Submission: Strategic Review of Health and Medical Research

Infrastructure and performance-dependent stability

There are several challenges and opportunities facing Health and Medical Research in Australia. Included among these are: Core operating and infrastructure support for health and medical research in the non-university sector, i.e., hospitals and independent medical research institutes. While research in clinical settings and medical research institutes has been encouraged and valued, especially in relation to translational outcomes, the necessary infrastructure (which is strategically provided to universities through Commonwealth research funding agencies) has historically been provided to hospitals and independent medical research institutes through some combination of cross-subsidy from hospital budgets (now largely gone, because of cost pressures) and philanthropy.

It is generally acknowledged to be best practice that a sustainable research environment, especially one that hopes to attract and retain gifted individuals that can forge new futures, requires ~45% of its operating budget as relatively stable core funding, for several purposes: provision of necessary administrative and physical infrastructure, provision or underwriting of the salaries of key scientific staff, and discretionary funds to allow opportunities and unexpected contingencies to be addressed, the latter of which might be provided from reserves, but over time amounts to a required core. The remainder (~55%) of the operating budget is obtained from competitive national and international sources, which guarantees that the entities are held to a high standard of performance and vision. This balance operates at the Walter & Eliza Hall Institute of Medical Research in Melbourne and the Institute for Molecular Bioscience in Brisbane, which are among the most successful and influential biomedical research institutes in Australia.

Some infrastructural funding is now provided to research institutes and centres of sufficient standing by the NHMRC and variably by State Governments, based on NHMRC research income obtained by those institutes. It also follows the past, and while past successes are a reasonable pointer to future success, this approach does not enable such centres to do other than live hand-to-mouth and mitigates against visionary ventures that can change the landscape. Essentially it encourages (as tacitly albeit unintentionally does the entire system) gradualism and conservatism. I suggest that a proper strategic framework be developed to provide the necessary infrastructure for health and medical research entities in Australia.

This will require definitional consideration both with respect to eligible entities and eligible sources of funding upon which to base the claim, and involve a consideration of lifting the pro rata matching contribution relative to all relevant competitive research funds obtained (rather than just NHMRC funds as at present). Additional core funds for lighthouse institutes of high standing need to be provided (suggested to occur on a 5+5 rolling basis; see below), against agreed, documented and monitored objectives and key performance indices. Together with an expectation that 2 these institutes will also energetically and successfully obtain philanthropic support (another indicator of community endorsement of their performance and relevance), such funds will allow those institutes to develop visionary plans ahead of the national funding agencies (whose

peer review processes can be stodgy and conservative). There is a balance ideally required between performance and stability of the workforce, especially if Australia wishes to attract and retain the very best researchers. A 5+5 rolling funding / performance assessment cycle would seem to provide this balance. In essence the proposal is that core funding (against agreed objectives and attainment of agreed KPIs) is pledged for 10 years, with annual review but a major quinquennial review of scientific, research impact (i.e., translational) econometric, strategic, and lateral outcomes, with one of two outcomes: (a) if high performance, then the support is pledged for years 11-15; (b) if not, the centre has 5 years to lift or face loss of funding. Hence the state has dynamic control, but concedes (a maximum of) 5 years for recovery or wind down. Importantly, none of the affected employees is under immediate threat and there is a grace period to make organizational or personal adjustments to the situation.

The transformational impact of genomics

It is clear that 'next gen' science and medicine is upon us. Molecular biology (1972-present) has delivered many benefits, including recombinant hormones such as insulin, erythropoetin, growth hormone and cytokines, as well as insights into cancer pathways, leading to an expanding range of new anti-cancer drugs and treatments, and has set up the technical and knowledge base to explore the genetic programming of the entire system. This period began with the draft sequence of the human genome in 2001 and is accelerating at an incredible pace. The first genome sequence cost >$3 billion, but technological improvements in DNA sequencing (which extend to epigenomic and transcriptomic sequencing) have brought the expense down and increased the volume of data by 2-5 fold per annum, to the point that the cost of sequencing a human genome is currently ~$4,000 (a thousand fold increase), and the number of human genomes sequenced will exceed 3,000 by the end of the year, and 10,000 next. Further advancements in the existing technology and radical new technologies are close at hand, with concomitant reductions in cost and expansions in data availability. This revolution creates considerable challenges, opportunities and imperatives. It will transform health and medical science, and clinical practice, the latter increasingly being demanded by aware individuals.

