Submission No 275

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

Name: Name suppressed

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Personal Submission

My background to this submission is from my career of more than 40 years in medical research (see summary CV in Appendix to this submission). I have been personally involved in the full range of research from laboratory bench and animal-based experiments to clinical and public health research involving people. This spanned many scientific disciplines but mainly the genetics and pharmacology of reproductive function. This career included establishing and leading a medical research institute that conducted small animal research for over 20 years till last year. Since then, I continue laboratory, clinical and public health research.

From that perspective, this submission aims to reinforce **the indispensability of animal-based research** to decisive medical research into human health and disease in the 21st century. A vibrant, incisive medical research sector is essential for not only scientific and medical knowledge for its own sake, but also for improved clinical applications and commercialisation in developing new treatment including drugs and devices for disease. This also has major economic implications for incorporating high value-adding employment in medicine and science. Careful cultivation of this focus is essential for NSW medical research to continue to be at the forefront of the growing edge of medical sciences. We have no alternative to being producer of new knowledge and inventors of new drugs and devices rather than being relegated to being passive consumers of advances produced elsewhere, for which we pay a premium to subsidize those original inventors in other places.

From observing debates about animal use in research over decades, it is evident that a small but disproportionately vocal minority of the community insists on imposing its sentimental preferences of the inviolable sanctity of all animal life over the community good of advances in knowledge in science and medicine with its contingent improvements in health and medical care. All these important communal good outcomes depend on the thoughtful and unavoidable use of animal in research, while minimising needless suffering. Eliminating animal-based research is virtually impossible under any scenario which envisages a vibrant and competitive state-of-the-art medical research sector in Australia. Nevertheless, the relentless slow-burn campaign against animal use in research, never expecting to abolish it entirely in a fiat, has instead concentrated on its slow strangulation by progressive tightening of a noose that combines further increasing the already tight regulations with imposing higher costs. Each twist of that screw aims to incrementally deter and hinder animal-based research. With every turn, these steps further disadvantage medical research in NSW with manifold deleterious consequences in scientific and economic terms for this State and its standing in Australia and the world. Above all this is flagrantly anomalous in a community which

accept the very large-scale farming of agricultural animals for food and goods. Presumably the scientific community is an easier and less defended political target than the important socio-economic interests of the agricultural sector.

Highest quality of medical research For NSW and Australia to make important contributions to medical research, it is essential to embrace its highest quality. This requires the community to support continued working at the frontiers of knowledge with state-of-the-art discovery and invention. If we accept a subordinate role by hobbling animal-based research, we would forfeit our roles as producers of new knowledge and inventors of new medicinal products to become passive consumers paying a premium price to subsidise knowledge and inventions produced elsewhere. The vulnerability of Australia to long international supply chains as experienced during COVID reinforces the imperative for Australian medical science to be as self-sufficient as possible and not depend on long and precarious supply chains from overseas.

The field of modern genetic research is a key example. The major genetic discoveries of the second half of the 20th century included deducing the DNA sequences of humans and animals. That progress facilitated major discoveries recognized by Nobel Prize-winning discoveries and inventions. These include the 2007 Medical/Physiology Nobel Prize for inventing the genetic modifications of the mouse genome that made possible creating genetic mouse strains. In the subsequent 15 years the majority of Nobel Prizes depended crucially on the use of genetically modified mice strains to elucidate their major scientific discoveries. These represent the highest achievement of global medical science with countless flow-on benefits to human health and medical care. It would be inimical and self-defeating for NSW to turn its back to such phenomenally beneficial medical research for investigating pathophysiology, disease mechanisms and therapeutics. Furthermore, every major advance in 21st century medical research, especially but not only in genetics and pharmacology, involves intelligent use of informative animal models. Systematic inhibition of this crucial field of medical research can only result in handicapping the creativity and productivity of NSW scientists.

