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Introduction

In this submission, we consider the future of health and medical research in Australia from the point of view of the field of regenerative medicine. Herein, the term regenerative medicine is broadly defined as encompassing basic and applied stem cell biology, the use of pharmaceuticals or biologics to enhance the body's capacity for tissue and organ repair, and cell therapies. We also include for consideration the application of stem cells as tools in research and development, because the technologies underlying such applications are the same as those in regenerative medicine.

The field of regenerative medicine presents a particularly instructive example for assessment of the future of Australia's health and medical research, because:

1. It is a new and rapidly growing area of biomedical research with widespread ramifications
2. It comprises a potentially disruptive set of technologies whose future implications are difficult to predict
3. It is a highly interdisciplinary field
4. The scientific, clinical and economic basis for product development and health care delivery in this sector is evolving and remains largely undefined

These features are not unique to regenerative medicine, but characterize many emergent health care technologies. In the future, the organizational structures that support, assess, and manage health and medical research in Australia will increasingly be faced with paradigm shifts such as that presented by regenerative medicine. It is therefore timely to review this field as a test case of the ability of our system to address radical change in biomedical research.

We address the four questions posed by the Review Panel in turn.

Why is it in Australia's interest to have a viable, internationally competitive health and medical research sector?

Implications for the health of the population: Regenerative medicine presents potentially curative solutions to a number of serious medical conditions that affect millions of patients and are currently intractable. These include many chronic diseases that result in massive public health, societal, and economic burdens here and elsewhere.

Economic considerations: Health care represents a significant proportion of the gross domestic product of countries across the globe, and regenerative medicine is a very rapidly growing part of this sector. A decade ago, the cell therapy industry was worth perhaps several million dollars a year. In 2011, the value of the industry was in excess of $1billion with rapid continuing growth projected into the future (Mason et al., Regen. Med. 6: 265, 2011).

Over 2500 trials of cell therapies have been conducted in the past 10 years, with 50% of these in Phase 2 or 3. Coupled with the increasing market share of regenerative therapies is the consideration that potentially curative treatments to debilitating conditions may offer considerable savings to health care providers.

The Track Record of Australian Scientists in the Field: Australia has made major contributions to regenerative medicine. Don Metcalf at the Walter and Eliza Hall Institute was a pioneer in the field of blood stem cells, a system that serves as a paradigm for understanding stem cells in mammals, and this tradition is carried forward today by Metcalf and his colleagues there. Some of the most important work in mesenchymal stem cells originated from the University of Adelaide, which remains a leading center for this research. One of us was fortunate to contribute to the beginnings of human embryonic stem cell research while at Monash University. Perry Bartlett at the University of Queensland and his colleagues are well known for their work on characterizing stem cells in the nervous system. Stem cell research rests on the intellectual foundations of developmental biology, and we have internationally recognized experts in that area. And today, biotechnology companies founded in Australia, or those built in part on their intellectual property, are amongst the leaders in translational research and clinical development, including Mesoblast here, and Viacyte, Stem Cells Inc, and Biotime in California.

Broader implications for Australian Research: Stem cell technologies, particularly human induced pluripotent stem cells, are now recognized as a cutting edge research platform for functional genomics, disease modeling, and drug discovery and development, in both the academic and commercial sectors. Our future competitiveness in the biomedical field will rely on ready access to such technologies and the expertise to exploit them.

The importance of local engagement: Maintaining and growing capacity in regenerative medicine here in Australia is important for several reasons. First, the model for health care delivery of cell therapies is often not centralized, as in the pharma and biotech sectors, but distributive, similar to a service such as in vitro fertilization. The distributive model requires local expertise, infrastructure and equipment to deliver health care products. Secondly, many cell therapies are likely to remain experimental for many years, and as such are best delivered in the context of an academic medical centre conducting clinical trials. If Australian patients do not have access to participation in such trials locally, they will demand access to new treatments overseas, most often at considerable expense. Or they will seek treatment outside the context of a trial setting, incurring not only expense, but risk to health with limited prospects of proper followup.

Importance of skilled workforce: The growth of basic and translational research in regenerative medicine, combined with the establishment of many well funded centres with top class infrastructure for this research around the world, mean that it is important to offer incentives to attract and retain established leaders and prominent new talent in this field. In particular, properly trained physician scientists are critical to the future translation of regenerative therapies. Opportunities for research training and careers for physicians in this country must be improved.

