



Australian Academy of Science

THE STEM CELL REVOLUTION

Lessons and imperatives for Australia

***RECOMMENDATIONS FROM THE 2015
THEO MURPHY HIGH FLYERS THINK TANK***

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Cover image: Graphic rendition inspired by the increasing structural and functional complexity uncovered by current stem cell research. Differentiated tissue (depicted by the orderly patterns towards the bottom of the image) derives from a multitude of stem cell precursors, some containing a complete blueprint of the mature tissue (large circles containing tissue motifs) while others (smaller coloured circles) pick up local cues from the tissue niches (red stroma) to follow more restricted outcomes. In cancers, stem cells abandon these cues, and in some cases exhibit random differentiated outcomes (circles containing multicoloured circles). Artist: Nadia Rosenthal



FOREWORD

The 2012 Nobel Prize in Physiology or Medicine was awarded to Dr John B Gurdon and Dr Shinya Yamanaka for the discovery that mature cells can be ‘reprogrammed’ to become stem cells with the ability to develop into skin cells, brain cells or any other type of cell in the body. Their discoveries—made 50 years apart—overturned the longstanding paradigm that cell differentiation is a one-way process, and opened the door to the future of regenerative medicine.

Specifically, medical science is now moving towards the point where it will be possible to take cells from one part of a person’s body and turn them into any other type of cell for use in replacement of lost cells or repair of damaged tissue in diseases such as Alzheimer’s disease, multiple sclerosis and cardiovascular disease.

This emerging field of regenerative medicine has become a hotly pursued subject in medical research, but the potential of stem cells does not stop there. As Dr Yamanaka highlighted in his Nobel Lecture, stem cells also have the potential to revolutionise how we understand disease pathology as well as the development and use of pharmaceuticals and treatment therapies for personalised medicine:

all that is needed is a tiny amount of blood cells from the patients. We can then generate ... (stem cells which) ... have the same genetic information as the patients and will provide unprecedented opportunities for predicting the toxicity of drugs, making disease models in Petri dishes, performing drug screening and for cell transplantation therapies.

Yamanaka and many stem cell scientists around the world see a future in which we can test potential drugs on a patient’s own cells to see if they are effective and whether there are side effects before administering the therapeutics. They see a future in which we have donor banks of stem cells that allow tissue and patient-matched cellular therapies to be widely available to treat currently intractable diseases. They envisage a time when we can replace aged or diseased cells in our bodies and live fuller, more productive lives.

Australian researchers have much to contribute to this field. This document outlines how Australia can best support their work and enhance the national effort to fulfil the promise of stem cell science.

Professor Richard Harvey FAA

Chair, National Committee for Cell and Developmental Biology
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EXECUTIVE SUMMARY

Stem cell science is poised to revolutionise the field of medicine. In the future, stem cell therapies may contribute to a range of new therapies, including:

- the repair or replacement of damaged heart tissue in the one in six Australians affected by cardiovascular disease
- the restoration of vision for the one in seven Australians over the age of 50 who are affected by macular degeneration
- the replacement of insulin-producing cells, resulting in the 120 000 Australians living with type 1 diabetes no longer needing insulin injections multiple times a day.

Such outcomes are possible because stem cells have the ability to differentiate into any of the approximately 200 types of specialised cells in the human body. Recent advances in medical science have made it possible to take mature adult cells from one part of the body—as a blood or skin sample, for instance—and turn them into stem cells that can then be programmed into any other type of cell in the human body: for example, liver, heart or brain cells. And because such ‘replacement’ cells can be grown from our own bodies they will not be fraught with the problems of incompatibility or immune rejection that have made person-to-person tissue transplantation such a challenge.

To achieve these potential outcomes, however, systematic and significant support for stem cell science will be required. The Theo Murphy High Flyers Think Tanks aim to apply novel thinking to issues of national significance, such as the impact of stem cell science. To do this, the Think Tanks bring together early- and mid-career researchers from a broad range of relevant disciplines—in the case of the 2015 Think Tank, stem cell scientists from academia and industry, clinicians, ethicists and business experts. This report summarises their deliberations and recommendations. They examined the Australian stem cell landscape from four perspectives:

- **Future directions for Australian stem cell science:** This group projected the possibilities that stem cell science might bring in the future. They then identified the steps needed now to enable Australia to be a major contributor to this future and to reap the benefits it will bring.

- **Facilitating basic and applied research:** This group examined the way stem cell research is conducted in Australia, including the technologies currently used and those needed for stem cell research and development. They assessed the barriers for Australian scientists and looked for ways to improve how stem cell scientists work in Australia.
- **Facilitating clinical translation:** This group determined how best to improve Australia’s capability to take ideas from the bench and translate them into clinical outcomes for patients.
- **Public expectations and regulatory oversight:** This group discussed public perspectives on, and expectations of, stem cell science and assessed whether current regulations, guidelines and education initiatives are adequate.

Despite the enthusiasm for the potential of stem cell science, the participants identified a significant concern that the field is currently being undermined by the proliferation of a ‘stem cell tourism’ industry. This includes practitioners who are prepared to meet a demand for treatment that the promise of stem cell therapy has created, despite a current lack of robust evidence to support the effectiveness and safety of these treatments. This ‘industry’ is potentially unbeneficial, even harmful, to patients. It will also reduce the credibility of stem cell therapies and researchers in the eyes of the public, slowing progress in the field. This report presents several recommendations to address this matter.

The potential benefits that stem cell science could bring to Australia are enormous, and Australia needs to support research in this exciting field to realise the benefits in both economic returns and the health and wellbeing of Australians. These are the same goals stated by the Australian Government in establishing the Biomedical Translation Fund as part of the National Innovation and Science Agenda. The following report outlines recommendations made by the Think Tank participants on how best to achieve these goals. The recommendations are summarised below.

Summary of recommendations

IMPROVE AUSTRALIA'S CAPACITY AND COMPETITIVENESS IN STEM CELL SCIENCE. To ensure a place at the forefront of stem cell science over the coming decades, Australia needs a strong cohort of stem cell scientists with access to world-class infrastructure and incentives to encourage local and international industry investment. This will require a prioritised program of investment in students and early-career stem cell scientists, including **education that encompasses clinical translation**. The promise of stem cell science will be more readily realised by **facilitating cross-disciplinary collaboration** between stem cell researchers and scientists from other fields. Australia needs a centre with the resources and support to turn great ideas and scientific discoveries into new treatments and therapies—**a centre to accelerate clinical translation**. This centre would act as an information portal to allow researchers and industry to facilitate access to new developments, provide advice about intellectual property (IP) and regulation, and link researchers with collaborators, clinicians, industry and entrepreneurial and commercial concerns.

INVEST NOW FOR THE FUTURE OF STEM CELL SCIENCE.

Prioritising investment in stem cell science now will result in healthcare savings in the future. Stem cell science should be a **national research and development priority**, and systems should be put in place to create a **sustainable workforce for the future**.

ENHANCE AWARENESS AND UNDERSTANDING OF STEM CELL SCIENCE AND REGENERATIVE MEDICINE. Improving **community engagement and awareness** of stem cell science will create a community that supports stem cell research and is better able to avoid the risks of unproven therapies. It is important to **establish a boundary of practice** for health professionals utilising stem cells in their medical practice, which meets the accepted standards set by the medical and research community and is acceptable to Australians. **Improving patient access to clinical trials** will also help to progress the field.

ENSURE REGULATION AND STANDARDS ARE WORLD CLASS.

