Submission No 233

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

Organisation: Western Sydney Local Health District (Animal Ethics Committee)

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Professor Wayne Hawthorne
Chair, WSLHD Animal Ethics Committee
Dr Ross Matthews
Executive Officer, WSLHD Animal Ethics Committee

WESTERN SYDNEY LOCAL HEALTH DISTRICT
ANIMAL ETHICS COMMITTEE

29th March 2022

Hon. Greg Donnelly
Chair of Portfolio Committee No.2 Health
Legislative Council
Parliament of New South Wales
Macquarie Street, Sydney NSW 2000

RE: Response to Inquiry into the use of primates and other animals in medical research in New South Wales

Dear Hon. Greg Donnelly and Committee members,

This response to the parliamentary inquiry into the use of primates and other animals in medical research in New South Wales, is lodged on behalf of the Western Sydney Local Health District Animal Ethics Committee (WSLHD AEC). Our Animal Ethics Committee (AEC) oversee and provide counsel on all animal ethics matters relating to research utilising non-human primates and other animals across the Westmead Health Precinct that encompasses the Western Sydney Local Health District (WSLHD), Westmead Institute of Medical Research (WIMR), the Kids Research Institute, Westmead Children's Hospital and the Children's Medical Research Institute (CMRI).

We oversight and promote the ethical, humane, and responsible care and use of animals for scientific purposes on all active animal research projects for the many thousands of research staff on the campus as legislated by the Animal Research Act 1985 No 123 and Animal Research Regulation(1). We work to the Australian Code for the Care and Use of Animals for Scientific Purposes (2).

Our AEC, like all others in NSW, is responsible for approving and monitoring research within our Accredited Animal Research Establishments. We regularly perform inspections of animals actively involved in medical research studies and the research facilities in which the animals are housed. Our AEC provides avenues for public participation in the regulation of animal research by having several lay members of the local community as members of our AEC Committee, and by providing yearly animal use statistics to the Department of Primary Industries (DPI). No animal research on the campus can be carried out without our AEC review and approval. The AEC considers and evaluates applications to conduct research based on the researchers' responses to a comprehensive set of questions, including their justification for the research with reference to any work in the same field, its likely impact on the animals, care of the animals including environmental enrichment and care,

along with the procedures for preventing or alleviating any pain and or distress. NO activity can be undertaken at any time without AEC review, approval, and oversight. The AEC provide guidance and support to researchers on matters relevant to animal welfare through the provision of training, ethics and governance workshops, provision of guidelines and dissemination of relevant scientific literature. In addition, all genetically modified animals have additional regulation via the Institutional Biosafety Committee (IBC) under the federal Office of the Gene Technology Regulator (OGTR). The secretary of the WSLHD IBC sits as a non-voting member of the AEC to provide oversight and advice on all transgenic animals or projects proposed.

In reference to the use of non-human Primates (NHPs), there are additional levels of scrutiny, oversight and regulation as is appropriate. Our AEC oversights several NHP protocols. As background to the extremely rigorous oversight of NHP protocols we are but one AEC that must oversight these protocols. All protocols that utilise primates are reviewed and approved by multiple animal ethics committees that are separate and independent; when an AEC application comes to the WSLHD it must first have been oversighted by the AEC of Royal Prince Alfred Hospital, who oversight the Baboon colony. Subsequently, it must also be approved by the University of Sydney AEC and the WSLHD AEC report directly to the ARRP on these matters. Additionally, there is also oversight from the NHMRC non-human primate (NHP) committee that has responsibility for NHMRC funded projects using NHPs under the "principles and guidelines for the care and use of non-human primates for scientific purposes".

Regarding transparency, the membership and duties of an AEC are outlined in the Animal Research Act 1985 (2)), which also provides guidance on how AECs should operate. Our AEC holds regular inspections of the animal holding facilities across the Westmead campus and reports the proceedings of the AEC annually to the Chief Executive Officer of the WSLHD. This report is also reviewed by the Animal Research Review Panel (ARRP).

