Submission No 219

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

Organisation: Garvan Institute of Medical Research

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Garvan Institute of Medical Research

GARVAN INSTITUTE OF MEDICAL RESEARCH (GARVAN) SUBMISSION IN RELATION TO THE PARLIAMENTARY INQUIRY INTO THE USE OF NON-HUMAN PRIMATES AND OTHER ANIMALS IN MEDICAL RESEARCH

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1. *INTRODUCTION AND BACKGROUND*

The Garvan Institute of Medical Research (Garvan) is an accredited medical research establishment authorised to use animal models for research and teaching purposes by the NSW Department of Primary Industries (DPI). The Garvan also holds an animal supplier license, to breed and supply laboratory mice, at the Australian BioResources (ABR) facility located in Moss Vale. The Garvan uses rodents and zebrafish for biomedical and clinical research.

Garvan's Animal Ethics Committee (AEC) is the committee established by the Garvan Board of Directors for reviewing and overseeing animal usage in research and teaching at the Garvan Institute of Medical Research, St Vincent's Hospital, The Kinghorn Cancer Centre. The AEC fulfils all the operational and governance requirements of the NHMRC and the NSW State Government.

The AEC meets every month to review submissions from investigators who wish to carry out studies with animals in the Biological Testing Facility (BTF), the BioCORE and Australian BioResources (ABR). Additional subcommittee meetings or inspections are held on average every other month as a standard practice. The AEC, whose membership includes veterinary, scientific, animal welfare and lay representatives, also provides ethical advice on standards of animal care, welfare, and housing. The AEC is committed to the principles of reduction, refinement and replacement and ensures that the use of animals is justified, taking into consideration the scientific or educational benefits, and any potential effects, on the welfare of the animals.

The Research Ethics, Governance and Integrity team provides secretariat support to the AEC, and supports researchers with education about the limitations of, and good practice in, animal research design. Garvan's Animal Welfare Officer monitors animal wellbeing and provides researchers with training in animal handling techniques.

2. *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.*

Animal models used in medical research, in NSW, typically fall within 2 broad categories – to advance basic science or for use *in vivo* animal trials to examine preliminary drug efficacy,

toxicity and pharmacokinetics. Early *in vivo* studies examine safety, which helps researchers determine whether a candidate drug has scientific merit to justify further development.

Garvan has an international reputation in excellent medical research outcomes across many research disciplines ranging from cancer, immunology to rare genetic diseases. Much of the success can be attributed to the role laboratory animals play in the building blocks of scientific knowledge advancement. The Garvan's position is that of a utilitarian one underpinned by animal welfare. It is with considered, intelligent and respectful use of laboratory animals that groundbreaking work, including scientific inroads into SARS-COV2 (Covid) can advance. Please refer to **Appendix A** for a curated list of recent and proven success outcomes from Garvan. **Garvan supports responsible animal research.**

Use of laboratory animals is vital to medical research as current technology is not advanced enough to completely replace live animals for some aspects of research, particularly those that investigate complex physiological interactions and live tissue or cell mechanics. However, efficiency and efficacy in using animal models relies on intelligent planning of experimental design and on being honest about, and cognizant of, the limitations animal models pose. Animal models are useful in providing *in vivo* information that can complement in vitro systems but may not always be useful in providing direct translational data between species. Therefore, education must play a role in enabling sound experimental designs that truly incorporate the essence of the 3Rs — replacement, reduction and refinement. The Research Ethics Governance and Integrity team and AEC provide tailored advice to researchers to help ensure animals that are destined for research purposes are used in a sensible, responsible and respectful manner that balances the animals' sacrifice and the research output.

Intelligent study designs also rely on multi-disciplinary and AEC collaboration. A biostastician, for example, can advise on sample sizes and smaller pilot studies to reduce unnecessary animal sacrifice, while veterinarians and animal welfarists can focus on the latest advances in animal care, husbandry and clinical support to refine the study better to improve animal welfare. The fundamental driver of meaningful use of animals for research is collaborative communication. The administration and practice related to the use of laboratory animals in research has a very significant impact, and is likely the main cause of variation between different establishments. Promoting and inculcating a research culture of respectful animal use is vital.

Complete eradication of laboratory animal models is not a viable option as this will expose gaps in research elements that simply cannot be addressed using *in vitro* or computer modelling methods. Furthermore, without preliminary pharmacokinetic and safety testing in animal models, any drug, vaccine, device, or treatment development will have to rely exclusively on human participants. Notwithstanding the human ethics and safety challenges this situation will pose, progress will likely be stymied by inadequate recruitment of willing study participants in the first instance. This becomes a bigger issue of research progress versus recruiting enough willing long term study participants or patients, as well as peripheral but associated matters such as insurance, indemnity and funding. Additionally, by ceasing all animal research locally, researchers may be forced to move animal studies offshore beyond NSW jurisdiction and oversight, and potentially subject animals to less stringent regulation, safety and welfare measures. This will inadvertently feed into a cyclical ethical issue.

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Use of laboratory animals, particularly in well characterized and genetically annotated species like rodents, is also a form of global scientific language, and subjected to peer review standards. Genetically engineered mouse models form a foundational framework where many global collaborations share the same stage. Researchers across the world understand the scientific and clinical significance as well as interpretation whenever a particular strain or line of mice is used for a study. Completely eliminating use of all laboratory animals for research in NSW would drastically impact global scientific collaboration opportunities.

There is also the concept of 'One Health', which refers to the approach that scientific advances made possible through use of animal models to enhance human quality of life, can also be extrapolated to improvements in veterinary medicine to benefit other animal species including livestock and companion animals. Companion dogs and cats, for example, share the same suite of chemotherapy drugs for treatment of cancer.

