Submission No 227

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

Organisation: Kolling Institute

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30th March 2022
To The Hon. Greg Donnelly MLC
Committee Chair
Use of primates and other animals in medical research in New South Wales Committee
NSW Parliament House
6 Macquarie Street
Sydney NSW 2000

Dear The Hon. Greg Donnelly MLC,

RE: The Kolling Institute submission to the Inquiry into the use of primates and other animals in medical research in New South Wales

The Kolling Institute is Australia's and New South Wales' oldest and most established medical research institutes. From its humble beginnings as a cottage on the grounds of Royal North Shore Hospital, it celebrated its centenary in 2020 and continues to investigate, treat and address diseases that affect not only the local but national and global communities.

A joint venture partnership between the University of Sydney and the Northern Sydney Local Health District, the Kolling Institute is a research hub for researchers to conduct medical research alongside clinicians and patients in a health care environment. The Institute has over 140 researchers (100 FTE), 61 postgraduate students, and 47 support staff working in the three priority research areas of Cardiovascular and Renal, Musculoskeletal and Neuroscience and Pain. It also conducts research in Cancer and Maternal Health.

The research conducted by the Kolling ranges from laboratory (basic science) research to translating these discoveries for use in the clinical setting. Throughout the process, the need to determine the safety, effectiveness and efficiency of any discovery is of the upmost importance. This will ensure that the benefit of treatment to patients outweighs any risk. The use of primates and other animals to understand the mechanisms of disease is therefore a core element for the discovery of treatment to human diseases. For these reasons, the Kolling Institute is making its submission to this inquiry to stress the importance of the involvement of animals in medical research. It will refer to the terms of reference of the committee in its submission.

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 Kolling, similar to other NSW based medical research institutes, seeks to understand the cause of human disease and to determine treatment avenues to cure patients of the disease. In this discovery pathway, the need for animal models is critical, as the committee would appreciate, it is often unethical, arguably immoral

and potentially dangerous to conduct experiments on human subjects without initial experiments in animal models to demonstrate safety and efficacy.

Animal involvement in medical research has three main purposes; it allows insight into the progression of disease, the assessment of disease response and the evaluation of therapeutic interventions that halt the progression of disease. It also allows exploration of 'off-target effects', (i.e. side effects) that may preclude use in humans. Although we use tissue culture and organoid models where possible, determination of unexpected effects necessitates the use of whole animal models. In summary, animal modelling acts as proof of concept (evidence) to a research hypothesis which can then infer what humans may experience. This has been accepted as a basis of medical research as it is an effective means to model disease progression and treatment.

There would be more harm and risk to public health if animal models were not used. Clearly, it would be unethical and immoral to introduce disease or to test treatment on human subjects without providing evidence of how disease progresses or how it can be cured. In effect the use of animals allows us to define the mechanism of action of interventions and refine and target their use. Additionally, the level of evidence needs to be of statistical significance to determine its impact on the human population.

The research and development of vaccines in response to the COVID-19 pandemic demonstrates both the benefits and risk to public health if animals were not involved in medical research. To develop the vaccine, it required animals to be inoculated with the virus to determine disease progression and to then use the data to formulate the vaccine. The vaccine is tested in animals to determine response to treatment and side effects. Once the safety, efficiency and effectiveness of treatment is at an acceptable level in animal modelling, it can be approved to be tested in humans. Following further clinical trials, the vaccine proceeded to approval by regulatory bodies such as the Therapeutic Good Administration (TGA) in Australia. Animal modelling data is used as part of the TGA assessment. Without animal modelling, there would not be a vaccine available for COVID-19 and this would be a greater risker to public health.

Similarly, there have been discoveries made by Kolling researchers involving animals that have led to a better understanding of human health. A recent paper published by Professor Chris Little, Director of the Raymond Purves Bone and Joint Research Labs at the Kolling Institute discusses the use and impact of animal models to understand the disease mechanisms and develop therapies for osteoarthritis (Appendix A). Using such models Prof Little identified the enzyme responsible for cartilage breakdown and loss in osteoarthritis. This knowledge was used by pharmaceutical companies to develop new therapies, which then underwent mandatory evaluation in animal models to confirm safety and efficacy, prior to their testing in human clinical trials. In a similar approach, Prof Carol Pollock (another Kolling Institute researcher of world renown) was the first internationally to demonstrate the mechanism underpinning kidney protection with the use of Sodium-Glucose-Linked Transport SGLT (2) inhibitors in an animal (rat) model of diabetic kidney disease. These drugs are now the most highly capitalised drugs in the world, supporting people with diabetes, heart failure and kidney disease.

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

Animals involved in research are specially bred for research purposes. In the case of mouse models for example, some mice have been genetically modified to replicate specific human diseases by knocking out an existing gene or replacing it or disrupting it with a synthetic piece of DNA. Complex diseases such cancer, obesity and diabetes can then by studied.