The current framework of regulation should be amended to align with international standards. Australia should aim to maintain a **permissive evidence-based regulatory balance** that fosters research and innovation while restricting unacceptable practice. Assessing the future directions of stem cell science by **horizon scanning** will allow Australian regulations to keep pace with emerging technologies and with informed public opinion. It is also important to set out scientific **standards for stem cell science** to ensure quality and reproducibility of basic research and resulting clinical therapies.

FUTURE DIRECTIONS FOR AUSTRALIAN STEM CELL SCIENCE

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Introduction

Our group focused on imagining and predicting what is possible in the future of stem cell research. We asked what were the likely directions for the field and what will be the outcomes delivered to the Australian economy, and the health and wellbeing of Australians. We also took time to consider novel applications of stem cell research that may be possible if stem cell research is well supported in this country. Finally we articulated recommendations to support stem cell science in the future to allow it to deliver all the potential we imagine and predict that it can.

To realise the potential of stem cells in health and biomedical industry, we first need a comprehensive and fundamental understanding of the basic biology—a **stem cell road map** (Figure 1). This knowledge will facilitate further technical advances in isolation, expansion and manipulation of stem cells both in a dish (*in vitro*) and in the body (*in vivo*) for applications to health and industry. It requires that we understand the cells and their niche (their local environment within the body), as well as the impact of ageing, disease, injury, lifestyle factors and the use of therapeutics on both the cells and their niche. The expansion of this scientific knowledge can proceed simultaneously with the application of existing knowledge, creating a continuously flowing pipeline facilitating the development of new applications.

FUTURE APPLICATIONS TO HUMAN HEALTH AND BIOMEDICAL INDUSTRY

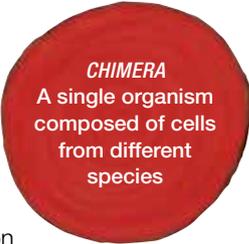
With regard to human health, we anticipate two areas where broad investment in stem cell research will deliver results: 1) cell-based platforms and 2) cellular therapeutics.

Stem cell-based platforms are already coming through the 'pipeline' and will enable a range of applications including:

- modelling of diseases and human development
- generation of new diagnostics
- screening for new drugs
- measuring toxicity or responsiveness of existing and repurposed drugs in the context of personalised medicine
- minimising the need for animal models.

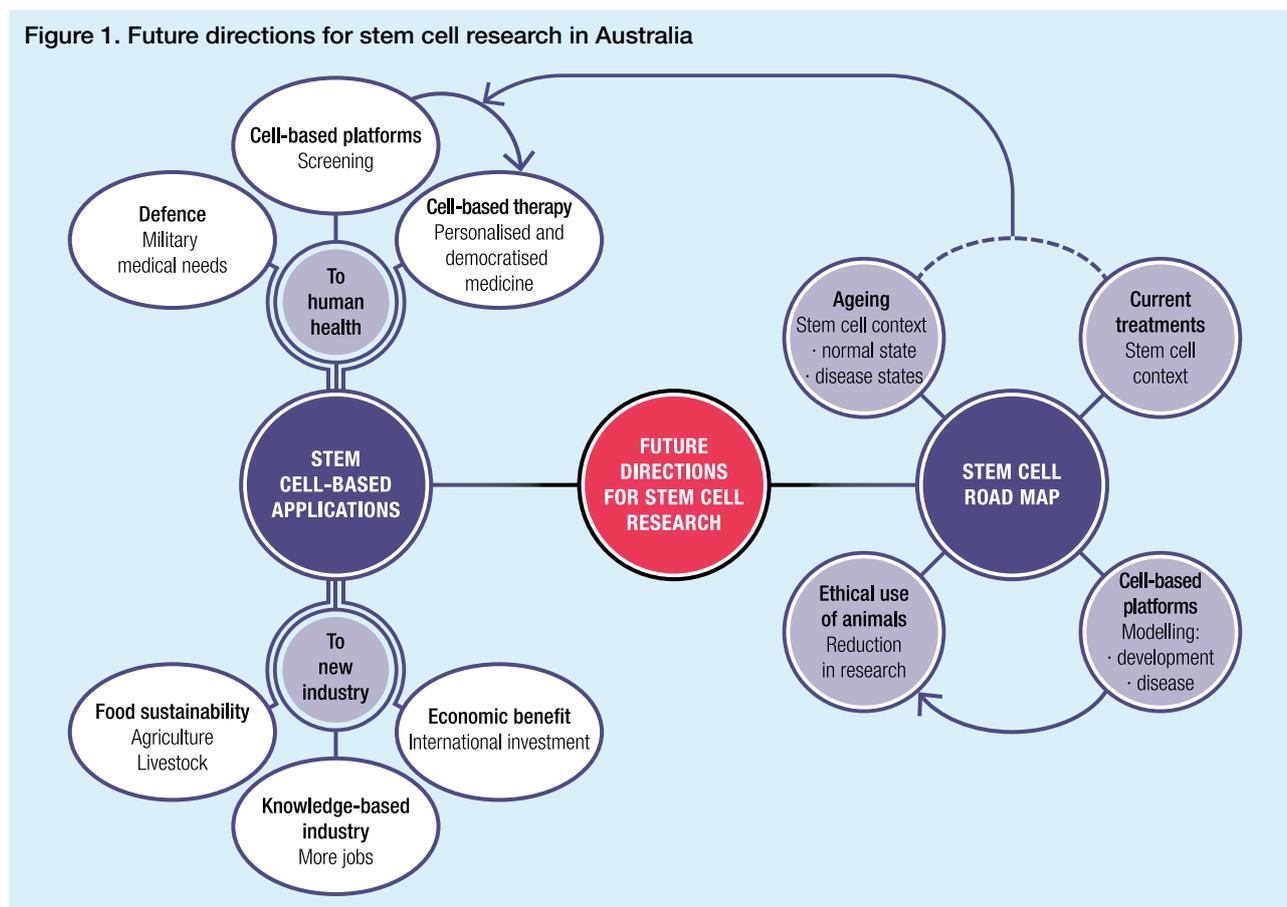
Utilising stem cells to develop safe and effective cellular therapies will require further time and investment to advance through the pipeline. Optimal delivery of tissues and/or cells into patients remains a challenge; however, this clinical translation is highly promising and worthy of significant investment. Future applications include:

- engineering multicellular tissue by combining cells in 3D structures, for example organ fabrication via 3D printing and organ formation via inter-species chimeras
- engineering cells for correcting genetic defects or introducing synthetic functions to enhance safety or efficacy. Examples include:
 - performing genetic repair to correct a disease-causing mutation
 - introducing markers to enable post-transplantation live cell tracking
 - introducing a 'kill switch' to selectively eliminate cells to mitigate risks of adverse effects
 - incorporating a biosensor function into cells that informs practitioners of potential post-transplantation outcomes.
- developing cell-based biologics or medical devices, where the cells act as living 'factories' to deliver specific therapeutic products by design, such as growth factors, hormones or peptides
- cell-based therapies for personalised medicine (i.e. transplantation of patient-matched stem cell-derived tissues that avoid immune rejection) and democratised medicine (i.e. off-the-shelf cell products that meet broad population needs including 'universal donor cells' and cell-derived products that promote regeneration).



CHIMERA
A single organism
composed of cells
from different
species

Figure 1. Future directions for stem cell research in Australia



Basic research in the stem cell field is building a ‘stem cell road map’ to provide in-depth understanding of the basic biology of stem cells. From this knowledge, new stem cell-based applications will benefit human health and potentially initiate new industries.

