new treatments for human diseases.

Animals are used in medical research for pre-clinical studies to show the safety and potential usefulness of new drugs, vaccines, devices, and other therapeutics prior to them being tested on humans in clinical trials. Pre-clinical studies are essential as they are needed to ensure that potential risks to human participants in clinical trials are reduced as far as possible. For example, drugs need to be tested in animal models to help determine the maximum human tolerance dosage for a drug.

Without pre-clinical animal studies, the risk of harm to humans participating in clinical trials would be unacceptably high and ethically unacceptable. The increased risk of mortality and morbidity amongst trial participants would make it very difficult to recruit volunteers for trials and would see the development of new drugs, devices, and other therapeutics grind to a halt.

4.2 The public health benefits of using animals in medical research

Some of the most notable examples of research involving animals leading to significant new treatments in Australia include the development of the artificial replacement heart valve, and the development of IVF treatment. Neither of these developments would have been possible without the use of animals in discovery research. This is true both in terms of the fundamental discovery science that underpins them, as well as the subsequent pre-clinical development into real-world application, which includes safety testing on animals.

The public health benefits of using in animals in medical research are substantial. Nearly all major discoveries and developments that have led to improved health outcomes have involved animals at some stage. Improved cancer treatments, identifying new drugs to combat cardiovascular disease, anti-viral treatments to prevent the development of AIDS in people living with HIV, the development of medicines to reduce high blood pressure, and the development of the cochlear implant (bionic ear) have only been made possible by using animals in research.

4.3 The risks of not using animals in medical research

The risks to humans of using animals in research for human health are extremely low. The use of animals in research in Australia is highly regulated and controlled. There have been no known adverse outcomes on human health through the use of animals in research, while the benefits delivered are substantial. Furthermore, if animals were not used in medical research there would be a significantly increased risk to public health as it would slow the pace of discovery for new treatments and elevate risks of mortality and morbidity during early phase clinical trials.

The risks to humans of not using animals in medical research are substantial. There would be an unacceptably elevated risk of mortality and morbidity to humans taking part in early phase clinical trials of drugs that had not been tested first on animals. There would also be an increased risk of unknown side-effects of new drugs and treatments that had not been subject to sufficient testing in animal models. An example of where this has happened is the thalidomide tragedy in the 1960s occurred in part because there was insufficient testing in pregnant animals for a drug indicated for use in pregnant women. .[ii] This led to thousands of babies being born around the world with limbs that had not fully developed due to the toxic effects of the drug on developing embryos. This finding was subsequently confirmed in animal models and helped lead to the withdrawal of the drug as a treatment for morning sickness. Current protocols require pre-clinical testing on animals and would have prevented this tragic outcome.

5 Terms of reference B & D:

(b) the costs associated with animal research, and the extent to which the New South Wales and Federal Government is commissioning and funding the importing, breeding and use of animals in medical research in New South Wales;

(d) the ethical and animal welfare issues surrounding the importing, breeding and use of animals in medical research;

5.1 The costs and benefits associated with using animals in medical research

While there are costs associated with using animals in medical research, the economic and health benefits are substantial are far outweigh any economic cost incurred. For example, the time taken for a new discovery to enter clinical use is between 7 and 17 years, and many phase 3 clinical trials for cancer and cardiovascular conditions in humans can cost many millions of dollars. Recent estimates put the average cost of a single phase 3 clinical trial at $19 million, with trial costs reaching as high as $347 million[iii].

Given the timeframes and costs involved only those drugs that stand the best possible chance of success can proceed to clinical trial. Therefore, animal studies must be used to identify those drugs with the best chance of success.

Developing and providing new treatments for patients is necessary to help give everybody the best chance of a healthy life. Disease is a great drain on the economy which prevents such participation as well as increasing health and social care costs. In addition, locally conducted medical research is the foundation of our home-grown biotechnology industry, which is a key driver of Australia's knowledge-based economy. Given the outstanding health and economic returns medical research delivers it represents the best investment any government can make. Estimates from KPMG show that for every $1 invested in medical research there are returns of about $4 to the population.[iv]

In terms of the costs associated with using animals in research it should be noted there are costs of purchasing or breeding animals, and there are costs associated with complying with the appropriate regulations associated with using animals in research.