All major peer-reviewed medical research journals encourage relevant animal-based research. In many instances, animal-based experiments are pivotal in the background of the highest quality studies reported in leading top journals. The most universal benchmark of productivity of medical scientists is their publication record, judged by various quality criteria including publication in top peer-reviewed journals. In that setting weighing down animal-based medical research with needlessly burdensome regulations, designed by some to hinder animal-based research, can only be detrimental to the productivity, achievements, and careers of NSW medical research sector scientists. In the medium term, that would encourage a flight from NSW of the best clinical and medical research scientists to more hospitable environments for their cutting-edge medical research.

Patents & Intellectual Property Protection Commercialisation of new discoveries or inventions leading to potential drugs or devices requires protection of Intellectual Property (IP). The economics of commercialisation requires negotiation with private sector entities supplying the necessary capital required to complete very costly market development programs. Those who risk substantial money by investing in early-stage medicinal products require strong IP protection. In turn, that requires strong, secure patents. In themselves such patents need to have a solid background of animal-based research. By undermining the ability of NSW discovery and clinical scientists to conduct crucial animal-based research efficiently and with minimal bureaucratic hindrance, adding to the obstacles in conducting necessary animal-based research are ultimately self-defeating.

Toxicology The introduction of new drug treatment for any disease must undergo safety (toxicology) testing as an essential pre-clinical component of drug registration by all major drug regulatory agencies including Australia's TGA, US FDA and Europe's EMA. One limitation of Australian commercialisation of its discoveries is the weakness of this country's commercial Toxicology sector. This essential discipline is heavily based on animal research and any further restrictions on animal-based research could further hinder the ability of Australian researchers to conduct the necessary pre-clinical toxicology within this country. That would have the effect of further alienating development of our new medical research knowledge into effective medicinal products. In forcing the use of overseas facilities, it again makes us consumers rather than producers of the valuable products of our country's new discoveries and inventions.

Limitations of the 3 Rs mantra. It would be a grand folly to overestimate the utility of the 3 Rs policy. While this policy represents sound common sense, a worthy ultimate goal and forming a useful and widely applied discipline, it can never substitute for all or even most animal research. As a well understood recent example, the COVID experience of mathematical models reminds thoughtful observers that prediction models are fallible and depend critically on the reliability of inputs. The same reservations apply to wishful thinking that prediction models could replace animal testing for drug pharmacology. Bypassing animal pharmacology is simply nowhere near safe enough for development and testing of new drug therapies in humans in this century. Ultimately the validity of hypothetical models must be evaluated by real world experience. Conversely, hindering animal-based medical research including in pharmacology and toxicology will inevitably come at a high price for health and medical care. No major drug regulatory agency would contemplate registering a new drug without sound pre-clinical and clinical pharmacology except for immunogenic drugs.

Sentimental reservations by a minority of motivated individuals and organizations are a luxury which must be balanced against the greater good for the whole community of a thriving medical research sector for employment, advancing medical and scientific knowledge, and commercialization of scientific discoveries. If arguments against use of animals in medical research forces by hostile regulation or indirectly by increased costs, that would come at the cost of hindering progress in health and medical care, notably developing new knowledge leading to inventing new medicinal products for human disease

Present Regulations on Animal Welfare

The present animal welfare issues are already well catered for. All animal holding facilities in NSW are licensed subject to regular and rigorous inspection of their quality. Reporting on animal usage is also already universal and provides public accountability for animal usage numbers.

Current regulations require animal ethics committees to approve any animal-based research and these committees serve to reduce animal suffering in medical research. These create a well-meaning but significant practical obstacle of ethical concerns including the 3Rs which inevitably adds costs and delays in progress of essential medical research. These barriers are widely accepted as necessary to ensure to reduce animal suffering but also to display public accountability for use of animals. But further restrictive regulations would only further hinder scientific progress in the environment where maximal efforts to reduce animal suffering are already in place.

A good example of careful progress in regulation of animal-based research in Australia is the recent change in AQIS regulations permitting importation of frozen mouse embryos. Still subject to rigorous quarantine, facilitating for the first time such importation facilitates crucial Australian medical

research involving the unique resources of genetic mouse strains. This now avoids the excessive cost, delay, and stress of importing live mice which usually involves the wasteful redevelopment of those genetic mouse strains again in Australia.