Investment in stem cell research will undoubtedly lead to wide-ranging applications in other industries beyond health and medicine, such as livestock, agriculture and textiles. For example, spider silk fibres provide an ideal biomaterial for tissue engineering due to their elasticity, strength and inert nature (that is, they do not elicit an immune response). There are many potential uses of diverse, non-human biologicals produced using stem cell technology, including the fabrication of medical devices and industrial materials, such as silica-based glass-like materials produced by marine sponges cultured from stem cells.

A well-supported stem cell research community could potentially address other national priority areas such as biodiversity. Emerging applications of stem cells may help to tackle disease epidemics that threaten native Australian species, such as the Tasmanian devil facial tumour.

Supporting basic research into defining the stem cell road map will not only provide the basis for these potential applications, it will likely also lead serendipitously to new discoveries and applications in industries we cannot yet predict. Australia has a strong history of basic research in a variety of fields leading to important applications, including the discovery of penicillin, the development of the human papillomavirus (HPV) vaccine (Gardasil and Cervarix), the discovery that the bacterium *Helicobacter pylori* causes

peptic ulcer disease and subsequent development of a diagnostic breath test, and the commercialisation of scar-free healing with the development of ‘spray-on’ skin technology. These examples highlight the importance of supporting the entire pipeline of innovation from basic stem cell research through translation to commercialisation.

Recommendations

RECOGNISE STEM CELL SCIENCE AS A NATIONAL PRIORITY FOR RESEARCH AND DEVELOPMENT

National benefit to Australia—The importance of supporting basic research is demonstrated by the development of *in vitro* fertilisation (IVF) technology, stemming from basic research into how fertilisation occurs and how it can be manipulated therapeutically. Australia was the second country in the world to implement IVF treatment and benefited from early access to this technology. IVF also provides an excellent example of the continuously flowing pipeline from fundamental knowledge to new applications.

The potential economic benefit from stem cell research, in particular the use of new stem cell platforms for drug screening and personalised medicine, has also become increasingly appreciated by funders of health care. Basic research into the development of ‘mini-organs’ is now facilitating personalised medicine to accelerate

implementation of effective treatments and avoid adverse effects. Beyond the economic benefit of reducing healthcare costs, in the future such platforms will enable better, individually tailored treatments and will contribute towards a healthier and more productive population.

Enhancing avenues for funding stem cell research—

There is concern among researchers in Australia that current funding strategies do not adequately allow for the translation of scientific discoveries made in basic research to medical and non-medical biotechnology domains. This concern was recently recognised by the Government in the release of the National Innovation and Science Agenda. We recommend that more coordinated cross-agency funding of stem cell research would better support the full suite of research and development activity of stem cell science from blue sky research to translation and commercialisation. This could be achieved using existing funding earmarked under the Medical Research Future Fund and the Biomedical Translation Fund.

Furthermore, we recommend broadening the scope of funding to encompass research, networking, enabling infrastructure and training of the workforce. This could be achieved in part by establishing a national funding body similar to the California Institute of Regenerative Medicine, which is mandated to support research and development in stem cell science, research infrastructure and workforce training. Another mechanism would be the development of larger collaborative research programs driven by calls for targeted funding similar to that in the US National Institutes of Health (NIH) biomedical funding system.

SUPPORT A SUSTAINABLE WORKFORCE TO MEET THE FUTURE NEEDS OF RESEARCH AND INDUSTRY

To compete internationally and benefit economically in the long term from the fruits of stem cell research, Australia needs to continue to train talented stem cell researchers with a broad range of expertise. Australian PhD programs should aim to provide students with a variety of skills and the ability to compete successfully with their international peers for prestigious postdoctoral positions. We recommend the following measures to improve the training of Australia's future workforce at universities and research institutes:

- more flexible training for PhD students, including some cross-disciplinary training such as in bioinformatics or clinical translation to ensure they have the necessary skills and experience to undertake stem cell research in a competitive environment
- greater flexibility in funding allocation to institutions to support training programs based on academic achievement, rather than years of enrolment
- support for universities to develop cross-disciplinary higher education programs to develop expertise across complex fields in areas including bioinformatics and bioengineering

- support for universities to develop and foster educational/training partnerships with industry, such as the Monash Translational PhD program.

In addition to training the future workforce, Australia needs to retain existing experts as well as recruit them from overseas to an environment of research excellence. Australia has a proven ability to provide this environment: an example is Mesoblast Ltd, a world leader in regenerative medicine. It was founded as a result of numerous patents stemming from basic research conducted initially in South Australia, showing that high quality research conducted in Australia can attract industry development and international investment with economic benefit.

Internationally there are examples of coordinated approaches to stem cell research and development which could guide Australian efforts to becoming a sought-after place for stem cell researchers to work. The Canadian Stem Cell Network has identified and filled structural gaps in the Canadian stem cell research landscape. Australia could take a similar approach focusing on the following measures which will support the current and future workforce, and create a productive research environment that supports innovation and meets the needs of industry.

- adequate career support for early- and mid-career researchers to retain talent domestically and to ensure Australia has a critical mass of researchers to meet the needs of a future knowledge-based economy
- acknowledgement of the sustained achievements and mentoring provided by senior researchers to early- and mid-career researchers by ensuring ongoing support of group leaders who hold competitive research fellowships
- an expanded, structured career path for scientists where excellence is appreciated, retaining skilled scientists to run research projects and maintain 'institutional knowledge' within a laboratory
- stable funding for research projects, with varying lengths and amounts of funding to match the needs of the particular project
- a streamlined and transparent grant review process. Study sections similar to the NIH model would provide constructive feedback and continuity of assessment. Experts in the subject should be able to evaluate research proposals for funding (with appropriate disclosure of interest) rather than perpetrating the current situation that those who are most knowledgeable about the work cannot participate in the peer-review process due to 'perceived' conflict of interest.

IMPROVE COMMUNITY ENGAGEMENT AND PROMOTE ADVOCACY AND AWARENESS

Stem cell research and regenerative medicine is driven by a range of factors including patient need, technological innovation, clinical realities and health economics. There needs to be an understanding of community needs and

expectations, and transparency in communicating the potential of stem cell science and regenerative medicine as well as its limitations. Communication needs to be improved between the research sector and the general community.

Firstly, we need to raise awareness within the research sector of how research advances are communicated to the community. For instance, widely promoting research advances through institutional media offices can promote the potential benefits of stem cell and regenerative medicine research and build key support that helps maintain success within the sector. It is important, however, to recognise that promotion of research advances can also lead to unrealistic public expectations about not only the risks of emerging stem cell interventions, but also the likelihood of receiving a safe and effective intervention.

Secondly, a national program to increase community awareness of stem cell research and cell-based and regenerative therapies will contribute towards a stem cell-literate public. This is critical to furnish Australians with information to understand the boundaries between proven stem cell-based treatments (such as blood stem cell transplants), promising new therapies being evaluated in clinical trials (available on the registry at www.australianclinicaltrials.gov.au) and unproven treatments offered by 'rogue' clinics. A stem cell-literate public will also ensure support of government investment in stem cell research in the future.

Ongoing consultation is therefore needed to tailor communications about the risks and realities of stem cell research to better inform the public. A range of methodologies, from social to traditional media, is needed to facilitate the flow of information within the sector and among relevant community groups. Improvements to the ways in which the community is engaged and information is exchanged can be achieved by:

- ensuring that information on emerging stem cell therapies and stem cell tourism through existing government health advisory sources (e.g. www.healthdirect.gov.au/stem-cells) is accurate and regularly updated to keep pace with the rapid changes in the field
- establishing a dedicated government source of information exchange with sufficient resources to provide timely and up-to-date communications that covers the full breadth of the stem cell and regenerative medicine field (similar to the National Prescribing Service or Consumers Health Forum of Australia)
- conducting empirical research into community needs and expectations to tailor communications and inform the ethical and regulatory processes that are shaping the sector

- establishing an education program in primary and secondary schools, support for scientist–classroom outreach programs, as well as greater support for physicians to educate their patients.