The costs of purchasing animals varies greatly according to the species, its age and genetic status. For mice and rats the cost can vary between $25 to $500 per animal. The cost of a primate (which are not used at medical research institutes in NSW but are used by other research organisations in NSW) is upwards of $25,000, with this price rising because of global supply chain issues. The substantial cost of using primates as well as highly regulated governance frameworks surrounding their use ensures that only a relatively small number are used.

5.2 Decreasing use of animals in health and medical research

As every dollar invested in medical research is a precious resource, and with institutes aware of their ethical obligations, animals are only ever used in research where there is no other feasible alternative.

The number of animals used in research at medical research institutes has been falling. This is because of the high cost of undertaking such research, the availability of some alternative methodologies, institutes' commitment to the 3Rs[v], as well as the high threshold that most be reached before ethics approval is granted to use animals in research. According to the NSW Department of Primary Industries, the number of animals used in research relating to human or animal welfare has fallen from 299,000 in 2010 to 130,000 in 2019[vi]. This has happened at the same time Australian Government investment in health and medical research has increased substantially from $1.2 billion in 2010-11 to just under $2.0 billion in 2020-21.[vii] This trend of decreasing use of animals is occurring overseas too. Within the EU there has been a fall in the number of animals used from 9.6 million in 2015, to 8.9 million in 2018 (the most recent year which data is available).[viii] Of these animals, 88% were mice, rats, or fish, with cats and monkeys accounted for 0.3% of the total.[ix] In the United States there has also been a decline with the number of non-rodent animals used more than halving between 1985 and 2019 (noting that figures for rodents and fish are not collected in the United States).[x]

These data are direct evidence that the medical research community is continuing to adhere to relevant guidelines to reduce the use of animals used in research wherever possible.

5.3 Ensuring high standards of animal welfare

Medical research institutes ensure the highest standards of animal welfare by making substantial investments in animal husbandry, staff training, managing animal ethics application processes, and ensuring compliance with both National Health and Medical Research Council (NHMRC) and state regulations. This requires the employment of qualified animal house staff, engagement of veterinarians, the build and maintenance of dedicated animal house facilities, and the management of animal ethics processes.

The welfare of animals used in research is of the highest concern to those working in medical research. High standards are set out in the NHMRC *Australian Code for the care and use of animals for scientific purposes* and through state regulations. Regular inspections and audits of facilities provide assurance that animal welfare standards are being maintained. Providing care for animals requires highly skilled and experienced staff. It has become increasingly difficult for research organisations to find the skilled staff needed for animal house facilities. There are no mandated or accredited training standards which makes both training and recruitment difficult. The inquiry should consider whether the NSW Government could work with the sector to develop and credential such a training program.

Recommendation

1. The NSW Government should work with stakeholders to develop accredited training standards and training programs for staff working with animals in research.

5.4 The occasional importation of animals used for medical research

Nearly all animals used in medical research are bred in Australia and therefore importation does not take place frequently (either directly or through a supplier).

For mice and rats it is occasionally necessary to refresh genetic lines back to their genetic source, or to import new lines which have specific characteristics needed for a particular research project. Relative to the number of mice and rats used in medical research the number imported is extremely small.

The national breeding colonies for non-human primates have been established to manage and maintain viable colonies of primates that can be used for medical research, and the highest standards of animal welfare. To ensure genetic diversity is maintained very

occasional importation of primates is also required. When this importation does take place, it is from other verified breeding colonies overseas, never with non-human primates taken from the wild. These stipulations are made by the *Principles and guidelines for the care and use of non-human primates for scientific purposes*, which are periodically reviewed and revised by the NHMRC to ensure the standards are among the highest in the world.

Without the very occasional importation of primates, the national breeding colonies would become unviable as genetic diversity could not be maintained. This genetic diversity is essential as it reflects similar diversity in humans. Not ensuring genetic diversity would present a huge setback for medical research in Australia, slowing or preventing new discoveries and treatments from being developed, and it would not lead to any animal welfare improvements. Medical research with primates would continue but it would take place overseas. This would leave Australia dependent on other nations, including those where standards cannot necessarily be monitored and might not meet the world-class standards maintained in Australia.

5.5 The use of non-human primates in medical research

Only a relatively small number of non-human primates are used in research in NSW each year. For 2019 this was 53 animals, with the average number each year over the last ten years being 72.[xi] Non-human primates make up just 0.003% of animals used in research in NSW. This relatively low number reflects the fact that all other options are pursued first.