As a committee that oversights all animal research across our large campus, we believe we have sound oversight and comprehension of what animal research encompasses and the huge number of benefits that it provides to research, patients, veterinary treatments and the broader community. We see the great importance of animal research in improving patient outcomes for many diseases and health conditions, improving the safety and efficacy of new therapies and technologies, improving our understanding of diseases, their causes and how to prevent or to cure them! Without animal research our understanding of disease would be severely diminished, the introduction of new therapies severely curtailed, and an unreasonable burden and risk placed on sick, vulnerable and desperate patients who will either have their medical needs unmet or face an increased risk to inadequately tested therapies which may be put forward for clinical trials without thorough safety and efficacy testing in pre-clinical models. We suggest that appropriately governed and oversighted animal research provides significant benefits that can NOT be achieved in any other way.

In reference to the specific questions raised we provide the following responses.

(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.

The broader areas of research undertaken on the Westmead campus include studies into cures and treatment strategies for patients suffering major and chronic diseases. This included the broader categories of cardiac, renal, liver, diabetes, neurological, vision, immunological, allergic, infectious, degenerative, deficiencies, haematological, and inherited disorders. Multiple research protocols are also based upon the treatment of Diabetes through islet transplantation, gene therapy and Vitamin D treatments. There are far too many studies that have provided successful outcomes from the research that has been translated to cures or clinical treatments for patients to put them in this submission. However, by providing a broad example of these successful outcomes we can say that

hundreds of individual cures, treatments, or prevention strategies have been developed and translated to the clinic to save, assist, or cure these sick patients.

Some examples of notable medical research studies, include cardiac scar modulation and regeneration, ventricular arrhythmia and engraftment of stem cell derived cardiomyocytes from the Centre for Heart Research. In Ophthalmology, studies on the treatment of corneal neovascularisation and increasing corneal graft success. The Storr Liver Centre is continuing to investigate liver cancer and diseases including hepatitis and non-alcoholic steatohepatitis. Renal researchers are investigating kidney disease such as acute and chronic renal failure and autosomal dominant polycystic kidney disease (ADPKD).
Other research has focused on cancer treatments, therapeutic device testing (cardiac catheter development, and the evaluation of new single dose COVID vaccine.

A more specific example of direct translation is that of transplantation to treat or cure various diseases. In Australia there are 1,850 patients waiting for organ transplants with only 421 organ donors last year and this imbalance means many patients may wait many years for a transplant. Development of the various health strategies can help prevent or slow the progression of their diseases and thereby hopefully provide an acceptable quality of life. An example of this is for those patients suffering from various forms of diabetes and kidney disease requiring a transplant. Researchers have developed new strategies on how to better retrieve donor organs, biopsy and/or detect rejection, diagnose changes to the graft, prevent long term damage to the graft, extend the life of the graft and ultimately change the quality of life these patients have. They have studied and developed how to transplant patients with type 1 diabetes and kidney failure curing their diabetes and kidney failure by transplantation of simultaneous pancreas and kidney transplants (SPK). This has developed into a national program that has been Federally funded for decades, treating more 600 patients with SPKs (3).

Additionally, on the background of additional animal research work they have developed new treatments for a sub-population of patients suffering from brittle type 1 diabetes who die from their disease due to an inability to detect low blood sugar levels. Again, a national program has been developed to treat these patients and the Islet cell transplantation unit has performed more than 300 pancreatic islet cell isolations for human patients after being developed in small and large animal models. This technology, identified and perfected in animal models, now saves and improves the quality of life of the children and adult patients that we transplant. This is also a federally funded transplant program from the National Funded Centres program.