INSTATE A PERMISSIVE EVIDENCE-BASED REGULATORY ENVIRONMENT

Advances in some areas of stem cell science have the potential to have tremendous impacts on human health, yet also present many ethical and legal concerns. For example, new techniques for cross-species organ production could provide a source of human organs for life-saving transplants. Similarly, experimental models involving human embryonic stem cells and human-non human chimeras provide crucial insights into early human development that may be key to solving problems of infertility or treating developmental disorders, but also raise legal and ethical issues of 'synthetic' human-like embryos. New tools being developed in molecular biology, such as gene-editing by the CRISPR/Cas9 system, are predicted to allow dramatic advances in stem cell knowledge and translation, but have also raised ethical concerns as a debate about the possibility of permanently modifying the human genetic code has begun in earnest.



While it is essential to maintain an awareness of these concerns, the potential impact of these types of research justifies finding a framework to allow it to proceed in an ethical manner. We need a balanced and scientifically grounded discussion to inform policy-making in this rapidly changing arena. In some cases, this may include creating a more permissive regulatory system for some areas of research to enable faster knowledge translation. This could occur particularly where risks are known to be very low, well-defined and manageable, and where it is largely accepted that the benefits outweigh the risks. Considering the initial hesitation and scepticism towards IVF during its inception, compared to its wide level of public acceptance today, we must keep an open mind about novel and challenging concepts and ideas. The future relies on forward thinking for our growth, development and sustainability.



FACILITATING BASIC AND APPLIED RESEARCH

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Introduction

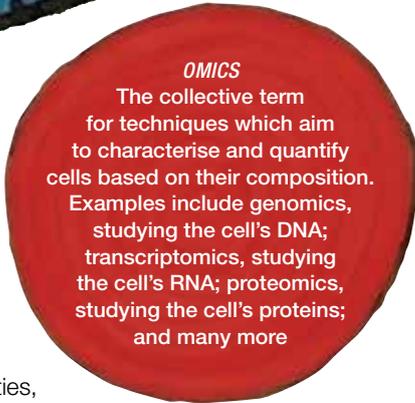
Our group aimed to determine how best to support stem cell scientists working in basic and applied research in Australia today. Some of these researchers are working on improving our fundamental understanding of the stem cells—that is, formulating our stem cell road map. Others are working in the early stages of applying our current knowledge using cell-based systems or animal models. The discoveries and research of these scientists will be the source of future applications to human health and industry.

While the field holds high hopes that innovations arising from basic research in the stem cell field will result in clinical therapeutics in the future, there are also likely to be far-reaching benefits besides therapeutics. For example, it is now possible to interrogate individual stem cells and their differentiated progeny using high throughput screening methods and molecular ‘omics’. Applying these analyses to patient samples has the potential to revolutionise the way we diagnose disease.

As highlighted in the ‘Future directions for Australian stem cell science’ section, there is also potential for innovations from stem cell science to impact on agriculture, biodiversity and other sectors. It is important to remember that advances made in these areas are likely to evolve from basic research in the stem cell field. For Australia to maintain excellence in health care for the future and potentially reap rewards from other industries, we must actively invest in basic research in this area.

The success of stem cell science is contingent on scientists, bioinformaticians, bioengineers and clinicians working synergistically, with technology platforms integrated into

both basic research and preclinical stages. It is imperative that cross-disciplinary collaborative research initiatives be supported by government, universities, teaching hospitals, research institutes and industry. Indeed, Australia’s geographical isolation and small population requires it to invest in the creation and maintenance of a scientific ‘critical mass’ for it to be competitive.



OMICS
The collective term for techniques which aim to characterise and quantify cells based on their composition. Examples include genomics, studying the cell’s DNA; transcriptomics, studying the cell’s RNA; proteomics, studying the cell’s proteins; and many more

Recommendations

The key to achieving successful outcomes from Australian stem cell research is investment in people, and this notion has inspired the recommendations of this group. The Australian Government should make stem cell science and regenerative medicine a priority area for investment over the next 10 years.

IMPROVE THE COMPETITIVENESS OF AUSTRALIAN SCIENCE

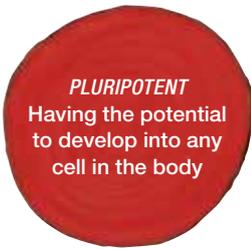
The nation needs to embrace the notion of Australia as a knowledge-based economy that can lead the Asia-Pacific region in regenerative medicine. Regenerative medicine will require an initial financial investment, healthcare systems will need to contribute to patient treatments, and a philanthropic environment to support stem cell research must be nurtured. Synergy between science, industry and medicine will need to be instated to treat patients. Currently, Australia invests a lower proportion of GDP in biomedical science than North America and Europe and there is limited representation of pharmaceutical or biotechnology sectors. Biotechnology and pharmaceutical industry partners are important for R&D to achieve scalability and effective delivery of new stem cell-based technologies and products.

We recommend the promotion of industry investment in research with appropriate technology transfer agreements to safeguard scientific intellectual property. This would be managed by specialised centres that act as bridges between university technology transfer departments and industry, such as the FastTRAC centre proposed in the

following section. Secondly, we recommend increased government and industry investment in science. Overseas investment in Australian research and technology could be encouraged by tax incentives, and translational programs could be jointly supported by government funding and industry investment.

ESTABLISH STEM CELL STANDARDS

We currently have the knowledge to isolate various stem cells and we understand how they can be manipulated to give rise to various cell types. However, concerns remain about the genetic variability and stability of these manipulated stem cells. Therefore protocols for their generation for clinical use need to be vetted and quality standards for their derivation should be established. Added safety measures to eliminate unwanted transplanted cells, such as an engineered 'kill switch', may be prudent. The future of regenerative medicine depends on scalable, efficient, reliable and reproducible methods for the differentiation of stem cells to desired outcomes.



To facilitate this, we propose the establishment of national stem cell repositories integrating curated induced pluripotent stem cells (iPSCs) and primary tissue banks with clinical information and genomics data that would fulfil quality control, data integration and distribution functions. Researchers

publishing new iPSC lines would be mandated (by public funding agencies) to deposit cell lines in these banks including details of their derivation.

We also recommend that legislated safety and efficacy standards for cellular therapies produced in good manufacturing practice (GMP) facilities be established. We believe GMP facilities should ideally be located in hospitals associated with research institutes that have imaging capabilities allowing for transplant monitoring.

FACILITATE CROSS-DISCIPLINARY COLLABORATIVE SCIENCE

Support for cross-disciplinary research teams is critical to the development of internationally competitive stem cell science and application. Engagement and consultation

with physicians and veterinary specialists early in the development process will be key to successful translation of research discoveries to medical and veterinary practice. Likewise, many aspects of stem cell research require collaboration with other scientific fields to facilitate the application of stem cells. Some examples of the interface between stem cell science and other fields include the following:

- Complex biological research now generates large quantities of data that must be expertly analysed. Therefore there is a need for bioinformaticians able to work in this field.
- While some stem cells can be injected, the effective delivery of others to the appropriate site in the body is more problematic. For example, complex tissues such as kidney might require engineering on 3D scaffolds.
- Once transplanted cells are in the body it is desirable to be able to track them to assess their therapeutic outcome. This could be achieved by collaboration with microscopists and other imaging specialists to develop these techniques.