While these numbers are small, the scientific contribution is substantial. There are no other animal models that are suitable for an array of research in areas such as cardiovascular disease, neurological conditions or reproductive health that could be used instead. The brain systems responsible for vision and control of skilled movements are far more sophisticated in non-human primates than in rodents, making the former necessary for some types of research that offer direct applicability to human patients. Moreover, it remains the case that non-human primates play an invaluable role in helping to develop new responses to intractable diseases. For example,

- The rapid development of COVID-19 vaccines has only been possible through using macaques.[xii] These vaccines will undoubtedly save millions of lives as well as reduce severe morbidity.
- Thirty years ago, HIV was effectively a death sentence. However, the development of antivirals has meant HIV can effectively be managed to prevent development of AIDS, saving thousands of lives, and preventing thousands of additional infections. This development has only been made possible by using non-human primates in medical research. It would not have been possible to make these advances by other means because of the characteristics of HIV infection are specific to humans and some other primates.

Given that it is clearly the case that medical research with non-human primates remains necessary, reducing Australian investment in research using these animals would mean that this activity would move overseas, where standards cannot necessarily be monitored, and might not meet the world-class standards maintained in Australia.[xiii]

6 Terms of reference C: the availability, effectiveness and funding for alternative approaches to animal research methods and technologies, and the ability of researchers to meet the 3 R's of Replacement, Reduction and Refinement;

6.1 The embedding of 3Rs in the research process

Over the last decade there has been significant growth in the size of Australia's medical research sector. As has been noted earlier in this submission, this growth has not been matched by corresponding growth in the number of animals used for medical research. This has been achieved in part through the continued use of the 3Rs – replacement, reduction, and refinement – in research design. At every step in the process researchers are required to consider alternatives and adjust methodologies to reduce the number of animals needed. The 3Rs are firmly embedded in the ethical guidelines that cover the use of animals in medical research, and this approach is strictly enforced by animal ethics committees during the application process.

6.2 Investing to developing alternative non-animal methodologies

Most alternative research methodologies have been developed overseas through government investment. An example of this investment has been the research funded by the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research. Since 2004 over £48 million has been invested in research to replace animals in research.[xiv] There is no corresponding investment being made in Australia into research to develop alternative methodologies. The NSW Government should consider specific funding initiatives that can help develop alternative methodologies that replace or reduce the number of animals used in medical research. The medical research community would strongly welcome such an initiative.

Recommendation

2. The NSW Government should fund initiatives that can help develop alternative methodologies to replace or reduce the number of animals used in medical research.

6.3 The current limitations of non-animal methodologies

Some recent developments provide alternative solutions to reduce the number of animals in research.[xv] This includes human simulation models, 3D culture of cells and tissues that replicate organ structures, and CRISPR technology. The latter being a new technology that can be used to edit genes.

While there have been scientific and methodological developments that provide alternatives to the use of animals in research, the point at which animals no longer need to be used has not yet been met.[xvi] Scientific advances are not sufficiently advanced or able to cover the range of techniques that would allow for the replacement of all animals in research. At present, the limitations on the usefulness and effectiveness of alternative approaches means that we are still some way off being able to reliably replace animal studies. It is notable that the EU scientific organisation that validates alternative methods to animal testing, EURL ECVAM, has approved just 50 alternative methods in the last 25 years.[xvii]

At present, alternatives techniques have not sufficiently developed to the stage that they can fully replace animals in all areas. For example, studies of neurological and mental health conditions deal with what is likely the most complex system in nature (the brain), and we are nowhere close to full understanding all parts of this organ and how they interact with each other and with the rest of the body. Further knowledge needs to be obtained before

computer-based simulations can become realistic. Furthermore, it is likely that some non-animal methods might still need to be validated in animal models, and there are areas of basic and behavioural research which are unlikely to ever be completely replaced.

7 Terms of reference E: the adequacy of the current regulatory regime regarding the use of animals in medical research, particularly in relation to transparency and accountability;

7.1 A well-developed and effective regulatory regime

The current regulatory regime regarding the use of animals in medical research is well developed and effective. It ensures the highest animal welfare standards, while also ensuring animals are only ever used in medical research where there is no other viable alternative.