However, they still can't transplant the large number of patients quickly or effectively enough and many will die while on the waiting lists. Using xenotransplantation, medical research scientists can potentially provide another source for transplantation and our studies have resulted in gaining valuable insight into the organ rejection process which provides major advances towards the clinical application of xenotransplantation as a solution to the organ shortage crisis in human patients. Here at Westmead, researchers have continued to develop treatments for such patients. Within their NH&MRC program they have developed a new technology which is being tested in NHPs (4). Research outcomes produced within our facilities have demonstrated the feasibility of utilising genetically modified pig neonatal islet cell clusters to cure diabetes. This is the first such study with success in producing long-term functional islet graft survival, in the very difficult to maintain preclinical model. Globally, no other study has been able to produce normoglycemia in this model, let alone for extended time periods up to two years post-transplant. This clearly demonstrates the utility of using transgenic neonatal islet cell clusters and clinically relevant immunosuppression to treat the many patients suffering from type one diabetes. This novel research could potentially benefit the millions of diabetic patients with this new technology. In addition, when viewed from a fiscal perspective and a health services perspective, the reduction of diabetic patient needs would be incredibly large reducing the health care budget by hundreds of millions of dollars in NSW and Australia.

There are limited public health risks associated with the research undertaken as all work is appropriately oversighted in appropriately designated and designed facilities. Prior to any studies they are examined by the AEC, IBC, and safety committees. Additionally, the facilities are either PC2 (Physical Containment level 2) or BC2 (Biosafety Containment Level 2) biocontainment facilities. All staff working in the PC2/BC2 facilities are trained and accredited, with strict adherence to PC2/BC2 procedures and standard operating procedures on cleaning and maintenance of the facility. The BC2 facility at Westmead passed the audit by the Department of Planning, Industry and Environment in September 2021. The work is also very well oversighted by not only the animal ethics but also for projects involving gene therapy or genetic modification by the Institutional Biosafety Committee (IBC), Office of the Gene Technology Regulator, Dept of Health) and safety committees. The health risks to our wider community are reduced through these highly regulated and policed processes.

(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.

We acknowledge there are costs associated with the use of animals in medical research, however, we would counter this point by highlighting the massive economic and health benefits that may ensure from medical research that substantially outweigh any economic cost incurred.

A good example of these costs are the extraordinary length of time it takes for a new treatment, drug or technology to enter clinical practice. This can be up to two decades, and many of the newer drugs such as the new line immunosuppressive agents for clinical trials in humans cost many hundreds of millions, even billions of dollars. Given the timeframes and costs involved only those drugs that stand the best possible chance of success can proceed to clinical trial. All of these have been developed and trialled in animal studies at several levels of testing. If these animal studies were not performed the safety and efficacy of these agents would not be known nor be able to be translated to patient treatments. Additionally, animal studies must be used to identify those drugs with the best chance of success and best safety profiles saving decades of unethical testing in human patients.

Medical research on our campus and in Australia is predominantly funded by government grants such as the NH&MRC grant, Medical Research Future Fund (MRFF) and CSIRO grants, etc. Additionally, research is also funded by not-for-profit organizations and private businesses. Most research programs undertaken across the Westmead campus are funded specifically by various grants from the NH&MRC, Cancer Council, National Heart Foundation, Juvenile Diabetes Research Foundation and several philanthropic organisations passionate about advancing science and medicine.

By testing new agents, techniques, and treatments for patients it gives everybody the best chance of a healthy life. Diseases and ill health in the population are a huge burden on society and the economy resulting in increased health and social care costs. In addition, locally conducted medical research underpins Australia's advancement to a smart country and helps drive the economy. Given the outstanding health and economic returns medical research delivers, it represents a worthy investment any government can undertake.

Most research animals (rodents) are bred in Australia at the Australian BioResources (ABR, Moss Vale) and the Animal Resource Centre (ARC, Western Australia). The WA government recently announced the closure of ARC on 2nd July 2021, a decision which will impact major universities, medical research institutes and large teaching hospitals. The WA government is trying to identify a new independent provider to deliver ARC services to its' clients. Additionally, the 2021 National Research Infrastructure Roadmap Exposure Draft (5)) revealed "the need for reasonably urgent

national consideration of animal model provision has been identified through Roadmap consultation."

(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.