We recommend the creation of stem cell research centres of excellence. These would enable cross-disciplinary scientific interactions and form national collaborative networks supporting interactions with scientists in other fields. These consortiums would support combined MD/PhD programs and would have the flexibility to incorporate additional clinical and cell production expertise as projects progressed to translation. The centres could facilitate the training of bioinformaticians with an increased understanding of biology by embedding them in wet laboratories. Alternatively, scientists could access bioinformatics support from national nodes with specific areas of expertise.

Furthermore, international collaborations could be fostered by expanding scholarship and fellowship schemes for international PhD students and postdoctoral scientists.

FACILITATING CLINICAL TRANSLATION

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Introduction

Australia's contribution to early stage research in stem cell and regenerative therapies has been significant. However, the relatively small population and small biotechnology sector in Australia are major disadvantages to the translation of preclinical findings. In contrast, North America and Europe have dedicated government-backed stem cell initiatives targeting diseases of significant burden. As a result many sponsored clinical trials of cell and regenerative therapies are under way. Despite relatively well-supported basic research in Australia, few clinical trials have been initiated here and there is a distinct lack of funding for early stage clinical

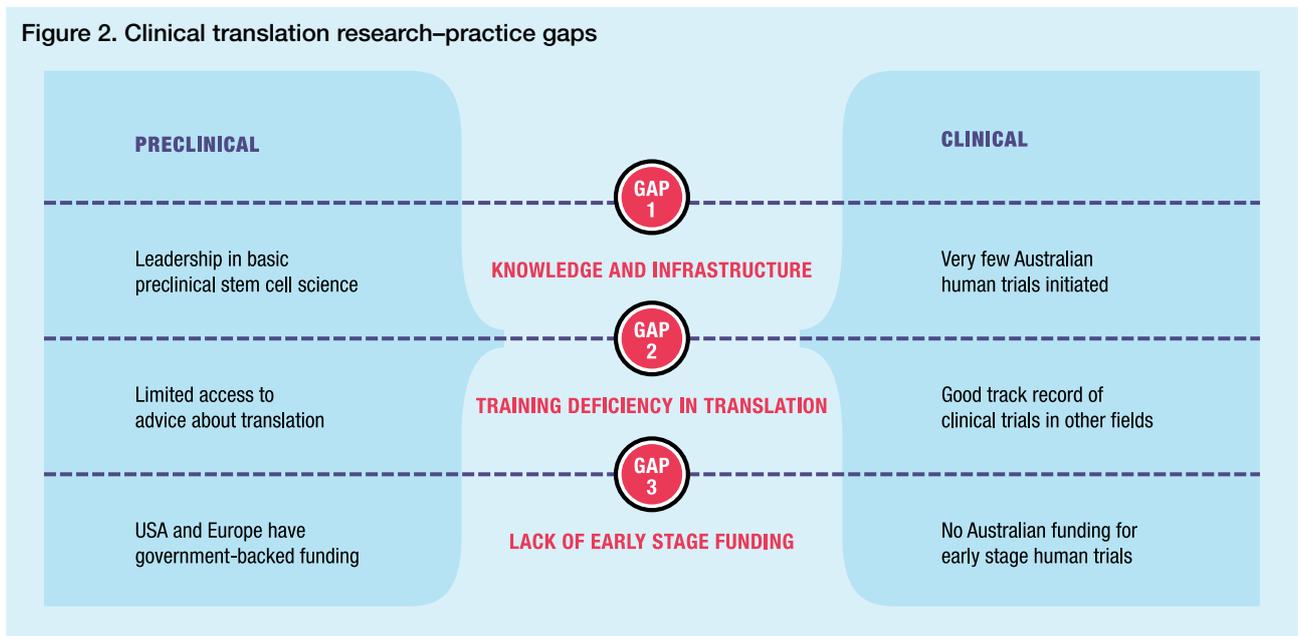
research. For Australia to meaningfully contribute to and reap the rewards of clinical stem cell translation and rejuvenation, the time for decisive action is now.

Our group had a diverse range of experience and points of view. We were composed of six clinician academics, six university scientists, three industry scientists and a business expert. There was a consensus that while Australia holds a good position in basic research in the stem cell field, there are several gaps in the path to clinical translation (see Figure 2).

The first is a gap in knowledge, project management and research infrastructure for basic researchers to progress into preclinical and clinical trials with their discoveries. Australia has solid GMP facilities in the major cities, but does not have a dedicated workforce focused on translating basic discoveries into clinical interventions. The second is a deficiency in training in translational paradigms for stem cell researchers. The third roadblock to translation is a lack of funding for early phase clinical research, such as Phase 1 clinical trials.

Addressing these three key impediments to successful translation is paramount for the future of Australian stem cell research, and failure to address them immediately will result in continued adverse outcomes for our research enterprise. Such adverse outcomes include loss of Australian intellectual

Figure 2. Clinical translation research–practice gaps



property to overseas companies, which will in the long term deprive Australian patients of early access to novel therapies and result in Australians paying higher prices to overseas companies when these therapies become commercially available.

It is important to recognise that cell and regenerative therapies offer the greatest potential for treating significant disability and easing economic burden. This includes debilitating conditions that have already been recognised by the government as areas of national health priority such as asthma, cardiovascular disease, osteoarthritis and diabetes, which cost the economy billions of dollars in treatments and lost productivity. In addition, the personal toll of these long-term illnesses is substantial in terms of pain, suffering, and loss of independence and productivity. Despite being recognised as national health priorities, investment into stem cell-based treatments for these conditions is relatively low in Australia. Financial support for translational research from the laboratory to the clinic through structured assistance in the areas identified in Figure 2 will—with the resultant development of successful biological regenerative treatments—invariably lead to enormous community and economic gains.

We recommend three key ways to streamline and improve translation of cell and regenerative therapies into clinical trials (Table 1).

PROBLEMS	SOLUTIONS
1 Knowledge and infrastructure	FastTRAC acceleration centre
2 Training deficiency in translation	Education on translation
3 Lack of early stage funding	Cost model a stem cell future fund

Recommendations

ESTABLISH FASTTRAC—A CENTRE FOR ACCELERATING TRANSLATION

There is an urgent and immediate need to establish a clinical translation acceleration centre—FastTRAC (Facilitating Stem Cell Translation and Regenerative Medicine for Australasia Centre). The role of FastTRAC would be to act as an advisory centre to facilitate and accelerate the clinical and commercial translation of cell therapies. This centre would provide basic scientists with a first port of call for expert advice on protecting and fostering IP, navigating regulation, developing clinical pathways to translation and finding funding sources.

While some universities currently offer some of these services, this centre would aim to integrate them in one place and function as a hub for all researchers in Australia.

This would eliminate resource duplication, streamline processes and ensure equal access to all researchers. This new centre would work collaboratively with existing stem cell research institutes throughout the region and would not be designed to replace them or recapitulate their research enterprises. The centre could be located within a stem cell research centre of excellence, proposed in the ‘Facilitating basic and applied research’ section.

The FastTRAC hub would draw together venture capitalists, industry, researchers, clinicians and the public for directed and focused collaboration towards translation of basic research discoveries into clinical trials (Figure 3, overleaf). Importantly, the centre would be outward-facing for talent development, reaching out to researchers in both academia and industry with a view to developing collaborative projects. It would also be able to engage and work with consumer groups to strive for better health outcomes for patients.