Present Status Of Animal Importation To Australia

Australia is a signatory to the CITES Agreement to ensure international trade in animals does not endanger their survival in the wild. In that context, Australia has effectively eliminated importation of non-human primates, whether endangered or not, so that the national non-human primate colonies are self-sustaining through selective breeding within population caps on colony sustainability. Australia's self-sustaining high quality breeding colonies of baboons and marmosets/macaque under the supervision of, and with support from, research-active institutions in NSW and Victoria. These facilities were supported by NHMRC between 1993 and 2018 when NHMRC direct funding ceased.

For non-primate animals, Australia maintains self-sufficiency of breeding colonies of animals for research, predominantly mice and rats. The main exception is the need to important unique genetic strains of mice into Australia for research. These are crucial for research into the genetic basis of physiology or disease. Previously importing such live mice came at high cost and delay (months) from international commercial animal suppliers (eg JAX, Charles River, Taconic) but the recent AQIS allowance of importing mouse embryos, subject to rigorous quarantine, substantially facilitates this essential process.

Indispensability of Animal Model for Research

In most area of modern medicine animal-based research has shed valuable and otherwise inaccessible insight into physiology - advancing knowledge of normal and pathological biochemical and physiological mechanisms of the body. These genetic models also shed light on disease mechanisms thereby creating novel therapeutic targets for improved medicines making them indispensable for making progress in human therapeutics.

In my discipline, reproductive biology and medicine, mouse genetic models have revolutionized knowledge and thinking about the normal and pathological regulation of reproductive function. In most respects, these mouse genetic models replicate with high fidelity human reproductive physiology providing indispensable insights into human pathophysiology. Thereby these genetic models reveal hitherto unrecognised disease processes and novel approaches to treating them. Not every aspect of human pathophysiology has had successful mouse genetic models, but where they have developed, they provide extraordinary valuable insight.

Non-human primate research

Regarding the use of non-human primates in animal-based research, the founder of the NSW baboon colony, the late Dr Andrew Phippard, had a strong working rule that experiments involving non-human primates could only be considered where (a) human experiments were not feasible for ethical or practical reasons and (b) smaller animal models such as rodents were either not feasible or not informative enough (eg due to major species differences or uniquely human diseases).

In some areas of medical research, the lack of animal models is a serious limitation on making progress. An important example is pre-eclampsia, a disease of (mostly first) pregnancies which causes hypertension, premature delivery, and damage to or even death of, mother, baby, or both. While

symptomatic treatments are reasonably effective so that few maternal or infant deaths occur in Australia, pre-eclampsia remains a major cause of maternal and fetal mortality and morbidity worldwide. As a characteristically human disease, its causes are still poorly understood with research being greatly limited by the lack of an animal model for what appears to be an exclusively primate disease. The disastrous legacy of thalidomide teratogenicity in the 20th century has left a lasting mandate in medicine to avoid drugs in pregnancy, especially novel substances not already used safely by historical precedent in pregnant women. This creates an even greater hurdle than in most other clinical setting to introduce new therapeutic drugs, the need for use in pregnancy. As a result, development of pre-clinical animal models are not only essential but unavoidable to develop safe and effective therapeutic drugs for pre-eclampsia. In that context the world-first research of Professor Annemarie Hennessy into a model of pre-eclampsia in the baboon has led to important research verifying findings about a cause and potential treatment for pre-eclampsia. This work originating in a collaboration between US and Australia scientists could only be completed in the NSW baboon colony.

Expenditure on Animal Research

A major route of State and Commonwealth government expenditure on animal-based research is through the peer-reviewed funding schemes of the Commonwealth (NHMRC and MRFF) and NSW (OHMR schemes). By competitive application and rigorous selection, these represent the highest quality of peer-reviewed medical research, and which can only be completed with approval from an animal ethics committee. In that sense these expenditures are oriented to achieving the best scientific and medical outcomes making them a virtuous form of governmental expenditure, not governed by political or personal gestures or whims.

Hopefully these comments may help the Committee's deliberations and I am prepared to appear before any hearing should there be one and my contribution may be considered worthwhile.

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