There have been significant changes in the effectiveness of the 3Rs, as can be seen by the growth in the medical research sector with an associated decrease in the number of animals used for medical research. This has been achieved in part through the adherence to the principle of the 3Rs by researchers, institutions, and an overall effort by the research sector to apply the 3Rs. Additionally, by the incorporation of strict adherence to policies all AEC applications are evaluated in relation to the 3Rs and at every step in the process researchers are required to consider alternatives and adjust methodologies to reduce the number of animals required. 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 all AECs during the application process and through each project's lifetime.

Additionally, there are several other ways that alternate approaches to avoid using animals are being undertaken, starting with the use of simulators for training and teaching. Although, in stating this, their effectiveness and broader ability to provide realistic responses is not on par with that of animal models, but it is a starting point for junior students, general concept training or basic testing of devices, instruments or techniques. There are also several levels of peer review for any research project to be undertaken which means it is externally peer reviewed, is innovative and of high value. This also protects against unnecessary duplication. New technologies such as advanced imaging, advanced flow cytometry and high throughput genomics and proteomic have meant that more information can be obtained with smaller animal numbers.

The way in which individual researchers that we have spoken to are trying to meet the 3Rs:

Replacement

- Literature review to ensure animal studies are not replicated with existing studies/data.
- Alternative approaches to animal research methods, such as in vitro and in silico models are used by researchers over animal models.
- These methods although highly prominent, still have limitations compared to animal models. They cannot accurately mimic the complex physiological systems of humans and animals.

Reduction

- Through sharing excess animals (specifically, mice), cadavers, tissues, etc. with other researchers and databases.
- Requesting the minimum number of animals required to give the study sufficient statistical power, based on statistical analyse and review.
- Pilot studies also use less animals to determine if the experimental methods are sound before conducting a full study using more animals.

Refinement

- Monitoring animals, minimising pain, increasing quality of life.
- Ensuring all staff handling animals are competent, capable, respectful, and well trained in all aspects of animal care
- Consultation with the facility Animal technical staff including Veterinarian staff.
- Providing housing and environmental enrichment appropriate to the species held.
- Ensuring best practice when conducting surgical procedures (asepsis, pain management)
- Seeking consultation from experienced personnel (facility veterinarian/animal welfare officer)

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

From the perspective of the WSLHD Animal Ethics Committee, the AEC feels there are limited issues in the importing, breeding and use of animals in medical research. This is because the field is already heavily legislated and maintains regulated conditions for undertaking all these activities. Additional to the appropriate regulations and guidelines that we work under there are various inherent and purposely inbuilt mechanisms to oversight and police such activities. These commence at the level of the evaluation of the ethics applications as the AEC consists of Veterinarian, Researcher, Animal Welfare and lay individuals, who review and assess each new protocol, adverse event reports and annual reports to ensure high ethical standards are maintained throughout all animal research projects.

The Code (2) is an important ethical framework and its governing principles are used to guide decisions while providing significant oversight. Additionally, the widespread application of the principles of replacement, reduction, and refinement in scientific research undertaken on the campus adds to the minimisation of issues. To provide an extra level of support we have experienced and qualified Animal Care staff that provide the care and husbandry required by each species onsite. All staff raise welfare issues with the Director of the facility who is a registered Veterinarian. Animal care staff also report to the researchers at the sign of ill health of any animal/s. Animals are provided with environmental enrichment and social/flock animals are kept with companions. In addition, animals are monitored closely for any indicators of pain, discomfort, distress or illness, and where appropriate are humanely euthanised.

(e) The adequacy of the current regulatory regime regarding the use of animals in medical research, particularly in relation to transparency and accountability.

As an oversighting AEC we feel 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 potential 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 (the Code) (2) and the Principles and guidelines for the care and use of non-human primates for scientific purposes (6). 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 (6). 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; the assessment of its clinical history and health is kept with the animal and is kept up to date in the same detail as for human patients. 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.