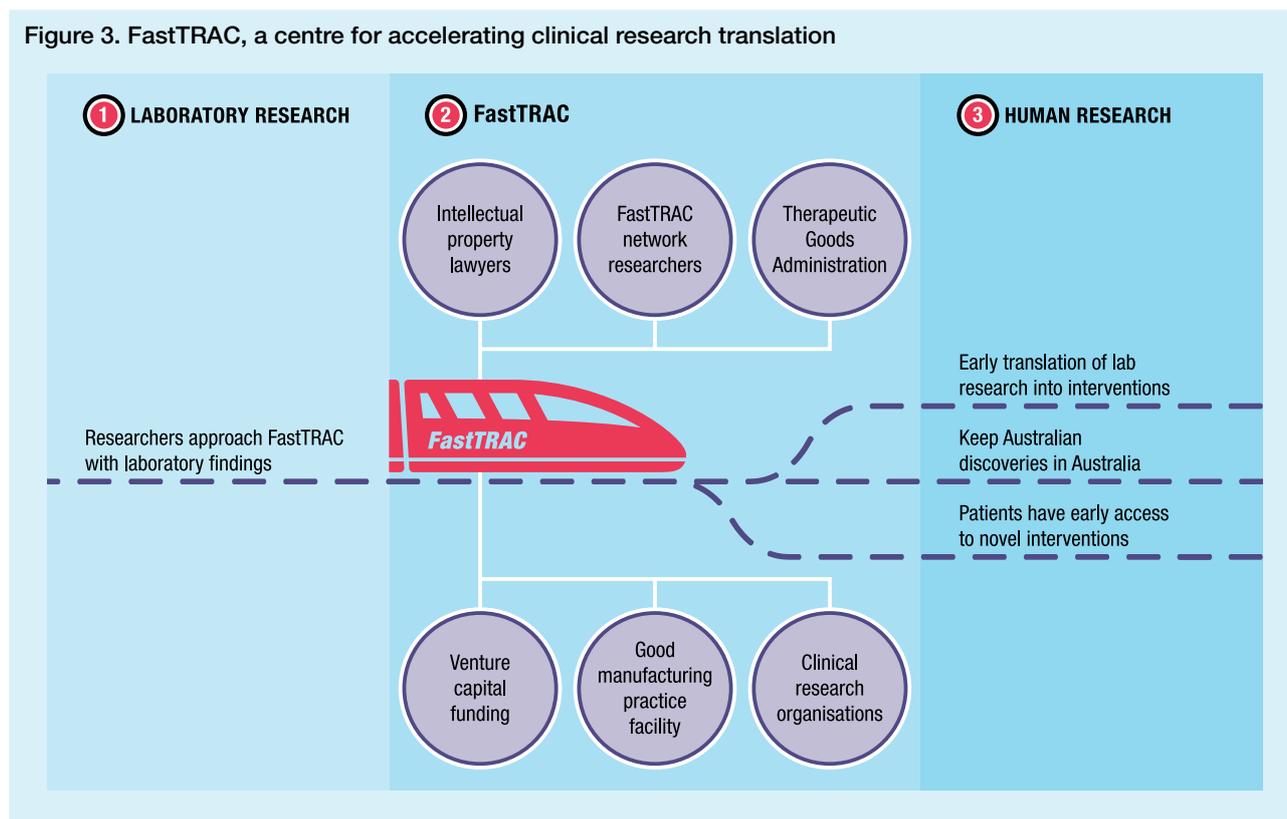
FastTRAC requires staff with expertise in each of the following areas: intellectual property, regulatory affairs/GMP, clinical trial design and performance, preclinical development of regenerative stem cell research programs, and fundraising. The centre’s priorities would align with the government-recognised areas of national health priority that represent up to three-quarters of the total burden of disease of Australians (arthritis, asthma, cancer, cardiovascular disease, diabetes, dementia and mental health) and other high-cost conditions such as cerebral palsy, the fifth most costly health condition. It would also assist the NHMRC Research Translation Faculty to identify research and funding gaps.

We also recognised a clear deficiency in preclinical large animal experimental facilities in Australia. As the centre grows, FastTRAC could solve this unmet need by providing on-site large animal surgical and high-end imaging resources. Another role of FastTRAC could also be to liaise between researchers and the Therapeutic Goods Administration (TGA), promoting regulatory reform, as well as building partnerships with clinicians to expedite research. With its advantageous position across academia and industry, it will develop novel metrics for successful clinical translation. It will become the home for a centralised body of early clinical trial registries and may serve a broker-like function matching researchers and clinical trial units with existing GMP and bioprocessing expertise throughout Australia.

SUPPORT EDUCATION SPECIFICALLY IN TRANSLATION

There is emerging recognition that translation is evolving into its own specialty area. It requires a unique mix of skills that most research higher degrees do not teach. We see a knowledge gap for current graduates of Australian research higher degrees in translating their findings to clinical studies. In fact, most would not know where to start. While obvious training paths for basic scientists and medical practitioners

Figure 3. FastTRAC, a centre for accelerating clinical research translation



exist, there is currently no training program for translational researchers who can successfully bridge these areas. Regenerative cell therapies have unique translation challenges. We propose several initiatives to improve training in translational medicine within our discipline of stem cell therapies.

First, translational skills need to be built into research higher degrees. It is currently acknowledged that many research higher degree candidates will not pursue traditional research roles, and are under equipped to move to newer areas such as industry or regulation. Moves are under way within academia in Australia to increase the amount of coursework in research higher degrees to make graduates more broadly skilled. We recommend that such coursework include training in translational medicine skills for candidates studying in the field of stem cells and regenerative medicine. Such skills include knowledge of IP law, familiarity with regulatory requirements for biological therapies, and an introduction to the commercialisation of scientific findings.

Second, it was acknowledged that there is a vast amount of knowledge, skill and scientific prowess within industry, and that our field demands interaction between academia and industry, perhaps more than most. Therefore we recommend that fellowships or cadetships with industrial partners be established for stem cell medicine researchers. These fellowships and cadetships would equip academic researchers with basic knowledge about how to start the process of developing a commercially viable therapy from their discoveries. It is envisaged that FastTRAC would facilitate these positions in the short term, and could

offer its own fellowship or cadetship training program in the longer term.

Third, medical schools and specialist colleges should be encouraged to combine clinical and surgical training with translational research within medical degree curriculums and fellowship schemes. Doctors and surgeons poorly trained in regulatory frameworks regarding the science of stem cell and regenerative medicine, and the foundations of clinical trials, such as good clinical practice, will become major obstacles to successful translational stem cell research in Australia. FastTRAC may become a portal for clinician academics with clinical trials experience to form new collaborative translational research networks with basic scientists.

UNDERTAKE A COST-BENEFIT ANALYSIS TO SUPPORT FUNDING OF STEM CELL AND REGENERATIVE THERAPIES IN THE FUTURE

This proposal aims to address the lack of funding that is hampering early clinical research in stem cell therapies in Australia by cost-modelling and public lobbying for a dedicated stem cell fund. We believe a bold and proactive solution is needed for this ‘black hole’ between early scientific discoveries and clinical therapies, an area that is virtually unfunded. The government has recently acknowledged this gap by directing resources into the Biomedical Translation Fund as part of the National Innovation and Science Agenda. We believe part of these funds should be directed to facilitating clinical trials in cell and regenerative medicine.

We draw on the experience of successful programs overseas where large government investments in cell and regenerative therapy programs have been successful in promoting clinical translation of new therapies as rapidly as possible. Direct government investment will build philanthropic and industry confidence to invest in the translation of stem cell and regenerative therapies in Australia.