There are two national guidelines produced by the NHMRC which govern the use of animals in research. These are the *Australian Code for the care and use of animals for scientific purposes*[xviii] (the code) and the *Principles and guidelines for the care and use of non-human primates for scientific purposes*.[xix] In addition to this legislation in New South Wales specifically governs the use of animals in research through the *Animal Research Act 1985 (NSW)*.

The *Australian Code for the care and use of animals for scientific purposes* has been incorporated into animal welfare legislation in states and territories.[xx] This Code was developed through consultation with stakeholders and sets standards which exceed those in most other countries. The Code provides an ethical framework and governing principles to guide decisions for those involved in using animals in research. The Code provides principles which must be followed by researchers, animal carers, institutions, and those involved in animal ethics committees.

The *Principles and guidelines for the care and use of non-human primates for scientific purposes* stipulates researchers must, wherever possible, obtain non-human primates from the national breeding colonies. Researchers are responsible for ensuring the documentation of the source of every non-human primate and the assessment of its clinical history and health is kept with the animal and is kept up to date. If any animals are imported by a researcher for NHMRC funded research, then the NHMRC Animal Welfare Committee must be notified after the relevant animal ethics committee has provided approval. In addition to this, permission from the relevant Commonwealth regulator must also be obtained.

7.2 The important role of animal ethics committees

Under the Code, each research organisation, which includes medical research institutes, is required to maintain an animal ethics committee. Before any research with animals can be undertaken approval must be provided by this committee. This is a process that takes many months both in terms of application and assessment. The committee's membership must include people from different backgrounds. This includes a veterinary scientist; a person with substantial experience of the use of animals in research; a person with a commitment to the welfare of animals that is employed by or otherwise associated with an institute and who is not involved with animal research; and an independent person who does not have a scientific background and who has never been involved in the use of animals in scientific or teaching activities.

Applications to the animal ethics committee have to demonstrate that the 3Rs have been considered in the research design. The members of these committees undergo training as part of their accreditation.

7.3 Ensuring animals are only used for research projects with the highest chance of success

The primary funder for medical research in Australia is the NHMRC. At present, limited funding and a rigorous assessment process leads to only around 10% of funding applications being funded each year. The assessment process sees research proposals assessed by experts (through peer review) and proposals are then subsequently ranked. Given the rigorous process used by the NHMRC it is reasonable to assume that any NHMRC funded research involving the use of animals is of the highest quality and has the greatest potential ultimately to bring about positive impacts for the community.

7.4 Transparent and open reporting of the use of animals in research

There is a high degree of transparency with respect to the use of animals in medical research. Each year the NSW Department of Primary Industries (DPI) collects data on the number of animals used in research (including medical research). Using this data, the DPI produces a comprehensive report which outlines the number of animals used and for what type of research, the purpose of the research, the species used, what procedure was undertaken, as well as the fate of the animals used. This report is published annually and can be downloaded from the Animal Ethics Infolink website.[xxi]

The medical research institute sector is committed to even greater transparency. AAMRI has been working with the Australian and New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART) to develop an 'openness agreement' which is expected to launch this year. Mirrored on developments in the UK, New Zealand and elsewhere, the openness agreement asks signatories to:

1. Be clear about their involvement in the use of animals in research or teaching.
2. Enhance communications with the media and the public about the use of animals in research or teaching.
3. Be proactive to in providing opportunities for the public to find out about research or teaching using animals.
4. Provide an annual summary of efforts to improve openness in the use of animals in research or teaching.

8 Terms of reference F: overseas developments regarding the regulation and use of animals in medical research

8.1 The use of animals in medical research continues in all comparable scientific nations

All major and comparable scientific nations continue to permit the use of animals in medical research. This is because having examined the evidence they have come to the same conclusion: there is not yet any other viable alternative that can deliver the same scientific and improved health outcomes.

Recently the European Parliament expressed a desire to move away from the use of animals in research. The European Commission subsequently investigated the feasibility of such a move and found that across a range of research domains, including medical research, that such an approach is not yet feasible.[xxii] Viable alternatives to using animals in research simply do not exist in most areas.

8.2 Investing in the 3Rs

The UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) was established in 2004 to increase the focus of the 3Rs in the research sector.[xxiii] This organisation not only promotes the use of the 3Rs but actively funds research that has the potential to lead to a reduction in the use of animals in research in the future. In addition to this, they also provide educational materials for researchers and help funders improve their review processes. Australia could benefit from developing a corresponding body that could help develop the new tools and techniques required to make further progress against the 3R goals.