The Garvan is in a unique position where laboratory animals have been used to provide tailored therapy for human patients suffering from conditions such as cancer to rare genetic diseases. One such example is the use of patient derived xenograft models whereby a biopsy of a patient's tumour is implanted and grown in a cohort of mice. The mice are then subjected to various chemotherapeutic combinations to assess efficacy which can guide treatment specifically for that individual patient. Similarly, through use of technologies such as CRISPR gene editing, mice models can be used to interrogate and find treatment for rare genetic diseases in human patients. With rare genetic diseases, there may be too few patients globally to initiate studies exclusively in human participants. Please refer to **Appendix B and C** for further examples.

Ultimately, animal models are used because different species possess special traits that allow rapid longitudinal study. For example, the generational lifespan of a mouse compared to a human is much shorter and their heightened metabolism allows for study of disease progression and treatment efficacy in a much shorter time. Other species like the zebrafish is prized for the translucency/transparency of their bodies allowing almost a direct visualization of real time organ development. Species like the axolotl have the ability to regenerate lost limbs and these unique traits provide insight into medical science in areas of tissue regeneration and repair. Because of unique species traits, a way to reduce and refine animal studies is to identify and use the most suitable animal model species, including selecting optimal genetically modified strains and lines, for a specific study. This will lead to the most efficient study outcome. However, current availability of certain species such as genetically modified and specific pathogen free rabbits, guinea pigs and pigs, remain limited locally compared to the USA and Europe, and contributed indirectly to inefficient animal use, particularly when less ideal species had to be used instead.

Public health risk from using laboratory animal species is low. Facilities that house laboratory animals are specific pathogen free and subjected to stringent regulation and inspection scrutiny. Biocontainment and quarantine practices are enforced to ensure that there is no disease spread within the facility and also to ensure animal models provide a clean canvas for scientific interpretation. Animals that are sick present with variability that confounds study data. Staff working with animals is also specially trained and vaccinated. Transgenic animals never leave the facility and so cannot cause ecological impact.

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3. *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;*

There are significant costs involved at all stages of animal research. However, the benefits of medical research advancement outweigh the financial costs. Moreover, animal research also creates local jobs and attracts skilled workforce and balances out the economy in other ways. A robust medical research industry also attracts both domestic and international students to pursue higher education locally in NSW, contributing to an enriched higher education sector.

With the announcement of the imminent closure of the animal resources centre in Perth (https://www.nature.com/articles/d41586-021-01896-x), it is anticipated that due to shortfall in laboratory animal supply that prices may rise further. Further government support and resourcing in this sector will help ensure prices remain stable and affordable for future research.

4. *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;*

Australia is lagging behind the USA and Europe in supporting alternative approaches to animal research methods and technologies, partly due to lack of government resourcing, funding and centralizing of such services. The educational seminars that were conducted by NSW DPI ceased about 5 years ago. Reinstating the NSW DPI seminars would help promote the 3Rs by driving active campaigns.

Many of the current opportunities available are smaller scale and initiated at the grassroots level by nonprofit organisations and special interest groups. Although these independent societies illuminate the path towards some practical alternatives and encourage discourse and step change initiatives, they do not have the capacity to cater to the entire medical research sector. Local organisations such as MAWA (http://www.mawa-trust.org.au/) , ANZLAA (https://www.anzlaa.org/) and ANZCCART (https://anzccart.adelaide.edu.au/) as well as international organization such as UFAW (https://www.ufaw.org.uk/) and FELASA (https://felasa.eu/) provide some level of competitive grants, conferences and educational support services to bring the animal research community together. However, not all medical research organisations are in the same position to invest as some initiatives are cost prohibitive.

Technologies such as tissue 3D printing can be helpful but again these technologies may not be cost effective for some organisations. A central government funded resource that shares such facilities would greatly aid in encouraging the 3Rs. The Australian Government has an obligation as part of the international scientific community to fund research and development of new alternatives, which would stimulate the overall push for increased industry, technology and discovery agenda in Australia, while also supporting an initiative with greater societal value.

5. *THE ETHICAL AND ANIMAL WELFARE ISSUES SURROUNDING THE IMPORTING, BREEDING AND USE OF ANIMALS IN MEDICAL RESEARCH;*

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Animal welfare is a continuously evolving area that indicates commitment by the industry in ensuring high standards of animal care. Animal ethics committee members, animal care staff as well as researchers undergo continuing education to upskill and upgrade their knowledge. Training requirement is mandatory, rigorous and involve dedicated learning and practice.

In terms of animal breeding, advances such as CRISPR technology, cryopreservation of sperm and embryos and other breeding approaches such as ultra-ovulation are strategies to minimize excessive breeding and are commonly used. Proposals that animals be used for research purposes are closely scrutinised by the Animal Ethics Committee and are guided by the Australian Code for the Care and Use of Animals for Scientific Purposes, and are subject to both internal and external audits to ensure compliance.

Even though animals cannot be used in research unless the protocol meets the rigorous test of the 3Rs, future revisions in the Code can be made around incorporating the five freedoms – freedom from hunger and thirst, discomfort, pain/injury/disease, ability to express normal behavior and from fear and distress as a standard baseline and justified if needed variation. The future of animal care should address mentation/stereotypic behaviour more routinely than the current emphasis on physical conditions.

Openness In communicating animal model-based research could also contribute to an improved ethics and welfare culture and promote greater understanding by the general public. ANZCCART is initiating an openness agreement project where research institutes can sign up to be part of a cultural drive to communicate openly and honestly about animal research.