Accountability

- Research institution, establishments, AECs and the individual researchers all adhere to the Animal Research Act 1985, Animal Research Regulation 2021 and the Australian code for the care and use of animals for scientific purposes.
- Annual Reporting to the Chief Executive of the Westmead Hospital on the number of projects, animal use, purpose, fate of animals etc.
- Annual Reporting to the Animal Research Review Panel (ARRP) under Department of Primary Industries. The animal use statistics are published yearly by the ARRP under the jurisdiction of the Department of Primary Industries.
- Inspections from ARRP, Auditing from ARRP every 3 – 4 years.
- Regular inspection of animals and animal research facilities by AEC members including Category C – Animal Welfare members.

Transparency

- The reporting of animal welfare issues, compliance, non-compliances, etc.
- Research findings are published and open to the public. Both positive and negative findings are published to avoid unnecessary repetition of experiments.

In summary, we believe that there should be high level accountability and transparency for animal research in Australia and encourage an openness to enable the general public to be more reliably informed regarding the use of animals in medical research.

(f) Overseas developments regarding the regulation and use of animals in medical research.

It is quite clear universally that all our internationally comparable scientific competitors continue to permit the use of animals in medical research. If we as a State and a Nation wish to remain internationally competitive in the medical research sphere, then we need to have the ability to still undertake cutting edge research with aspects of this being undertaken in animal research. These other countries have examined the evidence for undertaking animal research to provide cures and advance medical therapies and have shown there are no other viable alternatives that can deliver the same rigorous scientific appraisal of therapies and improved health outcomes.

A few examples of this are provided below;

The first example was developed in the United Kingdom where the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) was established almost twenty years ago in 2004 to help the research sector in its evaluation of the 3Rs. What they found was that animal research is essential and as such it now promotes the use of the 3Rs and actively funds the use of animals in research. In addition to this, they also provide educational materials for researchers and help funders improve their review processes. We would propose that the NSW state government or the federal government could benefit from developing a similar entity that could help develop the new tools and techniques required to make further progress against the 3Rs.

A further example was recently seen in the European Parliament as several member states 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. Viable alternatives to using animals in research simply do not exist in most areas.

Most recently, earlier this year the SWISS government ran a national referendum 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. This is the fourth time people in Switzerland have voted in a referendum against introducing a ban on the use of animals in research. We would suggest that if taken to a referendum in NSW or Australia that we would see

similar results as people realise the importance of animal research to the advancement of medical therapies and cures.

A very good example of this sort of amazing medical advances and direct translation of animal research to the clinical setting occurred on January 7th, 2022, in Baltimore, USA the XenoHeart team at the University of Maryland School of Medicine Led by Dr Muhammad Mohiuddin (President Elect, IXA) performed the world's first successful pig-to-human cardiac xenotransplant. The recipient had end-stage non-ischemic cardiomyopathy and he received a pig heart with 10 gene modifications. Permission for this procedure was granted under compassionate use by the FDA based upon outcomes of animal research data. This amazing advance was the direct result from years of medical research into Xenotransplantation using animal models, in particular the use of Baboons. This world-first is just the beginning of potentially reducing the organ-transplant shortage globally and could only have been done in testing in animal models (7).

The COVID-19 pandemic changed the way we all live. Positive results in testing for mRNA spike (S) glycoprotein of SARS-CoV-2 and the production of neutralizing antibodies for COVID19 vaccine in animal models lead to the clinical development of viable vaccines (8).
The results obtained from medical and biomedical research using animal models are crucial to the development of novel therapies and ensuring the safety, efficacy of treatments and to further our understanding of biological mechanisms of diseases.

It is essential that the New South Wales government have appropriate legislations which efficiently supports and regulates animal research. However, these legislations and regulations should not be increased to become overwhelmingly stifling of research or findings. By restricting the ability of surgeons, researchers and clinicians, the advances in medical sciences and in developing lifesaving treatments for our patients will be dramatically delayed, reduced and potentially stalled.

Please to contact us if you need any further information.

Professor Wayne Hawthorne
Chair, WSLHD AEC

Dr Ross Matthews
Executive Officer, WSLHD AEC

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