Recommendation

3. In conjunction with the federal and other state governments, the NSW Government should establish a National Centre for the Replacement, Refinement and Reduction of Animals in Research.

8.3 Public support for the use of animals in medical research.

In February 2022 there was a national referendum in Switzerland on whether to ban the use of animals in research. The result of the referendum showed that 79% of the population was against such a ban, and only 21% were in favour.[xxiv] This is the fourth time people in Switzerland have voted in a referendum against introducing a ban on the use of animals in research.

In 2018 research by polling company IPSOS commissioned by the UK Government has found that about two-thirds of the public are in favour of using animals in medical research where there is no other alternative approach, with only 19% against.[xxv] These figures have held steady since 1999 when IPSOS started researching attitudes towards animal research.[xxvi]

These findings of support for the use of animals in medical research are also reflected in recent research in Australia which shows when the context is explained about how mice are used to provide personalised cancer care there is support from survivor, patient, and the broader community.[xxvii]

9 Terms of reference G: any other related matters.

In this section AAMRI provides the committee with three case studies showing how animals have been used in research to help develop new treatments for patients. Without the use of animals, patients would not be able to access new life-saving therapies.

9.1 Case study 1 – ZERO Childhood Cancer study

The ZERO Childhood Cancer study is a comprehensive personalised medicine program being delivered in New South Wales for children and young people with cancer. As part of this study, researchers engraft tumour samples from high-risk cancer patients in mice to create avatar models. The researchers then use these individualised models to test potential therapies based on the tumour's unique genomic and drug sensitivity profile.

The results of this research are then discussed by an expert team and form part of the personalised treatment recommendations for the patient. The researchers have found that inclusion of this approach

- can provide independent proof of drug efficacy suggested by molecular analyses of the tumour,
- can identify treatment options that would not otherwise have been considered,

- and help avoid the use of ineffective treatments.[xxviii]

The research directly benefits human health by providing individualised treatment options for high-risk child and young adult cancer. These cancers have low survival rates and limited treatment options. The research also benefits human health through the development of high-quality animal models of high-risk cancer that can be subsequently applied to identify promising new therapies prior to their testing in clinical trials.

As part of the research, the researchers have consulted with patients, family and community to understand the acceptability of this research and have found significant support for the approach.[xxix]

Modelling in laboratory animals is currently the most rigorous approach to generating drug sensitivity data to inform patient treatment. Testing therapies requires that tumours are actively growing in an environment that is as close as possible to that of the patient, that drugs are in their active form (which sometimes requires metabolism in an organ), and that measures of drug response can be analysed and interpreted in a way that is analogous to that of a patient. These requirements cannot current be satisfied without the use of animal models while retaining confidence in the data that informs patient treatment.

9.2 Testing novel anti-cancer immune cellular therapies

Researchers in New South Wales are using mice for the testing of novel anti-cancer immune cellular therapies. The project will help determine whether the candidate drugs can cure cancer in mice transplanted with human cancer cells. The projects are part of the Sydney Children's Hospital Network's growing cellular therapeutics program, designed to propel the next generation of innovation in treatments for childhood cancer. If successful, these projects will form the foundation for a phase 1 clinical trial in humans to assess the safety and efficacy of administering novel cellular therapies in adult and paediatric patients with high-risk malignancies.

This work is being undertaken in the context of the research team's already successful translational cell therapy program which includes currently active clinical trials for B cell leukaemia and lymphoma, the only home-grown chimeric antigen receptor (CART) T cell trials of their kind in Australia.

The use of mice is essential to achieve the aims of the research project. The researchers have previous shown that long-term experiments demonstrating the durable cancer remission induced by some cellular therapies predict clinical performance of these therapies.

Although in vitro testing can potentially allow the researchers to reduce the number of mice needed for in vivo testing, severely immunocompromised mice transplanted with human cancer cells and in particular, patients derived cancer cells (patient xenografts, PDXs) is the best model that allows long-term analysis of novel anticancer treatments. These mouse models are the best platform for analysing and optimising cell therapies, since it can screen different cell therapy-based treatments in specific preclinical settings, study potential improvements to guide technical and clinical development of cell therapies, study the heterogeneity in patient responses and mechanisms of resistance to cell therapy, and test combination therapies to improve clinical outcomes.