When funding applications, whether it be to a Commonwealth or a NSW research funding agency, are submitted, the type, number and cost of the animal model are included. Therefore, both the NSW and Federal Governments are indirectly funding the use of animals for medical research purposes through the awarding of funding applications. The use of animals in such research can only occur with approval by a NSW government registered Animal Ethics Committee (AEC). In all AEC applications researchers must justify the use of animals including a specific section where they must explain why the work they are proposing cannot be done *in vitro* or with alternatives to animals (see additional information in the following sections).

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.

Cell and tissues cultures continue to be used to provide information on the cellular response to disease and treatment. New imaging modalities, 3D printing and the use of human tissue-based organoids are examples of emerging technology that have reduced the reliance on animal involvement. However, they cannot replicate the complex and dynamic interplay between multiple different cell types and body systems, that can and do change with time of day (both inherent body clock cellular regulation and effects of timed metabolite changes (with meals etc.) and mechanical loading (with wake/sleep cycles and exercise) etc.), month and year (e.g. ageing).

Researchers attempt to use the most appropriate methodology to answer their research hypothesis. For example, if a researcher uses organoids to test drug response, they do so as it is the most appropriate means to test their hypothesis. Whether this is done specifically to fulfils the 3R's requirements of being an alternative to animal involvement, is unknown. Cell and tissue-based research approaches are often not an "alternative" to animal use, but are complimentary to animal based experiments (see discussion in the attached article from Prof Little). This in vitro work thus contributes to the 3Rs in guiding researchers to consider what animal model to use and how this will best translate to develop treatments for human patients.

It is also worth noting that cell/tissue culture research itself often requires animals to be sacrificed to provide the cells/tissues to study. Using primary human tissue/cells is desirable but problematic in terms of getting "normal" or even early/pre-clinical disease samples. Typically, end-stage disease samples are available (e.g. at joint replacement), and these don't not necessarily represent the stage of disease that needs to be treated in patients. Immortilized human cell lines similarly do not replicate the biology of primary cells. Animals, both normal and at different stages of induced disease, are needed to provide the appropriate cells to study in vitro. Again such work enables Reduction and Refinement but will never replace animal use in translational medical research.

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

The animal facility at the Kolling Institute is operated by the University of Sydney. The importation, breeding and animal involvement in medical research at the Kolling are governed and managed by their Laboratory Animal Services and Animal Ethics Office. The committee is asked to refer to the University of Sydney submission on this matter.

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

Researchers, must apply and have protocols approved by an institutional AEC for research involving animals to be conducted. The AECs have a structure and composition mandated by NSW Gov't Department of Primary Industries and Animal Research Review Panel (ARRP). All AECs are constituted, approved and have their performance monitored and reviewed annually by ARRP. AECs have members representing the research, veterinary and general community, as well as members with a special interest in animal welfare. The committee assesses the purpose, the need and how the animals will be used for the research. In this respect, transparency in how animals will be used is mandated during the approval process. Without approval, the research cannot be conducted.

In all animal ethics applications there is a section where researchers must explain why the work they are proposing cannot be done *in vitro* or with alternatives to animals. In these sections researchers will explain the preceding *in vitro* studies and how knowledge gained in this has led to the need to now do studies in animals.

Upon approval, the committee also requires researchers to keep record on animal involvement and report back to the committee. The committee must be satisfied that the animals were used according to the approval provided. The committee can halt or even terminate the research should it deemed that the research deviated from the approval.

The Kolling believes that the current approval process for animal involvement in research, demonstrates both public transparency and accountability.

Overseas developments regarding the regulation and use of animals in medical research

It is the responsibility of the NHMRC to review, consult, adopt and to disseminate any overseas regulations that the NHMRC considers as being appropriate for the Australian setting.

The Kolling Institute has made significant discoveries to the understanding human health. The examples provided in this submission demonstrates its capacity as an established and distinguished medical research Institute in New South Wales. The Kolling recognises and acknowledges the contribution that animals have made to its medical research program. Their involvement has led to the understanding of the progression of disease and the development of treatments to halt disease progression. Ultimately, their sacrifice have improved the health and longevity of human society.

In recognising their contribution, the Kolling follows the governance and policy structure that is in place to ensure that animal welfare and that animal involvement is appropriate, transparent and essential. It follows the best practice guidelines and policies of the National Health and Medical Research Council (NHMRC) and all its animal research projects are conducted under the approval of the institutional Animal Ethics Committee (AEC). The Kolling believes the current established approval structure provides accountability, transparency and reasoning for the involvement of animals in medical research.

Additionally, the Kolling is striving to adopt new techniques and technology that can enhance how it conduct its research. Some of these may replace, reduce and refine the need for animal involvement, but will not replace it entirely.

I trust that this submission is of assistance to the inquiry and provides insights into the need and the current accountability measures for animal involvement in medical research. If the committee requires further information about the Kolling Institute and this submission, please do not hesitate to contact me.

Yours sincerely,

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Appendix A: OA Foundation – Experimental models of osteoarthritis