How might health and medical research be best managed and funded in Australia?

Current levels of funding in the sector: Current levels of funding in Australia for regenerative medicine are inadequate by international standards, particularly in the area of translational research. For example, the ARC Special Initiative in Stem Cell Science provides an excellent framework for a basic research consortium in the area, but at $3 million per annum, can only support a fraction of the country's meritorious research in this field. The NHMRC, despite its increasing focus on translation, has made little in the way of targeted strategic investment in this area of research, which represents a small fraction of their project grant portfolio. By contrast, federal spending in the US was US$950 million on regenerative medicine and an additional US$1.2 billion for stem cell research (Taking Stock of Regenerative Medicine in the United Kindgom, BIS, 2011). The California Institute of Regenerative Medicine (CIRM), a agency in a state with less than two times Australia's population and a focus on translational research, funds at a level of US$300 million per annum. Connecticut, a state with a population of 3.8 million, allocates US$10million per year to stem cell research. The United Kingdom estimates its spending in the field at UK£72.6 million in 2010 (A Strategy for UK Regenerative Medicine, Medical Research Council, 2012). The Canadian Centre for Commercialization of Cell Therapies, focused on strategies for translation alone, is funded at the level of CA$15 million for five years. Singapore, a city-state with a population of 5 million, dedicated US$75million over five years to stem cell research (Colman, A. Cell 22: 519, 2008).

Models for provision of funding: Australia needs to consider new funding sources for research in regenerative medicine, particularly translational research. A major barrier in this field (and in other areas of biomedical research) is that between basic discovery research and a Phase 1 clinical trial. Venture capital, which at one time would have addressed this gap, was never a strong sector of the Australian investment community, and is now even more restricted in availability and focused on short-term outcomes. From an investor point of view, this sector remains highly volatile and relatively high risk. Therefore, other agencies and jurisdictions are addressing this issue through various creative strategies (Reeve, B. Regen. Med. 7: 237, 2012), including: venture philanthropy, targeted at specific diseases and with considerable donor input into research management; public sector/ private sector alliances (CIRM funds research by biotech companies in the sector), specific bonds issues or specific tax initiatives to support research (California, Connecticut, Texas in cancer research,); partnerships with pharma or biotech (Harvard Stem Cell Institute and GSK).

Models for managing funding: The interdisciplinary nature of regenerative medicine requires combined expertise in a diversity of fields including cell molecular and developmental biology, bioinformatics and systems biology, animal modeling of disease, materials science, chemical biology, bioengineering, nanotechnology, imaging, regulatory affairs, and clinical medicine. It is difficult to see how existing Australian health and medical research governance structures will serve the requirements of interdisciplinary fields. The division of responsibilities for basic and clinical research between the ARC and NHMRC, and for health care provision between state and

Commonwealth, complicates an integrated approach. By contrast, the UK has brought together all its funding bodies involved in regenerative medicine to develop an overarching strategy for moving the field forward (A Strategy for UK Regenerative Medicine, Medical Research Council, 2012).
The project grant and program grant model, with its focus on individual investigators or small teams with narrow expertise in sharp competition with their peers, and its inherently conservative tendencies, is ill-suited to addressing most problems in this new science.
Elsewhere, in the US, the UK, Canada, and Japan for example, the drive in regenerative medicine is towards establishment of large multidisciplinary institutes that bridge the gap between basic and applied research, biology, the physical sciences, and clinical investigation. Such efforts do not sacrifice programmatic funding for infrastructure investment. CIRM is limited to 10% of expenditure on infrastructure, and the Harvard Stem Cell Institute is not a physical entity but instead a collaborative network with considerable resources to seed new projects across disciplines. In this respect, the Harvard institute resembles a startup or focused foundation.

What are the health and medical research strategic directions and priorities and how might we meet them?