9.3 Advancing our understanding of the immune system

Researchers in New South Wales are working to understand the parameters that determine the balance between tolerance and immunity in the liver, an organ known for its ability to induce tolerance. The researchers are using unique transgenic mouse models as well as advanced imaging technology and flow cytometry technologies to dissect how T cells

interact and are instructed by hepatic cells in both the healthy and diseased or transplanted liver. More recently, the researchers have extended their work to look at liver macrophages.

The research has important benefits for human health.

Firstly, the characterisation of the underlying mechanisms regulating intrahepatic immunity will inform the design of new approaches to interfere with this process, resulting in better clinical outcomes.

- **Tuning up immunity would benefit vaccination outcomes.** Boosting immunity by optimising immunisation protocols would improve the efficacy of vaccines against liver topic pathogens causing viral hepatitis and malaria.
- **Tuning down immunity would benefit transplantation and gene therapy**. Conversely, harnessing the "liver tolerance effect" in transplantation to enhance specific allograft tolerance would be expected to prolong the survival of liver transplants but also attenuate the allograft response to non-hepatic transplants. The same strategy might also allow acceptance of transduced cells after gene therapy.

Secondly, advancing our knowledge of liver resident macrophages and of T cell activation in this organ would help understand their contribution to inflammation and fibrosis during chronic liver diseases.

The immune system is dynamic and involves multiple cell types recirculating in different organs that have varying properties. For example, in the case of the liver, it is believed that it is the architecture of the organ itself that is essential to the immune properties of this organ. Given the complexity of the immune system, it is also necessary to study the immune system in an intact organism.

The confined environment of in vitro culture experiments is extremely limited in aiding understanding of complex interactions involved in the immune system. Furthermore, cell cultures do not allow for the study and development of diseases or tolerance. It is not feasible to analyse the immune system of humans in vivo. The initiation, development, and resolution of immune responses to liver antigens cannot be addressed in clinical studies that provide only a snapshot of the patient's immune status. Therefore, at present, there are no alternatives to using animals in this research.

[i] Nuffield Council on Bioethics (2022) *The ethics of research involving animals*. Available at: https://www.nuffieldbioethics.org/publications/animal-research#:~:text=The%20ethics%20of%20research%20involving%20animals&text=Research%20involving%20animals%20has%20been,This%20is%20overly%20simplistic.

[ii] Wendy, J. (2021) Sixty years on: the history of the thalidomide tragedy. *Understanding Animal Research*, 2 December 2021. Available at: https://www.understandinganimalresearch.org.uk/news/sixty-years-on-the-history-of-the-thalidomide-tragedy/

[iii] Mullard, A. (2018) "How much do phase III trials cost?". *Nature Reviews Drug Discovery,* 17(177). Available at: https://doi.org/10.1038/nrd.2018.198

[iv] KPMG (2022) *Economic Impact of Medical Research*. Available at: https://www.aamri.org.au/resources/reports/kpmg-medical-research-delivers-roi/

[v] Information on the implementation of 3 Rs in Australia can be found at NHMRC (2019) *Information Paper: Implementation of the 3Rs in Australia*. Available at: https://www.nhmrc.gov.au/research-policy/ethics/animal-ethics/3rs

[vi] NSW Government, Department of Primary Industries (2019) *NSW 2019 Animal Use in Research Statistics*.

[vii] Australian Government, Department of Industry, Science, Energy and Resources (2021) *2021-22 Science, Research and Innovation (SRI) Budget Tables*. Available at: https://www.industry.gov.au/data-and-publications/science-research-and-innovation-sri-budget-tables

[viii] European Commission (2021) *Summary Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union and Norway in 2018*. Available at: https://ec.europa.eu/environment/chemicals/lab_animals/pdf/SWD_%20part_A_and_B.pdf

[ix] European Animal Research Association (2021) Press release: EU statistics for animals used in research 2018. Available at: http://www.eara.eu/post/biomedical-research-sector-welcomes-the-eu-wide-figures-on-the-number-of-animals-used-in-research

[x] Speaking of Research (2022) *US Animal Research Statistics*. Available at: https://speakingofresearch.com/facts/statistics/

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