An example is the California Institute for Regenerative Medicine (CIRM), made possible by a US\$3 billion stem cell research fund allocated by the Californian government in 2004, which has recently (as of January 2015) initiated a new funding model to significantly increase the number of research projects moving into clinical trials. Under this scheme, funding for Phase 1 or 2 trials are not capped, while Phase 3 trials are capped at US\$20 million. The open application model (with monthly application deadlines) also eliminates potential time lost through the conventional annual application cycle. There are several other international models on which we could base an Australian Government fund for stem cell translational research.

Our long-term solution to support translation requires the establishment of the Australian Stem Cell and Regenerative Medicine Fund (ASCRMF), aimed at funding multidisciplinary teams of researchers (with clinical and commercial expertise) to conduct early stage translational research of cell therapies. We propose that the establishment of the ASCRMF be preceded by an actuarial analysis to ascertain the appropriate level of funding for this entity. Such an analysis will reveal that investment now in this critical area will save costs in the long term to healthcare budgets and will improve productivity by decreasing disease burden.

Funded research areas will align with Australia's health priority areas, maximising impact for the money invested. The mechanisms of application, review and awarding of funds will be decided in consultation with relevant stakeholders, including the Australian public, federal and state governments, academic research organisations, the National Health and Medical Research Council, industry, and FastTRAC. A reasonable time frame for launching the initiative—that is, to have an actuarial analysis completed and funding levels defined—would be two to three years.

PUBLIC EXPECTATIONS AND REGULATORY OVERSIGHT

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Introduction

The field of stem cell science and regenerative medicine has captured public imagination with its potential to develop new treatments for intractable diseases and injuries. Australian stem cell researchers have made (and will continue to make) valuable contributions to the stem cell science field. If Australian researchers and clinicians are well supported in their efforts as described in the previous sections, they will be well positioned to help deliver therapies that are safe and effective, while also ensuring patients have access to emerging treatments.

Achieving the greatest return on Australian efforts and investment in the stem cell and regenerative medicine field requires a robust ethical and regulatory framework that is both evidence based and incorporates accepted norms of patient protection. Such a framework needs to maintain currency in a rapidly evolving field, and must be integrated across all sectors including public and private research institutions and related industries.

Without an effective regulatory framework, Australia risks becoming uncompetitive within the global bioeconomy. For example, competitiveness could be lost through missed opportunities if the local regulatory environment inhibits identification or investigation of new research discoveries. Similarly, there is a real possibility for reduced competitiveness should the premature availability of unproven stem cell interventions within the community lead to instances of patient harm or exploitation.

EMERGENCE OF UNPROVEN STEM CELL THERAPIES

At present, *very few* stem cell-based therapies have been accepted as the standard treatment for a condition. The

best known example of an accepted ('proven') stem cell therapy is blood stem cell transplantation (often termed bone marrow transplantation) to treat some blood cancers. Cultured skin grafts are also commonly used for the treatment of burns and for wound repair, and limbal stem cells are becoming accepted for treating corneal burns.

Australian and international research efforts are aimed at identifying and testing new stem cell and regenerative medicine interventions. From these efforts there is growing preclinical evidence, as well as some clinical evidence, that a small number of these emerging stem cell-based interventions might potentially provide some patient benefit in defined circumstances. However, these as yet unproven interventions require further clinical trial testing and are currently not risk free. For instance, some patients have experienced tumours derived from autologous stem cell interventions.

Without rigorous clinical trials to test new stem cell-based interventions, the ability of patients and their carers to make informed decisions about pursuing a novel therapy is greatly diminished.

Unfortunately, across Australia and overseas, an increasing number of private medical practices and clinicians are marketing unproven stem cell-based interventions for a range of chronic diseases. For the most part, these interventions are offered as 'innovative' or 'experimental' therapies to patients suffering from chronic and debilitating illnesses, many of whom are vulnerable and are not getting what they want from conventional medical therapy. Strikingly, these commercially offered interventions typically provide limited or no relevant peer-reviewed scientific evidence to support commercial application of the intervention.

IMPROVING ETHICAL AND REGULATORY OVERSIGHT

In building a viable and internationally competitive regenerative medicine sector in Australia, it is essential that ethical and regulatory systems are designed to support basic research in stem cell science. In addition they need to facilitate the

LIMBAL STEM CELLS
Stem cells which maintain the cornea of the eye, for example replacing cells that are lost via tears. Also known as corneal epithelial stem cells

AUTOLOGOUS
Interventions which use a person's own cells. Stem cells are collected from an individual which are then reintroduced to the same individual

timely and responsible clinical translation of new therapies once the therapeutic benefits and risks are well established.

It is critical that policy-makers, researchers and clinicians, together with community stakeholders, engage with the ethical, legal and social issues related to current and emerging stem cell technologies. Failure to identify and address concerns in a timely manner, such as those associated with the marketing of unproven stem cell-based interventions, will place the health and wellbeing of patients at undue risk. It will also undermine the credibility of the Australian stem cell industry and compromise the viability of this emerging sector.

The following recommendations will reinforce public trust in, and transparency within, the stem cell research and regenerative medicine sector.

Recommendations

AMEND THE CURRENT FRAMEWORK THAT REGULATES AUTOLOGOUS STEM CELL-BASED PRODUCTS

The regulatory framework that oversees the manufacture, sale and distribution of autologous stem cells and cell-based products in Australia should be reviewed and amended to reflect international standards of clinical evidence and quality assurance in cell processing.

The relative ease with which some human tissues can be collected and processed has led to a rapid increase in the number of unproven interventions being marketed directly to patients in Australia. The majority of the clinics marketing these interventions to Australians claim that they represent effective and accepted medical practice with little to no risk. Most claim to use stem cells derived from the patient's own adipose (fat) tissues (i.e. autologous). However, very new technologies, such as cellular reprogramming to generate patient-specific stem cells, are now also being marketed in Australia despite the fact that these cells currently have no known or proven clinical benefit and are associated with significant risks such as the potential for tumour formation.

The sale of such interventions illustrates the weakness of the current regulatory system, which allows cellular products that fall far below the evidentiary standards of most other industrialised countries to be marketed in Australia. As this weakness has the potential to undermine the nation's reputation as a provider of world-class healthcare services, it risks our long-term competitiveness and immediate steps should be taken to:

- amend the Australian Regulatory Framework for Biologicals, paying close attention to the exclusion of autologous cells from regulation under the Therapeutic Goods (Excluded Goods) Order No. 1 of 2011. In early 2015 the Australian TGA carried out a public consultation regarding this topic and is currently in the process of preparing a recommendation on whether there should be regulatory change. It is the considered opinion of this group that a tightening of these regulations should occur

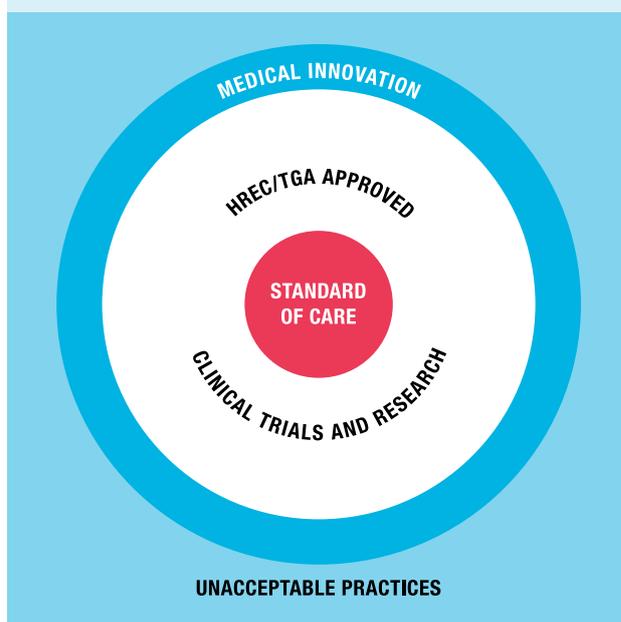
- limit the application of stem cells and cell-based products that have not been established as the standard of care to investigation within formal clinical trials that are overseen by a registered human research ethics committee (HREC) and, where appropriate, the TGA. Exceptions are experimental products obtained under the Special Access Scheme of the TGA.