Future scientific developments and challenges: There are many unmet challenges in this field that Australian researchers are well placed to address. Fundamental research questions that continue to face the field include the basis of cell fate determination including self-renewal, differentiation and reprogramming of cell fate, and the biology of tissue regeneration and repair. Some of the major current and future applications of stem cell technology in research include functional genomics, disease modelling, and drug development. Challenges for transplantation therapy include scaleup of cell manufacturing, barriers to functional integration of grafts into tissue, refining the effective use of cells as delivery systems for biologics, immune rejection, monitoring the fate of grafts through imaging, preclinical animal modelling, and safety and efficacy assessment of cell therapy. Two features are critical to success in the translational realm. The first is development of multidisciplinary teams to address diverse challenges in product development and manufacturing. The second is a clear awareness on the part of basic researchers of the clinical problems and the barriers to their solution, and an understanding on the part of medical practitioners of the scientific basis of regenerative medicine.
Alignment between research and public health priorities: Regenerative medicine targets many chronic diseases highly relevant to the Australian population. Examples of common disorders for which cell therapy based trials are currently underway or planned soon include macular degeneration, diabetes, AIDS, myocardial infarction, and many others. It is also important to remember that stem cell therapies have the potential to correct many serious congenital conditions with long-term adverse sequelae and healthcare cost implications, through prenatal, postnatal, or pediatric intervention. Indeed, when cell therapy is administered in early life, the environment of the

developing or maturing fetal or neonatal organ may in fact provide a more fertile soil for cell replacement than adult tissue.
There is merit in the concept that large academic centres here might focus on developing treatments for two or three medical conditions in which they possess special strengths, and address these through collaborative efforts with partners locally and overseas.
Global Perspectives: India, Brazil, and China comprise 40% of the world's population and they are rapidly undergoing an epidemiological transition towards diseases of affluence. Though perhaps only a minority of their populations may benefit in the near term, all three countries are actively pursuing stem cell research and regenerative medicine, often at a very high level. Unfortunately not all clinical activities in these countries or other nations with emerging economies are based on sound science. There is an urgent need to promote international standards for the assessment of safety and efficacy of cell therapy, in no small part to protect Australian patients from overseas clinics offering unsound and unfounded treatments. Australia can take a lead in this effort. Moreover, because research in regenerative medicine is advancing rapidly around the globe, it is very important for Australian researchers to develop and maintain international links.

How can we optimise translation of health and medical research into better health and wellbeing?

Challenges to translation: Given a promising early stage candidate therapy, some of the key challenges to translation in regenerative medicine include the provision of sustainable funding, a route to scaleable and cost effective manufacture (which may be local rather than centralized), and appropriate means for assessment of safety and efficacy of the therapy. This is best addressed by long term partnerships between the public and private sector, including pharma, biotech, health care providers, targeted philanthropy, and large academic centres.
The field would benefit through the formal establishment of tertiary referral centres specializing in particular aspects of regenerative medicine, with lead clinics working in conjunction with stem cell institutes. Better provision of funding for clinical trials, and related human infrastructure, is required to facilitate progress.
Whilst on the one hand cell therapy will likely be expensive, it will also have the potential to provide cost effective solutions for medical conditions that are currently are very expensive even to palliate and which incur large societal costs in terms of lost productivity. Therefore the health economics implications of advances in this field will require constant reassessment.

Recommendations

1. That the Panel recognize the level of funding for research in regenerative medicine in Australia is low, relative to other developed countries, and that in addition to enhanced support from the ARC and the NHMRC, new funding sources for research in regenerative medicine be explored, including targeted venture philanthropy, partnerships with pharma and biotech, bond issues and other targeted tax initiatives.
2. That new approaches to research funding and assessment be considered that will encourage large teams with interdisciplinary capabilities. At the heart of the process, it will be essential to achieve coordination amongst agencies with responsibility for research funding and health care delivery, to promote development of a coherent strategy.
3. That opportunities for physicians to undertake scientific training and research careers be expanded.
4. That Australia fund the establishment of 3-4 research institutes in regenerative medicine, incorporating a range of research disciplines and integrating basic applied and clinical research, at major academic centres combined with teaching hospitals. Where possible, the funding should focus on innovative programs rather than provision of infrastructure. Requirements for infrastructure for cell banking and GMP cell manufacture should be considered however. These institutes should be home to lead clinics in teaching hospitals that provide state of the art treatments and trial capability for a modest number of indications reflective of local expertise.
5. That adequate funding for the conduct of clinical trials and the necessary human infrastructure to support them be made available
6. That efforts to incentivize researchers in this field to establish and maintain collaborations with leading centres overseas be expanded.
7. That some support be directed towards ongoing assessment of health care outcomes and health economics in this field.