The sharp end is cancer diagnosis, where it is already clear that molecular genotyping can powerfully supplement and will quickly replace conventional cellular pathology, providing clinicians and patients with much greater detail and insight into the molecular events underlying tumour biology, the prognosis and the selection and aggressiveness of the treatment options. This will only accelerate as the knowledge base expands using the same technologies, e.g., from the International Cancer Genome Projects. Indeed, genomics is poised to deliver major benefits to patients, clinicians, hospitals and the entire healthcare system, and will transform pathology, clinical practice, epidemiology, and ultimately health economics. For historical reasons, NSW lags well behind Queensland and Victoria in having the necessary technological and informatic infrastructure to move forward and create futures in this area, which will quickly overwhelm us if we do not strategically plan for it, especially in accelerating the capacity in all research environments of genome informatics (broadly defined, to include genomic, epigenomic, transcriptomic and proteomic analyses, and the lateral deployment of these as incisive systems-wide experimental approaches).

Reform of the peer review system

The current peer review system in health and medical research is struggling, showing signs of dysfunction and crisis. It was designed for another time, and is statistically indefensible. At the national level, reviewers are provided with a small set of grant applications to review, which is done in the absence of knowledge of other applications in the same round, and requires (literally) hours of thoughtful composition to provide fair assessment and objective comments to both the applicants and the committee members that have to integrate the information across the other applications in their purview.

This is a highly fragile system, dependent on the idiosyncrasies and biases of the (2 or 3) reviewers (who only see a small fraction of the applications that must be ranked) and the committee spokesperson, all of which have a major influence on the outcome. There is too much potluck and unproductive use of time. This system also militates against visionary applications, which often fall foul of skeptical reviewers and of committees that are not sufficiently confident (i.e., knowledgeable) to adjudicate in their favour.

I would like to suggest that consideration be given to an alternative that is more efficient, fair, statistically defensible, and better equipped to identify innovative and potentially transformational proposals. This is based on my experience as one of the two NHMRC Nominees to the Council of Scientists of the Human Frontier Science Program, which sends all Fellowship applications to all Council Members, who simply rank the applications A-D, which means that *their time and thought is focused on the judgement, not the feedback*. The collective scores are then integrated prior to a face-to-face meeting to prioritise the applications. *Experience shows that about 10% of the applications score >95% A, which are then recommended for funding without further discussion. Attention is then focused on the small number of A-Ds, i.e., those that were rated very highly by a significant number and very lowly by others. These split into two groups, those that have some fatal flaw evident to some, and those that are truly innovative and had engendered different reactions. These are debated and the latter rescued, i.e., recommended for funding, an outcome rarely possible in our current system.* The discussion then focuses on discussing and final ranking of the A-Bs and A-Cs, meaning that the committee's time and experience is most efficiently utilised.

This system is also used by EMBO, and is highly robust and statistically defensible. It may be readily adapted to the NHMRC (and ARC), as well as state and philanthropic agencies, which are faced with the same problem. I suggest that consideration be given to some contextually-appropriate variation on this approach, *to ensure that the best and most innovative proposals for health and medical research be efficiently identified and supported, with the added benefit of being able to assemble high level committees (of ~30 individuals per research domain) because the required time commitment is reduced.* Successful applicants do not really need feedback, and unsuccessful applicants will be reassured that their application was not highly rated by a large cross-section of experienced peers and can seek guidance from others who have been successful in such competitions as to how the vision or approach of their grant applications may be improved.

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