ESTABLISH THE BOUNDARIES OF ACCEPTABLE PRACTICE

The boundaries of acceptable practice in research and clinical care must be clearly defined and secured with accountability mechanisms that are consistent with existing professional standards and reflect the current state of knowledge in stem cell science.

In defining the boundaries of acceptable practice, it is important to recognise that novel therapeutic approaches can sometimes emerge from within the context of clinical care, rather than through the formal clinical trial process. As shown in Figure 4, these activities, frequently referred to as 'medical innovation', occupy a grey zone beyond clinical research and practices that would be considered standard by suitably qualified peers.

Figure 4. The boundaries of acceptable practice in research and clinical care



Medical innovations with stem cells may, under a very limited set of circumstances, be suitable for introduction into clinical settings. These circumstances are clearly outlined in the *Guidelines for the clinical translation of stem cells*, developed by the International Society for Stem Cell Research in consultation with the Australian stem cell research community. These guidelines advise limiting innovation with stem cells to, at most, a very small number of patients who have few or no other medical alternatives.

Further consultation may be helpful in defining the specific conditions under which practitioners may justifiably

introduce unproven stem cell-based interventions outside the context of a clinical trial. However, the boundaries of *unacceptable practice* should, at a bare minimum, reflect the standards set out in the code of conduct of the Medical Board of Australia and the code of ethics of the Australian Medical Association.

These two codes should guide the boundaries of acceptable practice and should be supported with actions from the relevant agencies that govern medical and healthcare professionals in Australia. To best coordinate action from these agencies, it is necessary to:

- clarify the roles and responsibilities of existing governing bodies that oversee clinical research and practice in Australia. This will ensure that proposed stem cell-based interventions are supported by scientific evidence of safety and efficacy before they are introduced into clinical contexts and marketed to patients as therapies
- develop guidelines and educate medical and healthcare professionals about the circumstances under which they may justifiably introduce an unproven stem cell-based intervention into their clinical practice
- enforce sanctions against practitioners registered under the Medical Board of Australia and/or the Australian Health Practitioner Regulatory Agency who offer stem cell-based interventions or products outside the boundaries of accepted professional practice.

IMPROVE PATIENT ACCESS TO CLINICAL TRIALS

The process of clinical translation in Australia should be streamlined to improve patient access to high quality clinical trials that can generate scientific evidence of safety and efficacy for new stem cell-based applications.

Australia has a history of strong ethical and regulatory oversight to support the responsible conduct of clinical trials. However, uncertainty concerning the potential risks and benefits of many proposed stem cell-based interventions makes it difficult to adequately predict and protect against possible harm to patients. Current oversight systems have not kept pace with advances in stem cell research and so are ill equipped to identify and address the ethical, legal and social challenges of stem cell-based interventions.

Furthermore, lack of familiarity with and understanding of emerging evidence in stem cell science may hamper the ability of HRECs to review applications for clinical trials in a timely manner. Reviewers at the Australian and New Zealand Clinical Trial Registry (ANZCTR) may be equally challenged by the complexities of translational stem cell research. Consequently, fewer well-designed trials may be accessible to patients, which may, in part, contribute to demand for commercially available unproven stem cell-based interventions.

The competitiveness and ultimate success of the Australian regenerative medicine sector depends on the translation of safe and effective cell and regenerative therapies.

Therefore it is important that the necessary infrastructure and expertise be put in place to effectively oversee the inherent uncertainties of translational and clinical research with stem cells and cell-based technologies. Actions that may be helpful in supporting this goal include:

- providing HRECs with supplementary materials in support of the *National statement on ethical conduct in human research*, including specific guidance for evaluating research protocols for novel stem cell-based products or interventions
- establishing a specialist review board that HRECs and the ANZCTR may consult when evaluating human clinical research and trials involving stem cells.

UNDERTAKE HORIZON SCANNING

Mechanisms should be established to identify future possible threats and opportunities in stem cell research and regenerative medicine, and to proactively address the clinical, social, ethical and legal/regulatory implications of emerging technologies.

Exciting research advances arise frequently that have the potential to provide new therapies. However, the breadth and significance of these advances means that existing regulatory frameworks may often not adequately address the full set of implications resulting from the research progress. Current examples include: 1) the application of genetically modified stem cells; 2) the production of human gametes—eggs and sperm—from stem cells; 3) the recapitulation of early human developmental stages in the laboratory using stem cells; and 4) the emergence of new mitochondrial donation techniques such as pro-nuclear transfer and maternal spindle transfer to treat mitochondrial diseases.

The Australian regulatory environment therefore needs to ensure that it is sufficiently flexible to identify and investigate potential benefits and barriers to research, commercialisation and clinical translation that arise from advances in stem cell research. The outputs of these processes need to be closely tied to community engagement so that research progress is translated as efficiently as possible into improved outcomes for patients and stem cell biotechnology in a way that adds value to the sector. These structures could include:

- ensuring that stem cell and regenerative medicine research projects that receive government funding are required to consider the ethical, legal and social issues of the work (for example as part of the project proposal process)

- establishing streamlined mechanisms for updating existing guidelines and regulations when necessary in response to new stem cell and regenerative medicine discoveries (for example through formal liaison with appropriate professional bodies and regulatory authorities)
- establishing a formal horizon-scanning function for stem cell science within government or national scientific bodies, which will provide evidence-based policy to help Australia plan for emerging trends and address threats to the progress of the industry.

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Professor Hans Clevers Hubrecht Institute

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ABOUT THE THEO MURPHY HIGH FLYERS THINK TANKS

The purpose of the Theo Murphy High Flyers Think Tank series is to bring together early- and mid-career researchers from a broad range of relevant disciplines to engage in thinking about novel applications of existing science (including social science) and technology. They aim to examine issues of national significance and identify gaps in knowledge that should be addressed. These events are a unique opportunity for career development and networking among the nation's next generation of research leaders and their institutions. Think Tanks are one of the premier events of the Academy's calendar; this is the 14th that the Academy has held.

Previous Think Tanks

Previous Think Tanks have culminated in reports to government that have been timely, well received and instrumental in influencing policy development (available at www.science.org.au/news-and-events/events/think-tanks).

Past Think Tank topics have been:

- 2002** Australia's national research priorities
- 2003** Safeguarding the nation
- 2004** Emerging diseases: ready and waiting?
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- 2006** Innovative technical solutions for water management in Australia
- 2007** Extreme natural hazards in Australia
- 2008** Preventative health: science and technology in the prevention and early detection of disease
- 2009** Agricultural productivity and climate change
- 2010** Searching the deep earth: the future of Australian resource discovery and utilisation
- 2011** Stressed ecosystems: better decisions for Australia's future
- 2012** Australia's population: shaping a vision for our future
- 2013** Inspiring smarter brain research in Australia
- 2014** Climate change challenges to health: risks and opportunities

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