Submission
Strategic Review of Health and Medical Research

The Lions Eye Institute (LEI) is an independent Medical Research Institute affiliated with the University of Western Australia (UWA). It was founded in 1983 with the support of the local Lions Clubs in Western Australia and maintains a close relationship and receives support for the Lions Save-Sight Foundation. Its mission is to achieve excellence in scientific research and clinical practice to prevent blindness. The institute has both research laboratories and clinics with a long track record in bench to bedside research and clinical trials. Effectively the LEI is an ophthalmic version of an Academic Health Sciences Centre (AHSC).

LEI is contributing to the AAMRI and UWA submissions and thus this submission is brief and aims to highlight the example of research done at LEI and the challenges of long term funding and the time that important translational research actually takes.

Terms of Reference:

1. **Why is it in Australia's interest to have a viable, internationally competitive health and medical research sector? (*Terms of Reference 1 and 6)***

Research underpins delivery of health care. Regardless of research outcomes, the presence of high quality research centres attracts high quality academic clinicians to a region and thus improves the delivery of health care in that region. For example in Western Australia, prior to the establishment of the Lions Eye Institute in 1983 there was a major shortage of ophthalmologists in Western Australia.

2. **How might health and medical research be best managed and funded in Australia? (*Terms of Reference 2, 3 and 7)***

The major challenge of managing research funding is to improve the efficiency of the system. The RGMS system was very wasteful of researcher time and needs to be streamlined and improved.

Another challenge is a quality peer review system. Good research requires collaboration, but then all collaborators are deemed conflicted in reviewing a researcher's grants. Thus good collaborators are penalised particularly in small fields of research, where there are not enough reviewers with expertise to evaluate these grants.

3. **What are the health and medical research strategic directions and priorities and how might we meet them? (*Terms of Reference 5, 12 and 13)***

We need to maintain diversity of setting research strategy.
Problem/Disease based research is clearly needed **but** solutions also come from good basic science research.

For example, the major breakthrough in treatment of age related macular degeneration, by blocking Vascular Endothelial Growth Factor, relied on decades of basic research targeting the understanding of growth of new vessels, with no idea of application to ophthalmology.

4. **How can we optimize translation of health and medical research into better health and wellbeing? (*Terms of Reference 4, 8, 9, 10 and 11)***

TRANSLATION TAKES TIME

We can speed up and streamline the bureaucracy of ethics committees and regulatory authorities such as the Therapeutic Goods Administration (TGA).

Unfortunately the TGA is becoming more intrusive in research.

For example, I was instructed by our human ethics committee that the TGA wanted temperature monitoring on the containers taking blood specimens from the clinic to the DNA extraction facility. Researchers extract DNA from fossils that have had millennia without temperature monitoring, why have we suddenly been given this unnecessary impost?

It is critical that funding takes into account the long time that major research takes to produce truly significant clinical breakthroughs. In the attached manuscript (accepted for publication by the Medical Journal of Australia) I give examples of the biggest breakthroughs in ophthalmic research over the last century and the decades that these have taken to translate.

One of the key breakthroughs listed in my paper was the development of Anti-VEGF agents to treat Age-related Macular Degeneration (wet AMD). From a decade ago when ophthalmologists saw a patient once and told them "you are blind and there's nothing we can do, here is your referral to the Blind Association", we now have an ever growing number of patients returning every month for expensive top up injections. The cost of this treatment a mere six years later is a major portion of the national eye health budget; however offsetting this enormous cost is the fact that the patients are not blind and can continue to care for themselves.

In the late 1980s Prof Ian Constable at the Lions Eye Institute (LEI) wished to explore the possibility of genetic strategies to treat Age-related macular degeneration, the leading cause of blindness in Australia.
By the mid 1990s LEI established a gene therapy program, using recombinant adenovirus and recombinant adeno-associated virus and selected a natural anti-angiogenic molecule, the soluble fms-like tyrosine kinase-1 (sFlt-1 or sVEGFR-1) as the target molecule for wet AMD. A gene product used in one of the Briard dog model treatments for Leber Congenital Amaurosis was also developed and although the human trials for this treatment were approved in Australia, the rarity of this disease and the specific genetic subtype (RPE65) meant that no eligible Australian patients were available and thus the US and UK trials were those first published.
Subsequently Profs Constable and Rakoczy received grants from the Juvenile Diabetic Research Foundation USA and project and program grants from the National Health and Medical Research Council of Australia to develop a gene therapy program for human applications.
These grants enabled the detailed examination of safety and efficacy of gene therapy in the eye and the expansion of the scope of research. So in 2005 a team of immunologists led by Dr Mariapia Degli-Esposti joined LEI and commenced the immunological safety studies of the recombinant virus constructs.
By 2008 primate studies on the gene therapy treatment were concluded opening the way for human clinical trials. TGA approval was obtained in early 2009 and funding for the human trial became available in 2010. Production validation and quality control of the virus batch was completed in 2011 and subsequently Prof Constable injected the first three patients in January 2012. It is likely that the completion of the phase-2 and phase-3 studies will take another decade.

Thus although the work is now 20 years old it will be a full 30 years before this is 'translated' into routine clinical practice if it is successful.

The integrated clinical service and research model at LEI has been critical to the success of this program. To conduct the phase 1 clinical trial we rely on LEI's extensive experience of other phase 1, 2 and 3 clinical trials. With 45,000 patients a year through the clinic and one of the largest centres in the country treating AMD, we still have a challenge in recruiting patients who meet the stringent entry criteria for the study.

To maintain these programs - Bedside to Bench to Bedside - requires time lines beyond most grant funding systems and thus research institutes need to be able to sustain and help support ongoing research programs over decades, filling in funding gaps between competitive grants. In addition, in order to translate research we need comprehensive linkages between clinic and research to allow easy implementation of developments as happens at LEI.

I would be happy to provide the Review with further details if required

Yours sincerely

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